

1 Folks?

2 DR. TRACY: Warren, I think that's the
3 crux of the problem, is that both the subgroups,
4 symptomatic versus asymptomatic, and I think that's
5 where maybe the NASCET and the ACAS data have to come
6 into play to some extent, to look back at that and
7 what societies have regarded those results in terms of
8 their recommendations regarding endarterectomy or
9 stenting in asymptomatic patients.

10 I think the problem comes when you're
11 lumping these two groups of patients together.

12 CHAIRMAN LASKEY: Which precludes our
13 ability to generalize. I guess the other hooker here
14 is that we've heard a number of pleas for a medical
15 control arm, and I guess Dr. Zuckerman, you want to
16 address the nuances of that. That would help to put
17 some perspective into safety and efficacy. I
18 understand it's not --

19 DR. ZUCKERMAN: Okay. I'm not sure what
20 that has to do with Question 5 though. I'm sorry.

21 CHAIRMAN LASKEY: Well, we need a
22 comparator. We need a valid comparator.

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1 DR. ZUCKERMAN: Yeah.

2 CHAIRMAN LASKEY: And so comparing
3 symptomatic to asymptomatic I think is not, I think,
4 the end of the day for us, that there are other
5 patient subsets out there, if you will, many of them
6 in the medical treated arms that, again, we've heard a
7 great deal in favor of that this afternoon.

8 But why was that not -- why is that not
9 likely to work its way into today's discussion? Why
10 is it inapplicable or perhaps it is applicable. So
11 can you just speak to the inclusion of the medical
12 control arm?

13 DR. ZUCKERMAN: Okay. We're talking about
14 two important subsets, symptomatic and asymptomatic,
15 and the question for the asymptomatics was perhaps a
16 better trial design would have been a three-arm trial
17 with a medical control group.

18 However, from a legal, FDA regulatory
19 perspective, that sort of trial design is not
20 necessarily required if surgical endarterectomy for
21 asymptomatic patients is an acceptable standard of
22 care and the sponsor shows that compared to surgical

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1 endarterectomy in the asymptomatic group, there is a
2 reasonable risk benefit profile.

3 DR. TRACY: The problem is that there is
4 not agreement on that. I mean, the American Society
5 of Interventional and Therapeutic Neuroradiology and
6 the American Society of Neuroradiology and the Society
7 of International Radiology have a paper that was given
8 to us which indicates that asymptomatic endarterectomy
9 is at best controversial, not indicated in the
10 Canadian publications, sort of marginally indicated in
11 the U.S. publications, and that carotid stenting of
12 asymptomatic patients is listed as a relative
13 contraindication.

14 So it's a very difficult position for us
15 to be in. We're in a place where we may be asked to
16 approve something, approve a device for something that
17 it's not indicated for.

18 DR. WHITE: Wait though, Cynthia, wait,
19 wait. I mean, I agree there's some debate about
20 asymptomatic revascularization patients. There is,
21 but there's an AHA consensus statement about the
22 appropriateness of that revascularization that we've

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1 been practicing for a long time.

2 DR. TRACY: For endarterectomy or for
3 stenting?

4 DR. WHITE: Yes, for endarterectomy, for
5 endarterectomy greater than 80 percent.

6 DR. TRACY: Right.

7 DR. WHITE: The AHA consensus document.

8 DR. TRACY: Exactly.

9 DR. WHITE: The same group that was put
10 into this trial.

11 DR. TRACY: But not for stenting.

12 DR. WHITE: The question we have to ask is
13 is the stenting as safe as or equal to the surgery,
14 not whether the surgery is appropriate for greater
15 than 80 percent endarterectomy or greater than 80
16 percent lesion. Surgery is appropriate for greater
17 than 80 percent lesions. that's an established fact.

18 It's not that we can't debate it, but it's
19 an established medical fact. I do it every day. It's
20 standard of practice. We shouldn't go backtrack
21 there. We shouldn't get confused in that morass, and
22 Tony will tell you that. That is standard practice in

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1 the United States today.

2 Asymptomatic patient, greater than 80
3 percent stenosis, endarterectomy is indicated for that
4 patient. Now, you may not operate on every single one
5 of them, but it's an appropriate thing to do, and what
6 we have to decide is in that population of patients,
7 which were who were randomized in that trial, was the
8 stent as good as surgery or better or worse, but not
9 whether revascularizing 80 percent or greater lesions
10 is not what we're being asked.

11 I mean, I think if we go there we're never
12 going to get out of here.

13 DR. KRUCOFF: Yeah, I have to agree with
14 Chris. I think if the question is what's the optimal
15 treatment for asymptomatic carotid artery disease,
16 we're hosed. We have nothing to go on that's new.

17 But I think if you say in a population of
18 patients who are asymptomatic or scheduled for carotid
19 endarterectomy, is this a safe and effective,
20 reasonable alternative, I think that's what the
21 SAPPHIRE study a data set to think of.

22 DR. ABRAMS: Yeah, I would also say that

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1 several of the following questions also address the
2 same thing. I think really I agree with Chris. We
3 have to decide whether we're looking at safety or
4 we're looking at effectiveness and then maybe take the
5 issue of limitations of indications for things
6 somewhat later or at least open it to discussion, but
7 I don't think we want to discuss whether or not or
8 what the indications are for endarterectomy.

9 DR. TRACY: But even still there is a
10 higher risk of TIA in those treated with stent. Is
11 that a safety issue?

12 DR. WHITE: First of all, I don't believe
13 that's true. I don't think the data says that.

14 DR. TRACY: That's what the data says. I
15 mean it --

16 DR. WHITE: No, it was not a
17 statistically --

18 DR. TRACY: -- either says it or doesn't
19 say it.

20 DR. WHITE: It doesn't say they were
21 worse. It says they are the same. There was no
22 statistical difference that I saw. Was there a

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1 statistically different group?

2 The numbers were small, and the
3 variability was wide, and so it wasn't a higher risk.

4 CHAIRMAN LASKEY: Well, 6.6 is not small
5 in one year.

6 DR. WHITE: No, I'm sorry. the numbers of
7 the patients enrolled in the trial, the numbers
8 compared in the event rates were small, and so it
9 leads to difficulty in understanding the differences,
10 but there is no reason for me to believe that TIAs
11 occur more often after stenting than after
12 endarterectomy. Nothing. There's nothing that I know
13 that would indicate that.

14 DR. KRUCOFF: So maybe one other piece of
15 the last part of this question, Dr. Zuckerman, would
16 be that patient subgroups are tough to grapple at as
17 one result of premature stoppage of the trial, which
18 is very small, and it makes them very ambiguous.

19 DR. ZUCKERMAN: So you've looked at
20 Question 5(b), but Question 5(a) refers more to
21 Cordis' Slide 11, where you have the mechanisms by way
22 of higher risk patients were defined anatomic risks,

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1 medical co-morbidities. There were multiple pathways.

2 Is this an acceptable type of schema? Are
3 there any comments?

4 CHAIRMAN LASKEY: I think it is
5 acceptable, but they're still -- that's just the part
6 above water. I think, as with icebergs, there's so
7 much more beneath the surface. How do patients who
8 are asymptomatic with 80 percent stenoses wander into
9 the system and attract attention?

10 I think that is part of the crux of this
11 in terms of defining the appropriate patient
12 population for this device. Yes, it's clear if you
13 are in Class 3-4 CHF or you've had a recent acute
14 coronary syndrome, et cetera, et cetera, you're
15 certainly at high risk, but that's not the majority of
16 these folks.

17 And one does wonder how you get into the
18 system if you're asymptomatic and then discovered to
19 have an 80 percent stenosis. I think that's more to
20 the heart of how we practice and more to the heart of
21 who benefits from these interventions as well, but we
22 can't address that.

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1 I think the categorization of high risk is
2 certainly defensible. I haven't heard any arguments
3 about the classification scheme for what's high risk
4 today, but I think there's more to it than that,
5 particularly with a study in which two thirds of the
6 patients are asymptomatic.

7 How did they get into this study?

8 DR. COMEROTA: Warren, what responsibility
9 do we have? I mean, I agree with the comments that if
10 you take it on the surface, did you prove equivalence?

11 The answer is yes, but one way to prove equivalence
12 is to do any study with very, very small numbers, and
13 you're going to get equivalence no matter how
14 different the outcome is going to be.

15 Now, is --

16 CHAIRMAN LASKEY: I wouldn't say that in a
17 room with the statistical fire power that's sitting
18 here.

19 DR. COMEROTA: No, no, that's right.

20 (Laughter.)

21 DR. COMEROTA: But I think that it was
22 admitted that you need a fair amount of difference to

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1 have small numbers be statistically significant,
2 correct? I think we'd all agree on that.

3 And if our charge is only to look at the
4 difference between these two groups and the randomized
5 trial, the answer is clear. Do we have a little bit
6 more responsibility than that?

7 And I think that is what we're grappling
8 with. That's what I'm grappling with because we know
9 that the question addresses this variable way. So you
10 have recurrent carotid stenosis. You have
11 asymptomatic lesions. You have symptomatic lesions,
12 and the majority that were entered, the majority that
13 were treated with carotid angioplasty and stent had
14 less than 80 percent stenosis, the overwhelming
15 majority.

16 So we're looking at patients as I see them
17 who have relatively low risk lesions who are high risk
18 for intervention, and now we're choosing a high risk
19 intervention such as carotid endarterectomy, and we as
20 vascular surgeons are not proud of these results. And
21 I think to a person we would say these patients should
22 not be operated.

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1 But now we're asked to approve another
2 procedure that has equivalent outcome to outcomes that
3 we're embarrassed about, and that is the fundamental
4 disconnect of what we're being asked to do. That's
5 what I'm having problems with.

6 DR. WEINBERGER: But the reality is that
7 vascular surgeons are not turning those people away.

8 DR. COMEROTA: Well, look at the registry.
9 Vascular surgeons turned them away, and they were
10 intervened with.

11 DR. WHITE: No. That's not what happened.

12 DR. COMEROTA: Is that not correct?

13 DR. WHITE: No. Those patients were
14 referred for surgery. The decision for surgery was
15 made. The surgeon then said, "I can't operate," and
16 then they got into the registry.

17 DR. COMEROTA: Okay.

18 DR. WHITE: It has been said about 15
19 times today.

20 DR. COMEROTA: Well, I can't or I
21 shouldn't, or is there a difference? Is that not good
22 surgical judgment?

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1 DR. KRUCOFF: I have to take a little
2 exception at one other comment. Proving equivalence,
3 statistical proof of equivalence is not accomplished
4 just by doing small numbers. It's not the same as
5 seeing no difference because your numbers are too
6 small.

7 Now, we can question whether we actually
8 accept the methods used that would have terminated the
9 trial at 300 patients, but presuming that, in fact,
10 that is a legitimate statistic, and I think probably
11 when it's reviewed by FDA, it probably will be from
12 what we heard today, we're not just looking at a
13 casual finding from a small number of patients. This
14 is a significant noninferiority statistic that is a
15 little more than just something you get by doing too
16 little work.

17 DR. TRACY: Regardless of the question of
18 noninferiority, and I think to my mind it has been
19 satisfied as not being inferior to carotid artery
20 endarterectomy; however, the AHA guidelines indicate
21 it is approvable or recommended for 60 percent
22 stenosis if the stroke mortality rate is less than

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1 three percent.

2 That is what the AHA guidelines state.
3 That is what it states.

4 DR. WHITE: Well, I think you're just
5 misunderstanding just a little bit, and that is that
6 the consensus statement that was written by -- I'm
7 trying to think who the first author was -- there was
8 a consensus statement from the HA that said that not
9 60 percent was the indication for endarterectomy, but
10 80 percent.

11 DR. TRACY: With what mortality or stroke
12 rate?

13 DR. WHITE: Again, using the ACAS data,
14 but again, as you look, it gets a little complicated,
15 but the numbers you're looking at were guidelines for
16 programs to study safety. The indications for
17 operating on asymptomatic patients is greater than 80
18 percent, which is why it was used in this trial.

19 DR. TRACY: I think though that however
20 you cut this is controversial. I mean no matter how
21 many ways you look at this, and maybe this is what's
22 happening, but you're taking a carotid surgery and

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1 extending it to something that's even more --

2 DR. WHITE: Cindy, I'm telling you it's
3 standard of practice. It happens every day in the
4 hospital.

5 DR. TRACY: Sure, it happens every day,
6 but should it?

7 DR. WHITE: It's standard of practice.
8 It's not controversial.

9 DR. TRACY: Surgery happens every day.

10 DR. WHITE: Yes, greater than 80 percent
11 for asymptomatic patients. No question about that.

12 DR. TRACY: All right.

13 CHAIRMAN LASKEY: Therefore?

14 DR. WEINBERGER: One further comment that
15 speaks to this question. I think that the numbers
16 are too small to break out anatomic versus medical co-
17 morbidities, to break out symptomatic versus
18 asymptomatic, and I lament that very much together
19 with Dr. Comerota.

20 The fact is that surgeons in most
21 institutions operate on these patients, period. If
22 our surgical colleagues would turn them away

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1 routinely, then we'd have a very good argument here as
2 to whether or not we should be carotid stenting them.

3 But the truth is that the standard of
4 current surgical care is to treat people who are
5 asymptomatic, who have 80 percent stenoses with and
6 without medical co-morbidities. That is the reality
7 of what's happening in most institutions.

8 DR. COMEROTA: All we're saying is that
9 there are very, very few 80 percent stenoses and more
10 in this trial by angiographic description of diameter
11 reduction stenosis.

12 When you look at the symptomatic patients
13 that were randomized, there were probably ten or 12
14 patients with an 80 to 99 percent stenosis.

15 DR. WHITE: Are you looking at core lab
16 data? To get into the trial you had to have more than
17 80 percent lesions. I don't where this is coming
18 from.

19 DR. COMEROTA: Chris, they gave it to you
20 in your packet.

21 DR. WHITE: But I mean, are you telling me
22 that --

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1 DR. COMEROTA: Every patient had an
2 angiogram.

3 DR. WHITE: When I look at a patient to
4 get into this trial, he had to have more than 80
5 percent to get into the trial. Now, if two months
6 later --

7 CHAIRMAN LASKEY: That's asymptomatic. If
8 you're --

9 DR. WHITE: Asymptomatic that had greater
10 than 80 percent at trial. One hundred percent of the
11 patients had to have that. Now, two months later if
12 the core lab goes behind me and says, "You know, that
13 wasn't 80 percent. That was only 65 percent, Dr.
14 White," then that's what you're talking about.

15 DR. COMEROTA: Chris.

16 DR. WHITE: But to get into the trial 100
17 percent of the --

18 DR. COMEROTA: Look at the data, the
19 angiographic data in the panel pack.

20 DR. WHITE: Are you suggesting that
21 patients with asymptomatic lesions were enrolled with
22 less than 80 percent lesions?

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1 DR. COMEROTA: I'm suggesting that the --

2 DR. WHITE: Is that your criteria that I
3 don't know about?

4 DR. COMEROTA: I'm suggesting that the
5 overwhelming majority were less than 80 percent. If
6 you want the specific numbers --

7 DR. WHITE: But that was core lab. That
8 was post hoc data. That was analyzed after --

9 DR. COMEROTA: This is arteriographic
10 analysis.

11 DR. WHITE: After the fact.

12 DR. COMEROTA: This is at the time of
13 arteriogram before treatment.

14 DR. WHITE: You're wrong.

15 DR. COMEROTA: Chris, this is submitted to
16 us in the panel pack.

17 DR. WHITE: Maybe we could ask the sponsor
18 to clarify that for us, whether they would admit
19 asymptomatic patients to the trial with less than an
20 80 percent stenosis.

21 CHAIRMAN LASKEY: Well, the duplex was 80,
22 but then there's this carotid --

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1 DR. WHITE: Well, no. For stenting they
2 had to have an angiogram.

3 CHAIRMAN LASKEY: Right.

4 DR. WHITE: And at the time of that
5 angiogram if the investigator could not say it was 80
6 percent, they could not enroll that patient.

7 CHAIRMAN LASKEY: Well, let's put that on
8 the table.

9 DR. POPMA: Can I help?

10 DR. WHITE: Yes.

11 CHAIRMAN LASKEY: Yes.

12 DR. POPMA: We're going to pull up some
13 very quick slide. The hour is very late.

14 I'm Jeff Popma. We directed the
15 angiograph, the core lab analysis for this.

16 Very insightful comments. I had my travel
17 paid to come down here and also I'm on a coronary
18 stent advisory board.

19 That was an excellent question about the
20 disparity between the clinical site readings. The
21 average visual clinical site reading, which you can
22 see on this slide is perfect, was 85.2 percent. It's

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1 way too late in the afternoon to go to the differences
2 between NASCET and the ECST criteria, but when we
3 reapplied the ECST criteria from core lab analysis,
4 the stenosis was about 82 percent, and the NASCET
5 appropriately pointed out was a 68 percent stenosis.

6 And it's a huge issue about where
7 investigators actually take the reference vessel
8 diameter.

9 Having said all of this, the patients got
10 into the study based on the predefined Doppler
11 criteria for an 80 percent stenosis, which is in
12 clinical practice. Then we got the angiogram, as
13 Chris points out, months or two later. We've got very
14 detailed analyses about how we compare NASCET with
15 ECST, with visual readings that were performed and
16 provided in this.

17 Chris is exactly correct that the site
18 reported visual analyses, was an 85 percent NASCET
19 based visual analysis, but all of the patients got
20 into the study based on the Doppler criteria which
21 were predefined and standardized for this trial.

22 So I don't believe -- it's a long

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1 discussion which I can take care of later -- I don't
2 believe that inappropriate patients were put in the
3 trial. I believe that this trial reflects the type of
4 patients that are treated every day in clinical
5 practice and very comparable to what we've seen with
6 other clinical trials that are ongoing right now.

7 DR. COMEROTA: Could you answer then the
8 information on Table No. -- for every study, the
9 feasibility study, the randomized trial, the registry,
10 there's a patient-by-patient printout.

11 DR. POPMA: Correct.

12 DR. COMEROTA: And there's this column
13 that says "pre-procedure DS (percent)." Does that
14 mean pre-procedure diameter stenosis in percentage?

15 DR. POPMA: Your readings, which were
16 retrospectively late on down the line, yes, that's the
17 baseline percent stenosis.

18 DR. COMEROTA: Based upon an arteriogram.

19 DR. POPMA: Based upon our independent
20 core lab reading of the arteriogram.

21 DR. COMEROTA: Okay.

22 DR. POPMA: There's a subtlety to this

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1 question.

2 DR. COMEROTA: I'm not quarreling that the
3 patients didn't have your velocity criteria to get
4 into the trial. That is not the issue. All I'm
5 saying is by arteriographic analyses the number of
6 patients by angiogram defined 80 percent stenosis were
7 very, very few. There were about 19 percent, 80 to 99
8 percent stenosis, 19 percent in the randomized trial
9 and less than ten percent in the -- well, I have the
10 numbers, but there are very few relatively speaking by
11 arteriogram.

12 DR. POPMA: Using the NASCET criteria, the
13 NASCET criteria which takes the parallel portion of
14 the internal carotid, as we all know. You're correct
15 that the mean percent stenosis was 65 percent.

16 Having said that, it's a bit issue that we
17 can talk about now or later. The Doppler criteria
18 that were predefined and used for inclusion for
19 patients in the study were really initially validated
20 against the ECST criteria. We redid that based on an
21 imputed ECST criteria, and the Doppler readings are
22 very close to what they were initially validated with

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1 Gene Strandness and otherwise.

2 And having said all of this, most patients
3 who go off to carotid endarterectomy don't pass
4 through the catheterization laboratory before they go
5 to endarterectomy. This trial used standard Doppler
6 criteria for the 80 percent diameter stenosis.

7 We're in the process of writing the series
8 of validation papers, but basically I believe that the
9 patients who are enrolled in this trial met the
10 Doppler criteria, correlated with the ECST, and if we
11 were going to readjust everything, we would go back
12 and say that the NASCET criteria was a bit lower, but
13 that's what we would expect for every trial.

14 Having said that, one last slide which
15 I'll show here -- unfortunately I'm not going to be
16 able to blow it up to show it.

17 The real data that we should have been
18 talking about as we talk about the applicability of
19 NASCET criteria for this trial was a meta analysis
20 that was performed by Peter Rothwell along with Alan
21 Fox. We have had multiple discussions with Alan Fox
22 in our core laboratory over the last several months

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1 that really took all of the ECST criteria and went
2 back and reanalyzed them using the NASCET criteria.

3 All of the angiograms in ECST were re-
4 read, and the publication of this meta analysis says
5 two things to me. Without question, those patients
6 that had a greater than 70 percent -- in symptomatic
7 patients -- those that had a greater than 70 percent
8 stenosis did great with endarterectomy, but in
9 addition of an appropriately defined ECST and NASCET
10 meta analysis, there still is a statistical benefit
11 associated with anybody with more than a 50 percent
12 symptomatic stenosis.

13 That's coupled with this finding from
14 ACAS, and I know that we have focused on a greater
15 than 80 percent stenosis using a NASCET criteria and
16 ACAS, and Dr. Hobson is here and has spoken, and there
17 are a lot of subtleties to this, but this is the data
18 as was published in the JAMA article written for ACAS.

19 Even in those patients that had a greater
20 than 60 percent stenosis, there was still a benefit
21 with carotic endarterectomy. Absolutely we have
22 selected as a guideline for all the angiographic

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1 reasons we've talked about 80 percent, but if we
2 really drill in hard on the actual NASCET criteria
3 itself, there was still a statistical benefit at the
4 lower percent stenosis.

5 So having said all of this, I mean, if you
6 have questions I'll try to answer them, but I believe
7 that both in symptomatic patients and in an
8 asymptomatic patient this is the standard in clinical
9 practice today with respect to carotid endarterectomy,
10 and I believe that our results support the fact that
11 we're actually benefitting patients by
12 revascularization rather than with medical therapy,
13 understanding all of the limitations that we have with
14 the NASCET criteria.

15 I don't know if that helps at all, but
16 that's --

17 DR. COMEROTA: Well, I won't get into your
18 last comment, but very simply, we're just looking at
19 an angiographic definition of diameter reduction
20 stenosis. I'm not quarreling with the criteria. As a
21 matter of fact, I agreed with your criteria for your
22 noninvasive studies 100 percent.

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1 But when I look at the data that I
2 received for the angiographic analysis, it's what I
3 said, you know.

4 DR. POPMA: That's correct. And as we
5 talked --

6 DR. COMEROTA: And there's very few people
7 with a high grade stenosis that we would agree
8 angiographically had demonstrated.

9 DR. POPMA: I don't know that I agree with
10 that. By NASCET criteria, 95 percent of the patients
11 had more -- 95 percent of the patients had more than a
12 50 percent stenosis using the NASCET criteria. I
13 think virtually every lesion subset that we look at
14 there's a benefit with revascularization therapy.

15 Your point is well taken that we said 80
16 percent in the protocol based on the Doppler, and what
17 I'm trying to express is the Doppler was based on the
18 ECST criteria.

19 DR. COMEROTA: I know. You're trying to
20 get back to the Doppler. All I'm saying is the
21 arteriogram. That's all.

22 CHAIRMAN LASKEY: Jeff, your point is well

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1 taken, and I think this would be a hell of a time for
2 us to get back in to study inclusion criteria. So, I
3 mean, thank you. that's been very helpful.

4 And it's not the first time that actually
5 what is actually in a study is less than what you
6 think is there. That's lessons learned from QCA.

7 We have wandered far from the discussion
8 of the patient subgroups, but I think some important
9 territory has been aired out.

10 Number six?

11 MS. WOOD: Effectiveness of stroke
12 prophylaxis has historically required two to five
13 years' monitoring with safety outcomes generally
14 accessible within the lesser period of one year.
15 Please discuss whether chronic data presented in the
16 SAPPHIRE trial for the OTW configuration provide
17 evidence of sustained effectiveness of CAS in
18 preventing stroke in patients at high risk for CEA.

19 CHAIRMAN LASKEY: Well, panel members,
20 correct me if I'm wrong, but all I heard was that
21 there were extrapolations of the Kaplan-Meier curves
22 from the one year out to three and four years. So I

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1 think that's --

2 DR. WHITE: Well, I think they showed us
3 two-year data, three-year data.

4 CHAIRMAN LASKEY: The data on the median
5 survivals out to --

6 DR. WHITE: No, the stroke and death rate,
7 right? Was it stroke and death?

8 PARTICIPANT: There was stroke and death
9 for three years.

10 DR. WHITE: Was it for the complete -- it
11 was not for the whole data set. You don't have three-
12 year follow-up on the whole data set. Is that right?

13 DR. COMEROTA: If the question is did it
14 prevent stroke as well as CEA, the answer is yes. If
15 the question is did it prevent stroke in high risk
16 patients that are not going to undergo CEA, we don't
17 have that information.

18 DR. COHEN: Three-year data was presented
19 from the U.S. feasibility study, and the five-year
20 life expectancy for half of the patients was
21 extrapolated from the SAPPHIRE randomized data.

22 CHAIRMAN LASKEY: Right. Thank you.

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1 So there is no good, long-term data.

2 Number seven.

3 MS. WOOD: Is it appropriate for the
4 sponsor to employ OPCs developed from NASCET and ACAS
5 outcomes to assess outcomes for both symptomatic and
6 asymptomatic patients in the SAPPHIRE trial or should
7 the ACAS rates from the symptomatic trial be used for
8 comparison?

9 CHAIRMAN LASKEY: Well, we just had an
10 extended discussion about the study inclusion criteria
11 and how perhaps they were erroneous to start, and if
12 you re-look at them, the conclusions needed to be
13 modified certainly for the NASCET data.

14 So I mean, this is a very rapidly moving
15 target when you continue to reanalyze the data. I'm
16 not -- fellow members, is it appropriate for the
17 sponsor to employ OPCs?

18 DR. KRUCOFF: Well, Warren, you know, we
19 can maybe suggest to the agency that, on the one hand,
20 you have a SAPPHIRE cohort who are randomized, and you
21 have an hypothesis that you can test within that
22 population unto itself.

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1 Then there's all of the registries and
2 feasibility and the long-term data from the
3 feasibility, and how far you could extrapolate to use
4 historical point information from NASCET to ACAS might
5 be helpful there, but I think we've spent a lot of
6 time going over how many limitations you're going to
7 find in that particular question.

8 CHAIRMAN LASKEY: All right. So not
9 appropriate.

10 Number eight.

11 MS. WOOD: The ACAS and NASCET's did not
12 include myocardial infarction as an endpoint. The
13 SAPPHIRE trial included MI as a component of MAE. The
14 actual distribution of non-QA MIs are provided under
15 Tab 8 addendum of the panel pack. Please comment on
16 the sponsor's choice of this composite endpoint.

17 DR. COMEROTA: I think it's appropriate.

18 CHAIRMAN LASKEY: Well, it's appropriate
19 because it's contemporary, but is it appropriate when
20 you're looking at surgical outcomes versus non-
21 surgical outcomes, knowing that with surgical patients
22 you're stirring up the pro-thrombotic milieu. You're

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1 stirring up the pro-platelet milieu. You're stirring
2 up the flammatory milieu. You're stirring up a lot of
3 factors which go into postop surgical morbidity and
4 mortality, which are not applicable in the stent
5 patients.

6 Now, that's perhaps an advantage of this
7 study, but surgical patients were at a decided
8 disadvantage in this study because of the risk of
9 postoperative badness that happens when you give
10 general anesthesia to patients who are at high risk
11 for bad things.

12 I don't know what else there is to say.

13 DR. KRUCOFF: I happen to think that's
14 quite appropriate in the same way in thrombolytic
15 trials we look at stroke. You know, ultimately it's a
16 net clinical benefit concept, and I think it's pretty
17 clear that all current trials are looking in terms of
18 ultimately the net clinical benefit to patients in
19 this area.

20 CHAIRMAN LASKEY: Right, but we need to
21 tease out, especially when we're making comparisons to
22 studies that don't have MI as part of the event rate.

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1 We need to understand that this is a terribly
2 important difference about this trial and perhaps its
3 strong point, but there's no question when you look at
4 the Kaplan-Meier curves or mortality. Just look at
5 mortality out to two years. There is a clear and
6 distinct, early, sustained, and persistent -- I don't
7 care whether the log rank is significant or not -- but
8 the carotid surgical patients fare less well in terms
9 of long-term mortality, and I think that's telling us
10 something about their underlying risk not related to
11 the surgical procedure itself.

12 DR. COMEROTA: Does the fact that there
13 were significantly more carotid angioplasty stent
14 patients having had coronary revascularization, should
15 that come into our consideration in putting this into
16 perspective?

17 PARTICIPANT: No.

18 DR. AZIZ: I think it should because I
19 think you're already protecting against the event like
20 a myocardial infarct in the surgical patients. If
21 they have an underlying coronary artery disease, you
22 haven't tackled it, you know.

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1 DR. COMEROTA: I think if you look at
2 those curves that you're referring to Dr. Laskey, I
3 mean they continue to separate, and they separate a
4 great deal at about six -- start to separate at about
5 six or eight months and then really begin to diverge
6 as time goes by.

7 CHAIRMAN LASKEY: My point exactly. So
8 there's more than just the early hazard. There's
9 another hazard which is kicking in which we don't have
10 a good handle on, and certainly the long-term follow-
11 up data will be critical.

12 DR. ZUCKERMAN: Okay. Dr. Laskey, can you
13 give some advice for trials going forward? The point
14 of the question: is MI as significant as death and
15 stroke in these questions?

16 So that should be routinely in the primary
17 composite endpoint.

18 CHAIRMAN LASKEY: Is that a question?

19 DR. ZUCKERMAN: Yeah.

20 CHAIRMAN LASKEY: Yes, it certainly
21 belongs as an appropriate endpoint. I think we need
22 to understand its pathogenesis and its behavior and

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1 the risk factors IV. I mean there's a lot that goes
2 into this.

3 It's aggravating to sit here and hear that
4 50 percent of these patients were not treated with
5 beta blockers. They all had extensive coronary
6 disease. They all had extensive vascular disease, and
7 to be so under treated is, I think, a shame.

8 And we all know that if you intensely
9 monitor in the perioperative period and perhaps get
10 beta blockers on board preop, postop, there's this
11 whole area which has not been addressed, which is the
12 pre and postop management of the patients in this
13 study. That may certainly impact beneficially on the
14 postop infarction rates.

15 I'm astonished by the world class
16 cardiovascular caregivers who cannot see their way to
17 giving an adequate beta blockade to these patients at
18 high risk.

19 I'm done.

20 (Laughter.)

21 CHAIRMAN LASKEY: Nine.

22 MS. WOOD: The indications for carotid

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1 artery extending in the registry arm were largely
2 dictated by hazards of surgical exposure. The ability
3 to deploy a stent should not be affected by these
4 criteria or the outcomes achieved in this registry,
5 i.e., ten percent stroke and TIA at 30 days and an
6 additional 16 percent a one year acceptable.

7 DR. WEINBERGER: I don't know whether the
8 premise of this question is true. We've been trying
9 to ferret out how they got into the registry, and it's
10 true that the surgeons didn't want to operate on them,
11 but the analysis of those patients for the reasons
12 that they got into the registry is not heavily weighted
13 towards anatomic exclusions. It's also weighted
14 towards clinical exclusions. Am I wrong?

15 DR. ZUCKERMAN: Not all of the reasons for
16 entry are known, but for those patients who did have
17 anatomic reasons as the primary reason, those are the
18 results.

19 DR. COMEROTA: The registry followed the
20 randomized trial, correct?

21 DR. WEINBERGER: No, it was concurrent.

22 CHAIRMAN LASKEY: Parallel with.

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1 DR. COMEROTA: Parallel with? It did not
2 continue to enter patients into the registry after the
3 randomized trial was completed? No?

4 DR. WEINBERGER: No.

5 DR. COMEROTA: Okay.

6 DR. WHITE: I think you have to ask what
7 you compare the ten percent to. I think that, you
8 know, for example, we know that for stroke and death
9 if it's a reoperation on an endarterectomy, the HA has
10 told us the ten percent is an acceptable level.

11 So I think you have to say what are you
12 comparing it to because ten percent is high, one in
13 ten, and I think that I saw the sponsor present the
14 data for the registry compared to the surgery data,
15 which was questionable statistically in terms of its
16 honesty or the appropriateness of doing that.

17 But when I saw that comparison, the
18 registry data actually fell between the surgery arm
19 and the randomized arm. So it didn't appear to be
20 worse than the surgery arm.

21 So in that context of comparison, it seems
22 to be appropriate or acceptable.

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1 DR. KRUCOFF: If you will really take this
2 full circle, the conundrum becomes that patients who
3 are referred for endarterectomy for whatever reason,
4 symptomatic or not, who a surgeon evaluates and says,
5 "Huh-un, this is too high a risk," that's the group
6 who you probably ought to compare to medical therapy,
7 but that's a study, you know, that gets totally beyond
8 the pale here.

9 So in fact, we have data on sort of the
10 middle risk category, patients who are acceptable for
11 carotid and referred for carotid endarterectomy,
12 acceptable for carotid endarterectomy, who are
13 randomized, we have a data set that I think we might
14 be able to get to a conclusion on.

15 But those who are actually too sick for
16 surgery, we have these numbers, and really I think
17 we'd have to step back to say, "Compared to what?"
18 right to Chris' point.

19 CHAIRMAN LASKEY: And finally, because
20 they're only estimates and because the numbers really
21 are small, it would be helpful to just look at the
22 confidence intervals around these two. They may be

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1 rather unacceptable. I don't think we should just
2 look at the ra estimate.

3 Okay, ten.

4 MS. WOOD: Please comment on whether the
5 incidence of ipsilateral stroke is acceptable.

6 CHAIRMAN LASKEY: There's that word again.

7 (Laughter.)

8 CHAIRMAN LASKEY: And we need a comparator
9 here.

10 DR. KRUCOFF: So compared to
11 endarterectomy in a randomized cohort, it's
12 equivalent.

13 CHAIRMAN LASKEY: Not acceptable but
14 equivalent.

15 DR. WHITE: Well, I mean, again, compared
16 to what we understand. I think the largest single
17 subset of patients were redo endarterectomy patients.

18 Is that true, in the randomized trial? It was the
19 largest single indication, repeat endarterectomy. Is
20 that true, the largest?

21 I can't remember. Anyway, if ten percent
22 stroke and death is okay for those people, then we're

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1 well within -- if that's the accepted indication, then
2 we're well within the ballpark of that number, and
3 because it wasn't inferior, I think it is acceptable.

4 DR. COMEROTA: Would it be appropriate to
5 look at the registry patients as a comparator to
6 answer this question since they were deemed
7 unacceptable for operations or is that not
8 appropriate?

9 CHAIRMAN LASKEY: Well, it would be
10 appropriate, but we don't have the statistical -- we
11 don't have the methodology to do that. We're missing
12 a fair amount of data from my understanding. There's
13 a bunch of covariates there which haven't worked their
14 way into this analysis that may yet.

15 DR. COMEROTA: Well, we have the data on
16 ipsilateral stroke.

17 CHAIRMAN LASKEY: Yeah.

18 DR. COMEROTA: The data on ipsilateral
19 stroke for all patients in the registry trial, in the
20 registry, was 4.2 percent, and if you look at
21 ipsilateral stroke in the carotid endarterectomy
22 patients from SAPPHERE, it's 1.8 percent.

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1 If you look at symptomatic patients,
2 ipsilateral stroke in the registry was 6.5 percent,
3 and the carotid endarterectomy patient was zero.

4 If you look at asymptomatic patients, it
5 was too high in both. It was 3.2 percent in the
6 registry. It was 2.5 percent in the operative group.

7 So those are the data. That's why I asked
8 if it's appropriate or not.

9 CHAIRMAN LASKEY: Well, you just can't
10 compare them because they really are A and B. You
11 just can't compare the registry group in any way
12 easily to the randomized trial. They are different
13 and hence this effort to do at least a propensity
14 score if not more, but it's very difficult to just
15 look at those two numbers and say whether they're
16 different or not.

17 I think you need to drill down a little
18 further.

19 Number 11.

20 MS. WOOD: The various studies employed a
21 total of only four sized five millimeter stents. Does
22 the panel believe that there are adequate safety and

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1 effectiveness information for this size?

2 CHAIRMAN LASKEY: Tony, Judah? Not a lot
3 of data on this.

4 DR. WEINBERGER: Not a lot of data.

5 CHAIRMAN LASKEY: But needed; agreed?

6 DR. WHITE: I think that in the packet the
7 size, the iteration of these stents, the five to eight
8 is the same, essentially the same stent with the same
9 surface area, the same shortening.

10 I don't think this is the same issue as a
11 balloon expandable stent. I think it's a much less of
12 an issue than it is in a balloon expandable stent, and
13 I think that it would be -- I don't see why the five
14 millimeter stent would inherently be troublesome. It
15 would be used in a smaller artery.

16 And I think to not have a five if we're
17 going to do this would be putting some operators at a
18 disadvantage in a smaller area because then they'd be
19 using a six. So I think if a five is the right size
20 we ought to be able to use a five. It just doesn't
21 happen very often.

22 CHAIRMAN LASKEY: Okay.

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1 MS. WOOD: Has the totality of data
2 presented for the OTW configuration in the carotid
3 stent PMA shown reasonable assurance of safety and
4 effectiveness?

5 If not, what niche indications have been
6 shown to be safe and effective for carotid stenting?

7 CHAIRMAN LASKEY: Well, this is pretty
8 much why we're here today.

9 (Laughter.)

10 CHAIRMAN LASKEY: So -- what's that?

11 PARTICIPANT: This is.

12 CHAIRMAN LASKEY: Yes. So in terms of
13 safety, I think that the investigators have
14 demonstrated safety from the noninferiority
15 standpoint. I didn't hear anything to the contrary
16 today.

17 In terms of efficacy, I think there is a
18 lot of controversial material here in terms of the
19 reduction in the rates of stroke down the road, and
20 there's some unfortunate discordant outcome data with
21 respect to symptomatic/asymptomatic, men/women, other
22 subgroups which are annoying. You like to see all of

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1 the point estimates line up to the left of the hazard
2 ratio, but that's not the case here.

3 So that's my crack at this. Do you want
4 to round this out, folks?

5 DR. ABRAMS: I'd agree very simply. I
6 think we do agree that it's probably safe, but we have
7 real qualms about effectiveness, which is not a
8 question we're going to be able to answer today. So I
9 guess that's sort of what the agency is looking for.
10 I think that's kind of a black line answer to the
11 question.

12 DR. WHITE: But is the answer about
13 efficacy really noninferiority? I mean, there was no
14 superiority intended here. So efficacy, I think
15 sometimes we think of efficacy in terms of
16 superiority, but do we believe that not only did we
17 not cause harm, but are we not inferior to stenting?

18 And I think that's what the randomized
19 data set shows. So efficacy makes it sound stronger
20 than that, but I think the truth is that it's not
21 inferior.

22 DR. KRUCOFF: I think it's not a niche

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1 indication, but given the enrollment criteria for the
2 SAPPHIRE randomized cohort, and as Chris says, you
3 really want to sit not to the left of zero, but to the
4 left of the boundary that's appropriate for non-
5 inferiority.

6 But in that population, I don't know if
7 we'd call it a niche. Patients who are recommended
8 for revascularization or a carotid, symptomatic or
9 non, who are candidates for surgery despite having one
10 additional high risk characteristic; that in that
11 population, I think the equivalence of safety and
12 effectiveness out to the year of follow-up that's been
13 reported is pretty straightforward.

14 What goes beyond that year I think would
15 be a place we could think about.

16 DR. MAISEL: I respectfully disagree, and
17 I have particular concerns about the asymptomatic
18 group, and what do you call a stroke, a safety issue
19 or an effectiveness issue, I think, is a little murky.

20 But the 30-day rate for asymptomatic patients of
21 about five percent is very concerning to me.

22 I certainly recognize the troubles we've

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1 been having with the comparator group and that CEA is
2 performed in a lot of patients that have 80 percent
3 stenosis, but there's no CEA data on patients like
4 this that were enrolled in this trial. Many of the
5 data that we've been referring to are extrapolated
6 from much lower risk patients.

7 I'm particularly concerned about approving
8 this device for asymptomatic patients when we really
9 don't know whether it's the right thing to do for
10 patients who present better high risk with an 780
11 percent stenosis. We do not know what the best
12 treatment is for those patients.

13 DR. WHITE: You're right, but we've
14 backslid again. We just backslid again into the
15 indications for revascularization.

16 DR. MAISEL: But if you look at the
17 indications for the study, this study entry criteria
18 was not "you are going to be revascularized."

19 DR. WHITE: Yes, it is.

20 DR. MAISEL: No, it's not. It was "you
21 are referred for revascularization."

22 DR. WHITE: Bill, if you don't give me a

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1 stent, then these patients will be operated on with
2 their 5.3 percent --

3 DR. MAISEL: I disagree with that. I
4 think some of them will not be operated on. I think
5 some of them will receive medical therapy. I think
6 more than half of them will receive medical therapy as
7 evidenced by the registry data.

8 And so if a stent is not available, it's
9 conceivable that many of these patients will receive
10 medical therapy. I agree that the data suggests that
11 the asymptomatic patients are at very high risk,
12 better than carotid endarterectomy. I agree to that.

13 What I don't agree is that stenting these
14 patients is the best therapy for them.

15 DR. WHITE: I don't think they've
16 demonstrated superiority, and you used the word
17 "best." I think that what you have to say is that you
18 do not agree that it's not inferior to surgery.

19 DR. MAISEL: I agree that it is not
20 inferior to surgery.

21 DR. WHITE: But you're not sure that --

22 DR. MAISEL: I agree --

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1 DR. WHITE: -- the right thing to do is to
2 operate on these patients at all.

3 DR. MAISEL: I am saying I do not believe
4 that stenting these patients -- that there's evidence
5 here that stenting these patients is the right thing
6 to do.

7 DR. WHITE: But there's evidence that
8 stenting these patients is not inferior to surgery.

9 DR. MAISEL: I agree with that, but the
10 question is safety, and I am not sure that this device
11 is the right thing to do. I am not sure it is the
12 safest thing for the patients to receive this device.

13 DR. COMEROTA: Is it not true that in the
14 registry patients that if they did not have -- I mean,
15 seven patients were operated upon because it was
16 evident, at least the opinions were that it was more
17 appropriate to operate than not.

18 But if they were allocated to the registry
19 patients, if there were not a registry, these patients
20 would not have been intervened with; is that correct?

21 It's not correct?

22 DR. COHEN: Of the approximately 2,200

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1 patients who were screened, one third of them were
2 actually enrolled, and that compares favorably with
3 the trials that we are deciding whether or not are
4 appropriate comparisons. NASCET only enrolled one
5 patient for every three that received carotid
6 endarterectomy.

7 DR. COMEROTA: So we have a high risk for
8 an operation that we randomize to angioplasty and
9 stent versus operation. Now, how did they get to the
10 registry?

11 DR. COHEN: Basically the patient met
12 entry criteria, okay, and the surgeon decided that
13 they did not want to take the patient for surgery.

14 DR. COMEROTA: So we don't want to operate
15 on this patient. So you go ahead and put in a stent.

16 DR. COHEN: That's correct.

17 DR. COMEROTA: Okay, and then by virtue of
18 radiologists or the interventionalists saying in seven
19 patients, "We don't want to intervene on this patient.
20 You go ahead and operate," then they were operated.

21 DR. COHEN: Yes. I think a good analogy
22 to make here is a cardiology analogy. We have bypass

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1 surgery and we have multi-vessel stenting. There are
2 issues with both of them, advantages and
3 disadvantages. In assessing individual patients from
4 their history, their laboratory findings, other tests
5 that are obtained, we make our best clinical judgment
6 as to what the most appropriate therapy is, and
7 that's what we're talking about here, whether there
8 should be an alternative to what's already utilized
9 today in the United States.

10 DR. OURIEL: Tony, I was just going answer
11 your previous question about the asymptomatic side of
12 this, and I'll try to make it quick. But the data is
13 the data, and to split out asymptomatic patients is
14 really beyond the scope of the trial.

15 And that said, as we know, 70 percent of
16 our patients in this country are getting operated on
17 for asymptomatic disease, and they're not the low risk
18 patients. The New York study, seven centers circled
19 around New York City, many of these patients are high
20 risk.

21 So what do we do this procedure for? We
22 do it to prevent major ipsilateral stroke, and what

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1 was the major ipsilateral stroke in the treated
2 patients? Well, in the symptomatic treated patients
3 it was zero in the stent arm, and in the asymptomatic
4 treated patients it was zero, and that was at one
5 year. That was at one year.

6 So the results are obviously very good,
7 and let's look at a couple of other studies very
8 quickly. the first is ECST, and 9.8 percent risk of
9 stroke at three years in 80 to 90 percent stenoses.
10 It wasn't ACAS that split them out by stenosis. It
11 was ECST.

12 And in the 90 to 99 percent it was 14.4
13 percent stroke at three years, and then recently
14 presented data in London, about two weeks ago at the
15 Charing Cross study meeting ACST data, 1,500 patients
16 with severely stenotic asymptomatic disease, and at
17 five years, a 12 percent incidence of stroke, 2.5
18 percent per year.

19 So the goal of the SAPPHIRE trial was to
20 demonstrate non-inferiority of stenting and
21 endarterectomy in patients who we all treat, like the
22 patients at high risk for surgery, and this was

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1 conclusively demonstrated with a P value of 0.0035,
2 noninferiority. It's not that there just weren't
3 enough patients. It was well powered.

4 So the trial succeeded in proving in my
5 mind beyond any doubts that stenting is a safe,
6 effective, and appropriate alternative to
7 endarterectomy in symptomatic patients, in
8 asymptomatic patients that are at high risk.

9 DR. COMEROTA: You're very convincing, but
10 we're being asked -- I'm being asked; you're asking us
11 -- to change our entire paradigm of the management of
12 symptomatic patients on the basis of 50 symptomatic
13 patients being treated with the carotid angioplasty
14 and stent and 39 patients with atherosclerosis who are
15 symptomatic. That is what we're being asked to do.

16 DR. OURIEL: Well, I don't think so.
17 Respectfully, I think what we're asking you to do is
18 that if you have a patient that you are going to treat
19 that fit into this high risk criteria, that you ought
20 to be able to consider stenting in addition to
21 endarterectomy.

22 CHAIRMAN LASKEY: You may not get the

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1 answer now, but you're going to get it on the vote.

2 DR. ZUCKERMAN: That's fine.

3 CHAIRMAN LASKEY: Okay. Labeling.

4 MS. WOOD: Are the indications and
5 contraindications for the OTW configuration clear and
6 supported by the SAPPHIRE study findings?

7 If not, please identify the indication you
8 believe is supported by the sponsor's data.
9 Specifically, is stenting of asymptomatic patients
10 supported? Should any criteria stipulating when
11 stenting of asymptomatic patients is appropriate be
12 included in the labeling?

13 CHAIRMAN LASKEY: Well, we really just
14 addressed that. I'm not sure we're going to get any
15 further by any more dialogue, but I think people will
16 vote with their feet. Hopefully before they vote with
17 their feet, they'll vote with their hands about this
18 issue and whether the labeling should be so targeted.

19 So can we answer that in another way?

20 DR. ZUCKERMAN: Okay. Are there any
21 comments on Dr. Krucoff's prior suggestion that if you
22 can't cross with the distal protection device, this

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1 procedure should not be done?

2 DR. WHITE: You mean absolutely or
3 relatively?

4 DR. ZUCKERMAN: There was a comment before
5 that this should be a contraindication for --

6 DR. WHITE: I think it should be a
7 relative contraindication. I think you can use words
8 like "discourage" or "rethink it," but I think you
9 have to consider what your other options are. I think
10 the operator at that time needs to weigh the risks and
11 benefits knowing full well that -- I mean, there are
12 still people out there in the world who are not
13 convinced that protection devices are absolutely
14 required. So I don't know if we want to legislate
15 that, but I do think that we should encourage their
16 use as was done in this trial.

17 So I like the words "discourage" or "warn"
18 or "concern me," but I don't like the absolute
19 contraindication that says if I can't get a protection
20 device across I can't do it.

21 DR. MAISEL: I think if the label included
22 the data we were shown today with and without distal

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1 protection device and the risk of the procedure, that
2 would be very helpful.

3 CHAIRMAN LASKEY: Is that all the data
4 there is?

5 DR. TRACY: Warren, I don't want to
6 belabor this. Can I ask: is there such a thing in
7 anybody's mind then as a low risk high grade stenosis?

8 Okay.

9 CHAIRMAN LASKEY: Again, low risk for
10 what? Low risk for intervention or low risk for
11 subsequent events?

12 DR. TRACY: Well, since our concern is
13 stroke rate primarily in the asymptomatic patients, is
14 there a low risk, asymptomatic patient who should not
15 be exposed to this high risk procedure?

16 I mean if there was a way to state that in
17 the indications, really specifying that these are high
18 risk asymptomatic patients, it might make me a teeny
19 bit happier about it.

20 DR. KRUCOFF: Well, I think it would be
21 very reasonable to consider a phrase in the indication
22 labeling that the population of cohort for whom this

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1 is intended are patients who are considered good
2 candidates for benefit from carotid endarterectomy.
3 That's really where we have randomized data,
4 symptomatic and asymptomatic, whatever. That's the
5 group.

6 And if they're not candidates for surgery,
7 the registry arm of SAPPHIRE is actually a group who
8 are not candidates for surgery, and whether this
9 device is indicated in them or not, I think that's a
10 separate question, but at least to me the most clear
11 indication for use here would be in patients who are
12 candidates for surgery who would be anatomically
13 commensurate with stenting.

14 To touch on Bram's question, I don't know
15 to what degree a label or a condition can be applied,
16 but I think just based actually on the feasibility
17 data and the data where before the ANGIOGUARD wire was
18 available, there's clearly or appears to be a
19 different outcome with this stent than with the distal
20 protection.

21 For all of the different religions amongst
22 interventionalists, Chris, I think the data that's

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1 available would suggest at least a warning that the
2 risk of distal embolization appears to be higher based
3 on the data.

4 DR. WHITE: I believe that. I just don't
5 think it should be an absolute contraindication. I
6 don't like absolutes.

7 DR. KRUCOFF: Yeah, but some way to warn
8 operators that if you can't get the distal protection
9 system across --

10 DR. WHITE: Rethink whether you want to --

11 DR. KRUCOFF: -- this patient is a
12 candidate for carotid endarterectomy, and at least to
13 warn them that they should think that through.

14 MR. MORTON: Dr. Laskey, my only comment
15 about a warning, I'm not sure that the data from this
16 study showed that there was more danger in not using
17 the distal protection device.

18 DR. WHITE: No, but they presented
19 cumulative data over several -- they combined the data
20 for several of the trials that showed that the
21 patients who didn't have the device had a higher
22 stroke rate.

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1 DR. KRUCOFF: Yeah, the good news is that
2 they made the new version so good that 95 percent of
3 the time you're going to be able with a skilled
4 operator to get the distal protection system. It is
5 more flexible. It's more deliverable. That's the
6 good news, I think, that SAPPHIRE does sort of look
7 like is the expectable direction.

8 But I do think the meta analysis
9 ultimately with this stent, with and without the
10 angioguard at least operators should be warned if you
11 can't get into a distal protection position, be aware
12 that there may be a down side. And these are
13 candidates for carotid endarterectomy.

14 CHAIRMAN LASKEY: Okay.

15 MS. WOOD: Patients with complex
16 atherosclerotic disease of the aorta or highly
17 tortuous carotid arteries are not optimal candidates
18 for carotid stenting. Please comment on the adequacy
19 of the labeling with regard to patients with these
20 anatomic characteristics.

21 If there are candidate that are not
22 optimal that should be added, please also identify

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1 them.

2 DR. WHITE: I think the sponsor in the PMA
3 pretty well sets out the contraindications in terms of
4 thrombus and heavily calcified and tortuous lesions.
5 I think they're pretty well known, and I'm not sure
6 why the agency is asking this question. Do you think
7 there were additional things besides what were listed?

8 DR. ZUCKERMAN: We're not talking about
9 the clinical trial inclusion/exclusion criteria.
10 We're talking about how the warnings and precautions
11 presently read with respect to that factor. Is there
12 any other statement that you would put in regarding
13 lesion complexity that would make operators think
14 again about doing a carotid stent procedure or give
15 them pause to think?

16 DR. WHITE: It's very difficult to replace
17 good judgment at the table. Things change.
18 Angiograms look a certain way. You put a guiding
19 catheter or a sheath in. The carotids shift and kinds
20 appear where they weren't before. So it's a moving
21 target. It's very difficult to know before you get
22 into the cath. lab what the anatomy will actually be.

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1 So I think the warnings of the tortuosity,
2 the calcification, the thrombus, I think those things
3 are all up front, but I think it's just good judgment
4 and training that's going to teach operators when they
5 need to not be doing these things.

6 MS. WOOD: Should any other warnings
7 and/or precautions be stipulated in the labeling for
8 the over-the-wire configuration in addition to those
9 found in the proposed labeling?

10 DR. KRUCOFF: This is where I was going to
11 mention the distal, the ANGIOGUARD thing. I do think
12 that based on the data available that a warning to the
13 operator that of you are unable to position distal
14 protection, that the outcomes or risk of embolization
15 may be different should be clearly stated.

16 DR. WHITE: Can I ask the sponsor what was
17 the basis for the intracranial contraindication? I'm
18 trying to figure out why that's a bad thing to do.

19 DR. COHEN: Are you talking about
20 aneurysms?

21 DR. WHITE: No. You say here that
22 patients -- stenting of intracranial arteries is a

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1 relative contraindication. Just carotid stenting;
2 that if you're going to treat an intracranial lesion,
3 you shouldn't treat an extra cranial lesion.

4 DR. COHEN: Yeah.

5 DR. WHITE: Do you know why that's in
6 there, Jay?

7 DR. OURIEL: It's merely a carryover from
8 the exclusion criteria for SAPPHIRE.

9 DR. WHITE: Well, it's a good exclusion
10 criteria because you don't want to confound your
11 outcomes, but in reality sometimes we need to treat
12 outflow lesions to make the stent be latent and work.

13 DR. OURIEL: Sure.

14 DR. WHITE: So it probably shouldn't be
15 there.

16 DR. OURIEL: Point well taken.

17 CHAIRMAN LASKEY: But then again, wasn't
18 there something about tandem lesions?

19 DR. WHITE: The tandem is an indication,
20 but these are lesions up in the --

21 CHAIRMAN LASKEY: Yeah, okay. All right.

22 MS. WOOD: Please comment on whether the

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1 sponsor's post approval study plan is adequate. If
2 not, what additional information do you believe should
3 be collected post approval?

4 Specifically, do you recommend that an
5 independent neurologist make the neurological
6 assessments at each follow-up?

7 DR. ABRAMS: Yeah, I'd like to comment. I
8 definitely think so. I think it is a mistake or
9 perhaps it could have been thought out. There should
10 have been independent neurologists making the
11 evaluations during the current study. I'm sure there
12 were difficulties in doing it, and that's why it
13 wasn't done, but I think if the opportunity arises to
14 do it post marketing, I think it definitely should be
15 done, particularly if you're going to use minor
16 strokes as an adverse event as an important outcome.

17 CHAIRMAN LASKEY: And, yes, we think that
18 their post approval study plan is adequate, although
19 one always raises one's eyebrows at the nice round
20 number of 1,000. So you just might want to pursue
21 that.

22 DR. ZUCKERMAN: Okay. The agency needs

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1 clarification on where the neurologist is needed.
2 There is follow-up now planned at discharge 30 days,
3 nine months, et cetera. Is the independent
4 neurologist needed in the peri-stenting arena or is
5 there some reason for nine months to have an
6 independent neurologist?

7 What are we getting at here? Do we want
8 to assure in a post approval study that we can
9 replicate and generalize the acute carotid stenting
10 results?

11 DR. WHITE: How long will you ask the
12 sponsor to carry out the study of the randomized trial
13 patients?

14 DR. ZUCKERMAN: That's our next question
15 for an advisory panel.

16 DR. WHITE: Well, my point is that if you
17 want to know if events are occurring, you have to have
18 an independent neurologist. You cannot rely on an
19 operator. So if you want the data and you want to
20 know who had a stroke or who had an event, then I
21 don't care whether it's nine months or two years. It
22 has to be someone that didn't stand at the table to

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1 put that stent in.

2 DR. ZUCKERMAN: Okay, but there are two
3 different questions here. For a post approval study,
4 what is the main point that the panel wants to see?
5 Is it that when this procedure is generalized to
6 multiple hospitals in the U.S. we can replicate the
7 peri-stenting rates? That's one question.

8 The second question is in the IDE cohort,
9 if you want longer term, well documented follow-up,
10 you can ask the sponsor for a neurology examination of
11 those patients, but for this next 1,000 patients,
12 where is the neurologist critical? What is the point
13 of having a neurologist?

14 DR. WHITE: I think it's a 30-day
15 endpoint. A 30-day endpoint is going to be the
16 critical element here.

17 DR. ABRAMS: I would add one more, too, as
18 an endpoint in addition to the 30 days because I think
19 there's still the question about the low grade
20 embolization from devices that are placed in the
21 vasculature, and I think if it could be two points, it
22 would be 30 days and one year.

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1 DR. WHITE: Let me just say that I don't
2 necessarily disagree with that, but I think we ought
3 to be intensively studying the cohort of the subject
4 of the study intensively to determine that. I think
5 as we distribute this in post market surveillance, the
6 lion's share of the events are going to be peri-
7 procedural, and quality assurance issues and safety
8 issues are going to be all settled in 30 days.

9 So I think we should get emboli late
10 outcomes out of the cohort here followed for an
11 appropriate length of time, but as we go forward with
12 post market, I'm not sure that more than 30 days is
13 going to be much bang for our buck.

14 DR. COMEROTA: Is there going to be a
15 threshold above which there will be critical re-review
16 of the technique if there are major adverse events
17 occurring that exceed, substantially exceed, what were
18 observed in the SAPPHIRE?

19 DR. ZUCKERMAN: Yeah, the sponsor has a
20 data monitoring plan built into the post approval
21 study.

22 DR. COMEROTA: And would that include

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1 centers that were not part of the submission, or would
2 that be inclusive of the subsequent patients that
3 these investigators are entering?

4 DR. ZUCKERMAN: Your advice would be very
5 helpful here.

6 DR. COMEROTA: I would suggest that that
7 subsequent 1,000 be separate from the current
8 investigators. These individuals are very talented,
9 and their outcomes, I think, are going to set a
10 standard, and I think we need to insure that others
11 can match that outcome.

12 DR. KRUCOFF: I would, I hope, agree that
13 it should be both, and I think continuing to let
14 people who already have expertise use this in a post
15 market environment and making sure that new centers,
16 which I think they pretty explicitly made the plan to
17 include smaller hospitals, new operators. I think you
18 really need both, and that appears to me to be what
19 they have committed to.

20 The only other thing I wanted to mention
21 in this post approval is that I would at least put
22 special emphasis on or attention on areas where we

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1 have the least data from the pivotal trial, and that
2 would be the five millimeter stents and the cases
3 where distal protection was not able to be deployed,
4 but they were stented; that those are populations that
5 I would flag.

6 DR. ZUCKERMAN: So Part B of Dr. White's
7 response was the follow-up of the ID cohort. The
8 sponsor presently plans three-year follow-up. Is that
9 long enough to show durability of the procedure?

10 DR. ABRAMS: Yes, I'd think so.

11 CHAIRMAN LASKEY: Training?

12 MS. WOOD: Please comment on whether the
13 sponsor's training plan is adequate. If not, what
14 additional requirements do you believe should be added
15 to the training program?

16 CHAIRMAN LASKEY: Well, I guess this
17 morning's comments were it was accepted by the panel
18 that this was a reasonable training program, and
19 that's to be distinguished from qualification,
20 certification, confidence, and credentialing. Those
21 are all issues which are not within the purview of the
22 FDA or the panel, but are critically important.

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1 We've certainly heard a lot of testimony
2 in favor of those things today in the open public
3 session, but the training program seemed appropriate.

4 You know, I think we all have concerns about fly-by
5 carotid angiography in terms of acquisition of skills,
6 but I think looking at the best case scenario, people
7 will be well intentioned, will try and gain sufficient
8 experience.

9 The Cordis will adhere to a fairly
10 rigorous program, but it's really within the
11 governance of the local institutions to maintain some
12 quality assurance and some credentialing.

13 But having said that, there's not much
14 more that we can recommend. Any other thoughts on
15 training?

16 DR. KRUCOFF: Warren, I don't know if this
17 quite fits into a training program mold, but I guess
18 one of the things I've been sitting here thinking is
19 whether, given the controversy with regard
20 particularly to asymptomatic patients, whether just
21 the definition of a patient as a clinically indicated
22 surgical candidate would be something that should be

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1 maintained in a multi-disciplinary mode and whether
2 discussing how you identify the appropriate patients
3 belongs in a training program or not.

4 You know, one option would be almost like
5 the old brachytherapy approach, to involve several
6 disciplines in order to execute the procedure. It
7 does make things a lot more cumbersome, and I'm not
8 sure it really belongs in a training program.

9 But one thing might be to have surgical
10 and medical opinion that the patient is a candidate
11 for carotid endarterectomy as a way of describing the
12 patient population, who ultimately we know something
13 about the safety and effectiveness of the device.

14 CHAIRMAN LASKEY: Yeah, well, that's
15 certainly the high road. We would espouse that, but
16 that's probably not where most people travel
17 unfortunately, and as Chris said, you know, you let
18 people use their judgment, and hopefully they'll use
19 good judgment. There's no way to mandate that.
20 There's no way to inculcate that. You either have it
21 or -- so anyway, I think with respect to the device,
22 the training programs outlined is adequate, but the

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1 panel certainly has concerns with respect to
2 confidence and certification.

3 Okay? Before we move on to the vote, I
4 just want to ask Dr. Zuckerman and the agency if they
5 have any additional comments or questions prior to.

6 DR. ZUCKERMAN: No. We would just ask
7 that before any vote is taken that the panel members
8 pay particular attention to the regulatory definitions
9 of safety and effectiveness as read by Ms. Geretta
10 Wood.

11 MS. WOOD: I have one call for some
12 clarification. I had a question regarding who the
13 members are that would be voting on this device. If
14 you'd look at your attendees list, the voting members
15 and the consultants that are listed will all be
16 voting. The consultants were deputized, all of the
17 consultants here at the table.

18 CHAIRMAN LASKEY: Anything else?

19 I'd like to ask the sponsor if they have
20 any additional comments or questions.

21 DR. COHEN: No. thank you very much.

22 CHAIRMAN LASKEY: Okay. And, Dr. Hughes,

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1 do you have any comments prior to the vote?

2 DR. HUGHES: Yes. Thank you, Dr. Laskey.

3 I hope I can get my points across briefly
4 without loss of meaning. My comments are more along
5 the lines of general risk management as opposed to
6 specific medical and surgical criteria.

7 First of all, I want to commend the FDA's
8 staff and the sponsor for their presentations and, of
9 course, the panel for its review of the device. It's
10 as thorough a review as can be at this point.

11 And I also want to commend the presenters
12 in the open public session who, in general, I think,
13 did a fine job of illuminating the issues.

14 It's uncomfortable though to place the
15 panel in the position of either recommending approval
16 or non-approval with data and information, as well as
17 changes in protocol, you know, coming along, you know,
18 so close to the panel meeting, as well as some of the
19 apparent shortcomings in the pre and postoperative
20 medical therapies as has, you know, been brought out.

21 But anyway, I feel like the panel and the
22 FDA are at a point where there is a need for a balance

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1 of technological innovation, which I think that this
2 device and therapy represent an acceptable risk to the
3 ultimate consumer, certainly, you know, the patient.

4 Let's see. With the lack of statistical
5 analysis of the device, you know, in accordance with
6 strict adherence to FDA protocols, risk management for
7 this device if approved I think would require a
8 tremendous amount of cooperation among the
9 participants in the overall risk management system,
10 that is, you know, FDA constituents, the manufacturer,
11 as well as professional societies.

12 So input in the risk management system
13 from all of those parties would, indeed, be needed and
14 very aggressive, I think, and it would require the
15 aggressive enhancement of several attributes of the
16 medical device risk management system, in particular,
17 you know, those concerning labeling and post market
18 surveillance.

19 Of course, they have been addressed here,
20 particularly the labeling in terms of what's been said
21 by panel members and what was read into the record
22 from one of the parties in the public open session.

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1 Some of those aggressive measures, I
2 think, in post market surveillance would require what
3 I would consider some, you know, voluntary actions on
4 the part of the manufacturer, possibly beyond what the
5 FDA would be prepared to mandate, and I'm thinking
6 about such things as an aggressive device retrieval
7 program. I've noted some concerns for device
8 durability, and given the somewhat limited follow-up
9 time for the studies that we see here.

10 So I feel like there would need to be a
11 program set in place for aggressive device retrieval.

12 If we're talking about that, what also may need to be
13 considered is some form of an autopsy program coupled
14 with device retrieval.

15 Of course, if we're talking without device
16 retrieval it still may be possible; I'm not sure; it
17 may be possible to glean some insight in the form of
18 noninvasive autopsy, MRI, CT scans, and I'm thinking
19 in terms of, you know, whether or not that each
20 individual faces that ultimate ending point, whether
21 they're a patient or not, and so it's a matter of not
22 an issue of whether death is caused by some failure of

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1 the device, but there might be some information
2 gleaned from some form of autopsy program.

3 And then finally, I believe that the
4 manufacturer should also consider some form of
5 emergency compensation funds if it's determined that
6 there was something overlooked in this review, the
7 pre-market review and evaluation.

8 Part of risk management is to accept that
9 there will be some level of adverse events, and if
10 this level is higher than we've anticipated, I feel
11 that the manufacturer should be prepared to compensate
12 for any later intervention that might be necessary to,
13 you know, correct the device therapy, the device
14 situation, if that would, indeed, be possible.

15 And, you know, thank you for your time.

16 CHAIRMAN LASKEY: Michael.

17 MR. MORTON: I would acknowledge that
18 there have been some very intelligent and heartfelt
19 statements made by each member of the panel today. I
20 would also acknowledge Dr. Zuckerman's comments that
21 the role of the panel is to evaluate and make a
22 decision based upon the data that have been presented

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1 today and make a judgment based upon evidence of
2 safety and effectiveness.

3 And I understand that the Executive
4 Secretary is going to read that formal definition in
5 just a bit.

6 So thank you very much.

7 CHAIRMAN LASKEY: Thanks, Mike.

8 Geretta, if you can please read the voting
9 options.

10 MS. WOOD: Before I read the voting
11 options, just a point of clarification. Dr. Salim
12 Aziz, who is also a voting member, his name was
13 omitted from the attendees list. He also will be
14 voting today.

15 The medical device amendments to the
16 Federal Food, Drug, and Cosmetic Act as amended by the
17 Safe Medical Devices Act of 1990 allows the Food and
18 Drug Administration to obtain a recommendation from an
19 expert advisory panel on designated medical device
20 pre-market approval applications, PMAs, that are filed
21 with the agency. The PMA must stand on its own
22 merits, and your recommendation must be supported by

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1 safety and effectiveness data in the application or by
2 applicable publicly available information.

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

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

12 Your recommendation options for the vote
13 are as follows:

14 Approval, if there are no conditions
15 attached;

16 Approvable with conditions. The panel may
17 recommend that the PMA be found approvable subject to
18 specified conditions, such as physician or patient
19 education, labeling changes, or a further analysis of
20 existing data.

21 Prior to voting all of the conditions
22 should be discussed by the panel.

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1 The third option is not approvable. The
2 panel may recommend that the PMA is not approvable if
3 the data do not provide a reasonable assurance that
4 the device is safe or if a reasonable assurance has
5 not been given that the device is effective under the
6 conditions for use prescribed, recommended or
7 suggested in the proposed labeling.

8 Following the vote, the Chair will ask
9 each panel to present a brief statement outlining the
10 reasons for their vote.

11 CHAIRMAN LASKEY: I'd like to ask for a
12 motion on the PMA. Anyone?

13 DR. NAJARIAN: I make a motion that the
14 PMA be approved, but proof for the treatment of
15 symptomatic carotid disease in high risk patients.

16 CHAIRMAN LASKEY: We probably should back
17 that up, and then we will discuss the conditions to be
18 applied, but --

19 MS. WOOD: Excuse me. Dr. Najarian, are
20 you suggesting that you would like for the device to
21 be approved or are you --

22 DR. NAJARIAN: Approved with conditions.

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1 MS. WOOD: -- would like approvable with
2 conditions?

3 DR. NAJARIAN: Approvable with conditions.

4 MS. WOOD: Thank you.

5 CHAIRMAN LASKEY: Is there a second?

6 DR. WEINBERGER: I'll second.

7 CHAIRMAN LASKEY: Okay. It has been moved
8 and seconded that the PMA is approvable with
9 conditions, and let's take these conditions.

10 DR. TRACY: Warren, let me clarify this.
11 I believe he just voted for or he just recommended
12 approval for patients with symptomatic carotid
13 disease.

14 DR. WEINBERGER: No, a condition.

15 CHAIRMAN LASKEY: No, that will be a
16 condition that I'm about to ask for. It's approvable
17 with conditions is the motion which has been seconded.

18 DR. TRACY: I believe he stated though --
19 so you're making the distinction, just so we're clear.
20 What do you think we're moving for? what do you
21 think we're approving here?

22 DR. NAJARIAN: I will back up and

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1 simplify. My motion is vote for approval for
2 conditions, which we can now discuss.

3 DR. TRACY: Okay.

4 CHAIRMAN LASKEY: Which has been seconded.
5 The first condition of approval then is?

6 DR. NAJARIAN: That the use be limited to
7 symptomatic patients -- excuse me -- symptomatic high
8 risk patients.

9 DR. COMEROTA: Would that be with moderate
10 or high grade carotid stenosis? Symptomatic patients
11 with moderate or high grade carotid stenosis --

12 DR. NAJARIAN: Correct. This is --

13 DR. COMEROTA: -- carotid endarterectomy.

14 DR. NAJARIAN: Yeah.

15 DR. WEINBERGER: Do you mean limited or do
16 you mean indicated for? I don't think we're putting
17 limitations here. We're stating indications. The
18 indications should be indicated for patients with
19 symptomatic carotid disease with high grade anatomic
20 features.

21 CHAIRMAN LASKEY: Well, on the table right
22 now is the condition that they be symptomatic and at

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1 high risk.

2 DR. NAJARIAN: High risk, correct, not
3 high anatomic.

4 CHAIRMAN LASKEY: And the discussion that
5 ensued also put some quantification in as well?

6 DR. COMEROTA: I raised a point of
7 clarification with Dr. Najarian, did he mean to
8 include moderate to high grade carotid stenosis. In
9 other words, the NASCET terminology.

10 DR. NAJARIAN: Yes.

11 DR. COMEROTA: In patients at high risk
12 for carotid endarterectomy.

13 DR. WEINBERGER: And we're talking about
14 an indication recommendation or limitation?

15 CHAIRMAN LASKEY: An indication.

16 DR. NAJARIAN: I need some help here.

17 CHAIRMAN LASKEY: Yeah, an indication. I
18 think the process here should go through the generic
19 approvable with conditions, approved or disapproved.
20 We now have on the table the motion which has been
21 seconded, and we're moving forward with it. It's
22 approvable with several conditions, I'm sure, the

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1 first of which is that its procedure be applied to
2 symptomatic high risk patients, and that is high risk
3 for carotid endarterectomy. Is that accurate?

4 DR. COMEROTA: I asked for clarification
5 from Dr. Najarian. I think he clarified that was
6 accurate.

7 DR. MAISEL: Do you mean symptomatic
8 patients only or symptomatic patients?

9 DR. NAJARIAN: Only, only. I guess I'd
10 have to look back. Symptomatic patients --

11 DR. MAISEL: Are you trying to exclude
12 the --

13 DR. NAJARIAN: I'm trying to exclude the
14 asymptomatic group.

15 DR. KRUCOFF: So is this open for
16 discussion or do we need a second?

17 CHAIRMAN LASKEY: We're discussing this
18 condition.

19 DR. KRUCOFF: Right. Okay. Because I
20 think we're going to face a real conundrum here. The
21 only data that we really have that's interpretable is
22 for patients in whom carotid endarterectomy was

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1 indicated, symptomatic and asymptomatic.

2 As soon as you drop out asymptomatic
3 patients, you don't have enough data left to know what
4 you're doing. So I think the panel has got to face
5 the conundrum that for all of the miasma of our poor,
6 hapless asymptomatic patients going to get intervened
7 on where medical therapy might actually do just fine.

8 The data set that we have gives its
9 clearest look at the use of this device in patients in
10 whom the clinical consideration that they would be
11 better off revascularized has already been made
12 whether they're symptomatic or not, and as soon as we
13 drop the asymptomatic patients from that, there is no
14 data left to make database decisions.

15 DR. WHITE: I would support that, and I
16 really do think that two-thirds of this data was
17 asymptomatic, and I think we really run the risk of
18 inappropriately parsing this data to leave out that
19 population.

20 I think if you can't accept the
21 asymptomatic patients, then you probably can't accept
22 it on the whole.

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1 DR. KRUCOFF: Now, Bill, what you said
2 before, Bill, the registry patients here are not the
3 issue. It's the randomized patients.

4 DR. MAISEL: But the registry patients are
5 an issue in that the patients who would come to the
6 table in the real world are the randomized patients
7 plus the registry patients because those were the
8 patients that got sent in to be enrolled in the study.

9 So over 50 percent of those patients ended up not
10 being surgical candidates even though whoever referred
11 them in thought they were surgical candidates.

12 DR. KRUCOFF: Okay. So what we can do is
13 indicate that they're surgical candidates.

14 DR. WHITE: I think we have to be careful
15 with the word "surgical candidate." These patients
16 were indicated for revascularization, and it was only
17 after they were examined and looked at that they were
18 determined that it was high risk for surgery.

19 DR. TRACY: I think the problem is the
20 way the indication is written as it's being requested,
21 any old 80 percent asymptomatic stenosis gets a
22 procedure done. I think it has to be specifically

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1 stated that these are patients who require some form
2 of revascularization because they are at high risk for
3 stroke.

4 So I think if we can clarify that and make
5 it less nebulous, then I think we'll be happier, and I
6 agree, as much as I don't like having the asymptomatic
7 people here, I think we can't throw out two-thirds of
8 the patients. Otherwise we have nothing to work with.

9 CHAIRMAN LASKEY: No, but it's not
10 comfortable being up here espousing something just
11 because it's done. I think that's what we're
12 grappling with. Just because they would have surgery
13 and that's the standard of care, there's no data to
14 support that.

15 DR. COMEROTA: Mitchell, you said it was a
16 conundrum. that's a major understatement. You know,
17 we're looking at a procedure that in the asymptomatic
18 patients, and you can disregard the registry data if
19 you will, but in an asymptomatic patient at 30 days, a
20 death or ipsilateral stroke rate of 7.3 percent at 30
21 days in asymptomatic patients with many of these being
22 recurrent stenosis, and the overwhelming majority

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1 having angiographic lesions less than 80 percent, and
2 we're going to approve that if we include asymptomatic
3 in there, and I don't see how I can sleep at night if
4 I say that that's okay, that we're going to allow
5 that.

6 DR. MAISEL: Mitch, I completely
7 appreciate your point about doing subgroup analysis.
8 I think the issue is that there's no great way.
9 There's no right answer, and I think it's pick your
10 poison, and for me my poison is I'd rather see more
11 data convincing me that the asymptomatic patients are
12 not harmed by the procedure because I'm not convinced
13 of that.

14 CHAIRMAN LASKEY: Elaborate? Are you
15 speaking to the post marketing phase of this?

16 DR. MAISEL: I am speaking to the motion
17 on the table, which I would second.

18 DR. COMEROTA: I misquote. Sorry. It was
19 a death or ipsilateral stroke rate of six percent. It
20 was the symptomatic patients at 7.3 percent. So I
21 wanted to correct that.

22 DR. ABRAMS: Would the panel feel more

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1 comfortable if it was said that if the patient was a
2 high risk patient and a surgical candidate, leaving
3 the surgical, the concept of surgical candidate to
4 societies, to other data that has to be interpreted by
5 the person who is using the device?

6 MS. WOOD: Can't hear you.

7 DR. ABRAMS: I'm sorry. I agree with you.

8 I think there's a lot of discomfort about implicitly
9 approving this for asymptomatic patients, but I'm not
10 quite sure if that's our bailiwick to make a decision.

11 I think if we say that the device is approved for
12 high risk patients who are surgical candidates for
13 revascularization, we may be sort of able to kind of
14 walk a tightrope there and feel a little bit more
15 comfortable, as opposed to the indications that are
16 currently being proposed by the sponsor.

17 CHAIRMAN LASKEY: Well, no, I think we're
18 getting warmer. To rephrase the motion --

19 MR. WOOD: Dr. Laskey, a point of order.
20 We have a motion and a second on the floor. We have
21 to take a vote.

22 CHAIRMAN LASKEY: I'm not sure we're done

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1 discussing it, Geretta. That's the problem. So I'm
2 trying to rephrase, fine tune, be more precise in the
3 language. So we will vote when we appear to have some
4 consensus.

5 MS. WOOD: Then you will have to convince
6 Dr. Najarian to edit his motion that's on the floor.

7 DR. KRUCOFF: Or we can vote on it. We
8 can vote on the condition.

9 DR. TRACY: Or vote it down.

10 DR. KRUCOFF: Yeah.

11 DR. TRACY: Could somebody tell me what
12 the motion is?

13 (Laughter.)

14 DR. NAJARIAN: I can be more precise
15 because I can just read it. Vote that the Cordis
16 PRECISE nitinol stent system used in conjunction with
17 the ANGIOGUARD XP emboli capture guidewire is
18 indicated for the use in the treatment of carotid
19 artery disease in high risk patients. "High risk" is
20 defined as patients with neurologic symptoms, one or
21 more TIAs, or one or more completed strokes and
22 greater than 50 percent atherosclerotic stenosis of

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1 the common or internal carotid artery by ultrasound
2 and must also meet one or more conditions that place
3 them at high risk for carotid endarterectomy.

4 DR. COMEROTA: Ken, would you agree to
5 just say 50 percent stenoses and include all 50
6 percent or greater stenoses? Because I think that
7 recurrent stenoses are very appropriately included in
8 that group.

9 DR. NAJARIAN: Sure.

10 CHAIRMAN LASKEY: So all you've done is
11 just to reiterate what's in the label.

12 DR. NAJARIAN: Right.

13 DR. KRUCOFF: He took out -- but it's just
14 symptomatic in 50 percent is what I heard.

15 DR. NAJARIAN: That's the motion that I
16 put forth.

17 CHAIRMAN LASKEY: And the discussion that
18 I'm hearing is that delimiting this motion to just the
19 symptomatic segment is problematic.

20 DR. MAISEL: Can I make a suggestion?
21 Since we all agree on that, why don't we vote on that?

22 CHAIRMAN LASKEY: Yeah, that was my next.

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1 So just so we're all sure about what the motion is,
2 one more time, Ken, please. Just restate the motion
3 with the first condition.

4 DR. NAJARIAN: The motion is to approve
5 the PRECISE nitinol stent system in conjunction with
6 the ANGIOGUARD XP emboli capture guidewire for the
7 treatment of carotid artery disease in high risk
8 patients. "High risk" is defined as patients with
9 neurologic symptoms, one or more TIAs, or one or more
10 completed strokes and greater than 50 percent
11 atherosclerotic stenosis of the common or internal
12 carotid artery by ultrasound or angiogram.

13 DR. COMEROTA: I'm sorry. I hate to keep
14 beating --

15 DR. NAJARIAN: No, that's okay.

16 DR. COMEROTA: -- but I think you agreed
17 to recurrent stenosis, as well as atherosclerotic. So
18 neointimal fibroplastic lesions on --

19 DR. NAJARIAN: I think recurrent stenosis,
20 if I'm correct -- and maybe not -- is included in
21 the --

22 DR. COMEROTA: Well, you specifically said

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1 atherosclerotic lesions.

2 DR. NAJARIAN: Right, but also symptomatic
3 patients must also have one or more conditions that
4 place them at high risk for carotid endarterectomy.
5 And I believe recurrent stenosis is one of those
6 conditions if you look at the list, which I don't have
7 right in front of me.

8 DR. COMEROTA: But then you probably ought
9 to drop the atherosclerotic term and just say 50
10 percent or more stenosis. I just want to be clear on
11 what we're voting on, and I want to be clear that
12 patients who are very likely to benefit have the
13 ability to benefit by that procedure.

14 DR. NAJARIAN: To make matters a little
15 easier I'll withdraw the motion at this point and then
16 we can start anew.

17 CHAIRMAN LASKEY: Well, I'm not sure
18 that's any easier, but I think it may have been voted
19 down.

20 PARTICIPANTS: It has been seconded.

21 MS. WOOD: It has been seconded. The
22 second has to be withdrawn first.

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1 DR. MAISEL: If I seconded it, I withdraw
2 it.

3 MS. WOOD: Thank you.

4 CHAIRMAN LASKEY: All right. From the
5 top, I need a motion.

6 DR. KRUCOFF: For a condition.

7 MS. WOOD: A condition.

8 DR. KRUCOFF: All right. I would move
9 that the first condition be that with the indication
10 for patients include patients who have clinical
11 indications for carotid revascularization and an
12 attendant high risk condition as listed per the
13 inclusion criteria in the SAPPHIRE study.

14 DR. COMEROTA: So basically what is
15 requested for the indication as stated.

16 CHAIRMAN LASKEY: Yeah, I mean, that's not
17 much different than the current label.

18 DR. WHITE: And I'll second it.

19 CHAIRMAN LASKEY: Now, let's have some
20 discussion.

21 DR. TRACY: I think that the requested
22 indication by the sponsor did not specify that the

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1 patients who were asymptomatic be at high risk. I
2 think Mitch's attempt is to specify that the
3 asymptomatic patients are at high risk, if I'm
4 understanding the intent of what Mitch is saying.

5 CHAIRMAN LASKEY: But without mentioning
6 that word.

7 DR. TRACY: Without mentioning the word.

8 DR. WHITE: It's both.

9 CHAIRMAN LASKEY: Pardon?

10 DR. WHITE: It's both patients. You want
11 everybody.

12 CHAIRMAN LASKEY: Right, but we're not
13 mentioning symptomatic or asymptomatic. Your language
14 is attempting to cover the waterfront.

15 DR. KRUCOFF: My language, which is really
16 only mildly different from the indication as the
17 sponsor stated, but my intention is that this language
18 is commensurate with where we have data that we can
19 interpret, which is patients who for clinical reasons
20 across a range as we see of different approaches,
21 ultimately the end common pathway is that they are
22 patients who clinicians feel warrant

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1 revascularization. They are AHA -- we have standards
2 in print, professional society standards to help
3 already guide where this goes, and I think that's
4 where we have data on where this goes.

5 These are patients who have a clinical
6 indication for revascularization combined with a high
7 risk characteristic.

8 DR. MAISEL: I think the problem when you
9 make it so general, there is an indication for
10 asymptomatic patients with stenoses of more than 60
11 percent that might be considered candidates for CEA at
12 their lower risk, but now we're saying we're going to
13 include those as well?

14 DR. KRUCOFF: Well, except, Bill, the ACC
15 recommendation is 80 percent. I mean, you know, there
16 are guidelines already for who in an asymptomatic
17 population at least professional societies consider
18 appropriate for revascularization, and rather than
19 reinvent them or restate them, you know, I think
20 that's how patients got into this study.

21 And you know, we get into the vicissitudes
22 of what kind of angiographic or ultrasound cutoff, et

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1 cetera, et cetera, and I think we spin wheels. I
2 think the cut point here is the intended use of this
3 device is as an alternative to carotid endarterectomy
4 for patients obviously who have an indication for a
5 carotid endarterectomy. And that's where the
6 randomized data is that I think has most clear
7 interpretability.

8 DR. ABRAMS: In your motion, Mitch, are
9 you going to put a definition of high risk in or are
10 you going to leave it out?

11 CHAIRMAN LASKEY: It's as per the sponsor.

12 DR. KRUCOFF: The inclusion criteria in
13 the SAPPHIRE study was what I suggested, and I think.

14 DR. ZUCKERMAN: Okay. I think it's clear
15 that there has been a very active panel discussion,
16 and there has been some divergence of opinion today.
17 What would help the agency though is if the panel does
18 try to vote on specific recommendations, and if there
19 is disagreement, that's fine.

20 CHAIRMAN LASKEY: That's our next step,
21 Bram.

22 Okay. So we'd like to vote on this first

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1 condition then.

2 DR. KRUCOFF: Should we list all
3 conditions first or vote on them one by one?

4 CHAIRMAN LASKEY: We vote on each one
5 individually, and then we get to do it all over again.

6 So the first condition is to paraphrase
7 Dr. Krucoff, it's indicated in patients with a
8 clinical indication for carotid revascularization and
9 who are at attendant high risk for carotid surgery,
10 other definitions of high risk as per the RCT label.

11 So may I have by a show of hands all in
12 favor of this motion? Raise high.

13 (Show of hands.)

14 CHAIRMAN LASKEY: In favor. All against?

15 (Show of hands.)

16 CHAIRMAN LASKEY: Six against. So that
17 condition does not survive. I think we need to
18 entertain another condition.

19 DR. ABRAMS: Can I put forward another
20 proposal? I'd like to put forward the same proposal
21 without the definition of "high risk" in the proposal.

22 So it would be indicated for use in treatment of

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1 carotid artery disease in high risk patients.
2 Patients must also have one or more conditions that
3 place them at high risk for carotid endarterectomy.

4 And the reason for putting forth a
5 proposal like this is I think it takes it out of being
6 in a position of endorsing or it takes us out of the
7 position of endorsing what high risk is, and it does
8 put the burden back on the person doing the procedure,
9 but I think it's inappropriate for us to make a
10 decision about what a high risk patient is.

11 So I just put that forward.

12 CHAIRMAN LASKEY: Okay. Although I'm not
13 sure we were making that decision, we were just
14 deferring to the high risk definition from the
15 sponsors. I don't think we were --

16 DR. WEINBERGER: I think the ambiguity,
17 Warren, was that we're not sure if high risk means
18 this multi-faceted list of anatomic criteria or high
19 risk means the list of co-morbidities. If you mean
20 the latter, I think people could live with that. If
21 you mean the former, which is the definition that's
22 printed in this indications for use, that's what

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1 people are objecting to.

2 CHAIRMAN LASKEY: So do you care to
3 further elaborate on this definition of risk for this
4 condition? We clearly need to define some component
5 of the patient population for whom this is
6 appropriate, and risk is part of this.

7 Now, do you want to distinguish the risk
8 of the procedure from the risk of subsequent events or
9 how do you want to proceed?

10 DR. WEINBERGER: this is Gary's motion,
11 but what I would be comfortable with would be saying
12 patients who have a clinical indication for carotid
13 revascularization in addition to which have an
14 additional co-morbidity, which is listed as clinical
15 co-morbidities or anatomic features which put them at
16 high risk.

17 So that's what I put in specifically. I
18 don't want the threshold for revascularization to lie
19 within the indications for use. The threshold for
20 revascularization has got to proceed, entering into
21 the indications for use.

22 CHAIRMAN LASKEY: Okay. Well, that was

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1 certainly Mitch's -- that was the lead-in for Mitch.
2 It was patients for the clinical indication for
3 carotid revascularization. We all agree about that.

4 DR. WEINBERGER: Right.

5 CHAIRMAN LASKEY: And now the rest of that
6 sentence should --

7 DR. WEINBERGER: With co-morbidities
8 specified below, and then list the co-morbidities, and
9 that, you know, include the medical co-morbidities and
10 the anatomic features, but do not include the
11 statements with talk about symptomatology or lack
12 thereof.

13 I think that we want to put the onus of
14 that decision on the clinician prior to them pulling
15 out the IFUs on this device.

16 DR. ABRAMS: Can I accept that amendment.

17 DR. COMEROTA: But what's the difference
18 between what you said and what the requested
19 indication is?

20 DR. WEINBERGER: It's, I think, a fairly
21 substantial one. The requested indications for use
22 tell the physician that if he has a patient with a 60

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1 percent carotid stenosis and some TIAs, that he should
2 pull out the device. All right? And you might not
3 feel that that's the appropriate way to treat it, and
4 the neurologist might not feel that that's an
5 appropriate way to treat it.

6 And in that case, if the neurologist feels
7 that that's not appropriate, the patient shouldn't go
8 for revascularization. When the clinician thinks that
9 there's an indication for revascularization based upon
10 their analysis of the patient, that's when you meet
11 the threshold of looking as to whether or not this
12 device is appropriate.

13 DR. COMEROTA: Whether the patient is at
14 high risk or not?

15 DR. WEINBERGER: Right. What makes high
16 risk, what you're not distinguishing here is we're
17 talking about high risk at two different points. What
18 leads you to get revascularized is an assessment by
19 the clinician that the patient is at high risk for
20 stroke. That is not a decision that we should be part
21 of.

22 What indicates this device is that, in

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1 addition to the risk of stroke, there is a high risk
2 feature for carotid endarterectomy. That's what this
3 trial was about. In addition to having established an
4 indication for revascularization, there had to be an
5 additional co-morbidity or an additional anatomic or
6 clinical feature which made going ahead with standard
7 carotid endarterectomy more difficult.

8 What I'd like to reproduce in the
9 instructions for use is the requirement that prior to
10 looking at this instruction for use somebody make a
11 decision that the patient needs revascularization.
12 After that, in addition to that, the patient should
13 have heart failure, renal failure, radiation,
14 something else.

15 So your standard high risk patient that
16 needs the carotid endarterectomy is not what we're
17 talking about here. But your standard patient who
18 needs a carotid endarterectomy and in addition has
19 medical or surgical reasons not to have a carotid
20 endarterectomy, that's the ones we're talking about in
21 this indication for use.

22 DR. COMEROTA: So what you want then is

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1 the word "and" --

2 DR. WEINBERGER: I did.

3 DR. COMEROTA: -- inserted between the
4 second and the third bullet point, and that will meet
5 what you just said.

6 DR. WEINBERGER: I'm sorry. I'm not that
7 sophisticated.

8 CHAIRMAN LASKEY: Well, that's all right.
9 It's a just a one and a two. It's patients with,
10 one, the clinical indication for carotid revas. and,
11 two, have additional co-morbid factors as specified
12 below, colon, blah, blah, blah, right from the label.

13 DR. WEINBERGER: Yes.

14 CHAIRMAN LASKEY: Can we vote on that?

15 MS. WOOD: Once you have a second and
16 motion to put that on the table. Right now you have a
17 motion on the table that needs to be voted on or
18 amended, and it starts with the person who made the
19 second.

20 DR. COMEROTA: It hasn't been seconded
21 yet, Geretta. It hasn't been seconded.

22 MS. WOOD: It was a second?

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1 DR. COMEROTA: No, it's not.

2 MS. WOOD: Okay. Then the person who made
3 the motion either withdraws his motion or modifies his
4 motion and then we wait for a second.

5 DR. ABRAMS: Okay. I'd like to modify my
6 motion to the ones that we just discussed.

7 CHAIRMAN LASKEY: Now, wait a minute, wait
8 a minute. I thought it was Judah's motion that --

9 MR. WOOD: No.

10 DR. ABRAMS: Yeah, I'll modify my motion
11 to the one that Judah proposed.

12 DR. WEINBERGER: And I second my own
13 motion.

14 (Laughter.)

15 MS. WOOD: Which one of you would like to
16 read it again for clarification? Clarify the motion,
17 please.

18 DR. WEINBERGER: Okay. The motion would
19 say that the indications for use are Cordis PRECISE
20 nitinol stent system used in conjunction with the
21 ANGIOGUARD XP emboli capture is indicated for the use
22 in patients with symptomatic coronary artery disease

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1 requiring revascularization and having one of the
2 following features, colon, and list all of the
3 anatomic and clinical high risk features that were
4 used as secondary features for entry into SAPPHIRE.

5 DR. TRACY: I note the word "symptomatic"
6 just crept back in there.

7 DR. WEINBERGER: That was a mental lapse.
8 I'm sorry.

9 (Laughter.)

10 DR. WEINBERGER: I meant -- can somebody
11 read it back to me?

12 (Laughter.)

13 DR. WEINBERGER: I don't mean this to be
14 humorous. That's the problem. It's late, and this
15 process is arduous, if not absurd, but let's just try
16 and --

17 DR. WEINBERGER: Let's try and --

18 CHAIRMAN LASKEY: Let's try and just fine
19 tune the language.

20 DR. WEINBERGER: All right. So indicated
21 for use in treatment of patients who require carotid
22 revascularization and have the following high risk

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1 features, colon.

2 DR. TRACY: And those are stated in the
3 sponsor's Slide 11, I believe.

4 CHAIRMAN LASKEY: Is it allowable to have
5 Dr. Tracy append her comments to this motion or do we
6 need to have Judah restate the whole thing?

7 DR. TRACY: No, I'm just clarifying what
8 he --

9 DR. WEINBERGER: I think I said "et
10 cetera."

11 CHAIRMAN LASKEY: All right. We know what
12 you're referring to. Can the panel vote on that?

13 DR. WEINBERGER: That was Gary's motion to
14 my second.

15 CHAIRMAN LASKEY: Right. Can we have a
16 vote? All in favor? Higher, please.

17 (Show of hands.)

18 CHAIRMAN LASKEY: Four, five, six. Six in
19 favor.

20 All against?

21 (Show of hands.)

22 CHAIRMAN LASKEY: Two, three, four

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1 against. Sorry. Five. Six to five.

2 DR. ZUCKERMAN: Okay. Dr. Laskey, can we
3 read into the record who voted for this motion?

4 CHAIRMAN LASKEY: Sorry, guys. All in
5 favor again please raise hands. All in favor of this
6 motion with the condition: Drs. Krucoff, Tracy,
7 Pentecost, Abrams, Weinberger, and White.

8 And those against? Drs. Aziz, Comerota,
9 Dr. Nicholas, Maisel, and Najarian.

10 Still six to five. Motion passes.

11 Second condition, folks? It should get
12 easier from here. Okay.

13 DR. KRUCOFF: I think these are needed
14 conditions. If not, we can state it. But I would
15 propose a condition that a significant warning on the
16 label be established to operators that if distal
17 detection cannot be deployed, that the expected
18 outcomes with this device may be inferior or may be
19 inferior to if the device can be deployed.

20 That's not very good wording. Sorry.

21 CHAIRMAN LASKEY: Keep going.

22 DR. KRUCOFF: But a warning that if the

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1 distal protection system can't be deployed, that the
2 risks to the patient may be higher.

3 CHAIRMAN LASKEY: A second?

4 DR. ABRAMS: I'll second.

5 CHAIRMAN LASKEY: Discussion?

6 DR. WHITE: A good idea.

7 (Laughter.)

8 CHAIRMAN LASKEY: Dr. White thinks it a
9 good idea. It is a good idea. I think we should
10 vote.

11 All in favor.

12 (Show of hands.)

13 CHAIRMAN LASKEY: Call the names even if
14 it's unanimous? Drs. -- it's unanimous, all in favor.

15 Another condition of approval? Dr. White,
16 you wanted to fine tune the language in the -- now put
17 that on the table?

18 DR. WHITE: I'd like to make sure the
19 patient information booklet is revised. I don't know
20 if I can remember exactly what we said. Can we take
21 that from the minutes?

22 CHAIRMAN LASKEY: No, you'd better

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1 remember.

2 DR. WHITE: Oh, shoot. On page 7 you have
3 to add --

4 CHAIRMAN LASKEY: Don. I think --

5 DR. ZUCKERMAN: Dr. Laskey and Dr. White,
6 you can rest assured that all of the labeling
7 recommendations are in the transcript, will be very
8 carefully reviewed by both the sponsor and FDA. We're
9 looking for major league conditions, such as the
10 indication you just talked about, any comments about
11 post approval, the real show stoppers.

12 DR. WHITE: So perhaps then maybe we could
13 talk about the need for independent neurology
14 oversight for the 30-day visit for the post market
15 approval study.

16 CHAIRMAN LASKEY: Second?

17 DR. KRUCOFF: Second.

18 CHAIRMAN LASKEY: Discussion? Need for an
19 independent neurological --

20 DR. ABRAMS: Is that only a 30-day? We
21 had discussed using a longer follow-up for the pivotal
22 patients and 30 days for the post market surveys.

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1 CHAIRMAN LASKEY: Any discussion?

2 So just to clarify, Chris, the independent
3 30-day assessment refers only to which group now?

4 DR. WHITE: Well, my idea is that there's
5 three-year follow-up for the pivotal group with
6 independent neurological oversight at each of those
7 follow-up visits, and that for the PMA, post market
8 surveillance group, there should be independent
9 neurologic assessment at 30 days.

10 CHAIRMAN LASKEY: So this is for the 1,000
11 patient study?

12 DR. WHITE: Yes.

13 CHAIRMAN LASKEY: Is the independent
14 neurological input built into the PMA population?
15 This group that's being followed post approval.

16 DR. WHITE: The pivotal trial.

17 CHAIRMAN LASKEY: The pivotal trial.

18 DR. WHITE: Pivotal group. No.

19 DR. ZUCKERMAN: So those conditions are
20 what you need to either second or not second now and
21 just vote on them.

22 CHAIRMAN LASKEY: Okay. That's seconded.

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1 If we can have a vote in favor of.

2 (Show of hands.)

3 CHAIRMAN LASKEY: Drs. Krucoff, Tracy,
4 Comerota, Nicholas, Pentecost -- everybody, great.
5 Okay. That's for the independent neurology input at
6 30 days.

7 The fifth condition?

8 DR. COMEROTA: Can we attach only patients
9 who are symptomatic as a condition, or has that
10 already been addressed?

11 CHAIRMAN LASKEY: I think it has been
12 addressed all day, and I'm not sure we're going to get
13 any further with that because it is the subset,
14 because it is delimited, because we don't have the
15 statistical horsepower to defend that. So I think
16 we'd just be backtracking with number one. I'm glad
17 we got past the first critical condition.

18 DR. TRACY: Is it possible to -- it's
19 probably not possible or appropriate, but it would be
20 nice somewhere to say it is not indicated in low risk
21 asymptomatic patients, but that's like telling people
22 not to put their left shoe on their right foot. I

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1 mean, I don't know that --

2 CHAIRMAN LASKEY: Right. I mean, we've
3 just spent almost an hour talking about being
4 indicated in high risk as defined as follows. So I
5 don't think we'll get much more mileage out of that.

6 Are there any other conditions? Any
7 concerns about the post anti-platelet therapy regimen?
8 Is everybody happy with that? Plavix, aspirin, two
9 weeks.

10 DR. WHITE: At a minimum.

11 DR. KRUCOFF: Do you want to modify the
12 language?

13 DR. WHITE: No.

14 CHAIRMAN LASKEY: No? Okay.

15 DR. KRUCOFF: Warren.

16 CHAIRMAN LASKEY: Sir?

17 DR. KRUCOFF: I don't know if we can put
18 this up as a condition. I'll defer to Dr. Zuckerman,
19 but just in terms of this distal protection warning,
20 it seems to me that if the ANGIOGUARD wire is packaged
21 in with the stent, that its use pattern would be
22 significantly different than if it was packaged

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1 separately from the stent. So you could actually
2 deploy or not deploy the wire before you have opened
3 the package with the stent in it.

4 So I don't know if that's appropriate to
5 suggest as a condition in terms of packaging or if
6 that's just something we could mention.

7 DR. ZUCKERMAN: Well, it's presently
8 packaged separately, which would be the way you would
9 want.

10 DR. MAISEL: What if you need to use a
11 second one? What do you do if you need to use a
12 second one?

13 DR. WHITE: A second what?

14 DR. MAISEL: If it were packaged together,
15 if the ANGIOGUARD were packaged --

16 DR. KRUCOFF: Yeah, if it was packaged
17 separately, that's -- if that's the intention for the
18 commercial product.

19 CHAIRMAN LASKEY: All right. We have four
20 conditions on the motion for approval. Are there any
21 other conditions? Otherwise we will move to vote.

22 (No response.)

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1 CHAIRMAN LASKEY: No.

2 MS. WOOD: Dr. Laskey, we're presently
3 putting up the first condition, the change of
4 indications for use, and I've asked the summary writer
5 to clarify if that's what she also has in the record,
6 the summary writer or the transcriptionist, just to
7 make sure that we have it correct before we leave
8 today.

9 SUMMARY WRITER: The only clear indication
10 is my notes indicate that it was high risk for the CEA
11 procedure.

12 MS. WOOD; Right.

13 SUMMARY WRITER: So it might want to
14 specify that.

15 MS. WOOD: Dr. Weinberger?

16 DR. WEINBERGER: What we voted on was for
17 patients who have an indication for carotid
18 revascularization and in addition to that have either
19 anatomic or clinical features that put them at high
20 risk, and that's the list.

21 CHAIRMAN LASKEY: Can we see the rest of
22 the "or." You have anatomic factors. Just scroll

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1 down.

2 DR. WEINBERGER: She hasn't typed it yet.

3 CHAIRMAN LASKEY: Oh.

4 DR. ZUCKERMAN: Dr. Weinberger, the first
5 part though, is that correct?

6 SUMMARY WRITER: The question, I think,
7 has to do with where you want high risk patients or do
8 you want patients at high risk for treatment with
9 CEA.

10 DR. WEINBERGER: I want patients requiring
11 carotid revascularization, patients requiring carotid
12 revascularization. That's what we all agreed to
13 previously.

14 The intent there is that that decision is
15 made by the referring physician.

16 PARTICIPANT: So the four features at the
17 end should say "high risk," "one of the following high
18 risk features."

19 DR. WEINBERGER: And have one of the
20 following high risk features.

21 DR. COMEROTA: And also shouldn't that
22 include "and at high risk for carotid endarterectomy"?

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1 DR. WEINBERGER: No.

2 DR. COMEROTA: I thought that's what we
3 voted on.

4 DR. WEINBERGER: Those high risk features
5 are what defined the risk for carotid endarterectomy.
6 We're writing them out explicitly. That precisely
7 was what was used in the study to define high risk for
8 carotid endarterectomy.

9 CHAIRMAN LASKEY: Okay. Do we need to
10 wait?

11 MS. ABEL: You can look at the handout to
12 see the other things I'm typing in.

13 CHAIRMAN LASKEY: Because it really is
14 verbatim. Now, are we waiting --

15 MS. ABEL: It's Slide 64, Cordis.

16 CHAIRMAN LASKEY: Great. All right.
17 Folks, we will vote on the following motion: that
18 this is approvable with the following four conditions.

19 Condition number one, as you see up on the screen;
20 the second condition being that there be a warning
21 with respect to the inability to deploy the distal
22 protection component of this system; the third

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1 condition being to buff up some of the language in the
2 patient information brochure to make it more accurate;
3 and the fourth condition being that there be an
4 independent, 30-day neurologic consult built into the
5 post marketing approval process.

6 DR. ABRAMS: And one, two, and three-year
7 independent neurological evaluations for the pivotal
8 study population.

9 CHAIRMAN LASKEY: By a show of hands, can
10 I see all in favor of that motion?

11 DR. COMEROTA: Are we voting on the
12 condition or the overall.

13 PARTICIPANT: The whole ball of wax.

14 DR. COMEROTA: Don't we go around
15 individually?

16 MS. ABEL: Sorry. Can I interrupt before
17 you vote? These are the most critical criteria. It's
18 not inclusive of all the criteria for the study, and
19 so you should take that into consideration.

20 DR. WEINBERGER: Say that again.

21 MS. ABEL: These are just the most
22 critical criteria that were presented by the

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1 manufacturer. There are additional criteria that were
2 included in the protocol that are not listed here as
3 far as defining high risk.

4 MS. WOOD: Let's move on. We're getting
5 into too much detail. I think we have a pretty good
6 idea of what the panel wants added to this intended
7 use.

8 CHAIRMAN LASKEY: All right. Are you
9 happy with that?

10 MS. WOOD: Yes.

11 CHAIRMAN LASKEY: All right. We have the
12 motion. I need to see by show of hands all in favor.

13 DR. COMEROTA: Are we voting on the --

14 MS. WOOD: Actually we need a verbal vote
15 on this, a verbal. When it comes to the final motion,
16 we need a verbal vote. So we need to go around the
17 table and start with Dr. Aziz.

18 DR. AZIZ: You mean with the vote with
19 conditions?

20 MS. WOOD: Just yes or no.

21 DR. AZIZ: Approvable with conditions.

22 DR. KRUCOFF: Yes.

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1 DR. TRACY: Yes.

2 DR. COMEROTA: No.

3 DR. NICHOLAS: No.

4 DR. PENTECOST: Yes.

5 DR. ABRAMS: Yes.

6 DR. WHITE: Yes.

7 DR. WEINBERGER: Yes.

8 DR. MAISEL: No.

9 DR. NAJARIAN: No.

10 CHAIRMAN LASKEY: So I have seven in favor
11 and four against. By a margin of seven to four the
12 motion to approve with those conditions passes.

13 We just need to quickly go around the
14 table, reasons for.

15 DR. AZIZ: I voted -- actually I had voted
16 no with conditions earlier on. I think I got
17 confused. Mine should be no earlier on when we voted.

18 So I did not vote in favor actually.

19 The reason I didn't vote in favor was
20 because I think that it's safe. In my mind it didn't
21 really show that it was effective in the asymptomatic
22 cases.

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1 DR. ZUCKERMAN: Are you changing your
2 final vote so that the final vote should be six to
3 five?

4 DR. AZIZ: Sorry.

5 CHAIRMAN LASKEY: All right. sorry. I
6 misunderstood you, Aziz.

7 DR. KRUCOFF: I guess I shouldn't change
8 my vote.

9 (Laughter.)

10 DR. KRUCOFF: I voted in favor because I
11 think the data supports that in the randomized cohort
12 where we have interpretable data and they're
13 identifiable, that this is a safe and effective
14 alternative to carotid endarterectomy.

15 DR. TRACY: After much thought, I voted in
16 favor because I think there are a group of
17 asymptomatic patients in whom some revascularization
18 procedure is indicated, and I believe that the data
19 here supports the safety and efficacy of the stent.

20 DR. COMEROTA: First of all, let me
21 congratulate everyone. This was a long and arduous
22 affair, and I congratulate the company and the

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1 proponents. They were very convincing.

2 My worry is what I think everybody knows
3 what's going to happen, and at least what we fear is
4 going to happen is that when we look at the number of
5 patients who will be intervened with, there are going
6 to be many, many patients who will be suffering
7 neurologic events that if managed with best medical
8 care, who would not have undergone a procedure, will
9 now be having neurologic deficits and complications.

10 And I think that putting into relative
11 perspective, we're looking at a factor of ten to 15
12 based on what we know is the alternative to medical
13 care, and those are the asymptomatic patients.

14 I'm not quite certain that on the basis of
15 90 patients who were symptomatic and 39 patients who
16 had atherosclerotic disease who were stented. That's
17 the decisions that we're dealing with, and I think we
18 have set a standard that is far below what the medical
19 profession in the United States should demand in terms
20 of randomized trials to change an entire paradigm of
21 patient care. And that's what we've done today.

22 And I think that based on myocardial

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1 infarction and everything else that was addressed
2 today, in patients who ordinarily shouldn't have a
3 high risk procedure this decision was valid. If we
4 look at what's the best for patient care, I don't
5 think we achieved that goal today.

6 DR. NICHOLAS: I voted no because I feel
7 that on clinical grounds the information provided by
8 the sponsor demonstrated very nicely that carotid
9 stenting is a very useful tool for our patients. The
10 problem I have is although it is a subset -- and I
11 again apologize. I do feel that for the asymptomatic
12 patient we have opened a door that we probably should
13 not have done just yet. It may come, and I think that
14 with more data it may well be the standard. But I
15 think for clinical management right now, we shouldn't
16 jump too fast to change that.

17 DR. PENTECOST: I think this is more of an
18 issue of access than mandates, and I think the
19 manufacturer has proved that patients should have
20 access to this procedure, and it's not up to us to
21 mandate what kind of revascularization they have, but
22 I think the patient's end physicians deserve access to

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1 this type of therapy.

2 DR. ABRAMS: Well, I voted yes. I mean, I
3 share the concerns of the no voters, but I do think
4 that the sponsor showed that the device was safe and
5 as effective as carotid endarterectomy. I don't think
6 that we can be in a position of setting up clinical
7 practice guidelines. I'm not sure that's our purview.

8 So I voted yes based on the limited question I
9 thought was put before us.

10 DR. WHITE: I voted yes because I think
11 this is one of the most important things we could have
12 done, and certainly in my practice is going to be a
13 very important part of my practice. I think that we
14 need to be very careful about the indications, and I
15 think that the safe and proper use of these devices,
16 just like with any other device, is critical to good
17 patient care, but I can tell you that I can take
18 better care of patients if I have access to these
19 devices. I think it's very important that this be
20 available.

21 DR. WEINBERGER: I voted yes, and with
22 some of the same reservations of Dr. Comerota. I

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1 think that this is an incredibly useful technology.
2 It will be applied to the groups of patients that are
3 truly at highest risk.

4 We cannot legislate for physicians when to
5 send patients to revascularization. In evidence I
6 place the fact that vascular surgeons operate all the
7 time on, quote, low risk patients. I will be very
8 happy if the vascular surgeons were to spearhead a
9 study of vascular surgery versus medical therapy for
10 patients with high risk lesions, and if we find out
11 that in 2004 medical therapy is better, I will
12 congratulate you along with all of our colleagues.

13 However, the reality of life is that
14 patients are being referred for revascularization. If
15 they have multiple co-morbidities, I truly believe
16 they should probably not have surgery, and I would
17 very much encourage people who have high risk co-
18 morbidities, our 80 year old with renal failure and
19 hypertension, who are out of control. Those patients
20 really need an alternative to being put back to sleep.

21 So I do have reservations. I hope that,
22 you know, this doesn't get out of control. However,

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1 if it's applied in a reasoned fashion, this will be a
2 major advance for patient care.

3 DR. MAISEL: I voted no. Maybe I'm a
4 little altruistic, but rather than picking between the
5 lesser of two evils, I would rather pick the right
6 thing, and I don't know that we know what that answer
7 is.

8 I think many of us at the table struggle
9 with how patients who got the best medical therapy,
10 who were high risk would do. I certainly can't sit
11 here and say that giving them a carotid stent is the
12 right thing to do, and I'm very concerned that we're
13 going to be harming patients who receive it who are
14 asymptomatic.

15 DR. NAJARIAN: I'm very excited that this
16 was approved even though I voted no because I think it
17 is a technology that should be available to patients.

18 I have placed carotid stents, and I think it's
19 something that's necessary.

20 However, I voted no because I do not think
21 it should be used on asymptomatic patients at this
22 point in time. I'm sure that in a few years this will

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1 be the standard of treatment for carotid artery
2 disease, but at this point I'm not convinced.

3 CHAIRMAN LASKEY: Thank you all. This
4 concludes the report.

5 MS. WOOD: Before we adjourn, let me just
6 clarify something with the transcriptionist. We did
7 not read the names of the people who voted. Did you
8 get them into the record or do you need me to do that?

9 THE REPORTER: I got them.

10 MS. WOOD: Okay. Thank you.

11 CHAIRMAN LASKEY: Adjourned.

12 (Whereupon, at 7:26 p.m., the meeting in
13 the above-entitled matter was concluded.)

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