FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Cardiovascular and Renal Drugs
Advisory Committee

Prasugrel for Reduction of Cardiovascular Events in Patients with Acute Coronary Syndrome (ACS)

Tuesday, February 3, 2009

8:00 a.m. to 4:00 p.m.

HILTON - WASHINGTON, D.C.
8727 Colesville Road
Silver Spring, Maryland

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Cardiovascular and Renal Drugs Advisory Committee
February 3, 2009

Hilton Washington DC/Silver Spring, Maryland Ballroom
8727 Colesville Road, Silver Spring, Maryland

Agenda

8:00 a.m.	Call to Order Introduction of Committee	**Marvin A. Konstam, M.D.** Acting Chair
	Conflict of Interest Statement	**Elaine Ferguson, M.S.,R.Ph.** Designated Federal Official, CRDAC

The committee will discuss new drug application (NDA) 22-307, prasugrel hydrochloride film coated oral tablets, 5 *milligrams (mg) and* 10 *mg, for the proposed indication for use in acute coronary syndrome.*

8:05 a.m.	FDA Opening Remarks	**Norman Stockbridge, M.D.** Director, Cardiovascular and Renal Drug Products CDER
8:15 a.m.	**Sponsor Presentations** Introduction	**J. Anthony Ware, M.D.** Vice President, Lilly Research Laboratories Diabetes, Cardiovascular, and Acute Care Platform
	Unmet Medical Need	**Eugene Braunwald, M.D.** Hersey Distinguished Professor of Theory and Practice of Medicine, Harvard Medical School Chairman, TIMI Study Group Brigham and Women's Hospital
	Dosing Considerations	**Jeffrey Riesmeyer, M.D.** Medical Fellow, Cardiovascular Medicine Eli Lilly and Company
	Benefit-Risk (TRITON-TIMI 38)	**Elliott M. Antman, M.D**. Professor of Medicine, Harvard Medical School Senior Investigator, TIMI Director of Samuel A. Levine Cardiac Unit Brigham and Women's Hospital
	Special Topics	**William Macias, M.D., Ph.D.** Senior Medical Director, Cardiovascular Acute Care Eli Lilly and Company
	Closing Remarks	**Eugene Braunwald, M.D.**

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9:45 a.m.	Questions to presenters	
10:15 a.m.	**Break**	
10:30 a.m.	**FDA Presentation**	**Ellis F. Unger, M.D**. Deputy Director Division of Cardiovascular and Renal Products Office of Drug Evaluation-I Office of New Drugs CDER, FDA
11:30 a.m.	Questions to presenters	
12:00	**Lunch**	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Discussion of questions to committee	
3:30 p.m.	**Break**	
3:45 p.m.	Discussion of questions to committee (continued)	
5:00 p.m.	Adjourn	

C O N T E N T S

P R O C E E D I N G S

DR. KONSTAM: Welcome, everybody. I'm Mark Konstam from Tufts Medical Center and Tufts University, here to chair this FDA panel meeting on prasugrel. And I think we'll begin by going around the room and asking everybody to introduce themselves. So we'll start at that end.

DR. FOX: My name is Jonathan Fox. I'm the industry representative to the committee. I'm a cardiologist employed by AstraZeneca in clinical development.

DR. UDELSON: My name is James Udelson, from cardiology at Tufts Medical Center in Boston.

DR. DOMANSKI: Mike Domanski. I'm a cardiologist at NHLBI.

MR. FINDLAY: Steve Findlay. I'm from Consumers Union. I'm the consumer representative on the panel.

MS. FERGUSON: Elaine Ferguson. I'm the designated federal official.

DR. NEATON: Jim Neaton, biostatistician from the University of Minnesota.

DR. KRANTZ: (off mic) Mori Krantz, associate professor, University of Colorado.

DR. CANNON: Good morning. I'm Richard Cannon, cardiologist, National, Heart, Lung and Blood Institute.

DR. STOCKBRIDGE: I'm Norman Stockbridge, director of the Division of Cardiovascular and Renal Products at FDA.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs at FDA.

DR. KONSTAM: Okay. Thanks, everybody. So I'll read the following statement.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chair.

We look forward to a productive meeting. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We're aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

A press conference will be held in the Washington Room immediately following the meeting today. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

MS. FERGUSON: The Food and Drug Administration is convening today's meeting of the Cardiovascular and Renal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of industry

representatives, all members and temporary voting members 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 committee compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found in 18 USC 208 and 712 of the Federal Food, Drug and Cosmetics Act is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws under 18 USC 208.

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

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government

employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, the members and temporary voting members of this committee 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 USC 208, their employers.

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

Today's agenda involves a discussion of the new drug application NDA 22-307 Effient prasugrel hydrochloride film coated oral tablets, 5 milligram and 10 milligram, sponsored by Eli Lilly and Company and Daiichi Sankyo, Inc., the U.S. subsidiary of Daiichi Sankyo Company, Ltd., for the proposed treatment of acute coronary syndrome.

This issue is a particular matter involving

specific parties. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Jonathan Fox is serving as the nonvoting industry representative, acting on behalf of the regulated industry.

Dr. Fox's role at this meeting is to represent industry, in general, and not any one particular company. Dr. Fox is employed by AstraZeneca.

We would like to remind members and temporary voting members that if the discussions involve any 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 exclusions will be noted for the record.

FDA encourages all other participants to

advise the committee of any financial relationships that they may have with any firm at issue.

Now, I would like to recognize the FDA press representatives for this meeting, Sandy Walsh and Karen Riley, if either of you are here. Thank you.

I would like to also mention that there is not a formal press conference scheduled after this meeting. However, Karen Riley and Sandy Walsh will provide us direction at the end of the meeting, if there is interest and questions to be answered.

Thank you.

DR. KONSTAM: Okay. I'd like to ask Dr. Stockbridge for the FDA opening remarks.

DR. STOCKBRIDGE: I certainly want to welcome everybody and thank the committee particularly for their coming out to participate in this meeting this morning. I think the issues on which we need some advice from you are reasonably well laid out in the various background documents that you've received and the questions that we've posed for you.

I did want to point out that we are late bringing this to a Cardiovascular and Renal Drugs

Advisory Committee meeting. We are overdue on when we expected to have this application reviewed.

I think I bear most of the responsibility for the tardiness in this. And while it's certainly true that with the Food and Drug Administration Authorization Act, we will be bringing many things to you that we historically would not have, this particular application has some features that certainly merited some discussion here before we took an action.

In the past, a lot of the things that we brought to you, we took pains not to have taken an action prior to your seeing them because we didn't want to bias the committee with respect to the position that we had already taken, and we've certainly not taken an action here. You should also not interpret the delay in our taking an action to represent uncertainty about what we, office director, the division director and review team, think should happen here.

So we are certainly looking forward to the discussions this morning and this afternoon, and thank you again for your participation.

DR. KONSTAM: Okay. Thanks, Norman.

We're going to proceed now with the sponsor's presentation. Before the sponsor's presentation, I'd 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.

Now, I'm going to ask the panel, if they would, to allow the sponsor to go all the way through their entire presentation uninterrupted. I find it's better that way and we'll get through the day easier.

If there's something really burning and problematic about something that one of the speakers presents, you could bring it up; but if at all possible, I'd ask that you refrain until the end and we'll have plenty of time to question the sponsor in entirety at the end.

Dr. Ware?

DR. WARE: Thank you very much, Mr. Chair.

I'm Tony Ware and I lead the cardiovascular, diabetes and acute care programs for Eli Lilly.

On behalf of Daiichi Sankyo and Eli Lilly, I'm here to provide an introduction and an overview for

the sponsor's presentation for prasugrel or, as we are proposing that it be called, Effient.

I'd like to thank the FDA for the vigorous review and the discussions for the preceding months and we look forward to completing the steps necessary to bring this medicine forward to the patients who need it.

In particular, I'd like to thank the advisory committee members. From my days in academic cardiology, I know that to review an application such as this is very time consuming and we really appreciate your sacrifice.

When we began this, we began with this as a proposed indication in mind and this is for acute coronary syndrome, or ACS. This is a specific indication. Prasugrel is indicated for the reduction of cardiovascular events in patients with ACS who are undergoing percutaneous coronary intervention, or PCI. This is for both the patients with unstable angina or the non-ST-segment elevation myocardial infarctions, as well as for the STEMIs.

Effient has been shown to reduce the rate of

a combined endpoint of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke, and to prevent stent thrombosis.

We began this program several years ago in collaboration with our colleagues at the TIMI study group, and, of course, as most of you know, TIMI is a world renowned study group based in the Brigham and Women's Hospital and Harvard Medical School.

We began a program not to find the fastest way for approval or the most conventional or best trod path, but instead one that met the needs that were expressed by the cardiovascular community, and we have brought such a program to you today.

This program is extensive, 13,608 patients in the pivotal clinical trial, TRITON-TIMI 38, and nearly 9,000 patients or people have received at least one dose of prasugrel.

It's relevant to U.S. clinical practice. Unlike many of the large trials that have reported out, nearly one-third of the patients in TRITON-TIMI 38 were from the United States. Most importantly, it provides information that are important to practitioners. It

addresses patients who are critically ill with an unmet need, as Dr. Braunwald will detail for us in just a moment.

It is not -- and this will be an important point throughout the morning -- it is not a placebo controlled trial with a slower bar for approval, but instead it is a head-to-head comparison, a bold trial, with the standard of care clopidogrel, which itself has been shown to be effective when compared to placebo, and it provides meaningful endpoints that I think all of us would agree are important for patients; cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and stent thrombosis.

This entire clinical program was developed in close consultation with the FDA, who concurred with the design and the statistical analysis plan for the TRITON study. The database and adjudication procedures are very high quality and we're very confident in their integrity.

The benefit-risk analyses of our database are compelling. This application was granted a priority review by the FDA. We believe that it should be

approved by the FDA and available for the patients with acute coronary syndrome who are undergoing PCI.

The central hypothesis of the prasugrel research program is something I'd like for you to keep in mind through this morning's discussion, and this is the hypothesis; that is that a new thienopyridine, prasugrel, with a faster, higher and more consistent, that is, with fewer poor responders, any or all of these three characteristics, can produce important clinical benefits for the ACS patient.

We're pleased to have several external consultants with us today. Dr. Eugene Braunwald will follow me to the lectern and he is the chairman of the TIMI study group.

Dr. Elliott Antman was principal investigator for the TRITON-TIMI 38 study and is also with the TIMI group and the Brigham and Women's.

Dr. Jeffrey Barrett, from the University of Pennsylvania and the Children's Hospital of Philadelphia; Dr. Robert Ozols, of the Fox Chase Cancer Center; and, Dr. Philip Schein, of Oxford University.

The agenda is shown here. Dr. Braunwald will

present the unmet medical need in the patients with acute coronary syndromes. Dr. Jeffrey Riesmeyer, of Eli Lilly, will present information on dosing considerations. Dr. Elliott Antman, the principal investigator for TRITON, will present the benefit-risk section and the material on TRITON-TIMI 38. Dr. William Macias of Eli Lilly will present material on special topics. And Dr. Braunwald will provide some brief closing remarks.

I'd like to leave you with the four summary points that I'd like for you to take home from this morning's presentation.

First, that a substantial unmet need exists; secondly, that prasugrel is superior to clopidogrel in preventing cardiovascular events, including stent thrombosis; thirdly, that no credible evidence exists that prasugrel is carcinogenic or promotes a growth of tumors; and, finally, that the benefit-risk profile for prasugrel is favorable and we've developed a plan to effectively manage the risk of bleeding in the appropriate patients.

I'd like to invite Dr. Eugene Braunwald,

chairman of the TIMI study group, to come to the lectern and discuss the unmet medical need.

DR. BRAUNWALD: Good morning. Acute coronary syndromes are responsible for more than one and a half million hospital admissions in the United States each year. As such, this is the most common cause of adults being hospitalized in U.S. hospitals.

Now, acute coronary syndrome is a very heterogeneous population. On the left, you see unstable angina and non-ST elevation myocardial infarction, which actually makes up the majority of the 1.6 million hospital admissions and about a third of them being patients with ST elevation myocardial infarction.

Now, one thing that we have learned repeatedly and I think is beyond question now is that the aggregation of activated platelets play a central role in the development of the syndrome across its broad spectrum.

Usually, in ST elevation myocardial infarction, the platelet-led thrombus is totally occlusive and, in patients with unstable angina non-ST

elevation myocardial infarction, it is usually a subtotal occlusion. But platelets play a central role across the entire spectrum.

Now, the treatment of acute coronary syndrome really began in 1990 with Pierre Theroux in Canada doing a, at that time, large trial, but at this time it would be very small, a couple of hundred patients showing the benefit of aspirin and, shortly thereafter-- showing the benefit of heparin and shortly thereafter, aspirin was observed to be helpful in the TIMI 11 trial, also led by Elliott Antman, which showed that low molecular weight heparin was superior to heparin.

In the middle to late '90s, glycoprotein inhibitors IIb/IIIa receptor antagonists were developed and were found to be useful. In 2001, the CURE trial showed unequivocally that the addition of a second antiplatelet drug, a thienopyridine, added additional benefit.

High dose atorvastatin immediately followed and ACS followed and other antithrombotics, like fundaparinux and bivalirudin, came along.

Now, around the year 2000, critical trials began to show early invasive management, that is, taking the patient to the cath lab and, depending on the anatomy, proceeding with revascularization, usually, percutaneous coronary intervention with stent implantation, occasionally with coronary artery bypass grafting.

So this brings us here, at the end of 2008, into an integrated strategy that involve antithrombotic compounds and an early invasive strategy, and this was the basis of carrying out the TIMI 38 TRITON trial and, also, you'll hear a little bit about the TIMI 44 principle trial.

Now, these two trials were conducted by our group receiving grants to the Brigham and Women's Hospital from the sponsors, Daiichi Sankyo and Eli Lilly.

Now, why look for another thienopyridine? Because the results in CURE were really very impressive, but a number of limitations to clopidogrel have become apparent.

First of all, there is a modest antiplatelet

effect with high inter-patient variability. And as you'll see in a moment, about a third of the patients show no response or a very weak response. There is a delayed onset of action. It takes four to six hours. And in multiple small clinical studies, less a pharmacologic response to clopidogrel may increase the risk of adverse ischemic events.

Now, this is a slide that comes from a paper published by Dr. Paul Gurbel in Circulation and it is a distribution curve of the response to 300 milligrams of clopidogrel, the usual starting dose, and that shows the change in platelet aggregation from before to after.

So these are the most vigorous responses and on this side are the weakest responses. Dr. Gurbel used the term "resistance" and he defined resistance as no more than a 10 percent change in platelet aggregability and recorded from this work that this occurred in 31 percent of patients.

Now, this has been repeated many times and the numbers are more or less the same. They're not exactly the same, but this is a good measure.

Now, I'd like to show you the consequences of inadequate inhibition of platelets, and this comes from a paper -- this is the first paper that showed this by Matetzky, who is an investigator in Israel, carried out a small study, but very meaningful.

He worked on patients who had primary PCI for STEMI, only 60 patients, and he tested the response to adenosine on platelet aggregation and divided these responses into four quartiles of only 15 patients each.

Those that were most resistant showed no difference from baseline with clopidogrel, defined pretty much like Gurbel did, and these are progressively increasing effects of clopidogrel.

Now, on the right-hand side of the slide, you see the clinical outcomes. In this first quartile, where the resistance is highest, there was a 40 percent incidence of death, acute coronary syndrome or stroke, by six months, 6.7 percent -- remember, these are very small numbers -- in the second quartile, but none in the third and fourth, where clopidogrel had a positive response.

So this was the first time that we knew or

surmised that having an inadequate response would be translated into lack of clinical benefits.

This is a very busy slide and I know that you can't decipher it, although it is present in your material. And the reason it's posted like this is to show that by 2007, about a year and a half ago, there were nine trials and Matetzky, the one we just talked on, is at the top, and these move forward chronologically.

These are small trials, but they all showed the same thing, different kinds of measurements and different cuts, but they all showed that increased platelet aggregation resulted in an increase in post primary ischemic events, post PCI ischemic events, more myonecrosis and inflammation marker release. So bad outcomes in patients who had a hypo responsiveness to clopidogrel.

Now, getting back to my assignment, which is to talk about the unmet medical need, here are two trials that reported in 2008, two large trials, the ACUITY trial with bivalirudin, the ISAR REACT 2 trial. And you can see that there were robust numbers and

after one year, almost 19 percent of patients in ACUITY, 25 percent of patients in ISAR REACT 2, had an adverse ischemic event, death, myocardial infarction or the need for target vessel revascularization.

So this slide demonstrates the substrate for continued ischemic events in patients with ACS. So we start out with the patient who is managed with PCI, who then receives dual antiplatelet therapy, and the standard right now is aspirin and clopidogrel.

There are certain high risk features, clinical features, such as diabetes, such as ST elevation, myocardial infarction, such as advanced age, which contribute to continued ischemic events.

But there are also drug issues, and I showed you the inadequacy of clopidogrel in about a third of the population. There are genetic polymorphisms that are responsible, to an extent, for the reduced response. There are drug interactions which exist with clopidogrel. And so all of this factors combined lead to these ischemic events.

Going back to the slide that you saw earlier, here is the situation circa 2008. And what you'll hear

about this morning is the response to prasugrel and the comparison between clopidogrel and prasugrel in the outcome of patients with acute coronary syndrome.

Thank you.

Dr. Riesmeyer is going to continue and describe clinical pharmacology.

DR. RIESMEYER: Thank you, Dr. Braunwald.

Good morning. I'm Jeff Riesmeyer. I'm a cardiologist with Eli Lilly.

As in the Phase 3 TRITON trial, the early clinical development also focused on clopidogrel as the active control for the prasugrel studies.

What we found is that the key difference between prasugrel and clopidogrel is the metabolism. Both drugs are prodrugs. That means they're metabolized in vivo to active metabolites. Once metabolized, these active metabolites irreversibly bind to the P2Y 12 receptor, resulting in inhibiting ADP-induced platelet activation and aggregation, which persists for the life of a platelet.

In vitro, at equimolar concentrations, the active metabolite shows similar levels of platelet

inhibition. The doses of prasugrel used in TRITON, this equimolar concentration is never achieved at the platelet receptor, even with approved or higher doses or clopidogrel and we found that this is due to a more efficient metabolic pathway for prasugrel compared to clopidogrel.

I'd like to share that with you now. This is a schematic showing the metabolic pathway of clopidogrel to its active metabolite. The first thing you notice is that primarily the metabolism occurs in the liver.

Clopidogrel is hydrolyzed, approximately 85 percent of the prodrug is hydrolyzed to an inactive metabolite. The pathway to the active metabolite goes through two oxidative CYP dependent steps, shown here, the first of which is dependent on 2C19 and doesn't involve the higher concentration, the CYP 3A, which is in higher concentration in the liver.

This dependency on 2C19 may explain the recently described findings of the variants, the generic variants and inhibitors of 2C19 affecting both the pharmacodynamics and pharmacokinetics of

clopidogrel.

Prasugrel, on the other hand, is metabolized primarily in the gut. Prasugrel was designed to actually take advantage of hydrolysis, as shown here, instead of the inactive metabolite and intermediate metabolite is formed, which then requires only one oxidative step in the gut and the liver to the active metabolite.

Importantly, this step involves CYP3As, which makes up about 80 percent of the concentration of CYPs in the intestine. This may also explain why prasugrel has not been found to have clinically relevant interactions with CYP2C19 variants or inhibitors.

This difference in concentration is shown on the next slide, where we see both C_{max}, as well as AUC for prasugrel 60 milligrams, are much higher than that of clopidogrel 300 milligrams. Even doubling the dose of clopidogrel to 600 milligrams produces only a marginal increase in the level of active metabolite achieved.

Now, the C_{max} and T_{max} are important because they influence the onset of platelet aggregation, and

this means that for loading dose, this becomes important. The maintenance dose, because the platelets are inhibited at steady-state, this is much less important. What becomes important during loading and maintenance dose is the area under the curve, which influences the extent of platelet activation of inhibition.

This is shown on the next slide, where you see that a 60 milligram loading dose of prasugrel results in this rapid onset of platelet inhibition and achieves a very high extent of platelet inhibition compared to the 300 milligrams of clopidogrel or 600 milligrams of clopidogrel, as seen here.

Now, the 60 milligram loading dose was chosen for a Phase 3 trial, primarily because it achieves maximal level of platelet aggregation, as you see. The 40 milligram dose achieved a lower level of platelet inhibition and this response was somewhat abated by 24 hours.

What this slide shows then is why we chose 10 milligrams for the maintenance dose. This slide shows non-responders on the Y-axis and various doses of

prasugrel and clopidogrel on the X-axis.

What you see is a dose response here, that 5 milligrams of prasugrel resulted in 36 percent non-responders; seven and a half, 21 percent; 10 and 15, zero percent, compared to 45 percent with clopidogrel 75 milligrams.

The 10 milligram dose was chosen over the seven and a half milligram dose because of this difference in non-response and, also in the large Phase 2 trial, JUMBO TIMI 26, a favorable safety profile was noted with the 10 milligram dose.

So we've measured platelet inhibition and concentration at a number of different doses of prasugrel, and that's shown here.

This is an exposure response graph, with increasing levels of the active metabolite on the X-axis and maximal platelet aggregation on the Y-axis, so that a lower level now is associated with more platelet inhibition.

Well, you see this dose response, 5, 10 and 15 milligrams, for both the MPA, as well as the AUC. This relationship then allows us to construct a

mathematical model, a robust, non-linear mathematical model from which we can then predict platelet aggregation based on level of active metabolite. This provides the foundation then for exposure-based dose adjustment in those sub-populations who are identified to have higher exposure to prasugrel.

I'd just summarize briefly then the prasugrel clinical pharmacology program. Prasugrel metabolism is more efficient and less variable than clopidogrel. We found that a 60 milligram loading dose provided more effective platelet inhibition than clopidogrel. A 10 milligram maintenance dose provided superior pharmacodynamic response rate compared to clopidogrel. There is a predictable PK/PD relationship and no clinically relevant impact of drug-drug interactions or genetic variants.

With that, I'd like to thank you and turn it over to Dr. Antman, who will talk about the Phase 3 trial.

DR. ANTMAN: Good morning. Thank you very much. It's my privilege to present the results of the TRITON TIMI 38 study. I'll remind you that TRITON

TIMI 38 was supported by a research grant to the Brigham and Women's Hospital from Daiichi Sankyo and Eli Lilly.

This slide shows the design of the TRITON TIMI 38 study. Patients were candidates for the trial if they had moderate to high risk acute coronary syndrome presentations and for whom there was a plan to perform PCI.

Dr. Braunwald showed you the distribution of the ACS presentations in the United States and the trial mimicked that. We had the majority of individuals having unstable angina and non-ST elevation MI. We did what to have a representation of STEMI in the trial, as well. We capped that at 3,500 patients, which represents 25 percent of the trial. So 75 percent had UA and STEMI and the trial was powered around that form of the ACS spectrum, but we did have 25 percent who came in with STEMI.

All patients received aspirin and then were randomized in a double blind/double dummy fashion to receive prasugrel with the dose regimen that Dr. Riesmeyer just outlined for you and then a

comparison was made to clopidogrel. We had extensive discussions during the planning phase for the trial exactly what the dose regimen of clopidogrel should be.

The majority of practice during the planning phase for this trial was using the approved registered dose of clopidogrel, which is a 300 milligram loading dose and 75 milligram maintenance dose.

This is a dose for which there is extensive regulatory experience and we propose that that would be the regimen that should be the comparator. We also argued that if we used any other regimen of clopidogrel, it would be investigational. And also, if it was higher than this approved registered regimen, could result in higher bleeding and it would be difficult to dissect out any safety signals comparing prasugrel with a higher dose of clopidogrel.

The FDA found this rationale acceptable and we moved forward with the dose of clopidogrel that you see on this slide.

The median duration of therapy was 12 months, minimum of six months and a maximum of 15 months. The endpoint, the primary endpoint, was the composite of

cardiovascular deaths, nonfatal MI and nonfatal stroke. This is a hard series of events that are clinically important for patients and it is the same endpoint that was used in the CURE trial, which evaluated clopidogrel compared to placebo.

The primary endpoint here and the secondary endpoints that are shown here were all pre-specified and along with the statistical analysis plan, was submitted to the FDA and was approved before enrollment began. The safety endpoints are in that list, as well.

We did also have in our trial important sub-studies, such as the pharmacokinetic and genomic sub-studies, which provided critical information that was helpful to us in understanding the results of the trial.

I'm going to move right to the question of the balance of efficacy and safety, and, here, I'm going to present the all ACS population. And in a moment, I'll show you why we feel quite comfortable doing that from a bio-statistical perspective.

Throughout the slides that I'll be presenting to you, you'll have many ways that you can make your

own judgments about the balance of efficacy and safety, because you'll be seeing percentages for the treatment groups, the delta in the number of events, the hazard ratio, and, in some instances, we're also going to put up the number needed to treat or number needed to harm.

So let's look at this slide, which shows the primary endpoint, which occurred in 12.1 percent of clopidogrel patients through the end of the study and was reduced to 9.9 percent with prasugrel. That's a 2.2 percent absolute risk difference, 138 events prevented, 19 percent reduction in the hazard ratio, highly statistically significant, and is associated with a number needed to treat of 46.

This did come at a cost, shown on the bottom, of TIMI major non-CABG bleeds. These occurred in 1.8 percent of clopidogrel patients, 2.4 percent of prasugrel patients. That's in excess of 35 events in the prasugrel group, hazard ratio of 1.32. Here are the confidence intervals. The P value is 0.03, and the number needed to harm is 167. So roughly a relationship of NNH over NNT of about four-to-one.

Now, we are aware that there have been

discussions about the possibility of giving prasugrel for a period of time after the PCI is performed and then switching to clopidogrel. Let's say 30 days would be a time point when one might want to consider that, and I will offer some arguments as to why we do not think that is an advisable approach.

First, by 30 days, there was a highly statistically significant benefit of prasugrel over clopidogrel and that occurred because prasugrel was more effective in dealing with the ischemic events that patients were at risk for when they were treated with clopidogrel and, in a sense, therefore, by 30 days, prasugrel dealt with the hypo responsiveness that Dr. Braunwald outlined in patients who are receiving clopidogrel. It is very important to maintain that early benefit achieved with prasugrel as one moves forward over the course of long-term management.

Now, we have no evidence that it would be an effective way to treat a patient if we were to switch from prasugrel to clopidogrel. As a matter of fact, we do have some evidence from crossover studies that the level of inhibition of platelet aggregation, which is

higher with prasugrel, as you saw, deteriorates when one switches to clopidogrel. And this raises the very real concern that we could see a patient who had been protected at this point with prasugrel, who then switches over to this blue curve for clopidogrel and now has those events, but they're simply delayed in time, because they've switched to a less potent antiplatelet regimen.

This slide identifies the statistical approach to the testing of the endpoints in TRITON. The trial was powered around the UA/NSTEMI cohort and we found a statistically significant reduction in the primary endpoint favoring prasugrel. Conditional on having observed that, we then moved to the all ACS population and also saw a highly significant reduction in the primary endpoint. We then examined the STEMI population and, once again, saw statistical significance favoring prasugrel in that cohort.

We then looked at the array of additional endpoints that are shown on this slide, different composite endpoints or the primary endpoint ascertained at 30 or 90 days. In total, there are 24 comparisons

here. Every single one was significant in favor of prasugrel. The range of the P values are shown at the bottom from 0.023 to a very highly significant value with multiple zeroes to the right of the decimal point.

So we felt extremely confident that we had a robust observation about the benefit of prasugrel compared to clopidogrel across the range of analyses and endpoints that we were looking at.

The TIMI study group also felt that it was important to evaluate separately the benefit of the loading dose and the maintenance dose. To achieve this, we did a landmark analysis at three days. So by three days, we would argue that the events that were observed were, as a result, of the difference in the impact of the loading dose, prasugrel versus clopidogrel. There was a 17 percent reduction in the primary endpoint, which was statistically significant.

Now, the maintenance dose, shown on the right-hand side, showed actually a 20 percent reduction in the primary endpoint and I think, visually, you can appreciate that these curves continue to widen over time, underscoring the benefits of long-term treatment

with prasugrel.

In any trial, it's very important to examine the pattern of response across key pre-specified major subgroups and this slide shows the internal consistency in the trial, where the evidence is lined up here in favor of prasugrel across a range of subgroups, the ACS presentation, patient sex. There was no heterogeneity formally tested here, with formal statistical testing, with respect to age, but I think you can appreciate that there appears to be a gradient in the response to prasugrel compared to clopidogrel as one moves from younger to older age. And we'll have more to say about that in just a few minutes.

Diabetes or no diabetes, same beneficial effect; didn't matter whether the patient received a bare metal stent or drug-eluting stent, whether they did or did not receive a glycoprotein IIb/IIIa inhibitor at the time of PCI, whether they did or did not have impaired renal function.

Not shown on this slide is the statistical testing which showed that there was no significant impact of the aspirin dose used, the timing of the

loading dose of the study drug, or the anticoagulant selected at the time of PCI with respect to the relative benefit of prasugrel versus clopidogrel observed in the trial.

Now, as doctors, we are very interested in preventing all events in our patients with acute coronary syndromes, not just the first event in a composite endpoint. So this is an analysis that you may not have seen very frequently in previous trials. This plot shows, in a Kaplan-Meier fashion, the days from first event to second event or last follow-up for the primary endpoint, in fact, the recurrence of the primary endpoint.

So this is additional nonfatal events that occurred in the patient. You can see these curves widening. There's a significant benefit in favor of prasugrel. The inset on the right shows the distribution of these additional events. There were reductions not only in myocardial infarction, but also in cardiovascular death.

So the tally now moves from the 138 events that were prevented, just the primary endpoint of the

trial, pre-specified, in what I showed you on the first slide, to a clinically important observation, as well. We now have 195 events prevented with prasugrel compared with clopidogrel. And we recognize that we have a composite primary endpoint here. So it is important to evaluate the drivers for this benefit of prasugrel over clopidogrel.

The main driver for the composite endpoint was the 24 percent reduction in nonfatal MI. We did make observations that are particularly of note from a clinical perspective and I'll spend time talking about the nonfatal MIs, as well as, briefly, about stent thrombosis.

This slide summarizes the process for adjudication of myocardial infarctions. Investigators reported suspected MI endpoints on the case report form.

We also, as with most PCI-based trials evaluating treatments to support the PCI procedure, had a database trap or triggers for biomarker elevations indicative of myocyte necrosis. That information, plus the investigator-reported MI endpoints, were fed to a

blinded clinical events committee, who adjudicated the information and made the determination as to whether or not a myocardial infarction had occurred, and that's the 24 percent reduction that I've shown you.

Now, some individuals may be interested in asking what's the impact of the investigator report alone here. We'll call that clinical MIs observed by just the investigator, without this biomarker trigger on top of that. And we see here that, actually, that also was statistically significant in favor of prasugrel. In fact, the hazard ratio there is 0.67, so a 33 percent reduction in MIs when we look just at the clinical MIs that would be reported by the investigators.

I've been discussing the fact that there is evidence in the TRITON TIMI 38 trial of long-term benefit of treatment with prasugrel, and we can see that on this slide, as well, which shows you the Kaplan-Meier curves for myocardial infarction, which do diverge over time, ultimately culminating in that 24 percent reduction favoring prasugrel.

But these are not just peri-procedural

myocardial infarctions. They had a real impact on patients, because, as shown on the bottom of this slide, cardiovascular death after myocardial infarction was significantly reduced. The hazard ratio is 0.58 favoring prasugrel.

I told you that we were interested in comparing the loading dose experience and the maintenance dose experience, and, again, now we see a landmark, this time looking at myocardial infarction. We see the 19 percent reduction in response to the loading dose and a 31 percent reduction during the maintenance dose phase, and that actually is predominantly spontaneous myocardial infarctions, again, underscoring the pattern that we saw for the trial overall and the benefits of long-term treatment with prasugrel. The slides would look virtually identical if we repeated this landmark at 30 days for myocardial infarction.

Now, TRITON TIMI 38 is probably the first trial that used the myocardial infarctions that were observed in the trial to evaluate drugs according to the new universal MI classification scheme, which

divides myocardial infarctions into five types that are shown across the bottom.

We can see here type one, spontaneous myocardial infarctions, significantly reduced with prasugrel; peri-procedural myocardial infarctions, reduced with prasugrel; and, stent thrombosis-related infarcts, also reduced with prasugrel. So the peri-procedural infarcts, which include stent thrombosis, in grand total, that would be a 24 percent reduction, which is highly significant in favor of prasugrel.

Another very important observation in this trial was the impact of prasugrel on the size of myocardial infarctions. This slide depicts the peak biomarker that was used to make the diagnosis of myocardial infarction and here you can see one to less than two times the upper limit of normal all the way up to greater than or equal to 10 times the upper limit of normal.

Two-thirds of the infarcts in this trial were associated with a peak biomarker that was fivefold or greater. So these are large myocardial infarctions

which have clinical consequence to the patient.

In each of these comparisons, you can see that the incidence was lower in the prasugrel treated patients and, in particular, we note the very large absolute risk differences and the statistically significant reductions in the hazard ratio with prasugrel, indicating that it had a profound impact on large infarcts.

Now, this is consistent with the platelet hypothesis that Dr. Ware laid out for you. We would argue that the reduced amount of platelet thrombus burden in the coronary vasculature ultimately led to a smaller zone of myocyte necrosis.

So summarizing here, the impact of prasugrel on myocardial infarction, we observed significant reductions in spontaneous MIs, peri-procedural MIs, stent thrombosis-related infarcts. The number of MIs were reduced by 24 percent, those large MIs were reduced by 26 percent, and cardiovascular death after myocardial infarction was reduced by 42 percent, all of which were statistically significant.

Let's turn our attention to one of the most

feared complications of putting a stent in a patient's coronary artery, which is the development of stent thrombosis. And here, we're reporting the stent thrombosis according to the Academic Research Consortium definite-plus-probable categories.

This occurred in 210 subjects in the trial. They had a very high mortality rate, 25.9 percent, and this was 13-fold higher than the 2.6 percent mortality in those patients who were not adjudicated to have had a stent thrombosis.

Let me indicate to you that the overwhelming majority of stent thrombosis events occurred while the patient was on blinded study drug. So what I'm going to show you on the next slide represents the difference in the benefit of the drugs, not simply that the patient wasn't taking their drug.

We see here striking, clinically important, and statistically significant reductions in stent thrombosis, definite-plus-probable, with prasugrel, whether or not the patient received a drug-eluting stent or a bare metal stent, 64 percent reduction, 48 percent reduction.

In the interest of time, I'm not going to go through the landmark analyses, but we do have evidence of significant reductions in both early and late cases of stent thrombosis.

We also looked at key pre-specified subgroups in our stent thrombosis analysis and I want to call your attention to this one right here, which breaks out the age of our subjects as less than 75 or greater than or equal to 75.

You can see that the risk reduction was very similar both in the young patients and the old patients. There was actually a 1.2 percent absolute risk difference in the young patients, but a 2.6 percent risk difference in the elderly patients, a topic we'll return to when we try and figure out how to weigh the balance of efficacy and safety in elderly patients.

So the impact of prasugrel on stent thrombosis was substantial reductions, approximately 50 percent. It was robust across definitions, patient types, stent types, various subgroups, and it underscores the benefit of long-term treatment with

prasugrel and provides critically important information for clinicians who are managing patients with an acute coronary syndrome.

There are certain key subgroups in this trial who are known to have a high rate of events when they present with an acute coronary syndrome and they are also known to have very aggregable platelets. So it would be of particular interest to examine them and we would anticipate, in that situation, that if we had a more powerful antiplatelet regimen, like prasugrel, we might even see a bigger treatment effect than the trial overall.

That is in fact what we observed. Here is the diabetic subgroup, 3,146 subjects, a very large experience in diabetic patients, who actually had a 30 percent reduction in the primary endpoint with prasugrel. Please note on the bottom that there was no statistically significant difference in the rate of TIMI major non-CABG bleeds.

Here is another subgroup, also a very large experience, 3,500 patients with ST elevation MI, actually had a 21 percent reduction in the primary

endpoint, which was already evident at 30 days. They, too, had no statistically significant difference in the safety comparison here of TIMI major non-CABG bleeds.

Let's turn our attention to more details about bleeding. This is clearly a point that is of considerable interest.

Plotted on this slide are the TIMI major bleeds, on the left, 1.8 percent in the clopidogrel group, 2.4 percent in the prasugrel group, 0.6 percent absolute risk difference. I showed you the hazard ratio earlier and the NNH.

We then look at life-threatening bleeds, which were also higher in the prasugrel group. And we turn here to the infrequent fatal bleeds, but these occurred in .1 percent of clopidogrel patients, .4 percent of prasugrel patients, no difference in intracranial hemorrhage.

Now, I want to call your attention to the information at the top right-hand corner of this slide. Five hundred and eighteen subjects had a prior history of stroke or transient ischemic attack. None of the individuals in that cohort who were allocated to

clopidogrel had an intracranial hemorrhage. Six who were allocated to prasugrel did have an intracranial hemorrhage and that was a statistically significant difference. When we saw this signal, it raised concerns, in our mind, about the possibility of actually not using prasugrel in patients who had a prior history of stroke or transient ischemic attack.

This slide provides more information about the types of major bleeds. Instrumented bleeds were slightly more frequent with prasugrel, but the real driver was the difference in spontaneous bleeds and that was predominantly during the maintenance dose phase, no difference in trauma-related bleeds.

The issue about going to bypass surgery is an important one for consideration as well, and we found the format shown on this slide to be the most helpful way to analyze the information.

What you see on the Y-axis is the number of cases of a TIMI major bleed each day from the last dose of the study drug. And for both prasugrel and clopidogrel, there is a clustering early. So if a patient went to bypass surgery soon after they had

discontinued the study drug, we are more likely to see bleeding than if we waited a substantial period of time.

This was more frequent in the prasugrel patients compared to the clopidogrel patients. It would appear that if we waited at least five days, we would cover most of the risk period with clopidogrel. Since we have higher IPA we're dealing with with prasugrel, it would appear reasonable to wait seven days from discontinuation of the last dose of study drug to performing elective bypass surgery.

Glycoprotein IIb/IIIa inhibitors were used in approximately half the patients in this trial. This is another form of antiplatelet therapy and it has been associated with an increased risk of bleeding, so it's a logical question as to whether or not there is a different experience if we combined a IIb/IIIa inhibitor with prasugrel versus clopidogrel.

Here we see non-CABG TIMI major bleeding through three days, the time that's reasonable for an analysis for IIb/IIIa inhibitors. No difference in the TIMI major bleeds whether the patient received

clopidogrel or prasugrel. So one could elect to use a IIb/IIIa inhibitor if one were using prasugrel without a concern about an increase in the relative bleeding risk.

In the TIMI study group, we considered it important to provide a composite expression of the balance of efficacy and safety, and before database lock, we pre-specified this net benefit endpoint here, which is all cause mortality, MI, stroke and major bleed.

Also shown on this slide are some other composite endpoints that may be of interest for evaluating net benefit. We're going to focus on this one, which was associated with a 13 percent reduction favoring prasugrel. Over time, we can see that these curves culminated in that 13 percent reduction favoring prasugrel and this was statistically significant favoring prasugrel.

The events per 1,000 patients is a common metric that we use for evaluating treatment arms in clinical trials. So this is a ledger of benefit, on the left, and cost, on the right. The vertical line

here divides benefit from cost.

Now, on the left-hand side, I would argue that we have very important serious events which represent either loss of life or irretrievable loss of critical biologic tissue. So if we were to compare the hard events on the left side, it would be important to have a fair comparison on the right-hand side of the cost.

So let's see what we've got. Four fewer cardiovascular deaths that were not related to bleeds, 22 fewer nonfatal MIs, no difference in nonfatal ischemic stroke, at the cost of two more non-CABG fatal bleeds and three more non-CABG TIMI major nonfatal bleeds.

And I would argue at this point that we should stop our comparison on this ledger. Progressive inclusion of less and less severe forms of bleeding could be a misleading comparison when we compare it against these harder events on the left. But nevertheless, we have included, on the right, beyond this dash line, five additional non-CABG TIMI minor bleeds.

We were looking at the net benefit analysis and observed that individuals who had a prior stroke or TIA actually had more events and more bleeds and that ended up with a net benefit that favored clopidogrel and the interaction testing here was significant compared with those who did not have a prior stroke or TIA.

We also looked at age and body weight at the breakpoints that are shown on this slide. Both the elderly patients and the low body weight patients actually tended to have fewer endpoint events with prasugrel compared to clopidogrel, but they had more bleeds, ending up in a neutral net benefit. Those individuals who were younger or who had a higher body weight clearly had a net benefit in favor of prasugrel.

Here is an analysis that comes from observations made in a multivariable logistic regression model, trying to identify those features that would predict a patient's risk of bleeding. So advanced age, body weight, and prior TIA or stroke were all significant predictors.

This shows us the non-CABG TIMI major

bleeding in the prasugrel group after three days, which is when the signal was observed, in the elderly patients, in the front of the row, and the patients who have a body weight difference across the right-hand axis.

Now, clearly, having a younger age and a higher body weight is associated with the lowest risk of bleeding, but I submit to you that if we were to simply say we wish to avoid the use of prasugrel in the elderly or those with low body weight, that does not take into account the benefit that we could offer such patients if we could find a way to deliver the drug more safely.

I already showed you the stent thrombosis breakpoint for age. Here is another comparison. Consider the diabetics who had an absolute risk difference of 4.8 percent overall. The very elderly patients had a small absolute risk difference. But what if we look at the intersect of diabetes and age? That's actually an 8.1 percent absolute risk difference, which is four times what we saw in the trial overall.

So as we looked at this information that I've presented to you, we formulated these considerations for how we might use prasugrel.

Eighty percent of the patients in the trial, in this large piece of the pie, had a significant net clinical benefit with prasugrel and they could receive a maintenance dose of 10 milligrams. We might refer to them as the 10 milligram cohort.

I've already indicated to you that the four percent of subjects who had a prior stroke or TIA, we would wish to avoid prasugrel, just as we might wish to avoid clopidogrel, incidentally, in a patient who had aspirin and had had a prior stroke or TIA.

The question is what about these 16 percent of subjects who have low body weight or are an age greater than 75, and, there, it might be reasonable to consider a reduced maintenance dose guided by the pharmacokinetic type of observations that Dr. Riesmeyer outlined for you.

So as we return to the slide that Dr. Braunwald showed you, through its faster, greater and more consistent inhibition of platelet aggregation,

prasugrel intercepts all the various pathways by which patients who are treated with dual antiplatelet therapy with aspirin and clopidogrel have continued ischemic events and achieve the benefits that are shown on the bottom of this slide, which I've already outlined for you numerically as we went through slide-by-slide.

This does come at a cost. We can see that the cost here is 0.6 percent absolute risk difference in non-CABG TIMI major bleeding. There are certain considerations for potential mitigation of this bleeding risk that might include more radial catheterizations than femoral catheterizations, contraindication in patients who have had a prior TIA or stroke, and a dose reduction in patients over 75 years or who are less than 60 kilograms.

Now, let me close by stepping back and looking at the spectrum of antiplatelet therapy for patients with acute coronary syndromes.

The Antiplatelet Trialists' Collaboration provided a critical piece of information when they demonstrated that there was a 22 percent reduction in ischemic events when aspirin was used compared to

placebo. This was associated with an increase in risk of major bleeds.

A further advance occurred when clopidogrel was added to aspirin, and this comparison, therefore, is clopidogrel versus placebo. That's a 20 percent further reduction in events, with a further increase in the risk of major bleeds.

Now, in this head-to-head comparison with the current standard of care, there's a further 19 percent reduction in events with a further increase in major bleeds.

So a couple of major points to take home at this point. First of all, if we were to draw a line here, we could say that by extension, prasugrel would be anticipated to be superior to placebo.

The second point that I would like to make is really on behalf of the patients with acute coronary syndromes and the clinicians who have to care for them.

I submit to you that the benefit that we observed with prasugrel is a real and significant advance in the management of acute coronary syndrome patients. Let me remind you that when we have an

effective drug, we can find ways to use it even more safely and that is a topic that will be discussed by the next speaker, Dr. Macias, who will also provide information on additional special topics for this application.

DR. MACIAS: Thank you, Dr. Antman.

Good morning. I will review for you a variety of discussions that we have had with the agency as they have reviewed our application. And those topics that we will review are the incidence of neoplasms in the TRITON TIMI 38 trial, the sponsor's recommendation for a reduced maintenance dose in patients that are less than 60 kilograms or over the age of 75 years, the form conversion that occurs during the manufacture and storage of the prasugrel tablet from prasugrel solid to prasugrel base, and the proposed risk management plan.

As reviewed for you in the sponsor's briefing document and in the agency's briefing document, there were more prasugrel patients in the TRITON TIMI 38 that experienced a treatment emergent adverse event that fell under the neoplasm system organ class compared to

clopidogrel.

We've spent a substantial amount of time trying to understand whether this represents a true signal, whether this represents play of chance, but before we go through what our conclusions are and how we got to those conclusions, I just want to remind everybody that the TRITON TIMI 38 trial was not designed to ask nor answer questions related to cancer risk.

The inclusion and exclusion criteria did not exclude patients with cancer. They did not exclude patients with known risk factors for cancer. There was no prospectively collected data other than that collected on routine adverse events for risk factors for cancer, cancer history, recurrence of cancer, new cancers, tumor burden, evidence of metastasis or treatment, and most importantly, there was no protocol defined analytical plan for cancer.

This is the observation. There were 175 prasugrel subjects versus 138 clopidogrel subjects that experienced a treatment emergent adverse event under the neoplasm SOC for a hazard ratio of 1.26 and a

P value of 0.043.

This observation can be further refined in a post hoc analysis to those experiencing a new non-benign neoplasm, as defined by the preferred term in the MedDRA system, the MedDRA coding system. That was 135 patients versus 115 patients, for a relative risk of 1.18 and a P value of 0.21.

The only prospectively defined analysis as it relates to malignancies was malignancy-related death, because that was one of the classifications that the CEC adjudicated death in. And at the end of the randomized follow-up period in TRITON, there were 21 versus 17 deaths in the prasugrel versus clopidogrel group, for a P value of .63.

So beginning with the end in mind, we've spent a lot of time working through these data and the sponsor actually agrees with the FDA's Division of Oncology Drug Products, their advice that they gave to the Cardio and Renal Division that is summarized in the secondary review, and the sponsor believes that there are no data in TRITON to support the concept that prasugrel is a promoter, tumor promoter in humans. The

cancers diagnosed in TRITON are likely incidental and the finding is probably spurious, and no neoplasm analysis based on TRITON can be conclusive, for the reasons that I've already highlighted to you.

So how did we get to that conclusion? We've actually had a lot of discussion with the FDA on this topic. We reviewed the concept of whether the drug could be carcinogenic. We've talked about tumor stimulation. We've had a lot of discussion of whether assessment of bleeding could have led to the detection of tumors since bleeding was more common on the prasugrel treatment group, and, of course, there's always the play of chance.

Within the topic of tumors stimulation, we've looked very carefully at the toxicology data, including additional studies requested by the agency. We also looked to determine whether or not patients with prior cancers did worse as assessed by cancer-related mortality or whether patients with newly diagnosed cancers did worse, again, as assessed by cancer-related mortality, or whether there was any evidence that prolonged exposure to prasugrel was associated with

worse outcomes.

So in the pre-clinical toxicology data, prasugrel was not genotoxic in in vitro and in vivo tests. The two-year toxicology studies in rodents showed no increased development of any malignant cell type. There was an increase in benign hepatocellular adenomas observed in the mouse, but the FDA commented that these tumors are common in mice, most likely related to chronic enzyme induction, and are not considered relevant to human use. Both the sponsor and FDA agree that prasugrel is not a carcinogen.

Given the FDA's concern, we were requested to conduct additional toxicology studies that are specifically designed to test whether or not prasugrel stimulated the growth of tumors. These studies were recently completed. The final study reports were submitted to the agency, although the agency has not had time to formally respond.

These studies indicated that prasugrel did not stimulate growth of lung, colon or prostate tumor cells in culture, and in separate experiments, prasugrel did not stimulate growth of lung, colon or

prostate tumors when implanted in nude mice.

We also looked to see whether or not outcomes for patients who entered the trial with preexisting cancers were worse when treated with prasugrel compared to clopidogrel. This is the hypothesis that underlies erythropoietin, erythropoietin causing worse outcomes in patients with preexisting cancers.

We looked at malignancy deaths and the use of antineoplastic agents as relatively hard endpoints. There were 137 versus 132 clopidogrel patients with preexisting neoplasms and the number of malignancy deaths were quite similar between the two groups as were the use of antineoplastic agents. Antineoplastic agent use was not prospectively collected and we just needed to extract it from the concomitant MedPage.

We've spent a lot of time trying to understand which patients were diagnosed with new cancers, and this was probably the hardest thing that we could do in the entire database because we had no prospective definitions of what was a new cancer and what was a preexisting cancer.

To try to sort through that, the agency asked

us to do extended follow-up on a non-randomized cohort of subjects with a neoplasm adverse event. So we created a new case report form, sent the case report out to the sites after the trial was over and collected data from the investigator on the tumor type, whether the tumor was preexisting or new, the investigator's assessment of benign, malignant or unknown, what prompted the evaluation leading to the diagnosis, and the vital status.

These data were then submitted to the agency. Some of the analyses that you'll see in the review are on this follow-up dataset. However, there was still disagreement as to which cases would be considered a new non-benign neoplasm. So the sponsor met with the FDA to reconcile the database. We came up with a final list of 94 and 80, but we've continued to have some differences of opinion about certain cases and that's predominantly related to the fact that we had no prior prospectively defined method of determining what was preexisting versus what was recurrence or a new cancer.

The analyses I'll show you are based on the reconciled dataset.

The sponsor's analyses also include non-melanotic skin tumors. We've outlined the rationale for this in our briefing document. But briefly, the pre-clinical data do not support exclusion of any tumor type and exclusion of any tumor type was post hoc and subject to bias.

Additionally, the question that we're trying to answer is whether there's evidence for tumor promotion and, therefore, signal detection should look across a wide variety of tumors, particularly since biology of skin cancer is similar to that of other cancers.

This is the incidence of newly diagnosed cancers in the prasugrel group relative to the clopidogrel group, 94 versus 80, for a hazard ratio of 1.17 and a P value of .3. You can see that the lines do separate over time.

This is the outcome for those subjects with newly diagnosed cancers. Now, this is the outcome at the end of the extended follow-up period. So this is collecting outcome data after the trial is over on a cohort of patients defined by a post baseline event

that occurred during the trial, which was the diagnosis of a new non-benign neoplasm.

There were 30 malignancy-related deaths in the prasugrel group, 23 in the clopidogrel group, 32 percent versus 29 percent, for a relative risk of 1.11.

Now, our analyses differ a little bit from the agency's, because we used the at-risk population as those that had new non-benign neoplasms, 94 and 80, where, on occasion the agency will use the randomized or all treated population. And I will give you an example of that analysis because of the importance of this observation.

So this is an analysis now based upon the follow-up dataset. So it's going to be a little bit different than the reconciled dataset, but the numbers are very, very similar. The point is still the same.

In the follow-up dataset, there were 27 malignancy deaths in the prasugrel group versus 19 in the clopidogrel group, for a percentage of .4 versus .28 when looking at all treated subjects, for a relative risk of 1.42. However, in our analyses,

because we are collecting data in only a cohort of patients beyond the end of the randomized period, we only look at the at-risk population as being those subjects who have new non-benign neoplasms, and, here the percentages are 27 and 22.6, for a relative risk of 1.19.

Additionally, we looked to determine whether or not prolonged exposure to prasugrel was associated with a higher incidence of malignancy-related death. The idea behind tumor stimulation is the longer you're exposed to the stimulant, the more tumor growth, the worse the outcome.

However, we saw exactly the opposite when we looked at exposure related to number of malignancy deaths. So for subjects receiving prolonged exposure to prasugrel, there were a similar number of malignancy-related deaths and all of the difference in the observed malignancy-related deaths occurred in those subjects who received relatively short durations of exposure.

So in summing up this whole topic of tumor stimulation, there were similar mortality rates between

treatment groups for patients with prior or newly diagnosed cancers. The observed difference in the number of deaths in patients treated with prasugrel relates to the non-randomized cohort that was defined by a baseline event of new neoplasm and then extended follow-up in that cohort without follow-up of all randomized patients. And there were an unequal number of patients followed up; therefore, an unequal number of events, even though the percentages were similar.

Additionally, prolonged exposure to prasugrel did not worsen outcomes for patients with cancer relative to clopidogrel.

This was a similar conclusion as the Division of Oncology Drug Products came to. There are no data in TRITON TIMI 38 to support a belief that prasugrel is a promoter in humans; same support for that conclusion, short drug exposure to the study drug, no specified follow-up to detect specific cancers, and the cancers are likely to be incidental.

We also spent a lot of time trying to determine whether or not bleeding led to the detection of cancers. And here, what we're asking is whether or

not evaluation of bleeding prompts a diagnosis of cancer or leads to a diagnosis of cancer, and we can discuss whether or not that explains the difference between prasugrel and clopidogrel, but the focus was really whether or not bleeding led to the diagnosis.

This is the incidence of new non-benign neoplasms that I previously showed you. We saw an increase when we did the original analyses and when we analyzed those data, we analyzed them by tumor type. And in the original study report, we had noted that there were more colorectal cancers in the prasugrel group relative to the clopidogrel group and that many of those cancers were diagnosed during the evaluation of bleeding.

So when we designed the case report form that went back to the investigative sites, we asked the investigators, specifically, "Did something lead to the evaluation? Did something prompt the evaluation that led to the diagnosis?" And so for colorectal cancers, we asked the question, "Did anemia or bleeding lead to the diagnosis?"

For 16 of the 19 colorectal cancers diagnosed

in the prasugrel group and eight of the 10 colorectals diagnosed in the clopidogrel group, an evaluation of anemia or bleeding led to that diagnosis. So approximately 80 percent of colorectal cancers are diagnosed during the evaluation of bleeding and without an antecedent bleed or anemia adverse event, the number of colorectal cancers is quite similar.

We then looked to see whether or not colorectal cancers would explain the difference between the two treatment groups, and this is just looking at an analysis now excluding colorectal cancers and you no longer see separation of the curves late.

We also looked to see whether or not this is a chance finding and, obviously, this is a diagnosis of exclusion, but we were provided some data by the agency as to the incidence rate of colorectal cancer in the CURE trial. Here is aspirin versus aspirin-plus-clopidogrel. There were twice as many colorectal cancers in the aspirin-plus-clopidogrel group versus aspirin in CURE. Similar finding in TRITON, double the number of colorectal cancers in aspirin-plus-prasugrel versus aspirin-plus-clopidogrel.

You'll notice that patient exposure was a bit lower in CURE than it was in TRITON and if you index this up to about 6,500 patient years, you would have projected about 22 colorectal cancers in the CURE trial if it had the same duration of exposure or extent of exposure as in the TRITON trial.

So again, as we look across the totality of data, there is no biologic plausibility that prasugrel would be a tumor stimulator. There's no known mechanism of action. The pre-clinical data don't indicate any evidence of carcinogenicity or tumor promotion.

There is a higher incidence of neoplasms in the prasugrel group, but it relates predominantly to a higher incidence of colorectal cancers that are frequently diagnosed during the evaluation of bleeding. And there's no evidence that patients with preexisting cancers or newly diagnosed cancers are at higher risk of death with prasugrel relative to clopidogrel and no evidence that prolonged exposure to prasugrel is associated with a worse outcome.

Nonetheless, none of the analyses in TRITON

can be conclusive and the sponsor plans to prospectively collect additional data in the TRILOGY-ACS study, and we have convened an oncology expert panel to provide guidance on data collection and the analytical plan.

This is the sponsor's recommendation on labeling specific to neoplasms. The information included in labeling should reflect the uncertainty of the observation, should be useful to the prescriber, and should not create unfounded alarm for physicians or patients, and it should not have equal prominence to the risk of bleeding.

Labeling might include a statement that evaluation of GI bleeding should be undertaken because it may unmask previously undiagnosed cancers, comparable to what is included in warfarin labeling. The language would be included in the adverse events section and the information should not be used to restrict the duration of treatment.

So changing gears slightly, I'll review for you the rationale for dose adjustment in patients less than 60 kilos or greater or equal to 75 years. And as

Dr. Antman reviewed for you, the population less than 75 years of age, over 60 kilograms, and without the prior history TIA/stroke had a very favorable benefit-risk profile over time.

This is the efficacy profile over time. And for this population, there was really no difference in the incidence of TIMI major bleeding, at least through 360 days, with a slight splay at the end towards 450 days. So a very favorable benefit-risk program. Prasugrel was well tolerated in this population.

The exclusion of patients with prior TIA and stroke makes perfect biological sense. Dual antiplatelet therapy in patients with prior history of stroke has not been shown to be effective; has been shown to be associated with an increased risk of bleeding.

Age and weight were the two patient-specific characteristics that were retained in the population pharmacokinetic model, indicating that as age increased, exposure increased, and as weight decreased, exposure increased, and the sponsor has noted that exposure was higher in the population over 75 and under

60 kilos of weight.

Now, this is the balance of efficacy and safety in patients that are greater than 75 years of age. In this population of patients, prasugrel was not well tolerated. The discontinuation rate was approximately 32 percent. It was also not well tolerated in clopidogrel, with a discontinuation rate of about 28 percent.

This is the primary efficacy endpoint. We do start out with some benefit, but the benefit is lost and we don't really regain benefit throughout the entire 450-day period. However, we continue to accrue TIMI major bleeds. And as noted in both our review and the agency's review, it's not just that elderly patients have TIMI major bleeds, it's that the sequelae of those bleeds are much more severe.

However, there is evidence that patients over the age of 75 could benefit from prasugrel relative to clopidogrel. These are the data that Dr. Antman showed you in diabetics. This is just the Kaplan-Meier representation of those data.

This is cardiovascular death after a nonfatal

MI; reduction in cardiovascular death if the patient is on prasugrel relative to clopidogrel.

So the sponsor is making a recommendation that the maintenance dose in patients less than 60 kilos and over the age of 75 be reduced to five milligrams. This is because patients less than 60 kilos or over 75 years of age had higher exposure to the prasugrel active metabolite. Increased exposure was associated with increased bleeding during the maintenance phase and a reduction in dose would be estimated to maintain the exposure observed in the general population and reduce the risk of bleeding, and it should also maintain efficacy.

This is just showing us the AUC of the active metabolite for prasugrel 10 milligrams in the population over 75 years of age relative to the general population. So you see it's somewhat higher.

This is the predicted exposure once the dose is reduced to five milligrams. There is still overlap with the 10 milligram dose in the elderly and with the 10 milligram dose in the general population, and we have higher active metabolite exposure than one would

predict for 75 milligrams of clopidogrel.

Similar finding for patients less than 60 kilos. Here is the population receiving 10 relative to the general population. The predicted exposure to the prasugrel active metabolite following dose reduction overlapped with the general population and higher area under the curve compared to what you would expect to see for clopidogrel 75 milligrams.

The sponsor is providing the same recommendation to the agency as it did to the European Medicines Agency, and this is the CHMP recommendation for dosing in patients over 60 kilos and under 75 years of age.

Prasugrel should be administered as a loading dose of 60 milligrams and a once daily maintenance dose of 10 milligrams; however, for patients at special risk, the populations over 75 years of age or under 60 kilos, for that population, a dose reduction is strongly recommended. Following the administration of a loading dose of 60 milligrams, the five milligram once daily maintenance dose is to be given.

So a third topic that we've had a number of

conversations with the agency on is form conversion that occurs during the manufacture and storage of the prasugrel tablet. And just to simplify the story, we've created a little cartoon so everybody can understand exactly what happens.

The prasugrel tablet is manufactured with prasugrel hydrochloride and during manufacture and storage, some conversion to prasugrel base occurs. When the tablet is ingested, the tablet disintegrates into particles of prasugrel base and salt. The particles then dissolve. Prasugrel hydrochloride instantaneously dissociates the prasugrel base and only prasugrel base is absorbed.

So only the base is absorbed and converted to the active metabolite. At low gastric pH, the rate of dissolution, the extent of dissolution and the extent of absorption are unaffected by the base-salt ratio of the tablet. However, at high gastric pH, dissolution is somewhat slowed, but the extent of dissolution and the extent of absorption is, again, unaffected by the base-salt ratio.

The ratio of base to salt does not affect how

much prasugrel is in the tablet, the stability of prasugrel in the tablet, the potency of prasugrel in the tablet, or how much prasugrel the patient absorbs. It simply determines, under conditions of high gastric pH, the rate of absorption of the prasugrel base.

You can see that in pharmacokinetic studies in healthy subjects at normal gastric pH. These subjects are administered tablets of five percent base, 58 percent base, 70 percent base, and this is the active metabolite concentration time curve, showing that the curves completely overlap and they're bioequivalent.

Under conditions of elevated gastric pH, we can see that high base content tablets have somewhat of a reduced C_{max}, although the extent of absorption remains the same. So area under the curve remains the same. And so this reduction in C_{max} would only be appropriate, only important during the loading dose, and we can actually detect that pharmacodynamic effect in patients.

These are data from the TIMI 44 study, which compared a 60 milligram loading dose of prasugrel to a

600 milligram loading dose of clopidogrel in patients undergoing elective coronary stenting, and this figure looks at the maximum platelet aggregation versus time for prasugrel patients who were on a PPI at the time of loading dose or not on a PPI at the time of loading dose. And you can see, for those subjects receiving the PPI, there was less inhibition of platelet aggregation at 30 minutes, but by two hours, there was good inhibition, and at six hours, we were at now maximum platelet inhibition.

Even though there was less platelet inhibition in prasugrel patients being treated with a 60 milligram loading dose on the setting of a PPI, there was still better inhibition at 30 minutes than one would observe with a 600 milligram loading dose of clopidogrel.

We also looked carefully through a variety of analysis in TRITON to make sure there was no influence of base-salt ratio on the efficacy or safety.

This just summarizes the efficacy analyses, showing that through three days, the primary endpoint of cardiovascular death, nonfatal MI, nonfatal stroke,

always favored prasugrel, whether the patient was on a proton pump inhibitor or not on a proton pump inhibitor. So no evidence that efficacy was diminished.

So in summary, the PK/PD profile of the low base content tablets is equivalent to the base content -- the absorption between tablets with low base content and those with base content within the range used in TRITON.

The to-be-marketed tablets will have controlled base content. The dose purity, stability and appearance is not affected by the base content, and the sponsor has recommended the proposed label statement, "During manufacture and storage, partial conversion from salt to base may occur" and then in Section 16.2, under storage and handling, "Dispense product in original container."

Finally, I'll review briefly the risk management plan. This is really the world of risk management. It begins with safety specification, the identified potential unknown risks of prasugrel, and then moves to risk minimization as we attempt to

minimize the risks, to optimize risk-benefit balance, and then a very aggressive pharmacovigilance that provides ongoing assessment of risk that then feeds back into the safety specification and allows us to continually update the safety profile.

The identified risk for prasugrel is bleeding, particularly bleeding in subgroups that are at much increased risk of bleeding, such as patients with a prior history of TIA/stroke, the very elderly, the low body weight, those urgently undergoing CABG, or those receiving concomitant medications that might increase the risk of bleeding. Other events for focused follow-up include neoplasm, TTP, leukopenia, neutropenia, and agranulocytosis, and photosensitivity.

The sponsor's risk management plan includes a very aggressive risk minimization plan, driven by a communications plan to very carefully and extensively provide information to the practicing physicians and health care professionals who will be prescribing and managing patients that will be treated with prasugrel. The content of all the communications will be driven by the safety specification, as determined by the U.S.

package insert. We intend to have a patient medication guide and a variety of health care professional communications.

At the time of launch, we will provide a letter to health care professionals from our safety group. This is not something that we normally do. We will target this letter to a broad coverage -- a broad number of health care professionals and the letter will emphasize the indicated population, contraindications and warning, benefit-risk in subpopulation, and the management of bleeding risks.

We will also provide a prescriber brochure, again, something that we normally don't do, and this will emphasize risk management. And then there will be a very extensive pharmacovigilance plan, which will include an automated signal detection system, aggregated data reviews, and periodic safety reporting, and we are currently planning pharmacoepidemiology studies in the U.S. and in the E.U. And we have a number of ongoing clinical trials through which we'll collect additional information and we are planning observational studies in the U.S.

So I'm going to turn it over to Dr. Braunwald and then I'll come back and we'll take questions.

Thank you.

DR. BRAUNWALD: Well, you have been given an enormous amount of data to distill in a relatively short period of time and I would like to bring you back to where we started 90 minutes ago, with just two slides.

The first deals with the response to thienopyridines. We have to remember that these are prodrugs. They are converted to an active metabolite. That conversion is superior for prasugrel than clopidogrel, and that is shown by the PK studies, the PK sub-studies from TRITON TIMI 38 and other PK studies that the sponsor has undertaken.

So we have a much higher concentration of the active metabolite and that enhances considerably the platelet response. That enhances the pharmacodynamic response.

Then we have seen in this trial that this has also been related to a real clinical benefit. Of course, there is bleeding and it shouldn't be at all

surprising. About a third of the population given clopidogrel shows no response or a very weak response. None of the patients given prasugrel show an absent response or a very weak response. So you bring in a third of the patients with prasugrel that really had no platelet effect with clopidogrel and, lo and behold, as Dr. Antman showed, there is a 30 percent increase in major bleeding. It should come as no surprise.

The final slide are the public health implications and these are approximations and they are based on the U.S. cohort, about almost a third of the patients in TRITON TIMI 38.

So we started out this morning with my telling you there are about 1.6 million ACS admissions per year in the U.S. The data now show that somewhat over 50 percent, perhaps 55 percent, of these patients are treated with percutaneous coronary intervention.

The potential benefits of prasugrel or to replace clopidogrel within the U.S. cohort would be a reduction per year of 23,000 myocardial infarctions. And you heard from Dr. Antman that most of these are large infarcts. There would be a reduction of the need

for urgent target vessel revascularization of 8,600 patients; 7,400 stent thromboses would be prevented; and, 4,000 deaths would be prevented.

There is a cost, of course, that we have talked about and there will be in excess of 2,300 major bleeds, not associated with coronary bypass grafting. And I would say that this is a very, very good tradeoff and, as a physician, would very much like to be able to offer this to my patients.

Thank you.

DR. KONSTAM: Okay. Thanks very much, Dr. Braunwald. And I think we can move right to the questions.

Did you have something else to say at the end?

DR. MACIAS: No. I was just going to answer the questions.

DR. KONSTAM: Okay. Well, I want to thank the presenters for a set of really clear and cogent presentations and, also, for staying on time. So we've got plenty of time for questions.

I'm going to propose that we take the

questions in segments, if possible, beginning with questions to Dr. Ware and Dr. Braunwald, if there are any, and then questions regarding pharmacology to Dr. Riesmeyer, then questions regarding the TRITON study, its clinical implications and risk-benefit to Dr. Antman, and questions to Dr. Macias -- did I say it --

DR. MACIAS: It's both.

DR. KONSTAM: -- you'll answer to anything -- okay -- to Dr. Macias for the special topics; cancer, dosing, form conversion, and risk management.

Now, I've divided it into those segments, but the sponsor can feel free to substitute people if you think you've got better answers.

So if that's okay with everybody, I'd like to sort of proceed in those segments and I'd like to go around the table. So I'd like to start with asking, are there any question specifically related to the material or that you think particularly could be answered by Dr. Ware or Dr. Braunwald?

We'll start with Richard. Can we start at

your end? If you don't have any, that's okay. Don't feel obligated.

DR. CANNON: My questions are for Dr. Antman.

DR. KONSTAM: Okay. Anything over here? Yes, go ahead, Dr. Krantz.

DR. KRANTZ: Just a real quick one for Dr. Braunwald.

When he calculated the 4,000 deaths, does that include the increase in the fatal bleeding deaths?

DR. BRAUNWALD: Yes. That's an absolute number.

DR. WARE: If I could add a follow-up. There was no differential in fatal or life-threatening bleeding in the U.S. cohort between the prasugrel and clopidogrel groups.

DR. KONSTAM: I just wanted to ask Dr. Braunwald, and Dr. Antman could chime in on this, as well, just to put in perspective the types of MIs.

Elliott made the point that there's a reduction in the bigger MIs, as well, but I think it's important, when we get into the absolute risk-benefit, to sort of understand the impact of all the MIs.

I guess not focusing on TRITON, per se, but what can you tell the panel about the implication of troponin elevations, of smaller MIs that are just identified by biomarkers without symptoms perhaps or that set, and maybe if you can also separate between those that are peri-procedural and those that occur later.

DR. ANTMAN: Very important question, Dr. Konstam.

First, I want to point out that in TRITON TIMI 38, there actually was a core lab that was used for the evaluation of CK-MB with respect to the index events, and this was important because we could eliminate the difference in the upper limit of normal as we move from lab to lab to lab to evaluate the magnitude of a biomarker elevation. So all those related events that you saw, the peri-procedural MIs, were really from a core lab following the index procedure.

Now, if we could see the slide that's on the screen, because I think that actually provides important information here.

I did show you the distribution of size of myocardial infarction based upon the biomarker. And let me also point out that the majority of the biomarkers that we're talking about here are CK-MB, so that we're not talking about troponin for most of the cases here. I understand your point about the concern that troponin elevations may represent smaller infarcts. But we've taken care of that, because the majority of this was CK-MB and we also see the fold elevation here.

In specific answer to your question about spontaneous versus peri-procedural infarcts, we see the same pattern that I showed you a few moments ago, where there actually is a reduction in the size of the infarct.

Look here at these very large infarcts, which are spontaneous in nature, greater than 10 times the upper limit of normal. That was reduced with prasugrel as were the peri-procedural infarcts.

DR. KONSTAM: And I guess maybe I wasn't clear about what I was asking, so let me try again.

I get that about the effect across the board.

I guess I just want to hone in on the smaller MIs for a moment, and I think this becomes important, again, in trying to size the impact overall in absolute terms.

So I'm not necessarily asking for information from TRITON, but background information about the subsequent implication of a pure biomarker MI.

Let's take the peri-procedural situation. If I have, let's say, a CPK elevation above a certain lever peri-procedurally, what effect does that have on my natural history? That's the kind of question I'm interested in.

DR. ANTMAN: Okay. So we provided some answer to that already, because cardiovascular death is lower after myocardial infarctions.

We actually do have a slide that I think will be helpful -- I'm sorry -- cardiovascular death was lower with prasugrel compared to clopidogrel.

We do have a slide that shows a Kaplan-Meier for mortality for patients who have had a myocardial infarction or who have not had a myocardial infarction over time, and I think this will be helpful information for you.

It will take just a moment to pull up that slide.

What we are going to show you is the experience in a patient who has had a myocardial infarction compared to a patient who has not had a myocardial infarction and look at their mortality risk over time, under the assumption that they survived the first 30 days. That's the Kaplan-Meier analysis that we're looking for right here.

Just bear with us a second while we get that slide up. It is quite important to answer your question.

I'll tell you that, before we get that slide on the screen, if you track the mortality in a patient who has presented with an acute coronary syndrome but has not had a myocardial infarction, they have a low level, slow accrual of mortality risk throughout the course of this trial, TRITON TIMI 38.

There's a different shape to the curve for morality over time in subjects who have had a myocardial infarction and, actually, it is significantly higher compared to subjects who have not

had a myocardial infarction. The difference is roughly a rate of about 3.8 percent mortality at the end of the study if you've had a myocardial infarction and survived the first 30 days versus something in the range of about one or 1.5 percent -- okay -- so it's 1.7. All right.

So this slide, actually, I think is an important point to answer your question, Dr. Konstam.

So we see here Kaplan-Meier curves. This is actually a landmark analysis after the first 30 days and speaks to the long-term impact of having had initially a nonfatal myocardial infarction and having survived the first 30 days.

This is what happens. There's a slow, inexorable increase in your mortality risk over time to 3.8 percent at the end of the trial and that compares to 1.7 percent in subjects who did not have a myocardial infarction.

So preventing these myocardial infarctions is not only important for preventing the heart failure-related consequences of a myocardial infarction, but a hard event here, which is mortality.

And that's, I think, why we see the cardiovascular death being lower in patients with prasugrel compared to clopidogrel.

DR. KONSTAM: And I don't know whether you have data that speaks to this or not, but if you -- that's exactly the analysis I'm interested in. But if you limited it just to patients who had smaller MIs, just troponin elevations or CPK elevations, is there any data that speaks to that?

DR. ANTMAN: Yes, there is and we did have a slide that actually looked at the type of myocardial infarction based upon whether it was -- yes, we can look at this.

So I think this helps answer your question, as well. So we see the patients who had no myocardial infarction and, here, this one is actually set at time zero. This is not a landmark analysis.

But here are the patients who did not have a myocardial infarction and you're asking whether or not an individual who just had abnormal cardiac biomarkers or who had biomarker elevation and chest pain, or individuals who had cardiac enzyme or biomarker

elevation plus ECG abnormalities and chest pain, I think this is the gradient that you're looking for.

The majority of infarcts that we were talking about were large myocardial infarctions. To get at this, in answer to the questions that have been raised about this, we actually showed you the investigator call for MIs, which actually had a hazard ratio of 0.67. It was actually a bigger treatment effect than the CEC adjudicated MI.

DR. TEMPLE: It's tempting to believe that what you're seeing is increased risk of dying in people who have had an MI and that it has something to do with having had the MI. But isn't there an alternative explanation? We know the best possible predictor of the likelihood of a second MI is having had one in the first place. So maybe that just identifies a high risk population. That really could be.

DR. ANTMAN: You are absolutely correct. We cannot completely disentangle that nor can we talk about perhaps the differences in the baseline characteristics of patients who had a myocardial infarction who are going to put themselves, because of

those baseline characteristics, at higher risk of mortality. We cannot completely distinguish that, but this is a piece of evidence in support of the great importance of reducing infarcts.

DR. PAGANINI: Just a quick question, being the token urinal on the panel here as a nephrologist.

One of the issues that I think I'm very interested in is the absolute higher cortex, which is the renal cortex, and what the effect of having a defective renal function is on drug effectiveness.

We know that there's a combination of CKD and coronary artery disease; the worse the CKD, the worse the contrary artery disease, the higher, the more aggressive.

You've shown in your data creatinine occurrences of greater than 60 and less than 60. In your brief report, not brought out here, you noticed that there was a decay in the metabolite, decrease in the metabolite clearance of about 40 percent in the ESRD patients and in CKD patients, three and four and five.

Is there an effect -- since the bar, the

spray, in slide 46 is rather large for the thrombosis effect, is there an effect in decreasing renal function and longevity of the drug effectiveness over time, and should you be more careful placing folks with lower renal function into the 75 age lighter age group rather than just using the age and weight of people?

DR. ANTMAN: Fortunately, there's another nephrologist in the room, Dr. Macias, and I'd like to turn to him to help answer that question.

DR. MACIAS: This has really bad, because now there are two urinals in the room. Cardio/renal should have some renal, I guess.

Actually, what I'll do, very quickly, because I want to come back to Dr. Paganini's comment -- but I'll ask my colleague, Dr. Lan Ni, to comment very quickly on the pharmacokinetics and pharmacodynamics of prasugrel in patients with impaired renal function.

DR. NI: Lan Ni, in the Clinical PK/PD Group at Lilly.

We have done the clinical pharmacology studies in three types of patients. One is the mild to moderate renal patient, the other one is the ESRD

patient. We did not find any PK or PD changes in the mild to moderate renal impairment patient. But as you stated, we did find the reduced concentration, both C_{max} and AUC, in the ESRD patient. Interestingly, their PD, actually, is not changed in the ESRD patient comparing to the healthy subject.

Just to mention, also, in our TRITON PK subgroup, although the patient population in that particular group is mostly confined in the mild to moderate renal function, but we did not find any correlation of exposure with the serum creatinine.

DR. MACIAS: And then just very quickly, from the safety side of things, you do see an increase in bleeding as creatinine clearance goes down, but when you adjust for age and you adjust for weight, that all goes away.

DR. PAGANINI: Can I just -- I have two follow-ups, Bill.

DR. MACIAS: Certainly.

DR. PAGANINI: The first is what is the percentage of patients that had CKD-4 or 5 in all of your population, including the ESRD patient?

The second is did you see any interaction with erythropoietin or erythroid stimulating agents and the effect of this drug? In other words, was it less effective, more effective? Were there any drug-drug interactions?

DR. MACIAS: Four and five are going to be very rare in the study, very rare, because all of these patients are undergoing PCI with contrast. So a lot of those patients get screened out from the very get-go. So we didn't have very many at all.

I can ask the group to see if they can pull up the less than 30 mils population, if we have that efficacy slide. And we did not look for an interaction with erythropoietin, but we can go back and I can get you that answer, if you're interested in it; not necessarily today, but we'll talk.

DR. KONSTAM: Okay. Unless there are other questions for Dr. Braunwald, I think we're moving into pharmacology. And so maybe we could see specifically if there are any questions that we should address to the pharmacology and specifically to Dr. Riesmeyer or whoever would like to answer it.

Let's start around the table again.

DR. MACIAS: What I'll probably do is field the questions and then --

DR. KONSTAM: That's fine.

DR. MACIAS: -- and then funnel them over to the bullpen.

DR. KONSTAM: That's fine. I meant that segment of the material and anybody who wants to can answer.

Richard?

DR. CANNON: I have a question about the time course of platelet activation inhibition with clopidogrel versus prasugrel, and this is going to get at a question that I'll have specifically for Dr. Antman relating to whether there is a change in the benefit-risk ratio over time that might support consideration of transitioning from prasugrel to clopidogrel.

You touched on this and I want to pursue that, because this is an issue I struggled with and I think the FDA reviewers did as well.

So my question is are there data on the time

course of the relative inhibition of platelet activation, prasugrel versus clopidogrel, say, within 24 hours of the index event, 30 days, 60 days, 90 days and so forth, to support what I think your contention was, Dr. Antman, or refute, that if you were to switch, let's say at day 30, from prasugrel to clopidogrel, you might suddenly jump up to the higher rate of primary endpoint events and, therefore, lose the benefit that was achieved with the initial treatment with prasugrel?

So are there data to support that position or perhaps question that position, related to inhibition of platelet activation?

DR. ANTMAN: Can we see the slides from the principle TIMI 44 study and the ACAPULCO study? I think this will help answer Dr. Cannon's question.

So this slide actually is from the principle TIMI 44 study that was an effort that was chaired by Dr. Stephen Wiviott in the TIMI study group.

What you see here is a comparison of the IPA with prasugrel 60 milligrams compared to clopidogrel 600 milligrams. So this is talking about the onset of the loading dose. So this is a very important point

here.

Not that at 30 minutes, the level of IPA achieved with prasugrel is not achieved until at least about six hours in subjects who received even double the loading dose of clopidogrel.

The next slide actually speaks to the concern about crossover. It's one of many slides I could show you, but the concept is the same. This is from Dr. Montalescot and his colleagues who performed the ACAPULCO study.

What they did here was actually take it one step further and actually give a loading dose of 900 milligrams of clopidogrel and then started a crossover experience in their subjects, and they either initially received clopidogrel 150 milligrams a day -- that's twice the usual maintenance dose -- or 10 milligrams of prasugrel, the maintenance dose we used in the trial.

Now, on the Y-axis is actually plotted maximal platelet aggregation, so a lower number is a better thing in this particular plot.

So when a patient received prasugrel

10 milligrams, their MPA was lower. When they were crossed over, actually, to twice the usual maintenance dose of clopidogrel, their MPA increased. That puts them at risk for thrombotic events again.

That's what I was talking about, about my concern. This is an individual who originally received clopidogrel 150 and then was crossed over to the more potent regimen with prasugrel 10 milligrams and actually had a reduction in MPA.

So at this particular crossover, this one, going from prasugrel then over to clopidogrel, is what I was alluding to when I was concerned about the crossing from the green curve to the blue curve on the main results of the trial.

DR. CANNON: Just to make sure we're comparing apples with apples, I'm not familiar with the ACAPULCO study.

Is this after an acute coronary syndrome, is day 15 --

DR. ANTMAN: Yes. These are patients who had an acute coronary syndrome and they did undergo PCI and there was a two-week period of treatment with the first

drug given during the crossover, and then there was a crossover. At the end of another two weeks, you see the platelet aggregation information.

DR. CANNON: Were there any data beyond day 29 to show such a dramatic effect of crossing over from one to the other?

I guess my point is, is it possible that the further out you are from the index event, the less activated the platelets are and, therefore, the less need to have a more potent platelet inhibitor?

That's really the point and I think that figures into this whole discussion about whether the benefit-risk ratio changes over time such that whether it's 30 days or 60 days, or some time after the index event, it would be defensible to switch over from prasugrel to clopidogrel to try to spare some bleeds, but yet not lose benefit.

DR. ANTMAN: I'm not aware of any data that have looked at a crossover much later than what we see here, this two-week experience followed by another two-week experience. So you're asking something at 30 days or six months or something of that nature. I'm

not aware of data on a crossover done that late, but I know there are repeated observations very much like the ones on this slide. We have some from the principle TIMI 44 study for crossover, as well.

DR. KONSTAM: Michael?

DR. DOMANSKI: For Elliott Antman.

Elliott, I guess the concern that I have in this discussion is that one could try to reason from first principles that a crossover is or isn't reasonable. But what I'm concerned about is that would represent a fairly dramatic -- at least you help me out. If I'm wrong about this, tell me. It seems to me it represents a substantial change in strategy to do that, I mean, a dramatic change in strategy. And I wonder if there is any reasonable clinical endpoint data to suggest that that strategy works.

DR. ANTMAN: I'm not aware of any.

DR. DOMANSKI: Thank you. Okay.

DR. ANTMAN: Can we return to the main slide showing the balance of efficacy and safety? Because I think Dr. Domanski has really hit this on the head.

So let's just go back to that main slide of

the balance of efficacy and safety. And I did emphasize that --

So what you're referring to is that we have absolutely no evidence that it would be an effective way to treat a patient if we were to switch from prasugrel to clopidogrel.

I'll remind you of the crossover data, which does at least raise a very serious concern about the possibility that we would lose the benefit that had accrued over 30 days. We'd see the patients begin to switch over to this blue curve and all we would have accomplished then would be put those patients at risk of those events that were prevented by prasugrel, but put them at risk a little bit later.

DR. DOMANSKI: So one might conclude that it's an untested strategy.

DR. ANTMAN: It is an untested strategy and I personally would not recommend it.

DR. KONSTAM: So, Elliott, let me pick up on this a little bit more. So your point is well taken. We're sort of in uncharted territory from clinical trial data. So that's pretty clear.

But there are people who, and I'll just say suggested that if you look at the risk-benefit over time, that there might be at least a rationale for, at some point, in certain populations, say, okay, it might be reasonable to down-titrate the antiplatelet effect vis-a-vis the risk-benefit ratio. That's the question, I think.

So I guess it's not surprising, although you showed the 150 milligram switch, which is new information, but I guess it's not surprising that if you were to switch, you would down-titrate the antiplatelet effect across the population.

I guess maybe you could expand on this a little bit, because if you look at the ST elevation MI population, for example, and these are sort of two different populations, it looks like you do sort of have a flattening of the curve in terms of the difference. If you look at the unstable angina non-STEMI population, it's widening, although, interestingly, there seems to be no demonstrable effect on cardiovascular --

DR. ANTMAN: While you're speaking, can I

just ask the group? I think you're referring to a slide that Dr. Unger is going to be showing and it is in his briefing book, if we could just pull that up in the meantime.

DR. KONSTAM: That's right. Well, you know what? This is too long a preamble. I guess the question is it's not so much a matter of the pharmacodynamics. The question is is there some rationale for down-titrating the antiplatelet effect at some point in time.

DR. ANTMAN: Okay. I don't see a rationale for doing that and let me answer that by looking at this information. We found this of considerable interest.

We're going to need to see that slide again, please. Okay.

So you will, I believe, see this information from the discussion by Dr. Unger. And what is plotted here is the delta in the primary endpoint, expressing the difference in the development of a primary endpoint event with prasugrel versus clopidogrel. So positive numbers show benefit of prasugrel.

Here we see the unstable angina and STEMI cohort in the trial, 75 percent of the trial. And notice that there is a continuous rise in this delta in events, suggesting that there is ongoing and accruing progressive benefit over time.

What we see here in the STEMI population is a profound treatment effect early, which is then maintained. And I will remind you of my concern about an untested strategy of crossing over to a less potent platelet regimen, which could lose the benefits that we observed here.

Dr. Braunwald?

DR. BRAUNWALD: I have one additional point to get us back to basics.

In all of this, we're looking at groups of patients and we're looking in millions and millions. I think that if you switched to 30 days or 180 days from prasugrel to clopidogrel, you would expose one-third of the population to a very, very weak antiplatelet effect.

DR. NEATON: Related to this question, I think I -- if you had a slide, I'm sorry, I missed it.

Do you have the landmark analysis of 30 days for major bleeding events?

DR. ANTMAN: We do have that. So this would be a landmark analysis in the TIMI set of backup sides. So this would be TIMI major bleeds with a landmark at 30 days.

DR. NEATON: I guess I think that's probably the most relevant piece of data to this discussion.

DR. ANTMAN: Right. Well, it is, but with your permission, I'd like to actually follow it with another slide, which is the Kaplan-Meier curve of the long-term impact of having had a major bleed.

Right. So this is a 30-day landmark showing the difference between prasugrel and clopidogrel, and this makes no adjustment, of course, for that maintenance dose of 10 milligrams, because that wasn't tested in this trial. And, yes, you see that over time there is progressive widening of these curves, indicating that the signal of concern is during the maintenance phase and that's very much why the attention was turned to possible reduction in the maintenance dose and not doing anything to the loading

dose, of course. And so what you see here is this separation of curves.

Now, what I'd like to show you on this next slide, similar to what we looked at for the long-term impact of the myocardial infarction, and it's a very different pattern here, what we see is the high risk period after a major bleed will acknowledge perhaps, the first 30 days.

Now, the question is what's the long-term impact of having had a major bleed, and I think that you can appreciate that it would be a little bit difficult to draw a biological link between a bleeding event in the first 30 days and a death that might occur at, let us say, 450 days.

This curve actually helps us with that, because we can see that at the end of 450 days, comparing those patients who did not have a major bleed with those who did have a major bleed, there is no statistically significant difference in terms of mortality.

Now, this slide actually puts both of these pieces of information together, the Kaplan-Meier

landmark that I showed you a moment ago for myocardial infarction. That's on the right. Notice that it's a progressive widening here, ultimately ending in this difference, which is statistically significant, acknowledging all the points that Dr. Temple raised about how we can interpret this information and compare that to what we have over here.

So I see a long-term impact of the myocardial infarction. I do not see the long-term impact, in terms of mortality risk, of having had a major bleed. I certainly would not wish for any patient to have a major bleed, but I think the consequences of the myocardial infarction are greater to the patient than the consequences of the major bleed.

DR. NEATON: But this is a major bleed in the first 30 days.

DR. ANTMAN: It's a landmark analysis asking what the mortality is --

DR. NEATON: Following the major bleed.

DR. ANTMAN: -- 30 days following the major bleed.

DR. NEATON: Right. I guess I was speaking more in terms of the risk of a major bleed following 30 days.

DR. ANTMAN: That's what I showed you on --

DR. NEATON: Exactly.

DR. ANTMAN: And so that one was a comparison of prasugrel versus clopidogrel.

DR. NEATON: Right. And so one might presume that the subsequent risk of death following those bleeds would be similar.

DR. ANTMAN: Yes, if we argue from the landmark analysis, on the left side of this slide. Right.

Let me just say, speaking as a clinician, how I would interpret the left-hand portion of this slide. Dr. Macias showed you that the individuals who were found to have colorectal cancers probably were identified more frequently in prasugrel because there were more major bleeds in those patients.

So it is my hypothesis that having identified a patient who has malignancy as a consequence of having found that from the major bleed that they experienced,

more frequently on the more potent antiplatelet drug, is actually more likely to die from that cancer, but not as a consequence of that bleed itself.

DR. KONSTAM: Let me go to Dr. Udelson and then Dr. Domanski.

DR. UDELSON: A question for Elliott.

You made the case about diabetics. You made the point, Elliott, about the diabetics, particularly those over age 75, having a fairly significant efficacy benefit. But on the other hand, Dr. Macias made the case of lowering the dose in those patients.

Do you worry about loss of efficacy when you start doing dose adjustments in subgroups that may benefit?

DR. ANTMAN: Right. As a clinician, I do not, because I saw that relationship between AUC and MPA. And I'd like to have Dr. Macias and anybody else that he recommends discuss this relationship between AUC and MPA, because it's very relevant to your question.

DR. MACIAS: Could I see, very quickly the -- start with the AUC for -- let's go to the

75-year-olds first, and then I'd like to see against the EM RM for me, please.

So this is what we explained to you during the core presentation, and I apologize for going so quickly.

But what we're recommending is a dose reduction from the 10 milligram in the elderly to the five milligram in the elderly. And we do see overlap of the exposure to the general population and to the 10 milligrams in the elderly and higher concentration of the active metabolite than to clopidogrel. However, the important point is the inhibition of platelet aggregation.

So here is the inhibition of platelet aggregation and the 10 milligram tablet. Here is inhibition of platelet aggregation once we moved to five milligrams, and there is substantial overlap. So the dosage estimate is based not only on the exposure, but on the exposure-pharmacodynamic relationship, such that we maintain good inhibition of platelet aggregation.

Then to make sure that we were effective, we

split the clopidogrel population into extensive metabolizers of clopidogrel and reduced metabolizers of clopidogrel, and then we can demonstrate that five milligrams in the very elderly population has the same maximum platelet aggregation as good metabolizers of clopidogrel. And then if we look to see how good metabolizers of clopidogrel do relative to core metabolizers of clopidogrel in the population over 75, then we can assure ourselves that we can maintain efficacy.

So this is the population -- or at least we can strongly support an opinion that we would maintain efficacy. This is cardiovascular death, nonfatal MI or nonfatal stroke for the extensive metabolizers of clopidogrel, and this is the endpoint for reduced metabolizers of clopidogrel with a hazard ratio of about two.

So what these data tell you is that you have to have an exposure – a level of platelet inhibition that you would get as in extensive metabolizers of clopidogrel, and as long as we can maintain that level of inhibition of platelet aggregation, we should be

able to maintain efficacy, although it is all based upon PK/PD modeling.

DR. KONSTAM: Well, I just want to follow up, because a moment ago, Dr. Antman, in reference to the question about switching to clopidogrel, made the really cogent observation that there are no clinical data to support that or what the clinical impact would be. So now I think you're moving into defending using a lower dose in select populations based on PD information.

So I guess I'd sort of ask you, in reference to the comment that Elliott made on a different topic, do you actually have any clinical data to support what the efficacy effects or the risk-benefit ratio would be of actually doing this?

DR. MACIAS: Again, the recommendation for the five milligram would be based upon pharmacokinetic/pharmacodynamic modeling, and I'll ask Dr. Barrett to make a comment about the appropriateness of making dose adjustments based upon PK/PD modeling, because it is based on modeling, just like we would for pediatric patients or renal patients or hepatic failure

patients.

DR. BARRETT: Jeff Barrett, the University of Pennsylvania and Children's Hospital Philadelphia.

It's quite common to link together the clinical -- the pharmacokinetic and pharmacodynamic experience across the continuum of a drug development program and, certainly, the FDA has supported this practice from sponsors for a long time now. And, in fact, there's a lot of regulatory precedence for, in fact, recommending doses not studied in the pivotal trials on the strength of these kinds of relationships. That's been the case for gabapentin and for Enbrel, as well.

In the case of prasugrel, you do have the benefit of actual PK/PD studies with the five milligram tablet, and there's been seven studies in about 205 healthy volunteers and patients, and this spans across different ethnic groups, as well as normal and impaired renal function patients. So there is quite a bit of data to extend that relationship.

So if we take a look then at the continuum, as Dr. Macias mentioned, there is an underlying

pharmacokinetic/pharmacodynamic relationship that is well defined and the sponsor has gone through a lot of rigor in constructing a model that has been rigorously validated.

The strength of this, though, is that you can make these predictions with high fidelity. So the continuum of when one looks at all of the doses across this -- you saw this earlier in the clinical pharmacology presentation; when you look at maximum platelet aggregation as a function of exposure. The utility of the modeling, though, is that you can identify these at risk sub-populations within this relationship and pull out what would happen if we took the observed, in this case, under 60 kilogram patients, and adjusted them; this is a 10 milligram dose and you took a look at how that shift would behave, both in terms of the kinetics and dynamics in this relationship.

So you see you are able to affect the kinetics, but with minimal effect on the pharmacodynamic side. And you can portray that, also, if you take a look at the elderly patients as well. In

this case, we're looking at the observed greater than 75 years of age patients here receiving 10 milligrams and then what would happen if we gave a five milligram dose adjustment. So, in fact, there is data to support these recommendations.

DR. KONSTAM: Well, I'm going to ask Elliott this question.

So if you had a population that you felt should be exposed to a lower antiplatelet effect, for whatever reason, because it's a particular population at risk or whatever, would you rather give a lower dose of prasugrel that really hasn't been tested clinically or would you might consider using clopidogrel, where at least there's extensive clinical trial evidence to suggest what the clinical impact would be?

DR. ANTMAN: I would give prasugrel and I'll explain why.

Dr. Braunwald has been mentioning the large proportion and concerning portion of individuals who are non-responders or hypo-responders to clopidogrel. So I would have no way of knowing a priori, if I were to take a so-called higher risk individual and give

them clopidogrel, whether or not they would simply fall into that category where I effectively had given them no meaningful antiplatelet activity.

So I would prefer to give prasugrel, because I at least have a body of information that makes biologic sense to me. This PK/PD relationship makes sense to me and I would say that I would wish to find a way to offer the elderly patient and the low body weight patient some protection against these ischemic events. And if this could be done using this modeling from PK/PD, I would move in that direction.

Marv, let me actually make one other point that hasn't been brought out yet, and I was reminded of it when we were looking at the reduced metabolizers and extensive metabolizer concept here.

Please remember that you can take an individual who is an extensive metabolizer to clopidogrel and turn them into a reduced metabolizer of clopidogrel by giving them certain drugs for which there is an interaction. For example, an azole antifungal will convert that extensive metabolizer in clopidogrel to a poor metabolizer. That is not seen

with prasugrel. So that's an additional argument that buttresses my decision in response to your question.

DR. KONSTAM: Okay. Mike?

DR. DOMANSKI: I had wanted to force an explanation of why you'd recommend the lower dose in the absence of clinical endpoints, and the question is asked and answered.

DR. KONSTAM: I'm sorry. I was distracted.

DR. DOMANSKI: You asked my question and they answered it.

DR. KONSTAM: Okay.

Dr. Flack?

DR. FLACK: I have a question related to the age and weight cut points and, clearly, they appear to stratify patients. But what evidence do you have that they're really optimal, a cut point of 60 kilos versus 50 versus 54 or 70 versus 80 versus the 75 chosen?

Is there any sensitivity analyses or anything that you can point to that gives you confidence that these are really the optimal cut points to balance efficacy and safety? And as a follow-up, are you missing an opportunity to really individualize the

recommendations for dosing by combining weight and age in an individualized algorithm as opposed to just using blanket categories, which is really not individualized medicine?

DR. MACIAS: It's an absolutely excellent question. We had a lot of discussion about whether what we're seeing here is the interaction between low body weight patients and the very elderly. So it was the small, old person who is bleeding. And that explains a lot of the TIMI major bleeding, but it doesn't explain the worse outcomes associated with those bleedings.

So all of the fatal bleeding that we see in the population over 75, we have nine spontaneous fatal hemorrhages compared to none in the clopidogrel group. None of that is explained by low body weight. So just going to the low body weight is not going to solve the problem. We might get less TIMI major bleeds, but the sequelae is what we're actually worried about.

I showed you here just the cut points for weight and this is what we set up to do. We've had some discussion about whether we should be a little

more pragmatic here and this should be 60 and below and 65 and below, but this was the cut point for weight.

We see a similar pattern as we move, by bars, up age. When you get to 75-year-olds, it starts to take off. I'll bring this up. And if I had the bar graph for 80-year-olds on this one, it really takes off.

But the way we actually found the weight/age issue with bleeding was actually kind of independently. The TIMI group did their analysis with net benefit-risk, came up with the fact that these populations didn't appear to be benefitting.

We actually approached it from two different ways. One is we had the pharmacokinetic data telling us that age and weight were retained in the population pharmacokinetic model. So that focused us looking at low body weights and the elderly and we saw more bleeding.

Then we did the analyses I just showed you, and then we did the multivariable model. And these, interestingly enough, were the three patient-specific parameters that stayed in the multivariable model that

were predictive of TIMI major bleeding in the prasugrel population, and it was weight, age, and prior TIA/stroke.

And when you actually look at them, this is exactly what you see when you're looking at the univariates. So maybe it's 55, maybe it's 60, maybe it's 75, maybe it's 80. It's pretty close. It's going to be right in that ballpark. And we can't do a nomogram of the intersection between weight and age. I think Dr. Antman showed you that in his little four-bar graph, that old people that are heavy still bleed more; young people that are old really bleed -- excuse me -- young people that are -- that's good.

Could you fix that for me?

DR. KONSTAM: Okay. Dr. Cannon?

DR. MACIAS: You got my message.

DR. CANNON: Another question for Dr. Antman.

Elliott, I know the compliance overall was very good in this study, but there were some people who stopped therapy or maybe the doctors stopped the therapy because of bleeding.

Is there any evidence that there is increased

risk of a subsequent cardiac event if you stop prasugrel versus stopping clopidogrel?

So these are all people that got stents, drug-eluting or bare metal, and we worry about stopping clopidogrel or having a patient stop it when they receive a stent, particularly a drug-eluting stent.

Is there any reason to believe that that risk is greater with stopping prasugrel, for good or bad reasons, than stopping clopidogrel?

DR. ANTMAN: It's actually just the opposite. So here is a slide that helps answer your question.

This shows the primary endpoint from discontinuation of the study drug, for whatever reason that was, and you can actually see the rebound here going up much more sharply with clopidogrel, 9.5 percent, and a more blunted rise with prasugrel. So just the opposite of what you were concerned about.

This is the primary endpoint. Please disregard the print over here. That's primary endpoint; it is not bleeding. We have just a mislabeling right there.

DR. KONSTAM: Dr. Paganini?

DR. PAGANINI: Bill, can you put up your slide 26, please? And can you tell me now why you would recommend, in the elderly, a five milligram maintenance dose with a 36 percent non-responder versus a 45 percent non-responder with the 75 milligrams? And does this not speak for or against -- in other words, are you saying two things; one is don't change because if you do change, you will have a problem, but in these subgroups, go to a lower dose which, in fact, gives you a higher non-responder?

DR. MACIAS: This study is actually not in patients that are over the age of 75. There are no patients over the age of 75 in this trial. And the reason that you can dose adjust down is because you have higher exposure in the population over 75 and then when you dose adjust down, you stay somewhat within the range of what you see in the general population. But because of the PK/PD relationship, you don't lose as much of the pharmacodynamic response.

So we can actually estimate the percent of non-responders using the model that Dr. Barrett reviewed for you and that Dr. Riesmeyer pointed out for

you.

This is just looking at individuals who are -- this is where a quite a bit of the study information came from. This is just looking at prasugrel in the population that's heavier and less than 75. So you can see a very low non-response rate compared to what you see for clopidogrel. And then you can actually do the predicted non-response based upon modeling simulations. And here you are looking at now the population over 75 that weighs more than 60 kilos, and you can predict that you would only have a five percent non-response rate. And that's because PK is predictable, the PK/PD relationship is predictable.

It allows you to build the model, but you have to make decisions off of modeling. If you don't want to do that, then it's a little harder to make dose adjustments. But these data would tell us that five milligrams in the elderly would be associated with a relatively low non-response rate.

DR. KONSTAM: Could you put that previous slide up for a second, the one you just had, slide 26?

So I just want to use this -- there's

something nagging at me and -- to really challenge the whole concept of responder/non-responder for a moment.

I guess, just speaking for myself, I really haven't seen anything that clearly convinces me that there's something pharmacologic that we should call a non-responder. And I'd just like to see you guys expand on this a little bit, because I'm looking at that slide and it just seems that, number one, the definition of non-responder seems arbitrary in terms of the percent platelet inhibition. Secondly, it seems like you can dial the percentage up and down at least with prasugrel based on dose.

I'm not sure whether I've seen, for clopidogrel, a sufficient dose exploration to convince me that there truly is something called a non-responder. So I wonder if you guys could support that approach.

DR. MACIAS: I think probably the best thing to do is to walk through the genetic data from the TRITON TIMI 38 sub-study, focusing on the influence -- we can go back to our clinical pharmacology studies first, focus on the influence of

genetic variants on the generation of the active metabolite for clopidogrel and then what's the clinical implication of that.

So I'll ask Dr. Close to actually step up and just walk us through from the influence on PK to PD and then the clinical outcomes in the TRITON sub-study.

DR. CLOSE: Sandy Close, Genetics, Eli Lilly and Company.

So I'll do what Dr. Macias asked and I will start kind of at the beginning of some of the investigations on some of the biological plausibility behind the non-response that you see.

So as Dr. Riesmeyer showed you, the metabolic pathways between the two drugs were different, although both involved CYP enzymes. So these CYP genes have well known functional variants that caused either reduced or knocked out function of those genes, and they're very common in the population, between 30 and 60 percent.

So taking that information, we generated the hypothesis that said we need to investigate comprehensively these six genes in the population of

prasugrel and clopidogrel to see what the effect might be on response.

So the first place we investigated, to follow up on the slide that Dr. Braunwald showed, was in the pharmacokinetics, because the direct effect is on the development of the active metabolite.

So here, the middle line here, represents a zero difference in exposure between those within a reduced ability to metabolize and a normal ability to metabolize. So we just dichotomized the healthy subjects and said if you fall on the left side of this line, your reduced metabolizers have lower exposure. And you can see, for all the genes investigated, for prasugrel, we didn't see a difference.

For clopidogrel, for the CYP2C19 genetic variant, we saw that those with reduced ability to metabolize had a lower exposure rate. We saw this consistently in PD. We saw it consistently in 600 milligram dosing PD in patients, PK and PD, and then we, again, saw that it translated to something clinically meaningful.

So here, you have clopidogrel patients,

primarily outcomes, CV death, nonfatal MI or nonfatal stroke, from the TRITON TIMI 38 genetic sub-study. And what we show here is those with the ability to metabolize normally, or extensive metabolizers, had a lower event rate than those with reduced ability to metabolize.

That also translated into another important clinical outcome, definite or probable stent thrombosis, where we saw an increased risk of stent thrombosis in those with a decreased ability to metabolize.

DR. ANTMAN: Could we put up the slide that Dr. Braunwald showed from Dr. Gurbel, looking at the distribution of response to clopidogrel 300 milligrams?

DR. KONSTAM: While you're doing that -- I guess that's really interesting stuff and shows genetically-based variability, which is important, but I guess I'm not clear that you can't overcome that with dosing. You mentioned the 600 milligram load. But are you convinced that if you're in one of the genotype that has less exposure, that that can't be overcome by dosing?

DR. CLOSE: So this is a study of coronary artery disease patients who received 600 milligrams, because as in TRITON, you know we studied the 300 milligram loading dose.

So this is a study in patients that shows here is your exposure with clopidogrel for your extensive metabolizers versus your reduced metabolizers, and we saw a statistically significant difference here in exposure. And for prasugrel, we saw no difference between those two groups and a higher level of exposure regardless of what genetic group you were in, even in your extensive metabolizers.

So if you'd go to 622.

In the healthy subjects, we saw the same thing. So these are in -- this is, again, your exposure and we did a further breakdown here. I told you before that we broke it down into those with reduced ability to metabolize and normal, and we dichotomized it.

To do further investigation of what the effect of one allele, say the one from your mom with reduced ability to metabolize, versus both alleles, so

that both of your copies were knocked out function, we split them into ultra rapid metabolizers, those with two normal copies and one that's actually up-regulated, so an increased ability to metabolize; extensive, which is two normal copies; intermediate, those with one decreased copy; and, poor metabolizers, those with two knocked out copies of CYP2C19, and we do see a gene dose effect.

However, we can see that even those with the ultra rapid metabolizer genotype, with the 600 milligram exposure, have less platelet inhibition -- it translates less exposure and, thus, less platelet inhibition than your --

Does that help?

DR. ANTMAN: One other piece, because, Marv, I've had the opportunity to look at these curves, but I think the kind of curve, the one that Dr. Gurbel had, please, is maybe the kind that you and I have seen a little bit more frequently and perhaps we can answer this question from that, as well.

So Dr. Braunwald emphasized to you that this represents the response to clopidogrel, and this is the

kind of distribution curve that you would see if you gave the population 300 milligrams. And, indeed, it centers here at this position, but there are individuals who, depending upon where you want to make your cut point for the definition of hypo-responsiveness, might be called resistant.

You asked the question what would happen if you actually gave 600 milligrams to this group of individuals and I'm going to draw that with my laser pointer because I don't think we actually have the slide here. But what you would see is a higher peak and maybe shifted slightly to the right, but you would still have a substantial portion of patients who would be in this poor or hypo-responsive end of the spectrum.

If we did this with prasugrel, we would be shifted to the right, as you would imagine, and the width of the base of this distribution curve would be much narrower with prasugrel.

DR. KONSTAM: Okay. I'd like to –

Are you going to go into new territory?

DR. DOMANSKI: I'm going to go into cancer.

DR. KONSTAM: So hold that thought. It's

good, it's important.

We're over the time for break and I'm sensing that we do need more time to question the sponsor.

I'm going to suggest that we go ahead and take our break now, because it's 10:36, unless there's objection to that, and then come back and continue to question the sponsor.

So I have to read something to you for the break and that is that we're going to take a 10-minute break. Panel members, please remember that there should be no discussion of the proceedings during the break amongst yourselves or with members of the audience, and we'll plan to resume at 10:45.

(Whereupon, a recess was taken at 10:36 a.m.)

DR. KONSTAM: If everybody will sit down we're ready to get started. Can I have the rest of the panel up here?

I'd like to continue with the questioning of the panel and see if we can go another 15 or 20 minutes on that and then turn to the FDA presentation.

So let's continue the line of discussion, if there are additional questions regarding the core

findings of the TRITON study and the cardiovascular and bleeding risk-benefit relationship, and then we can turn to discussion of the additional areas, such as the cancer risk.

Jim?

DR. UDELSON: Elliott or Dr. Macias, can you shed any more light on the patients with TIA or stroke? Is there anything more to learn about that in terms of the characteristics? Were they more off and on -- a lot more off and on Aggrenox or Coumadin, and anything that might explain the bleeding beyond the history that clinicians could learn something from?

DR. MACIAS: We've looked pretty carefully at the stroke phenomenon. As you can imagine, it's not what we expected to see.

Certainly, in the TIA/stroke, there is more bleeding and that was seen, of course, with clopidogrel and aspirin versus clopidogrel in the match study. But the real issue in the TIA stroke is they have more stroke and the mechanism for that is unknown and it's not hemorrhagic stroke, it's ischemic stroke. So the questions you're asking me are not going to explain the

stroke side of things.

Most people who experienced a stroke came off study drugs, so we can't give you a lot of information on what happens afterwards. But there were very few events that actually occurred in individuals once they had a stroke.

Elliott, did you want to make a comment?

DR. ANTMAN: I just wanted to make a comment that puts things in perspective regarding the stroke guidelines from the American Stroke Association for secondary prevention of a stroke. And it's relevant here because the patients we're talking about are all on aspirin. And there's a Class III recommendation there that says that individuals who are on aspirin, you shouldn't add clopidogrel. Actually, it's stated the other way, that if you're on clopidogrel, you shouldn't add aspirin.

So they are underscoring the hazard of giving dual antiplatelet therapy to patients who have had a prior stroke, because this is a secondary prevention guideline. Based on what we've observed from this trial, we certainly would not wish to give prasugrel to

an individual with a prior stroke.

DR. KONSTAM: Elliott, I'd like to ask about the issue about the timing of CABG and maybe you could put up that slide. I think it's slide 51 from your presentation.

DR. ANTMAN: Right.

DR. KONSTAM: And I guess maybe you should tell us again how you interpret that slide, because I'm not seeing any clear breakpoint there that tells me that there's a certain number of days after which it suddenly becomes safe.

DR. ANTMAN: Right. I'll show you this slide and if we can also pull up the one on transfusion of four units, as well, that would be helpful.

So let me remind you, Marv, that what we're plotting here is the number of patients who have had a TIMI major bleed days from last dose of study drug.

So five days, which is the recommended period of withdrawal or washout from clopidogrel at the present time, does cover the vast majority of the clopidogrel-related bleeds. There are a few over here at day nine and we could discuss whether or not we

actually think that's any residual effect of clopidogrel or it's just a late signal that may or may not be related to having been on clopidogrel.

Because we're dealing with a more potent antiplatelet regimen that's going to have higher levels of IPA, it's logical that we would want to wait a longer period of time than with clopidogrel and seven days seems like a reasonable breakpoint.

But let's look at this another way, recognizing that one of the determinants for a TIMI major bleed is, in fact, the degree of hemoglobin drop and our cardiac surgeons remind us that there's a degree of hemodilution that occurs in association with surgery.

So they are interested in knowing the number of transfusions you have to give to a patient. So this plot is arranged the same way, but this time, we're looking at CABG surgery and the need for transfusion of at least four units of packed red blood cells or whole blood, and here I think we have information that is confirmatory to my suggestion; that we wait five days for clopidogrel and seven for prasugrel.

So here is transfusion of more than four units and, again, it's five days here for clopidogrel. I think we could discuss what's happening here at day nine, but by day seven, we've covered the risk period for prasugrel. So within the limits of what we can say, I would recommend five days for washout with clopidogrel and seven for washout with prasugrel.

But let me show you another perspective on this, because we're only looking at the bottom there. But please look at this curve, which actually provides additional information. Now, we're returning to TIMI major bleeds and what I was showing you on the preceding slides are the bottoms of the stacked bars that are shown here. And what you didn't see on the preceding slide, but is shown here is that among the individuals who underwent bypass surgery, the vast majority are able to undergo bypass surgery without experiencing a major bleed.

What we were focusing on was the actual episodes of major bleeds, those bottoms of the stacked bars. But this is an important clinical perspective here, which is that the vast majority of patients can

safely proceed to surgery.

DR. KONSTAM: Jim?

DR. NEATON: I had a question about this one, too, because I don't know how to interpret this without the denominators, if I'm understanding it correctly.

So this is the time from the last dose to CABG.

DR. ANTMAN: No -- yes, it is, that's right. Along the X-axis, those are the number --

DR. NEATON: So how many people had CABG a month after the last dose of medication versus more kind of proximal to it? Don't you need the denominator to make any sense of this?

DR. ANTMAN: I can tell that we had reported -- we reported in our *New England Journal* main results paper that there were 179 subjects who were allocated to prasugrel who went on to CABG and 189 who were allocated to clopidogrel who went on to CABG.

These plots that I'm showing here, I guess we can just put up this one, are carried out to day 27. I can't tell you, at the present time, whether or not there's actually an occasionally patient who had bypass

surgery more than a month after a study drug, but certainly it would be the minority of individuals.

DR. KONSTAM: Yes, but I think Jim makes a really good point. So the previous slide just showed number of events, but you really have to ask about rates per CABG operation, and the numbers are so small that it becomes really tough.

What I take out of this is that your recommendations make a lot of sense based on known pharmacodynamics, but it's a little bit unclear, to me, how much these data really support that.

DR. NEATON: I actually had the same thought. I thought your recommendations at the end made sense, but then I was kind of sitting there thinking, so what would you recommend in terms of how long would you stop drug before CABG surgery?

DR. ANTMAN: Well, five days for clopidogrel and seven for prasugrel is what I've said.

Let me also just remind you that we're seeing one piece, which is the cost side of this equation. There is actually a lower rate of the primary endpoint among the patients who were allocated to prasugrel who

did undergo bypass surgery compared to clopidogrel. So we do have to have the benefit and risk in our equation here when we calculate this.

DR. KONSTAM: So let me ask you a question that we're going to be asked.

As a clinician, do you feel like we can identify patients, and at what point, that are likely to have CABG. And if you can identify patients who are more than 50 percent, or whatever it is, likely to have CABG, what would be your recommendation in that patient?

DR. ANTMAN: Okay. That's a very good question and there are models that have been developed that factor in a lot of information about the patient's demographics and try and predict, with a score, whether the patient is likely to require bypass surgery.

But perhaps the most important piece of information that one needs is the coronary angiogram. So significant left main disease or significant multi-vessel disease is clearly an individual who is more likely to be referred for CABG than to be handled by PCI.

If we could actually put that up here. That's fine.

So this slide summarizes our thoughts on this, Marv.

So right now, because of the pattern of pharmacokinetic and pharmacodynamic response that we've been talking about for clopidogrel, many clinicians feel that pre-treatment is important. So that by the time a patient gets to the PCI, they've got the antiplatelet effect of clopidogrel onboard.

That is a liability, because it means if you actually then discover that you have left main disease or there is an urgent need to go to the operating room, you're going to be sending the patient to the operating room on antiplatelet therapy.

Consider the fact that there is a very rapid onset of the inhibition of platelet aggregation with prasugrel. We've shown you a number of slides now that show the time course being much faster. So one would argue that pretreatment would not be necessary, so that you could make the decision based upon whether or not the coronary angiogram showed a need for surgery. And

if it did, you'd go to surgery, you wouldn't have given a loading dose. The loading dose, if you decide to go to PCI, could be given at the time of PCI. You would have a very rapid onset of IPA into a therapeutic range with prasugrel. And in the bottom row, I put the proposal for the washout periods.

DR. KONSTAM: Mike?

DR. DOMANSKI: I'd like to explore -- a question that came up a little bit earlier, was the importance of MI to prognosis. And I want to explore that just a little bit, because I will begin by saying I would think it's an extremely important one.

I want to talk about -- I want you talk with me for a minute about Dr. Temple's observation, which is that when there are small elevations post-PCI, many of us, including people like me, who actually produce those elevations in the lab, would like to believe that they're just markers of a malignant plaque. But, in fact, there's a strong graded association that starts very low and goes -- and an increased strong graded association between enzyme rise and prognosis, which, in fact, suggests that maybe it's more than that,

because there is something to how much necrosis you're producing, because you wouldn't see that kind of strong graded association if it were just a marker of risk; because later on, I want to make sure that we're not debating the importance of what drove your endpoint, I'd like you to comment on that.

DR. ANTMAN: Okay. I agree with you that there is a signal of a graded risk of mortality after peri-procedural MI. The smaller the degree of biomarker release, the lower the risk, but it's not zero. The greater the release, the progressively greater the release of biomarkers, the greater and greater is the risk of mortality, which was why it was so important to me when I saw the size of myocardial infarction data comparing prasugrel versus clopidogrel. Two-thirds of those infarcts we're talking about are greater than five times the upper limit of normal. And remember, the vast majority of this is CK-MB. So the two thirds that we're talking about there, plus even the smaller ones -- in fact, we can put that slide up again here. Right.

So just to help you with this, the Ns on the

bottom show you the number of subjects in each of those bins. So we're talking about a substantial number of subjects who have these very large infarcts. And we can agree that the larger the infarct is, the more and more the concern is for the long-term implications with respect to mortality. But even these smaller infarcts are not without long-term mortality risk and it may simply take more patients and even longer follow-up to actually find that signal of risk.

I think we can agree that prevention of any myocardial infarction is a desirable goal. That is seen here with prasugrel, no matter how you wish to define the infarcts, and, as I've mentioned earlier, a particularly striking absolute risk difference as you get to the bigger and bigger infarcts.

DR. KONSTAM: Other questions? Dr. Paganini?

DR. PAGANINI: Just a quick -- four units of major as a major bleed, is that a standard definition of major bleed after CABG?

DR. ANTMAN: It's something that cardiac surgeons pay particular attention to and --

DR. PAGANINI: I understand that, but is that

a definition that you guys used or is it a standard definition?

DR. ANTMAN: It is often used in the medical literature for indicating a significant bleed that requires transfusion.

DR. PAGANINI: And in the operative suites, when people were on drugs, whatever drug they were on, was there any indication of what medications were used as an anti-bleeding medication that may have influence over postoperative stay, specifically in renal dysfunction?

DR. ANTMAN: I'm going to let Dr. Macias answer that in a moment, but I would just like to answer in one more general way first, which is you've hit upon something that is very important, which is that if a patient is on a potent antiplatelet regimen and they experience bleeding, the recommended response is to give platelet transfusions.

Now, that is actually something that was done, as best we can tell from the database, more frequently in the United States than outside the United States. We could discuss why they might have made that

decision, but, in fact -- and I think Dr. Ware pointed out that there was actually a much more muted signal of bleeding risk. In fact, there was no difference in major bleeding in the United States cohort compared to subjects enrolled in other parts of the world.

Dr. Macias, any comments about other drugs that were noted at the time of surgery? Do we have that?

I don't think we have enough information to answer it beyond what I've said.

DR. KONSTAM: Mike, you had a question about -- I don't know if there's any other questions about the cardiovascular events, but you had a question about cancer.

DR. DOMANSKI: Yes. I'd like to pursue that a little bit, if I could. Obviously, if prasugrel produced cancer, that would be a very negative sort of thing. But if it doesn't or if there's not compelling evidence to that effect, labeling the drug with some uncertainty and so forth has a downside risk, and the risk is that people who could benefit from it won't be given it because of the fear that any whiff of risk of

cancer brings.

We've had an extensive discussion of that by the sponsor. But there are also some analyses that are in the book and I'd like to ask that they respond to those.

The reconciled analysis shows no statistically significant association with cancer. The only analysis that does -- let me see if I can get the page right quickly -- or where there's some question raised is new or worsening -- new or worse cancer.

I'm concerned about new or worse. I'm worried about the word "worse" and that analysis doesn't resonate with me. But I'd like to hear some explanation of why that's a reasonable analysis or why it should be discarded.

DR. MACIAS: Obviously, the agency has not had their opportunity to present yet and so I want to be careful how much of the discussion we get into as regards to their data.

DR. DOMANSKI: We can hold it, also, if you wish, until after they do. But I'd just like to be able to hear what you guys say about it as well as what

the agency does.

DR. MACIAS: Well, with regards to "worse," we spent a lot of time trying to figure out what "worse" means, because in the trial, we didn't measure tumor burden, we didn't measure evidence of metastasis. We have no estimate of what "worse" would be. We do have cases where severity of an adverse event might go from one to two, mild to moderate, but if you look at all of the associated adverse events, we don't see anything.

So when we look across this concept of worse, we just don't have a concept of what worse cancer is, because the study wasn't structured to do that. We don't have an assessment of baseline staging, nothing like that.

I don't know if Dr. Ozols would want to make a comment about what worse cancer is, what the nature of worse cancers would be or is it appropriate to combine new and worse cancers.

DR. OZOLS: Bob Ozols, medical oncologist from Fox Chase Cancer Center.

I struggled over that categorization. Again,

I haven't heard what the FDA -- really, the details about it. But there are so many words to categorize cancer patients retrospectively and that's, obviously, the limitations of this study. If you're going to look at some type of risk factor, you'd want to do it prospectively. Obviously, there's histology, there's treatment, there's grade, there's all sorts of prognostic factors. And some of the things that were listed as worse, surgery and radiation, they're not kind of the classic criteria that we would lump as worse. So I don't know what "worse" means in this situation. It's not something that I've been seeing as far as a categorization of prognostic factors.

DR. DOMANSKI: I guess my concern is in the absence of the use of a standard metric, the analysis may, in fact, be vacant just based on the fact that it just is just that, not validated.

DR. OZOLS: Well, I, personally, do agree with the FDA Oncology Division's analysis of this that it may very well be spurious.

The only way to look at this is to look at prospectively, because of all the prognostic factors we

just talked about, and we don't have that. What we have here is a signal and, again, there's no hypothesis that this is a cancer drug or a promoter.

So when we look at this thing for a signal, I think there's two ways to look at it. One is to look at the site specifically to see is there some tumor that you're going to account for the increased incidence that you saw. If you make a hypothesis that, in fact, this is a stimulator, again, this is an unprecedented hypothesis that this type of a drug would cause a broad stimulation of a variety of tumors, then I think you have to include all the solid tumors and I think that you have to include the skin cancers, as well.

If you do that, the risk of increased incidence becomes small and is explainable, in my mind, by the fact that you've got this increased incidence of gastrointestinal tumors. And I do think that they're still -- the most likely explanation is that this is an ascertainment bias based upon increased bleeding that we see in that group of patients.

DR. DOMANSKI: Thank you.

DR. KONSTAM: Jim?

DR. NEATON: I have a couple of questions about the follow-up study that you did and trying to understand how much importance we should attach to that.

Can you just describe again who was followed there? I gather it was not everybody. I took it to be just the newly diagnosed cancers.

You have no data on long-term morality for cancer for the entire cohort. That's one question. And was this follow-up study done after the patients were unblinded?

DR. MACIAS: The population that was first -- first off, the sites were blinded when we did follow-up. In fact, we still haven't unblinded the sites. So that's an extremely important point.

Second of all, the request from the agency was to follow up everybody who had a treatment emergent adverse event that was in the neoplasm system organ class and that ended up being about 313 or so, of which we got information back on 311 subjects.

Can I have the slide that is from the core

for outcomes for preexisting, please?

We need to put that in context when we're talking about people with preexisting cancers. As Dr. Unger has pointed out and as a number of the reviewers have pointed out, we didn't have a case report form that really collected baseline cancer information.

Where some of the confusion was is we have preexisting conditions and we have past medical history, and the only module to collect past medical history was a checkbox, hypertension, diabetes, chronic renal disease, whatever the checkbox was. But there was no checkbox for cancer as a past medical history.

The only time the investigators were supposed to write in the preexisting condition boxes for cancer is if they believed, at the time the patient came into the trial, the cancer was, quote-unquote, "ongoing." And we didn't specifically explain about cancer. The medical condition is supposed to be ongoing, whatever ongoing means, and we can talk about whether or not our case report form was designed adequately. But this was an ACS trial, not a cancer trial.

But this was the outcome for the population that had a preexisting condition that would have been considered a non-benign neoplasm.

DR. NEATON: So that's a preexisting condition at study entry.

DR. MACIAS: That's at study entry. But also included in here are events that were diagnosed shortly after study entry but considered preexisting by the investigator when this case report came back.

So it's a very complicated way of looking at the data. Really, when you finish the randomized period, which is one of the very first slides --

If you show me the data at the end of the randomized period. It will be the second or third slide into the --

DR. NEATON: So let me just say, I think, I guess I don't know how to interpret this, if this is kind of a mixture of information collected prior to randomization with information collected post-randomization in a subset of people.

DR. MACIAS: At least where we have to stop is really at the end of the randomized period, because

we only followed -- so the trial was over when we got the request to do additional follow-up. We only followed up 311 of the 13,600 and some patients in the trial. So this is a cohort of patients that's defined by a post-baseline event. It's a non-randomized cohort for which we got extended follow-up and we had no follow-up for the other 13,300 or so patients in the trial.

So this is outcome at the end of the trial when we locked the database. And when we did our analysis, we saw this and then we did by tumor type. We did colorectals, we did breast, we did prostate. We never did this. This is a post hoc grouping, because it never -- we just don't analyze our data that way. And I'm not saying it's right nor wrong to do, it's just not how we analyze our data.

Where we thought the signal was was in colorectal cancers and then they were frequently diagnosed during the evaluation of bleeding. And I think bleeding certainly leads to the diagnosis of cancer, and I think it's clear from our data that you need to evaluated if you bleed, and whether that

explains the difference between two treatment groups, I think is a fair discussion. But I think what's really clear from the data is if you bleed, you have a high incidence of cancer if you get evaluated.

DR. NEATON: So I think you're telling me that probably I should focus on this and not so much on that follow-up study of 300 people that was done after the study was over with.

DR. MACIAS: Dr. Schein, would you like to make a quick comment?

DR. SCHEIN: I'm Philip Schein. I'm a medical oncologist, pharmacologist, currently at the University of Oxford.

I think that the take-home message for me, this is the end of treatment randomization, if you look at the very bottom line, it's not exactly highlighted in yellow, but you'll see a difference in malignancy-related deaths, and we're talking now of a database of 13,600 patients. But the difference is 21 versus 17, four, four patients out of over 13,000 patients is what we're talking about in terms of whether there is a risk.

One also has to recognize that the presence of a preexisting cancer or specific risk factors that might lead to cancer were not part of the randomization schema. In essence, the study took all comers.

So this was not controlled for. But even with that, and perhaps because there is a large number of patients that entered the study, you're talking about four deaths between the two arms. And, for me, that does not become a terribly meaningful number.

DR. KONSTAM: So I've seen different numbers here and I'm a little bit confused, because I've seen 27 versus 19 and I'm a little confused.

What is actually the number of cancer deaths in the two groups?

DR. MACIAS: So for clarity, this is the end of the randomized period, 21 versus 17. So when we locked the database, this is what was in the database. This is CEC adjudicated malignancy-related death.

The additional deaths that you're referring to came during the extended follow-up when we followed-up the cohort of patients that were identified by having an event during the trial and that follow-up

is beyond the trial and that's what --

DR. NEATON: That's the reason I was asking, because that number actually doesn't make a lot of sense to me. So that I'd be much more interested in your ability to do a mortality follow-up and understand cancer causes for all the randomized patients. That's what you want to do, potentially, if that's still possible, in terms of using the National Death Index or other mortality registers.

So this is a subset of deaths that occurred among a small subset of patients that were identified based upon post-randomization events.

DR. MACIAS: Yes.

DR. KONSTAM: Let me just say that when the FDA comes to give its presentation, I'd just like to get its take on this discussion, and I expect we'll hear that.

DR. DOMANSKI: Yes. If we could just put that slide up for one more second here. But the new non-benign -- I mean, new malignant neoplasms, 135 over 6,741 versus 115 over 6,716, very small numerical difference and a statistically insignificant result.

Why is that -- Jim, why is that a problem?

DR. NEATON: I'm not saying it's a problem. I'm actually trying to understand -- my original question was should I place any attention on this follow-up study that was done and I'm becoming more convinced, at least in my own mind, that it's less important than kind of what your overall findings --

DR. KONSTAM: Okay. I have another question for Elliott and it sort of moves into the question of what's the clinician to do, actually, and this may enter into how the drug is labeled.

Assuming this drug were to be approved, I'm wondering how you think the clinician should be advised. And so I'll give you a couple of choices and maybe there's another one.

One is that the guideline level one recommendation moves from antiplatelet therapy to prasugrel, as specified, as the preferential agent. And the alternative would be that actually it's a complicated risk-benefit analysis and that's to be left to the clinician and the patient on a case-by-case basis.

So maybe you could comment on your view about that.

DR. ANTMAN: So if I understand your question correctly, if I were sitting at the writing committee for a future guideline, you're asking how we might word that.

So the answer to that has to take into account the fact that when we do write our recommendations, particularly Class I recommendations, we are very careful not to call out one drug specifically unless we are confident that there have been all the comparisons that are needed against all the various other drugs.

So, for example, you can't really comfortably say that one particular anticoagulant is better than another, because there's many factorial combinations you'd have to consider. So we do talk about the use of anticoagulants and identify those drugs for which there has been evidence of efficacy.

We have a different situation here, because there's really one comparison and I think it would be an interesting discussion -- and this would be a

departure from what I said about the general rule on using the anticoagulant analogy.

So I'm not entirely sure how that discussion would turn out, but I think that we would have a pretty strong opinion favoring, mentioning the superiority of prasugrel over clopidogrel, and certainly when we have a situation like this, the benefit-to-risk must be brought to the attention of the clinician, so that would probably be factored into the recommendation as well.

DR. KONSTAM: But do you think that, if I'm a practicing clinician, it would be reasonable to sort of leave it to me to look at the benefit-risk, as the data show them, and make that decision for myself with that particular patient in mind?

DR. ANTMAN: Sir, you're asking about the guideline or the labeling for the drug at this point?

DR. KONSTAM: I'm asking about how you see the clinician interpreting the data and I think it may impact on the labeling.

DR. ANTMAN: Okay. So the way I think we could present this to clinicians, it is a complicated

story, is that metric. And maybe we could just look at that slide again, the events per 1,000 and I'll just remind you --

DR. KONSTAM: Well, that's okay. We can --

DR. ANTMAN: The ledger, what I showed earlier.

DR. KONSTAM: We can look at it.

DR. ANTMAN: I would actually put it in terms of the metric there and explain the benefit on the left side and comment on the importance of preventing myocardial infarctions and comment on the cost here. Personally, I would not go beyond this dashed line because I think it's a misleading comparison beyond that.

DR. KONSTAM: Yes.

MR. FINDLAY: In that same vein and context, can you elaborate a little bit more on the age cutoff issue that was raised before? The way I'm looking at the data, as a bit of a novice looking at data, is that the increase in risk is gradual starting at age 60, 65, 70, and as opposed to the weight cutoff issue, where it rose.

So for the clinician and, again, with potential possibly for labeling, how would you deal with the age cutoff, the clinician dealing, obviously, with a patient who is 72 and maybe has some risks?

DR. MACIAS: I can show you very quickly the data and where the univariate cuts came. Here we just did every five years and you can just see a continual increase. If you go to 80, this is going to bump up even higher.

But again, the major concern that we have with the very elderly is not just that they tend to bleed more. It's just that the sequela of the bleed is not good. I mean, we have more fatal hemorrhages, we have more intracranial hemorrhage.

Most of the TIMI major is life-threatening hemorrhage as opposed to for lower age patients and heavier patients, where most of the TIMI major or a large part of the TIMI major is not life-threatening. It's non-life-threatening TIMI major. But when you go to the elderly, you are going to a population where all of the difference is really driven by life-threatening.

So we look at this, and this is just the

population -- this is what Dr. Antman showed you; less than 75 years of age, greater or equal to 75 years of age, less than 60 kilos. So if you are less than 60 kilos and less than 75, you have a big jump up. The best group is this group here, less than 75, greater or equal to 60 kilos.

They are, obviously, not dichotomous cuts. You don't all of a sudden turn from 74 to 75 and your risk goes up. It's all a continuum. And the same with exposure, exposure is all a continuum.

MR. FINDLAY: But you would acknowledge that that makes messaging in labeling a little bit more complex, and particularly messaging to clinicians and to patients.

DR. MACIAS: It's why we left things as two different independent cuts. We said here is age, here is a cut, here is weight, here is a cut, because we thought it would be simpler to implement than a nomogram of some combination of weight and age and maybe gender. It's just you're really small or you're really old.

DR. KONSTAM: Okay. I see one hand raised

and I just wonder if, after this last question, we can move on to the FDA's presentation.

Okay. Dr. Flack?

DR. FLACK: I want to make one additional swing back at that. If you actually put that last slide up, you've got these different percentages by age and weight categories.

If you understood, though, what an acceptable level of risk for the TIMI major bleeding was, you could still do an individualized nomogram, and as opposed to simply saying these age categories kind of give me this and this, you could actually individualize it if you said the acceptable level of risk is 2.5 percent for above and below those categories. That gets you more into something that admittedly is probably more complex, but more precise, and there's always a tradeoff.

As this era -- we keep trying to move toward individualized and personalized medicine, it seems that we ought to give at least some credence to actually really trying to individualize things rather than taking broad strokes of the sort of things that

characterizes and not do it more precisely.

What do you say to that?

DR. MACIAS: You're asking me to speculate a bit as opposed to talk to the data. Actually, I actually agree with you that personalized medicine is a great way to go. I'm going to give you my opinion from the podium as opposed to all my colleauges' opinion. But as you look across the literature, it's becoming pretty clear that there is a threshold of the platelet inhibition above which you need to be to be protected, and Dr. Braunwald kind of spoke to that with all of these analyses of non-response.

As point-of-care testing for platelet inhibition becomes more and more common, more and more publications are coming out, and, boy, those targets are coming very close.

What we see in TRITON -- and we didn't have an opportunity to go through this with you. But what we see in TRITON is a very flat exposure-response relationship for efficacy. So we think we got everybody over that threshold.

What we also see in TRITON is a relationship

between exposure and increased bleeding, and we see it in patients less than 75, although it's not so pronounced, but, boy, over 75, you really see as exposure goes up in that population, the risk of bleeding goes up, which is our argument for bringing the dose down.

But if it's true that there is a threshold of efficacy and once you're above that threshold, increasing levels of platelet inhibition don't get you more efficacy, all they get you is bleeding, if you can establish that threshold of efficacy, then you can titrate. You get people over that threshold and if they go too far over the threshold, you titrate them down.

Now, we're not there yet. One, point-of-care testing is not that common. Two, we don't know the threshold yet for what is efficacy. I can tell you we have a range of exposure where you get into increased bleeding. We've got the upper part. But we're not there yet. We're not there yet. So we're kind of keeping it straightforward right now.

DR. KONSTAM: Okay. Thanks very much. Thank

you to all the speakers for the sponsor.

I'd like to turn now to the FDA presentation and Dr. Unger I think is going to give it.

DR. UNGER: Good morning, everyone. I'm Ellis Unger from the Office of New Drugs in the Center for Drug Evaluation and Research, and it's a pleasure to be here this morning. I'm going to try to underscore some of the difficult issues we've been grappling with in trying to reach a regulatory decision on prasugrel. And it's a pleasure to be able to be in a position to ask other people what they think.

I have to say that the presentation this morning is a product of a pool of very talented and dedicated reviewers, both from the Office of New Drugs here and the Office of Surveillance and Epidemiology, and I'd like to take just a second to acknowledge their extensive contributions.

I'm going to talk about efficacy, safety and quality. The quality is a chemistry type of material. We realize we don't have any chemists on the advisory committee, but what we're really going to talk about the clinical ramifications of the chemistry,

specifically the conversion from the salt to the base form you've heard about.

I was going to go over the highlights of TRITON TIMI 38, but Dr. Antman did it as well as it could be done. So I would like to just skip this slide and the next slide that just lays out the trial and go to the results, which you've also seen.

You remember that randomization was stratified by the presentation, whether it was a non-ST-segment elevation MI unstable angina was one stratum. The other was ST-segment elevation MI. This is the first stratum. You see the event rates, 12.1 for clopidogrel, 9.9 prasugrel. You see the statistical significance and the hazard ratio of .82.

This is the other stratum, ST-segment elevation MI. The components of the primary endpoint are laid out in this slide, and so cardiovascular death, nonfatal MI, nonfatal stroke, and the two strata are shown here, the unstable angina non-STEMI and STEMI, and then the overall population.

So if you just look at the overall population, for the sake of simplicity, on

cardiovascular death you have two percent versus 2.2 percent. So you have a favorable lean on cardiovascular death.

Nonfatal MI is where the money is in terms of what drove the composite endpoint. And you have neutrality on nonfatal stroke. Despite the fact that you have 13,000 subjects in the trial, you only have 60 events in each group.

So let's spend a little bit of time talking about the efficacy and, first, I'd like to address the time course of efficacy.

When you look at these Kaplan-Meiers, you've seen them presented many times, there's something rather strange about them and that is that they take off in a vertical way, which is most unusual for a survival analysis.

So let's examine this briefly and try to understand what's actually happening early, and, in fact, this is not the kind of landmark analysis that Dr. Antman showed, but it's simply breaking up the X-axis, changing the scale from the first day here to beyond the first day out to 450 days.

You see even within the first day, there's a lot of verticality to this relationship here. And what you find is that 54 percent of the events occurred in the first week and, in fact, 45 percent occurred in the first day and 23 percent occurred in the first hour.

So these are very, very early events, in general, although that's not to say that this isn't important. Obviously, beyond a week, you have 46 percent of the events, so we don't want to minimize that. But it is a bit unusual.

This is the landmark analysis, more or less, shown by the company. The reason for this is that one could reasonably postulate that you have this upfront superiority of prasugrel versus clopidogrel. Maybe that's just related to the loading dose, per se, or maybe it's only peri-procedural events that you're preventing with prasugrel versus clopidogrel.

So the landmark analysis just takes the events for the first X days, this is one is three days, this is seven, and throws them out and starts over again. And when you do that, you still see superiority of prasugrel over clopidogrel. So even though the

results are frontloaded, the landmark analyses still argue that the superiority is not related solely to the loading dose or a reduction in a peri-procedural MIs.

Now, let's look further at the contour of these Kaplan-Meier curves. This is the non-STEMI unstable angina. This is the STEMI. And here you see the curves continue to separate with time and here they seem to be parallel. So you can look at that more critically by just doing a subtraction of the curves, which I'm going to present in the next slide. I'm going to basically take these four curves and compress them into two curves that are subtractions.

So this is the STEMI subtraction and this is the non-STEMI unstable angina subtraction. And what you see pretty clearly is that there's this rapid accumulation of superiority for prasugrel over clopidogrel, but at about two and a half weeks, things change.

Both curves have an inflection at that point and for the ST-segment elevation MI, the superiority is maintained, but there's no additional accumulation of superiority, whereas for non-STEMI and unstable angina,

you get about 60 percent of the superiority in the first two and a half weeks, but beyond that, there still is superiority of prasugrel versus clopidogrel.

Now, I'd like to spend some time talking about subgroups with marginal effectiveness.

So you've seen these plots. This is a hazard ratio of one and anything that leans on the left side of this is good. But here's the outlier. This is the group that had a prior TIA or cerebrovascular accident. It comprises about four percent of the population of TRITON.

So patients with a prior hemorrhagic stroke at any time or a non-hemorrhagic stroke within three months of screening were excluded from the study, but that allowed enrollment to subjects who had an ischemic stroke greater than three months prior to screening and anybody who had had a transient ischemic attack. So they were in the study. Again, they comprised about four percent of the study and they were unfavorable for prasugrel. So these patients were better off on clopidogrel.

Let's talk about patients 75 and over.

Prasugrel superiority over clopidogrel is less certain in this group. Here, the trial is dichotomized at age 70, here dichotomized at age 75. You look at the hazard ratio of patients above 70 versus below, you see it's not that far from unity, .93. You do it at age 75, it's the same, .94; so not that much superiority of prasugrel over clopidogrel for elderly patients.

Now, it's worth looking at the results from CURE, which was a registrational trial for clopidogrel. This is from the clopidogrel label. Overall, this is clopidogrel versus placebo. It was a 12,000-patient study. You see the event rates, 9.3 versus 11.1 in placebo. But for age greater than or equal to 75, the event rates are not that different, again, a small subset, 17.8 versus 19.2.

Now, ordinarily, we don't get too excited about a small subset on the fringe of age or fringe of weight. As long as it tends to go in the same direction as the study as a whole, it's okay. It's not a big deal.

But I'm pointing it out here because I want you to hold onto this in your mind, because we're going

to talk about the bleeding in the elderly patients. And so when we try to do a risk-benefit assessment for elderly patients, you need to keep in mind what the benefit is, and that's the purpose of this slide.

In terms of concomitant therapies, as Dr. Antman told you, prasugrel came out just fine; 94 percent of subjects had a stent and the hazard ratio in that group was .8. For the six percent of subjects without a stent, it was .67. It didn't matter whether it was a drug-eluting stent or a bare metal.

For GPIIb/IIIa inhibitors, about half of subjects had received them during the index procedure. The hazard ratio was the same irrespective of whether the patient was treated with a GPIIb/IIIa or not.

Aspirin was a little more complicated because virtually all the patients were on aspirin. It was a matter of dose. So the company did a dose response modeling and there was no interaction there. So this is all good.

So the key points on efficacy, TRITON was a large outcome study, enrolling 13,608 subjects. There were 1,424 events, 10.5 percent event rate. Mean

follow-up a year, median 15 months. It was multi-country. The patient management was consistent with contemporary practice. The results were statistically significant for reduction in the composite endpoint of cardiovascular death, nonfatal MI, nonfatal stroke. The risk reduction was 19 percent relative, two percent absolute. Results were persuasive across both strata, the unstable angina non-STEMI and STEMI, and, of course, for the whole population.

The results were driven by nonfatal MI, but there was a positive trend on mortality. The study was neutral on stroke. The superiority of prasugrel was very much frontloaded, particularly for ST-segment elevation MI. The results were positive across the demographic subgroups, concomitant diseases, stent type, GPIIb/IIIa use and aspirin use, the elderly patients being a bit of an exception. The key negative here was that patients with a prior TIA or non-hemorrhagic stroke did worse on prasugrel.

I'm going to move from the efficacy to safety. First, I'm going to talk about deaths. This

is a summary of all deaths in TRITON. All cause death is in the top line. The cardiovascular deaths are here, non-cardiovascular are here. These are the percentages and, again, this is basically taking the percentage difference and multiplying it by 10. So you get events per 1,000 subjects treated over in this column. And I color-coded it for you a little bit. Green is good and yellow is bad. So positive numbers indicate superiority for prasugrel. Negative numbers are positive for clopidogrel.

So overall, for all cause death, it's positive for prasugrel to the tune of 1.4 per thousand or .14 percent difference in all cause death. The cardiovascular death is positive in a large way for prasugrel, 2.6, and that's basically these two categories here, acute MI, sudden or unwitnessed death.

The negative here is in intracranial hemorrhage, ICH, where you have a negative .6. Then for non-cardiovascular death, overall, you have negative for prasugrel, 1.2 per thousand, and this is starred here to show you this.

Extra-cranial hemorrhage, so we're talking

about hemorrhage not in the head; your chance of actually exsanguinating was nine versus one on prasugrel. So you could do the arithmetic on the relative risk, I think. The absolute risk is small, but this is something worth noting. So your chance of exsanguinating, relative risk of nine. The malignancy is also a negative for prasugrel, .6.

Let's talk more about the bleeding. We've started the discussion. I'm not sure that everyone in the audience is familiar with the TIMI definitions, but a TIMI major bleed is any intracranial hemorrhage or overt bleeding requiring intervention associated with decrease in hemoglobin greater than or equal to five. TIMI minor is clinically overt bleeding associated with decrease in hemoglobin between three and five. And in TRITON, the bleeding was characterized as related to or not related to CABG surgery.

So here are the TIMI major and minor bleeding categories, and it's clear prasugrel causes more bleeding than clopidogrel. No one disputes that. So the relative risk is about 1.3.

When you're talking about fatal bleeding, now

you have very few events, but the hazard ratio is much higher. It's about four. The fatal bleeding, 21 events versus five, this is the non-CABG-related bleeding.

The CABG-related bleeding, here, the denominator is patients who had a CABG. You see it's about 200 in each group. So you can start to understand why it may not be so easy to understand bleeding related to how long in advance of a CABG the drug is stopped; don't have a lot of people. If you add the two categories together and just look at all fatal bleeding, you have 23 events versus five, for a hazard ratio of 4.59.

So this is very similar to the Kaplan-Meier I showed you for the efficacy. This is the percent with event. The events are TIMI major or minor bleeding. So the scale is broken here at seven days. This is through day seven. This is past day seven, out to day 450. And, again, you can see the bleeding is very much frontloaded. About a third of the events were reported on the very first day and almost half the events were reported in the first week. So you can remember that

both for efficacy events and for bleeding, you get half the events in the entire study in the first week.

This is a graph that you probably are not familiar with. It's not unusual for us to hear people talk about risk-benefit ratio and I always cringe when I hear it, because you can almost never quantity risk or benefit as a number and then divide them. But this study actually offers an opportunity to do that, because the events are nonfatal MI and death, and the events are bleeding and you actually can divide one by the other and figure out what kind of trade you're getting.

Here, what I've done is display it as a function of time. It doesn't matter too much which classification of bleeding you pick. That's why you have three curves here. These are bleeding serious adverse events, this is TIMI major or minor, and this is TIMI major. So what you're looking at on the Y-axis is the endpoints prevented per bleeding event.

Let's just focus on TIMI major bleeds. A high number is good. So that means you've prevented more events per bleed. That's the best trade.

So in the first month, you have a very favorable trade and it starts to decrease somewhat during the second month, and then it stays pretty much constant after that. That's because you don't really have a lot of events out here. You don't have a lot of endpoint events. You don't have a lot of bleeding events. All the action is loaded in the front of the study. So it suggests that the trade is good here and less good as time goes on.

This is conveying the same information as the sponsor's slide 52, but it gives you the denominators, which is what was missing in the sponsor's slide 52. The other difference between this slide and the sponsor's slide is the sponsor showed you only TIMI major bleeds, and there were very few. So the data look, I think, somewhat deceptively benign.

This is a combination of TIMI major or minor bleeds and these are days between the last dose of drug and CABG. The N’s, the capital N’s, represent the numbers of subjects who actually had a CABG with prasugrel and clopidogrel. The small n’s represent the numbers of TIMI minor and major bleeds. And the bottom

line is we don't really have enough data to be able to say that there is a point in time where it seems safe to have a CABG.

I would point out that the half-life of the platelet becomes more important than the half-life of the drug. The platelets live for 10 days or so. So it's hard to imagine that 10 days after the drug, that the drug could be having any effect all. I doubt that it does.

But the problem here, if you do the percentages, you see the percentages are very high in the first days with prasugrel, much higher than with clopidogrel, and you want to convince yourself, after the seven days, the risk goes away, but then, lo and behold, on day 10, you get a spike. Ten patients have a CABG, two have an event. You have 20 percent. So it's difficult to say when it's reasonable to have a CABG once you stop the drug.

This is one way of looking at it. It's a cumulative frequency of bleeding as a percent of patients who have a CABG to try to make some reasonable conclusion from this. And what this is showing you is

for each day here -- because it's cumulative, let's pick day five. So it's showing you, in terms of these bars, the numbers of subjects who had a CABG between day zero and day five and the number who had a bleed, TIMI major or minor, between day zero and day five and simply dividing them.

If you look at it this way, it's very nice, you can kind of convince yourself that day seven is reasonable. But it's a little bit deceptive and you can understand, when you're looking at the numbers of events, it's just too small.

So let's talk about bleeding and patient weight. If you do your standard subgroup analysis, say, dividing patients in quintiles on the basis of weight, you look at the relative risk of bleeding over here. But before we look at the relative risk, let's look within each weight category.

So these are the lighter people. It's confounded because women are overrepresented here, men are overrepresented here. But the point is that bleeding occurs more frequently in people who are lower weight, and it's like that in every study I've ever

looked at. And as you get heavier, you have less bleeding. So we should all keep eating hamburgers, I guess.

But that's true for both drugs. So when you look at the relative risk in each of this quintiles, it's hard to convince yourself that the lowest weight quintile distinguishes itself in any way from the other quintiles. There's kind of a U-shaped relation here, there are subgroups, it's hard to make too much out of it. But the sponsor has focused on patients who weigh less than 60 kilograms. It just turned out, when I did my analyses, I did less than or equal to 60 kilograms and I'll get to that in a minute.

But let's look at less than or equal to 60 kilograms. That's a subset of this first quintile and the relative risk of bleeding is a bit higher. It's 1.72. Is that meaningfully higher than this? I don't know. You don't have a lot of patients here. You only have 400 patients in that particular subset.

So it's kind of hard to know. The sponsors made -- they've done the modeling based on PK and PD and they have made the case that the maintenance dose

should be reduced in people who weigh less than 60, but, again, we don't have clinical data.

But there is one thing I'd like to point out and that is the difference between -- and it seems trivial, but it's not necessarily trivial -- the difference between patients less than 60 and patients less than or equal to 60, because it turns out that if you look at patients who are less than or equal to 60, a quarter of them weigh 60.

Well, we know that a quarter of the patients who weigh less than or equal to 60 don't weigh 60 and that's because patients are rounded. Their weights are rounded and their weights are estimated.

So one has to carefully consider patients who are said to weigh exactly 60, because depending on how you write the labeling, if it's less than or equal to 60, that means basically anybody who is less than 60 or rounded to 60 will have the same treatment; they might have their maintenance dose reduced. If it's less than 60, then people who are rounded are not going to have that dose reduction. So we've pointed this out to the company recently and they are cogitating on it.

So I think we'll move to the next slide. Let's talk about patient age.

Well, we know older patients have more bleeding and you can dichotomize by any of these ages and you see more bleeding at the higher age. But again, you can look at relative risk prasugrel versus clopidogrel across these dichotomized groups, and let's pick 70. The relative risk of bleeding is the same.

So it's not the issue of relative risk of prasugrel versus clopidogrel for age. As the sponsor pointed out, they're not at a particularly high relative risk of bleeding, but the outcome, the sequelae of bleeding was particularly malignant in patients who were older.

So specifically, fatal hemorrhage was nine of 891, which is one percent, for prasugrel versus one out of 894, .1, for clopidogrel. You could calculate the relative risk as somewhere around nine, and that's a problem. For symptomatic intracranial hemorrhage, the risks were -- there were seven cases versus three, as you see there. So, again, it was the result of the bleeding and not the relative risk of bleeding.

So we put that together with the somewhat marginal efficacy in patients who are older and it makes us want to discourage use in older patients.

So the three groups really that I think we need to focus on in terms of risk management then are older patients and then also patients who are having CABG or, by extension, probably any kind of surgical procedure where we have to mitigate risk. And then the third group would be patients with a prior stroke or transient ischemic attack, and we know those patients do poorly on prasugrel.

All right. We're going to move to neoplasia and I'll do my best to try to illuminate some of the issues and some of the differences between the sponsor and the agency.

Well, does prasugrel cause cancer? Well, the short answer is we don't think so. So the genetic toxicology studies are negative. The time course of events observed in TRITON is not consistent with carcinogenesis, and we just don't think there's any evidence that prasugrel causes cancer and the sponsor agrees with us, which is good.

You've seen the data. So what I'd like to do is -- I'll show you the data, but I'm going to go through our thinking for the next couple minutes and tell you where we're coming from and then I'll show you the data.

So the time course of discovery of new cancers and also worsening of existing cancers in TRITON could be consistent with tumor stimulation. I don't think anybody can argue about that.

Well, tumor stimulation is rare. It's been observed with drugs, but only drugs that are known to stimulate tissue growth, and prasugrel is not known to stimulate tissue growth.

The sponsor was asked to perform some cell culture studies and they obliged. They completed them and submitted them very recently. They appear to be negative. We're still reviewing them. Actually, the review team has reviewed them, but I haven't had a chance to look at them yet, to be honest with you.

But be that as it may, in those studies, prasugrel did not increase cell proliferation relative to starved cells, stimulated by addition of 10 percent

fetal bovine serum, and the drug had no effect on tumor xenografts, human tumor xenografts, from lung, colon or prostate in vivo. So that's encouraging.

One could posit that the effect of prasugrel has something to do with platelets. It's a potent antiplatelet agent. Maybe platelets cause tumors to thrombose and prevent metastases. I don't know, but it's not been demonstrated, and one would expect to see similar findings with clopidogrel, for example.

And Dr. Marciniak looked through the clopidogrel data very carefully in CURE, CAPRIS and CHARISMA, and didn't really see any effect there in terms of tumors.

The nonclinical studies are negative. There was a 24-month carcinogenicity study in rats. There was no dose response in excess tumors and no evidence of malignant tumors in the two-year lifetime study.

The 24-month carcinogenicity study in mice showed a statistically significant increase in hepatocellular adenoma. It was dose-related, but this causes induction of metabolizing enzymes and hepatocytes get revved up and they may smooth

endoplasmic reticulum and it's not that surprising, apparently. There was a trend in favor of hepatocellular carcinomas that was identified by Dr. Marciniak. It was not statistically significant. The Carcinogenicity Executive Committee did not think that it was important.

So as you've heard, there were some weaknesses in the data in TRITON. And I'm not criticizing the sponsor here. I'm not throwing any stones at them. But this was an outcome study for cardiovascular disease and so, of course, there's no baseline cancer screening. And investigators were to list -- I'm quoting the case report form -- "all ongoing medical conditions at the time of study screening."

So "ongoing" is somewhat ambiguous. It's subject to interpretation. If I had a patient who had had a breast tumor ressected five years ago, is that an ongoing problem or not? Well, I'm not sure. Different people might respond differently. So that's one issue.

Another issue is you would imagine that not much attention was paid to getting the histories in the

throes of ACS. As a cardiologist, when I'm faced with a patient who is having an infarct, I'm not really going to focus too much on "tell me about your prostate." I mean, seriously. So that's not what the study was designed to do.

Another issue was that, on rare occasions, some of the prior medical historical data were actually overwritten by adverse event data, and that was a coding issue and it was very infrequent and could not have influenced, I don't think, in our findings beyond a case or two.

Then as the sponsor has pointed out and the committee has pointed out, these analyses are post hoc and they are unblinded. So we can sit around and say we were blinded when we thought about this and thought about that, and we were, but all of us had access to treatment codes. So it's kind of silly. It's all post hoc.

The good news is that at baseline, the frequency of preexisting malignancies was the same, 2.6 percent in both treatment groups. That's what you expect with a large trial and that's good.

We have to talk a little bit about the nonmelanomatous skin cancers, because everything turns on them, as you've heard.

So they lack the clinical importance of most solid tumors and they're relatively common. They're readily cured by excision and they're largely ignored in cancer statistics. But they are malignancies, so they should be considered in terms of tumor stimulation, we think. They're just less important from a public health standpoint.

So this shows you the imbalance in neoplasia in TRITON. This was kind of the reconciled view between the sponsor and the agency as of October and I'll point out some of the highlights here.

So prasugrel is in red and clopidogrel black. So there's a significant excess here in lung and bronchus, colon and rectum, these are pretty well balanced. Kidney, you see more. Breast was three versus one, although women, unfortunately, only made up a quarter of the population of the study. So you can extrapolate that by doubling it and you'd get six versus two, a little concerning. Other and unknown

includes cancers that really were unknown, but it also includes a few other categories where there was maybe one tumor, I think, liver and a couple other categories.

But here it goes the opposite direction, nonmelanomatous skin. You have more than two-to-one clopidogrel versus prasugrel. So depending on whether you include the skin or you get a relative risk of 1.17, the kind of risk I call a shoulder shrug, it's like, okay, so what; but if you exclude the nonmelanomatous skin, now it's 1.31, so a little more concerning.

After we did this reconciliation with the sponsor, we thought about it more and convinced ourselves that there were four cases that should be reclassified and they all were unfavorable for prasugrel. So we added two neoplasms to the prasugrel group and we took two away from the clopidogrel group.

You ask, how can you take a cancer away? Well, these were supposed to be new cancers. So there were a couple cancers in clopidogrel that we thought were probably preexisting and shouldn't count.

So if you look at the data with the four cases reclassified, you see the relative risks are a little higher, 123 with skin and 138 without, and it becomes nominally statistically significant. But, again, it's all post hoc.

Here are the Kaplan-Meier curves including skin, excluding skin. You see the P value is .28 and .09. You've seen these before.

What's the makeup of the cancers relative to what you see in the U.S. population at large? Well, the U.S. statistics from 2004 are shown in black versus the prasugrel and TRITON in red. The contour is not that different. You see more lung and bronchus, colon and rectum, but in general, it's across the board kind of composition of the tumors.

Originally, the sponsor held strong to the view that the imbalance in neoplasia was due to ascertainment bias and it was pretty reasonable on its face. The relative risk of cancer was about 1.3. The relative risk of bleeding was about 1.3. Bleeding led to cancer diagnoses. So maybe that's what was going on here. The excess bleeding was leading to more

diagnoses of cancer.

We looked pretty carefully at this, basically, within organ systems. So if you had a gastrointestinal bleed or you had an anemia or even iron deficiency, then it was reasonable to conclude that if that had occurred before the diagnosis of a GI tumor, that, in fact, the anemia or GI bleed led to the diagnosis of the tumor.

So we did that for the GI system, the GU system, and respiratory system. In respiratory, we wouldn't accept -- we would accept hemophthisis as a tipoff to a diagnosis, but not an anemia, because one doesn't ordinarily do a bronchoscopy for iron deficiency or for anemia.

But it turns out that if you look at all of the cases for these three organ systems, and it's a fair percentage of the total neoplasia in TRITON, 61 versus 44, the relative risk is about 1.4. And if you look at people who had had an antecedent bleed, it's 1.4 and, therefore, when you subtract them and look only at people who haven't had a bleed, the relative risk is still 1.4.

So we don't buy ascertainment bias as accounting for the imbalance in cancers, and what we can say is bleeding led to cancer diagnoses, but it didn't account for the imbalance.

All right. Well, the sponsor showed some of my slides, so I'm going to return the favor.

These are the sponsor's tables from the May 9th submission. They split things up. So this is the vital status of subject with a preexisting non-benign neoplasm. These are subjects with a new non-benign neoplasm. And there are six deaths versus two, 27 versus 19. Add them up, you get 33 versus 21, for a relative risk of 1.57.

So just to be clear, and the sponsor can correct me after my talk, if I'm incorrect, but you had a number of patients who had a neoplasm, I believe somewhat over 300, where the sponsor went back at our request and knocked on the doors of investigators and said, "What's the vital status of these patients? We really want to know what happened to them." And they did that and came back with these numbers.

So because the relative risk of any kind of

neoplasm was about 1.25, they sought vital status information in 25 percent more patients who were in the prasugrel group than were in the clopidogrel group.

They're shaking their heads affirmatively.

This reflects that. So you have this imbalance in deaths, 33 versus 21, given that twist. But we're concerned about the imbalance in deaths and, certainly, I think it blows away the notion that this is ascertainment bias because we expect 100 percent ascertainment with death and nothing short of that.

Okay. Worse neoplasms. This was a classification that was worked out by Dr. Marciniak and there were 30 subjects. So by worse neoplasm, these are people who were not identified as having a new neoplasm. So they were identified as having a neoplasm when they entered the study, but things happened to them that suggested that the cancer got worse.

They required surgery, they died; that's worse. They developed mets, the cancer recurred, they had an adverse event or they received radiation therapy.

In this analysis, when these 30 subjects are

added to the subjects who had a new non-benign neoplasm, the Kaplan-Meier looks like this. Now, this is really the worst case scenario. We've excluded nonmelanomatous skin cancers. Dr. Marciniak excluded a brain tumor, but there was only one. So I put that up there for accuracy, but it doesn't matter.

One thing about this that's kind of interesting is when you see this, it suggests latency and if you were back at the beginning of this and thinking what's going on, you might start to worry about carcinogenesis, because you might expect a latency period if something was actually causing cancer. I think it has nothing to do with that. I can't necessarily explain it, but I don't buy that it supports carcinogenesis.

So in terms of neoplasia, there are some reasons to be reassured and there are reasons to be concerned. A lot of reasons to be reassured. The nonclinical data are negative. We don't have a putative mechanism of action. We have multiplicity of safety analyses. That's always a problem. So you always have the potential for a false positive finding.

Then from a mechanistic standpoint, there's no good reason to exclude the nonmelanomatous skin cancer and if you include them, then the signal largely disappears.

There are a couple concerns, however. One is the excess malignancy deaths. They're a concern. They can't be explained by bias, although you could say there's bias in terms of ferreting out some of the deaths. But there was some imbalance initially. And the other part of this that hasn't been brought out too much is that the risk of cancer would seem to be continuous during therapy, whereas the benefit is largely frontloaded. So if you're exposing someone to a risk of a tumor stimulator long term, that would be a bad thing.

I'm going to move on to quality and we'll talk about this conversion from salt to base. I thought the sponsor described it very well. I'll give you the history here, from our perspective.

The development was initiated using the free base form of the prasugrel drug substance, but the sponsor became aware that the salt form had better

bioavailability at higher pH, so they altered the manufacturing process to produce the salt form. But late in development -- and by late in development, I mean when prasugrel -- when the TRITON study was basically done -- the sponsor discovered form conversion from salt to base that ranged from 42 to 87 percent base content in the tablet batches that had been used in TRITON. So it was a problem.

So why do we care about this? Well, we care. These are the regulations and we may refuse to approve an application for any of the following reasons. Bear with me while I read this.

"The methods to be used in and the facilities and controls used for the manufacture, processing, packing or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability and bioavailability." So we care.

The way the sponsor approached this was to assess the pharmacokinetics and the pharmacodynamics, and I'll show you our view of that. It's not really very different from their view.

You have to recognize, again, that prasugrel is a prodrug and it's not readily measurable in plasma. The active moiety, fortunately, is measurable. It's R-138727, and the pharmacodynamics can be assessed through studies of platelet inhibition.

So the relative bioavailability of the active moiety was compared in lots with low, medium and high percentages of conversion; so five percent, 58 and 70 percent of the 60 milligram loading dose. And bioavailability was found to be pH-dependent, as the sponsor told you. So it was looked at in the absence of a proton pump inhibitor and in the presence, which was lansoprazole, was used in these studies.

Now, in the absence of a proton pump inhibitor, there is just no problem. The prasugrel lots with low, medium and high conversion are bioequivalent and there's no issue. But in the presence of a proton pump inhibitor, those three lots are bioequivalent with respect to the area under the curve, but they're not bioequivalent, they are bioinequivalent with respect to C_{max}.

These are the data here. These are ratios of

means. I hope you can read this. This is all in the presence of a proton pump inhibitor. So a ratio of means between medium conversion and low, high and low, high and medium, and you see the AUCs down here, the 90 percent confidence intervals are fine. They're all within 80 to 125 percent. But for C_{max}, the 90 percent confidence intervals are not within 80 to 125 percent range. So we have a problem for C_{max} in the presence of a PPI.

The platelet aggregation studies get at the pharmacodynamics. And you'll see here the low conversion lot, medium and high conversion. High conversion is the one to pay attention to, in black. This is percent inhibition of platelet aggregation. This is time in hours; so at half an hour and one hour, there's a statistically significant difference between the high conversion and the other two, medium and low conversions, and same with one hour. But the effect accumulates. So when you get to two hours, you could see that these are virtually superimposable. So out to 24 hours, they're the same.

So the way that one could conceptualize this

is a shift in time. There's a delay in reaching maximal inhibition of platelet aggregation with the high conversion lot in the presence of proton pump inhibitors.

Now, this would affect the loading dose, of course, because the patient hasn't seen the drug. You could say, "Well, look, that shift is nothing. Why would I care about a little shift like that?" And I would turn around and say, "Look, it can be important, because 45 percent of all the events in TRITON occurred in the first hour." So the first hour -- excuse me -- 23 percent in the first hour.

So it actually is important what happens early. It's also important to recognize that for the maintenance doses, this doesn't matter at all. I mean, if you reach maximal inhibition of platelet aggregation X minutes later every day for perpetuity, it doesn't matter; it's just like taking the pill a little later. It doesn't matter. But this could be an issue.

If you look at the pharmacodynamics, prasugrel versus clopidogrel, straight up, the loading doses, you look at inhibition of platelet aggregation,

here, prasugrel and clopidogrel, you'll notice that at one hour, clopidogrel has reached only about half of its maximum inhibition of platelet aggregation, whereas prasugrel is almost the maximal in its inhibition of platelet aggregation. Prasugrel exceeds clopidogrel at all time points.

So this was an analysis that we did to try to understand whether this form conversion was important or not. The way the study was set up, the patient's loading dose was actually six tablets of prasugrel and it was from a particular lot of the drug. For days two through 30, they got drug from a second lot.

So one could look at the lot of drug that the patient received on day one, the loading dose, and look at events that occurred in the first day. Again, a lot of events occur in the first day, so that's the 45 percent. Forty-five percent of all the events occurred within the first day of the study. So this shows you the triple endpoint, cardiovascular death, stroke and MI, by lot.

I've switched colors on you. So now clopidogrel is red. The prasugrel lots are the black

lines. And with the exception of these three outliers -- these are very small subgroups, obviously, 40 patients out of 6,500 or something like that. With the exception of these, clopidogrel subtends all of the prasugrel survival curves, which suggests that prasugrel is at least as good as clopidogrel on day one, irrespective of the lot given.

The analysis was repeated for the first month. So now we're talking days two through 29. We're looking at the lots received during that point in time. And, again, with the exception of a couple small lots here -- not small lots, but small groups of patients who received a particular lot -- the results look good.

The sponsor told you that some of the form conversion occurred during manufacturing. Apparently, most of it did, but there was still some form conversion during storage. So we did the best we could with that.

We looked at the age of the tablets given to patients and divided them into quintiles by age from the newest to the oldest and looked at performance. So

we're looking at the triple endpoint over the first month, both in the presence and in the absence of a PPI, and the ordering of these quintiles is random. In fact, the black line tracks the newest pills, the freshest prasugrel, and it actually looks the worst compared to clopidogrel. So maybe it's like a good wine.

So there's no relationship between the age of the lot and efficacy in the presence or absence of a PPI. And, also, the hazard ratio is the same with or without concomitant PPI use. I actually didn't show this on here, but the sponsor showed it.

So a summary, salt-to-base conversion. We have bioequivalence and AUC for all levels of the product conversion from five to 70 percent with or without PPIs. In the absence of a PPI, we have bioequivalence in C_{max} for all levels of product conversion from five to 70 percent. With concomitant PPI use, we have bioinequivalence in C_{max} for all levels of product conversion.

So what are the ramifications of this? The inequivalence in C_{max} is tantamount to a delay in

reaching the maximal effect as determined by the platelet aggregation study, and the delay would affect the loading dose and could definitely impact peri-procedural events, and the delay would not affect daily maintenance therapy. We don't have any evidence that the delay did affect peri-procedural events.

In the absence of PPI use, form conversion from five to 70 percent has no effect on bioavailability. It's important to note that approximately 60 percent of the subjects in TRITON never received a PPI at any time. So for the non-PPI users, the safety and efficacy are well characterized. That's a lot of patients. So with concomitant PPI use, the form conversion could only decrease bioavailability. So it shouldn't impact safety if you're getting less of the drug.

The concern regarding decreased bioavailability is decreased efficacy. In TRITON, prasugrel's efficacy was fairly consistent in all lots tested, you saw that, and across the spectrum of tablet ages, with and without PPI use.

So based on the current manufacturing control

strategy, the to-be-marketed batches of prasugrel tablets may contain significantly lower levels of base than the batches used in TRITON. So for non-PPI users, as long as the form conversion of the to-be-marketed product is within the range that was studied, five to 70 percent, it would be bioequivalent to the product tested in TRITON.

For PPI users, a marketed product with less conversion than the lots used in TRITON, but within that range of five to 70 percent would have enhanced bioavailability, but the data from TRITON in the non-PPI users supported safety.

This is basically the same analysis the sponsor showed you in terms of overall risk-benefit. I like what they showed with the graph. I used colors, red and green.

But for 1,000 patients treated with prasugrel instead of clopidogrel, you prevent 24 endpoint events. We're talking about 21 nonfatal MIs, three cardiovascular deaths, no strokes, and the cost of that in terms of excess bleeding is 10 TIMI major or minor bleeding events. Two of them would be bleeding deaths,

three would be nonfatal TIMI major bleeds, and five would be TIMI minor bleeds. And I agree that the 19 TIMI minimal bleeds belong in a slightly -- I wouldn't subtract them straight out. They'd have to be weighted.

The cancer, the causality is uncertain. The main problem there is if it is causally related, the risk is continuing as you give the drug.

I believe that is all. Yes. Thank you for your attention.

DR. KONSTAM: Okay. Thanks, Dr. Unger.

I actually want to thank the entire FDA staff for really excellent documentation and really a very clear presentation.

We're running a little bit late. We were supposed to break for lunch at 12:00. I want to go ahead and have an opportunity for questions for Dr. Unger now. Let's see if we can do it in about 20 minutes and then break for lunch. If we can't, we'll keep going, but let's give it a shot.

So let's start on this side of the table. Questions for Dr. Unger? Nothing? Okay.

DR. NEATON: I'll come back to the cancer.

So I just don't think, given the information you presented, I have the same concern that you expressed in your slide, because I can't interpret that relative risk of 1.57 at all.

So as I understand the information that the sponsor presented this morning earlier, a relatively small percentage of the cancer deaths are preceded by a diagnosis of cancer. Most of the cancer deaths that were -- the numbers were 22 versus 16 or something like that, had not had a history at baseline, for example,

So what you have done is selected out people with a newly diagnosed cancer during follow-up, and I think what you've established is that the subsequent survival in each treatment group is around 20 to 25 percent. If you put the numbers together in that table, it's somewhere in that ballpark.

But what the problem with the relative risk is, is you don't know anything about the cancer deaths among the people that occurred that were not newly diagnosed in that period. So I don't understand how you can compare the -- your randomization is no

longer -- your comparison is no longer protected by randomization, because there are deaths almost certainly occurring from cancer that you just have not ascertained.

DR. UNGER: I think that's fair. I think this probably paints the worst case, which I'm obliged to do, I think. This would be the worst case, the 1.57, 33 versus 21 cancer deaths. And, again, this is from the sponsor's table. It's just that the sponsor went out and beat the bushes to obtain vital status on the original patients who showed up with a neoplasia in the SOC, as an SOC term.

DR. NEATON: I think that's fine, except that there's clear limitations, as you mention, and there were only 2.6 percent, something around that, that had a history of cancer. From the table we saw this morning, there were only a handful of deaths in that group.

DR. DOMANSKI: Marvin, could I come back to this slide for just a second? I would appreciate hearing the sponsors respond to that.

DR. MACIAS: I'll use the same slide.

So what these two tables are is this is the reconciliation of the 311 patients that we went to get extended follow-up on. So when the information came back, the investigators pointed out to us that of the cancers that we had queried about, 28 versus 10 were actually preexisting. And then 100 versus 84 were new, and this is consistent with what we saw in the original dataset, that we had more cancers. When we did the follow-up dataset, we had more; when we reconciled, we had more. So it's always been consistent with regards to new.

However, when we calculated the risk of death, if you wanted to calculate the risk of death over all patients, we would have added 28 to 100 and got 128 and six to 27 and got 33 and done the percentage, because we no longer can index this against the randomized population because it's not a randomized comparison anymore.

But what you do when you divide 33 by 21 -- and what's missing here is you're just putting a denominator of 6,700 and some patients under each one. You're indexing those against the randomized

population, and we don't believe that you can do that. You have to index it against the population at risk, and the population at risk is the population you did follow-up on.

DR. NEATON: Well, I just want to -- and let me just pursue it, since I asked the question, just for a moment.

I guess what I'm hearing you say is that you think this data are uninterpretable in terms of implicating this drug in producing cancer. Is that a fair statement?

DR. MACIAS: Well, actually, slightly different. What we would argue is -- and one of the things -- and I appreciate everybody has different ways of looking at this. So this is not trying to push one against the other.

But when we looked at the data, what we wanted to know was for subjects who got diagnosed with a new cancer, was the percent mortality the same in both groups. That's the question. And this comes pretty close. It may not be in -- obviously, 28 and six, 10 and two, those are basically the same

percentages.

So that's how we looked at it, because we said once you ask for follow-up of a cohort of patients that's defined by a post-baseline event, you have to use the at risk population, which is that cohort.

Do you want to comment, Phil?

DR. KONSTAM: All right, if you feel it's important, because I think the panel's got it, but go ahead.

DR. SCHEIN: Again, Phil Schein, University of Oxford.

I just want to put this whole discussion into perhaps a little broader context so that you have a perspective, at least as an oncologist would approach this. And we're talking about the issue of biologic plausibility.

The timeframes here are relatively short. How long does it take for a cancer to emerge and then grow sufficiently to kill? Is it biologically plausible that some of the tumors you're seeing here could have arisen de novo during the time course of the treatment and then gone on?

Richard Peto addressed this, as you probably remember, an important *New England Journal of Medicine* article relating to the SEAS trial, cholesterol-lowering therapy, back in September of 2008.

His conclusion there, which I agree to, but he approached it from epidemiologic evidence, having studied the development of cancers, smoking and other, was that it was implausible that a large number of tumors over a broad range of tumors, not with specificity, could have emerged and killed within a very finite period of a person's life.

I approach it perhaps more biologically. You have to recognize, from the initiation of the transforming event to the creation of a tumor that you might be able to find, let's say of one gram in size, we calculate there have to be about 30 doublings to create about 10-to-the-8th, 10-to-the-9th cells, 30 doublings. And for adult solid tumors, the doubling time is estimated to be about two months. To kill, you need another 10 doublings.

The latency period generally recognized for

most solid tumors in adults is at least five years. Smoking, it's much longer. Of things that we can measure more carefully, it's long.

The American Cancer Society provides guidelines for colonoscopy, how frequently should you have one, in order to find and interdict developing colon cancer. Their recommendation is 10 years, not 10 months, and certainly not six months. That's the length of time we're dealing with.

With hormone treatment, for example, in the postmenopausal period, the development of -- the first signs of development of a breast cancer emerging because of this new stimulus is about five years and the risk increases from there.

So the timeframes here are very short to imply that this drug has done anything to produce any small difference that might arise. So I think that has to be put into the conversation, in addition to the numbers, and what is the biologic plausibility. It's not that you shouldn't continue to study this in relation to the drug, but this would be an extraordinary precedent in that the stimulators that we

recognize, and I think Dr. Unger mentioned that perhaps in the beginning of his presentation, are largely growth factors. And EPO is one of the greatest concern, and hormones, but not simple chemicals like this.

Thank you.

DR. KONSTAM: All right. Thank you very much.

Can you help me? You had a number on your slide and in your document of a savings of three cardiovascular deaths per 1,000, and on Dr. Antman's slide, it was four per 1,000, if I remember right.

Can you help me out here? Is there a rounding issue?

DR. UNGER: I imagine it's a rounding issue. We don't disagree. We had to go back and -- if it's really -- is it really important to know which is -- I mean, it's --

DR. KONSTAM: It may be, I don't know yet.

DR. UNGER: I think it's a rounding issue. I'd have to go through the --

DR. KONSTAM: Okay. So we don't know

exactly. It's somewhere between three or four cardiovascular deaths, as defined.

DR. UNGER: Okay. We could go back to one of the early slides.

How come the sponsor can just make a slide appear and I have to do this? Government's got to work on that.

DR. TEMPLE: Ellis, could that be because of U.S. versus total?

DR. UNGER: No, no. I'm trying to find one of the first slides on -- that's what I'm trying to find. Okay.

So the question is a cardiovascular death or all cause death?

DR. KONSTAM: You had cardiovascular death on the slide I'm talking about.

DR. UNGER: Well, here's the cardiovascular death, two versus 2.2 percent. So again, they're rounded, so you're going to multiply them by 10 and then subtract, depending upon how you do it.

DR. KONSTAM: Okay. So you rounded down, they rounded up.

DR. UNGER: Yes, maybe.

DR. KONSTAM: I have another question for you and maybe the sponsor I'm not sure.

I didn't see anywhere CABG-related deaths pulled out. We have cardiovascular deaths. I assume deaths occurring postoperatively would be considered cardiovascular deaths.

I saw two, if I remember right, CABG-related bleeding deaths. But I guess I'm just wondering about it. But there's a lot of CABG-related bleeding and that might increase the likelihood of a CABG death, without being called a CABG death -- without being called a bleeding death.

So I haven't seen that anywhere, CABG mortality in the two groups.

DR. UNGER: Well, you're remember those numbers right. For bleeding, fatal bleeding, it's two versus zero. And I don't think -- unless Dr. Hicks thought of it, I don't think we considered CABG-related deaths.

Do you guys? Okay.

DR. MACIAS: Can you guys bring it up,

please?

DR. UNGER: See, here comes the magic.

DR. MACIAS: Don't say that yet.

Why don't you go ahead and bring it forward?

So this is just all cause mortality, CEC adjudicated, all treated patients who underwent CABG. So this is just prasugrel versus clopidogrel. This is death in patients anytime after CABG, 3.3 percent in the prasugrel group and 7.6 in clopidogrel; death within 30 days, if you're a cardiovascular surgeon, 1.9 percent and 5.8 percent.

Probably the most important one here is the question about who went to CABG within seven days of the last dose of study drug. Here, the mortality is 3.7 versus nine percent. So this is what we have as regard to CABG. I can show you the -- I'll just wait until you're done.

DR. KONSTAM: Well, that's good. If I'm looking at it, and maybe the panel can see it or the FDA can say that I'm misreading it, it doesn't seem as though the substantial, I'll use that word, excess bleeding in the CABG patients is translating into

excess CABG-related death, at least from these data.

Is that a fair statement?

DR. MACIAS: That's what we would --

DR. KONSTAM: I know you would agree with that.

Does anybody disagree with that? I don't hear anybody disagree with it either. So maybe that's right.

Jim?

DR. UDELSON: Can I go back to a question for Ellis?

Can we go back to your -- if you can magically make your last slide appear, with the deaths and the MIs?

DR. HICKS: Actually, Jim, do you mind if I just clarify one thing.

DR. UDELSON: Sure, Karen.

DR. HICKS: That all of the CABG-related bleeding in the clopidogrel group occurred on the first day of CABG and that all of the CABG-related bleeding in the prasugrel group either occurred on day one, the day of operation, or postoperative day two.

DR. UDELSON: Ellis, on your slide with the deaths, would I be correct in saying that those deaths are deaths that occurred as a component of the primary endpoint; in other words, deaths that were a first event, the cardiovascular deaths on top of that slide?

DR. UNGER: Are you talking about the slide that I showed that had the three --

DR. UDELSON: Yes.

DR. UNGER: Those are, yes, endpoints, because that is the endpoint slide.

DR. UDELSON: So what is -- because we've also seen that the recurrent events -- if you count from nonfatal events forward, the recurrent event deaths are seemingly much lower with prasugrel, whereas on the lower part of your slide, if you had a bleed and then died of intracranial hemorrhage, you were still counted as an intracranial hemorrhage death.

Do you have a sense of how it looks if you ignore the nonfatal events and just count cardiovascular deaths versus the bleeds?

DR. UNGER: Well, I would say -- I think the best way to look at deaths is just the -- I showed a

slide that showed all cause --

DR. UDELSON: All the deaths.

DR. UNGER: -- all deaths and you can -- I don't know if we could get to that very easily. But it shows pretty well. It's early, unfortunately, in the presentation, at the very beginning. There it is.

So I think this is the way to look at it. You could argue that some of the bleeding deaths -- sometimes it's difficult to make a distinction between what's a cardiovascular death, if a patient exsanguinated. So any way you slice and dice it, this is what you get.

DR. KONSTAM: Yes, Richard?

DR. CANNON: Ellis, can you go to slide 30, before we break for lunch, find it quickly? It's the one that shows the cumulative benefit-risk of prasugrel compared with clopidogrel by time.

So I found that slide to be helpful to me, if I interpret it correctly, and this is along the lines of the question that I asked Elliott earlier, because I'm struggling with, and I know you guys struggled with, is there a point in time beyond which continued

administration of prasugrel may not be defensible? I mean, the risks may outweigh the benefits.

This suggests to me that for the entire population, that you get the biggest bang for the buck early on, because you prevent so many primary events and, yes, there's bleeding, but on a ratio basis, you get more benefit than per unit harm. But even over time, it plateaus, there's still a net benefit related to the bleeding risk for continuation of prasugrel for the entire group.

So my question is, is that true for both the subgroups? Is that true for the STEMI population as well as for the unstable angina population, that that apparent benefit is maintained over time beyond that initial major benefit; that beyond 30 days or 60 days, that that benefit or that apparent favorable ratio of benefit to harm is maintained?

DR. UNGER: That's an excellent question. I don't think I actually plotted it out. But for the quarter of the subjects that had SC-segment elevation MI, you know that the curves were parallel past two and a half weeks. So it would look somewhat different if

you plotted it out.

If you were --

DR. CANNON: You're right, I do recall that the primary endpoint curves paralleled for the STEMI population. I don't recall the bleeding risk, whether the bleeding risk began to diverge for the STEMI population such that that might make that red line lower for the STEMI group.

DR. UNGER: I didn't show you bleeding by stratum.

DR. KONSTAM: If there are no incremental savings of endpoint events, of efficacy endpoint events, I'd think it would be pretty -- I think it's a good question. We should see that.

DR. UNGER: It's easy to do it, but not standing here.

DR. CANNON: Again, I'm struggling with, and I think that ultimately we'll have to come to grips with, this issue of the risk-benefit equation over time, and I'm sure you don't have that for men versus women. You don't have a similar plot.

DR. UNGER: No. No, but it's an interesting

concept.

DR. KONSTAM: Bob?

DR. TEMPLE: But in that, you have to distinguish between maintaining the difference that you got at the beginning and adding to it. It's very clear that you don't add to the difference in the STEMI population, but that doesn't mean that if you switch back, it wouldn't -- they wouldn't close up. You don't know have any data on that.

But can I ask Ellis something?

One of the possibilities raised by the last question and raised by others is that you might use one drug for a period of time and then switch, at least in people you were worried about bleeding on or whatever.

Do you have a view about whether, in the absence of data on making the switch, it's plausible to believe that you could at least, upon switching, get whatever benefit clopidogrel has? I mean, you wouldn't overshoot. Would you overshoot in some unpleasant way or would platelet inhibition dip away for a while? Do you have a view on that, again, in the absence of data?

DR. UNGER: The sponsor showed data, people

switching in both directions, and what they showed was that if you switch from prasugrel to clopidogrel, that inhibition of platelet aggregation is lessened.

Now, I don't know exactly how that was -- I mean, we -- I don't know exactly how that was done, if it was just you change maintenance dose with no load, that's it.

DR. TEMPLE: Ellis, was it lessened to where clopidogrel was or lessened below what clopidogrel would do? I don't remember those.

DR. UNGER: You guys showed the slide.

Just while he's putting the slide up there, I worry about the logistics of switching, which is a different issue.

DR. MACIAS: We're pulling that slide up. It's right here. We'll use our other magic wand here.

So this is the slide I think Dr. Temple is referring to. Right? Okay.

So remember that this actually is even different than what we're talking about with the usual dose, and even if you were willing to give 150 milligrams of maintenance dose of clopidogrel, this

is what would happen.

Here's the 10 milligrams of prasugrel and that's your MPA right here. If you then switch after two weeks, you've switched now to clopidogrel 150 milligrams, no load having been given by these investigators during this switch, your MPA is higher. So your ability to inhibit aggregation of platelets is less with 150 milligrams of clopidogrel compared to what it was when you had 10 milligrams of prasugrel.

So I reiterate what I mentioned earlier, and that's 150 milligrams of clopidogrel and 75 is, of course, the usual dose.

DR. TEMPLE: Okay. But that isn't my question. If someone were to switch, and it were possible, from prasugrel to clopidogrel, they would be doing it because they want less bleeding and they would know full well that platelet inhibition would be reduced to clopidogrel's level of platelet inhibition.

My question is would there be a problem -- let's say you wanted to do that. I'm not advocating it. I'm just saying let's say you wanted to do that.

Would there really be any difficulty in saying, okay, on day 30, I'm switching and I'm going to stop the prasugrel and I'll start clopidogrel on day two or something like that, and I know perfectly well inhibition will drop down, but it won't overshoot because there's two drugs, because clopidogrel isn't going to add significantly, and it won't drop down to nothing, because you're taking the clopidogrel.

If you thought that was the right thing to do, is what I'm asking, could you do it and get the clopidogrel benefit, whatever that is, plausibly, or is there something additional to worry about?

DR. MACIAS: We're asking a theoretical question here and the best we can do is provide the information. The crossover information is one. The other information is the discontinuation, the bump-up in events that we saw for the primary endpoint. I showed you this earlier in response to a question, where there is a rebound that's higher with clopidogrel than with prasugrel, which is much more muted.

So for some period of time while this crossover is occurring, your patient would be at

increased risk of events. We saw that after discontinuation of clopidogrel to a greater degree.

DR. KONSTAM: Okay. I'm hoping there are not too many more questions.

Would everybody be comfortable if this was the last question?

Okay, two more questions and let's see if we can break.

DR. KRANTZ: I'll try to be real quick.

I just had a question for Dr. Unger on slide 25 regarding heart failure death. I was struck by the fact that there was actually no difference in heart failure death, yet when the TIMI group presented, they mentioned that very large myocardial infarctions were substantially reduced.

So just as a corollary, ischemic heart disease is the leading cause of heart failure, might you expect that in preventing myocardial infarctions, you'd see a reduction in heart failure death? And I wonder, is that just a question of power, limited follow-up, or is it the over-reliance on our biomarkers to determine MI in terms a definition?

DR. UNGER: I can only take an educated guess, and I guess I would say that if you don't design a process and a case report form to carefully ascertain heart failure, then you're just getting whether the investigator said this patient had heart failure. So I would think it's not that careful. One would expect to see the same kind of relative risk in favor of prasugrel, but I'm only guessing.

DR. KRANTZ: And in follow-up, is there any ejection fraction data, Dr. Antman, that would support that there's a preserved ejection fraction amongst the prasugrel treated group relative to clopidogrel?

DR. ANTMAN: We don't have ejection fraction data. But since I'm here, I'm just going to actually point out one other thing to you, which I think helps explain your answer.

It's this one here, called acute MI, because when someone says why did a patient with myocardial infarction die, they might list, as a consequence of the acute myocardial infarction, well, there's only two reasons you can die after acute myocardial infarction, and that includes congestive heart failure as a

cardiogenic shock. So whether or not it got coded here as shock or whether it got coded here, I think this helps you understand there were 24 so-called acute MI deaths versus 36. That, I think, answers the question you had.

DR. KONSTAM: Okay. Yes?

MR. FINDLAY: You said that you had reached the conclusion, you and the reviewers, that use of prasugrel would be discouraged in older patients, older adults.

Could you elaborate a little bit on how you define older, given the conversation that occurred earlier and your sense of that?

DR. UNGER: Seventy-five and over. It's a bit arbitrary what you say the cutoff is, but we're not talking about an absolute contraindication. Then I guess it would be more important to actually pick the right age. But our thinking right now is 75 and over.

MR. FINDLAY: Thank you.

DR. KONSTAM: Okay. Actually, I had one suggestion that maybe with the stimulus package coming, maybe you could get somebody to help you with your

slides.

DR. UNGER: I'll take that under advisement.

DR. KONSTAM: I'll put a word in.

Okay. So we're now going to break for lunch. We'll reconvene again in this room. I'd like to try to reconvene by 1:30. Please take all personal belongings you may want with you at this time.

Panel members, please remember that there should be no discussion of the meeting during lunch among yourselves or with any member of the audience.

Thank you.

(Whereupon, a lunch recess was taken at 12:07 p.m.)

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

DR. KONSTAM: We're going to move into the open public hearing segment of the meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To assure such transparency at the open public hearing session of the advisory committee meeting, the 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 the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if

you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not prelude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair.

Thank you for your cooperation.

DR. WEAVER: Good afternoon, everyone. I'm Doug Weaver, President of the American College of Cardiology. And I have worked with Lilly in the past, but I don't have any known conflicts or relationships with them at the current time.

The American College of Cardiology felt that it was important to comment today because there is a seeming yin-and-yang in the approval decision of prasugrel to be used in cardiac patients who are at moderate to high risk of coronary syndromes and undergoing coronary stent implantation and require dual antiplatelet therapy.

The added effectiveness of prasugrel in reducing the rates of recurrent nonfatal myocardial infarction, re-hospitalization for ischemia, and stent thrombosis is clinically meaningful.

Over the past few years, we've learned a lot about the effectiveness of clopidogrel and sometimes the failures of the drug. There is mounting evidence that 15 to 25 percent of patients appear to have some resistance to the drug. Recently, we have learned that this may be, in part, due to some genetic differences among patients that could influence the way in which the drug is metabolized. We're also aware of possible interactions that released some proton pump inhibitors with clopidogrel, as well, and subsequent thrombotic events. However, I point out that the absolute

importance of these interactions is still unclear.

On the other hand, the large comparative study of clopidogrel and prasugrel showed added protection and benefit of prasugrel, particularly in patients under the age of 75 and in those without a history of possible or known cerebrovascular disease and those of normal or increased body weight.

Certainly, safety risks are inherent in all drugs and the studies presented here today show that prasugrel is no exception. So in the yang side of the equation that I mentioned in my opening remarks, we are concerned about whether the added bleeding risk, particularly fatal bleeding, can be mitigated.

Although the study showed that excluding specific groups of patients using clinical characteristics would ensure safety, there still remain two important questions, in my mind.

First, as I understand it, the segregation of patients using the set of clinical characteristics into those unlikely to benefit, as well as those having a high risk of bleeding, was done in a post hoc analysis. Can we be sure that the same findings would be present

if it was done in a prospective cohort of patients?

Second, in this country, where direct-to-consumer advertising and detailing to physicians is common, can we be sure that a product label alone will be adequate to prevent the prescription of the drug to a subset of patients having those high risk factors for complications?

To use the analogy, after clopidogrel became available for prescription, there was a great deal of marketing of the drug both in direct-to-consumer advertising and not only to cardiologists, but to primary care physicians, not all of whom were aware of which patients had been shown in trials to benefit, nor were they aware of the possible hazards of the drug.

Therefore, we believe that if the drug is approved, additional studies should be conducted to ensure its safety, as well as to ensure that it's prescribed to those patients who might benefit and who are unlikely to be harmed.

We believe that such additional studies are needed to improve the public confidence about prasugrel, but we also believe these could be done as

part of a post-market surveillance program.

The American College of Cardiology is committed to working with the FDA, the manufacturer, if asked, to help conduct such studies and provide the data required to ensure patient safety and improved health outcomes.

As many of you in the room know, the American College of Cardiology currently has several real world data registries of patients, including a cath and angioplasty registry, which includes the patient records on over seven million people, which includes clinical indications, co-morbid illnesses and drugs prescribed. These registries are, in fact, used in over 1,200 hospitals in our country and essentially every hospital that is doing stent implantation.

We also have an outpatient registry that's able to track patient conditions and outcomes. The American College of Cardiology has worked with the FDA in the past in other post-market surveillance issues. We believe that a rigorous study such as this is required and that we must go far beyond educational flyers to physicians and the simple post-market

reporting of possible drug-associated adverse reactions.

For one thing, patients with conditions in which prasugrel will be a benefit also commonly have other clinical conditions that can cause bleeding, stroke and fatal bleeding, and there would be a need for clinical characterization of the patient in order to adequately interpret the findings. Such an approach would be superior and more accurate than attempting to use case reports, simple administrative or pharmacy data in understanding the safety of this drug in the real world setting.

Therefore, it seems prudent to design a post-market registry outside the manufacturer's typical post-market analysis to monitor safety for a period of time to be certain about the safety profile of this new but important drug.

The FDA could additionally work with other agencies, such as CMS, to establish evidentiary review policies that collect data on prasugrel's safety and efficacy. Professional guidelines for the care of patients, such as those prepared by the American

College of Cardiology and the American Heart Association, will continue to evaluate the published studies to inform and help education physicians on the most appropriate treatment options for antiplatelet therapy.

So, therefore, in summary, we believe there is a benefit from access to an additional and more effective antiplatelet therapy and those patients who were at highest risk for a coronary event. However, we must also ensure that the drug is used appropriately, to the appropriate set of individuals, and that it is safe in the real world setting.

Thank you for allowing me to make these comments.

DR. KONSTAM: Okay. Thanks, Dr. Weaver.

We have one other scheduled speaker.

DR. SEREBRUANY: Good afternoon, everybody. I'm proud to talk in front of you today. I also want to express my deep empathy to the agency and to the panel, honorable panel, to allow me to express my view. I represent myself only and my wife paid actually for the travels here.

Next slide.

I also have a pattern to be disclosed with some of our friends with Lilly related to prasugrel development. I get research grants from both ends and I heavily consult on antiplatelet therapy on a variety of issues.

So the first piece of evidence I want to present, kindly, to you is in the question part between page 1 and 2 related to the benefit and, in lay terms, what the agency acknowledged, and it takes guts and glory to acknowledge it, is that only about half of the events were identified by investigators. In lay terms, again, it means that clinically relevant events were not necessarily the MIs which are presented in the final analysis of the TRITON trial.

So if we go to see how the definition of MI was actually emerging, there is a straightforward definition, which the respectful team used in the prove trial, which resulted in a pretty low MI rate in 18 to 36 months.

Then if we look at the JUMBO, there is certainly a lot of things going on peri-procedurally

and certainly the definition did not consist of one sentence. So if we look carefully what happened at JUMBO, then we realize when the change actually occurs. How TRITON was really justified by JUMBO, not really that much, because death and stroke go the opposite way and the only way to show that the trial was positive was to inflate the rate of MI.

Therefore, the rate of MI was calculated not precisely as clinically relevant MI, but this peri-procedural MI, which includes enzymatic flashes, enzymatic bumps, some chest pains, some unstable anginas, and the rate of 7.9 percent at 30 days is unseen and it should be about 4.5 and five compared to the relatively designed trial.

I was bombarded by people saying, "Victor, you don't understand cardiology," which is actually the case. I agree with that. But now when we know that the agency acknowledged that some of the MIs are actually not MIs and not all MIs are borne equal in this audience, then we need to think about it.

This is a TRITON, in my definition, which is present only in the design paper. Unfortunately, the

Maine New England Journal paper does not consist of any MI definition.

Now, we know that actually the definitions were changed during the course of the TRITON trial. The latest one happened in January of 2006, as reported in the wonderful review by the clinical team and the agency.

So the rate of MI and timing of the trial, obviously, TRITON stays away from the logic here, we use more hypertension control, heavily with statins, modify risk factors, look at me; we are very successful in doing that. And what we have there, we have 9.7 percent of MI rate and this MI is only in about 65 to 70 percent, as we now know, related to clinical events.

So this slide, you guys, we are not able to see somehow, but this is absolutely a pivotal critical slide. It suggests that in TRITON, when patients were loaded early or during the procedure, the benefit vanished. However, when you delayed the loading, when you do not allow clopidogrel to get onboard fast, then, of course, prasugrel 60 milligram has an absolute

advantage, because it works faster, it's more potent. It certainly blocks the vascular secondary events much for bigger situations. It's exactly so.

The most important part, actually, with regard to outcome are related to pages 329, 330 and 331. There are three Kaplan-Meier curves which suggest how the TRITON data look if only site-acknowledged MIs actually make the difference, and it makes a striking difference. Among the three Kaplan-Meier curves, when you can see in the binder from the federal agency, there is an immediate fast benefit of prasugrel, which certainly may be explained by these differences, and then the curves go absolutely in parallel; absolutely, again, in parallel. Go to page 329, 330 and 331. It's not my fantasies. It's what the agency actually tells us. What it means, that there is indeed the early benefit; however, the benefit does not expand later.

So when we start talking -- oh, this is a funny one. When we start talking about the net clinical benefits, people use the term here, we are comparing apples and oranges. No, we are comparing watermelons with raspberries here, because in reality,

now, when we know that all these MIs are real MIs and some of them are really enzymatic flashes, what we are balancing it with, we are balancing it with TIMI major non-CABG bleeds, which are the most difficult bleeds to get. This is only the absolute tip of the iceberg.

Okay. You want to deal with TIMI major bleeds, then pick up deaths and ST elevated MI only. You deal with these green juicy MIs which are there, then you should put minor bleeds. You need to put all of the data there, and then the benefit is for real.

What is even more important, that the agency acknowledge that self-defined MI by investigators is more predictable of death than the one which we are seeing here, and this is critical.

Moreover, on page 322, the agency says that if we count these MIs as it is compared to how the investigators say, the difference is not statistically significant. And the MIs reported by the investigators are of clinical significance. These MIs doesn't matter. Again, it's not me. It is what the agency says, when the death between MIs and non-MIs population, as reported in the green piece, are

different, meaning there is -- sorry -- not different, meaning MIs have no influence on death, how it is defined in the TRITON trial.

So this is so nice. This is so friendly. This is so like family-wise. We look at cancer and say, "Come on, it's nothing there." Are we kidding here? What are we doing here? Are we serious about all this?

So this is how the cancer may be, although I'm nobody from nowhere and I'm not an oncologist, but certainly there is a cause to that event. And this cause is definitely not direct carcinogenicity, that the risks have nothing to do with clopidogrel ticlopidine. It has nothing to do with tumor growth itself. But if the patient have already solid tumor, which is existing, preexisting tumor, and then you apply huge unseen chronic platelet inhibition, you break the barrier between the tumors and platelets, which are keeping it inside.

So solid tumors start to circulate, start to metastasize, start to disseminate, and that is why the curves diverge so highly at four months. This is not a

coincidence. This is a fact.

From the TRITON paper, we saw some of this balance in colorectal cancers, which was associated with bleeding. Well, a full truth, nothing but the truth. If you take the difference in two, number two, for new cases of cancer, this is how it looks. And all except skin cancer grows the wrong way.

Let's look at the total number of new cancers, which is 119 versus 87, by federal agency definition, which represents 27 percent of increase, based on my back-of-the-envelope statistics.

So what do we name? We name 18.2 percent vascular benefit, which is made from partly artificial MIs, which didn't yield any mortality benefit, a miracle invention; this is great news. However, 27 percent reduction in cancers for clopidogrel, meaning much worse results for prasugrel, we name a sporadic event. I rest my case.

The only last thing I will tell you, there is an ATM machine downstairs that says TRITON. It's where the money goes.

DR. KONSTAM: Okay. I think that that

concludes the open public hearing session.

The open public hearing of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

Okay. So I want to turn our attention to the questions and conduct the discussion for the rest of the afternoon along the outline of the questions and I'm going to propose a couple of things.

One is I would like to take the related questions en bloc and I'll tell you how I'm proposing that be done as we go forward. And I would like to go around the room for each block of questions that are related and get each member's opinion on each one. And through the questions, some of them are open-ended, some of them are more specific yes-no questions. So I'll cull out for you where I see the specific yes-no question that I'm going to ask you to speak directly to when we get to that.

I'm going to mention, Dr. Fox, you've been

quiet during the questioning period, which is great. I want to compliment you for that. As the industry representative, you don't get a vote, but I would like to solicit your opinion on these points, as well. So I'll take the prerogative, as we do go around the table, I'd like you to give your opinion on them, as well, even though we won't count you officially in the final vote.

So if that makes sense to everybody. The questions listing has a preamble, which I'll spare you. It's the basic aspects of the TRITON data. And so I'm going to begin with question one related to benefit, and I'd like to take the entire set of questions related to benefit as a block, and as we go around the table, ask each of you to comment on each of the elements that we'll cull out. So let me read through the question.

Prasugrel was associated with an 18 percent reduction in the hazard for the primary endpoint in the unstable angina non-STEMI population, a 19 percent reduction in the all ACS populations, P equals 0.0004, and a 21 percent reduction in the STEMI population,

P equals 0.019.

Half or more of the events occurred within the first few days and the difference between the groups was evident within the first day and either maintained, in the case of the STEMI group, or widened progressively in the case of the unstable angina non-STEMI group, through more than a year of follow-up.

Most of the first events were MI, that is, 73 percent of the first events, and that's where the difference between the groups was most clear. But cardiovascular deaths, 19 percent of events, trended in favor of prasugrel, as did all cause mortality. Strokes, eight percent of events were 0.9 percent in both groups.

So there's a series of questions now specifically related to what we get out of these data and let me sort of go through them for you.

So 1.1 says "Was the primary endpoint meaningful?" So as we go around the room, that's one yes-no question I'd like you to call out your answer to. You can explain yourself as we go.

In particular, comment on the strategy for

assessing MI. Ordinarily, the investigator reported events and the adjudicated events differed little, but in TRITON, only about half of the events were identified by the investigators.

So here is the second yes-no question. Is there a concern, yes or no, that the additional events, generally asymptomatic peri-procedural MIs, lack clinical significance? So I want your answer to that one. And what are the long-term consequences of nonfatal myocardial infarction? That's sort of an open-ended question you can comment on.

1.2. Clopidogrel has established benefits on these events compared to placebo. Based on the results of TRITON, can we infer that prasugrel would be superior to placebo? That's a yes or no.

1.3. Prasugrel was superior to clopidogrel in both unstable angina non-STEMI and NSTEMI populations. So 1.3.1, does the committee agree that these findings are sufficiently robust and the two populations are sufficiently related to support an overall claim for the ACS patient population? So that's a yes-no question and you can explain your

answer.

Finally, in this block, do the results support a superiority claim for prasugrel to the approved regimen of clopidogrel, noting that that's not a question of approvability. It's only a question of whether the efficacy data, per se, support a claim for prasugrel superiority to clopidogrel based on efficacy.

So with that, I want to start at this end. That's a mouthful, I know, but you can handle it, Richard. So let's start with you.

DR. CANNON: That is a mouthful.

Okay. So 1.1, so there are a couple of questions here. Primary endpoint meaningful, I thought that it was. The strategy for assessing MI, I think it was defensible and appropriate, because myocardial infarctions following PCI may not be clinically apparent and I do believe that muscle matters and that even though perhaps over the roughly one year follow-up, there weren't increased numbers of heart failure patients. Perhaps that's related to the way that they reported. But I do think, in time, the more muscle that one has, the less likely they are to have

adverse remodeling and congestive failure. So I think muscle does matter. So I think including biomarker evidence on infarction was reasonable in a trial that included an intervention.

Is there a concern that the additional events, generally asymptomatic peri-procedural MIs, lack clinical significance? As I said, I think they do matter and they might not show up immediately, but I think over time, peri-procedural MIs do matter. I think lost muscle means lost cardiac function, and over time, that will lead to heart failure.

Same thing for the long-term consequences of nonfatal myocardial infarction. The biggest risk is progressive adverse remodeling and development of heart failure.

So I think sparing any muscle is desirable and at the time that a patient presents with an ACS and PCI is being considered, you don't know. The tip of your nose may tell you that somebody is at particularly high risk of having a large infarct versus a small infarct, but the reality is you don't know at that point in time. So I think you have to assume that

someone could have a large enough MI that they would be left with substantial depression in LV function and, therefore, risk of heart failure.

1.2. Clopidogrel has --

DR. KONSTAM: Can I just ask you, for a second?

DR. CANNON: Yes.

DR. KONSTAM: So with respect to -- is there a concern -- I guess you've answered this. Is there concern that additional events, generally asymptomatic peri-procedural MIs, lack clinical significance? I guess your answer to that is no.

DR. CANNON: I think they do. I think they are significant.

DR. KONSTAM: So they do not lack clinical significance.

DR. CANNON: Right, right. I think they are important. It's just that one year may not be enough time to actually conventionally show that importance. It may take a longer period of time, but I think muscle matters, even a small amount of muscle saved matters.

Does that answer it?

DR. KONSTAM: Yes.

DR. CANNON: Do you want me to continue?

DR. KONSTAM: Yes.

DR. CANNON: Okay, 1.2 -- do you want me to just go through that?

DR. KONSTAM: Yes.

DR. CANNON: Clopidogrel has established benefits on those events compared to placebo. Based on the results of TRITON, can we infer that prasugrel would also be superior to placebo? And I believe yes. I believe had this been a placebo controlled trial, that prasugrel would have shown superiority over placebo. So the answer to that is yes.

1.3.1. Does the committee agree that these findings are sufficiently robust and the two populations are sufficiently related to support an overall claim for the ACS population? And I believe so. I think that the claim could be made -- based on looking at the data independently and collectively, that a claim, certainly for reduction in nonfatal myocardial infarction and stent thrombosis, can be made for the entire ACS population.

1.3.2. Do the results support a superiority claim for prasugrel to the approved regimen of clopidogrel? Yes, certainly with regards to preventing nonfatal infarction and stent thrombosis.

DR. KONSTAM: Okay. Dr. Paganini?

DR. PAGANINI: Was the primary endpoint meaningful? Yes. Strategies for assessing MI, clinical versus biomarker, I think that was well done by the study and well described.

Is there a concern over the additional asymptomatic peri-procedural MIs? I have no idea. I don't know. It's out of my field, so I won't comment on it. However, long-term consequences are nonfatal, higher risk for subsequent MIs, especially in the high risk population. So I think that's a big issue.

1.2. Is there established benefit over placebo with this drug versus the other? Yes, absolutely.

1.3. Does the committee agree? I don't know what the committee is going to do, but I'll tell you what I'm doing.

Finding robust, two populations is

sufficient, I think yes.

Then, is there a superiority? I don't know that. I can tell you that there is a superiority in non-responders. And so that I think is a very important issue, so that you have less non-responders. But superiority head-to-head in those that respond, I don't know that and I haven't really been convinced of that. So I don't know.

DR. KONSTAM: Can you explain that a little? I'm not sure what you're saying.

DR. PAGANINI: What I'm seeing is, at least initially, that there seemed to be less of a non-responder population with this drug versus the other drug, both in the loading dose, and then, also, if you go to the maintenance dose, you'll notice that there was a significant amount of non-responders by increased coagulation with either the prior drug and this drug.

I don't see -- I see the advantage of this drug being -- that it's more effective with less non-responders, the population with non-responders. As far as a head-to-head with all those that responded and

all those that responded, I'm not sure there's a superiority there.

DR. KONSTAM: But just looking at the clinical efficacy data across the whole population.

DR. PAGANINI: There is.

DR. KONSTAM: So do you feel that that clinical efficacy --

DR. PAGANINI: But I think it's more based on the non-responders.

DR. KONSTAM: Okay. So you're not sure about the clinical efficacy relative to clopidogrel. Okay.

Dr. Krantz?

DR. KRANTZ: So I think, in terms of the first question, was the endpoint meaningful, I think it was pre-specified and I think it was well designed. So I think I would answer yes to that.

I think the other question would be -- let's see here. The generally asymptomatic peri-procedural MI, I think I would echo a little bit what Richard was saying, that muscle matters, but, again, to my earlier comment, there's no objective data to suggest that they measured muscle function and, generally, that's

measured with an ejection fraction and, meaningfully, you're looking at cardiac performance, which wasn't done. So I'm really not convinced yet that the muscle matters argument is as strong as perhaps portrayed.

I do think that in terms of the peri-procedural MIs, that these are probably important, these biomarkers. It's a moving target with the way MIs become redefined.

I think Bob Temple is probably right; whether this is a simple risk marker of disease severity or disease burden or an independent prognostic variable is impossible to disentangle. But that said, in my clinical experience, I would say it is meaningful. So I would say yes, ultimately.

1.2. Based on TRITON, can we infer that it would be superior to placebo? I think that's beyond a doubt.

1.3. Does the committee agree that these findings are robust and the two populations sufficiently related to support a claim for overall ACS? I think for sure and certainly in the thrombus burden, it's probably greater in STEMI. It seems even

more robust.

Then 1.32, do the results support a superiority claim? I think as the primary endpoint was defined, I would say yes.

DR. KONSTAM: Okay. Jim?

DR. NEATON: Well, for the first paragraph, I think I'll respond yes, maybe, don't know. I guess I was reassured, in looking at the composite outcome, that the treatment benefit was present for the clinical MIs, those reported by the investigator.

The most common -- the prevalence of the size of the larger MIs, the treatment benefit was also there. And there was I think interesting data presented on the risk of recurrent events, although those could be some of the same type of enzyme-based MIs.

I think I agree with Dr. Cannon. You probably need longer data to understand the kind of clinical significance of these, unless there's other data sources.

Yes, I think it's superior to placebo and I think the findings are robust for the two subgroups and

I think the result supports a superiority claim.

DR. KONSTAM: Okay. I'm going to say yes for the fact that the primary endpoint was meaningful. I think the issue of is there concern about the additional events, I guess I'm going to have to answer yes and no. I don't have enough concern about it to detract from the clinical meaningfulness of the efficacy finding, but I guess I do have some concern in the approach that we'll get into later on to fully understanding the risk-benefit. And that's where I think that the issue of the relevance of the peri-procedural events and the purely enzymatic MIs becomes a little bit less clear.

I think we saw some nice data showing an association with subsequent adverse events and death, but as Bob pointed out, that could just be associative and not necessarily causal. So I think that does enter into an analysis later on of the risk-benefit that we'll have to think about.

Can we infer that prasugrel is superior to placebo? I would say yes. And are they sufficiently robust in the two populations? Again, I would say yes,

but I would sort of point out a couple of differences.

I do think that the two populations are different pathophysiologically. I think they behave differently clinically. I think their prognosis is somewhat different. And I think, as has been pointed out, the curves look different in them. It looks like the biggest bang for the buck efficacy-wise is -- most of the bang for the buck efficacy-wise for the STEMI population is at the beginning. whereas it's more continuous with the non-STEMI unstable angina group. And that's important because it's really only in the STEMI population that the CV death signal is evident or appears to be evident.

So I think the answer is, yes, that we can infer it with regard to both populations, but I think there are some caveats to that.

Let's see. Superiority claim for prasugrel over clopidogrel based on efficacy, I would say yes.

Okay. Mr. Findlay?

MR. FINDLAY: I'll answer these from my frame of reference, which is with less technical knowledge than most on the panel, but I think I have probably

enough to just nod at a few of these things.

1.1. Was the primary endpoint meaningful? Yes. I would agree with everyone else, for fairly obvious reasons. I would abstain from the other two questions in 1.1. I don't have the knowledge to answer to those.

1.2. Again, I think is sort of self-evident, yes. On 1.3.1, yes, I do believe that. And then 1.3.2, yes, but for most patients and not all.

DR. KONSTAM: Okay. Dr. Domanski?

DR. DOMANSKI: 1.1, was the primary endpoint reasonable? Yes.

Am I concerned about the adjudication or the event? No.

What are the long-term consequences of nonfatal myocardial infarction? I think there is strong evidence that the answer to that is death and probably, also, heart failure.

1.2. Based on the results of TRITON, can we infer that prasugrel is superior to placebo? Yes.

Do I agree, anyway, that the finding is sufficiently robust to support an overall claim for the

ACS population, that is, for both of them? Yes.

Do the results support a superiority claim for prasugrel to the approved regimen of clopidogrel? Yes.

DR. KONSTAM: Jim?

DR. UDELSON: So 1.1, was the primary endpoint reasonable? I think it was. And comment on the strategy. I've been thinking a lot about this and I think that if we, as a community, sort of buy into the ACC/ESC redefinition of MI, we have to search out these myocardial infarctions and, in fact, at this point, we'd probably be critical of trialists if this wasn't done. So I think at this point we have to do that and search these MIs out.

Is there a concern that the additional events lack clinical significance? No. I think we saw that the enzymatic MIs were associated with a higher risk, and that's been seen in many other datasets and I think they do identify a patient who is at risk. And I thought the analysis of the change in the recurrent events after the first nonfatal event was actually pretty compelling in that regard, as well. And the

long-term consequences of nonfatal MI I think identifies a high risk patient, even if it's enzymatic only.

1.2. Can we infer that prasugrel would be superior to placebo? I think so and I think when you line up CURE and the other clopidogrel trials, you can make that case as well.

Do we agree that the findings are robust in the two populations? I think there was a lot of internal consistency. I take your point about the different temporal effects, but I think the answer is yes.

1.3.2. Do the results support a superiority claim? I would think the answer is yes.

DR. KONSTAM: Okay. Dr. Flack?

DR. FLACK: Was the primary endpoint reasonable? Yes.

Is there concern about the additional events, the generally asymptomatic peri-procedural MIs lacking clinical significance? No, not really. They're different, but those bumps are associated with risk and whether it shows up immediately with pump dysfunction

or not, having an MI, big or little, is not good.

What are the long-term consequences of nonfatal MI? Not good. Death, pump failure, ultimately, dysfunction, and just not good.

Can we infer that, based on the results of TRITON, that prasugrel would be superior to placebo? Yes. And 1.3, was prasugrel superior to clopidogrel in both unstable angina and non-STEMI and STEMI populations and do you think that those findings are sufficiently robust? Yes. Those groups are different pathophysiologically, but the data looked pretty impressive for both.

The one caveat we might have to take with the STEMIs, particularly, the curves come together over time, is you have to remember that that was a much smaller group of people and when you start going out on survival curves and looking toward the later part of follow-up, you're getting into typically a much smaller sample size and things are getting biased out there. You're losing people.

So I don't necessarily know what that means or if you can just take it at face value that the

beneficial effect is still waning, but the beneficial effect appears to still be there.

1.3.2. Do the results support a superiority claim for prasugrel to the approved regimen of clopidogrel? Yes.

DR. KONSTAM: Okay. Dr. Fox?

DR. FOX: On the primary endpoint, I think this represents a traditional so-called hard triple endpoint. I have no quarrels with that.

On the strategy for assessing MI, I would agree with some of the comments others made that I believe the investigators and designers of the trial could have been lightly criticized had they neglected to collect those data, since it seems to be an evolving area of interest as to what, in fact, is the clinical importance of this group of events.

I think the analysis went to some length to emphasize that it was not disproportionately weighted towards minor biomarker elevations but, in fact, represented a spectrum and, if anything, a larger proportion of what most of us clinicians might consider real events.

I just would also maybe remember that these are unstable patients, that the enzyme elevations, whether you call them symptomatic or asymptomatic, in this patient population, probably differs from so-called asymptomatic enzyme leaks seen in patients coming for elective revascularization.

Long-term consequences, I'd just echo the thoughts of others. Whether it's causative of a subsequent event or merely a biomarker for risk of a subsequent event is, in my view, not particularly important to determine with respect to overall treatment effects.

On the question 1.2, I think the answer here is yes, but I would caution that it's probably not appropriate or, I should say, that you probably can't do a simple linear addition of the observed treatment effects or hazard ratios to come up with a final number, that either some fancy or statistical tricks would be needed to make an estimate of what the actual treatment effect versus placebo is. But I think the two observed treatment effects are large enough, so that the answer to the question is yes.

On 1.3.1, I agree with the comments of others. I think the results are consistent. And on the last one, I would agree, yes.

DR. KONSTAM: Okay. I'd like to take a pause now, ask the agency what they see as the issues.

Have we sort of resolved everything around this question? Do you have more concerns?

DR. STOCKBRIDGE: I think that's reasonably helpful. Your answer particularly to the question 1.3.1 differed some from the other people around the table and I wanted to explore that a little bit with you.

A question is whether there is a claim called ACS or whether the claim appropriately ought to be one in NSTEMI and one in STEMI populations, because, as you point out, they are different. If you look at the curves here, they look different.

How much would you expect that to be teased out in a label?

DR. KONSTAM: Yes. I'm not sure, but I do think -- and maybe there are more analyses that can be done. Okay. But I'll just give my reading of what I

see and ask others to comment.

It gets to a risk-benefit analysis for the clinicians at any time point in any patient and based on what I see in terms of -- and I don't usually read much into the shape of the curves. So I take that point. So, treading on tough territory, but as best I can see, it looks like there clearly is a continued effect over time in the unstable angina, non-STEMI population. I'm not clear at all that that's true in the STEMI population.

I think that the other sort of observation, which, again, I don't think you can take all the way home, but is interesting, is that the favorable trend in cardiovascular death was present in the STEMI population but not in the non-STEMI unstable angina population.

So I think both of those factors sort of weigh in on my thinking about, at any given point in time, what's the relative risk-benefit relative to the bleeds, and I think you could do more analyses on that. But it looks like it might be different in the two populations. It might be that in the STEMI population,

after a period of time, that risk-benefit starts to really narrow tremendously.

DR. TEMPLE: That's what I understood, too. But are you also saying that the mortality finding pushes you the other way in that group?

DR. KONSTAM: Yes, you're right. So actually, putting the two observations together makes me think that the risk-benefit actually -- that there's an attrition of the risk-benefit ratio across the whole population. But because the two things are -- you have the sort of flattening appearance in the STEMI ones, but the non-STEMI, which continues to spread, actually, you don't see the trend in the CV death.

I really wouldn't make too much out of those, except -- I guess just going back to the question, I do think that the STEMI and the NSTEMI population are different populations and I think they're behaving a little bit differently here. And it just isn't clear from the shape of the curves that there is a robust, maintained risk-benefit population in the STEMI population throughout the entire observation period.

DR. TEMPLE: So in answer to Norman's

question, that would lead you to think that labeling, should the drug be approved, should treat the two somewhat separately.

Is that true? That was a question.

DR. KONSTAM: I'd love other people's opinion. Yes, I know.

I wouldn't want -- okay. So I think that the efficacy findings apply to the entire population and I think that the labeling ought to reflect that this was a single trial with efficacy seen in the entire population. And I wouldn't sort of draw that line, from that perspective. However, in the description of the results, I think it would be reasonable to put some information about the fact that these two populations do differ pathophysiologically and there may be differences in the risk-benefit ratio in the two populations over time.

Does that make sense?

DR. STOCKBRIDGE: So compared to any of the other subgroup analyses that you've seen, all of which were pre-specified, too, weight group or sex group or gender group analysis, is that the way you're thinking

about this or is there something fundamentally different about this one, about the diagnosis, going in?

DR. KONSTAM: I'm not sure what you mean by fundamentally different. I mean, I don't think we -- we're going to deal with those other sub-populations when we get to the risk of bleeding and reflect back on the benefit, as well.

DR. STOCKBRIDGE: But typically, for a lot of the subgroup analyses that get done here, we put a whiskers plot in and say good luck trying to interpret any differences you may perceive here.

Is that sort of how you would expect to see this handled or are there two separate indications?

DR. KONSTAM: I don't see two separate indications, and I guess however it's handled, my reaction is it has to be something different than that. I mean, I just think where this comes in, if at all, it comes in in a discussion of the risk-benefit. If it's not clear in a very discreet, pre-specified, important sub-population that the benefit continues over a period of time, then I think that translates into a less

robust overall signal for risk-benefit in that population. I don't know how else to say it.

DR. TEMPLE: I think you said it a couple of comments ago, that you think overall, the overall result was what the study was about, so that's that; but that in discussing the trial, the safety data and so on, you might, as we do with lots of credible subgroups and are doing extensively here with credible subgroups, point out what some of the areas of uncertainty are.

That's how I understood you, anyway.

DR. KONSTAM: That's fair enough.

Jim?

DR. NEATON: I just want to add -- not directly related to this question, but we saw so many subgroup analyses today from both the sponsor and from the FDA reviewers, and I'm actually struck by the fact that for efficacy, there's absolutely nothing there.

So if you were to do any kind of test for heterogeneity among hazard ratios for the subgroups that were presented, the only one I can imagine that might even be close is a history of a TIA or stroke.

The rest of them are amazingly similar.

When we get to the bleeding, there's a risk-benefit issue that might be a little bit different, but I think we're dealing with a study with different populations, whether you call it STEMI or non-STEMI, men or women, older or younger, low weight or high weight, where the results are amazingly consistent in terms the treatment hazard ratios.

DR. KONSTAM: Mike?

DR. DOMANSKI: I hope I'm answering the question that's being asked, but if one sort of backs off and you're standing in the cath lab and you want guidance about whether this is an effective drug in a setting where you're revascularizing a patient with an ST elevation MI or a non-STEMI, I think the data from this trial are pretty clear in terms of guiding that therapy and guiding you to use this drug and guiding it as being a superior drug in that setting.

So that would be my answer to that question. Now, it may not be the question you asked, but if you didn't, ask it, there it is.

DR. KONSTAM: John?

DR. FLACK: Since we're dredging subgroups to death here, I just want to add one thing in the consideration of the STEMI cohort.

If you actually look back on the slide that was shown about the bleeding, the TIMI major bleeding, you actually don't really appear to pay a bleeding penalty with the STEMI MI group with the newer agent compared to clopidogrel, but you're getting better efficacy.

DR. KONSTAM: Okay. Any other discussion about this question before we move on to the next one? Okay.

So let's go on to question number two, risk. And what I'm going to propose is -- so the statement is made, "The primary risk was bleeding, which was clearly worse on prasugrel."

I'm going to ask the panel to take on questions 2.1.1 and 2.1.2 in a block, because 2.1.1 is pretty somewhat vague and open-ended, and 2.1.2 relates to CABG.

So 2.1.1 says, "What are the long-term consequences of nonfatal hemorrhage? So I'll let you

comment on that as we go around and then get into 2.1.2.

So in both treatment groups, bleeding was most frequent around the time of the index PCI and much more frequent following CABG. All types of bleeding are more frequent on prasugrel than clopidogrel.

Can patients likely to require CABG be identified prior to dosing and if so, should prasugrel be withheld in such patients?

I want you to comment on the first part of that, if you can, and then specifically answer the second part. If you can identify patients likely to undergo CABG, should prasugrel be withheld in such patients?

So let's start over here with Dr. Fox.

DR. FOX: On 2.1.1, I guess there have been some recent publications that have pointed out, at least in a retrospective look, the potential risks of transfusion. And it might be related to the age of banked blood. It might be related to just extracorporeal storage in general. But there does seem to be some sort of a signal there with respect to the

idea that blood transfusion is not an innocuous procedure.

So it may also be another one of these non-causative but relevant biomarkers of some aspect of clinical risk that someone needs a transfusion or has a bleeding episode that requires some sort of urgent intervention that it marks them for a poorer outcome.

So I guess my simple answer is, yes, that there are long-term consequences, but we probably don't understand them as well as we could.

As far as can patients at high risk of requiring CABG be identified prior to dosing, I guess my answer is maybe. If it's a relatively clinically stable patient, where you feel like you've got time -- and by time, I mean 20 minutes, 40 minutes, an hour or two, to thoroughly assess the coronary anatomy without the patient being in a state of shock or otherwise crashing, so that you feel pressed to perform an urgent intervention, as the operator, I mean, we have to leave that up to the interventional cardiologists and other clinicians taking care of these people as to use their best judgment of what's really

going on.

So if an operator or a clinician feels like they have time to ponder and determine the anatomy and the best clinical course beyond that determination, then the answer is yes. If the patient is clinically unstable, in the judgment of the clinicians taking care of that patient, and they want to get all potentially useful medicines on board in parallel to gaining an idea what's going on, then the answer is probably no.

DR. KONSTAM: Thinking about this, in the interest of trying to clarify what people are thinking, I might expand the question slightly.

So you have a patient, for whatever reason, you're pretty sure has a fairly high likelihood of needing a CABG, whatever that might be, 60 percent.

So should prasugrel be withheld? If you could comment -- if you say yes, do you mean in preference to clopidogrel or would you withhold any such agents?

DR. FOX: I don't think it would make any difference with respect to these two agents under discussion today, because if the patient needs urgent

bypass surgery, they probably don't have time to wait in an ICU with a balloon pump for three, five, seven days as opposed to hours.

DR. KONSTAM: So you'd withhold either one.

MR. FOX: If I thought there was a high probability the patient needed bypass surgery, I would probably advocate holding the agent until you knew what the anatomy was, unless you felt pressed otherwise.

DR. KONSTAM: Okay. John?

DR. FLACK: Long-term consequences, nonfatal hemorrhage outside of the risk of transfusing, I'm not sure about that and so I'm not going to pontificate about it.

Can patients at high risk of requiring CABG be identified prior to dosing? Probably, at least in some settings, situations, they might be.

Should prasugrel be withheld in such patients? I'm not sure that, despite the increased risk, that this doesn't fall under the heading of a physician judgment and the willingness for patients to accept a certain risk, because, clearly, in the short term, considering the patient who might need a CABG,

but then doesn't get one, and then you withhold this drug -- and that patient has really not been talked about -- as opposed to just simply the patient who might need a CABG, who gets one, who is probably going to get through the surgery without a major bleed, but might have one. And to me, I don't think that I can confidently say that if you're faced with that situation 10 times, that you might not decide one way or the other, depending on the patient.

So I don't have -- I think that's an area of physician judgment, with some guidance about the increased risk and all, but it may be acceptable, depending on what the patient and the physician's assessment of the situation are.

DR. KONSTAM: Okay. Jim?

DR. UDELSON: Well, I think nonfatal hemorrhage, really, depending on where it is, intracranial hemorrhage could be quite devastating, even if it's nonfatal, whereas, on the other hand, a GI bleed that you get treated for, beyond the risk of transfusion, might not be. So it's highly variable. I see that the intracranial hemorrhage, nonfatal

intracranial hemorrhage really wasn't very different.

In terms of predicting CABG in a particular patient, I think we're probably pretty bad at that, other than in the grossest sense. And I wouldn't think that we would have enough predictive power to be able to pick out who to withhold therapy.

But I think an advantage here is that the rapid onset really of the platelet inhibition, really for the most part, would allow you to wait until you know the anatomy. And I think there would be, on a clinical basis, really very few situations where you'd have to act before that and, for the most part, you would know the anatomy before you had to make a decision.

DR. KONSTAM: So let me just pick on you and make sure I understand what you're saying about that.

So somebody, like who might have been in this population, with unstable angina, non-STEMI, for example, coming into the cath lab, don't know his anatomy, you would not give this drug until you knew the anatomy.

DR. UDELSON: I think, for the most part, you

could do that, because from the data we saw, if you see the anatomy, the decisions are usually made very quickly and you give the drug within 20-30 minutes, you have a very high level of platelet inhibition. I think, for the most part, these are not emergent urgent patients, for the most part.

Now, the STEMI patients are a little bit different, of course, but I think if you look across all of the primary PCI, ST elevation MI literature, I mean, the percent of patients who end up needing urgent emergent bypass surgery is very, very low.

DR. KONSTAM: Mike?

DR. DOMANSKI: Well, I think in answer to the first question, I would -- I think from the standpoint of this discussion, I would not accept an increased risk of MI to lower the risk of transfusion for nonfatal hemorrhage. So it's a kind of backdoor answer, but I don't think I'd use that in any decision-making here today.

In terms of the second one, actually, prasugrel potentially offers us something we haven't had, and one of the problems is an awful lot of

patients, in many environments, certainly ours, go in as cath possible PCIs.

So with clopidogrel, you really have to decide that you're going to pre-treat them ahead of time. The rapid onset of action here actually gives you the option of at least seeing the anatomy before you commit yourself to it. So you don't hold up a bypass operation that's elective.

I think that it is hard to predict what procedure is going to go south if it's complex, particularly if it's a complex PCI, but they rarely do. I mean, it's very, very unusual to end up having to send a patient emergently to surgery. Clearly, we do sometimes, but it's pretty rare. So that certainly wouldn't stain my hands.

Actually, I think prasugrel offers a big advantage here in terms of the usual patient we see, which is cath possible, and letting us see the anatomy before we decide. If it's lousy anatomy and we want to send them to surgery on an elective basis, we're in a position to do that quickly without waiting a week.

DR. KONSTAM: Okay. Mr. Findlay?

MR. FINDLAY: I'll pass on these questions.

DR. KONSTAM: Okay. I don't know what the long-term consequences of nonfatal hemorrhage are, but I'll just take this opportunity to say that I do think that a TIMI major bleed is a big deal to the patient. I don't know -- so if the patient has a TIMI major bleed and recovers from it, I'm not sure we know that that has any untoward long-term consequences for the patient.

But I would just take the opportunity to say I just wouldn't dismiss the importance of a TIMI major bleed in terms of its associated morbidity to a patient. So I think it's a little bit more of a big deal than I think some have given it credit for.

With regard to CABG, yes, sometimes we can tell who is likely to have a CABG. I think it's tough. I do think there should be something in the labeling that very clearly provides a warning or a caution that proceeding to CABG while receiving prasugrel or soon after discontinuation of prasugrel is associated with a marked increase in intraoperative, perioperative bleeding, and I think that should be somewhere in the

labeling.

So I think I agree with the comments that I would, if at all possible, wait until after you know the anatomy. And then you may be faced with a little conundrum, because if you think, well, if the stent doesn't go right, I might have to wind up sending this individual to the operating room, but if I use prasugrel, maybe that will reduce that likelihood, although I'm not quite sure we know that from the data. But I would just leave it to say that if we think there's a very high likelihood of going on to CABG, you should be dissuaded from using the drug.

Bob?

DR. TEMPLE: I don't do this for a living, so this may be a naive question. But before you look at the anatomy, before you do the angiogram, how do you have any idea who is going to go on to a CABG or not? So if you don't, does that mean that what you're suggesting is you should always wait until you have that before you give the first dose?

DR. KONSTAM: Always is a big word, but I --

DR. TEMPLE: Well, usually.

DR. KONSTAM: I would say, and I think Jim and maybe others have said, that the preference would be to wait until you know the coronary anatomy.

DR. TEMPLE: Okay. But just to be specific, because we've got to write this into labeling, that would be a recommendation that you would usually wait until the angiogram is done before you give the first dose.

Is that what you mean?

DR. KONSTAM: Yes.

DR. TEMPLE: That's certainly not how the STEMI was done.

DR. KONSTAM: I guess that one would want to -- I think in the setting where somebody is coming to the procedure as an elective angiogram, cath possible angioplasty, that certainly would apply.

I think that somebody who comes in with unstable angina, on the other hand, somebody comes in with a troponin elevation and he's going the next morning, I think I'd go ahead and start the prasugrel that night.

DR. TEMPLE: Well, I'm thinking of the people

in this study, who I presume went pretty quickly to the cath lab and got treated. But weren't many of them -- and maybe the company those.

Weren't many of them treated right away?

DR. KONSTAM: Well, first of all, we might want to consider making a distinction between STEMI and non-STEMI unstable angina. So I think in the vast majority of STEMI patients, you would be going in being pretty sure -- in the vast majority of those cases, you'd probably be dealing with it with a PCI. I think this is a more important issue with the unstable angina non-STEMI population, where you just have no idea what you're dealing with.

DR. DOMANSKI: But we're already starting -- you know, again, maybe the practice around here, around the table, is different, but generally, you would start -- right now, you start clopidogrel right away and you've bought yourself some increase in bleeding complications with clopidogrel. Granted, it appears to be worse with prasugrel.

But I'm just thinking through the clinical scenario. A patient comes in, chest pain, chest pain

subsided, there's a troponin elevation. I think you would start him that evening and cath him the next morning already on prasugrel, and if you end up having to send him to surgery, hey, the risk is increased. But I think that's going to be the clinical pathway that people are going to take. If people disagree, then say so.

DR. TEMPLE: But I'm hearing two -- so I'm a bit confused.

DR. KONSTAM: There are a couple of points here. One is one that you made, which is the more rapid onset of action of prasugrel compared to clopidogrel, which you can take advantage of here. And the second point is you're right about a common practice with clopidogrel, but I think we've clearly seen that with prasugrel, the stakes have gone up with regard to intraoperative and perioperative CABG bleeding. So it's substantially worse with prasugrel than with clopidogrel. So I guess it's for us to think about this.

DR. DOMANSKI: Yes, it's a tough one because the benefits are more, too. And I suppose probably

different people may take different views of that. It's a little hard to work it all out here, but I'd be cautious about your labeling.

DR. TEMPLE: As Ellis pointed out, 23 percent of the events occur in the first hour. So if you take that hour to, I don't know, to something else, 23 percent of the events have happened.

DR. DOMANSKI: That's not how it would work, though. What you do, in the elective case, what would happen is, presumably --

DR. TEMPLE: I wasn't worried about the elective case. I was worried about the ACS.

DR. DOMANSKI: The ACS case, I can't imagine somebody waiting to just give the stuff. I mean, you want to prevent the MI that night, also, as you're waiting to do your procedure in the morning.

You're treating the patient. See him in the emergency room, you're going to write the orders to do that and, if they're really hot, you can take them to the lab emergently, but cath labs don't operate at night unless you call people in. So it's probably the next morning. You start the prasugrel or the

thienopyridine, you start one of them, and other drugs, of course, the usual cocktail.

DR. KONSTAM: First of all, if we look at what was done in this trial, if I'm not mistaken, for the unstable angina, non-STEMI population, there was a mix-and-match as to exactly when the drug was started. It was not uniformly started before the cath. Okay. And there is an analysis that we saw along the way that looked at it based on the different time of starting, and that might be examined a little bit more carefully.

But where we are right now, I don't think we can dissect out how much incremental gain you get from starting at -- getting the extra half-hour, or whatever it is, of starting it before the cath. I'm not sure we can sort that out in terms of efficacy.

DR. DOMANSKI: But I'm thinking again about the ACS patient who comes in, not the STEMI, but the person who comes in who you're going to do not three days from now and not right now, but the next morning. And I'm just trying to think through that pathway, and what I'm suggesting is I think that in writing the labeling, I don't know that we can do all of it right

now, but I would be thoughtful about not getting in a position where you tell people not to start something that night. So I'd be very cautious in your labeling that you don't write that out of it.

DR. UDELSON: Marv, I think if we're asking how this was done in the current trial, just looking at the *New England Journal* paper, "the coronary anatomy had to be known to be suitable for PCI before randomization in all patients with unstable angina or non-ST-segment elevation MI." So maybe the sponsor can correct it, but it sounds like the anatomy had to be known for those patients, and the ST elevation MI was different.

DR. KONSTAM: Yes. Well, let's sort of step through this a little bit.

First of all, the question is if you think a patient is highly likely to go on to CABG, what would you do. And I think the sense so far, though we haven't kept going around the room -- and we should do that, actually -- but is that the drug would be withheld.

I think, obviously, the knowledge of the cath

is the way you would know that and we don't have clear evidence from this trial that there's an advantage to starting prasugrel before the cath. So I don't know where we -- let's just keep going.

Jim?

DR. NEATON: I might skip that one, but I will just say that there were -- from the FDA's summary this morning, there were 170 major bleeds and 10 to 15 percent of them were fatal in prasugrel. So in terms of the first question, I think the long-term consequences can be very severe. And the data that was presented on time from CABG certainly suggested that within a few days, it may not be such a good thing to do.

DR. KONSTAM: But, Jim, it's asking for the long-term consequences of nonfatal hemorrhage.

DR. NEATON: Right. Well, I mean, you're alive for a while and then you die.

DR. KONSTAM: Okay. Dr. Krantz?

DR. KRANTZ: In terms of the long-term consequences, also, like Dr. Flack, I'm ignorant about the data on this, though I did see an analysis of the

sponsor, which is a little bit different than your perspective, which showed that the MIs actually drove a higher mortality relatively greater than the bleeding themselves that were nonfatal. So I think that is an important caveat.

I think in terms of can patients likely to be requiring CABG be identified, certainly, three-vessel disease, left main coronary disease, particularly in the setting of LV systolic dysfunction, is the perfect substrate for a bypass surgery, even in contemporary cardiology. So I think the answer to that is clearly yes.

In terms of withholding, I think, yes. I think really -- just to sort of address what Michael was saying earlier, I think really this is, in many ways, a blessing, because this whole notion of upstream use is no longer as important in terms of ADP-receptor antagonism. And I think you brought up a nice curve that FDA showed that basically if you start the drug too early, it's sort of like a U-shaped curve, you actually have worse outcome and if you start it within 30 minutes of actually doing your intervention, you

have the highest benefit.

So I would, again, disagree with Michael that you really want to load these patients the day prior. So I think, in some sense, in terms of looking at process of care, this may actually simplify it and create a better model for all of our patients.

DR. DOMANSKI: Let me just clarify that the only people I'm talking about doing the night before is not the electives, but the patients who come in with really unstable angina, the troponin-positive patients. So just to make clear what I'm saying. You may still disagree, but that's --

DR. KRANTZ: I still disagree only because this trial wasn't stable patients. This whole trial was unstable patients, by its definition. So that wouldn't really even be a relevant consideration, unless I misread TRITON.

Was elective patients involved?

DR. KONSTAM: Dr. Paganini?

DR. PAGANINI: The long-term consequences, I think, depend on the cause, whether there's an aligned pathology versus drug-induced, solid organ versus other

sites, and then the subsequent anatomical dysfunction that was a cause or an effect of either a hemodynamic consequence of the bleed or a dysfunction of the anatomical site or organ in which the bleed occurred. So I think that question is difficult to answer.

With regards to likely to require CABG, as a non-cardiologist, it's very difficult for me to understand which would and which wouldn't on their entry. You guys would have a better handle on that. Coming from the Cleveland Clinic, I would say that virtually everybody is a CABG candidate.

As far as the efficacy of the drug is concerned, it seems to me that one of the big issues that we have to find out is what happens in the OR if they're on the drug, and it was sort of spoken a little bit there. But I'd really like to know the effect of platelet therapy and other things on reversing some of the bleeding that happens in the operating room.

We saw a very nice bar graph of the green and the reds and we seemed to be looking at the reds all the time, but there were a significant number of folks who went through CABG who had no problems. So I'd

really like to have more information about what they did to those people, if, in fact, it was an increased bleed in the operating room, to either help that along or whatever.

So that then sort of frames my discussion by saying if we had a clear understanding of who was going to surgery, I would withhold it. That's easy. However, the effect of the drug seems to be more effective the earlier you give it.

Now, we'll discuss that, but it certainly is very effective early on. I think that's the purpose of giving the drug, why it's so quick to get in there, to get up there very quickly, to get the anticoagulant effect. So withholding it may, in fact, be a negative. The real question is how can you define likely to require CABG, which is, I think, in your field and not in mine.

DR. KONSTAM: Dr. Cannon?

DR. CANNON: As far as the first question, long-term consequences of nonfatal hemorrhage, I believe Elliott showed us a slide that, over time, the outcomes of people who survived -- they have a nonfatal

hemorrhage -- is about as good as people who don't have hemorrhage at all.

Now, that may be small comfort to people who have an intracerebral bleed and survive. The frequency of intracerebral bleeds, though, was fairly similar between the two groups. It's just that they were more severe in the prasugrel group; they were more likely to die from it. But it's 20 versus 16, slight more on the prasugrel.

The big difference was that the prasugrel group was more likely to die from it. So if we're talking about the survivors now, their outcome over time seems to be about the same as those who did not have a bleed. I believe, Elliott, you showed a slide of that.

Second, about the CABG, I'm glad that Jim read us that sentence from the study. I think the labeling has to be consistent with the way the study was performed. And for the unstable angina patients or the non-STEMI patients, drug was not given until the coronary anatomy was known. And I think that's important, because I think if you give it right away,

if you give it the afternoon that an unstable angina patient comes in, not knowing the anatomy, intending to do the cath the next morning, you're going to give it to some people that have unsuitable anatomy for PCI or you're going to enrich that group with perhaps people that would be better served going to surgery, in which case, the hemorrhagic complications may be greater.

So I think for the unstable angina non-STEMI patients, you should know the anatomy. Fortunately, the onset of action is fairly quick and I don't think there's a big price to pay.

I think for the STEMI patients, you know they're going to have an occluded artery. Even if they ultimately go to surgery, the surgeons will be delighted to have you open that artery and let them cool off a few days before they go to surgery. So maybe giving them prasugrel should be done, even though ultimately, a week or so later, they might go to surgery.

DR. KONSTAM: Okay. Norman, Bob, have we made it crystal clear to you guys?

(Inaudible response)

DR. KONSTAM: Oh, wow, that's impressive. We're going to ask you to summarize later, okay?

Let's go on, and what I'm going to ask is that questions 2.1.3 through 2.1.6 be discussed en bloc, and they relate to the impact respectively of prior TIA/stroke, weight, use of glycoprotein IIb/IIIa inhibitors, and age on the use of the drug. So I will just read this through

So, first, with regard to prior TIA and stroke, fewer than four percent of subjects enrolled with prior stroke or TIA -- I'm sorry. Fewer than four percent of subjects enrolled had prior stroke or TIA. Those randomized to clopidogrel had primary endpoint events about as often as did clopidogrel patients with no such history. However, prasugrel subjects with a history of stroke/TIA had primary endpoint events nearly twice as often as other prasugrel patients, and the risk of a subsequent stroke was much higher in prasugrel subjects with a history of stroke or TIA.

So the first question is, "Should labeling discourage use of prasugrel in patients with a history

of stroke/TIA or in whom stroke/TIA developed during treatment with prasugrel?"

Secondly, with regard to weight, quintile analyses of primary endpoint events reveal a fairly uniform advantage of prasugrel over clopidogrel, regardless of weight, and suggests no strong relationship between weight and bleeding risk.

In contrast, a dichotomous analysis demonstrates a statistically significant increase in bleeding risk for patients with a weight less than 60 kilograms. What, if anything, should labeling say about the use of prasugrel in patients according to weight?

Use of glycoprotein IIb/IIIa antagonists were used in about half of all ACS subjects in TRITON. The clinical benefit of prasugrel on the primary endpoint was similar, regardless of glycoprotein IIb/IIIa inhibitor use, and the risk of bleeding, although higher with the drug -- with the glycoprotein IIb/IIIa antagonist -- was not disproportionately worse on prasugrel. What, if anything, should the labeling say about use of prasugrel in patients according to

concomitant IIb/IIIa inhibitor?

Then, finally, age. For patients in older age strata, while bleeding was not disproportionately worse on prasugrel, fatal hemorrhage was more common with prasugrel, one percent versus .1 percent, and prasugrel showed less benefit over clopidogrel. In addition, older ACS patients in the study CURE received less benefit from clopidogrel over placebo. What, if anything, should labeling say about use of prasugrel in patients according to age?

Richard, we're going to start with you.

DR. CANNON: Okay. So 2.1.3, should labeling discourage use of prasugrel in patients with a history of stroke/TIA? Absolutely. I see no evidence of benefit. There is increased risk. So it should not be administered to those patients.

The second part of the question confused me a little bit; or in stroke/TIA developed during treatment with prasugrel, I don't quite understand what you meant.

Do you mean would I stop it? Yes, I'd stop it. If somebody has a stroke on prasugrel, I'd stop

the prasugrel.

Is that what you mean?

2.1.4, weight. So for those subjects less than 60 kilograms, they did seem to benefit, but there was more of a bleeding risk. The sponsor proposes to reduce the dose to five milligrams for those patients. I think that's reasonable. I don't have strong feelings. Maybe I could be persuaded to go ahead and give them 10 milligrams and just hope the bleeding is not that big a problem. But reducing the dose to five milligrams made sense to me and I think I would support that.

2.1.5, use of the glycoprotein inhibitors. There was no difference in risk-benefit, so I don't think there needs to be a particular warning about co-administration with the glycoprotein IIb/IIIa inhibitor.

2.1.6, age. So I really struggled with this, about the over 75 crowd, because I think there are some patients over 75 that are more fit perhaps or maybe the tip of my nose would tell me I'm less likely to have a problem than others over the age of 75. So I think

that there should be a warning perhaps or a statement that there may be greater risk with less benefit. On the other hand, I don't think I would absolutely limit its use to people under the age of 75. Plus, we saw with diabetics over the age of 75, there appeared to be substantial benefit. So I think that there should be maybe some kind of warning, but not a restriction of its use, based on age.

DR. KONSTAM: Okay. Emil?

Did you have a question for me? I'm sorry.

DR. TEMPLE: Yes. I just want to mention, stopping it after a stroke is in contrast to stopping it after a heart attack. I don't know if anybody showed those data, but we've seen it previously.

The effect is really very nice if you have one heart attack while on the drug and it's good to stay on it, but not a stroke, for the reasons that you've seen. So there is that contrast, for God knows why.

DR. KONSTAM: Okay. Emil?

DR. PAGANINI: Yes and yes to the first question. That's fair.

The second, I would probably -- the verbiage that I would use here would be sort of "may have a higher risk of bleeding at standard recommended dosing, thus lower dosing may be helpful." But I would question whether there's some way that they can evaluate a weight-based dosing vis-a-vis the pediatric dosing type of stuff that peds go through, and I guess that's one of the reasons why we have a pediatrician here. I don't know if there's anything that could come out of that, if they have any data on that, weight-based dosing for smaller people.

I'd also put in there some renal dysfunction people as well, as far as sliding scales of the dosing. But that's not one of the questions. I'll just throw it in because I'm here.

DR. KONSTAM: Can I stop you on that?

DR. PAGANINI: Sure.

DR. KONSTAM: Because you're the expert. So I was trying to remember the answer to your question about this and I --

DR. PAGANINI: Well, they didn't have any patients. They had very small -- the less than 30 mils

per minute with creatinine clearance seemed to do just as well.

I think, Bill, you had mentioned -- and I don't know if you're allowed to say anything, but you can nod. But I think that there weren't a large number of folks that had CKD4 or CKD5 in there and so that's an issue. Also, the dialysis patient, remember, they get stuck each time for their dialyses. So that's going to be a bleeding risk that's going to be there, as well.

So these are just issues that haven't been brought up by either their study population or brought up in the questions. I'll just throw it out there as things.

Then the third one, 2.1.5, I'd say there's a caution, but there's no statistically hard data to support that statement that there should be a caution. And then the last issue, as far as age is concerned, I think there was some fairly reasonable data on age. I do agree that age is not age. Somebody who is 60 or 70 or 80 can be different than somebody who is 60 or 70 or 80.

So I think co-morbidity analysis may be helpful. The older the patient population, the more co-morbidities they have. Perhaps some sort of an analysis of co-morbidity subgroups might help to identify the 75-year-old with A, B, C, D, E, F, might be a higher risk than a 75-year-old that runs the Boston Marathon.

DR. KONSTAM: Okay. Mori?

DR. KRANTZ: In terms of the stroke question, I think, both of them, I would say yes and yes.

In terms of the weight, I guess I'm not a big fan of dichotomization and continuously give you the information, but at the same time, I think it's probably reasonable to have a warning or label and consideration of the lower maintenance dose for an adjustment.

In terms of the IIb/IIIa inhibitors, I think certainly we don't want to discourage IIb/IIIas because obviously they had a significant benefit on or off the drug. The only concern I had was in the multivariate model; when you look at people receiving it for greater than three days, they actually had a significantly

increased risk for TIMI major bleeding. So I think in that respect, I might outline that as a precaution that people shouldn't receive extended post-PCI IIb/IIIa.

Then finally, for age, certainly, a caution seems warranted, although I'm really uncertain on this one in terms of the dose adjustment.

DR. KONSTAM: Okay. Jim?

DR. NEATON: I'll answer yes for the first two, as well. It seemed to me that there's strong data here that lower body weight and older age are important risk factors for bleeding in both treatment groups. There is no difference between the treatment groups in the relative risk of bleeding, however, by age or by body weight. And so I wouldn't say anything about body weight, except that it's a risk factor for bleeding.

For age, I'm a little bit torn, because there -- and I agree with the earlier comments. It's got to be more than just age. There's got to be other factors considered. But the piece that kind of leaves me kind of wondering what to say is the case fatality associated with the bleeding. So somehow that has to be mentioned. And I wouldn't say anything about the

GPIIb/IIIa inhibitors. So that's it.

DR. KONSTAM: Okay. And I agree with yes and yes for the stroke/TIA.

I agree with Jim that I don't know what to say about weight from the data. I think when you look at the first cut subset analysis by body weight, you don't see anything in terms of change in the relative hazard. It pops out when the sponsor does a multivariable analysis, plugging in weight less than 60, but as has been pointed out, that's a very small subset. I don't know why the choice was made to throw it into the multivariate analysis. So I don't know what to make of that.

So other than -- as Jim points out, low body weight for a given fixed dose seemed to increase the overall risk, but I don't see that it preferentially looks worse for prasugrel than for clopidogrel. So I don't really feel like anything obvious needs to be said there.

I don't see anything to be said about the glycoprotein IIb/IIIa antagonists. Concomitant use of potent antiplatelet agents is bound to increase

bleeding risk, but as the sponsor nicely pointed out, we don't see any subgroup differences between the two groups in that. So I don't see anything special to say about prasugrel.

I think age does come out and I like Dr. Unger's points that he made about this, because sort of both the efficacy side and the safety side make you less excited about prasugrel relative to clopidogrel as you get to older age. So I see that and I think that has to be attended to. Whether 75 years old is the key magic age or not, I'm not sure. It seems as good a cut point as any. But maybe there's a better one, but I think that might be reasonable.

I don't think I would go so far as to not approve it in patients over the age of 75, if we get to that point, but I think there should be some clear indication that the benefit-risk for prasugrel compared to clopidogrel declines substantially with increased age.

Okay. Mr. Findlay?

MR. FINDLAY: On 2.1.3, I would say yes, agree with others on both those, yes and yes, for

stroke and TIA. I agree with the five milligram dose on 2.1.4 on weight. That seems reasonable and cautious. I would pass on 2.1.5.

On age, I would concur with the FDA's take on this, the labeling should strongly discourage use in people over 75, although I'm also concerned about pegging that as a precise date. So labeling language would have to be developed there, I would say. I don't think the benefit-risk ratio for older folks justifies its use. If used, also, it should be at the lower dose in those circumstances where it's needed.

DR. KONSTAM: Okay. Mike?

DR. DOMANSKI: Well, 2.1.3, yes and yes.

I think that for 2.1.4 and, actually, 2.1.6, I wonder if one could just in the package insert say that with lesser weight, there appears to be more bleeding with agents of this type and not get -- because that's educational. It would be useful for people to know, and probably not everybody knows it. Obviously, prasugrel doesn't appear to be worse than the clopidogrel.

With regard to age, I think that the age 75

is arbitrary. So, again, in the text, one might say that older patients, in this case, ones over 75, appear to derive less benefit and that there was a risk. But I think that could be more educational than fancy warnings and stuff.

I probably wouldn't say anything about the IIb/IIIa inhibitors. There are a number of clinical scenarios that go with that and it's pretty hard to see how the labeling could help.

DR. KONSTAM: Okay. Jim?

DR. TEMPLE: Did you have a view on whether the dose should be lowered?

DR. DOMANSKI: Well, certainly, it's a reasonable maneuver, but it's a theoretical construct. I mean, they didn't really test that strategy. So we don't know anything about clinical endpoints. I would probably be silent about that, frankly, because we just don't have clinical endpoint data with that strategy.

DR. TEMPLE: Let me just mention something. I'm sure you all know this. But when we modify the dose for people with renal failure or people who are taking an inhibiting drug, believe we, we don't retest

it in that population that way. You just lower it to match --

DR. DOMANSKI: Yes. I mean, well, if that's your custom, I'd defer to you. I'd just point out that you don't really have data to support it.

DR. TEMPLE: Well, no, I don't know if that's the right thing to do here. I'm just telling you what we --

DR. DOMANSKI: I understand. I don't think there's a -- I'm not sure there's one right answer. I'm just hesitant to put formal labeling on something that you don't have hard evidence for.

DR. KONSTAM: What I would raise about that, as I raised with the sponsor, is there is another choice, which is clopidogrel. And there may be some specific downsides to that, but at least you do have extensive clinical trial evidence with a particular regimen of clopidogrel, which is less potent over the population and you have a lot of clinical information.

With the five milligrams of prasugrel, I mean, I think it sounds perfectly rational, but I guess the problem is we just don't have any clinical trial

data to support it.

DR. DOMANSKI: I entirely agree with that, too. I think that's well said.

DR. UDELSON: So on 2.1.3, I would say yes and yes. In fact, I think that was the only analysis with an interaction term, I think, as Jim was pointing out. So that seems pretty strong.

On 2.1.4, about the weight, it's a tricky one. I think it would be worth describing what was seen in the trial and giving some guidance with the PK data and let the clinicians decide. I think it's a very reasonable thing to do and I think, if I understand correctly, we will have a lot more information on the five milligram dose from the TRILOGY trial, and perhaps this could be revisited with the language when those data are available.

On 2.1.5, I think clinicians will want to know something about what the trials showed with IIb/IIIa inhibitors. I think it would be worthwhile putting something in there that there was no effect on the efficacy or the safety. I would want to know that if I was a clinician and wasn't familiar -- if I wasn't

here today seeing this shown to me.

On the older age, same comments really as in 2.1.4. I think a descriptive caution showing the PK data and suggesting the possibility of lowering the dose on the basis of that would be very reasonable, until we have more data on the five milligram dose.

DR. KONSTAM: Okay. John?

DR. FLACK: 2.1.3, for the stroke questions, yes and yes. I'm going to preface the rest of my comments by saying that clinicians face situations all the time that are not directly addressed in clinical trials, and I think it's too rigid to remain silent on very likely situations, and I think we have to give them our best evidence based on our interpretation sometimes of what we see in clinical trials, but also integrating other data from other sources, such as pharmacokinetic data. The only data that's useable is not just clinical trial data, and I think sometimes we get caught up in that. So I'm going to preface what I'm saying with that for the rest of my comments.

What about the weight issue for patients less than 60 kilograms? It seems to me that the net benefit

basically didn't favor either clopidogrel or prasugrel. And so what I would do is I wouldn't necessarily remain silent on it. I would simply say that the analysis -- really, the net benefit didn't favor one over the other, but one reasonable approach might be to lower the dose, because part of the reason you didn't get the net benefit had to do with the tradeoff with bleeding. And I think there's going to have to be some alignment of this insert, if it's approved, with clopidogrel, particularly since they were directly compared.

With the GPIIb/IIIa inhibitors, I think it's reasonable to say that there is increased risk of bleeding, but you still get efficacy, and I would leave it at that.

Finally, in the older age strata, first of all, if you even go into the older age group and look, even though it's not as definitive, the signal is still the same direction for clopidogrel not to be as good as the newer agent. So I would not necessarily whack prasugrel on this, but would essentially say that the net benefit appeared to be equivalent between the two

and I think it would be reasonable to offer an approach to improve the net benefit by reducing the dose.

The other thing is if that you keep cutting these trials up and looking at subgroups, you're going to find something that just doesn't quite fit the rest of it, and I have no idea if we're looking at something real or by chance. And we could argue until the cows come home and we could take polarized positions, but I just don't know. So I would not make a definite statement about it being much less effective. But in the trial, at least we know the net benefit appeared to be about balanced and I would just recommend that you could consider cutting the dose to try to improve it.

DR. KONSTAM: Okay. Jonathan?

DR. FOX: 2.1.3, that one seems pretty unanimous. The evidence is pretty clear, and so, yes.

2.1.4, I think that PK/PD modeling is helpful. I think that IPA, while not a validated surrogate for an outcome, does show dose effect relationships with this class of agent. The Phase 2 work and the clinical pharmacology work are supportive of the notion that -- along with the Phase 3

results -- that exposure is somehow related to benefit and to risk of bleeding, and that it seems that the data seem to suggest at least that you might not lose much benefit on outcomes while gaining some benefit on bleeding risk by reducing the dose in the less than or equal 60 kilogram group.

I think all the caveats others have said about the lack of really direct data for that are valid; however, I would agree with the comments of others that when you start dividing the data into smaller and smaller subgroups, you have to be careful about drawing conclusions there.

IIb/IIIas, I agree that just having some information in the label to -- even if it's neither here nor there, that tells clinicians that as long as they otherwise exercise precaution in the use of multiple potent anticoagulant/antiaggregational agents, that there's no special risk conferred by the combination, so I think that would be helpful information.

I agree with others that the age question is a very tough one. While the subgroup analysis suggests

that the magnitude of benefit wasn't as great as that seen overall or in some of the other subgroups; again, the numbers start to get smaller and at least it's in the right direction. It's not in the wrong direction.

I would agree with the comments of others that drawing a hard line at age 75 and not 74; 11 months is silly and should rather be constructed around recognizing that there is an increased risk of adverse effects with increased age and to try and construct some special kind of benefit-risk considerations when dealing with that patient population.

DR. KONSTAM: Okay. Great.

Let me ask Norman and Bob whether you're satisfied with these questions or you want more discussion.

DR. TEMPLE: I mean, we're delighted there's an absolute precise answer to every one of those.

DR. KONSTAM: I was going to say the same thing.

DR. TEMPLE: Those are very hard areas.

Just as a comment, 20 year ago, people

started looking at all these subsets. Every scholar and trialist in the room would throw them out. They'd quote Peto and use of don't look at subsets, all that stuff. But in the era of individualization, you're supposed to do that and I think it creates a very difficult tension for everybody.

DR. KONSTAM: I think you make great point, because in point of fact, we haven't figured out how to do this. So you're right. All sorts of things are going to pop up by chance. I'm worried about the weight less than 60. This might be an example of that. So, yes, it's a great point. We need to do personalized medicine, but I guess we haven't figured out how to do it yet.

DR. TEMPLE: Well, the journals, at least, and the submissions we get have made that decision for us. When have you ever seen a large study without a forest plot? It doesn't happen anymore, ever. So people are looking at all this stuff; what to make of it is the question.

DR. KONSTAM: But in this case, there's a problem, which is there's an excess bleeding, and I

think in that situation, I think it's reasonable to look for whatever guidance we can in the dataset. And I think you're going to have to use your judgment in the labeling about how strongly to make your statements. But I think it's the best we can do.

DR. TEMPLE: We totally agree. You cannot look at it; I mean, that's not possible. So you have to do it with care and some knowledge that you might be wrong.

DR. KONSTAM: Yes. Okay. We're going to go now to the simple question of cancer, and let's see. So let me read it.

Cancer was somewhat more commonly reported in the prasugrel group compared to the clopidogrel group. The strength of association depends largely on whether or not nonmelanoma skin cancers are included in the analysis. The pharmacologists and the Carcinogenicity Assessment Committee interpret the pre-clinical data as not indicative of carcinogenic or tumor growth enhancement.

The Division of Oncology Drug Products consultative review concludes that the trend in TRITON

was probably spurious. Although the review team has a range of views on the implications of these data, there is agreement that there should be some description in the labeling.

Does the committee recommend -- and I guess I'll take these as a series of yes-nos, so you might recommend none of the above, I suppose -- a section in warnings and precautions, a box warning, a restriction on use for limited time?

So let's open discussion on this issue. I'll start on this end this time with Jonathan.

DR. FOX: To 2.2.1, I would say not strong. I would agree with the Division of Oncology Drug Products and their assessment. I think Dr. Schein's comments were particularly pertinent in this regard.

On 2.2.2, I would say no, only because I think that the benefits --

DR. KONSTAM: Can I stop you for a second? You may have a previous draft of the questions. The one I have does not call out 2.2.1, 2.2.2 or any of those things. Yours does?

Use the one in your folder.

DR. FOX: And here I thought I was getting modern and paperless.

DR. KONSTAM: So the way I see it, really, the only -- and feel free to comment. I mean, you don't have to restrict yourself to yes-no answers here. So you may go back and comment. But the question that's specifically asked, what should be done. They want us to cut to the chase.

DR. FOX: I'm with you. No, no and no.

DR. KONSTAM: So nothing. You wouldn't even make mention of it in the labeling at all.

DR. TEMPLE: Can I just -- the question doesn't include putting it in adverse reactions. I think it's fair to say that none of us can imagine leaving it out all together.

DR. KONSTAM: I would agree with Dr. Temple.

DR. TEMPLE: But we don't want to over-influence you too much.

So this was whether it should be raised from the default up to one of these places.

DR. KONSTAM: You're not doing a good job of not overly influencing us.

DR. TEMPLE: Well, I'm sorry.

DR. KONSTAM: Okay.

DR. FOX: So to address Dr. Temple's comment, I think it merits mention somewhere in the product description that this observation was made, but it doesn't merit some of these higher level warnings.

DR. KONSTAM: Okay. John?

DR. FLACK: I don't think the cancer data's strong, but it's a little suspicious, and the problem is if you only assess things based on currently understood mechanisms, you never learn anything new.

So I think the verdict is out that it's a low level signal that I think ought to be included in some type of low level warning, but I don't believe that it's strong enough, or would I have a problem with this drug being given to one of my family members, based on the risk of cancer, and, to me, that's the litmus test.

But to discard this drug or even this class and simply say that it doesn't fit the biology -- which we did have an elegant explanation from an expert, which was really compelling. I would say, though, that we need to keep our minds open as to how this may not

be spurious and probably more basic, as well as epidemiological studies probably in this class of drugs needs to be undertaken.

DR. KONSTAM: Okay. Let me stop for a second, because I think the general comments are certainly very desirable. But I think the agency would like some specific recommendation about where you put it.

So since those of us around the table aren't in the business of writing labeling every day, maybe you could give us a quick tutorial about warnings and precautions, box warning and restriction on use for limited time, so that people could sort of tell you whether or not we want any of those things.

DR. TEMPLE: Okay. Most adverse reactions, if they are not very serious or if you're not really sure of them and things like that, go under a heading called "adverse reactions."

If something is more important than that, so you really want to get people's attention, we put them in warnings and precautions and many of those will be in the front part of the labeling, called "highlights,"

whereas adverse reactions may or may not be. But they would be likely there.

If we really want to draw people's attention to it, we box it or sometimes you dark print it, but you can also box it. Those have been publicly called "black boxes," as if it means you're not supposed to use the drug. That's wrong. They're box warnings and they're done to get people's attention, and, obviously, they have to be important. There isn't a rigid definition.

Use for a limited time would represent a conclusion that you thought this was real enough and the benefits of longer-term use were not well enough documented to say you should be cautious in using this longer, and maybe not do it or not do it in some subgroup. That would be a conclusion that you were reasonably worried about the finding, I would say.

Anybody want to add to that?

DR. KONSTAM: Okay. So let's go back to you, John.

So it seems pretty clear that there's going to be something about this in the labeling. So the

question is do you feel any of these specific steps are warranted?

DR. FLACK: I feel adverse reactions is most appropriate.

DR. KONSTAM: Okay. So not a warning or precaution, not a box warning and not a restriction.

DR. FLACK: Correct.

DR. KONSTAM: Jim?

DR. UDELSON: I would agree, possibly, in warnings and precautions. I think it doesn't merit a box warning and I think a restriction on time is almost more dangerous to suggest that people switch -- if someone has a drug-eluting stent, we really have no idea whether that's safe.

DR. KONSTAM: I'm sorry. Did you agree or disagree?

DR. UDELSON: Agree with warnings and precautions.

DR. KONSTAM: Okay.

DR. UDELSON: Not a boxed warning.

DR. KONSTAM: I understand. But that's different from what the two previous people said,

right?

DR. UDELSON: Well, I thought you were not giving us the choice of adverse reactions.

DR. TEMPLE: No, no. That's definitely a choice.

DR. KONSTAM: No, that's a given.

DR. TEMPLE: That's the default position, if you'd like. The question is whether to raise it.

DR. UDELSON: Okay. No, I would put it there in adverse reactions. I think the signal is present, but not very strong and we'll have 10,000 more patients coming up in another study and, again, this should be revisited when the TRILOGY trial is done.

DR. KONSTAM: Okay. Mike?

DR. DOMANSKI: I guess I didn't think the -- I thought the signal was insufficiently strong to discourage the use of this drug. So pending further data, I would make it as inconspicuous as you're willing to.

DR. KONSTAM: I think that's a no, no, no.

DR. TEMPLE: We can use our special small print stuff, the one that no one can see.

DR. KONSTAM: Steve?

MR. FINDLAY: With a magnifying glass.

Yes, mention in adverse reactions.

DR. KONSTAM: Okay. So none of the other things.

I agree with none of the above, no warnings or precautions or any of those things.

I guess just to explain, as I was reading through it, I was caught by -- the thing that was a "gotcha" for me was the deaths. So I really started getting worried when I looked at the deaths, because there's nothing that I could see that would explain that away, and even though the overall number is pretty small, that worried me.

But I think Jim really brought this point out that once you start going beyond the pre-specified period of the trial and the dataset lock and you're preferentially following those patients who have an adverse event having been identified during the course of the trial, that could've been on the basis of ascertainment bias or could've play of chance, it would seem natural that you would wind up having more deaths

in that group as well, or you certainly couldn't prove that it's really being from the drug.

So I sort of was much more relaxed about it after that discussion. I do think, as others have pointed out, it needs to be studied further. But at this point, I don't think it deserves anything more than a mention.

DR. NEATON: So I thought the sponsor and the FDA reviewers did a nice job. And what I understood eventually the methods in the trial for how this was ascertained, I just really think you have to think about that in terms of how these data arrived in this MedDRA table with this term.

I would say very little about it because whatever you say is probably going to be wrong. So I'm happy they're studying it carefully in a future trial, but I don't think there's much to say.

DR. KONSTAM: Okay. Mori?

DR. KRANTZ: I think I agree with the rest of the group. I wouldn't put it in a special place other than the adverse reactions. So I'd be transparent and tell the story as much as allowed in a short period of

time.

DR. KONSTAM: Okay. Emil?

DR. PAGANINI: The verbiage I would use is, quote, "We need tort reform," unquote. Beyond that, I'd put it in the adverse events.

DR. KONSTAM: Richard?

DR. CANNON: Adverse events sounds fine with me.

I want to just throw this out, and, that is, would it be worth adding in the adverse events section about this signal that the first manifestation of a malignancy may be bleeding? Are the data -- we talked about this ascertainment bias and so forth, but is there a message there that clinicians should know about, that if there is bleeding, and there is going to be bleeding with prasugrel, at least consider the possibility, particularly if it's GI tract, that there may be a malignancy that's responsible for this.

I'd be interested if other people think that's worth putting -- again, I wouldn't put it in warnings and precautions. I'd put this as a part of the adverse reactions. It might be important for

clinicians to think about.

DR. KONSTAM: Yes. So I guess I was always taught that if somebody bleeds, go and figure out why, even if they happen to be on a drug that's an anticoagulant or something like that. And what you're saying is remind physicians of that in the labeling, maybe.

DR. TEMPLE: So this becomes part of -- use of the drug could be part of practice like colonoscopy.

DR. KONSTAM: So it's a diagnostic. So giving the drug is a diagnostic test. Is that what you're trying to say?

Okay. Emil?

DR. PAGANINI: Can I ask? Wherever these warnings or adverse events or whatever are placed, what does that have to do with advertising on television or direct advertising in magazines? Is there not a relationship with where you place that as to what the company is required to do when they disclose for advertisement or direct advertising, or not?

DR. TEMPLE: Well, they have to make a fair and balanced summary of the bad news in association

with the good news. It seems likely that a mention in the adverse reactions would have to probably manifest itself in an advertisement. But I would leave that still to our advertising people to be specific about. I think the rule is it has to be balanced. If you say good things, you have to say what the bad things are. So obviously, bleeding is going to be prominent. My guess is if it's in the adverse reactions section, there would be an expectation that it would show up.

DR. KONSTAM: Okay. That one is pretty clear, I think. Right? Okay, good. We did something right.

Okay. Now we go to the simple matter of salt-to-free base. I'm not going to read this through.

The question, at the end, is "What, if anything, should labeling say about the formulation issue?"

I wonder whether we couldn't just open it up to the panel to see if anybody has anything they want to say about this.

John?

DR. FLACK: This is one I wouldn't say

anything about. I would work this out with the company to a satisfactory manner on the base from the FDA. But I really would not stick this in the label because I don't think it's going to serve any useful purpose, except for crazy marketing and all, and I don't think it's going to inform the practitioners at all.

DR. KONSTAM: Jonathan?

DR. FOX: I would agree with John. I think that this is more of a regulatory chemistry manufacturing controls discussion and control situation, where I think the sponsor has done a nice job with the clinical pharmacology work to define what the risks are associated with conversion of free base, what the implications are for pharmacokinetics and pharmacodynamics. That is, none and some.

I remember seeing a statement somewhere in the documentation that said that the current lots are being controlled to a level of 25 percent free base or less, and as long as that can be ensured, I think it should be fine.

DR. KONSTAM: Yes, Jim?

DR. NEATON: I just was going to make kind of

one suggestion. I thought the analyses that Dr. Unger did, in particular on slide 63, at first, I thought they were reassuring. But I've thought about them a little bit more and perhaps it's worthwhile looking at them a little bit more carefully, where you classified the response rate according to the newest versus latest batches.

I think the problem with that analysis is that you need to compare like with like temporally in the control arm for -- it doesn't make much sense, because the patient characteristics may change enough during the course of the study to have some bearing on this. So I would encourage looking at that a little bit more closely. But given the whole totality, I wouldn't say anything at this point.

DR. KONSTAM: Okay. Anybody feel differently?

DR. UNGER: Can I ask --

DR. KONSTAM: Ellis? Sure.

DR. UNGER: Can I ask for some clarification?

By the compare, you mean the age of the lots of clopidogrel?

DR. NEATON: I'm assuming, for example, when you talk about newest, that that refers to some temporal calendar time period that you could kind of compare the controls during the same time period.

DR. UNGER: Right. Well, for prasugrel, we know when the lot was released and when it was given to the patient. For clopidogrel, we didn't have that information and I don't think the sponsor has it, either.

DR. NEATON: I don't think you need it for clopidogrel. I think you just need to compare it to clopidogrel for the same calendar time period that the lots were used for the test drug.

DR. TEMPLE: So you're worried about changing the population over time and whether you've accounted for that.

DR. NEATON: Right.

DR. KONSTAM: Okay, good. Let's go on.

So now we get into risk-benefit and let's tackle 3.1, which is the cardiovascular event risk-benefit shown above and there's a table that we've been hearing about much of the day.

Even if the risks of hemorrhage could not be mitigated, does the committee believe that this represents a favorable benefit to risk relationship, yes or no?

So, Richard, let's start with you.

DR. CANNON: I'll say, yes, I think it does favor prasugrel. Hopefully, the hemorrhage risk can be reduced by targeting or eliminating some population from receiving the drug. But even if that weren't the case, I would say it does favor prasugrel.

DR. KONSTAM: Emil?

DR. PAGANINI: I would agree, it does favor prasugrel.

DR. KONSTAM: Mori?

DR. KRANTZ: Yes, I think it favors prasugrel.

DR. KONSTAM: Jim?

DR. NEATON: Yes.

DR. KONSTAM: I would say yes, also.

Steve?

MR. FINDLAY: Yes.

DR. DOMANSKI: Yes.

DR. UDELSON: Yes.

DR. KONSTAM: John?

DR. FLACK: Yes.

DR. KONSTAM: Jonathan?

DR. FOX: Yes.

DR. KONSTAM: Would the agency like any further discussion of this question?

Okay. So we can move on.

Does the committee believe -- and we'll tackle 3.2 in its entirety. Does the committee believe that the following restrictions are likely to improve the benefit-to-risk?

So first is avoiding use around CABG or other surgical or invasive procedures. I'm not sure what "invasive" means. I assume you don't mean PCI.

Other invasive procedures, to the exclusion of PCI; avoiding use in patients with prior stroke/TIA and discontinuing use in patients who develop stroke/TIA; avoiding use or lowering the dose in low-weight patients; avoiding use in elderly patients.

So let's start with Jonathan.

DR. FOX: Well, I guess my answers here are

focused on the word "restrictions," and I guess I would prefer a different word, being more like "advice" and "information" around these special topics.

DR. KONSTAM: Fair enough and you can comment, unless the agency wants to change the question.

But I guess they're asking -- maybe we owe them to answer the question, which is would restrictions improve the benefit-to-risk ratio. So unless there is an urgent -- to change the question, you could comment, but I'd like you to answer that question.

DR. FOX: I guess others have commented about not wanting to take away too much of the judgment of the clinician on the scene at the time in terms of how they make their decisions in taking care of patients. So it's just being well aware of the prolonged pharmacodynamic effect with respect to the potential need for urgent surgical procedure.

DR. KONSTAM: Dr. Stockbridge, did you want to make a comment?

DR. STOCKBRIDGE: I was just going to say

that "restriction" wasn't a key word in that, as far as we were concerned. If you manage somehow to get people to avoid using it around CABG, is that a good idea or not. And you can think about that, whether we -- depending on how strongly you feel about it, we might restrict it or we might just generate advice around it. But do you think that it's probably not a good idea to use it in the settings that are --

DR. KONSTAM: So, Norman, would dose adjustment be part of that?

DR. TEMPLE: Dose adjustment is in the fourth bullet there -- third bullet, third bullet. But I think you can assume it could range from anything to -- from a contraindication, for example, to use in people with prior stroke, which we've certainly contemplated, all the way to something more of an advisory nature, and we'd be interested in your views on this.

DR. KONSTAM: Right. So let me first ask, because you're right, so dose adjustment is called out in that bullet number three, but it's not called out in the others. So I'd point out, in elderly patients,

it's not called out there. It might be.

DR. STOCKBRIDGE: But their problem wasn't an exposure-related problem. So I'm not sure what the rationale would be for contemplating a lower dose there.

DR. TEMPLE: Let me mention one other thing. We have considerable new authority under FADA (FDA) to impose formal restrictions and have limited use and all that. We're not talking about that. We're talking about labeling here.

DR. KONSTAM: Okay. So I guess the spirit is does doing something to influence physician practice around these set of questions, one at a time, do you believe that any of them would influence benefit-to-risk? And if you want to say more about what you think, you can do it, if you want to.

DR. FOX: The comments by the agency are very helpful in terms of -- this is restrictions with a small "R," not with a capital "R." That's very helpful.

So I think that the special risks for bleeding complications that the study identified in and

around CABG merit mention somewhere in the label around the care with which clinicians should manage their patients in that setting. I hope that answers the first question for you.

I think the prior stroke/TIA, we covered that already, that's a clear, yes, it should be avoided.

The low-weight patients I think we covered already. I think the data support a dosage adjustment, even though there may not be any direct outcomes data in a dedicated trial in people of that size, that the weight of the evidence supports a dose adjustment without sacrificing much in the way of efficacy.

The last one, again, I still struggle with that one. I think we're a lot more lacking specific data about that age group, and I think just some general comments reporting the results in the subgroup with some caveats around the reliability of that small subgroup and care in the elderly, frail and co-morbidly burdened patient is probably reasonable.

DR. KONSTAM: Okay. John?

DR. FLACK: I certainly agree with the spirit of this and I think 3.2.1 about CABG is very

reasonable. 3.2.2. stroke/TIA, no argument there. 3.2.3., avoid use or lower the dose in low-weight patients, yes. And 3.2.4, in the elderly, I'm just not as negative on the data as maybe the agency or some others around the table. The signal is still in favor of this drug compared to clopidogrel.

So I certainly would not avoid the use in this group and I might consider lowering the dose, but still it appears -- at least the way I look at the data, and maybe it's wrong, but I think that it is probably the best therapy in the older patients.

DR. KONSTAM: Jim?

DR. UDELSON: So I agree with having some guidance for clinicians about trying to avoid use in people who you know are going on to CABG. That signal was clear. 3.2.2, it's very clear about the TIA/stroke patients avoiding use.

In the other two, I wouldn't say avoid use, but I think, as we talked about before, a description of the trial data and the PK data and the suggestion of possibly lowering the dose would be sufficient.

DR. KONSTAM: Okay. Mike?

DR. DOMANSKI: I think for 3.2.1 and .3 and .4, I would provide enough information in the label to tell people, in effect, that they're probably operating at somewhat increased risk and then they'll have to use their clinical judgment. I think with regard to the use in stroke and TIA, I would try to really discourage the use of that. I would restrict that.

Again, I guess I've said it a few times before, I feel uncomfortable recommending a lower dose in this setting, because I just don't think we have any clinical data.

DR. KONSTAM: Steve?

MR. FINDLAY: I would agree. I think it's strong language of advice and information is needed on all these points, making it very clear to clinicians. I won't try to parse out the language. The word "avoid" is not appropriate in some of these cases, and in previous questions, we had the word "discourage." But I think strong language is needed.

The sponsor has put forward a risk minimization and communication plan that, at least on paper, would go a good way to informing clinicians and

the public and consumers about the risks associated with this drug.

DR. KONSTAM: Okay. I think I'm confident about yes for number one, number two and number four, and I think I've already commented about how I feel about each of those and I agree with most of the comments before.

I think with regard to the low weight, I think the answer is probably yes, but I just don't get a clear answer from the data, because we just don't see it in the pre-specified subgroup analysis and it pops out in the less than 60 kilograms. So it makes sense, but I don't think I can infer it from the data.

Jim?

DR. NEATON: Actually, I think my point of view is the same as Mike Domanski's. I would definitely, for 3.2.2, use the term "avoid" and then, for the other ones, I think clearly point out some of the data, and for the first one, for the CABG, but also for the last two, these are important risk factors for bleeding that should be taken into account.

DR. KRANTZ: I think I might be a little bit

more declarative around the CABG. I think, at least in my own neck of the woods, it's sort of standard of care to call out a five-day period for clopidogrel. So I would think about a seven-day period. But again, hazard ratios were very favorable, .71 for prasugrel in that population. I certainly would avoid in the TIA.

I guess I'm still sticking with my first opinion that at least throwing out the option of a dose reduction for the lower weight might be reasonable. I probably wouldn't throw out or give the recommendation for lower dose in the elderly, but just a very general precaution about the risk.

DR. KONSTAM: Emil?

DR. PAGANINI: I'd discourage the use around CABG and other surgical procedures as opposed to avoid. I would avoid use in TIAs and strokes. I like the verbiage there. On 3.2.3, I would lower the dose in low-weight patients. And in 3.2.4, I would state cautious use in the elderly.

DR. KONSTAM: Richard?

DR. CANNON: I think one and two are pretty clear. One, I think, should be warning. Number two I

think rises to the level of a black box warning, as far as use in patients with stroke or TIA.

For three and four, as I said previously, I think lowering the dose in those individuals less than 60 kilograms is reasonable and defensible. That's what the sponsor recommends or advocates, and hopefully that would reduce the risk of bleeding. I think caution rather than avoiding use in elderly patients seems prudent and hopefully that would reduce the bleeding risk.

DR. KONSTAM: I'd actually like to just go back for a moment about the CABG and welcome other comments. But I am troubled by the fact that I don't really see a cut point in the number of days that suddenly makes it safe. I just don't see that from the data at all.

So although you'd think it should be true, based on the half-life of platelet survival, but I don't know. I don't know how that works from a clinical dynamic perspective and I'm troubled by it. So I'm just not sure about what exact recommendation to give to clinicians about how many days to wait after

discontinuation of the drug, and maybe we could get some more information about it.

DR. CANNON: But is it necessary to put the number of days they should wait? Just say that there is an increased risk of bleeding if a patient undergoes CABG or other surgeries and not put five days, seven days.

DR. KONSTAM: And so just say what? Say that there is an increased risk for bleeding –

DR. CANNON: Major bleeding.

DR. KONSTAM: -- for anyone receiving the drug or who has been on the drug for some unknown period of time.

DR. DOMANSKI: I think it would be useful, though, for the FDA to gather and garner enough data to make some kind of recommendation to people, because you're really just ceding it to folks who know less than some of the wisdom that the FDA can supply. So I would make some kind of a reasonable cut point. I think the reality is, for the elective cases, you can probably wait as long as seems reasonable. And for the ones that crash in the cath lab, the discussion is

going to be over anyway.

DR. KONSTAM: So wait a minute. What cut point would you recommend?

DR. DOMANSKI: I'm thinking through the half-life -- through the lifetime of platelets. I think probably if you waited seven -- certainly, if you waited seven days, you should be okay. But I'm subject to -- I don't want to make some kind of -- I want to be careful about saying too much on this one. I would look a little more carefully, get some other input and see. But I would put a number on it that's the best you could estimate.

DR. KONSTAM: Bob?

DR. TEMPLE: Didn't you think the risk looked like it declined some after, say, seven days or so? I thought that's what their presentation and Ellis' --

DR. KONSTAM: Well, I had problems with it.

DR. TEMPLE: Ellis didn't --

DR. KONSTAM: And Jim I think was the one who pointed out that we don't know the denominator.

DR. NEATON: Well, I think we do. In Dr. Unger's analysis, you do. It goes from like

17 percent to eight and a half percent, from the first week to the second week.

DR. TEMPLE: But don't forget, his eight and a half percent is a cumulative value.

DR. NEATON: I'm just taking the raw percents from his table that among the people that had CABG within a week of stopping, it was 16.8 percent, and, in the second week, 8.5 percent.

DR. TEMPLE: I mean, you know the first few days is 30, 40, 50 percent. It's huge.

DR. KONSTAM: But there seemed like there was a big problem in the first few days, first, I don't know, three days or so, and then it seemed to decline. And I'm just not sure there was -- I'm just not sure what seven -- I'm not sure about the seven days, that's all.

DR. TEMPLE: Maybe we can find a way to show the data in a way that's understandable.

DR. KONSTAM: Right.

Ellis?

DR. UNGER: A couple points. I mean, the ambiguity, in part, stems from the fact that at day 10,

you had two bleeds in 10 subjects, so that's 20 percent right there.

I'm sitting here, I had a couple thoughts. One thought we had had for labeling was basically waiting longer is better. That's general advice; it doesn't give you a cut point. But the other thought I had just sitting here is that we could analyze all bleeds by time and use all bleeds as a surrogate for bad bleeds and maybe get a better concept of the shape of the relationship.

People may have comments on that.

DR. DOMANSKI: Marvin?

DR. KONSTAM: Yes.

DR. DOMANSKI: I'm not so sure that this problem is all that tremendously complex. I mean, you irreversibly inhibit the platelets that are there. The platelets are then replaced over a time course that's reasonably well understood. I'm not so sure why this is a heavy oar to pull.

DR. KONSTAM: It's fine and we don't necessarily have to do it today. I just was commenting that I can't personally figure it out from the clinical

data that were shown. And I know we think we know what, around the table at least, what the half-life of platelets are. I don't know. I believe what I'm told on the subject. But it still can get pretty complicated. So, yes, half-life, so, okay, there's still half of the platelets around that still have the drug on board.

DR. DOMANSKI: Yes, but I was thinking my hematology runs out a little bit more quickly than I want to admit in this erudite group. But I would think as you get out 10 days, you've pretty much replaced them, haven't you? Anyway, so you can work on that.

DR. KONSTAM: Okay. You guys have homework. Good.

Yes, Mori?

DR. KRANTZ: Just a quick question for the record.

Does the agency recall what the label says for clopidogrel? Is it declarative in that label, for curiosity? Is it five days? I see a lot of nodding heads behind us. So I just would -- in terms of consistency, in terms of messaging to providers, we

have to maybe take that into account.

DR. KONSTAM: Jonathan?

DR. FOX: At the risk of sounding somewhat in contrast to my earlier comments, in general, I'd like there to be not so rigid instructions to clinicians. But I would agree with Dr. Domanski that, as opposed to Dr. Cannon, to leave it vague I think is maybe not a great idea, because then people will probably tend to underestimate the risk rather than overestimate it and say, "Oh, three days have gone by, it's probably okay now." So whatever number you pick, just to the agency, I think I would favor a reasonably well defined recommendation.

DR. KONSTAM: Okay. Norman?

DR. STOCKBRIDGE: Just one other thought on this. The drug is gone in one day. That's several half-lives. So why don't you wait a day, if you can, and give some platelets that work?

DR. DOMANSKI: I think we need to think about that one. The fact that the drug is gone doesn't mean anything. It's what it's done to the platelets that you've got floating around that counts.

DR. STOCKBRIDGE: Fine. They're out of commission. Forget about them. You're not ever going to get them back. They're gone.

DR. DOMANSKI: You do what you have to do, but giving platelet transfusions -- I'm not even so sure that's going to work. I guess if the drug is gone, it should. But I'm a little nervous about telling people to give platelet transfusions for an elective procedure.

DR. KONSTAM: Well, we don't have to tell them to do it, but I guess I'm not sure how to interpret Norman's comments. It would seem that if that's a concern of yours with the patient in front of you and you've stopped the drug two days ago, I guess it's something to consider, isn't it?

John?

DR. FLACK: I'll just throw out this. I hope that perfection, and that is absolute knowledge of when the risk is gone, does not become the enemy of the good here and giving some guidance, because I agree with the comment that was made that the FDA, and hopefully some input from this group, is going to have a better handle

on this than some of the people making decisions about this, and I think some guidance would be helpful, even if it is not absolutely definitively rigidly known that it's exactly right. I think we should take the best look at this data and make a reasonable recommendation.

DR. TEMPLE: I think we hear you. Also, I think you can say, beyond any question, that it's worst in the first few days, so even telling people that is true. And then it's got to be back to normal by 10 days because the platelets are back. Anyway, we'll figure it out.

DR. KONSTAM: Okay, good.

Okay. So we're up to the final question, which is sort of -- I don't know if the rest of what we've done is unofficial, but this is more official.

Before we go into the question, so we're going to vote on the approvability. Before we do that -- and we're going to do that in a pre-specified way, so don't do it yet. But I just guess I'd give the panel an opportunity for any last discussion on if anybody feels like there's some aspect of this that's going to impact on our decision-making for this vote

that really hasn't been given enough service, and sort of open that up. Okay.

So in that case, we will be using the new electronic voting system for this meeting. Each of you has three voting buttons on your microphone, yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on a screen.

I will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record as well as the reason why they voted as they did. And, Jonathan, we're going to leave you out of this, I'm sorry. Okay.

So if there's no further discussion on this question, we will now begin the voting process. Please now press the button on your microphone that corresponds to your vote.

Wait. I guess I should read the question, make sure we're voting in the right direction, no double-negatives.

Should prasugrel be approved to treat patients with acute coronary syndromes presenting with either unstable angina non-STEMI or STEMI? After the vote, please comment.

So let's please go ahead and vote.

DR. FLACK: I must say that I think it's an improvement --

DR. KONSTAM: Hold on, hold on. Press your button.

DR. FLACK: I already pressed it.

DR. KONSTAM: That's all right. Well, we didn't ask for any comments yet. Hold on.

DR. FLACK: I thought you said make the comments after you pressed it.

MS. FERGUSON: If you'll just wait a second, Thiep will let me know when the vote is in there.

Are we good, Thiep? Okay.

I can push the button three? All right. Here we go.

DR. KONSTAM: Okay. So the vote is yes-nine, no-zero, abstain-zero.

So now we can go around the room and I don't

know whether we need everybody to read their -- I guess -- all right. Everybody read your vote into the microphone and tell us why you voted the way you did.

So now, John, we can start with you.

DR. FLACK: Yes, for the reasons I've already articulated.

DR. KONSTAM: Jim?

DR. UDELSON: Yes. I think we're able to make a determination of benefit and risk. And I just want to say I think we'll be seeing this more and more in the coming years as we sort of push the envelope of pathophysiology and we'll need programs of this size to really get the kind of data we had today to really make that decision. So I voted yes.

DR. KONSTAM: Mike?

DR. DOMANSKI: I voted yes. I think that prasugrel is demonstrated to be effective and safe in appropriately selected patients.

DR. KONSTAM: Steve?

MR. FINDLAY: Yes, for the reasons we've discussed in the last hour and a half. I do hope that the sponsor would seriously consider DTC ads when those

happen, assuming the drug gets approved by the FDA, that are very forthright in presenting the risk-benefit ratio of this drug. I think that's critically important with this agent.

DR. KONSTAM: I voted yes. But I'd like to just make one or two comments.

First, I guess with every new antiplatelet agent or antithrombotic agent that came along, there's often been sort of a promise of dissociation between benefit and risk and that you could somehow move to having incremental benefit without incremental risk. And I think there was an anticipation, based on the Phase 2 data here, that that might in fact be the case with the dosing regimen that was prescribed, and I think we should point out that it didn't work that way. There was incremental benefit with what was clearly a greater antiplatelet effect, but it came with a cost, the cost being, clearly, incremental bleeding risk.

So I think we voted with our feet or with our fingers to the effect that everybody feels it's approvable. I would just say that there is a risk-benefit ratio. And I guess I'd just say my

questioning earlier to Elliott was sort of trying to understand what the community's message -- and, to some extent, this may be reflected or maybe not in the labeling -- the message is the right thing to do with all these patients who might've gotten into TRITON is to give prasugrel and not an alternative.

I guess I don't quite feel that way. I feel that it's a bit of a complicated risk-benefit tradeoff. I agree that there clearly is an incremental benefit over risk vis-a-vis the cardiac events and I think that's an individual decision to be made by the clinician with the patient in front of him or her on a case-by-case basis.

DR. NEATON: I voted yes. I think this was an extremely well done study. I think the analyses were quite clear for the overall efficacy and safety outcomes, and I think both the sponsor and the FDA did a nice job summarizing them for us.

DR. KONSTAM: Mori?

DR. KRANTZ: Yes. I think this really is a scientific advance. I think it's nice, to me, to see an incremental value rather than a new add-on therapy

that creates more complexity for care. And I thought the other thing that was nice about this was I think it moves us away from sort of the voodoo of preloading people in the dark without knowing their anatomical substrate. So I think that's a big advance. And, again, the documentation was really good on the sponsor and FDA side.

DR. KONSTAM: Emil?

DR. PAGANINI: I voted yes. I enjoyed the level of both quality and quantity of the data presented. I really enjoyed the quality of the analysis and discussion from both industry and FDA sides. I thought they were superb. And I believe that this drug is an effective drug as an advance on the front end to encompass a greater number of patient responders. So I see this as being an advance.

DR. KONSTAM: Richard?

DR. CANNON: Well, obviously, I voted yes. I do think there was a compelling need for a drug that had more predictable pharmacokinetics and pharmacodynamics than clopidogrel. I think the issue of clopidogrel resistance is real and it matters, and I

think this drug is a major advance in that regard.

I do hope that there will be future research on the possibility of maybe after a period of time, whether it's 30 days or 60 days, whether perhaps lowering the dose of prasugrel may reduce some of the bleeding risk without sacrificing the platelet inhibitory benefit.

I would be interested to see such data forthcoming and, also, I think we need more clarity about treating the elderly, because with large infarcts, they have the most to lose and potentially the most to gain. And perhaps in some way altering the administration of the drug or the dosing interval, perhaps there might be benefit that outweighs the risk of bleeding.

I also want to thank the sponsor and the FDA for their presentations. I thought they were excellent.

DR. KONSTAM: Okay. Let me ask Norman and Bob if there's anything else you need of this committee.

DR. TEMPLE: No. I think it's been a very

good discussion and I, too, admired the presentations of our people and I thought the company's presentation was pretty good, too.

DR. KONSTAM: Okay. So let me join the others in commenting about the quality of the discussion. I thought it was outstanding and it really was a terrific trial and that shows up. And I do want to thank the agency for their hard work on this and the clarity of their presentations. And I want to thank the panel for, I think, a lot of good, hard work today. And with that, we'll adjourn.

(Whereupon, at 3:52 p.m., the meeting was adjourned.)