

1 resulted in adverse events from air embolism. This
2 rate has been increasing and is not up to an estimated
3 0.14 percent.

4 Cordis investigated these events to try to
5 determine the root cause followed by some testing on
6 the bench to try to simulate this problem and correct
7 it. The problem seems to occur in the RX
8 configuration because of the tolerance and the length
9 of the pod in the RX. We are concerned that the bench
10 testing performed by the sponsor to date is not
11 optimal because saline was used in the testing and the
12 viscosity of saline is different than that of blood.

13 We believe that additional animal and
14 possibly clinical testing may need to be performed.
15 After this slide was finalized, Cordis called to
16 indicate that animal testing had been performed but it
17 was not included in the amendment for review. Based
18 on the bench and animal testing, the sponsor has
19 proposed stipulating larger guiding catheters for
20 introducer sheaths and more detailed instructions for
21 preparing the delivery system.

22 FDA will continue to work with the sponsor

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1 to resolve this issue since we believe that further
2 testing is probably warranted and the results of the
3 animal studies will need to be submitted and reviewed.

4 The indication sought by the sponsor is provided on
5 this slide and provides options for patients with and
6 without symptoms and stipulations relating to degree
7 of stenosis as well as comorbidities making them a
8 high risk for surgery.

9 The IDE for this device has had a long
10 history beginning in 1998. Since the first
11 submission, there have been many changes made to the
12 device, materials of construction, sizes, and profile,
13 with the most significant being the introduction of
14 the ANGIOGUARD Embolic protection device during the
15 latter part of the FEASIBILITY study, lowering the
16 profile of the device, and the development of the RX
17 configuration.

18 The sponsor terminated their randomized
19 study early and gave the reasons detailed in this
20 slide. Regarding the first bullet, these competing
21 studies were facilitated by Cordis in that Cordis
22 provided each investigator with a letter of

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1 authorization to allow FDA to access the Cordis file
2 for background information. Cordis also supplied
3 most, if not all, of the single investigators a copy
4 of their FEASIBILITY protocol, which was a registry
5 design, and the case report forms and consent that was
6 developed for that study.

7 Most opted to follow this protocol with
8 little modification, but Cordis was not privy to
9 interactions between these single investigators and
10 FDA. Most investigators were approved to perform
11 somewhere between 50 and 100 carotid artery stenting
12 cases.

13 While there was no contractual
14 relationship between Cordis and these single
15 investigators, a sponsor is required under the PMA
16 regulation to provide FDA with all data known to them
17 or that should be known to them. So Cordis
18 coordinated with most of these investigators to obtain
19 their 30 day data for inclusion into the PMA. It
20 should be noted that all of these studies stipulate a
21 minimum of 12 month follow up.

22 As stated earlier, there have been many

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1 design changes made throughout the history of the
2 file. For each change the sponsor made, they provided
3 testing appropriate to the specific change. Testing
4 has included fatigue, simulated use, device
5 specification, and integrity testing sometimes on the
6 bench, sometimes in animals, sometimes in both.

7 We met with the firm just prior to the
8 submission of the PMA and agreed that the RX
9 configuration of the stent and ANGIOGUARD could be
10 approved without clinical data since the working ends
11 have not been modified. In the original animal
12 testing results submitted prior to the proposed fix of
13 using larger guiding catheters or sheaths, one comment
14 in the report was that a larger guide would be needed
15 for the 10 by 40 centimeter size.

16 While we did not suspect a problem with
17 this statement, the new developments in humans, with
18 devices being used off-label, may warrant further
19 evaluation clinically and we may have to reconsider
20 our agreement. To date, the engineering reviews have
21 been completed, at least those performed prior to the
22 proposal for larger guiding catheters and sheaths, as

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1 have biocompatibility. These are considered adequate
2 and complete.

3 The review of the sterilization validation
4 is not yet complete, but no major issues are
5 anticipated from that review. As noted earlier, each
6 additional bench, animal, and possible clinical data
7 may be needed to fully validate the RX configuration.

8 Another non-clinical issue has arisen
9 recently. The FDA issued Cordis a corporate warning
10 letter on April 1, 2004. Our investigators noted many
11 serious non-compliance issues with respect to the
12 current Good Manufacturing Practices requirements.
13 The letter quoted that there were systemic problems
14 noted at many facilities.

15 Obviously these are going to need to be
16 rectified before approval can be granted for the
17 PRECISE and the ANGIOGUARD. I m going to now turn
18 over the podium to Dr. Heng Li, the FDA statistician
19 for a brief discussion of the statistical issues.

20 DR. LI: In my presentation, I will make a
21 few comments on the SAPPHIRE randomized trial, the
22 SAPPHIRE stent registry, and the statistical procedure

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1 of propensities for analysis followed by some
2 concluding remarks. First, let me talk about the
3 SAPPHIRE randomized trial.

4 This randomized clinical trial, whose
5 objective is to compare stenting with carotid
6 endarterectomy, had a group sequential statistical
7 plan in which the sequential triangular test was used.

8 Unlike a fixed sample sized plan, the group
9 sequential design does not pre-specify the sample size
10 of the trial. Instead, the design establishes a set
11 of stopping rules and schedules a series of interim
12 analyses.

13 At each interim analyses, the available
14 data are examined and the trial is either stopped or
15 continued according to the stopping rules. The
16 stopping rules and the schedule of interim analyses
17 are specified so as to control the frequent error
18 probabilities at their intended or specified levels.
19 For the SAPPHIRE randomized trial, the interim
20 analyses are scheduled at intervals of every 100
21 patients.

22 The maximum sample size was specified to

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1 be 2,400. In the original protocol, it was expected
2 that the trial would be stopped at a sample size of at
3 least 600. I will come back to discuss the original
4 group sequential trial in some more detail for the
5 SAPPHIRE randomized trial in a minute.

6 But before I do that, let me point out
7 that the sponsor made no claims that the original
8 group sequential protocol had been followed. As a
9 matter of fact, in the current PMA submission, the
10 message appeared to be that the original group
11 sequential statistical plan had not been followed. In
12 particular, the scheduled interim analyses had not
13 been conducted. However, FDA was not aware of any
14 change in the statistical plan.

15 In the current submission, data from
16 SAPPHIRE randomized trial were used to make the
17 declaration that stenting is non-inferior to CEA.
18 This declaration is based upon statistical inference.

19 We know that statistical inferences for design
20 studies need to be made according to the statistical
21 plan in the current study protocol. Otherwise, they
22 are unplanned.

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1 Therefore, the statistical inferences in
2 the current PMA submission that led to the declaration
3 of non-inferiority of stenting relative to CEA based
4 on the SAPPHIRE randomized trial is unplanned since it
5 made reference to a statistical plan that is not in
6 the current study protocol, namely a fixed sample size
7 design based on 334 patients, the number at which the
8 trial happened to be discontinued. We all know that
9 statistical inference based on unplanned analyses are
10 less reliable. So we don't think it's necessary that
11 the inference be based on an unreliable, unplanned
12 analysis.

13 Now, let us describe the original group
14 sequential protocol in a little more detail using a
15 picture. In this picture, the label of the horizontal
16 axis V represents the amount of information that has
17 accumulated at a given time or before a given time.
18 The label of the vertical axis Z represents the
19 difference in treatment effect as reflected in the
20 data at that time.

21 At any stage of the clinical trial, the
22 values of V and Z can be calculated from the available

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1 data. So we can imagine that as the trial progresses,
2 it traces out a sample path on the V-Z plane. Because
3 the amount of information increases as more data
4 became available, the sample path goes from left to
5 right starting at V equal to zero.

6 As it moves to the right, it may wander up
7 and down. The triangle on the graph defines the
8 stopping rule in the original group sequential plan
9 for the SAPPHIRE randomized trial. If the trial is
10 continuously monitored, then when the sample paths
11 cross one of the triangular boundaries the trial is
12 stopped.

13 If the sample path crosses the upper
14 triangular boundary, then the trial is stopped and the
15 non-inferiority tested. When the sample path crosses
16 the lower triangular boundary, the trial is stopped
17 and no non-inferiority can be claimed. As long as the
18 sample path is within the triangular region, the trial
19 continues.

20 The inner boundaries are called the
21 Christmas tree boundaries because of their shape.
22 These reflect the adjustment necessary for discreet

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1 monitoring. Since the scheduled monitoring is
2 discreet with interim analysis planned for every 100
3 patients, the Christmas tree boundaries would have
4 been used for the SAPPHIRE randomized trial.

5 This slide summarizes the stopping rules
6 described earlier according to the original protocol.

7 For the SAPPHIRE randomized trial, based on the data
8 contained in the PMA submission, we can calculate Z
9 and V as mentioned before. So we can plot a point in
10 the Z-V plane. Of course, this single point wouldn't
11 tell us what would have happened had the original
12 group sequential protocol been followed.

13 In the sponsor's presentation, there is
14 one slide that contains very valuable information
15 which is the attempt of reconstructing the group
16 sequential plan or a reconstruction of what would have
17 happened had the original protocol been followed to
18 the best approximation. As far as I'm aware, this
19 information wasn't contained in the PMA submission.
20 As far as I know, it wasn't submitted. If it was
21 submitted, it wasn't submitted before 4:00 p.m.
22 yesterday. I'm looking forward to reviewing this very

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1 valuable information in the near future.

2 Let me now turn to the SAPPHIRE stent
3 registry. For the SAPPHIRE stent registry, the
4 predefined objective performance criteria is to reject
5 a null hypothesis that the 360 day major adverse event
6 rate is greater than 16.94 percent. The observed 360
7 day major adverse event rate is 15.76 percent.

8 A 95 confidence interval for a 360 day
9 major adverse event rate has a lower bound of 12.36
10 percent and an upper bound of 19.68 percent. The
11 upper confidence limit, 19.68 percent, exceeds the OPC
12 of 16.94 percent. The pre-specified OPC has not been
13 met.

14 After realizing that the OPC is not met,
15 the sponsor made unplanned comparisons between the
16 stent registry and CEA arm of the randomized study.
17 Since the patient characteristics of those two groups
18 by the nature of how they are assigned are not
19 necessarily the same, a straightforward comparison as
20 was conducted in the current PMA submission is not
21 appropriate.

22 To address this issue, the sponsor used a

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1 propensity score method to compare the two groups
2 attempting to make post-hoc claim of non-inferiority
3 of stent registry to randomized CEA. The phrase
4 propensity score method, as it is commonly used,
5 refers to a class of statistical procedures that can
6 help evaluate difference in treatment effect when the
7 treatment groups are not necessarily comparable by
8 balancing a set of chosen covariates.

9 It works by first introducing a model for
10 the probability of a subject being assigned to one of
11 the treatment groups given the values of the
12 covariates. This probability is called the propensity
13 score, hence the name propensity score method. The
14 issue of missing data in the modeling, the issue of
15 missing covariates in propensity score modeling could
16 be addressed by multiple imputation.

17 The result of propensity score modeling is
18 that each subject is assigned a propensity score. One
19 way of using propensity score analysis to compare
20 treatment effects after a propensity score is
21 calculated for each subject is to divide the patients
22 into five strata according to their propensity scores.

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1 The first stratum consists of patients
2 with propensity scores in the top twentieth percentile
3 and so on all the way down to the last stratum
4 consisting of patients with propensity scores in the
5 lowest twentieth percentile. It turns out that all
6 the covariates included in the propensity score model
7 could be simultaneously balanced to a great extent
8 within each stratum. Therefore, bias due to imbalance
9 of those covariates could be removed to a great extent
10 when treatment comparison is made within each stratum.

11 The potential of being able to
12 simultaneously balance a large number of covariates to
13 a great extent is a very attractive feature of the
14 propensity score method. However, the sponsor may not
15 have taken full advantage of the propensity score
16 analysis in carrying out their propensity score
17 analysis.

18 The potential issues include not all
19 observed, clinically relevant covariates were included
20 in the propensity score model, not all patients are
21 included in the treatment comparison, and of course
22 the analysis itself is unplanned. Given the

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1 sensitivity of the results to any improvement of
2 methodology, this is all the more of a concern.

3 Now, let me get to the concluding remarks.

4 In conclusion, original group sequential protocol was
5 not followed and FDA was not informed of any change in
6 protocol for a new statistical plan. Evidence of non-
7 inferiority under original group sequential protocol
8 was not supplied in the current PMA submission.

9 For the stent registry, it fails to meet a
10 pre-specified operating OPC, objective performance
11 criteria. Any non-inferiority claim based on the
12 sponsor's post-hoc propensity score analysis is
13 problematic for the reason mentioned above. Now, let
14 me turn the podium to Dr. Weintraub.

15 DR. WEINTRAUB: Good morning. The
16 SAPPHIRE pivotal clinical study was designed as a
17 multi-center randomized group sequential study studied
18 by intention to treat as a comparison between patients
19 undergoing open operative carotid endarterectomy and
20 those being treated with the carotid angioplasty in
21 the Cordis PRECISE stent system. In addition to the
22 334 patients randomized to the stent and

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1 endarterectomy arms, there was an additional stent
2 registry cohort.

3 This presentation will examine the
4 comparative results of the randomized arms, compare
5 subgroups within the randomized arms, examine the
6 results of the non-randomized stent registry, and look
7 at the relative clinical effectiveness of the stent
8 and endarterectomy techniques. Finally, a brief
9 survey of historical randomized trials comparing
10 endarterectomy with medical management of carotid
11 stenosis will be introduced as a frame of reference.

12 In order to be considered for enrollment
13 in the SAPPHIRE study, patients were required to be
14 considered high risk by a neurologic or anatomic
15 criteria in addition to having one or more technical
16 or medical comorbid features considered to present
17 high risk for carotid endarterectomy. These include
18 the following and are defined in greater detail in
19 your panel packs. The sponsor also introduced these
20 in detail earlier this morning.

21 There were a number of exclusion criteria
22 which are also enumerated in these next two slides and

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1 in detail in your panel packs and again were discussed
2 by the sponsor earlier. I ll just take a second so
3 you can look at them.

4 There were 167 patients in each arm.
5 These serve as the basis of comparison in the pivotal
6 trial. In the non-randomized registry, 406 patients
7 met inclusion criteria but were determined by the
8 surgeon at each site to be at too high a risk for
9 carotid endarterectomy and inappropriate therefore for
10 randomization.

11 First of all, I skipped a page obviously
12 so I m going to have to go back. The names of the
13 various laboratories are provided in your panel packs.

14 Data analysis was performed by the Harvard Clinical
15 Research Institute which also provided the
16 adjudication committee.

17 The primary end points. Please note that
18 the composite of major adverse events at 30 days post-
19 procedure includes myocardial infarctions. These are
20 not included unless they were fatal in the historical
21 randomized trials comparing endarterectomy and medical
22 therapy. The second primary end point consists of the

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1 composite 30 day major adverse events plus death
2 and/or ipsilateral stroke at one month to a year.

3 Secondary end points are listed in the
4 next two slides. Again, they were detailed in your
5 panel packs. For the pivotal randomized trial, 29
6 centers enrolled patients. A total of 334 patients
7 were enrolled equally divided between stent and
8 endarterectomy. Five centers however enrolled the
9 majority of patients. The one year major adverse
10 event rates are listed for those five centers in the
11 slide shown here.

12 Let s look at the primary events. The
13 primary end point of 30 day adverse event rates for
14 the randomized stent and endarterectomy arms are
15 displayed here. Please note the confidence limits in
16 the far right columns. Let me review for the panel as
17 well as for myself that if the limits embraced by the
18 brackets encompass zero, the values of the two arms
19 are not considered to be statistically different. As
20 shown here, several pairs of data points approach but
21 do not reach statistical significance.

22 Here are the one year or 360 day major

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1 adverse event rates. There are no statistically
2 significant differences between the two groups.
3 Moving forward, we look at the two year major adverse
4 event rates and again no statistical difference
5 between the two groups.

6 In this slide, the data are presented in
7 several ways. First, both randomized and registry
8 data are presented. They are also divided into
9 neurologically symptomatic and asymptomatic cohorts.
10 Finally, the 30 day major adverse events are scrubbed
11 of their non-fatal myocardial infarctions making them
12 more comparable to historical randomized control
13 trials. That s done in this third column.

14 Again, there s no significant difference
15 between the randomized arms. The incidents and
16 severity of myocardial infarctions in the randomized
17 stent and endarterectomy arms was examined. It did
18 not differ significantly. The same data for the
19 registry are displayed though no formal statistical
20 comparison can be made. Again, no differences.

21 As previously mentioned, a total of 406
22 patients were entered into the stent registry. The

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1 sponsor states that they were entered at the choice of
2 the surgeon investigators who felt they were too high
3 risk for randomization. On this slide are represented
4 the reasons stated for surgical turndown. Note that
5 the reasons were not enumerated in 50 percent of the
6 patients. Please also note that approximately 70
7 percent of the patients were neurologically
8 asymptomatic.

9 Represented here are the 30, 360, and 720
10 day adverse event rates among the registry patients.
11 Take note especially, if you would, of this figure of
12 15.8 percent for major adverse event rates at one
13 year. To briefly review Dr. Heng Li s analysis,
14 objective performance criteria were set at 12.94
15 percent.

16 This figure was determined by calculations
17 derived from review of the literature of randomized,
18 controlled, endarterectomy trials as well as site
19 reviews of the relevant study populations of the
20 SAPPHERE trial. Since the original delta of four
21 percent was specified, the null hypothesis assumed a
22 360 day major adverse event rate of the 12.94 percent

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1 plus four percent of 16.94 percent or higher.

2 The observed rate in the trial however was
3 15.76 percent as presented in the previous slide.
4 Therefore, the sponsor could not reject the null
5 hypothesis. In other words, the criterion for non-
6 inferiority was not met. It s clear that the
7 propensity score method has not been thoroughly
8 explored. Questions remain about the adequacy of
9 analysis.

10 Let s return to the randomized control
11 study. The following slides show the patients
12 subdivided into neurologically symptomatic and
13 asymptomatic cohorts. Examination of the 30 day major
14 adverse events demonstrated non-inferiority of the
15 stent with respect to endarterectomy. I direct your
16 attention to the number of patients in the symptomatic
17 trials. Here s the 30 day adverse event rates.
18 Subgroup analysis at 360 days also showed non-
19 inferiority of the stent.

20 Turning to the asymptomatic randomized
21 patients, they were also compared with respect to 30
22 day major adverse event rates. Also note the rather

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1 larger number in these cohorts. There were over twice
2 as many asymptomatic as symptomatic patients in
3 randomized pivotal trial. Once again, there were no
4 significant differences between randomized stent and
5 randomized endarterectomy groups at the 30 day mark.

6 Results at one year were similar. There
7 were no differences between the randomized stent
8 patients and those who underwent endarterectomy,
9 although the superiority of stent approached
10 significance - you see the zero - at about the 0.07
11 level.

12 Subgroups other than symptomatic and
13 asymptomatic were examined. Here are displayed male
14 and female sex and diabetes in the randomized stent
15 and endarterectomy arms and in the registry at 30 and
16 360 days. At 30 days, major adverse events in the
17 diabetics occurred more frequently in
18 endarterectomized patients actually reaching
19 statistical significance with a p-value of 0.03.

20 One year major adverse events occurred
21 more frequently in males almost reaching statistical
22 significance. The subgroup of elderly patients was

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1 examined but the numbers were relatively small. No
2 differences were noted. Recurrent stenosis occurred
3 with similar frequency in all the groups.

4 Secondary end points were reviewed. In
5 this table, lesion, procedure, and device success and
6 protection for all patients randomized or selected for
7 stent are displayed. Success defined by these various
8 parameters ranged between 88 and 96 percent. The
9 column to the far right represents the individual
10 investigator sponsored trials.

11 Other secondary end points are shown in
12 here in the different cohorts; trapped material,
13 freedom from lesion restenosis, and freedom from major
14 adverse events at one year. There s probably no other
15 surgically treated disease entity that has been
16 studied so thoroughly in randomized control trials
17 than carotid stenosis. Thus far, carotid
18 endarterectomy has been compared with optimal medical
19 therapy in a series of trials over the period of a
20 decade or more.

21 Because the SAPPHIRE study is itself a
22 randomized study comparing a new technology with

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1 carotid endarterectomy as the gold standard, it would
2 be appropriate at this point to consider conclusions
3 derived from those historical randomized studies which
4 compare to endarterectomy with the then standard
5 medical therapy. The best known studies are the
6 asymptomatic carotid artery atherosclerosis study
7 called ACAS which looked at patients with asymptomatic
8 stenosis greater than 60 percent and the Veterans
9 Administration study of asymptomatic males with
10 greater than 50 percent stenosis.

11 The ECTS European study examined
12 symptomatic patients. The NASCET, North American
13 Symptomatic Carotid Endarterectomy Trial, also studied
14 symptomatic patients. In the interest of time, I have
15 condensed the conclusions of these several excellent
16 studies into three slides. If the panel were to find
17 it germane, we have more detailed slides available for
18 the discussion period.

19 Here are the conclusions. For symptomatic
20 patients, high grade stenosis carotid endarterectomy
21 was very effective, greater than 50 percent reduction
22 in the risk of stroke and any death at two years. Not

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1 only that but risk reduction varied with stenosis,
2 that is, the greater the stenosis, the greater the
3 risk reduction of operation.

4 For moderate stenosis, success was less
5 certain. It was calculated that 23 operations were
6 required to prevent each severe ipsilateral stroke at
7 five years. Not only that but each two percent
8 increase in 30 day perioperative event rate reduced
9 the five year benefit by 20 percent.

10 In the asymptomatic patients with greater
11 than 60 percent stenosis, endarterectomy was very
12 effective with approximately a 50 percent reduction in
13 the risk of ipsilateral stroke or perioperative stroke
14 or death if the procedure could be performed with a
15 perioperative, major adverse event rate of less than
16 three percent. Not only that but angiography alone
17 entailed a risk of stroke of 1.2 percent.

18 These conclusions are consonant with the
19 American Heart Association guidelines for stroke
20 prevention and for guidance for the appropriate use of
21 endarterectomy published in 2001 and 1998
22 respectively. Finally, there are data that caution us

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1 about the indiscriminate employment of endarterectomy.

2 First, the risk of stroke in asymptomatic
3 patients is statistically low. Second, in a study of
4 NASCET patients who had asymptomatic stenosis in the
5 artery contralateral to the symptomatic side, 45
6 percent of subsequent neurologic events were of
7 lacunar or cardioembolic etiology. Both of these
8 diagnoses are most common in those patients who are
9 elderly or who have major medical comorbidities.

10 Finally, the application of mechanical
11 technologies in patients with a limited life
12 expectancy should be approached quite cautiously. In
13 the following four slides, the respective symptomatic
14 and asymptomatic historical randomized control data
15 for endarterectomy cohorts are appended to the
16 corresponding SAPPHIRE cohort.

17 Because the historical studies excluded
18 non-fatal myocardial infarction in the definition of
19 major adverse events, as pointed out by the sponsor,
20 these have been scrubbed from the SAPPHIRE data or a
21 range given where it was not entirely possible to get
22 the exact numbers. I gave a range.

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1 Some historical study data have been
2 estimated for Kaplan-Meier curves. As you look at
3 these tables, please understand that they are being
4 offered merely as a frame of reference and not as a
5 scientific comparison. Consider also the relative
6 size of the cohorts.

7 For symptomatic patients, the NACSET
8 cohort illustrated here is for the patients with high
9 grade stenosis. The recruitment of these patients was
10 discontinued at a mean follow up of 2.7 years because
11 of the demonstrated superiority of endarterectomy
12 compared to medical management. These are the same
13 cohorts presented at the one year point. Remember
14 these are symptomatic patients in the randomized
15 control study stent arm and the carotid endarterectomy
16 arm.

17 Moving to the asymptomatic patients, here
18 the asymptomatic SAPPHIRE patients are displayed and
19 juxtaposed to the ACAS asymptomatic trial patients.
20 The same cohort groups are followed to one year. This
21 completes the data presentation.

22 What are the limitations of the sponsor s

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1 study? The pre-specified enrollment plan and study
2 analysis was not carried to completion in the SAPPHIRE
3 randomized study. This resulted in a smaller size
4 study with small sample sizes in important subsets of
5 carotid populations.

6 But what can we conclude? The randomized
7 study suggests non-inferiority of the stent to the
8 carotid endarterectomy. Registry cohort failed to
9 meet the OPC pre-specified criteria. The
10 comparability of the registry to the control
11 endarterectomy patients has not been optimally defined
12 or conducted. Thank you.

13 CHAIRMAN LASKEY: Are there questions from
14 the panel to any of these three presentations? Mitch.

15 DR. KRUCOFF: A question for Dr. Li. I
16 just want to make sure that I understand what you said
17 with regard to your triangular method, Christmas tree
18 slide that went onto a picture with a point with a dot
19 on it. That was your sixth slide. So is that dot
20 your data assessment from the randomized cohort at 334
21 patients that lie within the boundaries?

22 DR. LI: Right, it s based on a Z and V

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1 value calculated from the 364 patients data included
2 in the PMA submission.

3 DR. KRUCOFF: Right, and so the next
4 slide, you have a based on the above graph comment.
5 Is what I understood that you are saying based on the
6 information in the sponsor s presentation today that
7 was not present by 4:00 p.m. yesterday, would you
8 change this conclusion? Is that what I m
9 understanding you to say?

10 DR. LI: Basically the short answer is
11 yes. The sponsor, based on what I understand of the
12 one slide presentation, is trying, to the best
13 possible extent, to reconstruct what might have
14 happened had the original group sequential protocol
15 been followed.

16 My impression is that, based on the
17 sponsor s presentation, their conclusion is that had
18 the group sequential protocol been followed then the
19 trial would have been stopped at 300 patients and then
20 subsequently non-inferiority can be declared. But it
21 is important to make a distinction that in actuality
22 the protocol hasn t been followed as was implied by

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1 the presentation.

2 So it s impossible to know what would
3 actually have happened, but it s to a best
4 approximation. For example, had the protocol been
5 followed to every detail, then enrollment, recruitment
6 would have been stopped at the 300 patients, when 300
7 patients have had the 30 day data, which might not
8 have been the case. So it s not possible to repeat
9 all the detail. But it s only a rough approximation
10 and this approximation needs to be verified.

11 DR. KRUCOFF: I take it you are talking
12 about Dr. Cohen s slide that had the outcome columns
13 conclusion at 100 and --

14 DR. LI: Right, 100, 200, and 300.

15 DR. KRUCOFF: It was continue, continue,
16 stop.

17 DR. LI: Continue, continue, stop, right.

18 DR. KRUCOFF: But you at 300 have a dot
19 that s still within the boundaries which would not
20 imply stop. So I guess what I m asking is - and
21 understanding you haven t had the chance to review
22 this yet - do you have any sense of why one

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1 retrospective reconstruction of this would say stop
2 and 300 where it appears your retrospective
3 reconstruction of this would say continue at 300?

4 DR. LI: Okay, so remember when I
5 described the group sequential protocol, I mentioned
6 that the sample path may wander up and down. Although
7 it always go from left to right, it wanders up and
8 down. That dot in the previous slide is calculated at
9 334 patients. Apparently at 300 patients, if the
10 sponsor s calculation was right, then the boundary
11 would have been crossed at that time, and it s
12 completely possible.

13 DR. KRUCOFF: Okay, thank you.

14 CHAIRMAN LASKEY: Other questions from the
15 panel?

16 DR. ABRAMS: I have a question for Dr.
17 Weintraub. In your additional slides, do you have
18 data on the ACAS study for higher grade stenosis of
19 asymptomatic?

20 DR. WEINTRAUB: I m having trouble with a
21 touchy mouse. I m sorry, you asked for NACSET.

22 DR. ABRAMS: ACAS.

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1 DR. WEINTRAUB: Oh, for ACAS. It should
2 be pointed out in the European trial. The problem
3 with the European and North American data are that the
4 Europeans measured stenosis differently from the North
5 Americans. But in an excellent editorial published at
6 about the time that the final NASCET trial came out,
7 the writer actually compared the two.

8 The take away message was that at moderate
9 stenoses, which were about equivalent to about 40 to
10 50 percent stenosis in the American system, that
11 results particularly in asymptomatic patients probably
12 did not favor endarterectomy. Whether that would be
13 different because endarterectomy is not the same as
14 stent, we just don't know. But certainly on the basis
15 of the historical record, one has to approach moderate
16 to less than 50 percent stenosis with a great deal of
17 caution particularly in asymptomatic patients.

18 DR. ABRAMS: Is it actually possible from
19 this data to do a subgroup analysis on the greater
20 than 80 percent --

21 DR. WEINTRAUB: Yes, this was done.
22 Unfortunately, it's in there somewhere. To answer

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1 your question - and we can find that slide at the
2 lunch break for you - in an NASCET, the degree of
3 stenosis was broken down into three subsets.

4 Interestingly, the greatest effectiveness
5 was in the middle subset. When it got up to 85 to 99
6 percent, it dropped off a little bit. But there was
7 clearly a separation depending on the degree of
8 stenosis. That was also certainly true in the
9 European study. I think it was true in the ACAS but I
10 would have to look at it again.

11 DR. COMEROTA: One question. I hate to
12 belabor this point, Dr. Weintraub. And you don't
13 need to pull up the slide.

14 DR. WEINTRAUB: Very wise.

15 DR. COMEROTA: In your analysis, you
16 compared the symptomatic patients with the NASCET
17 group. Obviously we all know that there's two
18 publications for NASCET; the 70 to 99 percent stenosis
19 and then the less than 70 percent stenosis. You
20 compared the NASCET group greater than 70 percent.
21 They all had arteriographic documentation of that
22 degree of stenosis.

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1 DR. WEINTRAUB: That is correct to my
2 understanding, yes.

3 DR. COMEROTA: All of the patients in the
4 SAPPHIRE had arteriographic documentation to the
5 degree of stenosis. Was that compared on your slide,
6 the definition of the arteriographic stenosis?

7 DR. WEINTRAUB: This is a question that I
8 had raised in my original evaluation. I was told by
9 the sponsors that angiography was not used routinely
10 in those patients undergoing carotid endarterectomy.

11 DR. COMEROTA: Right, I m talking about
12 the registry and the randomized stent patients.

13 DR. WEINTRAUB: The randomized stent
14 patients, of course, all had angiographic analysis
15 preoperatively.

16 DR. COMEROTA: All patients having a stent
17 had an arteriogram.

18 DR. WEINTRAUB: That s correct.

19 DR. COMEROTA: But you are not sure what
20 the distribution of the degree of stenosis was in the
21 stented patients, correct?

22 DR. WEINTRAUB: I would really have to ask

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1 the sponsor about that. It s in the panel pack
2 because the degree of stenosis was broken down quite
3 exactly. But in terms of grouping them, I can t tell
4 you that. The sponsor might be able to.

5 CHAIRMAN LASKEY: Well, if there are no
6 further questions, since my hypoglycemia has taken
7 hold, let s break for an hour lunch. I have 12:25
8 p.m. Let s resume at 1:25 p.m. Thank you. Off the
9 record.

10 (Whereupon, at 12:22 p.m., the above-
11 entitled matter recessed to reconvene at
12 1:34 p.m. the same day.)
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22 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

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1 1:34 p.m.

2 CHAIRMAN LASKEY: On the record. All
3 right. I d like to thank everybody for coming back.
4 We ll resume this afternoon s session starting with
5 Dr. Judah Weinberger s queries. Judah.

6 DR. WEINBERGER: Thanks very much. First
7 of all a comment to the sponsor. I think that the
8 data presented is interesting, thought provoking and
9 hopefully we can sort through it and figure out
10 precisely what to do with it.

11 First an administrative question. I would
12 just like to ask the sponsor to explain why the FDA
13 wasn t aware of the latest changes in terms of
14 statistical analysis that was pointed out. It s
15 really hard for me to interpret a study when there s a
16 disagreement between the FDA and the sponsor as to
17 statistical validity.

18 DR. COHEN: The answer to your question is
19 that we were made aware that there was a question
20 about the statistical methods being applied last
21 Friday. We really did not have time to prepare
22 materials to send to the Committee beforehand.

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1 DR. WEINBERGER: So it is your position
2 that there was no deviation from the original plan.

3 DR. COHEN: That s correct.

4 DR. WEINBERGER: And it s the FDA s
5 position that there was a significant deviation from
6 the original plan. Is Dr. Li here?

7 DR. ZUCKERMAN: Ms. Kennell, would you
8 come to the podium?

9 MS. KENNELL: You re talking to the wrong
10 person when you re talking statistics, but I believe
11 that that is our understanding about the original
12 plan. I looked up the protocol last night just so I
13 would make sure that it was fresh in my mind. The
14 original protocol said that they were going to do
15 interim analysis at every 100 patients and that was
16 not done.

17 DR. WEINBERGER: All right. I m not a
18 statistician, but maybe you can explain to me how not
19 doing an analysis prejudices the interpretation of the
20 study. Rather I would imagine the less you look the
21 more powerful the statistic is because we re taught
22 that repeated analyses actually require higher -

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1 MS. KENNELL: I don t know that I would be
2 comfortable answering that question. I don t think I
3 have enough statistical expertise. I can try to find
4 out for our statistical session.

5 DR. ZUCKERMAN: Dr. Weinberger, let s try
6 to answer your questions. 1. The FDA and the sponsor
7 had a protocol with a prespecified statistical
8 analysis plan that has been reviewed by FDA. That
9 prespecified statistical analysis plan was changed at
10 some point. FDA was unaware of when it was changed
11 and what went into making that change.

12 Usually we would expect a major supplement
13 and meeting with FDA to discuss a major change in a
14 clinical trial like that. As such because of the
15 events that transpired, it becomes somewhat
16 problematic to interpret the statistics as presented
17 by the sponsor. It doesn t mean it s impossible, but
18 it does throw another question mark. Dr. Greg
19 Campbell, our Chief of Biostatistics, is also here and
20 he may want to add a point.

21 DR. CAMPBELL: Greg Campbell, FDA. Dr.
22 Weinberger, your question is a good question. It s

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1 always a good idea to follow the original plan that a
2 company has to analyze data. When they do not follow
3 that plan or we at the FDA do not follow that plan,
4 we re doing post hoc analyses and those are not
5 recommended. The issue as to how often you look is a
6 very complicated one in this case and I think I would
7 prefer not to try to comment on it only because it s
8 different if one looks all the time versus one looks
9 at particular intervals.

10 DR. WEINBERGER: Okay. I d like to dig
11 around a little bit in the data if we might and deal
12 with a couple of issues of trying to understand who s
13 getting the biggest bang for the buck or who is really
14 benefitting in this trial compared to standard
15 therapy. So if we understand the trial, the patients
16 have to have been previously identified by their
17 referring physician as people who need carotid
18 revascularization. This comment is directed at the
19 sponsors. Is that correct? So these are patients who
20 are previously identified by their referring physician
21 as needing revascularization.

22 DR. COHEN: That is correct.

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1 DR. WEINBERGER: All right. So this is
2 not anyone in the trial identifying the patient. Then
3 that patient gets referred in for revascularization,
4 has an anatomic study, has a clinical stratification
5 and based upon that is eligible for the study.

6 DR. COHEN: That s correct.

7 DR. WEINBERGER: All right. In that group
8 of patients that are the symptomatic ones and the
9 asymptomatic ones, you ve done stratification of those
10 two groups in your analysis as has the FDA. I d like
11 to focus on a different sort of a stratification that
12 is among the patients who ultimately ended up in the
13 registry, people who were not operated on because the
14 vascular surgeon decided that this was inappropriate.

15 Some of those patients ended up for anatomic reasons
16 and some ended up for medical comorbidities.

17 One of the things that s really counter-
18 intuitive here is a statement that you have in Panel
19 Pack where you said that the people ended in the
20 registry group for anatomic reasons did better with
21 surgery than they did with stenting. Let me read it
22 to you correctly. There was significant differences

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1 in major adverse events at 360 days when patients were
2 stratified by anatomic and medical criteria. I m
3 sorry. This is in the randomized group. The
4 anatomic, high risk patients had major adverse events
5 of 10.3 percent for stent patients and 5.6 percent for
6 carotid endarterectomy patients. Now the reason that
7 people are high risk if for anatomic reasons, how is
8 it that they do better with surgery than they do with
9 stenting?

10 DR. COHEN: One of the figures of the
11 design of this trial if I understand your question
12 correctly was that it allowed the surgeons to take
13 patients that they felt were at high risk and not
14 operate on them. Those patients then went into the
15 non-randomized stent registry. That would be expected
16 then to have the high risk surgery patients in the
17 stent registry as opposed to the surgical arm.

18 DR. WEINBERGER: Let s go back to the
19 randomized trial.

20 DR. COHEN: Okay.

21 DR. WEINBERGER: In the randomized trial,
22 you get into the randomized trial with having a high

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1 risk anatomic feature or high risk medical features.

2 DR. COHEN: That is correct.

3 DR. WEINBERGER: Okay. If you have high
4 risk anatomic features, I would expect that you would
5 do better with stenting than you would do with
6 surgery. If you have high risk clinical features, it
7 might be that you would do - That s unclear.

8 But certainly if you had high risk
9 anatomic features, it would appear to be that you
10 would be more likely to expect a good result from
11 stenting. It s rather counter-intuitive that patients
12 with high risk anatomic features at least not appear
13 to do significantly better, not in a statistical
14 sense, but do much better in terms of major adverse
15 events when they have a surgical approach rather than
16 a percutaneous approach.

17 DR. COHEN: I m sorry. Could I ask you to
18 tell me where you re looking at in the Panel Pack?

19 DR. WEINBERGER: Sure. This would be in
20 the summary of FDA Review Memo and this is with the
21 marked up memo that we got last week on page 12. That
22 includes your comments.

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1 DR. COHEN: I m sorry. This is not in the
2 Panel Pack.

3 DR. WEINBERGER: Geratta, do they have
4 that in their Panel Pack now? That s what I had Fed
5 Ex ed last week.

6 MS. WOOD: They should have that. It was
7 the FDA Memo as edited per the company s request.

8 DR. COHEN: I d like to ask Dr. Ken Ouriel
9 to answer this question.

10 DR. OUIEL: Okay. If I understood the
11 question.

12 DR. WEINBERGER: All right. Let s go
13 through it slowly so it s a point that s at least
14 important to me. I don t know about the rest of the
15 panel. If you take patients who are randomized in
16 this study, they get into the study because they are
17 either symptomatic or they are asymptomatic with high
18 grade stenosis plus they have to have another feature
19 that puts them at high risk.

20 DR. OUIEL: Correct.

21 DR. WEINBERGER: And that other feature
22 can be either medical comorbidity or anatomic problems

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1 or radiation to the neck or both.

2 DR. OURIEL: Right.

3 DR. WEINBERGER: All right. So if you
4 look among patients who get into the trial and you
5 look at those people who get in for anatomic
6 comorbidities primarily, those are the people you
7 would expect would do worse with surgery because the
8 anatomic comorbidities are defined as comorbidities
9 that are important to a surgeon. That is radiation to
10 the neck. That s important to a surgeon, not to an
11 endovascular therapy.

12 DR. OURIEL: Well, we know that it s
13 important for surgery. We didn t know whether it was
14 important or not for stenting. It may be that
15 radiation arteritis is a high risk for stenting.

16 DR. WEINBERGER: Okay. Or a contralateral
17 recurrent laryngeal nerve palsy, etc., all those
18 things that push you anatomically to worry about doing
19 that.

20 DR. OURIEL: Correct.

21 DR. WEINBERGER: All right. So in that
22 anatomic high risk group, you report a major adverse

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1 event rate at 10.3 percent for stented patients and
2 5.6 percent for carotid endarterectomy. I m not being
3 critical of the surgeons. In fact, I m congratulating
4 the surgeons. I m trying to understand how it is that
5 stenting interacts negatively with anatomic
6 comorbidities.

7 DR. OURIEL: I don t have that data in
8 front of me, but I wonder what the confidence
9 intervals are there. The numbers get very small when
10 you get down to the subgroups. I m just wondering if
11 those two numbers really are similar.

12 DR. COHEN: Can you tell us where this is
13 again?

14 DR. WEINBERGER: Sure. This is page 12 of
15 the section that s labeled Section 4, Summary of FDA
16 Review Memos. It s in the revision of that section
17 that came by last week. Do you have that? I don t
18 know what it was in the original document because the
19 page numbers have changed.

20 DR. COHEN: Let me make a couple comments.
21 First of all, only about 20 percent of the patients
22 in the randomized portion of the trial had anatomic

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1 comorbidities. That means that the number of patients
2 we re talking about is very small. So when you re
3 then making a subgroup of that subgroup, a standard
4 error on those endpoints alone, I m sure it overlaps
5 significantly. As you stated, there was no
6 statistical significant difference. If you could
7 point us to the exact sentence that you re looking at.

8 DR. WEINBERGER: All right. There s a
9 page in my book that s entitled Minor Deficiencies
10 (*FDA Questions*). Do you have that page?

11 DR. COHEN: Yes, this is page 12?

12 DR. WEINBERGER: This is page 12.

13 DR. COHEN: Questions 1, 2 and 3?

14 DR. WEINBERGER: Questions 1, 2 and 3. If
15 you go down to the next to the last paragraph.

16 DR. COHEN: Yes.

17 DR. WEINBERGER: There were significant
18 differences in major adverse events at 360 days. The
19 flip side of that is actually a very complimentary
20 finding for stenting and that is in patients with
21 significant medical illnesses. There seems to be a
22 very decided benefit to the stenting arm over the

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1 surgical arm. What I m trying to tease out here is
2 the statistics at least to a non-statistician are
3 quite borderline. I m trying to figure out who s
4 going to benefit from this approach.

5 What it seems to me is that based upon the
6 data admittedly the subgroups may contain smaller
7 number of patients. The patients who are more likely
8 to benefit at least based upon what you re reporting
9 are the patients with medical comorbidities rather
10 than anatomic problems.

11 DR. COHEN: I don t think that s a fair
12 comment.

13 DR. WEINBERGER: You don t think that s a
14 fair comment.

15 DR. COHEN: No.

16 DR. WEINBERGER: All right. Then let me
17 ask you this. Why do surgeons refuse to operate on
18 patients? You told us that 50 percent of the patients
19 who were put in the registry got into the registry for
20 reasons you could identify. Fifty percent had no
21 identifiable reason for being in the registry.

22 DR. COHEN: Actually if I might just

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1 correct that statement. It s not that we didn t have
2 information. We were asked this question three weeks
3 ago to provide information on what were the factors
4 that led to patients being entered into the non-
5 randomized stent registry. That data is not on the
6 case report forms. That s on the screening logs and
7 we had no database containing that data. In order to
8 answer the question that was posed, we accumulated as
9 many screening logs as we could. That s why there is
10 incomplete information.

11 What I would point out is that the items
12 on that list are nearly identical to the list of
13 demographic features which were at increased frequency
14 in the patients in the non-randomized stent arm. So
15 even though the data is incomplete which is more
16 because of lack of time as opposed to not having the
17 information necessarily, the factors that were
18 identified were similar.

19 DR. WEINBERGER: So if you re a vascular
20 surgeon and you get a patient you is 75 years old with
21 two or three medical comorbidities, is that sufficient
22 in your practice not to operate on them?

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1 DR. OURIEL: That would probably be a
2 patient that would be eligible for the randomized
3 portion of that study. Now if that patient had a
4 lesion at the C1 vertebral body or if the patient had
5 an MI within the last four weeks or other compounding
6 things, then you might decide that this patient needed
7 treatment but they were just too high a risk to have
8 an endarterectomy. It really varied from site to site
9 and surgeon to surgeon. Since some of the things are
10 subjective, it s very difficult to capture. Certainly
11 you can t capture it in a case report form.

12 DR. WEINBERGER: I think what I m
13 struggling with is that everything about this is very
14 much interpretative. In other words, the decision to
15 put someone in for revascularization is
16 interpretative. The decision whether or not to push
17 towards surgery is interpretative. Although we have
18 some rigorous reasons that when patients accumulate
19 enough of objective reasons to push them towards
20 revascularization, that s when the vascular surgeon
21 will make some comment as to whether or not he wants
22 to do it. Somehow they were eligible for the study

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1 without a vascular surgeon agreeing up front that they
2 would do the case.

3 I was wondering why that was not a
4 required part of the protocol. Why are patients
5 eligible for enrollment and in fact enrolled before a
6 vascular surgeon agrees that they would do the
7 procedure if the patient is randomized?

8 DR. OURIEL: Well, in fact, they were not
9 enrolled. They were actually eligible - There was a
10 certain number if you remember the slide was eligible
11 for randomization and in those patients, you needed
12 the surgeon and the interventionist to agree that they
13 could have either form of therapy. Now if they were
14 eligible by the criteria for enrollment, but the
15 surgeon said that they did not want to do an
16 endarterectomy then they ended up in the non-
17 randomized stenting arm.

18 DR. WEINBERGER: All right. And the
19 outcomes among those patients, those are patients who
20 if we believe met the bulk of them, two-thirds of them
21 are asymptomatic. Is that right?

22 DR. OURIEL: Correct. Roughly.

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1 DR. WEINBERGER: Roughly. And ACAS would
2 say that those asymptomatic patients would benefit
3 from having an operation would have a
4 revascularization under normal circumstances. But
5 ACAS doesn't report stroke frequencies that are
6 anything close to what you are seeing with this
7 patient population. So help me understand that
8 particular conundrum.

9 DR. OURIEL: I think I can do that. ACAS,
10 first of all, is a different set of patients because
11 they didn't have the medical comorbidities and
12 probably didn't have many of the anatomic
13 comorbidities that this trial did. That said, if you
14 remember some of the slides and you really look at the
15 stroke rate which I think is what you mentioned
16 despite the higher comorbidities in SAPPHIRE and the
17 higher comorbidities for sure in the non-randomized
18 stent arm, the 30-day stroke rates aren't all that
19 different.

20 DR. WEINBERGER: Okay. Then the last
21 issue that I wanted to raise before I turn this over
22 to somebody else is in terms of looking for subtle

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1 neurological deficits that occur post-procedure
2 whether they be whatever the method of
3 revascularization the nature of the neurological
4 examination involved cognitive testing as well.

5 DR. COHEN: First of all, there s an
6 independent exam by an neurologist. Second, there are
7 three tests that were used which are tests for
8 deficiencies due to stroke, the NIH Stroke Scale, the
9 Rankin and the Barthel. I think it would be best to
10 have Dr. Pierre Fayad comment specifically on the
11 components of those tests.

12 DR. FAYAD: Good afternoon. I m Dr.
13 Pierre Fayad. I m a circ neurologist and professor
14 and chairman of neurological sciences at the
15 University of Nebraska. I am paid for my expenses
16 today and for my time by Cordis. I am on the
17 executive committee for the SAPPHIRE study. To answer
18 the question, there were no specific
19 neuropsychological testing that was requested as part
20 of the SAPPHIRE trial. However, the neurologic exam
21 would assess some basic neuropsychological functions
22 and the NIH Stroke Scale would just direct the basic

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1 orientation and speech functions and so on. But there
2 were no specific testing for neuropsychological
3 function.

4 DR. WEINBERGER: Okay. Thanks very much.

5 DR. COHEN: May I? Just one little
6 response. You had asked about the differences in
7 outcomes on whether or not they were helping guide
8 whether or not you should or should not enroll
9 patients if this were approved. I would just like to
10 point out that the numbers that you are referring to
11 for anatomic reasons there were 35 patients who got
12 carotid endarterectomy for anatomic reasons, 36 who
13 received them who received the stent. The number of
14 patients who actually had events in those two groups
15 was two patients and four patients. So that s why I
16 say the difference between those are statistically
17 meaningless. The numbers are so small.

18 DR. WEINBERGER: Thank you.

19 CHAIRMAN LASKEY: Thank you, Judah. Dr.
20 Comerota.

21 DR. COMEROTA: Well, thank you, Dr.
22 Laskey. I m going to go about this a little bit

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1 differently. First of all, I think the sponsors are
2 to be commended. They submitted detailed analyses
3 from the studies that they have performed in bulk to
4 the panel. They laid out a logical plan of
5 investigation beginning with the FEASIBILITY study,
6 moving to a randomized trial and then moving on to the
7 registry for the reasons previously stated and then
8 giving additional supporting documentation from IDE
9 and CASCADE.

10 The pivotal clinical study as we saw was
11 the SAPPHIRE trial which was performed under the IDE
12 as you know. It did present supporting and safety
13 data and the presentations were very elegant. At the
14 end of those presentations, I thought this was going
15 to be a very short day because the decisions would be
16 quite obvious.

17 But let s look at the studies a little bit
18 and let s look at some of the information. First of
19 all, this began with the FEASIBILITY study which
20 evaluated device and procedure safety and provided
21 SAPPHIRE investigators experience with the angioplasty
22 and the stent system. I would say in reviewing the

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1 investigators, the interventionalists, involved in
2 this study, they are to be commended because these
3 represent the top interventionalists in the country
4 and I suspect if we were to rank them, they may fall
5 within the top one to two percent of
6 interventionalists in the world.

7 So the FEASIBILITY study was performed at
8 33 sites in the United States and it included 262
9 patients and 177 underwent angioplasty and stent and
10 85 patients had angioplasty and stenting with distal
11 protection. They were followed for a year and then
12 longer term follow-up was presented.

13 No demographic profile however was
14 reported to us. Therefore, differentiation between
15 symptomatic and asymptomatic patients as may have
16 surfaced from this morning's discussion was not
17 presented. Subsequently we learned what the data were
18 on atherosclerotic disease versus neointimal
19 fibroplasia in this patient group.

20 Now it's interesting that the stopping
21 rules for the FEASIBILITY study were determined and
22 were projected on the basis of the NASCET trial data

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1 of a major adverse events rate of 6.7 percent which
2 was the second study from NASCET. The first study had
3 a death and 30-day stroke and death rate of 5.8
4 percent. So that was chosen as the higher and perhaps
5 the better number would have been the mean of the two
6 if we re dealing with symptomatic patients alone.

7 However, when we look at the data in the
8 FEASIBILITY trial, major adverse events at 30 days was
9 6.9 percent and at one year, 10.7 percent. Death rate
10 at 30 days was 0.8 percent and at one year was 3.8
11 percent. Stroke at 30 days was 6.1 percent and 8.4
12 percent at one year.

13 Now we did subsequently receive a
14 differentiation of atherosclerotic patients versus
15 recurrent stenosis or neointimal fibroplastic lesions.

16 The major adverse event rate in the atherosclerotic
17 patients was 10.8 percent. It was 8.5 percent in the
18 recurrent stenosis group. The death rate was the same
19 in both groups, 3.6 and 3.4 percents. Ipsilateral
20 stroke was 7.7 percent in atherosclerotic lesions and
21 3.4 percent with recurrent stenosis. I think this is
22 a trend and an appreciation that most of us have had

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1 that patients who have a recurrent carotid artery
2 stenosis are a lesser risk for percutaneous
3 interventions than patients with atherosclerotic
4 disease. The mean pretreatment stenosis in the
5 FEASIBILITY study was 66 percent and patients who had
6 50 percent or more restenosis at the end of the year
7 numbered 24 percent of those treated with angioplasty
8 and stenting.

9 So as I mentioned above, the distribution
10 of patients was not given up front in the FEASIBILITY
11 study. If, however, the distribution of the run-in
12 patients were similar to SAPPHIRE patients in terms of
13 disease and symptoms status, it can be assumed that
14 nearly 70 percent of the patients would have been
15 asymptomatic and about 25 percent would have had a
16 recurrent carotid stenosis. Both of these groups are
17 relatively low risk for ipsilateral stroke.

18 So if the stopping rule was actually
19 calculated based upon lesion risk and if it was
20 apportioned to the distribution of symptomatic versus
21 asymptomatic patients, then the 30-day major adverse
22 event rate should have calculated at about 2.9 to 3.0

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1 percent rather than the 6.7 percent. If this were
2 actually used as the guideline, the stopping rule
3 would have been invoked and the FEASIBILITY study
4 would have been terminated based upon that
5 calculation.

6 When we look at the actual disease
7 distribution in the patients in the FEASIBILITY study
8 according to the angiographic description of the
9 diameter percent stenosis, less than 10 percent of the
10 patients had an 80 to 99 percent stenosis. About 38
11 percent of the patients had a 70 to 99 percent
12 stenosis. The balance had less than 70 percent
13 stenosis. So the magnitude of the severity of the
14 disease was not too severe in terms of an angiographic
15 diameter reduction stenosis.

16 As we move into the SAPPHIRE study,
17 obviously these are the principal data supporting the
18 submission for this IDE. The primary objective of the
19 SAPPHIRE trial was to compare the safety and
20 effectiveness of carotid stenting with distal
21 protection using these devices versus carotid
22 endarterectomy in the treatment of patients who are

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1 considered at high risk for carotid endarterectomy.
2 It was an one-to-one randomization, multi-center
3 trial.

4 The diagnosis initially was made on the
5 basis of a duplex and I think the velocity criteria
6 was certainly very appropriate. The primary endpoints
7 which I think are very important to consider are the
8 composite endpoints as clearly elucidated earlier
9 including death and stroke and myocardial infarction
10 at 30 days post procedure and then those additional
11 data up to 12 months and beyond. The high risk
12 criteria were well defined.

13 As we know, the SAPPHIRE trial was a
14 randomized study and it was targeted for 600 to 900
15 patients, the thought with the interim analysis and
16 that discussion has already proceeded so I won t get
17 into that. And we ve seen the results in the
18 randomized trial. We know that the death and stroke
19 rate at 30 days in the stented patients was 4.2
20 percent and the death and stroke rate in the carotid
21 endarterectomy patients was 4.8 percent. The overall
22 stroke rate in the carotid angioplasty and stent

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1 patients was 3.6 percent. It was 3.0 percent in the
2 carotid endarterectomy patients.

3 There were other associated events with
4 procedures that didn't surface in the discussion today
5 as yet. A severe hypotension occurring during the
6 procedure was 17.4 percent occurring in the carotid
7 angioplasty and stent group and 3.0 percent in carotid
8 endarterectomy patients. Bradycardia and/or asystole
9 occurred in 8.4 percent in the carotid angioplasty and
10 stent patients and 3.0 percent in the carotid
11 endarterectomy patients. Those numbers barely reached
12 statistical significance, not quite. That was 0.6
13 percent but the severe hypotension was very
14 significant. Cranial nerve injury obviously 4.2
15 percent in the CEA patients and none in the
16 angioplasty and stent patients. Distal vasospasm at
17 the time of intervention occurred in 22 percent of the
18 patients having carotid angioplasty and stenting. The
19 analyses were presented and I think they were
20 presented very well. I just supplemented some of
21 those data with what I've reviewed.

22 Now when we look at the degree of stenosis

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1 of the lesion and I think we would all agree that a
2 patient who has a high grade stenosis especially a
3 patient who is symptomatic with a high grade stenosis
4 is one who needs to have that carotid lesion
5 corrected. If you look at the patients that we have
6 data on that were submitted to us in the carotid
7 angioplasty and stent group who had an 80 to 99
8 percent stenosis represented 22 percent of the
9 patients in the randomized trial undergoing carotid
10 angioplasty and stenting. Fifty-five percent had 70
11 to 99 percent stenosis. Therefore 45 percent of the
12 patients who were randomized and received the stent
13 had less than 70 percent stenosis.

14 Looking at the available data for carotid
15 endarterectomy patients, 45 percent of the patients
16 had an 80 to 99 percent stenosis. Eighty-five percent
17 had an 70 to 99 percent stenosis. If we look at the
18 registry data, 19 percent of the registry patients had
19 an 80 to 99 percent stenosis. So we re dealing with
20 patients who underwent a percutaneous procedure that
21 did not have relatively high grade stenosis in
22 general.

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1 A comparison was submitted to us regarding
2 the registry patients and that comparison which was
3 performed by the company compared the registry
4 patients versus the carotid endarterectomy patients.
5 They included of course death and stroke. When we
6 look at the 30-day results of death and stroke, 5.9
7 percent in the stent patients versus 4.8 percent in
8 the carotid endarterectomy patients.

9 If we look at overall registry patients
10 versus carotid endarterectomy patients, ipsilateral
11 stroke at 30 days 4.2 percent in the registry stented
12 patients, 1.8 percent in the carotid endarterectomy
13 patients. Then if we look at all strokes to 30 days,
14 eight percent for stent and 5.8 percent for carotid
15 endarterectomy.

16 If we look at symptomatic patients because
17 this is real crux, I think, of what we re dealing
18 with, symptomatic patients with high grade stenosis, a
19 death and stroke rate at 30 days is 8.1 percent in the
20 stent patients and 6.5 percent in carotid
21 endarterectomy patients. Ipsilateral stroke at 30
22 days, 6.5 percent in the stent patients and zero

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1 percent in carotid endarterectomy patients. And death
2 or ipsilateral stroke 7.3 percent and 6.5 percent
3 obviously. Then if we look at all strokes to 30 days,
4 8.1 percent in the carotid angioplasty and stent
5 patients, two percent in the carotid endarterectomy
6 and that one patient had a contralateral stroke.

7 Then if we move on to the asymptomatic
8 patients, ipsilateral stroke was really no different,
9 3.2 percent and 2.5 percent respectively. Death and
10 ipsilateral stroke at 30 days, 6.0 percent in the
11 stented group and 3.3 percent in the carotid
12 endarterectomy group. Death to 30 days in the stented
13 group was 2.8 percent, 0.8 percent in the carotid
14 endarterectomy group. So I think once we begin to
15 look at the data, things do become clarified.

16 The CASCADE results were presented to us
17 and 121 patients were reported in the CASCADE trial
18 which was a European study. Ninety of those patients
19 underwent angioplasty and stenting with no ANGIOGUARD
20 protection and 31 of those patients had ANGIOGUARD
21 protection. There were no deaths in the CASCADE
22 study. There was an 8.2 percent stroke rate, ten

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1 percent in those patients who had no ANGIOGUARD
2 protection and 3.2 percent in the 31 patients who had
3 protection with ANGIOGUARD. Obviously we see a trend
4 developing here that protection seemed to have been
5 effective in that group. There were many more TIAs in
6 the patients who had no ANGIOGUARD protection versus
7 those who did have ANGIOGUARD protection.

8 Then the IDE data were presented. But I
9 think since none of the IDE data were adjudicated, I
10 think we have to look at it just as that. I don't
11 think we can accept the IDE data with very much vigor
12 since it was not adjudicated. The FDA has asked us to
13 address a number of questions. Warren, should I
14 answer those questions from my perspective or should
15 we wait until later?

16 CHAIRMAN LASKEY: We'll have a turn at
17 them as we go around. Do you have other queries or
18 clarifications?

19 DR. COMEROTA: Well, yes. I have one
20 other major point that I would like to address and it
21 was asked by the FDA, but I would like to make it part
22 of my preliminary comments. It has to do with the

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1 issue of myocardial infarction as an endpoint. I
2 would just like to find my comments here.

3 The question was raised whether myocardial
4 infarction either non-Q-wave or Q-wave myocardial
5 infarction was a valid endpoint for this study. I
6 think we just need to take a step back and look at
7 what are we doing and why. Obviously the purpose of
8 any procedure to treat carotid artery atherosclerosis
9 is to reduce the risk of stroke, predominantly reduce
10 the risk of ipsilateral stroke assuming that the
11 procedure that we re performing does not put the
12 patient at risk for contralateral stroke.

13 Carotid endarterectomy has demonstrated
14 its effectiveness in reducing stroke and death due to
15 stroke in very large randomized trials and every one
16 of them has been adjudicated by neurologists and
17 compared to best medical care. Now this endpoint was
18 achieved in reasonable risk patients.

19 If high risk patients were to have been
20 included in these trials, the operation itself may not
21 have proven beneficial compared to best medical care.

22 If that were the case, carotid endarterectomy would

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1 not be available today for comparison to carotid
2 angioplasty and stenting. The comparator would be
3 best medical care.

4 In order to achieve equivalence with
5 carotid endarterectomy in patients considered at high
6 risk for operation, the SAPPHERE included myocardial
7 infarction as a component with major adverse events.
8 None of us want our patients to have an MI and there
9 is a substantial associated subsequent
10 morbidity/mortality associated with anyone who suffers
11 a myocardial infarction be it Q-wave or non-Q-wave.

12 However, if one looks at that as a
13 endpoint obviously MI inherently favors a percutaneous
14 procedure compared to an operative procedure in high
15 risk patients. Furthermore, the premature termination
16 of this study appears to bias this outcome in favor of
17 carotid angioplasty and stenting. The reason why I
18 say that is because it is well established that
19 patients who have had a coronary artery bypass graft
20 and who subsequently undergo noncardiac surgery have
21 approximately a 50 percent risk reduction of a
22 mortality associated with that operation. They have a

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1 70 percent risk reduction of a nonfatal myocardial
2 infarction.

3 In the SAPPHIRE trial in the randomized
4 trial, 43 percent of the stented patients had a prior
5 coronary artery bypass graft. 30.8 percent of the
6 carotid endarterectomy patients had a prior coronary
7 artery bypass graft. This difference is statistically
8 significant. Furthermore, 35 percent of the stented
9 patients had a prior percutaneous transluminal
10 coronary angioplasty (PTCA) versus 23 percent of the
11 carotid endarterectomy patients. This difference is
12 statistically significant. The sum of that is that 80
13 percent of the stented patients had prior coronary
14 revascularization versus 54 percent of the carotid
15 endarterectomy patients.

16 So in the SAPPHIRE trial if coronary
17 revascularization was equivalent and therefore the
18 carotid endarterectomy patients were protected to the
19 same degree as carotid angioplasty and stent patients
20 were protected, would the difference in cardiac events
21 have been observed? I think there s a real chance
22 that those difference would not have been observed.

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1 The bias of prior coronary
2 revascularization in favor of carotid angioplasty and
3 stenting patients deflates the importance of the
4 difference in myocardial infarction outcome between
5 those two groups in the SAPPHIRE trial. Furthermore,
6 carotid angioplasty and stent patients were treated
7 with Clopidogrel in addition to aspirin. We all know
8 that the combination of aspirin and Clopidogrel
9 protects patients at high risk from coronary events.

10 This pharmacologic protection was not
11 offered to patients undergoing carotid endarterectomy
12 and perhaps for good reason. But there is now a
13 revascularization bias and a pharmacotherapy bias in
14 favor of the reduction of myocardial events in
15 patients undergoing carotid angioplasty and stenting
16 compared to carotid endarterectomy. I think that will
17 conclude my comments for now. Thank you.

18 CHAIRMAN LASKEY: Did you wish the sponsor
19 to respond to any of that or all of that?

20 DR. COMEROTA: Well these are observations
21 based upon all the information that was presented in
22 the Panel Pack. I had no additional information than

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1 what everybody else had.

2 CHAIRMAN LASKEY: Fair enough. Okay.
3 Well, thank you. Let us go around the table for
4 thoughts comments and queries. That s right. Dr.
5 Aziz. Thank you.

6 DR. AZIZ: Thank you. I would also like
7 to commend the sponsor on an excellent presentation.
8 Let me go straight to the topic of coronary artery
9 disease in some of these patients and this is a
10 question for the sponsors and maybe one of you could
11 answer. Once a patient is identified as having
12 carotid stenosis, what investigations are done to rule
13 out underlying coronary artery disease particularly in
14 patients who are going to go for a carotid
15 endarterectomy? Do they have any noninvasive tests
16 done or do they go straight to surgery?

17 DR. COHEN: Again, patients in this trial
18 would have otherwise received the same type of
19 preoperative evaluation that any patient undergoing
20 either surgery or an interventional procedure would
21 have undertaken, so whatever was appropriate given the
22 individual patient s history and physical exam, the

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1 EKG findings, whatever.

2 Having said that, I d like to take the
3 opportunity to mention that the distribution of
4 patients with coronary disease in fact was equal
5 between the different arms of the trial. Second of
6 all, there was data captured in terms of patients who
7 had a positive exercise test. So yes, that was
8 obtained and those were equally distributed for
9 patients who had positive exercise tests.

10 The other thing is that first you can t
11 simply sum the percentage of patients who have had
12 bypass and who have had percutaneous coronary
13 interventions because obviously those two groups
14 overlap significantly. The other thing is that we
15 actually looked to see whether the presence of
16 coronary disease, the presence of bypass surgery or
17 whatever played an important role in any of the
18 individual outcomes as well as the composite outcomes
19 and they did not.

20 DR. AZIZ: Let me see if I understand you.

21 If a patient was found to have coronary artery
22 disease or suggestive on the testing, would that

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1 patient have that corrected first before he had the
2 carotid endarterectomy?

3 DR. COHEN: Yes, and it was explicitly
4 stated in the protocol that if there was coexisting
5 coronary disease or if another surgical procedure
6 needed to be undertaken, be it, a carotid procedure or
7 cardiac or otherwise, it could not occur within 30 days
8 of the endarterectomy procedure.

9 DR. AZIZ: And then if a patient had,
10 let s say, carotid angioplasty and stenting done,
11 obviously the patient would be put on Plavix I would
12 presume for a long period of time. That would clearly
13 delay him having coronary artery surgery for a number
14 of months.

15 DR. COHEN: Actually the duration of
16 Plavix was two weeks as mandated in the protocol.

17 DR. AZIZ: That s one. Were there any
18 patients who during the course of the carotid stenting
19 develop carotid section?

20 DR. COHEN: I ll ask Dr. Ouriel to answer
21 this question.

22 DR. OURIEL: A long walk for a short

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1 answer. No.

2 DR. AZIZ: Now in terms of the emboli
3 protection, I see these two groups of patients,
4 clearly patients who are having intervention done on
5 the carotid artery. The danger is obviously having
6 emboli going in and you've obviously included an
7 emboli protection device. I'm sure that the emboli
8 protection device captures some of the emboli. But I
9 guess we really had no way of knowing what percentage
10 of the emboli it captures.

11 DR. COHEN: Actually there is data in the
12 Panel Pack that speaks to that and I can summarize
13 that. The percentage of emboli-capture devices,
14 ANGIOGUARDS, actually had debris in it. It varied
15 somewhat between the trials, but it was easily between
16 50 and 80 percent amongst the trials that we presented
17 today. The average number of particles was six to
18 eight particles per filter in filters that had debris,
19 although the number ranged all the way up to, I
20 believe, 20 particles per filter. The particles could
21 be as large as 1 X 1-1/2 millimeters in size. The
22 composition was basically what you would expect of an

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1 atherosclerotic plaque. There were smooth muscle
2 cells, foam cells, cholesterol crystals, necrotic
3 core, collagen, elastin and clot basically.

4 DR. AZIZ: Are you aware of any studies
5 that were done, not necessarily for this trial, but
6 patients may have had MRIs pre- and post-carotid
7 extending procedure with or without protection
8 devices?

9 DR. COHEN: No. There have been no
10 studies that I m aware of that have completed,
11 although, I believe there are studies underway
12 directed at neuropsychiatric changes as well as
13 perhaps imaging studies.

14 DR. AZIZ: Okay. And you aren t aware of
15 any studies where TCD monitoring was being done at the
16 time. Maybe you might be able to answer that
17 question.

18 DR. OURIEL: You re not talking about
19 studies related to this particular panel.

20 DR. AZIZ: No.

21 DR. OURIEL: I m sure there are TCD
22 studies that are available. Of course, it s a

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1 surrogate endpoint. There are studies that show that
2 if you have protection that you get fewer hits, but
3 it s not part of this analysis.

4 DR. AZIZ: All right. I think I have one.

5 Now I think it was earlier stated that there was a 17
6 percent incidence of hypotensive episodes during the
7 placement of the stent. Do you have any ideas as to
8 why that happened or what could be done to prevent
9 that?

10 DR. OURIEL: Sure. I think of that as
11 part and parcel of the stenting process just like for
12 those of us who are surgeons what we know when the
13 anesthesiologist puts our patient to sleep we get
14 hypotension frequency. Now it s not recorded in many
15 cases, but we know that it occurs when the patient is
16 put to sleep. We know that in a patient who has a
17 carotid lesion that you stent especially a tight
18 stenosis, maybe one with a lot of calcium, they are
19 going to get a vagal impulse and it s not surprising
20 that you get hypotension and Bardycardia.

21 DR. AZIZ: Nothing else for the time
22 being.

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1 CHAIRMAN LASKEY: Dr. Krucoff.

2 DR. KRUCOFF: Dr. Cohen, you may as well
3 hang around. Have a seat. Obviously one of the
4 things we're all wrestling with here is the
5 statistical analysis plan, its origin and then what's
6 actually eventuated. Certainly I'll echo everybody.
7 You guys have done a great job in taking what's a very
8 complex dataset and at least presenting it in a very
9 cogent and understandable fashion. In general,
10 studies in this realm are conducted with Data Safety
11 and Monitoring Board. Was there a DSMB for this
12 trial?

13 DR. COHEN: Yes, there was.

14 DR. KRUCOFF: And did they have a role in
15 the original triangular analysis plan or can you help
16 me understand who was going to look at the data along
17 the way in the original plan for these 100-patient
18 cohorts and how was that originally envisioned from
19 your perspective?

20 DR. COHEN: Perhaps what would be useful
21 would be to have a little bit better understanding of
22 exactly what this data analysis, interim analysis,

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1 plan was and how it played out. I think I would like
2 to ask Dr. Rick Kuntz to come up and provide an
3 explanation.

4 DR. KUNTZ: My name is Rick Kuntz. I m a
5 cardiologist in Boston. I m mostly the chief of the
6 Division of Clinical Biometrics at the Brigham Women s
7 Hospital. I functioned as the chief scientific
8 officer and CRO run by Harvard which ran this trial.

9 The statistical interim analysis was
10 contracted with a group in England called the
11 Whitehead group. We have a representative from here
12 who developed the triangular test that was used. We
13 performed the analysis using that methodology. The
14 sponsor and the group in England worked on the
15 analysis plan and actually conducted the analysis
16 plan.

17 Let me just explain my perspective on
18 this, but being a clinician and having a little bit of
19 background in statistics on this. It was clear from
20 the beginning in the design of this trial that we
21 didn t know what the final sample size would be.
22 There were a lot of unknown variables. An interim

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1 analysis was actually quite an effective way of
2 potentially looking at this study. The study was
3 going to be as large as 2400 patients if in fact our
4 estimates were off and possibly as small as 300 or 400
5 patients if we had really good results. We estimated
6 from our best analysis of the literature that probably
7 600 to 800 patients would result in a final analysis
8 demonstrating non-inferiority. Maybe if there was a
9 bang-up job done by the stents there would be
10 superiority at some point, but our main goal was to
11 look at non-inferiority.

12 In this analysis plan, the triangular test
13 follows most interim analysis theory. That is in fact
14 the more you look the more alpha there that you have
15 to spend because you are rolling the dice each time to
16 look for a positive result. In this study, the
17 triangular test allows you to alter the times when you
18 look during the conduct of the study. That is that
19 you can actually use other cues to determine whether
20 or not you want to look or not look and that s part of
21 the analysis plan and part of the textbooks that are
22 written, part of the theory that s been published in

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1 biostatistical literature and part of the program.

2 There were non-data driven reasons to not
3 look at the first 200 patient intervals. That was
4 because this was a new break-through therapy and it
5 was very unlikely that regardless of the result of 100
6 or 200 patients that this would result in anything
7 convincing to anybody because you just don't have
8 enough patients. The first reasonable time to look
9 would be at 300 patients and that was decided at the
10 beginning of this study. There was no data reviewed
11 at all.

12 When it came to the point where the first
13 planned interim analysis now, 300 patients, was going
14 to be done, it was very clear on those curves that
15 this study wasn't going to be enrolling much more than
16 350 or 400 patients. So a decision was made to do the
17 first look ever as the final look. The notion about
18 not using the monitoring portion of the Whitehead test
19 was omitted under the complete allowances of this
20 Whitehead triangular test.

21 This was not communicated by the sponsor
22 to the FDA. That probably was a mistake. They should

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1 have communicated that with the update and tell them
2 what they were doing. But technically speaking as far
3 as I understand it and as far as the program goes,
4 this was all allowable in the analysis.

5 There was only one analysis done during
6 the study and that was the final analysis. There were
7 no decisions made anywhere based on any of the data
8 and I can verify that. Nobody got any of the data
9 except Data Safety and Monitoring Committee during
10 this study.

11 So in the end, this study which started to
12 peter out quickly at around 280 patients enrolled did
13 peter out at about 350 patients, 334, when the
14 enrollment was so slow that it wasn't worth the money
15 and the resources to continue and it was clear that it
16 wouldn't continue any further because many studies
17 were having problems randomizing and there were the
18 registries available that were chipping into the
19 abilities randomized. So because of that, all
20 analysis were presenting as a first time and final
21 analysis as is appropriate.

22 There were irregularities with respect to

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1 the communication with the Food and Drug
2 Administration about exactly what was going on, but I
3 think the communications dealt with the fact that they
4 didn't know that this was appropriate to communication
5 since it was all within the design of the triangular
6 test. Looking back at it since this was a not typical
7 traditional test that was used although very valid,
8 there should have been better communication.

9 There is no doubt about it, but the
10 statistical analysis we feel stands as is. It's a
11 one-time analysis. There were no increased chances to
12 look at a positive result. Nobody rolled the dice
13 more than once to understand whether results came up
14 positive or not and these are the final results of the
15 study. That is the best way that I think we can
16 clarify on a clinical level what actually happened in
17 this study with the interim analysis.

18 DR. KRUCOFF: Thank you. That at least
19 for me clarifies some really key things. So what I'm
20 hearing you say, Rick, is that nobody peeked at these
21 data along the way. The original Whitehead
22 triangular, somebody, not including the FDA, decided

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1 up front that the options for earlier interims which
2 were within the statistical plan were going to be
3 delayed until the 300 patient point. The decision was
4 made before enrollment had begun.

5 DR. KUNTZ: No, actually I think that
6 decision was made after enrollment was done, but
7 within the allowances of the play of chance of the
8 Whitehead triangular. That method can be explained
9 theoretically by our statistician from England on this
10 and he would be more than happy to explain that. But
11 I think the key is that there were people looking at
12 the data. We still use the 100-patient interval for
13 the Data Safety and Monitoring Committee to review the
14 data. They did see it at 100, 200, 300 patients to
15 make sure that there were no safety concerns.

16 DR. KRUCOFF: But then just to make sure
17 that I m following you. Data and Safety who saw the
18 data along the way, were they involved in the decision
19 to go to 300 as a first formal Whitehead triangular
20 look or were they independent of that decision?

21 DR. KUNTZ: They were independent. The
22 decision to do the first interim analysis at 300

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1 patients was a decision made by the sponsor.

2 DR. KRUCOFF: Okay. And last, was there
3 anyone from the sponsor involved in the Data and
4 Safety Board?

5 DR. KUNTZ: No. Nobody from the sponsor
6 saw any of the data.

7 DR. KRUCOFF: Okay. Thank you. I d like
8 to shift gears a little bit and understand a little
9 bit more about where angiograms were used and where
10 they weren t. As I understand for the randomized
11 SAPPHIRE patients, Dr. Cohen, the patients would come
12 in through whatever clinical evaluation recommended
13 for carotid revascularization.

14 DR. COHEN: Correct.

15 DR. KRUCOFF: It sounds like there is a
16 cohort of patients who were operated on based on
17 ultrasound Doppler without a concomitant angiogram.

18 DR. COHEN: That s correct.

19 DR. KRUCOFF: All of the patients on the
20 percutaneous side had angiographic information. Do
21 you know how many of them had a diagnostic angiogram
22 independently from the interventional procedure? My

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1 questions are twofold. One is just how you knew
2 whether a patient was a candidate for a stent or not
3 in order to decide whether or not they were
4 randomizable or should be put in the register without
5 an angiogram.

6 DR. COHEN: My understanding is that for
7 the surgical intervention or surgical treatment that
8 because of the risk of doing angiography in patients
9 who have significant carotid disease that it is
10 usually omitted. So you go directly from ultrasound
11 to surgery. I believe the majority of patients in
12 this trial - we can conjecture to make sure that this is
13 correct - their diagnostic angiogram was done at the
14 time that they received their treatment with the stent
15 and distal protection.

16 DR. KRUCOFF: So my only question is then
17 how did you know you could randomize them if you
18 didn't have angiographic criteria to know whether they
19 were tortuous or calcified or some of the things that
20 would make you think stenting was not an option?

21 DR. OURIEL: Sure. In fact, some of the
22 difference between the intent-to-treat and the treated

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1 is because you did an angiogram and you found out that
2 this patient should not have been treated with the
3 assigned therapy.

4 DR. KRUCOFF: Okay. So then if I
5 understand, patients came in clinically. If they
6 randomized to surgery, they could get operated on on
7 the basis of the Doppler ultrasound data.

8 DR. OURIEL: Or could have an angiogram in
9 the minority of patients.

10 DR. KRUCOFF: Okay. Or if they randomized
11 to stenting, then most all of these patients had their
12 first angiographic delineation of the anatomy at the
13 time of their interventional procedure. Is that it?

14 DR. OURIEL: I can't give you the numbers
15 on that? But what I can tell you is that if a patient
16 had an angiogram in preparation for a carotid stent
17 and let's say you found the stenosis was only 30
18 percent, then they would still stay in that arm
19 intent-to-treat but they would not have been treated.

20 DR. KRUCOFF: Okay. And importantly then,
21 patients who got angiograms with the 1.3 or so percent
22 risk of a complication from that angiogram would

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1 already be in the intention to treat analysis. So
2 complications from a diagnostic angiogram are in fact
3 in the intention to treat.

4 DR. OURIEL: Sure. Once they are
5 randomized. Although the 1.3 percent risk of stroke
6 with angiography hopefully is no longer the case.

7 DR. KRUCOFF: Right. Understood. Then if
8 I can, Dr. Cohen, ask you a little bit about the use
9 of the ANGIOGUARD. As I look through the CASCADE and
10 FEASIBILITY data at least my interpretation of what
11 there is that patients who did not have the ANGIOGUARD
12 didn't have it because it wasn't available.

13 DR. OURIEL: That's correct.

14 DR. KRUCOFF: And then the percentage of
15 the denominators that did receive it was presumably
16 because it was available. Is that it?

17 DR. COHEN: That's right. It became
18 available later on in those trials.

19 DR. KRUCOFF: Okay. And I guess in
20 looking at these data, one question that will come up
21 that I'm just going to go ahead and ask is obviously
22 the ANGIOGUARD seems to have an important function in

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1 all of this. What I m wondering is whether it s your
2 inclination in the instructions for use to suggest
3 that since that s deployed first - you put the wire
4 up, the distal protection system first - if you are
5 for whatever reason unable to deploy the ANGIOGUARD,
6 are you going to suggest that the procedure be
7 terminated?

8 DR. COHEN: No, I don t believe that s
9 what occurred in the trial. That would not be our
10 suggestion.

11 DR. KRUCOFF: Okay. And yet is it fair to
12 say that the data on stenting alone compared to
13 stenting with distal protection looks like there s a
14 significant role for distal protection?

15 DR. COHEN: But I d also offer that this
16 was early in the learning curve for some of the
17 physicians participating in the trials, so just the
18 learning of doing coronary stenting. Second, this was
19 with earlier generation devices. Third, I would say
20 that there s a cohort of physicians who do carotid
21 stenting who do not believe in the benefit of distal
22 protection.

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1 The reason we did do exploratory analysis
2 of combining both CASCADE and FEASIBILITY was to
3 provide data that there is benefit to having distal
4 protection. The reason that we collected the filters
5 and had a pathology lab evaluate them was to
6 demonstrate that there is material captured on them.
7 However, the question I assume you're getting at is if
8 you are unable to pass it, should you not do the
9 procedure.

10 I don't know the percentage - and we can
11 look that up - of patients who had to have
12 predilatation before the ANGIOGUARD was actually
13 placed, but that is a component of the dataset. My
14 understanding is that those patients had outcomes that
15 were not different than the overall trial outcomes.

16 DR. KRUCOFF: Okay. We can come back to
17 this in discussions about labeling. At least the best
18 that I could get out of the three sets of data, the
19 CASCADE, FEASIBILITY and SAPPHIRE, SAPPHIRE, it seemed
20 like, you probably had a more advanced iteration of
21 the ANGIOGUARD end of the system because the
22 deployment rate was fairly high.

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1 DR. COHEN: That s correct.

2 DR. KRUCOFF: And again I think you ve
3 shown some of it particularly in the randomized
4 patients the noninferiority data for primary endpoint
5 with regard to the 334 patients you have in intention
6 to treat analysis. About 90 some percent of those had
7 distal protection. What I m concerned about is
8 whether the data would look the same if the 334
9 patients had been randomized to unprotected stent
10 versus not and what that ought to mean in terms of the
11 real recommendations. But we can come back to that.

12 Do you know offhand -- And I don t do
13 carotid so I m going to have to extrapolate from
14 coronaries. In self-expanding platforms in the
15 coronary arteries, there are times when all it takes
16 is the structural strength of the Nitinol to dilate
17 the lesion? There are times when you have to
18 predilate the lesion to get the stent across and there
19 are times when after deploying the self-expanding
20 platform you have to post-dilate. Do you have - or if
21 at least it was there, I m sorry because I missed it -
22 what percentage of the time was predilatation required

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1 and what percentage of the time was post-dilatation
2 required?

3 DR. COHEN: I don't have those percentages
4 off the top of my head. I would need to look them up
5 and we can see if we can get that. But both
6 predilatation and post-dilatation were done in some
7 cases.

8 DR. OURIEL: Well, I can tell you our
9 practice at the Cleveland Clinic is to almost always
10 predilate and always post-dilate because you do get a
11 significant stenosis if you don't post-dilate in
12 almost every case.

13 DR. KRUCOFF: Okay. Because while I'm not
14 going to go back to the marked hypertension and
15 Bradycardia, in cases I've actually observed certainly
16 the baroreceptors in the neck is a pretty richly
17 innervated territory managing patients. After carotid
18 endarterectomy, you sure learn that lesson in
19 patients. Obviously in a significant proportion of
20 these patients how much manipulation is involved may
21 also relate to that assault.

22 DR. OURIEL: And it's always on the post-

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1 dil that it occurs.

2 DR. KRUCOFF: That is goes. Yes. But at
3 Cleveland at least, you think that was most of the
4 time you ended up post-dilating.

5 DR. OURIEL: Yes.

6 DR. KRUCOFF: Okay. Last two quick
7 questions. One, it was pointed out in the
8 distribution that out of the range of devices that you
9 all manufactured the five millimeter device and the
10 tapered seven to ten millimeter device was rarely
11 used. Do you feel like you have sufficient data? Do
12 you think a five millimeter flow channel to the brain,
13 do we understand enough about that to say that s going
14 to behave identically to larger caliber vessels and do
15 we have enough information to understand the tapered
16 seven to ten?

17 DR. COHEN: I think it might be useful to
18 understand why the five millimeters and the tapered
19 are used. I would like to ask Dr. Nick Hopkins to
20 make some comments.

21 DR. HOPKINS: Hi, I m Nick Hopkins,
22 neurosurgeon from Buffalo, chairman of the Department

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1 of Neurosurgery there and professor of radiology
2 there. I m kind of a hybrid. I ve doing neurosurgery
3 and carotid endarterectomy since 1979 and doing
4 carotid stenting since the mid 90s. We have a large
5 experience. Cortis did pay my way here and paid for
6 my transportation and my lodging.

7 The question about the five millimeters.
8 First of all, almost every carotid artery narrows down
9 to somewhere near five millimeters somewhere near the
10 skull base and a five millimeter opening, if I
11 understand your question correctly, is plenty to
12 provide normal flow. We don t see significant
13 reductions in flow until we have stenosis somewhere
14 close to 60 percent. So a five millimeter opening is
15 plenty large enough for that.

16 The reason for the seven to ten I think is
17 the rare patient where you have a common carotid that
18 is so large that you wouldn t have good stent
19 apposition if you didn t have a ten millimeter stent.

20 So a seven to ten taper takes care of that situation
21 which is unusual, but it happens. So to not have
22 those two sizes available I think would put us at a

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1 disadvantage. Does that help?

2 DR. KRUCOFF: I guess the conundrum for me
3 is that five millimeters is the small end of carotid
4 which would be the huge end for coronaries and again
5 in my limited world of coronaries though smaller,
6 longer term durability of stenting interventions is
7 certainly different in smaller vessels than in larger
8 vessels. As we get out into larger vessels, carotids
9 and peripheral, there is some relatedness albeit the
10 total flow volume is different. I guess one of the
11 impressions I've gotten here is for ethical reasons
12 more than anything. We don't have a lot of
13 angiographic follow-up or detailed follow-up in the
14 whole cohort much less in how five millimeter stents
15 behave in carotids. Is that fair?

16 DR. HOPKINS: I think that's fair. You
17 made the point that the average carotid carries 250
18 millimeters of flow per minute. It's a huge
19 difference in terms of the flow volume to the brain
20 and the heart. A five millimeter stent, I think, is
21 critically important in a situation where for example
22 you have a lesion confined to the internal carotid.

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1 You want to limit your stent placement to the internal
2 carotid and you have an internal carotid that may be
3 relatively small. So you don't want to greatly
4 oversize, if you can avoid it, more than you have to.

5 We like to oversize a millimeter or two, but I would
6 hate to put a six or seven millimeter stent in three
7 millimeter carotid. I think a five millimeter is
8 extremely important for that situation.

9 DR. KRUCOFF: Okay. I lied. I actually
10 have two last quick questions, one really quick one
11 just to ask, your interpretation of the slide that you
12 put up and when I asked the FDA, Dr. Li, earlier. You
13 put up a slide for an FDA simulation of the V-Z
14 approach that had 100 patients continue it, 200
15 patients continue it, 300 patients terminate. Dr.
16 Li's impression was that at 300 patients in that
17 sawtooth, sort of, Christmas tree you were at a point
18 that you would say would reach the recommendation to
19 stop, whereas at 334, there was dot on his slide which
20 was still within decision matrix boundaries which
21 would be to continue. As far as you can tell, is that
22 still appropriate? Did you all get your continue

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1 option at 300 and did you look in the same way at 334
2 as to whether you would have been inside or outside?

3 DR. COHEN: I think what I d really like
4 to do is have the expert here that we have available
5 answer the question. I think if you don t mind,
6 Nigel, to come up. The short answer of that is that
7 we re trying to interpret this using our background
8 which is not applicable to this specific analysis
9 method.

10 DR. KRUCOFF: Maybe while he s setting
11 that up, can I ask you my last question? Why self-
12 expanding, not balloon-expandable and is Nitinol a
13 reasonable platform for a drug-eluding future?

14 DR. OURIEL: Well, we actually used to use
15 balloon-expandable stents in the carotid, but as soon
16 as the patient put their neck on their hand and rested
17 their neck against some pressure, it would crush. So
18 it s clear that balloon-expandable stents aren t going
19 to be good in superficial locations. Nitinol right
20 now is the best we have.

21 DR. COHEN: And just so people are aware
22 of this, Nitinol has the ability to self-expand. Plus

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1 if you crush it, it will expand back to a
2 predetermined size. That s it s major advantage and
3 why we use it in areas that are compressible.

4 DR. KRUCOFF: Okay. So while they are
5 setting up, have you all begun to explore whether
6 Nitinol is a reasonable platform for polymer and drug-
7 eluding configurations?

8 DR. COHEN: I m not sure that s an
9 appropriate answer to give in this forum.

10 DR. KRUCOFF: Okay. Never mind. It might
11 get you small vessel interest.

12 DR. STALLARD: Okay. I m Dr. Nigel
13 Stallard. I m a principal research fellow at the
14 Medical and Pharmaceutical Statistics Research Unit at
15 the University of Reading. I ve been paid as a
16 consultant by Cortis and they ve paid for me to come
17 to this meeting and paid for my time?

18 MS. WOOD: Could you please pull the mike
19 a little closer?

20 DR. STALLARD: I m sorry. Okay. So just
21 to briefly talk about the analysis that we would do
22 had we performed those interim analyses at 100, 200

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1 and 300 patients. But I want to start by just
2 outlining how we analyze at the end of a sequential
3 trial like this. Here s just a picture of the
4 triangular region and the triangular region is
5 designed so that the probability of crossing the upper
6 boundary during monitoring of the trial is controlled
7 to be 0.025 when the treatment difference is actually
8 the delta is the lower limit of the non-inferiority
9 region that we re interested in detecting. So that s
10 what we re controlling when we do this test.

11 As has been explained, you can monitor at
12 any time you wish so long as that time is chosen
13 independently of any observed treatment difference.
14 And the triangular region is calculated based on the
15 assumption that you re going to monitor continuously.

16 As soon as you monitor the number of discrete points,
17 the chance of stopping any one of those points is
18 reduced or the chance of stopping in its total trial
19 is reduced. So to control that to be at the 0.025
20 level, you need to bring in the boundaries further.
21 So the solid lines that you just saw are, if you like,
22 the most stringent ones. We actually adjust those

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1 bringing them in to allow for the analyses that we
2 did. The more analyses you do, the less you have to
3 bring them in because you re looking more often.

4 When you stop the trial at that point, you
5 can calculate a P-value and it s helpful just to
6 remember the definition of what we mean by a P-value
7 as statisticians. What we mean in the case of testing
8 for non-inferiority is it s the probability that if we
9 had a true difference of delta that we would see data
10 as strongly supporting non-inferiority as we ve
11 observed or more strongly supporting non-inferiority.

12 So that s what we mean by a P-value. It s that
13 probability which we need to calculate based on our
14 inter-monitoring to be able to perform a valid
15 analysis at the end of our test.

16 In order to work out the probability of
17 data that might have been more supportive, we need to
18 address the question What do we mean by more
19 supportive in terms of non-inferiority now that we
20 have a sequential test? For a standard analysis when
21 you just do one test, that s fairly clear. It just
22 means a larger test is at stake. For a sequential

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1 analysis, it s more complicated. It means either
2 stopping at the same interim with a larger test -
3 that s clearly more supportive evidence - or stopping
4 on the upper boundary earlier on because that also
5 would have been more supportive of non-inferiority.

6 Here s just a picture, not of the real
7 data, but just of some hypothetical trial. You can
8 just about see the dotted lines corresponding to the
9 Christmas tree boundary and you actually use these
10 inner points of that Christmas boundary. I m sorry
11 that it s so faint. So the probability of observing
12 data more extreme is the probability of either having
13 more extreme data at this look so that the solid line
14 above the plotted point or the probability of stopping
15 at either of the two previous looks, the two solid
16 lines which are drawn in there. It s the probability
17 of those three parts that we work out to get our P-
18 value if that was our sample path.

19 That s if we stop exactly when we cross
20 the boundary. If we don t do that, but cross the
21 boundary and then take another look, then we do what s
22 called an over-running analysis. The P-value here is

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1 calculated ignoring the point which led to stopping
2 and basing instead using our final value here of
3 looking at the probability of having a larger value
4 here. So in this case, we would sum up the
5 probability of being here, here or here. (Indicating.)

6 One thing to say is that this can be much
7 less than 0.05 or 0.025 in this case because the whole
8 probability of stopping on the upper boundary is
9 0.025. So by stopping very early on, we can get a
10 much more significant P-value. There is the real data
11 just taking that one look at 334 patients. You can
12 see that because we were above the inner point of the
13 Christmas tree boundary, we in fact would have stopped
14 the trial there if we would have the position to stop
15 the trial not already been taken. That leads to the
16 analysis which has been presented.

17 Here s the one reproducing the three looks
18 at 100, 200 and 300 and then treating the look at 334
19 patients as over-running data and allowing for that
20 over-running analysis I ve just described, then we get
21 the analysis results which have been presented. So we
22 get a P-value for testing for non-inferiority which in

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1 fact is almost exactly the same as the P-value
2 ignoring those three that we've seen.

3 DR. KRUCOFF: Okay. Thank you. That was
4 again very helpful. So again if I understand what
5 you're saying, your analysis in Dr. Cohen's table is
6 based on 334 using the over-run appropriate to the
7 model.

8 DR. STALLARD: That's correct.

9 DR. KRUCOFF: And we then would have to
10 resolve why the FDA would have put up a slide
11 suggesting that at 334 you would be reaching a
12 decision to make stop. We're using the same
13 denominator.

14 DR. STALLARD: We're using the same slide
15 here as the FDA because the last point is in fact back
16 inside the boundary.

17 DR. KRUCOFF: But it's the over-run
18 analysis.

19 DR. STALLARD: But nevertheless it's
20 because as you see here the over-run analysis that's
21 appropriate and that leads to the conclusion.

22 DR. KRUCOFF: Which is what you were

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1 representing in your slide.

2 DR. STALLARD: That s correct. So the
3 conclusion is exactly the same whether you include
4 those extra interim analyses or not.

5 DR. KRUCOFF: Yes.

6 DR. COHEN: Just to answer, Dr. Krucoff
7 had asked two questions. One, we do have data in our
8 case report forms concerning the percent
9 predilatation, but we don t have that available. We
10 can supply that to the FDA later. In response to your
11 other question about patients who do have an
12 ANGIOGUARD, in the randomized portion, there were six
13 patients who did not have an ANGIOGUARD. In the non-
14 randomized stent registry, there were 25 patients who
15 did not have an ANGIOGUARD. Reading through the
16 descriptors, there were no strokes albeit it is a
17 small number.

18 DR. KRUCOFF: Okay. What I m going to
19 come back to later is whether the instructions for use
20 should have any advice on preventing hypotension and
21 whether we have any sort of clue as to how you might
22 do that.

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