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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

NEUROLOGICAL DEVICES PANEL  
FIFTEENTH MEETING

10:00 a.m.

Thursday, November 16, 2000

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[All Open Session Speakers had PowerPoint Presentations.]

P R O C E E D I N G S

1  
2 MS. SCUDIERO: Good morning, everyone. I'm Jan  
3 Scudiero. I'm the Executive Secretary of this panel, and  
4 I'm also the Classification/Reclassification Team Leader in  
5 the Division of General, Restorative and Neurological  
6 Devices.

7 I'd like to remind all of you, if you haven't  
8 already done so, to please sign in at the door. There's  
9 agenda information at the door, and there's also information  
10 about how to order a transcript, if you wish one, after the  
11 meeting.

12 I am required to read the conflict of interest  
13 statement into the record, but before I do that, I wanted to  
14 ask all those who are speaking in the open public hearing  
15 and the industry portions of the meetings, if you're  
16 bringing your own computer, could you please be ready, have  
17 it ready to go when your time comes up? I've been in  
18 contact with everyone so you know about where you are in the  
19 program. And the person to see is Neil Ogden. Neil, would  
20 you just raise your hand a minute, please? So bring your  
21 computer over to Neil, and he'll take care of you. Thanks a  
22 lot.

23 And now the conflict of interest statement: The  
24 following announcement addresses conflict of interest issues  
25 associated with this meeting and is made part of the record

1 to preclude even the appearance of an impropriety.

2 To determine if any conflict existed, the agency  
3 reviewed the submitted agenda and all financial interests  
4 reported by the committee participants. The conflict of  
5 interest statute prohibits special government employees from  
6 participating in matters that could affect their or their  
7 employer's financial interest. However, the agency has  
8 determined that participation of certain members and  
9 consultants, the need for whose services outweighs the  
10 potential conflict of interest involved is in the best  
11 interest of the government.

12 Waivers have been granted for Drs. Kyra Becker,  
13 Richard Fessler, James Grotta, and Justin Zivin for their  
14 interests in firms and issues that could potentially be  
15 affected by the panel's deliberations. The waivers allow  
16 these individuals to participate fully in today's  
17 discussions. A copy of these waivers may be obtained from  
18 the agency's Freedom of Information Office, Room 12A15 of  
19 the Parklawn Building.

20 We would also like to note for the record that the  
21 agency took into consideration other matters regarding  
22 several panelists. Drs. Thomas Brott, Everton Edmundson,  
23 and Cedric Walker reported past or current interests in  
24 firms at issue, but in matters that are not related to  
25 today's agenda. Therefore, the agency has determined that

1 they may participate fully in the panel's deliberations.

2 Drs. Becker, Grotta, and Zivin reported past  
3 interests in firms and issues for matters related to today's  
4 discussion. Since the agenda involves only general matters,  
5 the agency has determined that Drs. Grotta and Zivin may  
6 participate in all discussions, and I believe Dr. Becker's  
7 name was inadvertently omitted right there.

8 In the event that the discussions involve any  
9 other products or firms not already on the agenda for which  
10 an FDA participant has a financial interest, the participant  
11 should excuse himself or herself from such involved and the  
12 exclusion will be noted for the record.

13 With respect to all other participants, we ask in  
14 the interest of fairness that all persons making statements  
15 or presentations disclose any current or previous financial  
16 involvement with any firm whose products they may wish to  
17 comment upon.

18 Thank you. And now I'll turn over the meeting to  
19 our Chairman, Dr. Alexa Canady.

20 CHAIRPERSON CANADY: Good morning. My name is  
21 Alexa Canady, and I'm the Chairperson of the Neurological  
22 Devices Panel. I'm professor of neurosurgery at Wayne State  
23 University and chief of neurosurgery at the Children's  
24 Hospital of Michigan, and I'm primarily a pediatric  
25 neurosurgeon.

1 In the first part of our meeting today, the panel  
2 will be making recommendations to the Food and Drug  
3 Administration on the design of clinical trials for devices  
4 to treat and prevent stroke and for devices to provide  
5 cooling neuroprotection during the treatment of stroke.

6 In the second part of the meeting, the panel will  
7 make recommendations on the design of clinical trials for  
8 hypothermia devices to provide neuroprotection during other  
9 neurosurgical procedures.

10 Before we begin the meeting, I'd like the  
11 opportunity to introduce our panel. I'd like to have them  
12 introduce themselves and their affiliation and area of  
13 expertise, starting to my left with Sally.

14 MS. MAHER: Sally Maher, Industry Representative,  
15 Director of Regulatory Affairs and Clinical Research, Smith  
16 & Nephew.

17 DR. WOZNER: Anne Wozner. I'm an assistant  
18 professor in the School of Nursing at the University of  
19 Texas-Houston.

20 DR. EDMUNDSON: I'm Tony Edmundson. I specialize  
21 in neurology, neuro-oncology, and pain management, from  
22 Houston.

23 DR. ROSSEAU: Gail Rosseau. I'm a neurosurgeon at  
24 CINN, Rush University in Chicago. I specialize in cranial  
25 base surgery.

1 DR. WALKER: Cedric Walker. I'm a biomedical  
2 engineer, professor of biomedical engineering at Tulane  
3 University in New Orleans.

4 DR. BECKER: Kyra Becker. I'm a critical care and  
5 stroke neurologist at the University of Washington.

6 DR. HURST: Robert Hurts. I'm an interventional  
7 neuroradiologist at the University of Pennsylvania.

8 DR. FESSLER: Richard Fessler, recently professor  
9 of neurosurgery at the University of Florida, just recently  
10 joined the CINN group, and professor at Rush Medical School  
11 at Chicago, and I specialize primarily in spine surgery.

12 DR. ZIVIN: Justin Zivin. I'm professor of  
13 neurosciences at the University of California-San Diego.

14 DR. GROTTA: Jim Grotta. I'm professor of  
15 neurology and Director of the Stroke Program at the  
16 University of Texas, Houston, medical school.

17 DR. KU: I'm Andrew Ku. I'm an interventional  
18 neuroradiologist at Allegheny General Hospital in  
19 Pittsburgh, Pennsylvania.

20 DR. BROTT: Tom Brott, professor of neurology,  
21 Mayo Medical School, clinical trials and cerebrovascular  
22 disease.

23 DR. MARLER: John Marler, Associate Director for  
24 Clinical Trials at the National Institute of Neurological  
25 Disorders and Stroke.

1 DR. WITTEN: Celia Witten, the Division Director  
2 of the Division of General, Restorative, and Neurological  
3 Devices at FDA. I'm the FDA representative at the table.

4 CHAIRPERSON CANADY: We'd like to, of course,  
5 thank the panel for taking the time to come to our meeting  
6 today and participate in this important business. For the  
7 record, a voting quorum is present, as required by 21 CFR,  
8 Part 14.

9 Before we begin the first topic, Mr. Stephen  
10 Rhodes, chief of the Plastic and Reconstructive Surgery  
11 Devices Branch, will provide an update on neurological  
12 devices activities since our last meeting on May 11, 2000.

13 MR. RHODES: Thank you, Dr. Canady. I am Stephen  
14 Rhodes. I am the branch chief of the Plastic and  
15 Reconstructive Surgery Devices Branch here in the Division  
16 of General, Restorative, and Neurological Devices. I'm  
17 going to give you a brief update.

18 CHAIRPERSON CANADY: You're a little bit tall for  
19 our microphone. If you could bend down a little bit? I  
20 think people are having a little trouble hearing you in the  
21 back.

22 MR. RHODES: Okay. This panel last met in May of  
23 this year and recommended that the Cordis Trufill  
24 cyanoacrylate PMA application for arteriovenous  
25 malformations was approvable on condition that the sponsor

1 modify their labeling, physicians undergo training before  
2 using the product, and the results of ongoing testing be  
3 submitted. This product was approved on September 25th of  
4 this year.

5 The panel met back in September of 1999 and made  
6 recommendations on the draft neurological embolization  
7 guidance document. This guidance document has been revised  
8 based on your recommendations and public comments and is  
9 available on the FDA Internet Web page.

10 Also at the September 1999 meeting, the panel  
11 recommended that the totally implanted spinal cord  
12 stimulators be reclassified from Class III to Class II. The  
13 notice of panel recommendation was published in the Federal  
14 Register on September 6th of this year, with a comment  
15 period ending November 3rd.

16 Now I'd just like to mention a couple of personnel  
17 moves in the division and the office since we last met.

18 Jim Dillard, who was the Deputy Division Director  
19 of DGRND, has moved to be the Director of the Division of  
20 Cardiovascular and Respiratory Devices. Mark Melkerson, who  
21 was the orthopedics branch chief in our division, is now the  
22 Deputy Director in our division. Russ Pagano, who was the  
23 branch chief of the Restorative Devices Branch in our  
24 division, has moved down to Division of Cardiovascular and  
25 Respiratory Devices to be a branch chief down there. And in

1 the interim, while we're selecting a replacement for Dr.  
2 Pagano, Diane Mitchell is the acting branch chief of the  
3 Restorative Devices Branch.

4 I want to thank you again for your participation  
5 in today's meeting, and, lastly, I would like to introduce  
6 our new Office Director, Dr. Bernie Statland, who would like  
7 to say a few words. Thank you.

8 DR. STATLAND: Good morning. I looked at the  
9 calendar today, and I realized it's my fourth-month  
10 anniversary, so I'm relatively new. I've been at the FDA  
11 for four months, and I'm the Director of the Office of  
12 Device Evaluations. I'd like to say a few off-the-cuff  
13 remarks, and then I'll read what I have out here.

14 First of all, I really want to, on behalf of the  
15 FDA, acknowledge all the participants at this meeting. I  
16 think it's a most timely get-together where representatives  
17 from academia, the clinical side, industry, and other  
18 observers deal with this very perplexing and important  
19 issue.

20 I was very fond of my grandfather, and he died in  
21 1959 of a stroke, and I remember a few years earlier  
22 visiting one of the relatives who always showed sign of  
23 stroke. And here, 40 years later, I feel very fortunate to  
24 be in a position where the technology has advanced and  
25 intelligent people can get together to discuss strategies

1 and opportunities that may help so that the future may be  
2 different from the past. So I just wanted to say that on a  
3 personal level as we embark upon this very important event.

4 But I also am here to share some commendations and  
5 awards to individuals who have participated so well in the  
6 advisory panel. We so much depend upon all of you, your  
7 time, your expertise, your commitment, your careful  
8 assessment of the situations and to give us the best that  
9 you have that will help us make decisions. So today I do  
10 have the great pleasure to present letters and plaques of  
11 appreciation to four of you for your faithful service in  
12 assisting our agency in its mission to protect and promote  
13 the public health.

14 The work that all of you do is a most valuable  
15 service to our country, and I will read a letter that Dr.  
16 Jane Henney, the Commissioner of the FDA, wrote, and also  
17 give appropriate plaques to four individuals. Let me read  
18 the letter first, and then I will acknowledge it  
19 appropriately. And the first one is to our Chair, of  
20 course.

21 "Dear Dr. Canady: I would like to express my  
22 deepest appreciation for your efforts and guidance during  
23 your terms as a member and Chair of the Neurological Devices  
24 Panel of the Medical Devices Advisory Committee. The  
25 success of this committee's work reinforces our conviction

1 that responsible regulation of consumer products depends  
2 greatly on the participation and advice of the non-  
3 governmental health community. In recognition of your  
4 distinguished service to the Food and Drug Administration, I  
5 am pleased to present you with the enclosed certificate.  
6 Jane E. Henney, Commissioner of Food and Drugs."

7 So the first plaque--I guess my assistant will  
8 give that to you--will go to Dr. Canady.

9 CHAIRPERSON CANADY: Thank you very much.

10 DR. STATLAND: And the second, who also is leaving  
11 after a period of time, is Dr. Edmundson.

12 Dr. Anne Wozner.

13 And Sally Maher.

14 [Applause.]

15 CHAIRPERSON CANADY: Our class graduated.

16 We're going to go ahead now and present the FDA  
17 presentation and move on to the subject matter: the  
18 treatment and prevention of stroke. Our first presentation  
19 from the FDA will be Ms. Janine Morris introducing the  
20 topic.

21 MS. MORRIS: Good morning. My name is Janine  
22 Morris, and I'm a senior reviewer for the Division of  
23 General, Restorative, and Neurological Devices in the Office  
24 of Device Evaluation at CDRH. I'm also the division point  
25 of contact for neurovascular devices.

1 Today I plan to briefly describe the scope of this  
2 panel meeting today and briefly discuss some of the  
3 background that led to organizing this meeting. I will  
4 conclude with an overview of the targeted panel questions  
5 that will be the focus of your discussion later today.

6 We have called this meeting to address two general  
7 issues--acute ischemic stroke and hypothermia for  
8 neuroprotection--because we foresee the emergence of device  
9 modalities in the treatment of and prevention of acute  
10 ischemic stroke and the use of cooling devices for  
11 neuroprotection in various patient populations.

12 It is the goal of this meeting today to discuss  
13 how to study these device modalities and their respective  
14 targeted patient populations.

15 We have structured the panel meeting into two  
16 separate sessions.

17 The first session will focus on endovascular  
18 therapies or treatment for cerebrovascular disease,  
19 specifically endovascular treatment of acute ischemic stroke  
20 and prevention of recurrent events in patients with  
21 completed stroke or resolution of transient ischemic  
22 attacks.

23 The second portion of the panel will address  
24 devices designed to induce hypothermia for neuroprotection  
25 for indications including cardiac arrest, traumatic head

1 injuries, stroke, and aneurysm surgery.

2 In accordance with the agenda, I will present  
3 FDA's perspective on the emergence of endovascular therapies  
4 for the prevention and treatment of acute ischemic stroke  
5 and then summarize by outlining several general questions we  
6 are asking you to address and make recommendations regarding  
7 clinical trial design for the treatment modalities.

8 There are other very important topics associated  
9 with the treatment and prevention of stroke including the  
10 current work being done with the NIH-sponsored CREST trial  
11 as well as device modalities to treat hemorrhagic stroke and  
12 other cerebrovascular disease.

13 However, the focus of the discussion for the first  
14 session is intended to address the clinical trial design  
15 considerations of potential endovascular therapies of the  
16 intracranial arteries in the prevention and treatment of  
17 ischemic stroke. We hope that you will keep that in mind  
18 during your discussion.

19 Atherosclerosis of the major intracranial arteries  
20 is an important cause of ischemic stroke. It is estimated  
21 that up to 10 percent, or 40,000 per year, of ischemic  
22 strokes in the United States are related to disease  
23 involving the major intracranial arteries. Treatment of  
24 patients with symptomatic intracranial atherosclerosis falls  
25 into two broad categories.

1           The first category is the prevention of recurrent  
2 events in patients with completed stroke or TIA resolution.  
3 Current medical intervention to prevent ischemic events is  
4 medical antiplatelet therapy.

5           Endovascular treatment of atherosclerosis is  
6 widely used in the coronary and peripheral arteries and  
7 include stenting and percutaneous transluminal angioplasty.  
8 As a result of the successes developed in the cardiovascular  
9 area, there is an emergence of cardiovascular device designs  
10 being modified for intracranial arteries. And the clinical  
11 literature has reported the use of stent and balloon  
12 placement in the intracranial arteries using modified  
13 stents, catheters, and delivery systems.

14           The second category is the treatment of acute  
15 ischemic stroke. Presently, the only FDA-approved treatment  
16 of acute ischemic stroke is the intravenous delivery of tPA,  
17 tissue plasminogen activator.

18           The literature has described interest and attempts  
19 to use various endovascular methods in the management of  
20 acute stroke including laser thrombolysis devices,  
21 mechanical thrombectomy devices, as well as other physical  
22 means to disrupt a clot, for example, snares, catheters, and  
23 guidewires.

24           As devices are modified or new devices are  
25 developed for use in the intracranial circulation, treatment

1 paradigms, including some combination of mechanical  
2 thrombectomy or thrombolysis, PTA, and stenting, are  
3 evolving.

4           FDA believes that the clinical trial issues such  
5 as patient population, clinical endpoints, time of  
6 treatment, combination therapies, and identification of  
7 controls require early consideration for the regulatory  
8 process of evaluating, the safety and effectiveness of these  
9 future device modalities.

10           We have provided you with a list of five questions  
11 in your packet and ask that your recommendations be  
12 structured into two parts that are related to: one, the  
13 endovascular therapies for the prevention of stroke, for  
14 example, intracranial stenting and angioplasty; and, two,  
15 endovascular therapies for the treatment of stroke, for  
16 instance, thrombectomy and clot disruption devices such as  
17 laser thrombolysis.

18           Now I would like to just briefly review each of  
19 the questions that you will be discussing later on in the  
20 day.

21           The first question is for you to discuss what  
22 characteristics should be considered in defining the  
23 appropriate patient populations for each respective  
24 treatment modality. That includes when considering  
25 inclusion and exclusion criteria in the design of the study,

1 what specific criteria should be considered: symptomatic,  
2 non-symptomatic, primary and/or secondary treatment, the  
3 vascular region of treatment, the degree of collateral  
4 circulation, thrombus composition, as well as length of time  
5 after stroke treatment.

6           Additionally, provide considerations of specific  
7 patient groups that may require assessment of their own data  
8 since the outcome could be expected to be different from the  
9 larger more homogeneous group.

10           Finally, provide considerations for the role of  
11 imaging techniques used to diagnose and assess stroke when  
12 describing the patient population for the trial.

13           Question 2: Discuss what characteristics should  
14 be considered in defining appropriate control populations  
15 for each respective treatment modality.

16           Question 3: Discuss what considerations need to  
17 be incorporated when identifying appropriate outcome  
18 measures to establish safety and effectiveness. What  
19 specific considerations are needed to establish safety?  
20 What specific considerations are needed to establish  
21 effectiveness, that is, the primary efficacy endpoint? And,  
22 finally, what secondary safety and effectiveness measures  
23 should be assessed?

24           Four, what sources of bias and confounding factors  
25 should be considered in the design of these studies? How

1 should the combination therapies be considered with respect  
2 to trial design? And how should concomitant medication be  
3 considered with respect to trial design?

4 And, lastly, when should evaluation of these  
5 outcome measures be made? When should the primary and  
6 secondary effectiveness endpoints be measured? And what  
7 length of follow-up is appropriate to establish the safety  
8 of these therapies?

9 Now, again, we will first have the open session,  
10 but we wanted to review these questions for you, and I'll  
11 leave it to Dr. Canady to continue. Thank you.

12 CHAIRPERSON CANADY: Thank you very much, Ms.  
13 Morris.

14 We're going to move at this point to the first  
15 open public hearing on the design of clinical trials for  
16 devices to treat and prevent stroke and for devices to  
17 provide cooling neuroprotection during the treatment of  
18 stroke.

19 I'd like to remind the speakers of several things.  
20 One, we would appreciate it if you would speak carefully  
21 into the microphone as there will be a transcript created  
22 from these presentations, and it's very difficult without  
23 the microphone.

24 We also would ask that you name yourself, your  
25 affiliation, and also list your financial interest in the

1 materials today.

2           Finally, I would remind you that there is no  
3 public participation in these hearings, although they are  
4 open, obviously, for observation, except at the specific  
5 request of the panel.

6           We have a number of speakers who will speak today.  
7 They have been informed in advance that there is a ten-  
8 minute time limit. There is a timer today because of the  
9 number of speakers. We have divided the timer so you will  
10 be in the green light for eight minutes, the yellow light is  
11 to warn you that your time is coming, and I expect that you  
12 will, in fact, stop when the red light comes on. If you  
13 need help, I will provide it.

14           [Laughter.]

15           CHAIRPERSON CANADY: Our first speaker this  
16 morning is Dr. Christopher Loftus. He is representing the  
17 American Association of Neurological Surgeons and the  
18 Congress of Neurological Surgeons.

19           DR. LOFTUS: Thank you very much. She's asked me  
20 to wait until she finished with the handouts. Is that  
21 acceptable to you?

22           CHAIRPERSON CANADY: Sure. We're not trying to  
23 stint discourse, just make it timely.

T1B 24           DR. LOFTUS: Thank you very much for the  
25 introduction and for the opportunity to speak. My name is

1 Christopher Loftus. I'm the Chairman of the Department of  
2 Neurosurgery at the University of Oklahoma, and I represent  
3 the Joint Section on Cerebrovascular Surgery, which I served  
4 as the past Chairman.

5 I formulated this talk hopefully to discuss  
6 exactly what you have requested, and that is, how should we  
7 design clinical trials for endovascular interventions for  
8 intracranial atherosclerosis, and just touch briefly upon  
9 extracranial atherosclerosis.

10 So we must address, according to the charge that I  
11 found on your website last weekend, prevention, intracranial  
12 procedures, endovascular procedures following resolution of  
13 a stroke. The patient is now okay, and we're trying to  
14 prevent ongoing ischemic problems in the future. And,  
15 second, the quite different topic, acute treatment of acute  
16 ischemic stroke. Two very different questions and two very  
17 different study designs.

18 This is familiar, I'm sure, to most of you but let  
19 me just go through it again regarding clinical trials  
20 methodology and how the power of clinical trials, our  
21 ability to influence in my own experience, surgical  
22 practice. A Level 1 trial, of course, is what we all want  
23 to see: a randomized trial with a low likelihood for false  
24 positive or negative errors. A Level 2 trial is also  
25 randomized, but with a higher likelihood. And beyond this,

1 we get into decreasing levels of certainty of evidence:  
2 Level 3, a nonrandomized concurrent cohort trial; Level 4, a  
3 nonrandomized trial with historical cohorts; and level 5,  
4 representing simple case series reports, a very low validity  
5 for clinical decisionmaking.

6 I would emphasize to you again that in the  
7 experience of us as--in our experience as cerebrovascular  
8 surgeons, randomized cooperative trials--and I talk about  
9 government-funded trials, which may be somewhat different  
10 than what we address a little bit today. Government-funded  
11 trials have changed the practice of cerebrovascular surgery,  
12 specifically the EC-IC bypass trial, which is the reason why  
13 when we talk about an endovascular intracranial trial, there  
14 is no proposed surgical arm to be discussed because EC-IC  
15 bypass is basically knocked out for treatment of ischemic  
16 intracranial disease.

17 The NASCET trial for carotid surgery has clearly  
18 influenced our practice; likewise, I would suggest to you,  
19 although somewhat more controversial, the ACAS trial has  
20 significantly influenced carotid surgery. And I would  
21 suggest previous studies are virtually obsolete when Level 1  
22 studies become available, including all those lesser levels  
23 of evidence that I mentioned.

24 Specific aspects of trial design which we're asked  
25 to address today: first of all, the first issue, prevention

1 following resolution of a stroke. These patients are okay,  
2 and we just want to find a way to keep them from having an  
3 ongoing problem regarding an endovascular intervention. I  
4 would suggest to you and I would suggest the Joint Section  
5 would suggest to you that symptomatic patients should  
6 clearly be studied first. It is very tempting based on  
7 angiographic appearance to consider manipulations  
8 intracranially and intracranial endovascular procedures for  
9 asymptomatic patients. I don't believe that's what you're  
10 about today from my understanding, and I would suggest that  
11 clearly the efficacy of an intracranial endovascular  
12 procedure, which, to my mind, to our minds, is a high-risk  
13 and innovative procedure, should be proven in patients who  
14 are at higher risk, i.e., symptomatic patients, before any  
15 asymptomatic trial is considered.

16 This is the same situation we faced in aneurysm  
17 surgery. This is the same situation we faced in carotid  
18 surgery. The risk/benefit ratio is clearly much thinner  
19 margin for asymptomatic patients.

20 The study design for a therapy--for an  
21 endovascular therapy for prevention following stroke  
22 resolution should be endovascular versus best medical  
23 therapy alone. Because of the EC-IC bypass failure, there  
24 is no surgical arm proposed in any trial for endovascular  
25 intracranial work. There is likewise no real possibility of

1 a sham procedure. So the trial design should be--it's not  
2 endovascular versus medical therapy. It's much as it was in  
3 the carotid trials, which are surgery plus aspirin versus  
4 aspirin alone. It has to be endovascular plus medicine  
5 versus medicine alone. And this is an important  
6 distinction.

7           The technology, I would suggest to you, needs to  
8 be stabilized, and I'm not here for industry and I'm not an  
9 interventionalist. So I don't know as much about the  
10 technology as most of the other people in this room. But I  
11 would suggest the technology needs to be stabilized before  
12 embarking on a trial to ensure the durability of the  
13 results. And we see this once again with aneurysm surgery  
14 where the technology is constantly evolving, and if one  
15 technology is proven in the randomized trial and then it  
16 changes, how much can those results be extrapolated to a new  
17 technology? So I would suggest it should be stabilized to  
18 ensure the durability.

19           Now, how should the trials be designed regarding  
20 endpoints and complications? And this is first for, once  
21 again, intracranial endovascular procedures for prevention,  
22 and it's the same for complications but it differs in terms  
23 of endpoints for the two different trials I would suggest to  
24 you. Complications, I started with wound complications, of  
25 course. This is an endovascular procedure, wound

1 complications, and then immediate outcome much like--I just  
2 took this from the carotid trials. TIA, stroke, or death  
3 within 30 days. These are your complication endpoints,  
4 medical versus surgical therapy--medical versus endovascular  
5 therapy, I should say.

6 Now, follow-up endpoints, I would suggest that  
7 since this is a prevention trial, you're going to need a  
8 design at least five years of follow-up, much like were  
9 designed in the carotid trials, although, as you know, they  
10 were stopped early because it wasn't necessary to go to five  
11 years to get a significant difference.

12 The endpoints are TIAs and/or stroke or death.  
13 And an assessment, I would suggest, by an independent  
14 neurologist be performed every three months. Potentially  
15 this could be blinded, and, of course, like in any  
16 randomized cooperative trial, there can be no crossovers.  
17 So no patients who go on to have negative endpoints should  
18 be allowed to cross over.

19 Now, what about the second issue, treatment of  
20 acute ischemic stroke? For endovascular procedures, you can  
21 talk a little bit about extracranial here, and I think  
22 you're here today talking about intracranial. But I would  
23 just suggest to you that if you have extracranial acute  
24 stroke, you could have a three-arm trial, i.e., endovascular  
25 plus medicine, medicine, and an acute surgical intervention.

1 Right now no real surgical trial has been done--we have  
2 surgical trials for carotids but nothing for acute stroke.  
3 So you could have a three-arm trial. Intracranial, there is  
4 no three-arm. There's no surgical strategy for intracranial  
5 acute stroke. It is medicine plus endovascular or  
6 endovascular alone.

7 The trial design, we heard a little about tPA in  
8 the introductory comments. The trial design needs to  
9 replicate the tPA data because they are the gold standard,  
10 i.e., entry criteria must replicate, i.e, within two or  
11 three hours, fast entry of patients into the system. What's  
12 it mean? Many patients, like tPA, will not qualify for  
13 inclusion in the study. Most will not because they can't be  
14 assessed that quickly.

15 Technology, I would suggest to you again, must be  
16 stabilized and must be reproducible, and much like surgical  
17 trials, the interventionalist must be certified by a panel  
18 to ensure high quality in the participants of the study.

19 Regarding follow-up for acute stroke  
20 complications, just like the first design: wound  
21 complications, TIA, stroke, or death within 30 days.

22 Endpoints are different from the first design, and  
23 this is because you can not only have a negative endpoint,  
24 but you can have a positive endpoint here. The patient gets  
25 better. So positive, immediate or early neurological

1 improvements, means hourly or daily neurological assessment  
2 for the first two weeks, and I take this from the IHAST2  
3 design, which is our hypothermia aneurysm trial that I'll  
4 talk about this afternoon. Negative is the same thing,  
5 TIAs, stroke, or death. Assessment every three months by  
6 hopefully a blinded and independent neurologist.

7           Common features to both trials and intention-to-  
8 treat analysis, i.e., pretreatment neurological declines.  
9 Once you get randomized--one more slide, if I may. Once you  
10 get randomized, you're charged to the randomized group, so  
11 you need to be treated quickly or you can have patients in  
12 an arm who didn't get the treatment but have a negative  
13 outcome and decrease the validity of that arm.

14           Randomized but not blinded for treatment,  
15 certified interventionalists, blinded follow-up is possible,  
16 and I emphasize no crossovers.

17           In conclusion, the opinion of the Joint Section,  
18 as hopefully I can express to you, properly designed and  
19 conducted trials change the practice of cerebrovascular  
20 therapy. We have seen this. Government-funded trials with  
21 independent monitoring clearly have the greatest validity as  
22 Level 1 evidence. And we feel strongly that treatment of  
23 intracranial atheromatous disease is one of the major  
24 frontiers in stroke research as proposed today and clearly  
25 should be a top priority for study.

1 Thank you.

2 CHAIRPERSON CANADY: Thank you very much, Dr.  
3 Loftus.

4 Is Dr. Connors available and ready? Thank you.  
5 Don't forget to introduce yourself as we change the  
6 computers here.

7 Dr. Connors will be speaking for the American  
8 Society of Interventional and Therapeutic Neuroradiologists.  
9 He is director of Interventional Radiology at INOVA at  
10 Fairfax Hospital.

11 DR. CONNORS: It's actually Inova Fairfax  
12 Hospital, and I get grief all the time for that not being  
13 said right, when I say it wrong. I'm also representing the  
14 American Stroke Association today. Dr. Loftus did an  
15 excellent job of presenting some fundamental data on  
16 intracranial atherosclerotic disease. I'm going to address  
17 more of the philosophy of acute stroke therapy, simply due  
18 to the fact that there's no way that I can answer all the  
19 thousands of questions having to do with certain of the  
20 trial designs. So I'll just try to give an overview of the  
21 viewpoint of the American Society of Interventional and  
22 Therapeutic Neuroradiology as well as the American Stroke  
23 Association concerning acute stroke.

24 Basically, the reason we're doing all this is  
25 because of the situation with stroke. We know that the

1 mortality of true middle cerebral artery clot is  
2 approximately 30 percent in a month. Morbidity is severe;  
3 only about 10 to 30 percent of these patients do reasonably  
4 well at all, and the ones that really do well are the ones  
5 that really don't have an MCA occlusion.

6           Intracranial stenosis, a quick word about this.  
7 This is the most dangerous neurovascular condition I  
8 personally see. It is more cumulatively dangerous than  
9 carotid stenosis. It is more dangerous than AVMs. It is  
10 more dangerous than aneurysms. It is more dangerous than  
11 dural AV fistulas. This is the most dangerous disease that  
12 I routinely see. That's why we need to address this, and I  
13 agree with the previous statements concerning symptomatic  
14 disease as being the targeted population.

15           As far as emergency stroke therapy goes, what  
16 we're trying to do is rescue salvageable brain, and the  
17 problem is that neuroprotective drugs have been proven to be  
18 ineffective by over \$1 billion of medical expenditure.  
19 That's a problem. And it is a crisis in the neurological  
20 community in that they are now funding trials that the  
21 pharmaceutical companies are tired of spending money on.  
22 And, fundamentally, the only procedure that has worked for  
23 stroke therapy is revascularization by whatever means  
24 possible. Get rid of the occlusion. The one hope that we  
25 have in the future is possibly some sort of physical

1 neuroprotection, which is hypothermia.

2           The interesting thing about this is that the NINDS  
3 trial was based on the fact that there was no proven  
4 ischemia. It was purely symptomatic based with no evidence  
5 of any physical defect, whereas the trials now are going to  
6 have physical evidence of defect, in other words, occlusion.  
7 You're going to have a visible target for therapy so we can  
8 measure that. But we cannot ignore the fact that what we  
9 have to come out with is positive clinical outcomes.

10           The ASITN and SCVIR feel that active intervention  
11 is appropriate for stroke and that we can now justify this,  
12 and we have an official statement that you all have been  
13 provided that is in your packet, which will be published  
14 simultaneously in two medical journals coming up in the next  
15 couple of months.

16           The current situation is that in the United States  
17 there's no firm count, but polling indicates that there are  
18 over 1,000 interventional stroke procedures performed now  
19 currently. This is just simply catheter-based fibrinolysis  
20 with combination medical therapy. I don't think it is  
21 appropriate, unfortunately, for there to be any single  
22 therapy these days for most anything. We're going to have  
23 combinations of drugs and devices almost from now until  
24 eternity.

25           As said previously, clinical outcome is what my

1 society and the American Stroke Association both believe is  
2 the fundamental outcome that we have to look.  
3 Recanalization is wonderful, but in the coronary literature  
4 it has been shown that recanalization sometimes makes things  
5 worse. You can't just grind up clot and send it downstream.  
6 You have to have getting rid of the clot to get positive  
7 benefit. And we've shown this with no reflow phenomenon in  
8 the cardiology literature and elevated triponins now that  
9 are showing eventually increased MIs from just grinding up  
10 clot and sending it downstream.

11 So patient controls, what are we supposed to do  
12 with that? Well, this is a difficult issue for all of us,  
13 but the ASITN and the SCVIR now feel that we cannot just  
14 ignore patients that come in. We know what the outcome is  
15 going to be if they have an insult. The NINDS trial was  
16 based on the fact that we knew that after a severe insult  
17 over one or two hours, they had an extremely high percentage  
18 of this being a permanent deficit. So this means that we  
19 have justification for going ahead and treating.

20 Now, we can possibly get MRA and CTA at  
21 institutions that offer no intervention, or if the  
22 interventionalist ain't around, then maybe we can use  
23 concurrent patients in the same institution for the same  
24 situation. But it is difficult for me personally to ignore  
25 a patient that I'm looking at and just say, well, tough

1 luck, sucker, I'm not going to do anything to help you.

2 Device complications for new things coming up. We  
3 can look at direct evidence of vascular damage for these  
4 devices, which we can see with the resolution of our  
5 monitors. Direct evidence of subarachnoid bleed indicating  
6 vascular damage we can look at for these things. Indirect  
7 is statistical worsening of predicted infarcts, which is  
8 obviously a difficult thing to do. And also we can compare,  
9 as the previous speaker mentioned, a device versus a drug,  
10 and I think that this is potentially a decent way to go  
11 about some of these evaluations because that gives us a  
12 moral standing to judge previous effects without actually  
13 doing nothing.

14 Proven facts, as I said previously, is that  
15 devices and drugs are synergistic. The example of this is  
16 that stents have now been proven to require antiplatelet  
17 medications, and there are numerous articles written that  
18 actually coronary stents, it's unethical not to use  
19 antiplatelet medications and that stents are proven to be  
20 beneficial far more when used with antiplatelet medications.  
21 I think that is going to be absolutely the truth in the  
22 brain. As far as intracranial angioplasty, it's absolutely  
23 the truth that these things stimulate thrombus formation in  
24 a delayed fashion. I think we have to be aware that  
25 sometimes people have strokes in the recovery room after

1 they have these things. So we have to be aware that  
2 medication is beneficial for revascularization.

3 Our society hopes that there is an open-minded  
4 approach by the FDA as well as inter-communication between  
5 you all's various branches to somehow get together on  
6 working with devices and pharmaceuticals to be allowed to  
7 work together for an eventual positive benefit.

8 What we're trying to do is to gather data because  
9 we need data on this same thing, and the problem is that we  
10 don't have data, so our societies are forming a registry  
11 just to keep track of some of the outcomes of what we are  
12 now doing. I think it is necessary for us to find out how  
13 well we're doing and how well we can eventually improve  
14 this. As a famous politician once said, a million here and  
15 a million there and pretty soon you're talking real money.  
16 If we get some patients and enough of them, maybe we'll have  
17 some decent data, although everybody's doing something  
18 different.

19 But this goes along with the fact that our  
20 societies believe that interventional stroke therapy is  
21 warranted. Why are we having this problem? That's because  
22 of champions. Pharmaceuticals have champions, new drugs  
23 have champions in the pharmaceutical companies. Devices  
24 have champions in the device companies. But there are no  
25 champions for procedures. And we, the physicians, have to

1 be the champions simply for procedures, particularly when  
2 we're not even paid for most of these stupid things. So  
3 we're the ones that have to go to the trouble to do this,  
4 and so we urge the committee to be open-minded for some of  
5 the things that we're trying to get accomplished and to  
6 cooperate with industry.

7           Basically we're saying that we need all the help  
8 we can get, and we appreciate the opportunity to be able to  
9 address you today. Thank you.

10           CHAIRPERSON CANADY: Thank you very much. You  
11 were very well prepared, 12 seconds left.

12           [Laughter.]

13           CHAIRPERSON CANADY: You're the "A" recipient so  
14 far of the timing award.

15           Dr. Helmi Lutsep from the Oregon Stroke Center, if  
16 you'd set up and identify yourself and, again, any financial  
17 interests?

18           DR. LUTSEP: I'm Helmi Lutsep, a stroke  
19 neurologist at the Oregon Stroke Center, and our stroke  
20 center is involved with more trials using mechanical  
21 thrombolysis, as we call it, than probably any other center.  
22 We've also been involved in the design of a number of these  
23 trials. So that's the perspective that we bring.

24           Now, we've already seen that there are a number of  
25 questions raised by the FDA, and we find that all of the

1 others hinge upon certain ones of these. So I would like to  
2 address just three of the questions, referring especially to  
3 acute stroke treatment.

4 The first question is regarding the control  
5 population, and beginning with background regarding this,  
6 there is one main point that investigators at our  
7 institution and many others, both the neurologists and the  
8 neuro-interventionalists, find a placebo group unethical for  
9 intra-arterial trials. And we also lump the heparin  
10 treatment into this since the outcomes with heparin have  
11 been no better and in some cases worse than with placebo.

12 As we've already heard from the previous speaker,  
13 these are particularly large strokes. They occlude large  
14 vessels, and their median NIH Stroke Scale scores are much  
15 higher than we see in the intravenous trials.

16 Of the NINDS subgroup population with an NIH  
17 Stroke Scale score of 20 or more, a good size middle  
18 cerebral artery stroke, only 2 percent in the placebo group  
19 recovered, and this was only 8 percent in the tPA group. So  
20 we really have a need to want to treat these patients.

21 Also, the procedure is very labor-intensive.  
22 Sometimes there is a referring physician who first has to  
23 give up the patient to another institution for treatment,  
24 and a large group is involved in the treatment of these  
25 patients. So, again, the group is compelled to want to

1 treat.

2 And then, finally, we do have a positive intra-  
3 arterial trial that does suggest that treatment is of  
4 benefit.

5 So our recommendation is to use a historical  
6 control. As I've outlined, a placebo group is not an  
7 option, and also no approved therapy exists after three  
8 hours, and even that under-three-hour therapy was assessed  
9 in a different population of patients.

10 Now, within this framework of the historical  
11 control, there are two potential options for outcome  
12 measures: either angiographic or clinical. And unlike the  
13 previous speaker, we have actually come to find that there  
14 are many benefits to using an angiographic outcome.

15 First, it is more objective, that independent  
16 investigators can evaluate this. It's less affected by  
17 changing medical care practices. For example, even since  
18 the PROACT II trial was published, there has been increased  
19 attention given to increased glucose levels and the adverse  
20 effects that they have on outcome. So already the emphasis  
21 has been to treat these glucoses which may be changing our  
22 outcome in these patients.

23 It also avoids the dilemma and the ambiguities of  
24 clinical scale selection. We've had numerous trials  
25 already: the neuroprotectants, the IV, IA, thrombolysis

1 trials. Most of them have used varying clinical outcome  
2 scales, and even within these scales, used different values  
3 with which to assess outcome, sometimes making this clinical  
4 outcome measure difficult to interpret and not nearly as  
5 straightforward as it might appear.

6 And then, finally, last, but certainly not least,  
7 it requires a smaller number of patients to show power, to  
8 provide sufficient power. The PROACT II trial again  
9 provides an example. Even a center as active as ours  
10 produced approximately one patient or less a month for that  
11 trial with an M1 or M2 occlusion. tPA was approved toward  
12 the end of the PROACT II trial. We're concerned that we may  
13 be able to find even fewer patients to enroll into future  
14 trials.

15 So our recommendation is to use the angiographic  
16 outcome measure as a primary endpoint along with safety  
17 data, and then to use clinical efficacy as a secondary  
18 measure. And once we have this objective angiographic  
19 measure already in place, we do not believe that MRI or  
20 lesion volume studies are then necessary.

21 So given the need for, as we see it, a historical  
22 control and for angiographic data, this leads us to the  
23 PROACT II trial for the standard, but what we ask is that  
24 the studies look beyond the middle cerebral artery. For  
25 example, the internal carotid artery has a lower

1 recanalization rate than the MCA. This is suggested by a  
2 number of small studies. So if we were to compare MCA  
3 recanalization--or compare the ICA recanalization to the MCA  
4 data, we would be setting a higher standard, if anything.

5 So our recommendation here is that you do consider  
6 other vessels in addition to the middle cerebral artery and  
7 simply set the recanalization data or standard to PROACT II.  
8 This would allow us to offer treatment to a greater number  
9 of patients and, again, help to increase that all-important  
10 end value.

11 Thank you.

12 CHAIRPERSON CANADY: Thank you very much, Dr.  
13 Lutsep.

14 Our next speaker will be Dr. Alexander Norbash.  
15 Again, if you would identify yourself, your affiliations,  
16 and any financial interests?

17 DR. NORBASH: My name is Alexander Norbash. I'm  
18 the head of neuroradiology at the Brigham and Women's  
19 Hospital. I'm a practicing interventional neuroradiologist.  
20 I have been involved in the development and testing and  
21 implementation into practice of novel tools intended to  
22 treat stroke, and I'm here today to specifically ask that  
23 recanalization be considered an appropriate primary  
24 endpoint, to inform the committee that distal clot  
25 embolization on first glance is a low-risk consequence in

1 the hands of those of us who intentionally perform  
2 angioplasty of a clot, and that historical controls be  
3 considered in lieu of blinded randomization.

4 CHAIRPERSON CANADY: Do you have any affiliations  
5 other than Brigham?

6 DR. NORBASH: It is in the capacity of a  
7 transarterial stroke therapy researcher that I've been  
8 contacted by legal regulatory counsel for Ecos (ph)  
9 Corporation, manufacturers of a catheter that can be used to  
10 deliver a variety of diagnostic and therapeutic agents and  
11 for first-generation use to transarterially administer  
12 thrombolytics, to share my perspective as a researcher and  
13 clinician in this field. Ecos has modified an existing  
14 ticket which is taking me to San Francisco today. I am not  
15 accepting an honorarium. I am not on their Scientific  
16 Advisory Board, and I have not been a scientific or clinical  
17 counselor, nor do I have an equity position, stock options,  
18 or intellectual property shared with them.

19 CHAIRPERSON CANADY: I think that does answer the  
20 question.

21 [Laughter.]

22 DR. NORBASH: I have treated strokes in patients  
23 ranging in age from several months to the ninth decade. I  
24 have successfully treated speech disorders, paralysis, coma,  
25 and even patients who have absent cranial nerve responses,

1 suggesting brain death. Among the patients I have treated,  
2 I include nurses, school children, police officer, and at-  
3 home mothers.

4 In contrast to the gratitude I feel with  
5 successful procedures, I am more often than not unable to  
6 treat the majority of acute strokes to my satisfaction.  
7 Patients I have treated with deficits have died, many of  
8 them, and many of them are permanently institutionalized.  
9 When I am unsuccessful, I personally deal firsthand with the  
10 consequences of my failure.

11 There are few tools available for the treatment of  
12 stroke. Our conventional micro-catheters and thrombolytics  
13 fail to produce the desired result in up to 33 percent of  
14 the PROACT II patients. Please keep that in mind. I have  
15 resorted to balloon catheters, micro-snare, intracranial  
16 stents, and rheolytic catheters when I am desperate.

17 Our lack of success with primary intra-arterial  
18 thrombolysis is not unusual. We now have over 30 cases of  
19 shared intracranial angioplasty of clots with which we've  
20 successfully recanalized 25 of 30 vessels not responding to  
21 intra-arterial thrombolysis.

22 My disappointment in our inability to predict the  
23 result of chemical thrombolysis is compounded by my  
24 disappointment in our understanding for the basic principles  
25 of neuronal injury reparation in the envelope for treatment.

1 I'd like to take this opportunity to discuss three  
2 representative cases with good outcomes following  
3 unsuccessful catheter-based therapy necessitating  
4 alternative treatments.

5 The first is a 34-year-old patient presenting with  
6 coma who has occlusion of the superior sagittal sinus, the  
7 main venous drainage of the brain. This is confirmed  
8 angiographically, and we see a stasis of contrast in  
9 multiple parietal and post-frontal venous branches.

10 Intravenous thrombolysis on three occasions was  
11 unsuccessful. Patient remained in coma. Using a Possis  
12 AngioJet rheolytic device, superior sagittal sinus was  
13 reopened. Patient regained consciousness, left the hospital  
14 one week later with a mild upper monoparesis.

15 The second patient, 56 years old, paralysis of the  
16 right half of his body, inability to speak; using a snare,  
17 extracted a very dense clot that has (?) compatible with  
18 calcification in the left middle cerebral artery.

19 Thrombolysis was unsuccessful. Balloon angioplasty was  
20 unsuccessful. Rheolytic devices cannot reach this location  
21 currently.

22 CT angiogram confirms the finding. Diffusion MRI  
23 emergently shows that there is no irreversible tissue damage  
24 as of the time of the scan. The snare is engaged. The clot  
25 in this location is extracting it, and in the supraclinoid

1 internal carotid artery here. And the final image shows re-  
2 establishment of adequate(?) flow. The patient left the  
3 hospital four days later with no residual deficits. Stent  
4 technology has remarkably advanced.

5 This next patient is a 72-year-old gentleman who  
6 benefited from the placement of an intracranial stent. He  
7 did not respond to thrombolysis or to angioplasty. His  
8 right carotid is occluded at its origin. The left carotid  
9 is occluded immediately above the ophthalmic artery. A  
10 contour abnormality suggests a lesion in this location.  
11 Micro-catheter negotiated above that level shows patency of  
12 the intracranial vessels. Angioplasty performed at that  
13 level did not allow filling of the right hemisphere, and you  
14 can see that there is a residual stenosis in the  
15 supraclinoid position. In spite of pressure elevation,  
16 intracranial stent placed above the siphon in that location,  
17 improvement in supply with circulation restored to both  
18 hemispheres, patient left the hospital one week later with  
19 no residual deficits.

20 Randomized trials and outcome analysis are the  
21 gold standards of clinical research. We have small,  
22 individual, meticulously stratified patient pools exposed to  
23 each individual institution. As an example, in the PROACT  
24 trial, as Dr. Lutsep mentioned, average enrollment for each  
25 of the 54 high-volume centers over a 30-month period of time

1 was less than 0.1 patient per month, and that's why we have  
2 difficulty in parsing out meaningful information, even from  
3 large-scale trials at this point.

4 Again, 12,000 thousand patients were the input  
5 function; only 180 after 30 months at 54 cents came out and  
6 were enrolled in a trial.

7 Realizing the dramatic nature of stroke therapy  
8 complications and the terrible cost of long-term  
9 complications created with stroke interventions gone awry,  
10 those of us who are engaged in therapy accent and encourage  
11 the maintenance of a rigid safety standard above reproach to  
12 avoid any unacceptable complications, complications which we  
13 currently do see in European trials. This demands rigid and  
14 accountable bench-top and in vivo pre-patient testing.

15 So I am here specifically to ask that  
16 recanalization be considered an appropriate primary  
17 endpoint, to inform the committee that distal clot  
18 embolization is a low-risk consequence in the hands of those  
19 of us who have been experienced in its implementation by  
20 doing intentional clot angioplasty, and that historical  
21 controls be considered in lieu of blinded randomization to  
22 controls with stroke trials.

23 I thank the committee for granting me the  
24 opportunity to share my views.

25 CHAIRPERSON CANADY: Thank you very much, Dr.

1 Norbash.

2 Is Dr. Alberts with us?

3 Our next speaker will be Dr. Mark J. Alberts from  
4 Duke University.

5 DR. ALBERTS: Good morning. My name is Mark  
6 Alberts. I'm head of the stroke unit at Duke University  
7 Medical Center. I do not have any financial interests. I  
8 have been an investigator in two stent trials. I'm going to  
9 limit my remarks to talking about stenting of extracranial  
10 carotid disease, which I believe is the most common  
11 endovascular therapy now used for cerebrovascular disease.

12 Carotid endarterectomy is a good operation for  
13 carotid stenosis with the complication rates of 2 to 6  
14 percent. However, there are some possible advantages of  
15 carotid stenting over carotid endarterectomy. It may be  
16 less expensive. It may have reduced complications. It may  
17 have reduced costs. It may be an option for high-risk  
18 surgical patients. And it may be an alternative for  
19 patients who have surgically inaccessible lesions.

20 There seems to be a notion that there is no data  
21 from prospective, randomized trials of carotid stenting in  
22 the extracranial circulation, but that is not the case.  
23 There was a trial that was performed called the Schneider  
24 WALLSTENT Study. This was a prospective, randomized trial  
25 of carotid stenting versus carotid endarterectomy in

1 patients with symptomatic stenosis.

2           The study design is that this was a prospective,  
3 multi-center, randomized but non-blinded study. It included  
4 patients only with symptomatic carotid stenosis of 60 to 99  
5 percent by angiography using the NASCET criteria. Patients  
6 had to have a life expectancy of at least two years. All  
7 patients got aspirin, and those who got stented also got  
8 ticlopidine because the study was begun before Clopidogrel  
9 was approved.

10           In order to be enrolled in the study, the  
11 operators had to have a ten-patient stent run-in phase with  
12 a complication rate of 10 percent or less. The surgeon had  
13 to have a complication rate of 6 percent or less for  
14 endarterectomies at that institution.

15           The primary hypothesis of the study was that  
16 carotid stenting would be equivalent to endarterectomy in  
17 the patient population enrolled in the study. The 12-month  
18 endpoint rate for carotid stenting will be within 2 percent  
19 of the 12-month endpoint rate for endarterectomy, and the  
20 endpoint for the study was ipsilateral stroke, vascular  
21 death, or peri-procedure any stroke or any death.

22           The study was terminated early based on  
23 recommendations of the independent Data Safety Monitoring  
24 Board. A futility analysis showed essentially no chance of  
25 proving the primary hypothesis. Detailed results will be

1 presented at the American Heart Stroke Meeting in February  
2 of next year.

3           The study will be criticized because some will say  
4 that the study did not have a long enough training period to  
5 reduce complications, but all the operators had to do ten  
6 stent patients with only one complication or less. The  
7 study will be criticized because newer stent devices and  
8 techniques may reduce peri-procedure complications, and that  
9 may be true, but these newer devices and techniques have not  
10 been subjected to prospective, randomized trial.

11           The question will be asked: Are these results  
12 atypical of the overall stenting experience or typical?  
13 It's hard to know without further data from prospective  
14 studies. And the question will be raised, once these  
15 results are presented in February: Should there be a  
16 moratorium on stenting outside of prospective, randomized  
17 trials? Which I think is a reasonable question to ask based  
18 on the results that you'll see in February.

19           Worldwide stenting data focusing mostly on the  
20 extracranial carotid circulation from 36 centers, including  
21 over 5,000 procedures, have shown a technical success rate  
22 of 98.4 percent, 3.5 percent restenosis rate at 12 months,  
23 and 30-day complication rates of stroke and death of 5.1  
24 percent, which certainly approaches that seen in the NASCET  
25 trial. What is, however, important to note is that perhaps

1 the majority of patients included in this data were  
2 asymptomatic patients, whereas the patients in the NASCET  
3 were symptomatic. So you have data from many anecdotal,  
4 nonrandomized, nonmonitored trials showing a stroke and  
5 death rate at 30 days of almost 6 percent, which approaches  
6 that for symptomatic stenosis, which may be unacceptably  
7 high considering the majority of these patients were  
8 probably asymptomatic.

9 In terms of study design, some of the key aspects  
10 for stent utilization in patients with extracranial  
11 cerebrovascular disease can be divided up into four major  
12 categories: the patient, the personnel, the device, and the  
13 procedure.

14 In terms of patient selection, how were patients  
15 selected? Were they really symptomatic or asymptomatic?  
16 It's hard to know because many times they are not being  
17 examined by physicians with neurologic expertise. Were  
18 alternative therapies discussed with the patients? Were the  
19 risk/benefit ratios of stenting adequately presented to the  
20 patient? And since stents are being used for a non-approved  
21 indication, did all patients sign informed consent? Many  
22 times this is not the case.

23 In terms of personnel issues, we feel strongly,  
24 and in the Schneider WALLSTENT study it was mandated, that a  
25 multidisciplinary team had to be assembled, examine, and

1 sign off on every patient enrolled. Before stenting is  
2 done, we feel strongly that the personnel should have  
3 expertise both in stenting and cerebrovascular disease. We  
4 feel strongly that there should be neurologic expertise on  
5 site that examines the patient and that there should be  
6 prospective auditing of procedures and complications.

7 In terms of the device, many devices are being  
8 used in the cerebral circulation without any past experience  
9 in the cerebral circulation, without any indication whether  
10 the device is safe and effective, or using the device in a  
11 prospective, randomized trial. Data sometimes is not  
12 collected about results and complications or it's not  
13 collected in an independent, objective manner, and little  
14 data is collected about the use of concomitant medications.

15 Procedure issues. Where is the procedure  
16 performed? Is it performed in a neuroradiology suite, a  
17 cardiac cath suite, or an OR? When is the procedure  
18 performed? Is it performed soon after a stroke or a TIA?  
19 Is an angiogram performed prior to the stent? What  
20 techniques are used for stenting? How is the patient  
21 monitored? Typically there is no standardizations for any  
22 of these questions, and what assessments are done to  
23 evaluate safety and efficacy?

24 What's the current status of stenting? Many  
25 procedures are performed by operators with minimal

1 experience or training in cerebral vascular disease. A  
2 variety of devices and techniques are used, although none  
3 have been shown to be safe and effective versus  
4 endarterectomy in prospective, randomized trial. Patient  
5 selection is not based on a uniform set of guidelines or  
6 criteria. Many procedures are not performed under the  
7 guidance of a multidisciplinary team. No formal  
8 requirements for careful, independent neurologic monitoring  
9 are stated, and data from prospective trials are limited, as  
10 I mentioned before.

11           Recommendations are as follows: Number one, only  
12 well-trained physicians should be performing stenting for  
13 cerebral vascular disease, and these physicians should have  
14 training in cerebral vascular disorders. Patient selection  
15 must be overseen by a multidisciplinary team to ensure  
16 proper screening and definition. Independent neurologic  
17 monitoring must be performed to evaluate per-procedure  
18 complications and long-term safety and efficacy. And all  
19 patients and results should be tracked in a national  
20 registry with individual and center benchmarking.

21           All patients should have a diagnostic four-vessel  
22 cerebral angiogram prior to stenting and as a separate  
23 procedure. There must be evidence that the device used is  
24 safe and effective in the cerebral vessels. A standard  
25 protocol should be established for post-stent monitoring,

1 including neurologic examinations and neuroimaging studies,  
2 and 30-day and one-year results should be reported.

3 Thank you very much.

4 CHAIRPERSON CANADY: Thank you very much, Dr.  
5 Alberts.

6 Before we move on to the industry presentations,  
7 is there anyone else who'd like to speak in the open meeting  
8 portion--the public hearing portion, rather?

9 [No response.]

10 CHAIRPERSON CANADY: Very good. If I could ask  
11 the industry representatives, are we okay with the computers  
12 on that side? If the industry representatives, if you'd  
13 also, if you haven't, would arrange for the computers, and  
14 we'll move on to our first speaker, Dr. Ajay--I'm going to  
15 get in trouble again--Wakhloo. Again, if you'd identify  
16 yourself and your affiliations and financial interests.

17 DR. WAKHLOO: Good morning. Thank you for this  
18 opportunity. I'm professor radiology and neurological  
19 surgery at the University of Miami School of Medicine. I  
20 have been working in stent technology, and I have done the  
21 basis research as far as the biomechanics and the fluid  
22 mechanics parts done for the last 12 years. I have been on  
23 advisory panel recently for Medtronic AVE as well as for  
24 Cordis. I'm not a shareholder, I don't have monetary  
25 interest directly related to either Cordis, Johnson &

1 Johnson, or Medtronic AVE. But I receive, of course, as a  
2 member of the advisory Board, some support--and travel, of  
3 course, yes.

4 Now, I will focus my talk on neurovascular  
5 stenting. The reason why I think it is time now to move on  
6 in this direction is that we have enough data from basic  
7 research, in vivo as well as in vitro, to support this  
8 concept. But we don't have enough data whether there are  
9 long-term benefits, all of that. That means if we design  
10 any kind of study where we are working with bioimplants in  
11 small vessels--I'm talking about 2 to 3.5 millimeter in  
12 atherosclerotic diseased segments as well as on aneurysm  
13 affected segments--we need to start somewhere, and I think  
14 we should start in smaller centers with excellent expertise  
15 in dealing with the neurovascular system. And I agree with  
16 the presenter before, that was not appropriately done and  
17 it's still not done in many places, because it seems to be  
18 easy but it's not in the end.

19 Is the laptop ready? Okay. Can I have a laser  
20 pointer, please?

21 Now, there are two different diseases of the  
22 cerebrovascular system which are of great interest in our  
23 setup and which might be addressed by intracranial stenting.  
24 The one is atherosclerotic disease, which is the major risk  
25 factor for ischemic stroke, and ischemic stroke accounts for

1 83 percent of all strokes. And the other disease is  
2 intracranial aneurysm, which we have been currently treating  
3 more and more aggressively with endovascular tools such as  
4 GDC. It affects about 400,000 people worldwide each year  
5 and about 30,000 in the United States which present with  
6 brain hemorrhage, and there are, of course, a larger  
7 population which incidentally have the finding of aneurysm.

8 Now, why do I believe that stenting and why do I  
9 think that the technology should be promoted? There are  
10 several reasons. The current challenges in treating  
11 atherosclerotic diseased segment of the cerebrovascular  
12 system is that not often if we do PTA, we see a restenosis  
13 or recoil, generally because we are hesitant to yield  
14 certain or exceed certain pressures during angioplasty or we  
15 underinflate the balloon or we undersize the balloon. We  
16 believe that primary stenting is the way to go because we  
17 provide a mechanical reinforcement to the diseased segment.

18 The other thing which has not been addressed I  
19 think strong enough in the past, but biomedical engineers  
20 know, fluid mechanics know, is that we have flow  
21 disturbances in the diseased segment, and even if we don't  
22 see diseases of that segment angiographically, but yet there  
23 is something going, which then ultimately leads to a damage  
24 of the endothelial lining, there is a lot of evidence for  
25 that. And I--and we have done a lot of work showing that

1 after stenting, you establish a laminate positive flow and  
2 you get rid of the disturbances, especially of the boundary  
3 layers.

4 Now, the other thing is if you do a PTA, a balloon  
5 angioplasty of atherosclerotic plaque, you create a rough  
6 edge, a rough surface, ulceration and breakdown of plaque,  
7 which is thrombogenic. And I think that stent might and may  
8 be a solution as a matrix in the native form or in  
9 combination of some drug factors, growth factors, which then  
10 provide a smooth neointimal regrowth. So what you are  
11 doing, you are creating a new bypass, endovascular bypass  
12 within that segment.

13 Then the other thing is that intra-arterial  
14 disease can serve as an embolic source, and we believe that  
15 with changes in the porosity of the stent, decreasing the  
16 porosity under certain limitations, can work as a potential  
17 trap for those embolic particles. And last but not least--  
18 and I will show you in the second presentation that we see  
19 not quite infrequently PTA dissection, and my colleague who  
20 is in the audience has a lot of experience with PTA sees in  
21 about 10 percent of the population a dissection, and in his  
22 hands, he's an expert in that. Other centers have probably  
23 a dissection rate of 20 percent, and I think the primary  
24 stenting or PTA combined with stenting, we can basically  
25 realign that flap nicely.

1           Here is a case, IV-tPA in an elderly patient who  
2 presented with speech problems and double vision, diplopia  
3 dysarthria, and the tPA showed an opening of the clot, and  
4 this is what we find in many of our patients. The patient  
5 was put on heparin. Two days later they present with  
6 similar symptoms again. So what do we do? We have a team,  
7 neuro-stroke team, and that's what we decided to do. We  
8 stented the entire basilar system, starting up here with  
9 four different stents up to this area. And this is the  
10 follow-up six months later. You wouldn't find the stent if  
11 I wouldn't point it out.

12           So the response in the neurovascular setup due to  
13 implants is different than in the coronary, and there are  
14 three different major factors for that, and we can discuss  
15 that later.

16           Now, what is the patient indication currently? I  
17 strongly would emphasize to start patients who are  
18 refractory to medical therapy at this point. However, we  
19 have to keep in mind that drugs don't change the progression  
20 of the disease. We get basically rid of aggregation of  
21 clot, but as the population is growing older, a patient who  
22 has such a basilar artery, in two years that may be closed  
23 off. We don't know that. And not infrequently in Afro-  
24 American population--I have a big community of Afro-  
25 Americans in Miami and Latin--we see that the patient with

1 intracranial disease all present with a stroke. So it is  
2 different than in the carotid disease where there is a  
3 precursor. People present with TIA, amoroso (?),  
4 headaches, but with intracranial disease, they generally  
5 come with major devastating stroke.

6 So I think that it would be justified at this  
7 point--and let's stick to centers with expertise--to treat  
8 even high-grade stenosis, ulcerative blocks which are not  
9 symptomatic.

10 Now, what is the problem of the medical treatment?  
11 You know there is a big WASID trial in 50 centers going on,  
12 and, unfortunately, the data may come out nice in favor of  
13 warfarin as versus aspirin. However, you should keep in  
14 mind that that randomized trial, patients who are very sick  
15 are not enrolled because we know they won't do good. They  
16 come to us, the neurologists, the colleagues who are  
17 involved, and they ask us to do a PTA and stenting. So at  
18 this point it would be not fair enough to compare a new  
19 device with this ongoing WASID trial. And I agree with Dr.  
20 Loftus. If you want to compare, then you have to compare  
21 with the new arm only presenting patients with medical  
22 treatment and stent combined with medical treatment.

23 The other thing is that we have a problem of  
24 compliance. Patients, not often, are on drugs and five days  
25 later they stop taking the drugs. The other thing is long-

1 time expenses by taking drugs. And, once again, I want to  
2 emphasize, drug, warfarin or aspirin, doesn't mean that you  
3 alter the pathology of the disease. You alter basically  
4 only the aggregation of the clot.

5 Now, what are the endpoints and the clinical  
6 outcomes? Our suggestion would be the recanalization, of  
7 course, of the diseased segment, no neurological deficit,  
8 and, of course, death and major or minor stroke. As follow-  
9 up, based on our initial trials, initial experience, we  
10 think a follow-up of six months as far as the angiographic  
11 follow-up is justified because we don't see any change after  
12 six months in the neurovascular system once you have  
13 stented. Clinical follow-up, I would go for 12 months and  
14 compare the natural history of the intra-arterial disease.

15 CHAIRPERSON CANADY: If I could get you to wind  
16 up, please, Dr. Wakhloo?

17 DR. WAKHLOO: Yes. The last point I want to make  
18 is the role of stenting for aneurysms, and I think this  
19 should be an own(?) protocol, and because of the rush in the  
20 time, I would like to emphasize a few things. Let me go  
21 fast through this.

22 The stent in the aneurysm setup is meant to  
23 basically endovascularly bypass the aneurysm while you then  
24 can later treat the aneurysm by any other means. This shows  
25 you this cross-section where the entire vessel to 27(?)

1 degree is involved in this diseased segment. So what you  
2 create, you create a new lumen within the aneurysm and the  
3 vessel.

4 So the bottom line, to summarize that, is that  
5 stenting presents, I believe, a breakthrough technology for  
6 endovascular repair of diseased neurovascular through three  
7 components: it's the outer(?) structure, the biomechanics,  
8 the biology, as well as the hemodynamic. And, therefore, it  
9 promotes the healing of that segment in aneurysm as well as  
10 in atherosclerotic disease.

11 Thank you.

12 CHAIRPERSON CANADY: Thank you, Dr. Wakhloo.

13 Our next speaker will be Dr. Gustafson.

14 MR. GUSTAFSON: Good morning, Dr. Canady and  
15 panel.

16 CHAIRPERSON CANADY: Good morning.

17 MR. GUSTAFSON: I'm actually not a doctor. I'm a  
18 "Mister."

19 CHAIRPERSON CANADY: Ah, I'm stuck today.

20 MR. GUSTAFSON: And it's Gustafson, but no one  
21 outside Minnesota can pronounce that correctly.

22 CHAIRPERSON CANADY: Oh, I go down big time. I  
23 lived there five years.

24 [Laughter.]

25 MR. GUSTAFSON: But you got smart and moved.

1 CHAIRPERSON CANADY: I was just too far away from  
2 the Scandinavians.

3 MR. GUSTAFSON: There you go.

4 [Laughter.]

5 MR. GUSTAFSON: I'm vice president of Quality  
6 Systems and Regulatory and Clinical Affairs for Possis  
7 Medical. We're a publicly traded company based in  
8 Minneapolis, and so as an executive officer of the company,  
9 I've got oodles and oodles of stock options, all of which  
10 are way under water right now because Nasdaq has tanked. So  
11 my financial interest right now is mostly theoretical.

12 [Laughter.]

13 MR. GUSTAFSON: So I expect to enjoy an enhanced  
14 sense of veracity in front of you today.

15 Okay. I'm also, I think, the only presenter that  
16 actually represents a medical device company or that is an  
17 employee of a medical device company. And that offers a  
18 certain perspective which I hope will be valuable to this  
19 panel.

20 Our interest particularly is our device, which is  
21 the AngioJet thrombectomy catheter system. As it's  
22 currently marketed, this is a 4 or 5 French catheter used  
23 for mechanical removal of intravascular thrombus. It's  
24 currently marketed for coronary applications in both native  
25 vessels and saphenous vein bypass grafts, peripheral

1 arteries, and AV access grafts, and it is currently under  
2 IDE clinical studies for the treatment of ischemic stroke in  
3 a much smaller version, which I can't tell you too much  
4 about.

5           The device in its various iterations has undergone  
6 extensive clinical trials. The VeGAS trial for coronary use  
7 involved a Phase 1 registry of 90 patients, a Phase 2  
8 randomized clinical trial in 350 patients. In addition, we  
9 enrolled 500 patients in concomitant nonrandomized  
10 registries, and we did this at 40 trial sites around the  
11 U.S. Our peripheral approvals are based on Phase 1 and 2  
12 trials: a Phase 1 trial registry in 30 patients, a Phase 2  
13 randomized trial in 280 patients. This was done also under  
14 IDE and at 13 sites. So this is the background that we  
15 take, and it's the perspective that we bring into the  
16 questions before the panel today.

17           I want on the basis of that background to offer  
18 some considerations for the panel.

19           We recognize that the randomized clinical trial is  
20 the gold standard for medical device clinical trials, but  
21 when we look at stroke, ischemic stroke, the only approved  
22 therapy suitable for use as a control, as an active control,  
23 is IV-tPA used within three hours of stroke onset. The next  
24 point there is no longer true. There are quite a few  
25 centers now that are using IV-tPA on suitable patients. But

1 even so, only about 1 percent of all stroke patients  
2 actually receive IV-tPA because they don't make it to the  
3 hospital in time for the indication to apply.

4           Looking at this, we offer some other options, and  
5 some of the previous speakers have brought this point up as  
6 well. Stroke and its outcome under conservative management  
7 or medical management is already well studied. And so we  
8 propose or we suggest the panel consider using literature  
9 objective performance criteria as the control. That's a  
10 term of art that comes over from the cardiovascular side of  
11 things. An objective performance criteria is really nothing  
12 more than a literature control generated through a meta  
13 analysis of the available and applicable literature.

14           Using such a control allows a smaller study  
15 overall with the same statistical power. It's not limited  
16 to a three-hour treatment window, which it would have to be  
17 if we were using IV-tPA as our control. And we believe that  
18 such a setting or such a trial design would allow it to be  
19 more realistic to the eventual clinical setting in which the  
20 device, our device or any other, is eventually going to be  
21 used.

22           I can point out that the concept of OPCs is  
23 already one accepted by FDA. The FDA guidance document for  
24 clinical investigation of replacement heart valves  
25 incorporates the concept of using OPCs, that is, literature-

1 derived, meta-analytical performance criteria for clinical  
2 outcomes for heart valves.

3           The second point is multiple treatments. The  
4 background here is that because stroke has few active  
5 treatments and those that are available have perhaps modest  
6 value, we have found in designing our clinical trial, which  
7 we call a time trial for our AngioJet in ischemic stroke,  
8 that our investigators want to use multiple treatments  
9 concomitantly, mostly in medical treatment, along with our  
10 AngioJet. And good principles of science tell us that  
11 multiple concomitant treatments can confound evaluation of  
12 the investigational treatment.

13           I'm not sure we have any suggestions for the panel  
14 at this point, but basically the challenges are: Can the  
15 trial design ethically forbid concomitant treatments? If  
16 the doctors really want to use them to the benefit of their  
17 patients, how can we as sponsoring manufacturers say they  
18 can't?

19           But if we accept them, can the trial separate  
20 treatment effects that are due to the different treatments  
21 being employed? If concomitant treatments are allowed, must  
22 the approved indication which we seek in order to market our  
23 product to make money and get my stock options back up, can  
24 the approved indication or must the approved indication  
25 which we receive from FDA specify its use only in the

1 presence of concomitant treatments? And all those questions  
2 become even more interesting when you consider that some of  
3 the treatments which our investigators and others will want  
4 to use concomitantly are currently off-label treatments,  
5 which means they are even less well studied and less well  
6 understood.

7           The third area is outcome measures, and this was  
8 also addressed by some of the earlier speakers. With  
9 apologies to some of the cardiologists that might be in the  
10 room, we recognize that the brain is more complex than the  
11 heart. The heart's a pump and you can measure its pumpiness  
12 to a fare-thee-well. The brain is more complex and,  
13 therefore, stroke symptoms are complex, dynamic, and they're  
14 difficult to measure and interpret.

15           Clinical recovery from a stroke is a high order of  
16 measure of treatment outcome, and it is, therefore,  
17 susceptible to many other influences than just the acute  
18 treatment that was used for the single ischemic stroke  
19 event. We view our product and others like ours as being  
20 recanalization treatments. The thrombus is there before the  
21 treatment. The thrombus is gone after the treatment. The  
22 benefits to the patient are assumed to be--if the offending  
23 thrombus is not there anymore, the patient should get  
24 better. Certainly there is a need to measure that, but we  
25 propose that the primary endpoint should be an angiographic

1 one, as has been proposed by other speakers, and the  
2 important secondary endpoints can consider clinical outcomes  
3 for the patient.

4 I guess I got ahead of myself. We should use the  
5 primary endpoint to be the immediate treatment effect, that  
6 is, the angiographic effect, on the visible culprit lesion  
7 seen at presentation because it's highly quantifiable and  
8 its repeatable and it's clearly related to the disadvantage  
9 treatment, and secondary endpoints can consider patient  
10 outcome.

11 In summary, we view these things as fundamental  
12 questions of clinical trial design and that they should be  
13 freshly rethought. In other words, we should borrow  
14 relatively little, perhaps, from the experience of other  
15 areas of medicine such as we ourselves have and freshly  
16 rethink these issues so that we can accommodate the unique  
17 elements of stroke and the interventional treatments being  
18 developed for it before a guidance is issued to establish  
19 standards for their evaluation in investigational clinical  
20 trials.

21 Thank you.

22 CHAIRPERSON CANADY: Thank you very much.

23 Our next speaker will be Dr. Lee Schwamm.

24 DR. SCHWAMM: Very well done.

25 Good morning, panel members. It's a pleasure to

1 be here. Let me just begin while my presentation is being  
2 loaded. I'm an assistant professor of neurology at Harvard  
3 Medical School, and I'm the associate director of the Acute  
4 Stroke Service at Massachusetts General Hospital. I'm also  
5 an ad hoc medical consultant for Boston Scientific Target  
6 Therapeutics, and they've asked me to appear here today.

7 I'd like to share with you today my thoughts and  
8 opinions on the proposed use of stents in the treatment of  
9 symptomatic intracranial atherosclerotic disease, and I  
10 bring to this my perspective as a treating physician. I'm a  
11 stroke and critical care neurologist, and I work very  
12 closely with my interventional neuroradiology colleagues in  
13 the treatment of these patients.

14 I'm going to try and briefly touch on what I  
15 consider to be key points in the topics that were addressed  
16 in the background material for the panel, and I'll start by  
17 talking about patient group selection. I apologize to some  
18 of the panel members if some of this information seems very  
19 rudimentary.

20 Intracranial atherosclerosis, as we know, can  
21 produce symptoms either through ischemia or low flow--excuse  
22 me, low flow or embolic mechanisms, and we typically regard  
23 this as surgically inaccessible. It's also important to  
24 recognize that we have a heterogeneous group of diseases:  
25 anterior and posterior circulation stenoses have differing

1 prognoses, different collateral blood supply, and likely a  
2 different response to therapy. And I think the panel should  
3 bear that in mind as they look at different intracranial  
4 stent design submissions in terms of what are the  
5 appropriate outcomes in these populations.

6 In addition, some patients actually respond quite  
7 well to antiplatelet or anticoagulant therapy. The number  
8 of patients presenting to us with ischemic stroke symptoms  
9 who are not on antiplatelet therapy has decreased  
10 dramatically in the last decade, and so it may be very  
11 difficult to find patients who have not been on any  
12 antiplatelet therapy at the time of their first symptoms.

13 But I think there is clearly a subgroup of these  
14 patients who present with failure of medical therapy and are  
15 recognized to have a very poor prognosis. And I think in  
16 particular the posterior circulation intracranial disease is  
17 a group of patients that have been recognized to have a very  
18 poor prognosis, and they might be the ideal candidates in  
19 which to test a novel intervention that has some  
20 unassignable risk. I think that we have heard before that  
21 there's some concern about enrollment in studies like WASID  
22 (ph) that these most difficult patients are not actually  
23 being enrolled, that they are essentially removed from  
24 randomization, and that's an important point.

25 Just to remind you again, we are talking about the

1 posterior circulation here. The vertebral arteries and the  
2 basilar arteries, a sagittal view of the brain, and the  
3 other important issue in posterior circulation disease is  
4 that because of its blood supply to the brain stem, very  
5 small strokes in the posterior circulation can have a very  
6 devastating effect on outcome, whereas similar sized infarct  
7 in the anterior circulation likely would not.

8           So what is the risk of stroke following  
9 intracranial posterior circulation ischemic symptoms? No  
10 one knows. We have some data. While we have some  
11 relatively good data about risk of ICA siphon in MCA disease  
12 from previous randomized trials, WASID looked retro-  
13 spectively at a cohort of patients with angiographically  
14 proven intracranial stenosis, and in that cohort, there were  
15 68 patients with symptomatic vertebral-basilar stenosis, 23  
16 percent in the aspirin group and 10 percent in the warfarin  
17 group. So 33 percent of those patients had a second  
18 ischemic stroke in the stenotic vessel territory in the  
19 median follow-up of about one year.

20           What about the patients then that fell out of  
21 WASID? They had their second event. They had their medical  
22 endpoint. Now what happens to them? Dr. Alberts recently  
23 published a retrospective review of the Stanford experience  
24 looking at precisely those kinds of patients and found 29  
25 patients who continued to fail medical therapy, 20 of whom

1 had vertebral-basilar disease. Eighty percent were on  
2 warfarin, which many consider to be at least part of the  
3 ideal medical therapy. The next event in those patients was  
4 a stroke in 10 patients and a TIA in 19. So it brings up  
5 the point that if we wait to randomize patients to a medical  
6 control arm who have already failed therapy, we may be  
7 looking at some devastating strokes in that patient group.

8           Of the 25 patients who were followed continuously,  
9 the median time to an event was 36 days, suggesting that the  
10 distribution of events over follow-up may not be a randomly  
11 or normally distributed curve but, rather, a bimodal or  
12 heterogeneous curve where there may be a significant number  
13 of events in a relatively short period of time, which poses  
14 difficulties in randomization in the clinical trial where  
15 clinicians feel the need to urgently provide therapy.

16           Failure of best medical therapy I think is  
17 reasonably considered as recurrent ischemia despite therapy,  
18 but I would also encourage you to think about other types of  
19 failure of best medical therapy. They would include an  
20 intolerance to therapy, bleeding or allergies, with  
21 acceptable side effect profiles but that discourage patients  
22 from continuing therapy; also, an inability to actually  
23 maintain the adequate medication target effect. We all know  
24 the trouble that WARS (?) has had in maintaining INRs in the  
25 desired range. And, thirdly, the serious adverse life-

1 threatening events such as systemic hemorrhage or intra-  
2 cerebral hemorrhage.

3 I would argue that you need to take those factors  
4 into account when you consider the risk/benefit  
5 stratification of the trial, and a lifetime of warfarin  
6 therapy is something that has an associated risk that we'll  
7 discuss in a moment.

8 Is randomization to continued medical therapy an  
9 ethical alternative in patients who have failed it? I think  
10 we've heard a lot about that today. Also, can patients be  
11 retained in the medical arm of a randomized, prospective  
12 device trial when the intervention is available off-label,  
13 either at the same institution or around the corner? And  
14 one of the risks is that you will deprive the medical arm of  
15 meaningful data because all the patients who are randomized  
16 to the medical therapy may select the stent option at  
17 another institution off-label.

18 So, really, what method is the least burdensome to  
19 patients and fulfills the FDA's mandate to try and study  
20 these patients in a careful and controlled manner? And I  
21 would argue that there's certainly enough data to strongly  
22 consider the use of historically controlled, single-arm  
23 trial design where we could capture very accurately criteria  
24 for enrollment, true complication rates, and an  
25 independently verified outcome.

1           Conventional outcome assessments. Certainly  
2 functional outcomes at six months have been talked about;  
3 incidence of major stroke stratified against minor stroke or  
4 TIA; adverse events and procedural complications. I would  
5 emphasize again the risk of hemorrhagic complications over  
6 years of anticoagulation, and also the impact on the quality  
7 of life of patients to suffer continuous monitoring of  
8 warfarin therapy and also living with the knowledge that  
9 they have a high risk of recurrent stroke, much as patients  
10 who have unruptured aneurysms experience a deterioration in  
11 their quality of life with that information.

12           I'll just briefly remind you that risk of  
13 hemorrhage in the brain with warfarin therapy is well  
14 documented and poses a significant threat over a lifetime of  
15 therapy, which most of these patients are committed to.  
16 They receive best medical therapy. And I'll end by talking  
17 about the potential biases in these kinds of trial designs.

18           Length of follow-up, as I mentioned before, is  
19 going to be very difficult. Procedure-related complications  
20 should manifest within 7 or 30 days at the latest of any  
21 intracranial manipulation. But how do we try and understand  
22 the long-term risks associated with both disease  
23 interventions? Angioplasty and stenting may lead to  
24 restenosis and other angiographic complications. Six months  
25 probably is enough time to recognize those. But the natural

1 history progression of the disease in the medically treated  
2 arm and the risk of hemorrhage over time may not be captured  
3 in a short period of follow-up.

4 We're going to be enrolling the highest-risk  
5 patient group. These are the ones that the physicians are  
6 going to want to enroll in a stenting trial because they're  
7 afraid they're going to fail medical therapy. So they are  
8 the higher-risk pool patients compared to a randomized,  
9 controlled trial like WASID, which is going to enter more of  
10 the patients with what physicians presume to be a stabler  
11 medical course.

12 And then you've heard before about the problem of  
13 off-label use of concomitant therapies, the need for  
14 clinical efficacy for physicians and patients to accept the  
15 requirements of the trial design; and, finally, the  
16 unpredictable advances in antithrombotic therapeutics that  
17 might improve best medical therapy, although I must say  
18 those are likely decades off rather than years off.

19 Thank you.

20 CHAIRPERSON CANADY: Thank you very much, Dr.  
21 Schwamm.

22 Our next speaker will be Dr. Charles Strother.

23 DR. STROTHER: Charlie Strother, University of  
24 Wisconsin-Madison. I'm professor of radiology, neurology,  
25 and neurosurgery. I'm also chairman of the board of

1 EndoVasix, Inc. And my remarks are limited to trials for  
2 devices that are intended for revascularization in the  
3 treatment of acute stroke.

4 To start, I would just like to try to make the  
5 point that just as you've considered the Cordis Trufill (?)  
6 as a single component in the treatment of arteriovenous  
7 malformations, devices intended for revascularization can be  
8 considered and I think should be considered as one of the  
9 single components in the overall treatment of acute ischemic  
10 stroke.

11 The philosophy--and we're tried to address the  
12 questions that you've given to us, and I've provided the  
13 panel with a detailed description of our thoughts on all of  
14 those questions. Stroke, as we have seen and as we all  
15 know, is a catastrophic illness that has massive social and  
16 economic consequences. There aren't great treatments out  
17 there. Large randomized trials have demonstrated that  
18 treatment can improve outcome, and there likely is going to  
19 be no silver bullet therapy for stroke. In my view,  
20 clinical success will come from a combination of successful  
21 component therapies.

22 Two important criteria, time and location. For  
23 comparison to previous trials, we're going to be really  
24 limited to treatment M1 and M2 segment of the middle  
25 cerebral artery. Separate studies are probably warranted

1 for patients at greater than six hours after onset and for  
2 those with extensive thrombus and large thrombus burdens.

3 The question about imaging. Currently CT is  
4 surely the key for detection of hemorrhage and for excluding  
5 patients with extensive evolving infarcts that are likely to  
6 be injured by intervention. MRI is incredibly exciting and  
7 powerful, and we're using it actively in our practice, but  
8 at the current time, it's not proven to actually improve  
9 outcome of acute stroke therapy. It's not universally  
10 available, and it imposes a significant time cost. It may  
11 be very valuable for use after the six-hour limit in trying  
12 to stratify patients who still will benefit from therapy.

13 Control populations. The natural history of  
14 middle cerebral artery infarct is well documented,  
15 especially by the PROACT II trial. Given the outcome of the  
16 NINDS and PROACT II studies, placebo controlled studies will  
17 be difficult to justify ethically. And historical controls  
18 allow access to a placebo control group for both technical  
19 and clinical endpoints.

20 Safety is the primary concern, obviously, in  
21 testing new devices. Vascular injury I believe is likely  
22 the greatest risk when devices whose purpose is  
23 recanalization are used. That should be evident both from  
24 angiographic and other imaging studies.

25 Intracranial hemorrhage is part of the natural

1 history of acute ischemic stroke, and potential new  
2 therapies must document the degree to which they modify the  
3 incidence of hemorrhage.

4           Efficacy. Stroke will eventually be managed with  
5 a combination of therapies designed to address different  
6 aspects of the disease. Devices should be tested against an  
7 appropriate technical endpoint chosen according to the  
8 intended purpose of the device. For recanalization devices,  
9 the endpoint would be the TIMI flow in the occluded artery  
10 as measured on an angiogram immediately after treatment.

11           Secondary endpoint data on clinical endpoints are  
12 obviously also critical not only for assessment of overall  
13 efficacy but so that studies can be integrated into meta  
14 analyses. The endpoints of the PROACT II trial should  
15 become standard secondary endpoints for device studies.  
16 These scales should be measured at 90 days.

17           Confounding variables. Obviously, analysis of  
18 appropriate technical endpoints such as recanalization rate  
19 avoids many of the difficulties of confounding variables.  
20 When you look at the TIMI flow immediately after a device is  
21 used, the confounding variables have very limited influence.  
22 As we combine therapies and concomitant medications are  
23 used, these are obviously lifesaving, but they could make  
24 interpretation of clinical outcome data nearly impossible.

25           In conclusion, comprehensive stroke therapy should

1 be considered as being comprised of several components.  
2 Each of these should be tested individually against  
3 appropriate technical endpoints. Comparisons can be made to  
4 well-studied historical controls. And individual successful  
5 therapies can be combined into a total stroke treatment plan  
6 in the clinical setting, hopefully giving us more to offer  
7 patients with this devastating disease.

8 Thank you.

9 CHAIRPERSON CANADY: Thank you very much, sir.

10 Our final speaker for the industry section of the  
11 discussion today will be Dr. Wakhloo again in a different  
12 capacity, representing Cordis.

13 DR. WAKHLOO: This time I'm speaking on behalf of  
14 Johnson & Johnson, Cordis Neurovascular. I am advisory  
15 board and receive honorarium. I don't have any other  
16 financial interest in the company.

17 What I would like to do with the second talk, I  
18 would like to focus on the protocol design and go into the  
19 detail for the stent trial intracranially.

20 Now, the primary objective of the whole study will  
21 be to evaluate the safety and effectiveness of PTA, primary  
22 stenting, or combination of both of them to treat  
23 intracranial atherosclerotic disease.

24 The post-procedure, we will have a follow-up  
25 clinically at 30 days and at six months, and we will have an

1 angiographic follow-up at six months. The endpoints will be  
2 the incidence of major or minor stroke and neurological  
3 outcome will be based on three different scales as listed  
4 here.

5           What is the effectiveness of the stenting? It  
6 will be defined angiographic outcome with a residual  
7 narrowing between 10 and 20 percent. Why did we choose the  
8 10 to 20 percent? Because in case we expect neointimal  
9 formation, generally that occurs in the dimension between  
10 150 and 250 microns. On each side that would mean 0.5  
11 millimeter narrowing, and if you work in the realm of 2.5 to  
12 3.5 millimeter, this would be the justified. We can't  
13 extrapolate the data from the carotid where we think that if  
14 we have residual stenosis of 50 percent or less this is  
15 sufficient. That cannot be extrapolated to the intracranial  
16 system because of the hemodynamics and the cross-section  
17 size of the vessel.

18           The other thing is post-procedure once again  
19 follow-up angiography six months is justified, and we don't  
20 see in our preliminary data any difference between six  
21 months and 12 months. There will be a core lab assessment,  
22 quantitative and according to the NASCET criteria.

23           Now, the study population would include patients  
24 who have neurological symptoms referable to the target  
25 lesion, de novo or restenosis, angiographically documented

1 target stenoses larger or equal to 50 percent, asymptomatic  
2 as well as symptomatic. The minimum reference diameter  
3 should be 2.5 millimeters because we believe going below  
4 that at this point would have the risk of in-stent  
5 thrombosis. We don't have enough data to justify that, but  
6 it would be safer to limit it to 2.5 millimeters.

7 No intracranial hemorrhage, hemorrhagic stroke,  
8 major stroke, or any stroke with mass effect within six  
9 weeks of procedure should be present. No lesions with  
10 angiographically evident thrombus. If you have a thrombus,  
11 you have to go for thrombolysis, get rid of the thrombus  
12 burden, and then for stenting.

13 The most common location--and I go to our first  
14 speakers--we will, of course, include the internal carotid  
15 artery, different segments, and the most common location, of  
16 course, the carotid bulb itself, that won't be included into  
17 the intracranial stent trial, but the petrous, supraclinoid,  
18 main trunk of MCA, PCA, vertebral artery as well as basilar.

19 Now, the significance of intracranial  
20 atherosclerotic lesions is not currently fully understood.  
21 However, we have enough data from different smaller group  
22 populations, 50 to 100 patients, including in different  
23 studies, that the risk of intracranial stenosis of an  
24 aneurysm or stroke is between 7 and 40 percent. In middle  
25 cerebral artery stenosis it's approximately 8 percent per

1 year. So as comparison, we have the natural history  
2 currently available. Why not, as Dr. Loftus mentioned this  
3 morning, take the surgical EC-IC bypass study? The reason  
4 is although the results were excellent, vein graft patency  
5 was very high, the arterial bypass the patency was very  
6 good; however, it failed to show, first of all, that it's  
7 effective for intracranial arterial disease with associated  
8 stroke, and then the mortality was between 3 and 14 percent,  
9 major complications 20 percent, major stroke. This is  
10 unacceptable. So the surgical arm is definitely not the way  
11 to go.

12 Now, what is our current knowledge? PTA is  
13 associated with complication between 10 and 50 percent at  
14 major centers. Primary stenting has, in those centers which  
15 it is performed, around 5 and 10 percent depending on the  
16 location, anterior versus posterior circulation.

17 Now, long-term results of PTA or stenting, we  
18 don't know them. We know PTA restenosis is approximately 10  
19 percent in excellent hands. Stenting restenosis, the  
20 earlier data coming from Japan, Europe, as well as from  
21 United States say approximately less than 10 percent, again,  
22 depending on which (?) and cross-section of the artery.

23 Here are a few examples of PTA. That's how we  
24 would like to see the M1 stenosis here in a gentleman with  
25 TIA to the left hemisphere. That's how we would like it,

1 but that's not how it happens. Generally, we have problems  
2 as such, and that's why we are thinking of stent technology.  
3 A lesion of the petrous internal carotid artery dilated, a  
4 patient who failed medical or was refracted to medical  
5 treatment, we dilate, you have a significant dissection of  
6 intimal flat floating in the vessel. We decided to do  
7 stent. That's how it looks, and that's how it looks like  
8 six months or 12 months later.

9 Now, the medication. Of course, that's what we do  
10 generally for our patients with endovascular treatment, but  
11 we would like to have those three drugs on board during the  
12 procedure: aspirin, Clopidogrel, heparin during the  
13 procedure and 20 hours after the procedure in combination  
14 with a IIb/IIIa receptor blocker. That's the problem what  
15 we are seeing. Tight stenosis of the right distal vertebral  
16 artery, post-angioplasty recoil. You see missing perfusion  
17 of the right PCA as well as the right anterior circulation.  
18 This patient has an occlusion of the right internal carotid  
19 artery so he lives from the perfusion from the posterior  
20 circulation. We stent it. Now you appreciate the increased  
21 perfusion as well as perfusion to right middle cerebral  
22 artery.

23 Another case of post-proximal vertebral artery  
24 stenosis, because there has been the issue raised if you  
25 cross a larger (?) vessel what happens. We do

1 angioplasty. The residual is not very nice. We do stenting  
2 and you see now the filling of the con-(?) vertebral artery  
3 coming down here after stenting.

4 Now, the reason is the pressure drop, which is the  
5 driving force, in fact.

6 Here, another case of petrous stenosis showing you  
7 the long-term or longer-term follow-up. Stenosis after  
8 stenting six months follow-up and at 12 months unchanged.

9 Now, there are, in summary, new generations of  
10 stents available, and I think the trackability and the  
11 flexibility are not an issue. The issue will be the long-  
12 term result as well as the peri-procedural complication  
13 associated. And I think that there are three different  
14 diseases which we can address and we should include in the  
15 study, which is the intracranial atherosclerotic disease to  
16 prevent stroke, and acute arterial occlusion treatment in  
17 conjunction with thrombolysis, as well as complex aneurysms.

18 Thank you.

19 CHAIRPERSON CANADY: Thank you very much, Dr.  
20 Wakhloo.

21 I'd like to thank all of the participants in the  
22 open portion of our discussion as well as the industry  
23 portion of the discussion.

24 We are going to have a slight change in agenda. I  
25 think we have time that I'd like to proceed with the open

1 panel portion of the meeting with the presentation by Dr.  
2 Justin Zivin, who is a consultant with the FDA's Peripheral  
3 and Central Nervous System Drugs Advisory Committee. He's  
4 prepared an analysis for the panel regarding this topic. At  
5 your pleasure, sir.

6 DR. ZIVIN: Thank you very much for this  
7 opportunity to speak with the panel. It's customary in  
8 these types of talks to give a little bit of the magnitude  
9 of the problem and try and put things in a little bit  
10 broader perspective, and so I start out with demographics.

11 Stroke is the third leading cause of death in the  
12 United States. It's responsible for approximately 150,000  
13 deaths per year, which is about 8 percent of the total.  
14 It's the leading cause of disability in adults. There are  
15 approximately 750,000 new strokes per year and at any given  
16 time approximately 3 million survivors in this country.  
17 It's the leading diagnosis from hospitals to long-term care.

18 The incidence in Europe is approximately the same  
19 as it is in the U.S. and the Far East. It is higher in  
20 China. It's said to be the number one cause of death.

21 There has been a 40 percent decline over the past  
22 30 years in the stroke rate, and this is most probably due  
23 to reduction in risk factors. Now, of course, there are two  
24 basic categories of risk factors. They include unmodifiable  
25 and modifiable ones.

1           The unmodifiable risk factors--well, I suppose  
2 device manufacturers might be able to change some of these  
3 things, but first we have age. Stroke risk increases with  
4 age, particularly after mid-50s. The gender incidence, it's  
5 approximately 30 percent higher in men. And race, the  
6 stroke risk is particularly high in African Americans.

7           The modifiable risk factors include hypertension--  
8 hypertension is the most important issue that we deal with  
9 in that it is a high risk factor and a high prevalence in  
10 the population, and most epidemiologists believe that the  
11 primary reason for the reduction in stroke rate over the  
12 past number of decades has been the fact that the  
13 hypertension control in the general population has markedly  
14 improved.

15           Heart disease is a major risk factor for stroke.  
16 Atherosclerosis is the same disease in both the brain and  
17 the heart, and as a matter of fact, that's one of the  
18 reasons that a number of groups have advocated changing the  
19 name to "brain attack."

20           Incidentally, the stroke victims ordinarily do not  
21 die of recurrent stroke. They ordinarily die of their  
22 concomitant heart disease.

23           Previous strokes and TIAs are risk factors for  
24 subsequent strokes. Diabetes and smoking are also important  
25 risk factors.

1           Now, there are two fundamental types of strokes.  
2 First we have almost--most, the overwhelming majority of  
3 them are ischemic strokes in various different categories,  
4 caused by occluded vessels; then there's the distinct  
5 minority which are caused by ruptured vessels of one sort or  
6 another.

7           Now, what are the proven medical and surgical  
8 therapies for stroke up to this point? These are generally  
9 widely accepted in the literature or FDA approved. The  
10 medical therapies for stroke up to this point using stroke  
11 as an endpoint--and I'll get back to that point as being an  
12 important issue later--we have the prophylactic methods, and  
13 those include--and they were tested primarily in secondary  
14 prevention or in non-atrial fibrillation--non-valvular  
15 atrial fibrillation patients. There are the antiplatelet  
16 agents. They include aspirin, ticlopidine, Clopidogrel, and  
17 recently the combination of dipyridamole-aspirin. The  
18 anticoagulant that has been proven up to this point is  
19 warfarin.

20           For acute stroke therapy, the only FDA-approved  
21 management method is intravenous tissue plasminogen  
22 activator. There are two other acute managements that have  
23 been shown to be effective in clinical trials but are not  
24 yet proven for--have not been FDA approved. One is Ancrod,  
25 which is pit viper venom, by intravenous methods, and

1 Prourokinase, which is a drug that's relatively similar to  
2 tPA, and that has been shown to be effective in intra-  
3 arterial studies. That's the PROACT II study that some of  
4 the previous speakers mentioned.

5 The surgical management, the one method that has  
6 been proven to be effective for stroke endpoints alone is  
7 carotid endarterectomy for secondary stroke prevention.

8 Now, getting on to the trial designs, there are a  
9 variety of designs that can be used, but, generally  
10 speaking, they fall into two general categories. One is the  
11 prophylaxis trials, and up until this point, most of them  
12 have been secondary prevention trials. Trying to show  
13 primary prevention in stroke patients is a very, very  
14 expensive business, and nothing has been proven to be  
15 effective that way. I would anticipate that most of the  
16 stenting trials and a number of the other device trials  
17 would fall into these categories.

18 Then we have the acute treatment trials, and as I  
19 mentioned, up to this point only the thrombolytics have been  
20 shown to be effective in that way. I would expect that some  
21 of the catheter-based studies of the device manufacturers  
22 might fall into the acute treatment trial design issues.

23 The principal, the major difference between these  
24 two trial designs is time from onset to randomization. In  
25 prophylaxis trials, this has been typically days to months.

1 For the acute management studies, it's been hours. And now  
2 I'd like to explain why it is that it's so important to get  
3 it down to hours in the acute studies.

4 It is at the present time impossible to measure  
5 the duration of ischemia that human beings can tolerate. We  
6 have no method for continuously monitoring the occluded  
7 vessel in a person, and so we don't know when it reopens.  
8 Therefore, we do not have information about the maximum  
9 duration of ischemia tolerance.

10 The next best information we can get that way is  
11 from primates, and this is a study that I'm showing you here  
12 that was done looking at neuropathological endpoints. This  
13 study was done approximately 20 years ago. The data are  
14 still every bit as valid as they ever were, showing the  
15 fraction of neurologic injury, again, measured by a  
16 pathological endpoint, as a function of the duration of  
17 ischemia. And I've marked out three points there. The CR  
18 point is complete recovery, in other words, a TIA. And what  
19 you can see is that an absolute complete recovery can occur  
20 within between 5 and 15 minutes. That goes along fairly  
21 well with our understanding of it from a variety of other  
22 sources of information, for example, asphyxia studies for  
23 global ischemia or drowning accidents, things of that  
24 nature, cardiac arrest.

25 At the other end of the scale you have no

1 recovery. That is, in fact, at least in these animal  
2 studies, the maximum duration of ischemia the animals can  
3 tolerate. And that turns out to be approximately six hours,  
4 and that was one of the justifications for the six-hour time  
5 limit in many of the studies. After that time point you  
6 cannot get renewed or restoration of function, and all you  
7 can provide at that point is side effects. This is for  
8 revascularization procedures. This data would apply to the  
9 revascularization procedures.

10 The ET50, the average duration of ischemia that a  
11 group of people, or animals in this case, can tolerate is  
12 approximately 100 minutes. That's the best defined point on  
13 the curve and has the minimum variance. And ideally that's  
14 when patients should be randomized to decrease the number of  
15 patients to a minimum.

16 Now, I'm going to be talking--extrapolating from  
17 the clinical trials that we've had for medical and surgical  
18 devices--medical and surgical management to device trials.  
19 And I'm going to be talking first about inclusion and  
20 exclusion criteria.

21 Age of patient. In the past we had both lower and  
22 upper limits. We still in most of our trials have lower age  
23 limit because there's so few patients who have strokes at  
24 relatively early ages. Increasingly over the years we've  
25 gotten rid of the upper age limits. Now, that's not to say

1 that for a device trial, particularly for something that is  
2 moderately invasive, it might be sensible to include  
3 something like that. It's something that's ordinarily in  
4 these trials, but I just wanted to give you a feeling for  
5 what the thinking is on these issues.

6 Interfering medical conditions. Anything that  
7 causes death or neurologic signs before the therapy can be  
8 adequately assessed is a sensible reason to exclude a  
9 patient. These typically are patients who are very sick to  
10 begin with and are not expected to survive to the endpoint  
11 because of their primary medical condition aside from  
12 neurologic disease.

13 Concomitant medications. At this point, for  
14 device trials, anticoagulants and antiplatelet agents might  
15 well be interfering, particularly if the patient is  
16 adequately anticoagulated at the time the device is to be  
17 tested. That will have to be considered.

18 Now, the possibility is that neuroprotectants will  
19 ultimately end up interfering with device trials, but for  
20 the time being they don't because we don't have any.

21 Stroke mechanism. I'll get into this in more  
22 detail shortly, but there's been arguments in favor of  
23 eliminating varying ischemic stroke subtypes. Whether  
24 that's sensible or not to some extent depends on the type of  
25 device. For example, if all you're doing is revascularizing

1 large vessels, then it might be sensible to exclude some of  
2 the small vessel type strokes. Most studies have excluded  
3 hemorrhages up to this point, and, again, for devices that  
4 seems to me to be reasonably sensible unless there's a  
5 specific reason to do otherwise. And time from onset is  
6 what I discussed previously.

7 Now, endpoints. Which ones should we be using?  
8 Well, for prophylaxis trials, in the past we have typically  
9 used recurrent stroke and death, and I have no reason to  
10 believe that that should change. Also, a number of years  
11 ago, transient ischemic attacks were commonly used as an  
12 endpoint. However, transient ischemic attacks by definition  
13 means the patient is not harmed. There is no neurologic  
14 long-term deficit. And we have increasingly gotten away  
15 from using TIAs as either a primary endpoint or as part of a  
16 composite endpoint. And I think that they should be  
17 excluded from a major endpoint.

18 For acute therapy, it's been a variety of rating  
19 scales, and now I want to go through the rating scales in  
20 some detail because I think that we've learned a lot about  
21 that, and they're more controversial than death and  
22 recurrent stroke.

23 A variety of scales have been studied over the  
24 years, and I'm not going to go through these in any detail.  
25 I put them in mostly for documentation purposes so that you

1 would have a chance to take a look at them more.

2           The Barthel Index is one that has been commonly  
3 used for stroke studies for many years. This is the first  
4 part of it, and here's the rest of it. Basically what it  
5 consists of is it's an activity of daily living scale, and  
6 you receive an arbitrary number of points for each function  
7 that you can perform, adding up to a total of a hundred  
8 points.

9           Now, this scale was not originally designed as a  
10 stroke scale. It was originally designed as a technique for  
11 helping nurses and physicians to assign patients to nursing  
12 homes. And so to get 100 points on this scale, to get a  
13 perfect scale, you can still be a fairly badly damaged human  
14 being. As a matter of fact, one of our nurses, I think,  
15 most nicely summarized what this scale tells us is: Can you  
16 get to the bathroom by yourself? And do you know what to do  
17 when you get there?

18                   [Laughter.]

19           DR. ZIVIN: Now, the next general category of  
20 scales that have been used are the NIH Stroke Scale and  
21 there's a variety of others that are similar that are  
22 essentially simplified neurologic examinations. Again, they  
23 are stylized examinations which, in this case, includes  
24 these sets of questions. There's an arbitrary number of  
25 points that are assigned to each one of these tests, and the

1 score is ultimately added up, although it's not an ordinal  
2 scale.

3           It does nicely summarize the exam, and I believe  
4 that a number of people find this particularly useful who  
5 are not neurologists who are trying to assess patients  
6 because it forces them to go through the exam in detail and  
7 remember to do everything. That's the good feature--those  
8 are the good features about this study method.

9           One problem with it is that it does take about  
10 five minutes to administer it, and when time is of the  
11 essence, that's not helpful. And the other more important  
12 problem is that there's a fair amount of inner-rater  
13 reliability problem with it. There are many of the  
14 questions that have some problems with getting the same  
15 answers amongst examiners.

16           Now, here's a scale that I can like. This is the  
17 Modified Rankin Scale. This is a global assessment scale.  
18 It's a one-question test which has seven possible answers.  
19 Are you mild, moderate, severe, or dead, with appropriate  
20 definitions, and it takes about two minutes or less to  
21 answer this question for any given patient.

22           The Glasgow Outcome Scale is another that's  
23 virtually identical, just a smaller number of points and the  
24 definitions are slightly different.

25           Okay. Well, how well do these things perform?

1 Well, the shining example that we all have to talk about is  
2 the NIH tPA trial. And what I want to show you is how these  
3 various different rating scales worked in that trial. And,  
4 in particular, I will--I have all four of the scales up  
5 here, and you have them in your notes so you can take a look  
6 at them, but I'll just confine my discussion to the Rankin  
7 Scale.

8           Again, one of the things that I really like about  
9 the Rankin and the Glasgow Outcome Scales is they're simple  
10 for people to understand and they're ordinal.

11           Now, what you can see here, just looking at the  
12 Modified Rankin Scale, in the tPA trial approximately a  
13 quarter of the patients ended up--of the placebo patients  
14 ended up in each of the various control--in the various  
15 groups, 0 to 1 being normal, 2 to 3 being mild to moderate,  
16 4 to 5 being severe, and 21--and death being death.

17           The treatment group, you can see there was  
18 approximately a 50 percent improvement in the number of  
19 patients who benefited from the treatment, whereas there was  
20 no significant increase in any of the other outcomes.

21 That's a particularly important point, particularly noting  
22 that there was not an increase in the death rate or bad  
23 outcomes. We'll get back to that.

24           Now, looking at them overall and saying in the  
25 primary endpoint of the NIH tPA trial was a measure of--the

1 way they did it was to take those scales and dichotomize  
2 them into normal versus abnormal. That was really what they  
3 were doing as a primary outcome measure, and the question is  
4 which of these scales worked best. And if you take a look  
5 in the lines on the end there, the odds ratio, relative  
6 risks, and p values, there was no difference. So  
7 essentially they all performed, at least in that  
8 dichotomization schedule--paradigm, approximately equally.  
9 And so, therefore, I think it makes--based on this and some  
10 other information that we don't have time to discuss, I  
11 think it makes little sense to include the Barthel Index to  
12 any appreciable extent. The Modified Rankin or the Glasgow  
13 Outcome Scales are very simple, and I think that they are  
14 sensible primary outcome measures.

15           The NIH Stroke Scale performs equally well, but it  
16 takes more training to learn how to do it, and it doesn't  
17 perform any better. However, there is some information from  
18 our literature that suggests that it may be useful as entry  
19 criteria to keep out patients who have too mild strokes,  
20 because we have had some trouble in some of our trials with  
21 include too many patients who spontaneously recover and that  
22 dilutes out the final endpoint.

23           Now, what about surrogate markers? And I'm going  
24 to take the hard-line view here. The only surrogate markers  
25 up to this point that have been truly--have been evaluated

1 to any significant extent are a variety of images. Now, one  
2 is measurement of blood flow or vessel patency, and a number  
3 are members--people who came to talk here before were  
4 advocating use of those techniques. My view is that those  
5 are poorly correlated with neurologic function. You can  
6 have a beautifully open vessel and dead brain and the  
7 patient doesn't benefit, so I think that is an inadequate  
8 method for assessing a patient outcome. It is a surrogate  
9 marker, but I don't believe that it's usable for assessment  
10 of patients. It might be useful for preliminary and Phase I  
11 and Phase II testing.

12           Image volumes have been recommended by many.  
13 These are primarily CT and, increasingly, MR techniques.  
14 Again, the lesion volumes are poorly correlated with  
15 neurologic function, and the reason for that is fairly  
16 uncomplicated. A large stroke in a relatively silent area  
17 causes no more damage than a tiny stroke in a critical area.  
18 And, therefore, trying to correlate the image volumes with  
19 the neurologic function is, at best, tricky and, at worst,  
20 impossible.

21           Now, there have been a variety of types of  
22 specialized analysis of these imaging techniques, and the  
23 claim has always been that since they're more precise  
24 measurements that they will be more useful. But as it turns  
25 out, if you look at it more carefully, the variance of these

1 lesion volumes may be very large and is not necessarily any  
2 better than the clinical rating scale which more directly  
3 measures what it is that we care about, which is functional  
4 improvement in patients.

5           An additional problem is that making these  
6 measurements is time-consuming, and in a situation where  
7 every second counts in treatment, that's not helpful, or at  
8 least the burden of proof is on the people who are  
9 advocating those types of methods. The bottom line is up to  
10 this point none of the surrogate markers have been proven to  
11 be useful for stroke.

12           Now, there's been controversy about every one of  
13 the approved stroke therapy methods, and no more so than  
14 tPA. The FDA approved the drug for patient care for stroke  
15 in 1996, and it's only been within the past year or so that  
16 a lot of the European regulatory agencies and others from  
17 around the world have finally agreed as well.

18           At the present time, as was mentioned,  
19 approximately 2 percent of stroke patients are receiving tPA  
20 therapy for their strokes, which amounts to maybe 4 to 5  
21 percent of the potential eligible patients. So there's a  
22 very long way to go. And the controversies have interfered  
23 with that, and I'll go in--I want to talk a little bit about  
24 the controversies.

25           Now, probably the biggest single reason that

1 stroke patients have not been receiving tPA to any  
2 appreciable extent is the three-hour window. All the  
3 studies of all the neuroprotective agents had longer time  
4 windows. They were all failures.

5 The only other study that had the same time window  
6 was the Ancrod study, and that was positive. The only study  
7 that had a six-hour time window and found a positive effect  
8 was the Prourokinase trial, which was intra-arterial  
9 therapy.

10 I think the message there is clear, at least for  
11 revascularization. It certainly is a maximum of six hours.

12 The standards of care are in the presence of  
13 changing--are currently changing, and I believe that this is  
14 helping to improve recruitment into the short time window  
15 studies. To do this requires stroke teams. It just can't  
16 be done in any other way. The patients have to be--you have  
17 to be ready for the patient coming in and have somebody  
18 basically standing there and shepherding the patient through  
19 the various procedures in order to get them in. If you just  
20 simply wait for a patient, you're not going to get them.

21 There were a large variety of protocol concerns  
22 that came up in the thrombolysis trials, and one was the  
23 concern about the ischemia subtypes. As it turned out, the  
24 ischemia subtypes were equally well treated with tPA as not,  
25 although there was plenty of controversy about that at the

1 time. For neuroprotectives it's not clear, and there's been  
2 arguments as to whether some of these--including some of  
3 these stroke subtypes has interfered with our findings in  
4 the neuroprotective trials. Again, you may on a selective  
5 basis consider including these types of reservations in the  
6 device trials.

7 A side effect that everybody was concerned about  
8 at the time when we were doing the tPA trials was whether  
9 hemorrhages would be so bad that it would be impossible to  
10 conduct the trials. That turned out not to be the case.

11 Now, there's been a lot of criticisms of the tPA  
12 trials that have come from a lot of different areas.  
13 There's been a lot of controversy in the literature, and if  
14 you end up approving a device for stroke management, my best  
15 estimate is that you will come into some of these types of  
16 criticisms as well.

17 The problem has been particularly for tPA that  
18 it's necessitating a major change in the style practice of  
19 many physicians, and there are disincentives to doing this,  
20 and I'd like to go through some of them.

21 There have been a number of publications that have  
22 come out that have claimed that the drug is useless or  
23 worse, and, again, these same types of criticisms are likely  
24 to be applied to anything that you end up approving, so I'd  
25 like--I'm doing this more as an example than anything else.

1           The claims have been--and a number of papers came  
2 out immediately after the trials came out, and they have  
3 subsequently been mostly knocked down, but the literature  
4 still exists out there, and so people use these things as an  
5 excuse for not giving the therapy.

6           One has been that it's ineffective. Well, the  
7 fact is that it is a relatively restricted patient  
8 population, the time window being the critical thing that  
9 reduces the population, potential population. But within  
10 that population, 50 percent relative risk improvement is  
11 really quite robust. It's much better than aspiring, for  
12 example, for treatment in the appropriate aspirin  
13 populations, and it is more cost-effective than surgery.

14           Another claim has been it's excessively dangerous.  
15 Well, the risks involved are about the same as the risk of  
16 endarterectomy, and as I pointed out, there is no net  
17 increased risk in bad outcomes or death out to six hours,  
18 even though it's not recommended that far out.

19           It's inconvenient, no doubt. Again, stroke teams  
20 are required. They have to be organized and maintained.  
21 There is an expense involved in doing all of that that is  
22 not adequately compensated, and that's the worst problem as  
23 far as I'm concerned. Next the time window, the biggest  
24 reason for the lack of success of tPA therapy up to this  
25 point is that the physicians are getting inadequately

1 compensated for giving it. And that's not the FDA's  
2 concern, but that does explain a large part of the reason  
3 for the lack of adoption.

4 Now, just so you won't think that I believe that  
5 we've got this all sorted out and we've figured out  
6 everything that we need to know about how to do stroke  
7 trials, this is what I call my humility slide. Here is our  
8 list of neuroprotectives. We have failed in all of our  
9 attempts up to this point. Pick your mechanism. It is on  
10 that list.

11 Now, as is the custom of the FDA, you received a  
12 series of questions to help frame the final discussions that  
13 you're going to have, and I realize that a number of the  
14 industry representatives have already answered the  
15 questions, but I'm going to try it, too. And I'll be very  
16 interested to see how well you end up agreeing with me.

17 Now, the first question had to do with what  
18 patient populations ought to be included. For exclusion, I  
19 believe that hemorrhages and small vessel strokes of various  
20 types might be excluded, but, again, this has to be looked  
21 at carefully and it shouldn't be a blanket statement one way  
22 or the other.

23 Inclusions: I believe that ischemia subtypes  
24 should be included in the trials, at least in the Phase I  
25 and Phase II trials, in order to identify the patients who

1 certainly will not benefit. And unless there's a very good  
2 reason, I think that that ought to be looked at carefully  
3 before they're excluded.

4 Now, another strategy that has been advocated by  
5 some is to use a patient population where you try to protect  
6 them from embolization during high-risk procedures,  
7 particularly CABG procedures. And the idea is that you  
8 would protect them--you have the patients in front of you.  
9 You have a preliminary exam. Then you have one after  
10 surgery, and you see if you've protected them from strokes.  
11 And this is an attractive strategy, but it's only been tried  
12 once or twice that I am aware of. And the problems with  
13 that technique are that actual substantial strokes are  
14 relatively rate in those patient populations, fortunately,  
15 and so trying to get enough events in order to use that  
16 technique requires a very large number of patients.

17 Now, there are more subtle things that go wrong  
18 with patients in the immediate aftermath of a CABG  
19 procedure, and that includes little things like losing--  
20 having a decrease in your IQ. The fact is, however, that  
21 those appear to be transient events in the overwhelming  
22 majority of cases, and so it's not clear that measuring  
23 those types of neuro-behavioral endpoints is a particularly  
24 useful thing in terms of trying to approve a therapy or a  
25 procedure.

1           Use of surrogate markers, I believe that in the  
2 not too distant future they will be useful for patient  
3 selection, but I believe that they are unacceptable as a  
4 primary outcome measure.

5           Controls, which ones should be included? Strokes  
6 cause permanent damage and are frequently fatal, and so I  
7 think up to this point the only ethical thing to do is add  
8 on designs. That means that for patients who come in within  
9 less than three hours, they should be offered tPA if they're  
10 eligible. Over three hours, placebo is acceptable up to  
11 this point as long as they're in acute therapy trials.  
12 Prophylaxis with best current medical and surgical  
13 management I think will be required for the prophylaxis  
14 studies.

15           Safety and efficacy outcome measures for the acute  
16 studies. The rating scales are the best thing that we have  
17 at the present time. As I pointed out, a number of them  
18 have been proven to be useful. I don't believe that they  
19 should be considered cast in stone at this point. There are  
20 certainly improvements that are likely to come along, and so  
21 I think that we could consider modifying them.

22           Quality of life scales, everybody's interested in  
23 them but none of them have been proven useful for stroke to  
24 the present time.

25           For prophylaxis trials, stroke or stroke-related

1 death are conventional, and I think that they're perfectly  
2 reasonable things to continue to use, and TIAs should not  
3 be.

4           Confounding factors. Concomitant medications  
5 should not interfere with devices aside from anticoagulation  
6 and that can be stopped temporarily, ethically.  
7 Combinations with proven treatments should be required.

8           When should we measure the outcomes? For acute  
9 studies, three months has been conventional, but that is  
10 arbitrary. And most of the spontaneous recovery in the  
11 placebo patients occurs within the first month, so it might  
12 be possible to shorten that to some extent.

13           For prophylaxis trials, death and recurrent stroke  
14 have generally been low in most of these trials, which  
15 necessitated following the patients for a considerable  
16 period of time. Generally, the standard has been two years,  
17 although a number of these trials have been stopped for both  
18 futility and efficacy reasons, and I think that that's a  
19 reasonable approach to the problem.

20           Thank you very much.

21           CHAIRPERSON CANADY: Thank you very much, Dr.  
22 Zivin. You've given us a lot to think about during lunch  
23 here today.

24           We're going to now break for lunch. I'd ask that  
25 we reassemble at 1:10.

1 Just one moment please.

2 MS. SCUDIERO: Lunch is being provided that's been  
3 brought in. It's catered. So you can just help yourself to  
4 the lunch there.

5 Thank you.

6 CHAIRPERSON CANADY: For a small fee.

7 [Whereupon, at 12:20 p.m., the hearing was  
8 recessed, to reconvene at 1:10 p.m., this same day.