UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

CIRCULATORY SYSTEM DEVICES PANEL

+ + +

June 20, 2019
8:00 a.m.

Gaithersburg Holiday Inn
Grand Ballroom
Two Montgomery Village Avenue
Gaithersburg, MD 20879

PANEL MEMBERS:

RICHARD A. LANGE, M.D., M.B.A.	Panel Chair
JOAQUIN E. CIGARROA, M.D.	Voting Member
KARLA V. BALLMAN, Ph.D.	Temporary Voting Member
JAMES C. BLANKENSHIP, M.D., MHCM, MACC	Temporary Voting Member
EDWIN C. GRAVEREAUX, M.D., FACS, FACC	Temporary Voting Member
JOHN W. HIRSHFELD, JR., M.D.	Temporary Voting Member
KEVIN E. KIP, Ph.D., FAHA	Temporary Voting Member
MICHAEL W. KRUCOFF, M.D., FACC, FAHA, FSCAI	Temporary Voting Member
ELLIOT B. LEVY, M.D.	Temporary Voting Member
FRANK W. LoGERFO, M.D.	Temporary Voting Member
TODD E. RASMUSSEN, M.D., Colonel USAF MC	Temporary Voting Member
JOHN C. SOMBERG, M.D.	Temporary Voting Member
DUXIN SUN, Ph.D.	Temporary Voting Member
GARY JARVIS	Industry Representative
PATRICIA M. DAIGLE, RN, FNP	Consumer Representative
PHILIP POSNER, Ph.D.	Patient Representative
EVELLA F. WASHINGTON	Designated Federal Officer

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly, the Food and Drug Administration makes no representation as to its accuracy.

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

BRAM D. ZUCKERMAN, M.D.
Office Director, Office of Health Technology 2 (OHT 2: Cardiovascular Devices)
Office of Product Evaluation and Quality

YU ZHAO, Ph.D.
Mathematical Statistician
Office of Surveillance and Biometrics

ANDREW FARB, M.D.
Chief Medical Officer, Office of Health Technology 2 (OHT 2: Cardiovascular Devices)
Office of Product Evaluation and Quality

MICHAEL FELBERBAUM
Press Contact

FDA PRESENTERS:

ELENI WHATLEY, Ph.D.
Senior Lead Reviewer
Office of Health Technology 2 (OHT 2: Cardiovascular Devices)
Office of Product Evaluation and Quality

KAREN MANHART, V.M.D., DACVP
Veterinary Medical Officer
Office of Health Technology 2 (OHT 2: Cardiovascular Devices)
Office of Product Evaluation and Quality

DONNA BUCKLEY, M.D., M.S.
Interventional Radiologist
Office of Health Technology 2 (OHT 2: Cardiovascular Devices)
Office of Product Evaluation and Quality

INDUSTRY PRESENTERS:

LAURA MAURI, M.D., M.Sc.
Vice President, Global Clinical Research and Analytics
Medtronic

DANIEL CLAIR, M.D.
Chair, Department of Surgery
University of South Carolina
Palmetto Health-USC Medical Group

ERIC A. SECEMSKY, M.D., M.Sc., RPVI, FACC, FSVM
Director, Vascular Intervention
Beth Israel Deaconess Medical Center

INDUSTRY ADVISORS:

IAN T. MEREDITH, A.M., M.B.B.S., Ph.D., FACC, FSCAI, FAPSIC, FAHA
EVP & Global Chief Medical Officer
Boston Scientific Corporation

TED LYSTIG, Ph.D., FASA
Senior Director, Corporate Biostatistics
Medtronic

KENNETH OURIEL, M.D.
President & CEO
Syntactx

AARON LOTTES, Ph.D.
Lead Scientist for Zilver PTX
Director, Regulatory Science/PAD Therapies
Cook Medical

J.D. MELER, M.D.
Vice President, Medical and Clinical Affairs
BD Interventional

WILLIAM A. GRAY, M.D., FACC, FSCAI
System Chief of Cardiovascular Services
Main Line Health
President, Lankenau Heart Institute

PETER A. SCHNEIDER, M.D.
Professor of Surgery
Division of Vascular and Endovascular Surgery
University of California, San Francisco

OPEN PUBLIC HEARING SPEAKERS:

LINDSAY MACHAN, M.D.
Department of Radiology
University of British Columbia
Vancouver, British Columbia, Canada

RENU VIRMANI, M.D.
President, CVPath Institute, Inc.

ERICA L. MAYER, M.D., M.P.H.
Susan F. Smith Center for Women's Cancers
Dana-Farber Cancer Institute

RAMON L. VARCOE, M.B.B.S., M.S., FRACS, Ph.D.
University of New South Wales
Prince of Wales Hospital
Sydney, Australia

ALIK FARBER, M.D., M.B.A.
BEST-CLI Leadership

YANN GOUEFFIC, M.D., Ph.D.
Department of Vascular Surgery
Institut du Thorax
Nantes, France

KIM J. HODGSON, M.D.
President, Society for Vascular Surgery
Chair, SVS Paclitaxel Safety Task Force
Professor/Chairman of Vascular and Endovascular Surgery
Southern Illinois University

DANIEL J. BERTGES, M.D.
Vascular Quality Initiative
Society for Vascular Surgery

W. SCHUYLER JONES, M.D.
National Cardiovascular Data Registry
The American College of Cardiology
Interventional Cardiologist/Associate Professor of Medicine
Duke University/Duke Clinical Research Institute

ROSEANN WHITE, M.A.
Independent Statistical Consultant
Your 3rd Opinion, Inc.

STEPHANIE FOX-RAWLINGS, Ph.D.
Senior Fellow
National Center for Health Research

JOHN WINSCOTT, M.D.
Professor of Medicine and Surgery
The University of Mississippi Medical Center

ROBERT YEH, M.D., M.Sc., M.B.A.
Director, Smith Center for Outcomes Research in Cardiology
Beth Israel Deaconess Medical Center
Associate Professor of Medicine
Harvard Medical School

INDEX

INDEX

M E E T I N G

(8:00 a.m.)

DR. LANGE: Howdy. I'd like to call the first day of the Circulatory -- the second day of the Circulatory System Devices Panel to order.

I'm Dr. Richard Lange, the Chairperson of this Panel. I'm President of the Texas Tech University Health Sciences Center in El Paso and Dean of the Paul L. Foster School of Medicine and previously was an interventional cardiologist.

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

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

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

DR. RASMUSSEN: Good morning, my name is Todd Rasmussen. I'm Professor of Surgery and Associate Dean for Research at the School of Medicine at the Uniformed Services University and attending vascular surgeon at Walter Reed National Military Medical Center.

DR. LEVY: Good morning. Elliot Levy, interventional radiologist at the National Institutes of Health.

DR. LoGERFO: Good morning, I'm Frank LoGerfo. I'm Professor of Surgery at the Beth Israel Deaconess Medical Center, Harvard Medical School, retired from vascular surgery practice and now engaged in research on injury to blood vessels.

DR. BLANKENSHIP: Good morning, I'm Jim Blankenship. I'm an interventional

cardiologist and Professor of Medicine at the Geisinger Commonwealth School of Medicine and Chair of Cardiology for the Geisinger system.

DR. KRUCOFF: Good morning, I'm Mitch Krucoff. I'm a Professor of Medicine and Cardiology at Duke University Medical Center, and Director of the Cardiovascular Devices Unit at the Duke Clinical Research Institute.

DR. CIGARROA: Good morning, I'm Joaquin Cigarroa. I'm Professor of Medicine at Oregon Health and Sciences University, Chief of Cardiology, Clinical Chief of the Knight Cardiovascular Institute, and a general cardiologist with added qualifications in interventional cardiology.

DR. SOMBERG: John Somberg, Professor of Medicine, Rush University, Chicago.

MS. WASHINGTON: My name is Evella Washington. I'm the DFO.

DR. BALLMAN: Good morning, I'm Karla Ballman, and I'm at Weill Cornell Medicine in New York. I am the Chief of Biostatistics and Epidemiology, and my expertise is in statistics and epidemiology.

DR. HIRSHFELD: Good morning, I'm John Hirshfeld. I'm Professor of Medicine at the University of Pennsylvania and an interventional cardiologist.

DR. SUN: Good morning. Duxin Sun, University of Michigan, Professor of Pharmaceutical Science and Director of Pharmacokinetics Core.

DR. GRAVEREAUX: Ed Gravereaux, vascular surgery and endovascular surgery at Brigham and Women's Hospital in Boston.

DR. KIP: Kevin Kip, Professor of Epidemiology and Biostatistics, College of Public Health, University of South Florida, Tampa, Florida.

MS. DAIGLE: Patricia Daigle, nurse practitioner, LSU Health Sciences Center in cardiology.

MR. JARVIS: Gary Jarvis, the Industry Rep, with Alfa Medical.

DR. POSNER: Phil Posner, patient and courtesy Professor of Physiology, University of Florida.

DR. LANGE: And I appreciate everybody returning after a stimulating day at the first day. So thank you, everybody, for being here. And if you have not already done so, please sign the attendance sheets that are on the tables by the door.

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

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

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

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and consultants of the Panel who are special Government employees or regular Federal employees have been screened for

potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for 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 and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on information related to recent observations of increased long-term mortality in peripheral arterial disease patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents compared to patients treated with uncoated comparator devices. FDA requests Panel input regarding the presence and magnitude of the signal and potential causes. FDA also seeks input regarding appropriate regulatory actions associated with the findings.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208.

Gary Jarvis is serving as the Industry Representative, acting on behalf of all related industry, and he is employed by Alfa Medical.

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

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

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

For the duration of the Circulatory System Devices Panel meeting on June the 20th,

2019, Dr. Duxin Sun has been appointed to serve as Temporary Non-Voting Member. For the record, Dr. Sun is a member of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee at the Center for Drug Evaluation and Research. This individual is a special Government employee who has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting.

The appointment was authorized by Russell Fortney, Director of the Advisory Committee Oversight and Management Staff, on May the 13th of 2019.

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

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

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

The press contact for today's meeting is Mr. Michael Felberbaum. If anyone from the press desires to speak with him, please see Mr. Artair Mallett at the desk outside the meeting room to obtain his contact information.

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

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

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

Finally, please silence your cell phones and all other electronic devices as I turn the

meeting back over to Dr. Lange. Thank you.

DR. LANGE: Thank you, Ms. Washington.

And as you're silencing your cell phones, just a couple things. I would remind the Panel that this is a public hearing, so do not have any sidebar conversations. Any conversation should be available for the public to hear.

All of our presentations have a specified time limit, and that's not to discourage participation or limit discussions, but it's actually to encourage participation. There's a lot of interest, and we have a lot of speakers today from FDA, manufacturers, and during our Open Public Hearing as well. So I'll ask people to adhere to their time limit so that we can get all those comments in.

As Evella mentioned, if you don't identify yourself, I'll ask you to do so, it makes it easier for the people that are transcribing it, and I apologize if it appears I'm being rude. We just need to get it up for the public record.

And speaking of transcription, I want to thank Lynn Peterson, senior writer for *Trends in Medicine*, who noted I made a comment yesterday, and I just want to clarify that for the record. It was in response to Question 2 from the FDA regarding a class effect, please discuss the strength of the evidence supporting a late mortality risk class effect, and in summarizing the comments of the Panel, and I think I'm quoting what I said, the strength of the evidence is low and no one feels one device is superior to the others, nor do they feel patients should be informed of the data. It should have said "nor do they feel patients shouldn't be informed of the data." So for anybody transcribing that and was here yesterday, I hope you're here today and don't quote what was said yesterday. So that's for the record, and I apologize for that. Thank you, Lynn, for pointing that out, and to others who noticed that as well.

We'll now proceed to the FDA's introduction. I would like to invite Dr. Eleni Whatley

to approach the podium and to begin FDA's presentations, after which each speaker will come to the podium and identify themselves before they begin.

And I will 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 Chair.

And, Dr. Whatley, you may begin and I believe you have 45 minutes for your presentation.

DR. WHATLEY: Thank you. Hi, I'm Eleni Whatley. This is Day 2 of FDA's presentation at the general issues panel meeting for the potential paclitaxel-coated DCB and DES late mortality signal.

This is the agenda for FDA's presentation for Day 2. I'll begin by providing a brief recap of what was discussed yesterday. We will then summarize our additional analyses including preclinical study review, dose effect, benefit-risk assessments, as well as discuss potential next steps and the effect of our conclusions on other indications.

To summarize Day 1, FDA concluded that there's a signal associated with an increase in mortality through 5 years for paclitaxel-coated devices as compared to non-coated devices and that a class effect cannot be excluded.

We made attempts to acquire missing data and assessed for the impact of missing data and believe that the mortality still exists given this missing data. However, no relationships were determined based on specific subgroups and to date, no causality could be attributed to this increased mortality.

The Panel generally agreed with FDA's conclusions. They indicated that they agreed that a signal exists but that there is uncertainty regarding the magnitude. While they do not believe sufficient data are available to suggest a class effect, they also noted that the data were evaluated in aggregate and did not believe that any specific device should be excluded. The

Panel believed that the amount of missing data was unfortunate and any previous and future attempts to gain missing data are important. Finally, the Panel were also not able to determine relationships with any specific subgroup or causality for the signal.

I will now discuss the reevaluation of all available preclinical data by FDA.

After determining the increase in all-cause mortality, one of the major questions FDA had was the potential reasoning or causality for the increase in mortality. In addition to the clinical analyses that were already being conducted, FDA thought it pertinent, given the new information, to reevaluate all preclinical and animal studies in order to see if any data including safety and pharmacokinetic, or PK, evaluations are available to associate a potential cause for the increase in mortality.

As a reminder, the approved DCBs and DES have varying characteristics, including drug dose density, which ranges from 0.167 $\mu g/mm^2$ to 3.5 $\mu g/mm^2$, and the maximum total drug load, which ranges from 0.1 mg to 17 mg based on the specific delivery size. However, in many instances in both the clinical and animal studies, multiple devices were used. Thus, additional drug was introduced.

I would also like to point out that although the paclitaxel dose administered during DCB and DES treatment may be significantly less than intravenous administration for cancer, it's important to consider the differences in drug formulation and route of administration, which may affect the drug activity and metabolism.

A summary of the detectable drug levels in local tissue, plasma, and downstream organs and tissues when using DCB and DES to treat lower limb vasculature in preclinical animal models is provided in the next few slides.

So as noted, given the new information regarding long-term clinical mortality, FDA reevaluated the preclinical animal studies that were conducted on the five approved devices. Over 30 animal studies were assessed, which included one-time dose safety studies, three-time

dose safety margin studies, and PK studies which specifically assessed the drug levels in various tissues and how the drug was eliminated.

However, some of the studies were conducted over 10 years ago and thus do not include data for current FDA feedback, such as assessment of various tissues and organs and appropriate study duration. For example, some studies were terminated after 60 days when there was still detectable levels of drug in the tissue and healing was yet to be completed.

For the PK studies, drug levels are assessed in the local arterial vasculature, where the DCB or DES are deployed, the plasma and various downstream tissues and organs. For the local vessel concentrations in these studies, drug levels were generally detectable beyond 60 days with some studies demonstrating local arterial tissue levels above the level of quantitation at 180 days and beyond, up to 270 days in some cases.

For the plasma concentration, paclitaxel cleared rapidly from systemic circulation. Immediately post-procedure, detectable levels were generally low and declined to levels below quantitation between 6 to 24 hours.

Paclitaxel concentrations were also evaluated in downstream tissues and organs of elimination. The downstream tissues evaluated for drug dosage were typically distal vasculature, though safety evaluations also included evaluations for the gluteus maximus, gracilis, semitendinosus, semimembranosus muscles, and coronary bands. In some cases, these tissues were also assessed for drug content.

Drug levels were also evaluated in organs of elimination such as the kidneys, liver, lung, and spleen.

The detectable drug levels in these tissues and organs were assessed at acute time points and through study termination, which is usually 180 days and beyond or when totals were below quantitation level, or BQL. As noted previously, in some cases the study duration did not extend until the detectable levels were BQL.

In general, drug levels were detectable in most downstream tissues and organs of elimination beyond 90 days. Paclitaxel is detected in the lungs in all cases and demonstrated the highest concentration of all organs. Further, the highest drug levels in the lung were within the cytostatic potency range for paclitaxel for one device; however, overall the levels in the lungs were generally low and declined steadily. Levels were lower in the liver and kidneys and cleared more quickly. In downstream and distal tissues, levels were also low but persisted until Day 90 or beyond in some cases.

Dr. Karen Manhart will soon discuss any adverse findings that were detected in the preclinical animal studies. Please note, however, that these studies were not designed to specifically detect any long-term adverse effects related to paclitaxel. The studies, in general, only lasted for a short duration, and the long-term effects of paclitaxel exposure and retention in local and downstream tissues after DCB and DES exposure and how it could be inferred for patients with PAD are largely unknown.

Before going over these studies in detail, we believe it's pertinent to point out some known adverse effects associated with paclitaxel when used to treat cancer which includes neutropenia, hypersensitivity reactions (such as skin reactions and dyspnea), cardiovascular effects (such as hypotension, bradycardia, and hypertension), anaphylaxis, and nausea.

There's also some evidence in the literature to suggest that paclitaxel's cellular effects are concentration dependent. At clinically high concentrations, paclitaxel is cytotoxic, meaning it kills cells and can act as a chemotherapeutic agent. In contrast, at low concentrations, concentrations similar to those administered with paclitaxel-coated devices, the drug has been shown to be cytostatic and exhibit pro-inflammatory and pro-angiogenic activity, which may result in other unattended adverse effects.

While numerous scientific papers have reported effects such as these regarding low doses of paclitaxel in preclinical animal studies, this is not being pointed out to definitively

come to any conclusion regarding clinical effects of paclitaxel at this dose. This is solely being pointed out to note that even though low doses of paclitaxel are used in DES and DCB, much lower than that administered for cancer, it does not imply that no adverse effects can be experienced at this dose.

To conclude, paclitaxel is present in the local and downstream vasculature and tissues for 60 and 90 days and beyond and in some cases for as long as 270 days, even though the dose administered is considered very low.

While a relationship between this drug residence and any vascular or tissue effects could not be determined, as discussed in more detail soon, the potential that the drug could be having long-term effects on various tissues or organs during its residence and allowing for chronic effects cannot be definitively ruled out. Additional studies would have to be conducted to specifically assess for this.

To provide more detail regarding the animal study results and conclusions, Dr. Karen Manhart will now provide an overview of her analysis of the preclinical safety study data.

DR. MANHART: Good morning. I'm Dr. Karen Manhart, a veterinary medical officer and animal study reviewer in the Office of Cardiovascular Devices. I will briefly present the results of a review that was conducted of the preclinical vascular safety studies that were submitted to the Agency to support in vivo safety of PMA-approved paclitaxel drug-coated balloons and peripheral vascular stents. The goal was to assess for patterns or trends across all studies, which may provide insight into the paclitaxel safety signal that may not have been obvious during the initial review.

There were a total of 22 separate GLP vascular safety studies conducted between 2004 and 2018, which is not inclusive of the pharmacokinetic studies which are often conducted in parallel and have different objectives, design, and endpoints.

All treatment procedures were performed in the iliofemoral arteries of non-diseased

domestic swine or Yucatan mini-swine, for a total of 512 animals across all studies.

Peripheral arteries were treated with either the paclitaxel test devices or non-drug-coated angioplastic balloons or bare-metal stents.

As animal study design is not standardized, some studies were performed with the test and control in contralateral arteries. Others had separate tests and control animals.

For each DCB device, both nominal and 3X safety margin paclitaxel doses were evaluated. The safety margin dose was achieved by increasing drug coating density or overlapping nominal treatments. For drug-eluting stents, single and overlapping vessel segments were evaluated.

For each dose, cohorts of an average of 6 to 10 animals were exposed to the test and control devices for varying lengths of time post-implantation, generally 1 to 7 days, 30 days, 90 days, and 180 days prior to sacrifice. One study also included a 210-day cohort.

Study endpoints typically included:

- Acute device delivery and handling;
- General animal health and in-life clinical observations;
- Angiographic imaging;
- Comprehensive gross pathological evaluation;
- Downstream and major systemic organ;
- Histopathological evaluation; and
- Arterial target tissue histomorphologic and histomorphometric analysis.

As study cohorts in large animal safety studies are traditionally low by design, statistical analysis was typically not performed other than in conjunction with target tissue arterial semi-quantitative or histomorphometric analysis.

In regard to results, there were extremely low animal mortality and relatively low morbidity rates. There was no evidence of device-related bone marrow suppression, hepatic or

renal toxicity, and no reports of malignancy or unusual gross findings in any of the reviewed animal studies.

The most common finding associated with target tissues treated with paclitaxel versus controls was, as expected, medial smooth muscle loss with proteoglycan and collagen deposition due to paclitaxel drug effect.

Drug-eluted changes were also noted in downstream skeletal muscle and coronary band arterioles in drug-coated balloon-treated hind limbs at low levels in acute, 30-day and 90-day time points, sometimes containing crystalline drug material. However, no skeletal muscle regions were large enough to produce clinical symptoms in any of the animals. Downstream findings were rare to absent in drug-eluting stent-treated tissues.

Overall, there were no systemic pathological changes which appeared to be directly related to the drug or devices. Animal mortality and morbidity were low, and all studies to 210 days post-exposure, and therefore no distinct patterns of data trends suggestive of a potential mechanism for the increased late mortality in human study subjects was observed. However, it is important to note that animal study data is relatively short term, with the longest follow-up at 210 days, well before the time in which the signal has been detected clinically.

Additionally, as Dr. Whatley previously presented in regard to pharmacokinetics, the dose and detectable levels were evaluated in the animal studies with no clear conclusions regarding effects of paclitaxel or dose.

Dr. Donna Buckley will now present on the dose analysis conducted for the clinical studies.

DR. BUCKLEY: Thank you. Again, I'm Donna Buckley, interventional radiologist, CDRH.

To further elucidate a potential biological relationship between mortality and paclitaxel exposure, an evaluation of the association between dose and all-cause mortality for each pivotal trial was conducted based on the as-treated population of patients who were treated

with paclitaxel-coated devices.

Patients with known 5-year mortality status were separated into seven to nine dose groups based on the total paclitaxel dose received. Because dosage ranges differed by device, dose group ranges also varied.

Numbers in blue indicate the number of patients with known mortality status included in a specific dose group. The horizontal axis with the blue dot represents the mean paclitaxel dose, and the vertical axis represents the mortality rate per dose group. The red line segment indicates the 95% confidence intervals for the group mortality rate.

In addition to plotting mortality as a function of dose, a univariate Cox proportional hazard model for all-cause mortality status was conducted with dose as the only exploratory variable.

Here, patients treated in the Zilver PTX group received a mean total paclitaxel dose during the index procedure of 1.1 mg. The graph shows no definitive trend between the dose and 5-year all-cause mortality, and a lack of association is supported by the univariate Cox model with a p-value of 0.5.

Patients treated in the Lutonix group received a mean total paclitaxel dose during the index procedure of 3.5 mg. The graph suggests a possible trend of increased 5-year mortality with increased paclitaxel dose, but there's overlap in the 95% confidence intervals. The possible association between the dose and survival time is supported by the univariate Cox model with a p-value of 0.04.

Patients treated in the IN.PACT Admiral DCB group received a mean total paclitaxel dose during the index procedure of 7.5 mg. The graph suggests no definitive trend in the 5-year all-cause mortality by dose. The Cox model resulted in a p-value of 0.09.

Finally, patients treated in the Stellarex DCB group received a mean paclitaxel dose during the index procedure of 4.2 mg. The graph indicates no evident trend between paclitaxel

dose and 3-year mortality. The p-value of the Cox model is 0.8.

Overall, in the Zilver, IN.PACT SFA, and ILLUMENATE trials, there was no clear relationship between dose and mortality identified. The LEVANT 2 study suggested a possible increased mortality with increased dose but small numbers in overlapping confidence intervals, limited assessment. Overall, there was no consistent association between dose and mortality detected across all studies.

I'll now provide an overview of the benefit-risk considerations with regard to paclitaxel-coated devices.

FDA considers both the benefits and risks of a given therapy in its regulatory decision making. Factors that are considered include the extent of the probable benefits and risks including the type, magnitude, probability and duration, the uncertainty associated with these factors, whether alternative treatments exist, patient perspectives on benefits and risks, and the public health need.

FDA's original approval of paclitaxel-coated devices for the treatment of femoropopliteal disease was based on the available data which consisted of 1-year follow-up at the time of primary endpoint assessment, as well as limited supplemental long-term clinical data beyond 1 year. FDA determined that the probable benefits outweighed the probable risks. It's important to note that no mortality or safety signal was seen at the time of FDA approval.

Currently, additional long-term data are available, and FDA believes that it is prudent to consider this new information regarding potential adjustments to the benefit-risk profile of this group of devices.

To facilitate that effort, FDA examined the benefits of these devices, primarily demonstrated by a decrease rate of reintervention, especially, clinically driven target lesion revascularization. Risk ratios were estimated at 1, 2, and 5 years for the as-treated population. And for all time points, the risk ratio values remained less than 1.0, favoring the paclitaxel-

coated devices compared to the non-coated devices for both the fixed and randomized effects models.

Up to 2 years for this model the risk of TLR is significantly less for the paclitaxel group compared to the control groups, since the 95% confidence interval range excludes 1.0.

At 5 years, although the confidence interval crosses 1.0, the risk ratio is approximately 0.8, representing an approximately 20% decreased risk of clinically driven TLR at 5 years in patients treated with the paclitaxel-coated devices.

In further examining the TLR benefit, the number needed to treat was examined. The number to treat indicates, on average, the number of patients who need to be treated with the experimental treatment to avoid one clinically driven TLR. An estimate of number needed to treat is derived by inverting the absolute risk difference estimate of clinically driven TLR obtained from the meta-analysis.

In the display table, the numbers are based on a random effects meta-analysis and for Years 1 through 5, the number needed to treat ranges from 9 to 13. At 5 years, the results suggest that on average, 13 patients need to be treated for one additional patient to experience benefit; in this case, avoidance of a revascularization procedure.

To further explore the mortality risk, the number needed to harm was examined. The number needed to harm measures the number of patients needed to be treated with an experimental treatment for one additional patient to experience an adverse clinical outcome. Again, the reported numbers are based on the random effects model from the meta-analysis.

Here, the number needed to harm decreases from 1 to 5 years. At 5 years, the results suggest that on average, 14 patients need to be treated for one additional patient to experience harm, in this case, mortality.

Overall, the class of devices that includes use of a paclitaxel coating to inhibit restenosis have shown consistent and generally sustained benefit in the reduction of reintervention to

treat femoropopliteal disease.

Here, from the meta-analysis, the number needed to treat to avoid a clinically driven TLR at 5 years is 13 patients. At 5 years, the number needed to harm, that is, to experience a mortality event, is 14 patients.

It's important to emphasize that a qualitative comparison of these findings should be cautioned, given that TLR and mortality events are not comparable given differences in severity. Also, these events do not fully characterize the totality of the device benefits and risks.

I'll now discuss potential next steps, given the data shared over the past 2 days. Before discussing next steps, however, it's important to reiterate the limitations of the currently available data and FDA analyses.

There are currently five approved paclitaxel-coated devices to treat stenosis in the femoropopliteal arteries. Approval of these devices was primarily based on 1-year data and only three trials have reached 5 years of follow-up totaling fewer than a thousand patients. So the available data may not be sufficient to definitively determine the magnitude and causality for this late mortality signal.

Though the missing data rates were generally similar for the treatment and control groups in the pivotal trials, there were many patients for whom data were missing due to withdrawal and consent or lost to follow-up. This ranged from approximately 3 to 26% missing data at 5 years with as much or more missing data in the studies conducted outside the United States. This amount of missing data reduces the robustness of the statistical analyses and introduces greater uncertainty.

With regard to additional paclitaxel treatments patients may have received, there's ambiguity in the current data. Most of the clinical trials did not allow for treatment with the additional paclitaxel-coated devices in the ipsilateral limb within the first 12 months; however, subjects may have received a device in the contralateral limb or 12 months thereafter.

Overall, detailed information regarding additional paclitaxel exposure was not rigorously captured across all trials, which may include treatment of femoropopliteal disease, other interventional procedures such as treatment of arteriovenous fistula or intravenous used for cancer treatments. These additional exposures were not accounted for and their impact on the mortality analysis results is uncertain.

With regard to causes of death, no deaths were adjudicated to be device- or drug-related; however, the information available may not have been sufficiently granular to fully assess potential drug-related adverse effects. In many cases, adjudication categorization lacked precision and many deaths were categorized as other or unknown. Patients typically had numerous comorbidities and the death categorization may not have fully captured all events that led to death. As a result, there are important challenges in identifying trends associated with increased mortality with respect to cause of death.

Overall, based on the review of the available data, there appears to be trend of increased mortality 3 to 5 years following treatment with paclitaxel-coated stents or balloons in the femoropopliteal arteries. However, as previously emphasized, there are numerous limitations with the currently available clinical data and the results of analyses. In addition, a biological or non-biological cause responsible for this late mortality signal is not evident.

The Panel will be requested to comment if additional clinical data collection should be considered to address questions related to this late mortality signal.

If so, there are numerous approaches that can be taken to gather additional clinical data. As an example, for a new enrollment post-approval study, an individual manufacturer or an industry consortium can proactively design a new clinical study to evaluate specific clinical outcomes to address concerns. This would need to be developed in consultation with FDA. Also note that under Section 522, FDA can require a manufacturer to collect necessary data.

With regard to the collection of real-world evidence, FDA recognizes the wealth of data

available from clinical experience derived from electronic medical records, claims and billing data, data from product and disease registries, and data gathered from other sources. As noted yesterday, there are several registries and consortia that capture data specific to peripheral interventional procedures. For these reasons, it's prudent to explore the feasibility of this information to inform the outstanding questions related to mortality.

These data, however, may have substantial limitations that may create challenges with utilization which may include, but aren't limited to, suboptimal data, quality and reliability, lack of follow-up, lack of internal controls, and potential selection bias.

If additional post-approval data collection is considered, potential sources of new data may include:

- Continued follow-up of ongoing pivotal trials that have not reached 5 years;
- Non-U.S. RCTs;
- Analysis of nonrandomized registry datasets; and
- A new randomized trial.

Regarding a new RCT, a fundamental question for the Panel is whether a randomized trial of paclitaxel-coated versus uncoated devices is feasible. Important study elements would include:

- Clinically acceptable relative risk or hazard;
- The appropriate Type I error;
- A feasible sample size;
- Optimal duration of follow-up; and
- Independent safety monitoring.

If the Panel were to consider a new randomized trial to assess mortality associated with paclitaxel-coated devices, FDA offers these sample size estimates to facilitate discussion. In these tables we show the estimated sample size for the total number of randomized subjects.

The top table shows estimates for a binary outcome analysis and the bottom table shows estimates for a time-to-event analysis.

In the binary outcome in the top table we see that a total sample size of over 43,000 patients is required for the most stringent approach where there would be no more than a 10% increase in relative risk. That is a risk ratio of 1.1 for mortality at 3 years using the paclitaxel devices compared to uncoated devices tested at the 2.5% significance level.

As less stringent parameters are included, sample size predictably decreases with later times of evaluation -- here, 5 years -- with larger tolerance for a Type I error and as the relative risk tolerance increases.

If the Panel were to consider further study in this regard, FDA would be particularly interested in the Panel's views if that would be an acceptable relative risk or in the case of a time-to-event analysis, below the hazard ratio.

In the bottom time-to-event model, we provide primarily sample size calculations to test a non-inferiority hypothesis in terms of hazard ratio to assess treatment effect for mortality over time.

Note that this calculation includes assumptions that may or may not hold. It assumes a constant hazard ratio in the control arm and the hazard ratio is constant over the total follow-up period. This calculation also requires specifying accrual time, which is 2 years in this calculation, and total study time, which is the sum of accrual time and follow-up time.

Including these assumptions, a total sample size of approximately 32,000 patients will be needed to reject the null hypothesis that the hazard ratio is greater than 1.1 of the 2.5% significance level when assuming an accrual period of 2 years and a total study time of 5 years.

Note that these estimates are intended only to facilitate discussion regarding feasibility and study parameters, should the Panel consider additional RCT data collection, and are not intended to convey particular FDA recommendations.

Considering FDA's least burdensome principles approach, it may not be possible at the time of device approval to fully predict long-term safety and effectiveness.

Note that FDA required for all paclitaxel-coated devices that the pivotal study subjects be followed for up to 5 years as part of a condition of PMA approval.

Product labeling may be updated following the collection of these post-approval data, whether related to the post-approval studies currently in place or related to new agreed-upon data collection efforts. In addition to updating the clinical data, other appropriate modifications may be made to the labeling in order to convey appropriate safety information. The Panel will be asked to discuss this issue.

It's important to note that today's discussion has been focused on paclitaxel-coated devices used to treat femoropopliteal atherosclerotic disease. Paclitaxel-coated devices are also approved or under study for use to treat stenosis in arteriovenous fistula and for the treatment of peripheral arterial disease below the knee. Only the Lutonix DCB is currently approved for use in arteriovenous fistula. FDA approval was based on improvement of target lesion primary patency at 6 months in the absence of major offsetting safety concerns. All-cause mortality at 12 months was 12.8% in the Lutonix DCB group and 9.7% in the uncoated PTA group.

There are no FDA-approved devices for the treatment of PAD disease below the knee to treat critical limb ischemia; however, a number of studies are currently being conducted for this indication.

The FDA-approved Boston Scientific Taxus family of paclitaxel-eluting stents indicated for improving luminal diameter has been approved for the treatment of coronary arteries. Taxus stents are no longer in use in the United States as newer-generation
-limus eluting stents demonstrated lower rates of repeat revascularization.

Note that limited long-term data exists for paclitaxel-coated devices for all of these

indications. Also, different patient populations may have different tolerance for the probable risks given the anticipated benefits. Therefore, the Panel will be asked to discuss whether concerns regarding paclitaxel devices used in femoropopliteal PAD should be considered when these devices are being used for other indications.

This concludes today's presentation. In summary, FDA reevaluated previously conducted animal PK and safety studies and did not identify information that may suggest a potential mechanism for late mortality.

We investigated the observed paclitaxel doses in the pivotal trials and did not identify a relationship between mortality and paclitaxel dose that was consistent across all trials.

We also investigated clinically driven TLR in the pivotal studies for all time points. The risk ratio values favored the paclitaxel device group and at 5 years, FDA identified approximately a 20% decreased risk of clinically driven TLR in patients treated with paclitaxel-coated devices.

Benefit in this regard should be considered as we discuss the risk and overall adjustments to the benefit-risk profile of this class of devices.

We must also examine how the benefit-risk relationship may vary across other indications for paclitaxel-coated devices.

And because there is tremendous uncertainty around these questions, FDA is asking the Panel to provide discussion and input on these topics.

Thank you for your time and attention.

DR. LANGE: Great. I would like to thank the FDA speakers for their presentations. This is the time at which Panel members can ask clarifying questions to the FDA, so let me open it up to the Panel.

Dr. Somberg.

DR. SOMBERG: Yes, I would like -- John Somberg.

I would like to go back to your data analysis slide for the dose relationship with mortality and the first slide you presented. They're not numbered on -- well, maybe they are. Number 20 -- 18, rather. Number 18. So that's much better than this one in my small thing here. But it seems to me that the last three data points confuse the graph markedly, and you know, when I do experiments and I have one or two that stream with that variance there, and I like to hear my statistical expert colleagues talk about that, but if I walked in with a graph like that, I think they'd both kick me in the butt and say, you know, do more experiments at the latter end of things. Now, clearly, we can't do that at this point.

So I would say it's not that there is no dose -- and I would ask you to clarify this but, you know, when you have 37, 64, 48, and 27 deaths and then you, all of a sudden at the end, have four, two, and two, one goes one way and two go the other, it completely off balances. So I think there is, you know, something distorted there and I'm not sure how to deal with it.

And also, just a comment from a pharmacologist. Sometimes there's a threshold that's reached that a drug concentration would trigger something and you would not necessarily need to show a dose response, but there is -- you know, for the first things there seems to be some sort of trend and then, you know, for between 2.5 and 3.0 dose milligrams, there is continuation but those two other things are outliers. So maybe the FDA wants to comment on their thinking and maybe -- I don't know if the Chair would let our statistical experts comment as well.

DR. LANGE: So I'll ask the FDA to comment. Then I've got Dr. Krucoff, Dr. Ballman, and Dr. Sun who want to speak after that.

So Dr. Whatley.

DR. WHATLEY: Sure. I think Dr. Yu Zhao will comment on this.

DR. ZHAO: So this is Yu Zhao.

So for the graph, it's just a visual presentation of, you know, what would be the trend of

the mortality as the dose increased. So FDA tries a different way, you know, how to show this. The reason that we, you know, have -- so basically, the strategy here is we're trying to have, you know, a reasonable group and a reasonable number of group, and within each group we can have a reasonable number of patients so that we can show the mortality rate within each group. However, you know, at the -- particularly at the right end, you know, there are only like a few patients falling in each group, there is nothing we can do about it.

For the Cox model, we do try some sensitivity for some of the studies, you know, if we identify before like there is one patient or two patients that is really far away from the other. Regarding the dose, we remove them and we do the Cox model and yeah, that's what we did.

But for here, for example, for the -- I think for this graph is for the Zilver. You know, at the end, there are like eight patients in that, you know, the far right three groups and if I remove all of them, you know, we lose a lot of data. The data we have currently is already, you know, very limited, so that's why we still presented here. But corresponding to the rate, you will see kind of a -- you know, up and down. We also show the confidence intervals so basically it shows that, you know, it's overlap everywhere. So I don't know whether this answered your question or not.

DR. LANGE: John, any other comments? I mean, I think what we hear is -- and I think you're right, this and the other studies that follow, the endpoints at the higher doses are always small numbers, and all of us lack confidence in those. Your point is well taken.

DR. WHATLEY: Dr. Buckley, did you have anything to add?

DR. BUCKLEY: No. I mean, I think you'll have more discussion on this later, but I think it indicates the challenges in just looking at these small numbers of data and trying to do trends. And I think this would've been most helpful if it were exceedingly clear across trials that there was a trend, but I think what we're coming up with is it's not clear that there is, but I don't think that we can completely exclude that.

DR. LANGE: Dr. Krucoff, Dr. Ballman. And then Dr. Sun, then Dr. Kip.

DR. KRUCOFF: Yeah, I think we saw and discussed yesterday, too, even the calculation of dose is a little complicated in this area. My question is to Dr. Manhart with regard to, you know, in 35 years of working with innovative drugs and devices, we have this ongoing challenge of determining what can we learn from preclinical animal models and then where does that stop being informative and we just have to move to human beings who have the disease. And you mentioned one issue with regard to the existing data, preclinical exposures, with regard to the duration of follow-up in the animals being in the range that we don't see a signal of concern in humans and not having data further downstream.

My other question, which, you know, if this isn't just noise at the end of trials creating a weird signal, if this really is a biological event, whether the distribution of deaths across different causes that we're seeing could imply that preexisting conditions in patients who are complicated with comorbidities interact in some way with the paclitaxel exposure, in animals, by and large, the animals cited here, the other end organs, in fact, all the end organs are fundamentally healthy.

So my question is, based on the existing animal data, do you see any range, as we might think about for later discussion, in additional prospective data that would be informative coming from preclinical animal models relative to what we have, longer follow-up, disease models in animals? Is there any way that we could explore some of this territory, not in human subjects, but learn more from preclinical animal models?

DR. MANHART: As I mentioned --

DR. LANGE: I'm sorry, please identify yourself.

DR. MANHART: Sorry, I'm Dr. Karen Manhart.

As I mentioned, the animal safety studies were not standardized across all the studies, so we got different types of data from all of the different sponsors. I would have liked to have

seen more -- such as bone marrow, downstream bone marrow, examination; examination of peripheral lymph nodes, things like that. And, of course, longer time points.

DR. LANGE: Dr. Ballman.

DR. BALLMAN: So going back to the dose-response relationship, I mean, we saw yesterday, you know, there was sort of a meta-analysis done of the dose response. Here, we're seeing the individual studies and yesterday we saw, when we looked at the individual studies, we didn't really see any mortality signal, we didn't see a signal until there was a meta-analysis. So did the FDA do a meta-analysis across the different studies, in terms of dose relationship?

DR. ZHAO: At this time we didn't do a meta-analysis regarding the dose effect. So at this time, because there's a tremendous difference regarding the device and the drug formulation and the drug releasing, for example, in our DCBs and in the DES, so FDA review team has some suspicion regarding, you know, whether the assumption needed for the meta-analysis is still holding, you know, at this time. So that's why we didn't go that approach. We just, you know, focused on the individual study.

DR. WHATLEY: I would like to point out that we didn't calculate dosage. We had the actual dosages that were received by every patient, and just to kind of reiterate Dr. Zhao's concerns, we had some thoughts about specifically pooling that data since the devices and the dose ranges were so different in some cases.

DR. LANGE: Dr. Sun.

DR. SUN: Can you help to clarify or confirm maybe later a few numbers? One is you mentioned that undetectable level after 90 or 180 days. Based on the FDA's Executive Summary, it said less than 0.5 ng/mg. Can you confirm that number? So, really, the reason I'm asking, because currently the undetectable level is less than 1 ng/g of tissue. That level is 500 times higher than the current standard. So please confirm that number.

Number two is, you said also, in the lung there is a therapeutic level concentration

present. Can you provide that number, too, if you have an animal? I don't know if you can find it because that may change the discussion even from yesterday. What the level of that be?

Number three point is for that dose, yesterday's sponsor presented there's a lower dose, 100 µg. Seems all the analyses minimum is 400 µg. So do you have the 100 µg dose/mortality data? Three clarifications.

DR. WHATLEY: Thank you. Okay.

DR. LANGE: Just because they're clarifying questions, Eleni, do we have that information now, or should we get that after lunch?

DR. WHATLEY: So that's what I was going to point out. Eleni Whatley.

I did want to point out we do have all the data from all the five individual sponsors. They did report it in various units, so some of them were presented in nanograms per gram, some in nanograms per milligram. We did convert it to get it all in the exact same units. So I will get you that information with my CDER colleagues and present it after lunch.

DR. LANGE: So three things. One is confirm the dose of 0.5 ng/mg.

DR. SUN: Or gram.

DR. LANGE: Or gram. The lung level, and looking at the hundred microgram dose. We'll look for that information after lunch.

DR. WHATLEY: And the cytostatic potency in the lungs, you were interested in that, as well?

DR. SUN: The concentration in the lung.

DR. LANGE: The concentration in the lung.

DR. WHATLEY: The concentration in the lung.

DR. SUN: Yeah.

DR. LANGE: Thank you.

Dr. Kip.

DR. KIP: Kevin Kip.

This is probably more of a -- it will be a question, but maybe more of a suggestion. So I don't think I've ever seen an example where a particular -- we'll call it an exposure of the drug here, has such heterogeneous concentrations across these different devices. I mean, that's about as wide a range as you'd ever see in terms of dose. So in terms of pooling the data, did you consider, within each study, just simply taking -- breaking up the sample size into quintiles so, you know, one-two-three-four-five groups and within each study and then pooling them? Because the range is so dramatic across the studies, I think that would be a more powerful test of dose response.

Now, you wouldn't be able to zero in on what the -- if there was a dose that really seems to matter the most, because you're standardizing by doing that, essentially, than if you take the distribution of dose within each study, put that into quintiles, those individual persons, now you're standardizing, essentially, but I think it would give more insight into whether there's a dose response.

DR. WHATLEY: This is Eleni Whatley.

Are you interested in seeing that for individual trials or for the pooled data?

DR. KIP: I think that would be most informative for the pooled, but you'd want to see the individual. But the pooled is what you'd really want to get at because, again, this issue, it's a massive range of dose across the devices. So somehow I think you have to standardize it, the analysis.

DR. WHATLEY: I believe we looked at that slightly but didn't include it. Is that something we can do during lunch, you think?

(Off microphone response.)

DR. WHATLEY: No.

DR. LANGE: Great. Dr. Zuckerman and then Dr. Cigarroa and then Dr. Rasmussen.

DR. ZUCKERMAN: Okay, this has been a very helpful discussion because, regardless of which aspect of the science we're talking about, preclinical, clinical, the theme here is we need better standardization between companies and use of better methodology, and certainly, the Agency, in follow-up, will be looking at the proposal by Dr. Kip. Certainly, I think Dr. Somberg's comments are very apropos. When we don't get a positive p-value, it doesn't mean that there isn't something there and we recognize that.

A question for Dr. Lange is that the industry has also looked at different methodologies. I think it might be helpful if Dr. Lystig from Medtronic describes the careful way that Medtronic tried to look for a dose-response relationship, not the meta-analytic technique that Dr. Ballman was referring to. Would you like a few comments now regarding other techniques or wait until this afternoon?

DR. LANGE: We're going to have a clarifying question time period, and if they can present that then, that would be great, and if not, we'll do it right after lunch. That will give you time. I know we're putting you all on the spot. All right, good. We'll look for that.

Thank you, Bram.

Dr. Cigarroa.

DR. CIGARROA: So thank you to the FDA for the presentation this morning. So I remain challenged in contemplating the ability of our current construct to address the issue of what we all agreed was a signal, and that is, we have preclinical testing and we have dose responses with the variable dose, as my colleague just mentioned, and what we're trying to assess is mechanism in a context of a signal where we saw excess death across cardiovascular and malignant conditions, as we saw yesterday in each of those histogram bars at 5 years in the data that we have access to with the recognition that that data is challenged. And so, you know, my question to you and your colleagues, are -- I think that there -- the model of acute toxicity in dose response is not the right way to think about it because the signal begins to

occur between Years 3 and 5, and so I think the models that we need to contemplate are different. For example, in the last 2 to 3 years, the issue of clonal hematopoiesis, which is present in the 10 to 20% of individuals over the age of 70, which is associated with an increased potential in cardiovascular events and malignancy, is present. We know that paclitaxel is associated with neutropenia and has an impact on bone marrow.

So, you know, my question to you is, in the animal models that we're contemplating and as we set the stage for discussions later on, I think we have to think differently. We saw no signal in the aggregate of data at 1 year. The preclinical models that are present here, if you simply interpret it in that context, are unlikely to provide us any additional clarity, so I would ask us to think about the models that we're using and the putative mechanisms and to think a little bit broader as we move forward today.

DR. LANGE: Dr. Rasmussen and then Dr. Ballman.

DR. RASMUSSEN: This is Todd Rasmussen.

I have a question or I'd like to have the slide projected that pertains to the target lesion reintervention, TLR, please. There was one or two. I appreciate the opportunity to provide a little bit of balance to what I am concerned is a one-way discussion about risk.

And so as I look at one of the questions we will be tasked to answer or address, it says benefit-risk profile, and in this discussion, everything has been focused intensively on risk, which is appropriate, but I also think -- and as we look at risk, I think there's ambiguity that is a bound, meaning we struggle with is this a signal, what's the cause, the lack of data. As I jotted down here, under the category of risk it is unclear, there's ambiguity.

Under the other word, that we need to balance with risk the word benefit, there is clarity to benefit, and I want to make sure that we don't lose track in our pursuit of this signal, lose track of the clear benefit in the data that we do have that benefits patients treated with this technology, and I think it's projected here, and it pertains to significant reduction in target

lesion reintervention, if I'm not mistaken.

So I want to put that as context to the group to encourage us to -- as we approach Question 8, we don't just get down the rabbit hole of risk, which is going to be ambiguous until the end of the day, and miss what is unambiguous, which is partly described in this slide, in the concept of TLR for patients, reduced TLR.

One question I guess I have specifically, and maybe you can remind me as I haven't read these studies in detail recently, when we talk about reduction in target lesion reintervention are we only talking about the reintervention being endovascular or is it also a reduction in open reintervention, meaning if a lesion in either group failed and needed reintervention, was that reintervention only endo or was it -- could it potentially have been open bypass as well? Or do we have that fidelity of data?

DR. BUCKLEY: The individual industries can correct me if I'm wrong, but it should include all reinterventions to --

DR. RASMUSSEN: Sure.

DR. BUCKLEY: -- revascularize.

DR. RASMUSSEN: And if that's the case, I raise that question because that should not be overlooked. If there is a reduction in reinterventions, and many of those reinterventions are open, that shouldn't be overlooked because that has also been a reduction in subsequent reoperations or operations and I think that, again, I just want to not overlook what, to at least me, is a clear benefit as we appropriately delve into risk as well.

DR. LANGE: Great.

DR. WHATLEY: Sure.

DR. LANGE: And we're going to be talking more about this during the deliberations. I only have about 10 minutes left for clarifying questions, so we're going to try to get those taken care of now so the FDA and/or sponsors can get the data. I've got a couple of hands up. I've

got Dr. Ballman, Dr. Somberg, and Dr. Zuckerman, so in that order. But so noted, and we'll talk a lot more about that, Dr. Rasmussen.

DR. BALLMAN: So just a clarifying question and a follow-up on that with respect to the benefit. It's my assumption that if you don't know if patients are alive or dead at 5 years, you wouldn't know what their reintervention status is, either, at 5 years but I look for clarification on that. So I'm not sure that the benefit is any clearer at 5 years than the death or risk is.

And then just a question, and I think it would be really, really difficult just given there's no standardization in the first place. Was there any sort of analysis done on dose-response relationship with respect to the benefit?

DR. WHATLEY: This is Eleni Whatley.

I can confirm your first point, that that information would be unknown as well.

Dr. Zhao, do you want to comment on the --

DR. ZHAO: We haven't done any dose analyses regarding the benefit.

DR. LANGE: So if, in fact, industry has that information and you would like that, we'll ask for that after lunch, if it's available. And that is the dose relationship versus benefit, TLR.

DR. RASMUSSEN: And I think both, also --

DR. LANGE: I'm sorry, this is Dr. Rasmussen.

DR. RASMUSSEN: I'm sorry, Todd Rasmussen.

We should also, then, know -- I think we do know the reintervention in those patients who were re-intervened on. I mean, we know whether they were open or endo. Otherwise, we wouldn't be able -- I mean, I don't want to talk against each other.

DR. LANGE: Okay, I'm going to -- we're going to talk about this. This is for clarifying questions. I understand both points --

DR. RASMUSSEN: Yes.

DR. LANGE: -- and I want to bring those up, so let's not leave those.

Dr. Somberg.

DR. WHATLEY: I would also like to point out the dose response in terms of TLR is also directly related to lesion length and that might make it murky.

DR. LANGE: Yeah. And that was Ms. -- that was Dr. Whatley. I'm sorry.

Dr. Somberg, Dr. Krucoff, and then I think we'll go to industry presentations.

DR. SOMBERG: Yes, I'd like to change the topic for a minute to the area of number needed for sample size if one was designing the study, and I appreciate the FDA's efforts in this regard. The numbers are substantial and I think pose a difficulty for designing a study in this area. And with that said, has the FDA looked at possibilities of enriching the population? And, specifically, I was looking last night to see if there was an association of cigarette smoke, smoking, because I remember the old days where, you know, everyone with peripheral vascular disease was a smoker, and I think that is to a large extent somewhat correct today as well, and the highest mortality in the neoplastic area was lung cancer. So there seems to be a thread there. So I was wondering if in your sample size were you able to say hey, these people have the highest risk? If we put those in, maybe we would be able to lower the sample. Any thoughts on that --

DR. ZUCKERMAN: Okay, Dr. Somberg, great comments for our discussion this afternoon. We're interested in any and all comments to develop a real trial that can be done in a reasonable time period.

DR. SOMBERG: I'm just asking was there any higher risk in the cigarette smoke.

DR. ZUCKERMAN: Yes, and we have many other suggestions --

DR. SOMBERG: Okay.

DR. ZUCKERMAN: -- this afternoon. The point that you're making about enrichment of population is a good one, and we'll discuss other things we can do.

DR. LANGE: So we're not going give you the information until this afternoon to make

sure you come back, Dr. Somberg, okay?

(Laughter.)

DR. LANGE: Dr. Krucoff.

DR. KRUCOFF: Yeah, just back to the benefit-risk because I agree a thousand percent that we have to keep the balance in mind. I'm trying to --

DR. ZUCKERMAN: Okay, Dr. Krucoff, there's no question, and I would ask Dr. Whatley to put our benefit-risk slide back up so that when the Panel discusses that question this afternoon all the factors that Dr. Rasmussen mentioned are included. However, I would point out that the values we're seeing in a meta-analysis right now are average values, and I think where we need Panel input is how can we develop better data to understand better risk stratification in this complicated field.

DR. KRUCOFF: Yeah, I just have a quick question to the FDA team because maybe I missed, but I don't think I've seen whether patients who benefit in the short term, in the absence of TLR, are survivors more than -- or the short-term benefit and the long-term risk are not related, so -- which from the histograms, as we've seen, I would expect. But I actually don't know if you have or if I missed, but I don't think I've seen whether short-term patients who do well have better survival at 2 to 5 years than short-term patients who don't do well.

DR. WHATLEY: This is Eleni Whatley.

I don't believe we have evaluated that, and we can look into it.

DR. LANGE: If you're able to give that information to us after lunch, that would be great. A great question. Any other clarifying questions before we move on?

(No response.)

DR. LANGE: All right. Again, I'd like to thank the FDA for your presentation.

DR. WHATLEY: Dr. Lange, would you like us to clarify the OUS/U.S. RCT baseline characteristics really quickly?

DR. LANGE: Sure, we'll do that after lunch as well.

DR. WHATLEY: Oh, okay.

DR. LANGE: Okay, I mean there was -- so things we talked about, Dr. Sun mentioned -- again, the three items he mentioned we've already been over. If there's any information regarding pooling of the data or quintiles or meta-analysis, it would be lovely to look at that. We appreciate Medtronic -- and I see Dr. Mauri shaking her head yes, that they can show us if there's a dose effect relationship in terms of TLR. And then if there's -- yeah, regarding TLR and versus dose, if the industry has that information, that would be great. We can present it after lunch. And I think I captured the summary of data we're asking for.

Dr. Rasmussen, something else you wanted?

DR. RASMUSSEN: Todd Rasmussen.

I think it's -- is there clarity on what the R is in TLR, do we know whether it was endo only, the reintervention, or was it endo and/or open?

DR. LANGE: I saw industry shaking their head, and it was endo and open.

DR. RASMUSSEN: Yeah.

DR. LANGE: And everybody's shaking -- this whole side of the room is shaking their head yes right now. Okay.

(Laughter.)

DR. LANGE: So they're either nodding off to sleep or agreeing, one of the two. Great.

(Laughter.)

DR. RASMUSSEN: I think they're telling me I should have read it more carefully.

DR. LANGE: It's a great question, and I didn't know the answer to it, but thank you for clarifying that.

We'll now have a combined presentation from the manufacturers. Speakers, please approach the podium. And, again, 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 Chair. Also, I ask the Panel to hold all questions until the end of the presentation. This will be a 30-minute presentation, and afterwards we'll ask any clarifying questions.

Dr. Mauri, you have the podium.

DR. MAURI: Thank you. I'm Laura Mauri, and I'm speaking now on behalf of the combined manufacturers here today. I want to thank the FDA and the Panel for this opportunity. We realize that this is a lot of information to digest and we appreciate the opportunity to discuss it with you. It's very important, obviously, to us to be able to provide guidance to our patients and also ensure their safety. On the one hand, if there is an important concern with mortality, it's very important that we get to the bottom of it. And on the other hand, it's also important that we ensure that patients have access to effective devices that are so important in improving their quality of life.

So today I'm joined by several other colleagues from academia, Dr. Clair, Dr. Secemsky, and this is the -- oh, I see. Okay. This is the agenda. Dr. Clair will talk about the multiple other vessel beds that have been treated in other studies. This is an important area of many trials and this is also a question that the FDA has asked the Panel to address.

I will talk a little bit about the different sources of safety data with an attempt to summarize and integrate what's been presented, and also some of the evolving studies that you're seeing over time, there's a lot of new data.

We invited Dr. Secemsky to speak for a few minutes because, as you heard yesterday, he presented data on 150,000 Medicare beneficiaries, but there was limited time to address some of the questions from the Panel about the methods and the selection, questions about selection bias.

And then, finally, I'll close with a review of the FDA questions that have been posed, as

well as the manufacturers' proposed next steps and actions.

DR. CLAIR: Thanks very much. I'm Daniel Clair at the University of South Carolina. I told you yesterday my conflicts. I serve as an advisor for Medtronic and Boston Scientific, and I serve as a consultant and a DSMB member for Bard, and the compensation for those go to the Medical Group, for which I work. And my travel and lodging have been paid by Bard, but my time is my own.

Before I start on reviewing data from the use of these products in other vascular beds, I think it's helpful for Panel members and for FDA members to get a sense of how this affects practice, and I'm just going to tell you a quick story about the national vascular meeting which happened a week ago and at the end of the meeting, there were a group of nearly 80 to 100 surgeons in the room dealing -- who deal with patients with peripheral vascular disease, and a moderator. An informal poll was taken of how many patients -- how many physicians are actually using these devices currently, and there were two, two of us, who raised our hands. And the moderator then asked how many of you were using these before this information became available and there were about 40 to 50 physicians who raised their hands. So this has had a significant impact on physicians' either ability or hesitation to be able to use these devices. So coming to some clarity on this will be very helpful for clinicians in general.

You saw some of this data yesterday, and this reflects two particular areas. One is the use of these devices in the coronary circulation. On the left, you see evidence from the largest group of literally thousands of patients who have been put in multiple trials to look at the use of paclitaxel-coated devices compared with bare-metal stents in the coronary circulation. Again, these were trials that were performed along similar protocol lines, so the definitions were the same, the CEC and the DSMB definitions and groups were the same, the assessments were designed so the studies could be pooled, and you'll see that there is no difference out to 5 years in the mortality in these groups.

There was some concern regarding the amount of drug on these devices that were placed in coronary stents, and for that reason, on the right, you will see the SPIRIT VI data, which looks at long coronary lesions that were randomized and treated with bare-metal stents versus paclitaxel stents, and you can see the survival there on the graphic in the right. But, again, this was the amount of drug on these stents in this long coronary lesion trial, was about the amount or within the range of the Eluvia stents that have been implanted in the trial using the drug-coated stent.

The next vascular bed that we will look at is the use of these devices in AV access. These are, again, relatively short-duration studies, but in both the -- both the trial from Lutonix and from Medtronic, you can see that there is no difference in survival among these patients and the hazard ratios did not reach statistical significance in either case.

This is a look at the use of paclitaxel in below-knee patients. These are usually critical limb ischemia patients, so these are clearly sicker patients. You would expect the mortality in all of these groups to be higher. Two of these studies have carried their duration out to 5 years, again, without a difference in survival visible from these mortality curves. In the largest of these trials that now has mortality out to 3 years, again, there's no difference in mortality in the patients treated with these devices.

And, finally, in the last -- other vascular bed in which these devices have been evaluated, this is a look at paclitaxel-coated stents in the renal arteries. Again, here are data out to 5 years. No difference in mortality in any of these trials looking at the devices in other vascular beds. And these are essentially the best data we have on the use of these in other vascular beds.

So you've seen data on coronary artery usage, on arteriovenous access usage, and on below-the-knee uses, along with renal arteries.

And paclitaxel devices have been commercially available, as you well know, for over 15

years without any mortality signal seen from any of these randomized trials in other vascular beds, obviously with some limitations to these.

I'd like to ask Dr. Mauri to come back to the podium.

DR. MAURI: Thank you. So I'm going to speak to the multiple sources of data. As the Panel, I think, have been alluding to, it's really difficult to integrate all these different sources. We spent a lot of time yesterday mainly on three trials that have 5-year follow-up but really just a handful of studies. You've seen in other multiple vascular beds no signal. And we recently have had many important observational studies that have been presented just even over the past few months and at this meeting.

So it's complicated to interpret these different sources of information, but it's very important that we understand the totality of evidence so we can have informed discussions with our patients.

When we think about interpreting sources of safety information, we have randomized trials, we have the meta-analyses of those trials, and then we have comparative analyses that can be done with real-world data. And randomized trials, of course, we all think of as the gold standard because we can eliminate selection bias. But the thing that we often don't discuss in detail is the limitations that they have, especially when they're done with very small sample sizes. In this case, the small sample sizes really limit the precision, especially in understanding the comparator arms where those sample sizes are half the size of the drug-coated size. And so they are also not designed to detect something like mortality, they're not powered to do that, and they just don't have the precision to do that.

On top of that, the trials that we discussed yesterday are really focused on a narrow patient population, the patients with -- certainly, these are patients with extensive disease, that are patients with claudication and don't represent the full spectrum of practice that clinicians see.

And then meta-analyses, you know, overcome the challenges that we have with power within these smaller studies. But the thing that we have to be careful of is that the requirements of a meta-analysis are really that it's a high quality of information that's put into these meta-analyses and that there's homogeneity and what you've seen, you know, from the presenters, both from the FDA and independent analysts, is that there's a challenge with the data that are being incorporated into these studies because of the lack of homogeneity and problems with the individual randomized trials, especially with their follow-up and missing information.

Now, real-world analyses, when they're done properly, can be helpful but the thing that they're not good at is avoiding selection bias, and that's the main limitation, but they can provide much greater precision. Now, precision is not enough. If you can't address selection bias, it's not convincing to have a more precise but biased estimate.

And so what's incredibly important, and I what I spent a lot of my previous career looking at is, well, when do we believe that these methods are sufficient? On the strengths of comparative analyses using real-world data, they're generalizable, they represent the full spectrum of what we see in clinical practice. And so that's very important to the actual safety that we're looking to ascertain from these.

So, really, at the end of the day, the only time we can really rely on real-world data is if there are very robust methods that we're confident about to address for selection bias.

Now, the randomized trials we had spoken a lot to, and I won't spend a lot of time on this slide, but you can immediately see the limitations that we've been discussing over the past day. The study designs were not designed for long-term mortality.

Paclitaxel treatment, one important thing to point out that hasn't been stressed before is that we also don't know the treatments that were received before randomization. In almost all of the studies, drug-treated products were available to patients before they were entered.

Many of these patients had prior procedures and were being treated for a second time and that was not recorded, whether they received paclitaxel before randomization. We have already spoken a lot about how it wasn't completely recorded after randomization, particularly absent when the opposite limb was treated, we just don't know that.

The small sample sizes we talked about, the instability that that creates, especially in the small control arms.

The missing data, with this high degree of missing data, we can't assume that it's missing at random and our experience within the Medtronic study was that it was not the adherence to medications. And risk factor modification, which is so important in this patient population, was not ascertained after randomization.

And then blinding was incomplete in these studies. We haven't spoken a lot about that, but patients were unblinded after a year, and the blind was only single blind, and it was only the patients who were blinded for the first year.

The meta-analyses then take these data from these randomized trials that are limited by the quality of information collected and heterogeneity and lump them all together, which does not -- it increases, certainly, the power but it doesn't necessarily increase the reliability of the estimation. In fact, it may be misleading.

And to their credit, the investigators who have done these analyses have looked at multiple sensitivity analyses to adjust for these things as much as possible, and when you get down to being able to ensure both that there are similar patients being compared and that there's secondary randomization to show actual treatment but accounting for all of the time, from the time of Time 0 forward and not censoring that data, that those estimates are no longer significant and the hazard ratio actually approaches 1.0, if you look at the VIVA analysis progression along that chart.

But at the end of the day, the meta-analysis is only as good as the data that you can put

into it, and so there's a limit to how well we can ascertain this, even with really trying to do our best to get the best follow-up as we would like.

The observational studies in this space have to be evaluated very carefully, and we have to look at those that have been conducted with a high attention to methods. They increase the precision and, if they are reliable in terms of the methods, can be quite important.

It's important to note that there are some unique strengths in this area for observational data. One of them is that the completeness of mortality ascertainment may actually be better than in the randomized trials, which is shocking but true. And Dr. Secemsky's Medicare analysis has ascertainment, we believe, in 99% of subjects, which is much more than we can do in most randomized trials.

In addition to that, the precision of these estimates gives us better power to be able to look at subgroups, which we can't do in small randomized trials, which is important so we can understand whether there is a diversity of treatment effects according to risk.

But, overall, the take-home message has been, from these well-conducted studies, some of which you'll see in more detail later on today, is that there are a large number of patients studied, representing non-overlapping groups of patients, and hazard ratios are really all right around 1.0 with very tight confidence intervals.

So I'll have Dr. Secemsky have some time to be able to speak to the questions raised yesterday.

DR. SECEMSKY: Thank you, Laura.

So, again, I'm Dr. Secemsky. I was invited by the industry group to speak here today to address some of the questions raised yesterday during the afternoon session. I am not receiving any compensation to speak today. So I am a vascular interventionalist and practicing physician. I'm also a clinical researcher, and the majority of my time in my clinical research is spent evaluating statistical methods to deal with issues like selection bias and comparative

safety analyses.

So we understand the concerns when we're comparing two devices, and we spent a lot of time on this in the coronary device space. I think we were all very -- felt very unique to be in the position to compare the safety of drug-coated devices, which we felt, from the clinical side, that the treatment selection bias is minimal in this situation.

Drug-coated devices are a first-line therapy for femoropopliteal artery revascularization. There are no patients that are identified that we would not treat with this therapy. The procedure itself is not changed by delivery of drug-eluting therapies, and we're not obligated to change any portion of our management after treating these patients, including duration of dual antiplatelet therapy. So this is different than when we compare coronary stents or other types of cardiac devices, but really, we feel that we're not changing the overall management of our patient when treating with a drug-coated device.

Now, we do note that there is variation in how drug-coated devices -- and that's how we have a control group here, and we feel that a lot of this is due to one operator preference. This is a newer technology, and some practitioners feel very comfortable on the devices they train with and use, and so they tend to keep using these devices. And, two, there is an additional cost to drug-coated technology and an investment required at an institutional level.

And so the decision may be more drawn based on whether these devices are available on the shelf than whether there's a patient characteristic requiring that use or not use of the device.

And yesterday we had to move really quickly through a large portion of our data, and I wish we had more time, but I want to highlight in this figure here, these are the baseline characteristics of our patients and I know the texts are small, but again, between patients who were treated with drug-coated and non-drug-coated devices, and this is before we've touched the data. And we use a standardized difference when we have such large patient numbers to

evaluate whether there's balance and meaningful characteristics between patients and we use a threshold of 10%.

And I want to highlight that all these characteristics -- and, again, these are measured characteristics, so I understand there is a contribution of unmeasured factors here, but all these measured characteristics, age, critical limb ischemia, prior amputation, tobacco use, diabetes, renal failure, liver disease, obesity, any of those that we typically use to determine whether treatment should be used or not, are balanced before we apply any adjustment or weight to these data. So I do think there's some strength in the idea that selection bias is a smaller component in terms of when we determine to use drug-coated therapy.

The second comment I want to make is just the idea of comorbidities and how the comorbidities negate the impact or of the potential harm of drug-coated therapy. One of these strengths of our Medicare analysis in the size is not that we have 150,000 patients, but that when we do look at separate subgroups we have enough patient population to find a meaningful -- or look at a meaningful amount of time and follow-up.

And I want to highlight here that 60% of our patients are non-CLI patients. In the PAD world there's two groups of patients, there's high risk and low risk. High-risk patients are CLI and the lowest patients are the claudicants and the non-CLI.

And here, when we see the patients with non-CLI, over 90,000 patients, we have more than 17,000 patients contributing data through 1,250 days, we find that there is no associated risk or evidence of harm with drug-coated therapy, with an upper limit of our confidence interval at 0.96, so not lending support that there could be a point estimate that's above 1.0 suggestive of harm. And that is similar to the CLI group where we again show that there's safety with this device with an upper limit of that confidence interval of 0.97.

I'm going to have Dr. Mauri come back to the stand now.

DR. MAURI: So we spent, as I said, yesterday reviewing multiple analyses. They've

actually been of overlapping datasets. Over time we've seen, since the initial meta-analysis, methods to try to adjust for missing data or variation in the designs of trials and with that, we've seen a decline in the hazard ratio even down to 1.1 in the most recent VIVA analysis. And yet it's difficult in a meta-analysis to lump together trials that have all these limitations and ascertainment is still unfortunately limited, and it needs to be addressed in future studies as well as ongoing data collection in the ongoing studies.

But when we look across the observational studies, what you see here is that, first, these are datasets that are complementary, they're not overlapping populations. They're large. That's reflected in the size of the samples, the bubbles there that you see, and they're very tightly -- with the confidence intervals, we're very confident about the narrowness of those confidence intervals because of the precision and estimating mortality across these datasets.

And so what you see is a hazard ratio that really has been flat and overall, we don't see a mortality signal in these studies. So this is an important finding because these are data that we didn't have 6 months ago, and it's important to consider them in the totality of the data that we have.

So we've looked at some of the questions that the Panel has been asked to consider and wanted to provide to you some of our thoughts. I won't go through these one by one because I don't think we have time, and there's already been a lot of discussion on these questions for Day 1.

But one thing we wanted to point out on Number 1 is that we do believe there is a signal in the meta-analyses that have been presented, but we don't see the signal in the observational comparisons and that's an important factor to acknowledge.

Two, the missing data bullet, which is Bullet Number 3, that this really has been a problem that's introduced a tremendous amount of uncertainty and what I would call out here is it's not just the statistical issue with missing data, there is that, and we saw that that was not

missing at random in our own study, but there is also the fact that we just don't collect a lot of this information in trials right now and that needs to be corrected, so things like additional paclitaxel use and whether our patients, who deserve good medical therapy, are actually receiving it.

On the questions that the Panel is asked to address today, just to focus on some of the last few questions, I would say, you know, we would emphasize the benefit-risk profile on Number 8, that we believe that there's still an important -- it's important to consider all of the evidence when we think about the uncertain risks versus the clear benefits that these devices provide.

For the postmarket studies and surveillance question, we believe that it's very reasonable to continue to extend follow-up in these large sample sizes and these observational studies and that we'd like to continue to work with the FDA, as we have done prospectively in some of these studies, to make sure that the methods control adequately for bias and meet the FDA's standards that have been published for real-world evidence.

For labeling, we would like to continue to work with the FDA as well, to update the data and make sure that there's uniformity of our understanding of the data. And our ongoing trials have really focused on completeness of data.

And I'll go on to talk about the implications for the other trials. And this is an eye chart, and I know that even me standing here, I can't read all these numbers, but it's to emphasize that there are many trials that are actually being done in this space right now, and over the next 5 years these studies will yield data, randomized data, on over 10,000 patients. And these represent, in the majority, independent studies more so than industry studies in terms of the numbers, and they represent the range of patients that we're talking about who are being treated in practice today, both under the femoropopliteal indication as well as in the more complex patient populations with below-the-knee or dialysis access.

It's critically important that we get this right going forward. I think there have been limitations in the past for the way that studies have been conducted. And so we strongly support efforts to collaborate with all the stakeholders who are involved, professional societies, investigators, patients, regulators, and that way we can improve the care of patients in this field, as well as the quality of the information that we can provide to them.

For the ongoing studies, it's important that we educate our sites through how important it is to maintain good follow-up, and then think about methods in the consent to provide for complete vital status ascertainment with linkage. We can ensure that there's better recording of additional information, post-procedure as well as pre-procedure, and maintain that throughout the follow-up, not just at the time of randomization, as well as the important factors of medical therapy that are now incompletely ascertained.

There are efforts to use EHR to implement structured minimum core datasets that will be useful for future device evaluation, and we are participating and will continue to participate in those efforts.

For real-world data, it's very feasible to extend and even bolster the methods that are used for addressing selection bias, using methods like instrumental variables approaches that simply take a little bit more time, but we will have that time to do that, and then extending the follow-up that will accrue in these large datasets for patients who have been treated, and working together with the FDA to ensure that we follow their standards to do so.

For labeling recommendations, as I've mentioned, we would like to work with the FDA to update our datasets and analyses and reflect that in the labeling and maintain the current indications.

Patient and physician guidance and patient access are probably two of the most important things that we want to talk about. We really think that this convening and discussion about this patient population is actually an opportunity for us to really address gaps in medical

care, which are evident even in the trial population where we usually think of those patients as getting better treatment, but we need to really evaluate this as a multi-stakeholder community and set up guidelines for the appropriate treatment of patients.

We also think, to guide the medical community and discussions with patients, it's important that the data that are presented here are published in a peer-review fashion and a timely fashion because it's only with that source of information that we can really inform decision making.

And then it's critical, really, that we continue to ensure patient access to treatment. These are very effective products, and we believe that the totality of the evidence is supportive in terms of the benefits and risks of these devices and right now, healthcare providers are not fully able to do what they think is appropriate for their patients.

So we respectfully request the FDA to update the March 15th letter to healthcare providers, really to convey the totality of the evidence that's being discussed now that is available in support of the benefit and risk profile of these devices for their intended uses.

Thank you.

DR. LANGE: Now we're open for clarifying questions. I've got Dr. Somberg, Dr. Hirshfeld, and Dr. Kip.

DR. SOMBERG: This is for -- this is John Somberg.

This is for Dr. Clair. I was confused with your presentation because it seems the slides you presented were that there's no signal in different vascular beds, but I would wonder if you can clarify the dose based on the dose of the device, the length of the device, the length of follow-up, and also the numbers in each. Some slides have -- you can figure out the numbers exposed, others you can't. Can you clarify that, please?

DR. MAURI: So you're asking for -- I'll just preface before you go in. Each of us can speak to our -- more generally, and I can speak for Medtronic, but -- and generally for the

industry. But if you have specific questions on the study, I'll invite the specific manufacturer for that study to come to the podium.

DR. SOMBERG: Well, my specific question was to the gentleman who presented those slides, that they were just -- and it seems to be in a general way, but if we're balancing out the meta-analysis of the -- all the paclitaxel devices, etc., with what, about 8000 patients, something. I wanted to know the number of patients in each one of these groups and the relative dose that would -- you know, with all the understanding that we talked about and the limitations of that so we can put this in perspective.

DR. LANGE: So is that information we could provide after lunch? That may take a little bit of time, and I don't want to -- so with adequate time.

Dr. Zuckerman.

DR. ZUCKERMAN: Zuckerman.

Two comments to the industry. First, thank you for responding in a very serious and constructive manner with an initial presentation. But there are, I think, a few key points that you need to continue to develop. For example, where you indicate the number of randomized trials that are ongoing right now, it looks like a very, very small minority are set up right now for 5 years of follow-up. In fact, I can only count two. So the first thing is the industry needs to work with these current trialists as soon as possible, and certainly, FDA is interested in that.

A second thing is I think it's very important to understand what these products are actually labeled for currently in the U.S., which is claudication, really. A lot of times we see claudication and CLI being mixed or other varieties. It would be more helpful if we keep things separate. It's not to say that the whole issue of peripheral vascular disease needs to be really addressed in a much more scientific way, but for purposes of the FDA, we need to speak about what is currently on label and off label.

DR. LANGE: Dr. Hirshfeld. I've got Dr. Kip, Dr. Ballman, and Dr. Krucoff, and then

Dr. Cigarroa.

DR. HIRSHFELD: Okay, this is a question for Dr. Clair, and it relates to further thought about the robustness of this signal of potential harm. So you showed the data from Gregg Stone's meta-analysis of Taxus versus bare metal and showed identical mortality curves for the BMS versus the drug-treated stents. However, that was a trial that was actually spectacularly more successful than any of these or the other number to treat of 11 for benefit in the heart, and yet you chose no benefit and mortality in the heart. So is it possible that the cardiac benefit and mortality is actually being offset by a detrimental effect of the drug in the heart or in the patient, so that you wind up with no difference in mortality but two offsetting phenomena?

DR. LANGE: Go ahead, Dr. Clair.

DR. CLAIR: So Dan Clair.

There are a number of trials that have looked at interventional therapies compared with alternative therapies for treating patients with coronary disease and benefit is not necessarily exclusively measured as mortality alone. In many of those trials there is improvement in benefits for the patients that reduce revascularization and reduced hospitalizations that are not necessarily reflected in mortality improvement for those patients, and I think this is the same issue.

DR. HIRSHFELD: I understand that. Now, however, if you were ever going to see a mortality benefit, it would be in 2,500 patients with a number needed to treat of 11.

DR. LANGE: Dr. Kip.

DR. KIP: Kevin Kip.

I believe this is for Dr. Secemsky. First, I applaud you for your analysis and trying to mine these observational data. I'm a big fan of observational data to the extent that we can use them and overcome the limitations. So keep doing it, is what I'm saying.

My question, though, I'd like to get your take on the interpretation of the results and I think this will impact our discussion this afternoon about future study designs as well. So in this Medicare population, what you've seen is, it looked like over about 4 years across the board, in the non-CLI population the mortality rate was about 40% and in the CLI it was 60%, and we heard yesterday from Dr. Katsanos the presentation on the inverse relationship between patient risk and the hazard ratio associated with paclitaxel.

So what you have in the context of this analysis of people with a mean age of 76, 77 is massive competing risks of mortality, massive, which theoretically or at least practically, I'd like to get your take, is masking any potential signal that might be for a mortality excess with paclitaxel in, let's say, a younger population with less comorbidities. So what's your general thought on the interpretation of these data in the presence of massive competing risks of mortality in this group?

DR. SECEMSKY: Great. Eric Secemsky.

Thank you, Dr. Kip. I appreciate the question. And I think this has come up a lot since we started publishing this in December, and I just want to highlight again that the randomized trial population is a sliver of our PAD population. So what I'm showing you of 150,000 U.S. patients is our PAD population. And so the idea that there is a level of harm that can occur in a care patient who has very few risk factors and have a long prognosis is a small population, and I think that when we're looking at these drug technologies, we're looking at how do they affect the patients that were treated and their prognosis.

And as we can see in this data, the patients that we are treating, who do have comorbid diseases, it's not all true in their prognosis. So I think that the idea of competing risks is very important, particularly when you're looking at young people who have an 80-year prognosis. When you're looking at the patients here who are 65, 70, 75, they're all going to have competing risks, and I think it's reassuring that we're not out-competing the competing risks

with toxicity from paclitaxel.

DR. LANGE: Apropos to this question, and you may or may not be able to provide this, Eric, you may have an analysis of the low-risk patients to see if there's any difference between the two treatments, and if you have that available, show that after lunch.

DR. SECEMSKY: Great. This is Dr. Secemsky.

Can we have now the opportunity to do that? Yeah, we were thinking exactly that and we can actually replicate the randomized trial population within the Medicare population and show what that -- those groups would look like. We do have patients who range in age from 66 all the way up to 80-plus years and we can replicate a lot of that. So we'll work on that. I won't have it for you until after lunch, unfortunately.

DR. LANGE: You won't be offended if we don't extend the meeting?

DR. SECEMSKY: Yeah, I can stay a few more days. Thank you.

(Laughter.)

DR. LANGE: We'll look forward to that.

Dr. Ballman.

DR. BALLMAN: Yeah, I'm a bit hesitant, I don't know if it's appropriate here or more in the discussion, but I just want to make the observation that, you know, I think we need better clinical trial design. When there's an issue with randomized data, you cannot rescue it with very large observational datasets. I mean, you know, we would take a huge step back if all of sudden we say we don't even need to do clinical trials, we just need the observational datasets. I mean, we could even -- you know, we could extend this to that extreme. Why do any clinical trials in the first place? So I think there is a place for observational studies, I think they're good for hypothesis generating, but they're not good for confirming efficacy or clinical benefit. I mean, this is why we have clinical trials. Even if they're done well, you can minimize some of the biases that are in there, but you cannot eliminate them, and as pointed out, you get great

precision but you get great precision around an incorrect estimate. So I just think we need to keep that in mind as we're sort of moving forward. And I don't think industry is trying to suggest we don't need clinical trials.

DR. LANGE: I see Dr. Mauri shaking her head no, that's not what she's suggesting.

I've got Dr. Zuckerman, Krucoff, Cigarroa, and Rasmussen.

DR. ZUCKERMAN: So, Dr. Secemsky, how would you respond to Dr. Ballman? For example, in your analyses there's no ability to include acute angiographic data, so you never know what the two groups are in that respect, a major contributor to long-term effect.

DR. SECEMSKY: Dr. Secemsky.

I just want to highlight that when we revascularize claudicants, it has nothing to do with survival. So we've never tried to revascularize a leg to extend life. We've never studied therapies to try to extend someone's life based on the delivery of a local treatment like a stent or a balloon. Our goal for lower extremity revascularization is purely quality of life, improvement in walking. And so the angiographic result has never been predictive of future mortality, and that's why we can exercise these patients, and that's why we can do medical management.

So I think that that is a key point here, is that the technology, the reason for the intervention, everything we're doing at the patient level is not actually something we're considering that's influencing mortality, trying to study mortality. We're trying to look for an improvement in quality of life, and usually it's on a short term; it's usually on a 1-year term.

And so I don't think that there's an angiographic endpoint that would cause me to say I think this patient is going to live less longer than another patient. There is not a procedural technique or an amount of drug that I deliver that I was ever concerned about would be altering their expectancy. It was only whether I can alter their quality of life on the short term.

DR. LANGE: We'll talk about that later.

Dr. Krucoff.

DR. KRUCOFF: Yeah, we'll talk about that later, I'm with you. And I do want to first just commend the industry representatives for the spirit, as Dr. Mauri voiced it, of collaboration and dedicated to collaboration, reaching out to Dr. Secemsky to pull him in and, etc., and I think we're -- boy, are we really going to need that, as well as the presentation of additional evidence, which you probably heard yesterday. On the one hand, it's just very confusing at a certain level, but I think it's vital, for as much unknown as we have, to reach out as much as we can.

I have just a couple of things that I'd love to clarify, if possible. And Dr. Kip helped a lot and I totally think, from the Medicare population, the ability to subgroup patients with multiple comorbidities and not multiple comorbidities and look independently would be useful, although it's not a randomized trial.

My two clarifying questions: One is with regard to the non-PAD vascular beds data that were shared. Is the assumption that the quality of that data and the follow-up in those datasets is better than or the same as what we're wrestling with in the peripheral disease randomized trials where quality of long-term follow-up deteriorates?

The second is with the benefit-risk discussion. I think we've been talking a lot about risk and you've shown a lot of mortality related data in different subsets, but that leaves us sort of with the assumption that there's benefit. So we saw numbers needed to treat, numbers needed for harm this morning, and so my second question is, from any of these additional observational or larger datasets, do we have a sense of number needed to treat, number needed to harm, basis? So, first, quality of follow-up data in the other beds. And, secondly, do we have anything like numbers needed to harm, numbers needed to treat, to give us the full scope of what you think we're getting from these larger data?

DR. LANGE: If it's available, and it may be different for the different companies, and I'll

ask to present that after lunch so we can give you a little bit of time to work on that. NNT and NNH, if that's available. And then the quality of data in the non-PAD patients as well. Thank you very much.

Dr. Cigarroa, Dr. Rasmussen, and Dr. LoGerfo, and I think that will probably take us to the break.

DR. CIGARROA: So, again, thank you for a wonderful presentation and, again, for the collaborative spirit amongst different industry and academic colleagues in your presentation this morning.

This is directed to Dr. Clair. With a focus on the conclusion that there was no signal present in randomized trials in other vessel beds, I'd like you to comment on, for example, the AV fistula bed in which the number of overall patients was just under 300 patients, the mortality at 24 months was about 23% in the DCB and about 18% in the PTA in the context of the overall sample size and duration. Would you consider that a directional trend in signal that's underpowered, or would you consider that no signal?

DR. CLAIR: Dan Clair.

There are few specifics about that particular trial which I think are relevant here. This is, overall, a high-risk population. They have an incredibly high mortality. Their average mortality after 2 years is about 40%. It's at least 20% per year, if not more.

The second thing is, in this particular trial there were five patients who refused to continue on dialysis or committed suicide by stopping their dialysis treatment. It just so happens that four of those patients were in the drug-treated arm and one was in the non-drug-treated arm. So, again, I'm not sure you can say this was a signal because if you actually take those patients out, the patients who committed suicide, the hazard ratio is about 1.1.

DR. CIGARROA: Thank you so much.

You know, this is really a challenge of competing risk as demonstrated in peripheral

arterial disease below the knee and/or an end-stage renal disease that at 5 years has a 50 to 60% mortality. So I think, you know, the point being is relative to the FDA indications for which we have approval in the fem-pop distribution, the ability to use or not use this information as to whether or not there's a signal or not due to the competing risk, I guess, is the question that we'll be deliberating, you know, over the next several hours. Thank you for that clarification.

DR. LANGE: And, again, just because of the limited time, limit the comments because we'll be having comment during deliberation, but certainly clarifying questions I want to bring to industry.

And so Dr. Rasmussen and Dr. LoGerfo.

DR. RASMUSSEN: I think, in that -- this is Rasmussen.

I think, in that context, I don't have a clarifying question. I have comments that relate to improving fidelity of data collection in current ongoing or future studies, so maybe I should reserve those.

DR. LANGE: If you would, Dr. Rasmussen, because that will be very important during our discussion and I certainly want to hear those.

DR. RASMUSSEN: Yes, sir.

DR. LANGE: Dr. LoGerfo.

DR. LoGERFO: I have a recommendation, it's a comment but also a question with regard to the calculation of TLR and if you're -- in risk-benefit, if you're calculating TLR in survivors, in other words, using life table analysis, TLR in surviving patients, you might consider that the patients who died may not have had a TLR. So those patients had life-long avoidance of TLR. This is the goal. So at 5 years you have to include those patients as in a way continuing to achieve the ultimate goal. So I think both the FDA people and the industry might look at this. I think you'll like it. We did it for amputation, for distal bypass, and it really improves the outcome as relevant to the patient. After all, the patient just wants to know how's this going to

be for my lifetime? Now, it depends on how you calculated the TLR and I don't know that, so that's sort of a question.

DR. LANGE: Dr. Clair.

DR. CLAIR: So Dan Clair.

I think what you're talking about is intervention-free survival, which is what we would like to know long term, and I don't know that we have that data for all of these trials, but I think it's probably something that could be provided.

DR. LANGE: Excellent point. I mean death is a hard way to avoid TLR, okay?

(Laughter.)

DR. LANGE: So we've come to the time for a break. We'll reconvene at 10:00. Again, I want to thank industry sponsors for excellent presentations, and the FDA as well, and we'll see you back in 15 minutes.

(Off the record at 9:59 a.m.)

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

DR. LANGE: We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views that are relevant to the meeting agenda. Panel members may ask clarifying questions to the speakers at the end of the last presentation. At that time, if you raise your hand and identify yourself, I'll call on you and then we'll identify the speaker to whom your question is directed.

Ms. Washington will now read the Open Public Hearing Disclosure Process Statement.

MS. WASHINGTON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA

believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of today's meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging or other expenses in connection with the attendance at the meeting. Likewise, FDA encourages you, before you begin your presentation, to advise the Committee if you do not have any such financial relationships. However, if you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Finally, if any speaker is reading for someone else, please state this at the beginning of your statement as well.

DR. LANGE: Thank you, Ms. Washington.

The FDA has received 14 requests to speak prior to the final date published in the *Federal Register*. After I call your name or your group up to the podium, you will have 6 minutes for your presentation. Please limit your time to that which you've been given so that all the speakers have a chance to present. At 6 minutes I will thank you for the comments you've made and express regret for those that we're not able to hear. So please confine it to 6 minutes.

The first speaker is Dr. Bruce Chabner. Dr. Chabner, if you'll please come forward to the microphone.

(No response.)

DR. LANGE: He is not here, that will -- okay. Super. I don't mean super, I don't mean that he's not here. I'm glad we identified this, okay?

(Laughter.)

DR. LANGE: Yes, strike that from the record.

All right, Dr. Lindsay Machan. Is that pronounced correctly? Mason or Masan?

DR. MACHAN: Yes, Mahcan.

DR. LANGE: Please correct me if I pronounced it incorrectly.

DR. MACHAN: My name is Lindsay Machan.

DR. LANGE: Okay, Dr. Machan, thank you. We appreciate you coming to present and to hear what you have to say.

DR. MACHAN: So I'm Lindsay Machan. I'm an interventional radiologist at the University of British Columbia. My travel was paid for by Boston Scientific, and I'm a medical advisory board member of Boston Scientific. I'm one of a group of three that patented paclitaxel in vascular disease. Sadly, I had no financial conflict of interest when it comes to paclitaxel.

(Laughter.)

DR. MACHAN: My main conflict is that I strongly believe that paclitaxel-coated devices are a safe and effective treatment for my patients with peripheral arterial disease.

Around the time when I started my career, the biological cascade of restenosis was just being worked out and it was elucidated that in response to any vascular injury you get platelet aggregation, and these platelets release various cytokines that stimulate pluripotential reparative cells to proliferate and migrate to the site and then secrete a proteinaceous matrix that constitutes the bulk of the restenosis lesion.

At the time, we were working on angiogenesis inhibition thinking that that was a way to inhibit overgrowth of a stent, and in fact, our findings were really in contradistinction to the data presented earlier by Dr. Whatley. We actually found that paclitaxel is an exquisitely potent inhibitor of angiogenesis at nanomolar concentrations, in fact, even lower than that. It was the strongest angiogenesis inhibitor that we identified.

And so we swapped over to CEF at the same concentrations, we could inhibit those

steps in the biological cascade, and we found that paclitaxel, in fact, did in vitro inhibit smooth muscle proliferation and migration at nanomolar concentrations without any sign of smooth muscle or endothelial cell toxicity. And it wasn't really until we got to 50 µM concentrations, at least three orders of magnitude greater that we actually even could detect smooth muscle cell apoptosis and not until we got 100 µM that we got nonspecific cell death.

And just parenthetically, just the tissue concentrations, for instance, from an Eluvia stent maximizes it to 2 weeks and it's 2.6 µM/L and then decreases from there. And, again, parenthetically, just these are -- if you see, from a polymeric paclitaxel stent release and also from drug-eluting balloons, that we get very low tissue concentrations in the arterial tissue.

So veering back to the talk, so in addition to showing that at those low concentrations we can inhibit smooth muscle cell proliferation and migration, we also can inhibit cytokine-mediated vascular smooth muscle cell migration, and in vivo I showed that at non-cytotoxic doses smooth muscle cell proliferation and extracellular matrix secretion were inhibited, and this was subsequently validated in the peer-reviewed literature by multiple other labs. So virtually every step in the restenosis cascade has been demonstrated to be inhibited by paclitaxel at cytostatic doses.

A common thing, particularly since this meta-analysis came out, is to show the cell cycle and show that the kind and gentle -limus drugs act in the cytostatic portion of the cell cycle and the nonspecific evil, poison paclitaxel, kills everything in the cytotoxic region. And, in fact, it is acting in that part of the cell cycle when it's used as a cytotoxic, as a chemotherapeutic. But, in fact, like many drugs, paclitaxel has multiple mechanisms of action depending on the local tissue concentration.

And so, in fact, there is profound activity in this portion of the cell cycle, and again,

independent validation has been shown by other researchers that in order to stimulate -- when platelet-derived growth factors stimulate those classic smooth muscle cells to migrate and proliferate, it's stimulating to enter the G_1 phase, again, the area where we say at cytostatic doses paclitaxel is acting.

The other thing we found is that the biological effect is extremely localized. If you balloon-injure a rat common carotid artery, as you see on the right, you'll get profound animal hyperplasia. And on your left, if you put perivascular paclitaxel in a rat, you get complete inhibition of this process but the effect is extremely localized. Early on, we didn't know how to create those rats, and we could actually see, in this longitudinal section, that submillimeter distances from where the paclitaxel is, you have absolutely no biological activity and this is both circumferential and longitudinal.

So, in conclusion, Panel, paclitaxel was chosen to inhibit restenosis because it's a potent inhibitor of virtually every step of the restenosis cascade non-cytotoxic doses and because it's very insoluble; therefore, you get an extremely localized effect.

And I'd like to finish by saying that I work with a group of basic scientists who, among us, have greater than 100 man-years of experience investigating the local application of paclitaxel and none of us can conceive of a mechanism for this nonspecific mortality. And our comfort with that is enhanced by, for instance, there's a 10-year follow-up study from the era of full-metal jacket following a prospective trial of paclitaxel and sirolimus-eluting coronary stents showing no difference in all-cause mortality and no signal from uncoated stents.

Thank you for this opportunity to present.

DR. LANGE: Thank you, Dr. Machan.

The next speaker, Dr. Renu Virmani.

DR. VIRMANI: Thank you. I am Renu Virmani. I am a cardiovascular pathologist and

have been practicing for the last 40 years. I worked for the government as well as the private sector. I started CVPath Institute in 2005, which is a nonprofit organization, and then performing device work for the FDA approval, European CE mark, and Japan PMDA work.

CVPath has performed the preclinical studies for DCB Lutonix, Medtronic, Spectranetics, now Philips, and Boston Scientific. We have the largest registry of stented human coronary arteries with over 800 cases, and have published more than 200 publications regarding stents. I have examined over 100 autopsies of individuals receiving coronary paclitaxel-eluting stents. The cause of death was in no way related to paclitaxel.

Here I show the causes of death in the United States by age greater than 65, and 55 to 64 years. The major cause of death in individuals greater than 65 years is heart disease followed by malignancy.

Shown here is the data that the FDA presented from the Executive Summary in bar graphs. The cause of death by categories by PTX trials versus controls are listed. As you can see, total deaths are higher at 5 years than at 2 years in both PTX and control arms. Non-cardiovascular deaths are more frequent than cardiovascular deaths and malignancy. There's something wrong.

On the left are shown mortality data from a PAD population by age less than 75 and greater than 75 years, with and without diabetes, and control without PAD are shown at 5 years in black bars. Note that the mortality rates are higher in those with diabetes, irrespective of age. The mortality rate is highest in control, greater than 75 years without diabetes, 22% versus 7% in individuals less than 75 years with diabetes. Death rates are higher in the PTX arm than the control arm in the PTX trials and PAD, 12.5%. How can we reconcile the outliers of our PTX control group?

Now I would like to switch to cancer patients and the untoward effects of PTX.

The doses of PTX in these cancer patients, on average, are 128 to 380 mg per dose, and life-threatening toxicity is hematologic; that is, bone marrow suppression only observed following nine courses of 175 mg/m^2, whereas the largest PTX balloon with the highest dose carries 21.7 mg. That is close to 10 times greater in cancer patients. As far as I know, no blood changes were observed of any significance in the PTX PAD trials.

Preclinical studies in swine, as was presented this morning by the FDA, do not support a toxic effect of paclitaxel with use of DCBs or DES for the treatment of PAD. Lifespan of a pig is about 16 to 18 years as compared to a human whose lifespan is over 80 years. So, therefore, we must take in context what is 180 days, 270 days in a lifespan which is only 18 years.

So PTX in vessel wall at 24 hours was 20 ng/mg decreased to half at 7 days and was 1 to 2 ng/mg at 30 days. Remember, this PTX is in solid phase, that's why the levels are that high, and it is not that the -- it's the available one that matters. It's a very small quantity that is available.

So the histologic analysis of the artery wall distal emboli and organs, including heart, did not show any safety issues in the animal studies, and bone marrow did not show any changes in the ones that did through the bone marrow.

On the left is PTX trial as-treated, and the total mortality rates are lower than in the Cardiovascular Health Study, shown on the right, in individuals with AI group, which is less than 0.9 or greater than 0.9. Total mortality is highest, 32% and 25% in individuals with and without underlying CAD.

In the current PTX trial, the total mortality is lower than all other trials with at least 5 years follow-up. To my knowledge, I have not reviewed any trial that has had this low a mortality in the control arm, 12.8%.

So, in summary and conclusions, the major cause of mortality in PAD patients is

related to underlying CAD.

Preclinical trials in large animals with over 400 swine and coronary paclitaxel-eluting stents in humans do not suggest systemic paclitaxel toxicity.

The increase in mortality seen in patients receiving PTX devices is not related to paclitaxel, having done a large number of RCTs myself.

I suggest unrestricted use of DCBs and DES, monitor and perform autopsy studies moving forward to be certain of the cause of death.

Thank you.

DR. LANGE: Thank you, Dr. Virmani.

Dr. Erica Mayer will be our next speaker.

DR. MAYER: Thank you. My name is Dr. Erica Mayer. I'm a breast cancer medical oncologist at Dana-Farber in Boston. These are my disclosures. I receive funding for my oncology related research. My travel here today is supported by my own funding. I received no support from any of the industry partners here today. I wanted to speak with you today about paclitaxel from an oncology perspective and breast cancer, specifically.

So you know a fair amount about paclitaxel, but this is a chemotherapy drug we've had for 30 years and for the past 25 years as part of breast cancer management. There are currently four FDA-approved indications for paclitaxel, including breast cancer, Kaposi sarcoma, non-small cell lung cancer, and ovarian cancer. There's a variety of off-label use as well, which is all advanced malignancies.

I want to stress that breast cancer is the only approved indication in the curative setting where patients are expected to possibly survive their diagnosis, and I want to focus on that dataset.

There are many well-known adverse effects from systemic paclitaxel exposure. Cytopenia certainly, as you've heard, is one of those, although that's quite rare at standard

dosing. More common is peripheral neuropathy, which is quite bothersome for patients. There's also a risk of hypersensitivity reaction which we can control with steroid premedication.

Many therapies for breast cancer have known cardiovascular toxicity, including several chemotherapies: anthracyclines, antimetabolites such as capecitabine, alkylating agents such as cyclophosphamide. Paclitaxel is not thought of as a chemotherapy agent with cardiovascular toxicity. There can be asymptomatic bradyarrhythmias, but we don't monitor for these. There's no long-term cardiovascular toxicity that's known.

I wanted to review some of the data from our adjuvant population showing the benefits of adjuvant paclitaxel. These are two of the large U.S.-based studies that led to the adjuvant approval of paclitaxel, randomizing a total of about 6,000 patients to an anthracycline-based chemotherapy treatment or anthracycline plus paclitaxel. The addition of paclitaxel reduced the risk of breast cancer recurrence and this is what led to FDA approval in 1999.

Long-term follow-up from these studies, a total of 7-year follow-up, show that there was a decreased risk of all-cause mortality at 7 years in patients who received paclitaxel. So receiving paclitaxel helped to save lives here. There was also no increase in cardiovascular toxicity or secondary malignancies in patients who received paclitaxel.

A different study helps us to perhaps isolate effects of paclitaxel versus anthracyclines. This is 4,000 patients randomized to receive anthracycline or paclitaxel. Long-term follow-up of this study showed no increase in treatment-related death with paclitaxel compared to the anthracycline-based regimen. In the AC or anthracycline arm there was more acute leukemia and more cardiac toxicity that was not seen with paclitaxel.

There was a numeric increase in deaths from other causes and those causes were fairly well balanced between the arms, malignancy and cardiac. As we've heard, these are

common in older patients.

Finally, in the breast cancer world, we do meta-analyses every 5 years of all of our randomized trials. A meta-analysis has been done looking at trials with or without adjuvant paclitaxel. There's a total of 123 randomized trials with 44,000 patients. We have overall mortality data for 11,000 patients, and it shows that patients who received paclitaxel in addition to anthracycline have about a 15% lower chance of dying from any cause. So, again, we see here that paclitaxel is helping people live longer.

We've heard a bit about paclitaxel dosing, and I would just point out that in a typical adjuvant regimen for a breast cancer patient, the patient receives perhaps 1.5 g of paclitaxel and in contrast to receiving a paclitaxel-containing device where perhaps it's as high as 10 mg. And if we think about this graphically, the woman in the slide would be the dose for a breast cancer patient, and the very small device next to her is the cardiovascular dose, which is about half a percentage point of what we would be giving to a healthy cancer patient.

One of my clinical interests is treating breast cancer patients who are pregnant. We can give chemotherapy in the second and third trimester. Most of the safety data has been with AC, but my group has studied the safety of paclitaxel and pregnancy, and we recently presented data showing no increase in maternal or fetal toxicity or abnormalities with exposure to paclitaxel. So we feel comfortable enough with this agent that we can give it to pregnant patients.

Finally, I want to touch on a point that was raised earlier today related to the long-term toxicity of having low-dose paclitaxel and in particular, the concept of CHIP, which is clonal hematopoiesis of indeterminate potential. This is thought to be a precancer to hematologic malignancies and it's known to be enriched in cardiac populations. A paper that is currently in press from the Cleveland Clinic has looked at 25,000 cardiac patients

compared to the SEER general population. All the cardiac patients had an intervention, CABG or a coronary device, and looked at the rates of developing a myeloid neoplasm.

What was shown is that the patients who had cardiac history did have more rate of getting a myeloid neoplasm, again, going along with the CHIP hypothesis, but specifically in patients who received a drug-eluting stent, this included paclitaxel, everolimus, sirolimus stents, there was no increase in myeloid neoplasm, so again suggesting no secondary hematologic malignancy from continuous low-dose exposure to paclitaxel.

So, in conclusion, paclitaxel is well established as a safe and effective chemotherapy for oncologic management and breast cancer patients, specifically, for the past 25 years.

We have no data in the breast cancer setting to suggest a long-term mortality risk, either cardiovascular or oncologic, from the limited exposure to parenteral paclitaxel.

And we have no data to suggest long-term mortality risk from prolonged exposure to low-dose paclitaxel in humans.

We also see no association between the paclitaxel drug-eluting stent and hematologic malignancy beyond the known CHIP connection.

I'll end my comments there. Happy to take questions later. Thank you.

DR. LANGE: Thank you, Dr. Mayer.

Dr. Ramon Varcoe will provide the next presentation.

DR. VARCOE: Thank you, Mr. Chairman. My name is Ramon Varcoe. I'm a clinically academic vascular surgeon from the University of New South Wales, Sydney, Australia.

So in the absence of a clear and biologically plausible mechanism for paclitaxel toxicity, I think it's beholden upon each of us to explore other alternative explanations, and over the next 6 minutes I'm going to shine a spotlight on clinical trial design as one of those possible influences.

My travel was funded by Medtronic to come here and these are my disclosures.

So I don't have to tell anyone in the room here that randomized controlled trials are the best method of estimating the impact of surgical and interventional procedures. But randomization itself doesn't prevent biased outcome assessment; blinding does that. And we know from the *JAHA* meta-analysis that all of the interventional trials that were included, all 28 failed to blind the participants or the healthcare team and the authors decided that that possibly introduced a high risk of bias.

It's also well established in the literature that failing to blind results in a 30% on average exaggeration in treatment effect compared to those trials that do blind their healthcare teams.

And these are the people who should be blinded, and you can see them here. I'll make two points, the first one being that clinicians and the healthcare team are very hard to blind in interventional trials, and when it comes to the adjudication of mortality as an endpoint, it generally is the investigators or a healthcare team that do that.

So this leads to a combination of performance and detection bias, which is when, either unconsciously or consciously, the participants and the healthcare team, who are not blinded, can introduce bias into the outcome measures and specifically, ascertainment bias. Now, this is when the investigators launch a more intense surveillance program onto this experimental group which, of course, they're more interested in following up. And this is particularly relevant with mortality when, obviously, people who have died become un-contactable, they're easily classified as lost to follow-up when, in fact, they should truly be classified as mortality.

So it comes down to the tenacity of the follow-up on behalf of the investigators. What we're talking about here is an unblinded research team taking a more tenacious approach to following up those patients in the experimental arms. And this can lead to fewer subjects being labeled as missing in those particular experimental arms with a

corresponding increase in the number of mortalities recorded.

So this is how it normally works. If someone doesn't answer the phone twice, they get sent a registered mail letter, but if they don't respond to that, then they're called lost to follow-up.

There are alternative options, of course. If you want to be tenacious, you can ring the family, you can ring the healthcare physician, you can check local hospital records or the Medicare database, and this is where classification issues do come into the discussion.

So we've seen a table like this many times over the last day and a half. These are the percentages of patients in the 5-year studies that were lost to follow-up or withdrawn or missing data, and that missing data ranged between 14 and 46% with an average of around about 25%. So a quarter of patients in these studies potentially are misclassified as missing when they were, in fact, mortalities.

So how can we determine whether the findings of this meta-analysis were due to paclitaxel or due to bias from clinical trial design? We have this idea that what if we performed an identical meta-analysis of randomized controlled trials in the SFA but we excluded all drug-coated devices. So we took paclitaxel completely out of the equation. I won't bore you with the details of this PRISMA flowchart, which is to say that our systematic review identified 22 studies that fulfilled the inclusion criteria. So these were patients that were involved in randomized controlled trials for PAD. They needed to be comparing an endovascular experimental device with a standard control endovascular strategy. They had to have at least 1 year of clinical follow-up. We excluded all studies that looked at drug-coated devices and any studies that did not denote overall survival numbers or designate them to individual arms of the study.

This is the most important slide I'm going to present. So just to orientate you, the top left panel is the forest plot from the *JAHA* meta-analysis at 1 year. The bottom left is

our own forest plot. And if I can guide your attention to the table, you see here that we had marginally fewer studies, 22 versus 28, and about half the number of subjects. But what was really impressive was that our risk ratio was highly statistically significant at 12 months, showing that the patients in the control arm had around 69% fewer mortalities compared to the experimental arm. We thought this was quite compelling. This represented an absolute risk difference of just under 2% and a number needed to harm of 52, but statistically significant, which was impressive.

At 2 years we had half the number of studies as Katsanos and about a fifth the number of subjects, but you can see the risk ratio is very similar, very similar to what we're talking about, again, the same direction favoring the controls over the experimental arm. There's a pattern developing here. It was underpowered and it failed to reach statistical significance, but the pattern continued on to 3 years. We didn't have any studies at 5 years, but we had five studies at 3 years and marginally fewer subjects than Katsanos. But, again, you see the same direction of effect favoring the control arm with fewer mortalities.

So how can misclassification of missing participants affect a meta-analysis? In the next couple of slides I'm going to show you some forest plots which I hope can illustrate this.

The first forest plot is the Katsanos forest plot at 5 years. You see the risk ratio of 1.93 and the three studies we've discussed ad nauseam. But if you add in here LEVANT 2 and the 5-year data from IN.PACT SFA, you see a slight change in the risk ratio down to 1.57.

Now, just think for a moment, what if a proportion of patients in the control arm were misclassified? Say 5% of patients were misclassified. This is what it does to the risk ratio. So it's 5%, the risk ratio is 1.37 and it's marginally statistically significant. But what if that number were 10%? You lose statistical significance. The risk ratio drops to 1.29. And

if you consider 20%, it basically is at parity with the diamond right on the number one. So I think that's really quite impressive as well.

In conclusion, what we've demonstrated here is that randomized controlled trials which compare treatment of experimental devices for the SFA find additional risk of death compared with controls at 12 months.

We saw the same direction of effect at 24 and 36 months, although our analysis was underpowered and failed to reach statistical significance.

But I want to make the point here is that these effects were independent of paclitaxel completely, and in my view, that casts considerable doubt as to the causal link between paclitaxel and mortality.

So could it be that SFA interventions in general cause increased mortality amongst our patients? Or more likely, in my opinion, could it be that this association between experimental SFA interventions and a high rate of death could be due to a combination of the interaction of bias through clinical trial design, a more tenacious follow-up protocol in those subjects in the experimental arms combined with high rates of medical interaction and enhanced medical therapy in those RCT arms that had more frequent TLRs?

Thank you for your attention.

DR. LANGE: Thank you, Dr. Varcoe.

Dr. Alik Farber will provide the next presentation.

DR. FARBER: Good morning. I'm going to talk about the use of paclitaxel in the BEST-CLI trial. I do not have any relevant disclosures. I'm here on behalf of my co-investigators, Matt Menard, Kenny Rosenfield, and Sandy Siami.

There is significant variation in amputation rates, revascularization rates, and intensity of vascular care delivered in patients with CLI across the United States.

There are two ways we treat critical limb ischemia: distal bypass and endovascular

therapy. And there's significant variation in the way these two treatment strategies are applied across centers in North America.

There's also a significant evidence gap between coronary artery disease, cerebrovascular disease, and CLI. Just take a look at the number of randomized trials performed in CAD and CVD and only one lone trial, the BASIL trial, performed in CLI, and a commensurate number of patients that are enrolled in these trials.

So this is why we're running the Best Endovascular versus Best Surgical Therapy in Patients with Critical Limb Ischemia trial, which is a prospective, randomized, multicenter, pragmatic, multi-specialty, open-label, superiority trial that aims to enroll 2100 patients at 160 clinical sites. We're funded at the level of $27 million, and the goal is to assess treatment efficacy, functional outcomes, cost and value in patients with CLI and infrainguinal PAD who are candidates for both open vascular surgery and endovascular therapy.

BEST is funded by the NHLBI, and again, patients with CLI who are candidates for both are randomized into open surgery or endovascular therapy, and the projected follow-up, mean follow-up, is going to be 4 years. We have 130 sites actively recruiting patients, and as of this morning, we have 1,733 patients enrolled and as such are 83% complete with our enrollment.

There's also a companion CLI registry that has been funded by the NIH that will be starting shortly which aims to enroll 1200 patients at 40 BEST-CLI sites and we'll have 24 months of follow-up.

Now, paclitaxel-eluting stents and coated balloons have been used widely in BEST-CLI over the past 5 years. This is the event timeline with regard to paclitaxel in our trial, and after all the information came afloat, we had multiple conversations with the FDA, NHLBI, our DSMB. We sent a letter to the BEST-CLI investigators from the leadership in December

28th, 2018.

And then after the FDA delivered its second letter, we sent a letter again to the trial site personnel on April 30th, 2019, and in that second communication we told the investigators that they were allowed to use paclitaxel products within the trial at their own discretion, reinforcing the FDA directive that physicians using paclitaxel are required to have full discussion of risks and benefits with their patients, and the principal investigators at each site participating in BEST was to personally acknowledge the receipt of the FDA and BEST memorandum and to inform all co-investigators of what was going on.

So paclitaxel use in BEST-CLI, in terms of the proportion of the patients treated, is similar to what is being treated now in the Vascular Quality Initiative. And the BEST-CLI trial and companion registry will provide a comprehensive and granular dataset on a sizable cohort of patients with CLI treated with paclitaxel devices. So we will be able to provide the use of paclitaxel during index procedure, by calendar year, by specific arterial segments throughout the course of the study, including reinterventions. We're going to be able comment on all-cause mortality and specific causes of death.

Now, there are some limitations that we have. The trial is not designed to compare safety and efficacy of paclitaxel devices against other endovascular technologies. The history of paclitaxel use before enrollment is not captured as is contralateral limb use with paclitaxel.

Yet, BEST-CLI trial and registry promises to provide a large cohort of patients with CLI treated with paclitaxel devices. Procedures are performed by multidisciplinary CLI teams in two-thirds of the sites and a dataset is captured in a prospective, detailed, adjudicated fashion within the scientific rigor of a randomized controlled trial. And there will be opportunity to obtain mortality at very long follow-up periods.

Thank you.

DR. LANGE: Thank you, Dr. Farber.

The next presentation is by Dr. Yann Goueffic. And if I've mispronounced that, when you approach the podium, please correct it for the record. And me as well.

DR. GOUEFFIC: Yann Goueffic.

I am Professor of Vascular Surgery and Chief of the Department of Vascular Surgery in Nantes, France. And so I am also the PI of the BATTLE trial. These are my disclosures. My travel was funded by Boston Scientific.

Definitely, I think that you should split DES and DCB. It's complicated, for instance, in terms of platform, in terms of drug amount, in terms of drug release, in terms of polymer. And also if you looked at the Katsanos data and if you look more at the DES results, we have only three randomized trials about DES. We have the FINN-PTX trial, we have the Zilver PTX, and we have the BATTLE trial at 1 year with 686 patients.

If you look at 2 years we have only two trials, the FINN and the Zilver PTX trial, because at this period BATTLE was not evaluable at 2 years. If you plot the results of FINN and Zilver PTX there is a trend, a signal, to have more death for in the DES group.

So let's go now to the BATTLE trial. What is the BATTLE trial? It's a French multi-centric randomized trial comparing Misago BMS versus Zilver PTX DES for the treatment of femoropopliteal lesions. The BATTLE trial has been funded by Terumo, and so far, the manuscript is under review at the *Journal of the American College of Cardiology*.

Trial BATTLE, it's an investigator-initiated study, randomization 2:1, and multicenter study with rigorous data collection process and completely independent. We have a monitoring of all the patients and the protocol has been published. We make a comparison between the Misago bare-metal stent versus Zilver PTX, which is a polymer-free paclitaxel-coating stent.

The main objective of the BATTLE trial is to demonstrate the clinical superiority of

the primary stenting using Zilver PTX stent versus a bare-metal stent, the Misago, in the treatment of femoropopliteal lesion. We use, as the primary endpoint in this study, the freedom from in-stent restenosis at 1 year and it is assessed by duplex scan at 1 year.

Very briefly, as the main inclusion criteria of the BATTLE trial was patient presented Rutherford Stage 2 to 5, de novo atherosclerotic lesion of the SFA and P1 or both, the target lesion should be comprised between 2 and 14 cm, and the reference vessel diameter should be comprised between 4 and 7 mm. We exclude from the BATTLE trial asymptomatic lesion, restenosis, and no atheromatous disease.

This is a flowchart of the BATTLE trial. We include all the patients schedule, 186 patients and at 2 years of follow-up, 68 patients completed their follow-up in the Misago arm and 76 patients completed their follow-up in the Zilver PTX arm.

These are the baseline clinical characteristics of the patients. They are pretty similar -- and we treat mostly claudicant patients. Misago, 82% of the patients were claudicants, and in Zilver PTX, 79% of the patients were claudicants. However, in the primary endpoint we didn't see any significant difference between both arms. In the Misago, we have 85.7% of patients free from in-stent restenosis versus 90.3% of the patients in the Zilver PTX arm.

Now, regarding the secondary endpoints, we didn't see any difference, but in terms of major adverse clinical events, we have a trend to have more MACEs in the Misago BMS versus the Zilver PTX, 6.4 versus 1.2%.

So looking at these MACEs, these MACEs was related to all-cause death because we have seven deaths in the BMS group at 2 years versus one death in the DES group at 2 years. We have no major amputation and no device- or procedure-related death in the BATTLE trial.

If you look at the causes of deaths, we can see that in the groups the death was what I think is a pulmonary cancer for three patients, sepsis for two patients, and traumatism for

one patient, and finally, one patient presented with multi-system organ failure. In the Zilver PTX group, only one death related to the hemorrhagic shock.

Now, if you update the Katsanos meta-analysis with the BATTLE trial at 2 years and we do this random effect forest plot of all-cause patients, we have no more signal of death in the DES group at 2 years.

So to conclude, in the BATTLE trial there is a trend to have more death in the BMS group rather than the paclitaxel-eluting stent group.

But BATTLE was not powered to assess safety data, and no conclusion can be drawn from this secondary endpoint.

Update of Katsanos meta-analysis with BATTLE did not support a signal of death following application of paclitaxel-eluting stent in the fem-pop lesion at 2 years.

Thank you for your attention.

DR. LANGE: Thank you, Dr. Goueffic.

Dr. Kim Hodgson will provide the next 6-minute presentation.

DR. HODGSON: Good morning, I'm Kim Hodgson, and I'm here representing the Society for Vascular Surgery, the largest vascular surgery society in the world. As its President and Chair of its Paclitaxel Safety Task Force, I'm here today to present to you on our thoughts about a pathway forward for the continued use of paclitaxel devices in PAD.

As an SVS officer, I'm disclosing no personal or family income or gifts from industry for over 4 years other than for compensation for serving on trial DSMBs or CECs.

In response to the concerning Katsanos analysis, the SVS established a paclitaxel safety task force, led by myself, to develop a strategy to get answers for our patients, our members, and our industry partners. As you can see by the composition of the task force, we envisioned a strong role for our AHRQ-structured patient safety organization and its national registry, the Vascular Quality Initiative.

The SVS Vascular Quality Initiative was launched in 2011 with the mission of improving the quality, safety, effectiveness, and cost of vascular healthcare by collecting and exchanging information. At the heart of the VQI are 12 national registries, so the various vascular diseases we treat and our 18 regional quality improvement groups. The VQI is currently the only AHRQ-designated vascular disease registry patient safety organization.

Participating VQI centers are proportionally distributed across the United States and there has been steady growth over the 9 years of its existence, currently with 565 participating centers in North America.

As of May 1st of this year, there were over 585,000 total procedures logged, including over 185,000 peripheral interventions and 53,000 infrainguinal bypasses with, I might add, 76% 1-year physician-evaluated follow-up. One-year follow-up provides a unique opportunity for patient and device evaluation and can be further fortified by linkage to claims data and the SSDI.

This graph shows the steady growth and procedures logged over the last 5 years for all registries.

There is virtually equal representation in VQI of all practice types, and despite being a vascular surgery society construct, there is healthy and diverse representation from the specialties involved in the vascular space.

The VQI incorporated the FDA GUDID system on its introduction in 2016 and is the only PVD registry using GUDID today. GUDID enables device-specific linkage to CMS, FDA, and other databases. The VQI is widely regarded in the vascular space as the most granular and robust to the PVD registries.

So with that brief introduction to the SVS VQI, let me now move on to our vision for a pathway forward.

Based on the Katsanos and other subsequent analyses, we assume that a mortality signal would be confirmed. We also assume that this Panel would be hearing a lot of reference to patient safety, a concept that can be difficult to define, but that our SVS appropriate use committee has defined here.

Striking the right balance requires weighing the increased risks associated with extra interventions against the presumed increased mortality of paclitaxel.

But if durability trumps a certain level of increased mortality, the safety equation really needs to include the alternatives of endarterectomy and open surgical bypass, which have demonstrated superior patency over endovascular revascularization and for most states of PVD and certainly for the severity of lesions likely to lead to the most paclitaxel exposure are treated that way.

The SVS would like to offer a portfolio of options that the FDA could consider depending upon where on the spectrum of concern the presented data at this Panel leads us.

If the mortality signal is reproduced but considered acceptably low, the SVS believes that the FDA should consider allowing use of paclitaxel devices only if participating in an approved registry, much like the current collaboration between the FDA, CMS, and the VQI that allows reimbursement for TCAR.

We can conceive of some other limitations that the FDA, depending upon the strength of the mortality signal, might want to consider.

While off-label use of endovascular devices is more the norm than the exception, in this case the FDA could consider limiting the use of paclitaxel devices to patients with the anatomic inclusion criteria of the original IDE trials, at least until the cause of the paclitaxel mortality signal is clarified and especially if a dose-response relationship is confirmed.

Recognizing that CLTI patients treated with paclitaxel devices will be exposed to

greater doses of paclitaxel, the FDA might consider limiting paclitaxel device usage in CLTI to those patients with no surgical revascularization options.

So, in summary, the SVS understands the interest in a multidisciplinary paclitaxel registry for the purpose of getting real-world evidence, but that prototype for that initiative already exists in the SVS VQI database.

We believe that the VQI's granularity, robustness, device identification, long-term follow-up, and its ability to add customized variables and time points make it an ideal, immediate option for an FDA-sanctioned paclitaxel registry.

The SVS VQI is committed to exchanging information and it has embraced the RAPID program, a public-private partnership that Dr. Bertges co-chairs and will be describing some projects in shortly.

RAPID is an already existing collaborative multidisciplinary group whose initial vision was to harmonize all the PVD variables across the major registries to dramatically enhance our statistical power.

The VQI incorporated all of the RAPID core data elements in September 2016, but to date, none of the others in this multi-specialty collaborative have done so. Consequently, it remains impossible to combine the different society registries.

So while there is no need to reinvent the wheel, RAPID variable implementation needs to occur in all registries to put some air in its tires and allow it to achieve its full potential, not just to help sort out the paclitaxel safety signal, but to be able to address the next signal that comes down the pike.

If this is not a project best handled by RAPID, then the SVS questions just what is RAPID for?

The SVS looks forward to working with RAPID, which has years of established collaboration, infrastructure, and trust to get these answers now and in the future.

Thank you.

DR. LANGE: Thank you, Dr. Hodgson.

And as alluded to, Dr. Daniel Bertges will give the next 6-minute presentation.

DR. BERTGES: Thank you. I'm Daniel Bertges speaking to you as a member of the SVS VQI as one of the co-leads for RAPID, which I'll elaborate on, and also a concerned vascular surgeon. I have no disclosures. I do have an academic interest in the subject.

I have two goals of my time. First is to present the current data from the SVS VQI PVI registry and second, to elaborate further on Dr. Hodgson's mention of a potential pathway forward using the SVS VQI's real-world data in collaboration with MDEpiNet's RAPID project and the VISION coordinated registry network, or CRN.

First, the current data. This is a retrospective propensity matched analysis that was recently presented at the vascular meeting in National Harbor last week, the VQI PVI registry from October 2016 to December 2017. This time frame was chosen because this was when the registry first began to capture devices with specificity, with linkage to the GUDID.

The outcome was looked at in three comparators, was all-cause mortality, DCB versus PTA, DES versus bare-metal stent, and finally, any paclitaxel device versus any non-drug device.

This flowchart depicts the construction of the cohort. We started with over 166,000 patients within the registry and derived a cohort of just over 8,000 patients. Importantly, the inclusions are shown in the text box. I'm going to call your attention to the fact that we excluded some 2,000 patients who had a prior PVI, and that was done intentionally to try to avoid the possibility of inappropriate assigning of paclitaxel exposure to the control group. We ended up with the four groups, shown at the bottom of the slide, with over 3500 DCBs over that approximate 1-year time period and 700 drug-eluting stents. Mortality was linked

to the SSDI. We considered the first procedure and did a sensitivity analysis for the second.

Propensity matching included demographics, comorbidities, and lesion characteristics. I want to call your attention to the fact that, as was mentioned, in the real world, a large percentage of patients are being treated for the indication of CLI. Between 34 and 51% of patients in the VQI registry treated with a paclitaxel device had CLI as compared to, on average, less than 10% across the pivotal trials.

The following two slides show the results. This is the Kaplan-Meier estimate for drug-coated balloon versus PTA, DCB in blue, PTA in red. We saw no survival difference with estimates of 9.6 and 12.6, respectively.

This shows the comparison of DES versus bare-metal stenting. Again, no difference in mortality, 8.8 versus 9.8%.

And then, finally, when combining drug versus non-drug, there was a slight mortality advantage in the paclitaxel group of 8.5% versus 11.5% with a hazard ratio of 0.82, a p-value of 0.03. This is at a mean follow-up at approximately 12.4 months.

Secondary procedures were performed in about a quarter of the patients, which was equally distributed between groups. The crossovers from drug to non-drug was approximately 12%. And, importantly, we found no difference in mortality within the crossover group.

So in summary to this part of my talk, in this real-world sample we saw no difference in mortality with paclitaxel devices at this early time point. Results were similar for DCB and DES, and we're continuing this analysis forward.

I want to switch gears to talk about a possible pathway forward, leveraging real-world evidence through MDEpiNet and VISION and the SVS VQI.

We envision two possible projects we can offer. First is a retrospective look within the VQI by linking to Medicare claims back to 2012 to 2017 through VISION's methodology,

which is the Vascular Implant Surveillance and Interventional Outcomes Network.

The second is continued surveillance with prospective near real-time tracking of mortality within the registry using DELTA, the Data Extraction and Longitudinal Trend Analysis.

I want to emphasize that both of these efforts are a collaborative effort between the SVS, the task force, RAPID, and the VISION CRN.

This slide shows the leadership of RAPID.

RAPID itself is a public-private partnership which started in 2015 as a NEST, the National Evaluation System for health Technology, demonstration project. RAPID's mission is to improve the national system for peripheral device evaluation throughout the total product life cycle. Paclitaxel is very much within RAPID's core mission.

As mentioned, it's a public-private partnership with several governmental agencies, including the FDA and CMS. There's good representation by the societies including SVS VQI, ACC/NCDR, SIR with support by the DCRI. And there's good representation across the board from industry.

A word about VISION, the Vascular Implant Surveillance and Interventional Outcomes Network. This is a CRN led by Drs. Phil Goodney and Art Sedrakyan at Dartmouth and Cornell Medical Center, and it's a collaboration effort between FDA, MDEpiNet, and registries. It focuses on developing a CRN for all vascular devices and connects data linkages. They have proven methodology for linking Medicare claims to registries such as the SVS VQI.

Through this tool, we are working on a registry-based link analysis from claims from 2012-2017, which will offer 5-year survival analysis for DES and 4-year survival for DCB and a real-world population with granular data.

Furthermore, we have a plan for prospective real-time tracking. The registry is going

through a process of embedding the DELTA process within the PVI in collaboration with Dr. Fred Resnic, who is co-director of the MDEpiNet methodological center, and this is a near real-time risk-adjusted tracking through propensity matching of mortality within the registry for patients receiving the paclitaxel device and the controls. And this is done in coordination with the VISION CRN.

I'd like to thank the Panel for their time.

DR. LANGE: Thank you, Dr. Bertges, for those comments.

Dr. Schuyler Jones will provide the next presentation.

You're next, Roseann.

DR. JONES: Thank you. Schuyler Jones from Duke University. I'm the ACC/NCDR representative. It's a pleasure to be here. I traveled on my own accord today. I do have grants that Medtronic funded for DCB work. I'm not talking about that research here today. I don't have other disclosures that I think are pertinent.

And as an interventional cardiologist that treats vascular patients routinely, I use this framework to think about patients who have SFA popliteal disease. Like Dr. Secemsky said earlier, I think when we treat the leg we often think about symptom improvement and not so much about cardiovascular risk. And we do care about our patients. We do want the devices to be safe.

And as we think about the things that are least studied, certainly medications, devices, and anatomy are the most frequent things that I think about that we could use more definition to improve our care of patients.

But what's the problem? The problem is there are few ongoing studies. We have limitations or inadequate data sources with a lot of missingness. A lot of that's been discussed here. There's heterogeneity in terms of approaches for treatment. And I think that we really need real-world data and treatment information from multiple sources, not a

single source, but multiple sources, to truly understand how to treat our patients better.

NCDR, as many of you know, is the ACC's suite of cardiovascular data registries, and it helps hospitals and practices measure, benchmark, and improved quality of care.

When we look at what NCDR has the opportunity to do, and that's to study patients both in the premarket but also in the postmarket realm, there are currently great examples of this with SAFE-STEMI as well as many valve projects, valve-in-valve as well as TAVR projects, from IDE to continued access to post-approval and then postmarket surveillance. I think this suite of registries is well suited to study this in the PVI space.

When we look at longitudinal follow-up, longitudinal follow-up is critical, and I think we've been talking about it for 2 days here. When we think of ways to add to the traditional measures of follow-up, we have to add follow-up from health plans. Health plans know exactly what happened to their participants almost all times without a drop-off. NCDR is deterministically linked to CMS data, as well as National Death Index data, and that allows us to be capably able to follow these patients over time.

So what is the ACC PVI registry? It's a PVI registry that assesses the prevalence and demographics, management, and outcomes of PAD patients undergoing endovascular therapy. At this time, the NCDR will expand to offer open surgical surveillance in the next 2 years. Data is collected at standard time points, captured from multiple vascular specialists including cardiologists, surgeons, and radiologists at the participating institutions. And these procedures can occur in the cath labs as well as IR suites and operating rooms, so a vast array of places within hospitals.

There are 208 hospitals currently participating in ACC PVI. As many of you know, NCDR PCI is over a thousand hospitals, but here, for lower extremity procedures, we've captured this in 200 hospitals with almost 50,000 procedures captured.

We likewise plan to do a PVI analysis looking at paclitaxel-coated devices. We've

limited it to SFA popliteal segments only. We were linking, as I told you, to CMS. Unfortunately, the data use agreement was unable to be completed in time for this presentation, so I'll only be able to show you baseline characteristics. You can see the device names, we tried to include all of the devices that contain paclitaxel and are used in the legs.

As Dr. Bertges commented, I think it's important to get the really granular details of a registry at the front end and then be able to link these outcomes over time to basically supplement that registry and that's what we had planned to do here. We have about 20,000 patients who underwent SFA popliteal intervention. Almost half of these or a little over half of these patients had paclitaxel devices during the index procedure. By this time last year, 60% of patients within the registry underwent paclitaxel devices. You can see that the patient characteristics are pretty similar. There are actually more claudicants who received paclitaxel devices than CLI. And the other characteristics are relatively standard for the types of patients that are being treated around the country.

As we think about what are the next steps here, I'd like to offer my insight into this. I think you're getting everyone's opinion and I might as well give you mine. As we think about linking CMS, I think there's the opportunity to do traditional observational analyses with adjustment for patient and procedural characteristics that have been described already.

I think our huge challenge and -- and with that the opportunity is to do prospective registry based randomized controlled studies with, not just our registry, but multiple registries for all of our patients that are cared for in the vascular space.

I put together this slide for a publication on pragmatic ways of studying vascular disease a few years ago, and I really think that we need detailed data for comparative effectiveness studies that really can build in randomization into these evaluation platforms,

whether or not that's the registries or PCORnet, the SPEED initiative that has just been talked about or others.

Thank you for your time.

DR. LANGE: Thank you, Dr. Jones.

Dr. Roseann White will provide the next presentation.

DR. WHITE: Thank you for allowing me to speak this afternoon. I work as an independent consultant. I work with several of the people here. C.R. Bard funded me to come here. I also work as an unpaid consultant for several of the academics here. However, I am presenting just my opinion of one humble statistician who has poked and prodded at the data that FDA provided.

One thing I want to bring across to the Panel is you're only as good as your assumptions.

If we take a look at some of the data from FDA, you can see that the assumption of proportional hazards is probably not appropriate. You can see FDA has shown that the hazard changes quite a bit over time. Though VIVA tested to see whether proportional hazards, whether there was violation of the proportional hazards, Dr. Austin, in his paper in 2018, said you would need between 200 and 1,000 events to be able to detect severe departures from proportional hazards. Luckily, people smarter than me have taken a look at this particular issue to look at an alternative way of looking at this information when we have violations.

The proposal they made was the restricted mean survival time. The restricted mean survival time is area under curve. Please note the word restricted. Mean survival time is over a period of time, according to the rules that have been laid out, so that you're not looking, like with proportional hazards, over all the follow-up that could have possibly happened or in binary where you're only looking at the patients that survive. The restricted

mean would say we're going to look between, let's say, 0 and 5 years because we have sufficient information to make that kind of assessment.

The paper showed that the restricted mean has just as much power as proportional hazards when the assumptions are there for proportional hazards, and then has more power when the assumptions are violated.

There's also some advantages in terms for clinicians, in terms of explaining this to the patient. It's hard to talk about hazards or number needed to treat. But if you could say to a patient over a 60-month period the average survival time is 55 months with Device A versus 52 months with Device B, now they can look at what their life is going to look like in the next 60 months and make a decision.

Unfortunately, it was not me who noticed this. This was actually from a presentation by FDA. Several very smart statisticians had talked about the restricted mean and have made recommendations on using it for both proportional violations and for its interpretation.

The second thing I want to say is that I think clinicians learn over time.

This is the first trial of the drug-coated balloons that started enrollment in 2010. I have truncated it at 3 years. The start of enrollment of the second trial, the Lutonix trial, started in 2011. And then you have the Stellarex trial which was started in 2013.

If you follow the PTA arm, you see that the PTA arm seems to be getting worse over time, worse over time where the DCB seems to be getting better. My supposition is that we are learning over time as to the best patients that need to be treated and also, that perhaps patients themselves are living longer and so maybe the patients themselves are at higher risk.

The best way to address this is according to a platform design. This was proposed by Scott Berry, a very smart statistician, smarter than me. The best way to think about it is to

think about it like these panels. We have these panels over and over and various different industry members present; however, FDA is always there. And though the industry and the devices may change, FDA does evolve its opinion over time and so in a platform design, we are sort of reflecting that change in the opinion or the treatment of patients over time by having a common control arm for all the different devices.

This is a more efficient way for industry to function since they don't all need to have their own individual control arm. It takes into consideration changes in practice over time and also involves the clinical community because it could be the professional societies, the VQI, the NCDR, who could be the ones that maintain this common control arm among all the different statistician -- among the different industries.

One other thing is what if you happen to drop and we stop for a while in terms of the control arm. We do have the advantage, if it picks up again, of being able to maybe interpolate between the times in which it was dropped and then picked up again.

In conclusion, I think we need to be aware of the assumptions. I think we do change over time due to learning, and so does our practice. And we can be most efficient through cooperation.

Thank you very much.

DR. LANGE: Thank you, Dr. White.

Dr. Stephanie Fox-Rawlings will provide the next presentation.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Stephanie Fox-Rawlings. Our Center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We've been very impressed by the discussion yesterday and today, and we agree

with the FDA and the Panel that the increased risk for death for patients treated with the paclitaxel-coated balloons or eluting stents, as shown in the meta-analysis of randomized pivotal trials, is very concerning. Any potential increase for death is important for healthcare professionals and patients to know about so that they can make appropriate decisions about whether to use a product. And we greatly appreciate the efforts that FDA is undertaking to evaluate the safety signal.

We also agree that there are unanswered questions about the clinical trial data and the cause for the increased risk. More research is clearly needed. While many kinds of studies can contribute to our understanding of the risks of these devices, the best source of information will be additional high-quality, long-term clinical trials.

Meanwhile, information about the signal for increased risk of death should be included in the labeling for these products. This information is important to help patients and their physicians make informed healthcare decisions.

Even though we still have questions about the meaning of the data, a 50% increase in deaths from the meta-analysis of numerous studies is the information that patients and physicians deserve to have. However, it may be more informative and possibly less frightening if it were provided in terms of absolute risk and not just relative risk. For example, if the absolute risk is only 2%, then a 50% increase may not be of great concern for many patients. However, an absolute risk that is much higher, then a 50% increase may have a much greater impact on their decision.

In conclusion, while there are still many questions, the fact that this signal was seen in a solid meta-analysis is important. It is a reminder of the value of long-term studies conducted after products are on the market. It also shows the importance of FDA's continued role in postmarket surveillance and communicating about their findings to physicians and patients. This information is absolutely vital for healthcare providers and

patients to make informed decisions about their care.

Thank you.

DR. LANGE: Thank you, Dr. Rawlings.

Dr. John Winscott will come to the podium and give the next presentation.

DR. WINSCOTT: Thank you. I'd like to thank the Panel for giving me this time to give my input, and thank Ms. Washington for organizing this. Very well done.

I'm Dr. John Winscott. I'm a Professor of Medicine and Surgery at the University of Mississippi Medical Center. My travel was -- I was allowed to be here today by a travel grant by Medtronic, but my time today is my own. In fact, today is a vacation day for me.

And so what I want to bring to you is my experience in this field. We have 26 cardiologists, of which I'm the only one that does vascular work. I also have a dual appointment with vascular surgery, and I spend most of my time training interventional cardiology fellows and vascular surgery fellows. And we are a Mecca of healthcare in our state. We're the only Level 1 trauma center, the only organ transplant center. In fact, our medical center represents 2% of our entire state economy.

I've been there for 11 years. I did all my training there and stayed as faculty, and I now have a dual appointment with interventional cardiology and vascular surgery. I direct our cath lab, I direct our interventional cardiology fellowship program, and I also direct the endovascular portion of our vascular surgery program, but 95% of my practice is vascular, and I do greater than 600 cases a year, the vast majority of which are critical limb ischemia. And we serve five wound care centers that are positioned throughout our state, trying to salvage limbs. And we also do onsite courses for physicians who are trying to learn new techniques for treating vascular patients.

What's unique, I think, to my opinion today is my volume. If you look at the number of patients that I've personally treated with drug-coated balloons in the last 4½ years, I've

treated almost 2,500 patients with drug-coated balloons, which is more patients than the meta-analysis and the randomized controlled trials all combined.

What's also unique in my practice in Mississippi, because we are part of the diabetes belt and have extensive disease, we say our patients only have one lesion; it starts around the middle cerebral artery and ends around the dorsalis pedis. But the lesion length in my practice is near 25 cm. So if you look at over 22,000 patients treated with a lesion length of 24 cm, I've delivered about three times as much paclitaxel as has been delivered in the trials combined.

My patients couldn't come today, but I wanted to bring some messages to you from them, and you can hear their voices.

This is a lady that I met several years ago, and she was requiring about three or four interventions per year to keep her leg open, and she had critical limb ischemia. We treated her with an IN.PACT Admiral treatment in 2015, and she has not had any further treatment since that time.

AUDIO: I feel like the medicine you have used on my leg, it was a miracle. I don't have to run back and forth to the doctor every 6 months, every year. It meant a lot to me. My husband was sick. I had to take care of him. I had no problems with the leg after Winscott had done the procedure on it, and I'm so glad I didn't lose my leg. I don't think I could live --

DR. WINSCOTT: She actually had to bury her husband in November from lung cancer. Not related to any PAD treatment. But she got to spend a lot more time with him because she was not going to the hospital every month to have procedures.

This is also a lady who had had greater than a dozen interventions prior to me meeting her, including a bypass that had been revised twice and then we were able to rescue that bypass with drug-eluting stent.

AUDIO: I want to thank Dr. Winscott and his crew. The procedure they done on me, I was having to have so many procedures done, and if it hadn't been for the procedure Dr. Winscott done my leg, I would not have a leg to walk on today. And I thank God for it, tried the -- I had to shave my legs a lot because of it. And I think it's a wonderful procedure for anybody that the trouble that I had with my legs.

DR. WINSCOTT: This is a man that I met in 2010. He had a 65 cm occlusion of his leg and was a really poor surgical candidate. We were able to recanalize that with directional atherectomy, but he required a lot of interventions over the next several years to keep it open. But after being treated with drug-eluting technology in 2015, he has not required another procedure in over 4 years.

AUDIO: And it is, it is beneficial to anybody if you don't have quality of life and to be able to keep walking and doing things you've always done. And like I say, without it, I would have no legs or no feet at all. I think it's the greatest thing that's ever happened, and the technology, what they do now and how they could prolong it, or if you don't have to go back very often, go back in a year sometimes and do well.

DR. WINSCOTT: So, in conclusion, I would say I have an extremely busy practice, and I fight for limb salvage every day. The most powerful tools I've been able to put in my toolbox over the years have been directional atherectomy and drug-coated balloon. But the most palpable change I've seen in my practice over the past 11 years has been drug-eluting technology. And after treating over 2,000 patients with this technology with lesion lengths around 25 cm, I personally don't have any concerns for safety or increased mortality. And I can tell you honestly that if my mother needed a procedure tomorrow on fem-pop segment, I would not only request but I would demand that she be treated with this technology.

Thank you.

DR. LANGE: Thank you, Dr. Winscott.

And the final presentation will be by Dr. Robert Yeh.

DR. YEH: Thank you members of the Panel. My name is Robert Yeh. I'm the Director of Smith Center for Outcomes Research in Cardiology at Beth Israel Deaconess Medical Center and Associate Professor of Medicine at Harvard Medical School. I'm going to present to you today preliminary analysis of a second study that we've done in addition to the Medicare analysis you saw earlier using another national claims database.

These are my funding. Predominantly, my funding source is the National Heart, Lung, and Blood Association, but I do have investigator-initiated research grants from Abbott Vascular, Boston Scientific, and Medtronic, and sit on scientific advisory boards for those companies.

Real-world data has been the predominant source for discovering long-term unexpected safety signals for approved devices. Not efficacy, but safety. They have more power to detect rare events and small signals, and they study the populations that are most relevant to public health as opposed to more concentrated randomized trial populations.

You already saw earlier that among fee-for-service Medicare beneficiaries, there's no association for the use of drug-coated balloons or drug-eluting stents for percutaneous fem-pop revasc and mortality. And evidence regarding the association between these devices and mortality, among other broadly generalizable populations, is lacking.

So the objective of this study was to examine the association between drug-coated devices and mortality among commercially insured and Medicare Advantage patients undergoing fem-pop revascularization.

This protocol was developed in collaboration with the Smith Center for Outcomes Research and Medtronic. We developed a pre-specified protocol jointly between academic and industry investigators and shared this protocol with the FDA for review and comment

prior to the start of the analysis. The analysis was performed by Medtronic Health Economics and Reimbursement, jointly supervised by the Smith Center and Medtronic. Statistical code and primary output were reviewed independently by both groups. The study was funded by Medtronic.

The data source, Optum Clinformatics Datamart, which is a dataset that includes de-identified monthly enrollment records, medical and prescription claims for greater than 60 million Medicare Advantage and commercially insured enrollees in all 50 states, and is matched with the Social Security Death Master File.

Our study sample: all patients who had these devices used between April 2015 and December 2017 identified in claims. Our primary outcomes: all-cause mortality through December 2018. And our covariates included more than 40 demographic and clinical comorbidities, including history of critical limb ischemia, prior amputation, prior cardiovascular disease, assessed the ICD-9 codes. Unique to this dataset, baseline medication use accessed via scripts filled within 90 days prior to index were also included.

Our statistical analysis, very similar to the Medicare population, we had an identical protocol effectively, so I won't belabor this, but we'll show a cumulative incidence of unadjusted all-cause mortality graphed and compared using log-rank tests and the statistical adjustment approach employed development and propensity score model based on these 40 covariates, using statisticians and datasets that were blinded to the outcomes, and then reweighting these integral procedures based on inverse probability treatment weighting to create adjusted cumulative incidence curves for all-cause mortality and comparing those curves between groups. We also calculated the adjusted mortality hazard ratio between drug and non-drug exposed groups, estimated using Cox proportional hazard models.

This is our final study sample: 20,536 patients undergoing procedures with drug or

non-drug-coated devices. You can see the distribution of drug use versus non-use. About a quarter of these patients received drug, three-quarters not drug, and the median follow-up was 763 days; within the interquartile range, up to 1028 days.

Here are the baseline characteristics of the complete cohort. You can see that this is a very sick population, similar to what we've seen earlier. High rates of critical limb ischemia, but typically high rates of diabetes and hypertension and tobacco use. The medications were used. I think there's an opportunity to do better on the pre-procedural medication use, as we know.

The most notable thing is when we look at the drug-coated balloons and the non-drug-coated balloons as well as the DES versus the BMS, what we see is that these patients, before weighting, are quite evenly matched on these patient characteristics. And I think even the most ardent critics of comparative effectiveness research, which I suspect there might be some in this room, would state that it's better to have balance in these characteristics rather than not balance in these characteristics before you do statistical adjustment.

Here's the unadjusted all-cause mortality between groups. Cumulative incidence of combined drug versus no drug, we see that the cumulative incidence at the end of follow-up was 14.85, of death it was 14.85 for drug, 14.94 for non-drug, p = 0.11, non-significant. For balloons only, similar results with a DCB mortality of 13.6%, PTA 14.7, a p-value of 0.52 for log-rank test. Stents only, 14.3%, 15.4, p-value equals 0.52.

These are the before and after treatment -- standardized mean differences of the covariates we looked at and again, you'll note that the blue -- that the red lines, excuse me, are prior to weighting. It's hard to see on the screen, but these are the covariates. And the vertical line you see is the standardized mean difference of 10% cutoff and before adjustment, the vast majority of these variables are already balanced between groups.

After reweighting, we see that there is balance between those groups with standardized mean differences of less than 10%.

Here's the adjusted all-cause mortality, adjustment meaning IPTW-weighted for drug-coated versus non-drug-coated devices. A hazard ratio of 1.09 -- rates 14.9 and 14.9%, non-significant log-rank p-value and confidence intervals for the hazard ratios crossing unity. Similar results were observed when we looked at balloons only, and the stent only subgroups after adjustment.

So the study limitations, we've talked about this. This is an observational comparison with claims data.

So while acknowledging that these may have limitations, we would argue that they should be used not in conjunction with the randomized data, and they are pieces of evidence that I think are useful.

There are no differences in guideline treatment of patients who received drug-coated and non-drug-coated devices. That's very different than patients treated with DES and BMS in the coronary circulation. In fact, when we looked at follow-up medication adherence, I haven't shown you that data for the weighted sample, we didn't weight on post-procedure drug adherence, but afterwards we followed and they had very similar rates of medication adherence afterwards.

Most clinical characteristics were well balanced prior to adjustment, which is what we would expect when there's not a ton of treatment selection bias happening. And, of course, we did adjust for observable characteristics between the troops, differences between those.

DR. LANGE: Dr. Yeh, would you give your concluding comment, please?

DR. YEH: Yes. So our interpretation, in this large national cohort of PAD procedures, drug-coated devices were not associated with a difference in mortality.

And, finally, compared with limited RCT subjects, these real-world cohorts are more representative of patients undergoing treatment in routine practice, and device safety is most relevant to the public health of these patients, not those ones that are seen in the trials.

Thank you.

DR. LANGE: Dr. Yeh, thank you for those comments.

At this point, the Panel will now have the opportunity to ask questions to any of those Open Public Hearing speakers. Panelists, please identify yourself and address the speaker by name so they can come up to the podium. We have a limited amount of time, so I want to make sure that we do use it for any clarifying questions.

Dr. LoGerfo.

DR. LoGERFO: This is with regard to the presentation by the American College of Cardiology.

DR. LANGE: Come on up, Schuyler.

DR. LoGERFO: In your presentation, on the first slide you showed a period of exercise testing or exercise treatment, but that was not part of any trial and I raise that question as to why that isn't there in the face of the experience with coronary stents for stable angina, which is a good analog of claudication. And isn't it in the public interest not to go down that road again and conduct a randomized clinical trial in spite of all we've heard about other types of trials because there were many cardiology trials until, say, the COURAGE trial and a couple of other trials showing that patients with stable angina did just as well if they did not have a procedure?

DR. LANGE: This is Dr. Schuyler Jones. Please go ahead, Schuyler.

DR. JONES: Thanks, Dr. Lange.

And so I think your question really revolves around treatment strategies and so

having done a lot of comparative effectiveness reviews for AHRQ and other things, there's a dearth of data on that, even less data than paclitaxel versus regular balloons and stents. So there's no question we need more evidence. I think when we were at the MEDCAC and supervised exercise was being discussed, Josh Beckman, who was here yesterday, said PAD is the disparity. That is still true. We have a dearth of data throughout the kind of extent of PAD. I don't think I answered your question. If you have more specifics, I'd be happy to try.

DR. LANGE: I'll go to Dr. Krucoff for a clarifying question, then Dr. Rasmussen, Sun, and Kip.

Dr. Krucoff.

DR. KRUCOFF: So I have a question for Dr. Farber and a question for Dr. Yeh.

DR. LANGE: So please approach the podium.

DR. KRUCOFF: Dr. Farber, you shared very nicely, thank you, the sort of sequence of decision making within the BEST-CLI trial registry in conjunction with FDA alerts and the awareness of these data and just based on, I think, where we're going to go with the discussion maybe later today, I was curious, do your patients, in order to participate in the registry, sign an informed consent document and did you change the informed consent document in conjunction with the different phases of information and FDA letters that you obviously discussed with your investigators and DSMB?

DR. LANGE: I'm sorry. Please, for the transcript, please identify yourself, Dr. Farber.

DR. FARBER: Alik Farber.

So we did not mandate the change in informed consent. However, we've had a number of IRBs come back to us and demand that and because of the difficulties involved, many of these particular sites opted out of using paclitaxel within a trial rather than undergo this very cumbersome, difficult process.

DR. KRUCOFF: Thank you very much. I think that's going to be relevant.

DR. LANGE: Thank you, Dr. Farber.

Dr. Yeh, please.

DR. KRUCOFF: Dr. Yeh, it was a beautiful presentation and I have a question, but I also have what I'm sure is a correction to your last statement there; you don't really mean to say that we shouldn't be concerned with the patients in randomized trials? The real-world evidence is more representative, but that both give us a different level of human concern, right?

DR. YEH: Yes. No, that's right. Sorry --

DR. KRUCOFF: Just because this is on the record.

DR. YEH: -- it was a statement under time duress.

(Laughter.)

DR. KRUCOFF: And just because I know you so well, I'm sure that what you meant should be --

DR. YEH: I think my main point is that the patients that we see in these observational datasets are actually the ones that are representative --

DR. KRUCOFF: Yeah.

DR. YEH: -- of the patients that we're all treating in practice --

DR. KRUCOFF: Yeah.

DR. YEH: -- and the ones that have public health relevance.

DR. KRUCOFF: Okay, so my question for you is that --

DR. LANGE: By the way, that statement was by Dr. Robert Yeh, for the transcript. So please go ahead.

DR. KRUCOFF: Sorry. Thank you.

My question for you is on this same sort of theme that we've talked about so many times, that we're in this kind of paradoxical setting where, as we and as your data clearly

include a lot of patients with multiple comorbidities, these are sick folks and we're trying to make them feel better, that we might actually hide or bury a signal even by matching that doesn't solve the problem. So have you or potentially could you look at patients who don't have the other comorbid risk factors that we know drives mortality as a way of understanding whether even in your certainty with the conclusions you shared, whether or not paclitaxel may play a role that none of us expect in patients who may have less or a single comorbidity?

DR. YEH: Yeah, I think it's a great idea. We haven't yet done that analysis. I think I'm partially reassured that the point estimates that we saw in the Medicare analysis, when you look at the CLI versus the non-CLI, which is going from level of sickness to less sick, are spot on with each other. So we didn't see, sort of, a widening gap there. This analysis of Optum data includes commercially insured, less than 65, age 65, as well as Medicare Advantage, which are known to be healthier than Medicare fee-for-service. We don't necessarily see that signal there. Certainly, we can look at both of these datasets and cull it down to the most healthy populations to see if we see separation of the curves, and that's something that we probably ought to do.

DR. KRUCOFF: Yeah, I hope you will because age alone -- and one of the realities of Medicare is 65 and older, which I'm very sensitive about these days, but --

(Laughter.)

DR. KRUCOFF: But the fact that you have taken the approach you've taken, you have younger patients in the same sort of spirit, so I hope you will.

DR. LANGE: Thank you, Dr. Yeh.

I have Dr. Sun, Kip, Ballman, and Cigarroa. And these are clarifying questions.

Dr. Sun.

DR. SUN: Yeah, I have a question for Dr. Ramon Varcoe. Hope I pronounced

correctly.

DR. LANGE: Please come up, Dr. Ramon.

DR. SUN: While you approach the podium, you analyzed the mortality data, mortality data based on the -- some of the assumption if there is a misclassified dataset, then you get a conclusion the difference is much smaller. Have you used the same way to analyze the benefits, the TLR, the difference is also similar, smaller or they stay the same?

DR. VARCOE: Ramon Varcoe.

We had a very focused meta-analysis subjective when we conducted the study, and it was really only about mortality. There was a lot of heterogeneity in the studies that were collected. The commonalities were I did not evaluate drug-coated devices, but other than that, they were evaluating all sorts of different types of technologies, so we didn't think it was even reasonable or of value to look at effectiveness and we focused our attentions on mortality.

DR. LANGE: And that was Dr. Ramon Varcoe. Thank you, Dr. Varcoe, appreciate that.

And I missed Dr. Rasmussen. He had raised his hand earlier, so Todd, please.

DR. RASMUSSEN: Todd Rasmussen.

I have one question, point of order, and then one heads-up for the experts, our FDA experts, about a point of deliberation I'd like their opinion on in the afternoon.

The point of order is, as this is the end of our public hearing sessions, were there any submitted by writing or outside of what we heard at the podium?

DR. LANGE: No, sir, we have -- what we have experienced is what was submitted.

DR. RASMUSSEN: Okay, so there aren't any in writing pending. My question for the deliberations this afternoon, I just want to give the FDA experts a heads-up. I would value their opinion and take on Dr. Varcoe's ascertainment bias. I'm interested in that and

whether or not they think they've studied that and whether or not they think that has strong merit in this discussion, and I wanted to give them some time to think about that.

DR. LANGE: Thank you, Dr. Rasmussen. We'll ask the FDA to respond to that after the break.

Dr. Kip, Dr. Ballman, and Dr. Cigarroa.

DR. KIP: Kevin Kip.

Dr. Rasmussen, that's a perfect lead-in. And, Dr. Varcoe, could you come back up because --

(Laughter.)

DR. KIP: So you've proffered a very interesting hypothesis that essentially says that this mortality signal that we've agreed upon seems to be present, could be due to some methodological flaws, so in the conduct of the randomized controlled trials that are the basis for that signal. Now, I'm not sure that the manufacturers, in and of themselves, will be thrilled to hear that maybe there were some, you know, concerns with their studies, but nonetheless, let's walk through a little bit of it quickly, and then maybe you can provide a little more explanation for your thesis on this.

So you first mentioned blinding, which I would suggest is probably not critical here because lack of blinding is usually more of a concern for subjective endpoints rather than mortality notwithstanding cause of death, but I mean, we're counting dead or alive, basically. And, secondly, that the lost to follow-up rate in both groups across the pivotal studies is about the same. So that, in and of itself, doesn't seem, at least at face value, terribly problematic. So what we're left with is what Dr. Rasmussen just referred to, is potential ascertainment bias among those with data between the paclitaxel and non-paclitaxel groups.

So what we need here today, if you have some more insight into how that might

occur. As I've been educated here today, today and yesterday, patients treated with paclitaxel essentially get the same regimen post-treatment compared to those without. So that, in and of itself, would not impose more ascertainment, such as more engagement with a healthcare system and better ascertainment.

Secondarily, if you're in the control group, non-paclitaxel, you're more likely to come in for a new procedure, correct, which we've acknowledged which, if anything, would engage more encounters with a healthcare system and potentially better ascertainment. So it's a long question, but if you have anything, particularly empirically data-wise, how those trials were conducted that would suggest that the ascertainment among those treated with paclitaxel versus not is different, that would be extraordinarily helpful.

DR. VARCOE: Ramon Varcoe.

So I think there were several points to your question, and I'll try to address them all individually. The first one, I think, was about numbers and proportions lost or missing data and this also troubled me a little bit at the beginning. When the FDA released the pack, there wasn't a clear trend with more losses in the control arm. But I would remind you that even though the proportions lost were high, the actual numbers lost were quite low and therefore easily influenced by chance. What we don't know is, in the control arms, what those numbers would have been if there were no bias involved, and I can't say that this disputes the theory, specifically, but it maybe doesn't support it.

One thing that's different about the two arms, the control versus experimental arms, is not the baseline characteristics, because they're dealt with by randomization, but the postoperative outcomes are different, and that is, I think, unequivocal that we know that there are more TLR events in the control arm. Therefore, they are different in that they return for medical touch points.

I would actually dispute the comment that they aren't -- that they are treated the

same medically because I think, generally, when patients come back for repeat interventions we do treat them quite differently, medically. We often enhance their medical therapy; we take a lot more care in providing attention to their risk factor control, making sure they're off cigarettes. We often increase the dose of statins or add additional antiplatelet or anticoagulation agents, and all of those things are known to positively affect long-term mortality. So I think that that is particularly relevant, and I hope that answers the first part of your question.

DR. KIP: It does, but I don't think that it addressed if there's an ascertainment bias, why the control group would be disadvantaged, that they would be followed and ascertained in a less rigorous manner.

DR. VARCOE: Yeah. Well, I think that that really comes down to classification. So in terms of more -- I think what we're observing here is a difference in classification of the two arms of the studies after the treatment has occurred. So I think that these are patients that are lost to follow-up because they're not answering the phone and it's a matter of how hard you pursue them as to find out whether they're dead or alive. I think that was illustrated quite nicely yesterday in the Medtronic data where, when they did reduce those lost to follow-up numbers, the two curves did come back together and to me, that's the strongest evidence we've seen so far of proof of this ascertainment bias, and I would really like to see those other trials and what happens when -- if they are able to reduce their lost to follow-up numbers as well.

DR. KIP: Not to belabor, but you're correct that that's one explanation. When the lost to follow-up was improved upon and the hazard ratio went down, that would be supportive of this type of bias. On the other hand, we also heard that the lost to follow-up is amongst those that are at the absolute highest risk and that's where the hazard ratio seems to be diminished because of the competing risk. So, therefore, you would expect a

diminished hazard ratio when you included a lot more of those very high-risk patients. So it could go either way.

DR. VARCOE: I think my last point I would make was that -- and in my last slide I suggested that I think there were multiple components to this, one being the unblinding, but the second one being the ascertainment bias and the third one being the difference in medical compliance and medical regimens that come with increased TLRs.

DR. LANGE: Dr. Ballman.

DR. BALLMAN: So I'd like to say I think registries aren't really good in terms of --

DR. LANGE: You want him to stay at the podium?

DR. BALLMAN: Oh, no. Well, it's to any of the registry --

DR. LANGE: Okay.

DR. BALLMAN: -- people, so if they just say yes or no. And I didn't identify myself. I'm Karla Ballman. So I do agree that registries are really good at picking up, sort of, adverse events that are quite rare. But the people that do the registries, do you agree or disagree with the viewpoint that these registries are good for acute adverse events and not long-term adverse events that are influenced by prognostic variables?

DR. LANGE: All right, this is going to be fun. If you did a registry presentation, come to the podium and this is a yes or no question.

DR. JONES: Schuyler Jones.

No, currently at least the registry that we have is not well designed for acute adverse events.

DR. HODGSON: Well, I think that --

DR. LANGE: Please identify yourself for the transcript.

DR. HODGSON: Sorry. Kim Hodgson.

Obviously, they're best for acute, but they provide the power when coupled with

other databases to be able to give you longer-term data and longer-term follow-up and that's what, in fact, we would want to do in the VQI. And just to further amplify that, it's the granularity -- Kim Hodgson again -- the granularity of the VQI and the GUDID, it gives us the device-specific information in that database that would allow us to get that longer-term follow-up and give us some answers.

DR. YEH: This is Robert Yeh.

I don't know if you're counting claims data as one of the registries in that question, but I think claims data are actually very well positioned to do long-term follow-up, particularly Medicare claims among Medicare fee-for-service beneficiaries because they, in fact, track something like mortality in 100% of patients quite well. Where they are less good, perhaps, than the registries is capturing certain important clinical information at the index procedure. So I like this idea of merging the benefits of a claims database which has complete ascertainment for mortality, if mortality is the question, the hospitalization, etc., with the detailed granular information one can get at the time of index from a registry.

DR. BALLMAN: Thanks, everyone. I think that the point was sort of missed, though, that in general I think the viewpoint is that registries are really good for acute, sort of short-term, close to the treatment type adverse events, and then once you have an adverse event that is influenced by prognostic variables, they sort of lose their punch.

DR. LANGE: Dr. Zuckerman and then Dr. Cigarroa.

DR. ZUCKERMAN: Yeah, I just want to go back a moment. Drs. Rasmussen and Kip brought up a very important issue in clinical study design, especially for chronic trials, the issue of ascertainment bias given that these trials are unblinded and probably will stay unblinded. Dr. Rasmussen asked the FDA to get together their data, which will be limited. I'd like to ask the Panel Chair to also ask the industry group to comment on this particular aspect of the U.S.-only trials so that we can get a full-fledged discussion because this will be

an important part of trials going forward.

DR. LANGE: Okay, so at the completion of the break, I'd like the FDA to address the ascertainment bias that was discussed. We'll ask -- and also to present the U.S. versus non-U.S. data so we can take at look at it and then ask industry to respond as well. That will be after lunch.

Dr. Cigarroa, you stand between this very intentional group and lunch, so your final clarifying question, Dr. Cigarroa.

DR. CIGARROA: The good news is since I raised my hand they've already been addressed, so I don't stand.

(Laughter.)

DR. LANGE: All right. At this point, I will pronounce the Open Public Hearing officially closed. We're going to proceed with today's agenda. We're going to break for lunch, and Panel members, I'll please remind you not to discuss the meeting topic either during lunch among yourselves or with any member of the audience. We'll reconvene promptly at 12:40. Actually, 12:35. 12:35, 12:35.

(Whereupon, at 11:56 a.m., a lunch recess was taken.)

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

(12:40 p.m.)

DR. LANGE: All right, it's 12:40, and there were several clarifying questions posed by the Panel, and I'd like to give the FDA and our industry representatives an opportunity to address these.

Dr. Sun had questions regarding the concentration in the artery, concentration in the lung, and what the data looked like with a 100 µg dose. And so any of our industry sponsors --

DR. WHATLEY: I have a chart for that.

DR. LANGE: Dr. Whatley, please come. For the record, this is Dr. Eleni Whatley.

DR. WHATLEY: So I actually got some clarification on what the questions pertain to and the values. The first question was based on the appropriate assessment method and the level of detection for drug levels in the animal studies. Dr. Sun noted that one company noted a level of detection or a level of quantitation, I'm sorry, an LOQ of 0.5 ng/mg. We couldn't recollect which company presented on that, so if they could potentially identify themselves after I finish, that would be great. But he noted that was relatively high and wondered what FDA's current thoughts were for the method and for the limit of quantitation. So our current feedback is that LCMS or an appropriately sensitive method be used for that assessment and the LOQ should be 1 ng/g.

DR. LANGE: Dr. Sun, does that answer that question?

(Off microphone response.)

DR. LANGE: Please proceed, Dr. Whatley.

DR. WHATLEY: He also was wondering and made a comment that for one specific device the observed levels in the lungs were within the cytostatic range and he was wondering what those concentrations were. So this was for a one-time safety dose study.

There was also a three-time safety dose study where the concentrations were higher. But the concentrations in the lung for the one-time dose were 1.18, 0.203, 0.097, and 0.023 ng/mg at Days 1, 28, 60, and 90, respectively.

DR. LANGE: Did you get that, Dr. Sun?

DR. SUN: Yes, I got it.

DR. LANGE: Okay, thank you.

DR. WHATLEY: And his final question pertained to some mortality assessments. We believe Boston Scientific was presenting for their 100 µg dosage. I don't have that information, so I'll leave it to Boston Scientific to present on that.

DR. LANGE: Does somebody from Boston Scientific want to address that? No? Again, please identify yourself for the transcriptionist.

DR. MEREDITH: My name is Ian Meredith. I'm the Global Chief Medical Officer.

So I have a slide up here, and this firstly deals with the patient doses related to those in the meta-analysis, the double-blind meta-analysis, the Gregg Stone paper that we talked about all-cause mortality, and the dose range there based on the stents used, as you can see, the paclitaxel dose was between 50 and 406 µg based on the stents actually used in that study.

If I could also take this opportunity to address one question. We had talked about the study as saying that we should have seen a cardiac survival signal, and therefore, the all-cause mortality might be actually masking a non-cardiac death signal because we -- the argument was that there was a reduction, we should have expected in this study that stenting actually afforded an advantage in terms of survival. I'll just point out that these were stable patients. There's no evidence that stenting actually provides a mortality advantage. In fact, actually there was a slight non-statistically significant difference in terms of increased cardiac death in this study offset by slightly lower non-cardiac death.

But the assumption that we would expect a mortality advantage from a drug-eluting stent in stable patients and therefore we might be masking a mortality signal, I think, needs to be corrected for the record. So this is addressed.

There was also a question by Dr. Krucoff regarding the quality of the study, so I just thought that I'd show there the patient-level follow-up, 195, 95, and 83% follow-up in the trials.

With respect to the doses used in the -- I'll actually jump, I think, to these. This is an easier summary to show the range of doses in the IMPERIAL trial, the IMPERIAL long lesion trial, and the Taxus trials. So this is based on -- calculated on the loaded doses on the stents, so 135 to 652 µg in IMPERIAL, 517 to 1,034 µg in the long lesion, and you can see the Taxus long lesion study, indeed, was comparable. And, again, we pointed out that there was no excess mortality signal in the Taxus long lesion study, either. And these are the clinically driven target lesion revascularization rates at 2 and 5 years. Of course, it's only 2 years because that's the data we have available for the current Eluvia platform.

Thank you.

DR. LANGE: Does that answer the question you had regarding dose versus efficacy TLR?

DR. SUN: Can I confirm? You said there's no mortality at 5 years?

DR. MEREDITH: There is no mortality. Let me go back and just show that. So there's no all-cause mortality difference between bare-metal stents and the paclitaxel drug-eluting stent --

DR. SUN: Okay.

DR. MEREDITH: -- in double-blind trials --

DR. SUN: Okay.

DR. MEREDITH: -- with up to 100% follow-up and the main trial driving this has a

95% follow-up.

DR. SUN: Okay.

DR. MEREDITH: And with common endpoint definitions.

DR. SUN: Thank you.

DR. LANGE: Not that there's no mortality, no mortality difference. You can have a stent be immortal and we won't be getting stents put in.

(Laughter.)

DR. MEREDITH: Most definitely. There's no mortality difference. But not that you would expect that because these are stable patients being treated --

DR. LANGE: Yes, sir.

DR. MEREDITH: -- for symptomatic coronary artery disease.

DR. LANGE: Thank you.

There was a question, and I'm not sure that anybody has this data, but Dr. Kip and Dr. Ballman had asked about either a meta-analysis or pooled quintiles regarding dose versus mortality. And if anybody has that information, please approach and identify yourself.

DR. LYSTIG: I'm Dr. Ted Lystig from Medtronic. I represent the global biostatistics function there.

And this is a question that Dr. Zuckerman had originally posed. We'll put this up. So we had previously shown this slide on Day 1 and this is an analysis where we're looking -- okay, sorry. This is an analysis where we looked at splitting doses up into terciles. And so to Dr. Kip's point, would there be possibly a better effect in terms of trying to group the doses together given the fact that there's a fairly broad range and these are possibly subject to leverage effects, so we put them into terciles, as shown here, and this is the Kaplan-Meier plot. The overall log-rank test, as you can see, for the significance of this overall

effect is 0.73. This is one particular way in which we can try to tease out if there is sort of a differential effect related to mortality. Now, certainly, these are small numbers and they do jump around but within the estimates that we do see, in fact, there's actually an ordering, a reverse ordering, from what you might expect so the most mortality is at the lowest tercile than the mid and the high. So if you were to posit that there was a dose-response relationship, you would actually have to see a reversal of what we see in here. Now, another question -- oh, and part of the issue with this is that the subjects were not randomized to dose, they were randomized to treatment, so we don't know that there's comparable risk at baseline.

So we had also gone ahead and performed a multivariate analysis where we adjusted for multiple factors. This was also shown on Day 1. And in this model the predictors that you might expect were there. This actually has multiple things where it's both the age, as you would expect, the renal insufficiency, smoking, and this shows that the dose tercile was not effective as a predictor, that if you put in a treatment arm there's a point estimate but not significant. You'll also note that if instead of using the paclitaxel dose tercile, if we use paclitaxel dose as a continuous variable, we also do not see that as significant.

Now, another question was if you were to treat -- this is a meta-analysis, this is within our own study. What if you combine the studies together from multiple companies? Now, it's not something we have immediately available but talking together with industry persons, several of the other companies were able to perform their own multivariate analyses. The terms do not all align, so the interpretation of coefficients differ. However, for the impact of one additional milligram of dose, we saw estimates from 0.97, 1.02, and 1.0. So this is something where it's -- there's definitional issues, they don't necessarily mean the exact thing but again, if our best understanding is that if you were to pool this, this is not indicative of relationship between dose and mortality.

DR. LANGE: Dr. Kip and Dr. Ballman, does that at least address the question you have?

DR. KIP: Yes. If anything, it looks in the opposite direction based on, at least, your data right here.

DR. LYSTIG: Right, thank you.

And now I'd like to turn to Dr. Mauri, who had some similar information on a multivariate model for the TLR information.

DR. MAURI: Laura Mauri, Medtronic.

This is to follow up on the related question about whether there's a dose effect for efficacy and we were able to, during the break, do a multivariable model for efficacy. I'm hoping we can pull it up. I think we have copies of it if you'd like to see it because you obviously don't have access to it. Is that all right to show?

DR. LANGE: Yeah, it is. And by the way, I just want to thank you all. We're eating lunch, and you all are working, and we realize it's a difficult task, so we appreciate it very much. Thank you very much, Laura.

DR. MAURI: Are we able to show this slide?

(Off microphone response.)

DR. MAURI: Oh, we just have a copy of it. Okay, great. So as you pick this up, this is a multivariable model for efficacy measured as CDTLR, which is the endpoint that you've seen with the FDA, and the first thing is that we didn't think to do it before because there's a large treatment effect. In our trial, we had an 85% relative risk reduction and so as you expect, you see a hazard ratio of 0.13 for the use of a DCB versus PTA, which is highly significant, p-value less than 0.001. So that's the first thing, the treatment is effective. And that's true after adjusting for the one factor that was an additional independent predictor, which is prior peripheral revascularization, which is an independent predictor of TLR as we

would expect, clinically. If you look then by continuous paclitaxel dose or dose tercile, the continuous paclitaxel dose was protective, so for increasing dose you see a significant value of the p-value of less than 0.001. For dose tercile, here I think we're limited because it's confounded potentially by something that we haven't adjusted for, which is lesion length. The longer lesions get more treatment, but it appears to have a dose effect for efficacy.

DR. LANGE: Thank you very much.

Dr. Ballman and Dr. Kip, you all fine with that?

DR. KIP: Yes.

DR. BALLMAN: Yes.

DR. LANGE: Again, thanks to Medtronic.

There were two issues Dr. Krucoff mentioned and that is the quality of data and the non-PAD -- actually, not quality. I think what he's asking for is completeness of follow-up and I think you all presented that already. Did you mis-see that?

DR. KRUCOFF: For the other targets?

DR. LANGE: Yeah.

DR. KRUCOFF: For fistula and for --

DR. LANGE: Yeah.

DR. KRUCOFF: So it's all coordinating.

DR. LANGE: Come on up, please. Thanks, Mitch. So for the coronary, what do we have for PAD for fistula and non-PAD?

DR. OURIEL: Dr. Kenneth Ouriel from Syntactx.

This is the BD data. AV access and BTK follow-up data, Dr. Krucoff. In the AV study, the primary endpoint was at 6 months, 90.5% follow-up at 6 months, 91.2 at 24 months. In the BTK study the primary endpoint at 6 months, 91.7% evaluable. At 12 months follow-up, 92.3%. Preliminary data at 3 years, because it's ongoing, it's more than 80%. But that's the

best we can do right now at 3 years.

DR. LANGE: Dr. Krucoff, does that answer your question?

DR. KRUCOFF: Yes.

DR. LANGE: Terrific. Thanks very much.

And the issue in that looking -- the industry looking at NNT and NNH. And you may not have had time to do that analysis, but if you did, I wanted to give you the opportunity to present that information. Please, come on.

DR. LOTTES: Aaron Lottes, Cook Medical.

So looking at number to treat for the Zilver PTX stent through 5 years, we had a 40% reduction in reintervention. It relates to a number needed to treat of 6.5 patients. Number needed to harm is an interesting one. It depends quite heavily on what population you look at. If we're looking at the population that FDA reviewed that had the primary and the secondary randomization but not the crossover, so the crossover patients with Zilver PTX in the control group, number needed to harm is approximately 16. If you shift those patients and looked at actual treatments, all Zilver PTX patients in one group, that jumps up to 62 number needed to harm.

DR. LANGE: Please, come on.

DR. MEREDITH: Thank you. This is Ian Meredith from Boston Scientific again.

This is number needed to treat to avoid clinically driven target lesion revascularization in the Eluvia trial, was seven patients. The number needed to harm -- and you're calculating that, of course, against the bare-metal -- the figure in the -- treated figure in the FDA panel pack for the non-treatment arm, which was a 7% mortality because, of course, in this trial it was a comparison of Eluvia versus Zilver PTX. So we're comparing the mortality from two different studies here and trying to create an absolute difference which, of course, you can't because it isn't one study and there is no bare-metal control, but to the

best of our ability, if we did that, that would be 98.

DR. LANGE: And by the way, I appreciate all those caveats because they're all very true.

DR. MEREDITH: They're all very true.

DR. LANGE: Yeah.

DR. MEREDITH: We don't have the -- but in order not to get up and say there is no harm, we have made an effort to say what the harm might be if the panel pack 2-year mortality data for the untreated arm were true.

DR. LANGE: We've already established there's no death of coronary stents, so no harm there.

(Laughter.)

DR. LANGE: Thank you.

DR. MEREDITH: Excellent. Thank you.

DR. LANGE: Mitch, to the best of their ability, does this address some of the issues?

DR. KRUCOFF: I think I do really want to say thank you, and I appreciate the efforts from our industry colleagues. I think, again, my emphasis in asking that question we may come back to in terms of the utility of nonrandomized much larger data, but I would say yes.

DR. LANGE: And is somebody else standing to speak? Come, please.

DR. MELER: Dr. J.D. Meler, Becton Dickinson.

I'm going to add some number-needed-to-harm data from our 5-year data. For LEVANT 2 RCT, it was 58. For the LEVANT 2 RCT including continued access, 111. And for the LEVANT series of studies, which is LEVANT 2 continued access, LEVANT 1, and LEVANT Japan, it was 143. So we'll get that material to you.

DR. LANGE: Okay. Now, that was a combination for all three trials combined?

DR. MELER: In the final, yes.

DR. LANGE: Okay. So for a couple of those, each of those individually --

DR. MELER: Sure.

DR. LANGE: -- and not combined.

DR. MELER: Sure.

DR. LANGE: Just again for --

DR. MELER: LEVANT 2 RCT was 58. LEVANT 2 with continued access, so the mandated piece by the FDA utilizing the same inclusion criteria, the same sites, that kind of thing, was 111. And then if we looked at the entire LEVANT series, LEVANT 2, LEVANT CA, the original LEVANT 1 study, and LEVANT Japan, we got to 143.

DR. KRUCOFF: Sorry, that's how many years?

DR. MELER: Five.

DR. KRUCOFF: Five.

DR. MELER: Five. I'm sorry.

DR. LANGE: Thank you very much.

DR. GRAY: William Gray speaking for Philips data.

Number needed to harm at 5 years based on Kaplan-Meier estimates was 71. And the number needed to treat -- to benefit would be somewhere in the mid to high teens. We're still working on that number, but in that range. At 5 years.

DR. LANGE: So it looks like the data we're getting for number to treat is somewhere between about 7 to 20 or 7 to in the high teens, okay. And the number needed to harm, difficult based upon these. Great.

Dr. Krucoff, is that okay? Great.

DR. KRUCOFF: Yes.

DR. LANGE: And with regard -- we had tasked the FDA with doing a couple things.

One is to address the issue of ascertainment bias based -- and I assume this was primarily from Dr. Varcoe's talk about it. And the other issue is as we -- we're going to wrestle with possible additional studies, inside the U.S., outside the U.S., and if you have any insight based upon your data about how those populations have compared over the previous trials and your analysis, that would be very helpful.

DR. FARB: Andrew Farb. Thank you, Dr. Lange.

There was also a question of blinding, which we can get to. So just to get that out of the way, the studies were not blinded with respect to operator. They were blinded out to 1 year with respect to patients, patients single blinded. And there was inconsistency among the studies in terms of their research personnel conducting follow-up visit. In Lutonix, the research staff was blinded to treatment assignment. We don't believe the other studies had that, and the industry can correct me.

Regarding the ascertainment bias and the discussions we've had, particularly today, it's a very interesting type of analysis and how that might impact studies. You know, we have some data from the trial that we'd be interested to see if that's generalizable to the other sponsors of the devices and actually goes beyond even the peripheral artery space. This could be applied to all types of studies. So this is an area that requires more thought.

So I don't have any data. This is, for us, a data-free zone but I think we need to speak a little bit more broadly because these data are based on, from what we can tell, site visit follow-up. But let's remember that these patients are elderly, they have multiple comorbidities, likely multiple physicians. So just looking at a single dataset such as compliance with the schedule of follow-up visits may be not seeing the entire totality of the picture of these patients and what type of medical care they're getting in terms of the touch-point argument that in some way the control patients were getting superior care as opposed to the treated patients. So this is an area for more discussion.

With regard to missing data, I think we've gone over that as much as we can with our data. I think the question fundamentally is likely that the missing data, if we had known what's in that missing data, would likely change our general interpretation of the data we have. From what we've seen, the differences between those patients for whom we know vital status compared to those who we don't know vital status, were not compelling enough to show that it's likely to change the signal that we have in front of us.

DR. LANGE: Please, we certainly would like to hear industry's assessment of the ascertainment issue as well. So thank you, Dr. Farb.

DR. MELER: Dr. J.D. Meler, BD.

So over the break, we had an opportunity to follow up on the Panel's questions regarding the ascertainment bias, and we were able to pull data from our RESILIENT trial, and we thought it was relevant because it compares a bare-metal stent to PTA in the femoropopliteal segment and as you can see, though not significant, a significant difference, there is a numerical difference here with the difference in mortality of BMS and PTA with BMS being slightly higher. So we just wanted to give you an example of a non-drug-related study where we also saw this ascertainment bias as an example. And Dr. Ouriel has a couple of additional pieces on that.

Thank you.

DR. OURIEL: Ken Ouriel, Syntactx.

This is the LEVANT 2 RCT data, and it is corroborating the findings of Dr. Varcoe. So lost to follow-up not being at random. Before the additional follow-up earlier in -- right after the 1st of the year, the hazard ratio was 1.68 with 85% follow-up. After a May 2nd data cut, the hazard ratio dropped to 1.59 with 88% follow-up.

DR. LANGE: So 1.68 with 80% follow-up, you say?

DR. OURIEL: Eighty-five percent follow-up, hazard ratio of 1.68, 88% follow-up, 1.59.

DR. LANGE: Okay, thank you.

DR. MEREDITH: Ian Meredith, Boston Scientific.

Again, referring to the IMPERIAL trial, there is no control arm. It's the Zilver PTX versus the Eluvia DES in the IMPERIAL trial. At 2 years this is where we are today, missing data is 5.2% in the Eluvia arm and 5.8 in the Zilver PTX arm, and that's a combination of both lost to follow-up and withdrawn consent.

DR. LANGE: Okay, thank you.

Dr. Mauri.

DR. MAURI: So as --

DR. LANGE: Dr. Mauri. I'm sorry, Dr. Mauri.

DR. MAURI: Laura Mauri.

As you know, we were able to go from 85% -- sorry, 83% follow-up to 97% follow-up with our vital status collection efforts. And if you look at the before and after you can see that the before is in the dotted lines and the after is in the solid lines. And you can see the two lines of purple and blue, which are the two different treatment arms, approach each other. So while we can't weigh what would happen in the other randomized trials, if they were able to obtain more complete follow-up, this is our empiric observation, that we didn't know what we'd find until we found the patients and they did bring the treatment difference closer together.

DR. LANGE: Okay, great. So what I'm seeing is that in all the companies there's an improved follow-up, there was still a change, it was just not quite as big, 1.68 to 1.59 and again, 1.6 to 1.4.

Go ahead.

DR. GRAY: Bill Gray from Philips data.

For the U.S. dataset, the total missing data is 9%, 7% withdrawn and 2% lost to

follow-up. And our OUS was 13%, about the same proportion of withdrawn and lost to follow-up.

DR. LANGE: Dr. Mauri.

DR. GRAY: We have more data coming which has cut that number into the signal digits, but that's not available yet.

DR. LANGE: Thank you for doing that.

DR. MAURI: Laura Mauri.

Just to make one point briefly. I think we'd emphasize the missing data on something very specific, on vital status, because that's something that we should collect as completely as possible. But I think what we haven't really talked as much about is the fact that we really don't know how patients might be treated differently after randomization, especially beyond 1 year, because we simply just didn't collect that information. It wasn't even part of the plan to collect, but it may be important.

DR. LANGE: And that's going to part of our discussion this afternoon, by the way. Thank you for bringing that up.

And as far as I can tell -- and by the way, there's one other piece of information that might help the Panel, information we have about U.S. versus non-U.S. or outside U.S. studies, as we frame out discussions this afternoon. What can you tell us based upon the information we currently have?

DR. ZHAO: This is Yu Zhao from FDA.

So FDA conducted the baseline comparison between U.S. and OUS patients for each of the four pivotal RCTs and the observed difference at an alpha level of 0.1 was summarized in this slide and the next couple slides. So here is a table that presents the results from Zilver PTX RCT and in general, it appeared that the U.S. patients were relatively sicker compared to the OUS patients.

DR. LANGE: Dr. Ballman, you had specifically asked. Does this address --

DR. BALLMAN: Yes.

DR. LANGE: Okay, it's very helpful. Thank you.

DR. ZHAO: That's for Zilver. This is for the one.

DR. LANGE: But wait, there's more. I'm sorry.

(Laughter.)

DR. ZHAO: So the trend is similar. It appeared that the U.S. patients were relatively sicker compared to OUS patients. And the same thing happened for the IN.PACT SFA.

(Off microphone comment.)

DR. ZHAO: Okay. So this is result for the IN.PACT SFA. So I want to point out there appear to be some data issue regarding the baseline medication status, so FDA will follow up with the sponsor to resolve this issue. With that, a caveat, it's still the same trend, U.S. patients appear to be sicker.

DR. LANGE: I assume the 0% medication was a high co-pay?

(Laughter.)

DR. ZHAO: And this is the result for the ILLUMENATE. Still the same thing.

DR. LANGE: Thanks for that information.

Dr. Ballman, was that helpful?

DR. BALLMAN: Very helpful. Thank you very much.

DR. ZHAO: Thank you.

DR. MAURI: Laura Mauri from Medtronic.

I just wanted to offer a point of clarification. So the FDA has shown our IDE study, which had U.S. patients and European patients. We also have a similar Japan trial, so we have another group of very similarly randomized OUS patients. Patients in Japan actually were sicker in some ways, they were significantly older and more frequently diabetic with

more frequent carotid artery disease as well. And so there's not a simple categorization because we saw that effect in the U.S. and we didn't see the effect in Japan or in Europe.

DR. LANGE: Okay, thank you.

And I think the industry and FDA has addressed all the questions we posed. If there's anything that's outstanding, please let me know, otherwise we'll go into our Panel deliberations.

Dr. LoGerfo.

DR. LoGERFO: This is a question for Dr. Clair, since he's chosen to sit in the front row. But with regard to all these studies, how do you avoid bias in the timing of TLR and why not use patency?

DR. CLAIR: Dan Clair, University of South Carolina.

I would answer that question simply by saying these trials are designed to try and be set up to evaluate the effect on patients. Stenosis has an effect on us, as clinicians. TLR has an effect on patients in terms of what they're subjected to. I agree with you, it may be much easier to standardize how you evaluate stenosis with duplex criteria, but it's a lot easier to get a sense of what the impact on a patient is by looking at TLR.

DR. LoGERFO: Why not use patency?

DR. LANGE: Thank you, Dr. Clair.

I mean, you know, we're going to be deliberating -- I'm sorry, do you have a question, Dr. LoGerfo?

DR. LoGERFO: Just why not use patency? It's so easy.

DR. CLAIR: Patency is often included in these trials as well. TLR tends to be the major focus of these because, again, it's patient focused.

DR. LANGE: Dr. Blankenship.

DR. BLANKENSHIP: Yesterday I asked about other indices of quality of life besides

TLR and heard a little bit about one -- I think, one quality of life survey. But to me, the question benefits versus risk revolves around more than just TLR, and I'm just curious if there is any other data from any of the folks from industry about other measures that would indicate that quality of life is generally improved with paclitaxel-eluting drug or stents or balloons and whether that affects sort of global quality of life or any other measures of it.

DR. LANGE: It seems there was a slide yesterday. Did you present that, Dan?

DR. CLAIR: I don't think I did.

DR. LANGE: Don't think.

Dr. Mauri, do you want to -- well, actually, there was somebody that -- yeah, don't make a fool of me now, I don't remember. Okay.

DR. SCHNEIDER: Peter Schneider, vascular surgery, UC San Francisco.

Yes, the slide that we talked about yesterday is -- is, I think, coming up here and what we looked at was the EuroQol 5D, it's a quality of life survey. The key thing, though, here is that when the patient undergoes one treatment or the other and then subsequently develops problems, that is to say, for example, the current symptoms which happened dramatically more frequently in the PTA group, we cannot just continue to survey their misery year after year, we have to do something about it. And so this is where this concept of the repeat revascularization becomes so important. So in order to maintain these indices, what you see here is a significant better mobility and significantly less pain among the DCB group at 6 months and then a strong trend in all five indices at 12 months. At the same time there were 48% fewer repeat revascularizations in the DCB group at 3 years, and that trend continued through 5 years.

DR. LANGE: Thank you.

I'll entertain two more comments regarding this.

DR. GRAY: This is Bill Gray from Philips data.

I'm going to repeat the same thing Peter said but in a different way with different data which is, that as it's currently constructed, the evaluation of patients at the 6 -- from baseline, 30 days, 6 months, 1 year and beyond, where both quality of life, ABI, Rutherford index, walking distances and so on, are all constructed to do that at the sample time point with a window. That means that we don't count them at their worse, so it's an "at" function, not a "through" function. So it's not through 12 months, it's at 12 months, and we don't measure, let's say, the ABI at 12 -- at the time prior to the intervention, so we don't get the worst-case scenario.

So the data that I'll show you will basically -- sorry, I need to go way down, like 43 or something. So the data I'll show you will basically recapitulate what Peter showed you, which is that there's a marked improvement in all those indices I just listed, hemodynamic, Rutherford classification, walking distance, and quality of life across the board from baseline to 6 months all the way out to 5 years.

And so here's the -- here's some of the datasets. They're hard to read, but you can see -- and they're not well shown here, but you can basically see there's a shift from walking distance, walking -- this is EQ-5D scales -- get better after the intervention in both groups and were maintained in both groups all the way out to 5 years. This is 12-month data, this is 24-month data, and 36-month data. We have only 36-month data in this trial. So that's for quality of life. Walking distance and again, too small to see, but take my word for it, all walking distances improved and are maintained. This is at 6 months and at 12 months. So, again, I don't like to go through it, it's boring, but the bottom line is, to your point, everybody gets better and the quality of life improves significantly with fewer re-interventions.

DR. LANGE: Yes, sir.

DR. MELER: J.D. Meler, Becton Dickinson.

Just similar to the other speakers, looking at our EQ-5, in 6 months we saw a persistent and maintained improvement with paclitaxel products.

DR. LANGE: Thank you.

DR. MEREDITH: So this is just -- Ian Meredith from Boston Scientific -- just addressing the results for the IMPERIAL trial and shown here you can see the Rutherford classification distribution at baseline, 1 month, 6 months, and 12 months showing sustained improvement in patients who received revascularization. And on the right you can actually see the walking distance, the walking impairment, but there's sustained improvement out to 12 months. This is the data that we actually have thus far, so significantly improved symptoms with respect to the Rutherford category, improved hemodynamics and walking function.

Thank you.

DR. MAURI: Laura Mauri, Medtronic.

We have one additional analysis that I think pertains to the question at hand, which is we looked at the impact of TLR. This was a question, I think, that came from Dr. Krucoff about patients who do well with TLR, without having had TLR at 1 year compared to those who do and how do we look at the outcomes that follow that subsequently. So only looking at outcomes beyond 1 year, understanding that it's not adjusted for the differences between the patients who would have had TLR or not, just looking at this in crude fashion, you see that on the left column you see patients who've had TLR within the first year; on the right, patients who've had no TLR; and there's no significant difference in terms of mortality, but there is a higher rate of target limb amputation and thrombosis in the patients who suffer TLR in the years subsequent to that. So this is obviously quite meaningful to patients. I can ask Dr. Schneider to comment on the clinical significance.

DR. SCHNEIDER: Peter Schneider, UC San Francisco.

Yes, the -- so just a brief mention of -- you heard some of the patient testimonials this morning and some of the other discussion we've had about what it's like to talk to a patient. So one might imagine that the avoidance of a major target limb amputation and/or a sudden vessel thrombosis creating obviously an emergency, which could happen any time of the day, these are highly significant, I think, in reducing a person's worry and also improving quality of life.

DR. LANGE: Dr. Rasmussen had his hand up. If this is a clarifying question, we'll take it now, and if not, we'll go into Panel deliberations and then let you make a comment.

Dr. Rasmussen, which would you --

DR. RASMUSSEN: You can be the judge on the question. I think it's pertaining to target lesion revascularization, just a point of fact that a percentage of those are open revascularizations, so it's not -- and I think it's for the Panel, those who aren't operating on these patients in the Panel, I think it's important to emphasize that it doesn't -- TLR doesn't just mean another angiogram and angioplasty, it may mean the lesion has recurred and now the patient needs an operation, open operation, which has probably a greater incidence of morbidity and decreased quality of life once they get into the open operation category.

DR. LANGE: Yes, sir. And I appreciate you bringing that out, and I see the heads bobbing over here on the industry side saying agreed, agreed.

Are there any other clarifying questions that were posed previously that have not been answered?

(No response.)

DR. LANGE: All right. With this, I'm going to close this part and move into our Panel deliberations. Before we do that, I'd like to ask our nonvoting members, Ms. Patricia Daigle, our Consumer Representative; Mr. Gary Jarvis, our Industry Representative; and Dr. Phil

Posner, our Patient Representative, if they have any additional comments, and I'll start at the end, Dr. Posner, with you and then work this way.

DR. POSNER: No, you guys have covered absolutely everything; my mind is full.

(Laughter.)

DR. LANGE: Thank you.

Mr. Jarvis.

MR. JARVIS: Yeah. First of all, I'd like to thank FDA and the industry here for pulling all of this together and all the hard work that's been involved because I know there's -- I know there's people on both sides that are working on very little sleep here to pull all this stuff together and get out the most recent data that we have to try to get to the bottom of this.

You know, over the last one and a half days we've seen and heard a lot about clinical data and what we've seen is we know what we know now, we know what we don't know and we don't have, and we're going to discuss here in a minute where we're going to go, so -- or what we would like to see. But, you know, I think when we -- especially when we're talking about a mortality signal here, we should look at the data in its totality and that's RCTs, that's registries, that's single-arm, that's coronary, that's whatever we have out here, we should be looking at that to get this to potentially look at the safety signal.

And I travel around a lot going to different conferences around the globe and talking to different physicians about things, and I can tell you that when this meta-analysis came out and was published in December, it threw the industry and physicians for a loop. Everywhere, all the meetings you go to, they all have sessions now, everybody's talking about this, and everybody's getting real collaborative and trying to work on this, and that's one thing I hope that the industry does, is they continue this collaboration beyond this meeting. Okay, I think that's really important that we all work as one on this and try to

move this together. But, you know, as other physicians had mentioned today here, you know, on March 15th FDA came out with this letter and this letter has put a chilling effect across the clinicians in this country and how they treat patients because all of a sudden now devices that they're sitting on their shelves that are indicated for use, all of a sudden now they're thinking am I putting my patients at risk by using these devices?

So if there's anything I could ask FDA here today would be, you know, please give the clinicians and industry as much reassurance as you can that when they continue to use these devices within their indications that they are safe and they are effective and they're not going to harm their patients because I think that's going to be a very important thing.

And one other thing that was brought up to me here was that some of the people who have these ongoing clinical trials, they're starting to see difficulty in enrolling patients because of this issue out there. So, you know, I want to say again that this is important; we need to have these devices out there to treat these patients.

And then, finally, from a personal piece and a potential prospective patient for these devices is I want to make sure there's continued access for physicians to have these devices and to be able to treat patients with these devices in the way they're indicated right now.

So thank you.

DR. LANGE: Thank you, Mr. Jarvis.

Patricia.

MS. DAIGLE: Yes, Patricia Daigle.

I'm going to kind of piggyback on you. First, let me thank the FDA for having me here and the cooperation of all the people who gave great testimony. But I represent the consumer, and the one thing that I would like to say, I think, on behalf of consumers is that one of the statements that really stuck with me was Dr. Daniel Clair's statement about the poll of physicians that he gave and that, you know, prior to this recognition of this alarm

that, you know, all the physicians, 40 to 50% of the physicians there were giving the stents, and now there's only two out of the group that will now offer the drug-eluting stents. So as a consumer, my concern is the consumer choices. I know there's high risk factors and I think the patient has or the consumer has the right to be aware of the risk-benefit, you know, that they have, but ultimately the choice should be up to the consumer. And so they should have a choice for that to be one of their choices to choose from, regardless of the risk, the risk should be up to their -- the consumer has a right to have a qualitative or a quantitative life, and it's their choice to decide which type of life they would like to live. So I think it's very important to have a choice for them to decide what their lifestyle is going to be.

Thank you.

DR. LANGE: I really appreciate the comments. Thank you all very much. And as you can tell, both from the extensive public hearing and the discussion we've had yesterday and today, is that everything that's been said is important to everybody on this Panel, and we take it very seriously. So I thank everybody for participating.

At this point I'd like to focus our discussion on the remaining FDA questions. Panel members, you have a copy of those questions in your folders. I'll ask Dr. Whatley to read Question Number 6 and then as you respond, again, if you'll identify yourself. And, again, I want make sure that we -- the full armamentarium of opinions is represented. We don't have to -- we may not have to say the same thing over and over, but I want to make sure everybody feels like they've had an opportunity to offer an opinion or a perspective to the FDA. At the end of our discussions I'll try to summarize things and ask the FDA whether we've been fully responsive or whether they want additional information or clarification.

So with that, Dr. Whatley.

DR. WHATLEY: Hi, my name is Eleni Whatley. I'll be reading the questions for the

Panel. The following slides will depict a summary of the questions and the data it pertains to. The full question can be found in the panel materials. I would like to note that Question 7 was edited heavily.

Question 7 (sic) pertains to paclitaxel dose/mortality relationship. FDA conducted statistical analyses to determine a potential relationship between paclitaxel dose delivered and mortality. From these analyses, there was no consistent dose trend across the four pivotal RCTs that had a non-paclitaxel-coated device control group. One study suggested increased mortality with increased dose, the LEVANT 2 RCT, and three studies did not show a relationship (IN.PACT SFA I & II, ZILVER PTX RCT, and ILLUMENATE RCT). Please discuss the relationship between paclitaxel dose and mortality.

(Off microphone comment.)

DR. ZUCKERMAN: That's correct.

DR. WHATLEY: Yes, that was Question 6.

DR. ZUCKERMAN: For the record, it's Question 6. Now we're going to discuss it.

DR. LANGE: Dr. Somberg.

DR. SOMBERG: This has been discussed many times in the last day and a half, and I would say that the data is inconclusive, the analysis is inconclusive because we have certain limitations. But the suggestions of our two statisticians on the Panel, I think, were excellent and maybe that could be returned to at some point because we're looking at the power of the meta-analysis to show us the signal, so I think we have to use the power of the meta-analysis to look at a dose-response relationship and not pool the individual studies with, as I pointed out earlier, the variability. So, in summary, I don't think at this point, with the data we have, we can make any further comments on a dose/mortality relationship.

DR. LANGE: When you say no more further comment, you don't want me to ask anybody else on the board?

DR. SOMBERG: No, you can ask whoever you want.

(Laughter.)

DR. LANGE: Dr. Ballman.

Dr. Ballman then Dr. Krucoff and then Dr. Blankenship.

DR. BALLMAN: I struggle and I agree, I don't think -- it's inconclusive at this point because it's not even clear to me what the measure of dose is and if you don't have a correct measure of dose, it's hard to do a dose-response relationship. So I think the data are inconclusive.

DR. LANGE: Dr. Krucoff.

DR. KRUCOFF: Yeah, I agree for even just the differences in design, continued complete tissue coverage versus limited surface area from a device. Knowing what the dose really is, is part one. But I think the other important thing, from my point of view, is that this is not a dose assigned, this is a dose driven largely by anatomy, by lesion length, etc. So I think the dose-response relationship here is fundamentally confounded and the data available don't make it simple.

DR. LANGE: Dr. Blankenship and then Dr. Sun.

DR. BLANKENSHIP: I agree that the data is not clear, and I don't think we can make a definite statement about dose relationship, but I do think that the ALARA principle holds that as you move forward that as low as reasonably efficacious would be a good strategy in the future.

DR. LANGE: Dr. Sun.

DR. SUN: Yes. To answer this question, I agree, I think dose is not very well defined. Based on this particular study, this range is very hard to conclude, but that does not mean there's no dose-response relationship. I'd like to put a little background because FDA clarified the number then for the Panel to have better information.

The lung concentration is somewhat surprising to me. Day 1 is 1,000 nM, 1,000 ng /mL per gram of tissue. That's equal to a 1,000 nM. Day 90 is 25 nM. Day 60 is 100 nM. Day 28 is 260 nM. If patients are exhibiting -- the concentration is somewhere between 1 to 10 nM. Some of the study early, the presentation is for smooth muscle endothelial cells and angiogenesis may be peak molar. So those concentrations emerge higher than the application's concentration. Of course, in vitro/in vivo, you don't know how much correlation they have. That's number one.

Number two, put in the cancer perspective, when you give 400 mg dose to the cancer patient, 3 hours infusion, the concentration plasma is around 3600. That's about 4,000 nM. Within 3 days they drop to around 20 ng. So 3 days is lower than 90 days. In lung, nobody has a human lung concentration but, from an animal study, the lung tissue for this particular drug were similar to plasma. A little bit higher.

So therefore does not -- does not add up in terms of the concentration in lung is one-third or 25% of a human cancer patient concentration. That's a bit high, that's a bit higher than -- but the dose really 1% or 2.5% of dose. Only possibility -- I'm assuming also when company reported those data, I'm assuming they measured all other tissues -- only found those in the lung. Otherwise that would be reported. So my assumption is that they only found in the lung. Only possibility hypothesis I can have is this really strange, this low dose reach lung concentration that high for that lung.

One possibility I can think of, speculate, is when you inject something in the bloodstream, if there is pieces more than half micron or 500 nm, if there's a piece, the first organ they stuck is the lung. Then if a smaller nanoparticle, then perhaps the liver or the spleen. It is possible, then, in the coating during this process that some of the pieces of particle peel off, stuck in the lung. That's the speculation I have, but the concentration is very strange. Not extremely surprising, but I would not expect that high concentration.

So in terms of dose, another comment I'd like to make is I'm in the cancer field, as you are. We load the cancer patient. We use MTD. We use as much as we cannot load anymore because we want to save their life. They'll be dying. Paclitaxel in vitro anti-cancer -- is 10 nM. We give the dose reach 3,000 nM. Threefold micromolar. We load tissue with the same concentration. This particular case is somewhere in between. In cardiovascular drug, we never load drug. Cardiovascular you see their PK is always in 50, 10 ng. You never see a drug in 3,000 ng/mL. This one in lung is 1,000 ng/g of tissue; is a bit high. Now, this number changed my viewpoint somewhat to Dr. Somberg's point yesterday. I said yesterday I don't believe it's systemic effect. This one somehow will change my view. In lung, it's a bit high. So I stop there.

DR. LANGE: Dr. Kip.

DR. KIP: I'll be quick. I agree that the data are clearly insufficient to establish dose-response relationship and I just want to make one point and that was from yesterday, we had two presentations in the Hill criteria for causation, and they seemed to highlight the importance of dose response, which is one of the 12 criteria that are just used, but just keep in mind, none of those 12 criteria are de facto requirements for causality, other than temporality. And when that was published in 1965, Hill was very circumspect in saying don't rely on just one of these criteria. So the data don't support right now, are indicative of, dose response but that's not an obligate requirement for causality.

DR. LANGE: Dr. Ballman and then Dr. Krucoff.

DR. BALLMAN: I just want to follow up on that, and Hill criteria was developed for observational studies to establish causation. It was assumed that, in clinical trials, that the two groups are the same, other than the treatment.

DR. LANGE: Dr. Krucoff.

DR. KRUCOFF: So I do want to emphasize a point that's come out very briefly, but

just because we don't have data to show a dose response which is, what we have does not mean one does not exist. And I think, as Dr. Sun's point, that what is an isolated organ, I think that's in an animal model with normal organs. What we have in human subjects in this PAD space are patients with multiple abnormal organs and we're seeing multiple different kinds of mortality. So, again, this may all just be data noise, but I don't think we can lose track of the fact that this question of dose relationship, if I have a predisposed abnormality that could be touched through other means shouldn't be lost and whether we could look at lung disease or others stratified by dose for outcomes, again, we get into the conundrum mentioned yesterday, subgroups mean smaller denominators, but the hazard, this is the limitation of the data. So I think just because we can't see it does not exonerate our ignorance about whether or not it's there.

DR. LANGE: Okay. Now, I'm going to summarize for the Panel's discussion is they feel like it's inconclusive based upon the data. It's complicated by patient variables including length of lesion, and there's a concern about high tissue levels, intra-arterial and intrapulmonary as well.

DR. ZUCKERMAN: An excellent discussion, and we also received, both for FDA and industry, further things to look at post-panel. Thank you.

DR. LANGE: Great.

Dr. Whatley, Question 7, please.

DR. WHATLEY: So this is the question that was edited.

FDA reevaluated the preclinical animal studies that were previously conducted for approved devices in order to determine if any data were available, including safety and PK evaluations, to associate a potential cause for the increase in mortality. From this review, no conclusive evidence was available to FDA to attribute causality. Drug-related changes in downstream tissues for treated hind limbs were noted at low levels in acute 30-day and

90-day time points, sometimes containing crystalline drug material. However, no skeletal muscle lesions were large enough to produce clinical symptoms in the animals. There was no evidence of device-related bone marrow suppression, hepatic or renal toxicity. There were no reports of malignancy or unusual gross findings in any of the reviewed animal studies. Extremely low animal mortality and relatively low morbidity rates were observed. However, the animal studies were relatively short in duration and were not designed to specifically evaluate for late effects of the drug. Please comment on whether any of the preclinical animal data provided mechanistic insights into the late mortality signal, and discuss and describe what new animal studies, if any, may be helpful.

DR. LANGE: Great. I'm going to take that in two parts. The first part is address, again, whether any of the preclinical animal data provide mechanistic insights, and so let's take that first and then -- so I've got Dr. LoGerfo, Dr. Cigarroa, and Dr. Somberg.

DR. LoGERFO: Yes. I noticed in the animal studies that the arterial wall was injured into the medial layer. I have some thoughts as to pull together some things here. Why is it a preponderance towards the left side? Why is it associated with cancer? Why is it delayed? And how does it do it with such a small dose of paclitaxel?

This relates to the anatomy at the adductor hiatus between the femoral artery and the femoral vein. This is a very tight enclosure, it's fibrous, and with atherosclerosis, it's almost scarred in. Any surgeon who has dissected in that area would only describe the veins as being plastered to the artery. When a balloon is blown up in an atherosclerotic vessel, the intima cracks and it usually cracks longitudinally, thankfully, so there's not a dissection. The artery expands. In this case, the vein is crushed against the adductor hiatus.

Now, a small amount of paclitaxel can get through that arterial wall. It doesn't have to get to the lumen of the vein because the saphenous arm of the vein nourishes the entire

vein wall, unlike arteries. So it's easily picked up and cause an injury to the vein, and it doesn't cause thrombosis immediately because the patient is on anticoagulants. If a small thrombus occurred or if an injury to the vein has occurred, it quickly becomes endothelialized within 2 weeks. Any surgeon who's looked inside a vein, seeing any cubital fossa where we put needles, often there's these strands that go across those veins, these senequii, but blood still flows through there. So now you have kind of a sleeper, occult venous lesion on the left side where a venous thrombosis is more common because of the crooked anatomy of the left common iliac vein. The pressure in that vein is higher. So things go along fine. Now, we get a hypercoagulable state from cancer, for example, or just dehydration, which would cover a lot of things. That kind of fulfills almost the triad of stasis, injury, and hypercoagulable.

Venous thrombosis is seldom detected in autopsies, in fact, pulmonary embolism is seldom detected in autopsies. If a patient is at home and these events occur, you would never know it. We have a large category of other causes of death and they're just unknown.

So I submit, this is a mechanism that brings these things together and that tiny dose of paclitaxel can cause the injury, as we see here, anti-angiogenic. I think that was a stronger view that I heard today. That can injure the vein, especially if it disrupts the base of this arm of the vein in which it's so dependent. So I pass along that thought for a mechanism. One easy thing to do is to start looking at blood flow in the superficial femoral vein at the time of the procedure.

DR. LANGE: Thank you, Dr. LoGerfo.

Dr. Cigarroa.

DR. CIGARROA: I'll defer until we get to part two of -- since you separated it.

DR. LANGE: Dr. Somberg, insight with regard to the first part of the question?

DR. SOMBERG: Well, the studies that the industry initially carried out and FDA reviewed, I don't think were -- well, I know were not aimed to discover a mechanism for long-term toxicity, none was suspected and it was not that helpful. There are some studies that are cited in the literature where you take situations that may contribute to mortality, like an increase in neoplasia, an increase in atherosclerosis, and it is plausible that certain concentrations of paclitaxel may contribute to that, specifically the cytostatic doses where you have enhanced inflammation where you're all aware of the literature where inflammation is deleterious to the vascular system, and also in terms of neoplasia. So I would say no, the studies to this date have not been, for the most part, mechanistically informative. But knowing what little we know and that there, I think, is a potential problem, we can then look at specific animal models in the future to evaluate new drugs, I think, even more importantly than old drugs.

And I would say that why would one think that a normal animal would not take 3 to 5 years to -- well, maybe their life spans are shorter but still, it would take a long time to see something as opposed to acute studies. So instead of doing animal studies, you know, it would probably be better to do human studies except in specific cases where we're trying to test a hypothesis for a specific mechanism like changes in immunosurveillance of tumor and facilitation of atherosclerosis.

DR. LANGE: Apropos to Dr. LoGerfo's question, the FDA -- we talked about the animal models and studies. Was there any look at the ipsilateral vein where the procedure was done? Anybody know?

DR. WHATLEY: No, we did not.

DR. LANGE: Okay, thanks.

So Dr. Sun.

DR. SUN: The crystal found in the lung is a little concerning to me. I think, based on

what I said earlier, that's the number also does not add up. Low dose, high exposure in the lung, I think that needs to be -- figure that out, either industry or somebody, in animal model. If it's human, you can have somebody to figure it out, that would be great, but I don't know you can do that, but that's -- actually, it would be another piece of suspicion, maybe a piece of coating fall off and went to lung. Otherwise you would not see the crystal in the lung.

DR. LANGE: Dr. Posner.

DR. POSNER: Just a thought about a model and a lot of the studies that are done are in older individuals, in humans, and the possibility of using Long-Evans 18 rat as your model because they've already deteriorated, they're closer to death, and it might have an effect that shows up faster in that particular animal model than it does in the ones that you've been using.

DR. WHATLEY: Was the question have we been using older models or --

DR. POSNER: It's just a suggestion that if you haven't been using older models, would you consider using older models since it's closer -- the Long-Evans is closer to the human aging model and there's a whole colony of them at the NIH.

DR. LANGE: So what I'm hearing for the first part is none of the current animal data provides mechanistic insights, if I've summarized that correctly. There's been some talk -- and Dr. Somberg, you had addressed a concern of using normal animals and Dr. Posner, younger animals may not provide any additional information. Dr. Sun was concerned about some of the crystalline paclitaxel in the lung and wanted to know more about local concentrations. Is there any other additional animal models or studies that should be done, other than what's been done?

Dr. Krucoff.

DR. KRUCOFF: So I definitely think that, in this type of safety signal exploration, that

anything and everything that we can learn from preclinical models we should maximize our efforts to adding knowledge, rather than having to explore a human risk to change ignorance into knowledge. And I think this is a particularly good example, potentially, for the kind of industry collaboration that we've seen throughout the past couple of days, to think about working together rather than everybody doing their own animal models but really sitting down with FDA and thinking about -- earlier it was suggested bone marrow or a little longer, thinking about longevity and what animal, but possibly thinking about where or what we could learn that might not necessarily be a hair-raising mechanism, it might actually be quite reassuring that, in fact, generating toxicity is not part of the picture. But I think that, to me, is the most important side of what could be done with preclinical information going forward.

DR. LANGE: I've got Dr. Levy, Dr. Zuckerman, and Dr. Cigarroa.

DR. LEVY: Elliot Levy.

I think we've been tacitly assuming that the peripheral disease patients who are treated with these devices are on the same drug regimens as the patients with coronary lesions that are treated and that may not be true, and an animal model might be a good way to investigate drug interactions because paclitaxel, at least in the oncology world, is known to be -- known to have several highly toxic drug interactions.

DR. LANGE: Dr. Zuckerman.

DR. ZUCKERMAN: Okay, I would just like to underline the importance of Dr. Krucoff's thoughts. Dr. Lange, I think you gave a very good summary up to Dr. Krucoff. There are very important scientific issues to elucidate here, but these are very expensive and time-consuming trials and certainly, the Agency would be very interested in continuing to develop a project in this area with the industry.

DR. LANGE: Dr. Cigarroa.

DR. CIGARROA: So I agree wholeheartedly with the last two statements. I think that, as designed, the current approach to preclinical animal studies will be unable to adequately address the question of is this signal associated with a biologically plausible model and so I think, as we move forward -- and you know, in aortic aneurysm studies, for example, assessing the impact of a drug in tobacco-naive versus tobacco-exposed produces, you know, different responses. So as we look at the consideration of preclinical, I would certainly encourage us, understanding the prevalence of diabetes and tobacco exposure and the fact that we're administering a drug, to better understand the drug-drug interaction milieu and the comorbidities to study potential mechanisms. So I would think new animal studies are absolutely essential. I would simply ask that we be more creative and learn from other areas of vascular disease including mechanisms of adding morbidity into the host.

DR. LANGE: All right, interest. Just a show of hands for the FDA and I'm just going to ask a simple yes or no question. Do you feel additional animal studies would be helpful? Yes or no. And if you say yes, let's show hands.

(Show of hands.)

DR. LANGE: No, show of hands.

(Show of hands.)

DR. LANGE: All right. And so I want to get real granular for just a moment to help the FDA. We want to be creative, we want to pick the right models, we want to do -- so the same stuff, we want to make it least burdensome and least costly and most informative. So those of you that raised your hand, in just one or two sentences each, what would that animal model be like? Would it be an extension of what we currently do? Would it be something different? Will we do some additional analysis we're not doing? For those of you that raised your hand yes. So Dr. Hirshfeld and I aren't going to say a word here, okay?

So just briefly and so everybody can have a say.

Dr. Somberg.

DR. SOMBERG: Inflammation. Specifically looking at animals with atherosclerosis, for instance, rabbits on high-fed atherogenic diets, etc. Maybe aged rabbits to deal with that situation. Look at tumor, animals bearing tumors, animals with metastases placed in them and also, animals with pre-cancerous hematologic nexuses that may be facilitated by this. But you have to look at a dose-response relationship and what Dr. Krucoff said, you know, it's not injecting an intravenous concentration of the drug but putting in a device that would mimic the release characteristics, either a balloon or a stent.

DR. LANGE: Dr. Somberg, thank you. Others?

Dr. Posner.

DR. POSNER: Well, as part of an alcohol and aging study, I can tell you that our aged rats had all the things that these patients that are showing mortality have. And so I again would suggest the Long-Evans, exposing to alcohol, exposing to cigarette smoke. I think the pharmacokinetics are really important because just giving them an IV of the med or the dose or whatever, I think the development of an indwelling plaque where you could actually apply it in a vessel for a period of time and then take samples of that vessel wall and the rest of the anatomy to see where the spread has gone and what damage has occurred. I also heard yesterday about the neutrophil, neutropenia, and I haven't heard anything about that today, but I think that's something that needs to be looked at, if there is actually an immune response that's being incurred, and in that case, I would use a mouse model and look at effects on the immune system.

DR. LANGE: Dr. Rasmussen.

DR. RASMUSSEN: So I just want to speak as one of maybe one or two individuals who said I do not think further animals would be useful.

(Off microphone comment.)

DR. RASMUSSEN: I voted that animal models would not be useful. And I'm overstating that, I don't say there's no use, but I think that my perspective is that we have thousands and thousands of patients who are getting this treatment. It is the easiest thing in the world to say we're going to do animal models, that is, we're going to launch a whole new institute of pig research on paclitaxel. I think that is going backwards. I think we have clinical studies that we can do that can ascertain all of this much more quickly, much more rapidly translatable than animal studies.

I say that just in balance. I don't think there's no use to animal studies, I'm not trying to be argumentative, but I just offer the balance that, you know, when we have something that is acknowledged now as a standard of practice, to go back to the animal lab, that is a -- maybe it's the wrong analogy, but that's a rabbit hole that is quite deep and often not productive, frankly, when you can just study patients.

DR. ZUCKERMAN: Your comments are well taken, Dr. Rasmussen, and the FDA understands the discussion here. We've got a lot of good information.

Dr. Lange, I think we can move on.

DR. LANGE: And the rabbits particularly liked your comment, by the way, Dr. Rasmussen.

(Laughter.)

DR. RASMUSSEN: Just a point of disclosure. As a member of the United States military, I am not sponsored by any animal rights activists.

(Laughter.)

DR. RASMUSSEN: So my comments were not influenced by that.

DR. LANGE: Your middle name is not PETA.

DR. RASMUSSEN: No, sir.

DR. LANGE: All right. All right, thank you.

Let's move on to Question 8, then.

DR. WHATLEY: Question 8 pertains to the benefit-risk profile. Paclitaxel-coated products have been shown to demonstrate sustained benefits with increased patency rates and reduced clinically driven target lesion revascularization rates. Prior to FDA approval, no concerning or unexpected safety trends were noted for these devices. However, an increase in late mortality has been identified. Given the totality of the data, please discuss benefit-risk considerations related to paclitaxel-coated DCB and DES for the treatment of symptomatic femoropopliteal disease. In your discussions, please comment on the continued marketing of paclitaxel-coated devices for patients with symptomatic SFA/PPA disease.

DR. LANGE: Dr. Rasmussen first. Then I've got Cigarroa, Krucoff and Blankenship, Dr. Hirshfeld, Dr. Kip, Dr. Posner. In fact, I hope everybody talks a little bit about this, all right, and we'll try to -- did you get all of that, Evella? No, okay.

DR. RASMUSSEN: I'll try to be brief and organized in my comments to allow time for others. I appreciated a couple of words in this question, both the word "benefit" and then the word "totality." I think that we are appropriately focused. Partly, our task is to focus on risk and the specific meta-analysis, but I think -- as I had said earlier, I think it's important that we maintain balance in this discussion and I picked up on the words "benefit" and then "given the totality of data." And so as I organized my thoughts and I -- under the context of totality, I have sort of a balance scale here and on one side of the totality scale I have a clear benefit that is appreciated through five or six different mechanisms here and it's balanced on the other side of the scale by risk that we are seeing in the form of something called a signal from really one type of study, a meta-analysis. They're both important and we have to acknowledge both sides of the scale. But on the

benefit, I see the benefits that we have ascertained from individualized rigorous randomized controlled trials. We have benefits observed from five, at least five, observational studies from a variety of different databases and methodology. We have near unanimous, if I'm not mistaken, public testimony in front of this Panel from academia, including one well-funded NIH investigator.

We have an oncologist, Erica Mayer, who gave compelling testimony on the safety and benefits of paclitaxel. We had public testimony from professional organizations and even the National Center for Health Research. We have quality of life or at least effectiveness data in the form of reduced clinically driven target lesion reinterventions, and we have really the inability to establish a cause.

And then on the other side of the scale, with regards to risk we have this meta-analysis. It's really one meta-analysis that's been done extremely well and it is highly important. I acknowledge its accuracy. It has been repeated by our FDA and I appreciate their efforts and acknowledge that accuracy as well. But to me, you know, the benefits in this scale -- and I think the meta-analysis, actually this afternoon, in my mind, have actually been drawn into question or at least challenged by the concept of ascertainment bias. So I would, as I look at this scale of benefit-risk, to me -- and I'm asked to comment on the continued marketing, I think that my comment is, from my perspective, that continued marketing of the paclitaxel-coated devices for patients with symptomatic SFA disease should be allowed.

DR. LANGE: Thank you, Dr. Rasmussen.

Dr. Cigarroa.

DR. CIGARROA: So I'll start with the benefit. The burden of peripheral arterial disease in the United States and worldwide is substantial. It markedly hinders the quality of life in the individuals to be able to function within their family units and function, you know,

within society without adverse limitations.

There's no doubt that the addition of paclitaxel to either (a) a balloon or (b) a stent in five developed devices today has favorably impacted quality of life, markedly decreased the need for repeat revascularization, and as it has been approved, has had a rapid adoption and a positive impact as it relates to the endpoints that we have talked about. So there's no doubt that there, in my mind, is a very consistent and clinically, clinically profound benefit to our patients which has created an opportunity for us, as clinicians, to provide alternatives to open vascular procedures and an associated morbidity in healing and avoiding that in many of our patients. So no doubt, benefit.

In terms of risk, as we think about the typical risks associated with procedural-based components, no increase in acute risk. The therapy is delivered in the same way. Non-drug-coated balloons are used in the same way we use stents. So as we think about the acute challenges, I see no acute issues as it relates to the risk to the patient. There is a clear and consistent signal of excess mortality in randomized clinical trials and in individual trials that have had follow-up through 5 years, there are signals. Now, they cross the line of identity in many of them because they're underpowered and so is that a real risk? Well, it is offset by additional datasets that, to me, tell me we need to understand more, but it doesn't tell me that we shouldn't, in discussions with our patients and in guidance to our providers, put a pause on this. And so I would say clear benefit. In the vast majority of risk, no excess risk, and there may or may not be an issue of excess mortality that, you know, I think we need to address and we'll talk about that later.

DR. LANGE: Dr. Krucoff.

DR. KRUCOFF: So I won't repeat because I agree with Dr. Cigarroa's assessment of benefit. This is unequivocally a class of devices that have emerged and created an immediate clinical benefit for patients with symptomatic or tissue-threatening, even, limb

ischemia. The conundrum, though, and in some ways the disappointing side is that that benefit doesn't lead to longer life and we now have a much less distinct but new question about does it actually shorten life to achieve that benefit.

And I think the dialogue with patients which, a year ago, prior to this meta-analysis, we wouldn't even have had that conversation with patients, that we really need to understand how to communicate about short-term benefit which is certain in the face of a long-term risk which is uncertain, even at the level that we've been talking about it here today. And part of this, I think, is to really retain the patient perspective here because the likely answer is one size won't fit all. And I was an investigator for the BARI study, the bypass angioplasty randomized trial the NIH first did in multi-vessel patients, and had many patients say well, if you could flip a coin over surgery versus angioplasty, angioplasty, I go home the next day and surgery, I'm in the hospital for a week and don't feel well.

So the tangibility of early benefit to patients, I think we really have to also protect our patients in their interests and in this dialogue. So I think the work to clarify, and hopefully we'll talk more about this, how to clarify what the risk really is, whether it is a mortality risk based on the devices or the drug, at all, I think that conversation really needs to go forward. The degree to which you can have an informed conversation with patients -- and here, I think the doctor side is when we use a tool and I remember the first generation of coronary drug-eluting stents, we operators tend to be very enthusiastic. So how to open the door to this milieu of devices where we're confident of the benefit, short term, and we're very unclear about the full implications of the risk 2 to 5 years later, we really need to be careful about how we do that, what we commit to learning, if we do that, and bringing these devices back online and I think ultimately create a clear window for patient preference to be a part of that discussion going forward.

DR. LANGE: Dr. Blankenship, Hirshfeld, Kip, Posner, Ballman, and LoGerfo.

Dr. Blankenship.

DR. BLANKENSHIP: So I agree with the comments of Dr. Cigarroa. Jim Blankenship.

I agree with the comments of Dr. Cigarroa and Dr. Krucoff. It seems like we look at the ratio of number needed to harm versus number needed to benefit and that's clearly more people will experience a benefit versus experiencing a harm. There is a cognitive bias called temporal discounting where persons tend to value something that happens sooner or place greater importance on, than something that happens later. So a benefit of less chance of TLR in the immediate future may be valued more highly than the risk of dying later on.

I think those two factors lead us to the point that Ms. Daigle made, which I think was right on the money, that we owe it to patients to let them make the decision and each person will come up with some different weighting of those factors, but I think we owe it to the patients to allow them and their doctors to collaborate to make a decision which, for a given patient, may be quite different from another patient. But to do that, these devices have to be available, and I think that mandates that they continue to be available.

DR. LANGE: Dr. Hirshfeld.

DR. HIRSHFELD: This is John Hirshfeld.

I will do my best not to repeat some of the excellent comments that have been made already, but I think I have a couple additional thoughts that I think are worth considering. And I think you want to think about this from both the standpoint, the regulatory standpoint of the FDA and the clinical practice standpoint of those of us who take care of patients.

From the regulatory standpoint, I think there's sufficient evidence that there may be a signal of harm, that the FDA really can't walk away from this issue and just decide that things are okay. I think if it turns out with further study that this is real, the FDA would be

really in the box if they had brought -- gone to where we've gone so far and then walked away from it. So I think it's really going to be impossible for FDA to ignore that.

From the standpoint of us, the users, we have to figure out how we're going to use this information to practice and looking at the data that we've seen, I think we see that in higher-risk populations, whatever signal there is, is drowned by the intrinsic risk of the patient. And so the problem really exists more in the lower-risk patients in terms of whether or not one would apply this to a given patient.

The second thing that really hasn't been discussed at all today, which is a real issue in the coronary world, is what the patient's intrinsic risk of having a recurrence problem is and that's really well understood by anatomic criteria. And so I would think that if you start to think about this you would begin to think that it would not be justifiable to use a device like this in a patient who was low intrinsic risk and low recurrence risk. But if the patient is high risk and high recurrence risk, then it would be very justifiable to give this patient every edge that they could possibly get. And then there's going to be a spectrum of people in the middle who are low or intermediate intrinsic risk, but moderate or high recurrence risk. And so I think that's going to be the role of clinical judgment in terms of how to apply this technology. So I think the technology clearly has value, we need to learn how to use it properly, and FDA needs to continue to work with industry and with us to try to define what the actual magnitude and importance of this signal is.

DR. LANGE: Dr. Kip.

DR. KIP: Yes. These estimates of number needed to treat/number needed to harm are kind of all over the map and so I'm not going to focus on those. I'm just going to summarize to say that I view the benefit-risk ratio as high and I'm not sure of the best way to say this that's politically correct or sound compassionate, I hope I come off that way. I'm struck by the industry presentations out in real-world clinical practice as to the patient

population that's seen every day, the mortality out at 4 -- 3, 4, 5 years, how exceptionally high it is in this group and that mortality risk occurs irrespective of whether or not you're treated with a drug-coated device or not. You're just an exceptionally high risk. So given that the drug-coated devices do substantially, I'm compelled, favorably impact quality of life, and I don't want this to come off, well, they're going to die anyway, so that's the point I don't want, but if you can get 2, 3, 4 more years out of high quality of life, I do think that needs to be taken into account.

DR. LANGE: Dr. Posner.

DR. POSNER: I'm going to be the real patient this time. My uncle was a Type 1 diabetic on one leg. My dad was Type 2 diabetic, a career three-pack-a-day unfiltered cigarette smoker with intermittent claudication. I'm a prediabetic and done everything healthy. The family, as a whole, would prefer to have their mobility. Now, I think of Mickey Mantle who said if I knew I was going to live this long, I wouldn't have done all the things when I was younger. And the key here is we're not talking about an acute instant death, we're talking about death from all causes as the marker. We're talking predominantly of cardiac and cancer, pulmonary cancer. And so given the option of taking something that's going to make my life worthwhile and knowing my major risks are going to be hit by a car, strangled by my wife --

(Laughter.)

DR. POSNER: -- heart disease or cancer, I can do all the preventative things that you can possibly do. Every male member of my family, except for my father and me, didn't make it past 55. But he gave up smoking, he started exercising and he got into good diet, he got everything under control. I never smoked except living in New York.

(Laughter.)

DR. POSNER: He made it to 80. I'm at 75. And so I think when you talk to the

patient, you have to have the patient learn what the risk really is, what are the things that can be done to modify that particular risk, and then what's the reward.

The FDA had a wonderful symposium last month that I attended on risk-benefit analysis and I listened to all those patients and some people said what I would gain from this is not worth the risk. Others, it was going to relieve me of chronic pain, constant pain, inability to have a good life and I'd rather be dead; it was worth the risk. And so from a patient's point of view, you need to talk to every individual patient and explain what the real risk is and how to minimize that and then let them make their decision.

DR. LANGE: Following the meeting, I want to talk to you about what preventive measures you're going to take to help prevent getting strangled by your wife. That would be helpful to me.

(Laughter.)

DR. LANGE: But no --

DR. POSNER: I love her.

(Laughter.)

DR. LANGE: Thank you, Dr. Posner, for those comments.

Dr. Ballman.

DR. BALLMAN: So I don't have much to add. I do think the benefit data are compelling that there definitely is a benefit. I also think, though, that there is a troubling harm signal and the reason why it's not seen in every individual study is, first of all, you know, patients weren't followed very well out to the 5 years and also these studies were not powered to detect that, so you have to rely on the meta-analysis and just because it's a meta-analysis, I don't think it makes it any less real.

But I do echo what Dr. Hirshfeld said, that we need to figure out the patients that have the more benefit versus the more risk, and I think there are subgroups and I think he

outlined those very nicely.

And, finally, I too think that it should be up to the patient and that each patient should be advised of what the benefit for that particular patient might be and what the risk might be. And so that's --

DR. LANGE: Dr. LoGerfo, any additional comments?

DR. LoGERFO: Yes, I have a very different view of the treatment of claudication, 35 years of vascular practice, as chief of vascular surgery, with a focus on lower extremity disease, patients with diabetes. I maintain that the well-educated, accurately educated patient will not choose to have an intervention for claudication. Now, I'm talking about 90% of people 70 years or older, when informed that they're not going to lose their leg, in fact, their leg is protected by collateral circulation, they're not going to wake up with a suddenly dead leg, walking is good. The pain is okay. Push it, walk a couple of times a day. Stop smoking. We're more effective at that, these days.

That does more for that patient than any 10 surgeons or interventionalists could ever do. Come back and see me in 3 months. You see how easy it is for me to assess your circulation with my blood pressure cuff and my little Doppler. I do this and I did this in patients for 35 years. It was extremely rare, I was thinking here of two patients who opted at some point for revascularization for claudication. It rarely progresses. This goes back to 4,000 patients followed for 5 years or more, reported in the '60s by Begen Jurgens (ph.), and subsequently 2,000 patients reported by Charles Robb and his associate, about 1,000 reported by Tony Inferato (ph.) around 1980; the same result, no intervention for claudication. At 5 years, the risk of limb loss is about 8%. If people stop smoking, it's zero.

Now, the well-educated patient thinking about this, knowing that there is no intervention without risk, will not want something done. There are risks to interventions. One that hasn't been mentioned here is that the patient with claudication has some

limitation on how far they can walk, although they feel very good when they learn that they can walk further if they do some exercise. This helps them in many ways. When that vessel occludes with a stent in place, the evidence is the vessel winds up worse than it was prior to any intervention. So the options for revascularization become more and more limited; it made the patient worse. You've taken away his options.

So I don't think there's urgency about this and I think it's time to look at -- I've mentioned this several times here -- in any future trial, an arm that includes exercise and it doesn't have to be Medicare-funded exercise, there is a whole category of self-directed exercise which works almost as well as the Medicare -- the people arguing that Medicare should pay for exercise, supervised exercise training. That's wonderful, but you don't need it. So I'll put a word of caution here. Trading life for something that's not limb threatening and you can help get better yourself is a stretch and you don't have to tell the patient, they will say doc, I don't want it, I don't want anything done right now.

DR. LANGE: Dr. Zuckerman.

DR. ZUCKERMAN: Yes. Dr. LoGerfo, your comments are very important and you've continued to stress the importance of conservative treatment, which is an important one for public health. Where the Agency is going, though, is we really don't know, in many fields, patient preference to the degree that we would like to know and while you describe your clinical experience, it has been interesting that in other device areas where there have been significant mortality and/or other adverse event signals of significance, patients look at things a little bit different from docs. So maybe we need to better understand patient preference in this area, which is a focus of the Agency currently. We've got in a good discussion of the benefit-risk. The FDA appreciates where most of the Panel members sit right now. I do think the need to best communicate between physician and patient still remains a challenge with accurate data. But, Dr. Lange, is there anything else that you can

help us flesh out from this question?

DR. LANGE: I don't know, but if there's something that hasn't been said, that you want to say, otherwise the other three things we have to cover --

DR. SOMBERG: I'll take that challenge and I just want to emphasize, number one, I don't think anyone on the table is talking about taking the drug off -- not the drug, the device off the market. I think the question is -- most concerning is the -- given a signal, which I think the majority of people do see here, is the risk-benefit ratio.

And I'm glad we've heard some talk of some physicians who believe that, you know, for TLR and the intervention is not always as critical as some other physicians think it is because that's reassuring to me, because when I heard -- to be succinct, when I heard that within the confines of the meta-analysis the number needed to treat for benefit is 13 patients and the number needed to treat for adversity was 14 patients, I mean, that was jaw-dropping.

And I think that has to be expressed, from my point of view, to the patient because they are trading maybe convenience and not having enough -- as many procedures and maybe walking a little bit more versus a 3- to 5-year enhanced mortality, if those numbers are correct. So I think there's something out there. When 50 or so physicians were using the procedure, when they raise their hands now only two are, there's some concern out there from people who deal with this problem all the time.

DR. LANGE: I'm going to truncate it only because you're not going to get unanimous opinion, but I think what you've heard, if I'm going to summarize, is there's a clear risk in terms of quality of life, I don't think there's any debate about that. There is some concern that the signal is weak, but people are unwilling to trade death for a marginal -- well, what could be a marginal clinical benefit at 3 years, but an acute immediate benefit and -- but in every case, I think everybody has said that the patient should be involved, should be

informed fully with the information we had, whether it's complete or incomplete, and should be involved in that decision-making process.

You hit the red light because you want to say something, Dr. Rasmussen? Because I want to move on, because the other stuff we're going to talk about is important as well.

DR. RASMUSSEN: I mean, I just think it's -- I think we digressed there because the question isn't given the signal, it's given the totality of data, and I think that's a big difference and I hate to -- I don't want to drag this on but I think, as a matter of point, the question says given the totality of data, please -- not given the signal. It's two different starting places and I don't -- I'll just make that point and stop, but I think it's a -- it is --

DR. LANGE: All right.

DR. RASMUSSEN: They're two completely different starting places and totality of data is what's in the question.

DR. LANGE: Yes, totality of data means both the risk and -- potential risk and proven benefit.

Dr. Gravereaux.

DR. GRAVEREAUX: I just want to echo what Dr. Rasmussen just touched upon and we're thinking the same thing. I think the -- you know, I came in here very curious to hear and I was very comforted to see all the industry and society responses and I'm very comforted by what I feel is a comprehensive experience. The reality, too, is that this is a claudication result we're looking at and we have critical limb patients, which is very different from Dr. LoGerfo's very well-stated, you know, points about life over limb and we don't have be hyper-aggressive in a claudicant. But, you know, for the critical limb ischemic patients, this might make much more of a difference and there the imperative isn't measured in 10 years of life, they're usually more end stage and the acuity and urgency to treat them with something which might have a modest benefit in TLR is very important to

them.

DR. LANGE: So I guess the other thing you heard was looking at the risk of the patient, low-risk patients subjected to any potential increased risk of mortality people aren't comfortable with. Obviously, there's a high-risk patient, either a high risk of not benefiting from revascularization or a high risk of dying, is that the mortality signal is less of an issue. So is there any other clarification the FDA needs?

DR. ZUCKERMAN: No, this has been a very helpful discussion on a challenging topic and I can assure the Panel members that the FDA is required to look at the totality of the data to best put this problem into perspective. Thank you.

DR. LANGE: Okay. And we'll get a little bit more of the application in the next three questions, which I want to cover. So let's go to Question Number 9.

DR. WHATLEY: Question 9 pertains to postmarket studies and surveillance. If you conclude that the totality of the available data shows that the benefits outweigh the risks for paclitaxel-coated devices, but the potential late mortality signal is not fully understood, please discuss whether post-approval studies or postmarket surveillance assessments are recommended. Please discuss the objectives of new postmarket data collections, what information should be collected, study endpoints, and study design. In addition, please comment on the feasibility of conducting new studies of paclitaxel-coated devices in patients with symptomatic SFA/PPA disease. And specifically, maybe mention the possibility of RCTs.

DR. LANGE: Dr. Kip and then Dr. Ballman.

DR. KIP: I'm pessimistic about, I hate to say it, launching a new large clinical trial based on the sample size calculations, all of this high competing risk. By the time you got the answer to that, I think you'd be too far removed. So having said that, my suggestion is, to the extent possible, for the existing randomized controlled trials, all in aggregate, try to

form a consortium or some other effort where they just extended the length of follow-up and equally as important, since our exposure assessment, and I mean exposure to paclitaxel is so variable, let alone prior to the procedure but what happens after the index procedure, that at all costs those existing randomized controlled trials have to try to find that information that what happened to the patient, okay, after their index procedure, did they transition over to paclitaxel, because, quite frankly, 5 years is probably not long enough so, you know, for a longer-term signal. So I just think you have to capitalize on what's in place the best way possible for feasibility.

DR. LANGE: So before we get additional comments, is there anybody that disagrees with that? We'll have additional things that may be complete. Is there anybody that disagrees that we're not going to instruct the FDA and industry to get all the data and as much follow-up information as possible? Okay, it may or may not complete the answer.

I've got Dr. Ballman and I've got Dr. Rasmussen and Dr. Krucoff.

DR. BALLMAN: Yeah, I agree completely with Dr. Kip's comments. I also just want to emphasize that I do not think the registries that are in place or the Medicare data are adequate for assessing sort of the signal long term, just because of all the biases that are in there, and it has been well established that, you know, registry-type things are good for short-term adverse events. They are not good for long-term events, especially events that are related to prognostic factors of the patients to begin with.

DR. LANGE: Drs. Zuckerman, Krucoff, and Rasmussen.

DR. ZUCKERMAN: First of all, I think Dr. Kip's suggestions are excellent clinical trial design points. However, I do want to caution the Panel to put the RCTs that we presently have in the right context. Certainly, the FDA team has been working very diligently with industry to get the best available data. I'm not confident, frankly, right now that even with a continued full-court press we can get to where Dr. Kip wants us to get to and I think the

Panel needs to seriously consider that.

DR. LANGE: In fact, I was going to make that comment. You get all of the data and it shows the same thing, is everybody going to say oh yeah, now it's conclusive or not. So let's address that.

Dr. Ballman, Dr. Krucoff, and Dr. Rasmussen.

DR. BALLMAN: But there are also some ongoing trials right now where you can really intervene and make sure that they know how important it is to get that 5-year data.

DR. ZUCKERMAN: Again, the FDA has limited authority. We need to work as a community, as people have pointed out. The most important slide shown in the industry presentation this morning was the one you were pointing to, Dr. Ballman, but when you look at those trials, most of them have a 1-year endpoint. I am afraid that if the industry doesn't work quickly with FDA and investigators, we will still have the same conundrum.

DR. LANGE: Dr. Krucoff, Rasmussen, Somberg.

DR. KRUCOFF: Okay. Well, I'm definitely on the bandwagon of maximizing whatever it takes and whether it's just the goodwill of an ecosystem that, I think, from every stakeholder we've heard talk in the past 48 hours is interested in improved outcomes for these patients with the lowest possible risk, that the industry -- and the ability of the industry to respond as well. There's a whole wave. We've heard multiple examples of ongoing data being collected in patients who have already been exposed and in clinical trial construct. And I think all efforts at all levels to collect as complete as possible data from those efforts would be the first salvo of what we'd all really like to go home and believe, which is that this is noise, not signal.

And the best effort, the quickest way we have to prove that and whether it's for patient options or whether it's for business revenue, the best way to get fully back online is to maximize the actual evidence that is maturing and whether that's outside or inside of the

FDA's purview to mandate, I think that's really where, as an ecosystem, we can recognize that's the best we have in the most immediate frame.

That being said, I don't personally think if we take a 21st century look at the power calculations that were shared by FDA earlier today, that a 6000-patient study, if it was done collaboratively where the devices -- even though yesterday we said we can't prove this is a class effect or not, but the signals across these trials, to me, would make me very sanguine about saying let's just take all of the available devices, work together and collect data prospectively through registry based means so it's less work for the site, it's faster, it's less expensive, there could be a uniform approach to informed consent. The medical-legal vulnerability goes away. The dialogue with patients becomes the centerpiece and we can continue to collect prospective data. That is not so cumbersome to do.

In 2006-2007 we collected, the industry, and formulated the DAPT study that Dr. Mauri led and reported, to take a class effect concern, safety concern, about drug-eluting stents. The denominator for that is twice what the denominator we're potentially looking for depending, of course, on what risk tolerance we have. So I think there are 21st century ways of going forward collaboratively, using registry based prospective randomization, if that was a best fit that would ease the burden, increase the speed, reduce the cost, even share the cost and whatever device is used, let it be used. International partnerships with groups like the Sweetheart -- you know, people who were already going down this road, I think there's a lot of room to think about making this very reasonable to consider going forward, not just as kind of an ongoing noise and surveillance of a postmarket, but with a prospective structured collaborative approach that reduces cost and reduces time.

DR. LANGE: Dr. Rasmussen.

DR. RASMUSSEN: I would put in a pitch for -- to me, this is the term or the principle

of focused empiricism comes to mind and if you look at Don Berwick and the Institute of Medicine and their proposal of this concept of focused empiricism, which applies to clinical scenarios where there's particular urgency for answers, you have a significant amount of data, but the data is imperfect. You use and implement the data you have at the moment. You continue to use pragmatic and registry-based data in conjunction with RCTs, if you can afford them and have the time for them. And then you implement and iterate based on -- based on new available data.

I think it's something certainly in situations where resources are limited, we don't have endless $50 million RCTs, we don't have -- to perform those, we don't have endless time to wait, we have a rapidly evolving field with different dosage, mechanisms, with different patients; it's very difficult to freeze and be fixed on only an RCT. And I think the concept of registry-based focused empiricism, improving and iterating, is really important and I say that in balance to the RCTs and I know, you know, we -- I think too often in this discussion we've said well, it's got to be the FDA and industry. I mean, we've had tens of thousands of clinicians represented here and highly technical registries now, that they are willing to listen. Many of those registries have outcomes modules. They're going to be better at collecting outcomes data in the registry than we will be and they'll be faster at it than we will be in waiting for RCTs. So it is prone to bias, it is -- and so it's not perfect in itself, but I do put a plug in and try to raise this point for the importance of focused empiricism and registry-based study.

DR. LANGE: Dr. Somberg, then Dr. Zuckerman.

DR. SOMBERG: There are two pathways forward that I see as reasonable. One is, as everyone said, you take all the randomized trials, emphasize randomized controlled trials and you try to improve the dataset, but that will only get you part of the way. I'm a little more optimistic than you are, Dr. Zuckerman, but I think it will get you part of the way, but

that should be in conjunction with the Swedish study because that was one and a half years in and if it is left to complete and continue to enroll, it will have at least, I think, 50% more patients and that will considerably add to the ability to determine if the signal is this or not. It's a randomized controlled trial, they have the Swedish system which permits adequate mortality determination, etc. So I think that's one pathway. And that would bring a result in maybe three, three and a half years.

The other one is how can we start a new study and get to go in three and a half, four years? And the only way that's at all possible is everyone joins together, works with an existing platform, if you will, to initiate and collect the data, but also to have a study with enriched patients. And that's not, per se, higher risk because you have to go back to what Katsanos was saying and that was that maybe you mitigate the mortality signal with the highest people and multiplicity of risk. So you have to go back to figure out what is the way to increase your signal of toxic -- paclitaxel toxicity without increasing the noise signal of enhanced mortality. That could be done, but there's considerable inertia against that.

DR. LANGE: Dr. Zuckerman, a comment or a question?

DR. ZUCKERMAN: The first thing is I am interested in is a response from Dr. Ballman and Dr. Krucoff to Dr. Rasmussen's comments a moment ago. Certainly, Dr. Rasmussen puts the problem in perspective, we have to find practical and efficient ways to move forward to better characterize what we're dealing with. But I think that awhile ago, Dr. Hirshfeld also made an extremely important comment. The FDA and public health agencies around the world cannot just lose sight of the signal we have. So while I do think there's going to need to be a combination of efforts, we can't do a new randomized trial of 40,000 patients.

On the same token, I do think to convince, rightfully so, perhaps people like Drs. Ballman and Krucoff, we need as part of this a new prospective trial where we have the highest quality data. The relative risks that we're trying to rule out doesn't necessarily have

to be 1.1. It can. But I would like their views on also seeing new prospective, high-quality data that complements a fuller total effort.

DR. LANGE: Dr. Ballman.

DR. BALLMAN: I mean, yeah, of course, if we could get sort of high-quality randomized data. And if the intent is just to get a better understanding of what this potential signal for harm is, you wouldn't need to -- it depends upon on what you want to get out of the trial, right, and how much to pay. So, you know, if the intent is just to follow up on the signal and see if it's there, I mean, you just randomize patients and you follow them and you don't do much data collection and that would be relatively cheap. On the other hand, if the intent is to try to understand how subsequent treatments might sort of interplay and so forth and get all that other information, that's going to drive up the cost considerably.

And I don't think the trial has to be quite the size you want. I mean, that's an ideal trial looking at non-inferiority as the endpoint. You know, you could -- you know, if the intent is well, you know, it looks like right now maybe the risk ratio is about 1.4, you know, we just want to rule that out, you could do that with a much smaller trial. So I don't know. I mean, I don't have much more to offer. I still think that there are ongoing randomized trials that the easiest and quickest way to do it is those are already up and running, is just to try to do a push or get buy-in from the community moving forward working as a collaboration to get the data from those trials.

DR. LANGE: Dr. Krucoff.

DR. KRUCOFF: Yeah, I certainly agree. I think, again, to me, the biggest bang for the buck is to try and push current active trials, both in and outside the U.S., to provide data and the randomized trials that have been meticulously analyzed here, to try and emulate the Medtronic approach of closing the gap with missing data. But I think if we're still in a

conundrum, I'm also in the -- I think if we could deal with a 1.3 or 1.4 sort of bottom line, that we're in a zone where it's not 40,000, it's about 6,000, if I remember the chart, and we could even debate about 0.0125 versus 0.05 and get to more manageable. And if it is, again, with multiple devices as a single class effect, that means the actual burden to industry is that denominator divided by five or six or whatever.

I think the biggest bell to ring is that we still discuss things and with registries and with randomized trials, as if they're separate entities, and I think that the lead in this -- in the Sweden group, but we've done this in conjunction with the NCDR in a coronary environment in the United States, where we've heard from the RAPID group and the peripheral space with the VQI as well, that it's poised with common data elements. We have sites that are already putting 100% of our interventions in detail into registry-based case report forms. If you compare those case report forms to the content for pivotal randomized trial submissions to FDA for devices in that same space, 85 to 90% of the data being entered is identical. So why do double service? We can put a prospective randomized design into workflow that already exists.

And then, I think, Dr. Ballman's repeated point, we just have to attach how do you do the long-term follow-up and how much granular information versus just mortality numbers really matter and the incremental burden for what we have to learn, particularly shared across manufacturers, becomes a much more manageable conversation. To me, that's the 21st century, that's what the National Evaluation System for health Technology is designed to pull us into. This is not using lousy registry data retrospectively analyzed. This is not using electronic health data randomly and diversely collected and retrospectively analyzed. It's using existing site-based workflow, high-quality, monitored information that's already in flow in this space to do a prospective randomized trial. That's a different path and it's not an either/or. We're in a position to follow the Swedish model and do both.

DR. LANGE: The last comment, Dr. LoGerfo.

DR. LoGERFO: Yes, I think we've all learned a lot here about the status of surveillance and what happens when we get behind the eight ball. And then we've got a tremendous investment, not just money, people, jobs on the line and it creates an inertia that we shouldn't get into. So it's in everyone's interest to avoid having that happen. So what's worked that I have seen, physicians can't do this, what's worked best with physicians monitoring is to have their work externally verified. For example, one group, the Noonan study group, you had to fund them. A nurse practitioner would come to your hospital, review the operating room output and make sure that everyone is in that database. That sort of thing was a big help.

External review systems, I think we really need to look at them. The one I'm familiar with, VQI, is an example, but there are several and we heard them presented today. They have to be involved in this in some way. But we've got to do better at this so we don't wind up in this situation too late.

DR. LANGE: Let me summarize what I've heard. There's data that's available already and it needs to be cleaned up, that's the randomized controlled trial collected as much data. There are studies that are either just initiated or ongoing and I would push those studies to get the information we need, primarily mortality data is what we're interested in. So long-term follow-up. I've heard the word collaboration from everybody on the Panel and from industry as well, because I don't think anyone wants to tackle this or can tackle it by themselves. So it's incredibly important to do that. We have the Swedish study we can get data from as well. There are studies outside the U.S., but the FDA has to be convinced the data are good so we can include them in the analysis. And I think, at the end of it, you ought to be or I would hope you would be able to look at the totality of number of patients and say what is the absolute number we need to get to the information we want. And if it

requires a smaller randomized controlled trial to get us to that number, then I would urge the FDA to do it with the least minimal -- least amount of information necessary, that's mortality, survival, what -- how their treatment is going and whether they've been revascularized.

And I think what you've heard there is a divergence of opinion about the value of registry data and we can talk about this all day long and you're not going to convince Dr. Ballman and myself that's the information, okay? So by the way, I think that represents the scientific community at large. There are people who are firmly in the registry camp and there are people that firmly say that you cannot get this kind of information. Other information is useful, but it can't answer this question. And so I don't think debating that is going to convince Dr. Rasmussen otherwise or Dr. Ballman otherwise, and so -- but I think that's representative of the scientific community. So if you rest upon that information, there's going to be a large amount of the scientific community that's not going to buy it.

And at the end, what we want is we want an answer and that is, at the end, what we would hope from industry and the FDA is not to come back here 2 years from now or 3 years from now and say it's still in question and we don't know the answer because at that point we would demand a randomized controlled trial of 10 or 20,000 individuals.

So, Dr. Zuckerman, does that address --

DR. ZUCKERMAN: Yes, I think that's a very good summary, but I think I heard something else from Dr. Ballman that really needs to be underlined. We have potentially a very powerful way forward. Certainly, the devil is in the details. For example, we don't know yet what the cooperation will be of the Swedes. Two, there's a device in that trial that's not U.S. approved and we need to consider those factors in. So Dr. Ballman indicated that today we can't -- if we need a new trial, we can't decide whether the relative risk to rule out is 1.2, 1.3, or 1.4. It's putting it all in context, which means that the industry and

FDA have to do a lot of work soon.

So does that summarize your best advice, Dr. Ballman?

DR. BALLMAN: Yes, it does. And also I want to echo in terms of the population that you choose, too, if you're going to move forward with some new data and picking the group that looks like, you know, it's the lower-risk people because there's where the differential is the greatest.

DR. LANGE: I'm not going to debate this anymore and so what I need from the FDA is do you have sufficient information or do you want any additional opinion, from the FDA?

DR. ZUCKERMAN: We have sufficient information to move forward on this challenging problem.

DR. LANGE: All right. Let's go to Question Number 10, involving labeling.

DR. WHATLEY: Based on your conclusions regarding the presence and potential cause of a late mortality signal, please discuss modifications, if any, that should be made to the labeling of all approved paclitaxel-coated devices for PAD, as well as devices being studied in clinical trials, in order to convey appropriate safety information.

DR. LANGE: Dr. Cigarroa and Somberg.

DR. SOMBERG: Can I just ask a quick question? Can I just ask a quick question? What is the current labeling because I haven't looked up the most recent -- does it include the warning material that was in the letter?

DR. ZUCKERMAN: No, it's very nonspecific. To put it bluntly, it says, I believe, there's a warning about paclitaxel use in pregnant patients. So what we're really looking for is how can we update the labeling in a transparent fashion that will be of use to practicing physicians and patients who read the label.

DR. LANGE: Dr. Cigarroa.

DR. CIGARROA: Given that the preponderance of this Panel has recommended

moving forth to study the issue of a late mortality signal, we can have differences of opinion of the use of prospective datasets through registries or randomized clinical trials or use existing new clinical trials to try and answer this. I think that the totality of the FDA Panel believes that there is a signal. We just don't know whether it is secondary to the paclitaxel or not. I think that the labeling must incorporate that sentiment. I can't tell you off the top of my head what the existing exact verbiage is, but labeling that indicates that there may, not that there is, that there may be a late mortality signal should be included.

DR. ZUCKERMAN: There you go, Dr. Cigarroa. We're just interested in high-level ideas. Our general approach is to actually present the data. If I've heard you correctly, you think that the current meta-analysis might be -- should be presented in each label, as well as the data for the particular device, as well as a discussion of the implications of the data from a high-level perspective?

DR. CIGARROA: I think that, from a high-level perspective, the totality of the data should be presented because we can include the CMS datasets, the observational sorts of data, as a countering. So I would say, at a very high level, that there is a potential mortality excess that's been identified late, but I think also included in there are additional datasets that might suggest that's not present. I don't want it to be, in my opinion, a unidirectional, that there is only a singular new dataset that raises a signal, because it has its flaws just like observational does. So I think a balanced approach, the totality should be wordsmithed into a labeling.

DR. LANGE: Dr. Somberg, Kip, and Rasmussen.

DR. SOMBERG: Well, I agree with some of what Dr. Cigarroa just said, but I do not think that the label can be a recapitulation of the Panel discussion. A physician is not going to read it, patients are not going to understand it. So I think you have to say, if you -- if you think there is a signal, the label should say something to the effect, as Dr. Cigarroa said, that

when looking at a meta-analysis that combined all studies with stents and with balloons that carry paclitaxel, there may be a late mortality which must be balanced against an early and sustained benefit in terms of pain on walking and potential loss of circulation to your extremity or to the extremities.

And I think that type of information to a general physician and also an insert that could be distributed to the patient would be helpful, in discussion with the patient, because many times patients can't concentrate when they're talking to the physician, they haven't -- they need notes and they need something to look upon later on. So something simple in layman terms that uses the word "may." But if you're saying okay, there was a meta-analysis that maybe said a signal, but there's this 50,000-patient observational study that sort of vitiates any of the consequences of the meta-analysis, because most people won't understand what causes -- what may give an implication to causality while the other may vitiate that signal. So I warn against being too thorough.

DR. LANGE: Dr. Kip.

DR. KIP: If you focus on the meta-analysis randomized controlled trials, I think you have your work cut out for you in terms of language, that when you use the terminology "may have an increased risk of late mortality," to the extent that the public can digest this, you're going to have to really wordsmith. You need to have relative risk and absolute risk, because if you put relative risk of 40 or 50%, people are going to run for the hills. They have to know the absolute risk. So it's hard to convey it, I realize, but both pieces are necessary.

DR. LANGE: Appreciate it.

Dr. Rasmussen.

DR. RASMUSSEN: Yeah, I just think I would just say that -- and I jotted this down. I don't think that we -- I mean, I think we have -- what we do agree on is that all of these

studies have limitations. I wrote the word flawed. I mean, whether it's the prospective, the RCTs or the meta-analysis, they all have limitations. And what I don't think the Panel should do is get into the business of picking and emphasizing the best of one of those flawed studies. I think, to Dr. Cigarroa's point of somehow conveying the totality of evidence for patients and providers without emphasizing one or the other, trying to distill it down because, you know, I think we're here because of a "signal" in a well-done study, but it has significant limitations.

We have a host of observational and registry studies that also have limitations and flaws. But I'm not sure the Panel can be in the business of picking the best of a flawed study, I mean, and I think the label should not -- should not convey that. We should try to provide as much evidence in a distilled manner, wordsmithed for the patients and providers, not underestimate their ability to make these decisions, and then move forward.

DR. LANGE: The industry, I mean our Industry Rep, Gary Jarvis.

MR. JARVIS: Yeah, just a question for everybody. Is it fair to include data within the labeling for studies that aren't included in the meta-analysis?

DR. LANGE: I'm sorry, one more time.

MR. JARVIS: Well, you know, for the -- you have this meta-analysis, but what about the data on the devices out there that weren't included in the meta-analysis, should those devices be included in the labeling aspect here?

DR. LANGE: Dr. Cigarroa, Dr. Levy.

DR. CIGARROA: So if I remember to early pre-FDA meetings during training, we have been instructed by the federal government to look at the totality of the evidence when making our recommendations to the FDA and I've always interpreted that as information that has been presented and ideally have had some peer review and using all of the information in order to provide guidance to our colleagues at FDA.

DR. LANGE: Dr. Levy, I'm sorry.

DR. LEVY: The same point, peer-reviewed material.

DR. LANGE: Dr. Posner.

DR. POSNER: Yeah, I just had one question. You mentioned the warning on the current label might be for women and one of our oncology presenters said that they are now using it in, I think, the second or third trimester in women safely. And so I --

DR. ZUCKERMAN: Sure, we will review that particular point, but my main point was that there's nothing in the individual device labels about the current dilemma that's been discussed over the last 2 days.

DR. LANGE: We're meeting because of the signal, I mean, of a concern, an honest, well-meaning concern of increased mortality and I think my opinion is that patients need to be informed of it. All right. And presenting all the data we can present and try to get all the data we've had here in a package insert won't be very helpful. And if we weren't concerned about it, that would've ended yesterday and we wouldn't have to inform the patients about it. It's not definitive we're going to get the answers to it, but until then, for a patient to make an informed decision, they need to have that information.

So, Bram, is there any other information you need from the Panel to hear at this particular time?

DR. ZUCKERMAN: No, the FDA has got a lot of good information.

DR. LANGE: And a lot of this around some of the other things we talked about.

Number 11. And I think we've started -- we've talked a little bit about that, but there may be some things we need to round out, so please.

DR. BUCKLEY: So Question 11: Given the limitations in the available studies of paclitaxel-coated devices for PAD, please discuss any study design recommendations to better evaluate these devices. For example:

a. Please comment on whether an assessment of the primary safety endpoint at 12 months is sufficient to ensure the safety of these devices to support PMA approval. If you believe that a longer-term endpoint would be more appropriate, please discuss your recommended primary analysis time point and its feasibility. In addition to mortality, please discuss other clinical events that should be included in primary or secondary safety endpoints.
b. Please comment on how the death adjudication process can be improved to help determine potential causes for late mortality.
c. For ongoing and future IDE studies, please identify what information, if any, should be included in the informed consent document related to the late mortality signal.
d. Please provide recommendations for future clinical IDE studies of paclitaxel-coated devices regarding study design, control population, statistical analysis plan, and efforts to minimize missing data.

DR. LANGE: I'm going to tackle (a) because I think the answer is evident. I'm going to state it and if anybody disagrees, now's the time. I don't think anybody here thinks 12 months is going to give us the answer because the information we're looking at takes longer, at least 3 to 5 years. Is there any disagreement with that?

MR. JARVIS: Well, I think we're talking about -- Gary Jarvis.

I think we're talking about primary -- the primary endpoint and I think the safety comes down to longer-term follow-up, potentially. But I think the primary endpoint, if we're looking at patency or TLR, I still think 12 months is an accurate time frame to look at that.

DR. LANGE: And by the way, I think all of us would agree with that, so -- but I guess what I'm saying is the study shouldn't end at 12 months, it ought to be going longer. But yeah, I agree in terms of TLR and quality of life.

Dr. Cigarroa.

DR. CIGARROA: Sorry, this is Joaquin Cigarroa.

I may be misinterpreting this. As I think about efficacy as a primary endpoint, I think about TLR. As I think about safety, and it's probably because it's influenced by the last 2 days, I'm thinking about mortality, and therefore, I would state that the answer is no and 5 years.

DR. LANGE: So efficacy at 12 months, safety at 5 years. Does anybody else have any other comments?

DR. ZUCKERMAN: So let me clarify the question in simple terms, Dr. Cigarroa. No, it's not clear to the Panel. What we're asking is, for a new PMA device, given what you said, you would wait until we have 5-year safety results for a new paclitaxel drug-eluting stent.

DR. LANGE: Dr. Ballman.

DR. BALLMAN: I guess I wouldn't wait for that for the efficacy thing, but I would have teeth behind getting that long-term safety and not letting sort of, oh, we only got it on like 75% or something like that.

DR. ZUCKERMAN: Okay, so right now our general stratagem is that we have to have 1-year data on all patients with the conditions of approval to go out to 5 years. Would you want the primary PMA cut-point at 2 years or do you think 1 year with good data and more teeth would cut it, Dr. Cigarroa or Dr. Ballman?

DR. LANGE: Dr. Ballman first.

DR. BALLMAN: Yeah. I mean, I think the 1-year, that makes sense to the community. I don't know this disease that well, but it seemed like 1 year was an acceptable sort of benefit-type thing or maybe 2 years, I don't know. But I mean, in terms of the safety, I mean, I know that, you know, in the oncology world where I come from, there is, you know, fast approval. But if the OS signal is not verified, the drug gets pulled. So, you know,

something --

DR. LANGE: Dr. Somberg and Cigarroa.

DR. SOMBERG: One year for approval in terms of efficacy seems reasonable, that's been the standard. I would continue that for paclitaxel devices. Five years follow-up is certainly desirable. At least 3 years. But I would also add a question. This is the only device -- you're not only talking about paclitaxel devices, because I would doubt if anyone else is going to come up with "I'll just stick another drug on the balloon or the stent." So the question is what would you want for a new drug/device combination? And I think if it's outside the paclitaxel family, you might go back to the least burdensome. If it's within the paclitaxel family, you would probably, because of this potential signal, demand more.

DR. LANGE: Dr. Cigarroa.

DR. CIGARROA: So to answer Dr. Zuckerman's question, I would follow under 1 year for efficacy, additional teeth, and attention to the detail of ascertainment of subsequent clinical events with a methodology and an adjudication process that we can feel confident of through 5 years.

DR. LANGE: General agreement? Head nod. One-year approval, 5-year with teeth, like real teeth, like getting the data back, the industry understanding the importance of it so we're not debating this later on because we don't have enough information and it's inclusive, and the FDA really holding their feet to the fire. And I'm not quite sure how we can do that legally but morally, it's imperative. Whether it's legal or not, it's morally imperative.

Dr. Hirshfeld.

DR. HIRSHFELD: This is John Hirshfeld.

Some of us are having a déjà vu all over again moment remembering December 2006 when we had the late stent thrombosis issue and paclitaxel and sirolimus-eluting stents.

That was, again, like this situation and was discovered by independent investigators not in any way affiliated with a regulatory agency, but it turned the industry and the clinical world on its head and at that time, there was a lot of discussion about we need better postmarket surveillance. That was 13 years ago and we're having the same conversation now and I certainly recognize the issues on FDA in terms of their regulatory authority to enforce this, but I think this should be a message to everybody here that this is something that will happen again if we don't close the loop on this process.

DR. LANGE: And I would suggest, having sat on many of these things for about a decade now, nobody coming with a premarketing study were missing 30 to 40% of the data and expect to get it approved. So I don't think people should come with 30 to 40% of the postmarketing study, if that's demanded as part of the approval of the device, I don't think that's acceptable, either. So I think we've beat that dead horse. All right.

Good, Question Number 12. Is there any other -- anything left on Question 11? I didn't realize we had a Question 12.

DR. ZUCKERMAN: Yes, we're talking about other parts of the --

DR. LANGE: Right.

DR. ZUCKERMAN: Yeah.

DR. LANGE: Anything on Question 11 that you'd like? Oh, what should be included in informed consent that's not there. And I think, mortality.

Dr. Rasmussen.

DR. RASMUSSEN: Well, I think we've learned -- if we've learned one thing over the last 2 days and from this study is that we probably are evolving on our understanding of dosing and dosing mechanisms of this drug and this disease condition. And I almost feel like it should -- future studies should really separate out drug-coated balloons from stents and different types of delivery mechanisms. I almost feel like, in looking at this data in the past

2 days, we've been -- it would be like comparing a tablet versus an extended release capsule. We should evolve in 2020 to probably a better definition of how the drug is being delivered in a stent or a balloon or other technology. I would keep that into consideration for future studies.

DR. LANGE: Dr. Kip.

DR. KIP: Really quick. Any new study must place a premium on paclitaxel exposure prior to the index procedure and after the index procedure, so that you know that over the course of time and follow-up, who was exposed and who wasn't.

DR. LANGE: Treatment, as well?

DR. KIP: Pardon?

DR. LANGE: Post-procedure treatment --

DR. KIP: Yes.

DR. LANGE: -- information thought to be important? Good. And the informed consent ability to identify whether the person's alive or dead. That's a part of the procedure.

Anything else in the informed consent?

(No response.)

DR. LANGE: With regard to (b), can death adjudication processes be improved to help determine potential causes? I'll look to Dr. Kip and Dr. Ballman, who have a tremendous amount of experience, and if Dr. Sun wants to speak with regard to oncology as well.

DR. KIP: All I can say is put it in the budget to have a committee, it gets paid for. I mean, it requires work to do adjudication so somehow, some way, I mean it's labor, it's sweat. So I mean that's a punting answer, but it's critical. But it's time consuming and you've got to be able to pay for it.

DR. BALLMAN: I guess I take a different take, I mean. I think, you know, it's important to get whether or not patients are alive or dead. I come from oncology and I've done studies and blinded trials with placebo and 60% of the adverse events are attributed to placebo. So attribution, especially death attribution, I think -- I mean, we saw none of the -- none of the deaths were attributed to drug. And so I mean, I think if you're just looking for a late signal, I don't think I'd spend too much time worrying about cause of death until you see a signal and it may be -- yeah, because it's just too expensive to do that well.

DR. LANGE: Dr. Rasmussen.

DR. RASMUSSEN: A short point of -- just a point of context to keep in mind, though, that this procedure is not intended to extend life. I mean, it's -- if we don't do this procedure. It's different than oncology and I think we forget that every once in a while this procedure is really explicitly done to improve quality of life. Not that mortality is not important, but I don't want it to get lost.

DR. BALLMAN: No, even in oncology we usually do not do cause of death, it's usually all-cause death.

DR. LANGE: And we've talked about (d) in terms of -- a little bit in terms of study design, control population in terms of the different studies available. Do you want additional information from this Panel regarding that?

DR. ZUCKERMAN: Yes.

DR. LANGE: Okay.

DR. ZUCKERMAN: But let's go back to (b) and Dr. Ballman's point. Unfortunately, you know, we have a signal here that remains undetermined. One of the reasons why, and Dr. Buckley can go into more detail, is that the death adjudication uniformly in these FDA trials was poor.

John, you've been associated with many cardiovascular trials adjudication processes. Would you agree with Dr. Ballman or would you say we can improve things, including having an oncologist on these committees?

DR. HIRSHFELD: I think that the question of attribution of cause of death is probably something that's going to be done retrospectively once the tabulation has been made. I think it's probably a lot to ask of a death adjudication committee to try to make attribution with respect to the device or not when it's a death that's 5 years after the exposure. But I think that if you would work in a fashion whereby if you discerned a death signal, then you would have to go back and look at the population of deaths and try to decide where that came from, which is basically what we've done this time and I think we've done as well as could, given the heterogeneity of the causes of death.

DR. LANGE: Dr. Zuckerman, does that -- what additional information can we help you with?

DR. ZUCKERMAN: Well --

DR. LANGE: At this point.

DR. ZUCKERMAN: -- any practical additional suggestions that people may have because the bottom line, as Dr. Ballman points out, is this is very tough, but doing a very thorough analysis at 5 years doesn't get you a lot.

DR. LANGE: And I guess the point I would make is almost all of us, either in cardiology research or vascular research or oncology research, if it's a prospective study and mortality is one of your endpoints, adjudicating that process is not terribly difficult. It just requires money to do it. But I think, retrospectively, I think you're just behind the eight ball and I'm not sure there's -- my personal opinion is I'm not sure there's anything you can do at that point to improve the information you have.

So Dr. Ballman and Dr. Kip.

DR. BALLMAN: Yeah, I was just going to say, I mean, these patients have a lot of comorbidities and if you weren't sort of -- that wasn't your primary endpoint, I mean, someone sort of going back, it could be attributed to any one of these. I mean, someone brought up earlier in the public thing that they should all undergo autopsy and sort of short of that, I don't know what more you're going to find.

DR. ZUCKERMAN: Okay. I think the FDA has gotten good comments. I do think, though, that going forward mortality will be given a higher priority and we'll need to think about how it can be best assessed and adjudicated.

DR. LANGE: And, again, I guess what I would say is that we have a number of studies that we have done in the past in which we've done a good job of identifying it prospectively and getting -- examine in close proximity to the death and having the right committee to do that with the right definitions.

Question Number 12.

DR. BUCKLEY: Question 12, other indications. The data --

DR. ZUCKERMAN: We haven't finished Question 11 --

DR. LANGE: Oh, I'm sorry.

DR. ZUCKERMAN: -- Dr. Lange. And to put it simply, certainly, the FDA impression is, in nutshell, is that the quality of these studies going forward needs to be improved substantially. Comments were made about need for uniform definitions and certainly, FDA would be interested in improving upon the present RAPID definitions, the use of a uniform case report form throughout the industry was very difficult to meta-analyze these trials because different definitions and attributes are being collected, the more uniform agreement on how patients can be ascertained long term. So I think the basic thing that we're looking at in this question is a whole rethink of the clinical trial design and execution in this field, potentially making it more uniform, which should add efficiencies and better

understanding of the data. How would the Panel react?

DR. LANGE: Dr. Ballman.

DR. BALLMAN: Well, I don't know, I think there's lessons that can be learned and it depends upon what each individual agency does. I mean, within oncology, it's come down to common data elements that the whole group sort of agreed upon. Also like for, you know, oncology FDA has come down with there are certain endpoints, there are certain diseases where OS is the primary endpoint and that's it. I mean, I know that's not the case here, but if it's in other -- you know, in early stage diseases, you know, there's a definition of like disease-free survival that the FDA has, you know, approved and so forth before it could be used. So I don't know what to say beyond that.

DR. LANGE: Is there anybody on the Panel that doesn't feel that common data points are -- would be helpful?

DR. RASMUSSEN: I mean, I feel that common data elements would be helpful. And then I have a comment. I sense that Dr. Zuckerman's asking for more information or more help with this question and I guess my comment is that, you know, our observation is we're tasked to be more efficient in the future, both efficient in time, because we can't wait until 2025 for some of these answers or 2030, and efficient with money. So we need to think of new creative ways to do clinical studies in the future.

And one of the things that I can't help but think, as I hear our societies and these registries, not thinking of registries in the past, but is there a way to talk to our societies and these whether it's VQI or other clinical registries, as they look to 2020, that we can work with them to be more efficient in common data elements across the registries? So, you know, we can be again iterating our processes, that's our responsibility. We can't have a registry in 2020 that was as bad as it was in 2010. So how do we and the Agency work and leverage the partnership of these registries in the future to establish common data

elements to make these registries that are available -- moving forward, make them more efficient and amenable to the types of studies and endpoints that you would need?

DR. ZUCKERMAN: I think you just did by underlining the importance. There are two reasons for doing this. One is to lead to better scientific knowledge and understanding. Two, as you point out, it's a more efficient way of doing things if the industry doesn't need to rewrite their case report form or definitions each time. And it's good to hear that oncology is doing this. We have a recent example in the heart failure arena where the Heart Failure Collaboratory had come up with a lean case report form, which is where you're going, and we look forward to doing it in this field.

DR. LANGE: And I guess, Bram, in that respect, the FDA can be a leader. Again, we have a number of different organizations with different databases and to the extent that the FDA can work to develop that common data element so that all registries are collecting the same information in the same way and the information that you get now can be helpful for looking retrospectively at stuff, that would be very helpful.

DR. ZUCKERMAN: There you go, the theme of cooperation among all involved stakeholders is critical here.

DR. LANGE: For the remaining Panel members, I don't think there's anybody that wouldn't want common data elements. I assume the ones that didn't hear, the missing data would also agree with me, by the way.

(Laughter.)

DR. LANGE: My ascertainment bias, by the way. And I'm sorry, I certainly didn't mean to cut this short. Is there other information panel-wise regarding this that you would like? Do you feel like you have enough information of what the Panel feels like?

(Off microphone response.)

DR. LANGE: Let's go to Question 12, then.

DR. BUCKLEY: Question 12, other indications. The data discussed above are relevant to paclitaxel-coated devices used to treat symptomatic SFA and proximal popliteal arterial disease. However, there are some paclitaxel-coated devices approved for other indications (e.g., for the treatment of stenoses in arteriovenous dialysis fistulae), and there are ongoing studies for other indications (e.g., the treatment of critical limb ischemia below the knee). Based on the available data, please comment on whether you believe any of our above recommendations are applicable to paclitaxel-coated devices with other indications for use. Please also discuss whether you believe benefit-risk considerations for these indications are likely to be different than those for SFA and proximal popliteal disease.

DR. LANGE: Dr. Somberg.

DR. SOMBERG: I think that for all indications for paclitaxel-coated devices, except for drug-eluting stents, it should be the considerations with -- talked about previous should be applied. So you're looking at me askance. So in other words, for other places you're going to put a balloon or a stent, you should collect the efficacy data for a year and the safety data for at least 3 and up to 5 years.

And I just want to interject. One other comment is that there's a difference between the intensity of protocol surveillance for a short period of time and then making it into a simple study later on, because I think we have to be concerned about doability of these studies and cost. So we're interested in a mortality signal out to 5 years, but we don't need to collect the totality of the data. That wouldn't do in the first year.

DR. LANGE: Patricia, I saw you shaking your head yes. As the Patient Rep, would you want this information in your package that you're having this procedure done for these other indications?

MS. DAIGLE: Patricia Daigle.

Yes. Yes, I would be wanting to have that information before consenting to any type

of procedure. The more information you have, the more the patient or person, consumer, is able to give a thorough consent.

DR. LANGE: Does anybody feel otherwise? Now, is the time to --

DR. SOMBERG: You got rid of all of the naysayers.

DR. LANGE: The naysayers are gone, that's right. You will outlast them.

(Laughter.)

DR. LANGE: And I guess the second part of that is do you believe that the benefit-risk considerations are likely to be different than for SFA/PPA?

Dr. Levy.

DR. LEVY: Well, I suspect the mechanism of response is going to be different in the dialysis graphs because it's a venous anastomosis that's the most common target.

DR. LANGE: Concerning in that population it would be different. Do other people share that concern?

Dr. Hirshfeld.

DR. HIRSHFELD: I think that it should be a class effect because we think that the effect is due to exposure to paclitaxel and release of paclitaxel. The only difference with arteriovenous fistulas is it's straight into the venous system rather than without going through a capillary bed.

DR. LANGE: Dr. Blankenship.

DR. BLANKENSHIP: Jim Blankenship.

I think it's likely to be different, but I don't think we know how it's going to be different, so we have to check it out anyway.

DR. LANGE: I guess I would say it may be different if we're looking at a 5-year increased mortality and we're looking at a group of individuals on dialysis that are likely to die at 2 or 3 years, or those with chronic limb ischemia that have a 60% mortality at 3 years,

it may be different. And I guess that would be my point. Not because the mechanism is any different, but just because of the longevity and risk of the patient. However, I would agree with Patricia and agree with my colleagues, is that individuals that are receiving this, until we have a final determination, at least should have that information so they can make an informed consent. Even if we need to say it's in a different vascular bed or it's a different indication, I think providing the patient that information is important. And I think the Panel does as well.

Does this address Question 12 for the FDA?

DR. ZUCKERMAN: Yes, I think the comments that you just made, Dr. Lange, are where -- are what the FDA was really looking for. Certainly, the general principles need to be applied to all areas but if we were to take, for example, a very sick dialysis patient population, would we really gain much from follow-up to 5 years as opposed to 3 years? That's where different benefit-risk considerations may be applicable and should be perhaps discussed further between FDA and industry.

DR. LANGE: I would agree. And I would also say there's a number of studies ongoing with critical limb ischemia and I would urge that the information that we know that we need in terms of looking at longer-term mortality and looking at either repeat revascularization or previous use of paclitaxel, is we would have those studies extended now so we can have that information available. It would be nice at the end to say no, there is no increased risk signal in these patients and to be able to pull that off the labeling if we need to. Great.

All right, are there any other comments from the Panel members?

(No response.)

DR. LANGE: Any comments from the FDA about additional ways we can help you?

DR. ZUCKERMAN: This has been an extremely helpful 2-day presentation because

the FDA has gotten a lot of help from this Advisory Panel, especially the people who are still seated here.

(Laughter.)

DR. ZUCKERMAN: And I want to thank them, as well as the participation from industry and academics has been outstanding. We've learned a lot, but there's a lot to do now and we look forward to continued collaboration in this field.

DR. LANGE: Great. And, again, I would like to thank the FDA, and I want to thank the manufacturers for their contributions to yesterday's Panel and today's Panel. And this meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee is now adjourned. Thank you.

(Whereupon, at 3:31 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

June 20, 2019

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

TOM BOWMAN

Official Reporter