

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGIC HEALTH
CIRCULATORY SYSTEM DEVICES PANEL MEETING

OPEN SESSION

THURSDAY, OCTOBER 11, 2007

The meeting came to order at 10:00 a.m.
in the Grand Ballroom of the Hilton
Washington DC North, Gaithersburg, MD. Dr.
Clyde Yancy, Chairman, presiding.

PRESENT:

CLYDE YANCY, MDCHAIRMAN
JOHN C. SOMBERG, MDVOTING MEMBER
GARY M. ABRAMS, MDCONSULTANT
EUGENE H. BLACKSTONE, MD CONSULTANT
DAVID C. GOOD, MDCONSULTANT
E. CLARKE HALEY, MDCONSULTANT
JOHN W. HIRSHFELD, MD CONSULTANT
VALLUVAN JEEVANANDAM, MD CONSULTANT
KENNETH JOHNSTON, MD CONSULTANT
NORMAN S. KATO, MDCONSULTANT
DEAN KINDLER, MDCONSULTANT
JOANN LINDFELD, MDCONSULTANT
DAVID MILAN, MDCONSULTANT
DAVID NAFTTEL, PHDCONSULTANT
JUDAH WEINBERGER, MD CONSULTANT
MICHAEL D. FLEMING, DDS, CONSUMER
REPRESENTATIVE
JAMES P. SWINKEEXECUTIVE SECRETARY
BRAM ZUCKERMAN, MD, FACC, FDA REPRESENTATIVE

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P R O C E E D I N G S

(10:01 a.m.)

CALL TO ORDER

DR. YANCY: My name is Clyde Yancy. I am chair of the circulatory devices panel. Welcome to the open session of today's meeting.

I am from Dallas, Texas, a medical doctor with the Baylor Heart and Vascular Institute at Baylor University Medical Center. And my area of interest and experience is heart failure, heart transplantation, cardiomyopathies, and hypertension.

I would like to call this meeting to order, and in doing so request that each of the panel members themselves, identify your institution and your area of expertise. Begin with Dr. Zuckerman.

DR. ZUCKERMAN: Good morning, Bram Zuckerman, director, FDA Division of Cardiovascular Devices.

DR. KINDLER: Good morning, Dean Kindler, stroke neurologist, Kalamazoo, Michigan.

DR. GRAVEREAUX: Good morning, Ed Gravereaux from Brigham Women's Hospital, vascular and endovascular

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surgery.

DR. MILAN: David Milan cardiac electrophysiology, Massachusetts General Hospital.

DR. NAJARIAN: Ken Najarian, University of Vermont; I'm an interventional radiologist.

DR. ABRAMS: Gary Abrams, University of California San Francisco, neurology.

DR. BLACKSTONE: Jim Blackstone, head of clinical research, department of thoracic and cardiovascular surgery, Cleveland Clinic.

DR. WEINBERGER: Judah Weinberger, interventional cardiology, Columbia Presbyterian, New York.

DR. SOMBERG: Hi, John Somberg, professor of medicine and pharmacology at Rush in Chicago, cardiovascular pharmacologist, clinical cardiology and electrophysiology.

DR. KATO: Norman Kato, cardiothoracic surgery, private practice, Los Angeles, California.

DR. LINDENFELD: Joanne Lindenfeld, University of Colorado. My interests are heart failure and heart

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transplantation.

DR. HIRSHFELD: John Hirshfeld. I'm an interventional cardiologist at the University of Pennsylvania in Philadelphia.

DR. NAFTEL: David Naftel, professor of surgery and professor of biostatistics at the University of Alabama at Birmingham.

DR. JEEVANANADAM: Val Jeevananadam. I'm the chief for cardiothoracic surgery at the University of Chicago.

DR. HALEY: I'm Clark Haley. I'm a vascular neurologist at the University of Virginia in Charlottesville.

DR. GOOD: David Good, professor, chair of neurology, Penn State University. I'm interested in stroke and stroke rehabilitation.

DR. JOHNSTON: Wayne Johnston, University of Toronto, vascular surgeon.

DR. YAROSS: Marsha Yaross, vice president, clinical, quality, regulatory and health policy, BioSense Webster in Diamond Bar, California, an industry

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representative to this panel.

DR. FLEMING: Good morning, Mike Fleming, dentist and North Carolina consumer representative.

CHAIRMAN YANCY: Thank you very much. I'd like to thank the panel members for being present, and acknowledge the expertise that is around the table.

If you haven't already done so, please sign the attendance sheets that are on the tables by the door. If you wish to address this panel during one of the open sessions, please provide your name to Ms. Anne Marie Williams at the registration table. This is very important.

Also, if you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to FDA please arrange to do so with Ms. Williams as soon as possible.

I'd note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14.

I would also like to add that the panel

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participating in the meaning today has received training
in FDA device law and regulations.

No one from the public or the press office is
allowed into this immediate panel area at any time
during a break or during the conduct of this meeting,
because proprietary information is on the table, and we
are not allowed to disclose that information to others.

Mr. Swink, the executive secretary for the
circulatory system devices panel, will now make some
introductory remarks.

Mr. Swink.

INTRODUCTORY REMARKS

EXECUTIVE SECRETARY SWINK: The Food and Drug
Administration is convening today's meeting of the
Circulatory System Devices Panel of the Medical Devices
Advisory Committee of the Center of Devices and
Radiological Health, under the authority of the Federal
Advisory Committee Act of 1972.

With the exception of the industry
representative, all members and consultants of the panel
are special government employees or regular federal

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employees from other agencies, and are subject to federal conflict of interest laws and regulations.

Following the formation and the status of this panel's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC Section 208, and Section 712 of the Federal Food, Drug and Cosmetic Act, are being provided to the participants in today's meeting, and to the public.

FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208 Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FT&C act Congress has authorized FDA to grant waivers to special government employees or regular government employees

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with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this panel who are SGEs have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor child, and for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, in contrast to grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda the panel will discuss and make recommendations regarding clinical trial designs for carotid artery stenting, and patients not at high risk for adverse events from surgical revascularization.

This is a particular matters meeting during which general issues will be discussed.

Based on the agenda and all financial interests reported by the panel members and consultants,

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conflict of interest waivers have been issued in accordance with 18 USC Section 208 and Section 712 of the FT&C act to Drs. Edward Gravereaux and Clyde Yancy.

Dr. Gravereaux's waivers involve two consulting arrangements with manufacturers of carotid artery stents, both for which he receives less than \$10,001. Dr. Yancy's waives involve unrelated consulting arrangement with an unaffected unit of carotid artery stent manufacturer, for which he receives less than \$10,001.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov.

Copies of these waivers may also be obtained by submitting a written request to the agency's Freedom of Information Office, Room 6-30 of the Parklawn building.

A copy of this statement will be available for a review at the registration table during this

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meeting and will be included as part of the official transcript.

Marsha S. Yaross, Ph.D., is serving as the industry representative, acting on behalf of all related industry, and is employed by BioSense Webster, a Johnson & Johnson company.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or an imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the panel of any financial relationships that they may have with any firms at issue.

Before I turn the meeting back over to Dr. Yancy, here are a few general announcements.

Transcripts of today's meeting will be available from Neil Gross & Co. Information on purchasing videos of today's meeting can be found on the

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table outside the meeting room. And presenters to the panel who have not already done so should provide FDA with a hard copy of their remarks, including overheads.

The press contact for today's meeting is Heidi Valetkevitch.

Thank you.

CHAIRMAN YANCY: We are on time, which is very much appreciated, and we will go forward with the FDA presentation.

FDA PRESENTATION

MR. CAVANAUGH: Thank you, Dr. Yancy.

My name is Ken Cavanaugh. I'd like to start off today by thanking everybody for attending this meeting. And I'd especially like to thank the panel members for taking some time out of their schedules to offer their recommendations on some important clinical topics today.

The two main topics today are clinical trial designs to evaluate carotid artery stenting in patients who are not considered high surgical risk, and the optimization of the quality of clinical data collected

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in these trials.

FDA's main goal for this advisory panel meeting is to use the recommendations of the panel to develop clinical trials capable of demonstrating the safety and effectiveness of carotid stenting in a non-high risk population.

To this end these studies should be expected to produce valid scientific evidence which is required to support approval of a pre-market approval application, or PMA, for this indication.

One of the key issues of optimizing the design of these studies is mitigation of the potential challenges to the conduct of carotid stenting studies, such as the rate of subject enrollment, and the interpretability of the resulting data.

Before we get started I would like to provide an overview of today's presentation. I will begin with an introduction to carotid artery disease and stenting, followed by a summary of FDA's current recommendations on this topic.

Dr. Will Sapirstein will then present the

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currently available clinical evidence regarding carotid revascularization.

Dr. Cho Ahn, a biostatistician, will follow with an explanation of some of the challenges that a carotid stenting study in non-high risk subjects may face.

Dr. Michael Barnett will then present the positions of key stakeholder medical societies on carotid endarterectomy and stenting.

A summary of the presentation will then follow, and afterwards, we would be happy to answer any questions the panel may have.

So let's get started with some background information that explains why we're interested in this topic.

The clinical problem at the heart of this discussion is stroke. Stroke is defined by the World Health Organization as a persistent neurological deficit of cerebrovascular cause. It is the third leading cause of death in this country, and the leading cause of disability.

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Recent figures suggest that 700,000 strokes occur each year, resulting in 160,000 deaths, 500,000 new stroke victims, and 200,000 recurrent strokes.

The annual total cost has been estimated at \$57 billion. So we're talking about a disease that is very costly in many ways.

Now what causes stroke? While it is not easy to determine the root cause of a particular stroke, one estimate of stroke etiology is that 30 percent of strokes occur due to extracranial disease of the carotid artery supplying blood to the brain, with an equal proportion resulting from ischemia unrelated to the carotid artery.

Twenty percent of strokes result from hemorrhagic causes, and vertebral-basilar disease contributes to the remaining 20 percent.

I'd now like to focus on carotid artery stenosis as a significant contributor to stroke.

The health risks posed by carotid stenosis are different from the risks resulting from stenosis in other vessels such as the coronary arteries in that the

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main concern is the generation and downstream migration of embolic debris from the embolic plaque - the stenotic plaque, excuse me.

The speed of blood increases as it flows through the stenosis, which is believed to increase the shear forces acting on the plaque, and increasing the likelihood that debris will be dislodged and include an important vessel downstream.

The presence of the stenosis itself typically does not limit the flow of blood to the brain, because the brain possesses a rich network of collateral vessels that is capable of maintaining adequate brain oxygenation provided there is no downstream occlusion.

Carotid stenosis is considered clinically significant in about 5 to 7 percent of patients 65 years of age or older. Significant stenosis can initially be detected through non-invasive means, such as duplex ultrasound, or more invasive methods such as angiography are often used to confirm the initial diagnosis.

In the context of clinical trial design and analysis, carotid stenosis is typically characterized as

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either symptomatic or asymptomatic, depending on whether or not a neurological event affecting the ipsilateral hemisphere has previously occurred.

Symptomatic status is frequently defined using a specific time frame such as six months. Subjects who last experienced an ipsilateral neurological event outside of this time frame would be defined as asymptomatic for purposes of this study.

Therefore it is important to note that subjects who are classified as asymptomatic may not in fact be completely free of prior symptoms.

There are currently three main treatment options for symptomatic and asymptomatic carotid stenosis. These are best medical therapy, carotid endarterectomy and carotid artery stenting.

Optimal medical therapy can take many forms depending on the health and co-morbidities of the patient. Clinical trials have benefits to anti-platelet regimens such as aspirin and clopidogrel which lower the risk of secondary stroke in symptomatic patients.

The use of a dual or triple anti-platelet

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regimen may be effective when patients do not respond to a single drug, although such a strategy increases the risk of hemorrhage and other bleeding complications.

In addition to the anti-platelet therapy, statins and ACE inhibitors have been shown to reduce the risk of stroke in patients with the associated risk factors, namely, hyperlipidemia and hypertension.

Another treatment strategy for carotid stenosis is carotid endarterectomy which consists of surgical excision of the stenotic plaque in the carotid artery.

This procedure was first introduced in 1953, and by the mid-1980s it had become the most common vascular surgical procedure in the United States.

Today over 130,000 procedures are performed annually, and it represents the current gold standard for carotid revascularization.

However, the role of carotid endarterectomy in the prevention of stroke is not always clear. This role was established through the conduct of several landmark clinical trials from the late-1980s to the

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early 2000s, which I'll now briefly summarize. In symptomatic patients a treatment strategy of carotid endarterectomy in combination of optimal medical therapy was shown to produce long term outcomes superior to medical therapy alone in two randomized controlled trials, the NASCET trial in North America, and the ECST trial in Europe.

The benefits provided by surgery were mitigated by the degree of carotid stenosis, with greater benefit observed when tighter stenoses were treated.

The mortality and morbidity rates associated with the endarterectomy procedure itself also affected long term benefit.

Similar superiority results were demonstrated in asymptomatic benefits in two more randomized trials, ACAS in North America, and ACST in the United Kingdom.

While the treatment group in both studies consisted of carotid endarterectomy plus medical therapy, the control groups differed slightly.

The ACAS control group was medical therapy

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alone, while the control group in the ACST was deferred endarterectomy. In other words endarterectomy was not to be performed unless the subject became symptomatic or presented some urgent need for a vascularization.

More detailed presentation of these four studies will be provided later in the presentation by Dr. Sapirstein.

While carotid endarterectomy was shown to have a role in treating carotid stenosis, not all patients make good surgical candidates for a number of reasons. If a high procedural adverse event rate is expected for a given patient, endarterectomy becomes a less acceptable option for them.

However, these patients may provide benefits from carotid artery stenting, the most recently introduced treatment option for carotid artery stenosis.

In this minimally invasive procedure, a stent or tubular mesh structure is inserted endovascularly, and delivered to a target vessel on a dedicated stent delivery system.

Once within the target lesion the stent is

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expanded, and it provides a scaffolding function to the vessel to stabilize the plaque, and it also provides a gentle outward force to the vessel wall to main patency.

With the introduction of the carotid artery stenting in the late 1980s was associated with a high incidence of procedure-related embolism, carotid stenting procedures are now most often performed in conjunction with an embolic protection device, which is placed distal to the lesion to capture and remove embolic debris generated during the procedure.

The specific effects of embolic protection on the overall procedure event rates have not been definitively established.

It is important to note that while stenting may now present the same set of risks as surgery, this does not mean that stenting provides less overall risk than surgery. These each present particular types of risk for the patient.

To date there are five carotid stent systems approved in the United States: the Guidant Acculink, which has since been purchased by Abbott Vascular; the

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Abbott Vascular Xact; the Cordis Precise; the Endotex Nextstent which has since been purchased by Boston Scientific; and the ev3 Protege.

These systems were all approved over approximately a 2-1/2 year time frame from August 2004 to January 2007.

These stent systems were all approved with nearly identical indications. The stents are indicated for the treatment of patients at high risk for adverse events from carotid endarterectomy who require percutaneous revascularization, and who have either neurological symptoms and at least 50 percent carotid artery stenosis, or no neurological symptoms and at least 80 percent carotid artery stenosis.

The target vessel must also be appropriately sized to accommodate the stent.

The safety and effectiveness of carotid stenting was last discussed by the advisory panel in April, 2004, in a public meeting to discuss a PMA for the Cordis Precise carotid stent system.

The panel recommended that the PMA be found

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approvable with certain conditions. These conditions mainly involved labeling restrictions, limiting the use of the device to subjects who are at high surgical risk.

Another set of conditions involved the need to conduct a post-approval study to evaluate the safety and effectiveness of the device outside of controlled clinical studies.

The panel underscored the need for careful followup in the post-market cohort.

We're happy to say that published results from post-approval carotid stenting studies have been consistent with pre-market study results, and follow up compliance has been robust.

The panel also made a number of important points that are relevant to this current panel meeting.

First the panel noted that current challenges involving the appropriateness - excuse me, certain challenges involving the appropriateness of comparability arise when using historical data as controls for a given clinical study.

The panel also stated that composite study

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endpoints were challenging to implement for studies comparing surgical and non-surgical treatment options due to the different gross profiles for each procedure, as I previously mentioned.

In a similar vein, the panel commented that subjects with certain anatomic risk factors may not make suitable candidates for carotid stenting, again demonstrating the different sets of risks posed by stenting and surgery.

Finally, and as stated on the previous slide, follow up in this post-approval phase was considered essential to evaluate this technology.

Now the five previously mentioned stent systems were all approved for use in high surgical risk patients. There's currently no carotid stent system approved for use in patients who are not at high risk for adverse events from carotid endarterectomy.

These patients represent the majority of potential patients with carotid artery disease, and may outnumber the high surgical risk population by two to one according to some estimates.

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Given the impact on public health on this large potential population, FDA believes that robust, prospective, multi-center clinical trials involving these patients are needed to demonstrate both the proof of concept of carotid stenting procedures in general, and to evaluate the safety and effectiveness of specific carotid stent systems with the goal of supporting PMA applications for the non-high risk indications.

This is why we're here today.

That concludes the introduction. I will now present our current recommendations in this area, and I will outline our questions for the advisory panel to be answered later.

When considering how best to evaluate carotid stenting in a non-high risk population we frequently turn to several key resources. The first is our guidance document on carotid stenting which was published in 1996. Despite its age the clinical trial recommendations are still mainly applicable to the non-high risk population. FDA guidance documents are used to communicate our current thinking on a given topic,

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and tend to represent best practices for collecting and presenting information to support a marketing application or clinical study protocol.

However, I'd like to emphasize that these documents are not at all binding on FDA, device manufacturers, or clinical study sponsors, and their contents should not be considered requirements unless there's a specific regulatory or statutory basis.

In addition to the guidance FDA considers both relevant published literature involving carotid revascularization as well as input from the advisory panel when considering recommendations for clinical studies.

Our overall recommendation for conducting a clinical trial to evaluate carotid artery stenting in a non-high risk population is to conduct a prospective multi-center randomized controlled trial comparing carotid stenting to endarterectomy. Such a design is expected to minimize the impact of bias and confounding on data interpretability. And Dr. Ahn will be discussing the significance of these two factors

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shortly.

A non-inferiority approach can be taken, which allows a specific non-inferiority margin to be used as the maximal allowable difference between the stenting and surgical study arms.

This non-inferiority margin, or delta as we sometimes call it, should be small enough to rule out a clinically meaningful difference in event rates.

Non-inferiority margins are usually pre-specified as an absolute number, or defined as a proportion of the observed control primary event rate.

As the primary endpoint of such a trial, FDA recommends a composite endpoint in incorporating periprocedural morbidity and mortality to assess the procedural safety and the longer term rate of stroke ipsilateral to the stented vessel as a measure of the durability of the procedure.

An example of such an endpoint is the rate of death, stroke and myocardial infarction within 30 days of the procedure, plus the rate of ipsilateral stroke from 31 to 365 days after the procedure.

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In addition to these recommendations, FDA recommends long-term follow up of the study cohort to assess the continued durability of the procedure, and to determine if any new event types occur.

FDA also recommends that all clinical assessments be as independent and objective as possible. Some ways towards this goal are: use of a clinical events committee to adjudicate adverse events; a data safety monitoring board to evaluate the ongoing safety of the study participants; and core lab analysis to objectively analyze the clinical data.

Finally, FDA recommends a multi-specialty team approach to treating subjects at each investigational site to minimize the effects of bias. For example such a team might include a vascular surgeon, a neurologist, and an interventional cardiologist or radiologist.

So these are our recommendations to date. However, we recognize that these recommendations could be optimized to enhance the quality of data collected in these studies.

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To that end we have the following questions for the panel.

Question one: Can acceptable non-randomized control trial designs that compare carotid artery stenting to carotid endarterectomy in patients who are not at high risk for adverse events from surgical revascularization be developed? If so, please provide recommendations regarding the choice of control, subject eligibility criteria, endpoints, and selection methodologies for minimizing bias and confounding.

Question number 2a: Does sufficient clinical equipoise still exist so that the performance of randomized control trials to evaluate carotid stenting is sufficiently scientifically and ethically validated? If so, what are the current barriers to enrollment in randomized control trials involving carotid revascularization?

Question 2b: What if any study parameters can be modified to facilitate enrollment in randomized control trials without unduly compromising the validity of the resulting data?

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Examples of study characteristics that may affect enrollment are subject eligibility criteria, follow up type in duration, and subject recruitment methods.

Question number 3: If the proof of concept of carotid stenting in non-high risk patients is successfully demonstrated, would your study design recommendations change? If so in what way? For example would you recommend a non-inferiority randomized control trial comparing two carotid stent systems?

Finally, question number 4: What other recommendations do you have that may facilitate initiation, enrollment, completion and interpretability of clinical trials for this indication?

We welcome the panel's input on these topics, as well as any other related topics that arise during the panel's deliberation.

Now, Dr. Will Sapirstein will present the available clinical evidence regarding carotid revascularization.

DR. SAPIRSTEIN: Good morning. I will be

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summarizing the important clinical trials involved in carotid revascularization that will provide a background for issues involving stent studies. These studies include landmark carotid endarterectomy trials by - for symptomatic and asymptomatic subjects that have been previously mentioned, as well as important randomized and non-randomized carotid stenting studies involving both high surgical risk and non-high risk populations.

For randomized controlled trials establish the effectiveness of carotid endarterectomy for eliminating the extra cranial carotid arterial disease responsible for up to 30 percent of the 700,000 strokes that occur annually in the United States.

These trials are the North American Symptomatic Carotid Endarterectomy Trial; the European Carotid Surgery Trial; the Asymptomatic Carotid Artery Study; and the European Asymptomatic Carotid Surgery Trial that were all concluded and published between 1991 and 2004.

The conclusions of these studies provided the definitive data for the etiologic relationship for

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cerebrovascular actions to arterial embolism originating from extra-cranial carotid or atherosclerotic disease.

The risk of stroke in neurologically symptomatic patients is substantially increased as a function of their stenosis severity as seen in this slide. This is also emphasized in the number needed to treat with endarterectomy to prevent a stroke.

The stroke risk is also significant in asymptomatic patients as demonstrated in the ACAS and ACST studies. The stroke risk, the number needed to treat, and the cerebrovascular actions prevented by treatment of 1,000 patients is similar in both these seminal carotid endarterectomy trials involving asymptomatic subjects.

The NASCET and ECST trials provided level one evidence for the benefit of carotid endarterectomy in preventing stroke in certain patients with symptomatic carotid stenosis. The benefit increases with the severity of the stenosis, and is much diminished when stenosis severity is less than 30 percent.

These benefits for carotid endarterectomy are

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attenuated by any increase for the procedural risk of mortality or morbidity due to the occurrence of stroke.

The two-year follow up for lesions greater than 70 percent was obtained in the NASCET study. The five-year data for less than 70 percent lesion stenosis, quoted here, is from the European ECST study.

A lesser degree of benefit was demonstrated in the ACAS and ACST trials for carotid endarterectomy in asymptomatic patients if the carotid stenosis exceeded 60 percent.

Severity of stenosis above the watershed of 60 percent did not, unlike symptomatic patients, modify risk for stroke in the medically controlled arms of these trials.

A much reduced peri-operative risk is necessary to achieve this benefit in the asymptomatic patients than is required for the larger benefit in symptomatic patients with at least 3 percent risk versus 6.7 percent risk for the symptomatic patients.

With the introduction of carotid arterial stenting to a less - for a less invasive option to

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carotid stenosis, several studies were conducted comparing these two interventions.

Study designs included randomized control and nonrandomized concurrent trials control to carotid endarterectomy as well as single armed observational studies controlled to historical endarterectomy data.

The key eligibility criteria for these studies typically focused on the subjects' surgical risk status, symptomatic status, and the severity of stenosis.

Other enrollment considerations included the age and gender of the patient.

Many studies involving high surgical subjects have been recently conducted in the United States. Seven of these studies are summarized in this slide. Of these, six were single arm studies, and one, the SAPPHERE study, was a randomized control trial with registry arms included.

The studies all incorporated similar eligibility criteria with respect to the subjects' symptomatic status and the percentage of symptomatic

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subjects controlled in each study was comparable.

Just go back - I missed the slide. These are the variables categorized as anatomical and co-morbid conditions which were applied in various combinations to designate patients at high risk for a surgical carotid intervention.

Subjects classified by co-morbidity outnumbered by far those with anatomic risk factors in every case. No criterion was included for high risk of a stroke due to the characteristics of the lesion such as a thrombosis or mobile embolism or excavated ulcerated plaque.

These four stent systems have been approved by the FDA for treatment of patients at high risk for carotid endarterectomy, and these have been single arm studies. Almost identical composite primary endpoints were employed in the analysis of these studies, which consisted of all-cause mortality, all stroke, and myocardial infarction occurring for the procedure and out for 30 days to capture pre-procedural risk for safety.

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The rate of ipsilateral stroke occurring from 31 to 360 days was also captured for assessment of effectiveness. The single contribution of major importance in the primary response variable was a 30-day stroke for all of these studies, which as noted there is 15 and 20 percent - 20 cases.

In contrast to these previous four studies, the SAPPHIRE study was designed as a randomized control trial to demonstrate non-inferiority of carotid stenting with embolic protection to carotid endarterectomy in patients at high risk for surgery.

Patients enrolled but deemed to be at too high a risk for adverse events from either surgery or stenting were placed in registry arms for either carotid endarterectomy or a CAS tied to the randomization process.

In total 334 subjects were randomized to either stenting or carotid endarterectomy, and 406 patients were placed in the stent registry, and only seven in the carotid endarterectomy registry.

The primary endpoint was the cumulative

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death, stroke or myocardial infarction occurring within 30 days, as well as death or ipsilateral stroke between 30 days and one year.

No statistical difference by intent to treat analysis existed in the primary endpoint at 30 days. At one year a difference of 7.2 percent in composite endpoint between the two randomized arms of the study statistically supported the non-inferiority of stenting to carotid endarterectomy.

This latter outcome has been criticized as attributable in large measure to the incidence of non-Q wave myocardial infarction in the carotid endarterectomy arm based on a twofold elevation of creatinine kinase with a positive MV fraction.

The outcome in the stent registry and in the stent randomized arm were comparable.

The randomized component of this study experienced very low enrollment and was not completed as planned. The onset of poor enrollment occurred at the time when single armed carotid stenting studies, including those using the Cordis system, became more

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prevalent possibly usurping candidates suitable for randomization.

Due to the low randomized sample the study did not have sufficient power to conduct a planned intended alternative analysis for superiority of stenting to surgery.

Now I would like to discuss some non-high risk carotid stenting studies, two of which have been concluded and published, and some of which are ongoing.

The SPACE trial was conducted from 2001 through 2006 in 35 centers in Germany, Austria and Switzerland. SPACE was a randomized trial designed to determine if carotid stenting is non-inferior to endarterectomy. The primary endpoint was the rate of death and ipsilateral stroke at 30 days per procedure.

Enrollment was originally planned for 1,900 symptomatic patients with severe carotid stenosis. Subjects were excluded from the study if any of several risk - high risk factors existed for surgical intervention.

This is the 30-day result obtained as an

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interim analysis of the first 1,200 patients enrolled. The upper confidence limit for the absolute difference in the primary endpoint between the two arms exceeded the non-inferiority margin for the study.

The results also failed to demonstrate that endarterectomy was superior to stenting. But based on the interim analysis an unacceptably high number of additional - and the high number of additional enrollments, subjects that were calculated to be required to demonstrate the non-inferiority of stenting, the further subject enrollment was terminated mainly for lack of funding.

The EVA-3S study was very similar to the SPACE in that it was a randomized multi-center European study investigating the non-inferiority of carotid stenting to endarterectomy in non-high risk symptomatic subjects.

Study enrollment took place from 2000 to 2005, and the patency endpoint was - and the primary endpoint was the rate of all death and stroke at 30 days

These are the results for 30 day followup of

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the first 520 subjects. At this time the data safety committee halted enrollment due to study concerns associated with the high rate of stroke in the stenting arm, especially in the elderly patients, as well as the futility to demonstrate the non-inferiority of stenting.

While SPACE and EVA-3S resulted in similar conclusions, both have been criticized for study design that some observers believe may have affected the outcomes.

First, the use of embolic protection devices was not required throughout the duration of either study. In SPACE embolic protection device use was always an option of the operator. In EVA-3S embolic protection device use was recommended by the data safety committee in 2003, three years after the study inclusion.

Another criticism is that the training requirements for operators in the stenting and endarterectomy arms were unbalanced, being less rigorous for stent use than for the surgical arm participants, and afforded a possible advantage to the carotid

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endarterectomy arm.

However the EVA-3S investigators failed in very stark analysis, subset analysis, to show any stent learning curve. The sponsors did determine that there was a statistically significant difference between the results of subjects treated with and without embolic protection. However only 20 patients underwent unprotected stenting compared to 227 that had cerebral protection devices used during the deployment of stents.

This slide illustrates the demographics of the CaRESS enrollments. Sorry, I've got these slides all mixed up.

SPACE and EVA-3S were randomized trials. The CaRESS study was a multi-center nonrandomized concurrently controlled study designed to compare carotid stenting to surgery in both symptomatic and asymptomatic subjects.

In an attempt to mimic real-world clinical practice subjects were treated with either stenting or surgery based on the preference of the patient and the treating physician.

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In addition enrollment was not adjusted for surgical risk data. The primary endpoint was the 30-day use of death and non-fatal - the primary rate of death and non-fatal stroke.

During the feasibility stage of the study, 397 patients - 397 patients were enrolled at United States centers between 2001 and 2002, with enrollment at each site conducted to maintain a two to one ratio favoring the surgical arm.

More than two-thirds of the subjects were asymptomatic, and 86 percent were considered at high surgical risk.

The demographics of the CaRESS phase one subjects indicate a significantly higher incidence of repeat carotid interventions, either endarterectomy or angioplasty, in the stent arm.

In other respects, clinically relevant characteristics were well balanced between the two arms.

The outcome of the two CaRESS arms were not significantly different at both 30 and 365 days. Surgical risk data was not a predictor of study

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outcome. However, because of the relatively low number of non-high risk subjects enrolled extrapolation of the outcomes to a non-high risk population is problematic. A phase two study based on the feasibility - on this feasibility study results has been proposed.

So in brief summary the randomized SPACE and EVA-3 trials failed to prove the non-inferiority of carotid stenting to endarterectomy in non-high risk subjects. The presence of potential confounding factors that afford - has afforded interpretability problems and limited the impact of the results on community clinical practice except perhaps to avoid carotid arterial stenting in the artery. And this underscores the need for well designed and conducted trials.

The non-randomized CaRESS phase one study suggests non-inferiority of stenting to surgery in a population with mixed surgical risk and symptomatic status. Because this was a feasibility study, however, the overall significance of the results is not clear.

Although the non-randomized study was able to enroll subjects with balance of clinically obvious

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relevant covariates in each arm, the extent of confounding for unknown clinical relevant covariates is uncertain.

In addition to these studies there are a number of randomized trials of the other currently - that are either currently enrolling or under development. This slide summarizes the design of four of these studies that are representative of a broad range of geographic sites, control treatments, and subject populations.

FDA is looking forward to the completion of these studies and hopes that the results can be used to optimize the treatment of all patients with carotid artery disease.

That completes my rather confused presentation, and Dr. Ahn will now present a statistical commentary on the trial design issues for non-high risk carotid arterial stenting.

DR. AHN: Thank you.

Good morning, my name is Charles Ahn. I'm a statistician in the division of biostatistics.

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Today I will present some challenges to clinical trial conduct and development in carotid stent studies.

This is the outline. I'll present a brief introduction of randomized control trials and nonrandomized concurrently controlled trials, and then discuss some issues with these two types of trials in carotid stent studies.

In particular slow enrollment with randomized control trials and treatment comparability and selection bias with nonrandomized concurrently controlled trials.

In well designed and well conducted randomized controlled trials we expect that all patients covariates, major or not major, are balanced between the two treatment groups. So the two treatment groups are comparable, and observed treatment difference is an unbiased estimate of treatment difference.

While FDA recommends that randomized controlled trials be conducted to evaluate carotid stenting in the non-high risk patient population, conducting the studies is not without its own set of

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challenges. The potential issue with this is, these studies may enroll patients more slowly than anticipated.

Slow enrollment may increase the likelihood that clinical practice or the device design will change over the course of the investigation. Such changes may call into question the generalizability and the clinical relevance of the resulting data.

Slow enrollment may be due to preferences of enrolling investigators who may often believe that potential subjects would be better served by one treatment versus the other, and therefore should not be involved in the study.

In addition the potential subjects themselves may decline to enroll in the studies because they are uncomfortable with the concept of randomization.

Especially if the subject is faced with treatment via either a surgical procedure or a minimally invasive alternative that may be perceived as more desirable.

Let me give you concluding remarks for

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randomized control trials.

A well designed and well conducted randomized controlled trial provides the highest level of clinical trial evidence. However, reliance on randomized control trials may paradoxically not allow investigators to acquire the required evidence in a reasonable time frame leading to premature study termination of well designed trials.

Another study design option for comparing carotid artery stenting and carotid endarterectomy is a nonrandomized study design where subjects are allocated to either stenting or the surgery arm based on factors such as physician judgment and subject agreement, not through a full randomization process.

Such a study will experience more rapid enrollment because patient can be involved based on physician and patient preferences. However there is no guarantee that patient covariate measured or unmeasured are balanced between the two treatment groups. So the two treatment groups may not be comparable.

In a nonrandomized study, allowing the

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investigator to exercise judgment in recruiting subjects and selecting treatment options for them can introduce considerable bias. This is a selection bias which will be discussed in more detail later.

Bias may also occur when a subject receives a treatment, or study endpoints are evaluated. It is also important to note that a randomized controlled trial and carotid stent study may also be subject to these two types of biases, treatment bias, and assessment bias, because the investigator will not be blinded to the study arm.

Now selection bias. Let me start with an example. There might be a situation where the investigator may prefer one particular treatment for their healthier subjects, which is likely to result in this particular treatment appearing to have more favorable outcome relative to the other treatment regardless of its actual merit.

If the treatment characteristics are not comparable between the two study arms due to selection bias, whether it is intention or unintentional, the

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study result may be confounded, because any perceived treatment effect may in fact be due to an imbalance of clinically relevant prognostic factors between the stenting and the surgery arm.

So if there exists a significant difference in two arms, we cannot differentiate whether this difference is due to treatment or due to confounders.

Here's an example of confounding. If control group has older and sicker patients than treatment group, the low success rate with the control group may be due to this patient characteristics, not because of the new device being more effective.

Other potential confounding factors include investigational site and physician training and experience.

Here is a dilemma with nonrandomized control trials. Known and major confounders may be controlled by a statistical method, such as covariant adjusted analysis or propensity analysis. But there are still unknown or unmeasured confounders.

Therefore we never know whether we were

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entirely successful.

Here is another one. If two control groups were not comparable, any statistical method cannot correct this to make them comparable. Furthermore, we cannot know whether they are comparable or not until the treatment is assigned to all of the patients or the end of the study.

For these reasons nonrandomized controlled trials may not be least burdensome, and in fact, it may pose a high risk for the sponsor in terms of meeting this primary endpoint.

In summary, bias and confounding cannot be expected to be completely eradicated in the nonrandomized control trials. There will always be concerns regarding these potential problems.

A key power question, however, will be whether potential problems related to bias and confounding in the nonrandomized carotid artery stenting trial can be sufficiently minimized through a careful study design and execution, such that it is reasonable for a study sponsor to choose this pathway.

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Now I would like to introduce Dr. Michael Barnett. He will present the professional society perspectives.

DR. BARNETT: Good afternoon. I'll present the professional society perspectives on carotid revascularization.

As a general overview, I'll present the recommendations given for endarterectomy and carotid artery stenting, as well as the American Heart Association and ACC recommendations, and a brief summary of how those recommendations are classified.

They are classified by class level, which is the strength of the recommendation, and the level of evidence supporting that recommendation.

The recommendation classes are class one, two, and three. In class one there is general agreement or evidence that the procedure or treatment is useful and effective; class two is that there is conflicting evidence or divergence of opinion on the utility of the procedure, and that's further broken down into class 2a and 2b; while class three is general agreement or

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evidence that the procedure is harmful or not useful.

Level of evidence are outlined in A, B and C. Level A evidence is data derived from multiple randomized control trials. Level B, data derived from a single RCT or from a nonrandomized study; and level C is expert opinion or case studies.

The ANA/ASA guidelines on carotid endarterectomy in symptomatic patients break the patients down into three broad categories: those with 70 to 99 percent stenosis; 50 to 69; and those with less than 50 percent stenosis.

They state that carotid endarterectomy is recommended by a surgeon with a perioperative morbidity and mortality of less than 6 percent. This gets a class one A level recommendation.

Carotid endarterectomy for the moderate stenosis group is recommended depending on specific patient factors such as age, gender, the comorbidities, and severity of initial symptoms; while those with less than 50 percent there is no indication for endarterectomy.

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The guidelines for carotid artery stenting in symptomatic patients state that among patients with severe stenosis those greater than 70 percent, that carotid artery stenting is not inferior to endarterectomy and may be considered in patients who are difficult to access surgically; in patients who have medical conditions that greatly increase their risk of surgery; and when other specific circumstances exist, for example, a prior radiation.

They go on to say that carotid artery stenting is reasonable when performed by operators with established periprocedural morbidity-mortality rates of 4 to 6 percent similar to that observed in endarterectomy and stenting trials.

The guidelines published in 2006 for asymptomatic patients with respect to endarterectomy and carotid stenting include the prophylactic carotid endarterectomy is recommended for highly selected patients with high grade stenosis when performed by surgeons with a less than 3 percent morbidity and mortality rate. And that received a class 1 level A

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recommendation.

Prophylactic carotid artery stenting they state might be a reasonable alternative to endarterectomy in asymptomatic patients at high risk for endarterectomy. However they go on to say that there is uncertainty whether these patients should have either a stenting or endarterectomy due to periprocedural and one-year event rates.

In 2007 the American College of Cardiology along with the other mentioned professional societies produced an expert consensus document on carotid artery stenting. And they summarized by saying at the present time, there is insufficient evidence to support carotid artery stenting in high risk patients with asymptomatic stenosis, less than 80 percent, or in any patient without high risk features.

This is consistent with the FDA's determination that the safety and effectiveness of any stenting device has not been shown in a non-high risk population.

And with that I'll turn it over to Dr. Ken

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Cavanaugh.

DR. CAVANAUGH: Thank you.

So I'd now like to summarize the key points from this presentation.

The carotid artery stenting is currently only approved by FDA for the treatment of carotid stenosis in high surgical risk patients. This approval was based on a reasonable assurance of safety and effectiveness in the indicated population.

However the safety and effectiveness of carotid stenting has not been demonstrated in the non-high risk population which includes the majority of patients with severe carotid stenosis.

FDA currently recommends conducting a randomized control trial to gather these data because this design is expected to optimize the quality of clinical data collected.

FDA respectfully requests advisory panel input to answer the question of whether clinical evidence from a randomized control trial is necessary to demonstrate the equivalence of carotid stenting in

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endarterectomy and necessary to support the safety and effectiveness of specific carotid stent systems.

FDA also encourages the panel to recommend specific study design elements intended to increase the robustness of these studies.

That concludes our presentation. We'd be happy to answer any questions you may have.

PANEL QUESTIONS

CHAIRMAN YANCY: Dr. Cavanaugh, thank you very much for the presentations from yourself and the FDA team.

We have several minutes that we can use to query the FDA team before we go into our first open public hearing.

I was especially struck by the one statement from Dr. Ahn that I thought had quite a bit of merit, and demonstrated that ironically there are certain circumstances under which the non-randomized trial might be more burdensome. And so I think it might be helpful to develop that thought process a bit further.

Dr. Johnston.

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DR. JOHNSTON: This is a very basic question which I've not heard answered. What is a high risk patient? Is this a high risk patient for surgery? Or a high risk patient for stroke? Or both?

And therefore what are we debating today when we're talking about low risk? I wonder if the FDA would address it.

DR. CAVANAUGH: Sure, and so these patients have been traditionally defined as high risk fo adverse events from carotid endarterectomy, so they don't present a good risk profile for the surgical procedure itself, not necessarily any risk associated with stenting, or any risk for future stroke if they were to be untreated. It's more about the specific surgical procedure itself.

Does that answer your question?

DR. JOHNSTON: I think it does. On tab 2 on page 17 of 26 at least from some of them, are those risk factors, I find them personally somewhat vague. And I'm not sure where I personally would draw the line if it weren't for a protocol.

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So are you implying that the proposal we would have for low risk would simply be the converse of all of these, for example, the converse of a hyate, converse of the presence of angina, and so on?

DR. CAVANAUGH: In general that's how we've considered the non-high risk studies to be. So just thinking about it conceptually - other people can chime in - you would have these high risk studies that we heard about, SAPPHIRE and other, registry studies, let's say, single arm studies.

And then you would have non-high risk studies. And I can't really think of a patient that could potentially have been enrolled in either study, because the inclusion criteria for the high risk studies, namely, the presence of one of these anatomic or comorbid factors would be an exclusion criteria for the other studies, because we're focusing on patients who appear to present a similar risk profile for either procedure, so they're suitable and comparable in that respect.

DR. ZUCKERMAN: So, Dr. Johnston, you've

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raised a key question. Does that help you out? The other slide of merit is slide #42 in the FDA presentation. Where generally in these clinical trials I think you had to have two significant comorbidities, or one anatomic risk factor.

And the key point is as you say, perhaps we should change the nomenclature for these prior FDA trials to higher risk surgical patients, and now we're going towards lower risk.

And we acknowledge that there are some surgeons who would operate on any of these patients in this matrix on slide #42.

DR. CAVANAUGH: That's helpful.

CHAIRMAN YANCY: We have had one panel member join us since we started. If you would introduce yourself please, and then proceed with your question.

DR. COMEROTA: Well, first of all, I'd apologize for being late. I was under the impression we were starting at 10:15.

My name is Anthony Comerota. I'm a vascular surgeon from Toledo, Ohio. I'm the director of the

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Jobst Vascular Center, and I have an academic appointment as an adjunct professor of surgery at the University of Michigan.

CHAIRMAN YANCY: Thank you.

DR. COMEROTA: May I proceed? Question: Does the FDA wish to address the risk of the lesion being treated? There's an awful lot of focus on the risk of the patient undergoing a procedure. I think it's well recognized that recurrent stenoses, fibrous lesions, lower grades of stenoses have a much lower risk of neurological event treated medically or non-operatively, nonprocedurally, versus the atherosclerotic lesion which is high grade stenosis.

And then of course stratifying for whether that lesion is symptomatic versus asymptomatic.

So my question is, what degree of importance does the FDA place on the type of lesion which is being treated in the framework of either medium risk or routine risk versus high risk patients?

DR. CAVANAUGH: Well, I can take the first attempt to answer that question.

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So I think I see kind of two components to what you're asking. The first with regards to constructing a clinical trial and how does - how do those lesion factors, let's say, enter into it?

I think, for the purposes of this discussion where we're focusing on non-high risk for adverse events from carotid endarterectomy, if there were lesion characteristics that were believed to contribute, especially to adverse events due to surgery, those might be appropriate to be inclusion-exclusion criteria depending on how you're looking at it for those types of studies.

At the same time the risks may be - they may present a different risk profile with respect to stenting. So there may be different stenting risk factors in all of that, which may represent a different patient population. It may very well represent a different population.

There may also be lesion characteristics that say, don't touch me at all, because something is going to break off.

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So I think by the meeting today we only envisioned talking about the non-high surgical risk population. So if we were to focus on lesion characteristics as eligibility criteria for those studies, I think it would be important to couch them within that framework.

And if we're going beyond that, then we may have to think about a different indication for those patients.

Another issue I thought of with that would be, a lot of the decision of whether or not to treat a patient using a certain treatment modality, or whether to treat them at all, a lot of that really gets back to representing what's best for clinical practice.

Those may make clinical practice decisions which FDA doesn't get involved in. There are treatment options that may be available to physicians. FDA can determine for specific devices whether there is a reasonable assurance of safety and effectiveness for the indicated patient population. However, physicians are ultimately going to know what's best for the patient,

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how they think their patients can best be treated.

And so a lot of this may go - may go beyond the scope of a clinical study designed to demonstrate the safety and effectiveness of a single device, because you are focusing more on well defined patient characteristics and things like that, because that facilitates our getting an answer.

So to some extent those issues may relate to a broader issue of clinical practice in determining what's best for the patient.

I'm not sure I answered your question, and other people should feel free to jump in. But that's my initial take on the issue of lesion characteristics.

I agree, I think that's an issue that needs to be explored a little further from studies. I hope that gets done.

DR. SAPIRSTEIN: Dr. Comerota, we have determined risk on the basis of procedural risk and access to the lesion and not on the lesion characteristics, so that the actual lesion treated should be comparable in the two arms, so that for

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instance a flaccid embolus would be excluded from a study of CAS and as is elderly patients over 80 because of the increased risk of a nonsurgical and direct operation.

And so that's what we have relied on in order to accurately determine the comparability of the stenting versus the carotid endarterectomy procedure.

CHAIRMAN YANCY: Dr. Somberg.

DR. SOMBERG: I wanted to continue the discussion that you were sort of bringing up, and that is, are we talking about approval of a device? Or are we talking about different medical practices?

And it seems to me - or my question really is to the FDA, have you considered that perhaps we are more in practice management considerations? And what I mean by that is, SPACE and EVA for asymptomatic patients failed according to their specified endpoints, which is fine for the specified endpoints, and it is if you will an academic study for practices.

But in terms of devices, I could conceive if you had an intervention that offered some benefit over

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some specified control like medical therapy for instance, and it wasn't as good as another intervention, but the other intervention required surgery, there are all sorts of lesion characteristics, severities, that maybe we have important focus here, and I agree on that, but maybe there's another focus that we should look towards how to define the efficacy of the device and how would it fit into practice for a very large number of patients who were not treated with the standard of care, if you will, carotid endarterectomy.

I'm not sure I'm saying what I mean very precisely, but it seems to me a fundamental undercurrent of this conundrum today, and in part the FDA presentation.

DR. CAVANAUGH: Sure. And to answer I think the first part of your question with regards to, what specifically are we talking about here today. Again, I think there may be two parts to that.

So I think before - one of the early questions that needs to be answered is, does carotid stenting have a place for the non-high risk population?

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And the second question is, okay, let's assume that gets established, how do we then go about proving whether specific devices are safe and effective for that indication in those patients? And it may very well be that some of those studies may be tied together, focusing on specific devices early on. They may be answering the same question.

So I think that if the panel has input on both of those questions it's going to be very helpful for us as a regulatory agency and for other potential study sponsors to know what are the key study considerations here? If there's any difference between those two types of studies it's good to know.

And to get to the second part of that, I think going to the broader patient population, we would - you're aware of the FDA's consideration of post-market data. We have post-market studies in place for approved carotid stents in the high surgical risk populations. And we could envision that if a stent were to be approved for the non-high risk population, there would be a post approval study performed with that as well,

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and we might be able to capture some data about how these stents are used, and that may - that may inform potential - that may inform potential treatment of patients later by knowing, okay, here's how these patients with specific conditions may have fared; maybe we want to be careful about treating them, questions like that.

I think for broader studies with regards to what's best for patients, as far as determining or influencing clinical practice, we may not have the regulatory authority to do that, but at the same time those would be important studies, and hopefully input from this panel could encourage and optimize the quality of data collected from those studies.

CHAIRMAN YANCY: No, I would agree that Drs. Comerota and Somberg and really helping us understand what kinds of input we need to provide FDA in terms of study design.

Dr. Blackstone.

DR. BLACKSTONE: Yes, I may be reflecting what the other two have said too. But if you look at your

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slide #84, the one just before this, when you were giving a charge for what you'd like from the panel, the framework is entirely framed in terms of carotid endarterectomy, that is to say, the comparison of stenting with carotid endarterectomy, the indications for carotid endarterectomy are not in high or low risk patients.

So this is a rather, I would say rather odd situation where you are instead of looking at a device, and whether that device is effective and safe, you are instead looking at it in terms of what is going on with another procedure, a surgical procedure.

And I think the idea that maybe the framework instead should focus on these devices, and what their effectiveness and safety is and particularly with respect to not doing anything, which is one of the things that you'd naturally think of. And on your first slides you said that was one of three arms. You're putting it all in they framework even in defining risk to surgical risk that one might argue may not even be germane to this argument.

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DR. CAVANAUGH: So what I'm hearing you say is that by considering the comparisons to endarterectomy we've been focusing on that and there may be other more suitable comparisons?

DR. BLACKSTONE: Well, we've already heard earlier in your presentation that this may be actually just the tip of the iceberg, and there are far more patients who one wouldn't even consider for carotid endarterectomy that these devices are probably going to - that the device manufacturers want to use them for.

So are we - is the framework for your questions to us proper, is what I'm really challenging.

CHAIRMAN YANCY: I think we all can contribute to that dialogue. Because there may be some around the table who believe that what some might call a conservative arm, or others might call medical therapy might be another reasonable comparator.

Dr. Abrams.

DR. ABRAMS: Yes, I would echo these thoughts that were put forth by Dr. Blackstone. I think the issue of best medical therapy is really the question

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that is I think on the mind of this panel.

It was also on the mind of the previous panel that looked at the high risk patient.

But I would like to ask the FDA, what are you currently considering a reasonable completion time for a randomized control trial?

And you want things to be completed reasonably. What are your criteria, what are you thinking of as a reasonable time for completion?

DR. CAVANAUGH: I'm not sure I have the answer to that, and I think that's where input from the panel might be helpful is to maybe inform us what you would consider to be a suitable completion time, if there are certain - depending on the time course of studies, if you can be able to tell that patients enrolled early on may not be comparable to those enrolled at the end, or medical practice may have changed and things like that.

Those are important for all of us to keep in mind. I don't we have any a priori guidelines for, okay, this study is going on too long. So that again would be an area where we could benefit from the panel's

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expertise is, what is too long?

Really what it comes down to for us is, are the data from the beginning of the study to the end, can they all be pulled together?

And that's really what it comes down to for that specific question. If we do encounter a study where it looks like there may be the question of comparability, we might ask for a specific analysis or rationale as to why they could be poolable. It may very well be a question for the panel for a specific marketing application. But if there are any guidelines or anything that the panel can provide on that point we would certainly be appreciative of that.

CHAIRMAN YANCY: Certainly depends on the rate of secular change and background therapy. I think Dr. Najarian, did you have your hand up? I'm sorry, Dr. Milan.

DR. MILAN: I didn't have my hand up but I do have a question. So and this has to do - I mean I think that there's legitimate questions around the choice of a comparator, and I think that is worthy of discussion.

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But I have a specific question about these non-inferiority trials, and how we decide what an acceptable delta is for non-inferiority.

And as you were making your presentations, which I was very impressed with, it struck me that in asymptomatic patients, for instance the recommendation is for high grade stenoses if the surgical risks or the procedural risk is less than 3 percent that you go ahead.

But I guess if the procedural risk is higher than that that the benefit is mitigated to some degree.

And the same - this is for CEA, for treatment of asymptomatic patients.

And then for symptomatic patients, the surgical risk is acceptable up to 6 percent. And I wonder if you've given thought to whether that should inform our decision about an acceptable delta when we compare carotid artery stenting to CEA?

DR. CAVANAUGH: Sure, and I can start off. Dr. Zuckerman, if you want to say something you can.

But there was - just to clarify, so those

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recommendations were medical society recommendations involving expertise beyond what we have, and they are great recommendations. They are not considered regulatory requirements or anything. So I just wanted to clarify that point.

With regards to selection of appropriate let's say non-inferiority margins, et cetera, I'm not sure again we have any prespecified, here's how you'd define that, but that could be a potential way to do that is to say, we have medical expertise that says, these rates are clinically significant. Here's the clinically significant difference, and this is how we - this is how we can develop the non-inferiority margin based on that information.

I think we envision that maybe the panel might want to talk about that a little bit, about how to incorporate the recommendations from medical societies, and so that's a good topic for discussion later. We'd be certainly happy to hear some of that.

DR. ZUCKERMAN: Okay, this has been an incredibly rich discussion, and I feel confident that

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the panel is moving in the direction that we wanted the panel to move in, which is, one, to consider that this is a very complex area that is going to need very careful trial design and considerations, especially with respect to this so-called delta.

But I want to emphasize that it's very important to use good clinical judgment here. For example Dr. Milan just had a great question: How do you frame a delta around 1 percent or 3 percent, and make it clinically meaningful?

Probably with 40,000 patients. But we would frame the question a different way. Certainly from the FDA perspective, or a clinician's perspective, when we are talking about a chronic implant, the minimum time point where we could consider a primary endpoint analysis would be at one year, or perhaps later, where we're generally talking about a rate, just in the ballpark, of about 6 percent.

Certainly we want the panel's input on considering a minimally acceptable clinical delta, which again would generate extremely large sample sizes, but

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at the same time you need to weigh that against clinical reality et cetera. And the agency has been thinking about something in the 30 percent ballpark, which may or may not be acceptable.

But there are multiple issues here that, after you hear more about proposed clinical trial designs, we'd like to turf these questions back to you.

The only other point that I'd like to mention is that people are really questioning what is the question here. And there really are two questions.

One is, you need to generate enough data in this trial or a series of trials such that on a per patient basis you're reasonably confident that doing a treatment strategy with this device is a reasonable thing to do.

It doesn't mean that this device needs to necessarily be better than a different - than a standard of care, A. B, it means that you also need to cull out enough information from this trial that the device works as intended.

But a reasonable assurance of safety and

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effectiveness does not allow us to forget that the principal analysis needs to be on a per patient basis such that we're confident that with performance with use of an elegant device we're still demonstrating some clinical utility for a PMA device.

CHAIRMAN YANCY: Please, Dr. Kindler.

DR. KINDLER: Thank you.

Well, I'm certainly intrigued by the discussion. And I would follow up what Dr. Zuckerman is saying by two thoughts. And the question is, in a sense it's not just two questions, but if I'm reading the explicit and implicit questions here, there are really two things that are being put on trial.

One is, is a relatively robust procedure that's been used for a long period of time in need of a replacement? And that would be CEA. Has current technology advanced to such a degree that we should reconsider that?

And the second one, in terms of answering, how we answer that question, has been our gold standard, which is randomized control trials in need of a revision

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as well.

And I think that is sort of what I'm hearing here as we try to discuss issues about delta, try to discuss issues about patient selection.

And I think great caution needs to be taken before either one of those are significantly revised.

CHAIRMAN YANCY: Dr. Jeevanandam.

DR. JEEVANANADAM: Looking at the - I mean this is a question to the FDA - the basic reason it seems like we're here is randomized clinical trials are probably the gold standard, but you can't enroll patients fast enough. And that's why we're here to try to figure out if there's alternatives to randomized clinical trials, and especially in this patient population.

And it seems to me that the question is why can't we enroll people fast enough? And are we close enough to enrollment that this point becomes moot? That's one question.

The other thing is, from a practical point of view, reimbursement always drives a lot of why people

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can or cannot be enrolled in clinical trials. And can you give us a perspective on the actual reimbursement state right now for carotid stenting?

DR. ZUCKERMAN: Okay. I think there are good reasons why, within HHS, Congress specifically designated that there's an FDA, and that there's a center for Medicaid services, or CMS, and these two organizations shall stay separate.

Our charge today is not to worry about reimbursement or per se what CMS is going to do. Our principal charge today is to construct a framework, considering use of the total product lifecycle concept, meaning what combination of critical premarket plus post-market data could we utilize to possibly approve these devices with a reasonable assurance of safety and effectiveness such that on a per patient basis we see clinical utility?

Now it might turn out that the trial designs suggested here would also be satisfactory for CMS, which has a different charge, reasonable and necessary. But that's a discussion for a different day, and we would

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just really recommend that sponsors have that discussion with CMS and see if approaches are congruent.

We have a big enough charge here today just to design these FDA trials.

CHAIRMAN YANCY: We need to take just two more brief questions.

Let me just make reference for Val's benefit that under tab 4 in the consensus document on page 129 there are several statements referencing CMS and how they approach carotid stenting.

Very brief segment, please, Doctor.

DR. YAROSS: I think that there is no question that those are separate standards, and appropriately so.

I think though that these get to the issue of sometimes a burden which is within the scope of FDA. And Dr. Cavanaugh, I noted in your presentation as in many FDA materials there is a suggestion that non-RCTs may not be least burdensome.

And yet industry that bears the burden often feels differently.

I wonder if you could elaborate a little more

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on that in the context of this study population.

DR. CAVANAUGH: I think when we're talking about least burdensome I think there may be a different weighting of the risks along the timeline of conducting studies. But the randomized control trial, you may have challenges for enrollment and all that. You can monitor that as time goes on. You may take some time to get rolling with those types of studies. But at the end you have a randomized study. And provided it was well designed, the data should be interpretable.

With the non-randomized study, the study may get off the ground a little bit easier. And you may collect data. But you may not, you probably won't know until the end of the study whether the data are in fact interpretable.

So there is more of a risk being assumed by the sponsor of such study. We're investing a lot of time and resources into conducting the study, and you may not be able to control the interpretability of the data. You may get to the end and find that you are making an apples to oranges comparison.

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And so that's really - that's the aspect of the burden that we're thinking about with a non-randomized study is that there is more risk weighted toward the end of the study that you may not know about during the conduct of the study and you may not be able to account for at the end.

So really what the question is here is, what our main question here I think today is, do you need a randomized control trial? Do you need one? There is no other alternative. And if there are alternatives, what can we do to control some of these issues? How can we implement them to gather sufficiently interpretable data?

And if the non-randomized studies won't work, why specifically not? Why can't those be used to gather data?

CHAIRMAN YANCY: Dr. Yaross, thank you for that question. It parallels an observation I had as well.

I think there was one brief comment from here? Please, Dr. Somberg.

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DR. SOMBERG: Someone raised the point, are we going to replace a very robust procedure which is endarterectomy with another intervention.

I don't really think that is the question of the day. I think the question of the day is, are we going to be able to judge the effectiveness versus safety of an interventional device? And I think it's important to make that comparison at some point in the medical practice, but I'm not sure that's the critical issue. And I think it comes down to something very, very precise, and that is, could you facilitate, decrease the burden and increase the yield and potential success of doing a randomized trial in patients where you were comparing the device to potentially medical therapy? Or would you compare the device to surgical intervention, but willing to accept maybe even a 60 percent difference, because the intervention offers some benefits over the alternative intervention.

And I don't say I have the answers to these things. There are neurologists here, vascular surgeons, et cetera, et cetera, who deal with this everyday.

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But I'm just bringing this up because, as other people have said in this meeting so far, as I see, we're conducting a study for best practices, and this is sort of like the American Physicians Society dealing with these patients. We're deciding best medical practice, and I don't think we're having per se a very detailed and precise regulatory discussion of efficacy versus safety of an interventional device.

CHAIRMAN YANCY: We'll take one more comment in this section, and that is from Lindenfeld.

DR. LINDENFELD: This is just a little different question. I noticed in the materials we were given that having a standard neurologic evaluation of patients increases the detection of CVA threefold. And I have two questions for you about that.

If that is the case, and if those ones that are picked up by neurologists are reflected of the death and obvious stroke rate, then wouldn't requiring that in a clinical trial substantially decrease the numbers of patients that would need to be enrolled? And that would then get rid of a lot of this problem of large enough

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numbers. So my questions are, do these evaluations by neurologists - and I think that was in the consensus document, that statement - if that's the case, then do those reflect other events and we would be confident in having a standard neurological evaluation to increase or detection of the stroke rate threefold, wouldn't that be one way to really decrease the numbers and therefore allow us to do randomized trials?

DR. ZUCKERMAN: I'm not sure I can answer that question.

DR. ZUCKERMAN: All trials, as you are pointing out, Dr. Lindenfeld, are fundamentally sample sizes depend on number of events. I wish we could say that with good neurological exams being done by neurologists the number of events is going to increase substantially, and sample size isn't an issue. We just haven't found that to be the case. But there will be other speakers here also.

CHAIRMAN YANCY: Certainly we have a number of neurologists around the table, so hopefully we can have that input.

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Let me, if you will, proceed with closing this part of the meeting and proceeding on to our first open public hearing. For the purposes of just being able to keep our thoughts clear, the kind of things I heard the panel bring up in response to the FDA's presentation had to do with the risk of the treatment per se, the natural history of the disease, and importantly, the definition of what constitutes non-high risk; the requirement to look at per patient outcomes, and understand if we can extrapolate this to clinical practice; the specific requirement to respect reasonable signs of efficacy and safety for the device; important questions about clinical trial design; persistent questions about determining and setting an inferiority margin; and then a very provocative discussion about what constitutes burden and what truly is the least burdensome. So I think we are getting a start on where we need to go, and at this point we'd like to move forward with our first open public hearing.

We have three speakers scheduled for this session. Each speaker has been allotted a maximum of 10

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minutes to speak. In the interests of time we ask each speaker to be as brief as possible, less than 10 minutes if that's possible, and for the panel to hold all questions until everyone has presented.

It's important for me to read the following statement.

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The first scheduled speaker is Dr. Stan Fink on behalf of Abbott Vascular.

ABBOTT PRESENTATION

DR. FINK: My disclosure is, I am an employee of Abbott.

I'd like to thank the panel for the opportunity to address them regarding this issue.

Basically we'd like to provide an overview of Abbott Vascular's carotid stenting programs, and also support the use of randomized trials to determine the safety and efficacy of carotid stenting versus carotid surgery.

Just very briefly an overview of Abbott's involvement with carotid stenting. Abbott Laboratories acquired Guidant Corporations' Endovascular Solutions

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