

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH  
MEDICAL DEVICES ADVISORY COMMITTEE

CIRCULATORY SYSTEM DEVICES PANEL

MEETING

WEDNESDAY,  
APRIL 21, 2004

The Panel met at 9:00 a.m. in Salons B, C and D of the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Dr. Warren Laskey, Chairman, presiding.

PRESENT:

WARREN K. LASKEY, M.D., Chairman  
GARY M. ABRAMS, M.D., Consultant  
SALIM AZIZ, M.D., Member  
ANTHONY J. COMEROTA, M.D., Consultant  
ALLEN A. HUGHES, Ph.D., Consumer Representative  
MITCHELL W. KRUCOFF, M.D., Consultant  
WILLIAM H. MAISEL, M.D., M.P.H., Consultant  
MICHAEL C. MORTON, Industry Representative  
KENNETH E. NAJARIAN, M.D., Consultant  
GARY G. NICHOLAS, M.D., Consultant  
MICHAEL J. PENTECOST, M.D., Consultant  
CYNTHIA TRACY, M.D., Member  
JUDAH Z. WEINBERGER, M.D., Ph.D., Consultant  
CHRISTOPHER J. WHITE, M.D., Consultant  
GERETTA WOOD, Executive Secretary

FDA REPRESENTATIVES:

BRAM ZUCKERMAN, M.D.  
LISA KENNEL  
HENG LI, Ph.D.  
RONALD WEINTRAUB, M.D., Consultant

SPONSOR REPRESENTATIVES:

SIDNEY COHEN, M.D.  
KENNETH OURIEL, M.D., F.A.C.S., F.A.C.C.

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1 P-R-O-C-E-E-D-I-N-G-S

2 9:06 a.m.

3 CHAIRMAN LASKEY: On the record. If we  
4 can have everybody take their seats please. This is a  
5 good sign. Everyone listens. Good morning. I m  
6 Warren Laskey. I have the pleasure of calling this  
7 morning session to order. The topic this morning will  
8 be a discussion of the PMA for the Cordis PRECISE  
9 Nitinol Stent System P030047. I d like to start with  
10 our Executive Secretary reading the conflict of  
11 interest statement.

12 MS. WOOD: The following announcement  
13 addresses conflict of interest issues associated with  
14 this meeting and is made a part of the record to  
15 preclude even the appearance of an impropriety. To  
16 determine if any conflict existed, the Agency reviewed  
17 the submitted agenda and all financial interests  
18 reported by the Committee participants.

19 The conflict of interest statutes prohibit  
20 special government employees from participating in  
21 manners that could affect their or their employers  
22 financial interests. However, the Agency has

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1 determined that participation of certain members and  
2 consultants, the need for whose services outweighs the  
3 potential conflict of interest involved, is in the  
4 best interest of the Government.

5 Therefore, waivers have been granted for  
6 Drs. Mitchell Krucoff, Christopher White, and a waiver  
7 was previously granted for Dr. Judah Weinberger for  
8 their interests in firms that could potentially be  
9 affected by the panel s recommendations. Dr.  
10 Krucoff s waiver involves consulting with a competing  
11 firm on unrelated matters for which he receives an  
12 annual fee of less than \$10,001.

13 Dr. White s waiver involves grants to his  
14 institution for studies of the sponsor and several  
15 competing firms in which he had no involvement in data  
16 generation or analysis. Funding to the institution  
17 for the sponsor s study was less than \$100,000 per  
18 year. The total amount of funding for the  
19 competitors studies was less than \$100,000.

20 Dr. Weinberger s waiver involves stock  
21 holdings in competing firms in which the values are  
22 between \$25,001 and \$50,000. The waivers allow these

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1 individuals to participate fully in today's  
2 deliberations. Copies of these waivers may be  
3 obtained from the Agency's Freedom of Information  
4 Office, Room 12A-15 of the Parklawn Building.

5 We would like to note for the record that  
6 the Agency took into consideration other matters  
7 regarding Drs. Andrew Comerota, Mitchell Krucoff,  
8 Kenneth Najarian, Michael Pentecost, Cynthia Tracy,  
9 and Judah Weinberger. These panelists reported past  
10 or current interest involving firms at issue but in  
11 matters that are not related to today's agenda. The  
12 Agency has determined that these individuals may  
13 participate fully in the panel's deliberations.

14 In the event that the discussions involve  
15 any other products or firms not already on the agenda  
16 for which an FDA participant has a financial interest,  
17 the participant should excuse himself or herself from  
18 such involvement, and the exclusion will be noted for  
19 the record. With respect to all other participants,  
20 we ask in the interest of fairness that all persons  
21 making statements or presentations disclose any  
22 current or previous financial involvement with any

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1 firm whose products they may wish to comment upon.

2 CHAIRMAN LASKEY: Thank you. If we can  
3 just go around the table and have everyone introduce  
4 themselves.

5 DR. ZUCKERMAN: Bram Zuckerman, Director,  
6 FDA Division of Cardiovascular Devices.

7 DR. AZIZ: Salim Aziz, Clinical Associate  
8 Professor at GW and private practice in Washington.

9 DR. KRUCOFF: Mitch Krucoff, Cardiology  
10 Division at Duke University and the Director of  
11 Devices Clinical Trials at the Duke Clinical Research  
12 Institute.

13 DR. TRACY: Cindy Tracy, the Director of  
14 Electrophysiology at George Washington University,  
15 Associate Director of the Division of Cardiology.

16 DR. COMEROTA: Anthony Comerota, Vascular  
17 Surgeon, Jobst Vascular Center in Toledo, Ohio.

18 DR. NICHOLAS: Gary Nicholas, Lehigh  
19 Valley Hospital, Professor of Surgery, Penn State.

20 DR. PENTECOST: Michael Pentecost,  
21 Chairman of Radiology at Georgetown.

22 MS. WOOD: Geretta Wood, Executive

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1 Secretary.

2 CHAIRMAN LASKEY: Warren Laskey,  
3 Interventional Cardiologist, Uniformed Services  
4 University.

5 DR. ABRAMS: Gary Abrams, Associate  
6 Professor of Neurology, University of California - San  
7 Francisco.

8 DR. WHITE: Chris White, Interventional  
9 Cardiology, Ochsner Clinic in New Orleans.

10 DR. WEINBERGER: Judah Weinberger,  
11 Director of Interventional Cardiology, Columbia, New  
12 York.

13 DR. MAISEL: William Maisel,  
14 Electrophysiologist, Cardiovascular Division at  
15 Brigham and Women s Hospital.

16 DR. NAJARIAN: Ken Najarian,  
17 Interventional Radiologist, University of Vermont.

18 DR. HUGHES: Allen Hughes, Assistant  
19 Professor of MIS at George Mason University, the  
20 consumer representative.

21 MR. MORTON: Michael Morton, I m the  
22 industry representative. I m employed by Carbomedics.

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1 CHAIRMAN LASKEY: And Geretta, if you  
2 could please read the voting status statement.

3 MS. WOOD: Pursuant to the authority  
4 granted under the Medical Devices Advisory Committee  
5 charter dated October 27, 1990 and as amended August  
6 18, 1999, I appoint the following individuals as  
7 voting members of the Circulatory System Devices Panel  
8 for this meeting on April 21, 2004: Judah Z.  
9 Weinberger, M.D., Ph.D.; Kenneth E. Najarian, M.D.;  
10 Michael J. Pentecost, M.D.; Anthony J. Comerota, M.D.;  
11 Gary M. Abrams, M.D.; Gary Nicholas, M.D.

12 For the record, these individuals are  
13 special government employees and are consultants to  
14 this panel under the Medical Devices Advisory  
15 Committee. They have undergone the customary conflict  
16 of interest review and have reviewed the material to  
17 be considered at this meeting, signed by David W.  
18 Feigal, Jr., M.D., M.P.H., Director, Center for  
19 Devices and Radiological Health and dated April 16,  
20 2004.

21 CHAIRMAN LASKEY: I d like to begin this  
22 morning with the open public hearing portion of our

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1 session today. Prior to having the invited speakers  
2 come to the podium, I just want to read the following  
3 paragraph if I might.

4 Both the Food and Drug Administration and  
5 the public believe in a transparent process for  
6 information gathering and decision-making. To ensure  
7 such transparency at the open public hearing session  
8 of the Advisory Committee meeting, FDA believes that  
9 it is important to understand the context of an  
10 individual s presentation.

11 For this reason, FDA encourages you, the  
12 open public hearing speaker, at the beginning of your  
13 written or oral statement to advise the Committee of  
14 any financial relationship that you may have with the  
15 sponsor, its product, and if known its direct  
16 competitors. For example, this financial information  
17 may include the sponsor s payment of your travel,  
18 lodging or other expenses in connection with your  
19 attendance at the meeting.

20 Likewise, FDA encourages you at the  
21 beginning of your statement to advise the Committee if  
22 you do not have any such financial relationships. If

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1 you choose not to address this issue of financial  
2 relationships at the beginning of your statement, it  
3 will not preclude you from speaking. That being  
4 said, I would like to call our first speaker this  
5 morning for the open public session. That would be  
6 Dr. Janette Durham.

7 DR. DURHAM: Good morning. I am Dr.  
8 Janette Durham, a Professor of Radiology and an  
9 Interventional Radiologist from the University of  
10 Colorado Health Sciences Center. I have nothing to  
11 disclose or a conflict of interest. I am also the  
12 President of the Society of Interventional Radiology.

13 SIR is a non-profit, national, scientific  
14 organization of more than 4,000 physicians and Allied  
15 Health professionals committed to improving health and  
16 the quality of life through the practice of vascular  
17 and interventional radiology. This society promotes  
18 education, research, and communication while providing  
19 strong leadership in the development of health care  
20 policy.

21 SIR members have undergone training and  
22 cervico-cerebral angiography as part of our ACGME-

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1 approved residency program. Our members have  
2 extensive experience placing endovascular stents in  
3 multiple vascular beds. SIR recognizes the importance  
4 of carotid atherosclerosis and its appropriate  
5 management.

6 In a recent SIR member survey, 22 percent  
7 of respondents reported having performed 25 or more  
8 carotid stent cases and the collective total of  
9 carotid stent experience was over 5,000 cases  
10 performed. Of those surveyed, 90 percent responded  
11 that they are interested in training to perform  
12 carotid stenting.

13 SIR supports carotid stenting as an  
14 effective and beneficial new technology for  
15 appropriately selected patients. We believe that  
16 there is sufficient evidence to warrant approval of  
17 this technology. SIR has had an opportunity to review  
18 in a preliminary fashion the training program put  
19 forth by the sponsor. We feel it s a sound program  
20 for device training.

21 We intend to participate as needed to  
22 provide educational content and proctors. Procedural

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1 safety and effectiveness will be equally as important  
2 to device safety and effectiveness. As a physician, I  
3 am involved in the diagnosis, prevention, and  
4 treatment of stroke.

5 In my practice, I recognize that stroke is  
6 one of the most devastating events a person can  
7 experience. Those who survive stroke are often  
8 disabled and have extensive health care needs. It is  
9 important that appropriately trained and skilled  
10 physicians treat patients who are being treated with a  
11 device to prevent stroke so that stroke is not the  
12 result of treatment.

13 It is important that labeling include the  
14 endovascular skills necessary to ensure high quality  
15 outcomes. Physicians are responsible for having  
16 undergone the necessary procedural training in  
17 addition to device training to qualify them to perform  
18 invasive procedures and utilize new technologies.

19 Hospitals are responsible for overseeing  
20 that physicians in fact have appropriate credentials  
21 to perform procedures safely. Industry need not share  
22 the responsibility for procedural training. To do

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1 this would unreasonably burden industry and add to the  
2 cost of advancing technology.

3 SIR has provided CME training and  
4 education on carotid stenting at our national meeting  
5 the past two years. We plan to continue this effort  
6 locally in the next year. In addition, SIR  
7 participated in the development of guidelines for the  
8 performance of carotid arteriography and most recently  
9 has developed a multi-society document for the  
10 appropriate quality and performance criteria for  
11 carotid artery stent placement which was published  
12 last September in The Journal of Vascular and  
13 Interventional Radiology and The American Society of  
14 Neuroradiology.

15 These guidelines are based on published  
16 science which recognizes a learning curve in the  
17 performance of carotid arteriography and carotid stent  
18 placement. In respect to stroke, SIR has also  
19 participated in developing a multi-society reporting  
20 standard for product stent technology assessment and  
21 uniformity of reporting in the literature. This will  
22 be published this May in Stroke and The Journal of

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1 Vascular and Interventional Radiology.

2 We recognize that carotid stenting is a  
3 dynamic area. As additional peer reviewed studies are  
4 published, SIR looks forward to working with all  
5 specialities involved in carotid stenting to refine  
6 these guidelines and further improve patient care. In  
7 closing, I thank the panel for the opportunity to  
8 provide comments. I am pleased to be available for  
9 any questions that you may have.

10 CHAIRMAN LASKEY: Thank you much, Dr.  
11 Durham. We re going to try and minimize the Q and A,  
12 so I m going to limit this to one question per  
13 speaker. Dr. Krucoff.

14 DR. KRUCOFF: Just a quick question. I m  
15 sorry if I missed this. Is this a formal consensus or  
16 position statement on behalf of the society or is this  
17 an individual statement?

18 DR. DURHAM: It is on behalf of the  
19 society.

20 CHAIRMAN LASKEY: The next speaker who has  
21 requested time is Dr. Ken Rosenfield representing the  
22 ACC and SCA&I. Dr. Rosenfield. Please forgive the

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1 presence of the timer. We re limiting these comments  
2 to ten minutes.

3 DR. ROSENFELD: My understanding is that  
4 there is a shared presentation, SCA&I and ACC, is that  
5 correct?

6 CHAIRMAN LASKEY: That is correct. You  
7 will precede Dr. Gray.

8 DR. ROSENFELD: Okay, members of the  
9 panel, FDA staff, and guests, my name is Dr. Kenneth  
10 Rosenfield. I am the Director of Cardiac and Vascular  
11 Services at Massachusetts General Hospital. I have  
12 the pleasure of standing along side Dr. William Gray  
13 who is the Director of Endovascular Interventions at  
14 Swedish Medical Center in Seattle.

15 Dr. Gray and I very much appreciate the  
16 opportunity to speak on behalf of two prominent  
17 organizations, the American College of Cardiology and  
18 the Society for Cardiovascular Angiography and  
19 Intervention or the SCA&I. As we embark on our  
20 comments, we disclose that we each have served in a  
21 consulting role for several companies, Cordis amongst  
22 them, whose products may be used for carotid stenting.

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1           We have received modest compensation for  
2 time spent away from our practices while serving those  
3 consulting roles. In addition, Dr. Gray and I both  
4 have served actively as enrolling investigators in the  
5 SAPPHIRE trial. Our participation in this and several  
6 other trials of carotid stenting for high risk  
7 surgical patients as well as our role as busy and  
8 experienced cardiovascular clinicians caring for large  
9 numbers of patients with a high burden of  
10 atherosclerotic disease enables us to comment from an  
11 informed and seasoned perspective.

12           While we are formally here to represent  
13 physicians in our respective organizations, we believe  
14 that we are ultimately here to represent the patients  
15 we all treat. On behalf of those patients, many of  
16 whom are at risk for disabling stroke and who will  
17 benefit from the lowest risk carotid revascularization  
18 available, we, our college, and our society, come  
19 today in the strongest support for carotid stenting.

20           The position that we represent today is  
21 that of the ACC and SCA&I. The American College of  
22 Cardiology is a 30,890 member non-profit professional

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1 medical society and teaching institution whose mission  
2 is to advocate for quality cardiovascular care through  
3 education, research, promotion, development, and  
4 application of standards and guidelines and to  
5 influence health care policy. The college represents  
6 more than 90 percent of cardiovascular specialists  
7 practicing in the United States.

8 The SCA&I is a 3,150 member non-profit  
9 sub-speciality professional medical organization  
10 comprised of cardiovascular and vascular  
11 interventionalists from several specialities who care  
12 for patients with vascular disease and perform both  
13 cardiac and extra-cardiac invasive procedures.  
14 SCA&I s mission is to promote excellence in  
15 catherization and angiography through physician  
16 education and representation, clinical guidelines, and  
17 quality assurance to enhance patient care.

18 On behalf of their members and the  
19 millions of patients for whom their members deliver  
20 care, the ACC and SCA&I both support treatments and  
21 approaches that promise to optimize and/or improve  
22 care while minimizing the negative effects and degree

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1 of invasiveness for patients. Furthermore, the  
2 approach for our organizations and their members has  
3 not necessarily been to accept the status quo but  
4 rather to pursue advances in treatment in order to  
5 accomplish our shared mission.

6 The ACC and SCA&I are here today in strong  
7 support of carotid angioplasty and stenting as an  
8 example of innovation and opportunity for less  
9 invasive treatment options for our patients. It is  
10 perhaps for this reason that more than any other  
11 speciality cardiologists have championed this new  
12 approach to carotid revascularization and stroke  
13 prevention.

14 There are numerous patients in every  
15 cardiology practice who are burdened with comorbid  
16 conditions that render conventional endarterectomy  
17 higher risk. Perhaps more than any other specialty,  
18 it is the patients cared for by cardiologists who have  
19 the most to gain if less invasive stroke prevention  
20 therapies are available which simultaneously offer  
21 reduction in peri-procedure MI and other surgical-  
22 related complications while providing for equivalent

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1 stroke prevention.

2           Conversely, it is these same higher risk  
3 patients who will suffer most if effective new  
4 therapies are withheld or stymied. The college and  
5 the society believe that the results of the SAPPHIRE  
6 trial along with other data now emerging provide the  
7 evidence base to support approval of carotid stenting  
8 with this protection for the subset of patients  
9 identified by the inclusion criteria for the trial.  
10 The ACC and SCA&I organizations strongly support that  
11 approval. We would like to focus on several specific  
12 areas in our comments to follow.

13           These include the role of the  
14 cardiovascular specialist in carotid artery disease  
15 management, secondly, the current gap in care and the  
16 lack of evidence base for patients with high risk  
17 features undergoing carotid vascularization, thirdly,  
18 our society's interpretation of the SAPPHIRE and other  
19 data regarding carotid stenting, and fourthly, the ACC  
20 and SCA&I position regarding carotid stenting as an  
21 alternative for revascularization including the  
22 importance of training and post-market surveillance.

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1 A longer written version of our comments has been  
2 provided for the panel, the FDA staff, and the  
3 Register. With this, I ll hand the podium over to Dr.  
4 Gray.

5 DR. GRAY: Thanks, Ken. Members of the  
6 panel, atherosclerotic disease states our core  
7 clinical competency of our two societies and of the  
8 more than 30,000 specialists that they represent. Our  
9 broad view of cardiovascular patients includes the  
10 critical recognition that atherosclerosis is a  
11 systemic disease and that the longitudinal clinical  
12 care and education of the patient and not episodic  
13 intervention is the key to effective reduction of  
14 morbid, life altering, and costly events such as  
15 myocardial infarction, sudden cardiac death, ischemic  
16 cardiomyopathy, renal failure, stroke, et cetera.

17 Specific to carotid stenting with embolic  
18 protection, cardiovascular specialists have been  
19 dominant among the vanguard of this new and promising  
20 technology for almost ten years and account for  
21 roughly 70 percent of all carotid stent procedures  
22 performed worldwide to date. In trials now before the

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1 panel as well as others to come, cardiologists form  
2 the important core of principal investigators and  
3 produce nothing short of spectacular results often in  
4 hostile, local, regulatory, and reimbursement  
5 environments but always in consideration of expanding  
6 the safety and effectiveness of the options available  
7 to the patient with extracranial carotid artery  
8 disease.

9 The cardiology community prides itself on  
10 practicing evidence-based medicine. It is in that  
11 spirit that we participate with our peers from other  
12 specialties to complete trials such as SAPPHIRE which  
13 are designed to clarify the role of carotid stenting  
14 vis a vie the existing standard of care  
15 endarterectomy.

16 The cardiology community has gone to great  
17 lengths to define the learning curve associated with  
18 carotid stenting so as to minimize the chances of  
19 causing harm to patients by indiscriminate performance  
20 of these procedures by unqualified interventionalists.

21 It is on the background of this dedication to the  
22 evidence-based treatment, education, and research of

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1 cardiac and vascular diseases for our patients in  
2 general and stroke prevention specifically that ACC  
3 and SCA&I come before the panel today.

4 In practice for five decades, carotid  
5 endarterectomy for stroke prevention in a patient with  
6 extracranial bifurcation disease is an elegant and  
7 effective operation. However, not until 1991 with the  
8 publication of NASCET was endarterectomy shown to be  
9 effective in symptomatic patients versus medical  
10 therapy. The results of asymptomatic carotid trial,  
11 the ACAS trial, in 1995 extended surgical efficacy to  
12 the asymptomatic trial with severe carotid stenosis.

13 Based largely on these two trials, carotid  
14 endarterectomy is performed in over 150,000 patients  
15 every year in the United States. It is estimated that  
16 approximately two-thirds of these are asymptomatic.  
17 While the NASCET and ACAS landmark trials established  
18 surgical interventions effective in managing carotid  
19 stenosis, these studies excluded patients with  
20 significant comorbidities likely to increase their  
21 surgical risk.

22 Indeed, over 80 percent of the patients

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1 screened in NASCET and the majority of patients  
2 screened in ACAS were excluded mostly on the basis of  
3 one or more criteria which may have placed the patient  
4 at a higher risk of peri or post-operative procedural  
5 events. In high surgical risk patients, there are no  
6 randomized data comparing surgery to any alternative  
7 therapy. There are however data for multiple high  
8 risk surgical registries demonstrating that stroke and  
9 death rates are on average at least twice that of the  
10 aforementioned trials.

11 In spite of this lack of randomized  
12 control data, endarterectomy continues to be performed  
13 in these patients almost with a higher morbidity,  
14 mortality, and cost. In short, this patient cohort  
15 with endarterectomy has not been shown to be safe nor  
16 effective. This represents a significant national gap  
17 in the ability to offer these patients a proven  
18 therapy.

19 Endarterectomy has been clearly shown to  
20 vary widely with experience and volume. Even at  
21 NASCET investigational sites, outcomes are not as  
22 robust as those that were seen in the trial. This

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1 variability also represents a further gap in assuring  
2 predictable, quality outcomes for our high risk  
3 patients.

4 There is then, after review of available  
5 information, a clear and worrisome diversions between  
6 the clinical data available regarding the benefit of  
7 endarterectomy in patients without surgical risk and  
8 the current clinical practice of endarterectomy in  
9 patients with significant comorbidities in this  
10 country. It is on this background and with this gap  
11 in mind that we now consider the data in carotid  
12 stenting with embolic protection.

13 The panel is currently considering data  
14 from the SAPPHIRE trial, among other sources, in its  
15 deliberation regarding the application of Cordis  
16 Johnson & Johnson for premarket approval of its  
17 carotid stent and embolic protection device for the  
18 treatment of high risk patients in extracranial  
19 carotid artery disease. A presentation of the  
20 SAPPHIRE data has allowed several important  
21 observations.

22 This is the first randomized trial ever to

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1 explore any alternative to carotid endarterectomy in  
2 high risk patients. Although designed as a non-  
3 inferiority trial and in spite of its early stoppage,  
4 it appears to have demonstrated a significant  
5 advantage of stenting over surgery.

6 Late neurologic events after 30 days occur  
7 infrequently and demonstrate effective stroke  
8 prevention which is the goal of any effective carotid  
9 therapy. Repeated restorization rates for stenting  
10 are meaningfully lower than that for surgery, almost  
11 reaching statistical significance in this trial.  
12 These results, as sound as they are in and of  
13 themselves, are further supported by results already  
14 presented in print from other completed trials.

15 The results from those other trials,  
16 investigational carotid stenting in the U.S.,  
17 demonstrate a remarkable uniformity in nearly 2,000  
18 patients across devices, operators, and sites and  
19 endorse the results of SAPHIRE as consistent and  
20 reproducible. It is useful noting that compared to  
21 the aforementioned trials ratifying endarterectomy as  
22 a standard of care in this country studies reporting

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1 outcomes in carotid stenting now total almost four  
2 times the number of patients in NASCET and several  
3 hundred more than the number of asymptomatic patients  
4 study in ACAS.

5 After reviewing these data, the college  
6 and society believe there is strong evidence that  
7 rigorous testing of carotid stenting has demonstrated  
8 comparable results and even superiority in some cases  
9 to carotid surgery in several important categories and  
10 in a significant number of patients to draw such a  
11 conclusion. I finish comments with Kenny.

12 DR. ROSENFELD: Based on the current data  
13 available, the college and the society believe that  
14 carotid stenting with embolic protection should be  
15 made available as an option to patients with clinical  
16 or anatomical comorbidities as defined in the SAPPHIRE  
17 inclusion criteria in order that they may take  
18 advantage of this lower risk alternative to surgery  
19 and improve their outcomes. To deny these patients a  
20 clearly beneficial alternative to endarterectomy is  
21 neither in the best interest of the patient nor  
22 society as a whole.

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1           The remarkable results from stenting,  
2 achieved in a fraction of the time that it took  
3 carotid surgery to mature, will only be replicated  
4 through continued expert application of the technology  
5 and procedure and with careful patient selection. The  
6 necessary skills transfer therefore is important once  
7 systems are available out of an IDE setting. Both the  
8 ACC and the SCA&I are committed to training and  
9 credentialing as a critical component of device and  
10 procedural approval.

11           Competency in carotid stenting requires  
12 acquisition of certain skill sets. These include  
13 cognitive, clinical, and technical skills. There is  
14 clearly a learning curve associated with achieving  
15 competence in carotid stenting.

16           The ACC and SCA&I are in favor of  
17 establishing rigorous but not prohibitive training and  
18 credentialing requirements. Specifically, we propose  
19 that training and certification be obtained within a  
20 rigorous, well-defined program which is based on  
21 thresholds for achievement of competence but does not  
22 present unreasonable barriers.

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1           Several documents are currently under  
2 preparation by multi-specialty groups such as the  
3 AHA/ACC competency document as well as the AHA  
4 guidelines documents for cerebrovascular imaging.  
5 These documents will aid in identifying the requisite  
6 skills and numbers of procedures to achieve  
7 competence.

8           The college and society also understand  
9 the critical need for and support the implementation  
10 of careful ongoing tracking of outcomes post-PMA  
11 follow up using standardized definitions and measures.

12          This ongoing surveillance will assure the adequacy of  
13 training and appropriateness of patient care.

14           Indeed, the ACC and the SCA&I have been at  
15 the forefront of developing standardized and  
16 systematized mechanisms by which key clinical and  
17 procedural data elements can be collected and analyzed  
18 to create new benchmarks and compare to existing  
19 benchmarks. As an example, the ACC NCDR, National  
20 Cardiovascular Data Registry, in conjunction with the  
21 Cardiothoracic Surgical Database represents the  
22 largest such effort to date.

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1 ACC NCDR is already conducting two studies  
2 on behalf of the FDA. These are underway. We look  
3 forward to the opportunity to collaborate further in  
4 this regard. In spite of the robust nature of the  
5 SAPPHIRE and the other data at hand and the benefits  
6 already realized by the thousands of patients who have  
7 been treated thus far with carotid stenting in the  
8 United States and worldwide, there will be those who  
9 will be opposed to carotid stenting approval or  
10 critical of the trial design.

11 I would refer you to the longer version of  
12 our comments here, the written document, which would  
13 express our feelings about these various issues.  
14 Specifically the longer version addresses the issue of  
15 MI as an inclusion criteria in this trial, the issue  
16 of MI as an endpoint in this trial, the possible  
17 requirement for pre-approval by a surgeon before  
18 undergoing carotid stenting, and the absence of a  
19 medical arm for this trial.

20 Time precludes us from describing these  
21 sentiments in detail, but we would refer you to the  
22 written documents that we provided for the panel. We

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1 would like to focus on one key element or issue --

2 CHAIRMAN LASKEY: Dr. Rosenfield, excuse  
3 me, you have one minute remaining.

4 DR. ROSENFELD: Okay, I ll wrap up my  
5 comments then. The other issue that we would like to  
6 refer you to is the issue of the inclusion of  
7 asymptomatic patients in this trial and whether this  
8 should be applied to asymptomatic patients. ACC and  
9 SCA&I believe at this point that the focus should be  
10 on implementation and careful roll-out of the  
11 technique by ensuring that the procedure is made  
12 available to the appropriate patients and while at the  
13 same time making certain that its use is not  
14 overextended to those who are not high risk as defined  
15 in the trial and also recognizing the need for  
16 appropriate threshold criteria without creating  
17 barriers for talented operators of any specialty to  
18 ensure proper training for interventionalists.

19 Finally, the focus should be on  
20 instituting systems to enable meticulous monitoring  
21 results in the post-market phase to ensure compliance,  
22 proper patient selection, and integrity of the results

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1 as well as to provide a mechanism for continued  
2 quality improvement. Most importantly, we would like  
3 to reiterate that the ACC and SCA&I position regarding  
4 this procedure in the current era and as demonstrated  
5 by the SAPPHIRE trial is that this can provide a real  
6 and meaningful benefit for patients in this country  
7 who are at high risk for CEA or endarterectomy.

8 It is in the best interest of these  
9 patients, whose options are quite limited, to make the  
10 procedure available. We have been honored to be here  
11 today to represent our professional organization. We  
12 also are humbled by the opportunity to speak on behalf  
13 of the patients who have participated in carotid stent  
14 research and future patients who will benefit from its  
15 approval. Thank you very much.

16 CHAIRMAN LASKEY: Thank you both very  
17 much. It is clearly a full plate. In the interest of  
18 time, again, which is a precious commodity this  
19 morning, we will move on. The next speaker requesting  
20 time is Dr. Bacarach.

21 DR. BACARACH: Good morning, ladies and  
22 gentlemen of the panel. My name is Dr. Michael

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1 Bacarach. I m very pleased to have the opportunity to  
2 present to you today on behalf of the Society of  
3 Vascular Medicine and Biology.

4 I m a practicing interventional vascular  
5 medicine specialist. I m currently the Director of  
6 the Heart Hospital in Sioux Falls, South Dakota. I m  
7 also an Associate Professor of Clinical Medicine at  
8 the University of South Dakota. I m the Treasurer of  
9 the Society of Vascular Medicine and Biology.

10 It s my goal this morning to briefly  
11 describe the Society of Vascular Medicine and Biology,  
12 to present our society s position regarding carotid  
13 stent support angioplasty, and the SAPPHIRE trial  
14 before you today. I wish to disclose that I did serve  
15 as an investigator for the SAPPHIRE trial. I have  
16 been an investigator in three additional carotid stent  
17 trials.

18 I have no financial relationship or  
19 conflict of interest with Cordis or Johnson & Johnson.

20 I have received no compensation for my appearance  
21 today. I am here as an officer of the Society of  
22 Vascular Medicine and Biology to present our society s

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1 position.

2           The Society of Vascular Medicine and  
3 Biology is an non-profit professional medical  
4 organization. It was founded in 1989 to foster a  
5 broad mission of patient care, education, and research  
6 in the field of vascular medicine. Our goal is to  
7 maintain a high standard of clinical practice and  
8 patient advocacy in vascular medicine.

9           The Society of Vascular Medicine and  
10 Biology is the only national professional medical  
11 society representing physicians with expertise in  
12 medical, surgical, and endovascular strategies for the  
13 treatment of these complex patients. Our membership  
14 includes individuals with expertise in vascular  
15 medicine, cardiology, vascular surgery, radiology,  
16 vascular nursing, vascular technology, and vascular  
17 biological research.

18           Extracranial carotid artery disease is an  
19 area of expertise of the physician members of the  
20 society. The development of endovascular therapy for  
21 vascular disease has been profound and has led to many  
22 advances which have improved the care of our patients

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1 with vascular disease. Specific use of less invasive  
2 therapies and strategies for revascularization have  
3 made treatment for many of my complex patients deemed  
4 suboptimal candidates for surgical revascularization  
5 life saving.

6 Carotid stent support angioplasty using  
7 cerebral embolic protection devices is one example of  
8 such innovation and advantage to our patients. My  
9 colleagues and I see many patients with carotid  
10 lesions that are inaccessible to standard  
11 endarterectomy or have prohibitive surgical risk from  
12 serious comorbid conditions making treatment difficult  
13 and risky.

14 Carotid stent support angioplasty  
15 represents a major advance in my ability to care for  
16 these patients. The SAPPHIRE trial was performed with  
17 sufficient scientific rigor and oversight to  
18 demonstrate convincingly that carotid stent support  
19 angioplasty with embolic protection is an appropriate  
20 first line therapy for high risk symptomatic and  
21 asymptomatic patients.

22 The society was impressed with the results

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1 of the SAPPHIRE trial. Our society strongly supports  
2 approval of carotid stent support angioplasty with  
3 embolic protection for high risk patients deemed to be  
4 in need of revascularization for the prevention of  
5 stroke.

6 The benefits of carotid stent support  
7 angioplasty by appropriately skilled, trained, and  
8 experienced operators and interventionalists are  
9 established. We do not support however broad adoption  
10 of this technology and technique without responsible  
11 and adequate training. As a national, professional  
12 medical society, the Society of Vascular Medicine and  
13 Biology urges you to approve carotid stent support  
14 angioplasty with embolic protection for high risk  
15 patients.

16 We urge you to assure that the proper  
17 training and experience is required prior to the  
18 adoption of this technique. Physician thought leaders  
19 must be involved in the development of this treatment  
20 breakthrough so that responsible, skilled, and  
21 experienced physicians treat our ill patients in the  
22 best, safe, and most appropriate manner. I thank you

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1 very much for the privilege of representing the  
2 society before you today. Thank you.

3 CHAIRMAN LASKEY: Thank you, sir. Any  
4 questions from the panel? Is there anyone else who  
5 wishes to come forth and address the panel on today's  
6 topic or any other topic? Yes, sir, please come  
7 forward. Just identify yourself.

8 DR. HANLEY: Sure, I'm Daniel Hanley. I  
9 represent the American Academy of Neurology.

10 MS. WOOD: Do you have any financial  
11 disclosures?

12 DR. HANLEY: Certainly. I represent the  
13 American Academy of Neurology. They have paid for my  
14 transportation here. I have previous relationships  
15 with Jansen as a medical consultant. This is a  
16 Johnson & Johnson company. I have no relationship  
17 with Cordis.

18 I am a former board member of the National  
19 Institute of Health, American Academy of Neurology,  
20 and a current board member of the National Stroke  
21 Association. I'm a board member of a for-profit  
22 public company, NMT, which makes cardiologic devices

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1 which do not compete with this device.

2 Representing the academy, I wish to  
3 address the panel today. I bring to my comments 25  
4 years of experience as a stroke physician and  
5 neurologist with an emphasis on acute care neurology,  
6 interventional procedures, their complications, and  
7 post-procedural care and recovery of stroke patients.

8 I bring one decade of public advocacy for improved  
9 stroke care on the part of the American Academy of  
10 Neurology, American Heart Association, and the  
11 National Stroke Association.

12 I wish to comment in three areas: (1) to  
13 enforce the importance of the entire process today,  
14 (2) to make the panel aware of an academy white paper  
15 regarding training, and (3) to make a simple comment  
16 regarding the standards by which comparisons should be  
17 made.

18 The first issue, I m pleased to be here  
19 while the FDA deliberates on a new industry sponsored  
20 trial data set that could lead to reduction in stroke  
21 events and the improvement or the addition to the  
22 armamentarium of interventions for Americans with

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1 stroke risks. The AAN, American Academy of Neurology,  
2 doesn't presume to predict the outcome of today's  
3 deliberation. Rather, we hope that patient safety and  
4 benefit are enhanced by today's outcome.

5 My second comment, we wish to make the  
6 Committee aware of the last three decades' effort to  
7 improve stroke and stroke care by the systematic use  
8 of practitioner training pathways. The academy has  
9 not had the opportunity to comment on the training  
10 pathway suggested for this application but welcomes  
11 that opportunity now and hopes to submit its comments  
12 in the near future.

13 The specific neurovascular stroke  
14 coalition pathway has been developed and is brain-  
15 specific. It is to this that I wish to speak.  
16 Despite this pathway's sponsorship by organized  
17 radiology, neurology, and neurosurgery, it is not as  
18 well known as similar heart-based pathways for  
19 coronary angiography and coronary procedures.

20 The pathway is articulated in the American  
21 Academy of Neurology's white paper, a copy of which  
22 will be left today with this panel. The academy

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1 wishes to ask that the details of this pathway for  
2 training and competency in cranial-cervical  
3 angiography be incorporated into the decision-making  
4 today regarding the overall use of stenting devices  
5 and the protocol to place stents in patients with  
6 stroke.

7 The essence of the white paper is that  
8 patient safety is only protected when we apply to  
9 cranial-cervical angiography and carotid stenting the  
10 lessons we have learned in coronary angiography.  
11 These lessons have lead to improved heart outcomes.  
12 The deliberation today must consider how we can  
13 achieve a different goal, improved brain outcomes.

14 The lessons we believe are quite simple.  
15 (1) The procedure in question must be performed by  
16 practitioners with prolonged training times specific  
17 to diseases of the brain because patient selection,  
18 pre and post-procedure management, and procedure  
19 performance are all directed at brain processes. (2)  
20 The proceduralist must demonstrate both technical and  
21 cognitive competence prior to credentialing to select  
22 patients, perform carotid stenting, and organize the

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1 care of these patients after the procedure.

2 (3) Because stroke is the most feared  
3 medical complication, the standards for performance of  
4 brain vascular procedures should be at least as  
5 stringent and at least as specific as the standards  
6 for coronary angiography. Specifically, these are a  
7 minimum of experience of 100 procedures for technical  
8 competence and a minimum training period of one year  
9 in brain stroke patient care in an ACGME credentialed  
10 neurovascular program for cognitive training.

11 The issue of non-neurologically trained  
12 specialists is addressed in this white paper. We  
13 believe that these requirements should apply to all  
14 practitioners whether they are neurologically trained  
15 or not. We do not believe that training in coronary  
16 disease and coronary angiography alone prepare the  
17 practitioner for treatment of stroke.

18 We do not believe that short, CME courses,  
19 whether industry sponsored or otherwise, or simulation  
20 of procedures, not on patients, substitute for  
21 organized, credentialed training in brain vascular  
22 angiography. We make this recommendation because it

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1 is evidence-based and has been demonstrated in  
2 multiple brain angiographic domains to produce optimal  
3 patient safety.

4 We ask that the decision-making today  
5 regarding stroke, a brain disease, and this carotid  
6 stent device reflect our extensive knowledge about  
7 training and competency for brain angiography in the  
8 indications, in the labeling, and the instructions  
9 regarding competency of physicians who will perform  
10 this procedure. My third comment is directed towards  
11 the standards that should be applied today.

12 We suggest that the standard that protects  
13 patient well being be the current established medical  
14 therapy for stroke and that comparisons of the event  
15 rates for patients who are risk matched with medical  
16 treatments not requiring angiography or stent  
17 placement be considered in today s deliberations. I  
18 thank you for your patience and I m willing to answer  
19 any questions. We will provide you with a copy of the  
20 white paper which has been endorsed by all of the  
21 neuro-societies and radiology.

22 CHAIRMAN LASKEY: Thank you, sir. Any

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1 panel questions?

2 DR. HANLEY: Thank you.

3 CHAIRMAN LASKEY: Thank you again. Anyone  
4 else? Then at this point, I would like to close the  
5 open public hearing and move on to the sponsor  
6 presentation.

7 DR. COHEN: Mr. Chairperson, Committee  
8 Members, Dr. Zuckerman, representatives of the FDA,  
9 and representatives of the public, good morning. My  
10 name is Dr. Sidney Cohen. I m Group Director of  
11 Clinical Research at Cordis Corporation. I ll be  
12 presenting on behalf of Cordis this morning. I m also  
13 an Adjunct Associate Professor of Medicine at the  
14 University of Pennsylvania.

15 In the next hour and 15 minutes, I would  
16 like to cover the following topics. I d like to  
17 provide an overview of this project, go over some  
18 background information on stroke and carotid  
19 endarterectomy, provide a brief description of the  
20 devices that were studied, and provide an overview of  
21 the PMA clinical data which encompasses a total of  
22 1,619 patients.

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1           This includes both non-randomized carotid  
2 artery stent supportive data from two trials, the  
3 CASCADE study and a FEASIBILITY study done  
4 predominantly in the United States as well as the  
5 pivotal trial data from the SAPPHIRE trial which will  
6 be presented by Dr. Ken Ouriel. I will then briefly  
7 provide an overview of the training program that we  
8 have developed and discuss our plans for post-market  
9 surveillance study.

10           The requested indication is detailed here.

11        I m not going to read it for the sake of time. But  
12 to summarize, the Cordis PRECISE Nitinol Stent System  
13 used in conjunction with the ANGIOGUARD XP Emboli  
14 Capture Guidewire is indicated for the treatment of  
15 carotid artery disease in high risk patients. High  
16 risk is defined as at least 50 percent stenosis in  
17 patients with symptoms and at least 80 percent  
18 stenosis in patients without symptoms.

19           In addition patients both symptomatic and  
20 asymptomatic must have more than one condition or at  
21 least one condition that places them at high risk for  
22 carotid endarterectomy. We ll go into what those risk

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1 factors are in the course of this presentation.

2           These studies started with a U.S. study  
3 called the U.S. FEASIBILITY study which was begun in  
4 September 1998. The SAPPHIRE pivotal study was begun  
5 in August 2000. The PMA was filed in October 2003.  
6 There are three conclusions from these studies that we  
7 plan to prove this morning, and that is (1) that we  
8 achieved our primary end point of non-inferiority of  
9 carotid artery stenting to carotid endarterectomy at  
10 one year for the major end point of major adverse  
11 events, (2) that carotid artery stenting provides  
12 improved outcomes in terms of reducing myocardial  
13 infarction, reducing the need for reinterventions and  
14 producing a statistically significant decrease in  
15 cranial nerve injuries, and (3) that the benefit of  
16 carotid artery stenting is sustained, and we will  
17 provide data up to three years from our studies.

18           Finally, the PMA was granted expedited  
19 review status in November 2003 being considered a  
20 significant therapeutic advance. You may be aware  
21 that Cordis was issued a warning letter on April 1.  
22 Cordis continues to work with the FDA on GMP and

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1 quality systems issues.

2 I have some background information on  
3 stroke and carotid disease. There are over 700,000  
4 strokes that occur annually in the United States.  
5 Stroke is the third leading cause of death with an  
6 estimated 164,000 deaths per year. Up to 30 percent  
7 of strokes are caused by carotid artery disease. It s  
8 the number one cause of disability in the United  
9 States.

10 The costs to take care of patients with  
11 stroke are in excess of \$53 billion per year. If you  
12 are under the age of 65 and you have a stroke, you  
13 have an over 50 percent chance of dying within eight  
14 years. But by enlarge, this is a disease that affects  
15 the elderly and particularly those with comorbid  
16 medical conditions.

17 Carotid endarterectomy has a 50 year  
18 history of development and refinement to its present  
19 status. It s currently the interventional standard of  
20 care in treating patients with carotid disease with  
21 the purpose of reducing stroke. There are up to  
22 200,000 carotid endarterectomies performed each year

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1 in the United States.

2 It s estimated that at least 20 percent of  
3 carotid endarterectomies are performed on high  
4 surgical risk patients annually in the United States  
5 with high surgical risk defined based on anatomic and  
6 medical comorbidities where the anatomic issues  
7 increase the risk of the procedure and the medical  
8 comorbidities increase the risk of having a myocardial  
9 infarction and death. There are a number of  
10 randomized clinical studies which have supported the  
11 superiority of carotid endarterectomy over best  
12 medical therapy that was available at the time the  
13 studies were undertaken.

14 These studies have led to carotid  
15 endarterectomy again being considered the standard of  
16 care for the interventional treatment of both  
17 symptomatic and asymptomatic carotid artery disease.  
18 It s clear, however, that the current treatment of  
19 patient with carotid disease using carotid  
20 endarterectomy extends beyond the NASCET and ACAS  
21 inclusion criteria.

22 By enlarge, NASCET and ACAS studied a

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1 relatively healthy subset of patients. For example,  
2 ACAS screened 25 patients in order to enroll one  
3 patient whereas NASCET only enrolled one out of every  
4 three patients who underwent carotid endarterectomy at  
5 the participating institutions.

6 Patients considered at high risk for  
7 carotid endarterectomy, as defined by ineligibility,  
8 comprise up to 50 percent of patients in different  
9 published series. A study from the Ochsner Clinic  
10 encompassing 366 patients yielded 46.2 percent being  
11 trial ineligible. A study from the Cleveland Clinic  
12 encompassing over 3,000 patients indicated that just  
13 under 20 percent of patients were trial ineligible.

14 From a database for the Agency for Health  
15 Care Research and Quality, which encompasses over 7.5  
16 million admission during the year 2001, there were  
17 30,000 patients in that database who underwent carotid  
18 endarterectomy. And 35.1 percent of those had  
19 features that would have made them ineligible for  
20 NASCET and ACAS being considered them high risk.

21 The specific criteria that we re talking  
22 about include anatomic and medical comorbidities. The

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1 anatomic risks include tandem lesions, previous  
2 carotid endarterectomy, previous radiation therapy to  
3 the neck, and status post-radical neck dissection.  
4 The medical comorbidities include age greater than 79,  
5 a previous stroke, a previous myocardial infarction,  
6 unstable angina, atrial fibrillation, symptomatic  
7 heart failure, valvular heart disease, cancer with a  
8 less than 50 percent five year survival, and renal  
9 pulmonary and liver failure.

10 The data on the next several slides will  
11 provide evidence in two regards; first, that outcomes  
12 in patients undergoing carotid endarterectomy do not  
13 match what is in the literature and in addition that  
14 there are patients that are at high risk that are  
15 undergoing carotid endarterectomy. This is a study  
16 published by Wennberg in which mortality in patients  
17 in a Medicare database of 113,000 patients treated  
18 with carotid endarterectomy from 1992 and 1993 was  
19 investigated.

20 On the left side, you can see the  
21 mortality rates from the ACAS study. For the NASCET  
22 study, you see that the mortality for patients

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1       undergoing carotid endarterectomy in the same  
2       hospitals that participated in ACAS and NASCET are  
3       more than two-fold higher than the mortalities  
4       reported in the literature for those two studies. And  
5       non-trial hospitals had somewhat higher mortality.

6               In addition, non-trial data from a number  
7       of centers that includes both single center, Ochsner  
8       Clinic, Ohio Registry which is a composite of Medicare  
9       database from that state, and New York Registry both  
10      symptomatic and asymptomatic patients, a composite of  
11      six hospitals, yielded incidents of rates of death of  
12      up to one percent, rates of stroke between two and a  
13      half and four and a half percent, giving rates of  
14      stroke and death between two and a half and five and a  
15      half percent.

16             Another study of academic medical centers  
17      in a retrospective analysis of 1,160 patients at 12  
18      centers in the United States for patients undergoing  
19      carotid endarterectomy in the years 1988 through 1990,  
20      using an end point of in-hospital death, myocardial  
21      infarction, and stroke, and an end point that s  
22      similar to that used in the SAPPHIRE trial, yielded an

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1 overall outcome of 6.9 percent. Patients who were  
2 over 75 who were symptomatic or had angina had higher  
3 event rates than those overall.

4 If we break out that 6.9 percent overall  
5 rate into its individual components, we see a death  
6 rate of 1.4 percent, non-fatal stroke rate of 3.4  
7 percent yielding a combined death/non-fatal stroke  
8 rate of 4.8 percent and a MI rate of 2.1 percent.  
9 Certainly this study as well as the previous studies  
10 suggest both that patients currently undergoing  
11 carotid endarterectomy have risk factors that lead to  
12 outcomes that are not quite what is published in ACAS  
13 and NASCET.

14 In addition, there s data that the  
15 patients currently undergoing therapy are actually  
16 comprised mostly of asymptomatic patients. Again,  
17 data from the same registries mentioned before or  
18 single site data indicates that a low of 25 percent or  
19 anywhere between 60 and 75 percent of patients  
20 currently going carotid endarterectomy in the United  
21 States are asymptomatic.

22 While there is no contemporary data that

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1 would allow us to understand the outcomes with medical  
2 therapy of patients who have carotid stenosis and who  
3 are asymptomatic, there is data that is more  
4 historical in nature that could be brought to bear on  
5 this. This is a study of asymptomatic patients  
6 totaling 1,196 which indicates that the stroke rate is  
7 fairly flat until you get to the 80 percent level  
8 where the stroke rate increases rapidly from one  
9 percent up to over five and a half percent.

10 This value of 80 percent to 99 percent  
11 actually is supported by data published from the  
12 European Carotid Surgery Trialists paper of  
13 asymptomatic patients which indicated that the three  
14 year stroke rate for the same cohort of patients for  
15 the 80 to 89 percent was 9.8 percent and for the 90 to  
16 99 percent was 14.4 percent. In addition, I would  
17 remind you that of the patients enrolled in the ACAS  
18 trial, only one-third of those had an 80 percent or  
19 greater stenosis.

20 In fact, this data led to the choice of 80  
21 percent as the minimum stenosis for asymptomatic  
22 patients in the SAPPHERE trial. Thus, in the United

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1 States, the standard indications for surgical  
2 treatment of carotid disease include both NASCET and  
3 ACAS eligible as well as ineligible patients,  
4 symptomatic and asymptomatic patients, and higher risk  
5 patients with high risk being defined on anatomic and  
6 medical comorbidities and thus, SAPPHIRE trial study  
7 patients who currently are referred for treatment of  
8 their carotid disease.

9 We chose to study high surgical risk  
10 patients because in the initial evaluation of the new  
11 technology, it was decided to study it in a cohort of  
12 patients where carotid endarterectomy is technically  
13 demanding. It s demanding based on anatomic factors  
14 which difficult access surgically may lead to  
15 increased local tissue and nerve injury as well as for  
16 the presence of medical comorbidities where patients  
17 would be less tolerant of general anesthesia and  
18 surgery. Thus, carotid artery stenting is studied as  
19 an alternative and less invasive method of therapy.

20 I d like to move on now to a brief  
21 description of the devices used in these studies. The  
22 carotid artery stenting system consists of two

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1 devices; a stent delivery system and emboli protection  
2 device. The stent delivery system is comprised of a  
3 stent and a delivery catheter.

4 The Cordis PRECISE Nitinol Stent comes in  
5 two french sizes; 5.5 french and 6 french. The 5.5  
6 french comes in diameters of 5, 6, 7, and 8  
7 millimeters with lengths of 20, 30, and 40. The 6  
8 french system has sizes of 9 and 10 millimeters  
9 diameter by 20, 30, and 40 millimeters in length.

10 In addition, tapered stents were studied.

11 In the 5.5 system, that s a 6 to 8 millimeter taper  
12 diameter by 30 millimeter length. For the 6 french  
13 system, 7 to 9 and 7 to 9 millimeter diameters with a  
14 30 millimeter length. The stent delivery system has a  
15 usable length of 135 centimeters with a guidewire  
16 lumen of 0.018 inch.

17 Emboli protection is provided by the  
18 ANGIOGUARD XP Emboli Capture Guidewire. This is a  
19 polyurethane filter on a Nitinol frame. Basket  
20 diameters range from 4 to 8 millimeters. We oversize  
21 the basket in use by anywhere from 0.5 to 1.5  
22 millimeters versus the reference vessel diameter. The

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1 pore size of the filter is 100 microns. The crossing  
2 profile is 3.5 french. The wire diameter again is  
3 0.014.

4 I d like to show an animation of the  
5 system in use. What you will see is, first, the  
6 inside view of the artery. That s not good. What you  
7 would have seen is the inside view of the artery with  
8 first the ANGIOGUARD device being deployed past the  
9 lesion, the sheath being withdrawn, deploying the  
10 umbrella-shaped ANGIOGUARD. That would be followed by  
11 a balloon dilatation with release of material from the  
12 lesion being captured by the ANGIOGUARD which is  
13 distill to the lesion, the placement of the stent  
14 which is a Nitinol stent which self-expands upon  
15 withdrawal of the sheath, and then finally capture of  
16 the ANGIOGUARD device and then retrieval of that  
17 device from the body.

18 I d like to move on now to an overview of  
19 the PMA clinical data which encompasses a total of  
20 1,619 patients. Again, this is provided as supportive  
21 data from the CASCADE study done in Europe and the  
22 FEASIBILITY study done predominantly in the United

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1 States. The purpose of these two studies were to gain  
2 experience with the carotid stent system and provide a  
3 learning curve for investigators.

4 It allowed us to refine the stent delivery  
5 system and to evaluate the advantage of adding the  
6 ANGIOGUARD device. Two studies will be described.  
7 The CASCADE study done entirely in Europe was a non-  
8 randomized study of carotid artery stenting  
9 encompassing 121 patients. Even though the primary  
10 end point was 30 days, we have a one year follow up in  
11 those patients.

12 The FEASIBILITY study was done  
13 predominantly, again, in the United States. It s a  
14 non-randomized study of carotid artery stenting. A  
15 total of 261 patients were enrolled. That has a three  
16 year follow up even though the primary end point was  
17 not at three years.

18 Let s move on to the CASCADE study. The  
19 objective here was to evaluate the safety and  
20 performance of the SMART stent with and without  
21 ANGIOGUARD Emboli Capture in patients with high grade  
22 carotid artery stenosis. The primary end point was

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1 ipsilateral stroke or procedure-related death within  
2 30 days of stent implantation.

3 This is a multi-center, prospective, non-  
4 randomized study in nine centers in Europe using the 7  
5 french SMART system which is a predecessor to the  
6 PRECISE system, identical stent just a slightly  
7 different delivery system. There were 121 patients  
8 enrolled, 31 with ANGIOGUARD. It was conducted from  
9 September 98 through May 2002. It included  
10 symptomatic patients with greater than 70 percent  
11 stenosis, asymptomatic patients greater than 85  
12 percent stenosis with the stenosis occurring between  
13 the origin of the origin of the common carotid and the  
14 extra-cranial segment of the internal carotid artery.

15 The primary end point is shown here.  
16 (Indicating.) There were no procedure-related deaths.

17 Ipsilateral stroke occurred at a rate of 7.4 percent.

18 If we divide the data between the patients who were  
19 treated with stent alone in blue and stent with an  
20 ANGIOGUARD in red, we see a reduction of events in the  
21 patients we used with ANGIOGUARD with ipsilateral  
22 stroke rate of 3.2 percent and no major ipsilateral

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1 strokes.

2 Conclusions. From the CASCADE study,  
3 which is carotid artery stenting, was found to be  
4 feasible for the treatment of carotid stenosis. The  
5 ANGIOGUARD distal protection device functioned well  
6 and appeared to reduce the risk of distal embolization  
7 resulting in fewer strokes such that use with the  
8 ANGIOGUARD the 30 day stroke rate was 3.2 percent with  
9 no major strokes.

10 The U.S. FEASIBILITY study s objective was  
11 to assess the feasibility of carotid artery stenting  
12 in the treatment of obstructive carotid artery  
13 disease. It s also to assess and standardize optimal  
14 operator techniques as this also served as the run-in  
15 phase for the clinical trial. It was designed as a  
16 non-randomized prospective study of 33 centers using  
17 the 6 and 7 french SMART system, again predecessors to  
18 the PRECISE system, and the 5.5 french PRECISE stent  
19 delivery system.

20 There were 261 patients enrolled, 85 of  
21 whom received stenting with the ANGIOGUARD device.  
22 They were enrolled from September 98 through July

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1 2001. We have follow up out to three years.  
2 Inclusion criteria included patients who were  
3 symptomatic, needed to have at least 60 percent  
4 stenosis. Patients who were asymptomatic had to have  
5 at least 80 percent stenosis by ultrasound or  
6 angiography with again disease of the native common or  
7 internal carotid arteries.

8 Inclusion criteria here were somewhat  
9 different. They included anatomic risk factors which  
10 made the patients at somewhat higher risk for surgical  
11 endarterectomy. This included restenosis after  
12 carotid endarterectomy, a history of radical neck  
13 dissection, a history of contralateral carotid artery  
14 occlusion, a history of an ostial lesion of the common  
15 carotid, and a high take off carotid bifurcation  
16 disease.

17 The primary end point was 30 day major  
18 adverse events, MAE, defined as death, any stroke,  
19 and/or myocardial infarction. Key secondary end  
20 points included major clinical events at six months  
21 and yearly to three years, patency defined as less  
22 than 50 percent restenosis by carotid ultrasound at 48

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1 hours, 30 days, six months, and yearly to three years,  
2 and neurologic assessments that were performed by an  
3 independent neurologist at 28 hours, 30 days, six  
4 months, and yearly to three years.

5 The end points are depicted here with a  
6 death rate of 0.8, MI of 1.1, stroke of 6.1 yielding a  
7 major adverse event rate of 6.9. Again, if we take  
8 the data and separate it out between the patients in  
9 blue who received a stent only versus patients in red  
10 who were treated with a stent and the ANGIOGUARD, you  
11 see that the stroke rate with ANGIOGUARD is 2.4. Once  
12 again, there were no major ipsilateral strokes.

13 We have here the cumulative incidents of  
14 major adverse events. I'd like to take a second to  
15 review this slide as you will be seeing this  
16 cumulative incidents curve several times during this  
17 presentation. At the very bottom of the curve - and  
18 I'm sorry, I don't want to hit the gentleman's head  
19 with the back of the pointer here - but you see the  
20 table that indicates the number of patients at risk at  
21 the different time periods.

22 On the Y axis is the cumulative percentage

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1 of major adverse events. The X axis is the time after  
2 the procedure. The end points are indicated at 30  
3 days here by the numbers, one year, two years, and  
4 three years. Error bars are 1.5 times the standard  
5 error.

6 What you see here is an increase in the  
7 rate of adverse events over the three year follow up.

8 When we look to see what the components of this  
9 increase in curve are, first, we look at the  
10 cumulative percentage of all stroke to 30 days and  
11 ipsilateral stroke from days 31 through three years.  
12 What you see is a rate at 30 days of 6.1 which  
13 increases to 8.7 at three years. That an increase of  
14 just under one percent per year.

15 On the other hand, if you look at the  
16 cumulative incidents rate percentage of death to three  
17 years, you see an increase in the curve over the  
18 course of this time period. It is this increased  
19 death that contributes to the increased rate of major  
20 adverse events. This increase of death rate or the  
21 deaths are likely due to the elderly age and the  
22 significant medical comorbidities of these patients.

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1           In conclusion, for the U.S. FEASIBILITY  
2 study, we were able to demonstrate the feasibility of  
3 carotid stenting with the Cordis PRECISE Nitinol stent  
4 system. The ANGIOGUARD Emboli protection device  
5 appeared to reduce the incidents of stroke. Again,  
6 with use of the device, the stroke rate at 30 days was  
7 2.4 percent and there were no major strokes. This  
8 also provided a run in to the pivotal SAPPHIRE study.

9           Because the number of patients in the  
10 FEASIBILITY study and the CASCADE study were small, we  
11 did an exploratory analysis to see whether combining  
12 the data from those two trials would yield  
13 significance. So on the right side of the slide here  
14 is the combined incidents of stroke without ANGIOGUARD  
15 and the combined incidents of stroke with ANGIOGUARD.

16        You see the difference here, from 8.6 to 2.6, does  
17 reach statistical significance at the  $p = 0.02$  level.

18           From these two studies, we were able to  
19 refine the carotid artery stent delivery system with a  
20 reduction in profile from 7 french to 5.5 french.  
21 That allowed us to improve the design of the delivery  
22 system. The data supports the benefits of the

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1 ANGIOGUARD Emboli protection device in reducing  
2 stroke. It has demonstrated the feasibility of  
3 performing carotid artery stenting. At this time, I  
4 would like to ask Dr. Ken Ouriel to come to the podium  
5 to present the pivotal SAPPHIRE trial data.

6 DR. OURIEL: Thank you, Sid. Good  
7 morning. I m Dr. Kenneth Ouriel. I m Chairman of the  
8 Division of Surgery at the Cleveland Clinic Foundation  
9 and Professor of Surgery at the Cleveland Clinic  
10 Lerner College of Medicine at Case Western Reserve  
11 University.

12 I m one of the members of the executive  
13 committee of SAPPHIRE. I m going to present the  
14 methodology and results of this pivotal trial. I d  
15 like to disclose that my lodging for one night was  
16 paid by Cordis. My travel here was paid for by the  
17 Cleveland Clinic. I have no other conflicts to  
18 disclose at this time.

19 The objective of the SAPPHIRE study was to  
20 compare the safety and effectiveness of carotid  
21 stenting with emboli protection to endarterectomy in  
22 the treatment of carotid artery disease in high risk

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1 patients. There were a total of 2,294 patients  
2 screened for eligibility for the SAPPHIRE trial.  
3 Among these, roughly one-third or 747 patients met the  
4 inclusion and exclusion criteria as determined by  
5 concurrence between and interventionalist, a surgeon,  
6 and a neurologist at each site.

7 Within this cohort of 747 patients, both  
8 the surgeon and the interventionalist felt that either  
9 carotid stenting or endarterectomy were feasible in  
10 334 patients. This group underwent randomization to  
11 stent treatment in exactly one-half or 167 patients  
12 and to endarterectomy in the other one-half.

13 There were 406 patients who the surgeons  
14 thought were unacceptable for carotid endarterectomy.

15 These patients were not randomized. Rather, they  
16 were entered into a non-randomized stent treatment  
17 arm. There were seven patients who the  
18 interventionalists thought were at unacceptable risk  
19 for stenting. These patients were entered into a  
20 small, non-randomized endarterectomy treatment arm.

21 The primary end point of this trial was  
22 death (all cause), any stroke, and myocardial

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1 infarction to 30 days post-procedure plus death (all  
2 cause) and ipsilateral stroke between days 31 and 360  
3 post-procedure. There are real differences between  
4 SAPPHIRE and previous surgical trials.

5 First, the primary end point of SAPPHIRE  
6 included all cause mortality rather than just peri-  
7 procedural or neurologic-related deaths. The  
8 composite end point of major adverse events included  
9 myocardial infarction in addition to death and stroke.

10 The 24 hour post-procedure stroke evaluation was  
11 performed by a neurologist.

12 Stroke scales were utilized in addition to  
13 physical examination in the classification of stroke.

14 Vessel restenosis and patency was documented by  
15 duplex ultrasound. Lastly, a multi-disciplinary team  
16 provided input on the treatment strategy including  
17 eligibility and appropriateness for randomization.

18 Some have asked why myocardial infarction  
19 was included in the primary end point of SAPPHIRE.  
20 Myocardial infarction leads to disability, death,  
21 prolonged hospitalization, and health care costs and  
22 as such is thought to be a key safety end point. In

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1 patients undergoing vascular surgery who sustain a  
2 perioperative non-Q wave MI, there is a six-fold  
3 increase in mortality over the subsequent six months.

4 Perioperative myocardial infarction  
5 predicts mortality at one year. There is a 27-fold  
6 increase in the risk of another myocardial infarction  
7 over the next six months. Therefore, perioperative  
8 myocardial infarction is a strong surrogate for long-  
9 term mortality after vascular surgical procedures.  
10 Lastly, perioperative myocardial infarction is part of  
11 the primary end point for other carotid artery  
12 stenting trials such as CREST and ARCHER.

13 Myocardial infarction was defined as  
14 either Q-wave or non-Q-wave. The definition of Q-wave  
15 MI was relatively standard requiring acute symptoms  
16 and new pathologic Q-waves. Non-Q-wave MIs were  
17 defined using the WHO definition of a CK ratio of  
18 greater than two times the upper limit of normal and a  
19 CK-MB fraction greater than normal in the absence of  
20 new Q-waves.

21 The definition of stroke was standard  
22 requiring a focal deficit of abrupt onset lasting more

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1 than one day. While the presence or absence of a  
2 stroke was not determined using stroke scales, when a  
3 stroke did occur, it was classified as major or minor  
4 using the NIH, Rankin, and Barthel scales.

5 The SAPPHERE study was designed as an  
6 equivalence or in statistical parlance non-inferiority  
7 trial. The design was based on the following  
8 parameters. This was a high risk study. The majority  
9 of events were expected to occur within 30 days for an  
10 overall one year event rate of 14 percent. The delta  
11 was chosen to be three percent, a definition that was  
12 agreeable to the clinicians and the Agency.

13 The statistical power was set at 90  
14 percent. The one-sided type I error rate was set at  
15 0.025 which is conventional. What this means is that  
16 we would expect the results to be equivalent if we  
17 could be 97.5 percent certain that stenting was no  
18 more than three percent worse than endarterectomy.

19 We employed an interim analysis plan so  
20 that we could terminate the trial early if we could  
21 demonstrate either non-inferiority or superiority.  
22 Given the fact that this was the first randomized FDA

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1 IDE trial and had a potential for slow enrollment, the  
2 triangular method that we employed allowed for  
3 flexibility in choosing the timing of sequential  
4 testing during enrollment.

5 Our initial plan was to allow the  
6 performance of interim analyses every 100 patients.  
7 This statistical plan was also flexible to allow  
8 enrollment of up to 2,400 patients, if needed. For  
9 example, this is roughly the sample size of CREST.  
10 Based on conservative efforts of the stent s  
11 performance, we anticipated that a sample size of 600  
12 to 800 patients would result in a decision to stop the  
13 trial for non-inferiority.

14 As the FDA has pointed out, the initial  
15 analysis plan was changed. All changes were done in  
16 accordance with the flexibility allowed with the  
17 triangular method. We decided to omit the first  
18 interim analyses since a sample size of anything less  
19 than 300 patients was thought to be unconvincing.  
20 Before the revised planned analysis in the fall 2001,  
21 it was clear that enrollment was proceeding so slowly  
22 that we were unlikely to reach 400 patients.

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1           Therefore, with an expectation of the  
2 trial terminating for slow enrollment between 300 and  
3 350 patients, we decided to omit all interim analyses  
4 and perform a single final analysis when enrollment  
5 was inevitably terminated. It is important to point  
6 out that this change in interim testing was permitted  
7 under the triangular method. Since interim analysis  
8 was not performed in the study, the first analysis was  
9 the final analysis. Therefore, standard testing  
10 without correction for interim looks was appropriate.

11           This is a graphical representation of the  
12 rate of enrollment. (Indicating.) Enrollment was  
13 robust for the first 12 months of the study. At that  
14 point, enrollment diminished concurrent with the  
15 availability of competing stenting registries from  
16 other companies. There were now outlets for patients  
17 to be treated with stenting outside of the randomized  
18 SAPPHIRE trial. In fact, the Cordis site IDEs began  
19 after the termination of randomization.

20           Importantly, all patients enrolled in  
21 SAPPHIRE were referred for treatment of their carotid  
22 disease. All randomized patients would have been

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1 treated likely with endarterectomy if not for the  
2 trial. Symptomatic patients were required to have a  
3 50 percent or greater stenosis by duplex or  
4 angiography. Asymptomatic patients had to have a  
5 stenosis of 80 percent or greater.

6 Disease had to be located in the native  
7 common or internal carotid artery. Importantly,  
8 consensus agreement by a multi-disciplinary team was  
9 required which included an interventionalist, a  
10 neurologist, and a surgeon. A patient had to have at  
11 least one comorbid condition which increase the risk  
12 of endarterectomy. These comorbid conditions could be  
13 anatomic or medical.

14 Key anatomic inclusion criteria that  
15 assured a high risk subset included contralateral  
16 carotid occlusion, contralateral recurrent laryngeal  
17 nerve palsies, previous radiation therapy to the neck,  
18 previous endarterectomy with the presence of a  
19 recurrent stenosis, difficult surgical access such as  
20 a high internal carotid artery lesion, or severe  
21 tandem lesions.

22 Key medical comorbidities that assured a

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1 high risk subset included the following: congestive  
2 heart failure, open heart surgery within six weeks, a  
3 recent myocardial infarction, angina at a low workload  
4 or unstable angina, severe COPD, or age greater than  
5 80 years.

6 At this point, I would like to present the  
7 results of the randomized portion of the SAPPHIRE  
8 trial. Table 1 of any randomized trial is always a  
9 comparison of the demographics and comorbidities of  
10 the two treatment groups. The randomized stent and  
11 randomized endarterectomy arms of SAPPHIRE were  
12 similar with respect to all baseline variables except  
13 three: coronary artery disease, previous coronary  
14 bypass, and previous PTCA. These characteristics were  
15 more frequent in the stenting arm. So if anything,  
16 the randomized stent arm was slightly more ill than  
17 the randomized endarterectomy arm.

18 There was a high degree of procedural  
19 success in the stented patients. The stent was  
20 successfully delivered to its intended location more  
21 than 99 percent of the time. Deployment of the stent  
22 resulted in less than a 30 percent residual stenosis

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1 in approximately 90 percent of the cases. The 30  
2 percent threshold is currently used for coronary stent  
3 trials however.

4 Using a 50 percent threshold, possibly  
5 more appropriate for a peripheral trial, approximately  
6 99 percent of the patients were successfully treated.

7 The ANGIOGUARD filter was deployed on the first  
8 attempt and retrieved successfully in over 95 percent  
9 of the subjects in the randomized stent arm and in  
10 over 91 percent of the patients in the non-randomized  
11 stent arm. Ultimately, 98 percent of the randomized  
12 stent and 95 percent of the non-randomized stent  
13 subjects had successful deployment and retrieval of  
14 the ANGIOGUARD device.

15 Let s move on to study outcome presenting  
16 data on an intent to treat basis unless otherwise  
17 specified. Among the 167 patients randomized to  
18 stent, one year compliance was achieved with respect  
19 to clinical criteria in 93.5 percent of cases and with  
20 respect to duplex ultrasound in 80.6 percent of the  
21 cases.

22 In the endarterectomy group, complete

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1 clinical follow up was available at one year in 85.6  
2 percent of the cases and duplex ultrasound in about 69  
3 percent of the cases. To remind you, all clinical  
4 events were adjudicated by an independent clinical  
5 events committee and all angiograms and duplex studies  
6 by independent core laboratories.

7 This slide depicts 30 day data in the two  
8 randomized groups; endarterectomy in red and stenting  
9 in blue. There were no statistically significant  
10 differences in the rate of death, stroke, myocardial  
11 infarction, or the composite of major adverse events.

12 At one year, again, there were no statistically  
13 significant differences in the frequency of death,  
14 stroke, myocardial infarction, or major adverse  
15 events. In each case, however, the data trended in  
16 favor of stenting over endarterectomy.

17 This is probably the most important slide  
18 that we re going to show you today. This is the  
19 primary end point analysis. The percent difference in  
20 one year MAE is along the abscissa with a dotted red  
21 line demonstrating the target delta of three percent.

22 The horizontal line is the point estimate for the MAE

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1 difference with a raw value of 7.2 percent in favor of  
2 stenting over endarterectomy.

3 As you can see, the 95 percent confidence  
4 interval is to the left of the margin of non-  
5 inferiority. In other words, the primary goal of the  
6 study was achieved. We were more than 95 percent  
7 certain that stenting was no more than three percent  
8 worse than endarterectomy. In fact and importantly,  
9 we were certain that non-inferiority was achieved with  
10 a p-value of 0.0035. In fact, with this particular  
11 test, had the 95 percent confidence bar been slightly  
12 to the left of zero rather than slightly to the right,  
13 stenting would actually have been statistically  
14 superior to endarterectomy with regard to the primary  
15 end point.

16 The FDA statisticians asked us to perform  
17 the analysis as if we had performed interim testing at  
18 100, 200, 300, and 334 patients. This table displays  
19 the results of that retrospective interim analysis.  
20 There would have been three interim analyses and one  
21 final analysis. The recommendations are listed in the  
22 last column and would have been as follows.

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1           We would have chosen to continue the trial  
2 after 100 patients. We would have chosen to continue  
3 the trial after 200 patients. We would have decided  
4 to stop the trial at 300 patients. There would have  
5 been some additional run on patients. We probably  
6 would have ended up with somewhere between 300 and 350  
7 patients. The final analysis would have included the  
8 run ons.

9           The p-values for superiority would have  
10 been 0.066. Importantly, the p-value for non-  
11 inferiority would have been 0.003, well below our  
12 threshold of 0.025. So with interim analyses and with  
13 corrections for multiple sequential testing, our  
14 conclusion would have been exactly the same. Stenting  
15 is equivalent to endarterectomy.

16           Having demonstrated non-inferiority in the  
17 primary end point of one year major adverse events, it  
18 makes sense to look at the individual end points at  
19 one year. There were no statistically significant  
20 differences between the randomized groups. But again,  
21 as this slide demonstrates, all trends were in favor  
22 of stenting over endarterectomy.

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1                   Again, there was no statistically  
2 significant difference in the rate of stroke at one  
3 year, 7.2 percent in the endarterectomy arm and 6  
4 percent in the stented arm. Diving strokes into major  
5 and minor ipsilateral events, it appeared as though  
6 the strokes that occurred in the endarterectomy  
7 patients were more often major, and the strokes that  
8 occurred in the stented patients were more often  
9 minor. But these differences did not attain  
10 statistical significance.

11                   These two Kaplan-Meier curves represent  
12 the cumulative percentage of subjects experiencing a  
13 major adverse event over one year of follow up. The  
14 MAE rate was 20.1 percent in the endarterectomy group  
15 and 12.2 percent in the stented group. While the  
16 trial was designed to be a non-inferiority trial,  
17 stenting almost hit statistical significance for  
18 superiority. The p-value was 0.053 with a log rank  
19 test.

20                   Data out to two years is displayed here.  
21 The trends continued through 720 days of follow up  
22 with an MAE rate of 26.7 percent in the endarterectomy

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1 group and 19.2 percent in the stent group.

2 When the composite adverse event rate is  
3 split out by its components, we see that the rate of  
4 perioperative stroke was relatively low at just over  
5 three percent in both treatment arms. Importantly,  
6 the rate of stroke remained relatively flat thereafter  
7 with roughly a one percent annual risk of subsequent  
8 stroke over the next two years.

9 These two Kaplan-Meier curves depict the  
10 risk of death over two years of follow up. The risk  
11 of perioperative death was relatively low at 2.5  
12 percent in the endarterectomy group and 1.2 percent in  
13 the stent group. Over the next two years however,  
14 mortality increased to 20.9 percent in the  
15 endarterectomy group and 14.4 percent in the stent  
16 group, a rate representative of the comorbid  
17 conditions of the subjects enrolled in the trial.

18 Of note, the median survival for the  
19 stented patients was 8.5 years and for the  
20 endarterectomy patients was 5.0 years. The cause of  
21 death is broken out here. There were 33 total deaths  
22 over the first year of follow up; 21 in the

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1       endarterectomy group and 12 in the stent group. Only  
2       four of the 33 deaths were tied to a neurological  
3       event; three in the endarterectomy group and one in  
4       the stented group.

5                   By far, non-neurologic deaths  
6       predominated. Twenty of the 33 deaths occurred as a  
7       result of other causes. Those other causes are broken  
8       down here. At the bottom of the slide, cardiac causes  
9       were the most common occurring in 18 of the 29 cases  
10      of non-neurologic death. Other causes are listed here  
11      without significant differences between the two  
12      treatment arms.

13                   The complications in the randomized stent  
14      and endarterectomy subjects are listed here. Target  
15      lesion revascularization was performed in 0.6 percent  
16      of the stent group and 3.6 percent in the  
17      endarterectomy group, a difference that did not attain  
18      statistical difference. Vessel thrombosis, defined in  
19      the protocol as angiographically confirmed occlusion,  
20      was not documented in either group.

21                   Major bleeding occurred in similar numbers  
22      of the stented and endarterectomy patients, nine and

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1 ten percent respectively. There was a greater number  
2 of cranial nerve injuries in the endarterectomy group;  
3 4.9 percent and not unexpectedly zero in the stented  
4 patients, a difference that was significant at the  
5 0.01 level.

6 The rate of restenosis, defined in the  
7 protocol as 50 percent or greater, was 19.7 percent in  
8 the stented group and 31.3 percent in the  
9 endarterectomy group, a difference that just missed  
10 statistical significance. But using more clinically  
11 applicable definitions of greater than 70 or 80  
12 percent diameter reduction, the rate of restenosis was  
13 much lower. Using the 80 percent threshold, the rate  
14 of restenosis was 0.8 percent in the stent group and  
15 4.2 percent in the endarterectomy group, again, a  
16 difference that did not attain statistical  
17 significance.

18 Clinically driven target lesion  
19 revascularization, which for all intensive purposes  
20 represents a result of critical restenosis, this  
21 occurred with very similar frequency to the presence  
22 of an 80 percent or greater stenosis. Well, we showed

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1 you an intent to treat analysis. But a small number  
2 of patients never underwent treatment.

3 Therefore, it s interesting to present the  
4 outcome of the patients who were actually treated with  
5 a specified modality. The reasons subjects did not  
6 receive specified treatment included ineligibility  
7 found after the patient had been randomized,  
8 withdrawal of consent prior to treatment, and  
9 deterioration in the patient s condition prior to  
10 treatment.

11 Interestingly in the treated patients, the  
12 frequency of major ipsilateral stroke and MI was  
13 significantly higher in the endarterectomy treatment  
14 arm. In the treated patients, by Kaplan-Meier  
15 analysis, the one year major adverse event rate was  
16 20.1 percent in the endarterectomy group versus 12.0  
17 percent in the stented group, a difference that was  
18 statistically significant by the log rank test with a  
19 p-value of 0.048.

20 We ll move on to data from the 406  
21 patients in the non-randomized stent arm, patients  
22 that met the criteria for inclusion but for whom the

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1 surgeon felt open surgical repair carried an  
2 unacceptably high risk. Initially, the intent was to  
3 compare data from the non-randomized stent arm to an  
4 objective performance criteria or OPC from the  
5 literature.

6 The pre-specified OPC was 12.94 percent.  
7 This was not met. In fact, from an evaluation of the  
8 data from the SAPPHIRE randomized carotid  
9 endarterectomy arm, it had been underestimated. The  
10 true MAE was 19.2 percent. The Agency was consulted  
11 in March of last year. A supplemental non-inferiority  
12 was suggested using data from the SAPPHIRE  
13 endarterectomy group and adjusting for differences in  
14 baseline demographics.

15 A propensity analysis was necessary  
16 because of the higher rate of comorbidities in the  
17 non-randomized stent group compared to the  
18 endarterectomy group with a statistically high rate of  
19 Class 3 or 4 CCS patients, previous neck radiation  
20 therapy, high cervical lesions, prior endarterectomy,  
21 and prior stroke.

22 These three Kaplan-Meier curves

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1 demonstrate the rate of MAE up to 360 days. Despite a  
2 higher severity of illness in the non-randomized stent  
3 group, outcome was as good or possibly better than  
4 that of the randomized endarterectomy treatment arm.  
5 In fact, the curve fell midway between the randomized  
6 stent and the randomized endarterectomy outcomes.

7 This is the analysis the Agency suggested.

8 The outcome of the non-randomized stent group was  
9 non-inferior to that of the randomized endarterectomy  
10 group. The confidence interval falls just below the  
11 three percent delta that was pre-specified with a p-  
12 value of 0.05.

13 Looking at complications, the rate of  
14 target lesion revascularization and cranial nerve  
15 injury was significantly lower in the non-randomized  
16 stent arm. The rates of vessel thrombosis and major  
17 bleeding were similar in the two groups. Given the  
18 small number of patients in the non-randomized  
19 endarterectomy arm, data will not be covered.

20 While we will present data from subgroup  
21 analyses, the study was not powered for such analyses.

22 I will now present data from the symptomatic and

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1 asymptomatic cohorts numbering 96 and 237  
2 respectively. The 30 day MAE rate in the asymptomatic  
3 endarterectomy in red and asymptomatic stent patients  
4 in blue is illustrated here. There were no  
5 significant differences in any of the individual end  
6 points or in the composite MAE rate.

7 Corresponding data at one year is  
8 illustrated here. Again, there were no differences in  
9 the rate of the individual end points or in the rate  
10 of the composite end point. In each case, however,  
11 there were trends in favor of stent over  
12 endarterectomy. The p-value for the difference in the  
13 MAE rate by Fisher s Exact high-score test was 0.07.

14 With Kaplan-Meier analyses of MAE to one  
15 year, asymptomatic patients randomized to stent did  
16 better than those randomized to endarterectomy, 10.5  
17 percent versus 20.3 percent with a p-value by the log  
18 rank test of 0.04. The median survival of the stented  
19 asymptomatic patients was 12 years. The median  
20 survival of the endarterectomy asymptomatic patients  
21 was six years.

22 Moving on to symptomatic patients, the

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1 rates of the individual end points at 30 days were not  
2 statistically different in the two treatment groups.  
3 Point estimates favored the stented patients for all  
4 end points. At one year, similar results were  
5 observed without significant differences in any of the  
6 end points but with trends towards improvement in the  
7 stented groups for each of the end points.

8 These two Kaplan-Meier curves display the  
9 frequency of major adverse events in the symptomatic  
10 cohort estimated at 20 percent in the endarterectomy  
11 arm and 16.3 percent in the stent arm, a difference  
12 that was not statistically significant. Of note, the  
13 median survival for the symptomatic stent patients was  
14 five years and for the endarterectomy patients 3.5  
15 years.

16 To assure the technical expertise of the  
17 surgeons in the SAPPHIRE trial and to convince  
18 ourselves that it was representative of surgeons  
19 throughout the United States, we evaluated volume and  
20 outcome. The 53 SAPPHIRE surgeons were high volume  
21 operators reporting a pre-trial experience averaging  
22 36 carotid endarterectomies per year with a median of

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1 28 endarterectomies per year.

2 This histogram depicts Medicare data from  
3 Wennberg published in JAMA about six years ago.  
4 Dividing the number of endarterectomies a surgeon  
5 performs into terciles, the lowest tercile performed,  
6 the cut off, was less than six carotid  
7 endarterectomies per year. The middle tercile was  
8 defined as between seven and 21 endarterectomies per  
9 year. The highest tercile was more than 21  
10 endarterectomies per year.

11 As you can see from Wennberg's data, the  
12 mortality rate for carotid endarterectomy decreased  
13 from 2.5 percent for surgeons performing less than  
14 seven cases annually to just over 1.5 percent for  
15 those Medicare surgeons performing more than 21 cases  
16 annually. Same data here but now adding the pre-trial  
17 volumes of the SAPPHIRE surgeons below the X axis.

18 With few exceptions, the SAPPHIRE  
19 surgeons prior volume placed them in the highest  
20 tercile of experience. One index of surgical  
21 expertise is the rate of cranial nerve injuries.  
22 Despite the inclusion of re-do endarterectomies in the

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1 SAPPHIRE data set, the rate of cranial nerve injury  
2 was similar to both NASCET and the VA cooperative  
3 studies, studies that did not include repeat carotid  
4 endarterectomies.

5 To evaluate the SAPPHIRE surgeons  
6 outcomes, the rate of 30 day ipsilateral stroke was  
7 used since this was one of the few end points  
8 available from each of the trials. Overall in  
9 SAPPHIRE, this rate was 1.8 percent. The SAPPHIRE  
10 symptomatic endarterectomy patients were compared with  
11 NASCET patients. While the numbers are small, the  
12 SAPPHIRE rate of zero is certainly no worse than the  
13 NASCET rate of 5.5 percent.

14 Comparing SAPPHIRE asymptomatic  
15 endarterectomy patients with ACAS, the rates were also  
16 very close, 2.5 percent versus 1.8 percent. These  
17 observations suggest that the surgical outcome for  
18 SAPPHIRE was quite similar to NASCET and ACAS for the  
19 end point of perioperative stroke despite the greater  
20 frequency of comorbidities in the SAPPHIRE data set.

21 We also compared the results of carotid  
22 stenting in SAPPHIRE to the outcomes of previously

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1 published surgical data. For symptomatic patients,  
2 there were no significant differences in the rate of  
3 ipsilateral stroke at 30 days between the SAPPHIRE  
4 randomized stent group, the non-randomized stent  
5 group, and the endarterectomy arm of the NASCET trial.

6 For asymptomatic patients, there were no significant  
7 differences in the 30 day risk of ipsilateral stroke  
8 in the SAPPHIRE randomized stent arm, the SAPPHIRE  
9 non-randomized stent arm, and ACAS.

10 In symptomatic SAPPHIRE patients, the 30  
11 day rate for all cause mortality was zero in the  
12 randomized stent arm and 0.8 percent in the non-  
13 randomized stent arm. For asymptomatic SAPPHIRE  
14 patients, the 30 day rate of all cause mortality was  
15 1.7 percent in the randomized stent arm and 2.8  
16 percent in the non-randomized stent arm. These data  
17 compare favorably with corresponding data from NASCET  
18 and ACAS.

19 In conclusion, the primary end point of  
20 the SAPPHIRE trial was achieved. Carotid artery  
21 stenting clearly was non-inferior to carotid  
22 endarterectomy in high risk patients. In fact, there

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1 were trends favoring stenting over endarterectomy with  
2 respect to major ipsilateral stroke, myocardial  
3 infarction, target lesion revascularization, and  
4 restenosis.

5 Further, there was a significant decrease  
6 in the rate of cranial nerve injuries in the stented  
7 group. In the symptomatic and asymptomatic subset  
8 analyses, there was significant improvement at 360  
9 days in favor of stenting over endarterectomy in  
10 asymptomatic patients with a 50 percent reduction in  
11 the rate of major adverse events.

12 The MAE rate was similar in the  
13 symptomatic patients treated with stenting or  
14 endarterectomy. The risk of ipsilateral stroke in  
15 stented patients overlapped the risks from the NASCET  
16 and ACAS trials. In other words, the results of the  
17 SAPPHERE trial was in keeping with previously  
18 published data.

19 With respect to the non-randomized carotid  
20 stent arm, there appeared to be risk factors that  
21 identified patients that may be at too high risk for  
22 endarterectomy. These risk factors were anatomic,

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1 medical, or both.

2           Interestingly, the patients entered into  
3 the non-randomized stent arm because the surgeon  
4 considered them to be at too high risk for  
5 endarterectomy had outcomes that were not inferior to  
6 the randomized endarterectomy patients even though the  
7 stented group had significantly more comorbidities.  
8 This was true for both the symptomatic and the  
9 asymptomatic patients. I would now like to  
10 reintroduce Dr. Sid Cohen to continue with training  
11 and post-marketing surveillance.

12           DR. COHEN: Thank you, Ken. I d like to  
13 take the next couple of minutes just providing an  
14 overview of the training program that we re proposing  
15 to undertake as well as the post-marketing  
16 surveillance study and finish with conclusions. The  
17 carotid artery stent training system is intended to  
18 build upon existing catheter-based expertise to  
19 develop the physician s knowledge and technical  
20 abilities in performing carotid artery stenting.

21           The system was developed using a variety  
22 of experts including SAPPHIRE investigators, experts

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1 in Internet-based training, experts in simulator  
2 modeling, and experts in proficiency measurements.  
3 The process of this education encompasses five steps  
4 that are pretty traditional but with some  
5 modernization.

6 It includes an online didactic session,  
7 observation of actual cases, simulation using a  
8 simulator, a proctoring system, as well as training of  
9 adjunctive staff in performing the procedure. These  
10 trainings occur for the didactic at Internet delivery,  
11 for observation and simulation using regional  
12 education centers, for the proctoring network and  
13 staff training on-site training at the physician s  
14 facility.

15 What s unique here is that we have  
16 included very importantly a measurement of proficiency  
17 that occurs at each step to ensure that high quality  
18 patient outcomes would be generated from physicians  
19 trained in this system. For the online didactic  
20 training, the goal is to transfer expert knowledge  
21 through doing and decision-making as opposed to just  
22 reading. The goal is to ensure procedural success,

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1 providing a detailed understanding of carotid anatomy  
2 and brain anatomy, appropriate selection of cases, and  
3 high performance in terms of technical execution of  
4 the procedure.

5 Training at the regional educational  
6 center occurs in a small group setting where four  
7 modules are reviewed over two days. This includes  
8 both didactic presentations, observation of actual  
9 cases, simulation lab using a simulator, and a product  
10 lab to gain familiarity with the products used in  
11 carotid artery stenting. The physicians interact with  
12 realistic graphical simulations. Their task  
13 performance is formally assessed. The understanding  
14 of learning objectives is demonstrated.

15 On-site training at the physician s  
16 facility by physician proctors utilizes a network of  
17 physicians who are experienced in performing carotid  
18 artery stenting using the Cordis system. These people  
19 act as proctors. The proctors either sign off the  
20 training and experience an application is adequate or  
21 suggest additional training recommendations in order  
22 to meet minimal proficiency standards.

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1           The training program encompasses a total  
2 of 34 hours of training with exposure to a minimum of  
3 15 cases. This serves as the foundation for hospital  
4 credentialing. In order to demonstrate outcomes of  
5 this training system in an earlier form, I would like  
6 to present outcomes from investigator IDE studies that  
7 were performed independent of Cordis but whose  
8 investigators were trained using an earlier version of  
9 this training system.

10           These investigator IDEs occurred at 36  
11 centers, 30 of whom were non-SAPPHIRE investigators.  
12 All the investigators were trained and proctored on  
13 the use of the stent and the emboli protection system.

14           Patient selection criteria was similar to that of the  
15 U.S. FEASIBILITY study. The neurologists evaluated  
16 the patients at 24 hours and at 30 days post-  
17 procedure. The data that I will be showing you is  
18 site-reported and unadjudicated.

19           Thirty day event rates, again site-  
20 reported, included a rate of death of 0.6 percent,  
21 stroke 2.6 percent, MI 1.4 percent yielding a major  
22 adverse event rate of 4.3 in 491 patients. Comparison

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1 of these outcomes with the data previously presented  
2 from CASCADE study in green, FEASIBILITY in yellow,  
3 SAPPHIRE in blue with the institutional IDEs in red  
4 shows that outcomes for both stroke as well as for  
5 death are very similar.

6 I d like to move on now to the post-  
7 marketing surveillance study that we re proposing to  
8 undertake. The goal here is to compare clinical  
9 outcomes with historical control data from SAPPHIRE in  
10 the early time period following approval and assess  
11 the effectiveness of the training program. It s  
12 designed as a multi-center, prospective, non-  
13 randomized, open label study with a 30 day composite  
14 end point where major adverse events are defined as  
15 all death and all stroke.

16 Patients included will be those at high  
17 risk with *de novo* or restenotic lesions. We plan to  
18 enroll at least 1,000 patients with the inclusion  
19 criteria matching the labeled indications. Follow up  
20 will include neurologic exams at discharge and at 30  
21 days performed by a neurologist and clinical events  
22 tracking through discharge by a 30 day office visit

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1 and a nine month telephone contact. There also will  
2 be monitoring with a stopping rule to ensure safety  
3 with electronic data capture to expedite review of  
4 outcomes.

5 I d like to provide a summary and  
6 conclusions to this presentation. What we have  
7 discussed is that stroke is a disease that has  
8 significant morbidity and mortality. It s due to  
9 carotid disease in up to 30 percent of patients. The  
10 goal is to prevent stroke and improve the quality of  
11 life.

12 Carotid endarterectomy is the current  
13 interventional standard of care for NASCET and ACAS  
14 eligible and ineligible patients, for symptomatic and  
15 asymptomatic patients, as well as for low,  
16 intermediate, and high risk patients. We acknowledge  
17 that there are no multi-center randomized studies that  
18 define outcomes in high risk medical or surgical risk  
19 patients. However, SAPPHIRE is intended as an  
20 objective comparison of carotid endarterectomy, the  
21 current interventional standard of care, with carotid  
22 artery stenting, a less invasive approach to therapy.

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1                   Again, Cordis is seeking an indication - I  
2 will not read this but summarize it - for use of the  
3 PRECISE Nitinol Stent System in conjunction with the  
4 ANGIOGUARD XP Emboli Capture Guidewire for use in the  
5 treatment of carotid artery disease in high risk  
6 patients with symptomatic patients having at least 50  
7 percent atherosclerosis stenosis, asymptomatic at  
8 least 80 percent atherosclerosis stenosis with the  
9 symptomatic and asymptomatic patients having at least  
10 one of the conditions, either anatomic or medical  
11 comorbidities that place them at high risk.

12                   This indication is supported by data that  
13 we ve presented from the SAPPHIRE trial where we  
14 achieved our primary end point of non-inferiority of  
15 carotid artery stenting to carotid endarterectomy for  
16 the end point of major adverse events at one year with  
17 carotid artery stenting, improving outcomes in terms  
18 of reducing myocardial infarctions, reducing the need  
19 for reinterventions, and providing a statistically  
20 significant decrease, actually an absence, of cranial  
21 nerve injuries. We also have provided data in the  
22 supportive studies that the benefit of treatment is

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1 durable with data that we've presented with up to  
2 three year follow up.

3 Cordis will institute a training program  
4 to ensure that the outcomes of carotid stenting in the  
5 non-trial setting replicates the safety and  
6 effectiveness demonstrated in the SAPPHIRE trial. We  
7 will conduct a post-marketing surveillance study with  
8 the goal of quantifying patient outcomes and  
9 confirming the adequacy of physician training. Thank  
10 you very much. I would be happy to answer any  
11 questions.

12 CHAIRMAN LASKEY: Well, first of all,  
13 bravo for staying within the dreaded yellow and red  
14 lights. That was an excellent presentation from both  
15 of you. Realizing that each panel member will have an  
16 opportunity to query again this afternoon and that  
17 we're coming up to a short break, are there particular  
18 areas of clarification that we can try and resolve  
19 now? Dr. Aziz.

20 DR. AZIZ: Just for clarification, once  
21 the stenosis was diagnosed by ultrasound, did the  
22 patient have an angiogram as well before surgery was

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1 done?

2 DR. COHEN: For the patients who received  
3 carotid stenting, obviously an angiogram was  
4 undertaken. For the patients who underwent carotid  
5 endarterectomy, no angiogram was required. A minority  
6 of patients actually underwent angiography because of  
7 the dangers of angiography.

8 DR. AZIZ: Interesting.

9 CHAIRMAN LASKEY: Tony.

10 DR. COMEROTA: Dr. Cohen, that was a very  
11 elegant presentation. Both you and Dr. Ouriel did it  
12 beautifully and very convincingly. In the FEASIBILITY  
13 study, could you tell us how many patients were  
14 symptomatic and how many were asymptomatic and how  
15 many had atherosclerotic disease and how many had  
16 recurrent stenosis?

17 DR. COHEN: I would need to check the data  
18 tables to be sure. My memory is that over 60 percent  
19 were symptomatic. I do not know that we gathered data  
20 on how many were native *de novo* lesions versus  
21 restenotic, but we can check on that and get back to  
22 you.

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1                   CHAIRMAN LASKEY: One question I had for  
2 Dr. Ouriel I guess. With respect to the surgical arm,  
3 was there a standardization of the surgical approach,  
4 i.e. general versus local? How was that decided?  
5 What was the standard surgical approach?

6                   DR. OURIEL: Well, actually, it was left  
7 up to the surgeons. So we did not dictate that a  
8 surgeon had to use a patch or not use a patch, a shunt  
9 or no shunt, or general versus local anesthesia. I  
10 can tell you that most procedures were done with a  
11 patch and under general anesthesia.

12                  DR. AZIZ: So none of them had an eversion  
13 endarterectomy. They had the standard endarterectomy.

14                  DR. OURIEL: No, that s not necessarily  
15 true. I don t have those numbers, but again, it was  
16 left up to the surgeon. In fact, there were some  
17 cases that had vein patches, some prosthetic patches.  
18 Some re-do endarterectomies had a saphenous vein  
19 short interposition graph. So it was left up to the  
20 discretion of the operating surgeon.

21                  DR. COHEN: If I could answer the question  
22 that was asked before for previous carotid

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1 endarterectomy with recurrent stenosis, that occurred  
2 in 22.4 percent in the patients in the FEASIBILITY  
3 study.

4 CHAIRMAN LASKEY: Okay, well, thank you  
5 both again. Let s take a rigorous ten minute break.  
6 We ll see you back in ten minutes. Off the record.

7 (Whereupon, the foregoing matter went off  
8 the record at 11:03 a.m. and went back on  
9 the record at 11:26 a.m.)

10 CHAIRMAN LASKEY: On the record. If we  
11 can all regroup again please. Thank you all very much  
12 for your compliance, another watchword. We would now  
13 like to proceed with the Agency s presentation.

14 MS. KENNEL: Good morning, panel members  
15 and audience. Our FDA presentation --

16 MS. WOOD: Lisa, pull the mic a little  
17 closer.

18 MS. KENNEL: Thank you. I m trying to  
19 juggle the laptop as well. Our FDA presentation will  
20 involve three presenters. I will be presenting some  
21 background information and comments about the non-  
22 clinical information in the file.

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1           Our statistician Heng Li will present  
2 several slides detailing statistical issues and  
3 conclusions. Dr. Ronald Weintraub, a consultant to  
4 FDA on this project, will discuss issues relating to  
5 the clinical study. We have a substantial number of  
6 difficult questions for panel discussion, so I want to  
7 move through our presentation as quickly as possible.

8           I would like to acknowledge the people who  
9 helped me on this project. I had three engineers and  
10 three clinicians who provided input as well as Dr. Li,  
11 the statistician. I reviewed the remainder of the  
12 information in the submission as well as coordinating  
13 the reviews from the team members.

14           The next several slides detail  
15 configurations and sizes of the stent and embolic  
16 protection device that the sponsor proposes to offer  
17 for sale. The OTW, over the wire, configuration will  
18 be offered in either 6 or 5.5 french profile with the  
19 larger profile being for the larger stent diameters.  
20 Stent diameters in the OTW configuration will range  
21 from 5 to 10 millimeters in both tapered and straight  
22 configurations.

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1           The sponsor also makes an RX, rapid  
2 exchange, configuration that is compatible with a 0.14  
3 inch guidewire rather than the 0.18 inch needed for  
4 the OTW version in the same sizes as the OTW minus the  
5 tapered. However, due to a recent development, we are  
6 not considering this configuration today.

7           Similar to the stent, the ANGIOGUARD XP  
8 Emboli Capture Guidewire will also be made in both an  
9 OTW and an RX configuration. Filter sizes in both  
10 configurations will range from 4 to 8 millimeters.  
11 Again, the RX configuration will not be considered  
12 today.

13           There have been some recent developments  
14 relating to the RX configurations. The sponsor  
15 submitted an unsolicited amendment to the PMA just two  
16 weeks ago which proposed a change in the Instructions  
17 for Use for these devices. What prompted this  
18 submission were complaints received by Cordis relating  
19 to air being entrained in the RX configuration when  
20 used off-label in carotid and other indications.

21           While many of these instances resulted in  
22 no injury to the patient, there were a few that

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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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