

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

WEDNESDAY, OCTOBER 10, 2007

The meeting came to order at 8:00 a.m. in the Grand Ballroom of the Hilton Washington DC North, Gaithersburg, MD. Dr. Clyde Yancy, Chairman, presiding.

PRESENT:

CLYDE YANCY, MD	CHAIRMAN
JOANNE LINDENFELD, MD	VOTING MEMBER
JOHN HIRSHFELD, MD	VOTING MEMBER
JOHN C. SOMBERG, MD	VOTING MEMBER
JUDAH WEINBERGER, MD	VOTING MEMBER
MICHAEL J. DOMANSKI, MD	NON-VOTING MEMBER
RICHARD HOPKINS, MD	CONSULTANT
NORMAN S. KATO, MD	CONSULTANT
A. MICHAEL LINCOFF, MD	CONSULTANT
DOUGLAS MORRISON, MD	CONSULTANT
DAVID NAFTEL, PHD	CONSULTANT
MARCIA S. YAROSS, PHD	INDUSTRY REPRESENTATIVE
KAREN R. RUE	CONSUMER REPRESENTATIVE
JAMES P. SWINK	EXECUTIVE SECRETARY
BRAM ZUCKERMAN, MD, FACC	FDA REPRESENTATIVE

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TABLE OF CONTENTS

<u>ITEM:</u>	<u>PAGE</u>
Call to Order	5
Conflict of Interest and Deputization to Voting Member Status Statements	6
Introductions	15
1st Open Public Hearing Dr. T. Bruce Ferguson, on behalf of The Society of Thoracic Surgeons	18 20
Sponsor Presentation (Medtronic, Inc.) Sean Salmon, Medtronic, Inc. Vice President and General Manager of the Coronary and Peripheral Vascular Business at Medtronic	30
LeRoy A. LeNarz, Medtronic, Inc. Chief Medical Officer	41
Martin Leon, MD, Member of Medtronic's Coronary Advisory Board	50
Laura Mauri, MD Interventional Cardiologist at Brigham and Women's Hospital and Chief Scientific Officer at Harvard Clinical Research Institute	89
Richard Kuntz, MD Medtronic, Inc.	105
Sponsor Q and A	118
Additional Sponsor Q and A	153

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TABLE OF CONTENTS
(Continued)

<u>ITEM:</u>	<u>PAGE</u>
FDA Presentation	
Elizabeth Hillebrenner Biomedical Engineer and Lead Reviewer for the PMA	157
Dr. Andrew Farb FDA Medical Officer Clinical Review-Endeavor stent	161/204
Dr. Yonghong Gao FDA Division of Biostatistics	193
Dr. Duggirala	212
FDA Q and A	222
Further Sponsor Q and A	237
Dr. Laura Mauri	238
Dr. LeRoy A. LeNarz	241
Dr. Jeff Popma	242
Dr. Richard Kuntz	254
Panel Deliberations	261
and FDA Questions	276
John Hirshfeld, MD	261
Judah Weinberger, MD	267
FDA Questions to the Panel	314
2nd Public Open Hearing	
William H. Maisel, MD, MPH Cardiovascular Division, Beth Israel Deaconess Medical Center/Harvard Medical School	422

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TABLE OF CONTENTS
(Continued)

<u>ITEM:</u>	<u>PAGE</u>
FDA and Sponsor Summations	
Ashley Boam, FDA	435
Sean Salmon, Medtronic, Inc.	437
Deputization to Temporary Voting Member Status Statement re:	
A. Michael Lincoff, MD	439
Explanation of FDA Authority to obtain Recommendation from an Expert Advisory Panel and Definitions	440
Recommendation Options for the Vote	442
Panel Motions on Recommendations/ and Approvable Conditions	443
Panel Vote (Unanimous) of Approvable with Voted on Conditions	463
Panel Summary of Reasons for Vote	463
Closing Comments by Chair Yancy	476

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

(8:06 a.m.)

CHAIR YANCY: Good morning. I would like to call this meeting of the Circulatory Systems Devices Panel to order. My name is Clyde Yancy. I am from Dallas, Texas, Medical Director of the Baylor Heart and Vascular Institute and Chair of the FDA Cardiovascular Devices Panel. My area of interest and experience is in heart failure transplantation, cardiomyopathy and hypertension.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors as you enter the room. If you wish to address this panel during one of the open sessions, please provide your name to Ms. Ann Marie Williams at the registration table. This is very important.

If you are, in fact, presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to the FDA, please arrange to do that as well with Ms. Williams. Again, this is very important.

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I note for the record that the voting members present constitute a quorum as required by 21 CFR Part 14. I would also like to add that the panel participating in the meeting today has received training in FDA device law and regulations.

Let me request that everyone in the room, myself included, silence your cell phones and Blackberry's so that we won't be interrupted. Mr. Swink, the Executive Secretary for the Circulatory Systems Panel, will make several introductory remarks, and your attention is focused on him, please.

MR. SWINK: I 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 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.

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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 and Section 712 of the Federal Food Drug and Cosmetic Act are being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this panel are in compliance with the 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 who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary, to afford the committee essential expertise.

Related to the discussion of today's meeting,

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members and consultants of the panel who are special government employees have been screened for potential financial conflicts of interests of their own as well as those imputed to them including those of those of their spouses or minor children, in purposes 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 or royalties and primary employment.

Today's agenda involves a review of a pre-market approval application for the Endeavor Zotarolimus-Eluting Coronary Stent System sponsored by Medtronic Vascular. This system is indicated for improving coronary lumenal diameter in patients with ischemic heart disease due to *de novo* lesions of length less than or equal to 27 mm in native coronary arteries with reference vessel diameters of greater than or equal to 2.5 mm to less than or equal to 3.5 mm.

This is a particular matters meeting during which specific matters related to the PMA will be

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discussed. Based on the agenda for today's meeting and all financial interest reported by the panel members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Doctors Joanne Lindenfeld, David Naftel, John Somberg, Judah Weinberger and Clyde Yancy. And waivers have been issued in accordance with Section 712 of the FD&C Act for Doctors Lindenfeld, Naftel and Yancy.

Dr. Lindenfeld's waivers involve unrelated consulting with a parent of the PMA sponsor for which she receives less than \$10,001.00.

Dr. Naftel's waiver is covered to unrelated consulting arrangements. The first one is with a direct competitor for which she receives less than \$10,001.00. For the second arrangement with a parent of the PMA sponsor, he also receives less than \$10,001.00.

Dr. Somberg's waiver entails his employer's interest in the sponsor study. He has no involvement in the study. His institute received less than \$100,000.00 in funding.

Dr. Weinberger's waiver also involves his

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employer's interest in the sponsor study of which he had no involvement. His institute received between \$100,001.00 and \$300,000.00.

Dr. Yancy's waivers address consulting arrangements with both the parent of the sponsor and an unaffected unit of the parent of the competing firms. He received less than \$10,001.00 for both of these arrangements. His waiver under 18 U.S.C. Section 208 also involves his employer's interest in the sponsor study for which they received between \$100,001.00 and \$300,000.00 in funding. Dr. Yancy has no personal involvement with the study.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting

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and will be included as part of the official transcript.

Marcia S. Yaross, PhD is serving as the industry representative, acting on behalf of all related industry and is employed by Biosense Webster, a Johnson & Johnson Company.

I would like to remind members and consultants that if discussions involve any other products or firms already on the agenda for which the 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 that they have with any of the firms at issue.

I will now read the appointment of temporary voting members statement. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990 and as amended August 18, 2006, I appoint the following individuals as voting

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members of the Circulatory System Devices Panel for the duration of this meeting on October 10, 2007: Dr. John Hirschfeld, Dr. Joanne Lindenfeld, Dr. John Somberg, Dr. Judah Weinberger, Dr. Norman Kato, Dr. Richard Hopkins, Dr. Douglas Morrison and Dr. David Naftel.

For the record, these individuals are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Clyde W. Yancy, MD to act as a temporary Chairperson for the duration of this meeting. This was signed by Daniel Schultz, MD, Director, Center for Devices and Radiologic Health and dated August 22, 2007.

Before I turn the meeting back over to Dr. Yancy, here are a few general announcements. Transcripts of today's meeting will be available from Neal Gross & Company. information on purchasing videos of today's meeting can be found on the table outside the

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

I would like to remind everyone that members of the public and the press are not permitted around the panel area beyond the speakers podium. The press contacts today are Karen Reilly and Peper Long. If you could stand up? And I ask all the reporters to wait to speak to FDA officials until after the panel meeting. Thank you.

CHAIR YANCY: At this meeting, the panel will be making a recommendation to the Food and Drug Administration on the pre-market approval application, PMA P060033 with Medtronic Endeavor Zotarolimus-Eluting Coronary Stent System, an over-the-wire, OTW, rapid exchange, RX, and multi exchange 2 (MX2) stent delivery systems. The Endeavor Zotarolimus-Eluting Coronary Stent System is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to *de novo* lesions of length less than 27 mm in native coronary arteries with reference vessel diameters of

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greater than 2.5 mm to less than or equal to 3.5 mm. That is the precise language for which we are adjudicating this application.

Before we begin, I would like to ask our panel members, who have generously given their time today, and other FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position and affiliation, and we'll begin with Dr. Zuckerman.

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

DR. MORRISON: Good morning. Doug Morrison, Interventional Cardiologist currently in private practice in Yakima, Washington.

DR. HOPKINS: Richard Hopkins, Chief of the Adult and Adolescent Cardiac Heart Surgery at Children's Mercy Hospital in Kansas City as well as Director of the Cardiovascular Research Laboratories. My areas of clinical interest are in reconstructive cardiac surgery and research interest is in cell, gene and tissue engineering. I am listed in the panel roster as being

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from Brown University, where I was for 11 years, but have moved this year from Brown to Children's Mercy.

DR. WEINBERGER: I'm Judah Weinberger. I'm an Interventional Cardiologist and an Associate Professor at Columbia University.

DR. SOMBERG: I'm John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago.

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

DR. LINDENFELD: Joanne Lindenfeld. My interests are heart failure and heart transplant, and I practice at the University of Colorado.

DR. HIRSHFELD: John Hirshfeld. I'm an Interventional Cardiologist at the University of Pennsylvania.

DR. NAFTTEL: I'm David Naftel. I'm a Professor of Surgery and Professor of Biostatistics at the University of Alabama at Birmingham and I'm the statistician on the panel.

DR. LINCOFF: I'm Michael Lincoff. I'm an

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Interventional Cardiologist and Director of Clinical Research and Cardiovascular Medicine at the Cleveland Clinic.

DR. YAROSS: I'm Marcia Yaross, Vice President, Clinical Quality Regulatory and Health Policy at Biosense Webster in Diamond Bar, California, and industry representative to the panel.

MS. RUE: I'm Karen Rue. I'm consumer rep and I'm from Lafayette, Louisiana.

CHAIR YANCY: I'd like to thank our panel members and appreciate your time and attention to this matter and welcome our new consumer representative. Thank you for being here.

We will now proceed with the open public hearing portion of the meeting. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA

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encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement to advise the committee of any financial commitment that you may have with the sponsor, its product and, if known, its direct competitor.

For example, this financial information may include the sponsor's payment of your travel, lodging, other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have 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.

One individual has requested to speak. The panel will now entertain Dr. Bruce Ferguson. Please indicate your name, affiliation and any potential conflict.

DR. FERGUSON: My name is Bruce Ferguson. I'm with the East Carolina Heart Institute and Chair of the Department of Cardiovascular Sciences at the Brody

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School of Medicine at ECU. I have no conflicts to disclose and I am here on behalf of the Society of Thoracic Surgeons.

The perspective of my comments this morning relates not to that of a cardiothoracic surgeon and not to that of a specialty which represents a potentially competing technology to the device under discussion today. Rather, the perspective that I would like to bring to the table is that of a framework for evaluation of cardiovascular technology from the broad vantage point of clinical ischemic heart disease therapy as a necessary component to this process. This is derived from the Society's 18-year-plus experience with observational national adult cardiac database efforts linked directly to outcomes research and analysis, and from a more recently completed seven-year experience with continuous quality improvement in medicine funded by the Agency for Healthcare Research and Quality.

RCTs in the device pre-market approval process largely are directed to assess device efficacy, at least in the initial stages. There are

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characteristics of these trials which raise questions related to the design and execution of the trials themselves that have come up, particularly in the last year related to cardiovascular devices. Particularly, the inferiority, non-inferiority and superiority design of the cardiovascular device trials raise the question of whether the design itself can compound prior trial conclusion shortcomings, the so-called strawman phenomenon.

Design trials without adequate control groups raise the question of whether this further distances the trial results from applicability and relevance in the real world. And perhaps, most importantly, the use of composite endpoints in cardiovascular trials to achieve statistical significance results, in many cases, in endpoints of least importance to patients that typically contribute to the most events in the composite metrics used in these trials. And this leads to the question of whether the interpretation of data from these composite endpoints may be misleading to patients and physicians.

We find ourselves, as clinicians, in the

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position of interpolating between cardiovascular device trial results in our application to clinical medicine. The short cycle development of technology means that validation of randomized trial results in the real world is difficult, if not impossible. These trials provide inadequate information to provide guidance for population subsets outside of the trial design, so-called indication expansion. And pre-market evaluation and approval process, including the design endpoints and review criteria, can often limit the importance of the trial results for many patients across the cardiovascular disease spectrum.

Most importantly, perhaps, often the information given to patients is usually limited to the latest trial results without the context of a multi-disciplinary approach to care.

The Society would recommend on the pre-market side that there be caution advocated in the use of pivotal randomized trial data as the only criteria for evaluation of these new technologies in cardiovascular disease. We would urge the FDA that the labeling

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language should reflect the parameters and conditions defined in the trial design including the lack of overall clinical context of the trial data. To address indication expansion, this labeling language should also reflect the knowledge limitation about the anticipated post-market real world context of device use.

We would also make the point about the importance of the post-market domain. Safety and effectiveness of cardiovascular devices should relate directly to patient safety and clinical benefit, often not addressed in these pre-market pivotal trials. Current criteria, mechanisms, and funding to evaluate safety and effectiveness are insufficient, and the pre-market evaluation process, however, cannot ignore these considerations, because of their impact on patient safety.

Post-market evaluation would allow for testing in population subsets beyond trial populations and for evaluation of individual component endpoints from the overall composite metrics of trials. Indeed, the FDA and the Society have partnered together to

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create a mechanism for post-market evaluation of device therapy and cardiac surgery through a purchase order mechanism that is based upon the STS National Adult Database with linkages to Medicare data sets for long-term follow-up data.

We believe this is a first step in the new patient-centered, multi-disciplinary post-market system that evaluates new cardiovascular disease technologies in the context of clinical disease and in comparison with existing alternative treatments. Examples include current and future treatments and therapies in ischemic heart disease, percutaneous valve disease, heart failure devices, and arrhythmias, just to name a few.

There are consequences of the current system liabilities within the cardiovascular device domain as we have all experienced over the past year and a half. Indeed, it is a tenet that new information will always be forthcoming. Short cycle development of newer technologies doesn't always solve clinical problems related to this new information, viewed from a patient safety and effectiveness standpoint. Current system

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liabilities result in consequences that are destined to be unfavorable for patients because the overall process of device evaluation is fundamentally not patient-centered.

This is borne out in the inherent difference between trial and the real world, use of the technology relative to the clinical context of ischemic heart disease, the lack of post-market information or documentation of safety and effectiveness of therapy, often until it's too late and related to design factors that are primarily focused on the devices and not the patients. For example, the more complex scenarios of multi-vessel disease, left main disease and chronic total occlusions should have as control groups coronary bypass surgery and not bare-metal stents or an alternative drug-eluting stent for comparison.

Early mortality outcomes are of greatest importance to patients. However, mortality is the least frequent event in the composite outcome metric in cardiovascular disease trials. Late mortality cannot be determined in almost all these randomized trial designs.

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However, for most patients, mortality is the most important safety and effectiveness metric following cardiovascular disease intervention. We would stipulate that it can only be determined through long-term observational analyses.

In the context of multi-vessel percutaneous coronary intervention versus coronary bypass surgery, there have been a number of observational studies that have compared long-term mortality in patients with significant multi vessel disease undergoing either PCI or coronary bypass surgery. Four studies from Duke, the Cleveland Clinic, New York State and Northern New England each used independent, sophisticated statistical methods to correct for baseline characteristics and propensity, and in this analysis, a weighted average mortality difference was calculated from a total of over 32,000 patients for the duration follow-ups of one year, two year, three years and out to four years.

At each of these time intervals, there was excess PCI mortality compared to coronary bypass surgery that varied from 2.3 percent weighted average difference

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at 1 year to 6.3 percent at 4 years. This translates into out of every 100 patients treated, 6.3 patients who died as a result of PCI compared to coronary bypass revascularization.

In summary, the STS recommends, on the pre-market side, caution in relying just on pivotal RCT data for a decision-making process. We would advocate for strong labeling language to adequately address the findings of the pre-market evaluation, but language which also addresses indication expansion. On the post-market side, the aggressive development of observational database resources to evaluate safety and effectiveness of translating these FDA recommendations into real world use and significant industry investment in these observational database resources for development and sustainable implementation, and lastly, that there be more optimal communication of risks and benefits to patients on both sides of this review process. Thank you.

CHAIR YANCY: Thank you, Dr. Ferguson and thank you for the perspective from STS. Are there other

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members of the audience who wish to address the panel at this time? Since no one else has come forward, we will proceed with today's agenda. Please note that there will be another opportunity for open comments in the afternoon.

We'll now proceed to the sponsor's presentation for the Endeavor Zotarolimus-Eluting Coronary Stent System. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. We will begin with the sponsor presentation.

MR. SALMON: Thank you, Mr. Chairman. Good morning. My name is Sean Salmon. I'm the Vice President and General Manager of the Coronary and Peripheral Vascular Business at Medtronic, and on behalf of the employees at Medtronic and our clinical investigators, I'd like to thank the Food and Drug Administration and the panel members themselves for this opportunity to present to you the Endeavor Zotarolimus-Eluting Stent program.

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In today's presentation, we will cover a number of topics. I will begin with a brief overview of the project and give a product description. I will be followed by our Chief Medical Officer, Dr. LeRoy LeNarz who will cover the drug's substance and the pre-clinical characterization of this combination device. Dr. Martin Leon who is the principal investigation from the Endeavor III and Endeavor IV trials will cover highlights of the randomized clinical trial results, and Dr. Laura Mauri who is the Chief Scientific Officer from the Harvard Clinical Research Institute will cover combined safety analysis for this device through its trial experience. Finally, Dr. Richard Kuntz, who is the Senior Vice President at Medtronic, will summarize the day's presentation and discuss our proposal for a post-market evaluation of this device.

In addition to the presenters today, we have several consultants with us, including Dr. Jeff Popma and Dr. Peter Fitzgerald who served as the core lab for the angiographic and IVUS core labs respectively, also consulting statistician, Dr. Richard Chiacchierini and

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Dr. Sean Willis and Stephen Jones joined us from Biocompatibles.

The purpose of my presentation today will be to provide an overview of the pre-clinical and clinical data that provide assurances based on valid scientific evidence of the safety and effectiveness of the Endeavor Zotarolimus-Eluting Coronary Stent System. As you have heard, we are seeking a proposed indication for the use which is consistent with approved bare and drug-eluting stents for indicating the improvement of luminal diameter in patients with ischemic heart disease due to de novo lesions of lesion length less than or equal to 27 mm in length in native coronary arteries with a reference vessel diameter between 2.5 and 3.5 mm.

We are seeking approval in this application for three diameters of stents -- a 2.5, 3.0 and a 3.5 diameter stent in lengths of 8, 9, 12, 14, 15, 18, 24 and 30 mm. Importantly, we leverage a consistent, uniform dosing scheme whereby there are 10 micrograms of drug applied to each millimeter of stent length which is consistent across the stent matrix.

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The Endeavor clinical program will be overviewed for you today. This is a comprehensive program that includes pre-market safety and efficacy evaluation, ongoing post-approval international studies and a proposed post-market study. In total, there are about 22,000 patients in this proposed data set with 16,500 of those including Endeavor. For the purpose of this presentation today, we're going to focus on the three randomized trials Endeavor II, Endeavor III and Endeavor IV and safety data from the pre-market data set.

I'd like to briefly summarize the clinical program in this slide. We believe we have a substantial density of safety and efficacy data derived from the seven clinical trials, primarily from the three randomized trials with supplementary information from four single-arm studies. There have been 2,232 patients enrolled to receive an Endeavor stent in this program. And importantly, 1,287 of those patients have more than two or more years of follow-up with 675 patients receiving the Endeavor stent with three years of follow-

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up. In total, the experience for Endeavor in this pre-market evaluation constitutes a 3,980 patient-years of follow-up experience.

What we can conclude from these data, as you will see, is that the clinical and angiographic superiority of this stent has been proven compared to the bare-metal stent driver in randomized trial and that treatment effect has now been sustained through three years of clinical follow-up. We've also demonstrated clinical non-inferiority to an approved drug-eluting stent. We will demonstrate consistency in the clinical and angiographic outcomes across different geographies and across all of our studies. And finally, we have no observed safety signals before one year or after one year to three years of follow-up including low rates of stent thrombosis by all definitions, low rates of death, low rates of cardiac death and low rates of myocardial infarction.

I'd like to briefly describe the Endeavor product. This product is composed of four primary elements -- the stent, its delivery system, the polymer

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and the drug substance. The stent itself is based on -- it's identical to the currently improved Driver and Micro-Driver Stents for the 3.0 and 3.5 and 2.5 mm diameter stents respectively. The Driver Stent is approved on a rapid-exchange over-the wire and multiple exchange platform. We will seek, in this application, the approval of all three of these delivery systems as well.

As I mentioned, the product matrix does correspond to the proposed indications for use. The same platform itself has undergone a lot of evolution in its history. This modular stent technology was first commercialized in the United States in 1997. And as you can see, we've made progressively increasing improvements to the stent in its stainless steel platform, reducing the strut thickness in order to improve the profile and deliverability of this device. And more recently, the Driver Stent leveraged a new called Cobalt. It has a Cobalt alloy. This allowed us to reduce the strut thickness further to .0036 inches while retaining the radial strength and fluoroscopic

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visibility of the device.

The design itself is formed by ring structures which are put into sinusoidal waves. This is an edgeless design. They are modular in nature and their construction, welded together in 1 mm elements to provide very good flexibility for deliverability of the device and also coverage of the vessel for scaffolding, even on bend sites. It conforms well to the anatomy. The delivery catheters their selves are flexible and low-profile. We leverage the balloon material on the margins of the stent to add security to the stent for making sure that it stays within the balloon. We also minimize the amount of balloon that hangs over the margins of the stent to provide safety to the proximal and distal vessel. This device reaches its nominal diameter at 9 atmospheres of pressure across the product range and has a rated burst pressure of 16 atmospheres.

Moving to the polymer. The polymer has a long history of use in medical devices that includes, among other things, coronary stents. There is an approved coronary stent coated with this polymer without

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any drug substance, the BiodivYsio ASPC coated stent was approved in September of 2006. At the time of drug-eluting stent development, there was a global experience of over 150,000 patients receiving devices coated with this substance.

PC is a composite polymer which is primarily comprised of hydrophilic monomers intended to get along well in a aqueous environment. PC mimics the chemical structure of the phospholipid head group. As you can see in this depiction on the left-hand side of the screen, this is an erythrocyte cell membrane. The PC head group is contained in 90 percent of the outer surface of the membrane of a red cell chemical copy of that exactly. And this way, this biocompatible polymer is biomimetic.

This technology was original developed because of its ability to be hemocompatible in the earlier days of coronary stenting, before the understanding that high-pressure balloon inflations and dual lines of platelet therapy could assist in keeping stents from clotting. This coating was contemplated for

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its use. As I mentioned, this is a hydrophilic coating, so it does not bind proteins, monocytes, and, importantly, in the graph, you can see platelets do not adhere to this surface in a baboon-shunt model in a trial compared to an uncoated bare-metal stent.

Moving to the drug substance, Zotarolimus is a macrolide antibiotic in the class of limus drugs. It's an analogue to sirolimus. The difference is this substitution of the hydroxyl group with the tetrazole ring which has the effect of increasing the lipophilicity of the drug while retaining similar nanomolar potency to sirolimus.

The construction of the combination device is as follows. The stent strut is coated with a base coat of PC coating which is approximately 1 micron thick and a mixture of 90 percent Zotarolimus at a concentration of 10 micrograms per millimeter is mixed in with 10 percent phosphorylcholine and sprayed preferentially to the abluminal surface with a coating thickness of approximately 2 to 4 microns. There is a thin overspray of 1/10 of a micron applied to the device itself.

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On the bottom of the slide, you can see these are three millimeter stents by SCM shown at 500 times magnification to give you an idea of the scale. You can see the thin strut compared to the currently approved drug-eluting stents. Both the stent strut itself and the polymer thickness is reduced, thereby reducing the overall polymer load.

We looked at the elution kinetics of this device in a porcine model. On the top graph, you can see Zotarolimus rapidly elutes from the hydrophilic polymer within 14 days. The drug substance itself is hydrophobic. As you can see in the bottom graph, that lipophilicity of that drug comes into play as it is rapidly up-taken by the arterial tissue and remains at therapeutic concentrations within the tissue through 28 days.

I'd like to invite Dr. LeRoy LeNarz -- he's our Chief Medical Officer -- to discuss the drug's substance and the pre-clinical characterization of this device.

DR. LeNARZ: Good morning. LeRoy LeNarz,

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employee of Medtronic. I am going to discuss the characterization of Zotarolimus as well as the relevant pre-clinical information for today's discussion. Over 60 reports were submitted to the drug master file for review by CDER with a joint review of the combination product by the Device and Drug Divisions. This includes all of the relevant pharmacology and other studies needed to help characterize the new chemical entity.

Just a quick summary of the safety pharmacology studies would indicate that we would expect no significant toxicity associated with the respiratory system, although not on the slide, CNS, and that we would not anticipate any sensitization or antigenicity by our pre-clinical studies. In addition, Zotarolimus was mixed with platelets and at a concentration that would be at or equivalent to 50 times the highest anticipated C_{max} for 48 millimeters of stent length. We saw no affect on platelet aggregation and, when combined with known promoters of aggregation such as ADP, collagen or TRAP, again, no effect.

Standard comprehensive in vitro and in vivo

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cardiovascular assessment including hERG as well as action potential duration studies with the cardiac Purkinje fibers, and both hemodynamic studies in a conscious and anesthetized dog as well as the conscious primate allows for margins of safety to be discussed following the pharmacokinetic studies.

The ADME studies included wide range but the salient discussion should be that there is high protein binding across all species, that the drug is distributed to the red blood cell versus plasma in approximately a 20:1 ratio and that radiolabel studies across all species define the GI tract as the route of excretion with very little renal clearance. This is reflection of the metabolism by CYP 3A4 pathways and at relevant concentrations, the drug is a non-inhibitor, and when combined with ketoconazole as opposed to some of the other drugs in the class, we see minimal amplification in both the dog and man at less than two-fold.

Battery of toxicology studies, the genotox was negative. The reproductive toxicology characterized and the single- and the repeat-dose studies in the rat

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and monkey as well as 90-day studies in the monkey provide the safety margins.

The drug alone -- pharmacokinetic studies were conducted by Abbott with both single-dose and multi-dose studies defining that the kinetics are linear, dose-proportional and across all dose ranges and that steady state is reached at day 10 with predictable kinetics, and in the multi-dose study, no treatment-emergent affects and no deaths or serious adverse events noted in either Phase I pharmacokinetic study.

If you take then the combination product and look at the elution of Zotarolimus, there are three studies. Two are depicted. One is the Endeavor U.S. PK study and the other is a subset study of Endeavor II done internationally. And you look at the conventional stent links, that being 18, 24 and 30, and depicting 10 micrograms per millimeter of stent length, one sees consistency in the C_{max} and AUC, and, again, confirmation of linear, dose-proportional and predictable pharmacokinetics, and, again, confirmation that we saw no differences across the geographies.

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If we take those prior discussed studies and we extrapolate out to 48 millimeters of stent length, we can see that the combination of the monkey and the human experience allow for AUC margins up to 60-fold by the 10 micrograms per kilo of IV administration to the primate and C_{max} at 28 by the rapid bolus IV administration in man, and with the multi-dose study, an AUC of 15-fold. And, again, this reflects for 48 millimeters of stent length.

As we move from the drug alone to the combination product, it's very important to characterize the arterial findings, and we're going to run through a series of slides that look at the porcine model in histopathology, inflammation and confirmation that we have endothelialization, both by examination of the endothelium and defining coverage as well as function of the endothelium.

Standard porcine models allow for explants at days 7, 28, 90 and 180 days, and you see the histology compared to the Driver control with no evidence of thrombosis across all of these studies in over 127

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animals and no evidence of arterial necrosis.

When one describes inflammation, there are scoring systems as we go from zero to three, you see that as you increase the number of inflammatory cells around the stent struts, you see an increase in the score. Endeavor has demonstrated a consistent score of one or less. On the left-hand side of this slide, we see at 10 micrograms per millimeter, the dose that would be released commercially, single-stented animals and that we see, again, the standard explant dates of 7, 28, 90 and 180 days. On the right, we see allowance of usually 30 to 40 percent overlap, and once again, we see the expected early higher injury score by day 7 and resolution of the inflammation over time and the scores in the range of 1 or less. More importantly, the cells that are seen lack eosinophils or lymphocytes and are predominantly giant cells and macrophage.

If we then take this same sort of study and increase the dose in the single stent to three-fold or 30 micrograms per millimeter and then overlap allowing up to 60 micrograms for the overlap range, we again see

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low and consistent inflammatory scores. Looking then at the endothelial replacement using histology and scanning electron microscopy identifies by day 28 in this same sort of a single-stented and overlapped model, endothelialization that is complete by day 28. And once again, if we increase the dose to 30 micrograms and then allow for overlap, once again, up to six-fold the dose, we see the continued maintenance of endothelialization that is complete by day 28.

More important is not just the fact that this barrier is present, but that it is functional and there are a couple of ways that one can identify the presence of eNOS, or NitricOxideSynthase, which generates nitric oxide, well-known to maintain vascular tone as well as thromboresistance. And one can see that we have identified in the immunohistochemistry staining the presence of eNOS in the porcine arteries.

A challenge with acetylcholine should allow for vasodilatation which allows us to then know that we have, by day 28, restored vascular functional integrity. And you can see that, with a comparison of

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the Endeavor to the Driver at 28 and 90 days, that we have identified functional endothelium.

So, in summary of the pre-clinical data, we have no medial necrosis or evidence of abnormal histology, very low and consistent levels of drug polymer-induced inflammation, rapid complete, more importantly, functional endothelium.

Prior to going to the review of the clinical trials, I will show the body systems that are of interest for new chemical entity. I will tell you that we have reviewed across the body systems and, most especially, comparing to the studies in which we have a control.

Endeavor II allows for bare metal or, more or less, a placebo control. And the other two studies, Endeavor III and IV, allow for an active control of the same drug class and a control with a different drug class. We see for the areas that one is most concerned, no signal for the liver, the kidney or differences in the immunological effects.

And with that, we can now conclude from the

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both pre-clinical and clinical data that the porcine studies have demonstrated that our drug polymer is safe with respect to biocompatibility and we have, again, normal endothelial coverage and function, that we have demonstrated the drug has favorable safety margins, no anticipation of drug-drug interactions based on the CYP 3A4 interaction studies and the challenge with ketoconazole. And we've seen no significant treatment-emergent events as a combination product.

It's my pleasure to turn the podium to Dr. Leon who has been the principal investigator for Endeavor III and IV.

DR. LEON: Thank you, Dr. LeNarz. I'd like to disclose that I am a member of Medtronic's Coronary Advisory Board, and they did provide travel-related expenses for this FDA panel meeting. I also have been a non-paid consultant as principal investigator for the Endeavor III and Endeavor IV clinical trials. It's an honor to represent the many physicians, physician scientists, research coordinators and sites that participated in the worldwide Endeavor clinical research

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program.

For almost 30 years, I've been a practicing interventional cardiologist and clinical scientist trying to understand the biologic and clinical responses to new interventional device therapies. During that period of time, I've learned that it's important to reduce many of the data to specific attributes that resonate most with the practicing interventionalist and to compare these new devices to current or alternative device therapies using rigorous, evidence-based medicine standards.

From the standpoint of drug-eluting stents, there are both bare-metal predicate stents and currently approved drug-eluting stents. Clinical interventionalists look largely at the attributes of safety, efficacy and deliverability. I believe that most physician interventionalists would agree that from the standpoint of safety, given some of the more recently obtained data, that bare-metal stents probably have a slight advantage over current generation drug-eluting stents.

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From the standpoint of efficacy, defined as a reduction in restenosis, there is no doubt that the current generation of drug-eluting stents are highly efficacious, much more so than bare-metal stents under most circumstances in reducing clinical and angiographic restenosis.

From the standpoint of deliverability, the user aspects of the device, being able to negotiate the coronary anatomy, certainly, current generation drug-eluting stents are not as deliverable as the most advanced bare-metal stents.

So as we look at the Endeavor drug-eluting stent program, it's important to note that we should try to preserve the efficacy advantage of current generation drug-eluting stents while improving the safety and deliverability, which would provide value or incremental benefit to patients.

Over the past five years, we've learned a great deal about drug-eluting stents. In the earliest days, we had several assumptions. From the standpoint of efficacy, we assumed that there was a very close

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relationship between angiographic late loss and binary restenosis as a surrogate for target lesion revascularization, the clinical endpoint in that these were linearly related, that small changes in angiographic late loss which could be discerned by angiography would reflect clinically meaningful differences in target lesion revascularization.

From the standpoint of safety, we had the assumption that safety could be determined in the first year after drug-eluting stent implantation. Based upon these efficacy and safety considerations, clinical trial designs were blinded superiority, randomized, clinical trials in low and medium complexity patients with bare-metal stents as the control arm, and that these would be sufficient to demonstrate drug-eluting stent safety and efficacy. Well, since those early assumptions, we've learned a great deal. This is an analysis from Dr. Stewart Pocock, which is familiar to the FDA, and in press in JACC looking at this surrogate relationship between angiographic endpoints and clinical outcomes. In this figure we're comparing in-stent late loss on the

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horizontal axis versus the probability of clinical target lesion revascularization. Eleven randomized control trials were examined involving the CYPHER Taxus Endeavor and bare-metal stents in 5,381 patients.

I think what you can clearly see in the raw data on the left and the best fit curves on the right that there is a monotonic but non-linear relationship between in-stent late loss and the probability of target lesion revascularization. In the range of late loss, between 0 and perhaps .7 or .8, the slope of this is quite flat and measurable changes in late loss do not induce clinically meaningful differences in target lesion revascularization. When late loss begins to climb to above .7 or .8, the slope changes and we do see significant and important changes in target lesion revascularization.

That was an important lesson in efficacy which we first learned with the Taxus stent program and we are relearning with the Endeavor stent program. We also learned, and it was highlighted, that a new side effect of complication was associated with first

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generation drug-eluting stents. These are data from our group that were published earlier this year involving nine prospective double-blind randomized trials from either the CYPHER or the Taxus programs involving over 5200 patients. We're looking at stent thrombosis as defined by the protocol with four-year clinical follow-up.

I'd like to make two points. First, for both bare metal and for the drug-eluting stents in the first year, there is an event rate of stent thrombosis that is between .5 and 1 percent and equal in both arms. But after one year, these curves diverge in an almost linear fashion with an approximate 0.2 percent per year increase in stent thrombosis up to year four so that a landmark analysis after year one would indicate a clinically significant and statistically important difference in this new phenomenon of very late stent thrombosis, attributed to first generation drug-eluting stents. This, of course, changed our perspective of safety assessments for these new category devices.

Certainly, this also provoked a very

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important FDA panel meeting last December which I summarized on this slide. First, that this phenomenon of very late stent thrombosis occurs after one year at an event rate of .2 to .6 percent per year and this may represent the constant hazard, but little is known about drug-eluting stent safety for so-called off-label use indications. But preliminary data from large registries suggest a higher frequency of very late stent thrombosis versus on-label use, and that dual antiplatelet therapy should be extended in some drug-eluting stent patients, but the duration of therapy, associated risks and the impact on very late stent thrombosis is controversial.

These new lessons have really colored our thinking of drug-eluting stents and affect the way we look at efficacy, safety and clinical trial design. Now, we realize that the relationship between late loss and target lesion revascularization, although monotonic, is non-linear, and moderate late loss may still result in low target lesion revascularization. We recognize that angiographic follow-up has a profound impact on

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target lesion revascularization. In fact, our colleagues at the Cleveland Clinic, more than 10 years ago coined the term oculostenotic reflex suggesting that if an interventionalist saw a stenosis that he would likely dilate it.

From the standpoint of safety, drug-eluting stent safety evaluations can no longer be confined to one year as very late stent thrombosis is increased compared with bare-metal stents, and as a result, clinical trial design has to be modified, that larger non-inferiority randomized control trials versus approved drug-eluting stents and even larger real world studies, both with longer follow-up, are now required to accurately discern clinical safety and efficacy.

It's in this context that we look at the overall Endeavor program. You're seeing the seven studies that have been submitted to the FDA highlighted by the three randomized trials, which I'll discuss in a moment. There are additional ongoing trials involving over 16,000 patients in real world scenarios and additional proposed post-approval registries in the

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United States. It's this massive data in over 22,000 patients that ultimately will be required over a period of time to completely discern DES safety and efficacy.

What's been submitted to the FDA are three randomized trials involving 3,181 patients of which 1,694 received the Endeavor stent and four registries involving 538 patients all treated with the Endeavor stent. From the standpoint of follow-up looking at patient-years, the overall follow-up is 6,492 patient-years of which the Endeavor stent follow-up was 3,980 patient-years.

The goals of the Endeavor clinical program were to demonstrate superior reduction in restenosis compared with a bare-metal stent, both angiographic and clinical endpoints, to demonstrate, a bare-metal stent-like early and late safety profile, and the metrics we use are hard endpoints like death and myocardial infarction and stent thrombosis, the clinical event, to demonstrate comparable or non-inferior outcomes versus an approved drug-eluting stent in a properly powered clinical trial and to show consistency of angiographic

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and clinical outcomes across all randomized clinical trials.

We'll be presenting data on these three randomized trials involving over 3,000 patients starting with Endeavor II which is a 1:1 double-blind superiority trial comparing the Endeavor stent with the control bare-metal stent Driver. The primary endpoint was a 9-month composite clinical endpoint target vessel failure defined as cardiac death, myocardial infarction and target vessel revascularization. We now have follow-up to three years from this study.

This study was done outside the United States. Why was it done outside the United States? Because at the time this study began, we already had approved drug-eluting stents in the United States, and for various reasons, it was not felt that we would be able to randomize patients to control bare-metal stents. Endeavor III and Endeavor IV were performed in the United States.

Endeavor III is a single-blind study with a 3:1 randomization, comparing the Endeavor stent to the

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CYPHER stent. Now the endpoint was 8-month in-segment late loss. This was at a time when, certainly, the feelings concerning surrogate angiographic endpoints and clinical outcomes were thought to be linearly related at all points, and greater emphasis was placed on this relationship. We have two years' follow-up on the Endeavor III trial.

The new data presented for the first time in a public forum today is the Endeavor IV trial. It's the largest of the randomized trials, 1,548 patients equally randomized between the Endeavor drug-eluting stent and the TAXUS drug-eluting stent. The primary endpoint was 9-month target vessel failure, and we'll be presenting 9-month data. One of the strengths of this program is the fact that the data has been analyzed in a consistent fashion.

All of the endpoint definitions have been consistently applied using these laboratories. All of the angiography was assessed at the Brigham and Women's Hospital. The Director is Dr. Jeffrey Popma. All the intravascular ultrasound was assessed at Stanford

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University. The Director of the IVUS core lab was Peter Fitzgerald. The ECG core lab was at the Harvard Clinical Research Institute and Peter Zimetbaum was the Director. The data coordinating center was the Harvard Clinical Research Institute and Dr. Laura Mauri was the Chief Scientific Officer. The Clinical Events Committee and the DSMV, again, were at the Harvard Clinical Research Institute and Donald Cutlip supervised these assessments.

It's important to look at some of the key baseline variables across all of these randomized control trials. There are some differences. There were fewer diabetics in the non-U.S. Endeavor II trial compared to Endeavor III and Endeavor IV, slightly less than 20 percent compared to approximately 30 percent. There were somewhat fewer patients with unstable angina in the Endeavor II trial, 33 percent compared to approximately 50 percent in Endeavor III and IV. Lesion characteristics were quite similar -- reference vessel diameter and lesion length in the range of 2.7 to 2.75 in lesion length in the range of 13 to 14 millimeters.

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There was a higher frequency of more complex lesions, so-called B2/C lesions in the Endeavor II trial compared to Endeavor III and IV.

Another difference among these trials is the assignment to angiographic follow-up. In the Endeavor II trial, 44 percent of the patients received angiographic follow-up. In the Endeavor III trial where the endpoint was an angiographic endpoint, 86 percent of the patients actually received angiographic follow-up.

And by design, in the Endeavor IV trial, a very small percentage of the patients received angiographic follow-up, only 18.6 percent. Of those patients assigned to angiographic follow-up, there was an excellent angiographic follow-up rate of those eligible patients, 89, 86 and 88 percent among the three clinical trials.

One of the features that resonates amongst interventional cardiologists is the issue of deliverability. The Endeavor stent represents an advanced platform. The first drug-eluting stent made of a cobalt alloy with thin struts, strong, highly

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radiopaque with easy visibility, a low-friction, edgeless design that is very deliverable, flexible, low profile on a very good delivery system yet providing good scaffolding. It's difficult to quantitate this concept of deliverability. In clinical trials, we use an index that we call device success, which means being able to actually bring the device to the lesion and to expand the stent and achieve a percent diameter stenosis of less than 50 percent.

Among the three trials, Endeavor II, III and IV, the device success was 99, 99 and 97 percent. This is a highly deliverable platform. Starting with the Endeavor II trial, this is quite similar to previous drug-eluting stent pivotal clinical trials. A double-blind randomized study compared to a predicate bare-metal stent, the Driver. The principal investigators were Jean Fajadet, Richard Kuntz and William Wijns, this was a study performed in single de novo native coronary lesions with a reference diameter of 2.25 millimeters to 3.5. Lesion length was 14 to 27 millimeters.

The study was intended to enroll 1200

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patients at 72 sites outside the United States in Europe, Asia Pacific, Israel, New Zealand, then Australia with equal randomization between the Endeavor active arm and the Driver stent control arm. The primary endpoint was target vessel failure at 9 months. The first 600 patients were scheduled to receive angiographic follow-up at 8 months, the first 300 patients scheduled to receive IVUS during those angiograms at 8 months. There were multiple secondary endpoints assessed as well.

Drug therapy included aspirin and Clopidogrel for at least three months. The dose of Zotarolimus will be uniform in all these trials, 10 micrograms per millimeter of stent length. This is the patient flow chart. Eleven hundred ninety-seven patients were enrolled, 598 randomized to Endeavor, 599 randomized to Driver. Angiographic follow-up was achieved in 89 and 88 percent respectively in the assigned cohorts. Clinical follow-up obtained at 9, 12, 24 and 36 months is shown here and varies between 99 and 96.5 percent, both for the Endeavor and the Driver stent.

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These were baseline characteristics and there were no distinguishing differences among the Endeavor and the Driver stent. This was largely a male population, approximately 75 percent, just under 20 percent with diabetes, unstable angina 33 percent, reference vessel diameter 2.7 to 2.75, lesion length just above 14 millimeters, and just under 80 percent were complex B2/C lesions.

For all of the subsequent slides, the tables will have a similar appearance. These are clinical events to 30 days. We'll start with the safety endpoints of death and cardiac death, myocardial infarction, all Q-wave and non-Q-wave, the composite of cardiac death and all myocardial infarctions, stent thrombosis, and then the clinical efficacy endpoints of target lesion and target vessel revascularization, and then at the bottom, the composite endpoints of MACE and target vessel failure.

At 30 days, I think you can see that there are no differences, no statistically significant differences between the Endeavor and the Driver stent.

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Yellow shadowing will denote any significant differences. It is important to note that within the first 30 days, there were 3 episodes of stent thrombosis for the Endeavor stent, 0.5 percent, and 7 episodes of stent thrombosis for the bare-metal Driver stent, 1.2 percent that was not statistically significant.

The primary endpoint was target vessel failure at nine months, and there was a 48 percent reduction in target vessel failure from 15.1 percent to 7.9 percent between Driver and Endeavor, a highly significant difference.

One of the components of target vessel failure is target vessel revascularization. There was a 55 percent reduction from 12.5 to 5.6 percent in target vessel revascularization. And the most specific clinical index of anti-restenosis efficacy is target lesion revascularization, and there was an even higher reduction to 61 percent from 11.8 to 4.6 percent comparing the bare metal Driver to the Endeavor stent.

These are all the clinical events to 9 months, and you can see highlighted in yellow the target

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lesion revascularization, target vessel revascularization, MACE and TVF are all highly statistically significant, favoring the Endeavor stent in terms of showing an improvement. I'd also like to point out that there were no further episodes of stent thrombosis in either the Endeavor or the Driver arm between 30 days and 9 months, staying at 3 and 7 events, .5 and 1.2 percent.

These are the angiographic and IVUS results to 8 months and, again, highlighted in yellow are statistically significant differences both within the stent and within the vessel segment treated. All of the parameters, including percent diameter stenosis, late loss and angiographic binary restenosis showed improvement with the Endeavor stent versus the Driver stent. For instance, in-stent late loss was reduced from 1 to .62. In-stent restenosis was reduced from 33 to 9.5.

Similarly, from the standpoint of volumetric IVUS assessments, there was significant reduction in neointimal hyperplasia throughout the stent length.

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One of the indices that interventionalists look at is angiographic binary restenosis within the segment. And here you can see that, for the Driver stent, 34.7 reduced by 62 percent to 13.3 with the Endeavor stent in this blinded, randomized trial.

We have data out to 36 months in this study, and you can see interestingly, again, there are no further episodes of stent thrombosis either for the Endeavor or the Driver stent between that 9-month period and now 3 years. We do see increased numbers of events equally distributed amongst the Endeavor and Driver stent in other safety and efficacy parameters, but still, highly significant differences in TLR, TVR, MACE and TVF. That can be best represented by looking at these actuarial event tree survival curves. The primary endpoint target vessel failure shown here out to 3 years with no evidence of a diminution in the effectiveness over this 3-year clinical follow-up period. target vessel revascularization again showing no evidence of diminution in clinical efficacy. Target lesion revascularization quite similar -- no evidence of

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reduced or diminished efficacy now with 3-year follow-up.

The composite safety endpoint of cardiac and myocardial infarction slightly favoring the Endeavor stent but not statistically significant out to 3 years. In-stent thrombosis, there were no further stent thrombosis episodes out to 3 years with either the Endeavor or the bare-metal stent, reflecting the initial difference of .5 versus 1.2 percent that was expressed in the first 30 days.

So we can conclude from this Endeavor II trial when we compare the bare metal Driver stent with the Endeavor drug-eluting stent, there is a similar safety profile. Death, myocardial infarction and stent thrombosis were all similar through 3 years of clinical follow-up. There were improved angiographic results at 8 months follow-up, looking at the standard parameters of late loss and binary restenosis. There was superior target vessel failure with a reduction by 48 percent due largely to a diminished target vessel revascularization requirement by 55 percent which persisted through 3

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years of follow-up.

The next randomized trial is Endeavor III. And once again, to put this in context, this was at a time when we were looking more closely at surrogate angiographic endpoints. It's the smallest of the three studies. I was the co-principal investigator with Dr. David Kandzari. This was a 3:1 randomization of the Endeavor versus the CYPHER stent in single de novo native coronary lesions with a vessel diameter of 2.5 to 3.5 millimeters, a lesion length of 14 to 27 millimeters conducted in 436 patients at 30 sites in the United States.

The primary endpoint was in-segment late lumen loss by QCA at 8 months. This was a non-inferiority design with a pre-specified non-inferiority margin of .2 millimeters. Multiple secondary endpoints have shown the drug therapy was the same as Endeavor II, aspirin and Clopidogrel for at least 3 months. The Zotarolimus was the same. A total of 436 patient were enrolled -- 323 Endeavor, 113 CYPHER. Angiographic follow-up with 86 percent in the Endeavor cohort and 83

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percent in the CYPHER cohort. We have clinical follow-up out to 24 months varying from 99 percent to 96.9 percent.

This is a smaller study and, interestingly, there was a slight imbalance in some of the baseline characteristics. There was a highly statistically significant difference in gender with those randomized to either Endeavor or to CYPHER. There were more males or I should say more females, perhaps, in the Endeavor arm. There were no differences in diabetes and unstable angina, approximately 30 percent and slightly more than half in both arms. Reference vessel diameter was 2.75 and 2.79 millimeters. Lesion length approached 15 millimeters, and B2/C lesions were slightly favoring Endeavor with a higher frequency of more complex lesions. This is not uncommon in smaller randomized trials of this nature to see some imbalance of baseline characteristics.

These are clinical events at 30 days. It is interesting to note that, although not statistically significant, the rate of non-Q-wave myocardial

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infarction in the first 30 days associated with the procedure was .6 percent with Endeavor and 3.5 percent with CYPHER. There were no stent thromboses at 30 days with either device.

The primary endpoint was in-segment late loss with a non-inferiority design. And as I mentioned, the pre-specified non-inferiority margin was .20 millimeters. This study did not meet its primary endpoint. The P-value for non-inferiority was 0.791. The in-segment late loss for CYPHER was 0.13, and for Endeavor, it was 0.36. These are all of the angiographic findings and, certainly, there are important differences between the CYPHER and in the Endeavor stent at angiographic follow-up as discerned in this study.

For both in-stent and in-segment analyses of diameter stenosis, late loss and restenosis, the CYPHER stent had improved outcomes compared to the Endeavor stent. Similarly, intravascular ultrasound indicated less neointimal hyperplasia associated with the CYPHER stent compared to the Endeavor stent. We have clinical

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follow-up out to 24 months. It's important to note that for both of these devices, there were no stent thromboses out to 24 months, none. We saw no significant differences in any of the clinical outcomes out to 24 months.

If we look at target vessel failure, the composite index that were the primary endpoints of Endeavor II and IV and look at this event tree survival curves to two years, you can see some interesting observations. First, there's an early difference reflecting the lower frequency of periprocedural non-Q-wave MI's in Endeavor which narrows to the point of angiography balanced by a slightly higher frequency of target vessel revascularization for Endeavor, equalizing at approximately the 8-month angiographic follow-up time point. It's interesting to note the steepness of this slope or the influence of angiography on the clinical endpoint in this trial which had almost complete angiographic follow-up.

After 9 months, these curves are completely flat with no difference between Endeavor and CYPHER from

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the standpoint of target vessel revascularization, cardiac death or myocardial infarction.

We conclude from Endeavor III, that if you compare the CYPHER DES and the Endeavor DES in a trial designed such as this, that there was higher angiographic late loss at 8 months associated with the Endeavor stent. There were reduced periprocedural non-Q-wave MI's and low rates of death Q-wave MI and stent thrombosis through 2 years of follow-up for both arms and similar target vessel failure through 2 years of follow-up.

The final and the largest randomized trial is Endeavor IV, again, presented for the first time in public today. I was the principal investigator. This is a 1:1 randomization of the Endeavor drug-eluting stent compared with the commercially available TAXUS drug-eluting stent in single de novo native coronary lesions at a vessel diameter of 2.5 to 3.5 millimeters with a lesion length of less than 27 millimeters. It is a 1:1 randomization in 1,548 patients at 80 sites in the United States, an equal randomization between Endeavor

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in 774 patients and TAXUS in 774 patients.

The primary endpoint was target vessel failure at 9 months. There were several secondary endpoints including a powered angiographic secondary endpoint and other clinical endpoints. Drug therapy was aspirin and Clopidogrel now for at least 6 months, and this was associated with the requirement to give at least 6 months of dual antiplatelet therapy with a TAXUS stent to keep the arms balanced. The same Zotarolimus dose was used.

We, in fact, did enroll 1,548 patients, 773 to Endeavor and 775 to TAXUS. Angiographic follow-up was 88 percent for the Endeavor arm and 82 percent for the TAXUS arm. Clinical follow-up at 9 months was 96 and 95 percent respectively for Endeavor and TAXUS. I will again remind you this is largely a clinical follow-up study with only 18.6 percent of patients actually receiving follow-up angiograms.

These are the baseline characteristics which were equally balanced between the Endeavor and TAXUS arms, 67 and 68 percent males, diabetics is slightly

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lower than 30 percent, approximately 50 percent with unstable angina, reference vessel diameter 2.73 and 2.70, lesion length quite similar, 13.4, 13.8 millimeters and just under 70 percent had complex B2/C lesions, no differences.

These are clinical events at 30 days, and you'll note that there are a lot of yellow highlights here. First, I would like to point out that there were 3 episodes of stent thrombosis in the Endeavor arm in the first 30 days and 1 in the TAXUS arm. There was a higher frequency of periprocedural non-Q-wave myocardial infarctions with TAXUS, 17 events or 2.2 percent versus Endeavor, 4 events, 0.5 percent, and that higher non-Q-wave MI frequency affected overall MIs, the composite indices shown here which were all statistically significantly different.

We often wonder what the importance is of these periprocedural non-Q-wave MIs. Many people argue, and it's still very controversial, as to whether or not they have clinical prognostic importance. To try to better understand this, we looked at the CKMB rises

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compared to the upper limits of normal for each laboratory for each site for the 21 periprocedural non-Q-wave MI events.

People argue that whether a 5 times upper limit of normal or an 8 times upper limit of normal represents a large infarct with clinical prognostic significance, but very few people would argue that a greater than 10 times normal CKMB rise does represent a large clinical infarct. And certainly, there have been many studies to suggest that this is associated with future prognosis. In this analysis, you can see that 8 out of the 17 TAXUS non-Q-wave MIs, or 47 percent, had greater than 10 times CKMB rises. These were non-trivial myocardial infarctions.

The primary endpoint for this study was non-inferiority with a non-inferiority pre-specified margin of 3.8 percent of the target vessel failure 9-month analysis. As you can see here, the P-value of the non-inferiority was 0.001, so it met the primary endpoint. The TAXUS TVF rate was 7.4. The Endeavor TVF rate was slightly less at 6.8 percent. The clinical efficacy

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component of target vessel failure was target vessel revascularization. It was 5.5 percent for Endeavor and 5.0 percent for TAXUS, a non-significant difference. The target lesion revascularization rates were 4.2 percent for Endeavor and 2.7 percent for TAXUS, a non-significant difference.

If we now look at clinical events to 9 months, we can see that there are no important differences in any of the clinical parameters listed on this table. I will point out that death and myocardial infarction, there are non-significant differences. There were three additional stent thrombosis episodes that occurred in the Endeavor arm after 30 days. All of these three episodes occurred between 30 days and six months. Of these three episodes, one was associated with a myocardial infarction and two others were not associated with a myocardial infarction. There were no further episodes of stent thrombosis for TAXUS, so the over all stent thrombosis rate was 0.8 percent for Endeavor versus 0.1 percent for TAXUS, and no differences that were statistically meaningful in any of

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the other parameters.

When we look at actuarial event tree survival for the primary endpoint of target vessel failure, we can see that at 9 months, there are no significant differences between Endeavor and TAXUS. Target vessel revascularization at 9 months is almost superimposable with no significant differences. Target lesion revascularization, again, does not show significant differences at the 9-month evaluation time point. The composite endpoint of cardiac death and myocardial infarction also shows no significant differences.

These are the angiographic and IVUS findings in the small cohort that received angiographic follow-up at 8 months. There were meaningful differences in many of the angiographic parameters. For both in-stent and in-segment, both percent diameter stenosis and late loss showed a benefit of TAXUS versus Endeavor or lower follow-up percent diameter stenosis in late loss both in-stent and in-segment.

There were numerical, but not statistically significant, differences in angiographic binary

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restenosis, and in-segment binary restenosis was 10.4 with TAXUS and 15.3 with Endeavor. There were also significant differences in neointimal hyperplasia as discerned by intravascular ultrasound imaging with a volumetric determination.

It is interesting to reflect on the importance of angiographic follow-up. We're looking now at target vessel revascularization in those patients that did have angiographic follow-up and those that did not.

You can see that there's a drop-off immediately in the frequency when angiography is not applied and does not influence the clinical outcome. If we only look at the more than 80 percent of patients that had clinical follow-up, the target vessel failure rates are 5 and 4.8 percent for Endeavor and TAXUS respectively.

If we now look at target lesion revascularization, the same observation. If we only look at the 80 plus percent of patients which is the real world -- we don't obtain angiograms routinely in

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these patients -- 3.5 percent versus 2.7 percent, Endeavor versus TAXUS.

If we felt that these differences in late loss or these small differences, small numerical differences in target lesion revascularization were significant, they should become exposed in the higher restenosis risk subgroups, where the likelihood of restenosis would be greater and you might see an upward drift of late loss.

We're looking at five different post hoc subgroup analyses in diabetics, long lesions greater than 20 millimeters, small vessels less than 2.5 millimeters, multiple stents and LAD lesions. First, you can see that the composite index of target vessel failure shows no difference between Endeavor and TAXUS. The safety endpoint of cardiac death and myocardial infarction shows no difference with some of the safety indices slightly favoring Endeavor. Target vessel revascularization shows absolutely no difference.

Perhaps more relevant is target lesion revascularization. And again, target lesion

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revascularization shows no difference in these high restenosis risk subgroups between Endeavor versus TAXUS. And in the clinical-only follow-up cohort, again, absolutely no evidence of a trend suggesting a higher frequency of target lesion revascularization with Endeavor versus TAXUS in high restenosis risk subgroups.

So we can summarize the Endeavor IV trial, which is a comparison of the TAXUS versus Endeavor drug-eluting stents, by indicating that the Endeavor stent reduced periprocedural non-Q-wave MIs compared with TAXUS, and there was an overall similar safety profile looking at death, Q-wave MI and stent thrombosis through 9 months of follow-up, that it met its primary target vessel failure endpoint, that there was similar TVR and TLR rates, even in high restenosis risk subgroups through 9 months of follow-up, and there was higher angiographic late loss at 8 months follow-up associated with the Endeavor stent.

To finally summarize the Endeavor clinical program, it's important to note that there is consistency of these results across the entire program.

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Angiographically, if we look at Endeavor II, III and IV, you can see in-stent that in-segment late loss almost superimposable for all three studies. Similarly, for in-stent and in-segment angiographic binary restenosis, very similar across all three studies.

And finally, in this last slide, if you look at target vessel failure to 9 months in each of these randomized trials, I think you can see summarized the salient findings. Certainly, for Endeavor II compared to now a bare-metal stent with tight confidence boundaries, we see a reduction in both target vessel failure and target vessel revascularization, a significant improvement, and no difference in safety, cardiac death and MI. For Endeavor III and Endeavor IV compared to either a CYPHER or a TAXUS stent, no differences in the composite endpoint of target vessel failure, the safety endpoint or the revascularization endpoint of target vessel revascularization.

So to summarize, in these three randomized trials involving 3,181 patients, the Endeavor DES has demonstrated a safety profile similar to the Driver

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bare-metal stent from the standpoint of death, myocardial infarction and stent thrombosis, superior reduction in restenosis, both angiographic and clinical, versus the bare-metal Driver stent, comparable clinical outcomes as measured by target vessel failure which is a composite index but broken up into target vessel revascularization or cardiac death and MI or target lesion revascularization, versus the approved TAXUS drug-eluting stent, durable clinical outcomes during long-term follow-up to 3 years and consistent angiographic and clinical outcomes across all of these randomized clinical trials.

Next, I have the pleasure to introduce to Dr. Laura Mauri who is the Chief Scientific Officer of the Harvard Clinical Research Institute and is an Interventional Cardiologist from Brigham and Women's Hospital.

DR. MAURI: Thank you and good morning. It's my pleasure to present today a safety overview of the Endeavor clinical trial program. My name is Laura Mauri. I'm an Interventional Cardiologist at the

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Brigham and Chief Scientific Officer at Harvard Clinical Research Institute. By way of disclosure, I am an advisor to Medtronic.

My lodging and transportation to this meeting was paid for by Medtronic and I have been a co-investigator for the Endeavor III trial.

We recognize in the context of the current DES landscape that some of our attention has shifted from looking purely at efficacy to paying much greater attention to documenting the safety of new devices. And in this context, the FDA requested that the Endeavor clinical trial program be assessed for its safety across multiple different studies including the Endeavor stent.

What I'll present today is a safety overview of this analysis that seeks to compare the Endeavor stent to the Driver bare-metal stent as a benchmark for safety.

This analysis includes six different trials of the Endeavor stent, three of them randomized and three of them registries, but the bulk of the data stemming from the three randomized trials that Dr. Leon

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has focused on and consists of follow-up in these different trials ranging from 9 months to up to 4 years.

And to give you a scope of the total number of patients that were included, we have 2,088 patients with 270-day follow-up, 1,287 with 720-day follow-up which is consistent with 2 years of follow-up, and 675 patients with 1080 day follow-up out to 3 years, a smaller group with follow-up out to 4 years.

The objective of this overview was to evaluate whether the Endeavor stent was associated with increased rates of death, myocardial infarction or stent thrombosis compared with the Driver bare-metal stent. The method used was to pool data on an individual patient level from six Endeavor stent arms that you've seen and one Driver bare-metal stent arm. And these data are presented as cumulative incidence at 360 and 1080 days.

The strengths of this analysis are the consistent definitions that were used that are uniform across all the different trials, the uniform data collection that was maintained across the trial program

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and the density and the duration of follow-up that you'll see.

The limitations to this analysis are that because there were different control arms for each of the different studies, the randomization effect is not entirely preserved, but this limitation should be viewed in the context of what is intended to be a conservative analysis looking for any signal of harm associated with this new drug-eluting stent relative to the Driver bare-metal stent control.

So it's important to consider the context of the baseline characteristics of the patients that were included in these studies, and one can see, as Dr. Leon has presented, that there is some variation in the rates of diabetes across the trials with higher rates of diabetes being observed in the U.S. studies as opposed to the European and OUS studies that were performed.

There is a consistency of the recommended clopidogrel duration in that it was recommended to be a minimum of 3 months in all of the trials with the exception of Endeavor IV. In the Endeavor IV trial,

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since the comparator was the TAXUS stent, the required duration of therapy was 6 months in order to be consistent across the randomized treatment arms. So there is -- most of the data, however, that we're going to focus on extends beyond the duration of follow-up with the Endeavor IV trial, and so it's related to the recommended duration of 3 months.

Furthermore, the clinical follow-up I'll point out in each of these studies is ongoing, but at the durations that have been achieved so far, we have seen rates of clinical follow-up ranging from 96 percent to 99 percent. When one pools together the Endeavor data as we've done for this analysis and then compares some of the important characteristics that are associated with outcomes post-PCI, one can see that, if anything, there was a slightly higher rate of diabetes in the Endeavor group, as opposed to the Driver group. There were small differences in reference vessel diameter and lesion length that were not statistically significant.

It's also incredibly important to consider

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the usage of dual antiplatelet therapy and the duration of use in the context of the safety events that are observed, particularly in the long term. As most of the members of the panel are aware, there has been a shift in practice over the past year, probably since the December panel meeting, towards longer durations of use of dual antiplatelet therapy and some practice extending beyond the current ACC guidelines and to the extent that some patients are being treated even beyond 1 year.

And so we looked prospectively in the trials where this was clearly collected to be able to understand the rates of usage of either clopidogrel or ticlopidine plus aspirin to 1 year and to 2 years and what we found was that approximately 30 percent of patients were still on dual antiplatelet therapy up to 1 year, but at 2 years, that rate was down to 10 percent. So in both cases beyond 1 year, the minority of patients were still on dual antiplatelet therapy.

It's also important to note that this was not significantly different when comparing the patients treated with Endeavor versus Driver. And I'll remind

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you that the randomization there was blinded.

So as an overview, what I'll be presenting, you'll see in the next series of slides the cumulative incidence presented according to Kaplan Meier graphs. And one reason that this is presented as a cumulative incidence, that is the occurrence of events rather than event-free survival is to be able to present the actual rates and interval rates out to 3 years. In particular, we were interested in the outcome of stent thrombosis and whether there were any differences in the patterns after 1 year.

To summarize what you'll see, we found no evidence of an increase in adverse events for Endeavor as compared to Driver when comparing death, cardiac death, myocardial infarction or stent thrombosis. So first, starting with the cumulative incidence of death to 1080 days or 3 years, what you see is in yellow a rate of 3.1 percent for the Endeavor group as compared to a rate of 4.5 percent in blue for the Driver bare-metal stent control.

Looking specifically at cardiac death, the

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rates are 1.0 percent at 3 years for the Endeavor group and 2.4 percent for the Driver bare-metal stent control. The cumulative incidence of myocardial infarction up to 1080 days or 3 years was 2.7 percent for the Endeavor group and 4.2 percent for the Driver group. And looking at the composite endpoint of cardiac death plus myocardial infarction, one sees a lower rate for the Endeavor group of 3.5 percent as compared to 6.6 percent for the Driver bare-metal stent control.

Before I move on to stent thrombosis which was an important endpoint that we ascertained in the safety analysis, I want to review some of the definitions since there's been a lot of discussion over the past year about different ways to look at stent thrombosis. The original protocols for all of the Endeavor clinical trials use the same definitions, and these original definitions included patients with coronary symptoms and angiographic or pathologic confirmation of thrombosis. In addition, any patient with an unexplained death within 30 days or any patient with a target vessel MI or an MI that couldn't be

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attributed to a non-target vessel would be included as a stent thrombosis.

Patients who'd had restenosis and were treated with a target lesion revascularization were excluded from the possibility of having a stent thrombosis under the original definitions.

Now in 2006, in early 2006, really prior to the concerns about late stent thrombosis, there were a series of meetings together with FDA with industry representatives and academic research groups to come up with a uniform set of definitions for stent thrombosis. It was recognized that different trials were using different definitions and that our understanding of stent thrombosis in the drug-eluting stent era might be different than what we had been accustomed to in the era of bare-metal stents where the focus was really on the first 30 days.

And these definitions sought to account for different levels of certainty according the amount of evidence supporting a diagnosis of stent thrombosis and ranged from the most restrictive definitions, definite

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thrombosis, to the most inclusive possible stent thrombosis which would include any unexplained death.

The balance has favored the usage of a compositive, definite and probable stent thrombosis, although all of these definitions have been analyzed. In addition, these definitions did not exclude the possibility of restenosis leading to a stent thrombosis in the future and would consider any event that classified as a possible stent thrombosis under the series of definitions.

Furthermore, the timing was then classified according to early -- whether it occurred within the first 30 days, late -- between 30 days and 1 year, and very late -- occurring beyond 1 year, and this was to be consistent with the understanding of possible different patterns over time of healing in drug-eluting stents.

So moving on to the results for the Endeavor clinical program, we found that the rate of stent thrombosis according to the original protocol definitions was 0.5 percent at 3 years as compared to 1.2 percent for the Driver bare-metal stent at 3 years.

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And it's important to note here that the density of clinical follow-up there were over 1900 patients in the Endeavor group followed at least 360 days and over 570 with the Driver stent followed at least 360 days. And in that context, there were zero events observed under the original protocol definition after the 360 mark. So beyond 1 year, there were no stent thrombosis events observed in either group analyzed.

When one uses a more inclusive definition of ARC definite and probable stent thrombosis, one sees the rate of events for the Endeavor arm was 0.8 percent at 3 years as opposed to a rate of 1.5 percent for the driver bare-metal stent control. And in each group, there is one additional event that

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