

1 DR. TRACY: Thanks. I m very confused by
2 Christmas trees, but I think I just would like to ask
3 Dr. Li. If I understand, it depends when you look at
4 the data. Even the sponsor is indicating that it
5 would fall under the line if you had done the analysis
6 the way it was initially intended to be done. So my
7 question is that somebody made that decision somewhere
8 along the line to not do it the way that FDA and
9 everybody else including IRBs and if the patients had
10 any reason to understand the analysis that was going
11 to be performed, the patients would not have
12 understood the analysis would be performed this way.

13 Does the sponsor see any ethical dilemma
14 with not following their originally outlined program
15 or do you feel that you in fact did follow your
16 originally outlined program? Then I guess I would ask
17 the FDA also, the statistician, Dr. Li, if he concurs
18 with the analysis that was just presented? Maybe I ll
19 ask you that first, Dr. Li. Are you happy that the
20 dot falls outside the boundary if the analysis was
21 performed the way the sponsor indicated that it was
22 performed?

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1 DR. LI: You mean the final dot being
2 inside the boundary?

3 DR. TRACY: Yes. Is it in or is it out?

4 DR. ZUCKERMAN: Dr. Tracy, you are asking
5 an extremely difficult question.

6 DR. TRACY: I understand that.

7 DR. ZUCKERMAN: Let me take a first crack
8 at it. As you know, that analysis is not provided in
9 your PMA Panel Pack. Dr. Lee, I believe, saw that
10 analysis for the first time yesterday. These are very
11 complex analyses that cannot be done on the back of a
12 handkerchief or napkin. So all we can say at the
13 present time is this is very interesting and certainly
14 there s a lot to this, but these analyses that were
15 just shown need to be appreciated in the context that
16 they have not been thoroughly reviewed by FDA
17 statistics. Dr. Li.

18 DR. LI: I think if that satisfies your
19 question, then I have nothing further to add.

20 DR. TRACY: Okay. I think it does. The
21 answer is that the conundrum comes up by the fact that
22 the originally outlined program per the best of my

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1 ability to understand was not followed or it was so
2 darn complex nobody understood exactly what the
3 program was that was going to be followed. So I think
4 there s some kind of false there with setting
5 something up that is so difficult to adhere to. I
6 wonder about the ethics of the situation that we re in
7 right now. I wonder what the patient thinks. I
8 wonder what IRBs think.

9 DR. COHEN: I think I would like to make
10 two points clear. First, the method itself allows for
11 discretion in terms of whether or not to perform an
12 analysis. That s within the confines of this analysis
13 method. So there is nothing that s an ethical issue
14 in terms of response or non-response communication or
15 non-communication. What we failed to do was
16 communicate how we decided to enact this whole method
17 with the FDA. Does that help?

18 DR. TRACY: Yes, it helps and I agree.
19 You did fail to communicate. It puts this panel in a
20 bit of a difficult situation, but we ll let that go.

21 DR. COHEN: Well, let me make sure we
22 understand. The analysis, the triangular method, has

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1 to do basically with the stopping rule. It has
2 nothing to do with the actual separate analysis of the
3 primary endpoint as to whether or not it meets non-
4 inferiority. Those are two separate things. The only
5 relationship between the two is if you do a
6 preliminary analysis. Then you basically enact an
7 alpha penalty on your final analysis. Otherwise the
8 two are distinct.

9 DR. TRACY: Okay. There was a group of
10 patients who were not treated. That, I believe, was
11 slide 85 in your presentation. In our little packet
12 here, it s page 29. It s a total of 24 patients or so
13 who were not treated but who had been randomized. Do
14 you have any data on what happened to those patients?

15 DR. COHEN: Actually that was presented in
16 the main presentation. If you ll give me a second, I
17 can find the slide. But we gave the reasons why
18 patients - it was eight and 16 patients - were not
19 enrolled.

20 DR. TRACY: Right.

21 DR. COHEN: There was a mixture of reasons
22 as I m looking for this. One was obviously that we d

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1 already discussed upon angiography the patient was
2 found not to meet the inclusion or exclusion criteria.

3 I m sorry.

4 DR. TRACY: That was slide 85 in your
5 original presentation. My question was what happened
6 to those 24 patients.

7 DR. COHEN: They were included on an
8 intent to treat analysis. Are you asking what
9 happened to them in terms of treatment or were they
10 included in the analysis? They were included.

11 DR. TRACY: They were included in the
12 analysis?

13 DR. COHEN: Yes, in the intent-to-treat
14 because they were randomized.

15 DR. TRACY: Okay. So you have no separate
16 information on what happened to those patients
17 clinically.

18 DR. COHEN: We have the information. I
19 don t have it.

20 DR. TRACY: But you don t have any
21 analyzed. Okay. One of the things I m struggling
22 with is trying to figure out what the indications for

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1 the device would be. I was hoping that that group of
2 patients would provide some type of analysis or a
3 control group.

4 But I guess if we relied back on the
5 historic controls that were presented, in asymptomatic
6 patients even with high grade stenosis at about a year
7 it looks like the risk of stroke is about five percent
8 in historic controls. It looks like the stroke rate
9 is around 7.3 percent at a year with the stent treated
10 patients in asymptomatic patients, 7.7 percent stroke
11 at one year in asymptomatic patients. So I m
12 wondering how I would convince a patient who is
13 asymptomatic and faces about a five percent one year
14 stroke risk to undergo a procedure that will give them
15 a seven percent stroke risk.

16 DR. COHEN: I m not sure that I would
17 agree with the five percent stroke risk. What we had
18 presented in our major presentation is - the first
19 statement was - that there is no contemporary data
20 that allows us to understand what the risk of stroke
21 is in these patients. There is no study that s
22 followed medical therapy in these patients. That was

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1 not the goal of this trial. The goal of this trial
2 was to determine what the outcomes were in these
3 patients who are treated either with carotid
4 endarterectomy or with stenting. There is an absence
5 of historical data and we acknowledge that.

6 DR. TRACY: Yes. Even if you compare
7 within the asymptomatic versus symptomatic patients,
8 your 237, the outcomes in the 237 asymptomatics versus
9 the 96 symptomatic patients, it looks as though the
10 asymptomatic patients fare worse than do the
11 symptomatic patients which is of some concern.

12 DR. COHEN: Perhaps you could point to
13 exactly what you re looking at.

14 DR. TRACY: Slide 96.

15 DR. OURIEL: I think while Dr. Cohen is
16 looking for that what this trial shows is that if you
17 decide that a patient needs treatment and they are
18 asymptomatic, high risk and if you were going to
19 perform a carotid endarterectomy, they will do as well
20 with a carotid stent.

21 DR. TRACY: Okay. Then it becomes a
22 clinical issue of whether or not you want to subject

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1 somebody to that risk either of stent or surgery.

2 DR. OURIEL: Yes. You see with this trial
3 the decision was already made that they were going to
4 get treatment or they wouldn't have entered the trial.

5 DR. TRACY: Right. It just makes me
6 wonder what would go through my mind to get me to a
7 point of making a recommendation like that.

8 DR. OURIEL: Personally as a vascular
9 surgeon if I had a patient with an 80 or greater
10 percent carotid stenosis, asymptomatic, that fell into
11 this category, then I would probably recommend carotid
12 endarterectomy in the absence of a stent. If a stent
13 were available after this data, I would consider stent
14 equally with carotid endarterectomy.

15 DR. COHEN: And if I could just respond to
16 the other thing if I'm looking at the slide that you
17 are indicating with the stroke rate of 3.3 percent CEA
18 and 5.1 percent with stent, let me point out that the
19 total number of patients in each group is only 120 and
20 117. So you're talking about the difference in
21 outcomes of one or two patients. I would not suggest
22 making clinical decisions based on such a small

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1 number.

2 DR. TRACY: And I think that it s
3 comparing the outcomes ultimately in symptomatic
4 versus asymptomatic patients. There seems to be a
5 discrepancy.

6 DR. COHEN: Actually with regard to the
7 overall event rate of major adverse events which was
8 the endpoint of the trial, the asymptomatic patients
9 actually had numerically the lowest major adverse
10 event rates.

11 DR. TRACY: Who had the higher stroke
12 rater, asymptomatic or symptomatic?

13 DR. COHEN: I m sorry. At what time and
14 what type of stroke? Ipsilateral stroke?

15 DR. TRACY: Stroke.

16 DR. COHEN: All strokes?

17 DR. TRACY: All stroke.

18 DR. COHEN: I m sorry. At 360 days if you
19 look on slide 97 which is asymptomatic and slide 100
20 which is symptomatic at 360 days, the overall stroke
21 rate is 7.5. 7.7 for asymptomatic. 6.5 and 2.0 for
22 symptomatic.

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1 DR. TRACY: So it is the asymptomatic that
2 have a higher stroke rate.

3 DR. COHEN: Numerically, yes, but not
4 statistically.

5 CHAIRMAN LASKEY: Well, about that, we
6 keep going back. I think we need to be very clear
7 about the lack of utility of post hoc subgroup
8 analyses. I don't think it belongs on the docket.

9 DR. COHEN: I agree.

10 CHAIRMAN LASKEY: It should be qualified
11 as such and I think we need to be very careful about
12 playing this game.

13 DR. TRACY: I'll try to wrap up here very
14 quickly. There appeared to be a higher rate of TIAs
15 in the stent group at 360 days. Why was that true and
16 did it correlate the degree of restenosis or initial
17 stenosis or was there some predictor for that?

18 DR. COHEN: The observation is there that
19 there were an increased frequency of TIAs occurring.
20 We have no mechanistic explanation. We can make
21 guesses, but I don't think that's really useful in
22 this forum.

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1 DR. TRACY: Okay. That s all. Thank you.

2 DR. COMEROTA: I made the majority of my
3 comments. I have three quick questions.

4 CHAIRMAN LASKEY: Can you hold on? I
5 wanted to make one pass around the table.

6 DR. COMEROTA: Pardon me.

7 CHAIRMAN LASKEY: Sorry. Thank you.

8 DR. NICHOLAS: First I would like to thank
9 the sponsors and Dr. Ouriel for an excellent
10 presentation that clarified a great deal of the
11 information for me. I have a couple of questions and
12 I think the first one of why didn t you follow the
13 protocol has been answered several times now. I think
14 I have a grasp of that. Not that I have a grasp of
15 the Christmas tree, mind you, but at least I
16 understand that part.

17 The question I have was the inclusion
18 criteria of high risk patients. One, who decided they
19 were high risk? Was it done by at a committee, by
20 individual who then submitted the patient to the
21 protocol or was it all patients were selected at the
22 time of a group meeting when you had a new patient?

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1 DR. OURIEL: Well, if you mean the
2 eligibility criteria for the trial?

3 DR. NICHOLAS: Right.

4 DR. OURIEL: Those were pretty clear cut
5 and they were determined by this three-membered group,
6 surgeon interventionalists and neurologists.

7 DR. NICHOLAS: But my question was did all
8 three decide or did one of three decide?

9 DR. OURIEL: All three needed to decide
10 that the patient was eligible. Then there was this
11 secondary decision. The surgeon had to be willing to
12 do an endarterectomy. The interventionalist had to be
13 willing to do a stent for them to get randomized.

14 DR. NICHOLAS: Okay. The next question I
15 have is again related to inclusion criteria in that
16 you included high risk patients, people who have
17 unstable angina and a high degree heart failure,
18 people who I wouldn't normally consider for an
19 elective procedure. Did these patients have
20 intervention for their heart disease if we just pick
21 out that group of high risk people before they had
22 their carotid addressed?

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1 DR. OURIEL: Sure. There were a whole
2 subset of patients who would have been treated before
3 they entered this trial and also there s a subset of
4 patients who would never have entered the trial at
5 all, the 2200 patients screened getting down to 700
6 patients that were entered for instance. I think some
7 of the patients you re talking about really never
8 ended up in this analysis because maybe they had no
9 treatment at all.

10 DR. NICHOLAS: Okay. But for those who
11 did enter with high cardiac risk factors, I assume
12 those problems were treated before you went on to
13 either stenting or endarterectomy for, let s take an
14 asymptomatic lesion for instance.

15 DR. OURIEL: If the surgeon and the
16 interventionalist were unwilling to treat the patient
17 because of those factors, then they would not have
18 been in the trial until those were addressed. Does
19 that answer your question?

20 DR. NICHOLAS: Okay. Thanks.

21 DR. PENTECOST: Was there a correlation
22 with the size of the stent in the post-intervention

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1 stenosis, i.e. were the patients with smaller stents
2 have a higher degree of problems afterwards?

3 DR. OURIEL: I understand your question.
4 It s a good question. It s certainly been shown for
5 instance in renal artery stenosis and restenosis. Do
6 we have an answer to that now? I think it s not an
7 analysis that we ve yet done but a good question.

8 DR. PENTECOST: What about patients that
9 had collateral imaging? I would think a lot of these
10 patients just before they came into the trial had CT
11 angiography and particularly MR angiography, also
12 post-intervention. Were you blinded to that
13 information or how to do that factoring into your
14 decision?

15 DR. OURIEL: Well, the decisions were made
16 based on duplex ultrasound first irrespective of other
17 tests.

18 DR. PENTECOST: So if you had a patient
19 with a duplex ultrasound and an MR angiogram, you
20 didn t look at the MR angiogram.

21 DR. OURIEL: It wasn t used in the
22 decision-making process.

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1 DR. PENTECOST: Okay.

2 DR. OURIEL: But in all respects, the
3 angiogram would have overridden the duplex if it were
4 performed.

5 DR. PENTECOST: Even MR angiogram?

6 DR. OURIEL: No, contrast.

7 DR. PENTECOST: If you used MR angiography
8 or CT angiography at all.

9 DR. OURIEL: The contrast angiogram or the
10 time of the stent would override the duplex in the
11 decision-making process.

12 DR. PENTECOST: Okay. That s all.

13 DR. ABRAMS: I had some questions focusing
14 on the strokes and particularly on the minor strokes.

15 If I understood correctly, the decision about whether
16 somebody had a minor stroke is they had to have a
17 change on their NIH Stroke Scale essentially. There
18 was no standardization of neurological examinations.
19 Is that correct? Every neurologist just performed
20 whatever his standard neurologic exam was.

21 DR. COHEN: I ll ask Dr. Fayad to answer.

22 DR. FAYAD: The NIH Stroke Scale is a

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1 standardized neurological exam that tries as best as
2 possible essentially to make an examination or
3 deficits comparable between different patients. Along
4 with the Rankin Scale and the Barthel Index which the
5 Rankin Scale is a global disability score or outcome
6 score and the Barthel Index which is an activities of
7 daily living scale, all of these three were configured
8 to try to come out with the degree of disability
9 related to the stroke. So the stroke was determined
10 as minor when there were no disabilities related to
11 the NIH Stroke Scale or to the Rankin Scale or the
12 Barthel Index.

13 DR. ABRAMS: Let me follow up on that with
14 a second. The neurologists were blinded, right, to
15 the procedure that was done and how did you do that?

16 DR. FAYAD: I don t think they were
17 blinded.

18 DR. ABRAMS: So the neurologists knew
19 whether the patient had a stent or a CEA. Okay. Now
20 if somebody woke up after a procedure and said they
21 were a little dizzy or they were a bit foggy, it
22 didn t necessary qualify for a change on the NIH

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1 Stroke Scale. Was anything done? Were they imaged or
2 was it decided that no, this wasn't a stroke?

3 DR. FAYAD: It was left up to the
4 neurologist at the center. They had to have
5 neurology. If there were any neurologic symptoms,
6 they had to have the neurologist involved in the study
7 evaluate them and it was left to his discretion for
8 further work-up. If he or she determined that this
9 was a stroke, it was sent to the adjudication
10 committee.

11 DR. ABRAMS: So basically he had to
12 trigger, initiate, things on the stroke. If he
13 decided that something wasn't a stroke, it was post-
14 anesthesia.

15 DR. FAYAD: That is correct. In fact, all
16 patients were examined by the neurologist before they
17 were discharged from the hospital. It was within 24
18 to 48 hours.

19 DR. ABRAMS: Yes, it's a little concerning
20 because I understand at least a large number of
21 patients are going to have five or six minutes perhaps
22 of significant hypotension, Bradycardia. They may

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1 have some subtle watershed infarction or watershed
2 changes that might not necessarily show up on the NIH
3 Stroke Scale. If these are looked into further, we
4 could be missing a fair number of ischemic vascular
5 events.

6 DR. FAYAD: There is always a risk of
7 missing a few things, but there was nothing major
8 missed as they had to standardly be evaluated by the
9 neurologists and the NIH Stroke Scale was only used as
10 a standard measurement. But it did not replace the
11 neurologic evaluation.

12 DR. ABRAMS: Now there appear to be about
13 25 or 30 strokes that did occur during the study.
14 These strokes, I presume, were - These individuals
15 had imaging studies, had modern imaging with diffusion
16 studies. Is that correct?

17 DR. FAYAD: I don t have the answer to
18 that. I assume that it was left up to what was the
19 decision of the neurologist, but it was not mandated
20 by the study. So it was part of the care of the
21 patient.

22 DR. ABRAMS: So the Data Safety and

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1 Monitoring Board did not actually review the clinical
2 evaluations of these individuals at any particular
3 point.

4 DR. FAYAD: Well, it was adjudicated if it
5 was declared again an event. It was adjudicated by
6 the events committee. Then if it was adjudicated,
7 then it always went to the safety committee of course.

8 DR. ABRAMS: And one last question, post
9 surgery, the individuals with the stents received
10 Ticlopidine or Colpidogrel for two weeks. Was there
11 any standardization of medical treatment going beyond
12 that two week period and did you analyze that or do
13 any subgroup analyses to see if how many people took
14 Colpidogrel, how many people took aspirin or any other
15 stroke prophylactic agent?

16 DR. COHEN: Yes, we have limited data on
17 medications that were taken at the six month and one
18 year time point, but it s very limited information.
19 We can get the exact numbers for you. I know that
20 there were more patients in the stenting arms that
21 continued on oral anti-platelet agents, for example,
22 at the six month and one year time point. We did

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1 collect data on other cardiovascular medications, but
2 not in a careful fashion that would allow us to make
3 detailed comments.

4 DR. ABRAMS: Did you look, say, at atrial
5 fibrillation? I didn't see it as analyzed among the
6 two groups. Did you look at atrial fibrillation
7 between the two groups to see whether there was a
8 difference and whether they were warfarin therapy or
9 things like that?

10 DR. COHEN: You're talking about on
11 follow-up?

12 DR. ABRAMS: Yes.

13 DR. COHEN: Not on presentation, but on
14 follow-up?

15 DR. ABRAMS: Yes.

16 DR. COHEN: No, I don't believe so.

17 DR. ABRAMS: Okay. Thank you.

18 DR. WHITE: Thank you, Warren. I'd like
19 to congratulate the sponsor and the investigators on
20 completing such a trial and I ask these questions in
21 the context of having been a carotid stentor for more
22 than ten years now. We placed our first stent in

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1 January of 1994. I d like to actually make sure I
2 heard what Dr. Ouriel said clearly and that is I think
3 the questions that I ve heard some of the panel
4 members asking and I think many people would like to
5 know is who are the people that should be treated, but
6 that was not the question that was intended to be
7 answered by this trial. As you ve said, I think I
8 heard people were committed to revascularization and
9 the question to be answered was how the stent compared
10 to endarterectomy in patients who were committed to
11 have revascularization.

12 DR. OURIEL: Yes.

13 DR. WHITE: So it doesn t answer the
14 question about who should get revascularized.

15 DR. OURIEL: Correct.

16 DR. WHITE: I d like to just respectfully
17 as I can disagree with Dr. Comerota about what he said
18 about MIs. I think MIs are extremely important in the
19 management of patients particularly non-Q MIs. I
20 think they re an element of all current major
21 cardiovascular trials. You can t do one today without
22 looking at the instance of non-Q MIs. The fact that

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1 they weren't measured in NASCET and ACAS I think is
2 unfortunate, but in that time period, we weren't aware
3 of the importance. It wasn't that somebody said we
4 don't care about MIs then. It just wasn't an issue.

5 It currently is now for the CREST trial.
6 It certainly is important. I think it's recognized to
7 be an important part of this. Dr. Comerota mentioned
8 something about the Colpidogrel bias in the treatment
9 group and I want to make sure we clarify that. The
10 first point is the Colpidogrel advantage absolute
11 numbers is in single digits for cardiac patients.
12 It's a risk reduction from nine percent to seven
13 percent, a very small number. It's not a issue.

14 The second thing is that patients in this
15 trial were only treated for two weeks or mandated to
16 be treated for two weeks with Colpidogrel so it would
17 be a short interval. The third thing was the stroke
18 rate for surgery as I understand it something that
19 happened peri-procedurally. So it's wasn't something
20 so much that happened nine or ten months later that
21 might have benefitted from anti-platelet regime, but
22 something that happened in the 30 day window. Is that

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1 true?

2 DR. OURIEL: Yes, the stroke rate really
3 plateaued after the initial events. Both groups.

4 DR. WHITE: I wanted to ask you if you had
5 any idea about the issue of debris and the filter and
6 stratified that particularly redo patients because the
7 issue about filters and the necessity of having a
8 filter would obviously depend upon the yield of
9 debris. It would seem to me that an intimal
10 proliferative disease such as failed redos
11 endarterectomy would be a smooth muscle disease as
12 opposed to an atherosclerotic process. Were you able
13 to stratify the debris in the filters by those
14 patients?

15 DR. OURIEL: We can find out if we have
16 the data. I don't have the data, but I can tell you
17 anecdotally as, Chris, you already know that it's not
18 just an intimal hyperplastic lesion on the redo. You
19 also have this patchulous patch with a lot of very
20 friable debris. I've been surprised more than once on
21 a redo to find debris in the filter.

22 DR. WHITE: And I was also impressed by

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1 the high rate of restenosis by ultrasound. We ve
2 not seen restenosis at these rates clinically. I just
3 wondered. I see Dr. Popma in the audience. I know
4 you did an angiographic follow-up. Was there an
5 correlation between angiographic restenosis and
6 ultrasound restenosis? Was there an over estimation
7 because of increased flow?

8 DR. OURIEL: While either by Jeff or
9 Jeff is coming up. I ll answer that yes, at 50
10 percent threshold there s a high rate of restenosis.
11 But if you look really at the clinically-relevant 70
12 or 80 percent, it s really very low.

13 DR. WHITE: Do you believe though,
14 Michael, that you really did have 50 percent
15 restenosis or do you think you were looking at
16 increased velocities?

17 DR. JAFF: My name is Michael Jaff. I am
18 an vascular medicine specialist in New York City. I m
19 the medical director of the vascular core lab that was
20 contracted by Cordis for the SAPPHIRE trial. In that
21 capacity, I m a paid consultant to Cordis.

22 I m actually going to show a very small

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1 number of data that will answer Dr. White s question.

2 At the time that the SAPPHIRE trial was being planned
3 and these criteria for initial stenosis prior to
4 treatment, prior to randomization, and follow-up after
5 treatment was designed, we didn t know the impact of a
6 stent on carotid artery and the duplex velocities that
7 would develop. So we ve now learned some very
8 interesting data that was just published in January of
9 this year that I think sheds a lot of light on this.

10 But let me just show you a couple of quick
11 slides that I think will answer Dr. White s question.

12 This is data from the recently published late last
13 year Society for Radiology and Ultrasound Consensus
14 Conference on Carotid Duplex Ultrasonography. What
15 this slide shows you is that the initial important
16 criteria for stenosis in a non-treated or native
17 carotid artery is the peak systolic velocity (PSV).
18 Without going into the physics of this, as many of you
19 know, the faster the peak systolic velocity or the
20 faster the speed of blood flow the more severe the
21 degree of stenosis. This is shown very nicely on this
22 slide.

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1 However, what you ll also show is there is
2 a significant amount of overlap between these
3 categories. Carotid ultrasound cannot and has never
4 been touted to be able to identify 51 percent versus
5 55 percent versus 57 percent stenosis. It categorizes
6 ranges of stenosis severity. In fact, there have been
7 a number of studies that have demonstrated
8 correlations between carotid ultrasound and
9 angiography.

10 Let me show you the data on restenosis.
11 As you ve already seen in your Panel Pack, these are
12 the predetermined duplex velocity criteria that were
13 defined for enrollment in the SAPPHIRE trial. You can
14 see here again that the greater the peak systolic
15 velocity the more severe the stenosis and the
16 determinant that s separated out moderate to severe
17 degrees of stenosis was an additional increase in end
18 diastolic velocity (EDV). These criteria were chosen
19 to be quite conservative to make sure that we identify
20 the patients who had truly 80 percent or greater
21 degrees of stenosis.

22 When we followed these patients and

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1 reviewed this data what we found was that fewer than
2 five percent of patients in the SAPHIRE trial who
3 were randomized to carotid artery stenting had a
4 diameter stenosis less than 50 percent which
5 demonstrates the excellent accuracy of duplex
6 ultrasound to screen out carotid disease which would
7 not benefit potentially from revascularization based
8 on previously published data.

9 Now to answer the question about
10 restenosis, there have been some recent elegant
11 studies published from New Jersey from Hobson and
12 others that have demonstrated that once a stent is
13 placed in an internal carotid artery, the compliance
14 of the vessel decreases so that the velocities
15 increase artifactually. In fact, the data that we
16 saw, this slide which you've already seen which
17 demonstrated that the duplex defined restenosis of
18 greater than 50 percent was 19.7 percent in the stent
19 group, 31.3 percent in the endarterectomy group
20 demonstrates the high sensitivity of carotid duplex
21 ultrasound, but the likely overestimated degree of
22 stenosis based on loss of compliance and in addition

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1 in carotid endarterectomy especially in nonpatched
2 carotid endarterectomy, the same phenomenon has been
3 known to occur.

4 However, what I would like to again
5 present to the panel is that the area in which carotid
6 ultrasound excels in its accuracy is in the higher
7 degrees of stenosis. In fact, you can see here that
8 the greater than 80 percent diameter stenosis as
9 identified by duplex ultrasound was 0.8 percent in the
10 stent group, 4.2 percent in the endarterectomy group
11 which parallels quite impressively with the actual
12 target lesion revascularization rates.

13 DR. WHITE: Thank you. I have some
14 questions about the Patient Brochure. Warren, is this
15 the time or do you want to wait?

16 CHAIRMAN LASKEY: Now is the time.

17 DR. WHITE: Could you get your Patient
18 Brochure out so I can look at pages and talk to you
19 about some of the crazy things you're telling our
20 patients? I would like you to look at page seven
21 under section 3.1 of the Panel Pack. It's section
22 3.1, Patient Brochure and it's page seven of that

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1 brochure. That top paragraph the last sentence says
2 You ll be asked to take aspirin for one to two days
3 prior to the procedure. These are the instructions
4 in general for the patient. I would like to make sure
5 that you add or edit that sentence to include that
6 they will likely be asked also to take Plavix or
7 Ticlopidine before the procedure because at the end on
8 the discharge instructions, you do refer to that. I
9 think you should be consistent.

10 The next issue is on page nine. You talk
11 about after your procedure. You fail to mention
12 anything about closure devices. In fact in our
13 laboratory, closure devices are used in 80 to 90
14 percent of our patients. In fact, we use them in
15 virtually all of the carotid stent patients to avoid
16 hypotension from bleeding. So I think at least some
17 verbiage to prepare the patient that they might have a
18 closure device as opposed to the standard reaction
19 would be appropriate.

20 On the next page 10 in the second
21 paragraph, you reassure patients that MIs are not
22 contraindicated. But later in this document, you

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1 mention that it s only been tested to a testor of 1.5.

2 I think bigger (PH) magnets are now being widely
3 available and so you perhaps want to be more cautious
4 in your reassurance. You don t want a patient walking
5 in and saying No problem. I can have this MR if
6 somebody has a 3-Tesla mag.

7 CHAIRMAN LASKEY: Is that true for Nitinol
8 or is it a non-issue?

9 DR. WHITE: Well my problem is on page 29
10 of the next section you say that you have not tested
11 the precise stent. I m sorry. This is section 3.2,
12 the last page of the next section. You say the
13 precise stent has not been evaluated above Tesla 1.5.

14 That s 12.0 on page 26. So if you re going to say
15 you haven t tested above 1.5, I think it s hard to
16 give a blanket reassurance. It may be true but I
17 think the information ought to be consistent.

18 CHAIRMAN LASKEY: Or just take it out.
19 It s irrelevant. Nitinol, non-ferromagnetic, not even
20 close.

21 DR. WHITE: In the next paragraph under
22 Lifestyle Changes this is the interesting sentence.

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1 In the middle of that paragraph, you say Those
2 patients who are able to reduce fats and cholesterol
3 in their diets are less likely to redevelop blockages
4 in the stent. That s fabulous. It just isn t true.

5 Fix that.

6 I d like to go to the next section which
7 is 3.2 Precise Over the Wire IFU. It s the
8 instructions for use, page number six. You talk again
9 in this section about the indications for use for your
10 procedure, but you don t actually specify the anatomic
11 or comorbidity issues here for the operator. I
12 believe a table should be put in that actually
13 specifically lists the comorbid and the anatomic
14 criteria for the SAPPHIRE trial so that the operator
15 can follow those carefully.

16 At the bottom of that page, the last
17 bullet point says Stent placement is not recommended
18 for patients and the first one is with poor renal
19 function who in the physician s opinion may be at risk
20 for an reaction to contrast. I have a problem with
21 that sentence because we cannot obviously predict
22 contrast reactions. So I would like to modify the

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1 phrase in some way in these days of medical liability.

2 I would like for you to give me a way to have
3 physician judgment, perhaps even inserting the word
4 high in front of risk so that I would not be
5 putting the stent in a patient at high risk for
6 example because everybody is at some risk for renal
7 insufficiency.

8 Then on the top of the next page you go on
9 in the sub-bullets and you say that Aneurysmal
10 dilatation immediately proximal or distal to the
11 lesion is not recommended. In fact, most of my
12 patients have some element of ectasia, either
13 proximally or distally to these bifurcation lesions.
14 So if you want me not to treat aneurisms you have to
15 define what an aneurism is or take it out.

16 DR. OURIEL: Okay. We can define that.

17 DR. WHITE: The next line says In
18 patients in whom femoral or brachial access is not
19 possible. I m trying to think. Are you telling me
20 that I can t do this with a direct carotid puncture?
21 Am I in trouble if I do that?

22 DR. OURIEL: Well, I don t know if you re

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1 in trouble if you did that.

2 DR. WHITE: Well, you re telling me it s
3 not - Again I would be careful about the wording
4 because I m going to get hung by somebody I do direct
5 carotid puncture and has some sort of problem and some
6 plaintiff attorney is going to get their hands on this
7 and say We told you not to do that. I just want you
8 to think about what you re telling me not to do.

9 DR. OURIEL: Sure.

10 DR. WHITE: You say down under 6.0 on that
11 same page to avoid stent placement that would
12 obstruct access to a vital side branch. Do you see
13 that under that bullet? My concern is that I
14 routinely drop this stents across external carotid
15 arteries. Is that not a vital side branch?

16 DR. OURIEL: I would not consider that a
17 vital side branch and we ll address that line as well.

18 DR. WHITE: Okay. And then further down,
19 the third bullet down, you say Venous access should
20 be available. Do you see that one?

21 DR. OURIEL: Yes.

22 DR. WHITE: During carotid stenting in

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1 order to manage the Bradycardia and hypotension.
2 When you say that, are you talking about peripheral
3 venous access or are you telling me I have to have a
4 femoral venous sheath?

5 DR. OURIEL: Peripheral venous access.

6 DR. WHITE: Perhaps you could say that
7 because I'll tell you that it's going to come up.
8 Mitch has already asked about Bradycardia and
9 hypotension. We've really gone away from the routine
10 temporary pacemakers. We have more complications from
11 the sticks than we do from the hypotension. So we
12 really don't want to promote the idea that everybody
13 has to have a femoral venous stick because you don't
14 want hypotension two hours after you put a carotid
15 stent in somebody from a hematoma. That's a safety
16 issue.

17 DR. OURIEL: Sure.

18 DR. WHITE: That's all I have. Thank you.

19 CHAIRMAN LASKEY: Dr. Maisel.

20 DR. MAISEL: I wanted to focus for a
21 couple minutes on some of the described device
22 problems that occurred during this study.

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1 Specifically it s mentioned that there are eight
2 patients that had failure of stent delivery, although
3 most of these ultimately had successful delivery.
4 Another eight patients had difficulty in passing or
5 retrieving the ANGIOGUARD. In the registry, an
6 additional 25 patients had ANGIOGUARD delivery
7 failure. Could you comment and provide a little more
8 detail about what were the reasons? Particularly with
9 the ANGIOGUARD delivery failure, what actually was
10 limiting the delivery of the system?

11 DR. OURIEL: Well, I can t tell you
12 exactly on those particular patients, but I can tell
13 you that in general especially with previous versions
14 of the ANGIOGUARD, sometimes a lesion could not be
15 accessed very easily especially in the early portions
16 of this trial. That s basically why an ANGIOGUARD may
17 be difficult. If you ding up the wire, then you re
18 going to pull it out and get another ANGIOGUARD and
19 that would be an instance where initially the
20 deployment of the ANGIOGUARD was not possible, but
21 eventually it was.

22 DR. MAISEL: When you say can t be

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1 accessed easily do you mean it s stenotic, it s
2 narrowed, tortuous? What specifically are you
3 referring to?

4 DR. OURIEL: All of the above.
5 Angulations of the internal, tight lesions. It can be
6 difficult to get any wire through a tight carotid
7 lesion.

8 DR. MAISEL: And so were most of the
9 ANGIOGUARD delivery failures then early in the
10 registry and early in the randomized trial?

11 DR. OURIEL: We can look at that slide
12 again and see exactly comparing the FEASIBILITY to the
13 randomized trial. Let s see if you have that on one
14 of your -

15 DR. MAISEL: Simply because you re
16 suggesting it may have been related to inexperience or
17 trouble with the actual device.

18 DR. OURIEL: Well, I think that was
19 subsequently modified.

20 DR. COHEN: There are two aspects to the
21 answer. The first one is the patient s anatomy with
22 access toward tortuosity, lesion, severity, etc. The

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1 second one is that as we have mentioned early in the
2 presentation there have been several generations of
3 the device and the major improvements have been to
4 improve deliverability and lower the profile of the
5 device.

6 DR. MAISEL: Understanding that subgroup
7 analysis is fraught with danger, I m going to delve
8 into it a little bit, seeing as Dr. Laskey is several
9 seats away. I m particularly interested in talking
10 about the asymptomatic patients. I am struck as was
11 Dr. Tracy the high stroke rate particularly at 30 days
12 for these patients that were asymptomatic.

13 I certainly recognize as you ve mentioned
14 several times that there s contemporary data to know
15 what that rate would be in these higher risk patients.

16 It relates a little bit to the ANGIOGUARD delivery
17 system question. I m struck by the fact that the
18 asymptomatic stroke rate is higher than the
19 symptomatic stroke rate.

20 I wonder whether that might be due to
21 delivery of the system in more stenotic vessels or to
22 stent delivery in an 80 or 90 percent stenosis rather

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1 than a 50 or 60 percent stenosis. That might result
2 in more distal embolization. Do you have any data
3 either from the pathology, from the ANGIOGUARD devices
4 or from analysis of the relative stenosis and
5 complication rate?

6 DR. COHEN: The first part of the answer
7 is we obviously have expressed our disagreement with
8 any suggestion that the event rates are different.
9 The number of patients in each group is low. One or
10 two patients one way or the other can have marked
11 effects on the rates when you re looking at subgroup
12 analyses given the size of the samples. The second
13 part to your question is no, we don t have any data.

14 DR. MAISEL: I would also simply comment
15 that the design of the study I think could have
16 anticipated some of these issues. Grouping
17 symptomatic and asymptomatic patients which have
18 clearly different risks and clearly the acceptable
19 safety margin would be different in these populations
20 could have been anticipated. To my knowledge there
21 was no stratification of symptomatic or asymptomatic
22 at the time of randomization that might have helped

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1 address some of these issues.

2 DR. COHEN: That s actually not true. The
3 patients at the time of randomization were stratified
4 as to their symptom status. Just again, the goal of
5 this trial was not to provide detailed information on
6 subgroups. It was to analyze the primary endpoint.

7 DR. MAISEL: The other comment I ll make
8 and I simply would like to say that I certainly
9 recognize that it appears that the stent group did at
10 least as well as the CEA group overall, although we
11 can debate the statistics. What s not clear to me is
12 how these patients would compare to best medical
13 therapy. We were not provided really any data on the
14 medical therapy that these patients were receiving
15 which I think is a critical aspect of the care of
16 these patients.

17 Maybe you can just clarify. You mentioned
18 that you have some six and 12 month data. Can you
19 show us anything that shows what percentage of
20 patients were receiving anticoagulants which can
21 reduce stroke rates by maybe as much as 20 percent?
22 How many were on statins or other lipid-lowering

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1 therapy that can reduce stroke rates by 20 or 30
2 percent in these patients?

3 DR. COHEN: I can give you a limited
4 amount of data and unfortunately it will have to be
5 verbal. I don't have it in a slide. At the time of
6 discharge in terms of the category of anticoagulants,
7 in all this data I will give the stent data first and
8 then the carotid endarterectomy or the surgery second.
9 This is only for the randomized portion of the trial.

10 For anticoagulants, 31.6, 43.2 percent. For
11 antiplatelet agents, 98.1, 71.6 percent. For beta
12 blockers, 41.3, 59.0 percent. For lipid-lowering
13 agents, 69.9 percent, 65.5 percent. That's at
14 discharge. At 30-day follow-up, it was 94.3 percent.

15 I'm sorry. This is for clopidogrel specifically.
16 28.8 percent.

17 DR. MAISEL: Thank you. That's very
18 helpful.

19 DR. NAJARIAN: Hi, just a few questions.

20 DR. MAISEL: I'm sorry. Can I just ask
21 one more question? During the presentation, I can't
22 remember which of you mentioned it, but while showing

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1 some of the Kaplan-Meier you, on numerous occasions,
2 mentioned median survival. Sometimes that was
3 three, four, five, six years. Can you explain to me
4 how you had a median survival of that long in a trial
5 that was this short?

6 DR. OURIEL: How it was calculated?

7 DR. MAISEL: Yes.

8 DR. COHEN: I d like to as Joe Massaro to
9 come up.

10 DR. MASSARO: I m Joe Massaro. I m with
11 Harvard Clinical Research Institute, managing director
12 of Biostatistics and Data Management. I also am an
13 assistant professor of biostatistics at Boston
14 University. Cordis paid for my travel down here and
15 my lodging. Other than that, I have no financial
16 interest in Cordis.

17 Basically it s all extrapolated. We took
18 the one-year survival data and got an estimate of the
19 one-year maze rate for each group and then just
20 extrapolated that over the course of time until we
21 came up with an estimate of 50 percent of the patients
22 would be alive.

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1 DR. MAISEL: So it s safe to say that
2 those really are -

3 DR. MASSARO: It s estimated.

4 DR. MAISEL: Okay. Thanks.

5 DR. NAJARIAN: My turn? Just a few
6 questions. In both the carotid endarterectomy cases
7 and the stent cases, what percentage of each group had
8 general anesthesia versus local anesthesia?

9 DR. OURIEL: For carotid endarterectomy,
10 about 91 percent of the patients had general
11 anesthetic.

12 DR. NAJARIAN: And for the carotid stent
13 arm?

14 DR. OURIEL: It was done under local.

15 DR. NAJARIAN: All under local. Including
16 the 406 patients in the registry?

17 DR. OURIEL: Yes.

18 DR. NAJARIAN: Great. Another question.
19 I was just looking at in-hospital complications of
20 both groups. The randomized arm for the carotid
21 stenting, there were five out of 159 patients who had
22 a stroke. In the stent registry, ten out of 406

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1 patients had a stroke in hospital. Do you have any
2 data regarding those strokes like what percentage were
3 hemorrhagic and what percentage were ischemic? Were
4 any of the strokes since they did occur in hospital
5 treated interventionally with tPA or thrombolysis?

6 DR. COHEN: If I could ask you to divide
7 your question up. There were two parts to it. The
8 first part again?

9 DR. NAJARIAN: Two parts. I m sorry. The
10 first question is of the 15 strokes from all stent
11 patients what percentage were hemorrhagic versus
12 bland.

13 DR. COHEN: Yes. I know that there was, I
14 believe, a total - now this is in the entire trial
15 over the first year - of three hemorrhagic strokes.
16 We re going to check right now how many were in
17 hospital.

18 DR. NAJARIAN: I m sorry. How many were
19 hemorrhagic?

20 DR. OURIEL: Four or five were
21 hemorrhagic. I can t tell you which treatment arms
22 they were in. None were treated to our knowledge with

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1 thrombolysis.

2 DR. NAJARIAN: So approximately there were
3 five or six bland, non-hemorrhagic strokes then that
4 weren't treated.

5 DR. OURIEL: Approximately, but those
6 numbers aren't exact.

7 DR. NAJARIAN: Okay. This will come up at
8 some point. I'm not sure this is the appropriate time
9 to mention it, but in your training criteria, it says
10 The sponsor has proposed a training program called
11 CASES. This program must be completed prior to
12 shipment of any device to each center. This program
13 will be tailored to meet the needs of each physician
14 with more intensive training for those with little or
15 no experience. The more intensive training that
16 you're referring to, is that the third major bullet
17 down?

18 DR. OURIEL: I'm sorry. Could you tell me
19 what page you're looking at?

20 DR. NAJARIAN: I'm sorry. Page seven.
21 Actually I'm in the FDA packet, Introduction FDA
22 Questions No. 1.

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1 DR. OURIEL: I m sorry. Is this in the
2 Panel Pack you re talking about?

3 DR. NAJARIAN: Yes, the Panel Pack.

4 DR. OURIEL: The Panel Pack. Is this the
5 printed page number or the stamped page number on the
6 page?

7 DR. NAJARIAN: The one that refers to
8 training, page seven. It s also probably in your pack
9 as well.

10 DR. OURIEL: I have a page seven that has
11 a diagram on it. It starts out A Qualified
12 Physician with an arrow down to One online didactic
13 session. Is that what you re referring to?

14 DR. NAJARIAN: Maybe we can t find the
15 same page, but regarding training.

16 DR. OURIEL: Okay. I believe we have it.

17 DR. ZUCKERMAN: You re talking about the
18 last question.

19 DR. NAJARIAN: Yes, regarding the training
20 that you specified here. I was just wondering. It
21 says with patients with little or not experience.
22 Is that with stenting?

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1 DR. COHEN: No, specifically with carotid
2 stenting. Perhaps the explanation that will make this
3 clear is to turn it around the other way. What we did
4 in this program was to provide less intensive training
5 for those physicians who were experienced in
6 performing carotid stenting either with or without the
7 Cordis devices. If they had experience of 25 cases of
8 stenting and ten with the Cordis devices, then we
9 considered there was a need for minimal training in
10 those individuals. If there were people who were
11 experienced in carotid stenting but specifically not
12 in the Cordis devices, then they needed to have
13 training in the Cordis devices. For other physicians,
14 they needed to have the full program.

15 DR. NAJARIAN: Okay. Now there is no
16 experience here for documented cerebral arteriography.

17 I was just wondering. Does that mean that a
18 physician at a hospital, any physician, could go
19 through this training course and have devices shipped
20 to them?

21 DR. COHEN: Again, it s up to the hospital
22 to decide whether or not a physician is allowed to

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1 perform a procedure. We re not involved in the
2 credentialing process. All we are doing is assuring
3 that people who would be using our devices have been
4 adequately trained in that procedure.

5 DR. NAJARIAN: In that device.

6 DR. COHEN: Right.

7 DR. NAJARIAN: I ll just ask. Do you
8 think that minimal training in carotid access should
9 be necessary?

10 DR. OURIEL: On a local level?

11 DR. NAJARIAN: On a local level.

12 DR. OURIEL: Outside of the scope of this,
13 I think yes, someone needs training. In carotid
14 access, I don t think diagnostic angiography should be
15 encouraged however as a mechanism to get training if
16 you weren t going to do it anyway.

17 DR. NAJARIAN: That s all of my questions.

18 Thank you.

19 CHAIRMAN LASKEY: Are you sure?

20 DR. NAJARIAN: Yes.

21 CHAIRMAN LASKEY: Okay. We re two minutes
22 past an official break time. Did you want to requery?

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1 You had some additional quick question and I had one
2 quick question and then I think we should break before
3 the rounding third, heading home.

4 DR. COMEROTA: Sure. Hopefully these will
5 be quick. Dr. Cohen, if the FEASIBILITY study results
6 exceeded the projected major adverse events for
7 carotid endarterectomy which were calculated into the
8 trial - so if you had a projected event rate more than
9 two times that of CEA - would you have proceeded with
10 the randomized trial?

11 DR. COHEN: I m sorry. You re asking a
12 hypothetical question.

13 DR. COMEROTA: Yes.

14 DR. COHEN: And this is based on the U.S.
15 FEASIBILITY Study?

16 DR. COMEROTA: Correct.

17 DR. COHEN: Okay. There was this formal
18 stopping rule which was a twofold rule. I forget the
19 formal name of the rule.

20 DR. COMEROTA: Correct.

21 DR. COHEN: And that rule was followed.
22 So we followed the rules of what was agreed upon by

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1 both the FDA and us as being appropriate.

2 DR. COMEROTA: Okay. These are high risk
3 patients. We've more or less agreed. At least, they
4 have high risk characteristics. Do you think these
5 are high risk carotid lesions?

6 DR. OURIEL: Do you mean are they high
7 risk carotid lesions for stroke?

8 DR. COMEROTA: Correct.

9 DR. OURIEL: I'm not sure I understand.

10 DR. COMEROTA: Correct.

11 DR. OURIEL: Well, I really don't know the
12 answer to that, Tony, but I can tell you I just don't
13 know that answer to that. But I know what you're
14 thinking and we've thought the same thing that a
15 patient with diffuse atherosclerosis with a 70 percent
16 carotid lesion may be more likely to have an event
17 than a patient without diffuse atherosclerosis and a
18 70 percent carotid lesion, but no data.

19 DR. COMEROTA: Okay. The results as we've
20 mentioned before, these were top notched physicians
21 involved in this trial. We see what the data are.
22 When this gets out, where do you think the real world

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1 event rate is going to lie when all interventionalists
2 begin to use this?

3 DR. COHEN: I think the best answer to
4 that is to refer you to the details of the post-
5 marketing surveillance study. We've communicated with
6 the agency and the desire here is actually to obtain
7 data in a variety of settings including both academic
8 and non-academic centers, a geographically diverse
9 number of hospitals as well as low volume,
10 intermediate volume and high volume operators so that
11 we will gain insight into whether the training we are
12 doing is adequate and whether or not there is a
13 threshold as I believe what you're alluding to that
14 would have an effect on safety.

15 DR. COMEROTA: Do you have information on
16 the results of brain imaging that was performed on the
17 patients in both arms of the trial post-procedure?

18 DR. COHEN: No, that was not part of the
19 formal trial.

20 DR. COMEROTA: But when they were
21 performed, you don't have that information.

22 DR. COHEN: We don't have it. No.

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1 DR. COMEROTA: Okay. I know that with all
2 due respect, Warren, subgroup analyses and so forth
3 you did say that these were stratified up front
4 asymptomatic versus symptomatic. I mean we make our
5 clinical decisions in very large part on whether the
6 patient is symptomatic or asymptomatic and the
7 behavior of those lesions and the degree of stenosis
8 drives what we do. It has a direct impact on the
9 benefit that the patient receives from the procedure
10 or lack of benefit.

11 The absolute reason why any procedure is
12 deemed beneficial is when it s performed at a very
13 risk of an event. That defines how these patients are
14 going to be identified and who will benefit from that
15 technique. Just let me get your thoughts on these
16 high risk patients with potentially low risk lesions,
17 why they weren t considered to be put into a medical
18 management arm?

19 DR. COHEN: Then I would refer back to
20 what the major goal of this trial was. It was not an
21 NIH trial looking at trying to understand a disease
22 process, event rates, etc. It was a trial looking at

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1 patients who are treated in the United States and I
2 think we've provided sufficient information from the
3 literature and from different databases to support
4 that. These patients are being treated today in the
5 United States and what we were studying specifically
6 was an alternate form of treatment that we believe
7 from the data is less invasive and in some regards
8 safer. It offers an alternative therapy for these
9 patients.

10 DR. COMEROTA: Well, I understand. I
11 understand exactly. But our panel is charged with
12 identifying whether this is appropriate or if the
13 global idea isn't appropriate, what's the niche for
14 the technique. Without that information, it's
15 difficult to get to that answer. This is a discussion
16 that I'm sure we're going to have after the break.

17 What we do know is the stroke rate in a
18 very large study, unwritten national trial, medical
19 treatment from 10 to 15 years ago or 15 and more years
20 ago - we know that medical treatment is better today -
21 that 30 day stroke rate in those patients treated
22 medically is 0.3 percent. 0.3. We know what the 30-

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1 day stroke rate in symptomatic patients is. Well, all
2 the cerebral vascular events was 3.3 percent. Stroke
3 and death, neurologic deficit and death, is around 1.0
4 percent in symptomatic patients. The only way that
5 any technique can equal that over time is to have a
6 very, very low event rate. So I would give you across
7 the board that these patients should not be operated.
8 They should not have a carotid endarterectomy.

9 DR. COHEN: Well, I can understand and
10 respectfully I understand your opinion in that regard.

11 However, again what we have shown is that these
12 patients are being intervened upon in the United
13 States. Our goal here wasn't to determine whether
14 that's appropriate or inappropriate, but to point out
15 that they are being treated and to allow an alternate
16 therapy to be compared to the current standard of
17 care.

18 DR. COMEROTA: And if we approve that,
19 then you are asking us to put a stamp of approval on
20 this therapy.

21 DR. COHEN: As an alternative to the
22 procedure -

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1 DR. COMEROTA: As an alternative to
2 another inappropriate form of therapy.

3 DR. COHEN: Sorry.

4 CHAIRMAN LASKEY: I think (a) it s time
5 for break. Let s cool off. (b) Thank you very much.
6 We realize that this last ten minutes has been
7 speculative. We appreciate your patience. Thank you,
8 Tony. I have a quick question for Nigel. Can I catch
9 you on the break? Thank you. I have 3:55 p.m. Can
10 we reconvene in ten minutes please for the remainder.
11 Off the record.

12 (Whereupon, the foregoing matter went off
13 the record at 3:56 p.m. and went back on
14 the record at 4:14 p.m.)

15 CHAIRMAN LASKEY: Thank you again.

16 Before we finish up here and move to the
17 questions and the panel vote, we do need to reopen the
18 open public hearing portion of this afternoon's
19 meeting and prior to that, Ms. Wood wants to read a
20 statement into the record.

21 MS. WOOD: This is in addition to the
22 conflict of interest statement. We would like to note

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1 for the record that a waiver has been granted for Dr.
2 William Maisel. His imputed waiver involves a
3 contract to his institution for the sponsor's study in
4 which he had no involvement in data generation or
5 analysis. The waiver allows Dr. Maisel to participate
6 fully in today's deliberations.

7 A copy of this waiver may be obtained from
8 the agency's Freedom of Information Office, Room 12A-
9 15 of the Parklawn Building.

10 CHAIRMAN LASKEY: And the first speaker
11 requesting time for the open public session is Dr.
12 Robert Hobson.

13 Dr. Hobson.

14 I will remind this afternoon's speakers
15 that they're limited to ten minutes on the clock as
16 well, just like this morning.

17 DR. HOBSON: Thanks very much, Dr. Laskey.

18 It's a privilege for me to make a few
19 comments on behalf of the CREST investigators, a group
20 that is studying the efficacy of endarterectomy versus
21 stenting in a good risk sample of patients. That's
22 supported by the National Institutes of Health.

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1 I have no relationship with the Cordis J&J
2 Company. I have received modest support from the
3 Guidant Corporation in association with the CREST
4 trial.

5 These are data on the impact of clinical
6 trials on a number of carotid endarterectomies
7 performed in the United States annually. On the
8 vertical axis is the number of endarterectomies in
9 thousands, and on the horizontal axis, the year of
10 interest. These data are from the Dartmouth Atlas of
11 Vascular Health.

12 And notice that in 1985, the number of
13 carotid endarterectomies performed in the United
14 States was about 100,000. With the publication of a
15 trial that had little to do with extracranial carotid
16 stenosis, the EC-IC bypass trial, there was a
17 substantial decrease in the number of cases just by
18 association.

19 In other words, this was a trial primarily
20 interested in internal carotid occlusion in which a
21 branch of the external carotid, the superficial
22 temporal, was anastomosed to a temporal branch of the

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1 middle cerebral through a temporary trephine, and even
2 though there was no difference demonstrated between
3 that bypass and even though it stayed open in over 90
4 percent of cases, it showed no difference with medical
5 therapy, and as a result, there was a substantial and
6 significant decrease in the number of endarterectomies
7 performed until publication of the symptomatic trials
8 in '91, the North American symptomatic carotid
9 endarterectomy trial supported by NIH, the European
10 carotid surgery trial in Europe, and the VA
11 symptomatic trail.

12 And we are back up to about 100,000
13 operations in 1994-5, with the publication of ACAS and
14 the VAA symptomatic trial, up to the '96 data of about
15 140,000 operations, which has been sustained out to
16 2000 now.

17 Now, the CREST trial is supported by the
18 Neurology Institute of the NIH and looks at this same
19 question being asked by the SAPPHIRE trial. What is
20 the efficacy of endarterectomy versus stenting in a
21 conventional risk group of patients, that is, the 80
22 percent of patients treated by surgeons who do carotid

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1 endarterectomy.

2 This particular trial then looks at the
3 better risk patients and uses devices supplied by the
4 Guidant Corporation, the ACCULINK nitinol self-
5 expanding stent, and the ACCUNET anti-embolic device.

6 The CREST Executive Committee is populated
7 by many of the speakers who were also involved in the
8 SAPPHIRE trial. These are the experts in the field.
9 Tom Brott, the co-PI for CREST, is a neurologist.
10 Gary Roubin is co-PI for intervention in cardiology;
11 Bob Ferguson for intervention. Nick Hopkins is the
12 neurosurgeon and Wes Moore the vascular surgeon. Rick
13 Kuntz has done the data management in the past at
14 ACRI, and George Howard is the biostatistician. Jeff
15 Popma runs the core lab in angiography, and Kirk Beach
16 has taken Gene Strandness' position as the co-PI for
17 ultrasound.

18 The trial is being conducted at 70 centers
19 in the United States and Canada and is wrestling with
20 the issue of recruiting patients to a trial that is
21 randomizing symptomatic patients only. However,
22 progress is being made, and during the last month we

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1 had our most productive month with over 30 patients
2 randomized in the treatment categories.

3 However, I recognize that on my own
4 service, a group of vascular surgeons that perform
5 carotid endarterectomy as well as stenting, that these
6 are our current indications in higher risk patients
7 for the performance of carotid artery stenting.
8 Carotid restenosis was our first subset of patients
9 treated because it is acknowledged at low risk for
10 neurological events, and therefore, it's the ideal
11 training case for a new interventionalist.

12 High risk patients, radiation induced
13 stenosis, and there are very few anatomically
14 inaccessible lesions at the C2 or above.

15 On our service we initiated a program in
16 carotid artery stenting in September of 1996, and
17 we've done 204 cases now over that seven-year period.

18 During that same period we have done 885 carotid
19 endarterectomies. So this constitutes about 20
20 percent of a vascular surgeon's work load currently.
21 So we are sympathetic to the clearance of indications
22 for carotid artery stenting.

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1 As part of our work-up through CREST, we
2 wanted to look at the published data on the
3 prospective analysis, that is, the randomized clinical
4 trial data comparing carotid artery stenting and
5 endarterectomy, and these are the published reports.
6 I know the focus of our discussion today is SAPPHIRE,
7 and I'd like to make a few comments on that.

8 I would suggest, however, that the data
9 from Schneider and SAPPHIRE are only available to us
10 today by abstract format, and although the other three
11 trials are published, none have had much in the way of
12 outreach one way or the other in terms of preference
13 for stenting.

14 Now, as an observation, sitting in the
15 audience today, I think the SAPPHIRE investigators
16 right over here did exactly what this group told them
17 to do: go out and do a noninferiority trial.

18 And the dilemma you must have on this
19 panel is the results are an extraordinarily small
20 sample, and I wouldn't want to be in your position.
21 And although we will live with your decision, it's a
22 problem.

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1 As abstracted originally after the
2 original report at the American Heart, there were 307
3 patients. Thirty-two percent were symptomatic.
4 That's 96 patients. Now, recall my first slide that
5 had its data on the impact of a clinical trial. It
6 does change clinical practice. What we're suggesting
7 is that we change a clinical algorithm established
8 over the last two decades based on the analysis of 96
9 symptomatic patients, and I would submit that a great
10 deal of the discussion this morning regarding things
11 that I certainly didn't understand in terms of
12 triangular biostatistics come down to a very small
13 number of events.

14 If less than five events swung one way or
15 the other it would change the result of this very
16 small trial, and my lament to you is that we haven't
17 provided a higher standard for the SAPPHIRE
18 investigators to follow. Superiority trials have been
19 used in the impact on clinical trial algorithms, and
20 the smallest sample size was over 1,700 patients. So
21 it gives you an opportunity to focus in on stroke.

22 After all, we're interested in stroke

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1 prevention, and there was no significant difference
2 between those two treatments in terms of stroke
3 prevention. It's very possible, I think, that the
4 SAPPHIRE trialists have identified a subset of
5 patients that should be treated by neither
6 endarterectomy nor carotid stenting.

7 What's the impact of medical therapy? It
8 would have been magnificent. This trial would have
9 been a ground breaker if you had included a medical
10 therapy arm, and I know that wasn't your goal, and I
11 can understand that you wish you had done that.

12 Five-year survival data with such a large
13 number of asymptomatic patients would have been nice,
14 too.

15 CHAIRMAN LASKEY: Sir, you have one
16 minute.

17 DR. HOBSON: I've already commented on the
18 restenosis issue.

19 So with regard to the future of carotid
20 stenting, the CREST investigators can live with
21 approval of a device provided the data driven
22 introduction of carotid stenting is confined to

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1 SAPPHIRE-like patients.

2 The challenges, I think, have been covered
3 very nicely. One has been an optimal trial where
4 you've done what the federal government asked you to
5 do. There's no data on medical therapy which is
6 unfortunate.

7 I was reassured by Dr. Cohen's
8 presentation that the FDA can probably define post PMA
9 surveillance, that the FDA can monitor the results of
10 carotid artery stenting at trial and registry centers,
11 as well as centers just introducing carotid artery
12 stenting, and I'm pleased that the interventionists
13 will be trained in a way that is essentially
14 comparable to the recommendations made by many experts
15 in the CREST trial.

16 And if these things are followed, if these
17 challenges are met, then I think that we can proceed
18 with a randomized trial on conventional risk patients.

19 My concern, in conclusion, would be that approval of
20 this device based on a very small number of patients
21 might in any way interfere with the proof of purpose
22 trial, the CREST trial.

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1 Thanks very much.

2 CHAIRMAN LASKEY: Thank you, sir.

3 The next individual requesting time is Dr.
4 Ku.

5 DR. KU: Thank you.

6 My name is Andrew Ku. I'm representing
7 myself as an individual. I'm an interventional
8 neuroradiologist in practice since 1991.

9 Okay. Disclosure. No current ownership
10 or shares in the company being discussed or
11 competitors at the present time. I have had prior
12 ownership and probably will consider them in the
13 future, but mainly as an investor.

14 Currently my travel reimbursement is paid
15 for by myself. I am not representing anybody. There
16 is a possibility I may be reimbursed by ASITN, as I'm
17 also an observer for them.

18 The current data that has been presented
19 shows that the PRECISE stent and the ANGIOGUARD XP
20 distal protection device may be as safe as surgery in
21 high risk surgical patients. I don't believe that the
22 current data shows that the precise stent and

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1 ANGIOGUARD XP distal protection device is safer than
2 medical therapy in asymptomatic high risk patients, as
3 defined in the SAPPHIRE study. In fact, most studies
4 that have covered asymptomatic patients probably show
5 that this option is potentially inferior.

6 So that's my major concern because the
7 study does include asymptomatic patients.

8 This is just a review of the data that was
9 presented earlier. Of interest is even though it's
10 not statistically significant is the information
11 that's highlighted in red, which covers the combined
12 major mortality/morbidity rate, comparing stents in
13 symptomatic patients versus endarterectomy patients.
14 It is significant lowers. Well, it's not
15 significantly. It is lower, but not statistically
16 significant in stent patients.

17 So for patients who are symptomatic, i.e.,
18 having TIA, had recent prior stroke in that
19 ipsilateral territory, it seems like it works pretty
20 well.

21 Asymptomatic patients, same data. The
22 numbers are pretty similar. So you've got to wonder,

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1 you know. Is there a higher risk for these
2 asymptomatic patients when you use the device? Is it
3 worth it?

4 The information that was presented by the
5 FDA, reanalyzing the data that was submitted basically
6 shows the same thing. So I will go through that very
7 quickly.

8 But basically it shows that the patients
9 who are symptomatic were significantly benefitted by
10 the device, and the patients who were asymptomatic
11 didn't really do much better than endarterectomy.

12 There are trials. There's the University
13 Medical Center, and then there is the real world.
14 Most of these studies, including all of the
15 symptomatic and asymptomatic studies have been
16 performed in major medical centers with the best
17 trained physicians in the world.

18 For example, carotid endarterectomy in
19 NASCET, ACAS, SAPPHIRE. They were all done by
20 physicians who were very experienced. You didn't have
21 somebody who was doing three endarterectomies a year
22 doing these, in general.

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1 Review of endarterectomy results from
2 Medicare data shows that the outcome is not as good in
3 patients who are sampled from Medicare data, probably
4 because there are a lot of patients being treated by
5 physicians who don't do many procedures, or there's a
6 lot more variability in, you know, the patients'
7 clinical conditions.

8 So I think we must be very cautious about
9 comparing all of these trials versus the real world.
10 I would hope that you would be very conservative in
11 your analysis and allow the needed margin of safety
12 that real world conditions demand.

13 There are two major causes of stroke,
14 either embolic or nonembolic. Nonembolic I mean by
15 thrombosis of the vessel. So basically if you have a
16 diseased blood vessel, there's plaque potentially.
17 There could be a piece of stuff that forms and that
18 breaks off.

19 The other possibility is that due to flow
20 restriction, there's in situ thrombosis of the vessel,
21 and I think that most strokes fall into these two
22 categories.

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1 The NASCET study, which is a study that
2 covered symptomatic patients, did show benefit from
3 surgical therapy over medical therapy.

4 Studies in asymptomatic patients, however,
5 are somewhat different. There have been at four major
6 randomized trials covering medical therapy to
7 endarterectomy. Three out of the four showed no
8 positive benefit from endarterectomy. The Mayo Clinic
9 asymptomatic carotid endarterectomy trial was
10 prematurely halted due to safety issues from the
11 surgical arm. Only ACAS was positive in showing
12 benefit from surgery.

13 However, if you look at the actual data,
14 the five-year medical history of ipsilateral minor
15 stroke was 11 percent or 2.2 percent annually. The
16 surgical arm reduced that risk, but if you analyze how
17 many endarterectomies are needed to prevent one minor
18 stroke, it was about 83 endarterectomies, and the data
19 didn't show any significant prevention of major
20 strokes.

21 So if you look at it after you subtract
22 out the natural medical portion of the complication

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1 rate or stroke rate, surgery gave basically a one
2 percent per year improvement over those five years.

3 Eighteen-year follow-up, they had a 17
4 percent stroke rate, of which the contralateral non-
5 stenotic stroke was nine percent. So if you take out
6 that nine percent and divide it by 18 years, the
7 benefit was about half a percent per year.

8 And the Canadian Stroke Consortium in
9 their analysis found that they did not have any
10 indication for endarterectomy for any level of
11 asymptomatic stenosis.

12 Part of the NASCET trial reanalysis, one
13 of the comments was most individuals with asymptomatic
14 disease fared better with medical therapy. So here we
15 have a SAPPHIRE trial where two-thirds of the patients
16 were asymptomatic, and they were being treated. This
17 was presented, I believe, at the American Stroke
18 Association meeting. It's not published.

19 They did a reanalysis of ACAS and the
20 reanalysis showed no statistical improvement with
21 endarterectomy. So maybe there is improvement. Two,
22 point, three percent, you have to do better than 2.3

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1 percent complication rate to show benefit. Maybe not.

2 I have a major concern with the current
3 indication for use with this particular device. As I
4 stated in your packet, my major concern is in the
5 patients without neurologic symptoms and with greater
6 than or equal to 80 percent stenosis. It would make
7 common sense that if something is really narrowed, you
8 would have a high risk of stroke, but it's not proven
9 by the data.

10 So I feel that if you're going to operate
11 on these patients or stent on these patients, you're
12 taking a lot of risk for very little or negative
13 benefit, and I think that we would do a disservice.

14 So since I do use carotid stents, I
15 remember one of my patients in 1991 died because she
16 had bilateral carotid dissections from a car accident.

17 She had multiple injuries, and they could not
18 anticoagulate her. I did an angiogram, made the
19 diagnosis. She was neurologically normal. She was
20 dead the next day from bilateral infarcts.

21 So I think that there is a very strong
22 indication for a device for certain patients, but I

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1 would like the labeling to contraindicate the use of
2 this device in asymptomatic carotid disease because I
3 don't think the data that is available justifies it,
4 and I think that if we allow people to use it as a
5 physician driven device, in this particular instance
6 it may be a severe mistake.

7 I know that the FDA doesn't like to
8 regulate the practice of medicine, but if that
9 language is in there, the lawyer certainly will.

10 I would like to see a PMA showing safety
11 and effectiveness prior to use in an asymptomatic
12 device. I think that device may have potential.
13 Things are improving every single day. Our devices
14 are getting better. The techniques are getting
15 better. So there probably will be a point where our
16 complication rate is low enough that this device will
17 be useful.

18 So we as physicians or I as a physician
19 feel that I must treat the patient and not the
20 angiographic procedure or angiographic picture, and I
21 think that most clinicians will agree with that.

22 If you want any comment on training, I

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1 could do that, but that's a separate issue.

2 Thank you very much.

3 CHAIRMAN LASKEY: Thank you, Dr. Ku.

4 The remaining speaker who has elected time
5 is Dr. Rodney White.

6 DR. WHITE: Thank you very much.

7 My name is Rod White. I'm a vascular
8 surgeon from Torrance, California. I'm here today
9 representing the Society for Vascular Surgery in lieu
10 of a letter that Dr. Green submitted.

11 My own conflicts, I paid my way to this
12 meeting as an observer. My greatest conflict is I'm a
13 practicing vascular surgeon who does both open carotid
14 endarterectomies and carotid stents, and I make my
15 living doing this. So any of us who are here to tell
16 you that that isn't a conflict, I think it is probably
17 from both directions.

18 Now, Dr. Green had submitted a letter to
19 be read here today, and then was unable to attend. So
20 I am going to read this letter for him as the
21 Secretary for the Society for Vascular Surgery. This
22 is his letter from the SVS, and as I read it, this

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1 will obviously be him speaking rather than me.

2 "I am current President of the Society for
3 Vascular Surgery. I am also a practicing vascular
4 surgeon and Chairman of the Department of Surgery at
5 Lennox Hill Hospital in New York City.

6 "I am formally requesting an opportunity
7 to speak to the FDA panel concerning approval of the
8 Cordis ANGIOGUARD and PRECIS stent systems for carotid
9 angioplasty and stenting. I do so representing a
10 group with vast experience in the management of
11 patients with cerebral vascular disease.

12 "The Cordis Company and principal
13 investigators are to be congratulated for designing
14 and conducting a randomized trial comparing carotid
15 stenting with embolic protection to endarterectomy in
16 a selected group of patients considered at high risk
17 for endarterectomy. They hypothesized an equivalence
18 between stenting and endarterectomy in this defined
19 subset of patients, and their data appear to support
20 their contention.

21 "While the definition of high risk use in
22 the SAPPHIRE trial is not uniformly accepted by all

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1 vascular surgeons, we do agree that certain patients
2 are likely to benefit from carotid angioplasty and
3 stenting when performed at a level of expertise
4 similar to that of the trialists. These patients
5 include those with contralateral laryngeal nerve
6 palsy, a history of radiation therapy to the neck,
7 previous carotid endarterectomy with recurrent
8 stenosis, and those with medical co-morbidities that
9 might adversely affect the outcome and the opinion of
10 surgeons, interventionalists, and anesthesiologists
11 responsible for the patient.

12 "We believe, however, that this cohort of
13 patients in SAPPHIRE represents a small percentage of
14 those in the general population currently undergoing
15 carotid endarterectomy and that this study is not
16 reflective of current national practice.

17 "We cannot overstate how important we
18 regard trials with expanded indications powered
19 sufficiently to allow the data to determine any
20 subsequent expansion of indications for usage.
21 Pending results of large scale experience from a
22 single arm registry or dual arm randomized trial with

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1 independently adjudicated one-year outcome data, there
2 are little data to support the use of carotid stenting
3 in lower risk patients. We are concerned that
4 because the differentiation between high and low risk
5 is not always clear and the monitoring and usage
6 nearly impossible that the procedure will be utilized
7 in patients not adequately studied.

8 "The adjudication of high risk is best
9 done by a collaborative decision making process,
10 including multiple physicians and a surgeon that
11 performs carotid endarterectomy.

12 "If approved, carotid stenting should be
13 performed by those operators with expertise not just
14 on technical aspects of delivering a stent to a
15 target, but on all of the pre and post procedural
16 components carotid endarterectomy requires.

17 "This means that a thorough knowledge of
18 the natural history of carotid bifurcation disease,
19 medical co-morbidities, possible neurologic
20 consequences of both stroke and reperfusion and the
21 ability to provide post procedural care necessary in
22 addition to the requisite technical skills.

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1 "We are concerned that no one interested
2 group of physicians has expertise in all of these
3 areas. Multi-specialty coordination and cooperation
4 will be required to achieve outstanding outcomes that
5 we all deserve.

6 "Because carotid stenting is a new
7 procedure to the majority of vascular surgeons,
8 interventional cardiologists and interventional
9 radiologists, training and credentialing presents a
10 unique challenge. Each of the vested subspecialties
11 has a different skill set and knowledge base.
12 Specifically, there are groups that have more
13 expertise in catheter aspects of carotid stenting,
14 groups that have more expertise in diagnostic
15 components, namely cerebral angiography, and those
16 with more expertise in the management of patients.

17 "No one of these ingredients is more or
18 less critical to successful outcome. We are
19 encouraged that many interested professional societies
20 are working collaboratively for the creation of CPT
21 and ICD-9 codes and to address national noncoverage
22 decisions for carotid stenting over the past nine

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1 months.

2 "We are discouraged that similar
3 collaboration has not occurred regarding training,
4 competencing and credentialing standards. The
5 tendency of each group to emphasize its strengths and
6 minimize its weaknesses relative to carotid stenting
7 is self-serving and not in the best interest of
8 patient care.

9 "It is critical that each of the
10 representative societies establish it own set of
11 responsible guidelines for credentialing requirements
12 with the understanding that the final decision will be
13 made locally.

14 "We believe that anyone who wishes to
15 perform carotid stenting should possess a minimum of
16 skills associated with the advanced interventionalist
17 regardless of the target lesion treated. Certainly a
18 familiarity of the anatomy and behavior, the cerebral
19 vessels is essential, no less so than coronary, renal,
20 or lower extremity vascular anatomy. Many of the
21 skills and tools required to perform renal and
22 superficial femoral artery angioplasty and stenting

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1 are transferrable to the extracranial circulation.

2 "Other variables being equal,
3 practitioners experienced in coronary, renal and lower
4 extremity and subclavian interventions will require
5 fewer procedures to become proficient in carotid
6 stenting. Those without such experience will require
7 many more procedures.

8 "Vascular surgery training requirements
9 have not in the past included a minimum number of
10 cases as a requisite for certification. Rather, a
11 curriculum is approved. Training programs are
12 reviewed for competence, and individuals are certified
13 and then qualified.

14 "We believe that the case numbers are less
15 relevant than demonstrated competence. We agree
16 conceptually with the certification process developed
17 by CREST investigators whereby performance parameters
18 are included in the determination of competence.

19 "Lastly, I would like to comment on the
20 proposition that an arbitrary number of diagnostic
21 cerebral angiograms be a prerequisite credentialing
22 requirement for carotid stenting. The panel should be

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1 aware that there remain relatively few indications for
2 diagnostic angiograms performed as sole procedures.
3 To create any threshold for training on this basis
4 creates an unacceptable risk to patients, and there is
5 a definite instance of stroke from the diagnostic
6 procedure alone, irrespective of an intervention.

7 "Further, any diagnostic procedures do not
8 provide experience in the more complex techniques,
9 such as guide/sheath cannulation of the common carotid
10 artery, use of embolic protection devices and stent
11 deployment. We would hope that the
12 neurointerventionalists would agree to collaborate in
13 the care of these patients rather than to create
14 artificial and potentially dangerous barriers.

15 "In conclusion, the society for vascular
16 surgery is supportive of the efforts bringing this new
17 technology forward. While we still believe that
18 carotid endarterectomy is appropriate in the majority
19 of patients with carotid artery stenosis and
20 indications for intervention, we support the judicious
21 use of carotid artery stenting in bona fide high risk
22 patients.

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1 "We recognize the challenge of introducing
2 this technology in the larger community and will
3 continue to work with our medical colleagues in
4 industry to achieve our goals to improve patient
5 care."

6 This is submitted, "Sincerely, Richard M.
7 Green, President, Society for Vascular Surgery."

8 Thank you.

9 CHAIRMAN LASKEY: Thank you, sir.

10 Is there anyone else that wishes to come
11 forth? Yes, sir.

12 DR. DALL'OLMO: Thank you.

13 My name is Carlo Dall'olmo. I am a
14 community based vascular surgeon in Flint, Michigan,
15 member of a ten-man vascular group, and we have
16 performed up to 400, 450 carotid endarterectomies a
17 year, and over the past several years have been
18 involved in the four carotid stent training trials.

19 I believe that carotid stenting is an
20 exciting new therapy with several important questions
21 which remain to be answered because the applicability
22 of this procedure will depend on the answers.

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1 The first is the two questions that
2 carotid stenting initially raised. Sine carotid
3 stenting hit the scene, there were always two
4 questions that had to be answered. The first was:
5 could it be done as effectively and safely as a
6 carotid endarterectomy? And the second was: what is
7 its durability? Is it as durable as a carotid
8 endarterectomy?

9 I think that referable to the first
10 question, what we heard today is that, yes, it can be
11 done safely. So the initial step is there.

12 However, what is the longevity of this
13 procedure? What is its durability? Is three years
14 enough follow-up to answer this question?

15 I don't believe that's enough. I don't
16 believe that data is in. Carotid endarterectomy is a
17 durable procedure, and it's not unusual to see
18 patients who are ten, 12, 15, and 18 years post
19 carotid endarterectomy walking into your office.
20 Certainly in the community we see them in our
21 churches. We see them in our stores. We see them on
22 the streets.

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1 The second question is whether or not the
2 data on 334 patients in the SAPPHIRE in a randomized
3 arm is enough to extrapolate to an entire population
4 on a broad label. I believe more data is needed.

5 Finally, the issue of high risk. The
6 current criteria seemed to be loose and apply to too
7 many patients. Prior to the year 2000 when we weren't
8 involved in any carotid stent trials, we operated on
9 the high risk patients routinely. As a matter of
10 fact, high risk was almost used to exclude a patient
11 because it often meant that their longevity was so
12 short that it wasn't worth intervening.

13 I believe that the definition of high
14 risk, with the exception of anatomical lesions, such
15 as an irradiated neck or a high lesion or perhaps a
16 recurrent carotid stenosis, I believe the definition
17 of high risk needs to be stringently defined, and that
18 hasn't been done yet.

19 Until these questions are more
20 definitively answered with either larger randomized
21 studies or more data, I speak in favor of a limited
22 scope of applicability. There's nothing lost by doing

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1 this until better data is available. If it's good
2 today, it will be good a couple of years from now when
3 we get more data.

4 I think one of the risks that we really
5 run, and this is a serious problem, is applying this
6 on a broad label at this time and then having it go
7 out and having a number of problems develop at all
8 levels, which is a real risk.

9 Better, in my opinion, that we start
10 slowly and expand, and I thank you for the opportunity
11 to comment.

12 CHAIRMAN LASKEY: Thank you, sir.

13 Are there any other folks who wish to come
14 forth?

15 (No response.)

16 CHAIRMAN LASKEY: If not, we'll close this
17 open public hearing.

18 Geretta will read one more letter into the
19 record.

20 MS. WOOD: I received this statement from
21 Colin P. Derdeyne, M.D., Associate Professor at
22 Mallinckrodt Institute of Radiology in the Department

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1 of Neurology and Neurological Surgery at Washington
2 University School of Medicine.

3 "Dear Panel Members:

4 "The labeled indication for this device
5 should not include patients with asymptomatic carotid
6 stenosis. The data from the SAPPHIRE trial that has
7 been presented to date do not support safety and
8 efficacy for protected angioplasty and stenting in
9 this population. While outcome was significantly
10 better in the endovascular group than those who
11 underwent surgical endarterectomy, it is possible and,
12 indeed, highly likely that these patients would have
13 done better on medical therapy alone.

14 "We cannot conclude that this device is
15 safe and effective for asymptomatic patients. In the
16 SAPPHIRE data presented at the AHA scientific sessions
17 in Chicago in 2002, the 30-day rate for stroke,
18 myocardial infarction, and death was 6.7 percent for
19 the asymptomatic endovascular group. One year of
20 follow-up data reportedly are over ten percent for
21 these adverse outcomes in previously asymptomatic
22 patients.

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1 "I do not know how many patients in the
2 trial were asymptomatic, nor the co-morbidities that
3 led them to be categorized as high risk. Asymptomatic
4 patients were required to have greater than 80 percent
5 stenosis of the target carotid artery. This
6 categorization was used to select patients perceived
7 as high risk for revascularization, not high risk for
8 stroke.

9 "We do not know the natural history for
10 these patients. The best data we can have comes from
11 the asymptomatic carotid atherosclerosis study, or the
12 ACAS, published in 1995 in the Journal of the American
13 Medical Association. Sixteen hundred fifty-nine
14 patients were randomized to best medical therapy,
15 aspirin or surgical endarterectomy. A relatively
16 young, health, good surgical risk population was
17 studied. Overall, a very slight, but statistically
18 significant benefit was found with surgery.
19 Annualized event rates for ipsilateral stroke from
20 five-year projected data were approximately two
21 percent for ipsilateral stroke in the medical group,
22 and one percent for the surgical group. Thirty-day

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1 periprocedural surgical complication rates were 2.1
2 percent.

3 "Importantly, there was no stratification
4 of increased risk with higher degrees of stenosis.
5 Eighty-eight medically treated patients had greater
6 than 80 percent stenosis. Three, or 3.7 percent,
7 suffered a stroke during follow-up.

8 "Another group of patients that might be
9 thought to be high risk was not. The five-year risk
10 of stroke for 77 medically treated patients with
11 contralateral complete carotid artery occlusion was
12 3.5 percent while the five-year stroke risk in the 85
13 surgical patients was 5.5 percent, Baker, Stroke,
14 2002.

15 "Finally, women do not appear to benefit
16 from intervention, although the study was not powered
17 to make this determination. It is important to note
18 that since publication of the ACAS study, several
19 improvements have been made and medical therapy that
20 may further reduce the risk of stroke in asymptomatic
21 patients.

22 "Statin agents have been shown to lower

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1 the risk of stroke in patients with atherosclerotic
2 diseases published in Lancet 2004. Better anti-
3 hypertensive agents are also now available.

4 "In summary, surgical revascularization
5 for patients with asymptomatic carotid stenosis is of
6 marginal benefit even if the most healthy of patients
7 and with extremely low periprocedural complication
8 rates. This benefit may not be present in women or in
9 patients with greater than 80 percent stenosis or
10 contralateral complete carotid occlusion. The event
11 rates reported in the SAPPHIRE trial for both surgical
12 and endovascular treatment of asymptomatic patients
13 are extremely concerning.

14 "Even with the lower rates seen in the
15 endovascular group, the most rational conclusion that
16 can be drawn at present is that these patients should
17 be treated medically. A trial of stenting versus best
18 medical therapy is needed to determine if these
19 devices are safe and effective in asymptomatic people.

20 The label for this device should not include
21 asymptomatic patients.

22 "Thank you for your time and

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1 consideration.

2 "Sincerely, Dr. Colin P. Derdeyne."

3 CHAIRMAN LASKEY: And now the open public
4 forum is closed.

5 We need to consider the questions put to
6 the panel. In view of the hour and the fact that we
7 do need to vote and we cannot lose any of the members
8 up here who need to leave for the airport, I would
9 just request that we hold the discussion in response
10 to these questions to a minimum, panel. Let's try and
11 develop a consensus for the agency concisely.

12 So with that, can we have the questions,
13 please?

14 MS. WOOD: I'm going to go ahead and start
15 reading the first question while they're bringing up
16 the projector.

17 Can the data from the investigator-sponsor
18 studies be considered in the evaluation of high risk
19 carotid stenting given the differences in trial
20 conduct for the high risk investigator sponsor
21 registry?

22 CHAIRMAN LASKEY: Well, I'll take point on

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1 these and then please feel free to modify, amend,
2 chime in or correct.

3 I think that these IND studies which were
4 part of the panel packet are in no way representative
5 of the patient population that we are asked to
6 consider today for the randomized portion of the
7 trial. I think the event rates are rather low,
8 strikingly low, which speak to at least one problem
9 with the generalizability of these studies. There's a
10 lack of adjudication of these endpoints.

11 So in summary, I don't think that these
12 data from the IND studies can be used for today's
13 discussion.

14 Good. All right. Next.

15 MS. WOOD: Number two, how does the large
16 enrollment in the registry CAS arm affect
17 interpretation of results?

18 CHAIRMAN LASKEY: Interpretation of
19 results of what?

20 DR. ZUCKERMAN: The randomized trial.

21 CHAIRMAN LASKEY: All right. Well, point
22 number one, I think we went through great pains this

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1 morning to speak to the fact that these patients wound
2 up in the carotid stent registry for certain specific
3 reasons, some which were clearly identified and some
4 which were yet to be identified.

5 I believe Dr. Cohen alluded to the fact
6 that the data collection forms describing all of the
7 clinical characteristics in covariates really haven't
8 been culled yet to ascertain differences or
9 similarities that would allow us to draw conclusions
10 of same or different behavior.

11 Number three, the outcome of the
12 propensity score analysis remains in abeyance in part
13 because of this, the lack of sufficient number of
14 covariates examined, and I think those analyses are
15 still under study.

16 So without answers to those three, I'm not
17 sure that we can bring information about the
18 applicability or generalizability of the carotid stent
19 patients into this realm. We can certainly speak to
20 the randomized trial data separately and the stent
21 registry patients separately, but I think making
22 comparisons is premature and perhaps hazardous.

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1 DR. COMEROTA: Comment. Would it be
2 accurate then to assume that this would be a real
3 world type of scenario because these are patients that
4 are evaluated for an operative procedure deemed not to
5 be of adequate acceptance for the operation and,
6 therefore, directed for carotid angioplasty and
7 stenting?

8 CHAIRMAN LASKEY: Well, you're asking a
9 question in a question. We're supposed to --

10 DR. COMEROTA: Well, see, Warren, you said
11 they're not applicable, and I think that they may be
12 applicable in light of what is the role of carotid
13 angioplasty and stenting in these potentially high
14 risk patients.

15 CHAIRMAN LASKEY: In those patients.

16 DR. COMEROTA: Right.

17 CHAIRMAN LASKEY: These are different
18 patients than the ones in the randomized trial.
19 Agreed?

20 DR. COMEROTA: Some of them were, yes.

21 CHAIRMAN LASKEY: In ways that are both
22 identified and yet to be identified.

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1 DR. COMEROTA: Correct.

2 CHAIRMAN LASKEY: And therein lies part of
3 the problem of doing some of these additional analyses
4 to establish comparability of results across these
5 different patient subsets.

6 DR. ZUCKERMAN: Okay. The point of the
7 question though was that there was a large exit of
8 patients from the original enrolled trials to this
9 registry. Does it invalidate the results of the
10 randomized trial in any way?

11 CHAIRMAN LASKEY: No, I don't think I
12 heard that today. It doesn't invalidate it.

13 DR. ZUCKERMAN: Okay.

14 CHAIRMAN LASKEY: It certainly qualifies
15 it.

16 Judah, any comment? Okay.

17 Number three. How does premature
18 termination of the pivotal randomized study affect the
19 conclusions derived from this study?

20 Well, we went back and forth about whether
21 it was premature termination or not, whether it was
22 part of the up front decision to do sequential

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1 analyses, that that was built into the study design,
2 that perhaps it was not prematurely terminated. I'm
3 not sure from my standpoint whether this is just a
4 semantic issue between the agency and the sponsor, and
5 I'm not sure we should spend much more time on this.
6 We've really beat it up pretty well this morning.

7 DR. KRUCOFF: I would basically agree to
8 just turn it the other way. I think it's clear it was
9 administratively prematurely terminated. I think the
10 question then becomes of the range of statistical
11 expertise on the data available, how legitimate are
12 the conclusions from the randomized segment, and I do
13 think there are some discussion between the expertise
14 from London and Harvard and the agency would probably
15 be worthwhile.

16 CHAIRMAN LASKEY: That being said, the
17 goal and the endpoint was addressed and was found to
18 be adequately powered to reject the noninferiority
19 null hypothesis despite the fact that it was before
20 the target.

21 DR. KRUCOFF: I think the one other thing
22 I come away with, Warren, is that at least the

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1 premature termination was not the result of looks at
2 the data that would be inappropriate or biased in that
3 regard. That to me would be a much more fatal kind of
4 problem.

5 CHAIRMAN LASKEY: Absolutely.

6 Okay. the next question is?

7 MS. WOOD: How does premature termination
8 of the pivotal randomized study affect conclusions
9 derived from this study?

10 CHAIRMAN LASKEY: We just did that.

11 MS. WOOD: Please discuss how data from
12 previous carotid treatment trials NASCET, ACAS can be
13 used to analyze the current perioperative 30-day data
14 set with regard to safety.

15 CHAIRMAN LASKEY: Well, we just heard some
16 information during the open public session, data to
17 that effect. Do the surgeons wish to speak to these,
18 quote, control rates?

19 DR. COMEROTA: I think the basic issues
20 have been raised. The reference to NASCET and ACAS
21 have always been what is the operative
22 morbidity/mortality, but then you take that operative

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1 morbidity/mortality and then select instead of a good
2 risk group a high risk group of patients and then say,
3 "Okay. We're going to compare the operation to a new
4 form of intervention."

5 And if you look at the new form of
6 intervention, if we specifically focus on ACAS and the
7 30-day result rate, since the majority of the patients
8 in SAPPHIRE were asymptomatic, that 30-day result rate
9 is ten to 15 times higher what it was in the medically
10 treated patients in ACAS.

11 If you look at the 30-day result rate,
12 it's somewhere between -- it's some factor higher than
13 NASCET. If you look at the death and stroke rate at
14 the end of 30 days, it's probably a factor of two
15 higher.

16 DR. WHITE: I disagree with that. I think
17 that's not quite true, and I think the heart of this
18 issue is that NASCET nor ACAS provide a proper
19 comparator, and if we had had a sponsor here come and
20 try to use ACAS or NASCET to justify their response,
21 we wouldn't have heard it because they were not
22 properly controlled.

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1 It doesn't mean you can't look at NASCET.

2 It doesn't mean you can't use that as a --

3 CHAIRMAN LASKEY: We're just answering the
4 question.

5 DR. WHITE: -- as setting some limits, but
6 you cannot use ACAS or NASCET as a proper comparator.
7 they're just different populations of patients.
8 There's nothing to make you think they were the same.

9 CHAIRMAN LASKEY: Not only that, but the
10 ground breaking aspect of this trial was that they
11 included myocardial infarction as well, which was not
12 part of the composite endpoint in either NASCET or
13 ACAS.

14 So I think that's another variable that
15 was discussed this morning in terms of its relevance
16 as well, and it's probably a very key variable.

17 So to answer the question, it can't very
18 well properly be used in the context of redefining
19 your MAE rate.

20 DR. ZUCKERMAN: Okay, but, Dr. Laskey, I
21 just heard two opinions as to how usable the prior
22 randomized carotid trials are, one person saying yes,

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1 one person saying no, that there are major
2 differences.

3 What are the opinions of other panel
4 members? Is there a consensus one way or the other?
5 How generalizable are these trials?

6 CHAIRMAN LASKEY: Well, but before we do
7 that, we have to make sure we're talking about the
8 same thing. The event rates that were reported in
9 NASCET and ACAS are not the event rates discussed
10 today unless we throw out the myocardial infarction
11 data. So that's one problem.

12 But Mitch.

13 DR. KRUCOFF: I think a fundamental issue
14 here is around the issue of intention to treat.
15 Intention to treat is to try and capture a real
16 clinical scenario where you see a patient and would
17 intend to treat them in some way, and I think it has
18 been very clearly and repeatedly stated that SAPPHIRE
19 was focused on an intention to revascularize, and what
20 that patient population is and how it varies in the
21 practice of medicine is a whole series of discussions,
22 but I think to take studies that include an intention

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1 to randomize between revascularization or not is a
2 fundamentally different starting point than taking a
3 population in whom the intention is to revascularize.

4 And I think that to me is the biggest
5 chasm to leap here in trying to use historical
6 controls where the intention was to randomize between
7 revascularization or not in comparison to this set of
8 data.

9 CHAIRMAN LASKEY: Well, you're quite
10 correct, but the question refers to using the periop
11 data with respect to safety. So that we need to make
12 sure we're looking at the same variables here.

13 CHAIRMAN LASKEY: Gary.

14 DR. NICHOLAS: If I can, I think that the
15 applicability to the SAPPHIRE study and to try to
16 utilize it to cross-validate the study, I don't think
17 it can be done, but I do think that both NASCET and
18 ACAS can set a guideline for stroke and not looking at
19 myocardial infarction obviously or even death rate
20 which might be altered because of the population.

21 But if we look at stroke in both the
22 symptomatic and asymptomatic patients, I think they do

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1 set a standard, that pure and simply endpoint, the one
2 the patient worries about and the one we worry about.

3 So I do think they have validity in
4 assessing this type of protocol.

5 CHAIRMAN LASKEY: Even in the era of
6 Plavix and so forth, which was not --

7 DR. NICHOLAS: Yes, sir.

8 DR. WEINBERGER: I think that the older
9 studies don't seek out to enroll patients with high
10 risk co-morbid backgrounds, and I think that for that
11 reason alone you could not compare outcomes even if
12 they included MIs. I think that even if MIs were
13 included as endpoints in NASCET and ACAS, they still
14 would not provide valid comparators.

15 CHAIRMAN LASKEY: Suffice to say the use
16 of historical controls as controls is dangerous.

17 Next.

18 MS. WOOD: There were multiple ways for
19 higher risk patients to be entered into the SAPPHIRE
20 trial. Please discuss the impact of these various
21 patient subgroups on ability to generalize safety and
22 effectiveness results.

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1 CHAIRMAN LASKEY: Well, I'm not sure how
2 many multiple ways there were for patients to wander
3 into the study. Once it had been decided that they
4 needed something done was the very first step, and
5 then things evolved or devolved from there, but that's
6 a different issue than how they got to that point, and
7 we don't know how they got to that point.

8 The next sentence though speaks to various
9 patient subgroups which is kind of a disconnect from
10 multiple ways for high risk patients to get into the
11 trial. So there's two ideologically distinct concepts
12 being addressed here. I don't think we can speak to
13 how patients got into the study in the first place
14 because we're not privy to that data, but in terms of
15 the impact of the various patient subgroups, that's a
16 terribly important issue that I think we grappled with
17 all afternoon if we just used the symptomatic versus
18 asymptomatic division to begin with.

19 That clearly affects the data on safety
20 and effectiveness because it applies in the one group
21 but doesn't apply in the other group. So it's
22 confusing to us.

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