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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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May 24, 2016
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

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RICHARD PAGE, M.D.	Panel Chair
DAVID YUH, M.D.	Voting Member
DAVID KANDZARI, M.D.	Voting Member
JEFFREY BRINKER, M.D.	Temporary Voting Member
SEEMANT CHATURVEDI, M.D., FAHA, FAAN	Temporary Voting Member
KAREN FURIE, M.D., Ph.D.	Temporary Voting Member
NICHOLAS KOUCHOUKOS, M.D.	Temporary Voting Member
JEFFREY BORER, M.D.	Temporary Voting Member
GREGORY DEHMER, M.D.	Temporary Voting Member
RALPH BRINDIS, M.D.	Temporary Voting Member
DAVID SLOTWINER, M.D., FACC	Temporary Voting Member
SCOTT EVANS, Ph.D.	Temporary Voting Member
MICHAEL LINCOFF, M.D.	Temporary Voting Member
WARREN LASKEY, M.D.	Temporary Voting Member
JOHN HIRSHFELD, JR., M.D.	Temporary Voting Member
PATRICK NOONAN, JR., M.D.	Temporary Voting Member
RALPH D'AGOSTINO, Ph.D.	Temporary Voting Member
NAVEEN THURAMALLA, M.S., CCRP	Industry Representative
PHIL POSNER, Ph.D.	Patient Representative
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INDEX

INDEX

INDEX

M E E T I N G

(8:00 a.m.)

DR. PAGE: Good morning, everyone. I'd like to call this meeting to order. This is a meeting of the Circulatory System Devices Panel.

I'm Richard L. Page. I'm the Chairperson for the Panel. I am a cardiac electrophysiologist, and I'm currently Chair of the Department of Medicine at the University of Wisconsin in Madison.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel members participating in the today's meeting have received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information related to the premarket approval application of the AMPLATZER PFO Occluder, sponsored by St. Jude Medical.

Before we begin, I'd like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and your affiliation. And we'll start over here with Dr. Zuckerman, please.

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

DR. YUH: Good morning. My name is David Yuh. I'm the Chief of Cardiac Surgery at Yale University. My expertise is in the area of minimally invasive cardiac surgery.

DR. KANDZARI: Good morning. I'm David Kandzari. I'm the Director of

Interventional Cardiology and Chief Scientific Officer at the Piedmont Heart Institute in Atlanta, Georgia.

DR. BRINKER: Hello, I'm Jeff Brinker, interventional cardiologist at Johns Hopkins University.

DR. CHATURVEDI: I'm Seemant Chaturvedi. I am a vascular neurologist and Vice Chair for VA programs at the University of Miami Miller School of Medicine.

DR. FURIE: My name is Karen Furie. I am a vascular neurologist. I'm Chief of Neurology at Rhode Island Hospital and Chairman of Neurology at Brown University.

DR. KOUCHOUKOS: I'm Nick Kouchoukos. I am a cardiovascular surgeon, and I practice at the Missouri Baptist Medical Center in St. Louis.

DR. BORER: I'm Jeff Borer. I am a cardiologist from New York City, former chief -- Chairman of Medicine and Chief of Cardiology at State University in New York.

DR. DEHMER: Greg Dehmer, interventional cardiology and Professor of Medicine, Texas A&M College of Medicine, and I'm Chief of Cardiology at Baylor Scott & White in Temple and Medical Director of Cardiovascular Services for that organization.

DR. BRINDIS: Ralph Brindis, Professor of Medicine at UCSF Institute for Health Policy Studies, previously an interventional cardiologist, now general cardiologist and cardiovascular outcomes researcher.

MS. WASHINGTON: I'm Evella Washington, the DFO.

DR. SLOTWINER: David Slotwiner. I am a cardiac electrophysiologist at Weill Cornell Medical College and Director of Electrophysiology Laboratory at NewYork-Presbyterian In Queens.

DR. LINCOFF: I'm Mike Lincoff. I am an interventional cardiologist at the Cleveland Clinic. I'm Vice Chair of Cardiovascular Medicine and director of our academic research organization, C5Research.

DR. EVANS: Good morning. My name is Scott Evans, Department of Biostatistics at Harvard University, expertise in clinical trials.

DR. D'AGOSTINO: Ralph D'Agostino, statistician from Boston University, Harvard Clinical Research Institute, and the Framingham Study.

DR. LASKEY: Warren Laskey. I'm Chief of Cardiology at the University of New Mexico and a retired and reformed interventional cardiologist.

(Laughter.)

DR. HIRSHFELD: I'm John Hirshfeld, and I am a former colleague of Dr. Laskey's, and I am an interventional cardiologist at the University of Pennsylvania.

DR. NOONAN: I'm Patrick Noonan, Chief of Interventional Neuroradiology, Baylor Scott & White in Temple, Texas.

DR. POSNER: I'm Phil Posner. I'm the Patient Rep and a retired cardiac electrophysiologist and neuroscientist.

MR. FRANKEL: Good morning. Naftali Frankel, Consumer Representative.

MR. THURAMALLA: Good morning. I'm Naveen Thuramalla. I'm the Vice President of Regulatory Affairs with Arkray, Incorporated. I serve as the Industry Representative on this Panel.

DR. PAGE: Thank you very much. As you can see, we've assembled a really outstanding Panel that includes expertise in a number of different areas that are important

for the work we have to do today.

If you've not done so, please sign the attendance sheets that are at the tables by the doors.

Ms. Evella Washington, the Designated Federal Officer for the Circulatory System Devices Panel, will now make some introductory remarks.

Ms. Washington.

MS. WASHINGTON: Good morning. I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on 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 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of the Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have 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.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees or regular Federal employees 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 children and, for purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations and vote on information related to the premarket approval application for the AMPLATZER Patent Foramen Ovale (PFO) Occluder, sponsored by St. Jude Medical. The AMPLATZER PFO Occluder is a percutaneously delivered permanent cardiac implant for PFO closure. The device is indicated for preventing recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208, Subsection (b)(3), to Dr. Richard Page. Dr. Page's waiver addresses his institution's interest as a clinical site for the AMPLATZER PFO Occluder trial in which he is not a participant. His institution is awarded between $10,001 and $25,000 a year for patient follow-up activities. The waiver allows the individual to participate fully in the Panel deliberations. FDA's reasons for issuing the waiver are described in the waiver document which is posted on FDA's website at www.fda.gov/AdvisoryCommittees.gov. Copies of the waiver may also be obtained by submitting a written request to the Agency's

Division of Freedom of Information at 5630 Fishers Lane, Room 1035, in Rockville, Maryland 20857.

Naveen Thuramalla is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Arkray, Incorporated.

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 an FDA participant has a personal or 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 they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. Thank you.

I will now read the Appointment to Temporary Voting Status Statement.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter for the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August the 18th, 2006, I appoint the following individuals as voting members for the Circulatory System Devices Panel for the duration of this meeting on May the 24th, 2016:

Dr. Jeffrey S. Borer, Dr. Ralph G. Brindis, Dr. Jeffrey A. Brinker, Dr. Seemant Chaturvedi, Dr. Ralph D'Agostino, Dr. Gregory Dehmer, Dr. Scott Evans, Dr. Karen Furie, Dr. John Hirshfeld, Dr. Nicolas Kouchoukos, Dr. Warren Laskey, Dr. Patrick Noonan, and Dr. David Slotwiner.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This was signed by Dr. Jeffrey Shuren, the Director of the Center for Devices and Radiological Health, on April the 6th, 2016.

For the duration of the Circulatory System Devices Panel meeting on May the 24th, 2016, Dr. Michael Lincoff has been appointed as a Temporary Voting Member, and Dr. Phil Posner has been appointed as a Temporary Non-Voting Member. For the record, Dr. Lincoff serves as a consultant to the Cardiovascular and Renal Drugs Advisory Committee in the Center for Drug Evaluation and Research. Dr. Posner, a Patient Representative, serves as a consultant to the Peripheral and Central Nervous System Drugs Advisory Committee in CDER. These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Associate Commissioner for Special Medical Programs, on April the 28th, 2016.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. Thank you.

Before I turn the meeting back over to Dr. Page, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated.

Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Ms. Deborah Kotz.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing session today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Mr. Artair Mallett at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

Dr. Page.

DR. PAGE: Thank you, Ms. Washington.

Before we get started, I'd like to just make a couple comments. These microphones work very well. There's a light that I ask you not to use to get attention, but just when you turn on your microphone. We have one light on here. So thank you. And actually that improves the acoustics for the panelists as well. I will look for everyone in terms of anyone wanting to raise their hand and make a comment, and I will call on you, and I'll do my very best to be fair to everyone, whether you're in the corner or not.

We're going to have every conversation minuted. So I do ask the panelists not to

discuss between or among yourselves. Everything you say over the next 8, 10 hours is very important to this process, and we want to capture your comments and have any conversations in the minutes.

Finally, in terms of time, we're going to stay on time. I ask the Sponsor, I ask the FDA -- and likewise, we have a number of speakers for the open public comment period. We will have a 5-minute duration of time for each speaker. But to be fair to each speaker, we will cut you off at 5 minutes.

With that, I'd like to proceed with the Sponsor's presentation. I'd like to invite the Sponsor to approach the lectern.

I will remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor will now have 90 minutes to present. Please begin your presentation, Dr. Carlson.

DR. CARLSON: I am Mark Carlson, and I am the Chief Medical Officer and Vice President of Global Clinical Affairs at St. Jude Medical. We are pleased to be here today to share with you the results of the RESPECT trial, which evaluated the safety and effectiveness of the AMPLATZER PFO Occluder in patients who have experienced a cryptogenic stroke and are found to have a patent foramen ovale.

I'll start by briefly reviewing the condition. A patient foramen ovale, or PFO, is a hole in the wall between the right and left atria that in some people persists after birth. In many who have a PFO, the anomaly does not cause a complication, but a number of patients with

a PFO experience a stroke, often at a young age. A PFO can allow blood clots to go from the right side of the heart to the left side, travel to the brain, and cause a stroke. This stroke mechanism is referred to as a paradoxical embolism, the paradox being that a venous thrombus can occlude a systemic artery by crossing the PFO and bypassing the lungs. Let me illustrate how patients with a PFO may develop a stroke by paradoxical embolism from clots originating in the venous system.

In certain patients, clots may form in the leg, pelvis, or other veins and break loose, migrating through the inferior vena cava to the heart. In most patients, these clots end up in the lungs, where they are dissolved by an endogenous tPA, causing no harm. However, in patients with a PFO, these clots may travel through the PFO into the left side of the heart. There, they can be expelled from the left ventricle into the aorta and then into the systemic circulation or, in this case, into the cerebral vessels and to the brain, causing a stroke.

St. Jude Medical developed the AMPLATZER PFO Occluder to close the PFO, preventing recurrent stroke related to paradoxical embolism. This minimally invasive device is self-expandable and made from a nitinol wire mesh that has both shape memory and super-elasticity. It is comprised of two discs linked together by a short connecting waist. The discs contain a thin polyester fabric to inhibit blood flow through the vessel or through the device. Let's walk through the implant procedure.

Following percutaneous puncture of the femoral vein, a standard right-heart catheterization is performed. A diagnostic catheter is passed over a guide wire, across the PFO, into the left atrium. Thereafter, a sheath is used to deliver the PFO closure device. The AMPLATZER PFO Occluder is advanced until the left atrial disc is fully exposed in the left

atrium. The disc is then pulled tightly against the atrial septum. With gentle tension the sheath is retracted to deploy the right atrial disc and seal the PFO. Once proper position is confirmed, it is released from the delivery cable. The device gently sandwiches the atrial septal tissue, effectively closing the PFO. Over time, the device endothelializes through the body's natural healing process. Venous emboli are now deflected by the AMPLATZER PFO Occluder, preventing subsequent stroke related to paradoxical embolism.

The AMPLATZER PFO Occluder is a targeted therapy designed to prevent recurrent stroke due to this specific mechanism. It will not prevent strokes due to other mechanisms such as atherosclerosis.

RESPECT was designed to demonstrate superiority of the device over medical management alone, in reducing the risk of a recurrent ischemic stroke. RESPECT was a randomized, event-driven clinical trial in patients with cryptogenic stroke and a PFO. The expected event rates were based on published observational studies. The trial took four times longer to perform than anticipated. Let's discuss why.

The trial enrolled its first patient in August of 2003. Over the first 3 years, PFO occluders were available from two companies under Humanitarian Device Exemption, or HDE, which significantly slowed enrollment in RESPECT. In fact, during this period, 9,700 AMPLATZER PFO Occluders were shipped under the HDE, while only 259 patients were enrolled in RESPECT. In 2006 FDA determined that the eligible U.S. population exceeded the HDE threshold, and as a result, all PFO occluders were withdrawn from the market. Once the device was no longer available under HDE, the enrollment rate doubled. Enrollment continued until 2011 when the 25th primary endpoint event was observed. The

event rate was 50% lower than expected. This fact, coupled with the slower-than-expected enrollment rate, extended the duration of the trial to 8 years.

The PMA was submitted in 2012. Deficiency letters were received in 2013 and 2014. Understandably, the FDA requested multiple sensitivity analyses related to patient accountability and the trial's different analysis populations. In addition, FDA requested information on the testing done to assess exclusion of other potential causes of the index stroke, as well as information related to clinical evaluations conducted at the time of the recurrent stroke. We also met several times with FDA to discuss the appropriate indication. We will discuss many of these topics today.

RESPECT is the largest randomized clinical trial of a PFO closure device, with 980 patients enrolled. At the time of the primary assessment, the study had accumulated more than 2,700 patient-years of follow-up and a median follow-up of more than 2 years. The results were published in the *New England Journal of Medicine* in 2013. Our invited presenters, who were the lead authors of the pivotal paper, will go into more detail on the data in a few moments, but first I would like to highlight the key findings from RESPECT.

Treatment with the AMPLATZER PFO Occluder was associated with a 50% relative risk reduction for recurrent ischemic stroke, relative to guideline-directed medical management in the intent-to-treat population. As you can see, this difference did not achieve statistical significance. This indication of benefit was magnified in the per-protocol, as-treated, and device-in-place populations, which showed 63%, 72%, and 70% relative risk reductions. In today's presentation we will show data demonstrating that the AMPLATZER PFO Occluder provides an important option for young and middle-aged patients who face a

life-long risk for recurrent stroke.

We are asking that the device be approved for the following indication: The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Our agenda today is as follows: Dr. Jeffrey Saver from UCLA will discuss the unmet need of patients with a PFO who face a life-long risk for recurrent stroke despite medical therapy, and he will review the RESPECT trial design. Dr. David Thaler from Tufts University will present the effectiveness results, and Dr. John Carroll from the University of Colorado will present the safety results. I will return to review our training and post-approval plans. Dr. Carroll will close our presentation with a benefit-risk discussion. All of our external presenters are RESPECT steering committee members.

We are also joined by these additional experts. All of our external presenters have been compensated for their time and travel to today's meeting.

I now invite Dr. Saver to the lectern.

DR. SAVER: Good morning. My name is Jeffrey Saver, and I am a Professor of Neurology and a practicing stroke neurologist at UCLA David Geffen School of Medicine. I treat many patients who have suffered a stroke and have particular concerns about young and middle-aged, otherwise healthy stroke patients who face a life-long risk of recurrent stroke. Cryptogenic strokes are ischemic strokes of unknown cause, despite a thorough diagnostic evaluation. Cryptogenic strokes account for approximately one-quarter of all ischemic strokes and for 34% to 46% of the ischemic strokes that occur in young and

middle-aged individuals. These strokes may happen without any of the traditional risk factors such as hypertension, diabetes, high cholesterol, or a history of smoking.

PFOs are found to be present in approximately one in four adults in the general population. And while the vast majority of these individuals with a PFO never have any clinical issue, some do. The prevalence of PFO in cryptogenic stroke patients is twice as high as the general population, approximately 40% to 50%. The annual burden in the United States of young and middle-aged cryptogenic stroke patients with PFO is about 16,000 per year, a population of moderate but important scope and one that exceeds the threshold for Humanitarian Device Exemption.

Once these younger patients with a PFO experience a cryptogenic stroke, they face an extended lifetime risk of recurrent stroke during their most productive years. By 10 years after a cryptogenic stroke, the recurrent stroke rate is between 10% and 20%, and the recurrent stroke is most commonly also cryptogenic. Cryptogenic strokes are associated with substantial morbidity and mortality. At 2 years, 85% of patients have persistent neurological deficits, more than half are disabled, and 15% have either died or need assistance from others to make it through their day.

Now, let's consider the current treatment options. Upon diagnosis, current guidelines recommend prescribing a medication regimen of either antiplatelet or anticoagulant therapy. Presently there are insufficient data to establish whether anticoagulation is better, equal to, or worse than antiplatelet agents for secondary stroke prevention in patients with a PFO who have had a cryptogenic stroke. There are concerns in this younger population with long-term anticoagulation and dual antiplatelet therapy,

which may interfere with physical labor, sports, pregnancy, and other activities. Also real-world, long-term compliance for medical therapy in stroke patients is problematic, with documented noncompliance rates of 35% to 50% at 1 to 2 years post-stroke. And even when these patients are taking antithrombotic agents, there remains a 1% to 2% annual risk for another ischemic stroke.

A second potential treatment option is surgical PFO closure, but it is rarely used, and some series have reported high complication rates.

A third treatment option continues to be transcatheter PFO closure. Because there are no approved devices for PFO closure, this can only be performed with off-label use of devices that are not intended for this purpose. There is no evidence from randomized trials demonstrating that these off-label devices are safe or effective for that purpose.

To illustrate the current unmet need for treating PFOs to minimize the risk of recurrent cryptogenic stroke, let me present a case. This is a patient who was recently cared for by a physician member of the RESPECT steering committee. This male patient was 54 years old in 2010 when he had his first stroke. After extensive investigations, doctors found no conventional mechanism to explain the stroke; however, he had a PFO and an atrial septal aneurysm. He was started on aspirin as per current guidelines for medical preventive therapy. But then this year, in 2016, when bending over to pick up his gym bag, he had a sudden onset of stupor and loss of memory and vision. His basilar artery had become occluded, a life-threatening event. Fortunately his stroke was treated quickly with tPA at a local hospital, and he eventually had only three small areas of infarction, two seen here in the right thalamus and the left mesial temporal lobe. After investigations, the PFO

was again the only identified potential culprit. This active man suffered a potentially fatal recurrent stroke despite taking current guideline-directed medical therapy. For PFO patients like him, it is important that we have additional treatment options.

In summary, PFOs permit venous clots to paradoxically embolize and travel to the brain. A PFO-related cryptogenic stroke can be devastating to patients, causing substantial morbidity and mortality. These strokes can and often do occur in otherwise healthy people with few, if any, traditional vascular risk factors. And despite our best efforts, medical management does not eliminate risk of recurrent cryptogenic strokes and carries distinctive risks for this younger patient population. Transcatheter PFO closure could be an important treatment option to reduce the rate of recurrent strokes for these patients.

Now let's turn to the RESPECT trial design and baseline patient characteristics. The RESPECT trial was designed to evaluate whether PFO closure with the AMPLATZER PFO Occluder was superior to guideline-directed medical management alone in reducing the risk of a recurrent ischemic stroke.

RESPECT was a randomized, event-driven, open-label clinical trial with blinded endpoint adjudication. We randomized patients who had suffered a qualifying cryptogenic stroke 1:1 to receive either the AMPLATZER PFO Occluder or medical management alone. The trial enrolled patients at 69 sites in the United States and Canada from 2003 to 2011, and patients continue to be followed today in 2016. The trial entry criteria resulted in a well-defined patient population. Enrolled patients met clear inclusion criteria for having both a cryptogenic stroke within the last 9 months and a PFO confirmed by transesophageal echo bubble study. Stroke was defined in accordance with national guidelines as an acute

focal neurological deficit presumed to be due to focal ischemia. The stroke had to be confirmed either by MR or CT findings of a new neuroanatomically relevant cerebral infarction or by symptoms of a stroke persisting at least 24 hours.

We enrolled patients between the ages of 18 and 60. We did not enroll patients over the age of 60 because they are at higher risk of recurrent stroke from non-PFO mechanisms which PFO closure cannot prevent.

The trial excluded patients whose ischemic strokes had an identified cause such as large vessel atherosclerosis, atrial fibrillation, and intrinsic small vessel disease, among others. The trial also excluded patients with active venous thromboembolic disease who were unable to discontinue anticoagulation therapy.

Prior to randomization, investigators indicated which guideline-recommended medication regimen each patient would receive if he or she were randomized to the medical management arm. These options included either warfarin or one of the antiplatelet regimens listed here. We eliminated the aspirin plus clopidogrel regimen in 2006, based on changes in national clinical management guidelines.

Patients in the device arm were to undergo the implant procedure within 21 days of randomization. Following the procedure, these patients were to receive aspirin plus clopidogrel for 1 month, followed by aspirin alone until 6 months, and then further antithrombotic therapy at the discretion of the patient's neurologist. Patients in the medical management arm were to receive the medication regimen that had been specified for them prior to randomization. And patients were followed at 1, 6, 12, 18, and 24 months, and then yearly thereafter.

RESPECT's primary endpoint is a composite of any of the following events:

- Recurrent nonfatal ischemic stroke;
- Fatal ischemic stroke; or
- Early post-randomization death.

The definition of a primary endpoint stroke was the same as the definition I described for qualifying strokes.

To ensure we captured all primary endpoint events, we used multiple methods to identify potential strokes. We collected information from all unscheduled clinic visits and hospitalizations. Additionally, at every scheduled follow-up visit, site personnel administered the structured Neurologic General Symptoms Interview. This interview asked the patient about the occurrence of symptoms in any of five major domains, including weakness, dizziness, or problems with speaking, vision, or sensation. This instrument has been validated in randomized trials and epidemiologic studies as sensitive for stroke detection.

All potential endpoint events were referred for adjudication to the independent clinical events committee. The committee was blinded to treatment arm and independently determined whether an event met the primary or secondary endpoint definitions.

The trial sample size calculation projected an aggressive 75% relative risk reduction based on the best data available at the time of the trial design, which came from observational studies. The assumed 2-year rates of primary endpoint events were 4.3% in medically managed patients and 1% in device patients.

The trial was powered at 80% at the 0.05 two-sided significance level. This was an

event-based trial and was designed to enroll patients until there were 25 adjudicated primary endpoint events.

The initial analysis for the primary endpoint was a raw count analysis based on Fisher's exact test. During the course of the trial, differential dropout rates were observed between the two arms, making the raw count analysis inappropriate. When this was observed, we specified that the Kaplan-Meier method and log-rank test would be key supplementary analyses. This decision was made while enrollment was ongoing before data lock. In addition, we show hazard ratios and relative risk reductions from Cox proportional hazard models.

Today we will be covering results from multiple analysis populations that were evaluated to fully characterize the device effect. The first is the intention-to-treat population, which was the primary analysis population. The ITT population analyzes all patients according to the arm to which they were randomized, regardless of whether or not they actually received their assigned intervention.

The pre-specified per-protocol analysis population excludes patients who did not meet the inclusion/exclusion criteria, patients who never received their randomized therapy, and patients who were noncompliant to their medication regimen.

The as-treated analysis is also confined to patients adhering to the protocol but analyzes them according to the treatment they actually receive.

And the device-in-place analysis population considers all patients in the trial but analyzes them according to the treatment they actually receive.

In regards to baseline demographic and medical characteristics, the two arms were

well balanced. Most of the patients were healthy and had few comorbidities, as would be anticipated with a relatively young patient population. The average age was 46, and just over half of patients were male.

The prevalence of traditional vascular risk factors were similar to the overall U.S. non-stroke population of this age. The rate of serious cardiac, respiratory, and vascular conditions was low. Approximately 4% of patients had a history of deep venous thrombosis, over a third of patients had an atrial septal aneurysm, and approximately half of patients had a substantial shunt.

The site neurologist used clinical judgment to determine which guideline-directed medication regimen each patient would receive if he or she were randomized to the medical management arm. The planned medication regimens were distributed similarly for both arms, reflecting stratification of randomization on this factor. Approximately one-quarter of the patients were planned to receive warfarin if they were randomized to the medical management arm, and the remaining patients were planned to receive one of the various antiplatelet regimens.

Of the 499 patients randomized to the device arm, 32 did not receive a device. Seventeen patients decided not to undergo the procedure, and another 15 had an intra-procedural exclusion discovery; for example, other causes of shunting, such as atrial septal defect or pulmonary arterial venous malformation, or the absence of a PFO. An additional two patients did not have the study device placed. Therefore, a device implant was attempted in 467 patients, in whom 99.6% had a successful delivery.

The PFO closure status of all implanted patients at 6 months was assessed by TEE.

The protocol set a stringent bar to ensure accuracy, requiring that the echo core lab consider the images technically adequate to determine closure status both at rest and with Valsalva. Of the 465 successfully implanted patients, 95% had a TEE performed; 349 patients had TEEs that were assessed as technically adequate both at rest and Valsalva; 91 of the TEEs were considered not fully technically adequate.

The primary assessment for PFO closure was complete closure, defined as zero bubbles appearing in the left atrium both at rest and at Valsalva. This was observed in 71% of patients. The literature indicates that effective closure is also a useful endpoint to assess as it reflects substantial reduction in flow across the interatrial septum, and a substantial proportion of these patients will proceed to complete closure in ensuing months.

Effective closure was the lead technical efficacy endpoint in the other trials, CLOSURE and PC trials. In RESPECT, effective closure was defined as zero to nine microbubbles in the left atrium. The rate of closure based on this definition was 94%.

The enrollment of RESPECT took 8 years, which was more than twice as long as anticipated, so the rates of withdrawal were correspondingly greater than anticipated. The rate of withdrawal in the medical management arm was higher than the device arm. The difference between arms is driven primarily by patients' withdrawal of consent. Most patients in the medical management arm who withdrew consent did so because they were unhappy with their randomization assignment or stated they intended to seek PFO closure outside the trial.

The mean duration of patient follow-up at the time of primary assessment was approximately 3 years in both arms. The device arm had 1,476 total patient-years versus

1,284 in the medical management arm.

Finally, I'd like to review the antithrombotic medications taken by patients during the trial. Because of the differing protocol-driven strategies for antithrombotic therapies between the two arms, the profile of medications used differed. For example, at the time of 2-year follow-up, patients in the device arm were primarily on single antiplatelet therapy used in 88%. The use of dual antiplatelet therapy and warfarin were both very low. And about 5% were on no antithrombotic medication.

In the medical management arm, 70% were on single antiplatelet therapy and 9% on dual antiplatelet therapy. Warfarin was being used in 18% of patients, which is notably higher than the 2% in the device arm. This differential use of warfarin will be important to consider when we review the incidence of venous thromboembolic events later in this presentation.

I will now invite Dr. Thaler to the lectern to present the RESPECT effectiveness results.

DR. THALER: Good morning. I'm David Thaler, and I'm Chairman of Neurology at the Tufts University School of Medicine, and Neurologist-in-Chief at Tufts Medical Center, and I'm a practicing vascular neurologist.

My presentation of the RESPECT trial effectiveness results will follow this outline. First, I will present the primary endpoint results in the intention-to-treat and the per-protocol populations. Then I'll present a sensitivity analysis accounting for missing data in the per-protocol population, followed by primary endpoint analyses in the as-treated and device-in-place populations. I'll also present the data we have from our extended follow-up

period and finally a few slides on a patient-level meta-analysis. Let's now look at the primary endpoint analysis in the intention-to-treat and per-protocol populations.

The ITT population included all 499 patients randomized to receive the AMPLATZER PFO Occluder and 481 patients randomized to medical management. The ITT population for the device arm included 34 patients who did not receive a device; 465 patients had a successful implant. Of those 465, two patients were excluded from the per-protocol population, one because of a violation of a key trial entry criterion and the second for noncompliance to medication. Therefore, 463 patients are included in the per-protocol device arm.

Of the 481 patients randomized to the medical management arm, 7 were excluded from the per-protocol population, 4 due to violations of the trial entry criteria and 3 for noncompliance to their medication regimen. The remaining 474 patients are included in the per-protocol medical management arm.

As a reminder, the endpoint was a composite of recurrent fatal ischemic stroke -- I'm sorry, recurrent nonfatal ischemic stroke, fatal ischemic stroke, or post-randomization death.

There were three deaths in the device arm and six deaths in the medical management arm at the time of the primary assessment, but none of these deaths was adjudicated as a primary endpoint event. The only endpoint events that actually occurred in the trial were recurrent nonfatal ischemic strokes.

The raw count analysis of the ITT population shows an odds ratio of 0.53 in favor of the device; however, this did not reach statistical significance. As previously mentioned,

the differential follow-up rates make the raw count analysis inappropriate and indicated the use of survival analyses. The survival analysis of the ITT population found a 50% relative risk reduction for recurrent ischemic stroke among patients randomized to the device arm compared with the medical management arm. The two-sided p-value for the log-rank test was 0.089. While this analysis missed statistical significance, the 50% relative risk reduction is clinically relevant. The survival analysis of the per-protocol population found a 63% relative risk reduction.

Recall that the rate of recurrent ischemic stroke in this population is 1% to 2% per year. In the context of secondary stroke prevention in patients with decades of life ahead of them, the number needed to treat is an important consideration.

This slide shows the event rates in both groups as well as the number needed to treat in the intention-to-treat population, shown below, the figure in blue. You can see that the risk of a stroke accumulates with time, and the difference in the stroke rate between the device arm and the medical management arm gets larger. Because the treatment difference gets larger over time, the number needed to treat becomes smaller each year, going down from over 100 at Year 1 to 27 at Year 5. In the per-protocol population, the number needed to treat at 5 years is 22.

Given the rate of early withdrawal at the time of the primary assessment, we undertook sensitivity analyses to assess the impact of the missing data. In the intention-to-treat population, 50 device patients and 84 medical management patients withdrew from RESPECT without experiencing a primary endpoint event. The characteristics of the patients who withdrew from the trial were similar to those who remained, with a few exceptions.

Patients who withdrew were more likely to have had a stroke prior to their qualifying cryptogenic stroke and tended to be smokers or former smokers at the time of randomization. Therefore, patients who withdrew had a higher prevalence of risk factors for recurrent stroke than those who remained in the trial.

I'll present one of our sensitivity analyses for missing data. In the per-protocol population there were six observed events in the device arm and 14 events in the medical management arm, which equates to observed rates of 0.4% per year in the device arm and 1.2% per year in the medical management arm.

For the medical management arm, we simulated missing data assuming that the stroke rate is the same as that observed in the patients with complete data. And based on the 322 missing patient-years, four additional events were imputed, bringing the total to 18 events in the medical management arm.

We wanted to show what it would take to tip the per-protocol analysis from statistical significance to insignificance or a p-value greater than 0.05 and resolved for the imputed event rate. Based on the 90 patient-years missing from the device arm, the imputed event rate would need to be 4.4% per year or 10 times greater in the missing data than what was observed. This assumption appears to be clinically unlikely, providing reasonable assurance of the per-protocol results.

Next, I'd like to review the effectiveness results in the as-treated and device-in-place populations. The as-treated analysis evaluates patients based on the actual protocol treatment received, and device in place compares patients based on device received and in place at the time of the event, regardless of adherence to protocol. These analyses

demonstrated the relative risk reduction for ischemic stroke with the AMPLATZER PFO Occluder of 72% in the as-treated population and 70% in the device-in-place population. These findings of a magnified effect in these populations is consistent with a genuine positive effect of device closure in reducing stroke events.

Now I'd like to present the post hoc analyses of extended follow-up. These analyses were conducted in response to an FDA request for updated safety and effectiveness data.

Differential dropout persisted throughout the extended follow-up period, with more patients withdrawing from the medical management arm than from the device arm. One of the key assumptions of the RESPECT trial was that recurrent strokes in these younger patients would primarily be due to paradoxical embolism. This assumption becomes less valid with extended follow-up. One in five RESPECT patients were over the age of 60 at the time of data lock for the extended follow-up period. Such patients are at increased risk for recurrent strokes due to competing non-PFO-related mechanisms. I'll show two separate analyses designed to explore the impact of non-PFO-related strokes and aging.

Over the extended follow-up period, nearly one-third of recurrent strokes had a known mechanism according to ASCOD phenotyping. These included atherosclerosis, small vessel disease, and cardioembolism. As a note, four of the five cardioembolic strokes were related to atrial fibrillation, three of which were in the medical management arm.

In this slide you see the Kaplan-Meier plot for all recurrent strokes, regardless of mechanism, in the ITT population, through extended follow-up. There were 18 events in the device arm and 24 in the medical management arm. These yellow dots represent the strokes of known mechanism that I just discussed. When we focus our extended follow-up

analysis strictly on the strokes of undetermined mechanism that may be prevented by PFO closure, we see that the AMPLATZER PFO Occluder was superior to medical management.

In an effort to validate this finding, we conducted an additional sensitivity analysis that didn't rely on phenotyping. Here, follow-up was censored when patients reached 60 years of age. The result was consistent with the finding from the analysis using ASCOD phenotyping. The relative risk reduction in all recurrent stroke was 52%.

And here's why. This chart shows the percentage of strokes due to known non-PFO-related causes in gray and undetermined causes in light blue. Among patients who were still under the age of 60 at the time of their outcome stroke, only 18% of strokes had a known cause and could not have been prevented by PFO closure. In patients over 60, we see the opposite. Nearly all of the events in older patients were due to a known cause. These were not PFO related and, again, could not have been prevented by PFO closure.

Finally, I'd like to present data from a patient-level meta-analysis of two randomized PFO closure trials, which increases the power and precision of our ability to estimate the treatment effect. This analysis was conducted at Tufts University as part of a separate NIH-funded grant.

The meta-analysis combined the patient-level data from RESPECT with the PC trial, both of which studied the AMPLATZER PFO Occluder. The PC trial was conducted in Canada, Europe, Brazil, and Australia, and like RESPECT, the PC trial had a 1:1 randomization and was conducted during the same time period. The PC trial provides another 414 patients for analysis.

These are the results of the meta-analysis from the intention-to-treat and as-treated

populations for ischemic stroke. We used Cox models to evaluate the outcome, adjusting for the covariates indicated on the slide. In the intention-to-treat population there was a statistically significant relative risk reduction of 59% for recurrent ischemic stroke with the AMPLATZER PFO Occluder. And even stronger positive results was seen in the as-treated population.

To summarize, the RESPECT primary endpoint in the ITT population was not met, despite showing a 50% relative risk reduction in favor of the device. This did not reach statistical significance.

Analyses of additional populations support the study hypothesis that closing a PFO with the AMPLATZER PFO Occluder reduces the risk of recurrent ischemic stroke.

Through extended follow-up, benefit in preventing recurrent cryptogenic strokes was sustained. Strokes with conventional causes emerged as patients aged.

With pooling of patient-level data from the two randomized trials of the AMPLATZER PFO Occluder, there was a significant relative risk reduction in favor of the device for the prevention of recurrent ischemic stroke.

Thank you. I now invite Dr. Carroll to present RESPECT safety results.

DR. CARROLL: Good morning. My name is John Carroll, and I am a Professor of Medicine at the University of Colorado School of Medicine and a practicing interventional cardiologist at the University of Colorado Hospital. I'm pleased to present the long-term safety results of a trial that extended through extended follow-up. At this time we have over 5,000 total patient-years of follow-up, including more than 2,700 patient-years of follow-up with the device.

This slide shows the overall rate of serious adverse events in the device and medical management arms, expressed both as a percentage of the patients in each arm as well as a rate per 100 patient-years. There have been no unanticipated adverse device effects or deaths related to the procedure or the device through extended follow-up. Serious adverse events related to the procedure occurred in 2.4% of device patients, and SAEs related to the device occurred in 2% of device patients.

Next, I will spend some time reviewing the details of the SAEs related to the procedure or the device. First, serious adverse events that were related to the procedure.

Two patients developed pericardial tamponade, which required pericardiocentesis. One patient experienced a cardiac perforation and another a pericardial effusion, both of which resolved without intervention. There were three access site bleeding events. There was one right atrial thrombus detected at the time of the implant procedure. As a result, the investigator aborted the procedure prior to inserting the delivery catheter. There was one case each of deep vein thrombosis, atrial fibrillation, allergic drug reaction, and vasovagal response. All events resolved without known long-term sequelae. There were no serious adverse events of acute ischemic stroke due to air emboli or thrombus on the device, and there were no device embolizations.

Let's now turn to device-related serious adverse events. Two patients experienced ischemic strokes, which were adjudicated as device-related SAEs as well as primary endpoint events. One occurred 7 days post-procedure. The other occurred 3 months post-procedure. The patient was found to have a sinus venosus atrial septal defect that was not diagnosed at the time of enrollment, and the patient should not have been enrolled per the

trial entry criteria. There were no reports of atrial fibrillation or thrombus on the device related to these events. Two patients experienced a pulmonary embolism. One was at 5 days post-procedure and the other was almost 6 months post-procedure. An echo done on the second patient revealed a cardiac thrombus in the right atrium, not attached to the device. Both the cardiac thrombus and pulmonary embolism event resolved with warfarin 3 months later.

The device was surgically explanted in two patients. The first patient was the one with the sinus venosus atrial septal defect that I just discussed and who underwent surgical repair. The second patient had the device explanted due to infective endocarditis 18 months following the procedure.

There was only one SAE of atrial fibrillation attributed to the device. Three days post-implant after successful treatment of cardiac tamponade, the patient was found to be in atrial fibrillation with a rapid ventricular rate. He was given oral and IV metoprolol and spontaneously converted back to sinus rhythm. The patient was discharged home in stable condition the next day.

One patient had a residual shunt at the edge of the PFO closure device adjacent to the aortic root. An ASD occluder was placed without complication or residual shunt.

There were four other serious adverse events.

Importantly, there were no reports of thrombus on the device or device erosions in any patient during the trial.

Next, I'll review the adverse events related to atrial fibrillation, which has emerged as a risk factor to consider in the context of transcatheter-based PFO occlusion.

This slide includes both serious and non-serious atrial fibrillation adverse events. There was a numerically higher rate of atrial fibrillation in the device arm. Approximately one-third of the events were periprocedural, resolved prior to discharge, and no recurrences were noted thereafter. When we consider the post-procedure events in the device arm, the rate of atrial fibrillation was comparable with the medical arm. Four strokes occurred in the trial related to atrial fibrillation. Of these, one occurred in the device arm, and three occurred in the medical management arm.

During the trial, the RESPECT DSMB noted a higher rate of venous thromboembolic events in the device arm, including deep vein thrombosis and pulmonary embolism. Through extended follow-up, 18 patients in the device arm experienced 24 VTE events, and 3 patients in the medical management arm experienced 5 VTE events. The imbalance between the arms was an unexpected finding that was not apparent in other publications of PFO closure, likely due to their smaller size and shorter duration of those studies.

Intuitively, patients who suffer cryptogenic stroke are likely to be at a higher risk for a thromboembolic event. While the device protects paradoxical embolism from clots moving from the right side to the left side of the heart, it does not prevent clots from forming in the first place. Nevertheless, we have conducted extensive analyses to investigate the excess VTE rate in the device arm.

This is the distribution of the time to first venous thromboembolic event in the 18 device patients. Events that occurred within the first 6 months were adjudicated as procedure or device related. Subsequent VTEs were not adjudicated as device or procedure related. Most of the events occurred at least 1 year after implant.

The strongest predictor for a venous thromboembolic event in device patients was a history of deep vein thrombosis. Device patients with a history of DVT were 12 times more likely to experience a VTE during follow-up than patients without a history of DVT.

As Dr. Saver presented earlier, anticoagulation therapy with warfarin, an evidence-based therapy known to prevent VTE, was nine times more likely to be used in the medical arm than the device arm. At 2 years, warfarin was being used in 18% of patients in the medical arm but only 2% of patients in the device arm.

After randomization, the protocol resulted in warfarin therapy being discontinued in nearly all device patients because the protocol specified that aspirin and clopidogrel were to be used for the first month post-procedure, followed by 6 months of aspirin. No device patient with a history of DVT who experienced a recurrent VTE event was on warfarin at the time of their event. Since RESPECT was designed, the medical guidelines for antithrombotic therapy for VTE disease has evolved considerably.

The current evidence does not suggest that the imbalance in VTE events is due to the device for several reasons. First, most events occurred several years after implant procedure, and by that time, the device would likely have been endothelialized. Second, no thrombus was observed on the device on surveillance echoes at 6 months, which was concordant with other trials. Furthermore, no thrombus on device was observed on echoes done for other reasons throughout the course of the trial. Finally, there was no pathophysiologic reason for device thrombus leading to DVT. In fact, of the 18 patients who had VTE, 11 of them had DVT. Seven had an isolated PE.

In summary, the overall rates of SAEs were similar in the two arms. The RESPECT

trial has demonstrated that the AMPLATZER PFO Occluder can be safely implanted, with a rate of serious complications less than 5%. The rate of cardiac tamponade was 0.4%. We found no intra-procedure strokes or device embolizations. There were no reports of thrombus on any device or device erosions through extended follow-up.

Approximately one-third of atrial fibrillation events in the device arm were transient periprocedural events. The rate of atrial fibrillation post-procedure was comparable to the overall rate in the medical management arm.

There was a higher rate of venous thromboembolic events in device patients. Our analysis to understand this finding suggests that the difference was largely attributable to patients who had a prior VTE who were not being treated with warfarin. Therefore, patients undergoing PFO closure who have had a prior VTE should strongly be considered for anticoagulation, as is recommended in the proposed device labeling.

I'll now turn the presentation back to Dr. Carlson.

DR. CARLSON: Thank you, Dr. Carroll.

In the next few slides I will describe St. Jude Medical's post-approval plans, including our physician training program and proposed post-approval clinical studies.

Our physician training program covers patient selection, implanting physician qualification, and implant and post-procedural training. St. Jude Medical strongly believes that proper patient selection is key to ensuring that the benefits of PFO closure with the AMPLATZER PFO Occluder outweigh the risks. The company will train physicians per the American Heart Association and the American Stroke Association's published guidance regarding the diagnosis and treatment of patients with a PFO who have suffered a

cryptogenic stroke.

Our program will train physicians to use a multidisciplinary team approach to evaluate prospective patients. The team will include both a neurologist and an interventionalist. The didactic training will cover how to conduct a comprehensive workup to diagnose cryptogenic stroke, including elimination of other potential causes. The training will emphasize that a neurologist must confirm the cryptogenic stroke diagnosis and recommend the patient for PFO closure.

The AMPLATZER PFO Occluder training program will include mandatory components to ensure that implanting physicians are well prepared to implant the device. Only physicians qualified by their institution to perform left atrial procedures via the right atrium will be trained. The training will consist of mandatory physician didactic training and case support. The physician didactic training will cover appropriate patient selection, the device, clinical trial data, the procedure, and post-procedural care. Proctoring will be tailored to physician experience.

Next, I will review our proposed post-approval studies. St. Jude Medical plans to conduct two studies to evaluate the ongoing safety and effectiveness of the AMPLATZER PFO Occluder.

Our first post-approval study will continue to follow current RESPECT patients through their 5-year follow-up visit. The second is a non-randomized prospective study of newly implanted patients. The proposed sample size in this study is 806 patients, based on the statistical assumptions and calculations found in your Panel pack. Patients will be followed through 5 years.

The second post-approval study safety endpoint is a composite -- pardon me, composite of device- or procedural-related serious adverse events through 5 years in the categories shown here. The effectiveness endpoint is recurrent ischemic stroke through 5 years. Both of these endpoints will be evaluated against performance goals which were developed based on RESPECT's study results.

St. Jude Medical is committed to continuing to work interactively with the FDA to further define and finalize our post-approval study program.

Thank you. I now invite Dr. Carroll to close our presentation for today.

DR. CARROLL: Thank you, Dr. Carlson.

PFO closure provides a mechanistic therapy for the prevention of strokes related to paradoxical embolism. It is very reasonable to consider a targeted therapy in a carefully selected patient for whom a neurologist has excluded other reasons for stroke.

Surgical or device closure for other forms of right-to-left shunting is widely accepted in the cardiovascular community as the standard of care and is embedded in guidelines for the management of many other congenital heart diseases.

While PFO closure prevents strokes due to paradoxical embolism, closing the PFO does not prevent venothromboembolic disease, and it does not prevent strokes related to atherosclerosis, hypertension, or other known stroke risk factors. Patients with these risk factors will require ongoing medical therapy and monitoring, highlighting the continued importance of comprehensive risk factor modification.

Despite the intuitive rationale behind this therapy, closing the holes in a heart thought to have caused a stroke, it was an enormous effort to gather randomized

controlled data for PFO closure. In my 35 years as a clinical trialist in cardiology, I've never encountered a more challenging environment to get the answer to a fairly straightforward question, can we lower the risk of recurrent stroke by mechanically closing the PFO? It was assumed by many in the field that the question didn't need to be answered. The basic tenet of conducting a clinical trial demands equipoise, and a substantial proportion of the clinical community did not have equipoise. Thus, enrollment and retention in the RESPECT trial, and all PFO closure trials, were hampered by widespread off-label closure.

This slide demonstrates the number of cryptogenic stroke patients with PFOs enrolled in studies that were ultimately published in the peer-reviewed literature. As you can see, during the course of recruitment in the RESPECT trial, thousands of PFOs were closed and reported in observational studies.

Nine years ago, the FDA convened the Cardiovascular System Devices Panel to weigh in on the issues challenging the conduct of randomized PFO closure trials. That Panel strongly recommended that randomized controlled trials be completed to answer this question. This call was echoed in editorials by leading experts in cardiology and neurology, as shown on this slide. Despite all the challenges, many stakeholders, including St. Jude Medical, the FDA, professional societies, clinical sites, and most importantly the patients, committed to finding the answer to this important question.

The totality of data presented today leads to the conclusion that the AMPLATZER PFO Occluder provides a reasonable assurance of effectiveness and safety.

Considering effectiveness, current medical therapy provides only partial protection from recurrent stroke. PFO closure further reduces that risk in carefully selected patients.

As we saw in the RESPECT trial and in the meta-analysis, all point estimates showed a clinically meaningful treatment effect, and closure of the PFO with the device has an acceptable periprocedural and long-term risk profile.

Although not statistically significant in the ITT analysis, the 50% relative risk reduction for a stroke is clinically significant. This reduction was more pronounced in the per-protocol, as-treated, and device-in-place analyses. The totality of the randomized data evaluated in the patient-level meta-analysis strengthens the substantial relative risk reduction observed in RESPECT.

In extended follow-up, the AMPLATZER PFO Occluder was shown to reduce the risk of recurrent cryptogenic stroke. At 5 years, using the ITT analysis, only 27 patients needed to be treated in order to prevent a stroke.

In RESPECT, the overall SAE rates were similar in the device and medical management arms. Device- and procedure-related complications occurred in 4.2% of patients, and there were no long-term known sequelae.

VTEs occurred more frequently in the device arm, which appears to be largely due to differential use of warfarin between the two arms. As noted in the recently updated guidelines from the American College of Chest Physicians, extended anticoagulation ought to be considered for patients who experience an unprovoked VTE. Recommendations on the appropriate medical therapy for patients undergoing PFO closure are included in the proposed device label.

The AMPLATZER PFO Occluder is a needed option for these patients to safely close their PFOs, providing protection against paradoxical embolism for many years to come.

Approval of this device would lead to the replacement of off-label closure with a regulated device designed specifically for PFO anatomy, with reasonable assurance of safety and effectiveness based on data from randomized controlled trials.

As you heard from Dr. Carlson, St. Jude Medical would provide the clinical community with rational dispersion of this first-in-class therapy. This strategy includes proper physician training, appropriate patient selection involving teams of neurologists and their interventionalists, and postmarket surveillance.

In summary, for years we have known that we needed additional treatment options for the prevention of recurrent stroke due to paradoxical embolism in young to middle-age patients. The AMPLATZER PFO Occluder provides us with an option. The clinical data have demonstrated that the device reduces the risk for these strokes beyond medical management alone. The procedure is safe, and we should be able to address the risk for VTE with guideline-directed anticoagulation in patients who have had a prior VTE.

Overall, the benefits of the reduction in stroke risk achieved in the AMPLATZER PFO Occluder outweigh the risks among carefully selected patients for whom this therapy is appropriate.

Thank you for your attention. This concludes our formal presentation. Dr. Carlson will now moderate the question and answer session.

DR. PAGE: Thank you very much. I want to thank the Sponsor for a very clear presentation.

Before we move on, I believe Dr. Zuckerman has a comment.

DR. ZUCKERMAN: Yes. Thank you, Dr. Page. And thank you, Dr. Carlson, for your

team's excellent presentation this morning.

As many Panel members are aware, we allow for presentations by the Sponsor, and we generally require that the data being shown have been evaluated by FDA prior to their presentation in the open Panel meeting. There is one slide that the Sponsor showed for the effectiveness endpoints, CO-60 on your page 30, which is a very visually arresting slide which attempts to explain, through ASCOD scoring and other analyses, the convergence of the treatment effects with longer-term follow-up.

For the record, it's important to understand that FDA has not had a chance to evaluate these data in detail. It's not that the Sponsor can't show these data. Certainly after the Panel meeting we'll be very interested in learning about them, but we do want you to understand this slide in the appropriate context and ask the Sponsor that if there are other new data analyses not unique for a very complex dataset, that we appropriately recognize what has been shared with the FDA.

Thank you.

DR. PAGE: Thank you, Dr. Zuckerman.

I would like to now proceed with allowing the Panel to ask any brief clarifying questions for the Sponsor. Please remember, the Panel may also ask the Sponsor questions during the Panel deliberation session.

So I see Dr. D'Agostino.

DR. D'AGOSTINO: A very impressive presentation. There's one point that you may have covered I'm not sure I understand. You had 69 sites. You had blind adjudication, is that correct, for the events?

DR. CARLSON: Correct.

DR. D'AGOSTINO: Given the mechanism and the -- what have you, how blinded was the blinded adjudication? Was there a possibility that some of the events were discounted because of unintentional but possible --

DR. CARLSON: Unintentional but possible knowledge --

DR. D'AGOSTINO: Well, unintentional but possibly over-reading the records in terms of making the adjudication.

DR. CARLSON: I think that's unlikely. We do have a member of our CEC here.

DR. D'AGOSTINO: Yeah.

DR. CARLSON: So we followed the guidelines and our usual strict criteria in redacting information that could alert CEC members, meaning clinical events committee members, of information. But perhaps -- yeah, do you want to speak?

DR. SAVER: Yes. I sat on the ASCOD committee and the CEC committee when -- I served on the ASCOD blinded committee when we were presented with information from source documents. All information that would have unblinded was blacked out in each of the source documents. So not only were we formally blind, we were blinded at the detail level without a chance for being unblinded.

DR. D'AGOSTINO: You know, there are a number -- in your presentation there are a number of things where you discount certain deaths and so forth. And I mean, you're very rigorous and I'm not -- I'm just trying to sort through --

DR. CARLSON: Understood.

DR. D'AGOSTINO: -- if something happened along the way.

DR. CARLSON: And it's actually Dr. Larkin who's a member of the CEC, if Dr. Larkin wants to add to anything.

Do you have anything to add to that?

(Off microphone response.)

DR. CARLSON: Okay.

DR. D'AGOSTINO: Thank you.

DR. CARLSON: Thank you.

DR. PAGE: Thank you.

Dr. Chaturvedi.

DR. CHATURVEDI: So we know that one of the most common causes of stroke is intracranial atherosclerosis, and that's estimated to account for about 10% of all ischemic strokes. So my question was, was evaluation for intracranial atherosclerosis mandatory prior to subject enrollment in the RESPECT study? And if not, what percentage had evaluation for intracranial atherosclerosis?

DR. CARLSON: That's a question we're happy to address, and I think Dr. Saver would be the appropriate person to address that.

DR. SAVER: Thank you.

Yes, it was mandatory, and 100% of the patients in the trial had evaluation of the intracranial vessels. Those patients who received carotid duplex ultrasound as part of their evaluation also had to have received either a CTA or MRA or transcranial Doppler ultrasound evaluating the intracranial circulation. So all patients had their intracranial vessels assessed.

DR. PAGE: Thank you.

Dr. Borer and then Dr. Furie.

DR. BORER: Thank you. That was a very nice presentation. I'd like to hear some more detail about the four patients -- I believe it was four who had strokes after the implantation of the device and who had TEEs that showed total occlusion of the PFO so that it would have been virtually impossible for them to have had cryptogenic stroke. There were only four of them, as I recall, and I would like to know, first, among those four patients, what was the evidence that the initial stroke was likely to have been due to a paradoxical embolism? And what was their age at the follow-up stroke? Were they over 60? You made a good point there. And did they have other stroke risk factors? Those four trouble me because it makes me wonder whether they actually had a cryptogenic stroke in the first place. So if we could have some more detail about them, I would appreciate it.

DR. CARLSON: Thank you. A very specific question. And I'm going to ask Dr. Sethuraman if she can come to the lectern and if we have that specific information at this time or if we need to come back to you.

DR. SETHURAMAN: Barathi Sethuraman from St. Jude Medical, Vice President of Clinical Science.

You were asking about the six strokes in the device patients who had a stroke after device? I'm trying to make sure where you got the four from.

DR. PAGE: Perhaps I can clarify. I believe the question related to -- Dr. Borer identified four patients who had recurrent CVAs in the setting of what appeared to be 100% occlusion by the device. If you don't have those data immediately available --

DR. SETHURAMAN: Okay.

DR. PAGE: -- might we ask that you prepare a slide for us after the lunch break? Specifically the questions were what was the evidence of the nature of the original qualifying CVA?

Does that summarize properly, Dr. Borer?

DR. BORER: Partly, yes. And what makes you believe that, in fact, they were more likely to have non-cryptogenic stroke when they had the follow-up stroke? Yeah, that's it.

DR. PAGE: So Dr. Carlson --

DR. CARLSON: Understood.

DR. PAGE: -- you may have other homework to do over the lunch break, as you can imagine. Let's just have you keep track of that as being the first of the questions.

DR. CARLSON: We've got it, Dr. Page.

DR. PAGE: Thank you.

Dr. Furie and then Dr. Noonan.

DR. FURIE: I have two questions. The first has to do with the diagnosis of atrial fibrillation. Since the time that this trial was conducted, there has been a wealth of new data suggesting that more extensive monitoring increases the likelihood of detecting atrial fibrillation. Can you speak to the amount of monitoring that occurred in this trial and what your recommendations would be moving forward?

DR. CARLSON: I can. And as an electrophysiologist, I agree with you, the field has moved, and monitoring has changed. Patients with a baseline history of atrial fibrillation were excluded, and atrial fibrillation was determined during the trial by either

electrocardiogram or by Holter monitor. So it's entirely possible that there were some patients who had occult atrial fibrillation or had undiagnosed paroxysmal atrial fibrillation. Our best estimates are that this would have been a handful of patients, and it would have been equally distributed between the two groups, but we really can't say with any certainty.

DR. FURIE: And my second question has to do with the clause that implantation of the device is intended to prevent paradoxical embolism. That's a tricky condition to diagnose, and are you implying that there should be evidence for paradoxical embolism with regard to either a history or detection of acute DVT, pelvic vein thrombosis, or a history of a hypercoagulable state to make that the likely mechanism of stroke in patients who have a cryptogenic mechanism?

DR. CARLSON: I'm going to refer that question to one of our clinicians.

Dr. Thaler.

DR. THALER: Thank you, Dr. Furie. The field of cryptogenic stroke, as you know, is progressing, as you suggested, with the A-fib question. And the presumption that a patient's cryptogenic stroke is due to paradoxical embolus or, let's say, PFO relatedness is largely a function of the prevalence of PFO found in cryptogenic stroke patients. And by other work that's been done, the criteria used in the RESPECT trial, I think, identified a population of cryptogenic stroke patients, in part because of limiting it by age and excluding other factors, but successfully identified a population of patients who had cryptogenic stroke who happened also to have PFOs that, in fact, were likely to be pathogenic rather than incidental. But to answer your question directly, I don't think the plan is to require the presence of DVT or a hypercoagulable state or a thrombus in situ. As has been found

before, I think we presume it based in part on the epidemiology.

DR. PAGE: Thank you, Dr. Furie.

I see Dr. Noonan next, then Brindis, Brinker, and Yuh.

Dr. Noonan.

DR. NOONAN: Thank you.

I have a number -- I'm going to put my questions in two general categories. The first concerns the device. I know that it's made of two nitinol discs and connected by a waist. I assume, as it's delivered, it's in the catheter and it's strung out on delivered form.

DR. CARLSON: Correct.

DR. NOONAN: And when it is unconstrained, if you were to deliver it on the tabletop, it would make two sort of ovoid discs.

DR. CARLSON: Correct.

DR. NOONAN: Not necessarily flat, is that correct?

DR. CARLSON: They're pretty close to flat.

DR. NOONAN: Pretty close to flat. Now, between the two there's a waist. Is that waist made of the same metal? Is that nitinol as well, or is there a different metal in that waist?

DR. CARLSON: I believe it's the same metal, but I'm going to ask one of our engineers just to be absolutely certain.

Mike.

MR. MEYER: Hi. Mike Meyer, St. Jude Medical, research and development.

And yes, the waist is the same material. It is a continuous nitinol braid which is

formed into the shape of the discs and the waist.

DR. NOONAN: The picture in the patient information booklet, to me, is a different color. I don't know if that's intentional. Is that a weld?

MR. MEYER: No, the waist, there's no weld in the waist. It's just formed. There are welds on the end of the device, but not in the waist.

DR. NOONAN: What's the function of those welds?

MR. MEYER: To bind. On the one end it's to bind the screw, the delivery screw. On the other end it's just to bind. You've got 72 wires that come together. So, again, it's to attach the radiopaque marker band.

DR. NOONAN: What would happen if the welds failed?

MR. MEYER: We have data that -- we have a tensile spec at 12 pounds, and we have data that shows that, in tensile, it's about 75 to 90 pounds. So we have not seen any marker bands fail.

DR. NOONAN: Were the welds tested for corrosion?

MR. MEYER: Yes, they were.

DR. NOONAN: Okay.

MR. MEYER: Yes.

DR. NOONAN: All right. The device in a young person, a 20-year-old, might be in place 68 years, 70 years. I'm just concerned a little bit, which brings me to the pig data.

DR. CARLSON: One other point to make is that these devices become endothelialized. So --

DR. NOONAN: Do you have proof -- I'm glad you brought that up. What proof do

you have that the device becomes endothelialized?

DR. CARLSON: This is a human autopsy case in a patient who died for other reasons, in which you can see that the device --

DR. PAGE: Could the AV people please increase the volume and adjust according to each speaker? Thank you.

DR. CARLSON: Oh, am I talking -- I'm usually not accused of speaking too softly. This is a single case of a device that had been implanted for 15 months, and you can see that it's endothelialized.

DR. NOONAN: Was that true in the pigs?

DR. CARLSON: It was.

DR. NOONAN: Okay.

DR. CARLSON: And those were at 6 months, I believe.

DR. NOONAN: Now, 71% of the devices had full occlusion at 6 months, and you followed them after that point. Did they actually go on to full occlusion, the 29% or so that didn't have complete occlusion?

DR. CARLSON: I don't believe we had systematic follow-up on all of those individuals, so I don't have follow-up echoes on each of those individuals. But there are data from other studies that suggests that's the case.

DR. NOONAN: Okay. But not from your study?

DR. CARLSON: Correct.

DR. NOONAN: All right. Next, were there any patients -- you may not have this data -- who had full occlusion at 6 months that went on to develop a leak? Not occlusion.

DR. CARLSON: No.

DR. NOONAN: Okay. Regarding page 11 --

DR. PAGE: Dr. Noonan, a number of people are waiting. Why don't we just hold it to one or two more questions, and we'll get back to you as time allows. Go ahead, please.

DR. NOONAN: Me?

DR. PAGE: Yes, sir.

DR. NOONAN: Okay. My next question is, in the trial, you screened patients using ultrasound for the carotids. Were there patients who only got ultrasound on the carotids, but not CTA and not MRA? And then you included, for intracranial screening, TCD. Now, I would beg that TCD is not quite a standard-of-care means of evaluating intracranial vessels.

DR. CARLSON: One hundred percent of patients had intracranial vessel studies performed.

Dr. Saver, can you address the second question?

DR. SAVER: Yes. As was mentioned, every patient did have intracranial vessel imaging. The use of TCD was very low, largely confined to patients who had contraindications going into the MRA scan and to getting contrast, so neither CTA or MRA was an option for them. Almost all the patients had CTA or MRA for their intracranial imaging.

DR. NOONAN: Okay.

DR. PAGE: Thank you.

Dr. Brindis, then Brinker, then Yuh.

Dr. Brindis.

DR. BRINDIS: Yes, I have a question for the Sponsor, which may need some homework. And actually first to Slide 60, which Bram also mentioned, so I'll throw that up. And then it also refers to Table 31 in the package that you sent us, on page 67. I don't know if you have a slide of that available, showing the demographics and baseline characteristics of patients in the PFO ACCESS registry. And I bring that up because the average -- the mean age in the PFO registry was 59.5. So it's markedly older than the patients enrolled, of course, in the study. And again, looking at the data that you showed nicely in Slide 60, this raises a couple of questions in terms of a rational dispersion in the application of the technology.

So the question would be is there any difference in the entrance -- the rigor of the entrance criteria or screening tests in the PFO registry? Are we using the same recommendation of a team-based approach with a neurologist? Do you have any insight as to why there is this marked age difference? And to raise the question that we just heard earlier, related to occult atrial fibrillation, do you plan on having a more rigorous, aggressive evaluation for occult atrial fibrillation, particularly appreciating the older age group in the PFO ACCESS registry?

DR. CARLSON: I can answer some. I'm not sure we'll be able to answer all of those before the break. With regards to your last question and requirement regarding monitoring for atrial fibrillation, that's a conversation that we'll absolutely be having with FDA. And we recognize that the standard of care has changed over the last several years, as was mentioned before.

Dr. Sethuraman, can you comment on the registry and any differences that might

have existed between that and RESPECT?

DR. SETHURAMAN: Yeah. Barathi Sethuraman again.

The PFO ACCESS registry required patients to have had two cryptogenic strokes, and one of them must have occurred while the patient was on anticoagulant or antiplatelet therapy.

DR. CARLSON: Does that address your question, Dr. Brindis?

DR. ZUCKERMAN: Okay. So Dr. Brindis, the bottom line is that the ACCESS registry is for a different indication than what is being discussed here --

DR. CARLSON: Fair enough. Thank you, Dr. Zuckerman.

DR. ZUCKERMAN: -- and was just included in the Panel pack for the sake of completeness.

DR. CARLSON: Thanks, Dr. Zuckerman.

DR. PAGE: Thank you.

Dr. Brinker, Dr. Yuh, Dr. Slotwiner, and then Dr. Kandzari.

Dr. Brinker.

DR. BRINKER: Thank you.

I noticed that there was one patient that received an additional occlusion device to patch up an area that wasn't completely covered at the time of the implant. But do you have any other post-procedural information that supports -- that involves transseptal catheterization for any reason? The instructions for use are pretty mute on transseptal after one of these devices are put in, and there are a lot of potential needs. So it would be nice to have something in there and something you might be able to tell us from

experience.

DR. CARLSON: Absolutely. And let me ask Dr. Carroll to address that.

DR. CARROLL: It is certainly of concern that placing a device in the atrial septum may make it impossible or difficult for people to have subsequent transcatheter procedures for atrial fibrillation ablation, et cetera. Fortunately, the vast majority of patients having PFO closure within RESPECT had a 25 mm device. And so when you look at the remaining amount of septal tissue that is readily accessible for transseptal catheterization with access to the left atrium, it's quite a bit. So I think that's, in general, the answer. There have been reports of people doing transseptals through a device, although that would not be something I would personally recommend. So I think there is -- the point is, this does not preclude having other forms of transseptal procedures.

DR. BRINKER: So some of those other reports, the device is a bit different, as far as I can tell, than this particular device. Would you categorically say that no attempt should be made to cross this device with a transseptal system?

DR. CARROLL: I would hesitate to be quite so categorically dogmatic. I think clinical situations vary. But I think the bottom line is that there is almost, in all of these patients, the ability to do a transseptal catheterization elsewhere in the remaining normal septal tissue.

DR. BRINKER: So I would suggest words of that show up somewhere in the instructions for use.

DR. CARROLL: Thank you.

DR. CARLSON: Thanks very much.

DR. PAGE: Next will be Dr. Yuh, then Dr. Slotwiner, Dr. Kandzari, Dr. Chaturvedi, Dr. Lincoff, and Dr. Laskey. And several more perhaps.

(Laughter.)

DR. PAGE: We are going to break at or before 10:00. There will be opportunity for further questions of the Sponsor later. I would like to keep our questions single, if possible, and concise.

Dr. Yuh.

DR. YUH: Thank you. A great presentation. Thank you very much. I have a single question. Maybe you could help me better understand how you assigned the cryptogenic versus known causes for embolic stroke. I mean, how do you know that in those patients where it's been -- where they've been tagged with a known etiology of stroke, that it's not due to the PFO? And wouldn't you expect to see a concomitant rise in known stroke rates in the device group, you know, over time, over the full length of the trial, to the 8 years? In other words, after the 5-year inflection point, I would've expected to see a higher rate of known strokes, even in the device group.

DR. CARLSON: We are.

DR. YUH: You are.

DR. CARLSON: We did.

DR. YUH: Okay.

DR. CARLSON: And that's part of the explanation for curves coming together.

DR. YUH: Okay.

DR. CARLSON: I think it was eight in one group and nine in the other during

extended follow-up. So the known -- it was evening out as a result of known strokes. But let me ask Dr. Thaler to address your other question.

DR. THALER: Thank you very much.

I guess I'd admit, as a clinical neurologist, that all stroke diagnosis is presumptive, and it's somewhat probabilistic. So even in a patient who has atrial fibrillation, they may have a 50% carotid stenosis that was, in fact, responsible for their stroke. The way the ASCOD phenotyping works is that there are required investigations for each of the categories and if one of those -- and then there are definitions for assigning it as probable or possible or definite. So if one of those is discovered, then it received that score. If you don't know for sure that the 70% ipsilateral carotid stenosis was responsible for that MCA stroke on that side, but it counts as a Grade 1 cause of probable -- you can have more than one probable, which is another definition of cryptogenic. You can have atrial fibrillation and high-grade carotid stenosis. And, in fact, that's in some old literature, another category of cryptogenic.

DR. CARLSON: It's not in ours.

DR. THALER: Not in ours. No, that's correct. So I guess the short answer is we can't be absolutely certain, but the way the ASCOD criteria worked is that we identified a source that was recognized as definitely related to that potential stroke, potentially related to that stroke, and then we removed them because there seemed to be a cause, recognizing that it really is all probabilistic.

DR. YUH: Thank you.

DR. PAGE: Thank you, Dr. Yuh.

Dr. Slotwiner.

DR. SLOTWINER: Thank you.

I'm having trouble reconciling two pieces of information, and maybe you can help. I'm looking at figure C-48, Slide CO-48, the number needed to treat, and looking at the data lock, the early view of the data and then the later data lock with follow-up after in 2015, and the fact that in the extended data follow-up, the proportion of patients who met the primary endpoint in the device arm shrunk. So there were more -- fewer patients in the device arm; the ratio changed. Here, the curves are separating, and it continues to look like the device arm gets better, but that data would suggest that it may come together, and I'm just curious if you can help me try to understand the two.

DR. CARLSON: Let me ask our statistical guru, Barathi, to respond.

DR. SETHURAMAN: This graph is based on the primary assessment, which was the initial data lock, where the separation was very clear. The other data that you're referring is to the extended follow-up.

DR. SLOTWINER: I see. Would it be possible to see what this would look like with the extended follow-up?

DR. SETHURAMAN: Sure, we'll provide that after the break.

DR. SLOTWINER: Thank you.

DR. PAGE: So just to be clear, Dr. Slotwiner, you're asking the Sponsor to put together a presentation for extended follow-up in terms of the number needed to treat?

DR. SLOTWINER: Exactly.

DR. PAGE: Okay. Is that clear, Dr. Carlson --

DR. CARLSON: Will do.

DR. PAGE: -- to you and the crew? Thank you.

DR. CARLSON: We've got it.

DR. PAGE: Dr. Kandzari.

DR. KANDZARI: I'll try to be concise with two issues. Number one is that I want to raise -- and I don't think it will be the first time we discussed this issue of oral anticoagulation in this trial. But I think the Sponsor, you very appropriately showed this numerical excess of venous thromboembolism, deep venous thrombosis events in the device arm versus the medical management arm, and there was quite a disparity between the patients treated with oral anticoagulation after device assignment or randomization.

And I think it's fair to say, at the time of the conduct of this study, that the device might have been perceived as an alternative to oral anticoagulation. Therefore, many of the patients reduce the frequency of a prescription, of provider prescription of anticoagulation. And it turns out perhaps that might not have been the case, right? Venous thromboembolism is perhaps the -- is the presumed etiology of paradoxical -- cryptogenic stroke, and maybe perhaps a greater number of these patients should be treated with oral anticoagulation therapy. So, number one, I'm interested from the Sponsor to hear about what your recommendations might be around oral anticoagulation therapy, or might that mitigate the effectiveness of the device?

The second issue I'd like just to hear more commentary upon, and we'll see in later presentations, is that over longitudinal follow-up, depending on how the analyses and data are cut, that there seems to be a waning of effectiveness of the device. The event rates

seem to converge, depending on the analysis again. And what I'm hearing from the Sponsor is that this is principally driven by the emergence of other etiologies of stroke and as the patients advance in age. And so I'd like to just get greater clarification from the Sponsor, too. Is your explanation for potential waning effectiveness -- and, you know, notwithstanding patients less than 60 years of age in the overall population. Is that because of other etiologies of stroke?

DR. CARLSON: So both good questions. Both questions we've thought about and have discussed and we're prepared to address. I don't know that I could address your first point any better than you did yourself, and we have language in the proposed labeling that addresses the need for anticoagulation in patients who have a history of VTE and patients who otherwise are at high risk for a thromboembolic event. And we'll continue to work with FDA following this meeting to refine that language as necessary to bring down that rate going forward. It's something that we'll be monitoring carefully in the post-approval study as well.

With regards to the convergence, what you mentioned is one reason for it. I think there may be others, and I'd like to ask Dr. Thaler to address that so that we can have a comprehensive explanation of the potential reasons for the convergence.

DR. PAGE: And we have a few questions to go. We're going to be having a full discussion on this convergence over time.

DR. CARLSON: Okay.

DR. PAGE: We haven't heard the FDA presentation as yet. So unless there's a specific question for follow-up, Dr. Kandzari, I might put this discussion on hold until we've

heard both FDA -- heard the FDA presentation as well. Does that work for you?

DR. KANDZARI: That's fine.

DR. CARLSON: Will we have an opportunity to participate in that?

DR. PAGE: You will be called on. Thank you.

DR. CARLSON: Thank you.

DR. PAGE: Dr. Chaturvedi, please.

DR. CHATURVEDI: In the primary paper, you reported 16 stroke events in the medically treated group, and if one scrutinizes those events, 2 were judged by the review committee to be due to A-fib, 1 was thought to be due to small vessel disease, 1 was a primary hemorrhage, and then 1 patient had a history of atrial fibrillation prior to enrollment and appears to be a protocol deviation. So that's at least 30% of the events in the medical group, which were -- appear to be unrelated to paradoxical embolization. So do you have any thoughts on that?

DR. CARLSON: Dr. Saver, could you address that, please?

DR. SAVER: I can, just one of those. I think the patient who had a hemorrhagic event had an ischemic stroke first and then hemorrhage, had both an ischemic stroke and a hemorrhagic stroke. So it was not just a primary hemorrhagic event. But on the other question of the A-fib prior to entry, we'll have to get back to you on that.

DR. CHATURVEDI: And the patient description in the packet, it said the hemorrhage was discovered first and then low-density areas were discovered 5 days later, I believe.

DR. CARLSON: So we'd like to look into that more carefully and get back after the break.

DR. PAGE: Okay. So do you recall which specific question that was? Which specific patient, I mean, that was? Why don't you restate for Dr. Carlson, if they're going to be providing information after the break.

DR. CHATURVEDI: Yeah, sure.

DR. PAGE: Go ahead and restate.

DR. CHATURVEDI: I don't have the specific numbers of the patients right now, but I can provide that later.

DR. CARLSON: There were patients with atrial fibrillation and a patient with a hemorrhagic stroke. Those were the main points.

DR. ZUCKERMAN: Okay, during the break, Dr. Carlson can give you the information.

DR. CARLSON: Thank you.

DR. PAGE: Perfect, thank you.

Dr. Lincoff.

DR. LINCOFF: Well, I was going to ask about the convergence, but I'll defer that. But then briefly, did you collect any data regarding bleeding complications? I recognize the reduction in bleeding was not an intent of an endpoint, but either through adverse events -- I mean, the sparing of anticoagulation, is there any upside there that might add to the stroke reduction?

DR. CARLSON: We have.

And Dr. Sethuraman, do you have anything to add to that?

DR. SETHURAMAN: Actually --

DR. CARLSON: Here we go.

DR. SETHURAMAN: -- you can go ahead. Do you want to put it up?

DR. CARLSON: Go ahead. You're doing great.

DR. SETHURAMAN: We did collect major bleeding events, and the event rates were similar in the two groups.

DR. PAGE: Does that satisfy your question? Thank you very much.

DR. LINCOFF: Thank you.

DR. PAGE: Dr. Laskey.

DR. LASKEY: Hopefully a quick question here related to trial conduct. So you have a discontinuation rate of -- "discontinuation rate of 10% in the device arm and 17.5% in med management." Those are rather high, certainly high on drug trials, and I think they have a lot to do with your analyses. I wonder, lost to follow-up, but you have a footnote in Table 8, patient disposition shown only for patients who did not experience the primary endpoint. So how do you get follow-up on patients who did not experience the primary endpoint and so on? I go down this row because I think these numbers are high, not what we would call good clinical practice, and that there is some informative censoring here, which probably enters in through your K-M. So if you could just comment on this particular aspect of trial conduct.

DR. CARLSON: Well, let me ask Dr. Sethuraman to comment.

DR. SETHURAMAN: Yeah, we showed this table in patients who did not experience a primary endpoint event because the patients who did experience a primary endpoint are already included in the analysis. So we were looking at what is really still missing. But what are we missing in terms of events in patients who might have withdrawn before they might

have experienced a primary endpoint event? With respect to the -- the rates themselves are across all the follow-up that we collected over the course of this trial, which was a very long period of time. I don't know if you want a clinical interpretation of why there were all these withdrawals in that. I can ask someone else to talk about that.

DR. LASKEY: Well, I understand that things happen, but once randomized, you're obligated to find these things out. Certainly lost to follow-up and certainly withdrawal of consent is -- that's a new one. So I would just suggest that that's a major wrinkle.

DR. PAGE: And I think we'll be able to have a valuable discussion of that after lunch. Thank you, Dr. Laskey.

Dr. Dehmer. And then I saw Dr. Noonan.

Dr. Dehmer.

DR. DEHMER: I'm going to ask you about one of the slides that you showed. It's CO-39, if you're able to call that one up. This slide deals with PFO closure at 6 months, and it is up on the screen. So you show complete closure, meaning zero microbubbles in 71%, and if up to nine microbubbles got across in the follow-up, it went up to 94% effective. So does that mean that in 6% or the remainder, the device would be classified as ineffective? That's 20 patients.

DR. CARLSON: That is correct that it's 20 patients. I think the question of effectiveness in those 20 patients is -- I don't think that you can say that it's ineffective.

DR. DEHMER: Well, what happened to those 20 patients in follow-up?

DR. CARLSON: None of those patients had a stroke.

DR. DEHMER: Okay. So you have a device in place that's not working and so none --

but none of them had a stroke.

DR. CARLSON: Well, I don't think you can say that it's not working. You've got a device in place that is letting more than nine bubbles through, but it may be letting far fewer bubble through than if the device hadn't been implanted at all.

DR. PAGE: Dr. Dehmer, you raise a very good question, and I look forward to the full discussion, including our neurologists, about this specific issue, what is happening -- what is the benefit, or lack thereof, if there are still bubbles that are going across? So we'll hold that for discussion, but I really want to hear from you and others during that discussion.

Dr. Noonan, did you have a question?

DR. NOONAN: I think Dr. Chaturvedi's patient was Number 17 --

DR. PAGE: Can you speak up, please? Or can we turn up the mike, please?

DR. NOONAN: Patient Number 17 is the one Dr. Chaturvedi was mentioning, I think, with the craniotomy, who then had strokes.

DR. CHATURVEDI: The one with the primary hemorrhage, yeah.

DR. NOONAN: Yes. And so maybe vasospasm was a cause. I mean, he did have a hemorrhage. I don't know. You didn't tell me if it was subarachnoid hemorrhage. One thing, there was a slide -- I think it's page 11 and it's Slide 22, and it's an interesting case to me. A 54-year-old male for a stroke in 2010. No conventional cause at that time. And then suddenly, in 2016 he has a basilar occlusion. Now, the slide you're showing of the MRI, is that an MRI from 2010?

DR. CARLSON: I believe that's from the second stroke.

Dr. Thaler?

DR. THALER: That's from the recurrent stroke in 2016.

DR. NOONAN: Was the first stroke in the posterior circulation as well?

DR. THALER: I don't recall. I think it might have been anterior circulation, but I don't recall.

DR. NOONAN: Okay. I mean, I've seen a few in the patients, in the patients who had strokes, and they seem to be, you know, recurrent in the same circulation. I'm just curious because one thing, it's very easy to miss and it's very difficult to assess the vertebral artery depending on the standards now, which brings up the question of imaging. Were the imaging of these strokes, the qualifying strokes, done at hospitals other than the one at which the device was implanted? So, for example, if the qualifying stroke was, say, at a community hospital and was performed with standards at a community hospital, which may not include either a good quality CTA or an MRA with gadolinium, and then, you know, the treatment was done elsewhere, was there an over-read of those studies?

DR. THALER: So the inclusion criteria and the consent and admission into the trial was done by the site neurologist at all of the 69 sites. And so that neurologist, me, for example, would have reviewed all of the data that were available to determine whether or not the workup was adequate. So there would have been some circumstances where if the MRA was done without contrast, for example, and we think the contrast proximal MRA would be more revealing for a vertebral origin -- stenosis, for example -- then we would repeat it. So I suppose the short answer to your question is yes, some qualifying strokes would have occurred at non-study hospitals, but all study neurologists would have been responsible for reviewing the inclusion criteria.

DR. NOONAN: And who would the study neurologist have reviewed the studies with?

DR. THALER: I suppose it depends on which studies you're referring to. So the neuroimaging studies would have been reviewed probably by the neurologist, maybe with or without neuroradiological help. The cardiological studies, like the echo, would be reviewed with the cardiologist.

DR. NOONAN: Are neurologists credentialed to read neuroimaging studies in all of the sites?

DR. THALER: That's a complicated question. Neurologists typically in normal clinical practice review imaging themselves. Very few are actually credentialed as radiologists and bill for that service, but I would venture to say that the majority of vascular neurologists are comfortable reviewing their own images.

DR. NOONAN: Okay.

DR. PAGE: Thank you.

We're going to come to a break in just a moment, but before that, Mr. Frankel, did you have a question or a comment?

MR. FRANKEL: Two quick questions. To Dr. Kandzari's question, if I understand correctly, you said that the anticoagulation recommendations are going to be based on the specific criteria for higher-risk patients, for long-term anticoagulants even though they have the device implanted.

DR. CARLSON: One of the things that we learned in this trial is that patients who needed anticoagulation prior to implant still needed anticoagulation thereafter. It seems

intuitively obvious the device is not intended nor does it prevent a thrombus, and if you're at risk for a thrombus because you've had a history of a thrombus or for some other reason, that needs to continue to be treated appropriately.

MR. FRANKEL: How large was the patient population that didn't run into any problems but had those higher risks?

DR. CARLSON: Oh, gosh. I think the question is how many -- what's the denominator of patients in the study, particularly in the device arm, who had higher risks and didn't have a complication?

MR. FRANKEL: Correct.

DR. CARLSON: I don't know that we have that immediately available, so we can get back after the break with that.

MR. FRANKEL: The other quick question is the device patients that had a procedure-related adverse event was 2.4%, and then you have 2% for device-related. Do you have any assessment in terms of long-term risk due to those SAEs?

DR. CARLSON: We've got information on -- I think it was presented during the presentation that those patients, their symptoms, et cetera, resolved.

Dr. Carroll?

DR. CARROLL: That's certainly an important aspect of assessing risk versus balance. Certainly whether an SAE at the time of the procedure had some persistent effect on quality of life, et cetera, it's important, and that's where the vast majority of the SAEs that were device- and procedure-related did not have any long-term sequelae. They were transient intra-procedure and effectively treated, very different from recurrent strokes, which we

know have long-term sequelae.

MR. FRANKEL: Thank you.

DR. PAGE: Thank you very much to the Sponsor for your responses to our questions. We have three questions for work over the break, and I think you're clear on all of those.

DR. CARLSON: I think so.

DR. PAGE: If not, please let us know.

In the meantime, I'd like to now take a 15-minute break. Panel members, I remind you not to discuss the meeting topic during the break among yourselves or with any member of the audience. We will resume promptly at 10:15.

Thank you.

(Off the record at 10:01 a.m.)

(On the record at 10:15 a.m.)

DR. PAGE: Okay, it's now 10:15, and I'd like to call this meeting back to order. The FDA will now give their presentation.

I'd like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA will now have 90 minutes to present. Please begin.

DR. DRUMMOND: Good morning, and welcome to the FDA's presentation on the AMPLATZER Patent Foramen Ovale (PFO) Occluder, PMA Number P120021. My name is Arielle Drummond, a biomedical engineer in the Division of Cardiovascular Devices, and I'm the lead reviewer of this PMA.

For our presentation today, I will first present introductory slides. Dr. Rong Tang will give the statistical presentation. Dr. Andrew Farb will give an overview of the clinical review and will address specific issues the FDA identified during the clinical review. And Dr. Erika Tang will discuss considerations for a post-approval study. I will then conclude with a brief summary of FDA's review.

The FDA has conducted a comprehensive review of this PMA. I would like to thank everyone who has contributed to the review of this device.

The AMPLATZER PFO Occluder system, which I will refer to from here on as the PFO occluder device, includes two components. The PFO occluder implant itself, shown here on the right side of the slide, is available in three sizes. The 510(k)-cleared TorqVue Delivery System is used to deliver the occluder.

Testing of the finished product consisted of bench performance and material characterization studies, biocompatibility testing, MRI compatibility testing, and animal studies. Sterilization, shelf life/packaging, and manufacturing were also evaluated. FDA has found the results from the nonclinical testing acceptable.

The indications for use proposed by the Sponsor is as follows: The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Today we will primarily discuss the results of the Investigational Device Exemption (IDE) study RESPECT. The study was approved by the FDA in September of 2000 and enrolled the first patient into the pivotal study in September of 2003. During the trial, there

were multiple clinical protocol revisions, primarily intended to address slow enrollment and to include the supplementary statistical analyses, which Dr. Rong Tang will discuss in more detail during her statistical presentation.

Enrollment for the study closed in December of 2011. In November of 2012, the Sponsor submitted the PMA, and since that time the FDA and the Sponsor have had multiple interactions. The results presented today will include two data locks, the initial PMA data lock and the extended follow-up data lock.

Now I would like to introduce Dr. Rong Tang, who will provide the statistical presentation.

DR. R. TANG: Thank you, Dr. Drummond.

Good morning, Dr. Page and members of the Panel. My name is Rong Tang. I am a mathematical statistician in the Division of Biostatistics. I will present FDA's statistical review. I will at first briefly describe the design of the RESPECT study, followed by a discussion of various analysis populations, and then I will present the results of the statistical analysis. After that, I will summarize the statistical review.

The RESPECT trial is a prospective, multicenter, randomized, open-label, superiority clinical trial. The enrollment period lasted 8 years. At the time of the initial lock, a total of 25 events and 2,760 patient-years were observed. The extended follow-up analysis was based on the data lock in August 2015. A total of 42 events and 5,154 patient-years were observed.

In the RESPECT trial, the test group was the AMPLATZER PFO Occluder plus medication, and the control was medical management. A total of 980 patients from 69 sites

were randomized, 499 to the test group and 481 to the control group.

The primary endpoint was a composite of recurrence of a nonfatal stroke, fatal ischemic stroke, and post-randomization death.

According to the IDE protocol, the study objective was to show that the device group was superior to the MM group regarding the rate of primary endpoint event at two-sided alpha level of 5%. This analysis is also called the raw count analysis, to contrast with the survival analysis that was added in a later protocol revision. The primary analysis population was the ITT population.

Please note that the raw count analysis was proposed under the assumption that the follow-up time for patients in the two study arms would be approximately equal. During the course of this study, subjects in the two study groups had different length of follow-up. Consequently, the statistical interpretation of this rate comparison is not clear.

A decision rule for a superiority claim was also proposed for the study. In Stage 1 the enrollment would be stopped and the superiority would be declared if within the first 12 events the number of events for the MM group equals or exceeds 10. If the trial did not stop in Stage 1 for success, then in Stage 2 the enrollment would be stopped when 25 events were observed. Device superiority would be declared if within the first 25 events, 19 or more were from the MM group.

However, high and differential dropout rates were observed in the two study arms. The protocol was revised to include survival analysis to supplement the decision rule. The survival analysis was performed in the ITT population as well as the per-protocol, as-treated, and device-in-place populations.

Please note that even though survival analysis can accommodate censored data, it does not necessarily solve the issue of differential discontinuation. This is because differential discontinuation implies potential violation to non-informative censoring, a very important assumption for survival analysis.

To quickly recap, the enrollment was stopped once 25 primary events occurred. A total of 980 patients were enrolled in the study.

The raw count analysis was only performed in the ITT population for the initial data lock. There are four analysis populations and two data locks for the survival analysis.

The ITT population was the pre-specified primary analysis population. In the ITT analysis, all randomized patients are analyzed within the group to which they were randomized. FDA guidance recommends following the ITT principle in superiority trials. This approach avoids biases associated with patients switching treatment, selection bias, and dropout or withdrawal patterns that may confound the observed treatment effect. The ITT population had 980 patients, and all patients were analyzed within the group to which they were randomized.

The per-protocol population included 463 device patients and 474 medical management group patients who met all major protocol requirements, including meeting key eligibility criteria, at least 67% compliant with medication, and the device implantation for the device group.

This figure shows the subject accountability for the per-protocol population. The patients included in the device group are highlighted in green, medical management group patients in yellow. A total of 36 patients and 3 events were excluded from the device arm.

Among these exclusions, 34 did not receive a device. One had inclusion/exclusion violation, and one was noncompliant to medication. For the medical management arm, a total of seven subjects and two events were excluded due to inclusion/exclusion violation or noncompliance to medication.

The third population is the as-treated population. This population was based on the actual treatment received, regardless of the randomization. In addition to the 460 device -- 463 device group subjects and 478 medical management subjects who were compliant with the assigned treatment, 9 device subjects were included into the control arm. These nine patients refused the device, but agreed to the medical management.

This figure shows the patient accountability for the as-treated population. The green highlights the device group, and the yellow highlights the medical management group. A total of 36 subjects and 4 events were removed from the device group; 3 subjects and 1 event were removed from the MM group. The red arrow indicates the nine subjects and the one event moved to the control arm from the device arm.

The post hoc device-in-place population was proposed after enrollment was stopped. This population includes all the 980 subjects enrolled in the study. Patients were analyzed according to whether or not they received the study device. The no device-in-place group had 35 patients moved from the device arm.

In this flow chart, the yellow highlights indicate the no device-in-place arm, which has all the patients from the MM group and the 35 from the device group. The red arrow indicates the 35 patients moved to the no device-in-place arm. Among these 35 patients, one already had a stroke prior to device implant, and 25 of them did not receive device and

also refused to medical -- medication regimen.

The results from the pre-specified primary analysis as well as the supplementary analysis will be presented in the next few slides.

Based on the Fisher's exact test specified in the raw count analysis, the p-value was estimated to be 0.157. Based on this analysis, superiority cannot be claimed. The interpretation of the Fisher's test is not clear due to the violation of equal follow-up.

So the rate per 100 patient-years are also presented to provide a numerical comparison between the two study groups. The rate per 100 patient-years was based on the number of events divided by patient-years. In the ITT initial lock, the rates are 0.61 and 1.2, respectively. In the ITT extended lock, the rates are 0.65 and 1.0, respectively.

And in the RESPECT trial, only 16 out of 25 events were from the control group, which is less than the 19 needed for superiority claim according to the decision rule. Therefore, the RESPECT study did not meet the pre-specified decision rule for superiority.

So the survival analyses were performed to supplement the decision rule. This table has presented a nominal p-value for the ITT cohort, the primary analysis population. Please note that the Type I error will increase when statistical tests are used repeatedly for the same hypothesis. The confidence intervals for the hazard ratios are also presented, but they are not adjusted for multiplicity, just as the p-value.

So the ITT analysis based on the initial lock. The hazard ratio was 0.5 with an upper confidence limit of 1.131. This unadjusted confidence interval is relatively wide, and it covers 1.0.

In the per-protocol population, the hazard ratio is smaller with a point estimate of

0.371 and an upper confidence limit of 0.97, slightly under 1.0.

In the AT population, the result shows even lower hazard ratio and upper confidence limit. Similar results can be found in the DIP population.

The survival analyses were also performed for the extended lock in all analysis populations. Similar to the original lock, only the nominal p-value for the ITT analysis is presented. The extended lock occurred 3 years after the initial lock. It accumulated over 2,000 additional patient-years and 17 additional events. For survival analysis, study power is determined by the number of events. In the presence of a true treatment effect, the result is expected to be more pronounced with more data available.

In the extended ITT population, the hazard ratio increased to 0.65 from 0.5. The upper confidence limit increased to 1.2 from 1.131.

For the per-protocol population, the hazard ratio and upper 95% confidence limit were also increased comparing to the initial lock. The hazard ratio is 0.58 comparing to 0.371 in the initial lock. Upper confidence limit is now 1.12, greater than 1.0. Both the upper confidence limit for the AT and the DIP populations are much closer to 1.0 comparing to the initial lock. It appears that a signal of positive treatment effect in the initial lock has not become stronger with more data available.

These are the Kaplan-Meier curves for the ITT population. The curves are well separated after about 1.5 years in the initial lock. However, the separation becomes less evident, and the curves appear to approach each other after 7 years in the extended follow-up.

Similar trends were observed in the per-protocol, as-treated, and the DIP

populations. Again, the potential positive treatment effect observed in the initial lock appears to be less evident in the longer-term follow-up when more data is available.

In the RESPECT study, there was a higher rate of discontinuation in the MM group versus the device group for both data locks. The presence of differential discontinuation rates makes it difficult to determine whether the censoring is truly non-informative.

I will make some brief comments about the sensitivity analysis. Please note that primary analysis in the ITT population is not statistically significant. The Sponsor performed a tipping point analysis for the per-protocol population using log-rank test. That analysis shows device success in over 75% of the situations studied in the tipping point analysis. However, please note that per-protocol population is a post-randomization subgroup, and there is a large number of missing values comparing to a smaller number of events. Therefore, the outcome of sensitivity analysis would be largely dependent upon the assumption made on the missing data.

This table contains some boundary point information from the tipping point analysis. The Sponsor performed a tipping point analysis under two different scenarios. The first scenario is more favorable to the medical management group, and the second is more favorable to the device group. As has been noted earlier, the tipping point analysis shows device success in over 75% of the situations, but there are a variety of situations under which the p-value is no longer considered significant.

As you can see in the table, by applying different assumptions the p-value becomes greater than 0.05 by adding just one additional event in the device group. So the results of a tipping point analysis can be greatly impacted by different assumptions.

I will end my presentation with a statistical summary. The superiority objective of the primary endpoint was not met.

The extended follow-up analysis did not strengthen the treatment effect observed in the initial data lock.

The per-protocol, AT, and the DIP populations are post-randomization subgroups, and these supplementary analyses results should be interpreted with caution.

Differential discontinuation rates across study arms challenge the non-informative censoring assumption required for survival analysis.

This concludes the FDA's statistical review, and I would like to turn the presentation over to Dr. Farb.

DR. FARB: Good morning, Dr. Page and members of the Advisory Panel. My name is Andrew Farb. I am a cardiologist and medical officer in the Division of Cardiovascular Devices. I'll be providing FDA's review of the AMPLATZER PFO clinical results. Here is an outline of my remarks. I'll start by providing background information on stroke and PFO; then discuss the RESPECT trial in depth, going through the trial design and focused on enrollment criteria, cryptogenic stroke determination, and concomitant medical therapy; then trial results for the effectiveness endpoints and safety assessments; followed by comments on the RESPECT and PC trial meta-analysis. I'll close with a summary of clinical observations.

Stroke is the fourth leading cause of mortality and a leading cause of serious, long-term disability in the United States. It's categorized as ischemic, accounting for greater than 80% of all strokes, hemorrhagic, or undetermined. In patients under 55 years of age,

up to 30% of ischemic strokes are reported to be cryptogenic, that is, there is no identified cause.

The mechanisms for non-ischemic stroke can be broadly separated into diseases that increase the risk of thrombo- or atheroembolism and those associated with intracranial arterial disease. The conditions associated with thrombo- or atheroembolism include:

- Atrial fibrillation/atrial flutter;
- LV mural thrombus;
- Valvular endocarditis;
- Prosthetic heart valves;
- Thoracic aortic or carotid atherosclerosis; and
- Venous thrombus in the setting of a right-to-left shunt.

The intracranial arterial conditions that are associated with non-cryptogenic stroke include:

- Intracranial atherosclerosis;
- Arterial dissection;
- Vasculitis; and
- In situ thrombosis associated with an underlying hypercoagulable state.

In contrast, cryptogenic stroke is a diagnosis of exclusion, and the determination that a stroke is cryptogenic is highly dependent on the comprehensiveness of the evaluation to exclude alternative known stroke etiologies. Advances in diagnostic testing and monitoring, for example, cardiac monitoring to detect subclinical atrial fibrillation, have been able to identify underlying etiologies for more strokes that were previously classified

as cryptogenic.

Next, PFO, a common incidental anatomic finding in 25% to 30% of the general population. And its presence does not confirm risk of stroke among asymptomatic individuals, as reported in the NOMAS study, which showed that a PFO is not associated with an increased stroke risk in men and women or in those younger or older than 60 years of age. Similarly in the SPARC study, PFO was not an independent predictor of stroke among normal individuals greater than 45 years of age.

What about PFO and cryptogenic stroke? Several observational studies have reported a higher prevalence of PFO in cryptogenic stroke versus normal individuals or individuals with an identified etiology for stroke, suggesting paradoxical embolism as a potential underlying mechanism. Among subjects aged 30 to 85 years enrolled in PICSS, a PFO was detected in 33.8% of subjects and was present in 39.2% with a cryptogenic stroke versus 29.9% with a stroke in which the etiology was known. It's been suggested that the presence of PFO may play a more important role as a cause of stroke in younger compared to older patients. In the PFO-ASA study, a PFO was identified in 45.9% of young patients with cryptogenic stroke, a higher rate of PFO than in the general population. Another study reported a PFO prevalence of 43.9% in patients less than or equal to 55 years with cryptogenic stroke compared to 14.3% incidence in younger patients with a stroke due to a known cause.

What about a second stroke in individuals with a first cryptogenic stroke? Here, PICSS showed that stroke patients with PFO did not have a significantly increased risk of recurrent stroke or death at 2 years compared to stroke subjects without a PFO.

Further, no consistent association has been established between the risk of stroke or a PFO size, severity of right-to-left shunting, or the presence of an atrial septal aneurysm. Although there have been case reports from time to time of thrombi originating in the venous circulation traversing a PFO in stroke patients, venous thrombosis has only been rarely identified in patients with PFO and stroke.

Regarding treatment options for patients with ischemic stroke or TIA and PFO, the 2014 AHA/ASA and American Academy of Neurology guidelines recommend antiplatelet agents for patients who have not -- who are not otherwise being treated with anticoagulants. They give this a Class I level of evidence B recommendation. These guidelines note that there are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary prevention in patients with a PFO and cryptogenic stroke. Regarding transcatheter device closure of PFO in patients with cryptogenic stroke or at a PFO -- cryptogenic stroke or TIA, these guidelines state that available data did not support a benefit of PFO closure.

For clinical trials to evaluate the safety and effectiveness of PFO closure to prevent recurrent stroke in patients with a PFO and cryptogenic stroke, FDA has required randomized controlled trials to conclusively demonstrate the safety and effectiveness of PFO occlusion devices. FDA's requirement for randomized trials has been supported by the Circulatory System Advisory Panel on three occasions, and medical professional societies, including the AHA, ASA, the ACC, and the American Academy of Neurology, have also endorsed the need for randomized trials of PFO closure in this patient population.

We do have some randomized data for PFO closure versus medical therapy in

patients with cryptogenic stroke and PFO. CLOSURE I failed to show the superiority of the STARFlex PFO Occluder versus medical therapy for the primary endpoint of the composite of recurrent stroke or TIA at 24 months, all-cause mortality at 30 days, or death from neurologic causes between 31 days and 24 months.

In the PC trial, PFO closure with the AMPLATZER PFO Occluder, the same device used in the RESPECT trial, was not superior to medical therapy for the primary endpoint of the composite of death, nonfatal stroke, TIA, or peripheral embolism.

Which brings us to the pivotal RESPECT trial. The objective of RESPECT was to investigate whether percutaneous PFO closure is superior to current standard of care medical treatment for the prevention of recurrent embolic stroke in subjects who have had a cryptogenic stroke. RESPECT was designed as a prospective, multicenter, randomized, unblinded study in which neither subjects nor healthcare providers were blinded to the randomization assignment. Subjects were randomized 1:1 to either the AMPLATZER PFO Occluder, herein referred to as the device, or medical management, referred to as MM. Randomization was stratified by investigational site, presence of an atrial septal aneurysm, and recommended medical therapy.

The key inclusion criterion was PFO and cryptogenic stroke within 270 days of enrollment. Importantly, these were stroke patients, not those with solely TIAs. Stroke was defined as an acute focal neurologic event presumed to be due to focal ischemia, and either symptoms persisting for at least 24 hours or symptoms persisting less than or equal to 24 hours with neuroimaging findings of a new cerebral infarct. A cryptogenic stroke was defined as a stroke from an unknown cause. And a PFO required performance of a TEE

showing microbubbles in the left atrium within three cardiac cycles of right atrial opacification at rest and/or with Valsalva.

RESPECT had many exclusion criteria which are important to consider when thinking about potential candidates for PFO closure. Here are some general exclusion criteria which exclude those under 18 or older than 60, as well as patients with significant cardiac abnormalities, serious medical comorbidities, subjects who cannot take antithrombotic medications, and those with anatomic features that could preclude device implantation.

Here are the criteria intended to exclude subjects with other potential embolic cardiac or non-cardiac etiologies such as atrial fibrillation/atrial flutter, LV aneurysm, intracardiac thrombus or tumor, mitral/aortic valve vegetation or prosthesis, aortic arch plaques, atherosclerosis or arteriopathy of intra- or extracranial vessels with greater than 50% diameter stenosis, or another cause of right-to-left shunting.

There were other criteria to exclude patients with non-embolic stroke, such as lacunar infarcts probably due to small vessel disease, or evidence of arterial dissection as a qualifying event, or evidence of an underlying hypercoagulable state, defined by a battery of tests.

The baseline screening test for cryptogenic stroke determination started with a neurologist-investigator evaluating the qualifying stroke associated with testing, including a TEE, ECG, or Holter monitoring, comprehensive imaging of intra- and extracranial arterial circulation with brain MRI, CT, MR angiogram or CT angiogram or contrast angiography, transcranial Doppler, and/or carotid duplex and then screening for an underlying hypercoagulable state.

So in thinking about the utility of PFO closure to prevent recurrent stroke, one should appreciate that RESPECT subjects were evaluated by a neurologist and were highly selected to exclude patients who had a potential underlying cause of stroke based on a planned comprehensive neurologic and cardiovascular evaluation.

Now let's turn to the adjunctive antithrombotic medical therapy administered to randomized patients. Per the protocol, device subjects were to receive aspirin for at least 24 hours prior to the procedure. Following the implant, the antiplatelet regimen was clopidogrel plus aspirin for 1 month, then aspirin alone through 6 months. Beyond 6 months, medical therapy was at the discretion of the treating physician.

In the medical management group, subjects could be treated with any of the following regimens:

- Aspirin alone;
- Warfarin alone;
- Clopidogrel alone;
- Aspirin plus dipyridamole; or
- Aspirin plus clopidogrel.

Under a study protocol revision, aspirin plus clopidogrel was eliminated as an acceptable regimen to reflect the recommendations in the 2006 update to the AHA/ASA guidelines.

As you saw in the previous slide, heterogeneous antithrombotic regimens were built into the RESPECT trial. There is no evidence-based standard of care medical regimen to reduce the risk of recurrent stroke in patients with cryptogenic stroke. The use of multiple

acceptable combinations of antithrombotic agents in the medical management group present some challenges, including defining the probable benefits of the device versus medical therapy.

For the medical management subjects, investigators determined the recommended medication regimen for each patient. Subjects were allowed to change the antiplatelet or anticoagulation treatment as long as a new regimen was included amongst the protocol-defined options.

With regard to the actual antithrombotic therapy usage in device subjects, approximately 90% of subjects were taking antithrombotic medications throughout the study, and the vast majority of device subjects used antiplatelet agents. Therefore, the RESPECT trial is essentially a study of the device plus medical management versus medical management alone. In the medical management group, overall use of protocol-directed antithrombotic medical therapy was high throughout the trial. Except for very late follow-up time points in which data are limited, use of antithrombotic medication was greater than 95% at all follow-up assessments. Antithrombotic medication use or non-use at follow-up visits is not the same as medication compliance or noncompliance as defined in the trial. Medication noncompliance was defined as less than 67% cumulative compliance over the course of the trial.

However, it should be noted that there is no evidence-based standard definition for noncompliance with antithrombotic therapy in patients with cryptogenic stroke that establishes a threshold associated with an increased rate of recurrent events or with risk reduction. This issue will be revisited in the analysis of recurrent strokes in the

supplementary analysis populations.

Next are the RESPECT trial endpoints. You've heard that the primary effectiveness endpoint was a composite of recurrent nonfatal stroke, fatal ischemic stroke, or post-randomization mortality within 30 days post-implant or 45 days post-randomization in the device group and within 45 days after randomization in the medical management group. And as you have also heard, in RESPECT, all primary endpoint events were recurrent nonfatal strokes.

Two major secondary effectiveness endpoints are worth noting and will be addressed later in the presentation. The first is the occurrence of TIA. The second is complete PFO closure assessed by TEE bubble study at 6 months follow-up; this was applied to the device group only. PFO closure was adjudicated by the echo core lab. There were no pre-specified hypotheses for the secondary effectiveness endpoints, and secondary effectiveness endpoint rates were presented descriptively.

The safety endpoint consisted of serious adverse events as adjudicated by the DSMB, which included:

- Death;
- Life-threatening adverse events;
- Inpatient hospitalization or prolongation of an ongoing hospital stay;
- Persistent or significant disability or incapacity; and
- Medically significant events, including laboratory abnormalities.

There were no pre-specified hypotheses for safety, and safety events were also presented descriptively.

Which brings us to the results of RESPECT. There were 980 enrolled subjects in the ITT population, 499 randomized to the device, 481 randomized to medical management.

Looking at baseline demographics, RESPECT enrolled young to middle-age adults, with just over a majority being male and most with non-disabling strokes as their qualifying event.

With regard to baseline medical history, about 11% of subjects had a prior stroke -- had a stroke prior to enrollment of their qualifying event, with approximately 12% having a history of TIA. About 3% to 4% had had a history of DVT.

For stroke risk factors at baseline, just over 40% were current or former smokers, just over 40% had lipid abnormalities, and data were not collected on the use of lipid-lowering medications during follow-up. Just over 30% had hypertension. And here, too, data on antihypertensive medication use were not collected during follow-up. And just under 40% had a history of migraines, a more recently recognized risk factor for ischemic stroke.

To summarize some key baseline clinical features, atherosclerotic and non-atherosclerotic risk factors for stroke were common among enrolled subjects and were balanced between treatment groups, with hypertension present in approximately 30%, hyperlipidemia in 40%, current or former smoking in 40%, and migraine in 40%. These clinical features should be considered in categories in the qualifying recurrent strokes as cryptogenic and likely to be related to the presence of a PFO.

To exclude atrial fibrillation or atrial flutter, nearly all subjects had a screening ECG, with far fewer (13% to 16%) undergoing a Holter monitor. Both tests were performed in

only 11% of device subjects and 12.7% of medical management subjects.

Currently, there is greater appreciation of subclinical atrial fibrillation and extended cardiac rhythm evaluations with event monitors or implantable loop recorders, which are available as more sensitive A-fib screening tools. By today's standards, the investigations in RESPECT tended to exclude subjects with atrial fibrillation or atrial flutter and were quite limited in scope.

A confirmed ischemic stroke was a crucial inclusion criterion, and neurologists-investigators at the study sites assessed the clinical information regarding the qualifying stroke to support enrollment in the trial. However, the protocol definition of stroke did not require neuroimaging studies at baseline if the stroke symptoms lasted greater than 24 hours and were required if symptoms were less than 24 hours in duration.

Overall, 82% of subjects -- 82 subjects or 8.4% of enrolled subjects lack neuroimaging confirmation of the qualifying stroke. The rate of neuroimaging confirmation of the qualifying stroke versus confirmation based on symptoms alone was significantly lower in the device group versus the medical management group for the ITT population (10.4% of device subjects versus 6.2% of medical management subjects), raising the possibility that these image-negative device subjects may have been at a lower risk for recurrent events. Further, there were 968 subjects in whom an MRI was performed in the evaluation of their qualifying stroke. Of these, 67 or 6.9% of subjects had a negative MRI for an acute infarct.

There was an imbalance in MRI negative scans between treatment groups. MRIs were negative for acute infarct at 8.3% of the device group versus 5.4% in medical management subjects. As you can see in the table, there were few MRIs in each group

performed within 3 hours or at least 10 days after the qualifying stroke, which potentially could have represented false negative scans.

And among subjects with no MRI performed at the time of the qualifying stroke, a CT scan performed at least 2 days after the event did not show an infarct in five device subjects and two medical management subjects.

The following summarizes our concerns regarding cryptogenic stroke determination in the RESPECT trial. Investigations to exclude subjects with atrial fibrillation were limited in scope and could have under-represented the true frequency of atrial fibrillation in this population; 8.1% of RESPECT subjects did not have MRI or CT confirmation of their qualifying stroke, with an observed numerically higher rate in the device group versus the medical management group. Brain MRI, a highly sensitive method to detect ischemic stroke, did not show an acute infarct in 6.9% of subjects in which an MRI was performed, and the observed rate of negative MRIs was higher in the device group compared with the medical management group.

While the neuroimaging concerns involved less than or equal to about 10% of subjects, one should keep this potential imbalance of confirmed strokes in mind in the context of the very small number of recurrent events in the trial.

As you've heard, the RESPECT trial data were analyzed at two time points, an initial data lock in May 2002 and an extended follow-up data lock 3¼ years later in August 2005. In interpreting the statistical analysis of RESPECT, one needs to start with recognizing the differences in the cumulative follow-up between the two treatment groups due to differential subject dropout, which I'll address later.

For the additional data lock shown on the left, the mean follow-up was longer in the device group by 0.3 years, and there were 192 more patient-years in the device group. In the extended follow-up data lock shown on the right, the mean follow-up was 0.6 years longer in the device group, and there were 393 more patient-years in the device group versus medical management.

The difference in follow-up between treatment groups is explained by subject discontinuation rates between treatment groups. There was a higher rate of subject discontinuation in the medical management versus the device group for both the initial data lock (19.1% in the medical management group versus 10.4% in the device group) and for the extended follow-up data lock (30.1% in medical management versus 18.2% in device).

The difference in the overall subject discontinuation rate between treatment groups was driven by subjects deciding to withdraw from study participation (11.4% in medical management versus 4.8% in device in the initial data lock, and 14.8% in the medical management group versus 6.2% in the device group in the extended follow-up data lock). We'll return to the issue of subject discontinuation in the discussion about the interpretation of a possible superiority signal of the device versus medical management.

Now, let's examine the primary effectiveness endpoint results. You've seen the primary endpoint analysis presented by the Sponsor and reviewed by my colleague Dr. Tang. In accordance with the Sponsor's pre-specified decision rules, trial enrollment was stopped once 25 primary endpoint events had occurred. All events were nonfatal ischemic strokes.

In the ITT population, there were 9 primary endpoint events in the device group and 16 in the medical management group. This raw count analysis in the ITT population was the pre-specified primary analysis for RESPECT. The null hypothesis was not rejected and device superiority versus medical management was not demonstrated with a p-value of 0.157. Therefore, the primary endpoint of a stroke rate reduction based on the pre-specified ITT analysis was not met.

In the extended follow-up of the ITT population, there were 9 additional events in the device group and 8 additional events in the medical management group, resulting in 42 total events, 18 in the device group and 24 with medical management. Even with the extended follow-up, we are still dealing with a relatively small number of events.

Although the raw count analysis in the ITT population was the pre-specified primary analysis in RESPECT, recall that there was differential follow-up between treatment groups, driven by a substantially larger number of medical management subjects withdrawing from the trial. Therefore, event rates per patient-year of follow-up and Kaplan-Meier estimates provide additional insights into the strength of the evidence supporting or not supporting a benefit of PFO closure with the device and the magnitude of any potential benefit.

In the initial data lock, the observed event rates per 100 patient-years in both treatment groups, shown on the table on the left, was small but numerically favored the device group (0.61 versus 1.25). In the Kaplan-Meier plot on the left, one can appreciate curve separation starting at around 1½ years of follow-up with overlap of the 95% confidence intervals. The hazard rate is 0.50 with a wide confidence interval (0.22 to 1.13), and the p-value is not significant at 0.089.

With extended follow-up, on the right, it's important to note that the event rate has dropped in the medical management group to 1.01, and the difference between treatment groups has narrowed. In the Kaplan-Meier plot to the right, the event curves approach each other, raising the question about the durability of any potential device benefit.

What about antithrombotic medication use among the 42 subjects with primary endpoint events? Thirty-nine subjects had medication usage information at the time of the first recurrent stroke. Of these, 30 subjects were taking protocol-required medical therapy at the time of the event (16 device subjects and 14 medical management subjects). There were nine subjects who were not using protocol-required medications in the week prior to their recurrent event (two device subjects versus seven medical management subjects). These data might suggest that medication noncompliance in medical management subjects is a risk for recurrent stroke, but the numbers are far too small to draw any conclusions.

In considering the evidence supporting a possible benefit of device closure to reduce the risk of recurrent ischemic stroke, one should be mindful of the relatively small number of events compared to the number of subject withdrawals and the differential dropout of subjects between treatment groups.

In the ITT analysis, there were 9 events in the device group and 16 in medical management for the initial data lock. The number of events were notably lower than the number of subject withdrawals, excluding those who died or experienced a primary endpoint event (49 in the device group and 86 in the medical management group).

Similarly, in the extended follow-up data lock, compare 18 events in the device group and 24 in the medical management group being much smaller than the number of

subject withdrawals (84 in the device group and 134 in the medical management group).

To summarize the pre-specified primary analyses for the ITT population, there were a small number of events in the initial data lock. The primary endpoint of a significantly lower stroke rate in the device versus medical management group based on the pre-specified ITT population raw count was not met.

To address differential follow-up between treatment groups, event rates per patient-year of follow-up and Kaplan-Meier estimates may be considered more informative than raw counts. The observed event rates per 100 patient-years in both treatment groups were small and numerically favored the device. The Kaplan-Meier curves separated at about one and a half years, but with overlapping confidence intervals that are relatively wide confidence intervals around the hazard ratio with a non-significant p-value.

In the extended follow-up data lock, the event rate difference between treatment groups has narrowed, and the red rate curves for the two treatment groups approach each other.

Finally, the issue of missing data due to subject withdrawals, which were greater than fivefold higher than the number of events in both data locks and was disproportionally higher in the medical management group. Substantial missing data can lead to challenges in the interpretation of study results. Imputation methods can help but cannot fully address uncertainty regarding the strength of the evidence.

Next are the supplementary analysis populations: per protocol, as treated, and device in place. You've seen this diagram before for the per-protocol population as of the initial data lock in May 2012. A total of 43 subjects were excluded in the per-protocol

population. Among these 43, 36 subjects with three events were excluded from the device arm, and 7 subjects with two events were excluded in the medical management arm.

Although the exclusion of some subjects followed the protocol definition, an examination of some of the individual cases raises questions about whether the supplementary analysis populations expand our understanding of device effectiveness. For example, one subject was found to have significant CAD and underwent coronary bypass surgery with a PFO closed surgically. The stroke occurred 1 month later, and a definitive cause of the stroke was not found. Yes, the patient was not treated with the device, but in principle, the PFO was closed.

The other subject, age 53, decided not to undergo device implantation and agreed to follow the medical management protocol with aspirin. A stroke occurred almost 4 years later, but in the narrative summary it was noted that he had stopped his ACE inhibitor and statin therapy at the time before his event. This device patient was noncompliant with medical therapy over the course of the treatment but was on clopidogrel at the time of the stroke. And recall that the definition of medication noncompliance was not evidence based.

Two medical management subjects had their patient-years excluded from the per-protocol analysis only because their medication noncompliance fell just under the 67% threshold.

Here's another challenge to data interpretations as patients are excluded or reassigned in the supplementary analysis. Among the total of 34 device subjects who did not have the device implanted and were excluded from the per-protocol cohort, the following 17 patients were excluded based on evaluations or treatments performed at the

time of the implant procedure.

Eight device subjects were excluded because a PFO was not confirmed or crossed or the implant attempt was unsuccessful. One device subject was excluded because atrial fibrillation was observed at the time of the implant. Three device subjects were excluded because another source of right-to-left shunting was identified. Four device subjects were excluded because a PFO device was not placed or an ASD was found. And one device subject was excluded because of significant coronary artery disease, as presented previously, and this was identified at the time of the implant procedure.

The exclusion of some device subjects from the per-protocol analysis because of findings or treatments at the time of the implant procedure was consistent with the approved per-protocol definition. However, medical management subjects do not undergo an implant procedure, during which similar types of reasons for exclusion from the per-protocol analysis may have been found and which could lead to imbalances between treatment groups.

With these issues regarding subject exclusions in mind, in the per-protocol population we've gone from 25 total ITT events to an even smaller number of 20 events in the initial data lock (6 in the device arm and 14 in the medical management group). The observed event rates per patient-year, the table on the left, numerically favor the device, being 0.42 versus 1.19. In the Kaplan-Meier plot on the left, one can appreciate again curve separation but with overlap of the 95% confidence intervals at most time points and a hazard ratio of 0.37. With extended follow-up, on the right, the event rate difference between treatment groups has narrowed, and the event rate curves approach each other,

as was seen in the ITT population.

This figure shows subject accountability for the as-treated population as of the initial data lock. A total of 36 subjects were removed from the device group, of which 9 subjects were added to the medical management group as crossovers from the device group.

The variables of motivation that might be important to individual subjects to remain in the study and take protocol-directed medical management or refuse to follow protocol management medical therapy and how they may differ from those in the other group are unknown.

Once again, keep in mind that we are dealing with a small number of total events. And, for example, as noted previously, the medication noncompliance subject in the device group was on clopidogrel. The subject with a pre-device implantation event, in the lower left, was reported to have had a post-stroke transcranial Doppler study that was negative for microemboli. This event was excluded, but few patient-years were excluded from the device arm, lowering the event rate in the device group. And the subject that did not agree to medical management --

DR. PAGE: I'm sorry, I have to interrupt for a second. The numbers are off from your presentation in the booklets that the Panel has, and I think the Panel may be having some difficulty keeping up. I see people looking at their paperwork. Ideally, we would have the same numbers on the slides as in our books, but is the Panel all following where we are right now? Ms. Washington is working with me. What we see is 115 here is actually numbered what in our book?

DR. FARB: I think some information, Dr. Page, was added to the slide, but it should

still be 115.

DR. PAGE: I have a different set of slides that I was provided. So my 115 doesn't look like this. So does FDA have --

DR. SLOTWINER: I think ours do.

DR. PAGE: Does everybody else have their own?

DR. SLOTWINER: Ours match.

DR. PAGE: Yours are matching. Great. Keeping going then.

DR. FARB: I'm sorry, are we okay or not? Because there's --

DR. PAGE: Ideally, I would get a packet that matches what others are seeing and what you're showing, but unfortunately right now I don't have one. Go ahead, keep going.

DR. FARB: Oh, okay. So where we left off was the subject who did not agree to medical -- there was a subject who agreed to medical management and crossed over to the medical management group for the as-treated -- was the one who stopped his ACE inhibitor and statin.

Here's a listing of excluded as-treated patients who did not have a device implanted. Eleven subjects were excluded based on evaluations or treatments performed at the time of the implant procedure. Three device subjects were excluded because a PFO was not confirmed or crossed at the implant procedure or the implant was unsuccessful. One device subject was excluded because atrial fibrillation was observed at the time of the implant. Two device subjects were excluded because another source of right-to-left shunting was identified. Four device subjects were excluded because the PFO device was not placed when ASD was found and treated. And one device subject was excluded because of the

coronary artery disease in the per-protocol population.

Once again, recall that medical management patients do not undergo an implant procedure, during which other reasons for exclusion may have been found.

Notwithstanding the concerns noted, in the ITT population we've gone from 25 events to 21 (5 in the device arm, 6 in the medical management arm) with the observed event rates per patient-years favoring the device group, as shown in the left table (0.36 versus 1.33). In the Kaplan-Meier plot, there is curve separation with overlap at most time points of the confidence intervals. But with extended follow-up, once again we see that the event rate differences between treatment groups have narrowed considerably and the event curves approach each other.

The device-in-place population divided the ITT population into two groups to compare subjects with or without the device. The no device-in-place arm consists of all subjects from the medical management group, and 35 subjects crossed over from the device group that did not have device in situ. Here we see a good deal of subject crossover from the device group to the medical management or no device-in-place group.

In the device-in-place population, similar to the other supplementary analysis populations, the observed rates per 100 patient-years numerically favor the device group (0.42 versus 1.14 in the initial data lock). In the Kaplan-Meier plot on the left, curve separation is similar to the other supplementary populations. With extended follow-up, the event rate difference between treatment groups once again narrows and the event curves approach each other, as was seen in the other analysis populations.

This summary sheet is at the back of your Panel pack for today and provided as a

handout. And, in fact, we're not going to go through it. The point here is to appreciate the complexity of excluding and moving patients around among the different populations, with potential biases introduced and offering challenges to reaching conclusions about the overall effectiveness of the device.

So, regarding the supplementary analysis populations, hazard ratios and p-values suggest a benefit of the device versus medical management. However, one should be mindful of the small number of events, that excluding and reassigning subjects can compromise the balance among measured and unmeasured baseline covariates that is afforded by randomization.

The p-values get more impressive as events with limited patient-year follow-up are reassigned to the medical management group. None of the p-values were adjusted for multiplicity, raising the possibility of false negative results.

And concern regarding a high and disproportionate number of subject withdrawals also apply to the interpretation of supplementary analysis populations.

Next I'll turn to the extended follow-up analysis. With longer-term follow-up, as more patient-years and events accumulate, it would be expected that the effect size of a durable beneficial treatment would be maintained and be associated with a reduction in the upper bound of the 95% confidence interval. However, compared to the initial data lock, the extended follow-up analysis showed an increased hazard ratio and the upper bound of the confidence interval for all analysis populations.

In the ITT population, the hazard ratio increased from 0.50 in the initial data lock to 0.64 in the extended follow-up, and the upper bound of the confidence interval increased

from 1.13 to 1.20.

In the per-protocol population, the hazard ratio increased from 0.37 to 0.58, and the upper bound of the 95% confidence interval increased from 0.97 to 1.12.

In the as-treated population, the hazard ratio increased from 0.28 to 0.51, and the upper bound of the confidence interval increased from 0.77 to 0.99.

And in the device-in-place population, the hazard ratio increased from 0.30 to 0.52, and the upper bound of the confidence interval from 0.79 to 0.98.

These data suggest that any signal of a positive treatment effect becomes less pronounced over time as more data accumulate.

You have seen the Sponsor's data on the number needed to treat to prevent one ischemic stroke, which was based on the initial data lock and was presented as 27. With more data available in the extended follow-up data lock, the number needed to treat increases to 43 at 5 years.

The Sponsor performed a post hoc ASCOD analysis to try to gain insight into stroke mechanisms. And as you have seen in the Sponsor's presentation, this analysis suggested that PFO closure was associated with a reduction in the rate of recurrent strokes of undetermined mechanisms, that is, fewer ASCOD Grade 1 strokes.

Recall that ASCOD phenotyping assigns a degree of likelihood on causality for underlying diseases known to cause ischemic stroke. The five phenotypes are atherosclerosis, small vessel disease, cardiac pathology, other cause, and dissection. Each phenotype is assigned a grade, Grade 1 being disease is present and potentially causal; 2, disease is present and a causal link is uncertain; 3, disease is present and a causal link is

unlikely; and 0, disease is absent; and finally Grade 9, the workup is insufficient for grading.

The objective of the ASCOD analysis was that in identified Grade 1 strokes, those in which an underlying disease condition was present and likely causal, one might infer that the remaining events, those lacking a known cause or having a disease with an uncertain causal link to the stroke, are more likely to be cryptogenic, with a further inference that the untreated patent foramen ovale, present in the medical management group, plays a role in the pathophysiology of these recurrent stroke events.

The problem with this reasoning is that the ASCOD scale is a scale of likeliness, and the absence of evidence, or in this case uncertainty of causality, is not the same as the evidence of absence, that is, that these events are therefore cryptogenic and related to the PFO. The absence of a Grade 1 designation does not mean that the stroke is cryptogenic. In a patient with a Grade 2 or Grade 3 designation, one can say that stroke-associated diseases are present but that there is uncertainty about a direct causal link to the stroke. And remember that in RESPECT, many of these patients had conditions associated with stroke at baseline, particularly atherosclerotic risk factors, that should be treated to lower the risk of stroke.

Further, ASCOD phenotyping was developed to describe the degree of overlap among diseases known to cause ischemic stroke. It was not designed to characterize stroke etiologies as cryptogenic. Notably, there is no cryptogenic ASCOD phenotype. Also, the ASCOD algorithm was not designed to evaluate recurrent strokes.

Insights based on ASCOD analysis in RESPECT are of limited value. There was no standardized comprehensive evaluation of subjects to determine the etiology of the

recurrent stroke, and the ASCOD evaluation was reported as incomplete for 11 events. And in six additional events, it was noted that disease was present, but the link to the stroke was uncertain.

You've seen presentation by the Sponsor dichotomizing strokes in subjects less than or equal to 60 years of age or greater than 60 years of age, with 34 strokes or 82% being undetermined for ASCOD in the younger group, and 13% or 1 in 8 strokes being greater than 60 years of age being undetermined per ASCOD. Please note that this is a new analysis and not previously reviewed by the FDA, and the same limitations of the use of the ASCOD grading scheme apply to the 60 years of age cutoff analysis, which does not identify -- was not designed to identify cryptogenic strokes.

With regard to the totality of the evidence, effectiveness data in RESPECT, high levels of subject discontinuation, particularly in the medical management group, presents challenges to the interpretation of the effectiveness endpoint results. Although there were numerical trends for a reduced rate of recurrent stroke in favor of the device, statistical significance for the primary endpoint in the ITT population, the primary analysis cohort, was not met. Observed event rates were more favorable to the device group in the three supplementary analysis populations. However, the robustness of these analyses are limited by potential bias associated with imbalances in baseline evaluations and switching treatment groups.

Although the post hoc ASCOD analysis suggests that PFO closure was associated with a reduction in the rate of recurrent strokes of undetermined mechanisms, the scientific robustness of the ASCOD analysis is limited by the frequency of incomplete clinical

assessments and the absence of a uniform evaluation process to determine the etiology of the recurrent event.

Next, the secondary endpoints. TIA may be seen as part of the continuum to cerebral infarcts as related to cerebrovascular disease that may be due to thromboembolism. Although the diagnosis of TIA is less rigorous in stroke, since neuroimaging confirmation is absent, it would be expected that an intervention that reduced the rate of embolic stroke would also reduce the TIA rate. However, in RESPECT there was no signal that the TIA rate was lower in the device versus the medical management group.

Next, the actual PFO closure rate by the device. There were 465 device subjects who were eligible for complete PFO closure analysis by 6-month TEE. Of these, 338 had a shunt grade assessment both at rest and with Valsalva, with 11 subjects having a shunt grade assessed as Grade 1 or higher at rest or Valsalva, these subjects being included in the closure analysis as closure -- as PFO closure failures.

There were 116 subjects omitted for the PFO closure analysis, subjects who had either missing or incomplete shunt grade assessments or did not undergo a TEE as directed per protocol. Overall, the PFO closure data were incomplete or missing in 116 or 33.2% of subjects.

There were 249 of 349 subjects with a Grade 0 shunt at both rest and Valsalva at 6 months, corresponding to a complete PFO closure rate of 71.3%. Therefore, incomplete PFO closure was common, occurring in 28.7% of assessed subjects. And additional analysis performed by the Sponsor of the proportion of subjects with effective closure, defined as

either a Grade 0 or a Grade 1 shunt at rest and Valsalva, showed a 94.2% effective closure rate at 6 months.

Here is the PFO shunt status in the 18 device subjects who had a recurrent stroke. There were eight subjects who had no shunt at rest and with Valsalva, two with a shunt grade -- two with a Grade 1 shunt at rest or with Valsalva, three with a Grade 2 shunt at rest or with Valsalva, one with shunting across a previously unrecognized ASD, and one in which the shunt could not be classified.

There were three subjects with no device implanted at the time of the stroke. One had the stroke post-randomization but prior to device implant, and one decided -- opted out of undergoing device implantation but remained in the study, and then the subject with coronary disease who had the shunt -- PFO closed at surgery.

What can we make of these data regarding PFO closure status as it relates to recurrent stroke? It's not possible to draw definitive conclusions based on a very small number of events. Suffice it to say that events can occur despite complete PFO closure, and we really don't know what degree of PFO closure might be needed to prevent a stroke. And recall that in RESPECT, residual right-to-left shunting was present in 28.7% of assessed subjects.

The Sponsor performed a subgroup analysis of the following cohorts of interest:

- Age
- Gender
- Shunt size
- Atrial septal aneurysm

- Index infarct topography
- Planned antithrombotic medication

The forest plot shows no significant p-values for interaction. The analysis does suggest that the device may provide an increased benefit in subjects with a substantial shunt or an ASA. However, because the primary endpoint was not met, subgroup analysis should be considered as hypothesis generating for future evaluation.

Next, the RESPECT trial safety assessment. There were 16 deaths, 6 in the device group (1.2%) and 10 in the medical management group (2.1%), with 15 of 16 deaths occurring beyond 6 months post-randomization and 1 device group death within 6 months due to coronary artery disease. None of the deaths were adjudicated by the DSMB as being related to the device, procedure, delivery system, or study protocol. One device subject did have a fatal pulmonary embolism. And I'll discuss DVT and PE shortly.

The proportion of device subjects with serious adverse events related to the device or implantation procedure was 4.5%. There were no device- or procedure-related acute ischemic strokes resulting from air or observed thromboemboli on the device. There were two cases of pericardial tamponade, one cardiac perforation, three cases of major vascular access site complications, and two device explantation procedures.

In the medical management group, the overall rate for serious adverse events was 1%, and these events were adjudicated as related to antithrombotic therapy.

Here are the major bleeding events stratified by treatment group. The major bleeding events were low; event rates were low and similar between the device and medical management group.

The observed rates of atrial fibrillation, paroxysmal supraventricular tachycardia, and atrial flutter were numerically higher in the device versus the medical management group. On a per-subject basis, the atrial fibrillation rate was 4% in the device group subjects versus 1.9% in the medical management group.

Next, venous thromboembolic events. There were 18 subjects, or 3.6%, in the device group compared to 3 subjects, or 0.6%, in the medical management group who had DVT or PE. The reasons for the high observed rate of DVT or PE in the device group are not clear. One postulated mechanism is that some PFO patients are at increased risk for venous thrombosis, and the more frequent use of warfarin in the medical management group, in approximately 20% of subjects, reduced their risk of DVT or PE compared to warfarin use in the device group, which was less than 4% of subjects.

Additional studies, however, would be needed to identify patients who are at particularly high risk for venous thrombosis and to determine whether PFO closure plus anticoagulation is superior to anticoagulation alone to prevent ischemic stroke.

To summarize the safety assessment, subject deaths were uncommon, and there was no signal of increased mortality in either treatment group.

The proportion of device group subjects with serious adverse events related to the device or the implant procedure was 4.5%.

Major bleeding rates were low and similar between treatment groups.

The total observed atrial fibrillation rate was numerically higher in the device group (4%) versus medical management (1.9%).

And there was a signal for a higher rate of DVT and PE in the device versus the

medical management group (3.6% versus 0.6%, respectively).

You've seen the Sponsor's patient-level meta-analysis of pooling the RESPECT and PC trials. The result of this analysis suggests a significant ischemic stroke risk reduction in patients treated with the device. However, limitations regarding the meta-analysis should be considered. This analysis pools results from just two trials, RESPECT and PC, rather than a recommended practice of aggregating data from many studies. And the rates of multiple baseline characteristics, including those associated with ischemic stroke, differed between the PC and RESPECT trials.

The typical neurocardiac risk factors, except for stroke, except for smoking, migraine, atrial septal aneurysm, and a larger PFO, were more frequent in the RESPECT versus the PC trial. The PC trial had a high proportion of patients with prior stroke or TIA and as well as subjects receiving anticoagulation. Additionally, there were differences in available follow-up between the two randomized trials. Other limitations include high rates of patient withdrawal and loss to follow-up relative to the number of events, which were more frequent in the medical management group. Unascertained events may have influenced the results of the analysis.

Medical therapy for both the device and the medical management groups were heterogeneous within and between studies.

And the meta-analysis did not include the RESPECT extended follow-up data, which you have seen showed a narrowing of any potential treatment effect for the device. And most patients in the meta-analysis were followed for 2.5 years.

Finally, the PC trial manuscript reported that there was an imbalance in referral for

endpoint adjudication, such that events in the device group may have been less likely to be reported than events in the medical management group.

Other findings in the meta-analysis to consider include a high rate of atrial fibrillation with device closure versus medical management, and a higher -- and a large PFO or ASA did not identify patients likely to benefit from device closure from those unlikely to benefit.

To summarize FDA's clinical view, the RESPECT trial required a comprehensive assessment for cause of ischemic stroke, although the evaluation for atrial fibrillation and atrial flutter had limitations. It may be reasonable for conclusions drawn from RESPECT to be limited to a selected subgroup of patients with stroke and PFO in which known causes of ischemic stroke have been excluded by a neurologist and a cardiologist.

The initial data lock included a small number of events, with low event rates for both treatment groups. In the ITT population, superiority of the device versus medical management was not demonstrated in either the raw count or Kaplan-Meier analyses.

In the initial data lock, supplementary analysis event rates were more favorable to the device, but excluding and reassigning subjects can compromise balance in baseline covariates afforded by randomization, and the impact on study outcomes is difficult to predict.

There were no adjustments in the p-values for multiplicity, which raises the possibility of false positive findings.

The high number of subject withdrawals that were greater than fivefold higher than the number of subjects and unbalanced withdrawal in favor -- and high numbers --

unbalanced withdrawal that was higher in the medical management group reduces the strength of the evidence.

Challenges of subject retention in RESPECT are understandable in the context of the clinical landscape and were difficult to overcome. Imputation methods are helpful but do not fully address missing data concerns.

With longer-term follow-up, as more patient-years and events accumulate, it would be expected that the effect size of a durable beneficial treatment would be maintained, associated with reduction in the upper bound of the 95% confidence interval. However, compared to the initial data lock, the extended follow-up analyses showed an increased hazard ratio and upper confidence limit bounds for all analyses populations, raising a question about a durable treatment effect by the device.

The post hoc ASCOD analysis to determine the likelihood of recurrent strokes to be more or less likely to be an undetermined or cryptogenic cause goes beyond the intended scope of ASCOD grading and is limited by incomplete clinical assessments in the absence of a standardized evaluation process.

There was no evidence that PFO closure reduces the TIA rate, which would be -- which could be expected for an intervention that reduces thromboembolism. Incomplete PFO closure was common, observed in 28.7% of assessed subjects, and a full PFO closure assessment was not available in 33.2% of subjects.

The proportion of device subjects with serious adverse events related to the device or implant procedure was 4.5%.

Subject deaths or major bleeding were uncommon, and there was no signal of

differences between treatment groups. However, there were signals for an increased risk of atrial fibrillation and deep venous thrombosis or pulmonary embolism in subjects treated with the device that may warrant further investigation.

I'll now turn the FDA presentation over to Dr. Erika Tang to provide our post-approval comments.

DR. E. TANG: Good morning. I'm Dr. Erika Tang, the epidemiologist on the review team. I'm in the Division of Epidemiology in the Office of Surveillance and Biometrics, and I will be presenting the post-approval considerations for this device.

Before we talk about the post-approval study, we need to clarify a few things. The discussion of a post-approval study prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

The plan to conduct a post-approval study doesn't decrease the threshold of evidence required by FDA for device approval.

The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk-benefit balance.

FDA issues conditions of approval to refine the benefit-risk profile of a device. These conditions of approval fall into the following three general types: first, additional nonclinical or bench testing; second, extended follow-up of the premarket cohort; and, third, new patient data collection to address focused benefit-risk questions and/or evaluation of operator training programs either as a standalone post-approval study or comprehensive registry-based surveillance with shared responsibilities using components of the national

medical device evaluation system.

These are the postmarket concerns identified by the FDA review team through the review of the premarket data that should be addressed long term, if the device is approved:

- The safety and effectiveness of the device, including incidence of recurrent ischemic stroke;
- Device- or procedure-related serious adverse events;
- Deep venous thrombosis;
- Pulmonary embolism;
- Atrial arrhythmias; and
- Complete PFO closure.

Considering that this is a first-of-a-kind device and the providers participating in the IDE trial are experienced users, the review team is also recommending the evaluation of a training program for new operators. Therefore, FDA is recommending a post-approval study with new enrollment and long-term follow-up as a condition of approval for this device.

The following slides outline the post-approval protocol. Dr. Carlson already also presented an overview of the post-approval study. These slides are provided in your handout for the discussion this afternoon.

The primary endpoints and 5-year-long follow-up proposed by the Sponsor for a post-approval study are reasonable. However, for the reasons presented in the last hour, the FDA review team believes that the Sponsor needs to assess additional endpoints such as deep venous thrombosis, atrial arrhythmias, and complete PFO closure. We're also

recommending the evaluation of a training program for new operators. In order to evaluate the effectiveness of this program, differences in technical and procedural success and the rate of procedure-related adverse events should be assessed between newly trained operators and experienced users.

The Panel will be asked to comment on the post-approval study design and whether additional elements or objectives should be considered to provide surveillance on the safety and effectiveness of the device.

This concludes my presentation. And now Dr. Drummond will be presenting FDA's concluding remarks.

DR. DRUMMOND: Thank you, Dr. Tang.

The FDA's summary is in your Panel slides for your convenience, and it highlights the main points presented by Dr. Rong Tang and Dr. Andrew Farb.

So this concludes the FDA presentation. And I'd like to thank you for your time and attention, and we look forward to the Panel's discussion.

DR. PAGE: Thank you very much for that clear presentation.

I will make note that in the corrected handout, we're only off by one slide number. So when the Panel may have questions, we'll ask you to give the number as well as the description of the slide, and we'll make sure we have that up. Likewise, if there are questions that are going to require some more work over lunch, we will be directing those primarily to the Sponsor in terms of any further data analysis.

I'd like to now ask the Panel if there are any specific questions for the FDA, brief clarifying questions. And who would like to ask a question?

Dr. Hirshfeld, then Dr. Noonan.

DR. HIRSHFELD: I have two questions. One of these may actually be more of a homework assignment for the Sponsor. The first is the statistical power to interpret the data beyond 5 years. According to the Panel pack that we received, Table 16, at Year 6 there are 53 device patients and 40 medical patients still listed as being at risk, and so the numbers get very small. Now, I saw some Kaplan-Meier curves that were carried out on the slide that were carried out farther than the Kaplan-Meier curves were carried out in the Panel pack, and I wondered whether there are additional data that FDA is in possession of now that makes these numbers larger and more robust than they were before.

And my second question, which really doesn't require an answer right now, but all morning we've been talking about strokes as a categorical variable. Maybe the stroke either occurs or it doesn't. We haven't had a single mention of the NIH Stroke Score of these endpoint events. I know those data are available, and I wonder whether at some point during this meeting we couldn't have a structured presentation of the exact severity of these endpoint events, so we know whether we're talking about really serious neurological events or whether we're talking about minor neurological events. So I don't know whether that should come from the Sponsor or FDA, but I'd just like to request hearing that.

DR. PAGE: We will ask the Sponsor to provide a breakdown in terms of relative severity of the strokes.

Dr. Carlson, does that work for you?

DR. CARLSON: Yes.

DR. PAGE: And your first question about longer term was to the FDA. In terms of generating these Kaplan-Meier curves, there seems to be a paucity of data as you go out.

DR. HIRSHFELD: I don't know whether there are more data that are available to FDA, that they included this morning, than is published in the Panel pack or not. But the Kaplan-Meier curves seem to go out to 10 years, than the slides that they showed today, and they go to 7 years.

DR. ZUCKERMAN: Okay. John, simply put, there aren't more data. That's why there was an initial data lock and a subsequent look at the data. I think the small numbers are also well represented in the FDA slides that show large confidence intervals. After lunch, the Sponsor may want to respond to your question regarding numbers and consequently numbers needed to treat as we go out further.

DR. HIRSHFELD: Yeah, the reason I think this is important to be clear on is that there's an issue about whether the Kaplan-Meier curves are converging at late follow-up, and I'd just like to have real clarity on the precision of those estimates at that point.

DR. PAGE: So, Dr. Carlson, is that question clear to you? And any ability that you can provide in terms of numbers needed to treat out beyond 5 years would be valuable.

DR. CARLSON: It's clear, and we agree it's --

DR. PAGE: I'm asking you just to respond after lunch, if you don't mind. We don't have you on a microphone, so your comments right now couldn't be included in the minutes. Thank you.

Dr. Noonan.

DR. NOONAN: Thank you.

It was Slide 134 in your packet that was different than our Slide 134, by the way. So that's the one we didn't have. So that's how we got an additional slide that doesn't match our numbers.

Go back to the strokes. Ten percent of these patients in the trial had strokes prior to their qualifying event. I don't know who has the answer, but were those strokes in those patients cryptogenic or non-cryptogenic? I'd be curious, you know, that suddenly somebody had a cause and then they had a cryptogenic stroke, and just a little suspicious.

Regarding in the Executive Summary, which was a packet that was given to us on a disk, there are two tables of interest, their Table 7 and Table 8. Those are on pages 28 of 78 and 29 of 78 in the FDA Executive Summary. And in the group that got the device, very few of those patients were on clopidogrel alone, whereas in the medical management group the numbers were far more substantial. It ranges from 25% at randomization to finally at 8 years it's still 12.6% versus 1.1% in the device group. And that concerns me because having put other devices in where I need patients to be effectively -- have antiplatelet therapy being effective before I put the device, about 20% of patients getting clopidogrel alone may be found to not be responders. And if you have a large percentage of patients in the medical management group getting clopidogrel, I assume, among that group, there are probably some non-responders, and therefore the patient is at risk of stroke because they're really not treated at all.

DR. FARB: Yes, there's a known issue with clopidogrel and the non-responder population, but at the time when the trial was designed, that was the drug. But it does raise questions going forward with the knowledge we have, how to best manage these

patients knowing that they may be at increased risk for events.

DR. PAGE: Thank you.

Dr. D'Agostino, then Dr. Chaturvedi. And did I see Dr. Kandzari? Did you have your name or your hand up, as well?

DR. D'AGOSTINO: Thank you.

DR. PAGE: I'm sorry, actually Dr. Lincoff next.

DR. LINCOFF: Can we talk to both the Sponsor and the FDA at this point, or do you want --

DR. PAGE: Right now we're looking for brief clarifying questions to the FDA, unless there's something that needs to be addressed in the lunch break.

DR. LINCOFF: Okay. Then no.

DR. PAGE: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: Yeah. With regard to the movement from the ITT to the per-protocol, I'm having a hard time trying to sort this out. There were nine events in the ITT, and then it goes down to six events in the per protocol, but it turns out that two of those events come from individuals who had no device implanted. So does one want to look to the religion of ITT as randomized? But more important to me is why weren't the devices implanted on those 34 individuals? Was there something going on with these 34 subjects that put them at higher risk and they didn't get it, or did they withdraw from it? Can more explanation be given? Does the FDA have any insight on how it went?

DR. FARB: Thank you. We can provide the list, and the Sponsor can as well. A good

number of those who didn't have reasons for not having the device, that was discovered at the implant procedure, which is another issue that was alluded to. A good many of the others just decided -- what we learned from the Sponsor was they opted out. They decided they didn't want the device. A small number of those decided to stay with the medical management. Others dropped out.

DR. D'AGOSTINO: With the two that ended up having events, do you know what their posture was? Did they just decide not to pull out or --

DR. FARB: So yeah --

DR. D'AGOSTINO: -- I mean, to change?

DR. FARB: -- not beyond -- one of those decided not to have the device and stayed in medical management. The other had the coronary disease and then had the PFO closed at bypass.

DR. ZUCKERMAN: Okay, Dr. D'Agostino, maybe we can ask the Sponsor to enumerate on those two patients after lunch also.

DR. D'AGOSTINO: Thank you.

DR. PAGE: So, Dr. Carlson, you're clear on that?

(Off microphone response.)

DR. PAGE: Thank you.

Dr. Chaturvedi.

DR. CHATURVEDI: My question was with regard to the PE events, and I believe there were 13 in the device arm and 2 in the medical management arm. And has the FDA tried to ascertain how clinically significant those were in terms of how long were the patients

hospitalized? Were any of them fatal?

DR. FARB: There was one fatal PE. They're all considered serious adverse events per the definition, as opposed to non-serious adverse events. Most were treated with anticoagulants, and a good proportion indefinitely with anticoagulation -- anticoagulants, some more limited. But from the data that we were provided by the Sponsor, most stayed on anticoagulation indefinitely. But again, we can ask the Sponsor then to give the precise breakdown.

DR. PAGE: Thank you. On the subject of PE, Dr. Farb, you mentioned the open question as to whether there would be any benefit to the device in a patient with a history of PE or DVT who's anticoagulated anyway. We've heard the Sponsor say that they thought that if the patients were receiving the device, they should be anticoagulated fully, and some of the difference was mentioned as perhaps being related to the higher use of warfarin. I might ask whether the Sponsor might be willing to address your question as to the Sponsor's perspective and any data that might support whether if someone has a history of a DVT or PE and is committed to anticoagulation, as you suggest, whether there is any additional benefit in those patients, from the device.

Dr. Carlson, did I explain that question satisfactorily for you?

(Off microphone response.)

DR. PAGE: So if you could put that on your list of things just to briefly address after lunch, I'd appreciate that.

Moving on to Dr. Kandzari.

DR. KANDZARI: Thank you.

This is a question for Dr. Farb, and specifically I'm referencing, at least in our information, Slide 140, entitled PFO Shunt Status in 18 Device Stroke Subjects. And specifically, having been reviewing these data over the past 2 weeks or so, the number of different ways the analyses can be performed is dizziness -- is dizzying. And so amidst my vertigo, maybe one of the simplified methods I'm looking for is just a mechanistic understanding that the device is actually preventing what we think it's doing.

And in this slide, this is the extended follow-up data of the 18 stroke events in the device arm, and in a simplified assessment of this, looking from a mechanistic principle, 11 of 18 strokes by my estimate here occurred despite clear-cut closure with either the device or a surgical approach to this. And we can look at seven additional events that with some degree of shunting still occurred or one patient may have not been in the study. So 11 out 18. Clearly there's closure of the PFO, and yet the events still occur. Do you have a similar slide of these data for the 24 events that occurred over extended follow-up in the medical management arm, specifically with regard to the perceived etiology of the stroke? And to broaden that within that medical group, to broaden Dr. Page's comments, do we know how many of those patients were on oral anticoagulant therapy at the time of the event?

DR. FARB: Part 1, I think, gets to the ASCOD classification, which was applied in an effort to characterize mechanism and with a dichotomy of determined versus undetermined being applied, and I think what we tried to express is that we find some limitations with that type of analysis. There is a slide that we presented about the medical therapy at the time of the events in those patients, and again we have a small group that appear to be, I think, seven versus two that were -- seven in the medical arm and two in the device arm

who were not taking the protocol-directed therapy at that time. But the numbers are very, very small in terms of whether -- and then the heterogenicity of the types of treatments, to be able to come with a unifying theme about the effectiveness of this treatment.

DR. KANDZARI: I think putting it in another perspective of what I'm seeking is that of these 18 events, as I shared with you, maybe seven might still be perceived as potentially cryptogenic strokes. Eleven, there's full closure of the PFO. Seven, we could debate could still be cryptogenic. In the medical management arm, how many of those 24 events would still be considered cryptogenic?

DR. ZUCKERMAN: Okay. So, Dr. Kandzari, the Sponsor knows their data and the case histories. They can try, on the fly, to put together a table of those 24 patients.

DR. KANDZARI: That would be insightful.

DR. PAGE: Thank you.

Dr. Noonan.

DR. NOONAN: Regarding the PE/DVT -- focus on the DVT, is there any data that some of the DVTs were in the same leg as access, venous access?

DR. FARB: I would defer to the Sponsor for that information.

DR. PAGE: So the question being in terms of the actual cause of the DVT possibly being the access.

DR. NOONAN: Correct, correct.

DR. PAGE: I think we'd need to look at the temporal nature of the DVT development. Did we see a slide of that already? If not, perhaps you could show that to us after the break, Dr. Carlson, the timing and any attribution of the causality of the DVT related to

actually undergoing the procedure.

Mr. Thuramalla had a question or a comment.

MR. THURAMALLA: Sure. First, thank you for your presentation. On the extended follow-up review, do we know how many of these patients were over 60 years? Though they were recruited below 60 years of age, but as the extended follow-up was going on, do we know how many crossed and went beyond 60 years?

DR. FARB: Of the entire population?

MR. THURAMALLA: Yes.

DR. FARB: I don't know off hand. We can, again, get that information.

DR. PAGE: So what you're asking is what are the ages of the events? That ought to be something that could be generated for us by the Sponsor.

MR. THURAMALLA: Okay. On Slide 102 from our pack, there are a number of recurrent events. Do we know how many of them were of known nature?

DR. FARB: You know, I think what we tried to express here is it's not the -- it's a likelihood scale for the ASCOD, based on putting together information based on the patient's history, available laboratory and imaging studies, which, as recognized in the recurrent events, weren't a systematic compilation of procedures that all patients underwent. In fact, if the patient had a test within a year of the event, that may have been deemed by the committee as sufficient not to repeat that test. For example, if a patient had a carotid Doppler exam within 9 months of the recurrent event, that test may not have been repeated. Or an echocardiogram.

So that, for us, gave us some pause in terms of the strength of this evidence because

there are clinical judgments that are made as well as missing evaluations. And knowing how testing is, testing is not perfect, and sometimes repeat testing is indicated, especially if you are concerned about the etiology of a recurrent event. So I think there is a good-faith effort to do -- to assign likelihood to these events. But the big picture is there's a lot of uncertainty and lack of likelihood, and just because a certain definitive event was not found does not equal these are cryptogenic and potentially related to the open PFO.

DR. PAGE: Thank you.

I'm going to suggest we have one more question before the lunch break and then possibly break 5 minutes early.

Dr. Borer.

DR. BORER: Thank you. It's a follow-up to your point, Richard.

I'm wondering whether it's fair to look at the data that were presented to us about the temporal relation of the procedure to DVTs -- in many cases they occurred years later -- and assume that the lack of a close temporal relation means the procedure wasn't causative or may not have been.

You know, having done several thousand catheterizations myself -- and looking around the table, we're talking about upwards of 50,000 catheterizations' worth of experience. When you do a right-heart catheter, transseptal, and particularly when using fairly stiff and large devices as might be used here, modest injury to a vein is perfectly conceivable to me. It might not be evidenced early after the procedure. It might lead to scarring or late distortion or what have you that could predispose to a DVT years later.

So I'm not so sure that we should make the assumption that there has to be a close

temporal relation between the procedure and the DVT for the DVT to be related to the procedure. I'm wondering whether, in fact, the DVTs really do have to be looked at more carefully over time, and if this device is approved, that should be one of the things that's focused on in the post-approval study.

DR. PAGE: That's a very important point, Dr. Borer, and I think it will be valuable to discuss that very issue.

I'm reminded that part of the work for the Sponsor has already been done, and we'll ask the Sponsor to bring up, after lunch, CO-71, which does show the temporal relationship in terms of events after implant.

With that, I'm going to have us break for lunch. Panel members, please do not discuss the meeting topic during lunch among yourselves or with any member of the audience. We're going to convene at 5 minutes of 1:00. Please take any belongings with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

Thank you very much.

(Whereupon, at 11:55 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:56 p.m.)

DR. PAGE: Please consider this Advisory Panel meeting reconvened. We'll proceed now with the open public comment portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Washington will read the Open Public Hearing disclosure process statement.

Ms. Washington.

MS. WASHINGTON: Both the Food and Drug Administration (FDA) and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. FDA has received 10 requests to speak prior to the final date published in the *Federal Register*. Each speaker will be given 5 minutes.

DR. PAGE: So we'll be getting started with the open public comments. I will remind each speaker that the time we are allowing is the total amount of time. A light will go off, a beeper will go off at 5 minutes for all but one of the talks, and we will ask you to wrap up at that very moment. So basically, if you have a speech and the best part of your speech is in the sixth minute, I would hate for you to lose the opportunity to deliver that part of your talk, and I'd hate for us to miss out on that. So I will ask you to stay on point at 1 minute before. So 4 minutes in, you will see a yellow light at the lectern.

Our first speaker is Dr. Shunichi Homma from Columbia University. Please come forward to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

Welcome.

DR. HOMMA: Thank you very much for having me here. I'm Shunichi Homma from Columbia University. I have no financial conflict of interest. I came here on my own accord. I was on the DSMB for the RESPECT trial up until last October.

As a background, my group was the first to describe relationship of PFO stroke in 1992 in this country, and then I was the principal investigator for PFO in Cryptogenic Stroke trial, published in 2002, NIH supported, which showed that there was no increase in stroke rate as long as a patient took medication, in patients with stroke. I also published on such issues as size of PFO relating to stroke and surgical closure issues, amongst other issues.

I believe pretty much you ought not to approve the device at this stage. There may be patients who may benefit from this, but in general, I do not think that approval is appropriate. I do worry about the atrial fibrillation rate. For example, in some of the trials,

only the SAE atrial fibrillation or the ones that's standard during the hospital were considered as A-fib. So such things need clear analysis. And I very much worry about the increased rate of pulmonary embolism and deep venous thrombosis in patients who did receive the device in the RESPECT trial. So I think this needs to be carefully considered. This may have had something to do with, for example, the duration of the medical therapy, which was only 6 months in these patients. And these patients may have harbored such things as occult hematological abnormality leading to stroke, which was not taken care of by implanting a device.

The meta-analysis, I take some issues with it. There were several hundred patients that dropped out of the study, as you know, and it's very difficult to figure out what the outcome might have been if these patients would have stayed.

And also it's my suspicion that some of the patients probably had stroke with PFO closed, which does not make sense to me. And given the PFO issue, it's a very common issue. We have to remember that 25% of us have a PFO. In this room, I suppose about 30 to 40 of us have a PFO. And the potential misuse of this device after approval without the clear selection criteria, I believe it poses a clear danger to the public population.

As a physician, I believe in doing no harm. Primum non nocere, that's what I want, such at this point, I strongly oppose the approval of the device until such time that a clearly defined population that would benefit is defined. And I certainly hope that I'll be a part of this endeavor to figure out which patients might benefit so that we can we reduce the burden of stroke in the future.

And also I'd just like to just point out that myself along with co-authors that include

Ralph Sacco, Steve Messé, Horst Sievert, who's an interventional cardiologist, and Marco Di Tullio, we published a review in *Nature*, one of the *Nature* magazine's journals recently, and I think it basically goes through our thoughts very carefully.

And also American Academy of Neurology, as some of you might know, it's about to publish a guideline about PFO closure. I've asked if I can -- I was a part of it. So was Dr. Kent as well, and this was headed by Dr. Messé. I asked the academy if I can release this, but they denied such. But I certainly hope that you will take a look at it -- it should be online soon -- so that you can make a rational decision as to the approval for the device, which will have clearly a very large impact on many of our patients.

Thank you very much.

DR. PAGE: Thank you, Dr. Homma.

Our next speaker is Dr. Clifford Kavinsky from Rush University Medical Center.

Welcome.

DR. KAVINSKY: Thank you. Mr. Chairman, distinguished Panel, my name is Clifford Kavinsky, and I am Professor of Medicine and Pediatrics and Director of the Adult Structural Heart Disease Program at Rush University in Chicago. I have the privilege today to speak on behalf of the 4,600 physicians and cardiovascular professional members of the Society for Cardiovascular Angiography and Intervention.

My expenses today are paid for by the SCAI, and I will receive no other compensation from any entity for this, my testimony here today. The SCAI was founded in 1978 by the pioneers in this field whose mission is to provide the highest standards of cardiovascular care in the United States and around the world. I am a practicing

interventional cardiologist with over 20 years of experience in structural heart disease catheter-based interventions. While I was an investigator in two of the randomized clinical trials for percutaneous closure of foramen ovale in the setting of cryptogenic stroke, I have no conflict of interest to report.

As the Panel is aware, stroke represents a significant public health problem in Western industrialized countries. In the United States, it is the most common cause of major disability and costs our economy billions of dollars in healthcare and lost wages. The emotional and physical toll of cryptogenic stroke on patients and their families is enormous. Paradoxical embolism through a patent foramen ovale as a cause of stroke in young people has been understood for 140 years. It was first diagnosed in 1877 when thrombus was noted straddling the foramen ovale during the autopsy of a young woman. Since that time, there has been extensive case reports of thrombi noted within the PFO in patients with stroke.

Now, I did bring one slide today. Up, please. Here's a slide of a patient who had a recent stroke, from our hospital. This is an echo. This is the left atrium, the right atrium. Here's a massive thrombus straddling right through the PFO and was the cause of this woman's massive stroke. So while I finish my statement, I want you to study this hard.

Numerous retrospective studies document the increased presence of a PFO in young patients under 55 with stroke, and the association is even stronger when the PFO is combined with an atrial septal aneurysm. In the clinical community, it has been felt to be intuitive that a device for sealing the PFO to be effective in preventing future strokes in these types of patients. Along these lines, non-randomized clinical data have suggested

strongly that PFO device closure is better than medical therapy in preventing recurrent cryptogenic stroke and has an excellent safety profile over the mid to long term. However, three randomized clinical trials have failed to reach their primary endpoints. These studies have been hampered by significant limitations, in particular, routine off-label closure of high-risk patients resulting in low event rates in the remaining lower-risk populations. Further, crossover of patients randomized to medical therapy has been equally pernicious from a clinical trial design standpoint.

Finally, follow-up has been too short in this young population whose life expectancy and risks span over many decades rather than 2 to 4 years of follow-up, available at the time of the initial presentation of the study results. Recent data showing somewhat longer-term follow-up make, in our opinion, a compelling case for certain patient populations.

The SCAI believes that there is an important unmet clinical need in patients with cryptogenic stroke and PFO beyond what conventional medical therapy offers. Although randomized controlled trials have been -- have had inherent and likely unavoidable design problems, we feel that young patients with stroke are particularly at risk and represent a potential target population for PFO closure, perhaps focusing on those patients with large shunts and with atrial septal aneurysms.

The SCAI urges at least limited approval of a device for PFO closure with a multidisciplinary team approach, mandatory participation in a post-approval registry, and specific operator and institutional requirements that would lead to a safe and efficacious dissemination of percutaneous PFO technology to the public and fulfill this important unmet need.

Thank you.

DR. PAGE: Thank you very much.

Our next speaker is Dr. MingMing Ning from Massachusetts General Hospital.

Welcome.

DR. NING: Thank you. I have a few slides. I apologize because I have a cold, that perhaps the slide you can read if you can't hear me very well.

I want to thank the distinguished Panel and the Chair for giving me an opportunity to speak today. I am a vascular neurologist from Boston who has been caring for patients with neurovascular injury, and I have a focus on cardiac abnormalities over the last 15 years.

I have no conflict of interest, and I have not participated in any of these trials. And no one has paid for my lodging or travel, but I do travel economy class. I do participate in various professional organizations to advance patient-related research, in particular AFMR, and I do want to let you know, in the setting of today's topic, we are sponsored by the National Institutes of Health to study the mechanism of PFO-related injury.

I want to introduce you to my extended family of colleagues who dedicated their lives in treating patients with PFO-related injury. These include colleagues from cardiology, cardiac surgery, hematology, peripheral vascular disease, and neurology to individualize care in stroke patients with cardiac abnormalities.

Over the last 25 years, and sharing some of our clinic's experience, we have evaluated approximately 8,000 stroke patients with PFO. Of these, about 16% of patients underwent PFO closure, so we're rather selective. Our experience indicates that PFO closure is safe for high-risk patients, and it decreased the risk of recurrent stroke by more

than 60% to 70% compared to medical treatment. Having personally evaluated 2,000 stroke patients with PFO myself, this disease has taught me a lot of humility. PFO is a highly dynamic and complex disease. And I wish the echo would play, but this was given to me by my cardiology colleagues. But I wanted to show that this is a dynamic structure. We often say it's a hole, but it's not a simple hole. It changes over a lifetime. It's a three-dimensional backdoor to the brain that's open to a wide range of risk factors.

This is a busy slide, but I want to include all of the people. Many of them are extremely distinguished in describing the phenomenon of PFO over the last several decades. There are many secondary risk factors that we've learned from our patients, and no two patients are very much alike. As such, it's very difficult to do a clinical trial in these patients.

This is a multi-organ system disease affecting not only the heart and the brain but also the blood, the lungs, and the peripheral vasculature. For example, pregnancy increased the risk of PFO-related stroke, especially if there are additional risk factors such as May-Thurner's pathology. And so do risks with various occupations. In very physically fit individuals, in the rare individuals such as astronauts and jet pilots who is taken care of, who is exposed to high G's, and to all of us who actually travel extensively to meetings, there are many common risk factors that also come into play because of the high prevalence of PFO, as the previous speakers have mentioned.

So many of you have traveled afar to come today. I would say all brave some risk of PFO-related stroke because long-distance travel, itself, in raising the risk of PEs and DVTs, can also prolong immobility, especially when the airlines are skimping on beverages.

But despite all of these risk factors, there's an important paradox I want to raise. I know the previous two speakers both mentioned this as very important. There's only about 10% to 20% of all PFO stroke patients having acquired procoagulable state. Even with all the risk factors I talked about, only more than 70% of the patients do not have a known source of clotting.

So where did the clots come from? Look at the table very carefully. You can see that the highest risk in association of stroke is actually atrial septal aneurysm. If you could please help me play this echo and it will be -- well, that doesn't play either. But I wanted to show you that the atrial septal aneurysm, as I learned from my cardiology colleagues, is a sagging atrial septal flap that significantly increased right-to-left shunting.

This is my very last slide. Forgive me for oversimplifying a decade of work on this one slide, in looking at the molecular mechanism of shunting in PFO. Oversimplifying this, the gist of this slide is that we did look at shunting in blood and measured procoagulant vasoactive factors.

DR. PAGE: I'm sorry, we have to have you close now.

DR. NING: Of course. I wanted to just say that, in general, PFO can create a hypercoagulable state itself. Therefore, I think individualizing high-risk patients in PFO closure both objectified --

DR. PAGE: Thank you very much. Thank you very much for your presentation. I'm sorry, we have to move on.

Is Dr. Wolfgang Koehling here? Welcome. Dr. Koehling is a RESPECT study participant from Washington, D.C.

DR. KOEHLING: Thank you. I work at World Bank as an investigator, and I'm also a member of the UN task force on falsified and fake medicines. I'm Patient Number 2 in Washington, D.C. I was 30 years old. I was on a 36-hour flight from the Pacific Ocean back to D.C. My stroke occurred 72 hours after that flight, so it's most likely economy class syndrome.

My coagulation rates were always absolutely normal. I have a medical history that goes back for 44 years, with blood work that I have at home, so I can check that. I identified the stroke about 5:00 a.m. in the morning. My brother is a neurophysiologist in Germany, so I knew the symptoms of stroke. I had paralysis on the left-hand side, loss of vision on the left-hand side, and I self-medicated with about 3,500 mg of aspirin and went to G.W. Hospital for initial treatment. After 3 days I was released with no further symptoms. I was examined, and I had a PFO, and I was referred to Washington Hospital Center for further treatment.

I was accepted in the RESPECT trial. I have been always active. I have been a professional triathlete for several years before joining the World Bank. And upon discovering the PFO, I was asked to join the RESPECT trial. I believe in medical research and trials. My brother is a researcher, so I certainly joined. I was glad that I was chosen for the device. I was instructed not to do any strenuous exercise for 30 days. On Day 31, I ran the Marine Corps Marathon in my worst time ever at 4 hours and 15 minutes.

(Laughter.)

DR. KOEHLING: But I knew I was going to be fine. Despite my low coagulation rates or my normal coagulation rates, it wouldn't have been reasonable to take anticoagulants,

like warfarin or Coumadin, because it wasn't the reason for the stroke. I travel extensively to difficult countries, Somalia, Afghanistan South Sudan, so taking anticoagulants would have been dangerous for me.

Following my experience, knowing that heart defects usually have a congenital side to it, both my brothers were tested. My middle brother also had a PFO, and because he lives in Germany, he had opportunity to have the PFO closed with the same device proactively. I'm actually stunned that the FDA is discussing if this should be a voluntary option after stroke. I think this should be an option as the PFO is being discovered and not only after an incident.

When I look at the data and see that there were 9 incidents in the initial phase and 24 incidents in the follow-up phase, I would like to highlight that none of the data determines what the cause of the stroke is, if it's an emboli or if it's an aneurysm, if it's a high cholesterol levels, et cetera, et cetera. It is a significant lower level of incidence than the warfarin treatment, and I strongly plead with FDA to allow the choice made by the patients, especially in younger patients where there's still an active life ahead of them.

Actually, I wish the FDA would consider that the device was voluntary if a PFO is detected in children at age 16 and above, when the heart is sufficiently developed to accept such a device to prevent strokes. We know that aneurysm is another reason for strokes, but blood clotting seems to be the most important one in this case. I'm glad that I joined the study. You see I'm healthy, have no further incidents, and I wish that the FDA would consider this as a choice following an incident.

Thank you.

DR. PAGE: Thank you very much, sir.

Our next speaker is Mr. Jeffrey Weiss, a RESPECT study participant from Lincoln, Rhode Island.

Welcome.

MR. WEISS: Thank you. My name is Jeffrey Weiss. I have nothing to declare. I self-footed my visit to Gaithersburg today as I believe this is an important issue.

First, some background.

DR. PAGE: I'm sorry. If you can stand up fully and point the microphone towards yourself, that's perfect.

MR. WEISS: Oh, sure. Great.

DR. PAGE: Let's give him a few more seconds, please.

MR. WEISS: Okay. First, some background. I'm a highly functioning 61-year-old with degrees from MIT and Columbia in electrical engineering, a serial entrepreneur having built several telecommunication companies, and currently work as a clean technology venture investor. I'm an avid cyclist, swimmer, skier, and gym enthusiast. I have no signs of coronary disease, heart disease, arrhythmias, venous thrombosi, or other known contributory factors which will lead to multiple cryptogenic strokes. I'm happily married and maintain a modest stress healthy lifestyle. I also understand that a little while ago you saw my brain scan, my MRI.

In 2009 immediately following sexual activity, one of my legs became numb and remained so for several hours. I discussed my symptoms with my wife, who's a practicing physician, and we decided it should get checked out. An MRI showed that I indeed had had

a small stroke. An ultrasound followed by a TEE bubble study conclusively demonstrated a PFO with active blood leakage from my right-to-left atrium. I was put on a daily regimen of 81 mg of aspirin as a blood thinner.

In 2011 I was referred to Dr. Thaler at Tufts. As one of the world's leading experts in PFOs, with an active ongoing study on PFO closure versus medical therapy, he indicated that it was not yet known if PFO closure was more effective than aspirin for preventing recurrent strokes. He also explained that where rapid increased chest pressure is consistent with a PFO-induced stroke, Valsalva events happen throughout the day, and though a single correlated stroke episode may be indicative, it is by no means conclusive.

On January 2nd, 2016, after sitting in my bedroom reading, I stood up while lifting a gym bag. I lost vision on my right side, the effect of like looking through a kaleidoscope. I heard a loud buzzing noise in both ears. Fortunately my wife was present. I have no further recollection of what happened until I was in the hospital. However, apparently I remained conscious and cooperative, although drooling with a left facial droop and was confused and asking to go to sleep.

When I reached the hospital, I became more aware and recall much of what happened from that point forward. A CAT scan ruled out intracranial bleeding, and I was offered tPA in a form that carries a roughly 6% risk of bleeding that can result in death or permanently altered mental status. Given that I couldn't even do the most basic math in my head at this point, it was clear to me that I would go ahead and take the risk. I couldn't imagine spending the balance of my life so impaired. Within 30 minutes of receiving tPA, my mental status cleared, although I continued to have visual distortions for several more

hours. The test results over the next few days were disturbing. There was evidence of a total of five separate stroke sites, the original one from roughly 10 years ago, two which occurred in the peripheral areas of the brain and were asymptomatic, and two acute ones from the current episode: left occipital lobe and the thalamus. I was released from the hospital on aspirin and Plavix and warned to avoid activities which could cause bleeding, including both aggressive bicycling and skiing.

I returned to Dr. Thaler on January 8th. He reviewed my test results and explained his RoPE score research. He showed that during my first stroke, my RoPE score would've been a 7, which implies roughly 70% probability of my PFO as the root cause. My RoPE score for the most recent event was lower but would've been identical except for my increased age. However, my physical condition is such that age discrimination in a rubric is likely inappropriate for me. He discussed the closure procedure. And the devices were still considered to be experimental in the United States, but if I was interested in closure, he would refer me to Dr. Kimmelstiel, an interventional cardiologist at Tufts with extensive experience in PFO closure. With a pile of research papers in hand, I returned to review the situation with my wife.

There isn't statistical evidence that any combination of antithrombotic medicines would be more effective than aspirin alone. Therefore, I was exposed to an ongoing risk for recurrence. By the time we returned to Tufts to meet with Dr. Kimmelstiel, I had already resolved in my own mind to move forward with the procedure. Dr. Kimmelstiel ordered some additional tests, including another bubble study and a 1-month heart monitor to rule out A-fib, addressing the other physician's question.

On the day of the procedure, Blue Cross notified Tufts' billing department that they would not pay for the procedure. That was followed by several hours of phone calls between Dr. Kimmelstiel, my wife, and Blue Cross representatives, but they continued to maintain that there was no medical necessity to close a PFO, though I had had recurrence while taking aspirin. In addition, the closure device being used is listed as experimental and therefore isn't covered under the federal Blue Cross policy. I resolved at this point I could personally absorb the financial impact of the procedure but not the uncertainty associated with delaying having it done. Had I been anywhere other than with my wife during the stroke on January 2nd, the quality of my life today would be very different. Subsequent to my PFO closure, my life has returned completely to normal.

Any review of stroke literature makes it clear there are many causes, many possible causes for stroke. Given the prevalence of PFOs and a known ability to both develop and pass clots into the brain, it is clear that PFO closure should be an option for patients where there's no other identifiable cause for the stroke, and particularly when standard secondary prevention methods, as in my case, have failed.

Thank you.

DR. PAGE: Thank you very much, sir.

Our next speaker is Ms. Connie Gardner. She's a RESPECT study participant. She has personal experience in terms of herself as well as her son, who is also a RESPECT study participant from Wormsleyburg --

MS. GARDNER: Wormleysburg.

DR. PAGE: -- Pennsylvania. Welcome, Ms. Gardner.

MS. GARDNER: Thank you. Good afternoon. As he said, my name is Connie Gardner, and I'm a RESPECT study participant.

DR. PAGE: Could you pull the microphone a little bit lower there?

MS. GARDNER: Sure. Can you hear me now? I am a participant in the RESPECT study, as you mentioned. I have nothing to disclose. I supported my own travel here today because I felt it necessary for you to hear my story.

In 2003 I worked as a home health aide for Visiting Nurse of Central Pennsylvania in Harrisburg, Pennsylvania. I was 41 years old. Thirteen years ago tomorrow, I was writing out my bills at my kitchen table on a Saturday morning. I had spoken with my husband and my brother on the phone 15 minutes prior to my daughter and my two grandchildren coming to drop by for a visit. I told my daughter my hand wasn't working properly, but that's not what she heard. She heard a garbled mess. I kept calling my 6-month-old granddaughter a grandson. Nothing made sense. My hand wasn't writing.

So my daughter quietly closed the checkbook and called her dad, who was at work as a federal firefighter in the Mechanicsburg Navy base 7 miles away. She called him, and he came home, took me to the hospital, which in our case was only a mile and a half away, Holy Spirit Hospital in Camp Hill, Pennsylvania. My stroke was confirmed at the time, and scans showed that there were actually two strokes. We don't know if it happened consequentially or if it had happened -- one had happened earlier and gone unnoticed. The bubble test was also done to confirm my PFO.

At the time, Dr. Stuart Pink of Associated Cardiologists was my cardiologist. Other doctors in that group knew of the RESPECT study and thought I met the criteria with two

strokes and a PFO. The one thing I don't remember the specifics on are the dates of the original blood work I had and the first time I met the team at Washington Cardiology Center, the team of nurse Donna Whitman, Dr. Petros, Dr. Lin, Dr. Satler, and Dr. Slack.

I was accepted into the RESPECT study, and I was randomized on the side that received the device. Between May 2003 and August 2003, I had to take warfarin and have the P-time blood test done every other day for a while, every two or three days, and biweekly after that. Luckily for me, the work I did gave me the flexibility to do that.

On August 28th, 2003, I received the device. I had a 23-hour stay and was sent home with Plavix for 9 months. No more blood thinners than that. No more P-time tests. I was checked according to study protocol. I felt that I had done great. No issues, no complications, no side effects from the device, and the PFO had closed -- was closed by my device.

The reason I have to speak to you today is my story doesn't stop here. Nine months later my son, an 18-year-old, had a stroke in 2004. He was working at the Giant Center, a part of Hersheypark in Hershey, Pennsylvania. He only knew my symptoms and what he had been told, that I couldn't talk right, mom was talking funny. But he had his sense of speech, but he had lost all the use of his side. At that point he was sent to Hershey Med Center. On the way to the hospital, I called my cardiologist up home, but he was unavailable because that day he actually was in the midst of an MI himself. So being mom, my first thought once I got to the Med Center, explaining my history and a little bit of convincing to the Med Center, my son had the bubble test, and the PFO was confirmed. The next call was to Washington. After getting his records and seeing my son, he was also

accepted into the study. He was randomized on the medical side. My son has had a few of what we call spells. He's had strokes, we believe, in his eye. But by the time he gets to the eye doctor, the eye doctor says the clot's dissolved, but there is still evidence there that something's going on, even on the medicine.

In conclusion, I'm here to ask for your consideration that the PFO closure gets passed. I live my life not in fear of forgetting to take medicine or getting blood work done or being bumped or bruised or having to take blood thinners for the rest of my life or having to have open heart surgery to fix the PFO. I see the fear in my son's eye at times, and I think, even though he takes the aspirin once a day, when he forgets, he frets. The stress of forgetting that, the stress and anxiety of knowing of what mom went through and what he wouldn't have to go through, I just am asking that the device gets approved so that my son and others would have the opportunity, if they chose that option, to be able to live life to the fullest without the fears.

DR. PAGE: Thank you very much.

MS. GARDNER: Thank you.

DR. PAGE: Is Ms. Phoebe Dow here? Welcome, Ms. Dow. Ms. Dow is a patient from Houston, Texas.

MS. DOW: Good afternoon. My name is Phoebe Dow, and I'm here to tell you about how my life changed 10 and a half years ago. St. Jude Medical supported my travel here today, but I am here on my own time.

I felt it was important to be here today to share my story so you could begin to understand my experience with having used this device. My testimony will speak of my

personal experiences of when I had my stroke at 19 and had a stroke -- why I had a stroke at such a young age. Please keep in mind, at 19 I didn't know what a stroke was. I didn't even know what the symptoms were of having a stroke.

I was born with a hole in my heart and the hole never closed, which then allowed for the blood clot to go through my heart to my brain, causing me to have a stroke. If the PFO device was available to me at this time, maybe I wouldn't have had the stroke. I had to learn the hard way of what could happen to a person if you don't have the PFO device as an option. If the PFO device was available to me, it could have prevented the blood clot that caused my stroke, which would have made my life less traumatic.

When I had my stroke, I lost all the mobility on my right side and had to go through intense physical therapy to regain partial functioning on the right side of my body. I was in the hospital for about a month, and when I left the hospital, I had no health insurance, and I basically did most of the therapy at home. I had to withdraw myself from college because I was incapable of driving to and from class, and I struggled with writing. It was also an emotional roller coaster for me because I was just beginning my life, but yet I felt like it was taken away from me.

When I was in the hospital at Memorial Hermann in Houston, Dr. Richard Smalling came into my hospital room and said I'm going to help you. That is when he informed me of this medical trial called RESPECT, and it involved one of two options: having the small procedure with the PFO device, which will close the hole in my heart, or take oral medicine. And in 2006, I chose the procedure with the PFO device to close the hole in my heart, and I haven't had any side effects or complications to date. I have annual appointments with the

neurologist for checkups, but a few years into the study, they started offering to do phone interviews because of my success with the device.

I have since recovered from the stroke and have had achievements in my life since receiving the PFO device. I recently graduated from college with an accounting degree and work for Education Service Center in Houston. I look forward to what my future holds and think I will live a healthy life knowing my chances of having a stroke are reduced because of this PFO device. I believe the PFO device needs to be available for every person who stands to benefit from it, so we can prevent this from happening to someone else. If this device could save one person from going through what I did, then why not give them the opportunity?

Thank you.

DR. PAGE: Thank you very much, Ms. Dow.

Our next speaker is Ms. Peggy Mahrt from Redding, California, a RESPECT study participant and Secretary of the PFO Research Foundation.

Welcome.

MS. MAHRT: Chairman Page and members of the Panel, thank you for the opportunity to speak to you today. My name is Peggy Mahrt. I'm a founding board member of the PFO Research Foundation, which was founded by PFO patients, four PFO patients, and provided me travel support to be here today.

On May 19th, 2009, I suffered a cryptogenic stroke at the age of 42. After my stroke, I had to regain my speech, relearn to type again, learn to add and subtract simple math problems, drive, walk, and how to do simple everyday tasks like folding laundry. There is

nothing scarier than to have a stroke and being trapped in your body, not able to speak or move. I felt like my life was over, that I would never be able to be the person that I was before. I was also concerned with the potential of having another stroke at any time. After discovering I had a PFO, I was initially prescribed aspirin therapy. Two months after my stroke, I suffered a transient ischemic attack and was switched off aspirin to warfarin before enrolling in the RESPECT trial at UCLA.

After my physician explained the state of PFO science and talked to me about the trial, there seemed to be a huge gap in knowledge about tons of interest to patients like me who are making treatment decisions. I was frustrated that the quality of life issues and potential adverse events between both treatment options weren't emphasized or at all as part of the decision-making process. There were no answers here.

After conversations with my physician and undergoing informed consent, I went into the RESPECT trial with an open mind and no preference for device or medical therapy, and I was randomized to the medical therapy arm of the trial. As I remained on warfarin for over a year while in the study, I had difficulty tolerating the drug. I had no energy. My hair fell out. My skin changed for the worse, and black circles that I'd never had before, appeared under my eyes. I experienced episodes of dizziness that caused me to fall and split my head open twice and left me bleeding profusely in front of my two children, ages 9 and 12. And it was disappointing that I see none of these disturbing outcomes have been documented in the endpoints of the trial, which will be ultimately used to help patients make treatment decisions. Both incidents required trips to the ER and were upsetting to my family members. My kids to this day still talk about the events and say things like "the time mom

had to ride in the ambulance and almost died." My injuries also required multiple MRI and CT scans to make sure that there were no hemorrhages that happened 2 weeks after my injuries. And the financial costs were nothing near the emotional expense to my family, and my life and theirs became limited and filled with fear of another injury.

This type of lifestyle was not something I looked forward to doing for the rest of my life. I was only in my early 40s. I did not have the freedom to do things I used to do: skiing; hiking; fishing on the rivers, lakes, and ocean with my husband; white water rafting; kayaking; all in fear that I would fall and hit my head. Additionally, the diet restrictions and weekly blood draws became draining and depressing. They were a constant reminder that mom was sick. It was a daily source of concern and anxiety in our lives.

As time went on, I sought out additional PFO experts for consultation and held open discussions with my family. I came to the decision that this was not the way that I wanted to live the rest of my life, and my family agreed. We then researched device closure, traditional open heart surgery, and robotic closure for PFO.

In September 2010, I chose to close my PFO with the device professionally outside the trial, in hopes of reclaiming my life. The effects were overwhelmingly positive, and I was then amazed with the improvement in my life. Even the migraines, fatigue, and heart palpitation that I've had all my life are now gone. I was unsure of device closure at first, and thought of having a device in my heart was overwhelming at times. But after being on warfarin and seeing my lifestyle change for the worse, I'm grateful for the improved quality of life that the device closure offered me and understand why many patients on medical therapy have not been able to stay in the RESPECT trial. Patients in PFO Research

Foundation Facebook group frequently report being told by physicians that there's no difference between closure and medical therapy. But yet someone like me, the difference has been my life. The fact that no statistical difference is being reported between the two therapies means researchers left out the heart of the equation, and that's the patient.

It is time for the FDA to understand there are patients like me out there who desperately need access to this device. We are willing to accept the minimal risks discussed today and have access to the benefits we are most interested in. I urge the Panel to respect the patient voice and vote in favor of approving the AMPLATZER PFO Occluder.

Thank you.

DR. PAGE: Thank you very much.

Our next speaker is Mr. David Dansereau. He's consulting in private practice, a physical therapist. He's a stroke patient education and awareness -- he's involved with stroke patient education and awareness, and he's a former board member of the PFO Research Foundation.

Welcome, sir.

MR. DANSEREAU: Thank you. Good afternoon. My name is David Dansereau. I am the founder of Know-Stroke.org, a community for patients with stroke and PFO. My travel expenses are being reimbursed by the PFO Research Foundation, of which I was a founding board member.

I'm a husband, a proud father of three children, and a two-time stroke survivor. Almost 9 years ago at age 39, when my children were all under 7, I had a stroke without any known risk factors. As a physical therapist, I relied on my established treatment and

experience to work on my physical deficits and restore function. While I do not want to minimize the negative impacts a stroke can have on your body, I do want to emphasize to this Panel today, by far the largest obstacle my family and I had to overcome were those related to the stroke prevention options for patients with PFO, the same options that are being debated here today. I rapidly learned that there is no consensus in the PFO field for patients seeking answers and care, and depending on which specialist you spoke to, a cardiologist or a neurologist, the diagnosis and treatment pathways could diverge and lead you to vastly different options.

My eventual path to device closure was drawn out over 9 months. During that time I went to two cardiologists. One of those two physicians urged me to close the defect right away. He told me he had done about 20 procedures like this before and wanted to schedule the procedure by the end of the week, and I was not comfortable with this. The other suggested we conduct more tests and have me meet with more specialists in his group to review my case further. Of note, I also met with three neurologists in three separate practices during this time, one who urged closure, the other medical management, and one who simply did not provide much direction other than agreeing I was in this gray area.

I ultimately followed Neurologist Number 1's order to use Coumadin for blood thinning along with a beta blocker to offer an off-label alternative to managing my brain fog, migraines, and fatigue that relentlessly remained after my stroke. I recall being stuck at my desk in a stupor trying to work shortly after beginning this off-label combination of medicines. I was trying to complete a simple article I was writing for a PT journal. A quick

one-time task now took over 3 hours, and I could not focus clearly. Aside from fatigue and fogginess, I was anchored to regular blood draws to try to get my INR right, concern about managing my diet, and worried about bleeding. Before my stroke, I was an avid athlete. One of my long-term goals was to go back to playing ice hockey. I knew contact sports, Coumadin, and ice skates did not play well together. My quality of life and that of my family was only being made worse by medical therapy, and I knew I needed another alternative for stroke prevention. So I went to MGH to consult on PFO closure.

My doctor told me he had done more than 700 PFO closures and was enrolling patients to be followed in their patient registry, the CAMP registry, for which I participated to have my outcomes documented and help advance PFO science. I do not know the difference in off-label closure versus closure with an investigational device or registry versus a randomized controlled trial. I do know pursuing PFO closure was not -- was a decision my family and I did not take lightly.

My first choice to try blood thinners at the advice of my doctor left me with a horrible quality of life. I believe having closure at MGH with a skilled physician has allowed me a vastly improved quality of life. I have reached my goal to returning to skating and I play hockey to this day. I also completed another long-term goal, which was completing the Boston Marathon. I am certain I would not have been able to safely participate in a contact sport while on blood thinners, and I feel my preferences and values around quality of life were not taken into account at all, in all treatment decision making initially. In addition, it is important to note that something significant happened after closure. My head cleared. No headaches, no brain fog. I really wish the FDA and the company doing the RESPECT trial

would have included important quality of life outcomes like migraine, bleeding risk, the burden of managing INR, and fatigue in the trial, so the true story of what it's like to live with devices versus medical therapy could have been told.

I've been following the field of PFO for many years and communicating with thousands of PFO and cryptogenic stroke patients like myself. I've heard the evidence today, and I'm satisfied with the device. It's safe and effective. As I mentioned earlier, the lack of information available to patients to support treatment decision making is frustrating, and after more than a decade waiting for the answers from RESPECT, I can tell you, we won't have another shot at this.

I urge the Panel to consider what is most important to patients and recommend the FDA approve the AMPLATZER PFO Occluder for prevention of recurrent cryptogenic stroke. I'm also recommending that the postmarket study collect outcomes that are most important to patients. If you do not know what they are, we, as patients, are more than happy to tell you. I'd like to thank the Panel for listening to the patient side of the story.

Good afternoon.

DR. PAGE: Thank you very much, sir.

Our next and final speaker is Ms. Elizabeth Bray-Lake. She's president and CEO of the PFO Research Foundation. We had previously committed 8 minutes to Ms. Bray Lake. So, ma'am, you'll have 8 minutes with a 1-minute wrap-up light.

MS. PATRICK-LAKE: Got you.

DR. PAGE: Welcome.

MS. PATRICK-LAKE: Okay, thank you very much, Chairman Page, and certainly for

your courtesy, Dr. Zuckerman and the rest of the Panel. I am Bray Patrick-Lake. I serve as the President and CEO of the PFO Research Foundation, and it's a patient advocacy group that's dedicated to providing unbiased scientific information to patients for treatment decision making and also to advancing patient PFO science. We have been big proponents of raising awareness for clinical trials. We've worked to create a research match module for PFO, educational videos, a patient's guide to PFO. We've done surveys.

I just want to be clear that I serve in many other capacities, and I'm here today solely as a patient of PFO. I was here on my own accord, but my taxi was expensive, so I might actually submit that to the Foundation for reimbursement. I work at Duke University. I'm not here on behalf of Duke. I'm on detail with NIH for the Precision Medicine Initiative. And I want to be clear, I'm not here for any of that, other than serving as the president of the PFO Research Foundation. And my -- there we go. No. Got it. Okay, it's skipping slides. Are you helping me? Okay.

So I think the most important thing to note here is that there has literally been no patient involvement in trial design, conduct, or oversight. So the science of patient input has been an emerging science over the last decade, but we know now there are evidence-based practices that say that we should be actually taking in patient perspectives in our regulatory decision making. And so in this generous 8 minutes, I'm going to try to cover some interpretation, which is also a best practice. You want to engage patients in interpretation and dissemination of trial results, and I'll do my best in 8 minutes to cover the last 16 years. So in our online Facebook group for PFO Research Foundation, we have more than 1,000 patient members that have actually joined. We've discovered that we

have many more lurkers. We've made over two million contacts with patients over the last 8 years. And something that's really important to note is that patients with PFO and cryptogenic stroke really only wanted to know if device closure was as good as medical therapy and not better. So if you had actually engaged patients when designing this trial, we would've recommended a non-inferiority design.

And if I could actually produce Jack Winberg (ph.) and bring him into this room right now, I think that he might say that once this randomized controlled clinical trial, which I'm actually a fan of RCTs, got into trouble when we were making some of these multiple amendments, we might have actually considered doing what's called a patient preference trial where you have patients that you try to consent for randomization. Hopefully you'll get some patients in that. But then when the patients say I'm going to go off and do whatever is right for me, you still collect single-arm observational studies. So unfortunately that opportunity has now passed.

So we have also here a complete lack of respect and consideration for most -- what's most important to patients, and we've painted a very incomplete picture. So we're really not focused here on the unmet need and the therapeutic burden, which I've now heard, what, four or five patients testify about the quality of life. Patient-reported outcomes are completely zero. Patient preferences have not been taken into account in any way. It's interesting because CDRH has actually released guidance around that, saying that we should be taking in patient perspectives in benefit-risk assessments. We also have the Medical Device Innovation Consortium that's put together an entire patient-centered benefit-risk framework. I am one of the contributors to developing that framework. It's very important

because there is no one patient that is exactly like other patients. This is a very heterogeneous population, as we've heard throughout the day. This has actually become what I would call the common core of clinical trials. I'm sitting here thinking about how we're going to sort any of this out, and the one thing that you all can do is understand that patients need to be the ones who can weigh all the benefits and risks and make the decision that's appropriate for themselves.

So this is actually CDRH's own graphic on patient input and the device total product life cycle, which I find very interesting because it's very similar to certainly what the patient community and things that we've been working on and the evidence-based practices. But yet in this trial we have none of this. It is absolutely completely lacking in the RESPECT trial.

So I'm going to take just a couple minutes to try to respond to some of the FDA conclusions that were presented in their summary. Primary endpoint not met at initial data lock. So, again, it's been an entire circus of how we're going to, you know, I guess, analyze based on various assumptions. And somebody -- I think actually this person might be here -- I've heard say statistics is lies, lies, and more damn lies. And to me, that's what we heard today. So let's make it simple for patients.

Even though we know that tens of thousands of patients have undergone this procedure, at least off label, from the Panel that we met for on erosion actually 4 years ago today, I think in this very room we're now down to looking at 25 events. And so I can say, in the device arm, we know that 9 is less than 16. If you look at the Kaplan-Meier curves, you can actually see that they diverge, even though they converge and come back and then they diverge again. If you showed that to patients and talked to them about what we

discovered, even though you say there's no statistical significance achieved, trust me, patients can actually make some type of decision.

So the second point was that no patient subgroup with evidence presented for compelling benefit. I'll tell you that's because there was no information collected on quality of life, patient-reported outcomes, or preferences.

So Number 3, analysis suggests device benefit. It should be noted -- while someone else has suggested device benefit, it should be noted that the primary endpoint again was not met, and the results of this should be used for supplementary analysis to generate hypotheses for future studies. So from the patient perspective, we would say that the primary endpoint was completely arbitrary. It would be totally unethical to pursue another premarket study that's similar to this one.

Extended follow-up demonstrates benefit -- demonstrates small benefits that reduce likelihood of durable benefit. Again, while the curves converge around 5 years, at no time does the device group actually drop below the medical management group. Share this information with patients, and let them choose.

Number 5 is absolutely my favorite, the unbalanced rate of subject withdrawal from medical management limits the robustness of clinical trial results. No joke. When you don't engage patients and stakeholders in designing clinical trials, you give them nothing when they come in. This trial has now doubled in length. We're asking people to come in and share their lives and give their time to keep providing data. They haven't even gotten a single layperson's summary back. They don't even know what we're learning. Why in the world would they stay in this? Plus, you didn't have buy-in in the first place. So I actually

find it amazing that 75 -- 70% of the patients stuck with this trial and that 75% came back for a TEE, which if you've had one, they're not that much fun. It requires a site, it's a day off work, sedation, and you need somebody to drive you. Absolutely ridiculous. So let's move on from that.

Six, seven, and eight. Let's inform patients that they need to have a good stroke workup. This is what we really need. People need to be managing their stroke risks and their hypercoagulopathies for all of life. So we really need to inform them of risks. Talk to them about A-fib. Talk to them about the PE issue that we're hearing about and the potential for shunting. I was closed in an aborted device trial with migraine. I used to become paralyzed. I haven't been paralyzed since. And I'll tell you that I've got 15 to 18 bubbles in my left atrium on any day. I had a solid curtain of bubbles on my TCD and my whole atrium would be totally filled with bubbles, but yet I received benefits. So don't write that off.

Let me move on. I'm in my last seconds. So FDA's own strategic priorities actually say we should be taking in patient input into our regulatory decision making. We also have our strategic priorities from FDA the year before, saying we need to strike the right balance between premarket and postmarket data collection. We've been following some of these patients for 10 years. Do you think we've struck the right balance here? We've literally placed the burden on 980 patients when we know tens of thousands of patients might have undergone this procedure. So we're moving towards a system of national evidence generation. We really need to take the burden off these 980 patients and start capturing evidence in a much larger way.

So we know that the patient perspective is missing completely here. We really have proven that this device is safe and effective. If you would ask patients, we would tell you that you should actually be voting to approve this and then providing decision-making material so patients can choose which therapy is actually right for them. Also I'm not in support of the postmarket study that I see in this packet. It's much more of the same. We really need to recommend approval. Focus on a postmarket study in a larger population that can eventually provide useful information to patients for informed decision making.

Thank you.

DR. PAGE: Thank you very much.

Does anyone from the Panel have any questions for the Open Public Hearing speakers?

(No response.)

DR. PAGE: Seeing none, before I pronounce this portion closed, I do want to thank all of the speakers, especially the patients and representatives of patients. A comment was to respect the patient voice. I assure you, that's why we're here. And while we respect every person's perspective here, we, as a committee and panel, need to look at all of the data in terms of answering the questions FDA has put forward to us as to safety and effectiveness.

I'll now pronounce the Open Public Hearing to be officially closed. We'll now proceed with today's agenda. We're going to start with the Panel deliberations now. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons

who are asked to speak identify themselves each time for the record.

Now, over lunch, I hope the Sponsor had a chance to eat something, but we also gave you a few requests for further information. Dr. Carlson, I'll ask you to take the specific questions in the order that we prepared them to you. I will ask that you keep your comments brief because I really want this Panel to be able to discuss all the important issues we have before us.

DR. CARLSON: Thank you, Dr. Page and distinguished Panel members. I believe these are in order. We did our best there, and we have counseled one another to be brief.

So the first response is to Dr. Borer, who raised a question. In the four patients that had stroke after device implantation and complete PFO closure per TEE, it would be impossible for them to have a recurrent cryptogenic stroke. What is the evidence that the qualifying stroke was cryptogenic? What was the age at recurrent stroke? Did they have other stroke risk factors?

Dr. Thaler.

DR. THALER: Thank you. David Thaler again, from Tufts University.

Let me just provide quickly these data here, which should answer this question directly, and I'll try not to editorialize. If there are questions about them, I'm happy to address them. So there were four subjects after device implant with complete closure who had -- according to their 6-month TEE, who had recurrent strokes. And the first one you can see, at the time of recurrence, which is the third from the right column on the right, he was 50 years old, and he was still cryptogenic according to the ASCOD classification. The second subject was 51 at the time of his recurrent stroke, and that also was with no identifiable

cause. The third subject was young, 44, had radiation arteriopathy as the identified mechanism of their recurrent stroke. And the fourth one was even younger, 32 years old. This is now 5 years after the procedure, and the penultimate one was a year after the procedure. This one was adjudicated as being associated with small vessel disease and lupus.

DR. CARLSON: So one additional point is that 50% of patients with cryptogenic strokes do not have a PFO. There are other mechanisms of cryptogenic stroke outside of an embolus through a PFO.

The next question --

DR. ZUCKERMAN: Could we pause for a moment? I think Dr. Farb of FDA would like to respond to this, since this is an important point.

DR. FARB: So FDA had a question about the patient with the radiation arteriopathy, the actual side of the stroke, which was on the opposite side of the radiation arteriopathy. So this was an outstanding question for FDA to the Sponsor about the designation of this stroke being caused by the radiation, which was on the right side and the stroke on the left.

DR. PAGE: So otherwise you would say it was cryptogenic as well?

DR. FARB: Correct.

DR. PAGE: Okay, thank you.

Dr. Carlson.

DR. FARB: It could be, it could be.

DR. CARLSON: Thank you.

The next was a question from Dr. Slotwiner, who asked what is the number needed

to treat over extended follow-up?

Dr. Thaler.

DR. THALER: Thank you.

I'll direct you to the Kaplan-Meier plot, which you've seen before. This is a slightly different orientation, and you can see the number needed to treat above. This is in the extended follow-up with all 42 strokes, recurrent strokes, and the number needed to treat hovers in the 60s and then goes up higher as time marches on. And we will address this in a few minutes. If you limit it to those that did not have a Grade 1 identifiable cause, so therefore potentially still PFO related, the number needed to treat you can see here, and it tends to go down, from the 70s down to the 50s. And then later on it becomes harder with lower data density, but it tends to go down over time.

DR. PAGE: Thank you.

DR. CARLSON: Next was a question from Dr. Posner, who asked of patients with a history of DVT, how many did not develop VTE?

Dr. Carroll.

DR. CARROLL: Yes. In both arms there were 20 and 15 patients with a history of DVT, and we see, of those patients who were in the device arm, 25% of them had a VTE during follow-up, and zero in the medical arm had that. Of the medical management arm, 60% of them were on warfarin. And in the device arm, all patients who were initially on warfarin, it was stopped, and in this particular arm, long term, 10% of those patients were on warfarin. So there is an asymmetry of warfarin use.

DR. CARLSON: Next was a request from Dr. Chaturvedi. Five of 16 events in the

medical management arm appear to be unrelated to paradoxical embolism. Please provide further details on the patients.

Dr. Thaler.

DR. THALER: Thank you. David Thaler again.

So, very quickly again, not to spend too much time, these are the five patients in the medical management arm that were referred to by Dr. Chaturvedi. Thank you for the question. And the causes of stroke of these five was atrial fibrillation in the first subject. He did have a single remote episode of atrial fibrillation prior to enrollment in the study, but he was permitted entry into the study. That was apparently awhile before. Subject Number 2 had a Grade 1 cause interpreted as small vessel disease. That was almost a year after randomization, and he was 53 at the time of his recurrence.

The third subject was of unknown cause. There was a question about why we would call this unknown cause in someone who had primary brain hemorrhage. My memory was that he had a left intraparenchymal hemorrhage, but there was a decreased density which appeared over the first several days of the presentation on the contralateral hemisphere, deep in the contralateral hemisphere. So it appeared as if it was unrelated to the hemorrhage. There wasn't that much mass effect to suggest that there was arterial compression. So that was why that one, in spite of the intraparenchymal hemorrhage, was interpreted as without a Grade 1 cause.

And then there were two subjects with atrial fibrillation several years after the randomization.

DR. CARLSON: Thank you, Dr. Thaler.

Next, a request from Dr. Laskey. We would like to clarify three points regarding missing data: reasons, impact, and mitigation. Mr. Mullin and I will respond.

MR. MULLIN: Chris Mullin, biostatistician with NAMSA.

So if we try to address the challenging issues of missing data, I think there are a couple important pieces of data to go back to. One is that those patients who discontinued had a higher risk of stroke based on their baseline characteristics. And the second point is that the discontinuation rate was higher in the medical management group. So based on these two other data points, we agree with the FDA. As they stated -- I believe it was in their Executive Summary -- that if anything, this underestimates the rate of stroke in the medical management arm more than in the device arm. And I think this suggests the totality of data presented today. These analyses are conservative in nature.

DR. CARLSON: And then regarding mitigations, which was a very appropriate question, we took several steps -- you can see them here -- allowing transfer of patients between investigational sites for patients who moved. Reimbursement for patient travel expenses. The Sponsor, St. Jude Medical, provided funding for required tests in the case of financial hardship, allowed phone visits at 3 years and beyond, as you heard from one of our patients. And sites were required to make at least two phone calls and send a certified letter prior to considering a patient lost to follow-up. So we were aware of the challenges with patient dropout and did our best to reverse that.

Next was a question from Dr. John Hirshfeld. What is the NIHS score for the endpoint event, severity of strokes?

Dr. Thaler.

DR. THALER: Thank you.

There are several different ways to decide whether someone's had a major or a minor stroke. It's a question patients often ask, and I point out three general approaches to it. One is by measuring the volume of infarction in the brain itself, was it a big one or a small one, which does not always correlate with the impact of the stroke on the patient's daily life.

The second approach is the NIH Stroke Scale score, which was alluded to, which is a formalized neurological examination that gives a score of a neurological deficit.

The third and more standard way for stroke outcome studies is to look at the modified Rankin score, which is a disability scale that determines the ability of an individual patient to perform their activities of daily living.

I'd like to share with you, first of all, just the infarct sizes, if that's of interest, as a way of understanding what the recurrent strokes were like. You can see that three of the -- this is in the primary assessment, by the way, in the first 25 subjects. So 3 of the 25 were measured as small. This is the longest linear measurement on a single slice, and the rest of them, most of them were either medium or large. That's just one way to characterize the stroke as large or small.

A second way really, and one that's more important to the patients, is whether there's an impact on their activities of daily living, whether they have ongoing symptoms or not. This is the modified Rankin score. I suspect most of you are familiar with it. Zero means there are no residual symptoms. This again is in the primary assessment period of the first 25 subjects. You can see that 6 of the 25 recurrent strokes had no residual

symptoms. The rest did. Some had persistent symptoms, and you can see that there were many who were disabled or dependent at the time of their recurrent stroke.

DR. CARLSON: Okay, Dr. D'Agostino. What was the reason for the two patients who had a primary endpoint event but did not have the device implanted?

Dr. Carroll.

DR. CARROLL: Thank you.

Actually, there were three patients in the device arm that were randomized to the device who had a recurrent event and did not have a device in place. Three out of the nine. One patient was randomized to device, but before he had his closure procedure, he had a stroke. Another patient was randomized to device, decided not to undergo closure and subsequently had a stroke on medical therapy. And the third patient we've heard about, post-randomization to the device arm. The patient was found to have severe coronary artery disease, underwent bypass surgery with surgical PFO closure, and had a perioperative stroke. All the patients were included in the intention-to-treat in the device arm.

DR. CARLSON: Thank you, Dr. Carroll.

I'm not sure who asked this next question, but it was, in the medical management arm, how many of the 24 events were cryptogenic?

Dr. Thaler. Bring up the slide, please.

DR. THALER: Yeah, if we can bring up the slide.

DR. CARLSON: There we go.

DR. THALER: Thank you.

So this is all 42 of the follow-up strokes, and you can see that nearly one-third of them are now of a known mechanism, which is not inconsistent with the published literature on follow-up strokes in patients with cryptogenic stroke and PFO. And so just to describe the ones that we classified as known cause, there was one due to large vessel atherosclerosis in the device arm. You can see that there were six that were thought to be due to small vessel disease. There were five due to cardioembolism. Four of those were atrial fibrillation; three of them were in the medical management arm, and one was in the device arm. There was one due to "other" and that was, I think, the radiation arteriopathy. So that left 10 in the device arm and 19 in the medical management arm that were of undetermined mechanism.

DR. CARLSON: Dr. Thaler looked surprised because I skipped a question from Dr. Kandzari, whether the Sponsor has any data that if a subject is at risk of PE or DVT and is on an oral anticoagulant, does the device provide any additional benefit?

Dr. Carroll.

DR. CARROLL: Yes, thank you.

There has not been a trial of PFO closure in addition to anticoagulation in those with a history or with active venothromboembolic disease. That does not exist.

DR. KANDZARI: Actually, the former question was mine, but I think I did ask something related to this and this was --

DR. PAGE: And I asked a question.

DR. KANDZARI: -- were there any --

DR. CARLSON: Was that you?

DR. KANDZARI: -- were there any events in the medical treatment arm in patients who were on oral anticoagulant therapy?

DR. CARROLL: Yes, there were two recurrent ischemic strokes.

DR. KANDZARI: Thank you.

DR. CARLSON: Two of the 24.

DR. PAGE: And my question wasn't whether there --

DR. CARLSON: And I did have that.

DR. PAGE: My question wasn't whether there were randomized data that -- in this population, of course, but --

DR. CARLSON: You were asking if there were data in our study?

DR. PAGE: If there were data in the study, or if not, whether you have an opinion as to whether this device is indicated for patients who are already committed to lifelong anticoagulation, which, I must mention, in addition to warfarin includes NOACs.

DR. CARROLL: It's an excellent question for a very challenging group of patients who really do exist. And certainly given that NOACs/warfarin are not perfect, the protection against another paradoxical embolism giving a stroke may justify the combination of the two therapies in this subgroup.

DR. PAGE: Thank you.

DR. CARLSON: Agreed, we think it does.

Okay, now let's see. The next question is, in terms of causes of DVT, elaborate on temporal cause, timing, and potential attribution of DVTs to the procedure.

Dr. Carroll, you're back.

DR. CARROLL: So, again, this was an unexpected finding that was one of the benefits of having such long-term, robust data in this very important group of patients. So we looked carefully at different reasons. Six device patients experienced only a DVT for ipsilateral, that is, on the same side as their procedure. Two were contralateral. Eleven device patients experienced a DVT alone or a DVT in conjunction with a PE. Eight were ipsilateral. Three were contralateral. And then the remaining one device patient, making the total of 18, experienced a DVT in the arm.

Next, in terms of when did these occur, patients with DVT alone, two occurred in the periprocedural time period, which we listed as AEs. The rest were out multiple years, and whether there's an association with a prior right-heart cath from A-fib ablation, PFO closure, what have you, we do not know. It's a reasonable topic for a post-approval surveillance study.

DR. PAGE: Do you have similar data for the patients who did not receive the device in terms of timing of their DVTs?

DR. CARLSON: In the medical management.

DR. CARROLL: In the medical management. Not on the tip of my tongue.

(Off microphone comment.)

DR. CARROLL: There were three events. And so --

DR. PAGE: Okay.

DR. CARROLL: -- post-randomization, when did they occur on medical therapy?

DR. PAGE: Yeah, if you could let us know just those numbers sometime in the next hour or so, that would be helpful. Thanks.

DR. CARLSON: Okay. This question is what were the ages of the patients who had stroke in extended follow-up?

Dr. Thaler.

DR. THALER: Thank you.

So as the study went on, patients got older, strokes were occurring, and as we expect, strokes occur more frequently in older patients than in younger patients. By the time of extended follow-up, 20% or 1 in 5 RESPECT subjects were now over the age of 60, even though they had been enrolled under the age -- 60 years or less. Eight strokes in the extended follow-up were in patients who were over 60, and you can see the ages represented there. And as I mentioned before, as patients got older, again there seemed to be a recognizable mechanism in the older ones than in the younger ones.

DR. CARLSON: And what was the severity of pulmonary emboli in the device arm?

Dr. Carroll. Number 12.

DR. CARROLL: Yes. So we did perform risk stratification based on the CT findings, and here we see there was one patient that was approximately 5 years post-randomization, an individual who was found deceased at home, who did have an autopsy, and that's the way the diagnosis of a pulmonary embolism was made. And at that time they also examined the device and did not see a thrombus on device. The remaining 12 PEs were classified as intermediate to low risk based on this CT classification scheme. In terms of ongoing symptoms, nine of those patients who had PEs had no further symptoms. Three had some ongoing symptoms, and I described the one patient who died.

DR. CARLSON: Okay. Dr. Saver would like to make one brief comment regarding

ASCOD, since there was so much discussion about that this morning and how it was used in the study.

DR. PAGE: Sure, thank you.

DR. SAVER: Thank you.

So the ASCOD does have a variety of strengths in assessing the recurrent strokes that the ASCOD committee was tasked to do. It is one of the latest generation of instruments for classifying stroke subtypes. The current version was published just in 2013. It has a number of advantages over older approaches. It handles multiple categories well. It incorporates modern imaging approaches. And it has the advantage of being informative after the targeted workup that is typically done for recurrent ischemic strokes. It does result in probabilistic assignments. And no stroke classification is absolutely perfect, but we think it was a very strong instrument to use for this purpose.

DR. CARLSON: Thank you.

Finally, Dr. Page, my sense is you're going to convene a conversation on convergence at some point, and we have some points to make on that, but we'll wait if that's the case.

DR. PAGE: We had asked you to address it. I'm happy if you want to go ahead, Dr. Carlson.

DR. CARLSON: Okay, we can do that now.

Dr. Thaler.

DR. THALER: Thank you very much.

So we agree that the extended follow-up shows curves which are -- which need some interpretation. There was a suggestion that the data gets sparse the later out that we go,

and we agree with that. The confidence intervals get very wide. So it's unclear whether the curves are actually converging or whether they're apparently converging, and I think we accept that they become unreliable the later out we go. However, if they do converge, I would say that that's entirely what I would expect as a stroke neurologist. Stroke is not a disease. Stroke is the endpoint of many other diseases. As people age, those other diseases will come to the fore. And, in fact, cryptogenic stroke is not a disease. It's also the endpoint of many other diseases.

You've heard today already that cryptogenic stroke patients have a prevalence of PFO of roughly 50%. That means that there is half of the population who also have cryptogenic stroke with no PFO, but they've had a stroke and there's some other mechanism for those cryptogenic strokes. We mustn't use cryptogenic stroke and PFO-related stroke or paradoxical embolism as synonyms because they're not the same.

The perfect trial would have identified subjects with a paradoxical embolism and only included outcomes that were clearly related to paradoxical embolism. It's hard to identify those with absolute certainty, and so we selected patients' case identification at the beginning. I think it has to be as close as possible to cryptogenic stroke due to PFO that we can get. The outcomes of importance are the ones that are likely to be related to the PFO.

It would be wrong to claim that the PFO closure device can prevent all stroke. That would be silly. It's a little bit like claiming if you do a breast mastectomy for breast cancer, it will prevent all cancer. The outcome of interest is breast cancer and not colon cancer or melanoma. So it's for that reason that we think if you introduce noise at the beginning of

the trial by potentially including non-PFO-related index strokes, and you introduce noise at the end of the trial by potentially including non-PFO-related recurrences, the curves will just come together. Obviously, if we go long enough, the curves will be completely together. At 100 years, there will be complete mortality.

So the final observation is that the differential follow-up, I think, is important and because there was -- more often in the medical group we have more patient-years than the device group, who are older, there are more likely to be non-cryptogenic stroke causes in the device group. So the fact that we saw, with the noise at the beginning and the noise at the end, the fact that there's a signal for PFO closure-type strokes, I think, is remarkable and bears interpreting.

Thank you.

DR. CARLSON: Finally, we appreciate greatly the comments by --

DR. PAGE: Before you proceed, Dr. Lincoff -- please put up your name badge, if you don't mind, in front of you, Dr. Lincoff. Dr. Lincoff had a clarifying question or comment regarding that issue.

DR. CARLSON: Yes, sir.

DR. LINCOFF: I challenge some of those assertions. It's not the same as mortality curves. You can only die once. These are multiple strokes and having had it once doesn't -- I mean, ultimately, everybody has to die, but everybody doesn't have a stroke, and you can have multiple strokes. So for curves that are apart to converge that means the event rate has to be higher in the arm that was originally an advantage. So it's not just enough to say there's noise and there's lots of events happening here that have no relationship to the

treatment because that's a very valid point. I think the question a lot of us are stuck with is why were there more events over that longer period of follow-up and not the last three events that happened when there were 20 patients? But the period up to about 7 or 8 years, looking at this where the curves actually converge, that means there were more events in the device arm. And if there was an explanation for that, it would make us feel much more comfortable. I feel that's an issue that we'd like addressed.

DR. THALER: Thank you. I think I was running, I felt, out of time with my explanation, so I went quickly over why I think there might have been a differential increase in the non-cryptogenic or the identifiable causes in the device arm compared to the medical arm.

To address your point, if the curves are separated, why would there be more recurrences in the device arm later on? I think that's because we have differential follow-up. We have more older patients, older years of patients in the device arm. And so therefore these non-PFO-related recurrences, which is what it seemed to represent when we looked at the ASCOD classification, seemed to be occurring more often in the device arm than in the medical arm. That's where those yellow dots were.

And just to overcome the ASCOD classification thing a little bit, if you simple censor patients, don't ASCOD classify them, you just censor all follow-up at the age of 60 and we're observing the patients within the patient population that we anticipated studying, getting rid of older strokes, if you like, probable non-PFO-related strokes, this too seemed to bear out this interpretation, which is that non-PFO-related strokes were preferentially happening in the device group because of the differential follow-up.

DR. PAGE: Dr. Lincoff, thank you for that question. I want to make sure that we have an opportunity to discuss fully.

Dr. Laskey, did you have an issue right now for the Sponsor, or can this wait until we're in our discussion period?

DR. LASKEY: Well, both, but time me. As long as the Sponsor is here. So why don't you just age-adjust, which is what many people do for looking at the K-M or Cox? It's a very simple procedure to do.

DR. CARLSON: I'd like to ask Chris to address that.

MR. MULLIN: Chris Mullin, biostatistician.

So I don't know that we've done the particular analysis that you have, and I don't know that there's time to do it today, but I'm guessing you're thinking about a time-dependent covariate. I mean, there are difficulties with age because it's linear of a time, right? I think the analysis censoring patients at 60 years is one approach that's partially addressing that point.

DR. LASKEY: Okay, but you're hanging your hat awfully strongly on aging here as a powerful driver of the difference.

MR. MULLIN: I believe age is one factor, but I think also those other baseline risk factors that we identified earlier for patients who have withdrawn who are high risk show that those patients were more likely to leave the trial. I think that creates some potential issues around competing risk and such.

DR. CARLSON: Thank you.

Dr. Page, the answer to your question regarding the three VTEs in the medical

management arm, one occurred at 4 months; that was a pulmonary embolus. One at 2.9 years, that was a DVT. And one at 6.7 years, that was a DVT as well.

DR. PAGE: Perfect, thank you.

Dr. Kandzari had a brief question.

DR. KANDZARI: Yes, just a clarifying question back to the age issues. We're focusing on age. We hear that acknowledging 60 is no binary endpoint, but there's a lot of noise thereafter from your expert group. Your trial intentionally included patients 60 years or younger, but your proposed labeling doesn't say anything about age. Could you address that?

DR. CARLSON: It's a conversation we look forward to having with FDA, and we're -- you know, it's a complex issue as patients will become over 60 years of age after they get these devices, but -- and there are undoubtedly cryptogenic strokes with PFOs in patients who are over 60 years of age. But we are welcoming that conversation.

DR. PAGE: And I welcome that discussion among the Panel. I'm not going to take that up right now. Did you --

DR. CARLSON: Okay.

DR. PAGE: -- have any further comments or clarifications, Dr. Carlson?

DR. CARLSON: Just a last statement, that we appreciate greatly the comments made by the patients here today. We've been part of the patient preference activities with FDA, and we look forward to engaging patients in our postmarket trial.

DR. PAGE: Thank you very much.

Were there any further follow-up comments from Dr. Farb or the FDA?

DR. FARB: Thank you, Dr. Page. Just to clarify a couple things that were said in the back-and-forth. A statement was made about that FDA stated that we felt that the loss to follow-up actually underestimated the number of strokes in the medical management arm, but we don't agree with that statement. We just don't know. That's the problem with missing data.

Just another clarification point on the percentage of patients who -- in the medical management group who were treated with warfarin. There was about 20%. I'm not sure if it came to 16 or 60, but it was about a little less than 20%.

And then finally, of the three strokes in patients who were randomized to the device but who did not receive the device that were alluded to, again there was one patient, an 18-year-old, who had a stroke post-randomization. Prior to implant, that patient had a TCD that was negative for microemboli. We had the CABG patient who actually had the PFO closed. That patient also was excluded from the per-protocol analysis. And then finally the opted-out patient, the patient who decided to stay in the trial on the medical therapy who had the stroke about 4 years later, and that patient had come off their antihypertensive and statin medications prior to the stroke. Just other factors to consider.

Thank you.

DR. PAGE: Great. Thank you very much.

I'm going to take the Chair's prerogative in terms of the fact that we've got a lot to discuss; this is a very large Panel. And I'm going to direct the discussion around the questions. If there are further questions for FDA or the Sponsor, we will bring them to the lectern. So what I'm going to do in just a moment is actually take a break and then go

directly into questions so we have a format around this discussion, because it is such a broad discussion and we have so many voices around the table.

Before we do that, though, speaking of important voices, we have representatives from industry, from consumers, and from patients, and patients are the center of what we're doing here. I just want to make sure our representatives have an opportunity to comment before we go into the next session.

Dr. Thuramalla, do you have any comments at this point?

MR. THURAMALLA: No, I have no comments at this time.

DR. PAGE: Mr. Frankel?

MR. FRANKEL: The incomplete device closure, that percentage of patients, is there any correlation to operator experience? That's one question in terms of if that was looked at, at all, in terms of patient volume by individual sites.

DR. PAGE: As I recall, the procedural complications were fairly few. But, Dr. Carlson, do you have any comment about anything that was learned in terms of operator experience or increased adverse events related to procedure in the first cases by individual operators?

DR. CARLSON: We did not see a learning curve, and there were only 20 patients with incomplete closure. So I don't know that we've looked at that question specifically, but with those numbers I'm not optimistic that we're going to find --

MR. FRANKEL: And one other thing. In terms of older than 60 years old, in that patient population, is there any reason to think that the risk reduction in terms of strokes that would -- that this would be effective for in terms of the younger population, that that wouldn't be an equal reduction for the older population even though that there is obviously

an increase in risk for other cause of stroke?

DR. PAGE: I'm going to -- rather than put Dr. Carlson on the spot there, I want to hear from our neurologists as to --

MR. FRANKEL: Sure.

DR. PAGE: -- the cryptogenic stroke in the over 60. That's a very important point you bring up. So I --

DR. CARLSON: Over 60 --

DR. PAGE: That's okay. I'm not asking you to respond. We're going to move on here.

DR. CARLSON: Your neurologists, not our neurologists? Oh, you're asking your neurologists?

DR. PAGE: No, we will be discussing that.

DR. CARLSON: Okay.

DR. PAGE: Yeah, thank you. No, not your neurologists. Thank you.

DR. CARLSON: Oh, my God.

(Laughter.)

DR. PAGE: The neurologists on the Panel.

And finally, Dr. Posner, do you have any other comments?

DR. POSNER: Just a question. With all of the cardiac electrophysiologists in the room, I wonder whether we're going to have a little bit of discussion about the atrial fibrillation.

DR. PAGE: I assure you we will be discussing atrial fibrillation. Indeed, we're well

represented in terms of electrophysiologists.

So with that, I am going to -- we have a lot to do. I'm going to call a 10-minute break, and at 2:35 we're going to reconvene, and in that way we'll have structure around the discussion for each of these important questions. Thank you. We're on break. I do ask -- do remind everyone on the Panel not to discuss the matter at hand today.

(Off the record at 2:25 p.m.)

(On the record at 2:36 p.m.)

DR. PAGE: At this time I'm calling us back to order. At this time we're going to focus our discussion on the FDA questions. Panel members, copies of these questions are in your folders. I would ask that each Panel member identify him or herself each time he or she speaks or if called upon; you don't need to when I ask you to be called upon. This will facilitate transcription. Before we show the first question, I just want to remind us what we're here doing and thank you for allowing us to move forward to the questions to get some structure around our discussion. We are here to answer FDA's questions, to give our opinion regarding the answer to these questions. So we have a trial, we're here to discuss the safety and effectiveness of this device and its potential approval, but we're here to address the questions that are asked of us. So with that, Ms. Drummond is going to read the questions for us, and I'll ask you to go ahead through Question No. 1.

DR. DRUMMOND: The RESPECT trial primary endpoint was a composite of recurrent nonfatal stroke, post-randomization all-cause mortality, and fatal ischemic stroke. All primary endpoint events were recurrent nonfatal ischemic strokes. Per the pre-specified primary analysis plan decision rule, enrollment would be stopped once 25 events were

observed, and device superiority would be declared if there were ≥ 19 primary endpoint events in the medical management group. Since there were 16 events in the medical management group (versus 9 in the device group, with a p-value of 0.157), device superiority was not demonstrated.

Throughout the trial, there was a differential dropout rate (10.4% in the device group versus 19.1% in the medical management group in the initial PMA data lock). To account for differential follow-up, event rates per patient-year were calculated, and the primary hypothesis was tested with a supplementary Kaplan-Meier analysis and log-rank test and is shown in Table 1.

An extended follow-up analysis was based on the extended follow-up data lock. There were 18 primary endpoint events in the device group and 24 in the medical management group. The drop-out rate at the time of the extended follow-up data lock was 18.2% in the device group versus 30.1% in the medical management group. Table 1b shows the event rates per patient year in a Kaplan-Meier analysis of the primary hypothesis.

The event rates were 0.65 per 100 patient-years in the device group and 1.01 per 100 patient-years in the medical management group (with a p-value of 0.16, unadjusted for multiplicity). The wide 95% confidence interval around the 0.65 relative risk should also be noted.

So we're asking the Panel to comment on the clinical significance of these results.

DR. PAGE: Thank you very much.

I'd remind the Panel that this is the primary endpoint. This was agreed upon by the Sponsor and the FDA way back when this trial first was designed. Before we start the open

conversation, I'm interested in whether one of our statisticians care to comment on the extended follow-up supplementary per patient in Kaplan-Meier analyses, which is obviously an analysis that was taken up in response to the duration and dropout of this trial.

Dr. D'Agostino.

DR. D'AGOSTINO: Yeah, I think the -- Ralph D'Agostino. I think the shift to the analysis is appropriate in the sense that they want to respond to the data that's being shown there. I think we can give it in statistics interpretation. I'm going to jump in here and not answer the clinical question. This data should be viewed statistically, and then you can change it as you please and interpret it as you please in terms of the clinical, but the data shows, with the primary analysis, that we didn't see statistical significance being achieved.

It could be we made a mistake or it could be that, in fact, the data is telling us that, from a statistics point of view, you don't have the event rates you want, and the extended basically puts the two groups more and more together, saying that over time, based on this analysis, these curves are getting closer. And that's the statistics and you can give -- and I'll certainly join in also on the clinical interpretation, but I think that's the statistics interpretation. I don't really have -- I'd love my colleague here to respond. I don't really have any questions with the methods being used and the interpretation from the statistics point of view.

DR. PAGE: And, Dr. Evans, would you agree that you're satisfied with this analysis?

DR. EVANS: Yeah. No, I agree with the methodologies being employed. I do have a couple of comments maybe. I did want to thank the Sponsor and the FDA for their

thoughtful and helpful presentations. I know -- I understand there's a lot of complexities associated with today's proceedings, and I appreciate the efforts to understand the data. I do have some concerns about the interpretation of the data from the RESPECT trial, and I want to make a few comments.

So, first of all, given the number, small number of events, I am concerned about the stability of the results. A few events in either direction drastically changes interpretation, and you can see confidence intervals are wide, indicating a great deal of uncertainty in the estimation of effect. In the ITT count analyses, data are consistent with up to a 22% increase in risk. In other words, if you were trying to use the data from the RESPECT trial to rule out a 20% increase in risk, you'd be unable to do so with reasonable confidence. And even with the ITT Kaplan-Meier, you'd be unable to rule out 13%.

I think the big issue, or one of the big issues, is if there are lots of assumptions about the nature and the influence of dropout, before conducting any fancy analyses, there are three sort of preliminary analyses that are helpful. One is to assess the magnitude of the dropout, and in this case, the withdrawal rate is greater than the event rate, and this can be concerning because missing data may be more influential than the data we're observing. And with rare events, it's critical to have diligent patient follow-up; otherwise, you're sort of stuck making assumptions about what you're not able to see.

The second thing is that you compare the dropout rates between arms, and here you see, in the first part of the trial, 10 versus 18% differential drop in the main study, and 18 versus 30 in the extension, the long-term extension, with more loss in the medical management arm. Now, this is a clear treatment effect. Now, there are theories about,

well, it may be a positive treatment effect, in a sense, but it's informative censoring, as Dr. Laskey pointed out, and again, we're stuck sort of making assumptions about what do we really know about this.

The last thing is to sort of compare the completers to those that drop out, and patients that withdrew were different from those who didn't. They had risk factors, more likely to drop out. We can see some selection in the FDA's presentation Slide 113, there was information about if you move from an ITT to per protocol, that there's some selection of patients who don't get implanted. This opens the door for bias and selection based on post-randomized factors and also raises questions about generalizability.

So I'll stop there for now.

DR. PAGE: Thank you very much.

Dr. D'Agostino.

DR. D'AGOSTINO: I just wanted to comment. I was saving my comments about the discontinuation to Question 2, but I definitely agree they're important to consider in this analysis.

DR. PAGE: Fair enough. You set us up very nicely now for me to ask members of the Panel, be they cardiologists or neurologists or others, to comment about their perspective in terms of clinical significance of the primary endpoint results.

I'm looking to Dr. Lincoff.

DR. LINCOFF: Well, talking about clinical significance when you don't have statistical significance is always fraught with difficulty, but if we look at the face of it, what I see is a trial that was designed with assumptions that turned out to not -- particularly regarding

underlying event rates which turned out to be lower in the actual trial, which led to essentially an underpowered trial, this coupled with what turned out to be, as the Sponsors and others pointed out, some degree of noise in the initial event, the index event, how many of those were actually paradoxical emboli, not that that could've been refined any further, and the noise in the endpoint, how many of those are.

So in the end, what we're left with is essentially an underpowered trial. If it's real, if the difference were real, and we -- based on the primary analysis -- and I'm going to also reserve comments regarding the others for Question 2, but from the primary analysis and the lack of statistical significance, we can't say it's real. But if it is real, a 50% reduction would certainly be clinically relevant.

And the question then becomes do we throw away this 9 years of effort because it's underpowered, or is it valid and rational, and I think that's the topic of the next question, to try to get a better understanding, in reality, of whether or not there's a treatment effect and so what that magnitude is. So on the face of it, if real, I think this is clinically significant.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yeah, I would be very chary of throwing everything out because the p is lost in 0.05. There are many reasons why this may have worked out the way it did, and you know, we've heard about all that. I see one big problem, though, and if you take the 40,000-foot view and say, well, the central tendency of all these data are that something is being done that's effective, if you accept that, the FDA then will be left with a problem that

I don't know how to resolve, which is for whom? Dr. Lincoff indicates that we can't better refine the population that was treated to find out if they have actually paradoxical emboli, and that's true. But going forward, if we believe that that's who was helped, somehow the population has to be better defined than it was in this trial; you know, there are new techniques, et cetera, et cetera. So I think the big problem facing us is getting rid of the initial noise, moving forward, by defining the population at risk, and that's going to be hard.

DR. PAGE: If I may ask you to follow up, if you're saying might it be indicated for a subgroup, then I would remind you that we're not given the option in terms of our vote as to anything but the indication that's been put forward, which you've all seen and heard and we'll remind you of. But if, hypothetically, you were trying to identify a higher risk individual, recognizing I'm talking to a cardiologist among some neurologists, are there any risk markers that you might have identified to enhance your confidence that this would do the right thing for a patient?

DR. BORER: Not retrospectively in the trial that was done, but again, going forward, we talked about many of the techniques that now are available to seek causes of strokes. You know, it's possible to much more effectively, than with a 24-hour ambulatory electrocardiographic monitor, to identify people with paroxysmal atrial fibrillation. As far as I recall, hypercoagulable states weren't interrogated intensively in the trial; they might be going forward. That's not really trying to identify a subpopulation that we're not being asked about; it's suggesting that we ought to be very careful about how we define the indication for use based on a definition of paradoxical -- cryptogenic strokes probably caused by paradoxical emboli.

DR. PAGE: And ask for a place holder on the issue of A-fib because we will want to talk about that, whether there's a way to get rid of some of the noise before the device is considered.

Did anybody -- Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: Yes. I think this has been a very good discussion so far, but I want to explain the intent of Question 1 in a little bit more detail, such that the Agency, as Dr. Page suggested, can get the information that we need. As Dr. Borer just pointed to, you know, there are many complexities. This trial was designed roughly 15 years ago, and I think everyone understands that it's not the perfect trial per 2016 standards. That's why the Agency would like to take this discussion one step at a time.

The first thing is, as you heard from Drs. Evans and D'Agostino, statistically there are problems, and use of traditional statistical decision rules is somewhat limited. But as Dr. Lincoff pointed out, the question is specifically written to comment on the clinical significance of these results and using the totality of the data here. And that's where the Agency really needs the help of the clinicians on the Panel to understand these results in their understanding of the big picture. And especially, I would like to call on both Drs. Furie and Chaturvedi to help us here. As practicing neurologists, do these results here help you with clinical care? How do you interpret these results --

DR. PAGE: Thank you. Dr. --

DR. ZUCKERMAN: -- for these patients?

DR. PAGE: Dr. Chaturvedi had his hand up, and then I will ask Dr. Furie also to comment.

Dr. Chaturvedi.

DR. CHATURVEDI: Well, first of all, I think we can all probably agree that the event rate is very low, and even with medical management, the event rate was around 1 per 100 patient-years. And so that suggests to me that even with medical management, these patients have a relatively benign prognosis.

And then the other issue is, which I think was very important, which was one of the statistics we heard in the last session about during extended follow-up in the medical group, eight events occurred on patients across the age of 60, and out of those eight events, seven were due to alternative mechanisms. And so if you subtract those seven events, instead of being 18 versus 24, it then becomes 18 versus 17, which is virtually that 8. And then if you subtract the primary cerebral hemorrhage, which I mentioned this morning, in the medical group, it becomes 18 versus 16. And so I have significant concerns about the clinical significance of what the primary endpoint shows.

DR. PAGE: Thank you.

Dr. Furie.

DR. FURIE: As was previously stated, it's difficult to talk about clinical impact when the statistical analyses are negative. And so I don't think that this trial significantly moves the field forward in order to be able to counsel patients with regards to PFO closure being more effective than best medical management, which is another gray area of this trial that's been really highlighted based on the rates of venous thromboembolism. An element of this that is still troublesome is the issue of paradoxical embolism because that's the condition that we're trying to prevent, and yet, we rarely are able to actually detect venous thrombus

in the legs or the pelvis. And so the risk from that particular mechanism is largely hypothetical at this point in time.

And so as we heard, paradoxical embolism is being used synonymously with the presence of a PFO, and one in four people has a PFO. And so when you find them simultaneously in a patient with super vascular symptoms, the association, a causal association is often drawn, and it may not be accurate. And that's why we see patients in this trial who have other competing supravascular risk factors and other mechanisms of stroke later on, and this becomes more of an issue as patients age and potentially more of a confounder for alternative treatments or interventions that they might need as they age, so it's not a trivial issue.

DR. PAGE: Thank you.

I'll call on Dr. Dehmer and then Brindis and Slotwiner.

Dr. Dehmer.

DR. DEHMER: So I would probably disagree a little bit when I hear people say the event rate is 1 in 100. It is low, unless you happen to be that one person that has a devastating stroke, so I understand about the risks. You know, as a clinician, I came into this meeting kind of thinking I knew what to do for a PFO. I've learned an awful lot and now I know less about what to do for a PFO than I did before the meeting started. And I am not a statistician like Dr. D'Agostino and Dr. Evans, but we seem to be hung up on this magic p-value of p less than 0.05, and my rudimentary knowledge of statistics tells me that that means that if you don't achieve that, there's like -- if you do achieve it, there's a 5% risk that it could still be due to chance rather than a true effect of the study. And if you go back to

the really basic question, which was their intention-to-treat analysis, I mean, of -- not all these other statistical adjustments that were added on layer after layer after layer to try and sort out the data a little more. You know, the p-value, it's not like it's 0.5, it's 0.16, so that means that there's still -- if I'm correct, and I know they'll correct me if I'm wrong -- there's still an 84% chance that this is a real finding and, you know, those odds aren't that bad.

Yes, sir.

DR. PAGE: I'm sorry. Are you done with your comment?

I'll call on Dr. D'Agostino to respond.

DR. D'AGOSTINO: Yeah. No, the 0.05 says if there really is a difference, if the device really is kind of -- then you'll have "we don't know." But if the device is just like the medical, you have a 5% chance of seeing a result that's telling you it's significantly better. It doesn't give you a 95% the other way around in the sense -- you can go on and on. But that 5% is saying that they are the same, what's the chance I'm going to say they're different.

DR. DEHMER: I think we're kind of saying the same thing, just differently.

DR. D'AGOSTINO: But you don't like have an 84% chance that it's better.

DR. PAGE: So you're not saying the same thing.

(Laughter.)

DR. DEHMER: Not the same --

DR. PAGE: I want to make sure that everybody understands that and make sure that I understand it. Dr. D'Agostino, can you say that again for us, please?

DR. D'AGOSTINO: If the two things were exactly the same, the device and the

medical management, and you ran this test, you have a 5% chance of getting data that says they're different, and that's the so-called effect, whatever. If we -- yeah. So it isn't the case that you really can say that I have a 95% chance that they're really different or the same and so forth. You don't add those two numbers together to say here is -- I think of them as being the same.

I'm going to take a test, I'm going to put a test together where I could be 5% of the time saying that they're different, and that's what we have going on here with these 0.12s and so forth. So we don't have -- we don't have a way of quantifying what's the chance that they were right and what's the chance that they were wrong. If they were the same and if they were different, that's how the probabilities are generated. It isn't that because I have this, I now have a 95% chance of being correct. They're conditioned on the real state of nature.

DR. PAGE: Thank you.

DR. D'AGOSTINO: Am I clear?

DR. PAGE: I think you made that very clear.

Dr. Brindis.

DR. BRINDIS: Well, Dr. Page, I'm going to jump on or bite on your question there. Can we identify groups of patients who may possibly benefit? And, of course, the FDA said we do have some hypothesis-generating ideas related to two subgroups; that is, of course, with an atrial septal aneurysm and those with large shunt size. But building on Dr. Lincoff's comment about the low event rates and an underpowered trial, you know, meta-analysis has been done. Of course, we have the Kent meta-analysis, which of course

pushes forward the utilization of this device for cryptogenic shock for a PFO. But then when you do their meta-analysis of the high-risk group that maybe how our clinicians have been practicing and taking -- not enrolling patients in trials such as the septal aneurysms and large shunt size, in the meta-analysis it showed no difference. It's not significant. So there's your answer to that question.

DR. PAGE: So you're saying that you're not sure that there is any subgroup that you can identify?

DR. BRINDIS: We don't know yet.

DR. PAGE: Thank you.

Dr. Slotwiner and then Dr. Kandzari and then Dr. Brinker.

DR. SLOTWINER: Agreeing with Dr. Lincoff that clearly there are statistical limitations, but taking into account Dr. Zuckerman's request to try to interpret the data to see if there's -- based on the study limitations what we can make of it, I wanted to ask our neurologists how solid the data is that the medical therapy is helpful and are we comparing apples to apples?

DR. FURIE: The medical management of PFO --

DR. PAGE: And Dr. Furie --

DR. FURIE: Thank you, yes.

DR. PAGE: If I don't call on you --

DR. FURIE: Yes, sorry.

DR. PAGE: -- please repeat your name for the record. Thank you.

DR. FURIE: The whole issue of medical management for PFO is controversial, and I

think that's probably why this study adopted a more of a convenience approach to allow clinicians to choose. Dr. Homma, who spoke, did a study comparing aspirin to warfarin and failed to show a benefit to warfarin therapy in an older patient population with PFO, but it's unclear. And I think the issue of venous thromboembolism makes this more compelling and perhaps more nebulous, but there's no absolute right answer now.

DR. PAGE: Dr. Chaturvedi.

DR. CHATURVEDI: I mean, the current standard of care would be to use at least antiplatelets in somebody with a cryptogenic stroke, and that was recommended by the AHA/ASA secondary prevention committee led by Dr. Kernan. So, yeah, we don't have all the data we would like, but at least antiplatelets are recommended.

DR. PAGE: I'm going to keep our neurologists on the spot for a moment here, and I made note the AHA, ACC, and I think the neurology organizations signed off on the guidelines, and those guidelines were written after this pivotal study was published. To your knowledge, was this study incorporated in consideration of those guidelines?

DR. CHATURVEDI: Yes, the RESPECT study and the PC trial were both reviewed as part of those guidelines and the committee included -- gave it a Class III recommendation that PFO closure was not indicated.

DR. PAGE: And I think it's remarkable that that was a Class III recommendation or therefore lack of recommendation, that it was advised against doing that. What has changed since that time?

DR. FURIE: There haven't been any new trials to affect the level of evidence. I think there's been discussion in the community about keeping options open for patients and

perhaps revising the criteria that are used to distinguish between IIb and III.

DR. PAGE: Thank you.

Dr. Kandzari and Dr. Brinker.

DR. KANDZARI: Some of my comments have been addressed already, mainly that the -- there is no standard of care, it seems, or at least consensus despite societal recommendations regarding appropriate medical management for these patients, and we see that across the board with regard to differing antiplatelet agents and oral anticoagulation. And so the challenge in interpretation is relative to what therapy, and it was really a dealer's choice in many instances.

The second issue is that notwithstanding statistical significance here, and in the absence of a demonstration of superiority, it's hard to define numbers needed to treat. But if we think about it, the use of this device for a number needed to treat for reducing paradoxical embolism would be actually quite large, because despite directional trends favoring the device therapy, an important consideration is that among the stroke events that occurred in the device arm, still more than 50% of them had some identifiable etiology.

So if we truly distill down to the number of events that would be considered related to, potentially related to paradoxical embolism of those 18 events over longitudinal follow-up, fewer than half of them we could say was perhaps associated mechanistically with closure of the device. It doesn't mean -- I think that actually still supports the potential benefit of the device when we're talking about the effectiveness of it, but it's a very small -- it's a very difficult number of patients to define.

DR. PAGE: Thank you very much.

Dr. Brinker.

DR. BRINKER: I think that younger age is one factor I take into consideration, and I don't care if after 60 everything catches up. I don't think you need sustainability of an effect to have a benefit in treating those in their high-risk age, if that makes any sense. I agree with David's concept of really honing down on people who have some other -- it's sort of a contraindication rather than a group that you would specially want to target for having this device. We want to target all the people who are not going to get benefit from this device and try to use that, and I think that's what David said.

The other thing is, I think, more interested perhaps in multiple episodes of stroke, and of course, people who get this anyway, strokes on good medical therapy in reasonable patients, and it's amazing that all -- maybe not amazing, but all the people who had a stroke after an event, that's -- at least they're sick and in some cases they're -- so I think that repetitive episodes, in the absence of any other indication against putting in the device, would be something that I would think very strongly of.

And the other thing, just to consider, there's a lot of these devices going, and where the real issue in this device is for the first time saying yes, PFOs can be benefited by a device, and the impact of not approving this device will probably not change the overall number of people who are getting the device.

DR. PAGE: Thank you very much.

I'm going to -- you brought up the issue of age. I'm going to put our neurologists on the spot, and that is, we discussed the issue of increased noise because of more strokes for other reasons beyond the age of 60. In someone who is predisposed to a paradoxical

embolus cryptogenic CBA, does the frequency of that change as one gets older? Or do we know?

DR. FURIE: So the older folks are going to be put in situations, for instance, being sedentary after surgery, having hip fractures that might set them up for venous thrombosis that then causes paradoxical embolism. In general, though, I'm not aware of an increase with age, per se, for this particular mechanism that --

DR. PAGE: Neither increasing nor decreasing?

DR. FURIE: Right.

DR. PAGE: Okay.

DR. FURIE: The risk of cryptogenic stroke goes up, but it's for other reasons. It's clinical atherosclerosis, it's hypercoagulable state due to occult malignancy. So you certainly are going to see more cryptogenic stroke in the elderly, but not specifically related to paradoxical embolism.

DR. PAGE: Great. Thank you very much.

Dr. Hirshfeld.

DR. HIRSHFELD: Yes, I'd just like to make a remark about the -- being careful not to undervalue the event rate. The event rate is roughly 1 per 100 patient-years. Since we're considering a patient population which will frequently have 15 or 20 years at risk, a 1% per year risk of having an event, if it accumulates linearly over time, becomes 15 to 20% likelihood of having an event over that period of time. So I think that this raw -- that rate is actually a more important event rate than we might have been considering.

DR. PAGE: Thank you.

I'm hearing more positive sentiment from cardiologists than I'm hearing from neurologists. I'm not hearing anything different from the previous guidelines, and guidelines can get it right and guidelines can it wrong. Does anybody have any other comments before I bring to summary Question No. 1? Obviously, we're going to be going -- talking -- Question No. 2, we'll take this even further in terms of whether people are satisfied with the other interpretations.

I see Mr. Frankel, Dr. Posner, and Dr. Noonan.

Mr. Frankel.

MR. FRANKEL: Quick clarifying question with what Dr. Furie said. For the population that's above the age of 60, if the impact, it sounds like it's mostly lifestyle and just as -- and that would be the higher risk factor. Would you say that it would be reasonable, then, that a younger patient who has a similar lifestyle based on their specific characteristic comorbidities, that you would classify them at the same level of risk as the person above 60?

DR. FURIE: Karen Furie.

It's a very interesting question you asked because there's chronological age and there's biological age, and you can see 35-year-olds who are obese with diabetes and smoking who really have the bodies of a 75-year-old and vice versa. And I believe one of our speakers actually stated that he was technically over the age limit but had no vascular risk factors and a very healthy lifestyle. And so I do think there has to be some physician judgment about the age, particularly with people who are sort of in that in-between phase but are free of risk factors and, as I said, have very healthy lifestyles in general. They're

probably more like a 50-year-old than a 60-year-old.

MR. FRANKEL: So there is a substantial significance in patient selection other than chronological age that's worthwhile to be focused on?

DR. FURIE: You know, the trial used this 18 to 60 range, and so if you were going to follow, you're really dogmatic about following and only treating patients who fit into the trials, you'd probably set those age limits. But, in fact, what happens is people use their judgment, and so my guess is you'll see this extending out to an older population given the factors that we talked about.

DR. ZUCKERMAN: Okay. Again, Dr. Furie, we can talk about those sorts of interesting post-approval problems, but if you could get back to the question at hand, and I think it was nicely brought up by Dr. Brinker also, if you have a 20-year-old, someone in their twenties or thirties who has a PFO paradoxical embolism, no other risk factors, is the risk-benefit calculus in terms of what you see in these clinical data make it more compelling than talking about the 55-year-old who may have diabetes, lung disease, et cetera? Because, you know, there is a population of 20- and 30-year-olds who basically have strokes and don't have a lot of excess other morbidity.

DR. FURIE: Yes, that's a population where you would have grave reservation of committing a patient like that to lifelong warfarin. Unfortunately, we don't have the NOACs, or at least they haven't been tested in this clinical scenario, so you're either going to opt for an antiplatelet agent or warfarin as medical management, and I think that it would be reasonable to include a discussion of alternative approaches such as PFO closure with patients in that situation.

DR. PAGE: Dr. Furie, you just mentioned something I think is -- bears repeating. Is it then the case -- you said that NOACs have not been studied, and as such, the neurology community has not advocated NOACs for replacement of warfarin obviously in cardiovascular disease. There are some areas, such as prosthetic valves, where we're convinced there's a difference. In many cases, however, NOACs have an advantage. What is the consensus, if you and your colleague could summarize, in terms of the neurology world, regarding NOACs in this indication?

DR. FURIE: If there's evidence of venous thrombosis, then you have an alternate indication for a NOAC, and those patients may well be started on that class of drug. However, if it's cryptogenic stroke and a PFO, there's no evidence that a NOAC would be superior either to warfarin or to antiplatelet therapy, and that's not currently the standard of care.

DR. PAGE: Dr. Chaturvedi, would you agree?

DR. CHATURVEDI: Yeah, I'd agree. But I want to make a comment on a different topic either now or later.

DR. PAGE: Actually, I'll put you on the list.

Dr. Posner, our Patient Representative.

DR. POSNER: As a patient representative, I'm very confused. I happen to be a patient representative with paroxysmal atrial fibrillation. I'm a patient representative who, for 35 years, taught all my medical students that the first thing you do with atrial fibrillation is go on an anticoagulant. A lot has changed in the last 50 years. What I've seen in the study here is there's a large number of people walking around in the population with PFOs.

What I've seen here is there's no statistical difference in secondary strokes between the people that got the device versus the people that were on anticoagulants.

And so the question I have is, do you make the device available to everybody who has a PFO that's young and hadn't had a stroke yet, or if they had one single event, which may or may not be cryptogenic because we all know you don't know if it's cryptogenic or not. I have five friends and former colleagues that have had "cryptogenic strokes." They're on warfarin. They've never had a second event. And that statistic is probably as good as the studies with a group of *n* of 5, as an old animal researcher. So the point that I make is when we're talking about clinical significance, I think all of the clinicians are talking about more strokes, more damage. The clinical significance to the patient is making the decision.

And I think it would be important for them to get better data than we've gotten today to present it to the student. I'm big with PCORI. I'm one of their representatives on their advisory panels, and if I took this to a PCORI panel, they'd take a look at this data and say it needs more work before you could make a recommendation to a patient as to what to do, be they young or old. And I'll tell you when I had to make my decision -- I'm not on warfarin, I'm not on an anticoagulant. When I talked to my cardiologist and he says how many times do you fall down, as to whether you want to go on warfarin, do you want to continue skiing, and so that's just from a patient's point of view about all of this.

DR. PAGE: I appreciate that.

Dr. Noonan.

DR. NOONAN: I'm not sure I want to ask my question, but I know that they screen patients with imaging and MRA, CTA, and maybe the Sponsor can answer this question. If

the screening were adequate, we have nearly 1,000 patients. Did they detect the 3% of cerebral aneurysms that we ought to detect? So if we didn't detect them or we didn't see any at all to really rule out other causes of cryptogenic stroke -- cryptogenic stroke, if you have cryptogenic stroke, you got to be pretty darn sure that PFO is actually the cause. When we really start looking at things, I suspect that we're going to find more things, including as Dr. Furie mentioned, subclinical atherosclerosis; unstable plaques; intracranial stenoses above the level of an ultrasound of the neck, say in the skull base; even aneurysms.

DR. PAGE: Fair enough.

Dr. Chaturvedi.

DR. CHATURVEDI: There was some discussion about the event rate, and the comment was made that if you're the 1 out of 100 who has a devastating stroke, it can still be very important. But I think it's important to point out that in the events which did occur, they were mild. And, for example, if you look at Table 15 of the sponsor packet, they provided the NIH score in the patients who suffered a stroke, and the median NIH score in both the device group and the medical group was 2. And for those who are not that familiar with the NIH score, it's a scale which goes from 0 to 42, with 42 being high and 0 being normal. So the fact that the median score was 2 suggests that the events which occurred in both groups were very mild.

DR. PAGE: Thank you very much.

Dr. Laskey. And then I'm going to try to bring some conclusion to Question No. 1.

DR. LASKEY: I'm just going to react immediately to that comment that -- first of all,

there's this myth about the size of the PFO relating to outcome. There's no size to a PFO. It's deformable, it's dynamic as we've learned. And I think if you have a PFO, it could be miniscule and still devastating. And I, personally, when I was working at the Bethesda Naval Hospital, saw two young recruits with devastating first strokes whose careers were ended because of that, so it doesn't have to be mild and it may not be mild.

And the other dark tunnel that Dr. Posner was taking us down, it reminds me of a discussion I had in this room somewhere between 12 and 15 years ago with Dr. Brinker and Dr. Zuckerman: Well, why don't we just close all the PFOs because that's what was going on, that's why a trial was needed; never mind wait for an event, let's just close all the PFOs.

And then there was this genetic drift into, okay, after the first event because the rules were, if I remember correctly, you needed to fail medical therapy to get into the trial, and then that was loosened after a while. So this has certainly moved right along, as our thinking has, but I think we open up or actually go down a very slippery slope with every 18-year-old with a PFO, and then you need to get into numbers needed to treat, which are not at all logical. And finally about numbers. I think when -- I've learned that when you see a treatment effect of 50, 60, or 70%, it's probably not true. That comes from some very smart statisticians smarter than I. And the other thing that bothers me here is the uncertainty; the width of the confidence interval is as disturbing as the, perhaps, unreality of the point estimate itself.

DR. PAGE: Thank you.

So, Dr. Zuckerman, with regard to Question 1, there's been a robust discussion. I can't possibly summarize all of it, but thankfully we have minutes. No one contests the fact

that this did not meet its primary endpoint in terms of statistical significance for whatever that means. No one here is obsessed with the p-value, and we had a nice discussion of the p-value. There were concerns with regard to the conduct of the trial, with no blame, but the small number of events, less than were predicted many years ago; the fact that there are wide confidence intervals that actually there could be up to a 22%, or with the modified analysis, a 13% increase in risk with this device.

Dropouts played a significant role. And when you -- when dropouts exceed events, that's a real problem. And finally there were asymmetric dropouts. And so I think that -- we're all concerned by that. That being said, we discussed -- there is more warmth among some than others in terms of the clinical meaning of this trial and whether it might seem to be approvable. The issue of noise before and after is significant.

Younger age or less strokes for other reasons, so that makes it such that we feel more confident in the younger age perhaps, and that was the group in which this device was studied. The issue of ruling out atrial fibrillation, Holters weren't even done in most patients, and now you can put a 14-day event recorder that's the size of a big band-aid to see whether there's any A-fib, and further search for asymptomatic A-fib could be valuable in terms of noise, going out.

There wasn't a lot of enthusiasm for finding the higher risk groups otherwise in terms of FDA's mentioning large PFOs and the potential for aneurysm that was not brought forward in terms of the meta-analysis. In terms of our neurologists, I think they're more skeptical. The issue of 1 in 100 per patient-years is brought up as being important if you are the one in the hundred, but we need to look at statistics on both sides, and the fact that

some of these strokes tend to -- these strokes on both sides tend to be smaller relative to the worst grades of strokes that are used by the neurologists.

There's further confusion with regard to medical therapy. Aspirin and warfarin appear to be about as effective, but nobody feels very confident in what is best care for medical therapy, which is the comparison group, although I would point out that as much as this was device versus drug, this was device plus drug versus drug in many cases here, so the absence of any drug, any antiplatelet agent was fairly uncommon among the device group. And the issue on age was discussed further in terms of biological age. I don't know what to make of that, but certainly in terms of indication, this device was studied in patients 18 to 60, and nobody can argue that that is not the case.

So, to summarize, this is a tough area. We have cardiologists who are, I think, more favorably disposed than neurologists, but I think there's a variety of perspectives. There's agreement that this study did not meet its predetermined endpoint for statistical significance, but there may be more openness to other ways of looking at the trial, which would bring us to Question 2, if this is adequately -- answer to Question 1 in terms of FDA's perspective.

DR. ZUCKERMAN: Yes, this has been very helpful. I think we're ready for Question 2.

DR. PAGE: Great.

Dr. Drummond, would you please read Question 2 for us?

DR. DRUMMOND: Sure.

Table 2 shows a supplementary Kaplan-Meier analysis of the per protocol, as treated, and device in place populations using both the initial PMA data lock and the

extended follow-up data lock.

Although the per protocol, as treated, and device in place analyses suggest a potential device benefit in reducing the rate of recurrent ischemic stroke, it should be noted that since the primary endpoint was not met (as discussed in Question 1), supplementary analyses are typically used to generate hypotheses for future studies. In addition, the following issues limit robustness of the results of the supplementary analyses.

- Analyses conducted on the extended follow-up data lock demonstrate a smaller difference in recurrent ischemic stroke rates (that is, an increased relative risk) in the device versus the medical management group compared to the difference observed in the initial data lock.
- The rate of subject discontinuation was high in the RESPECT trial and numerically greater in the medical management group versus the device group [that was 30.1% versus 18.2% respectively, in the extended follow-up data lock], and the number of discontinued subjects was substantially higher than the number of subjects with recurrent ischemic strokes.
- Finally, the primary endpoint was tested in supplementary Kaplan-Meier analyses in a total of 8 analysis populations:
    - The initial data lock, which was the ITT, per protocol, as treated, and device in place population; and
    - Extended follow-up data lock: ITT, per protocol, as treated, and device in place populations.

  The p-values reported were not adjusted for multiplicity such that the

probability of attaining statistically significant results due to chance increases. Please comment on the clinical significance of these results.

DR. PAGE: Thank you, Dr. Drummond.

Before we dig in, I do want to point out that a statistician diligently pointed out it should be noted since the primary endpoint was not met, supplementary analyses are typically used to generate hypotheses for future studies. This has taken 15 years. So I think future studies are going to be hard to do. What we have are the data that we have. I'd like to ask the Panel to speak to this, to give your perspective one way or another as to the clinical significance of this trial in the context of these other analyses, whether you are satisfied with these analyses. And finally I will look for people who have not yet spoken, and to that end, we'll go to Dr. Yuh.

DR. YUH: So what's been bothering me throughout all these discussions, particularly as we follow the data out longitudinally, is that under the assumption of the etiologies of stroke change, the profile changes with time, that the contributions of the medical management versus the device would seem to change, as well. And so it's hard to derive any kind of meaningful conclusion, even with these additional analyses, in my mind, because you have the medical management folded in with the device, and then you have a changing landscape of the purported etiology profile of the strokes. And I was wondering if anybody could speak to that.

DR. PAGE: Dr. Furie.

DR. FURIE: I know, I agree with that comment completely. In terms of risk factors and management, there's a lot of heterogeneity, and you're quite correct, that the regimen

of antithrombotic therapy and perhaps other medications is likely to change over time as well.

DR. PAGE: I'm looking for other comments.

Yes, Dr. Lincoff. Dr. Lincoff.

DR. LINCOFF: So as a trialist who generally does drug trials, I'm a very strong advocate of intention-to-treat, but reality, particularly when we're talking about small numbers of endpoints in an underpowered trial is -- a device isn't going to work if it isn't in. So these secondary analyses are of some value. I'm less compelled by the per protocol because the reality in clinical practice is some patients follow what you prescribe and some don't, and I think you do need to account for that in part of -- in your analyses, and so I'm very skeptical of the per-protocol analyses, per se.

But I think what's compelling is the device-in-place analysis, and when that is looked at, even if one compensates for the sum of the per protocol that was built into that, I think we have a much clearer picture of what does appear to be a treatment effect. Again, you know, from a purely statistical standpoint, I recognize that it's not legitimate to base decisions on a subsidiary analysis when the primary analysis is negative, but we're trying to move beyond that and tease information out of this dataset, and I think that's an important and, I believe, compelling piece of information.

DR. PAGE: Before we go on to Dr. Slotwiner, I'll ask Dr. D'Agostino to comment on perhaps Dr. Lincoff's comment, as well as your perspective on which of these data you feel that we can use as we're making this important determination in terms of efficacy.

DR. D'AGOSTINO: As my colleague Bill Kannel and I used to have discussions -- Bill

was in the Framingham study. He said you keep feeding data until it confesses.

(Laughter.)

DR. D'AGOSTINO: And I think it's very important to do the analyses that were done. It's -- but you did the primary analysis, it didn't turn out to be significant, and now you want to get insight and the question may -- some people may say why in the world is he asking the Sponsor about two individuals. Well, they were two individuals with events. You know, can you start looking at the individuals, the ones who had events, and say something about them; what was the reason they had events, and how did it tie into the procedures and so forth? I must admit, from the discussion I've heard, and I spent quite a bit of time preparing reading the materials, I don't see them answering the question of do I really gain tremendous clinical insight. But that's your, you know, bailiwick and so forth.

I think the fact that they did the analysis is quite appropriate; don't get carried away with the p-value suddenly becoming significant, don't get carried away with trying to, you know, play a game with the missing data. I think they're missing so much data, the data -- missing data is surely clearly informative, and you're not going to be able to salvage that. All of that said, I think you do want to look at it and see if there's some insight you can gain. You said the study's been going on for a number of years, and so what kind of clinical insight, keeping in mind the lack of statistical significance -- but can we tell the FDA something that they may have not seen, or they've seen and they're waiting for us to say some other types of things? I don't know if my answer is what you're looking for, but --

DR. PAGE: Well, I'm hearing that you're kind of leaving it up to us, but we're in part asking you to help us interpret --

DR. D'AGOSTINO: Well --

DR. PAGE: -- whether there is a meaningful signal. We know that the primary endpoint didn't reach satisfaction --

DR. D'AGOSTINO: No, my --

DR. PAGE: -- but is there a meaningful signal?

DR. D'AGOSTINO: No.

DR. PAGE: And then we can decide whether it's clinically relevant --

DR. D'AGOSTINO: My response to that is that there isn't a tremendously good signal coming out of here. You're dealing with a small number of events; if you just take one or two events out of a group, which the per protocol did, you suddenly get statistical significance. But I don't think you get much clinical insight by that, so if you want my view as a statistician and just sticking to the statistics, I think that these are quite appropriate to do, but the large number of missing data, the imputation type of methods or the sensitivity analysis, the number of different secondary analyses they did, none of them give me, from a statistics -- and then trying to interpret clinically any real great insight, that a lot is coming out of it. I think it's a good exercise, but I don't get much out of it. But again, that's --

DR. PAGE: Fair enough. Is it possible to ask for a yes/no question of Dr. Evans as to whether you agree with that general interpretation? If not, please expand.

DR. EVANS: I do agree. If I could make a couple of -- I agree with my colleague, everything he just said. I do agree that looking at these analyses can be helpful in some ways, but I also caution, sort of second the caution about over-interpretation of the additional analyses. The intent-to-treat analysis is the only analysis that retains the

integrity of a randomized trial. It preserves the expectation of balance with respect to confounding factors regardless of whether you measure them, whether you know about them or whether it's a hundred years before you've even thought about it and it's the only place where you get it. Now, once you go to other analyses, they're subject to the biases of observational studies. That doesn't mean they're not helpful to look at, but they have more issues with them in addition to just the primary wasn't met. I'm talking about it's -- once you get to as treated and per protocol, you're not talking about randomized trials anymore; you're talking about observational studies because people are selecting themselves based on data observed after randomization.

So the dropout or the selection of patients could be selective, so on FDA Slide 113, they outline how did you exclude patients going from ITT to per protocol and why were these patients, 17 patients, not implanted. Well, if those are the patients that are perhaps more likely to have an event, then you've clearly got selection coming out of that, and this is what Dr. D'Agostino was trying to get at earlier. You may not be playing a fair game when you make that comparison.

The other thing I would note about the per protocol, intent-to-treat, as treated, et cetera, theoretically they -- although we sometimes consider them sensitivity analyses of each other, they address slightly different questions. They're not exactly the same question. So intent-to-treat, basically, is a question about strategy. If we employ a strategy of implanting a patient and so forth, how does that compare with a strategy of medical management? That's different from saying we're going to control for people who can't comply and exclude patients who are not implanted for one reason or another. It's a

slightly different question. And so you're going to decide about which question you're most interested in. But if you're going to be interested in the questions about as-treated and per-protocol analyses, you have to be prepared that the expectation of balance with respect to confounders is no longer there, and so you have to take that with that grain of salt.

And then, of course, there is, you know, the intent-to-treat issue is really a pragmatic one, that if you're going to apply this in practice, if I'm the next -- if this trial was still ongoing and I'm the next patient to come in, the only analysis you know that represents me is intent-to-treat because you don't know whether I'm going to be in per protocol, you don't know whether I'm going to comply, you don't know any of that stuff. So the only one that applies to me up front, that you know applies to me up front, is intent-to-treat. And then, of course, the multiplicity issue, you've got to be careful about that. So I think all of that is sort of on the table, and you just have to be aware of it.

DR. PAGE: Thank you very much.

Dr. Slotwiner.

DR. SLOTWINER: Well, I wanted to respond to the original question, which was if these numbers, these analyses have changed my view of the data as a clinician, and I think our statistician colleagues just gave the technical answer. As a clinician, I just worry that the confounding factors and missing data, the people who didn't enroll in the trial because they wanted to get the device off label, all of that is made more remote here, and so I worry that I won't know how to interpret it, so I don't think this helps me interpret the data any further.

DR. PAGE: Thank you, Dr. Slotwiner.

Dr. Borer.

DR. BORER: Yeah, I found the additional analyses helpful, not dispositive, but helpful. I think the ITT is the holy grail, of course, for all the reasons we've heard, but it's the most conservative analysis and, in this case, perhaps unrealistically conservative because of all the factors we've heard about four or five times now. And it was very reasonable for the investigators to want to ask other questions to see if they could clarify, in some way, the interpretation of the ITT results. And I think they did. Are these ancillary analyses the analyses on which we should make our decision, so to speak? No, I don't think so, but they help clarify why things may have worked out the way they did in ITT. Did they enhance the interpretability of the ITT results? Yeah, I think they do. So I find them helpful.

DR. PAGE: Thank you, Dr. Borer.

Dr. Chaturvedi.

DR. CHATURVEDI: Yeah, I think the additional analyses are of interest, but I still think that they suffer from the fatal flaw which I mentioned earlier, which is that the event rates are inflated because of including outcome events which were due to other mechanisms. And so, for example, as I mentioned, 7 out of 24 were due to other mechanisms in patients over age 60; if you include the hemorrhage, 8 out of 24. And so in the extended follow-up device-in-place analysis, instead of having an event rate of 1.09 per 100 patient-years, it's likely in the range of 0.8 or maybe even lower. And so I think the analyses are potentially misleading because they include a heterogeneous collection of events, some of which are undoubtedly unrelated to paradoxical embolization.

DR. PAGE: Thank you, Dr. Chaturvedi.

Dr. Kandzari.

DR. KANDZARI: So somewhat in the theme of Dr. Laskey's earlier comments, I also believe that these relative reductions, from a commonsense perspective, as a clinical trialist, they're a bit exaggerated to think that there's a 70% relative reduction. But that said, let me put it in another perspective to some of Dr. D'Agostino's comments about clinical -- the clinical relevance in the numbers. It's that if we look at the long-term follow-up cohorts, there were 18 events versus 24 events, so not very meaningful perhaps from a clinical perspective, or statistical perspective, I should say, but clinically, in follow-up, 10 of the 18 events in the device arm were unknown, and by the report that we saw in the follow-up, 19 of the 24 events in the medical cohort were unknown.

So that does translate to a roughly 50% reduction in events that are unknown. And if we think about this from a mechanistic perspective of what this device is intended to do -- I'm acknowledging the challenges of defining paradoxical embolism. We are looking at a potential 50% reduction in stroke events that have no identifiable cause, and I'd open that up for other comments.

DR. PAGE: Thank you.

Mr. Thuramalla.

MR. THURAMALLA: One thing I'd like to add to the ITT analysis discussion is -- and to see what -- is the meta-analysis that was presented showed a statistically significant reduction in the risk of stroke even in the ITT analysis with the device, so I just want to see what the Panel thought about the meta-analysis data that was presented. Thank you.

DR. PAGE: I'm not sure I understood what you were asking.

MR. THURAMALLA: So the discussion, especially by Dr. Evans and others, was primarily that the ITT analysis did not show or conclude that there was a reduction in the risk rate of stroke. But in addition to this randomized trial, the meta-analysis was also presented both by the Sponsor as well as FDA, and that showed a statistically significant reduction in the stroke risk with the device even in the ITT analysis. So I just wanted to see what the Panel thought about that.

DR. PAGE: Do any -- first of all, do our statisticians want to comment on whether they find the meta-analysis compelling in the absence of a positive endpoint in terms of the pivotal study?

Dr. D'Agostino.

DR. D'AGOSTINO: Ralph D'Agostino.

I thought the meta-analyses were interesting, and it's more, you know, do you sort of salvage by the possibility of some positive results by looking at that. I just didn't find it so compelling, and there seemed like there was some question with some of the components within the meta-analysis, so I think it's saying, you know, maybe there's something going on here, but does it sort of tip the balance and get you into a case, a situation, where you feel comfortable, like I don't think it is, and I lived through the situations where when I've had a number of -- and the FDA's much more expert -- a number of small studies that sort of look good, look good, look good, you put them all together, and they look really great, but it's more that you're sort of making things, selection bias, what you put into the meta-analysis and -- you know, because it looks good, because it will

reinforce it. You put it in, and does it really tip the balance? And I have all those types of concerns about carrying a really positive message.

DR. PAGE: Fair enough, thank you.

Dr. Chaturvedi.

DR. CHATURVEDI: If you'll look at the meta-analysis for the endpoint of recurrent stroke, the difference is 0.9%, and so that would translate to a number needed to treat of 111. And so earlier we were discussing a hypothetical patient, and so if you ask the average 30- or 40-year-old patient to undergo a procedure where only 1 out of 111 patients can potentially benefit, I think that would alter the risk-benefit equation significantly, which we'll probably discuss later.

DR. PAGE: Yes, Dr. Slotwiner.

DR. SLOTWINER: I think if you compare that to lifelong anticoagulation, you might get a different answer. And I guess that was my question in asking both of you how confident you -- on medical therapy, and I appreciate your answer, but it sounds to me that you would never consider recommending no treatment to a patient with cryptogenic stroke. And is it possible that this device is at least equivalent to anticoagulation, I think, is a question I'm wondering today.

DR. FURIE: Karen Furie.

And that's not the question that they tested here. I mean, is it non-inferior to any medical management or to aspirin might be an interesting question, but I don't think we can really say.

DR. PAGE: And also, Dr. Slotwiner, are you concerned about the fact that the

patients who received the device generally were on lifelong or ongoing medical therapy?

DR. SLOTWINER: Yes, that's a good point. It's muddy, and clearly, we don't have the data to answer, but as we try to extract and make meaning out of this 15 years of work, I'm just wondering.

DR. PAGE: Dr. Zuckerman, I'm going to try to summarize Question No. 2, and the Panel can correct me if I'm not getting this accurately. I think this is building on the discussion we had around Question No. 1. It's pointed out that, especially in younger people, we're looking at a long time that they would be potentially on drug therapy as opposed to a relatively short follow-up in terms of devices so far, so might that be additive, although one issue is that most patients in the device arm also were on some sort of drug therapy which we've heard is equivalent between antiplatelet and full-dose anticoagulation.

In terms of these other analyses, there at least was some general concern among our statisticians that these are difficult to even get a signal from related to a number of issues, so many data are missing. The fact that Dr. Evans made a point that once you get to the point where you're doing these other analyses, you're now looking at an observational trial where dropout and selection bias may be playing a role, confounders are playing a role, and you're answering perhaps a different question than the one which he pointed out is if you're looking at the patient across the table in clinic, the only data you really have here are the prospective data in terms of the primary endpoint.

In terms of whether these are helpful, I'm getting a sense that no one is expressing that they're swayed significantly from their previous comments, which I think, for Question 1, we're taking the entirety of the data in hand and part -- some members are seeing these

as quite helpful; others are worried that they're difficult to interpret. They're seen as of interest or muddy in different discussions. The issue of actually looking at what might be determined as a true cryptogenic stroke, the numbers seem to be less among the device patients although -- in longer-term follow-up, although those curves with large confidence intervals didn't seem to get closer to each other. The issue of meta-analysis was brought up, and while it is of interest, again, I'm not hearing any panelists completely swayed by the meta-analysis independent of their analysis of the data that we have before us, both the primary endpoints and the secondary analysis.

Does that satisfactorily address the FDA's question, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it does. Thank you.

DR. PAGE: Thank you.

Dr. Drummond, I'll ask you to read Question No. 3, please.

DR. DRUMMOND: There was no pre-specified safety endpoint; safety events were presented descriptively. The proportion of device group subjects with serious adverse events (SAEs) related to the device or implantation procedure was 4.5% (21 of 467 subjects with a device implantation attempt). Selected SAEs limited to the device or implantation procedure (device group subjects only) are shown in Table 3a.

Table 3b shows the rates of atrial fibrillation, including PAF, atrial flutter, and PSVT as either SAEs or non-SAEs, stratified by treatment group.

On a per-subject basis, the atrial fibrillation rate was 4% (20/499) in the device group and 1.9% (9/481) in the medical management group. Table 3c shows the rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) adjudicated as either SAEs or non-

SAEs, stratified by treatment group. There were 18 patients (3.6%) in the device group and 3 patients (0.6%) in the medical management group who had either a deep vein thrombosis or pulmonary embolism. Please comment on the safety profile of the device, the clinical significance of the safety events, and the rates of safety events between the device and medical management groups.

DR. PAGE: Thank you very much.

And I'll first ask for us to address Table 3a.

Dr. Yuh.

DR. YUH: So, you know, not diminishing the severity and impact of a cryptogenic stroke, but if you look at the numbers in a 4.5 or 4.2% serious adverse event rate in the study population, so that amounts to --

DR. PAGE: Which table are you --

DR. YUH: I'm looking -- I mean, 3a is the -- selected events.

DR. PAGE: Okay.

DR. YUH: But in the totality of the SAEs, these are a sampling of the SAEs, obviously. There's 21 of them. So then if you look at -- and correct me if I'm wrong, but the potential number of patients that have been helped, even under the best circumstances in terms of avoidance of stroke, is in the same range of about 16 to 24 patients, depending on how long you follow them out. You're asking a patient across the table to accept a 4.5% complication rate and SAE rate with an indefinite or uncertain benefit in terms of their risk reduction for stroke, and that gives me some pause. And that's not even counting the potentially heightened risk of atrial fibrillation and DVT.

DR. PAGE: Fair enough.

Mr. Frankel.

MR. FRANKEL: First of all, in terms of the short-term risk, the SAEs, like it was noted before, from what I understand, based on the data, all those actually will not affect the patient in the long term based on everything that was observed in that bracket. So my question is like this, towards -- if the neurologists on the Panel could address it. If you took the vantage point for a patient as a supplementary treatment, in other words, that you cover the base in terms of the device and you cover in terms of anticoagulants, would you feel more comfort in that respect, that you can tell a patient that, based on this data, that there's a likelihood of minimizing the risk from -- by taking both approaches?

Now, I know that, from listening to the patients that testified, there is a strong interest to be able to get off the anticoagulants, and that seems to be a big motivator that attracts people to the device, but looking at the data and the risks that were seen, it seems that if the source of the cryptogenic strokes are from multiple sources and that the device can cover one aspect of that and the medical therapy can cover other aspects; is there a benefit to be viewed in that line?

DR. PAGE: So do one of the neurologists want to try to respond to that question briefly?

DR. CHATURVEDI: Well, first of all, I just want --

DR. PAGE: Dr. Chaturvedi.

DR. CHATURVEDI: Yeah, I just want to sort of dispel the notion of lifelong anticoagulation because, I mean, that certainly wasn't part of the protocol, and it's not part

of the AHA/ASA guidelines that we mentioned before, and so for example, the guidelines mention that for patients with a PFO or stroke, PFO and stroke, antiplatelets are recommended, and we commented that we don't have the ideal data to know whether the anticoagulants are superior, but at least in the PICSS study published several years ago, there was no difference. And so I just think that the -- tossing around the idea of lifelong anticoagulation versus device is a bit misleading.

DR. PAGE: And it could be pointed out that the vast majority of the device patients were receiving anticoagulation. Would you agree? What is the percentage of patients in the device arm receiving anticoagulation? Let's go back to that, FDA, if you can find that for us.

DR. CHATURVEDI: I believe they were talking about --

DR. PAGE: I think talking antiplatelet. I'm just describing what -- thank you. I'm referring to the fact that anticoagulation and antiplatelet are equivalent, considered equivalent, but one of those therapies was present in a vast majority of the device patients. Usually antiplatelet, correct?

DR. FURIE: I believe the figure that was given was over 95%.

DR. PAGE: And maybe if FDA can put together that slide for us just to remind ourselves what were the patients taking who received the device at their last follow-up.

I saw Dr. Brindis.

DR. BRINDIS: Though with the comment that Bram said I shouldn't -- it's two -- the registry is very different, patients enrolled in the registry are very different than the trial. On Table 32 of the Sponsor's handout, looking at adverse events related to the device, they

had very low adverse events related to implantation in terms of 0% vascular complications, zero device explantation, no tamponades, and 1.5% major bleeding. So I thought that was relatively assuring.

DR. PAGE: So can we agree, at least, that for Table 3a, the overall instance of device-related SAEs is relatively low? I'm looking around the committee, and I'm seeing nods. We can put up -- if FDA is trying to get that together, we can put up Table 3b, atrial arrhythmias.

Yes, Dr. Noonan.

DR. NOONAN: I note that the numbers in Table 3b are for the intention-to-treat group, so we have 499 subjects. I would be curious to know, for the past treated, the people who got the device, which I think was a number of 463, what was the rate of atrial fibrillation among only those patients? Because, of course, there were a certain number that didn't get the device. And Table -- my comments on 3c will be exactly the same because, again, we have the denominator of 499. But really, I'm sort of interested in the denominator of 463.

DR. PAGE: Yeah, you're raising an interesting question, aren't you, in terms of -- if we're looking at the as treated or the -- in terms of follow-up, should we be looking at whether there's a difference in these complications?

DR. NOONAN: That's a more relative question for device safety.

DR. PAGE: Right.

Yes, Dr. Drummond, did you -- are you ready to comment in terms of -- or either of you?

DR. FARB: Sure.

DR. PAGE: Dr. Farb.

DR. FARB: So the idea, I think, has been stated that this is a trial with device plus medical therapy versus medical therapy alone, in view of the fact that about 90% of the device patients were taking -- therapy throughout the trial, even though at 6 months it was at the discretion of the treating physician, so that's how it's laid out.

DR. PAGE: Okay, thank you. So what we're seeing is that 90% were actually taking either anticoagulants, or more frequently antithrombotic medication at follow-up.

Thank you.

Dr. Lincoff.

DR. LINCOFF: Looking at the atrial fibrillation rates, the -- I mean, I think it's important to make the distinction between events that are happening at the time of the procedure. I mean, we know that invasive coronary procedures often trigger A-fib, which is usually self-limited; to my knowledge, it's not particularly associated with an increased risk of downstream complications and doesn't necessarily signal that they're at risk for spontaneous paroxysmal atrial fibrillation over the course of normal life. They have a wire in the atrium; it's not surprising. So -- and I don't remember the exact numbers, but my recollection was it was a fair proportion of these were acute intra-procedural that resolved over the course of the day or so afterward, so I think these are inflated. I mean, if they were real in terms of paroxysmal A-fib in the follow-up, that would be concerning.

DR. PAGE: So you raise an important question. I don't know whether the Sponsor has available -- I don't remember seeing in the sponsor packet an analysis of two questions

with regard to atrial fibrillation. One is in the as-treated comparison, whether that is available, and also the -- if you could remind us of the timing of the atrial fibrillation as to whether it's periprocedural or whether we're seeing a signal over a longer period of time.

Dr. Carlson, do you think you might be able to respond to that in a few minutes, or do you have some answer now?

DR. CARLSON: Where's my -- I don't have the magic pad. Can you put it up? Oh, it's up. Okay, this is one of the core slides that we presented and shows that there were seven patients and seven atrial fibrillation events that occurred during the procedure or in the time prior to discharge, in the first hours. And if you look at the post-procedural episodes of atrial fibrillation in the device treatment arm and compare them to the rate, compare the rates in the device arm to the medical management arm, they're very similar.

DR. PAGE: This is very helpful. My impression is that we're not seeing a strong signal in terms of 3b. Anybody showing great concern with regard to that?

(No response.)

DR. PAGE: All right. I'm going to move on to Table 3c. And this is the discussion, relates to discussion that we've had. The Sponsor provided us a picture of the timing of the DVT events. I'm interested in the Panel's perspective on clinical significance of the safety events, specifically with regard to DVT or PE. Looking for someone to make some comment.

Thank you, Dr. Kandzari.

DR. KANDZARI: Sure. And although we've -- has appropriately stated, that this is a trial of device plus medical management versus medical management alone, and although we've heard that 90-plus percent of the patients in the device cohort were on antithrombin

or antiplatelet therapy during follow-up, there was a change in the management of these patients with regard to their oral antithrombotic or antiplatelet therapy, and specifically there was a marked decrease from baseline to follow-up in the device cohort of the patients who are treated with oral anticoagulation. And I think this is salient because when we think about the patient and advocate presentations in our public session today, in many instances a theme was directed towards this device therapy as an alternative to anticoagulation or to antithrombotic therapies. And in many instances, this trial tells us that independent of the device, changing the therapy for some of these patients perhaps was associated with increased hazard. I don't think it's related to the device per se. I think it might, perhaps, be related to changing these patients who might be, for other indications, deserving of antithrombin therapy and removing it from them and resulting in these sequelae.

DR. PAGE: Thank you for pointing that out.

Dr. Laskey.

DR. LASKEY: I would agree with that, and I think, to further muddy what may be clean waters, there is, perhaps, a subgroup of patients who have, shall we say, a thrombogenic substrate? So sort of competing risk here. If you close the hole, then the PA has this -- becomes the route of alternative embolization. So these are people inherently at risk of clotting, which we've discussed. It's a theme that runs throughout this whole area, that there is a group of maybe 15%, 20%, who are inherently higher clotters, and maybe that's what we're seeing here. It might not have anything to do with instrumentation. But I wonder if there is a group at higher risk and you eliminate competing risk analysis, you eliminate one of those risks but you expose the other by doing so.

DR. PAGE: All right. And the Sponsor made the point that anticoagulation was discontinued in patients with a history of DVT and PE. I'm interested in the Panel as to whether you have any comment as to the Sponsor's assertion that full anticoagulation, if it's already going to be there for DVT PE, whether we feel comfortable that a device should be put in place in those patients who are already to lifelong anticoagulation with warfarin.

Dr. Furie.

DR. FURIE: There still might be a role --

DR. PAGE: Say again?

DR. FURIE: There still might be a role for considering PFO occlusion, given that maintaining patients in the therapeutic range is challenging, and so I can envision a discussion with a patient who opts to continue both the anticoagulation for venous thromboembolism but is concerned potentially about risk when the INR falls into subtherapeutic range and they choose to do both basically.

DR. PAGE: Thank you. I'm going to put you on the spot further in terms of antithrombotic therapy. We've seen that 90% of the patients with the device had antithrombotic therapy. Should that be part of the protocol? Because it's -- we've had discussions of drug or device, but the fact is 90% of the patients with the device were taking a drug. Would you see that as being an expectation or a requirement in terms of patients if they were to have this device put in place?

DR. FURIE: Well, I don't know that there's enough evidence to say that everyone should remain on antithrombotic indefinitely, but certainly during the subacute period early on, it seems like common sense. You know, with very young people who don't have any

other potential risk, committing someone to lifelong aspirin is not without risk of hemorrhagic complications either.

DR. PAGE: Mr. Frankel, I see your hand, but I need to keep asking the Panel about scientific questions. I'm not ignoring you, I promise. Others have a comment as to whether if your patient were -- or if you were going to approve this device, whether it should be recommended that the device have antithrombotic therapy?

Thank you, Dr. Noonan.

DR. DEHMER: Well --

DR. PAGE: Dr. Dehmer, excuse me.

DR. DEHMER: It's a little bit like the argument that we heard earlier about as patients get above the age of 60, there's all sorts of other reasons that they have a stroke. In this case, as patients get older, there may be other reasons that they need to be on antithrombotic therapy. It's for their coronary disease or for something else, so there may be this similar transition from being on antithrombotic therapy because you had a device put in to being on antithrombotic therapy, you know, if you want to lower your colon cancer or you have coronary disease.

DR. PAGE: So no takers in terms of the issue of antithrombotic therapy.

Dr. Brinker.

DR. BRINKER: Well, since the only data we have is overwhelmingly in the device group on patients who had continued at least antiplatelet therapy, there should, at the very least, be a statement in the instructions for use that over 90% of the patients were on antiplatelet or antithrombotic -- anticoagulants.

DR. PAGE: Thank you.

Dr. Zuckerman.

DR. ZUCKERMAN: Yeah. There you go, Dr. Brinker. When we look at the current sponsor's label, they just indicate that patients were instructed to take aspirin for 6 months after device implantation, but usually in a controversial setting like this, we describe what actually happened in the clinical trial. We heard a good discussion as to why we should include those data in the label.

DR. PAGE: And that's what I was driving at.

Dr. Noonan.

DR. NOONAN: Given that the Sponsor has shown us a slide in which most of these events seem to happen on the ipsilateral side of access, perhaps the Sponsor can come up with the means to reduce that incidence either by changing device profiles or recommending that certain things not be done in achieving hemostasis. Perhaps those are ways to solve some of this problem.

DR. PAGE: I'm sorry, I had to -- I was looking at something in my paperwork. Can you say what you just said again, if you have any --

DR. NOONAN: Sure. The Sponsor presented a slide in which most of these events, I think better than half, that that's happened in the ipsilateral side of access. So perhaps there are methods to reduce the incidence of these events by changing device profile or perhaps recommending certain ways of achieving hemostasis in the groin or the axilla or the arm.

DR. PAGE: Thank you. And that's something that could be taken up from the

interventional cardiologists in terms of what's known.

Dr. Evans.

DR. EVANS: Not sure I completely understood the sort of dismissal or the -- about the atrial fibrillation. Maybe I can describe why. So, you know, a number of speakers have sort of urged us to think like patients. So if I'm the next patient coming in and we just saw the results from the trial, 16 versus 9 events, and you can calculate a number needed to treat, and then if you go back to Table 3b, you get 20 patients versus 9 with atrial fibrillation. You could also calculate a number --

DR. PAGE: Can we see 3b again, please?

DR. EVANS: You could also calculate a number needed to treat for that. Well, the number needed to treat for that is less than the number you'd need to treat in order to prevent a stroke. And then when you go to 3c and you calculate a number needed to treat in order to see if DVT or PE be considerably less than both of them. So if I'm the next patient in the trial and you're saying, well, we want to perhaps apply this to prevent a stroke, but you also have a higher probability of gaining an atrial fibrillation or DVT or PE than you do with preventing a stroke -- or am I misinterpreting?

DR. PAGE: I'm not going to tell you that you're misinterpreting at all.

Dr. Lincoff and then Dr. Slotwiner.

DR. LINCOFF: If you're counting, you're not misinterpreting. But these are not equivalent events. We can't weigh them. I mean, you could try to put a utility on each event, but the reality is that a periprocedural A-fib event, the patient may not even know what happened. And even A-fib spontaneously, they're not the same thing as a stroke.

We've heard from patient after patient and any of us who have dealt --

DR. EVANS: Sure.

DR. LINCOFF: -- with these patients and we've seen the data. A stroke is devastating. These, in general -- a pulmonary embolism can be, but these, in general, are not. And certainly a periprocedural A-fib may not even be perceivable.

DR. EVANS: Right. So in -- but in a disease that appears to be -- or an event that appears to be rare, still worth the risk?

DR. PAGE: I think you raise a very good question.

Dr. Slotwiner and then the patient Mr. Frankel.

DR. SLOTWINER: Thank you. I think the table's misleading. From the explanation we got from the Sponsor, I think those are primarily events that occur at the time of the procedure when we're placing wires inside the atrium. So it's very, very common to tickle the atrium and induce atrial fibrillation in anybody. And when you look at the longer-term numbers comparing the A-fib later on, it's equivalent in both groups. So I don't think that those A-fib episodes acutely have any --

DR. EVANS: Sort of seen as transient?

DR. SLOTWINER: Exactly.

DR. PAGE: Mr. Frankel.

MR. FRANKEL: First, just to that point, I think obviously any of us over here are individuals, but if I had to guess what most patients, at least, if it's indicative what the patient said today, is that if there was a very small possible margin, but a chance to be able to avoid a devastating stroke, I think that they'd be willing to take treatable adverse events

that could be controlled and they won't affect their life in an extraordinary way. My question, just, in terms of 10%, 90% we know were followed with anticoagulation until the end of the study. The 10% that were not, are we able to isolate any data from there in terms of to glean whether or not there was an increase, a disparity and risk, amongst that patient body, just that 10% alone?

DR. PAGE: I don't remember that number from the Sponsor's or the FDA's table, but I believe that that number could be arrived at looking at the individual events.

MR. FRANKEL: I just mean in terms of the 10% that did not continue on anticoagulation therapy. That 10% of the population, did they have an increase in events seen, as compared to the 90% that did not have to have anticoagulation therapy after 6 months but did?

DR. PAGE: I'm going to ask Dr. Carlson if you're able to answer briefly the issues that we've raised in terms of the adverse events. The A-fib, whether we have any data with regard to the device in place and likewise whether you can -- your group can tell us any information about those who were not -- whether we're seeing the events in patients who were not on -- not receiving antithrombotic or anticoagulant therapy, recognizing these are small numbers. If that's easily available, we'll have you come to the lectern; otherwise, we'll keep going.

Dr. Carlson.

(Off microphone comment.)

DR. PAGE: I understand if you can't generate the numbers right now.

DR. CARLSON: I don't think I have it. I've got medications within 1 week prior to

stroke. I'm not sure this is going to address your question.

(Off microphone comment.)

DR. CARLSON: Yeah, it does a little bit. Can you put it up? This doesn't maybe get directly at it, but there were patients here you can see who were not taking any medication or missed doses, in both arms.

DR. PAGE: Okay.

DR. CARLSON: During the week prior to their stroke.

DR. PAGE: I don't know what to make of that one way or the other.

DR. CARLSON: I'm not sure what to make of it.

DR. PAGE: Okay. Thank you very much.

Dr. Zuckerman, I'm going to try to summarize with regard to Question 3. It's acknowledged that the overall procedural adverse event rates were relatively low, but any complication is raised as an issue. It needs to be balanced to potential benefit, as was pointed out. In terms of the atrial fibrillation, the signal does not appear to be strong in terms of long-term atrial fibrillation, but the transient, typically non-persistent procedural atrial fibrillation is not as troubling to the group.

With regard to the Table 3c, there is a signal here that causes some concern. There is consensus that anticoagulation would need to be maintained typically with warfarin and in the patients who have a history of a DVT or PE certainly. And beyond that, perhaps there are issues that could be addressed at the site because some of these venous thromboses were more frequently on the ipsilateral side of the puncture, and that probably could be looked at. This is a common procedural issue that could be looked at in perhaps other

databases. Do you have any further needs from us with regard to Question 3?

DR. ZUCKERMAN: No, I think you and the Panel have put the safety data into a good perspective.

DR. PAGE: Thank you very much.

I'll now ask Dr. Drummond to read Question No. 4.

DR. DRUMMOND: Complete PFO closure assessed by TEE and bubble study was a pre-specified secondary endpoint. Table 4 shows the rates of complete PFO closure (shunt grade 0 at rest and grade 0 during Valsalva) and effective PFO closure (shunt grade 0 or 1 at rest and grade 0 or 1 with Valsalva) in subjects implanted with the device and assessed by the Echo Core Lab. Complete PFO closure assessed by TEE and bubble study was a pre-specified secondary endpoint.

Among 349 device subjects with a Core Lab-assessed PFO shunt assessment at 6 months, 249 patients had a grade 0 shunt both at rest and with Valsalva, corresponding to a complete PFO closure rate of 71.3%. Therefore, residual shunting across the PFO was common, occurring in 28.7% of assessed subjects. It should be noted PFO closure assessment of the 6-month TEE by the Echo Core Lab was incomplete or not available in approximately 25% of subjects implanted with the device.

Please comment on the rate of PFO closure by the device.

DR. PAGE: Thank you very much.

I'm looking for comments from the Panel with regard to concerns about PFO closure, what it means to be complete, effective.

Dr. Borer.

DR. BORER: Okay. Of course, from these data, we don't know the answer to the question, but in order for a blood clot, if it exists, to be likely to cross a PFO, the flow across the PFO is the determining factor, the likelihood of a paradoxical embolism, must be proportional to the flow across the PFO. Therefore, I would say that the more complete the closure, the more likely you're going to avoid the problem you're trying to avoid. Having said that, of course, we don't really know the dose of PFO closure that causes -- that reduces risk. That wasn't studied; we don't know it. But we do know that even with total PFO closure, you don't eliminate risk of stroke, may not be due to paradoxical embolism. Those four patients that I asked about, none of them was over 60; one of them had lupus, probably shouldn't have been involved in the trial, but the other three had strokes even though the PFO was totally closed.

So I think that it may well be that with only 75% of the data available, we don't even know what the true PFO closure rate was because 25% of the data aren't available to us, but knowing that approximately 90% of those who could be studied had pretty good closure of the PFO, not complete, but pretty good, often complete, that probably reduces the risk of paradoxical embolization in an important way. Now, those are a lot of assumptions, and none of them is provable. But I don't think we can go any further than that. We just don't have any other data.

DR. PAGE: Fair enough.

Dr. Slotwiner.

DR. SLOTWINER: I agree with Dr. Borer. I believe the Sponsor told us that amongst the patients with the device who had strokes, none of them had any flow across the -- I

think those were all closed, I think they had mentioned that. So it's just the 25% that we don't know about. But I agree, it's proportional to flow, so I think it would probably reduce the risk.

DR. PAGE: Other comments about this?

(No response.)

DR. PAGE: Dr. Zuckerman, I'll take a stab at this. First of all, 25% are missing; on the other hand, we have to acknowledge that 75% of the patients came back for TEE, which I think is a fairly good sampling, assuming there's not a systematic reason for those 25% not to be available. The issue of whether zero bubbles or very few bubbles are going to be passing is one that I don't think we know the answer to, but it seems at least logical to -- some of the Panel, and I'm interested if others want to contradict, that getting rid of nearly all of the flow would be of benefit.

I saw Dr. Carlson wishing to address the lectern, and did you have a clarifying --

DR. CARLSON: A minor clarifying comment. Ninety-five percent of the patients had a TEE. There were an additional 20%, I think it was, who had the TEE, but the core lab said that either one or the other, the rest or the Valsalva or both, were inadequate.

DR. PAGE: Thank you for that clarification. So --

DR. CARLSON: Okay. If that changes your opinion, at least it might change your opinion about the conduct of the trial.

DR. PAGE: Ninety-five percent is even more remarkable. Thank you for that clarification.

Dr. Zuckerman, have we adequately discussed the PFO issue? I think the

assumption, without any real proof, is that the -- if the device is working, it's because it's working by blocking flow across the PFO, and the assumption is that blocking nearly all of it may be satisfactory, but we don't really know the answer to that.

DR. ZUCKERMAN: Yeah. I think this is a realistic way to look at things. If I could though quickly ask Dr. Carroll, you've had a lot of the experience, and currently the label says just use angiography and echo in the cath lab to try to get the best closure possible. After 10,000 St. Jude implants, are there any other tips and tricks that should be in the training program to help get the best closure possible? We can work offline with you and the Sponsor, but --

DR. CARROLL: I think that's a reasonable assumption because we have learned there are some anatomies that are more challenging than the other, in some ways, of potentially placing the device that may be more efficacious than that. But parenthetically, the main issue is 6 months, we've learned, is too early to look at the issue of complete closure, and that's been shown through multiple studies around the world, and it takes longer for the degree of closure to arrive at its final destination. So two things: we could do a better job intra-procedurally, I think, and we can assess it later.

DR. ZUCKERMAN: Great. So the Agency can work offline with the Sponsor on that point.

DR. PAGE: Thank you very much.

I'll now ask Dr. Drummond to read Question 5.

DR. DRUMMOND: The Sponsor proposed the following Indications for Use: "The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent

foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to presumed paradoxical embolism."

Please comment on this Indications for Use statement.

DR. PAGE: I'm looking for comments as to the appropriateness of this indication. This is the only indication that we're voting on. Is that correct, Dr. Zuckerman?

DR. ZUCKERMAN: It is.

DR. PAGE: So we -- I now need to hear whether, if you were writing this hypothetically, whether this is the way you would write the indications for this device.

Dr. Chaturvedi.

DR. CHATURVEDI: Yeah, I think even if you had a group of neurologists, there would be a debate about what constitutes a cryptogenic stroke, and so I think in the real world this is going to have considerable uncertainty, and so I would try to add greater specificity by saying -- using terminology such as after satisfactory exclusion of other causes of stroke, such as atrial fibrillation and atherosclerosis.

DR. PAGE: Very good point. And that could be either in the indication or in the package insert to give advice as to -- may I suggest, perhaps, among the things that we would do now as opposed to 15 years ago would be to do a long-term monitor looking for atrial fibrillation?

DR. CHATURVEDI: Yes, I would agree with that.

DR. PAGE: Dr. Slotwiner.

DR. SLOTWINER: I think that -- or at least we need to comment on the associated antiplatelet therapy that most of the patients in the trial received.

DR. PAGE: So you would want it in the indication or -- we'll be talking about the package insert in terms of --

DR. SLOTWINER: Well, I mean, it could --

DR. PAGE: I guess the issue is are you able -- with that being silent, do you feel that this is an adequate indication?

DR. SLOTWINER: I don't think the study looked at that, so I would have a problem with that.

DR. PAGE: Thank you.

Other comments?

(No response.)

DR. PAGE: Does anybody want to comment on whether age, if we're talking about how the study was conducted, whether age should be considered given the fact that this -- our pivotal study is 18- to 60-year-olds or is that -- are we talking biological age or leave that to the practitioner?

Yes, Dr. Borer. And then Dr. Brinker.

DR. BORER: Yeah, I think that these are all very important issues, and they should be in the label. But the indication, if we put too much in the indication, I think we will create confusion. I think the indication as it's written is okay; in the label itself, exclusions, inclusions, definitions of cryptogenic stroke, whatever, really should be in the label but not necessarily in the indication.

DR. PAGE: Fair enough. Dr. Brinker, is -- that answered your comment. And I'm seeing Dr. Yuh nod. And again -- yes. Dr. Posner, our Patient Representative.

DR. POSNER: Just from a patient's point of view. If I saw an insert that said presumed paradoxical embolism, that's a terrible word, "presumed." I want to know why, since we're already debating about the definition of cryptogenic. But a presumed paradoxical incident, if somebody's really hot to put one of these in, they're going to presume it was paradoxical.

DR. PAGE: I think the sad state of affairs is that may be the best we can do in terms of saying what the mechanism is.

Other comments with regard to this label indication?

(No response.)

DR. PAGE: So, Dr. Zuckerman, the Panel generally feels that -- and without saying whether they're voting in favor or not, that as the proposed indication for use as written seems appropriate, although the labeling would need to address the population that was actually studied and how the trial was conducted, issues being mentioned including anticoagulation issues and age perhaps and finally the issue of, as Dr. Posner mentions, the issue of presumption of the etiology. There are ways to pin this down better than there were available 15 years ago, at least in terms of cryptogenic stroke due to silent atrial fibrillation, but that would certainly need to be discussed in the package insert.

Dr. Brinker, did you have a question?

DR. BRINKER: Yeah. So this has to be a diagnosis of exclusion because there's no way to know that a given clot went through that if you're not visualizing in real time.

DR. PAGE: The point is well made. It is a diagnosis of exclusion, but perhaps the exclusion procedure could be done better now than it was during the time of the trial.

Dr. Zuckerman, does this adequately answer your question?

DR. ZUCKERMAN: Yes, but I have one follow-up question to Dr. Chaturvedi and Dr. Brinker. I think we've heard that we want to be very specific and exact in the diagnosis of cryptogenic stroke, and there are a whole range of factors. And similar to what we've done recently with the TAVR labeling, we've recommended that a certain team be a part of this evaluation, and here would it be perhaps better just to say that this evaluation should be done by a neurocardiac team with sufficient expertise, instead of listing every point such that we're sure we have a neurologist, an excellent neurologist involved in this evaluation?

DR. CHATURVEDI: Yes, Dr. Chaturvedi.

I would recommend the terminology that I mentioned before, after a satisfactory exclusion of other stroke etiologies such as atrial fibrillation and atherosclerosis, and then if you wanted to add somewhere else that these determinations should be made by a team experienced and consisting of neurology and cardiology expertise, I think that would be desirable.

DR. PAGE: Mr. Frankel, do you have a brief comment?

MR. FRANKEL: Just on the wording, "to prevent recurrent." Would it be perhaps more realistic, based on the data we have, "to decrease risk of" rather than "to prevent"?

DR. PAGE: We'll ask FDA to take that into consideration.

Moving on to labeling, I'm going to put forth, Dr. Zuckerman, that we've just been discussing labeling, and beyond that, unless I see any need from the Panel to further discuss labeling, I think we've given you some input. Is that satisfactory?

DR. ZUCKERMAN: Yes, it is.

DR. PAGE: Great. So we're moving on to Question 7.

Dr. Drummond, would you please read Question 7?

DR. DRUMMOND: Stroke can be a devastating clinical event for patients and families and has large public health implications. There are approximately 800,000 new or recurrent strokes per year in the U.S., of which 87% (or approximately 696,000) are ischemic strokes. It has been estimated that 25% of ischemic strokes (or approximately 174,000) are cryptogenic. PFO is a very common finding in the general population (present in approximately 25% of individuals). Therefore, it would be expected that many patients with cryptogenic ischemic stroke would be potential candidates for PFO closure.

The Sponsor has presented data from the RESPECT trial, including an initial PMA data lock and an extended follow-up data lock. There were relatively few primary endpoint events (42 in total) in a trial that enrolled 980 subjects with the vast majority of subjects followed for at least 4 to 5 years. The low number of recurrent strokes and the small event rate differences between treatment groups (0.65 per 100 patient years in the device group vs. 1.01 per 100 years in the medical management group in the extended follow-up ITT analysis) suggests that many patients could be potential candidates for an invasive cardiac procedure to implant a permanent device to prevent a relatively uncommon event (vs. medical therapy alone). There was no particular patient subgroup identified for whom there is strong evidence for an enhanced benefit associated with implantation of the device.

Based on the data presented from the RESPECT trial, do the probable benefits of the AMPLATZER device outweigh the probable risk? In answering this question, please

comment on the topics on the next slide:

a. Whether the results of the RESPECT trial support an important role of the presence of a PFO in the pathophysiology of cryptogenic ischemic stroke.
b. Whether the results of the RESPECT trial provides compelling evidence that the device provides a clinically meaningful reduction in the risk of recurrent ischemic stroke vs. medical therapy.
c. Whether the safety profile of the device implantation procedure and the device itself are acceptable in the context of the estimated reduction in the risk of recurrent ischemic stroke.

DR. PAGE: Thank you very much. I'm going to suggest that we really take Questions (a) and (b) together because if -- I think they're inexorably intertwined. I'm looking for someone to come out and tell me whether they are finding compelling evidence that cryptogenic stroke is (a) due to a PFO in many cases and (b) is meaningfully reduced in the RESPECT trial.

Dr. Hirshfeld.

DR. HIRSHFELD: I think the preponderance of what we've seen today would call for different modifiers, changing important to modest, and changing compelling to moderate, and changing clinically meaningful to modest.

DR. PAGE: But that would -- given this question, if you're saying it's modest and not meaningful, then are you saying it's not meaningful? Not to put you on the spot, Dr. Hirshfeld.

DR. HIRSHFELD: Yes. Well, we're getting into semantics here. I think the

statements, as written, overstate the value and efficacy of the device, and so I think that the statements could be focused to more properly reflect what we've learned about what this device is able to do if the modifiers are less emphatic.

DR. PAGE: Fair enough. Thank you very much.

Dr. Laskey.

DR. LASKEY: And I hate to use the "s" word, but to bring statistics in --

DR. PAGE: Which one?

DR. LASKEY: There is an uncertainty about this. I think uncertain instead of modest, and I think it acknowledges that there's a benefit, but it's of uncertain magnitude.

DR. PAGE: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: Yeah. I mean, to take this, we would have to ignore our answers in our discussion to the previous questions, wouldn't we, in terms of effectiveness and statistical significance and clinical meaningfulness and so forth? Isn't that being reflected in this question?

DR. PAGE: So in terms of Question (b), you would say no?

DR. D'AGOSTINO: Yeah.

DR. PAGE: Thank you.

Other comments, please.

Dr. Lincoff.

DR. LINCOFF: I have no problem with clinically meaningful because I think even a small reduction is, in this endpoint, is important. I realize we have to work with the

question we have; my only problem is "compelling" because I think we're working hard to extract a signal from the data that we have, so -- yeah. I guess, strictly speaking, I would call this no, but I call it no on the basis of the "compelling," the nature of the evidence.

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: I might share a bit of a different perspective. I think that the device certainly does not exclude the risk of stroke, as we've learned from this trial. Neither does oral anticoagulation in other settings, like atrial fibrillation, but it may reduce it. And secondly, this -- the use of this device, I think, importantly, also, for many patients at least, doesn't translate to the exclusion of antithrombotic or antiplatelet therapy. That said, however, we have to deal with what we have; we've said this many times today. This is a trial that took 8 years to enroll; I don't think we'll see another randomized trial like this in this indication, at least in the near term. And it was statistically underpowered for what the event rates turned out to be.

And that said, however, I think there's a directional change towards what I mentioned earlier of reduction and unexplained stroke and at least, by the best standards and the criteria we could apply in the context of this trial, it was about a 50% reduction over a long -- over the extended follow-up cohorts in reduction of unexplained stroke. And I think that the difference of about 10 events, as Dr. Lincoff said, is clinically meaningful independent of statistical significance.

DR. PAGE: Yes, Dr. Chaturvedi.

DR. CHATURVEDI: Yeah. In formulating my answers to this, I sort of conceptualized

a three-legged stool, and so the first leg is how well are the patients characterized at baseline, and I would contend that they weren't that well characterized because only 13 to 16% had Holter monitor; the vast majority were enrolled with ECG only.

The second leg is how well were the follow-up events characterized, and are we sure that the follow-up events are due to paradoxical emboli. And once again, I would contend that the follow-up events were not that well characterized, and from what we've heard today, I think at least 8 out of 24 events in the medical arm, which is one-third, are due to alternative mechanisms other than paradoxical emboli.

And then the third leg is does the overall trial have statistical integrity? And there I would echo the points raised by Dr. Evans about concern about the high level of lost to follow-up and patient withdrawals. And so at the extended follow-up period, there were 42 outcome events and 218 withdrawals, which is a ratio of over 5 to 1 withdrawals compared to follow-up events, and I find that deeply troubling. And so I would say that all three legs of the stool are very shaky.

DR. PAGE: So you are leaning toward answering no?

DR. CHATURVEDI: Yeah, I would answer no for (a) and (b).

DR. PAGE: Okay, thank you.

Other comments?

(No response.)

DR. PAGE: Dr. Zuckerman, can you clarify something for me? I think we all recognize, frankly, the heroic nature of conducting this trial and how much work has gone into it. We are faced with a single indication that I'm hearing some concern about, and I

don't know which way it would go, but hypothetically, if this were -- is this -- what would happen following if this were a negative vote? Would there be opportunity to hone the indications for use in a way, working between you and the Sponsor, so that this would be available, because there are compelling reasons for this to be available in certain populations at the very least? And again, I'm not tipping toward one outcome or another. I just want to be clear on -- you've been very clear, we have to vote on this indication as written, but I think among us, whether we're -- we agree with this indication, I think there is likely consensus that there is use for this device.

DR. ZUCKERMAN: Yes. Thank you, Dr. Page. I think we all have to remember that the science of clinical trials is evolving dynamically, and what was considered a good clinical trial design 15 years ago may not be in the bailiwick right now. So certainly the Agency is not going to throw the baby out with the bathwater, as suggested by Dr. Kandzari and others. And, you know, if this is not -- is judged not an appropriate indication, then I think there's further work that the Agency, Sponsor, and members of this Panel would be asked to do. However, before we get to that point, it's very important that we try to answer, as fully as possible, the questions that the Agency is asking today for the assigned indication, and I do want to underline that.

And that's why I want to go back to Dr. Kandzari's statements, as well as Dr. Hirshfeld. I think we've certainly learned from even the limitations of this clinical trial, if I'm interpreting Drs. Hirshfeld and Kandzari correctly, that putting in a device in a PFO in the right patient population can decrease the risk of subsequent stroke. It's not going to completely decrease the risk, but there is a risk reduction. We can't give you the certainty

of a statistical p-value today for obvious reasons, but I do want to hear from the other clinicians around the Panel, given that, you know, today you saw an echo with a thrombus crossing a PFO. We know that there's a certain risk for crossing from right to left; it's not going to happen in every patient. But we need to really hear about, given the whole spectrum of data in the literature, what can we say about (a) and (b)?

DR. PAGE: Thank you for that clarification.

Dr. Kouchoukos.

(Off microphone comment.)

DR. PAGE: Please turn on your microphone.

DR. KOUCHOUKOS: This is a very relevant issue because there are other options to deal with this particular problem. One is surgical closure. And I certainly have seen several cases such as the one that was showing the echocardiogram where these huge embolus, long strings of plaque are sitting in the orifice of the atrial septum or part of it has already gone to the brain. And there are other devices, correct me if I'm wrong, that are being used to close these defects now that are either off label, maybe the device is for closure of atrial septum defects. So there are other ways that these defects will be treated if this kind of a device is not made available. And there is, to my understanding, no other device available currently for closure of PFOs for this particular indication.

DR. PAGE: I'm not sure how we can comment on off-label use of other devices.

Dr. Zuckerman --

DR. ZUCKERMAN: I think that's the appropriate comment. We would like to deal with the data here today being presented, both the RESPECT trial data and the literature, to

see if this is an approvable device for the current indication. We'll deal with off-label use at a different time.

DR. PAGE: Thank you.

Dr. Furie.

DR. FURIE: I just wanted to respond to Dr. Zuckerman's comments. The first is that the upper boundary of the confidence interval does allow that intervention is potentially harmful, so it's not all on the benefit side based on the point estimate. But I also acknowledge that there is a population of patients for whom -- paradoxical embolism, because of PFO, is the likely mechanism and for whom this intervention may be beneficial. So the challenge is trying to prove that in the context of a clinical trial, and it may just be impossible to do.

DR. PAGE: Yes, Dr. Zuckerman.

And, Dr. Kouchoukos, can you turn off your microphone, please? Thank you.

DR. ZUCKERMAN: Okay. Dr. Furie, your comments have really been excellent today and reminding us that there's potential risk with this device and therapy that we always need to be cognizant of. Especially, I think you've been cautioning us that in any post-approval period, when the device becomes more generalizable, one usually sees more problems that are unintended. All I can say is that we need to make a decision on the data here today, but the Agency would be, if it does go forward, would be very cognizant of what could happen in the post-approval period and would call upon you and others to help us with those sorts of decisions. But I would ask you to comment on the current data here.

DR. PAGE: Thank you.

Dr. Lincoff.

DR. LINCOFF: I just want to comment. We've morphed somewhat the conversation from these two questions to whether or not the indication is -- or if a different indication would be more supportive. And I just wanted to say that I think the indication is correct. You know, to the best of -- this trial was a pragmatic trial, and that's what's going to happen in practice, to the extent that you can identify a group of patients that are likely to have had or have a good chance of having had an embolism by this mechanism. I think that's the best you can do in clinical practice.

Now, our tools get better every year, so now we have the patch that we can monitor for A-fib and that will continue to evolve, but I just -- from my standpoint, I don't see a better indication. I think that all our consideration should be on this, not that well, we may turn it down for this but there would be another indication, because I don't think in practical life there is a better way to make that indication. You use all the tools we have available to us to identify or rule out patients who have another more likely cause.

DR. PAGE: Dr. Slotwiner and then Dr. Brinker.

DR. SLOTWINER: I just wanted to echo exactly the same sentiment. I think there is an indication here. The degree of benefit, I think, may be over-expressed in the statements as written, but I think it's going to be impossible to do another clinical trial like this, and I think it has a role.

DR. PAGE: And you're echoing who now? Dr. Lincoff or --

DR. SLOTWINER: Dr. Hirshfeld.

DR. PAGE: Dr. Hirshfeld.

DR. SLOTWINER: And Dr. Lincoff.

DR. PAGE: Okay. Thank you.

Dr. Brinker.

DR. BRINKER: I'd like to air my thoughts in concert with all this. I think that we were doing pretty well until we reached this Question 7, and I think we were confronted with semantic issues: the term "important," the term "compelling," and I think that we could say it does play a role, it does support a role for PFO in the pathophysiology of cryptogenic ischemic stroke. Just the very fact that we're accepting a difference.

DR. PAGE: Yeah, we're accepting part (a). The issue is (b).

DR. BRINKER: Okay. So part (b), if you take out "compelling," and I think we're there.

DR. PAGE: So you think it's there, but it's just not compelling?

DR. BRINKER: Yeah. I think the term makes it sound like it's overwhelming evidence, statistical evidence.

DR. PAGE: So what you're saying is it's not overwhelming, it's not compelling, but it's satisfactory in your mind?

DR. BRINKER: Yes.

DR. PAGE: Thank you.

I'd like to move on to the safety profile.

Yes, Dr. D'Agostino.

DR. D'AGOSTINO: Yeah, Ralph D'Agostino.

What makes it -- even with "compelling" taken out, we don't have any solid data; we

have a lot of feeling for the data, but it's all in my stomach looks good as opposed to any kind of --

DR. PAGE: I think you ask a very good question. So you're asking those who are -- find this not compelling but satisfactory when you're not seeing satisfactory evidence of meaningful --

DR. D'AGOSTINO: Well, I don't know how to judge satisfactory from compelling and so forth. I mean, if the p-value was 0.01 and the event rate was -- or if the sample size was 1 million or something like that and they had a huge number of events, that would be compelling. We have a reasonable size study, but very small number of events and we see flip-flopping in terms of the statistical significance and even in terms of clinical implications on what makes -- you know, what leads us to this positive aspect? Are we being led by the questions, or is it something that was really going on?

DR. PAGE: Yes, Dr. Laskey.

DR. LASKEY: So with all due respect, you know, we're beyond the numbers here. I think we're all at the gut level. Did you say something about your stomach? And I think the question, the next question, if I were the Panel chair, and I was --

(Laughter.)

DR. LASKEY: -- you have six interventionalists here, would be to ask each of the six of us how did you feel when you were doing your next PFO closure, because that's what we're going to come down to, and that may be the most helpful, concrete, pragmatic conclusion to whether we think that there's a benefit here.

DR. PAGE: Well, I'm happy to have all the interventionalists speak, but I also think

it's important that the neurologists and the statisticians have a voice because our medical history is littered with doing a lot of things by specialists who we believe are doing the right thing, but we're -- especially as we're considering whether this device is both safe and effective for the indication as put forward, it can't be the stomach, it's got to be the brain. So I'm happy to hear the interventionalists, but I think the interventionalists need to listen to the neurologists and the statisticians and vice versa.

So Dr. Brindis.

DR. BRINDIS: Thanks. So I am convinced that there is a role for this device in certain selected patients. The trouble I have is trying -- is our ability to select the proper patients and when -- if and when the device gets approved, how it would be applied in clinical practice is my major concern in terms of numerator-denominator issues, appreciating that there are patients that would benefit with this device.

DR. PAGE: Are you worried that there are patients, for the indication, that would not benefit, and as such you're concerned about the indication and want to wish that you could narrow it?

DR. BRINDIS: Yes.

DR. PAGE: Okay.

Dr. Borer.

DR. BORER: Yeah, as I said earlier, I agree completely with Ralph about the primary issue, it being the selection of patients. But I think the indication is fine if you accept the fact that the FDA will make its best effort to put all kinds of information into the label to make the selection of patients who are likely to have paradoxical embolism as the cause of

their stroke much more rigorous than it was in the trial. I think they'll do that, and therefore I think that the indication is fine, and with better patient selection there will be a benefit for most patients.

DR. PAGE: Well, I need clarity from Dr. Zuckerman on this matter.

Dr. Zuckerman, the -- I'm hearing, I believe, a plurality, if a not a majority, that think this device should be available but believe it needs to be selected in a way that's less broad than the indication. That being said, we have two ways to go at that, and in terms of FDA, if we vote as a Panel in favor of that broad indication, is FDA able to narrow that, or contrarily, if we voted against this specific indication, would FDA then be able to work with the Sponsor to adequately narrow the indications to where I think this Panel is leaning? I see Dr. Borer. I'm interested in Dr. Zuckerman's charge to us.

DR. ZUCKERMAN: Yeah. Thanks for that very good question, Dr. Page. The rules of this Panel are that there's one vote at the end today where we vote on a specific indication. However, what's really important at this panel meeting is for the discussion that's ongoing right now. The vote may be yea, nay, or totally tied; that's immaterial. What the Agency needs is the best clinical-statistical discussion on what the data need, what the data mean, what would be preferable to this Panel, such that both the Sponsor and FDA get optimal guidance. So I would encourage you, Dr. Page, to continue with this very rich discussion.

DR. PAGE: As we shall.

Dr. Borer and Dr. D'Agostino.

DR. BORER: Yeah. Again, I don't think there's a problem with the indication. The indication says that this should be available and used for patients who have a cryptogenic

stroke due to a presumed paradoxical embolism. I think that's fine; that is the indication. The issue then becomes who is it that has a cryptogenic stroke due to a presumed paradoxical embolism? And that's a matter of making rigorous criteria that have to go into a label. And, you know, we may not be able to rewrite a label down here today, but I think that is what the FDA is going to have to do, and if that's done, I think the indication is fine.

DR. PAGE: Thank you.

Dr. D'Agostino and then Dr. Noonan.

DR. D'AGOSTINO: Yeah, Ralph D'Agostino.

I think where this conversation's heading, and one of the individuals making the comments earlier in the open public hearing raised it, is we're looking at a test of superiority. The data that's before us is, is this procedure, is the device better than medical? Basically, we said they're equal, and we're looking for rejecting for that, that somehow or other we've exceeded the medical. The discussion we're having right now is that it didn't statistically beat out the medical, but is there a lot going on with it that there's a population that we should be suggesting to the FDA that they really pursue and so forth?

So, in some sense, if I hear it correctly, we're abandoning the rigor of the statistics for superiority and the tests were based -- was it better than the medical? It isn't. We have data that it's better than medical, but now we're pulling out that it does have meaning and usefulness to it, and how does that shape up? Am I missing what's going on here in terms of how the question is --

DR. PAGE: Well, let me just ask you, you're not suggesting we go to non-inferiority --

DR. D'AGOSTINO: No. No, no. They raised the question of non-inferiority, but --

DR. PAGE: We've got drug and drug on both sides.

DR. D'AGOSTINO: Yeah. No, but I'm -- I'm raising the question is that the superiority test that we were looking at and we made -- had a lot of discussion on it doesn't exclude the possibility that there's something useful about this procedure, the device, even though it didn't beat out the medical.

DR. PAGE: Fair enough.

Dr. Noonan.

DR. NOONAN: I agree with Dr. Borer's comments. What we're really wondering is whether these strokes are cryptogenic at all, and if there's some indication based on better imaging available in 2016 that was not available when this trial started, maybe some more rigorous standard for what patients should receive, less choices for what they receive in determining how they're imaged, then perhaps we have a better idea of which ones are really cryptogenic and probably do the PFO and which ones are definitely not. So I don't have a problem with the indication, just prove that it's cryptogenic, prove that there's not something else that could've caused it.

DR. PAGE: Fair enough.

So with regard to (a) and (b), Dr. Zuckerman, there, I believe, is a consensus among the Panel that the indication is appropriate with very careful guidance as to who would most benefit from the device. I'm going to take a leap and just ask whether anybody has any concerns with regard to safety profile relative to the potential benefit. And then I'll call on you, Dr. Posner, in a moment. Do we need to discuss the safety issue further?

(No response.)

DR. PAGE: Dr. Posner, did you have a comment?

DR. POSNER: This is just a science question. I don't think you can make the statement with respect to the data that came out of this trial. I mean that's saying -- that says the results of the RESPECT trial support, the results of the RESPECT trial provide. Well, the results of the RESPECT trial were statistically insignificant. What you're all saying is yeah, there's a role for this, and I can agree with that; and yes, if there is a stroke that's caused by something coming across a PFO, blocking the PFO is going to predict that, but that doesn't come from the RESPECT trial. I mean it's just not science.

DR. PAGE: I think people are interpreting the trial in different ways, sir, but there is certainly -- and I hope Dr. Zuckerman is hearing, there is concern about the guidance that we're getting from this trial and as such, the -- I think the votes may reflect that concern. I think clear consensus is that there are indications for this device.

DR. ZUCKERMAN: The point is acknowledged, Dr. Posner.

DR. PAGE: Thank you.

I'll ask for briefly reading the Question No. 8.

DR. DRUMMOND: Please comment on any additional study objectives or design features that you recommend for the post-approval study and whether or not the Sponsor's post-approval commitments are acceptable.

DR. PAGE: The post-approval trial we've discussed at some length. Any other comments with regard to -- yes, Dr. Borer and then Dr. Brindis.

DR. BORER: I think that post-approval trial as -- post-approval study, I'm sorry -- as it was suggested is actually fine; it's a registry. With the addition of the two points that the

FDA made, that atrial fibrillation and DVTs have to be among the outcome events that are tabulated. But if that's done during the follow-up, then I think the design of the post-approval study is fine.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: The registry -- so I agree with the comments the FDA made and that Jeff has just made. I might ask, also, that we be tracking our anticoagulant use because that's been a significant issue. And I would strongly endorse the impassioned plea by Bray Patrick-Lake that we look at the patient-centered quality of life issues, maybe even look -- track issues such as migraine. That was a continued theme that was brought up today, and I think it will add to the understanding related to this device. That's lacking, to date.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Just --

DR. PAGE: And Dr. Evans. We need to get to the vote kind of quickly.

DR. SLOTWINER: Just close collaboration --

DR. PAGE: Yeah.

DR. SLOTWINER: -- between a neurologist and the implanting physician to make sure patients are selected appropriately, in the registry, documented.

DR. PAGE: Very good, thank you.

Dr. Evans.

DR. EVANS: You know, the rates that we observed in this RESPECT trial were very

different than what was expected, and whether that's evolution of medical practice or otherwise, but if you do a post-approval study, how are you going to interpret the rates there? Somehow you need context or a control, and you're going to have to be careful.

DR. PAGE: Point well made.

So, Dr. Zuckerman, in terms of post-approval study, I think generally it's seen as satisfactory, making sure that A-fib, DVT, anticoagulation are considered, likewise quality of life and potentially migraine. And finally, that there needs to be maintained a very close relationship between an excellent neurologist and an objective interventionalist as they make decisions as to the patient care. Does this satisfactorily answer the question, sir?

DR. ZUCKERMAN: Yes, but I would like to turn back to Dr. Furie, who's made very good comments about a post-approval period. So certainly, Dr. Furie, in terms of practical things, I think the role of a team approach with a neurologist as a key component helps us. I guess you would also like a specific detail such that in the year 2016 we have an adequate protocol for ruling out other types of stroke, and certainly Dr. Carlson and others have mentioned devices that are now available. And I guess the third thing that I'd like to ask you about is your ideas about a controlled rollout at centers of excellence initially such that this device is used appropriately.

DR. FURIE: Thank you. I agree with all of your comments, and I do think that a controlled rollout will provide information about how effectively these teams work and can collect the data. In particular, the neurologist is not only important on the front end for selecting patients who are eligible, but also --

DR. PAGE: Dr. Furie, can you point toward the microphone, please?

DR. FURIE: Oh, yeah. But also for monitoring patients post-procedure, given that these patients won't all receive imaging and there's some potential bias there, but to have somebody to look for perhaps more subtle manifestations of cerebral infarction or even silent brain infarction.

DR. PAGE: Thank you.

Dr. Chaturvedi.

DR. CHATURVEDI: Yeah, in the Sponsor's plans for the post-approval study, I didn't see anything about exclusion of atrial fibrillation using modern methods such as 2-week monitoring or 4-week monitoring or even longer.

DR. PAGE: Very good.

Okay, does that satisfactorily address the questions, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it does. And I think the Sponsor is also in agreement.

DR. PAGE: Thank you. So now we -- the Panel will hear summations, comments, or clarifications from the FDA. The FDA has 10 minutes.

DR. FARB: Thank you very much, members of the Panel. I think the discussion's been very helpful for us. We have the opportunity to reread the transcript and take your -- all your advice back home, and we look forward to the vote and continue to work on this project. Thank you very much.

DR. PAGE: Thank you, sir.

Yes, Dr. D'Agostino.

DR. D'AGOSTINO: D'Agostino.

As we go through these voting questions, I'm used to having the statement when

they say effective be that did I have a clinical trial, that somehow or other, one showed it's objective. That clearly, from the discussion we've had this last half hour, that clearly is not what we're talking about. Could we have some advice from the FDA or some guidance from the FDA, when they're saying effective, what is it that we're supposed to be pointing to?

DR. PAGE: We will read the definition of effectiveness, and if there are still questions at the time of the vote, please point that out for us.

I'd now like to offer the Sponsor an opportunity to give any concluding comments. You have 10 minutes.

DR. CARLSON: Okay. We'll try to beat that. My colleague, Dr. Thaler, and my colleague, Dr. Carroll, want to make brief remarks, and I'll wrap up very briefly.

DR. THALER: Thank you very much. David Thaler again. I just want to address the patient selection issue, which I entirely agree is absolutely crucial, and we've been spending a lot of time identifying patients who have cryptogenic stroke. Even within cryptogenic stroke patients who have a PFO, not all of those PFOs are pathogenically related to the index stroke. But I want to reassure the Panel that there are new methods that have been evolved in the last few years, published in 2013, that help to disaggregate within that population of cryptogenic stroke patients with PFO the ones who are more or less likely to have pathogenic or incidental PFO. So the science has moved forward. We're beyond where we were in 2000, when this trial was designed. And otherwise identifying -- starting with the cryptogenic stroke population with the caveats that Drs. Furie and Chaturvedi have been highlighting, I think, is entirely appropriate.

DR. PAGE: Thank you.

DR. CARROLL: Thank you. Your discussion has been very illuminating, and I think you all have appreciated the challenges we felt in the last 13, 14, 15 years in trying to come up with learning from this important clinical trial and not just a yea/nay, does the device do anything, but what is the optimal management of these patients? And one thing we have learned, it's individualized. They have different risk factors. Some are modifiable, sometimes they don't have any, but this should be part of the option that's available, and we need to get this into the regulatory world, and we need professionals to also further develop this team approach because we've learned that -- and I've learned this from my steering committee members -- how important this is in the individual patient evaluation and to have that option.

And finally, we have demonstrated that in patients younger than 60, even in the intention-to-treat, at 5 years we do see a 50% risk reduction, and that's substantial. And I can remember this grandmother from Wyoming with her daughter, granddaughter, down there after a stroke, talking about risk reduction and she -- and the uncertainty we had. We had a 0.08 in the RESPECT trial, and she said well, number one, 2.5 risk of having another stroke at 5 years, it's less than 5%. That's important. And secondly, my daughter, granddaughter needs a voice in this decision. She can assess risk and benefit in her own way. And that's why I think your vote is important in enabling at least this option to be available in a rational way.

Thank you.

DR. PAGE: Thank you.

DR. CARROLL: Thanks.

DR. PAGE: Dr. Carlson.

DR. CARLSON: Thanks. My handlers have written here "keep it short and thank you." So thank you all very much for contributing your time and your expertise over the last few weeks and all day today to addressing this very important issue. I want to reinforce that we agree with those of you who have asked that the labeling be specific and be focused on getting this device into the right physicians' hands and into the right patients' hands. A team approach. And not only in selecting the right patients, but optimizing their comprehensive therapy thereafter. So I'll end there. We look forward to working with the FDA and perhaps many of you on the Panel going forward. Thank you.

DR. PAGE: Thank you, sir.

Before we proceed with the panel vote, I'd like to ask our non-voting members, Mr. Frankel, our Consumer Representative; Mr. Thuramalla, our Industry Representative; and Dr. Posner, our Patient Representative, if they have additional comments.

Mr. Frankel.

MR. FRANKEL: Thank you.

I first want to just note and just in summary that the patient selection, obviously that's been spoken about a lot, and that's obviously a key focus. And the Sponsor had noted that there wasn't a noticeable learning curve, but at the same time it was also noted that there were new techniques, fine-tune techniques that have been learned based on experience; for example, to better avoid perhaps incomplete device closure. So I think that that's an important aspect as well, from that side. Two of the critiques that I heard today, in the analysis there were some striking quotes, from my vantage point. Dr. Homma, when

he noted the -- from a critical perspective in terms of the device, he actually started by saying, "There may be patients who benefit from this," and then there was a very long "but." And one of the distinguished Panel members in his critique noted that the strokes were mild, and then there was talk about clinically meaningful reduction. I think that from listening to the patients and just overall perspective from a consumer's vantage point, there is no small number when it comes to what we're discussing over here, which is the catastrophic result of a stroke, and I think that that's important to be mindful of, and, you know, sometimes from a statistical point of view, in a sterile sense, something may not seem significant, but looking at it from that vantage point, I think it is very significant. Someone once said that anyone who says that something is a mild surgery, it means that they're speaking about someone else. So I think that that's a key focus over here, and there's an overall trend, based on listening to everyone on this Panel, is that there's a strong consensus that there is a benefit over here.

The question is to what extent, and obviously there is important questions in terms of selection, and I think that with presenting the data to the patients and allowing them to weigh their risk versus benefits, knowing that there are benefits and the potential of decreasing the risk of such a terrible event in someone's life, like a stroke, I think that there is a strong difficulty in arguing against making that option available to patients, and that obviously is in the context that, as far as labeling is concerned and marketing, I think it's very important, from looking at it from the other side of the coin, that patients have to know, based on the data that we have, that this isn't an alternative to anticoagulation/antiplatelet therapy. There's no evidence that that's a reasonable

conclusion to make. And from listening to patients talking about it, it seems that that is an impression, for some reason, that they are under. So I think it is very important, from a labeling vantage point and ultimately marketing, that it has to be crystal clear to patients that by no means that this is an alternative in that sense, but that they should be able to make the option available to them with their eyes wide open and that they could select this and potentially avoid a stroke by taking that option.

DR. PAGE: Thank you very much.

Mr. Thuramalla.

MR. THURAMALLA: I'd like to first start by thanking both the FDA and the Sponsor for conducting such a large randomized clinical trial and for their presentations this morning. I'd like to also thank the Panel for their very thoughtful deliberations on this difficult subject. Having said that, we all know RESPECT is the largest clinical trial of PFO closure device, and although the primary endpoint did not achieve superiority, if you consider the totality of the data, it shows signs of relative risk reduction. The meta-analysis data for this supports this. In conclusion, I believe that this device should at least receive a favorable or-- and at least -- so that it could be used or offered to at least select patients, which will allow the clinician and the patient to discuss as a potential treatment option.

Thank you.

DR. PAGE: Thank you.

And Dr. Posner.

DR. POSNER: I want to thank everybody. This was a really good robust discussion; I learned a lot. I think the end result is what everybody wants, and hopefully, the applicant is

going to go forward with the postmarket studies following the suggestions that came here. I have one additional suggestion for postmarket, and that's marketing. Since there are already devices out there that do close PFOs that are being used off market, as a patient, I would like to know which one of those is the best, because if I'm convinced that I'm in a subgroup that needs my PFO closed, I want to know why I should select this one versus the other ones that are currently out there off market.

DR. PAGE: That's a great question, and unfortunately, the off-label devices are not -- have never been --

DR. POSNER: Oh, I know this.

DR. PAGE: -- subject to this sort of rigor. But thank you, Dr. Posner.

We're now ready to vote on the Panel's recommendation to FDA for AMPLATZER PFO Occluder. The Panel is expected to respond to two questions relating to safety and effectiveness. Ms. Washington will now read two definitions to assist in the voting process. Ms. Washington will also read the proposed indication for use statement for this device.

Ms. Washington.

MS. WASHINGTON: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert Advisory Panel on designated medical device premarket approval applications, PMAs, that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions for safety and effectiveness are as follows:

Safety as defined in 21 C.F.R. 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness as defined in 21 C.F.R. 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The Sponsor has proposed the following indications for use: The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to presumed paradoxical embolism.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three voting questions:

Question No. 1: Is there reasonable assurance that the AMPLATZER PFO Occluder is safe for patients who meet the criteria specified in the proposed indication? Please vote now.

(Panel vote.)

MS. WASHINGTON: Voting Question No. 2: Is there reasonable assurance that the

AMPLATZER PFO Occluder is effective for use in patients who meet the criteria specified in the proposed indication? Please vote now.

(Panel vote.)

MS. WASHINGTON: Question No. 3: Do the benefits of the AMPLATZER PFO Occluder outweigh the risk for use in patients who meet the criteria specified in the proposed indication?

(Panel vote.)

MS. WASHINGTON: Please give us a moment as we tally and verify the official votes.

(Tally of votes.)

MS. WASHINGTON: The votes have been captured, and I will now read the votes into record. On Question 1, the Panel voted 15 for yes, 0 for abstain, and 1 for no that the data shows reasonable assurance that the AMPLATZER PFO Occluder is safe for use in patients who meet the criteria specified in the proposed indications.

On Question 2, the Panel voted 8 for yes, 0 for abstain, and 6 for no that there is a reasonable assurance that the AMPLATZER PFO Occluder is effective for use in patients who meet the criteria specified in the proposed indications.

On Question 3, the Panel voted 11 yes, 0 for abstain, and 5 for no that the benefits of the AMPLATZER PFO Occluder outweigh the risk for use in patients who meet the criteria specified in the proposed indications.

The three voting questions are now complete.

DR. PAGE: I will now ask the Panel members to discuss their votes. I don't need a

long discussion, and if someone has already said what you believe, then you can just go ahead and provide your comment, but please, if you answered no to any question, explain why and go ahead and put forward how you voted individually. And we'll start with -- and again, we're just going to voting members. We'll start with Dr. Yuh.

DR. YUH: Thank you.

I voted yes for all three. I think, you know, all of my votes are somewhat through the prism of the consequences of stroke, and I think that it is safe, you know, considering the relative consequence of having a stroke. In terms of efficacy, that group is in there, it's in the group described by the indications. I think we just need to do a better job of defining it, as everybody kind of alluded to. And so Question No. 3 follows my responses to 1 and 2.

DR. PAGE: Thank you.

Dr. Kandzari.

DR. KANDZARI: I voted for yes for all three as well, and my votes were in the context of both the consequences of stroke relative to the safety of the device, as well as the limitations of the trials that we -- in the data that we have to date. Again, the device doesn't exclude formally altogether the risk of stroke, it doesn't exclude the potential need for medical therapy for patients, but I was most compelled by this directional signal towards reducing unexplained stroke with the device.

DR. PAGE: Thank you.

Dr. Brinker.

And could I have the votes put back up for Question 2 for us to see? Do you have those available? On my computer here, I believe we left out two votes in terms of the

effectiveness. Unless two people didn't vote.

(Pause.)

DR. PAGE: So Ms. Washington will read into the record Question 2, a corrected vote.

MS. WASHINGTON: On Question 2, the Panel voted 9 yes and 7 no, that there is a reasonable assurance that the AMPLATZER PFO Occluder is effective for use in patients who meet the criteria specified in the proposed indications.

DR. PAGE: Thank you.

Dr. Brinker.

DR. BRINKER: I voted yes for all three. I was encouraged by the fact that the term used in these questions were assurance, reasonable assurance, rather than statistical certainty, such as can be attained. I also think that there's a real clinical need, even if the group turns out to be much smaller than was overall studied in this group of research candidates, for some device to be helpful for the pathophysiology that most certainly exists in some portion of these patients of cryptogenic strokes. And I'm even further impressed and excited about once the ground rules are laid for the appropriate way to go about this, that nothing but improved endpoints will be obtained.

DR. PAGE: Thank you.

(Off microphone comment.)

DR. CHATURVEDI: Yeah, I voted no for all three. With regard to safety, I don't think we were given any sufficient information about the excess of DVT and PE in the device group. There was some speculation as to possible mechanisms. And also, we weren't given any information about the clinical significance of the pulmonary emboli events in the device

group. For Questions 2 and 3, I would just reiterate that we are in the world of evidence-based medicine, and we have two trials with this device, both of which failed the primary endpoint, and our colleagues at the AHA and ASA, which had a considerable wealth of expertise on their committee, they voted against PFO closure and said it's not indicated at the present time. And Dr. Homma alluded to an upcoming statement from the American Academy of Neurology, and I would await that with interest.

DR. PAGE: Thank you.

Dr. Furie.

DR. FURIE: I voted yes, no, yes. I think the additional data we received alleviated some of my concerns about safety. I, too, had concerns about the methodology of the trial and the negative results statistically. But although it may seem illogical, I voted yes on the third because I also see a clinical need for this device, and it's my hope that a population that would benefit from its use can be identified.

DR. PAGE: Thank you for clarifying.

Dr. Kouchoukos.

DR. KOUCHOUKOS: Yes, I voted yes for all three for all the reasons that you've heard previously. I think there is a definite clinical need for this device, and hopefully its usefulness can be identified and honed in.

Thank you.

DR. PAGE: Thank you, sir.

Dr. Borer.

DR. BORER: I, too, voted yes for all three based on the assumption, as I mentioned

earlier, that the FDA will provide labeling language that rigorously defines a way of reasonably selecting patients who are likely to have had paradoxical emboli causing stroke. Given that presumption, I think the answer to all three should be yes.

DR. PAGE: Thank you.

Dr. Dehmer.

DR. DEHMER: I voted yes for all three. I think -- I, too, feel like there's a strong clinical need to have this device available to patients. You know, I think the Sponsor was in a difficult position. They have made a valiant effort to try to do the study in the best possible way, but we're studying a very elusive entity which we don't even completely understand; it's been a moving target along the way. And I am persuaded that there -- that patients should be given the option of considering this therapy, so I voted yes.

DR. PAGE: Thank you.

Dr. Brindis.

DR. BRINDIS: Yes, for all three. I think that patients and clinicians need to have this device available as opposed to using other devices that probably are not as good in an off-label fashion. I think if I was on the writing committee of this particular guideline, I would give it a IIb indication as opposed to a III indication when you read the wordings for such. And my hopeful plea is that aggressive patient choice, particularly looking for occult atrial fibrillation, is done in making sure we choose the right patients for this device.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: I voted yes for safety, but I voted no for the other two questions

because I think the statements were too strong; but as we discussed earlier, I am confident that those can be reworded between the Sponsor and the FDA. I do think this device should be available. I want it to be available for the proper population.

DR. PAGE: Thank you.

Dr. Lincoff.

DR. LINCOFF: I voted yes for all three. My feelings have been summarized by the previous speakers, so I'll move on.

DR. PAGE: Thank you.

Dr. Evans.

DR. EVANS: I voted yes for safety based on comments from other Panel members about the transient nature of some of the harms. I voted no for effectiveness and benefit-risk. The question is about reasonable assurance. To me, that implies that it's supported by data, which I didn't see here. And the most reliable analyses told me that it was not supported by the data. And it seemed that much of the discussion and -- sort of turned towards speculation that we hope it works in some population, but medical need doesn't apply, that there's an effectiveness here.

DR. PAGE: Thank you.

Dr. D'Agostino.

DR. D'AGOSTINO: Ralph D'Agostino.

I voted yes on the safety and no on effectiveness and no on the last question also. In terms of the safety, I think it's been adequately discussed. In terms of the effectiveness, we basically are saying we're proving it -- or voting positive on it because it's a single-arm study

that showed something. We've thrown out the comparative study we have and basically are looking at one of the treatments and trying to draw off the effectiveness. That might be a useful way of doing it. I lived through a lot of the over-the-counter studies back in the seventies when we used to say it's effective, it's generally recognized as safe and effective, and we were telling people to take -- and we're telling them to do a lot of other things that we've sort of straightened ourselves out on. But there was always data that said they were effective, but always data that wasn't in the clinical trial -- in the clinical trial structure, and that's what I'm concerned about. I think there's something useful here, but I don't think that we have the data before us. And then the -- does the risk for use -- the risk is low, and the benefit is useful. I'm saying I'm not clear about the benefit, the effectiveness. I really can't answer in a positive way on that third question.

DR. PAGE: Thank you.

Dr. Laskey.

DR. LASKEY: I voted yes, no, yes. I should've been a neurologist. Yes for the reasons stated. No on effectiveness, although it was 51-49, I have to be honest here. And in the interest of being a clinician first and a statistically oriented concerned clinician second, that weighed into over the yes for the benefit-to-risk ratio. I think that there is a need, I think that there is a group out there, and I'm very hopeful that Dr. Carroll and associates can identify that group and that there would be benefit, but I have to say the benefit is of uncertain magnitude with the possibility of hazard.

DR. PAGE: Thank you.

Dr. Hirshfeld.

DR. HIRSHFELD: I voted yes, yes, yes. And many of my rationales were very similar to Dr. Laskey's. I think there is a beneficial effect, but I think that the size of that effect is uncertain, although it's likely modest and likely less than what the raw data that we saw show. I am concerned about the conversion of that rate over time, and I think that needs to be explored ongoingly in the future. I also am concerned that patients in the public may have an overly simplistic understanding of this technology.

We certainly heard today from a number of patient comments, comments that were clinically effective; they really believed that they had been cured by this device, and if they hadn't gotten the device, something terrible would've happened to them. And I think they may even have a false sense of security, so I think it's important that patients understand what this device can and can't do. Now, finally, I think it's a very important device for use in properly selected situations, so this is the reason I voted yes is that I would like to have this device on the shelf.

DR. PAGE: Thank you.

Dr. Noonan.

DR. NOONAN: I voted yes, no, no. I echo Dr. Slotwiner's, Evans', and D'Agostino's comments. I think as far as a catheterization procedure, putting in a device, it probably falls right in line with any other device by that means, so it's safe to place. Regarding effectiveness, I'm not sure there's reasonable assurance. I think there's a hint, and a hint has been mentioned, or a signal. If it's more than just a signal, I think you could say that there's a definite benefit, so I couldn't say a definite benefit. There's probably a group of patients who will benefit from it, but that remains to be seen.

DR. PAGE: Thank you.

And as the Panel knows, I don't vote unless there is a tie. If I were forced to vote, I would vote yes on safety and no on the other two. I believe this is an important technology. I'm confident it will be available to our patients. I'm just afraid that the data did not support the effectiveness based on this -- the indication as written and the data as presented. Nevertheless, I think we're in a good place in terms of this Panel; it's a split vote. And I think the discussion reflected the fact that I think we're unanimous in believing this device has a role, and the challenge for FDA and the Sponsor is to identify the best patients, the most appropriate patients who can most benefit from this procedure.

With that, I would like to thank the outstanding Panel that we had today and really thank you for your engagement and active discussion. I'd like to thank the FDA and the Sponsor, both of whom put forth very professional, concise, yet complete presentations. And finally I'd like to thank the patients and the representatives thereof who spoke at the open public comment. As always, we're keeping you in mind, and we're trying to do the best for patients and the safety of the United States patient population.

With that, Dr. Zuckerman, do you have any final remarks?

DR. ZUCKERMAN: No, I would just like to thank all the Panel members. This was an outstanding discussion this afternoon.

DR. PAGE: With that, this meeting of the Circulatory System Devices Panel is now adjourned.

Safe travels, everyone. Thank you.

(Whereupon, at 5:36 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

May 24, 2016

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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MICHAEL McCANN

Court Reporter