FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

Monday, May 2, 2011

8:00 a.m. to 4:15 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

MEETING ROSTER

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P R O C E E D I N G S

(8:02 a.m.)

Call to Order

Introduction of Committee

DR. PACKER: Good morning. I'd like to call this meeting to order. This is the joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. We'll be discussing the cardiovascular safety of ultrasound contrast agents today.

As we usually do, I'd like to go around the room and have everyone introduce themselves. Please keep it brief, and just your institution of origin and your discipline.

Shaw, you want to start?

DR. CHEN: Yes. Shaw Chen, deputy director, Office of Drug Evaluation IV. We're the Division of Medical Imaging Products.

DR. IYASU: I'm Solomon Iyasu. I'm the director of the Division of Epidemiology and Office of Surveillance and Epidemiology.

DR. FILICE: I'm Ross Filice. I'm the clinical reviewer from the Division of Medical Imaging.

DR. CHARLES: Janelle Charles, statistician, Division of Biometric VII, Office of Biostatistics.

DR. SACHDEV: I'm Vandana Sachdev, cardiologist. I run the echo lab at the Intramural NHLBI.

DR. TATUM: I'm Jim Tatum, radiologist and nuclear medicine physician from the Veterans Affairs.

DR. SUNDARAM: I'm Senthil Sundaram, cardiologist, Wake Faculty Practice, director of noninvasive lab. Thank you.

DR. WOODS: Good morning. My name is Mark Woods. I'm the clinical pharmacy coordinator and residency program director at St. Luke's Hospital in Kansas City, Missouri.

DR. VAIDA: Good morning. I'm Allen Vaida. I'm a pharmacist and the executive vice president at the Institute for Safe Medication Practices.

MR. COUKELL: Good morning. I'm Allan

Coukell. I'm a pharmacist with the Pew Health Group and the consumer representative on the Cardiovascular and Renal Committee.

DR. SANJAY KAUL: Good morning. Sanjay Kaul. I'm a cardiologist at Cedars-Sinai Medical Center in Los Angeles.

DR. BLACK: Hi, good morning. I'm Henry Black. I'm a clinical professor of internal medicine at New York University and member of the Center for the Prevention of Cardiovascular Disease.

DR. VESELY: Nicole Vesely, designated federal official, cardiovascular and renal drugs advisory committee.

DR. PACKER: Milton Packer, University of Texas Southwestern, cardiology and clinical sciences.

DR. HOCHMAN: Judith Hochman, cardiologist, NYU Medical Center, New York.

DR. KRANTZ: Good morning. Mori Krantz, cardiologist, Denver Health Medical Center, director of echo services.

DR. HALPERIN: Good morning. Jonathan Halperin, cardiologist at Mount Sinai Medical Center in New York.

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

DR. MORRATO: Good morning. Elaine Morrato, epidemiologist and health systems management and policy at the Colorado School of Public Health.

DR. WOLFE: Sid Wolfe, internist and with the Health Research Group of Public Citizen in Washington.

DR. D'AGOSTINO: Ralph D'Agostino, biostatistician, Boston University and Framingham Heart Study.

MS. PATRICK-LAKE: Bray Patrick-Lake, I'm the president of PRO Research Foundation. I serve as the patient representative.

DR. STROM: I'm Brian Strom, University of Pennsylvania. I'm a general internist, epidemiologist and clinical pharmacologist. My interest is pharmacoepidemiology.

DR. RICH: Stuart Rich, cardiologist,

University of Chicago.

DR. WEBER: Michael Weber, State University of New York Downstate, College of Medicine, cardiology.

DR. FOX: Jonathan Fox, I'm a cardiologist in clinical development with AstraZeneca. I'm the industry representative to the Cardio Renal Committee.

DR. PACKER: I'd like to welcome everyone today and also would like to welcome the sponsors. We have a very large committee. It's a joint meeting of two committees. It is going to be very, very important that we hear everyone's opinion. It's also important for everyone to try to be as concise as possible in presenting their views because there are going to be many views around the table.

If you want to be recognized, please put on your microphone. I'll see the red light at the top. You don't have to raise your hands. Nicole will keep a running count of who put on their microphones first, and she'll make sure that I do

things in a judicious order. If for some reason that system fails, please don't hesitate to raise your hands, wave them wildly and make sure that you're recognized in the old traditional manner.

It is very important that we stay on time today. There's a lot of material to go over. It's not just two committees meeting. It's also three sponsors presenting plus an FDA presentation. So we're going to try to keep the discussions and the presentations on time and focused. So let's make sure that everyone understands that.

Nicole, I'm going to have you go through the conflicts first before we kick things off.

Conflict of Interest Statement

DR. VESELY: The Food and Drug Administration is convening today's joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the

committees 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 these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has

authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today the committees will discuss safety considerations of ultrasound contrast agents particularly related to new information in development since the prior advisory committee meeting on the same topic on June 24th, 2008. The discussion will include the result of required postmarketing safety studies and data from

postmarketing surveillance.

This is a particular matters meeting during which specific matters related to the approved products, Definity by Lantheus Medical Imaging and Optison by GE Healthcare, as well as the investigational new drug application for SonoVue by Bracco Diagnostics will be discussed. Definity and Optison are indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

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.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the products at issue.

Dr. Sanjiv Kaul, who is a guest speaker with us today, has acknowledged a professional and

financial relationship with General Electric Medical whose product is under discussion today.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Fox is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Fox's role at this meeting is to represent industry in general and not any particular company. Dr. Fox is employed by AstraZeneca.

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

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

DR. PACKER: As we go forward, because there are three sponsors, if I could ask anyone who is presenting on behalf of the sponsors, be it an employee of the company or a invited consultant on behalf of the company, to please identify themselves before getting up to the microphone, and please remind us which company you're presenting. It would be very helpful since there are three.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes it's important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships they may have with the firm at issue such as consulting fees, travel expenses, honoraria and interest in the sponsor, including equity interest and those based on the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

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 gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair, and 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 advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or at lunch.

Without further ado, we'll go to the formal presentations for this morning. The first presentation is by Ira Krefting from FDA, who will give us a history of ultrasound agents.

FDA Presentation - Ira Krefting

DR. KREFTING: Good morning. I am Ira Krefting. I'm from the Division of Medical Imaging Products. I want to welcome you again to this joint meeting. I also want to welcome you here to a spring Monday in Washington.

We will be discussing, as you heard from Nicole, the safety of ultrasound contrast agents, which are used to improve visualization during ultrasound examinations. That is an imaging procedure that does not use radiation. We had a

previous advisory committee concerning these agents in 2008.

So why are we here today? Today, we will focus on a safety update. We will hear presentations about postmarketing studies and the reporting of adverse events. Our goal today is to obtain input from the panel on the impact of those studies and accumulated postmarketing data on the continued safe use of the ultrasound contrast agents. The sponsors of these agents have been invited to join us and provide their perspective.

Our panel of experts represents multiple areas of expertise, as you heard going around the table. There are experts here from cardiology, statistics, et cetera, and they've come to us from institutions from around the country. We have a new large room here. We have room for two Kauls, so we have Dr. Kaul from Oregon Health Sciences University who will be speaking, and there's another Dr. Kaul on the panel.

So as I bring you to the introduction to set the stage for today's discussion, it has nothing to

do with money, no money here. But I would like to acknowledge my longstanding friendship with Dr. Rupani, who is on the GE review team. In a past century, in another place, we worked closely together on many clinical issues not related to the issues under discussion today.

We view the ultrasound contrast agents as a class of products. They all have a similar mechanism of providing contrast with tissue through their interaction with ultrasound. The safety issues we will speak about are relevant to all of the members. The specific safety profile of each member may differ. Additionally, each agent has his own market share and has been on the market for different times.

Here are the ultrasound contrast agents we will be focusing on during our discussion. Note that Optison was approved first. Definity came on the market later. SonoVue is used in Europe and in many other countries around the globe but is not approved in the United States.

The indications for Optison and Definity are

the same. SonoVue in Europe has the same cardiac indications but is also approved for delineation of blood vessels in the central nervous system, breast and liver.

So as I mentioned, today I want to set the stage for the rest of today's meeting. Part of my presentation will be a review of the regulatory history and significant events that have occurred with the ultrasound contrast agents. We'll go over the basis of the approval for the ultrasound contrast agents. This review will also provide the audience with a brief insight into our approval process.

We'll talk about the adverse event reportings that reached the FDA in 2006. We'll discuss our safety labeling changes that occurred between 2007 and 2008. We will review the recommendations from the 2008 advisory committee. Then I will introduce to you the postmarketing studies, which will be a major point of discussion, and we'll then move on to the rest of today's deliberations.

First, let's talk about the approval of the two agents marketed in the United States. Each NDA -- and NDA is a new drug application -- have the same indications. In the Phase 3 studies -- those are the studies designed to show efficacy and also monitor for safety -- there were approximately 200 patients for each agent.

For patients to get into the study, the inclusion criteria, they had to have a suboptimal echocardiogram. Patients with unstable conditions were excluded from the study, but some patients with New York Heart Association Class 2 or Class 3 congestive heart failure were involved in the study. As will be important later, and this will come out in later discussions, there was no measure of pulmonary artery changes.

This is the safety database. This is the number of patients who received each agent over the course of the development program. That includes what we call Phase 1 through Phase 3 trials, the development program. Note that the deaths and other serious adverse events, particularly in the

case of Definity, occurred days after the administration of the agent. The serious events were mainly cardiac and attributed to underlying conditions. As you can read at the last bullet, Definity was discontinued for chest pain, dyspnea, back pain, and hypersensitivity reactions.

After these products were approved, the FDA worked with the sponsors for the development of an initial label. The initial label -- this is before 2007; this is when the products were approved -- had a contraindication. Now, if you look at the label, the package insert, there's a section that's called contraindications. The contraindications for each of the approved ultrasound contrast agents were for hypersensitivity and for cardiac shunts.

The concern about cardiac shunts was that large particles would pass from the right circulation, that is, the venous circulation, directly into the left or arterial circulation and lead to an embolus, perhaps in the brain or other vital organ. I'll provide you in the next several

slides with further understanding of labeling.

Over the years there has been additional uses of these agents, what we call the off-label uses, and this has served to broaden the patient population. These agents all have extensive off-label use. They have significant use in stress tests with a pharmacologic stress agent or with exercise. They are used for the diagnosis of complications of myocardial infarction, like ventricular aneurysm, and they're used in the ICU, particularly for patients who are too critically ill to be moved and also for the delineation of vascular structures.

Let's move forward now to 2006, 2007 when there were emerging safety concerns that reached us. Starting about 2006, FDA became aware of deaths and serious adverse events that occurred rapidly and dramatically following administration of the approved agents. The serious reactions included death. The serious reactions seemed to be of an anaphylactic/anaphylactoid nature or of acute cardiac pulmonary collapse. The risk factors were

of a cardiopulmonary nature or of chronic pulmonary disease, congestive heart failure or acute coronary syndromes.

About the same time, FDA became aware of animal testing -- and this was actually not new data, but became aware of animal testing that appeared to mimic the dramatic cardiopulmonary reactions seen in patients with severe events. Following an ultrasound contrast administration, there was an increase in pulmonary artery pressure and a concomitant simultaneous decrease in systemic arterial pressure. In pigs, this occurred at clinically relevant doses. In dogs and monkeys, at doses higher than the clinical doses.

Here is a graphic representation of the blood pressure effects that I just mentioned to you. Notice in yellow the pulmonary artery pressure dramatically increases, and there is a concomitant decrease in the blue of the systemic arterial pressure. This was from, as you see, experimental data in the pig model.

So all of this information coming together

led to the development by FDA of safety labeling changes. Our changes made in 2007 were based on postmarketing reports. There were five deaths within 30 minutes of contrast administration. The nature of the deaths was of acute pulmonary deterioration with or without anaphylactic or anaphylactoid symptom components such as hives or bronchospasm, et cetera. There were also 200 serious reactions shortly following the contrast administration. The majority of those again were of a cardiopulmonary nature, hypotension, respiratory failure and cardiac difficulties.

Before I show you the 2007 labeling changes, let me provide you with some background information, the definitions we apply when we are crafting a label. This is taken from the Code of Federal Regulations.

Let's talk about a boxed warning. A boxed warning alerts the prescriber to certain situations that could lead to death or serious injury. The boxed warning appears, obviously, at the top of the label. It is usually about 20-some-odd lines, and

it is fashioned to give a specific direction, a specific warning to a practitioner or to a prescriber so that that individual can take a specific action to avoid serious adverse events. So it alerts the physician, the prescriber, to be vigilant about a specific problem.

In the same area of the Code of Federal Regulations, we can talk about the definition of contraindication. The main point that I've highlighted in red is that the drug should not be given if the risk of use clearly outweighs any possible benefit. As you read on in the text from the CFR, you will see several examples of when contraindications would be appropriate.

So here is the 2007 label. The underlying was done, and the red areas were done for emphasis, so all of you could be aware of the parts that were different. Now, the label is a little complicated. I'll have to work you through it. It's in two slides.

So first this is the boxed warning, and remember I said it has to be short. The two areas

are in red: Assess patient for contraindications -- we'll move on to that in a moment -- and monitoring of all patients for 30 minutes for vital signs.

Now, if you take the label for each of these products, you go a little further in the structure of the label, here are the specific contraindications. These are the new contraindications in 2007. They were based on the risk factors we observed in the deaths and serious adverse reactions, which I presented to you a little earlier in the discussion. The contraindications divide between acute or deteriorating cardiac conditions. As you can see, acute coronary syndromes, et cetera, and severe pulmonary conditions. Hypersensitivity and intra-arterial injections remain as risk factors.

Following the new boxed warnings, the practice community became concerned that these agents might be withheld in certain medical situations where they could provide important diagnostic information. The community provided

data suggesting that the agents do not induce hemodynamic changes. We were alerted to literature again showing studies demonstrating relative stability after the administration of these agents in humans.

Here are some of the literature citations that came to light after the 2007 labeling changes. These were extensively reviewed, and, again, they seem to reveal systemic hemodynamic effects in humans at clinically relevant doses were minimal or nonexistent.

Having received all this input -- this is now in 2008. Having received all this input from the practice community and reviewed the publications, which I cited previously, FDA took further action. We again revised the boxed warning. Using our new authority under the FDA Administrative Act -- that's FDAAA -- we can require sponsors to do postmarketing studies. These studies are called postmarketing requirements, often referred to PMRs, and the nature of these studies is to further characterize

the safety of the drug or agent in question. We additionally, as you heard earlier, convened an advisory committee in 2008 to discuss all the issues at hand and issued web postings further explaining all of our actions.

So having done all those interventions in 2008, this is the boxed warning that was issued at that time. Again, let me work you through it. The areas in red represent the changes that were made. So each patient is to be assessed for contraindications, and only high-risk patients, those with pulmonary hypertension or unstable cardiac conditions, were to be monitored for 30 minutes.

In parallel to the earlier slide, we have to go to the contraindications section of the label, and this is the 2008 contraindications. As you can read there, it relates to a shunt and hypersensitivity, and, again, intra-arterial injection. Generally, it was a return to the contraindications that was on the previous earlier than 2007 label.

That all is a little complicated. We shunted back and forth there, so here is a summary of the labeling changes to make it clear for everybody on the panel and in the audience. So before October 2007, there was no boxed warning. The contraindications were shunt, hypersensitivity and intra-arterial injection. Between October 2007 and May of 2008, there is a boxed warning, and we had rather stringent contraindications. Then after May of 2008, we continued with the boxed warning, which you just saw in the previous slides. However, the contraindications reverted back to the earlier 2007 era of shunt and hypersensitivity and intra-arterial injection. However, very important, remember that monitoring is recommended for all unstable patients.

The concerns about ultrasound contrast safety, particularly the use in unstable cardiopulmonary patients, extended beyond the United States. Our colleagues in Europe had observed similar type of reactions. The European labels for the ultrasound contrast agents reflect

these concerns. Each one of these agents has a label that's a bit different, so I will present excerpts from each of the various labels to you.

For Luminity, which is Definity in Europe, I've highlighted the warnings section. As you can see, use extreme caution when considering the administration of Luminity to patients with unstable cardiopulmonary status. There is also a monitoring requirement for unstable cardiopulmonary patients. And finally, the bullet relating to shunts has also been mentioned by our colleagues in Europe.

Here is the EMA, the European Medical Association, label excerpts for Optison. Optison carries a contraindication for hypersensitivity and high levels of pulmonary artery hypertension. The special warning is noted there that the experience with Optison is quite limited in severely ill patients.

SonoVue, as I mentioned, is not approved in the United States. An excerpt from the EMA label for SonoVue, the contraindications section, you

will note cardiopulmonary conditions, angina at rest for within seven days, recent coronary interventions, we talked about the shunt, pulmonary hypertension and the adult respiratory distress syndrome, which, as you know, is a severe pulmonary condition where patients may be on a ventilator in the intensive care unit.

Moving on now to the other areas that the FDA took action on in the period from 2008 on, we'll talk about the advisory committee. The focus of the June 2008 advisory committee was a review of the ultrasound contrast agent cardiovascular adverse reactions and a review of the preclinical data demonstrating similar adverse reactions. The advisory committee provided guidance for further development of ultrasound contrast agents down the road.

Important recommendations made by the panel, as you can read there: They confirmed the importance of preclinical data in relevant species. There should be premarket randomized clinical trials for safety in populations likely to use the

ultrasound contrast agents. It's particularly important with these agents being used with cardiac agents because the comorbidities may mimic the serious adverse events. Also, observational trials should be instituted for safety.

As a result of all those discussions and with our new authority, as I mentioned to you, we did request from the sponsor three very important studies, which will be discussed later today. These are the postmarketing studies that will be used to help characterize the safety of these agents.

The first one, which was a longstanding request, was a study of a thousand outpatients using the contrast agent in routine practice. Then there would be an observational study of ultrasound contrast use in critically ill patients, those patients with acute cardiopulmonary conditions probably in an ICU or a cardiac care unit, and a study during cardiac catheterization during right heart catheterization to study pulmonary hemodynamics. The study should be performed in

patients with normal baseline hemodynamics and those with pulmonary artery hypertension.

So this is my introductory discussion to set the stage for today's meeting. Here's a brief overview of the major topics that we'll be discussing that you've heard about in some detail in the last few minutes. Obviously, there's going to be an extensive review of the postmarketing studies that I just presented to you. Then we're going to talk about review of postmarketing spontaneous reporting, particularly for rare events. Finally, the implications of the import of all this data for labeling, specifically related to boxed warning and contraindications.

So with the conclusion of my study, I will turn the podium back to the chairman. Thank you.

DR. PACKER: If we have brief questions before Ira steps down.

One very brief question. In your discussions with the sponsors for the observational studies, did anyone have a certain effect size in mind, or did you just sort of tell them they had to

be big enough?

DR. KREFTING: Well, I think I'll pass on the detail of that because you'll be hearing about that in the statistical discussion.

DR. PACKER: Okay. Thank you very much.

We'll go on to the invited speaker presentation, Dr. Sanjiv Kaul, and we'll take questions after Sanjiv's presentation as well.

Speaker Presentation - Sanjiv Kaul

DR. SANJIV KAUL: Good morning. Thank you. Thank you for inviting me to give an overview of the current cardiological applications of contrast echocardiography. And when I mean current, I mean the way we use it, which is way beyond the approved. So most of the use is outside the approved indication, which is resting opacification of the LV at rest.

I'll cover a little basics for those who are not familiar. Dr. Marzella asked me to talk about how ultrasound contrast agents produce signal, how they are detected, And for those who don't know echo, maybe a few slides about how we image these

patients.

So there's a history of ultrasound contrast agents here, very briefly. Europe, Levovist was a ultrasound contrast agent used in Europe and Japan. It's no longer made. Albunex was the first contrast agent approved in the U.S. by the FDA. It was not very effective because the gas in the bubble was air and it leaked out by the time it crossed this pulmonary circulation, thus producing very little opacification on the left side. And that was replaced by Optison, which is basically the same thing with a different gas, high molecular weight gas. And we learned that high molecular weight gases are very effective for shells that are diffusible.

Definity, you have heard of, and SonoVue is in Europe. Imagent was another contrast agent that reached market but never made it. The company did not survive. Sonazoid is also made by General Electric [sic]. It was first made by Amersham. It's used in Japan for hepatic opacification. CARDIOsphere and Imagify are two contrast agents

that are still in different phases of development, particularly for myocardial opacification.

So when we give ultrasound at clinical frequencies, which is about 2 million times a second, the bubbles will oscillate in the ultrasound freely, just like your ear drums are oscillating when I'm speaking to you. And so these oscillations, to be able to image these oscillations, you need cameras that are much faster than the Nyquist limit. So this is 20 megahertz camera, 20 million instructions for frames per second in Rotterdam, and they have been -- they gave ultrasound here, and you can see these bubbles oscillating. Of course, we are playing them at much slower speed than 2 million times a second.

The thing to notice is that the negative pressure of the ultrasound makes the bubble expand much more than it contracts. And this nonlinear property of ultrasound is what makes the images. So bubbles oscillate, they produce harmonics, and these signals, which are different from the signal you sent to the bubble, are then processed, either

offline and online. And most of the processing is now done online. And I'll just show you a simple one of those processes.

So in this way, you have the heart, and you give half a signal to the heart, and then you then give a full signal to the heart. So these are one after another quickly. You send half a signal, and then you send a full signal. And then you process it by multiplying the half signal by two times and subtracting it from the full signal. And since the heart is linear, it does not produce harmonics, you will subtract them, and there will be no signal.

On the other hand, when you give a half signal to a bubble, the bubble will not reproduce the exact signal because it produces a nonlinear response. And so the half signal and the full signal are not going to look like each other. It's not going to look like half of the full, and then when you multiply the half signal by two and subtract it from the full signal, you are left with the signal. And this is now done in real time, and this is how we detect the presence of bubbles

inside tissue and inside the left ventricle cavity.

For those who are not familiar with ultrasound, it's just a process by which we take images of a three-dimensional structure, mostly by cutting the heart in two-dimensional slices in different ways, although now we are moving to whole 3-D imaging and then cutting the heart. I am not going to share any 3-D data today.

I'll be talking about three areas where we use contrast, and the use of it varies institution to institution. One of the areas where we have used contrast a lot is in chest pain syndromes in the emergency department. So you are aware that 20 million ED admissions for chest pain occur annually in the U.S., and the EKG is diagnostic -- the first EKG is diagnostic in only about 30 to 40 percent with your classic ST segment elevation.

Cardiac enzymes take hours to become positive or to become available, and 5 million people are admitted annually unnecessarily to the hospital. And most of them are discharged even

without a cardiac diagnosis the next day, and this is $15 billion a year.

So we started using contrast in patients with chest pain syndromes with nondiagnostic EKG. This is about at least a 10-year-old radio, if not longer. On the left is a patient who's come in with chest pain syndrome, and we can see wall motion abnormality in the anteroapical region. Contrast is entering the LV cavity, and then we give contrast for the myocardium. And these are in systolic frames from one second to 10 seconds after bubble destruction, and I'll talk about that a little later so it will become clear to you what I am saying. But there is no contrast in the myocardium.

So this patient, who has a nondiagnostic electrocardiogram, has an anteroapical wall motion abnormality and no contrast in the myocardium; taken to the cath lab, found to have a proximal LAD occlusion. The occlusion was opened, and then right after that when contrast is injected, you can see there is evidence of immediate reperfusion and

transmural reperfusion with no evidence of no reflow, and a month later, wall motion is entirely normal. So this patient was helped by our doing contrast echo at the time of ED admission before anything else was abnormal.

Here is another patient. There is contrast in the LV cavity. You can see there is enlarged anteroapical wall motion abnormality, and we were sure there'd be nothing in the myocardium. But the myocardium opacifies beautifully. And we took this patient to the cath lab, and his artery had recannulated spontaneously, which you know can happen with 15 to 20 percent of patients, especially if you are giving them heparin and other antiplatelet agents. And the outcome of this patient compared to the last patient is different, as I will show later.

So in this initial study of 1,000 patients, we examined events in the first 48 hours, and this is, remember, patients who have non-ST segment myocardial infarction or non-ST segment acute coronary syndrome; excuse me. Out of these, 90

patients had acute myocardial infarction, 50 had unstable angina defined very strictly by dynamic EKG changes and small troponin leads, and we ended up having a 17 percent event rate in this population in the first 48 hours.

Excluding this population in the first 48 hours, we then followed the rest for the next two years, and we found an additional 13 percent event rate. So this is not a risk-free population. We have 13 percent event rate in two years.

What we found in the first 48 hours was none of the EKG changes -- none of the clinical things were of much importance. If you had an abnormal EKG, that means any abnormality; ST changes, nonspecific, whatever, you had a twofold chance of having an adverse event.

If you had regional function abnormality -- now, this is with contrast in the cavity, so we are delineating wall motion based on contrast, you had a fivefold higher incidence of cardiac events. And when you had both abnormal perfusion and function, you had a 14-fold chance of

having increased events.

On the other hand, when you took patients for late survival, after 48 hours, again, you can see if both perfusion and function were normal, you had hardly any events. In fact, this was patients requiring angioplasty after repeated episodes of chest pain. And if you had both abnormal, you had almost a 50 percent event rate. And those with abnormal function but normal perfusion like the patient I showed you, were those who either spontaneously revascularized or had wall motion abnormalities associated with cardiomyopathy or valvular disease that, of course, had normal perfusion, and their outcome was different than those who had acute coronary syndromes.

We then looked at the TIMI score. As you know as clinicians, we are all taught to look at TIMI scores. And the TIMI score, as all of you know, just for those who don't know, it's age over 65, three CID risk factors, known coronary disease, ST segment, deviation on EKG, more angina events in the last 24 hours, and use of aspirin and then

troponin. And each is given a score of 1.

Since troponin is not available at the time of admission, right at the time of coming to the ED, we derived a modified troponin score from the first six variables and showed that even in low TIMI risk score, we had the ability to further stratify into low, medium and high risk based on contrast echo. And also in moderate TIMI score, we can further stratify into low, medium and high risk.

We also showed that in hierarchical order when we add information in the emergency room, clinical information is about 68 percent of total information. When you add abnormal regional function, you bring it up substantially, but you increase it further by adding abnormal perfusion. Then when the TIMI score is complete; that is, troponin has been -- you have the troponin numbers and you try to develop a score, it doesn't add anything. In fact, once you have seen the myocardium with or without perfusion, you know the status of the patient and adding troponin has no

additional effect.

We also looked at cost because this is important. This was done by modeling based on our patients. So if patients are seen in the ED, usual care, clinical evaluation admit or discharge versus doing perfusion and function, we found that even adding contrast would save $900 per patient based on hospital stay, et cetera.

Finally, in the same vein, what we wanted to do was to see if we can use this as a predictive model. As you know, a lot of people have developed predictive models in the emergency room, simple models. So we looked at our main culprits and looked at multiple regression analysis, looked at the coefficients and gave them -- anything around 1, we gave it a score of 1, and abnormal perfusion and function, we gave a score of 2. So each patient was scored in the initial 1166 patients that we evaluated.

So we developed the model in these patients and tested it in this patient population, and you can see that the model prediction and the observed,

a risk score of zero to a risk score of 4 was pretty good. We then said, okay, let's look at this prospectively, and we did another 720 patients prospectively and applied the model in another group and found the model to work relatively well. So we can really use these variables to risk predict in the emergency room. And, quite frankly, we use it every day in our clinical practice in our institution.

I will show you some images where it makes a difference, and those who are not echocardiographers, excuse me. But those who know how to read echoes might get a little -- might enjoy this a bit.

Here is a patient with atypical chest pain in the emergency room, and this is a sort of an echo without contrast. And we would sort of not have known what to do. And when we give contrast, we see clear-cut apical hypertrophy, and we are now diagnosing apical hypertrophy much more with the use of contrast, even routinely in outpatient. Now, this is LV cavity use of contrast. This is

the use that has been approved by the FDA that I'm showing you here.

On the left is another patient. You can see there is an apical wall motion abnormality. Everybody would agree this is an apical aneurysm, but when we give contrast, now you can see there's not only an apical aneurysm, but there is a pseudoaneurysm within the apical aneurysm. This makes a huge difference because the first one on the left is not a surgical candidate. The one on the right goes to the OR soon.

Here's a patient again in the emergency room, had slight dysarthria and complained of chest pain. And you can see on the left, not very remarkable, maybe some reduction in LV function, but nothing to get very excited about. And when we gave contrast, as you can see on the right, we see noncompaction. And, obviously, the outcome of this patient is not to go to the cath lab. The outcome of this patient is that they have noncompaction and dilated cardiomyopathy as a consequence.

We are using this in all our dystrophy

patients now. We have myocardial dystrophy clinics, and they send us these patients. And before using contrast, we would never pick up most of these apical abnormalities with noncompaction. And it's much more common to see noncompaction in dystrophies than we had heretofore believed.

A very common indication is thrombus. We can see here. More importantly than picking up thrombus, we exclude thrombus. As you know, those who do echo, there are a lot of reverberations and things at the apex, and people say, oh, maybe there's a thrombus, maybe there is not. And giving contrast clarifies that really well.

On your right is a patient who had multiple myeloma, came in the emergency room with chest pain. And, of course, this is a fascinoma (ph). You see this here with normal wall motion, and when we do perfusion of this thing, there is myocardial perfusion in this area. An angiogram done here shows a cavernous hemangioma.

I'll show you a few cases. This is a patient. He's an employee of the hospital, comes

in with chest pain and a totally normal electrocardiogram. I mean, there are lots of experts here. If anybody disagrees with me, please raise your hand. And, obviously, we did an echo. We always do in the emergency room. And the noncontrast echo doesn't look all that bad, but on the contrast-enhanced echo, if you watch the lateral wall, this is nothing you would have picked up on a noncontrast echo. Systole, systole, systole, there is dyskinesis in the middle of the lateral wall in a very small segment, there, dyskinesis, dyskinesis.

So the guy goes straight with a normal EKG to the cath lab, has an intermedius totally occluded. We open it, and he comes to see me once a year.

Another patient -- and I promise you I'll stop after one or two and go on to some other stuff. But here is a patient who came in really with a seizure, and after seizure, she woke up and said she had chest pain. And you can see there are some ST-T changes. An echo was done, and you can

see echo showed an apical abnormal wall motion. And they were ready to take her to the cath lab, but obviously, we do contrast. And the contrast shows a totally different picture, the myocardial perfusion. These are in systolic frames, so you can see after destruction, the myocardium is completely opacified. So this is Takatsubo syndrome, then need to go.

Again, I don't know where the takatsubos (ph) were hiding, but they're all out now. And we're all finding them with contrast echo in patients with chest pain and abnormal wall motion.

An area where we use contrast in 100 percent of our patients is stress echo. Stress echo even when the baseline image is acceptable, when they're huffing and puffing and the image is going in and out, it becomes sometimes you lose segments, and you don't have a second chance. So we give it to 100 percent of our patients. And it's made an enormous difference.

This is not approved because this is a

stress test. It is not a resting echo. So this is an unapproved indication, and it completely makes the image -- it's beautiful, especially the anteroapical region and the proximal portion of the lateral wall where we always get into trouble. And also, more importantly, the posterior wall; the posterior wall, for all those who do echo, they'll tell you, this is an area where sometimes we fall on our face. And it's because the posterior wall is being interrogated not by the axial resolution but by the lateral resolution of echo. And this whole area becomes fuzzy because it's parallel to the echo beam. But with the introduction of contrast, it's very easy to see these walls and make accurate assessments.

My next area is going to be detecting coronary stenosis, and as all of you know and those who don't, we detect coronary stenosis by producing hyperemia because at rest when we have a coronary stenosis, it has to be 90 percent or greater to cause a reduction in coronary blood flow because of autoregulation.

But Lance Gould showed many years ago that if you produce hyperemia, you can separate stenosis of 50 percent or less from stenosis of 50 percent or more. And during this period of hyperemia, you can image this using contrast echo. And the way we do this really on all the images that I've shown you so far, what we do is we infuse contrast as a continuous infusion in a diluted solution with a syringe. It's a pump, syringe pump, and it goes at a known rate. And in about two minutes we reach steady state; that is, the concentration of bubbles in the system equals the elimination rate. And so anywhere you put the echo probe, you are going to look at the blood volume of that organ because these bubbles are within the vascular space of the organ.

So on the rightmost panel here, this is the blood volume of the myocardium, the echo beam or the thickness of any echo slide that you see is about half a centimeter, so it's a 5 millimeter thick beam. And when we reach that stage, we destroy the bubbles. I showed you the bubble

oscillation. You can give it a little bit more energy, and they pop. And when they pop, there is nothing in the beam. And then we watch the bubbles come back. And the rate at which they come back gives us red cell velocity.

In the myocardium, the velocity is 1 millimeter per second. The beam is 5 millimeters thick, so it takes about 5 seconds to fill under normal resting flow conditions. If flow is faster, it'll fill faster. If flow is slower, it'll take longer.

We can plot this acoustic intensity over time. And the slope of this curve is velocity, and the plateau of this curve is blood volume. So, quite frankly, we have a unique method here where we can measure flow by using two parameters of flow, volume and velocity, because flow is a certain volume of blood moving at a certain velocity. These are pure intravascular tracers, so they give us very good information.

Here is a patient on the left here. This is bubble destruction you saw and then bubbles coming

back at rest in the myocardium, and they opacify the myocardium homogenously.

When we give this patient dipyridamole, you will see bubbles come in, but they come in slower in the posterior wall compared to the anterior wall. So the posterior wall is slow bubble destruction -- this is slow, slow, slow -- while the interior wall has already filled. So we make a diagnosis of circumflex, probably circumflex artery stenosis. SPECT done in this multicenter study was normal in this patient, and coronary angiogram showed very proximal circumflex-artery-type stenosis.

In this study, we looked at -- it was a Phase 2 study. This is Sonazoid. We looked at 55 patients, and we plotted coronary artery stenosis versus positivity by MCE versus SPECT. And only at very levels of stenosis were they comparable. The velocity information, the rate at which flow comes in was more powerful, and we have shown that SPECT really measures blood volume and not velocity. And so MCE has this advantage of looking at milder

forms of stenosis and diagnosing them.

As you know, perfusion becomes abnormal before function in the classical ischemic cascade. This has been shown experimentally by us and others during demand ischemia. So it makes sense that we use perfusion. The question is should we use SPECT or should we use a contrast, and I use both. I practice both, and I believe that absence of radiation, a lower cost and a faster process. It's a much faster process. We are done in 25 minutes less than stress, and we don't have to have the patient come two days or stay a fully day for SPECT, that this has certain advantages.

Here is a patient again showing perfusion at rest at 20 microgram per kilogram per minute. Perfusion was abnormal but function was normal. You can see this in systolic frame, so thickening is normal. It was only at 40 microgram per kilogram per minute that the thickening was also abnormal along with perfusion.

So we have seen -- and I'll show you some data from Elhendy, et al. This is Tom Porter's

group. On the left are echo images. As you aware, is the four chamber and two chamber at rest. You can see totally normal perfusion. And then on right, during dipyridamole, you can see function is perfect, but perfusion is abnormal in the entire interventricular septum in the inferior wall and in the entire apex while function is totally normal. And this is multivessel disease that we are diagnosing by looking at abnormal perfusion while function is totally normal.

So Tom and his group looked at -- this is a comparison to stress echo, now, because stress echo, the other argument we get is why not use stress echo, why do you want to look at perfusion. And you can see here in this cohort of 170 patients, I think, he showed a superior sensitivity at high-dose dobutamine but also at medium-dose dobutamine. Just like we did in our other study, there is a much higher sensitivity and accuracy with perfusion. He also, in terms of multivessel disease detection, just like I showed you that example, it is better than stress echo.

Finally, he also showed that if both perfusion and function were negative, you had very good outcome. This is 788 patients. If both were abnormal, you had pretty bad outcomes and a moderate outcome in between.

Finally, I'll move on to the last topic, just three more slides, and this is carotid imaging. And this has been spearheaded by Steve Feinstein, who has really worked on this. One of the things, as you know, everybody tries to measure -- I won't say measure but tries to measure -- is IMT. It's such a small little measurement. There's a lot of error. And with contrast in the cavity, you can see on the right here, the measurement becomes much easier in terms of IMT. So this is one application that people are working on.

The other is to just look at the morphology of the plaque. So this is a plaque here you can see. And when contrast is -- and not only do you see the contrast very well in the cavity, you see the plaque, and you also see erosion of the plaque.

There is an ulcer in the plaque. So as you see towards the end, this is the plaque, this big atheromatous plaque, and here is an ulcer in the plaque. This is something that you cannot see without contrast.

Vasa vasorum is another area that is very fascinating. The atheroma acts like a tumor, so it needs more blood vessels to grow. And the vasa vasorum supply that blood vessel. In fact, the hemorrhage seen in plaques that are very important for plaque ulceration and for plaque disruption, also, occur through this mechanism. And you can see here a very nice example where there's contrast in the cavity, and you can see in here as you watch this is the plaque. And you will see as contrast comes through, there is a blood supply within the plaque that you see vasa vasorum.

So this is another area that is -- this adds to the entire evaluation of atherosclerosis in a target organ that is very easy to approach, which is the carotid artery.

Here is a case of Takayasu carotid

angiogenesis, a lot of atheroma, a lot of angiogenesis.

I would like to finish, and this is for Ira who likes volcanoes. I live in Portland, Oregon. It's one of the most beautiful places on earth, and that's the mountain from my office. Thank you very much.

[Applause.]

DR. PACKER: We have time. We're running a little behind schedule.

Ralph.

DR. D'AGOSTINO: Thank you for the presentation, very informative. If I hear you correctly, the place where you may have imposed some sort of decision rule to see just how much benefit you are getting from the contrast is when you did the prediction rule that's in Wei, et al. paper, and I have a couple of questions on it.

I'm not clear on what is actually the outcome for the prediction rule; is it short term, long term? And then also, if I followed the regression, it looks like in doing the regression,

the logistic regression that takes these variables, and they're all very sensible variables -- and then what would happen, if I follow here, is that you just follow the individuals to see what their outcomes are, where if you actually made a prediction rule out of it, you would impose -- if you get a score of four or something like that, you would put the person in the emergency room or the coronary care or so forth.

So I'm not sure that you have a prediction rule that has an intervention in it in terms of where the individual goes --

DR. SANJIV KAUL: Right.

DR. D'AGOSTINO: -- or if you just have a prediction rule that tells you what the outcomes are going to be.

DR. SANJIV KAUL: Right. So, basically, this was not done as an intervention to the patient.

DR. D'AGOSTINO: So when you say $900, we don't really know that. That's some sort of estimate --

DR. SANJIV KAUL: That's correct.

DR. D'AGOSTINO: -- people followed the rule.

DR. SANJIV KAUL: That is correct.

DR. D'AGOSTINO: So do we have anything from the material that you actually make an impact that you can quantify?

DR. SANJIV KAUL: Nobody has done a prospective study utilizing this.

DR. PACKER: There was a question -- no? I guess not.

Yes, please, Jim.

DR. TATUM: Excellent presentation, and I really agree with you that one of the things that you're moving with ultrasound is reducing the radiation that's being used and alternative methods. One thing that I did want to point out in reference to the discussion here today, almost everything you showed was relatively a low-risk patient. We're not talking a high-risk population. So let's be careful in deliberation not to cross-contaminate into what I think are some very, very

important uses that have been presented here as we begin to talk about higher-risk patients and what would be boxed warnings. So we need to be very careful about that.

DR. PACKER: One question, and please don't misunderstand. Is there anyone, in your opinion, who when they get an echo should not get contrast?

DR. SANJIV KAUL: Well, we follow the --

DR. PACKER: Is there any --

DR. SANJIV KAUL: We follow the guidelines about pulmonary pressures and shunting, like anybody else does. So, basically, PA pressure is very easy to measure, as you know, on an echo, so we immediately know if somebody has pulmonary hypertension. And the number of 90 millimeter of mercury or higher is a very rare patient for us in the emergency room.

DR. PACKER: Let me ask the question again.

DR. SANJIV KAUL: Okay.

DR. PACKER: Is there any role for echocardiography without contrast?

DR. SANJIV KAUL: Yes. If you can see the

endocardium very well at rest, you don't need to give contrast for a regular patient, like the ones I showed you. But in my practice, I will tell you, a third of my outpatients receive contrast because I don't see the endocardium well or I don't see the heart the way I wanted to.

DR. PACKER: Given your enthusiasm, why are you depriving two-thirds of your patients of noncontrast?

DR. SANJIV KAUL: Because if I get the information that I need, then I don't give the contrast at rest. We are talking only about rest. Stress, I give it to everybody because stress, I don't have the time window or the opportunity to go back and try to get their segment if I didn't get it the first time around.

DR. TATUM: Could I follow up, just one question?

DR. PACKER: Yes.

DR. TATUM: So since we went down that track, what about strain imaging? I mean, that's become more incorporated in the systems. And how

does that impact on your use of contrast?

DR. SANJIV KAUL: Right. So that's a very good question. Strain imaging in its current form is very noisy, and there will be development in strain imaging. But in terms of looking at the endocardium currently in our armamentarium of ways to look at the myocardium or looking at the cavity, it's still much better.

DR. PACKER: I don't know if it was Shaw or Bray who was -- Shaw, why don't you go and we'll pick it up. Yes.

DR. CHEN: Yes, I have a question. In your experience, is there any difference between the different agents in this class? For example, between Optison and Definity, any subtle difference in their behavior? I'm not talking about the data we're going to present today.

DR. SANJIV KAUL: Yes, I can tell you the differences in terms of imaging differences. As you know, these bubbles have to be made to oscillate, and there's a sweet spot for oscillation. And how much you can make them

oscillate without destroying them and how much energy you need to give each bubble to make them oscillate, this is something different between them. It's not the same. And so we optimize our echo system depending on which agent we are going to use. So there are differences, absolutely, in terms of acoustics.

We never administer our agents as bolus. We administer all our agents in a diluted -- through a syringe pump. So we see very few side effects, if any, and those are usually a little bit of back pain and things like that. So we really don't -- I don't think -- I think it's the bolus that may be a little bit more liable to cause some of the side effects that have been mentioned than a slow, continuous infusion.

DR. PACKER: Bray?

MS. PATRICK-LAKE: I was hoping you could help me get a better understanding of real-world practices versus the what's labeled. So when I read the ASE guideline document, it sounded like if there were greater than two endocardial borders

that were not visualized well and you had a suboptimal image, at that point, a patient would be deemed to receive contrast. But I think I heard you say that 100 percent of patients coming into your practice are receiving contrast with stress echo, which sounds like it's predetermined. And I was wondering if your practice is typical or if you would consider it to be aggressive with the use of contrast.

DR. SANJIV KAUL: For stress echo, I think there are other people who do the same. Maybe there are people in the audience who will address that. But I just -- we read the stress echo at the end of the day. We are not there during the stress echo. So I don't want to take the chance. So, yes, it may be a little bit more aggressive than others in terms of use.

MS. PATRICK-LAKE: Right, but are other physicians standing around waiting to read echoes on the spot or is everybody reading them at the end of the day?

DR. SANJIV KAUL: Most people read them at

the end of the day, and if contrast is not used, unfortunately, a lot of the tests are not of good quality.

MS. PATRICK-LAKE: Thank you.

DR. PACKER: Yes, please?

DR. SUNDARAM: One of the relative contraindications is the pulmonary hypertension, and if you look at the ASE documents, one of the other indications, even though it is not approved, is to enhance the Doppler signal in tricuspid regurgitation to measure the pulmonary pressures. So in those instances where you can't look at the tricuspid regurgitation, the velocity envelope, in which you can't measure the pulmonary hypertension, how do you reconcile that?

DR. SANJIV KAUL: Right. So there are lots of cues towards whether a patient will have pulmonary hypertension. RV will be enlarged, RV wall will be hypertrophied, there will be RV dysfunction, there will be the flying W sign on the N mode of the pulmonary valve. So there's a lot that tells us if there's pulmonary hypertension or

not. And if we are suspecting that there's pulmonary hypertension of the grade enough to 90 millimeters, you'll even have interventricular septal motion that will be abnormal.

So it's a different kind of a patient, and it's very easily identifiable at those levels of pulmonary pressure than, let's say, 45 or a 50 millimeter where they may not be much different.

DR. PACKER: Sidney?

DR. WOLFE: This is just further trying to hone in on questions that Dr. Packer and Dr. Tatum and others have raised. You said at the beginning that most use is off label. Could you just give us a rough -- what does that mean, 60, 70, 80 percent?

DR. SANJIV KAUL: I'm just talking about my practice.

DR. WOLFE: I'm talking about your practice, right.

DR. SANJIV KAUL: In my practice, I would say resting echoes would be -- without myocardial perfusion or without stress would be probably 40 percent, 35, one-third.

DR. WOLFE: Off label?

DR. SANJIV KAUL: One-third are label.

DR. WOLFE: Are label. Okay.

The follow-up question was, since at least one element of the labeling is the failure to be able to identify in a noncontrast echo what's going on, how many of the patients -- again, your practice, how many patients have not had any noncontrast echo preceding the contrast one?

DR. SANJIV KAUL: I didn't follow that question.

DR. WOLFE: In your practice, how many patients get a contrast echo without previously having had a noncontrast one?

DR. SANJIV KAUL: Oh, the resting echoes are all done without contrast first. Everything is done without contrast.

DR. WOLFE: But then on the stress, they're all done --

DR. SANJIV KAUL: With contrast.

DR. WOLFE: Okay. So thank you.

DR. PACKER: One last -- what happens to

these bubbles? Do they float around forever?

DR. SANJIV KAUL: No, no. A couple of things happen to them. Firstly, they get destroyed by ultrasound. So if I give you these bubbles and I don't want them in your cavity, I just raise the top power and they're gone. Now --

DR. PACKER: The bubble, the sphere is gone.

DR. SANJIV KAUL: Yes.

DR. PACKER: Okay. So what happens to the gas?

DR. SANJIV KAUL: The gas is expired in the lungs. Under normal conditions, if you don't destroy them, they are taken up by the reticulo-endothelial system, cleared and then exhaled in the lung. In fact, the amount exhaled in the lung is so small that you can't even measure it. We tried to measure it in intubated patients, and we couldn't measure it. So it's a very small amount of gas.

DR. PACKER: And do you give multiple doses?

DR. SANJIV KAUL: I only give in continuous infusion, so no multiple doses.

DR. PROSCHAN: I'm wondering about the size of the micro-bubble. Does that -- I mean, there was something in the briefing materials that indicated that perhaps larger bubbles help you see better. Is that the case?

DR. SANJIV KAUL: Yes. The acoustic backscatter is related to the sixth power of the radius. So, obviously, a 2-micron difference in bubble is a 64-time difference in backscatter. However, we have to have bubbles that have to cross the pulmonary circulation and the capillaries.

So we have to sort of come to that via media where we can have bubbles that will cross and yet be enough size. So somewhere between 2 and 5 or 6 microns is about the right size. Anything bigger than that in any bubble solution is going to be filtered.

DR. PACKER: Okay. Let's move -- thank you very, very much. We'll move the presentation along. Let me just --

DR. RICH: Milt, one final question.

I want to follow up on Milt's question about

the fate of the bubble. Absent the ultrasound bursting of the bubble, what is the half-life and how are they eliminated?

DR. SANJIV KAUL: As I said, through the reticulo-endothelial system, and it depends from bubble to bubble. I think the companies may be able to give you a more precise answer, but I don't think the bubbles last more than 10 minutes.

DR. RICH: But not seconds?

DR. SANJIV KAUL: No, no, it's minutes.

DR. PACKER: All right. Thank you very much.

We're going to move on to the sponsor's presentation. Just to let the committee know, we will -- I think probably the most efficient thing to do is let the sponsor go through the entire presentation, and we will take questions after each sponsor's presentation.

So we'll begin first with the presentation on Definity, and, again, there are three presentations. We'll go through them all, and then we'll take questions at the end.

Industry Presentation – Dana Washburn

DR. WASHBURN: Good morning. My name is Dana Washburn, vice president of Clinical Development and Medical Affairs at Lantheus Medical Imaging. Mr. Chairman, panel members, FDA representatives, thank you for the opportunity to present data on Definity this morning. On behalf of Lantheus Medical Imaging, I would like to thank you in advance for your deliberations.

We will have three presenters this morning. In addition to myself will be Dr. Mark Hibberd, senior medical director, Global Medical Affairs and Pharmacovigilance at Lantheus Medical Imaging, and Dr. Michael Main, medical director, echocardiography laboratory, St. Luke's Mid America Heart Institute, professor of medicine, University of Missouri Kansas City.

This is the overview of our presentation. I will provide a very brief introduction. Dr. Hibberd will provide the pharmacovigilance safety data focusing on the data since the last panel meeting of 2008. Dr. Main will discuss the

postmarketing studies and an overall benefit-to-risk assessment. And I will close with Lantheus' recommendations for label changes as requested by FDA.

Definity is a microsphere containing perflutren gas enclosed in an outer lipid shell. The approved indication, as reviewed this morning, is for patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Definity is short lived following administration with a circulation half-life of 1.3 minutes, and perflutren is not detectable after 10 minutes in blood or expired air.

I'll now turn the presentation over to Dr. Hibberd for the pharmacovigilance data.

Industry Presentation - Mark Hibberd

DR. HIBBERD: Thank you, Dr. Washburn.

I'd like to begin by giving a brief overview of our proactive global pharmacovigilance system which begins with a collection of spontaneous adverse events from healthcare providers who can

use a toll free number that exists in our product labeling or via our corporate or products-specific websites. We also collect adverse events from all our employees, contractors and distributors around the world who have been trained in adverse event reporting processes. And we do weekly literature reviews to look for adverse events that haven't otherwise been reported.

In addition to this, we manage product risk by tracking adverse events of special interest which for Definity include cardiopulmonary reactions and anaphylactic reactions and by doing trend analyses on a quarterly basis under a risk management plan in Europe.

Finally, we have an independent data monitoring committee who review clinical trial results and ongoing pharmacovigilance data on a periodic basis. That committee comprises a cardiologist, an immunologist, and an epidemiologist. And during their reviews over the past three years, they've not found any new trends in adverse safety signals.

This slide summarizes pharmacovigilance data at a high level since the last advisory committee meeting. In summary, we have seen no new adverse safety signals. The adverse events rates that we have seen have been stable, and serious adverse events typically occurred in patients with confounding factors, as we presented to the committee three years ago. Some of these confounding factors include serious underlying or rapidly progressive disease, concomitant medications with known adverse effect profiles such as dobutamine, and physiological- or pharmacological-induced ischemia during stress testing.

This slide shows the spontaneous and serious adverse event reports since the last advisory committee meeting, and there expressed is the number of reports we have received as a proportion of the total number of Definity doses sold. The top of the table, you can see all serious adverse events reported in the past three years with a rate overall of approximately 1 in 6,000 doses.

Beneath, you see the cardiopulmonary events occurred at less than 1 in 24,000 doses sold. And the anaphylaxis-, anaphylactoid- and anaphylactic-shock-type reactions occurred in less than 1 in 47,000 reports. There has been no meaningful change in the type of frequency of these reported events.

Since the last advisory committee meeting, there have been adverse events with fatal outcomes in a total of 10 patients. During that period, approximately 1 million Definity doses were sold, providing a rough rate of less than 1 in 100,000. Of these 10, six of the events had onset within 30 minutes of Definity administration. And of those six, two were cardiac arrests during stress testing with coadministration of dobutamine. Two of the six reactions had features making anaphylactic reaction plausible, and the other two of these six had no specific features of anaphylaxis and appeared to be due to the rapid progression of serious underlying disease. The fatal case rates since 2008 have not changed.

I'd like to put these data in context briefly by comparing the risks of various commonly used diagnostic tests in cardiovascular medicine. At the top of the table, the procedure fatality rate for coronary angiography has been reported at approximately 1 in 1,000. For exercise treadmill testing, the rate of myocardial infarction or death associated with the procedure, approximately 1 in 2500. The lifetime risk of fatal malignancy has been estimated from SPECT imaging to be somewhere between 1 in 1,000 and 1 in 10,000. And the procedure fatality or serious complication rate for transesophageal echo, estimated at about 1 in 10,000. By comparison, the contrast transthoracic echo serious adverse event with fatal case rate for Definity is less than 1 in 100,000.

So I'd now like to introduce Dr. Michael Main to present our postmarketing required studies.

Industry Presentation - Michael Main

DR. MAIN: Thanks, Dr. Hibberd.

Good morning. As Dr. Hibberd indicated, I'll start today with a review of our postmarketing

studies. These included a large retrospective ICU study, a study of pulmonary hemodynamics in patients receiving Definity, and a registry study in clinical practice seeking to determine the risk of severe cardiopulmonary reactions in patients receiving Definity.

Well, the first of these studies was derived from the Premier Perspective database. It's the largest hospital database in the United States, and it contains date-stamped records of all billed procedures for patients, including events or procedures like echocardiography. In this database, 1 million patients were identified who underwent echocardiography on the same day as their ICU admission. And included in this were 16,000 patients who were administered Definity on that day.

Since this was a retrospective study and treatment assignment was not random, or when it was assigned by the investigator, a propensity score was assigned for each patient, and that took into account a variety of demographic conditions and

also comorbid conditions as listed here.

Using a greedy match algorithm, we were able to construct a highly specific matched dataset of Definity and control patients. And as you can see, approximately 16,000 patients were in each group, the Definity and the control group. And we did this to five decimal places, and in doing so, we were able to include about 97 percent of the Definity patients who were eligible for matching.

As you can see here, the results from that study, about 3.1 percent of the noncontrast patients had died at 48 hours postechocardiogram in this study, which was the primary endpoint for the study. Only 2.14 percent of the Definity patients had died at that time. The odds ratio for mortality for Definity was .68, so a 32 percent lower mortality in the patients undergoing Definity-enhanced echocardiography.

Secondary endpoint in this study was in hospital all-cause mortality, and as you see, the benefit or lower mortality in the Definity patients extended throughout the hospitalization. At the

time of complete hospitalization, 16.56 percent of patients in the noncontrast group had died versus 14.59 percent in the Definity group, an odds ratio for mortality in Definity group of about .83, so a 17 percent lower mortality throughout the hospital stay in patients who had received Definity during their echocardiography while hospitalized in the ICU.

Well, when we look at a range of comorbid conditions, including things like congestive heart failure, myocardial infarction, acute coronary syndromes, pulmonary hypertension, cardiogenic shock, and then very high acuity patients undergoing mechanical ventilation, we can see that the mortality rate in the Definity arm, in the Definity group, was numerically lower for all of these conditions and statistically significantly lower for all except acute coronary syndromes where there were very few events, very few events during the hospitalization. So across this wide range of comorbidities, the survival advantage in the Definity group was maintained throughout.

Well, the third study was a pulmonary hemodynamic study. And as Dr. Krefting indicated in his opening remarks, there's been very little data of the effect of ultrasound contrast agents in general and Definity in particular on pulmonary artery hemodynamics. In this study, 32 patients were recruited at seven sites. Sixteen of these patients had elevated pulmonary artery systolic pressure greater than 35 millimeter mercury at baseline. Sixteen patients had normal pulmonary artery systolic pressure, so less than 35 millimeter mercury at baseline.

The primary objective was to determine whether there were any pulmonary artery hemodynamic changes in patients undergoing clinically indicated right heart cardiac catheterization. A secondary objective was to determine whether there were any other important safety or potential immunologic effects of Definity administration, and potential markers, including C3a, C5a, tryptase and interleukin-6 were assessed prior and then following Definity administration in this study.

As I said, all of these patients underwent right heart cardiac catheterization. They underwent then safety monitoring, including vital signs, clinical labs, pulmonary hemodynamic monitoring and immune response labs. Definity was administered in a clinically-relevant dose, and then pulmonary hemodynamics were monitored for 30 minutes. Safety monitoring continued for 60 minutes, including vital signs, clinical and immune response labs, the 12-lead ECG as well. Adverse events were followed for 24 hours, and serious adverse events up to four days following the procedure.

And these are the results of that study showing the baseline pulmonary artery systolic pressure prior to Definity administration in both patients with normal and elevated pulmonary artery systolic pressure. And as you can see, pulmonary artery systolic pressure remains stable in the patients with baseline normal pulmonary artery systolic pressure throughout the period of the examination. The same was true in patients with

elevated pulmonary artery systolic pressure. So following a clinically-relevant dose of Definity, no change in PA systolic pressure in patients either with normal or elevated baseline pulmonary artery systolic pressure.

Well, in addition to that finding, there were no deaths. There were no serious adverse events. There was a similar adverse event profile in both groups. No change in any of those immunological parameters, either, including C3 or C5a, tryptase or IL-6.

The final study was a large registry study assessing the incidence of severe cardiopulmonary reactions in 1,053 patients at 15 clinical sites throughout the United States undergoing Definity dosing during either rest, stress or both types of echocardiography. Thirty-minute safety monitoring was performed, an assessment that was done pre-dose, then at 5, 15 and 30 minutes following Definity dosing. Vital signs, ECGs and 02 saturation by pulse oximetry all were monitored during the study.

Adverse events were then followed for 24 hours; the primary objective, life-threatening cardiopulmonary events within 30 minutes, and a secondary objective was all adverse events within 24 hours.

The population included had a lot of comorbidity. It's typical of what we see in the echo lab on a daily basis. Previous MI in 21 percent of patients; 31 percent had undergone revascularization previously. And, importantly, 50 percent of patients were taking four or more cardiac medications.

Here are the results from that study. There were no deaths. There were no life-threatening cardiopulmonary reactions within 30 minutes. There were no serious adverse events within 24 hours of Definity dosing. The non-serious adverse event profile was also benign. Eleven percent of patients had at least one adverse event. However, only 3.5 percent of patients had an adverse event that was thought by the principal investigator at the site to be attributable to Definity. In

comparison, 15.4 percent of patients had an adverse event that was thought attributable to the stress test or the pharmacologic stress agent. There were new safety findings from this study.

In addition to these three large studies, these postmarketing studies which we've just reviewed, there's been a very large volume of investigator-led research published in the peer-reviewed literature since 2008. And shown here is a figure from a meta-analysis of severe cardiovascular events published by Khawaja and colleagues in the American Journal of Cardiology last year. And shown in this figure is the pooled odds ratio for mortality in patients undergoing echocardiography either with or without an ultrasound contrast agent. And as you can see, the group included over 5 million control patients undergoing unenhanced echocardiography and over 211,000 patients undergoing echocardiography with a contrast agent. The analysis favors an ultrasound contrast agent administration. The odds ratio for mortality was .57.

Also, in this same study, the authors summarized the allergic events that occurred during contrast administration throughout these studies. There were 110,500 patients in whom information was systematically gathered regarding incidence of allergy or anaphylaxis. And as you can see from this large group, almost 111,000 patients, only five anaphylactic events for an event rate of about 1 in 25,000, so a very low rate of acute anaphylactic events.

So to sum up the safety data so far, the pharmacovigilance data show no change in the Definity adverse event profile. Two prospective studies had no deaths or serious adverse events within 24 hours of Definity administration. The pulmonary hemodynamics study showed Definity had no effect on pulmonary artery systolic pressure in patients with either normal or elevated baseline pulmonary artery systolic pressure. And the very large propensity matched ICU study showed Definity was associated actually with lower mortality in these very high acuity patients, almost all of whom

would have been previously contraindicated based on the initial warnings back in 2007. Additionally, the peer-reviewed literature findings are all consistent with this data showing a very favorable adverse event rate for Definity.

In addition to the large body of safety data, which is now available, a very important efficacy study was published by Kurt and colleagues in the Journal of the American College of Cardiology in 2009. And in this study, 632 consecutive patients with technically difficult resting transthoracic echocardiograms were recruited. They each initially underwent an unenhanced echocardiogram and then a contrast enhanced study. The physician caring for the patient was contacted with the results of the unenhanced echocardiogram and then some time later with the incremental data that was now available following the contrast study. And the investigator -- rather, the clinician was asked what type of changes are you now going to make in this patient's care as a result of data available

from the contrast-enhanced examination.

Shown here, the top line results from this study, as you can see, we've shown here patients in blue with a procedure change; in red, patients who had a medication change only and in green, patients who had both a medication and a procedural change. And I'll draw your attention to the patients hospitalized in the SICU. Two out of three patients in the SICU had either a medication change, a procedural change, or both which resulted due to the incremental data available following contrast echocardiography. And although the effect was greatest in the SICU, it was also very strong throughout hospitalized patients and certainly present in outpatients as well. Overall, in total, 1 out of 3 patients had a significant change in medication, in procedures avoided, or both as a result of this incremental data available following contrast echocardiography.

Well, this is an example just in routine clinical practice of how this Kurt data applies on an everyday basis. This is an 82-year-old man who

presented with left arm pain and nausea. And this is an apical four-chamber view. This is the left ventricle, the right ventricle, the left and right atrium, the intraventricular septum, the cardiac apex, and the anterolateral wall of the left ventricle. And, initially, this appears to probably be normal, although endocardial delineation is quite poor.

Following administration of an ultrasound contrast agent, we can see that there's a very large zone of apical dyskinesis. This patient was taken urgently to the cardiac catheterization laboratory for coronary angiography. So in this case, similar to a case that Dr. Kaul earlier presented, management was affected in a very positive fashion for this patient. He received early care that was very critical.

This is a patient who had a history of remote myocardial infarction, and this is a similar view, an apical four-chamber view, the septum, the apex, and the anterolateral wall. There's an echogenic area near the cardiac apex, and then a

echolucent area distal to that. Difficult to tell exactly what that represents on an unenhanced image.

Following contrast administration, we can see to and fro flow of contrast within this cavity and then back into the LV. This is a left ventricular pseudoaneurysm, also known as a contained rupture of the left ventricle. This is an urgent situation. This patient needs to undergo open heart surgery for repair of this problem to prevent sudden cardiac death.

Another important finding of the Kurt data was the impact of contrast on left ventricular thrombus detection. As you know, left ventricular thrombus is an important risk for cardioembolic stroke and peripheral embolization. In the Kurt study, before contrast, 35 patients had a suspected thrombus. Following contrast, only one of those patients was suspected of having a thrombus. Before contrast, three patients were thought to have a definite thrombus, and then following contrast, zero patients were thought or actually

defined to have a definite thrombus. And perhaps even more importantly, five previously undetected thrombi were noted with contrast.

Obviously, this has real significant profound implications for patient safety both in the prevention of cardioembolic stroke and also in avoidance of systemic anticoagulation and patients who might be at increased risk of hemorrhage.

This is an example of that type of patient. This echocardiogram, again, all of these are apical four-chamber views, the left ventricle. This is a young woman who had suffered a recent anterior wall myocardial infarction while hospitalized and had just recently undergone bilateral mastectomy in treatment of breast cancer. She was recuperating in the ICU. And as you can see, there appears to be severe left ventricle systolic dysfunction. There's also an echo density at the cardiac apex, and the question is, is there a left ventricular apical thrombus or is this artifact?

Following contrast, we can see that there is absolutely no thrombus; very, very sharp

endocardial border delineation. We can now more accurately assess both regional and global LV systolic function. Not only were we able to exclude thrombus in this patient, but we were able to quantify left ventricular systolic function. And as a result of that, in the patient's clinical scenario, she underwent placement of a implantable cardio diverter defibrillator. I saw her in the clinic just a few weeks ago, and she's doing fine now, three years following that large infarction which was complicated by cardiogenic shock.

This is another case in which thrombus is the question, a 45-year-old man with known coronary artery disease. He had undergone percutaneous coronary intervention previously. We didn't know much else about him. Again, apical four-chamber, but really can't see very much at all. And, of course, 15 to 20 percent of echoes are technically difficult, usually due to patient-related factors, obesity as we'll see in a minute and lung disease.

Following contrast administration in this patient, we can see that he has a very large apical

mural thrombus, a squared-off left ventricle, as it used to be called in the cath lab, with left ventriculography. So very high risk obviously for cardioembolic stroke, systemic embolization; lifelong anticoagulation, then, as a result of the finding on this study.

Well, as we all know, there is a severe obesity epidemic in this country. These patients are very, very difficult to image. An 18-year-old man who was super obese, a BMI of 58, presented with dyspnea, and the question was, what is his LV systolic function? It appears reduced. Again, however, there is really no endocardial border delineation.

Following contrast administration in this patient, very sharp endocardial delineation. We're able to exclude intracardiac masses and thrombi and tell very definitely that this man has severe global hypokinesis, severely reduced LV systolic function.

This is another example. This is a 34-year-old super obese woman. Her BMI was 64, and the

same question arises. Is the left ventricular systolic function normal? We cannot tell. Following contrast in this patient, we can see that the left ventricle is actually very small and hyperdynamic, clearly normal LV systolic function, so a completely different outcome in this patient, completely different recommendations for clinical care.

Despite the demonstrated efficacy of ultrasound contrast agents, there seems to be really an apparent underutilization of these in clinical echocardiography in the United States, perhaps at least in part due to some lingering safety concerns.

In the single-center prospective study, which we reviewed, the Kurt study, there was a significant amount of suboptimal baseline echocardiograms just in routine clinical practice. As you can see, this increases to 21 percent in ICU patients. Of course, many of these are mechanically ventilated and very difficult to image. But across the board, a high proportion of

technically inadequate echocardiograms.

The ASE consensus statement estimates the suboptimal echocardiography frequency at about 15 to 20 percent. Despite that, however, current contrast use in the United States is only about 2 percent of echocardiograms.

So to sum up the Definity benefit-risk summary based on the safety studies, the efficacy data and overall day-to-day use, there's a strong and consistent safety profile for Definity. SAEs are rare. They're lower or similar to reported rates for other cardiovascular imaging modalities, as Dr. Hibberd previously outlined. Use of Definity has been shown to favorably impact patient management. We know that from the Kurt study. However, current use of contrast is low compared to published rates of suboptimal echocardiograms, both in Kurt and the ASE consensus statement.

Data from the postmarketing studies, the pharmacovigilance efforts and the literature all suggest that the product label should be revised at this point.

I'll now turn the remainder of our time over to Dr. Washburn, who will go over labeling recommendations.

Industry Presentation (con't) - Dana Washburn

DR. WASHBURN: Thank you, Dr. Main.

I will close on behalf of Lantheus Medical Imaging with the following requested recommendations regarding the Definity label: Number 1, removal of the boxed warning. The pharmacovigilance postmarket study and literature data presented this morning show that the conditions which require a boxed warning according to the Code of Federal Regulations are not present. Additionally, the relevant safety information currently in the boxed warning will be included in the highlights and warnings sections of the Definity label.

Secondly, remove language from the warning section regarding monitoring requirements and risk associated with specific disease states. And, finally, include summary of the three postmarketing studies reviewed this morning in the label.

These results presented by Dr. Main provide important information to the prescribing physician regarding the clinical use of Definity.

This concludes the Lantheus presentation. Thank you for your consideration.

Questions to Industry Presenters - Lantheus

DR. PACKER: All right. Thank you very much.

What I'd like to do in order to organize the presentation, just to remind the committee that -- a couple things. All three sponsor presentations are going to in many cases raise similar issues, and so you could decide that you want to raise some of those issues now or not. That's really up to you.

Second, the concept here is to ask questions, not necessarily present opinions. So this is a time to ask the sponsor for clarification, anything else that you would like.

Third, I'd like to organize the questions, so they're not haphazard, along three areas. The first is pharmacovigilance data, the second is the

hemodynamic study, and the third is the large observational study.

So let me first begin by asking does anyone have any questions on the pharmacovigilance data that were presented? Sidney?

DR. WOLFE: This is just really a methodological question. First, in the briefing package, you state that in the 1,000-patient pharmacovigilance study that everyone had previously had a noncontrast echocardiogram and they were picked because that was suboptimal.

Is that correct? You didn't mention it in your oral presentation. That's what it says.

The second question was the method of adjudication or determination of causality. You mentioned that in terms of the percentage of events that were due to the drug, the primary investigator looked at that. You didn't mention whether the determination, whether it was due to the stress test, was also done by the primary investigator.

So those are the two questions, adjudication and then, first, did all these people have a

previously abnormal echo, noncontrast.

DR. MAIN: Yes. In the registry study, these patients all qualified by virtue of having a technically difficult unenhanced echocardiogram. And you mentioned deaths. There were no deaths in that study. The adverse events were attributed by the principal investigator at each site.

DR. PACKER: Mike Weber.

DR. WEBER: Yes. I just want to be clear about the spontaneous reporting since the last advisory board apparently 10 deaths including six within 30 minutes of administering the product.

Are these included, in any way, in what was called the large retrospective observational study? Because that study talked about over a million observations. Are these six, or 10 and 6, how do they fit into the spectrum of that? Are they included or could there be things happening that we don't know about?

DR. MAIN: I don't believe that any of those patients were included in that retrospective ICU database study. I'll ask Dr. Hibberd for

clarification on that, but I don't believe so.

DR. PACKER: Sanjay, we're trying to do it in the order in which they were -- Sanjay.

DR. SANJAY KAUL: Regarding this particular --

DR. PACKER: Pharmacovigilance.

DR. SANJAY KAUL: Pharmacovigilance?

DR. PACKER: Yes. Yes, Brian.

DR. STROM: I think we have the answers yet to come to one of the prior questions.

DR. HIBBERD: So just to clarify, as far as I know, the pharmacovigilance spontaneously reported fatalities were not part of the systematic observational study on mortality that we performed in critically ill patients. The spontaneous reports come from events which occur during clinical practice outside of the study and are reported by individual physicians or healthcare providers.

The retrospective database study was a systematic review of all of the cases available in the Premier Hospital network's database system

during the period stated.

DR. PACKER: Yes, please.

DR. STROM: Yes. One comment now and two questions. The comment -- just in clarification of that last comment, Premier is a very large database. They were studying people in the ICUs. If any of the 10 were ICUs, there's a significant chance they were included, though the data was collected in a very different way.

Two questions, one is use of this product in children. And my reason for that will come out later. And the second is you quote a serious adverse rate of 1 in 6,000. FDA commonly estimates that 10 percent of adverse reactions are reported to the spontaneous system, which would give a rate of 1 in 600. I actually think that 10 percent is very optimistic.

Is there a reason to think that with this kind of product the rate would be higher, the reporting rate, the completeness of reporting would be higher or lower than you would expect with other drugs?

DR. HIBBERD: So we would agree that there may be some underreporting of spontaneous events. It's very difficult to know what that underreporting would be. I'm not sure I can say a lot more about it than that, at this point anyway.

The registry study we performed, the DMP-415 study which had over 1,000 patients in it, didn't have any serious adverse events reported at all. It's certainly fair to say that at around about a thousand, it's possible statistically that there might not have been a serious adverse event seen there. On the other hand, we didn't see any, and that provides some additional reassurance about the rates.

DR. STROM: Can I just follow up?

DR. PACKER: Sure.

DR. STROM: Obviously, zero out of a thousand is still compatible with a rate of 1 in 300 statistically.

In terms of use of kids?

DR. HIBBERD: These data are predominantly about adults. There are very few reports.

Steve, do you -- I'm not sure how many reports. I'd have to check from our database of adverse events in pediatric cases, but utilization in the pediatric population is extremely low.

DR. PACKER: Yes, please?

DR. PAPADEMETRIOU: My question is related to patients in the emergency department with chest pain. The unnecessary, perhaps, use of contrast evaluation may be counterproductive in some patients. Since time is of the essence and we need to move these patients quickly to the cath lab if they have acute MIs, how long does the procedure add to the routine evaluation and can sometimes be counterproductive?

DR. MAIN: Well, the data that Dr. Kaul presented and the way we would use contrast in the emergency department would really only be applicable to patients with nondiagnostic electrocardiograms. So if a patient has a ST-segment elevation infarction that's obviously evolving, they would be taken to the cardiac cath lab immediately. So this test would be useful in

patients with nondiagnostic ECGs, the suspected acute coronary syndrome patient to better risk stratify them.

DR. PAPADEMETRIOU: How long does it add to the procedure? How much time?

DR. MAIN: Just literally minutes. Done at the bedside with commercially available equipment and an injection of an agent, literally, 5 to 10 minutes, this study could be performed.

DR. PACKER: I have a question about when you get a report of an adverse event, a death, or a serious morbidity, in your pharmacovigilance program and you notice that there is significant comorbidity, how do you interpret that?

DR. HIBBERD: I think it has to be done on a case-by-case basis but --

DR. PACKER: But tell me whether you find the associated comorbidity a reassuring explanation for the event.

DR. HIBBERD: I think again it would depend entirely on the nature of the event. We gather all of these events regardless.

DR. PACKER: I'm still confused. When you get these data, how do you interpret them? You are trying to present, I think, based on the pharmacovigilance data a reassuring picture, but I just want to understand how do you interpret an event that occurs in a patient with significant comorbidity. How does the company or how does any physician actually establish the concept of a causal or non-causal relationship?

DR. HIBBERD: Okay. So I think when these events are reported by physicians, they look at features such as the temporal association of the event and the nature of either the procedure being performed or the underlying disease progression that they can see from the clinical situation, and they would make a judgment based upon those things.

DR. PACKER: Having been in that situation personally, I can't imagine how anyone would be able to do that.

DR. HIBBERD: It's extremely difficult, I think, to certainly ascribe causality either to underlying conditions or in some cases to

particular medicines or procedures. It's difficult to do that.

DR. PACKER: So how do you do that?

DR. HIBBERD: Dr. Washburn, do you have a thought?

DR. MAIN: I'd agree it's very, very difficult. Obviously, temporal relationship plays a role and other concomitant factors. In the sick patients, though, this issue of pseudo-complication comes up. These types of events occur due to progression of disease. And I think one thing that's very interesting from the data that we presented, particularly in the ICU patient population, is the very high ambient risk of death in these patients. Three percent of patients in the ICU study had died within 48 hours. However, it was significantly lower in the Definity patients.

DR. PACKER: Well, we haven't gotten to the observational study. On the pharmacovigilance database --

DR. MAIN: Fine. Okay.

DR. PACKER: -- how can you do this? Does anyone -- can anyone answer how that can be possibly done on a pharmacovigilance -- not an observational study. On a pharmacovigilance database, how can you do this?

DR. MAIN: So I think it's important to point out that what we do is we do an extensive evaluation of all reported events regardless of whether this appears to be associated with comorbidities or not. We would do extensive efforts outlined through our pharmacovigilance system to gain all the records that we can from the site, from the investigator, and then a clinical judgment is made similar to what would be done in the clinical setting for potential causality. But we understand and agree with you that an absolute causality can rarely be assigned.

DR. PACKER: I would go -- you're being optimistic. There is no methodology that exists that allows the presence or absence of a causal relationship to be defined in the setting that you have described. You can simply report the adverse

effect, that it occurred, but you cannot understand or define the relationship to the contrast agent with any reliable methodology.

Jim?

DR. NEATON: Well, my question was along the same lines. And just to point out, I guess, the obvious, which the sponsor indicated, that the mortality in their retrospective study was 2 percent. And now we're talking about 1 in 10,000, 100 in 10,000 in the pharmacovigilance. There's just some -- there's a disconnect there that is almost unbelievable in terms of attribution to the product.

DR. FOX: Just a comment from an industry perspective. I mean, for all these interventions, whether they be contrast agents or pharmaceutical products, this sort of pharmacovigilance work is done routinely for all these sorts of products. If the reporter indicates a suspicion of causality, that's taken face value. If they don't, but the company looks at the other aspects in the report and says, there is probably something here, the

company usually can upgrade and say suspected causality or relatedness but typically will not downgrade if a reporter suspects relatedness.

The other thing is, all these factors that you're talking about are confounders. And the more the confounders, the more you're right, Dr. Packer, that the more it's confounded, the less you can say about it. But if you have a case reported in which there are few confounders, that can help you. Then you might call that an index case. Then if you get two of them or three of them, then you think you might actually have something to stand on.

DR. PACKER: I agree with that, but, unfortunately, a lot of times adverse events occur in patients at risk as opposed to patients not at risk. So this is an impossible task. I understand everyone engages in it, but that doesn't establish its validity.

DR. FOX: It ranks pretty low on the ladder of strength of evidence, I agree.

DR. PACKER: Let's move it forward. The hemodynamic study. Questions? I know everyone

wants to talk about the observational study, which is why I'm leaving it for the last.

Hemodynamic study? Yes, please.

DR. PAPDEMETRIOU: In the hemodynamic monitoring, you had 16 patients with elevated pulmonary pressures. Your definition was above 35 millimeters of mercury. Were these patients with left-sided LV dysfunction and they have elevation of pulmonary pressures, or did any of them have any primary pulmonary hypertension?

The second question is, did you see any systemic -- the changes in systemic pressures? Does the agent have any vasodilating properties?

DR. MAIN: Well, these were a mixed bag of patients. Certainly, many of them had elevated PA systolic pressure on the basis of elevated left heart feeling pressures. I do not believe that any had primary pulmonary hypertension, although some had pulmonary arterial hypertension on the basis of other factors. There was no significant change in systemic hemodynamics during the study, either.

DR. PACKER: Yes, please, Jim?

DR. TATUM: You just mentioned that that was a heterogeneous group, right? But looking at the graph, it looks pretty homogenous, and your mean pressures that you're talking about is somewhere between 40 and 60 in that group with nobody in the high outliers.

Am I reading that wrong or is the graph misrepresenting it?

DR. MAIN: No, that's correct. And patients with PA systolic pressures greater than 75 millimeter mercury were excluded by study design.

DR. PACKER: No control group in that study?

DR. MAIN: Correct.

DR. PACKER: Why not?

DR. MAIN: Well, the study was designed in collaboration with FDA, and that was the agreed-upon methodology.

DR. PACKER: I'm sorry. Why not?

DR. MAIN: Well, there was no control group, but there was a run-in phase. So pressures were monitored, as you saw, prior to Definity

administration, during and then following. So there were baseline pressure assessments available for several data points prior to administration in both the patients with normal and elevated PA pressure.

DR. PACKER: Just for the record, you can get all sorts of nonintervention-related hemodynamic effects in the absence of a control group. So getting a control group for a hemodynamic study is really important.

Okay. Let's move on to the observational study.

Sanjay, you want to start us?

DR. SANJAY KAUL: Yes, I have several questions related to the observational study. Is there any particular reason why the analysis was confined to the pre-warning time frame?

DR. MAIN: Well, post-warning, especially the early phase of that, most of these patients would have been contraindicated to receive an ultrasound contrast agent. So that's really the dataset that we had to work with.

DR. SANJANY KAUL: So what was the utilization of these contrast agents pre-warning and post-warning?

DR. MAIN: I don't have exact figures available. Maybe somebody else can. Utilization, though, we have multiple lines of evidence that for the field as a whole, utilization basically plummeted following the initial warning in October of 2007. And, basically, I can tell you, for instance, in our institution in the early months, there was very little utilization in ICUs. Most practices throughout the country, in fact, for at least a limited period of time, stopped using ultrasound contrast agents altogether and certainly stopped using them in critically ill patients.

DR. SANJAY KAUL: The reason why I'm asking you is I'm trying to figure out what is the impact on patient management decisions to which you attribute the implied benefit. You're not implying that the treatment effect that you saw was due to some magical properties of the contrast agent; better information led to better treatment

decisions. And so I want to see what is the impact on those patient management decisions.

Did you capture that information in the pre-warning era, the 48 hours?

DR. MAIN: And you're referring then to the ICU study and the benefit observed there, correct?

DR. SANJAY KAUL: Yes, the observational registry.

DR. MAIN: Yes. Well, the treatment effect -- are you referring to the ICU study or the registry study in a thousand patients?

DR. SANJAY KAUL: The observational registry.

DR. MAIN: Okay, the observational registry. The efficacy really was not evaluated systematically in that study.

DR. PACKER: Ralph?

DR. D'AGOSTINO: I have a few questions. Thank you.

We're talking about the retrospective study, right? I'm curious about the propensity score matching that you get up to 97 percent matching,

which is sort of unusual to be able to accomplish.

Did you find or did you do any analysis that talked about a less decimal point matching and the sensitivity? If you had -- say, you're talking about the nine decimal place matching or the eight where you had about 50 percent of the sample versus the 97. Were there any -- did you do any sensitivity analysis to see how things would change as you did this greedy matching and changed the greedy matching, or did you just decide on the five decimal place and then go with that?

DR. BHAT: This is Gajanan Bhat, biostatistician, and I'm from Lantheus Medical Imaging. We had this study -- to answer one of the other questions, too. We had this study started soon after our boxed warning. So the data cutoff is 2008, 2002 to 2008, so it's pre-boxed warning.

We sent in the protocol. We discussed with the FDA about the methodology, and we clearly defined that in the study statistical analysis plan. So we did the five-digit matching based on the strength of match that we included

97.4 percent. But if we do the nine-digit match, it is only like 39 percent of the patients we can include in the analysis. We did the analysis, but we thought we were losing a lot of patients in that kind of matching, which is a very high, stronger match.

We also did three-digit matching, which when we identified the patients in both groups, contrast and noncontrast, and we try to compare baseline and comorbidities at three digit, we're not able to compare all the patients.

DR. D'AGOSTINO: It's not the three-digit I'm interested in, if it's the less. When you're getting up to 100 percent matching, you're basically looking at raw data, and then the question about you did the grouping. But it's the lower matching where you have a sort of pure group that really matches well, the two groups match well.

Did you do anything like that and see if your results would have change or your results did change?

DR. BHAT: We did that, but results did not change that much. It was within the odds ratio of less than .1.

DR. D'AGOSTINO: It never -- that .68 stayed. It went to .7 or something like that? Is that what you're saying?

DR. BHAT: Yes, that's correct.

DR. D'AGOSTINO: Let me go on to another thing.

When you have so many variables that you're matching also, then it's hard to say at the end that your matching does anything. Did you go and look at some primary variables, some cardiac conditions and what have you to see that in your matching you do, in fact, have a matching on those variables? What people oftentimes do when they do a propensity score is they match on the propensity score, then they go back and look and see did they actually achieve matching on individual variables, and you have so many variables.

DR. BHAT: Yes, we identified at least the variables we showed in the previous slide, that 48

or mortality, where congestive heart failure, SES, mechanical ventilation and there were a few other ones. We looked at them, how they were matched, and were able to match most of them.

DR. D'AGOSTINO: Then when you did your analysis -- can I have a couple more questions?

DR. PACKER: Oh, absolutely.

DR. D'AGOSTINO: Then when you did your analysis, you talk about the Cochran-Mantel-Haenzel, and I always appreciate Cochran being there. He was my thesis advisor, and you want him in that Cochran-Mantel-Haenzel test. That requires grouping of variables, and you obviously couldn't do it on all the variables that you use in your propensity score.

What were the groups that actually were defined in that Cochran-Mantel-Haenzel test?

DR. BHAT: That includes the comorbidities we included --

DR. D'AGOSTINO: But what ones? I mean, can you give us a flavor of it just so we -- you're adjusting over that, and you're getting your odds

ratio. What I'm wondering is, are your results being driven by one or two categories that are bizarre that are making the odds ratio look so good and the other ones are being washed away because of the grouping?

So were there any -- what are the groupings, and were there any groupings that really were driving your analysis?

DR. BHAT: So if you go to the next slide --

[Pause.]

DR. D-AGOSTINO: I don't remember anything in the main presentation that actually told me what these groupings were.

DR. BHAT: So here we presented two odds ratio. One is the CMH, which is .8668 (indiscernible), and the other way is a full model logistical regression odd ratio where we included some of the variables that matched that five-digit level. We included those variables back into the logistic regression model to calculate an adjusted odd ratio. So that came out to be .683 in the

primary endpoint.

DR. D'AGOSTINO: It's not the question I'm asking. The question I'm asking is, with the Cochran-Mantel-Haenzel test, you usually have groups that you're looking at, basically the contrast within the groups. And were there any groups -- you have a 48-hour mortality by comorbidity. But back to Dr. Kaul's question, there must have been some intervention in that.

Were there any groups that defined your Cochran-Mantel-Haenzel test where you see a big effect, or is it uniform across all those groups? And I don't know what those groups are. All you're telling me is that you did the Cochran-Mantel-Haenzel test.

DR. BHAT: We did the CMH based on these are the stratifications that we used, although we haven't presented that in the primary endpoint, but these are the main groups that we used.

DR. D'AGOSTINO: And then the question was asked before is that, how are you saving lives by the differing methods? What are you doing? This

would indicate that you have a superb treatment by giving the contrast. What are we missing on that?

I would have expected that once you match on different variables, that for some mere event, you would have gotten no difference, and maybe some later event, you would have done some intervention and saw the intervention happen.

How do you explain the differences?

DR. MAIN: Well, I agree with Dr. Kaul's assessment just a few minutes ago that the most likely explanation is that we are getting a more accurate and more timely diagnosis on these patients. And remember, these are critically ill ICU patients. Time is of the essence. Identify these problems earlier; render treatment if it's appropriate earlier, and I think you will save lives. Obviously, we don't know that, based on this study. We don't know what the mechanism is, but there's a clear association with improved outcome.

DR. PACKER: Before you leave that topic, what treatments do you think were administered here

or could conceivably have been administered based on the contrast information that would have resulted in a 32 percent reduction in mortality in 24 hours?

Do we have anything that reduces mortality by 32 percent in 24 hours, let alone something which is informed by contrast?

DR. MAIN: Well, for example, take a patient who's hypotensive in the ICU, and we don't know why that patient is hypotensive. Do a contrast echocardiogram in a patient whom we cannot image well at baseline, we might find that the ventricle is small and hyperdynamic. Perhaps the patient then is hypotensive due to hypovolemia, which could be treated. Maybe they're bleeding. Maybe they're hypovolemic for some other reason. Maybe they have a left ventricular outflow track obstruction due to hyperdynamic state. Maybe they have --

DR. PACKER: Those are -- that's a -- I can't imagine that hypertrophic cardiomyopathy influences your point estimates here very much. And a lot of these patients have right heart

catheterization, have pulmonary artery catheters in place. You'll know what their filling pressures are.

What I'm trying to figure out is, based on what information contrast can provide, what treatments could conceivably have been given that would have resulted in a reduction in mortality in a 24-, 48-hour period of time? We're talking about a reduction in heart failure, a reduction in myocardial infarction, a reduction in shock, a reduction in mechanical ventilation.

Do you have any idea what anyone could have done? I understand you didn't record it, but can you conceive of it?

DR. MAIN: Well, let's just get back to that example that I gave regarding hypotension, and you said that you don't think that a hypertrophic cardiomyopathy diagnosis could make a difference. I agree with that. But let's take, for instance, the post-op patient in the ICU. What's typically going on? They're getting a lot of inotropic agents. They're hypotensive. A lot of times, we

find out they're actually hypotensive because they have a small hyperdynamic ventricle with a dynamic intracavitary gradient, and the exact opposite treatment of what is necessary is being administered, positive inotropes. What they need is to have those medications discontinued, and they need to be given fluids.

So I think we see this every day in the echo lab where we actually do make a substantive change in therapy based on the results of the echocardiographic study. I guess the real question is, if echo isn't that helpful, I guess we just shouldn't be doing them at all. And I think it is. I think we make a positive difference every day, and what we're doing with the contrast agents is increasing the diagnostic efficacy of the test.

DR. PACKER: How do you get a reduction in myocardial infarction?

DR. MAIN: In the rates of death after myocardial infarction? Well, early and accurate diagnosis of mechanical complications, for one. Paul Grayburn has a very nice analysis showing that

in patients with pseudoaneurysm, the reported rates of diagnosis are actually very low with transthoracic echocardiography itself. When you add a contrast agent, you actually can diagnose these. You see extravasation into the pericardial space. You diagnose that earlier, you're going to save lives.

DR. PACKER: You had a reduction in the incidence of myocardial infarction.

DR. MAIN: No, these were patients with myocardial infarction --

DR. D'AGOSTINO: Those are comorbidities.

DR. MAIN: Those are not reduction in those; those are the comorbidities.

DR. PACKER: I just want to make sure that I understand. The type of patient that a physician would do a contrast study on could in some way be determined to be more stable than a patient that a physician would not order a contrast study on in ways that cannot be assessed by comorbidity.

Would you agree with that?

DR. MAIN: Patients undergoing contrast may

be more unstable in ways that cannot be assessed, you're saying? Repeat that.

DR. PACKER: The decision, the enthusiasm for a physician to order a contrast study might be greater in someone who was -- or they may be reluctant to order one in someone who was very unstable than someone who was stable in ways that could not be determined by a comorbidity. Your comorbidity determines comorbidity but not the stability of those comorbidities.

DR. MAIN: I would agree with that. Some of that is probably not measurable. That's correct.

DR. PACKER: And so we have no idea to what degree unmeasured confounders contributed to the point estimate.

DR. MAIN: Well, I think that's probably true. I think that's probably true to some extent, yes. Although these were very well matched otherwise, but, of course, there could be other confounding variables. I would agree with that.

DR. PACKER: You can only match on what you measure.

DR. MAIN: That's absolutely right.

DR. PACKER: Okay. Sanjay?

DR. SANJAY KAUL: My question is essentially an extension of this discussion. We're trying to figure out whether the treatment effects were real or not. And since the critical information, patient management decisions, is not available to us, we have to resort to some ancillary, indirect information.

So with regards to that, I'm interested in knowing whether this treatment effect that we saw at 48 hours is durable. You reported that in hospital treatment effect, it was a 13 percent treatment difference compared to a 32 percent -- or a 17 percent treatment difference compared to a 32 percent at two days.

Can you tell me what is the time frame for that in hospital? Because I didn't see that information provided. And why do you think that there is an attrition of this treatment effect?

DR. MAIN: I believe -- and I'll check on this. But I believe the mean hospitalization

period was 13 days for patients and eight days in the intensive care unit. So these were quite sick patients, prolonged hospital stays, a long time in the intensive care unit. Why is there less effect throughout the whole of the hospitalization? I'm not sure.

DR. SANJAY KAUL: While I have you there, also, on slide 26, which is the meta-analysis, could you please clarify for me, is that a meta-analysis of randomized trials or are those observational studies?

DR. MAIN: Those were all observational studies.

DR. SANJAY KAUL: And was there substantial clinical heterogeneity and overlap in those databases that should have precluded pooling to begin with?

DR. MAIN: Well, that's a good question. And if we could put that slide up, there was actually a heterogeneity index reported, I think, in the subtitle. There was substantial heterogeneity, that's true. These were not

randomized. This was observational studies. There was not substantial overlap in patients between the studies in individual patients.

DR. SANJAY KAUL: So all we are left with is an estimate, which is rather precise but could very well be spurious?

DR. PACKER: Elaine?

DR. MORRATO: Yes, thank you. I had a couple questions methodologically as well. The effect is dependent upon the population that we're assessing, so I'd like to understand your definition of critically ill that you chose and why. I understand from the briefing materials you chose site of care -- i.e., they're in an intensive care unit -- in selecting the patients. I'm trying to understand why and if you did any other analyses looking at alternative definitions such as comorbidity.

DR. MAIN: You're correct. The patient population was selected from amongst hospitalized patients who were in the intensive care unit. And, no, we did not do any other analyses based on

comorbidity.

DR. MORRATO: Why did you choose that definition then?

DR. MAIN: Well, we thought these were among the sickest patients of all, and that's where the question of ultrasound contrast agent safety had been most acutely raised, in the patients with very, very high clinical acuity. We thought these were the sickest patients and the best dataset to demonstrate the effect in.

DR. MORRATO: Okay. Part of the design is related to where you're seeing the signal, and the pharmacovigilance data would suggest that the deaths are occurring with the first few minutes, 30 minutes to 60 minutes. So I'm trying to understand why you chose a 48-hour same-day/next-day endpoint for your analysis and if you did any additional sensitivity analyses looking at day 1 deaths.

DR. MAIN: Forty-eight hours was chosen because the Premier Perspective database only includes deaths by day. So if a patient had

received a contrast, say, at 6:00 p.m. on day 1 but then had died seven hours later, that would have been recorded into day 2. So the decision was made to make sure that all early deaths were basically captured by using a 48-hour or two-day analysis.

DR. MORRATO: Did you do any sensitivity looking at same day?

DR. BHAT: We did the 24-hour analysis, and the odds ratio is a little bit better, actually, probably .63 or .64. And in the Premier database, we don't have the time to event. It's all based on the discharge, so we can only go by the day, and that's why we used 48 hours.

DR. MORRATO: And then the last question relates to -- and the FDA was sharing that at the time of the advisory committee there were five deaths but 200 serious adverse events reported in the pharmacovigilance. So I'm wondering if you looked at other alternative secondary endpoints such as resuscitation or any other of those kinds of measures that might have been taken.

DR. BHAT: We did not in the retrospective

ICU study because that was not part of the study design, and we did not do that analysis.

DR. MORRATO: So is there data from the study that would support your recommendation that the label should be changed to remove monitoring?

DR. MAIN: Well, certainly in the patients that we described in that retrospective study, all of those patients are in the ICU anyway and would be subject to monitoring. As you indicated, the attributable events have appeared always to occur very, very shortly after contrast administration. It doesn't seem to be any role for prolonged -- in other words, 30-minute monitoring due to the very short-term nature of any of those events.

DR. MORRATO: Right, but you just said that these patients are in the setting in which they are getting that level of monitoring; is that correct? So we can't necessarily extrapolate from this patient setting to what might be a setting that doesn't have those safety devices around.

DR. MAIN: That's right. But not all of the patients in the current product labeling would be

in intensive care units. I guess my point was these patients are in intensive care units. Based on the data, based on the data presented, we just don't see that there is any role or any help to the clinician, any help to the patient, with prolonged monitoring.

DR. MORRATO: Although you didn't look at it. Thank you.

DR. MAIN: Not in that particular study. That's correct.

DR. PACKER: Michael?

DR. PROSCHAN: Yes. I also pondered the idea of what could be causing this treatment benefit. One thing that's in the briefing materials that hasn't been mentioned so far is the idea that some of it might be that you're preventing some procedures that would result in death immediately, surgery that could be fatal right away, and maybe the contrast echo after looking at that, you decide that you don't need that. That would explain why there would be an early benefit and not as much later on.

The other thing I wanted to ask about related to what Dr. Kaul raised earlier about the meta-analysis. So those are observational studies. Were there methods used to adjust for bias such as the propensity matching in those studies or were those just unadjusted?

DR. MAIN: Each of those individual studies? No, there was no propensity matching. Those were unadjusted. A constant theme throughout all of those studies, however, was the fact that patients who received contrast tend to be sicker by a variety of different measures than patients who undergo unenhanced echocardiography. So they were not matched. The contrast patients were in general much more -- much sicker and had many more comorbidities than unenhanced echocardiographic patients.

DR. PACKER: Okay. We're going to go Vandana, Bray, Brian.

DR. SACHDEV: In your observational database, do you know if the patients received Definity as an infusion or bolus?

DR. MAIN: We don't know, and both techniques are used in practice in the United States.

DR. SACHDEV: And do you believe that the level of risk is comparable between the two?

DR. MAIN: I don't think that we have any firm scientific data that one is necessarily safer than the other. Dr. Kaul mentioned in his lecture that he believes that the continuous infusion is safer, and there are certainly a lot of people who believe that.

DR. PACKER: Bray?

MS. PATRICK-LAKE: I was really trying to understand the impact of the boxed warning on the patients who may be contraindicated, and I appreciate that you had trial design and study design that was agreed upon with your company and the FDA. But, for me, I thought it would be really helpful to understand outcomes for patients who are specifically contraindicated in how their clinical decision-making was impacted.

What I saw that seemed to be a little

helpful was the study that was on the impact of contrast echocardiography by Dr. Kurt at Methodist Hospital. And I was just wondering if Dr. Kurt or any of his co-investigators had a financial relationship with your company.

DR. MAIN: Apparently, no. No; no financial relationship.

DR. PACKER: Brian?

DR. STROM: Three questions. We heard earlier about a lot of use of the product is for stress echoes. I don't know if you have a sense of your entire market what proportion is for stress echoes. And analogously, in the Premier study, which is in ICUs, what proportion was for stress echoes? And I have two more.

DR. MAIN: Well, there has been some data from Arlington Medical Resources in previous years. I can tell you that pre-boxed warning contrast in general, ultrasound contrast agents were used in about, I believe, 10 percent of stress echoes but low single digits for other resting echocardiograms.

DR. STROM: My question is the opposite. Of the number of people who get the contrast agent, what proportion of them are getting stress echoes?

DR. MAIN: Thirty-five percent at present.

DR. STROM: And how about in the Premier study in an ICU setting?

DR. MAIN: None, none. Stress echoes were excluded, yes. Those were all ICU patients, so no stress testing.

DR. STROM: Okay. That's what I was expecting, so just to be clear that the entire use for stress echoes and safety in stress echoes, which was all the out-of-label use we were hearing about before, it's not represented there at all, just to be clear.

Second, Premier is a claims database. What efforts did you undertake to validate any of the outcomes with medical records?

DR. MAIN: No additional analysis based on that. You're correct. This is a claims database, and that was the analysis.

DR. STROM: Third, is the -- one of

the -- in the prep material, I don't remember whether it was yours or somebody else's, we saw unadjusted and sort of unmatched and matched analysis. I know the slide you just showed us had partially matched and matched analyses in terms of the Cochran-Mantel-Haenzel and the logistic regression.

Do you have unmatched and matched analyses that you can show us?

DR. BHAT: Yes, we included the full dataset, which includes all 1 million plus patients where the noncontrast is about 991. When we did the analysis of -- just an odds ratio. It came about similar; it's a little bit different. I can't remember exactly, but it's around .7.

DR. STROM: Yes. So my recollection was in the unmatched analysis the protective effect was not as marked. It was still there, but not as marked. It became more marked in the matched analysis, presumably indicating important confounding.

Can you tell us what those confounders were?

DR. BHAT: Well, when we did the matching, we included on all the demographic and comorbidities about 35 variables. I think when we looked at multiple digits of matching, I think one thing came out is the APR severity of illness where in the Definity group there are higher -- much severe patients than the noncontrast group. That was one of the main factors for imbalance.

DR. STROM: Okay. So the severity of illness was a confounding variable, and to the degree this is not a great measure of severity of illness, then controlling for more which means the answer is more.

DR. BHAT: Yes. So that made the odds ratio to be slightly lower in matched dataset than the full dataset.

DR. PACKER: Henry?

DR. BLACK: I just wanted to make a couple of comments. I'm not at all surprised that improved diagnostic accuracy would have better outcomes. If it were the other way around, I would be very surprised.

I wanted to focus on slide 30 from the Kurt study, which may not be exactly how Milt was doing it. The major thing this seemed to do was avoid procedures, and I can easily understand how doing unnecessary procedures could have bad outcomes.

Was this the case? Could you tell from your other studies whether or not this was also the case, or analyzing the single-center study, was there any particular procedures that were avoided, and how would that income [sic] short-range effects?

MR. MAIN: Yes, I think you're correct on that. The procedures avoided included other imaging procedures in this study. And I think in terms of the treatment effect, the fact that we avoid perhaps in the retrospective ICU study, avoid invasive diagnostic tests like coronary angiography, which as Dr. Hibberd outlined, is still today a 1 in 1,000 risk of mortality associated with that procedure. That probably did add to the effect, no question about it.

DR. SUNDARAM: Thank you.

Broadly speaking, among other variables, there are four important variables in performing and interpreting an echocardiogram: the technology, which is the ultrasound machine; the sonographer who performs; and the patient and also the interpreting physician. And, clearly, the ultrasound technology has significantly improved, especially with the harmonic imaging in the early part of this century.

My question is, as far as the decision to assign the treatment -- or in this particular case to use the contrast or not -- to what extent the two important variables, the sonographer and the ultrasound technology besides the interpreting physician, played a part and were they able to match in this?

I know it's pretty difficult in terms of the hospital claims data, but these are important variables. Were they ever matched?

DR. MAIN: No. Just don't really have any information from that claims database regarding any of those variables and the decision to use

contrast. I would agree with you, and I would agree that ultrasound technology has improved. Over the same period of time, however, patients have also continued to get much more difficult to image.

DR. PACKER: Can I just ask one clarifying question? How did you define the 48-hour period? I understand that Premier judges things based on a daily basis. So how was 48 hours defined?

DR. MAIN: Same day or next day. Same day or next day, so day of treatment and the next day.

DR. PACKER: Okay. So let me see if I understand. Let's say that the first day was a Monday, and the second day was a Tuesday. If a patient in the control group died on Monday, that would count no matter when they died on Monday.

DR. MAIN: Correct.

DR. PACKER: A patient in the echo group, in the contrast group, if they died on Monday would count, right?

DR. MAIN: Correct.

DR. PACKER: But the period of risk is not

the same because the patient in the control group could have died any time on Monday, and the patient in the contrast group could only have died after they got the contrast study.

DR. MAIN: Well, they both would have had to have died after their echo, though.

DR. PACKER: They both had to die after their echo?

DR. MAIN: Or they wouldn't have had one performed.

DR. PACKER: I see. Right. That's fine. I just wanted to make sure there wasn't a survivor bias here.

What's that?

DR. NEATON: I have a similar question just in terms of the validity of this database. And it even goes back a step.

So how confident are you that the predictors in developing your propensity score really occurred before the echo was done? You have a number of comorbid conditions here, and I'm just wondering with this database how much of this could be

chicken/egg versus how much is truly baseline pre-echo.

DR. BHAT: That's a good question, and we cannot really validate completely. Everything is from Premier database. That patient is admitted. The data obtained by the hospital, that's what we collected.

DR. NEATON: And in an earlier question about -- and the document indicated that there was some uncertainty about even capturing all the dust.

Do you have any sense for how many of the outcomes within 48 days [sic] might have been missed because of people transferring or other things?

DR. BHAT: Well, in some cases, if a patient dies late in the day on the first day, that will be reported next day. So that's why -- that's the reason we got 48 hours instead of 24 hours. So if a patient dies in the end of the next day, the report may come on the subsequent day which we're not able to catch it.

DR. NEATON: I have a couple more questions.

So just in terms of understanding the methods, so you did one-to-one matching. But as I understood your primary analysis, you ignored the matching. You adjusted for the covariates in the logistic model, all the ones that you considered for the propensity score; is that correct?

DR. BHAT: Well, the propensity scores were calculated based on 35 variables. It is whether a patient got the treatment or not.

DR. NEATON: Is there an analysis which takes into account the one-to-one matching?

DR. BHAT: It's a baseline comparison before and after.

DR. D'AGOSTINO: That was my question about the Cochran-Mantel-Haenzel test, was it maintaining the matching.

DR. NEATON: Right, exactly. I didn't see a single analysis here that actually was in keeping with what I thought the design was, which was the 1-to-1 matched pairs analysis.

DR. BHAT: No, we did not do the one-to-one matched pair analysis.

DR. NEATON: So can you do that and tell us whether the result is similar?

DR. BHAT: Oh, I cannot tell you.

DR. NEATON: And a third question, maybe you don't have the data, but it would seem like a reasonable thing to do here. And a good thing always to do when you do this type of matching would be to consider analysis, whether or not the treatment effect is comparable across stratum defined by propensity score.

In other words, among the people that had high propensity for the product, are there mortality differences among those whom the propensity is lower?

DR. BHAT: That's a good question. We haven't done that, to my knowledge.

DR. NEATON: This is just all kind of -- I'm just trying to think just methods and design in terms of the utility of the database and in summarizing the results, which I'm having some difficulty in understanding -- quite apart from the remarkable odds ratio -- which is understanding how

much weight to put on this.

DR. BHAT: Just to kind of summarize, when we calculated propensity scores, to answer your questions, we identified two groups with similar propensity scores, but we did not do the one-to-one matching and comparison. We still did the two samples studies. And also, we haven't done the high propensity score or low propensity score kind of stratification.

DR. NEATON: But the actual algorithm used produced one-to-one matching, right?

DR. BHAT: Yes, yes.

DR. PACKER: Okay. We have to go through this quickly. I'm actually getting some --

DR. D'AGOSTINO: I have two questions. One is a comment is to just back up what Dr. Neaton was saying. That's why I was trying to get up.

What went into that actual analysis they did and how did it preserve the matching?

The other is, just let me make sure I'm understanding it. In the facilities, you had two sets of facilities with noncontrast and the

contrast. Were these mutually exclusive facilities?

DR. BHAT: Can you clarify the facilities?

DR. D'AGOSTINO: Well, you say you had 536 facilities where it was noncontrast and 199 facilities where there was contrast.

DR. BHAT: No. The same facility can have both the noncontrast --

DR. D'AGOSTINO: Same facilities can -- but there's twice as many in the noncontrast.

DR. BHAT: Yes.

DR. D'AGOSTINO: I mean, a 1 percent mortality rate may not be very substantial, depending on the type of hospital involved.

Do you know if the hospitals were matched? I mean, you do some teaching hospital and so forth, but are you dragging in some hospital differences that aren't captured, some of these unmeasured variables?

DR. BHAT: Yes, so the facilities that there is a teaching hospital or nonteaching, that was one of the variables, but we did not really stratify

the facilities to calculate any odds ratio.

DR. D'AGOSTIO: Do you have a raw estimate of mortality rates for the hospitals? I mean, are they different, similar?

DR. BHAT: When we looked at the overall -- I haven't really seen any kind of outlier -- they are pretty similar.

DR. PACKER: Mike?

DR. PROSCHAN: Related to the issue about the matched analysis, what I would find to be helpful would be just a simple 2-by-2 table where you show for the pairs how many of the pairs had both people died, the contrast died and the other one didn't die, all the numbers in that 2-by-2 table, if you have that.

DR. BHAT: Like I said, it's not a 1-to-1 matching of patients in the end for the analysis. So it is still group statistics that we used. And we are trying to simulate. It's not the same, but we are trying to simulate a parallel randomized study where there is no one-to-one matching in a way.

DR. PACKER: I just want to make clear because I raised the question before that the effect size, the effect, is due to a survivor bias, and I just want to clarify one thing.

The noncontrast echoes are done all day long. Contrast echoes are not done 24 hours a day. They're done by echocardiographers that have contrast experience; is that correct?

DR. MAIN: Well, I know that this differs by institution. At our institution, sonographers administer contrast agents based on a decision at the bedside and a physician's standing order. And, obviously, I think fewer echocardiograms are obviously done during the night. At some facilities, that'd be by a cardiology fellow who could also administer those or a sonographer on call. So I'm not sure that that's necessarily correct.

DR. PACKER: Well, I'm going to assume it's correct because I know it to be correct. Therefore, an echocardiogram, noncontrast echocardiogram, done at 1:00, 2:00, 4:00 in the

morning would give that individual a longer period of exposure to mortality than a contrast echo done conveniently between 8:00 and 5:00.

Consequently, you're chopping off periods of time when only noncontrast echoes would have made a patient eligible, and, in fact, you're chopping a period of time approximately equal to your risk reduction. Your risk reduction is a survivor effect.

DR. MAIN: I don't have any data regarding the number of studies that were done in the early morning hours, so it's difficult to comment on that.

DR. PACKER: And that's the point, you don't know, but I can assure you that the noncontrast echoes were done in the morning, making a patient eligible for death the entire 48-hour period whereas a contrast study was done later in the day, making that patient 48-hour period a far shorter 48-hour period.

DR. MAIN: I guess I would just respectfully disagree with that. I don't think that there'd be

a very large quantity of patients who are imaged at 1:00, 2:00 or 3:00 in the morning. We do contrast echocardiography and noncontrast echocardiography all day long so --

DR. PACKER: But most hospitals don't.

DR. KRANTZ: Can I add to that?

DR. PACKER: Yes.

DR. KRANTZ: I would only say that there is a chance that when the reader, the interpreting cardiologist, looks at the study, he goes back and orders contrast later in the day. So there is that effect in addition to the on-call effect of the fellow. So I think there may be a number of operative things going on.

DR. PACKER: We're going to take a five-minute break.

(Whereupon, a recess was taken.)

DR. PACKER: Okay. We're going to go on to GE's presentation.

Is GE here? It's hard to do a presentation without the sponsor. Of course, it wouldn't be the first time we've done that.

Is GE here? I hate to rush you, actually, but I have to.

Industry Presentation - Paul Sherwin

DR. SHERWIN: Good morning, ladies and gentlemen. I'm Dr. Paul Sherwin, senior medical director at GE Healthcare. We're grateful for the opportunity to work with this joint committee to review the safety data on Optison and its support for labeling that will optimize safe access to this clinically important diagnostic tool.

There's substantial evidence demonstrating the safety of Optison as reflected in postmarketing surveillance, extensive peer-reviewed literature, and the three recent safety studies. All of these data support the safe use of Optison to assess cardiovascular function, even the most critically ill patients.

The boxed warning was based on concerns that arose before these data were available. The boxes had the impact of reducing access to what has now been demonstrated to be a safe tool for rapid and precise cardiac assessment. The specific warnings

on the box are fully addressed elsewhere in the package insert. Our presentation today supports the recommendation to remove the boxed warning but to reformat labeling using the Physician Labeling Rule format instituted in 2006, which will highlight upfront the warnings and contraindications.

After describing the use of ultrasound contrast agents in the U.S. and the original safety concerns that led to the boxed warning, I'll present the safety surveillance data for Optison that supports the removal of the boxed warning.

Dr. Jonathan Goldman, assistant clinical professor of medicine and staff physician at the San Francisco VA Medical Center and executive vice president of strategic development at ICON Clinical Research, will present the results of postmarketing studies, which will also support removal of the boxed warning.

Dr. Steven Feinstein, the cardiologist who is internationally recognized as an expert in the use of the ultrasound contrast agents, founder of

the International Contrast Ultrasound Society and director of the Ultrasound Laboratory at Rush University Medical Center, will summarize peer-reviewed literature showing that Optison is safe and recommending its use. He will illustrate how Optison can improve diagnostic accuracy and patient management. He will also describe how the boxed warning has hindered appropriate use in patients.

I'll then come back to conclude and lead the discussion on behalf of our team.

Ultrasound contrast agents are sterile suspensions of microspheres that are composed of a protein or lipid shell surrounding a gas such as perflutren. In echocardiography, these agents reflect ultrasound waves, increasing blood tissue contrast, resulting in better visualization of the ventricular walls with diagnostic benefit.

There are two approved ultrasound contrast agents in the U.S., Optison, approved in 1997 and Definity, approved in 2001. They share the same indications, and neither is indicated for stress procedures. Both agents are contraindicated for

right to left shunts, perflutren hypersensitivity and intra-arterial injections.

Optison is additionally contraindicated in patients with hypersensitivity to blood, blood products or albumin. They differ in microsphere concentration with Definity being 15 to 24 times more concentrated, and therefore slightly in the distribution of microsphere diameter, although the vast majority of microspheres are smaller in diameter than a red blood cell.

The shells are made of different materials, albumin in Optison and phospholipids in Definity. This is also the case for SonoVue, which is not yet approved in the U.S. The gas is the same in both, perflutren, which is an inert nontoxic gas, which is also approved as a medical device for treating detached retina via intraocular injection. Perflutren's elimination half-life is 1.3 minutes, and it's completely eliminated in 6 to 10 minutes by exhalation. Dosing is by volume for Optison and by weight for Definity.

The volume of perflutren gas per millimeter

of agent administered is 25 microliters for Optison and 150 microliters for Definity. These gas volumes are miniscule in comparison to the volume of the cardiovascular system.

In 2007, FDA had received reports of perflutren-associated serious adverse events. Based on the 2008 FDA press release, there were 11 fatal events of which followed Optison use and 199 nonfatal events of which nine followed Optison use. In response, package inserts were revised. We had a boxed warning and contraindications in patients with unstable cardiac conditions or pulmonary hypertension. Monitoring of all patients for 30 minutes after dosing was also required.

Subsequently in 2008, FDA revised package inserts based on two studies, one of Optison, one of SonoVue, which each reported no adverse effects of a contrast agent on pulmonary pressures. The revised package inserts required monitoring of high-risk patients instead of all patients. The majority of new contraindications were removed. The sponsors were also asked to conduct

postmarketing safety studies.

The current boxed warning for Optison warns of serious cardiopulmonary reactions, including fatalities, during or after the administration of perflutren microspheres. It recommends assessing all patients for the presence of contraindications and recommends monitoring of vital signs, ECG, and the oxygen saturation in patients with pulmonary hypertension or unstable cardiopulmonary conditions during administration and for at least 30 minutes afterwards. It refers users to the warning section and advises users to always have resuscitation equipment and trained personnel readily available. However, the postmarketing safety data and other data available for Optison demonstrate that the boxed warning is no longer warranted.

The postmarketing safety data are divided into two time periods, before and after the 2008 package insert revisions. Before the revisions, patient exposure was 1,095,000 vials. After the revisions, exposure included an additional 55,000 vials for a total of 1.15 million. Before the

revisions, 11 nonfatal serious events were reported for a rate of one-ten-thousandth of a percent. After the revisions, six nonfatal serious events were found through GE literature surveillance for a rate of 11-one-thousandths of a percent, and the overall rate is 15-ten-thousandths of a percent.

Since approval in 1997, a single fatal event has been reported for a rate of 900-thousandths of 1 percent both before and after the revision of the package insert. This event was not related to Optison use. It was a pericardial infusion due to myocardial rupture following a dobutamine stress test conducted three days after an acute myocardial infarction.

The postmarketing safety data after the boxed warning support its removal. The removal of the boxed warning is further supported by the three recent postmarketing safety studies, which Dr. Goldman will now present.

Dr. Goldman.

Industry Presentation - Jonathan Goldman

DR. GOLDMAN: Good morning. I'm

Dr. Jonathan Goldman, executive vice president, ICON Clinical Research, an independent contract research organization. And I'm also a practicing cardiologist at the University of California San Francisco where I'm an assistant clinical professor of medicine and also serve as a staff cardiologist at the San Francisco VA Medical Center.

I was responsible for the conduct of two of the three postmarketing studies. In terms of my financial disclosures, I have received consulting honoraria from GE Healthcare. I do not have any financial interest in the company nor in the outcome of this meeting.

Three studies, Studies, 3, 4 and 5, were designed to meet commitments to the FDA. Each study's design and analysis were agreed upon in advance with the FDA. Study 3 determined the rate of serious adverse reactions, or SARs, among Optison patients in clinical practice. Study 4 looked at the effects of Optison on pulmonary pressures and pulmonary vascular resistance. Finally, Study 5 assessed one-day and two-day

mortality in critically ill patients who underwent Optison-enhanced echocardiography. These studies showed no new safety concerns. They support the safety profile reflected in the package insert and support the removal of the boxed warning.

Study 3 examined the serious adverse reaction, or SAR rate, in patients who received Optison in routine medical practice. An SAR is a serious adverse event, SAE, believed to be due to the study drug, in this case, Optison. The study was prospective and open label and did not include a control group.

One thousand and thirty-nine patients scheduled for a clinically-indicated Optison echocardiogram between June 2008 and March 2009 were enrolled at 18 United States centers. Optison dose was chosen by each investigator based on clinical need. The primary outcome was the SAR rate based upon causality assessment by an independent data safety monitoring board or DSMB.

Of the 1,039 patients enrolled, 62 percent were male. Ages ranged from 20 to 97 with a mean

of 59. Eighty-three percent were white, 14 percent black, and 2 percent Asian. Body mass index ranged from 15 to 82 with a mean of 34. The dose of Optison ranged from 0.2 to 10 milliliters with a mean of 1.91. Forty-seven percent of the patients underwent a stress echocardiogram during the study, which is an off-label indication for Optison use.

There were no deaths or serious adverse reactions. Five patients reported six serious adverse events. None of these were deemed related to Optison by the investigator, GE Healthcare or the DSMB. There were no clinically significant changes from baseline in vital signs.

The six SAEs were as follows: A nonsustained ventricular tachycardia which ended when dobutamine infusion was terminated during a stress test, fluid overload and sustained ventricular tachycardia after a nine-hour radio frequency ablation procedure, and three events which were actually new diagnoses based upon the Optison-enhanced echocardiogram. These included coronary artery disease, a left ventricular

thrombus, and a left ventricular mass.

Cardiopulmonary adverse events reported by 17 percent of patients. Thirteen percent of patients experienced a cardiovascular event, and 7 percent experienced a pulmonary event. The majority of events were mild or moderate in intensity. Younger patients were more likely to experience adverse events than older patients. Women were more likely to experience events than men. And high cumulative doses were associated with higher event rates, but this is mainly a reflection of the higher event rate in stress echocardiography procedures in which high cumulative doses of Optison were used.

As expected, patients undergoing stress echo had much higher rates of adverse events than those who underwent nonstress echo procedures. The adverse event rate in the nonstress patients was less than that was reported in the Optison package insert.

In Study 3, Optison was generally safe and well tolerated with no deaths or causally-related

serious adverse reactions. Six serious adverse events in this study were not related to Optison. Adverse events were generally mild and most were not attributed to Optison.

While Study 3 focused on safety in terms of overall rates of serious events in clinical practice, Study 4 focused specifically on safety in terms of changes in pulmonary vascular resistance and pulmonary arterial systolic pressure. Study 4 compared Optison and placebo for their effects on pulmonary arterial systolic pressure and pulmonary vascular resistance.

This was a single-blind, randomized placebo-controlled crossover study. Thirty adults scheduled for a right heart catheterization for clinical reasons between May of 2009 to July of 2010 were enrolled. These subjects had either a normal or an elevated pulmonary arterial systolic pressure. Each subject received 0.5 milliliters of Optison and 0.5 milliliters of 5 percent dextrose, the placebo, in random order separated by 15-minute intervals. The primary outcome measures were

changes in pulmonary arterial systolic pressure and pulmonary vascular resistance at 2, 6 and 10 minutes after each injection.

The normal pulmonary artery systolic pressure group had a high percentage of males and a higher mean age than the elevated PASP group, but the two groups were comparable in racial composition and body mass index.

This table shows the mean pulmonary arterial systolic pressure in millimeters of mercury versus time from injection. There were no significant differences between Optison and placebo effects on pulmonary arterial systolic pressure except at 10 minutes in the elevated pulmonary arterial systolic pressure group where there was a significantly lower pulmonary arterial systolic pressure for Optison. The difference, 4.26 millimeters of mercury, is not considered clinically significant.

This table summarizes the mean pulmonary vascular resistance results. There were no significant differences between Optison and placebo

in either group. There were no deaths, serious adverse events or severe adverse events. The one reported adverse event was procedural pain due to withdrawal of the catheter. There were no clinically-relevant changes in other hemodynamic parameters, vital signs, oxygen saturation, clinical laboratory tests or ECG findings.

Study 4 showed that Optison was safe and well tolerated and that it did not increase pulmonary pressures or vascular resistance in patients with normal or elevated pulmonary arterial systolic pressure. These results are consistent with the Optison study conducted by Erb and Shanewise that was cited by FDA when they revised the package inserts regarding pulmonary hypertension in 2008.

The last study, Study 5, was designed to focus on mortality in critically ill patients. Study 5 retrospectively compared critically ill Optison patients in controls for one- and two-day mortality. The data source was Premier's 37 million-patient prospective comparative

database. Patients who underwent an echocardiogram from January 2003 to November 2005 were screened. Contrast use was based upon medical need. The primary outcome measures were same-day or same- or next-day mortality.

Eligible patients had to have at least one of six critical diagnoses that were related to the warning section in the Optison package insert. The qualifying conditions were as follows: acute myocardial infarction, pulmonary embolism, pulmonary hypertension, respiratory failure, serious ventricular arrhythmias, or worsening or unstable congestive heart failure.

The inclusion criteria were met by 2,884 Optison echocardiogram patients and 270,066 noncontrast echo patients. Each contrast patient was matched to four noncontrast controls using a propensity score and stepwise logistic regression model based upon 29 variables which were selected with a goal of identifying patients with a propensity of receiving contrast-enhanced ultrasound.

The 29 variables included demographics, indicators of clinical condition, medication usage, and various comorbidities. Before matching, there were 25 significant differences between the groups, and after, there were four. Before matching, 14 percent of critically ill patients received Optison compared to 9 percent of non-critically ill controls, suggesting that patients who received Optison were sicker.

In a study of this type, it is crucial that contrast patients and controls have similar baseline mortality risks independent of the treatment; namely, contrast or no contrast. Although the patients in the control group each had one of the same six critical diagnoses used to select the Optison patients, the original per protocol matching procedure did not match each Optison patient to controls who had the same critical diagnosis.

As a result, in most cases, an Optison patient was matched to four controls who actually had other critical diagnoses. This resulted in a

mismatch of baseline mortality risk because mortality risk is not the same across the six critical diagnoses.

To address this, the per protocol matching strategy was modified to include matching on the critical diagnosis as well as the other 29 variables. This alternative method resulted in every Optison patient being matched to four controls who each had the same critical diagnosis as the Optison patient allowing for a more balanced comparison.

Null analysis showed a significant increase in risk with Optison. The results for the GE per protocol and alternative analyses are shown in the first and second row. The FDA also analyzed the per protocol matched controls, and their analysis excluded six outlying patients. Their results are shown in the third row.

Finally, because the FDA briefing document refers to differences between the GE and Lantheus analyses, we reanalyzed the Optison data after including in the propensity model two variables

that Lantheus included in their database analysis presented at the 2008 advisory committee meeting. These included the 3M APR-DRG, which stands for all patients refined diagnosis-related groups indices for mortality risk and severity of illness.

Since this analysis directly includes mortality risk and disease severity, it may be particularly informative. All of these new analyses will be submitted to the FDA for their review.

The odds ratios ranged from 1.124 for the GE APR-DRG analysis to 1.40 for the GE per protocol analysis. Despite differences, all analyses had 95 percent confidence interval limits that included the value of 1, indicating no difference in same-day mortality. Importantly, no deaths were reported to GE Healthcare, suggesting that healthcare providers did not suspect a role for Optison. Although not shown here, similar results were observed for two-days, which is same or next day mortality.

The GE analyses of Optison and the Lantheus

analyses of Definity have applied different definitions of critical illness applied to the Premier database for the selection of controls. Optison data used ICD-9 codes for admitting diagnosis to match for at least one of six critical diagnoses. The ICU, CCU or mechanical ventilation status was not used for selection but was used for the propensity score model to match controls to cases. Thus the control group had a spectrum of severity of critical illness.

Conversely, the Definity analysis required patients in ICU to be included, whereas comorbidity as defined by ICD-9 code was used for the propensity score model to match controls to cases. Thus the control group was limited to the more severe end of the spectrum of critically ill patients. The two cohorts thus had different definitions of critical illness resulting in different event rates and controls and were extracted from different time periods from the Premier database.

We repeated all of the Optison analyses for

Definity using the same database and the same statistical methods. Similar results were obtained for Optison and Definity. All showed no statistically or clinically significant differences in mortality rates. The initial differences between the GE per protocol analysis and the Definity analysis seemed to reflect differences in the matching criteria rather than differences in the actual risks associated with the two agents.

When similar entry criteria are used for the definition of critical illness and the time period, namely, 2003 to 2005, similar odds ratios were seen for the effect of Optison or Definity when compared to controls. Use of most optimal methods, propensity matching, provides the best match for controls to cases and supports a conclusion of no adverse effect in critically ill patients.

The most severely ill patients are those who are critically ill and who are ventilated. When the Optison and Definity data for this subset of ventilated patients are analyzed, no adverse effect is seen, and the results are very similar for both

agents.

Studies of this type have inherent limitations. First, these are observational and not interventional studies. Because of this, selection of treatment is nonrandom. Only the date of death was available in the database, not the specific time of death nor the cause of death. The reason for the echocardiographic examination and its urgency were not available, nor could it be determined which patients underwent stress echocardiography. There may be an inherent selection bias in that many more patients who received contrast were critically ill compared with those who did not receive contrast, which is consistent with how contrast is used in clinical practice.

Despite these limitations, all of the analyses support the same conclusion, that there is no statistically significant nor clinically relevant increase in same-day or two-day all- cause mortality in the patients who received Optison.

Now, Dr. Feinstein will summarize peer-

reviewed literature on Optison human safety and will discuss the impact of the boxed warning on patient care. Dr. Feinstein heads the echocardiographic laboratory at Rush University Medical Center.

Dr. Feinstein.

Industry Presentation - Steven Feinstein

DR. FEINSTEIN: Thank you very much, Jon. It's a pleasure to be here.

I'm Steve Feinstein. I'm professor of medicine and director of the echo lab at Rush University Med Center in Chicago. We perform roughly 15,000 echoes a year. I've used contrast echo for around 25 years.

Along with Barry Goldberg, we founded the International Contrast Ultrasound Society. It's a grassroots organization dedicated to the safe and effective use of ultrasound contrast agent for our patients globally. We represent an international interdisciplinary membership, 58 countries strong, thousands of members, and we uniquely unite cardiologists, radiologists, vascular medicine

specialists.

ICUS was created three years and eight months ago in direct response to the boxed warnings placed on the ultrasound contrast agents. I am a paid consultant to GE. I have no financial interest in the company or the outcome of this meeting.

I will review the published literature on the safety of ultrasound contrast agents, and in particular Optison, from the period 2000 to 2010. Of particular interest to this group is one of the very first uses of ultrasound contrast agents was in the critical care units. These three prospective studies -- and their references are listed below -- were prospectively designed. It's 187 critically ill patients who received serial boluses of Optison. There were no deaths, no changes in blood pressure, oxygen stats noted. Each author independently recommended the safe use of Optison in the ICU setting.

What was the goal of the next study? It's an interoperative study by Erb by and Shanewise.

The study was designed to look at risk-benefit or benefit-risk and safety. Thirty-five patients received 97 central vein injections. That is in the central vein, they received the injections, not in the peripherally, in the OR under anesthesia. The physicians concluded Optison did not change hemodynamics, cardiac function, or oxygen saturation and was safely used in the very sickest of all patients, ASA Class 4 patients.

The results of their data seen here and the raw data has been available to the FDA since the year 2009. The peer-reviewed safety literature from 2008 to 2010, this was collected since the black box warning was instituted in September of '07. There have been over 20 peer-reviewed articles on contrast safety. I will highlight a few.

The meta-analysis, which you've seen and Dr. Main so aptly described, included some 211,000 patients. These were collected from eight studies. What was their endpoint? MI and death. The bottom line, there was no significant difference in the

incidence of MI or death in the patients who received ultrasound contrast in eight collected studies.

You've seen this demonstration. This is a graphic representation. One might say it favors the use of contrast versus not.

In 2008, the American Society of Echo convened an expert panel to review the safety of contrast echo in response to the boxed warning. Over 78,000 cases were reviewed. Twelve thousand were Optison. There were no deaths, no SAEs, and the adverse event rate was .0003 with Optison.

They concluded the incidence of SARs was lower than or similar to that of contrast agents used in other imaging modalities. And to quote, "The black box warning effectively eliminated the use of ultrasound contrast in those who these agents are of the greatest benefit."

The results obtained in this study occurred without routine monitoring and suggest the boxed warning recommendations for monitoring should be reevaluated and potentially eliminated.

A retrospective study done by Herzog published in JAMA in 2008, 112,000 echoes were reviewed prospectively reporting AEs with the nursing staff. There were zero deaths, zero SAEs observed with Optison.

In conclusion from the peer literature, there appears to be no safety signal based on the data presented.

The current boxed warnings have negative consequences for our patients. Why do we need Optison? Contrast ultrasound is critical for decision-making. Its need is 10 to 30 percent of all echoes and provides accurate assessment of LV function. Contrast is routinely used to monitor therapy in patients with heart failure and coronary artery disease.

In this particular case, as you have seen already, you'll note the center is the apical four-view. The apex is at the top. You will now see the contrast agent entering the right ventricle passing through the lungs and entering into the left ventricular cavity. This is a half cc. This

is 10 drops injected in an arm vein.

On the left is an unenhanced image. On the right is enhanced. As you can now clearly see, when you're trying to define segments, they are well defined after the contrast use. Numerous professional societies now require and/or mandate the use of contrast ultrasound. As you can see, I've listed six here.

As director of the echo lab at Rush, we adhere to the 2000 ICAEL guidelines. What does that imply? "Contrast," as I quote, "is indicated for use when two contiguous segments are not visualized as it provides greater accuracy in determining LV function. Contrast must be used if this is not accomplished with harmonic imaging," specific reference to stress testing.

The real world, an echocardiogram was performed. Two out of six contiguous segments were poorly visualized. Therefore, contrast is indicated and mandated. A nurse, physician, family member, pharmacist, supervisor or risk management then asks me, "Did you inform the patient and

family we're using a black box drug?" I discussed the boxed warning. I cite evidence-based literature describing safety and efficacy of contrast agents. I mention that contrast agents reduce additional testing, the risk associated with that, the complications and ionizing radiation. The family, the patient may then decline the boxed warning or may, due to the boxed warning, decline the use of contrast, thus leading to additional testing. Alternatively, if they agree to the contrast ultrasound, it can make a difference.

Let me give you an example in this critically ill patient. Precontrast images led to the wrong diagnosis, wrong treatment. The patient was seen after open heart surgery and consultation. She was hypotensive, tachycardic and treated with diuretics and sympathomimetics, the exact case that Dr. Main referred to, different patient. After intravenous injection of 10 drops in an arm vein or a half cc of Optison, the LV was well seen. It was actually hyperdynamic, and, in fact, the current therapy was contraindicated in this patient.

As you'll see in this videotape, in the apical chamber, again the apex at the top, the center of the image is the heart. And you can see, this is not a very clear echo, the ejection fraction although it was estimated at 10 to 15 percent.

Following the half cc injection in the arm vein, you can see that, in fact, that was completely wrong, and the medications needed to be completely changed as this was a hyperdynamic ventricle, not a poor functioning ventricle.

Another patient recently came in, routine defibrillator checkup, 66-year-old man. His echo quality was poor. His ejection fraction was reduced. He had a defibrillator placed to prevent sudden death. All these conditions are listed on the black box warning. This is his first image. You can see the defibrillator with the arrow, and you can tell this is a very poor quality image.

Shortly thereafter after a half cc injected, there is a mass at the apex where his heart attack was, and that's a very large thrombus. And when

you zoom up, you will notice that the thrombus is actually pedunculated as the contrast swirls around it. He was immediately admitted for full anti-coagulation.

Let me conclude. There's a clear and important medical need for ultrasound contrast agents and Optison. Six professional societies' practice guidelines mandate and require the use of contrast today based on certain criteria. There exists no safety signal based on peer-reviewed literature and the sponsor-completed data. After 10 years and 1.15 million doses of Optison, there are no related deaths. The boxed warning now limits contrast resulting in negative consequences for our patients. The current warnings and contraindications suffice. They are there. We recognize them. And in light of these considerations, removal of the additional boxed warning, or black box as clinicians know it, is justified because the data demonstrate no evidence of a safety concern.

I thank you. Dr. Sherwin will now conclude.

Industry Presentation (con't) - Paul Sherwin

DR. SHERWIN: Thank you, Dr. Feinstein.

There is ample evidence of the safety of Optison. The postmarketing safety surveillance data show a very low rate of adverse events. The three clinical studies showed no SARs or increase in mortality. The peer-reviewed literature recommends the use of Optison in critically ill patients. Finally, the boxed warning may create a barrier to appropriate use in patients and result in delayed diagnosis and referral to higher-risk procedures, including the potential for unnecessary exposure to ionizing radiation. All these support removal of the boxed warning.

The boxed warning was based on the data available in 2007 and 2008. Since then, however, a vast amount of additional patient experience has accumulated demonstrating the safety of Optison. In addition, the warnings and contraindications section of the current package insert provides adequate guidance for the safe use of Optison.

In light of these considerations, removal of

the boxed warning is justified because the data demonstrate no evidence of a safety concern. As an alternative, we suggest updating the package insert to the new format released in 2006 under the Physician Labeling Rule. This would present warnings and contraindications on the front page in the highlights section and maintain an appropriate level of awareness.

Thank you very much for the opportunity to speak today.

Questions to Industry Presenters – GE Healthcare

DR. PACKER: Okay. We'll open this up in the same manner. Let me just ask the members of the committee that perhaps many of the same questions that you asked in the previous sponsor applies here. You need not bring that up again unless you think the answer is going to be unique. And we'll begin the questions actually in an open-ended fashion. You can talk about anything you want.

Mori?

DR. KRANTZ: Just real briefly, the first

two studies, Jonathan or whomever was looking at that, is there any patient that got a contrast study that had a shunt? I think that was one of the questions. I know we can't get that from the Premier data.

DR. SHERWIN: A shunt was ruled out by history and also by the baseline echocardiogram.

DR. KRANTZ: So they were excluded then, essentially?

DR. SHERWIN: Yes, they were excluded.

DR. PACKER: We're going to go around. Sidney?

DR. WOLFE: These are the same questions, but I think the answers may be different. So the first question was, in the briefing material from you that we're handed, it says, "Patients" -- this is we're now talking about the prospective thousand-patient study -- "eligible to participate if they were scheduled for a stress or nonstress enhanced echocardiographic exam."

Question. Were all these people -- or what proportion of them - people who had previously had

an inadequate noncontrast echo? And that's the first question.

The second again is the question that Dr. Packer and others, including I, have raised. How do you determine causality? In the first company's case, they said the principal investigator decided, A, whether it was drug related and, B, whether it had to do with the stress test. I believe you mentioned here that you had some data safety monitoring adjudication group.

The reason I'm raising the second question -- you can answer the first one in a second or so probably -- is that the results of your 1,000-patient perspective study are radically different from the Lantheus ones in the sense that they had a larger proportion of patients who they felt were causally related to the product, whereas yours was down towards zero, not quite zero. I made a little table of it.

So the question is, did you have a different adjudication system or an adjudication system as opposed to just asking for the principal

investigator to decide whether it's causal? The causality question is obviously critical here. As Dr. Packer has said, it's very difficult. And when you see almost all the cases being wiped out on the basis they're not causal, I have a question.

DR. GOLDMAN: So I'm going to answer the second question first in the hope that you'll forget about the first one.

The second question was to do with the adjudication of the events. By methodology, the investigator would determine whether the patient had an adverse event or not, either because the patient gave a symptom by history or because some finding occurred on the echo. So if it was some critical diagnosis like a thrombus or a tumor, that might still make the investigator's criteria for a serious adverse event whether it was causally related or not.

So all of the serious adverse events were categorized by the investigator according to type and whether they thought it was related or not. Clearly, they were all temporally related to

Optison because that was by design. And, secondly, an independent DSMB then reviewed all of the data, recategorized the event as to what event they thought it was or was not, and then provided their own assessment as to whether it was probably causally related to underlying disease, related to concomitant medications or was related to Optison.

DR. WOLFE: Quick follow-up on that. In your data, you show a very, to me, striking relationship between adverse events and the dose. And if, in fact, the adjudication process eliminated almost all, not quite all but almost all, of these events as being causally related.

How do you explain the fact that with increased dose, you had more events? The two seem to be in conflict. Then you can get back to the first question, which I haven't forgotten yet.

[Laughter.]

DR. GOLDMAN: Well, when you do a stress echocardiogram, you have to administer contrast twice, of course. You have to do a rest injection; then you have to do a second injection actually

during your stress procedure. A proportion of the stress tests actually were performed with dobutamine stress, and a proportion were performed using exercise stress.

I'd like to show two backup slides. The first one is slide 45 that you have up there. So you can see here when you look at the dose that's administered when you compare the stress to the nonstress, very few of the nonstress patients got high dose of contrast agent, which is consistent with clinical practice. You don't need to give the higher dose if that is the case. Conversely, the stress patients sometimes did need a higher dose.

If we go to backup slide number 46, which I think I can control here, you can see here, when you look at the data according to stress type, that the preponderance of the cardiac adverse events are those who actually underwent a dobutamine stress echo.

So if you look at the data that I just showed you in slide 45 and the data that you can see here, it's predominantly the patients who

undergo the stress who have the higher dose, and the patients who get the adverse events are those who predominantly undergo dobutamine stress tests.

DR. WOLFE: That still begs the question, which Dr. Packer and others raised before, is do you attribute that to the stress test or to the drug as in the drug that you're giving, the Optison? I think it's difficult to do at best. And then if you can get down to the first question which was, were the patients all previously, as had been the case with the Lantheus patients, found to have an unsatisfactory noncontrast echo?

DR. GOLDMAN: It was for the determination of the investigator to decide whether the patient met the criteria to use contrast or not. So purely to have a technically difficult echo in itself by ASE guidelines was not the entry criteria, it was for the investigator's determination.

DR. WOLFE: That means they're different entry criteria for this study than the Lantheus, because Lantheus said 100 percent of these patients.

Do you have any idea what percentage of the patients of these thousand had had a previous unsatisfactory echo?

DR. GOLDMAN: No, I'm not aware of that.

DR. PACKER: Michael?

DR. PROSCHAN: Yes, I wanted to come back to the Packer hypothesis because this is something that I wouldn't know anything about being a statistician. The time bias hypothesis, one of the differences we just saw was that Definity used ICU and CCU only. And I'm wondering is there a reason to believe that that time bias might be worse for those patients than for others.

DR. PACKER: Yes.

DR. PROSCHAN: Okay. Thanks.

DR. PACKER: Allan?

MR. COUKELL: I'm interested in this assertion that hospitals stopped using contrast agents as a result of the black box warning, and perhaps you could shed some light on which hospitals and why. In your written submission, you cite Dolan, et al. 2001, which doesn't seem to say

anything of the kind, at least as I read it. So perhaps you could provide some clarification.

DR. SHERWIN: The Dolan reference, unfortunately, said 2001. That was an error. It was an 2009 reference.

DR. FEINSTEIN: It still has a chilling effect. Our institution, which is a large institution, we were some of the initiators of contrast back in the year 1998, stopped using contrast entirely for two months. I've talked to many of my colleagues in this room, around the country and overseas, same chilling effect. Many of us have not come back full. And as I mentioned to you in the presentation, the risk management nurses, Pharm.D., physicians, patients, all want to know about the black box. So it still remains a chilling effect in my office, my practice, and many of my colleagues.

DR. PACKER: Sanjay?

DR. SANJAY KAUL: Dr. Goldman and Dr. Feinstein both asserted that there is no statistically- or clinically-relevant increase in

same-day or two-day all-cause mortality for patients who received Optison.

Just a comment. I don't think the data are assertive enough to make you draw that -- or allow you to draw that conclusion.

So let me ask Dr. Goldman, what do you mean by a clinically-relevant and a statistically-relevant increase in mortality? How do you define that? Do you base that only on p values, which I don't think is an appropriate metric in observational datasets, or do you base that on point estimate, or do you base that on a 95 percent confidence limit upper boundary to rule out an unacceptable risk?

DR. GOLDMAN: Well, I'm not a statistician. Dr. Lupinacci will approach the podium to provide further guidance on the statistical question. But with respect to the clinical side of things, you would look at the point estimates and the magnitude of the difference between the treatment and the controls.

I think the point that we've tried to make

here is that when you look at all of these analyses, what it really comes down to is how do you adequately match the cases and the controls so that you're really truly comparing like to like.

DR. PACKER: I just want to make sure. Sanjay didn't ask you a statistical question. He really asked you a clinical question, which is that where -- when you want to make a clinical judgment, what are you looking at?

DR. GOLDMAN: Looking at the point estimates to see what the magnitude of the difference is.

DR. PACKER: And the 95 percent confidence intervals, you ignore?

DR. GOLDMAN: The 95 percent confidence intervals have to be taken in the context of the sample size that you're looking at. A small sample size is going to have wider confidence.

DR. PACKER: A small sample size means imprecise estimates.

DR. SANJAY KAUL: Right, but you have 137 events. Is that enough for you to have a confidence interval that will allow you to assert a

definitive conclusion?

DR. GOLDMAN: Well, you have 38 deaths that meet these criteria, and the confidence intervals are based around that and based around the magnitude of the effect, if there is one.

DR. PACKER: Maybe I can just pursue this just a second. Normally, one looks at the upper bound of the confidence interval because if you look at the point estimate and you have extremely imprecise data, you have to recognize that they're largely uninformative. So the upper bound gives you a sense of that.

So right here, we've got upper bounds ranging from 1.6 to 2.0.

DR. SANJAY KAUL: That's correct. And we haven't seen the in-hospital mortality data. You made a comparison with the Definity cohort regarding same day and/or same or next day, but I'd also like to see what happens to this treatment effect at the in-hospital time frame, whatever that is, because we saw an attrition treatment effect in the Definity cohort. And what happens to the

Optison cohort when you do the in-hospital?

DR. LUPINACCI: Good morning. My name is Paul Lupinacci, associate professor of statistics at Villanova University. I have received a consulting honorarium from GE. I have no financial interest in GE or the outcome of this meeting.

Though we don't have the results of the in-hospital mortality readily available, the in-hospital mortality results were performed, and the odds ratios were very similar to the odds ratios across the various analyses that were displayed.

DR. SANJAY KAUL: Did they exclude an odds ratio of 1?

DR. LUPINACCI: No. The confidence intervals did not exclude an odds ratio of 1.

DR. PACKER: Allen?

DR. VAIDA: Just a quick question since we're being asked some questions on the labeling, and it seems like both companies want to decrease some of the warnings and get rid of the box.

What's the use in the ambulatory setting of

this product? All the studies have been done in acute care. And do you even get any adverse events reported in through your pharmacovigilance from ambulatory? There was one study that showed about 14 percent. Do you have any idea how much this drug is used in the ambulatory?

DR. SHERWIN: Well, Study 3, which was the 1,000-patient registry study, all of those patients were ambulatory.

DR. VAIDA: All those patients?

DR. SHERWIN: So that was outpatient ambulatory patient cohort.

As far as your second question about pharmacovigilance, we cannot always tell from the report whether or not the patient was ambulatory or not. I think in most cases from the context, reading the cases, they were probably mostly inpatients, but we have a very small number of cases.

DR. PACKER: Okay. We have to swing this way.

Elaine, I think you had your hand -- and

then we're going to --

DR. MORRATO: Just an additional follow-up to what Dr. Kaul was saying around the statement that you made that there exists no safety signal.

If we accept that this is sort of a therapeutic class effect, I'm really intrigued by the fact that there is a strong temporal relationship between the administration of these contrast agents and the events, the majority occurring within 30 to 60 minutes. So I'm hoping you can help me understand why we should disregard the spontaneous adverse event data.

DR. SHERWIN: Could we have slide 11, please?

So these events that were reported to us in the postmarketing surveillance, there were 11 nonfatal events, a high proportion of these were in association with stress procedures. Six out of the total of 17 nonfatal serious were stress procedures. In many cases, the event was reported relatively long after the Optison administration, in some cases, one day or more following the

Optison administration.

So temporally, it wasn't always the case that there was a close temporal administration between Optison administration and the reported event.

DR. MORRATO: In the FDA materials when they pull out several cases, though, they're citing cases that are within 45 minutes, within 15 minutes, within 60 minutes. So are you saying that those are select cases; they're not representative?

DR. SHERWIN: There are some cases, yes. There are three allergy cases, and those had very close temporal association with Optison. In other cases, these events occurred during dobutamine stress procedure. And in some cases, the event terminated when the dobutamine was stopped. So not in every case was there a very close temporal association.

DR. PACKER: Okay. We're going to go right -- Brian and --

DR. STROM: And we're talking about all the

data now?

DR. PACKER: All the data.

DR. STROM: Okay. I've got a few questions related to the Premier study. Firstly, to be clear, what you did is you matched on ICD-9 codes. Did you validate with medical records the validity of ICD-9 codes?

DR. GOLDMAN: We were unable to validate against the medical record. The Premier database is anonymized with respect to patient.

DR. STROM: Okay. But what you showed very clearly is when you match on different things, you get very different answers. So you're matching on a variable that we don't know the meaningful of it.

Second, can you show us -- the question came up before in the prior presentation, the issue with your matching on exposures before or after the -- sorry -- matching on variables before or after the exposure.

Did you make that differentiation?

DR. LUPINACCI: In our propensity score models, we used 29 baseline covariates. Those were

pre-reported covariates prior to the administration of the treatment.

DR. STROM: Okay. So those were all pre-exposure, to be clear?

DR. LUPINACCI: Yes.

DR. STROM: Third is can you show us unmatched -- given all the issues of matching here and the answers, change whenever you match, and you don't know what your match -- and given it's ICD-9 codes, recognizing all that, can you show us unmatched versus matched results?

DR. LUPINACCI: No, those results are not available. We did not look at them.

DR. STROM: Okay. Again, given the results change based on what you match on, what about the -- this is sort of a classic problem with using propensity scores because it's a giant gamish. You don't know what things in the gamish matter.

Did you do analyses doing logistic regressions, not propensity scores, not matched analyses, adjusting for variables not controlling for it by matching?

DR. LUPINACCI: No, those analyses were not performed. All of the analyses that were performed used the propensity score matching algorithms. The different models, the different algorithms that were used included additional variables based on baseline mortality risk, the critical condition and the severity of the illness.

DR. STROM: Last question. Given propensity scores are simply a way -- another statistical approach to control for confounding, very useful when you're screening for adverse reactions when you don't know what the confounders are, but much more problematic for hypothesis testing because of the confusion that it results in, can you -- where they're mostly useful for is if you have many variables per outcome, but you have plenty of outcomes here.

Can you tell us why you chose to use propensity score matching rather than doing the analysis and in what, at least in the past, would have been a more conventional approach?

DR. GOLDMAN: A variety of different

suggestions were discussed with the agency prior to actually conducting the analysis, and this was the preference and the favored method that was used.

DR. PAPADEMETRIOU: My question will be again on the pulmonary hemodynamics. I see that you included patients with pretty high systolic pulmonary pressure, up to 176.

My question is, have you looked at those patients that potentially had primary pulmonary hypertension with very high systolic pressure, and how many of those patients did you include?

Can we say anything about this group of patients? Because they behave differently from the patients who have pulmonary hypertension due to LV dysfunction, did you have enough patients with primary pulmonary hypertension so you can say that it's safe in this group, too?

DR. GOLDMAN: I'd like to bring up backups. If I just show you this slide. All of the 30 subjects enrolled had a history consistent with cardiovascular disease. Nineteen had a history of pulmonary arterial hypertension of which 12 was

classified by the investigator as primary based on medical record. Of the remaining 19 who had elevated pulmonary pressures, seven had secondary hypertension, and I'm providing here the reason. So Eisenmenger, coronary disease, non-idiopathic dilated cardiomyopathy, other forms of hydrocardiomyopathy, heart failure, possible association with an obesity drug use and pulmonary vascular disease.

DR. PACKER: Stuart?

DR. RICH: I want to get a little better handle on the differences between Optison and Definity, so I do understand that Optison has a protein shell and Definity a lipid shell; is that correct?

DR. SHERWIN: Yes, that is correct.

DR. RICH: And they both have the same gas inside?

DR. SHERWIN: Yes, that's correct.

DR. RICH: And it appears that there is a clearly recognized anaphylactic and anaphylactoid -- I don't know what anaphylactoid

means, but reaction to Definity.

Has that never been seen with Optison?

DR. SHERWIN: We have had three cases of serious allergic reactions. One of them was anaphylactic. And by the way, to answer your question about anaphylactoid, that's often used in the contrast literature to describe a reaction which is anaphylactic-like in its symptoms but in which, generally, there's not a true antibody-related cause that's been established. So anaphylactoid just means looks like anaphylactic.

So, yes, we have had one anaphylactic postmarketing reaction reported to us and then two other non-serious reactions, where, clearly, there was evidence of allergies such as facial edema, hives, difficulty breathing in association with that as well.

DR. RICH: and other than what was reported to you, are you aware of any other than three incidences in the entire spectrum of use of Optison in the clinical world, any other evidence that there is a potential anaphylactic or anaphylactoid

response?

DR. SHERWIN: Those are the only three of which I'm aware from our database.

DR. PACKER: Yes, Jim?

DR. NEATON: The populations were very different in the two studies, and so if you believe -- kind of put aside the sampling variability and all the potential bias that may remain from kind of measured confounding and modeling, is an interpretation here that in very high-risk people in the ICU, there's a risk-benefit which seems to be favorable but in less seriously ill patients, there's an unfavorable risk?

DR. FEINSTEIN: I would say that the benefits of using ultrasound contrast in any patient who has a technically limited study, notwithstanding their conditions, is clear. If we cannot see the left ventricular chamber wall, that is two out of six regions, contrast is indicated. And as I have shown and others will show today, in outpatient settings, the patient walks in feeling fine, turns out to have a clot. And in the current

study, as you saw, five clots were -- or 35 potential ones after contrast, actually only one, but they found five new ones. And, no, we don't believe and the data supports us, there is no increased risk for an outpatient versus a critically ill patient for the use of contrast.

DR. NEATON: I kind of appreciate the fact that the case examples, and I like the schematic, I guess, of the modeling study, but I guess we don't have the results of that study, and it's too bad the trial wasn't done.

So how do you explain the differences between the two studies? Have you done an analysis with Optison restricted to ICU patients?

DR. FEINSTEIN: The very first three studies I showed you --

DR. NEATON: Well, no, just the retrospective analysis.

DR. FEINSTEIN: Oh, I'm sorry. Okay.

DR. NEATON: I saw the one with the ventilators. Does that include all the ICU patients or is it a broader group?

DR. LUPINACCI: So the subanalysis on only those patients that were on mechanical ventilation is a subset of those patients in the ICU and the CCU. An analysis of the Optison patients only restricted to the ICU was not performed.

DR. PACKER: One question about -- I like your hemodynamic study because you had a control group. Let me ask a question.

You said there weren't any clinically significant changes. Can you tell me how you would define a clinically significant change in pulmonary vascular resistance?

DR. GOLDMAN: That's obviously going to vary from physician to physician who's looking at the data, and there are people (indiscernible), the pulmonary world. However, a change of 50 percent you would say would be probably significant.

DR. PACKER: Fifty?

DR. GOLDMAN: Sorry. Twenty percent.

DR. PACKER: Okay. So 20 percent. Okay. The between group difference that you had was .8.

DR. GOLDMAN: The between group

difference --

DR. PACKER: Was .8, which is about 20 percent.

DR. GOLDMAN: So here's the data from the study showing you the differences in different times. For each of the time points, we saw a reduction in pulmonary arterial systolic pressure.

Can you just clarify the time point that you're concerned about?

DR. PACKER: Can you go to slide C-26? I'm looking at the cohort with elevated PA systolic pressure.

DR. GOLDMAN: Right.

DR. PACKER: And there was a -- in the group that got no contrast, there was a fall of .7, and the group -- I'm sorry, a fall of .6, and the group that got contrast, an increase of .2.

DR. GOLDMAN: Right.

DR. PACKER: Which is a difference of .8.

DR. GOLDMAN: The statistical analysis that we applied to these data were adjusting for the control within that.

DR. PACKER: That's not my question. I'm talking about the magnitude of the difference. Remember, you only have 19 patients. So lack of statistical significance here is readily attributable to your small sample size; .8 approximates a 20 percent difference. You're also getting a significant decrease in PA systolic pressure between the two groups. So you're having hemodynamic effects here in the pulmonary vasculature with the contrast agent, and the reason that you can pick that up is that you have a control group.

DR. GOLDMAN: Right. So that's -- when you take account of the noise that you, of course, see --

DR. PACKER: You have a control group in order to interpret the noise. That's why having a control group is so important, and that's why you did a really good job in that.

DR. GOLDMAN: So I think the data that we see here doesn't support a clinically significant effect --

DR. PACKER: The data here supports a clinically significant increase in pulmonary vascular resistance of about 15 to 20 percent.

DR. GOLDMAN: So when you consider what would the noise be in repeat measurements of pulmonary vascular –

DR. PACKER: No, no, no. That's why you have a control group. You have a control group over the same time period.

DR. SHERWIN: We should point out, too, that these changes were not associated with adverse events reported in those patients, and there was no intervention taken on the part of physician. So in that sense they're not --

DR. PACKER: You have 19 patients. You have average pulmonary vascular resistance of 4 to 5. These are clinically significant hemodynamic changes in pulmonary vascular resistance.

DR. GOLDMAN: I guess I would respectfully disagree with that.

DR. PACKER: On what basis?

DR. GOLDMAN: On the basis of the magnitude

of the change, the effect size --

DR. PACKER: You told me 20 percent was what you would consider clinically important.

DR. GOLDMAN: If it's greater, significantly greater than that, but I don't think we see that in these data.

DR. PACKER: Okay. Last question.

DR. SACHDEV: When we talk about adverse events and numbers and which ones are clinically significant differences, I think the temporal association is really important. So can you talk about whether the numbers that we're looking at occur within, say, the first 30 minutes as opposed to the whole 48 hours? Are we overestimating which numbers are important just because we're looking at a longer period of time than we should be?

DR. SHERWIN: Are you referring to the database study, the one-day and two-day mortality?

DR. SACHDEV: Either one, either one. So when we look at the numbers, I guess I'm remembering that the drug only stays on for about 10 minutes, and this is a high-risk population, so

it's hard to sort out the control from the treated. So if we had just looked at the within 30-minute numbers of adverse events, would they have been much lower, presumably?

DR. SHERWIN: For the Study 5, which was the database study which looked at one- and two-day mortality, that may be the case. We don't know because we didn't have access to the exact time of death for these patients. It was only the date of death, so really knowing what day, either day 1 or day 2, that they died.

For the other studies, for 003, for example, the 1,000-patient registry study, we do have the time from start of injection to onset of the adverse event in some cases, not all. There were six serious adverse events. In one case, the time of onset sustained ventricular tachycardia was about 8 minutes. This occurred during dobutamine infusion, and the ventricular tachycardia stopped when the dobutamine infusion was terminated. So I think that suggests that it may have been due to the dobutamine even though it occurred very shortly

after Optison.

In the other two cases which were not new diagnoses, this was a case of ventricular tachycardia and fluid overload, which both occurred in a single patient in a protracted procedure, about a 9-hour procedure which involved RF ablation. So I think even though it occurred relatively soon after Optison, there was a very complicated procedure ongoing which probably is a better explanation for the adverse events. So in that case, we think probably Optison was not the cause.

In the other three events, these were actually new diagnoses based on the findings from the Optison; so left ventricular thrombus, left ventricular mass and one other event --

DR. SACHDEV: Why are those adverse events? I mean, that's the reason for doing the contrast studies, to make the diagnosis, so why are those counted as adverse events?

DR. SHERWIN: Well, in a clinical trial, an adverse event is counted as any untoward event,

whether or not it's believed due to the drug or whether or not it's temporally related. So anything which is new is reported to us if it prolongs -- if it meets the criteria for a serious adverse event. So it prolongs hospitalization, or if it's fatal, or if it's life threatening, or is a disability, or a birth defect, all these criteria qualify, and we instruct our investigators to be very conservative and report everything to us.

DR. PACKER: Jon, you definitely have the last word.

DR. HALPERIN: Thank you. I have a simple-minded question. The sponsor argues for removal of the boxed warning based on the evidence that has been presented. The boxed warning calls for assessment of contraindications and monitoring for a period of time after administration of a contrast agent. All of the patients studied were, in fact, both assessed and monitored. So how can this evidence be used to support doing something differently?

DR. SHERWIN: We're not advocating

elimination of the monitoring or the contraindications or the warnings. We think those should stay in the label as they are. It's just the boxed warning itself be removed, and then we're advocating reformulating the labeling to move to the new format, which was instituted in 2006, which has a highlight section, basically a synopsis of the package insert. And these would be appropriately highlighted up front, the first page that someone sees and have the same warnings and contraindications that are currently there now.

DR. PACKER: Okay. Thank you very, very much.

DR. FEINSTEIN: Can I just make a statement to concur with Paul? We're here not advocating that contraindications be withdrawn. They're appropriate. We're not advocating that warnings be withdrawn. We're saying that based on the data, is there sufficient warning and safety signals here to warrant a higher level such as a boxed warning, which has a very different meaning.

We are cognizant as physicians of warnings

and contraindications. We follow them. We're asking --

DR. PACKER: So you think physicians shouldn't monitor and watch patients carefully because if you bury it in the middle -- I'm trying to figure out what you're arguing for.

DR. FEINSTEIN: I'm arguing the data doesn't support --

DR. PACKER: Careful monitoring of patients?

DR. FEINSTEIN: No, no. We're also careful. We monitor. We don't include patients who are contraindicated. What we're arguing clinically is the impression that a black box portrays to the patients, families, risk management, that this is among this most serious of all drug warnings you can lay on an application. If that's the case then, Dr. Packer, put it on. If it's not and the data supports it, take off the most severe warning. Leave it in the warning section. We'll read that. You understand.

DR. PACKER: Yes, I think you make a good point.

DR. FEINSTEIN: Thank you.

DR. PACKER: If you want to get physicians' attention to monitor patients, you put it up front.

DR. SHERWIN: And that's what we're advocating with the highlights section of the new format.

DR. PACKER: Okay. Let's go on to the next presentation by SonoVue.

As Dr. Spinazzi is coming forward, let me say one thing with the greatest respect and humor, that you will get extra points for ending early.

[Laughter.]

DR. PACKER: And you will earn the undying gratitude of the chair and the committee for every single minute you go under thirty minutes.

Industry Presentation – Alberto Spinazzi

DR. SPINAZZI: Okay, Mr. Chairman.

Good afternoon. Thank you for giving us the opportunity to present safety data on SonoVue even if it is just an investigational drug here in the United States.

This is the presentation of SonoVue. There

is a phospholipid cake that you can see here which is an gas atmosphere. The gas is sulfur hexafluoride, so different from the previous agents you have seen. And the product is reconstituted with a prefilled syringe of physiologic saline.

So following reconstitution, you have the microbubbles that are formed. They contain the same soluble gas. The other gas is insoluble, so they get out of the bubbles with more difficulty, in a much more difficult way. And the shell is made of phospholipids like for Definity.

The mean microbubble diameter is about 2.5 micron. So for 1 mL of contrast injected, it is about 8 microliters of gas that are injected, so a little bit less than the previous agents. So the recommended dose is about 2 mL, so this means there's about 16 microliters of gas.

This is a less fancy picture than Dr. Kaul presented before. This is just a picture, no oscillating bubbles, but just to show the bubbles together with red blood cells, and most of the bubbles are smaller or same size of red blood

cells.

Now, SonoVue is approved in Europe and Asian countries. It is approved in 36 countries and marketed in 25. In Europe, it is approved for echocardiography, similar indication like for Definity and Optison in the United States, but it is also approved for stress echocardiography. Then Doppler of macrovasculares, so Doppler of assessment of arteries and the portal vein to assess vascular abnormalities and also to improve the diagnostic performance in the characterization of focal lesions in the breast and the liver.

So the United States is developed for use in echocardiography for singular indication like the one that Definity and Optison already have, and we are also performing clinical studies in patients with cancer and focal liver lesions for liver lesion characterization assessment.

So this is the safety data will be presented from the safety database. This is the integrated database of completed clinical studies, plus we will provide you with data on the serious adverse

events in ongoing clinical trials.

The postmarketing surveillance is approximately 1.7 million patients exposed to the agent. This is the estimated. And then a literature review on 53 independent papers, so none sponsored by Bracco, and involving more than 39,000 patients.

So we wanted to give you an idea because we are discussing here possible predictable effects of this agent, and may be dose dependent, and something which is unpredictable like hypersensitivity reactions. And we are presenting data on the effects of SonoVue on ventricular repolarization in patients with documented coronary artery disease, the effects on pulmonary hemodynamics in patients with congestive heart failure and pulmonary hypertension, the effects on oxygen saturation and pulmonary function in patients with moderate to severe COPD, and the kinetics and the oxygen saturation in patients with restricted lung disorder and reduced gas transfer.

So the type of review -- so then we will

provide the rate and type of adverse events from clinical trials, postmarketing surveillance, and what is in the peer-reviewed literature.

So starting from possible predictable effects, the first was two studies that were agreed upon and with protocols reviewed and approved by the FDA about the possible effects on ventricular repolarization. This was in patients with documented coronary artery disease.

The first study, 112, was a continuous 12-lead monitoring of patients and the effects of the various ECG components. And there were two volumes of SonoVue, .1 and .5 milliliter per kilogram, which is approximately from 3.5 to 17 times higher what is recommended to use here in the United States, and matched volumes of placebo. And this was a crossover comparison, so each patient acted as his own control. And 113, same design, but this time one dose of SonoVue and matched volumes of placebo, so .1 milliliter per kilogram and different insonation modes, so regular as mechanical index and at the highest possible

mechanical index approved by the FDA.

So both studies have continuous 12-lead ECG monitoring. Data were sent to a central lab. They were selecting -- you see three beats from Lead 2 of the various ECG components, and then there were blinded and trained and experienced cardiologists that were assessing, so measuring the intervals and assessing the ECGs also for possible abnormalities like presence of pathological Q waves, clinically significant two-way changes and post-dose arrhythmia.

So these were -- so just to go through the design, so each patient received two doses of SonoVue and one of the volumes of placebo. So there were six possible sequences. And after each dose, there was a 48-hour monitoring of the patient.

You can see better how it was. You see all what was has been monitored in these patients. You can see that there was dosing periods a 1, 3 and 5. And so for each dosing period, the patient was receiving one of the treatments that I mentioned

before. And there was a 12-lead ECG monitoring from three hours pre-dose to 12 hours post-dose.

This was Study 112. All patients had significant cardiovascular history, especially congestive heart failure. And these were the mean values over time of the corrected QT interval, and you can see the dotted line are the reference values. But more than the mean values, I believe you are interested more in the changes from the baseline.

So you can see here, we selected two dose -- two time periods from zero to 20 minutes and from zero to -- from baseline to one hour because you are mainly interested in the acute effects of the agents. Anyway, these results were similar across the board. And you can see that the effects of placebo in terms of increases from baseline and the effects of the two doses of SonoVue were extremely similar. And there were no increases over 60 minutes. Milliseconds, you see for the corrected QT interval. And the same also next is for decreases from baseline.

So as for Study 113, there were again one dose, which is approximately 3.5 times higher than the one recommended for clinical use of SonoVue, matched volumes of placebo, and two different insonation modes. And so all the patients were exposed to this dosing and insonation regimens in a randomized sequence order.

The controls were exactly the same. For the sake of time, I go to the next slide. And all patients had significant cardiovascular disease in history, especially congestive heart failure.

So, again, the results are almost superimposable compared to the previous study. These are the mean values over time for the effects on the corrected QT interval. And also in terms of increases, this is the maximum increase from baseline in the time period zero to 20 minutes and then zero minutes to one-hour post-dose, and also in terms of decreases.

So, in conclusion -- and there were no ECG abnormalities observed, there were no serious adverse events, nothing that could lead to any

clinical -- nothing of any clinical significance.

So the magnitude of the changes from baseline were similar for SonoVue, and the placebo was similar for SonoVue, the two doses of SonoVue. And it was similar to normal high mechanical index, and there were no detrimental effects of SonoVue on cardiac electrophysiology.

This is a study that was mentioned before by one of the speakers. It was a study in patients with congestive heart failure Class 2 and 3, and ejection fraction below 45 percent, referred for cardiac catheterization and MUGA.

This is how the patients were randomized. One was group was randomized to SonoVue two doses of 2 mL, which is the recommended dose and twice that dose and matched volumes of placebo. And then there was also a control group just only with the placebo.

Different parameters were assessed, the right arterial pressure, systolic, diastolic and mean pulmonary arterial pressure, pulmonary capillary wedge pressure, cardiac output, stroke

volume, pulmonary system and vascular resistance, heart rate and systemic blood pressure and oxygen saturation.

This is the patient population. All patients had significant cardiovascular medical history. And as you can see on the bottom row, part of the subset of these patients had also significant pulmonary hypertension.

So we couldn't see any effect in any of the parameters nor could we see any serious adverse event. And I can show you on the next slide also what were the max changes observed for the 4 mL of SonoVue and the 4 mL of placebo. Now, you have the magnitude of the changes that was extremely modest and actually seem very similar for the placebo on the right arterial pressure, on the mean pulmonary arterial pressure, on the pulmonary capillary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance.

So, in essence, this was also reviewed by experts and we couldn't see -- and by the FDA at the time we submitted the first time the NDA, and

we couldn't see any effect on the pulmonary hemodynamics or systemic hemodynamics.

This is a study -- anyway, so we agreed with the FDA that the experience in these type of patients was limited, especially in the patients with pulmonary hypertension. And we agreed upon to run a new study to assess the effects on pulmonary hemodynamics similar to the one you have seen before presented by GE, and that product has already been approved by the FDA, and the study is ongoing.

Now, we also assessed the database of postmarketing surveillance to see any possible event that could actually come from a potential pulmonary embolism. We didn't have any spontaneous report of pulmonary embolism or any adverse events suggestive of anything that would increase the pulmonary hemodynamics or in patients with known pulmonary hypertension.

The only case recent from one of the clinical liver studies that we are conducting in the United States as a patient with prostate cancer

was inpatient, hospitalized and in bed for several days with unknown deep vein thrombosis, and he had symptoms of pulmonary embolism about 10 hours after receiving 2.4 mL of SonoVue. And the pulmonary embolism was confirmed by CT, and the principal investigator at the site considered this event unrelated to SonoVue administration. And for what it's worth, we agree with that.

This is a study to assess the effects on pulmonary function in patients with moderate or severe COPD. And there were a number of controls made. You see both the regular safety as lab vital signs for 48 hours as well as effects on the pulmonary function in these patients. And we couldn't see any effect on pulmonary function of the administration of SonoVue in this type of special patient population nor we could find any adverse event in the postmarketing surveillance database suggestive of such effect.

This was actually required by the European authorities differently from Dr. Kaul's excellent presentation. I only disagree on one point, that

these products, all the gas that is injected is recovered in expired air, certainly in healthy volunteers. So the question from the European authorities was, is that true also for patients with restricted lung disorders, but restricted lung disorders due to parenchymal lung disease and with known reduced gas transfer.

Actually, we conducted this study. We couldn't see any effect of the SonoVue on the oxygen saturation, and it's a high dose of SonoVue, actually, .3 milliliter per kilogram. And in the end, it was recommended not to have any dose adjustments based on the presence of a restricted lung disorder, nor we could find no effect in the oxygen saturation or could we find any adverse event in patients with restricted lung disorders.

So in conclusion, we couldn't find any significant effect on pulmonary hemodynamics, pulmonary function, blood pressure, oxygen saturation, vital signs, cardiac function, ECG components and laboratory tests in these studies. And the overall data from postmarketing

surveillance do not suggest any such effects in the patients exposed to SonoVue so far, at least what we have been reported.

From review of the literature, the safety of SonoVue from completed clinical studies, this is a comparison of the rate of adverse events in clinical studies. This is the integrated safety database with SonoVue, and what was reported in 2008 by Lantheus and GE for Definity and Optison. And more or less, the rates were similar, especially in terms of serious adverse events and also in the type of adverse events. And we have seen also from the briefing documents that actually this profile is even more similar. At that time, probably there were less stress studies you see performed with the other agents. We had also a number of stress echo studies in our clinical database.

We got 10 deaths from all clinical studies, and all were considered unrelated and how. So one occurred prior to SonoVue administration. And two patients had a safe echocardiographic procedure and

hours later underwent PCI and devascularization. Both got the PTCA and coronary rupture during the PTCA, so in this case, an endo pericardium. So in this case, we agreed with the investigators that they were unrelated.

One patient died three days after the SonoVue exam and right after right hepatectomy, and also, this event was considered -- this death was considered unrelated. And six patients died after a safe study with SonoVue and safe adverse events monitoring for 24 to 72 hours after the exam. And later on since we follow up patients up to 14 days after the studies, they died of underlying conditions, and all these cases were considered totally unrelated.

Now, if we put together the integrated database with the ongoing clinical studies, we are going now up to a total of 6,470 patients. We had serious adverse events in 33 patients, which is a total of .5 percent. Twenty-eight serious SAEs, including the nine deaths, not 10 -- because the one which occurred before SonoVue administration

was not counted as an adverse event for obvious reasons -- were considered unrelated to SonoVue administration for similar reasons as the ones that I mentioned before for the cases with fatal outcome. Five were considered with some type of relationship with the agent.

The first one was a patient that experienced severe chest pain at peak dose of dobutamine, stress with ST elevation, and then he developed hypertension and dizziness. This is in the database as an unknown relationship. The investigator later on reported that he believes this is unrelated to the SonoVue administration, but we still have in the integrated database this case with an unknown relationship.

Then this is a case of severe skin rash about one minute after SonoVue administration. The patient was treated later on with antihistamines and IV steroids. Just after the administration of an IV steroid, right after that, the patient has a vasovagal attack, a vasovagal reaction. And it turned out that the patient actually is

hypersensitive to the steroids, but in the end, we still have in our database this relationship as probable even if the investigator considered this unrelated.

This is a patient that had a confirmed -- complete occlusion of the left internal cerebral artery, and 20 hours after the administration of SonoVue, the patient developed sensory motor paralysis of the right arm. And that was treated and resolved, and the investigator reported this relationship as unknown.

The final case that was considered with a possible relationship to the SonoVue administration was an anaphylactic reaction. I started about one to two minutes after the injection of 2 mL of SonoVue, and this is a classical anaphylactic reaction. It's a clinical course that you may see with x-ray agents or MRI agents. And usually they start a few minutes after contrast administration. And this one at the heat sensation or asystole, loss of consciousness, and hypertension, treated as usual in this case with epinephrine and atropine

steroids, fluids and then recovered in 30 minutes.

This was the last of these five cases where the patient received 6 mL of SonoVue, safe rest and echocardiography, and then during dipyridamole and the second injection of SonoVue, the patient developed extrasystole, bradycardia, short-term asystole, and reaction was treated. It lasted about an hour and then was resolved. And the relationship was considered probable also for SonoVue.

Now, I'm not bothering you on what we're planning to do as a retrospective cohort study. We got a lot of input, and this was an excellent discussion. We learned a lot during this, so I would skip the next slide. So we have submitted a protocol to the FDA for comment. We're waiting for comments now. We understand why we didn't get comments. This discussion was definitely today fruitful to run a better study.

Then from the postmarketing surveillance, we got exposure of over 1.6 million patients, and we got a total of 217 cases of serious adverse events.

Part of them, 162, were hypersensitivity reactions, and some of them were anaphylactic reactions.

This is the trend over time of this serious adverse events, and as you can see in the next one, probably this is a similar graph that was prepared by the FDA in the briefing document. And you can see there is a constant increase in the exposure, so in units sold and similar trend also for the number of adverse events, so a constant rate of these serious events, but 2010 when we had a significant drop.

This is another way of presenting the same data. So constant increase in exposure in the use of this agent, and the trend of serious adverse events went down from 2001 from the launch till 2004 where there were contraindications decided by the European authorities. Then it stayed stable. It was declining before, and it declined again in 2009 to 2010.

Of note, you see these data are coming mainly from Europe and also some Asian countries, and in Europe, more or less you see -- I'm not sure

if Definity is marketed in Europe, and Optison has a very limited exposure in Europe. But this is all what is for SonoVue.

So if you compare what was presented in 2008, the SonoVue PMS data with what was presented by GE and Lantheus, you see that the different estimated exposure and rate of serious adverse events being similar for SonoVue and Definity, lower for Optison.

If you now compare 2008 to 2010 based on the briefing document that was actually released on Friday, this is the estimated exposure for SonoVue and Definity, much less for Optison. It's been off the market for a while. And you can see that rate of serious adverse events is similar for the three products, but there are no fatal cases for GE while there are fatal cases for SonoVue and Definity.

So the rate of fatal cases following SonoVue has been 1 in every 184,000 exposures. Three cases were considered totally unrelated by the reporters. For instance, one case was, during the procedure, a patient started to have asystole and hypertension.

So the patient died shortly after. But on autopsy, it was found that they had complete occlusion of the common (indiscernible). So that was considered by the reporter totally unrelated to the SonoVue administration.

Three cases are still unassessable. As you know, when we receive first information, we immediately report the cases, but then we have follow-up reports to the authorities based on the information we receive or we actively look for. But still three cases still do not have all the elements to come to a full assessment and three cases for which there is probably some relationship with the administration of SonoVue.

We have experience with other types of agents like x-ray agents, MRI agents, and what we have seen, especially for hypersensitivity reactions, is very, very similar in terms of these types and clinical course of what we have seen for the other agents like x-ray and MRI.

So, in conclusion, again, when compared to other imaging agents, the observed pattern is

similar. The underlying disease and the conditions of the patients may play a role in the severity of the disease and in the outcome. And we couldn't see any major trends in change of reporting rates we see over time but this drop in serious adverse events during 2010.

So from published papers, we have, as I mentioned before, 53 papers based on independent studies for over 39,000 patients, and we are reporting the most significant. One was an independent survey on 28 centers having registries of patients dosed with SonoVue for abdominal ultrasound, and there were a total of 29 adverse events reported for about .1 percent adverse events. Twenty-seven events were non-serious, mostly mild and self-resolving, rapidly self-resolving. And two were serious adverse events, hypersensitivity reactions, not anaphylaxis, for a rate which is similar to what we have seen in the postmarketing surveillance.

This is a comparison of stress versus nonstress echo. This was done in patients for

which in theory the product is contraindicated in Europe, so patients with chest pain within five days. And it was 500 consecutive patients with SonoVue, those that -- probably approximately 2.5 times higher than recommended in the U.S. and a historical group of 500 patients who underwent stress without contrast. And there were no deaths, no myocardial ischemia, no serious events, no allergic reactions and no differences between SonoVue and the control.

This is together with SonoVue and Optison and a total of 419 procedures with contrast. This is again stress with or without contrast. In 332 without contrast, no deaths, no myocardial infarction, no allergic reactions and no serious events, and there were no differences between the three groups.

This is -- I guess the most important part of this slide is the upper part. So these are all the cases of use of SonoVue in critically ill patients for a total of 528 patients. We got in touch with all the authors to make sure we

collected all the safety data, and there were no deaths within 24 hours. But most important, there were no serious adverse events, nothing that was of any clinical concern in these 528 patients.

So to conclude, in clinical trials, we couldn't see any significant effect that could be predictable or those dependent on pulmonary hemodynamics, pulmonary function, blood pressure and so forth. And the overall incidence of adverse events and the type of the most frequent adverse events as we saw similar among SonoVue, Optison and Definity.

The experience from postmarketing surveillance, the rate of serious events is one case approximately every 10,000 exposures. Even if for many exams, the use of the dose is not one vial. Anyway, serious adverse reactions were observed in fewer than every 10,000 exposures, and there were no major trends over time. And the peer-reviewed literature never showed a difference between SonoVue and the controls or no cases of death within 24 hours, even in critically ill

patients.

Thank you very much for your attention.

How did I make? Good?

Questions to Industry Presenter

Bracco Diagnostics

DR. PACKER: Very good. Thank you. The gratitude is conveyed. Thank you.

DR. D'AGOSTINO: I can't talk as fast as this speaker. Thank you for the presentation.

My general sense of what we heard is a substantial amount of data presented and so forth, that with the hemodynamics, you had small samples involved, which is not untypical. And when you got to the question of sort of the adverse events and what have you, we got a lot of description and what have you.

It sort of begs the question that was being raised before. If you start looking at confidence intervals, what have we ruled out? Some of these events are very small and so forth and some are large, and then you look at the three different agents that we have here.

I can't take away a message in terms of what have we ruled out. I mean, you say there's no difference, and the p values, I'm sure, confirm that. But I think the big question we have is are you dealing with so much noise in the data in such a small number of events even though you look at all of these that you could be dealing with a twofold increase of even higher.

So do you have any slides that you haven't presented that might give us an indication of what we actually have ruled out in terms of adverse event risk?

DR. SPINAZZI: So the question -- you're right. See, the rate is extremely low, and the data, there is a lot of background noise. The data are dirty. And so it's very difficult to -- actually, a definitive study should involve a vast patient population. And, again, we couldn't see anything different with at least SonoVue and what we have observed with other injectables.

DR. PACKER: Mori?

DR. KRANTZ: Very quickly. The 500-patient

study for stress echo, you showed no adverse events, not even myocardial ischemia. I would find that probability very low that if I did a stress echo, no one would get ischemic. So I guess I wonder are you tracking data the same way the other two companies would be?

DR. SPINAZZI: Yes, yes, definitely. And also, we got in touch with this center. I didn't say that no ischemia, but no myocardial infarction was seen in this patient population, no serious adverse events. There were non-serious adverse events reported, and I can't remember.

DR. KRANTZ: That's very surprising, isn't it? Not a single adverse event in the study.

DR. SPINAZZI: There were non-serious adverse events reported, and that was not that surprising. We had non-serious events but no serious adverse events. I'm sorry if I was not clear enough.

DR. PACKER: Great. Thank you very, very much.

We will take a break, and with the

committee's indulgence, can we reconvene at 1:15? I know this committee is quite used to Spartan conditions, and this will continue to add to those Spartan conditions. So we'll come back at 1:15, at which time we'll have the FDA presentations.

AUDIENCE MEMBER: Are we allowed to eat lunch?

DR. PACKER: Yes, but in a reasonably short period of time.

DR. VESELY: So for the panel, lunch is directly behind me in the back room.

(Whereupon, at 12:46 p.m., a lunch recess was taken.)

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

[1:20 p.m.]

DR. PACKER: I appreciate everyone getting back here on time, and we will begin with the FDA presentation, which will be in two parts.

FDA Presentation - Janelle Charles

DR. CHARLES: Good afternoon, everybody. Welcome back. My name is Janelle Charles. I am a statistician in the Division of Biometric VII in the Office of Biostatistics CDER. Today I will discuss the FDA analysis of the retrospective observational database cohort studies for Definity and Optison.

I begin my presentation with a brief background of the studies followed by description of the statistical methods employed. I will also discuss the individual study designs and results. I will then present a comparison of the study designs and conclude by summarizing the statistical findings and study limitations.

The studies presented in this talk, Definity study and Optison study, were conducted by Lantheus

and GE Healthcare as part of their postmarketing required studies. The primary objective of these studies was to compare in-hospital all-cause mortality in critically ill patients undergoing echocardiography with and without contrast agent. Following my talk, Dr. Filice will present the other safety data for the contrast agents.

These studies were retrospective observational database cohort studies. The data were observed from past records of critically ill patients who underwent echocardiography during hospitalization either with contrast enhancement or without. The treatment assignment was not randomized. Therefore, the choice to use a contrast enhancement and the type of contrast enhancement administered was determined by the healthcare provider attending to the patients during hospital stay.

This nonrandom treatment assignment may lead to differences in the baseline risk factors or covariates between the two treatment groups; that is, contrast and noncontrast, and unadjusted

treatment effect estimates may be biased.

Both studies use inpatient discharge data from Premier's Perspective database. This is one of the largest databases containing patient level data from all regions across the United States. The data submitted comprised patient characteristics, including demographics, comorbid conditions and concomitant medications as well as hospital characteristics. It is important to note that these data were limited with respect to a specific time to death following echocardiography.

I will now present a summary of the statistical methods used by the FDA in review of these studies. As mentioned, given the nonrandom treatment assignment, baseline differences may lead to bias treatment effect estimates in patients who received contrast relative to those that did not. Propensity score matching was a technique developed to address this issue. In these studies, the propensity score represented the probability for a patient to receive treatment given observed baseline covariates. Matching on propensity scores

attempted to adjust differences in measured baseline covariates.

Both FDA and the NDA holders for Definity and Optison estimated the propensity scores for each patient using multivariable logistic regression models. In these models, the outcome was treatment, and the inputs were baseline risk factors or covariates identified from the respective study protocols. There were no post-treatment or mortality outcomes included in the propensity score estimation models.

For each study, FDA determined the common support region; that is, the region of overlap of propensity score distributions between the treatment groups. Patients outside the common support would have little opportunity to form close matches on propensity scores. Therefore, only patients in the common support were eligible for propensity score matching conducted by the FDA. The matches were obtained using greedy matching algorithm. For each contrast patient, a noncontrast patient with similar propensity score

was selected without replacement.

The FDA assessed the balance of covariates before and after propensity score matching using chi-square tests. Further, the primary statistic for assessing mortality was the odds ratio; that is, contrast to noncontrast. For both studies, the FDA estimated the odds ratio and 95 percent confidence interval using unconditional multivariable logistic regression models based on the propensity score match data. In these models, the outcome was the mortality endpoint, and the inputs were treatment and risk factors for mortality. These models were not the same as the propensity score estimation models.

FDA also estimated the attributed risk of mortality as the difference in the risk in the contrast and noncontrast group using the matched data. This estimate compared the risk on an absolute scale rather than on a relative scale as with the odds ratios. In addition, FDA conducted sensitivity analyses, including those shown on the slide. The results are sensitivity analyses, that

is, conditional versus unconditional logistical regression, were consistent with those presented in today's talk.

I will now present the design and results for the Definity study. As you heard previously, this study was based on inpatient discharge data for critically ill patients who underwent echocardiography with or without Definity during study period noted here. Note that the study period includes the 2007 and 2008 label changes. Critically ill patients were identified as adults 18 years and older admitted to various intensive care units listed on this slide.

It is important to note that patients who underwent echocardiography with unknown contrast agent or agent other than Definity and those who underwent only stress echocardiography were excluded from this study. Emphasis here on the only stress echocardiography exclusion, this implies then that patients who underwent both stress echocardiography and rest may have been included in this study.

In the interest of time, I'd like to skip the endpoint definitions, as we've had them already, primary endpoint being 48-hour mortality, secondary endpoint in-hospital all-cause mortality.

On to slide 15. This slide shows the patient disposition for FDA analysis for the Definity study. The boxes to your right show the patients excluded from the FDA analysis, and those on your left show patients included at each stage. Lantheus Medical Imaging submitted unmatched data, that is, before propensity score matching, of just over 1 million critically ill patients of whom approximately 16,200 underwent echo with Definity, the remaining with noncontrast.

FDA identified patients for whom the identifiers were repeated. These patients represented those who underwent both Definity and noncontrast echocardiography. These patients were removed from the noncontrast group and only considered in the Definity treatment arm. Further, patients were excluded whose sex were reported as unknown.

The propensity scores were estimated for all remaining patients following these exclusions. Patients that did not lie in the common support of the propensity score distributions were also excluded from further investigation. For each Definity patient, a matched noncontrast patient was sought. The final 1-to-1 FDA propensity score matched dataset consisted of 16,199 Definity patients and 16,199 noncontrast patients.

This slide shows the results of the primary endpoint of 48-hour all-cause mortality from the matched data. The FDA and Lantheus' analyses were based on unconditional multivariable logistic regression models. These models estimated lower risk of mortality for Definity contrast compared to noncontrast. FDA obtained a mortality risk of 2.2 percent for Definity patients and 2.7 in the noncontrast patients. The odds ratio estimate, that is, odds of mortality for Definity relative to noncontrast, was .8 with 95 percent confidence interval, .7 to .9.

I will now present the design and results

for the Optison study. This study was based again on inpatient discharge data from Premier's Perspective database for hospitalized patients who underwent echocardiography with or without Optison during the study period noted on this slide. Note that this study period does not include the label changes of 2007 and 2008.

Critically ill patients were identified as adults 18 years and older, admitted with at least one of the medical conditions listed on this slide. Patients who underwent echocardiography with unknown contrast or contrast other than Optison were excluded. Patients who received stress echocardiography were not excluded from this study.

Again, in the interest of time, I'd like to skip the primary and secondary endpoint definitions. But I would like to mention that in today's talk, I will present the results of the secondary endpoint for Optison, which is the same as the primary endpoint for Definity.

So this slide illustrates the patient inclusion process used in the FDA analysis for

Optison. The boxes to your right represent patients excluded from further investigation. GE submitted a dataset of approximately 210,000 critically ill patients of whom approximately 2900 patients underwent echocardiography with Optison and the remainder with noncontrast. FDA excluded patients whose sex were reported as unknown. There were no patients with repeated identifiers in this data.

Following propensity score estimation, FDA further excluded patients who were not contained in the common support region of the propensity score distributions. For each Optison patient, four noncontrast patients were sought. The final 1 to 4, that is, Optison to noncontrast matched dataset, consisted of 2,883 Optison and 11,532 noncontrast patients.

This slide shows the results for same or next-day mortality risk estimates for Optison. Both the FDA and GE observed slightly higher risk of same- or next-day deaths in Optison compared to noncontrast treatment arms. The FDA estimated a

mortality risk of 2.2 for Optison and 1.9 for noncontrast. The odds ratio estimate, that is, odds of mortality in Optison relative to noncontrast, was 1.2 with 95 percent confidence interval .9 to 1.6.

The FDA odds ratio estimate was based on unconditional logistic regression models that did not account for the matched sets. GE used a conditional model that did account for the matched sets. However, both analyses resulted in 95 percent confidence intervals that included a null value of 1.

Although the Definity and Optison studies discussed use inpatient discharged data from Premier's Perspective data, there are some underlying design differences that may contribute to the results observed. This slide compares the study duration, patient population definition, and exclusion criteria for the Definity and Optison studies.

Of note are the study durations. The Definity study includes the 2007 and 2008 label and

changes, whereas the Optison study does not. Based on the 2007 label changes, Definity would not have been indicated for use in patients with certain medical conditions. In addition, given these study durations' overlap, it is likely that some of the same noncontrast patients were observed in both studies.

Further, the definition of critically ill; critically ill patients included in the Definity study were based on billing codes for intensive care unit, whereas for the Optison study, critically ill patients were those with particular unstable cardiopulmonary conditions.

Lastly, for the Definity study, patients who underwent stress echocardiography only were excluded, whereas for the Optison study, patients who underwent stress echocardiography were not excluded. Therefore, there's a possibility that patients who underwent both rest and stress echocardiography were not excluded from these studies. However, the effect of type of echocardiography cannot be assessed using the

submitted data.

This slide shows the FDA mortality risk and odds ratio estimates, contrast and noncontrast, for the Definity and Optison studies. These results are based on the same- or next-day all-cause mortality endpoints using the matched data. The estimated mortality risk for the contrast agents were similar for both studies. However, there were differences in the estimated background risk of mortality in the noncontrast patients. For the Definity study, the mortality risk for noncontrast patients was 2.7 compared to 1.9 for the Optison study. These differences in background risk suggest evidence of heterogeneity between the patient populations studied.

For the Definity study, there was a lower risk of mortality estimated for patients treated with Definity compared to those who underwent noncontrast echocardiography. For the Optison study, the estimated mortality risk was higher for Optison relative to noncontrast patients. However, the possibility of no effect cannot be ruled out

given the confidence interval includes the null value of 1.

This slide shows the FDA estimated attributed risk based on the same- or next-day mortality endpoint and using the matched data. For each study, the attributed risk was estimated as a difference between mortality risk estimates in the contrast group and that in a noncontrast group. For the Definity study, the estimated attributed risk was negative 6 per 1,000 with 95 percent confidence interval negative 9 to negative 3. For the Optison study, the attributed risk estimate was 3 per 1,000 with 95 percent confidence interval negative 3 to 9.

There are a number of limitations to consider when interpreting these studies' results. For these studies, patients may have undergone both rest and stress echocardiography. However, the effect of the type of echocardiography, rest or stress, on mortality cannot be assessed with the data submitted. The mortality endpoints in these studies were based on calendar day following

echocardiography and not the specific time of death. Therefore, a death 30 minutes after echocardiography and a death several hours after echocardiography on the same calendar day cannot be distinguished.

Another limitation of these studies was the reliability and accuracy of patient data submitted. The mortality endpoints are the studies were determined based on inpatient discharge codes. While mortality was an objective endpoint and assessed in only an inpatient population for these studies, there was a possibility of misreports of deaths.

Propensity score matching was used to account for differences in baseline covariates that may lead to biased mortality estimates. However, these covariates used in the propensity score estimation in these studies may not take into account all factors that contributed to treatment selection. While propensity score matching tends to produce balanced treatment groups, these methods can only address for observed baseline covariates

and not the unobserved ones.

In conclusion, the estimated mortality risk suggested that Definity may be associated with a lower risk of mortality relative to noncontrast. The specific dates that patients were in study were not submitted. Thus, the effect of label changes on mortality results cannot be determined.

The estimated risk suggested that Optison may be associated with higher risk of mortality relative to noncontrast, although the possibility of no effect cannot be ruled out. Furthermore, limitations of observational studies should be considered when interpreting the findings of these studies. While propensity score matching was used in both studies to account for nonrandom treatment assignment, there may be residual confounding and biased treatment effect estimates from these studies. As noted previously, the data submitted were limited with respect to specific time of death following echocardiography and type of echocardiography, rest or stress, that patients underwent.

Finally, it is important to consider all available sources of data when assessing the overall safety of the contrast agents discussed today.

Dr. Filice will now discuss the additional safety data available for the contrast agents discussed in today's advisory committee meeting. Thank you.

DR. PACKER: Ross, why don't we go to your presentation, and then we'll take questions for both.

FDA Presentation - Ross Filice

DR. FILICE: Thank you. My name is Ross Filice. I'm the clinical reviewer from the Division of Medical Imaging, and I'm going to try and go relatively quickly, especially through the first part of my presentation because a lot of the results have been presented already. So in the interest of time, I'll try and make it quick.

So this is a summary of the data we're presenting. Of course, Dr. Charles just very nicely presented the results of the observational

database studies. I'll be going over the other two studies as well as a summary of Bracco's clinical trial experience that they provided to us and then postmarketing data for all three agents.

So as has already been presented, the safety registries were performed for Definity and Optison where at least 1,000 patients were enrolled for contrast echocardiograms in routine medical practice. Some of the demographics here, which have been presented, the trials were relatively comparable with more males than females enrolled and mostly white patients enrolled.

As has been reported, no deaths in either trial. There were no serious adverse events in the Definity trial and six in the Optison trial in five patients, though none of those were considered related to Optison.

These are the most common adverse events reported in those trials, more than 0.5 percent of the time. And when looking at all adverse events, first we'll look at the Definity trial. On the very left-hand column, you can see the overall

adverse event rate and the associated adverse events that were deemed to be possibly caused by Definity. And as has been presented already, most of these were mild or moderate in intensity with only a very few being severe in intensity.

In the case of GE, again, an overall higher adverse event reporting rate, but as has been said already, very few of these have been deemed caused by Optison. The majority of these are in the cardiac or pulmonary categories, and, again, most of these are mild or moderate in intensity.

When looking at time to adverse event in both of these registries, the majority due appear to occur within 30 minutes, particularly seen in the Definity trial. And one interesting analyses we were looking at was if there's any relationship to dose and any relationship between rest and stress. If you look at the far left-hand column first, you'll see the overall adverse reporting rate -- again, this is Definity we're looking at first here. You'll see the overall adverse event rate in rest and stress. There are more adverse

events reported in stress, which is certainly not unexpected as the patients are being stressed.

Then as you progress to the right, we're going in increasing dose strata, so from low dose to high dose patients. And you can see in each one of those strata that more events were reported in those patients undergoing stress, again not unexpected. But no apparent dose relationship was seen in this particular trial.

In the case of GE, again in the far left, you can see overall adverse event reporting rate in those patients undergoing stress is much higher than rest. And then as we increase in dose strata, you can see that there is an apparent associated increase in adverse event reporting rates both in rest and stress as dose goes up; and, again, in all strata, more adverse events in stress than rest.

When looking at some of the demographic subgroups, more adverse events were reported in females in both of these trials. There was some heterogeneity in the ethnic subgroups you can see here, but because of the relatively low numbers of

non-Caucasian patients, it's a little hard to make conclusions there.

In terms of vital signs, I'll try and describe this very quickly. The Y axis represents the change from baseline. The X axis represents time points after administration. In the case of Definity, we're looking at heart rate here with the rest patients on top, stress on the bottom. The blue line looks at the mean change from baseline. The red boxes represent 25th to 75th percentile. The whiskers represent 10th to 90th percentiles, and each point represents an individual patient or, in some cases, clusters of patients, that they had the exact same change from baseline.

If you look at rest patient group heart rate, there's virtually no change from baseline over time, and, of course, there's some variability as would be expected in any clinical trial, but we didn't see any concerning patterns. When you look at heart rate in stress, you see an increase as the patients are being stressed with subsequent decrease, which is obviously expected, but, again,

no concerning variability patterns; and similar findings for respiratory rate and oxygen saturation.

In the case of the GE trial, we couldn't break them down into rest and stress based on the raw data we had, but similar findings in that there were no concerning patterns of variability for heart rate, respiratory rate, or systolic blood pressure.

There were ECGs documented in the Definity trial. No clinically significant changes were seen. They did note that more changes from normal to abnormal were seen in those patients undergoing stress, but if you look at the actual interpretations, a large portion of these are sinus tachycardia, which, of course, would be expected in stress and some other findings that you'd certainly expect with stress and in these patient populations, but no concerning arrhythmias were seen. In the Optison trial, they weren't collected routinely, so no conclusions were drawn.

So, again, no deaths were reported. Six

serious adverse events in the five patients in the Optison registry but none considered related. Some of the comments here about the adverse events that I've already discussed, no clinically important vital sign changes and no significant ECG changes seen in the Definity trial.

From the pulmonary hemodynamics studies, again, at least 30 patients enrolled. The focus was on pulmonary arterial hemodynamic data. These cartoons illustrate how the trials were run, which has been discussed. So in the Definity trial, they all just received a Definity echocardiogram. In the Optison trial, there was crossover, so each patient had an Optison and dextrose echocardiogram to provide some means of control.

The demographics are a little difficult to interpret because of the relatively low numbers here. There was a group here, the normal group in the Optison trial that was somewhat older. Again, most patients are Caucasian.

No deaths or serious adverse events reported in either one of these trials. There were nine

adverse events in the Definity trial split pretty evenly between the groups. Only one -- actually, this is two events in one patient that were considered possibly caused, but they resolved with medication and were also considered possibly related to the catheterization. Only one event in the Optison trial, which was the sheath removal pain that was commented on before, not considered related. And since there's relatively low numbers of patients, all the adverse events are listed here because they all occurred more than 0.5 percent of the time.

Again, the focus here was looking at hemodynamic data, so I'll go over these relatively quickly. In Definity, we're looking at systolic pulmonary arterial pressure on the top with mean values on the Y axis and minutes after administration on the X axis. The left-hand group is those with normal pulmonary pressures, the right, those with pulmonary hypertension. The red line is the mean, and the black bar is the 95 percent confidence intervals. You can see, of

course, the patients with pulmonary hypertension had a higher mean baseline pulmonary pressure, of course, but no significant changes are seen over time. Pulmonary vascular resistance is shown at the bottom here.

Looking at Optison, we broke it out into the different arms and different groups because of the crossover design of the trial. But, again, looking at systolic pulmonary arterial pressure here, no significant changes in either arm or either group and same for pulmonary vascular resistance.

We did the same thing for the systemic parameters that haven't been displayed yet, I don't think, but similar findings for Definity looking at a variety of systemic parameters and for Optison as well.

We were also interested in some of the individual variability in these trials. So because of the low numbers of patients enrolled, we could graph actually each patient's change from baseline over time. So in this case, the Y axis represents absolute change from baseline. The X axis

represents minutes after administration. And each line represents an individual's change from baseline. So here, we're looking at Definity systolic pulmonary arterial pressure, and there certainly is some individual variability, which would be expected in any clinical trial, but we didn't see any concerning patterns here.

The same thing for pulmonary vascular resistance. I've also labeled some of the outliers just so you get a sense for which group or which arm they come from in the case of Optison. Optison, we're looking at systolic pulmonary arterial pressure and pulmonary vascular resistance and same thing for the systemic parameters, so looking at Definity first here, and Optison.

The one interesting finding here, there was a number of lab parameters measured in both of these trials. This is looking at some of the immunology parameters measured in the Definity trial. The first thing I need to point out is that in the background package, I actually accidentally reversed the baseline and minus 3-minute time

point, so thanks to Lantheus for pointing that out, and I apologize. So these graphs should be in the correct order here of time points.

The Y axis represents mean values. The X axis represents the number of minutes before and after administration. And an interesting finding that's still present, you can see here at baseline the complement C3a level is just about the upper limit of normal, which is 1239 in this trial. At the 3-minute time point, this mean value is actually significantly higher than the baseline, and then you see a subsequent decrease over time. You see an associated decrease in the white blood cell count at the same time at 3 minutes, although this finding is not significantly different.

So to us, this raised the possibility of seeing some sort of immunologic response with complement activation to Definity. The one thing, of course, that I'm sure all of you have noticed here, is that there's this minus 3 time point. This mean value is certainly higher than baseline, and it's actually even higher than the 3-minute

time point, although there is a wide confidence interval because there are some outliers here. But this is minus 3 minutes, which means it's before Definity was even administered. So it's not clear why this change is seen, and certainly these are just exploratory results, but we thought these findings were interesting.

As I said, a number of other labs were measured. No other clinically important changes were observed in either trial. And ECGs were also recorded. Again, multiple baseline abnormalities seen, as you'd expect given this patient population, but no clinically significant change is seen in either trial.

So, again, no deaths or serious adverse events, no concerning hemodynamic changes from a pulmonary or systemic perspective, the exploratory immunology panel results I just discussed, and no other concerning findings.

So in terms of postmarketing, other data I'm going to review some of the United States postmarketing reporting for Definity and Optison,

and then Bracco has also provided us a summary of their clinical trial and foreign postmarketing experience to date.

Definity was approved in 2001, of course. Since that time, there have been 22 unique deaths reported of which 14 have occurred or appear to occur within 30 minutes and 17 within 60 minutes according to the narratives that were provided with those postmarketing reports. Five of these were associated with stress, three of which included dobutamine, and 10 were deemed possibly or probably related by the sponsor.

Of the serious adverse events reported, there are 330 which include those deaths. Again, a large number of those are reported within 30 or 60 minutes, although it should be noted that 133 of these don't have clear time to onset based on the narratives.

This is a graph of the fatal postmarketing reports over time just to show you that there are some fatal postmarketing reports that have occurred, even after the labeling changes, which

were in '07 and '08. And some excerpts from some of the narratives just to give you a sense of the kind of pattern that we've seen. A lot of these events, as I've shown, appear to occur relatively shortly after administration and commonly appear to be cardiopulmonary and/or anaphylactoid in nature, and some examples from their serious postmarketing. These are serious nonfatal postmarketing reports that show some similar descriptions.

Optison was approved in 1997. One death has been reported since that time and 13 serious adverse events with the correlating time, as you can see here. The one death was associated with a dobutamine stress test, and this is an excerpt from that narrative. It wasn't clearly related to Optison as the sponsor has already described because some of these findings seen at death were already present prior to echocardiography.

Some of the serious adverse events that we've received regarding Optison, again, to show you that similar pattern that I showed for Definity as well. And as you obviously saw, there's far

fewer Optison reports than for Definity, and I think this chart helps at least partially explain why.

This is U.S. sales data graphed over time. So, of course, Optison was approved first followed by Definity here. You can see a relatively sharp drop in 2005 in Optison sales, which is at the time when they pulled it off the market for manufacturing difficulties. And you can see it hasn't really recovered since that time. There's a fairly sharp drop in Definity sales as well around 2007, which is right after the initial labeling changes were implemented, and you can see it's rebounded since that time.

But I think one important point here is that over the last five to six years, Definity sales has accounted for essentially all of U.S. sales, which may at least partly explain why those postmarketing report numbers are different.

The other reason I show this graph is because when the sponsors have calculated reporting rates, they've used these numbers as their

denominator, that is, patients exposed, because they've both made the assumption that one vial sold equals one patient exposed. Well, we have some concerns with that methodology just because we are not entirely sure that each vial sold means that a patient is exposed. As I'm sure some of you can imagine, if a vial is discarded or not used or if a patient receives more than one vial for one exam or a series of exams, that may not necessarily be true.

Just to give you a sense for what some of the projections might look like, these extra lines I've added to the graph here over time are projected unique patients exposed to Definity and Optison. This is based on an FDA Office of Surveillance and Epidemiology report that uses the SDI inpatient healthcare utilization system database which takes utilization information from more than 650 United States hospitals to make a projection nationally of unique patients exposed.

Now, there are certainly limitations with this methodology as well. It doesn't include

federal hospitals or some specialty acute care hospitals, and it certainly is a projection nationwide. But just to give you a sense for some of the differences you might see, if you compare these estimates to the sponsor's estimates based on vial sales data, you can see about a four to fivefold difference at any given time point. And so, of course, regardless of the numerator you're using, you will end up with a four to fivefold difference in your estimated reporting rate.

Just to give you a sense for some of the preliminary calculations we've done, these are adverse events reported by Lantheus associated with Definity between 2002 and 2010 that have been associated with a MedDRA SMQ of anaphylaxis. So you can see the events listed here with projected unique patients by the SDI database projection and then the associated reporting rates here. So if you look, for example, at serious anaphylactic events, you can see 215 with a reporting rate of about 50 in 100,000 or a rate of about 1 in 2,000, which is much different than some of the other

numbers you might have seen today or in some of the background packages.

So now for SonoVue. So, to date, they've reported on 6700 patients who've been exposed in their completed and currently ongoing clinical trials and have sold -- at least the numbers I had at the time of this report, which is similar to what they reported today, about 1.5 million doses sold.

In terms of death, they report 10 deaths in their clinical trials of which none appear to be related both by their evaluation or ours. So we don't believe any of these were related to SonoVue, either.

In terms of postmarketing reports, there have been nine deaths reported, five of which were reported as possibly related and seven of which appear to occur within five minutes of administration.

In terms of serious adverse events, you can see 21 reported in their clinical trial experience as of the time of the report they submitted to us,

with three deemed as possibly related and 207 serious adverse events of which the vast majority were reported as possibly related and most of which fall in the immune, cardiac or respiratory categories. And, again, some excerpts from some of their sample postmarketing reports, just to give you a sense for a similar pattern that we've seen for all the agents.

So in conclusion, I think the postmarketing studies that have been reported are somewhat reassuring in that we do not see any further concerns. The pulmonary studies did not show any pulmonary hemodynamic changes that we felt were concerning. Of course, it's important to remember when we're evaluating for these rare or serious adverse events and fatalities. It's difficult to evaluate with the relatively low numbers of patients, particularly in the safety registry.

In terms of spontaneous reporting, we certainly still see serious events and fatalities even after the labeling changes in '07 and '08. Again, many of them appear to occur relatively

shortly after administration, and they commonly appear to be cardiopulmonary or anaphylactoid in nature. And then some of the limitations in SAE reporting rates regardless of the methodology used, we just would like to urge caution when looking at these rates because of the relatively low confidence in both the numerator, that is, the number of events, and the denominator, that is unique patients exposed. And then, as the sponsors have pointed out, it's important, especially in this population, to remember that there are many confounding underlying factors. There's a high background rate of serious and fatal events in these populations which certainly makes causality difficult to assess.

The impact of labeling changes in '07 and '08 on the selection of patients who were exposed to these agents as well as reporting rates and monitoring; and then the one thing we'd also like to urge caution is there have been some comparisons made between reporting rate estimates in some other clinical trial studies. One of the ones that seems

to come up relatively frequently is a study by Katayama in 1990 who was looking at adverse event rates associated with iodinated contrast. They looked at about 330,000 patients who were exposed to iodinated contrast, and it was a pretty well controlled clinical trial, or observational study that had much higher confidence in both the number of patients exposed as well as the adverse events that occurred.

So when you're talking about estimated reporting rates with what is a relatively much lower confidence in those numbers, we feel it's a little like comparing apples and oranges, and we just urge caution when you see some of those comparisons.

So thank you, and I guess questions?

Questions to FDA Presenters

DR. PACKER: Ross, why don't you have a seat, and we'll direct our attention to both of you at the same time. And we'll open it up for discussion.

Ralph?

DR. D'AGOSTINO: This is a question for Dr. Charles. I enjoyed your presentation and your clarifications on some of the issues that were mentioned earlier today. But now, if you look at the Definity study, some of the things that we were mentioning in our discussion here and exchange with the sponsor is the hospital difference, the fact that some of the hospitals didn't use contrast at all and you might be getting controls coming out of that group.

Another is that the -- we don't necessarily know that these baseline data are real baseline data, so we don't really know what the propensity score was necessarily matching on. And the one that was very important that the chair mentioned was the timing of the contrast procedure that it follows a noncontrast, and the timing for the follow-up was less. And, lastly, the matching, the analysis never took into account the matching.

Given these items and everyone wants to weight them, would you think that the confidence interval that you got of .7 to .9 for the mortality

actually could go over 1? I mean, there are lots of concerns that we were expressing that you didn't necessarily focus on in your presentation.

Then just one other thing is that with the other study, the Optison, is that they haven't ruled out a serious risk with their analysis, and I'd like a comment on that, also. But I'm really focused on the Definity study, please.

DR. CHARLES: So I'd address your first question regarding whether the confidence interval can go over 1. I think what was highlighted in the presentation is the limitations of these observational studies in terms of the propensity score can only do so much, and we could actually still have some biased estimates that is included in the confidence intervals.

So provided that we had different data, the confidence intervals may tend to go over 1. As you see, the upper bound there was .9, which is relatively close to 1.

DR. D'AGOSTINO: Yes, I didn't want to say it, but I'll say it now. I mean, one could ask is

the study really undermined with the problems that we had, that we had some very serious problems. And maybe we just have to say you did a nice -- you worked very hard and so forth, and you've got some indications, but we don't really know how to interpret it.

DR. CHARLES: Exactly. And I think the other thing that comes up as well is the background rate in the Definity study, which was relatively high in comparison to that observed in the Optison study, which may push the confidence intervals lower as compared to the Optison study.

DR. PACKER: Okay. Sanjay, Henry and Jim.

DR. SANJAY KAUL: Thank you. I was kind of hoping to get a little bit more information about the study methods as was promised earlier this morning. Specifically, what was the going-in hypothesis for the two studies, was this a class effect hypothesis, what were the assumptions for effect size, power and so on and so forth? And, quite frankly, I have as much, if not greater, concern about the methods than I do for the effect

signal that we see or don't see.

How did the model perform? I did not see anybody addressing what was the discriminative power, how was the balance assessed. I mean, do you -- I saw p values. Is that the right approach to assess balance in a propensity score match analysis? I saw a discriminative power C index of .70 in Dr. Goldman's publication in JACC Imaging. Is that sufficient discriminative power for the Optison matching? I didn't see that addressed.

So I would like a little bit more clarity as well as about -- I mean, there are sensitivity analysis approaches that you can take where you can say how much unmeasured confounding must exist to refute the findings. I mean, if it is 60 or 70 percent, then the data are more reliable, but if it is 5 or 10 percent, then you're a little bit more concerned.

So I'd like to see these issues, methodologic issues, addressed before we have any confidence in whatever effect size we see.

DR. PACKER: You've asked more than 10

questions.

[Laughter.]

DR. PACKER: Does any -- yes?

DR. SANJAY KAUL: That encapsulates the problem.

DR. PACKER: I understand but -- please.

DR. CHARLES: You mentioned the class effect hypotheses or class effect size calculations. As far as I recollect, there were no prespecified effect sizes that were requested; that is, the sponsors weren't requested to rule out a particular risk when they were conducting these studies. However, they were encouraged to submit sample size and power calculations to the agency.

DR. PACKER: Can I just ask a question about that? The concept of a class effect is a very complicated concept, and we don't want to spend a lot of time on that today. But the impression that this committee has is that these two contrast agents, at least mechanically, structurally, with the potential difference of anaphylaxis, which I don't want to get into, it's hard to imagine that

they're that different. And yet you have point estimates and confidence intervals that essentially don't overlap. So if you were to look at the point estimate and confidence interval of 1, the point estimate and confidence interval of the other, you would actually conclude that they're either both terribly unreliable or that there's a difference between the two.

Which do you think is true?

DR. CHARLES: Well, I'd like to point out here that the point estimates and confidence intervals shouldn't be looked at in isolation, which is the hope that I had in putting up that slide with the actual background risk estimates in the noncontrast groups. So a lot of the "difference," quote, unquote, that you're seeing in the results could be due to the underlying patient populations that were studied in both the Optison and Definity studies.

DR. SANJAY KAUL: I think the issue about the class effect hypothesis is critical. I would argue that at least the Definity hypothesis was

informed by external information. The Optison hypothesis was not informed by the external information, for whatever reason, whether that didn't have the market share or things like that. So I think it's important to address that because the data are not laying out in the same plane.

DR. PACKER: They're not laying out in the same plane for reasons that are difficult to attribute to the differences between agents, and, therefore, have to be, if you believe that, attributable to difference in the way the studies were designed, carried out, or analyzed; because, otherwise, we're faced with a distinction between two agents that, frankly speaking, I don't get the sense that a lot of people believe in.

Henry?

DR. BLACK: I want to talk a little bit about that. I can't resist trying to compare the two agents. I know that wasn't the idea. And when you're talking about timing, the one thing in timing that I don't think you really focused on is the changes in care from 2000 to 2010 versus what

you see in the other study. There were two years that overlapped where you might be able to see what the rates were before advances in care might have occurred.

Did you happen to think of doing 2003 to 2005 between the two compounds to see if one is better or worse or they're really the same?

DR. CHARLES: Well, the data that we obtained were limited with respect to the specific calendar year, date specific, so we couldn't do any such analyses to see the effect of label changes on --

DR. BLACK: There were things happening in the world that were caring for these patients that you might lose in an eight-year study that you would see in a four-year study or a two-year study comparing them. There are two similar years there.

Since I think this data is -- we have to extrapolate an awful lot from not having the specifics we'd like, that might be interesting to see if the rates were the same.

DR. CHARLES: Agreed.

DR. PACKER: Okay. We're going to go -- Judy, you just missed the gun on that, but we'll go around.

We're going to go Jim, Bray, Mark.

DR. NEATON: I have one question, maybe two for Dr. Charles and then one for Dr. Filice. And so I guess I'm getting the impression that you were sent some data that somebody had already put together because you knew that people were not in there, for example, for Definity if it only had a stress test, but you couldn't tell whether the echo that was done was stress or rest. So this was a dataset selected for you?

DR. CHARLES: Correct.

DR. NEATON: And so I thought I heard you say -- you seemed to have a little bit more confidence about the fact that the propensity score predictors were truly baseline. Given that this was prepared for you, is that -- did I read that right?

DR. CHARLES: Well, I based the baseline covariates based on what was submitted in protocol

as baseline by definition in protocol.

DR. NEATON: Right. Okay.

A question I had related to what Sanjay asked was, have you looked -- I guess you'd have to look probably to make it comparable at the ICU population and Optison. Are the predictors of using the Optison product similar to the predictors for using the Definity product?

So can you -- how confident are you that the selection process that these covariates predict the use of the two imaging products together? Are they really being considered as equivalent products by the investigators using them?

DR. CHARLES: Right. And that's an issue that came up as well in the analyses, that the covariates collected, they were varied in the two studies; so the baseline covariates that were included in the propensity score models for Definity as well as Optison. There was some overlap in terms of demographics, but comorbid conditions, concomitant medications, there was a lot of variation.

DR. NEATON: So why not get the data from this Premier database for both products and controls and do it together? It just seems like there's a missing piece here that could add a lot of value to the analyses that were done.

While I've got the mic, on slide 27 -- this is just one example, Dr. Filice.

Can you just explain what this is? I didn't see here how you were taking advantage of the crossover design.

DR. FILICE: This I think is Janelle's, Dr. Charles.

DR. NEATON: So what exactly are you plotting here?

DR. FILICE: So on the Y axis, this is Optison looking at systolic pulmonary arterial pressure. And on the Y axis, we have those patients -- sorry, the mean values. The X axis, of course, is minutes after time, and you can see in these cases, the patients all receive two injections. So one was dextrose and one was Optison.

DR. NEATON: So where does the dextrose kind of placebo -- where is the placebo versus treatment comparison?

DR. FILICE: Sure, sure. And I went through this pretty quickly trying to save a little time, so I apologize. So, for example, if you look at the left-hand patients are those patients with pulmonary pressure, and the top is those patients in arm A. So they received Optison first and then dextrose. If you look at just the upper left corner, those patients received Optison first, which is -

DR. NEATON: So, basically, it's the last four points kind of on the top curve are the dextrose --

DR. FILICE: Correct.

DR. NEATON: -- and the last four points on the bottom curve are the Optison.

DR. FILICE: I think maybe the other way around, I think. Maybe I misunderstood, but in the top left, it should be the first four are Optison followed by the last four are dextrose. On the

bottom for arm B, it'd be the opposite, so dextrose first and then Optison.

DR. NEATON: Okay. I'm struggling for an estimate here of what the treatment control difference is that this study was nicely designed to estimate.

Were you able to replicate the findings shown on the one slide that the sponsor showed?

DR. FILICE: I'd have to see that to know exactly which one that was. I mean, we didn't think that there was any significant difference introduced by either Optison or dextrose because we thought that it stayed at baseline throughout.

DR. PACKER: Okay. We'll go along to our initial -- Bray, I think you were next, and we'll sweep again.

MS. PATRICK-LAKE: So first forgive me for being inarticulate. I'm troubled by a couple things. I'm troubled by the fact that it took -- there are 30 of us sitting around this table. It took me a number of hours to read through all this material and to fly out here. And

at the end of this, I'm looking at summary conclusions that say, "Magnitude of risk difficult to assess with low numbers and a low confidence in accuracy." But yet when I look at the number of doses sold, I see in 2010 one company is reporting close to half a million doses sold.

So where's the disconnect? I don't know who's responsible or who designed these postmarketing surveillance studies, but why aren't we collecting the information we need to answer the questions?

I don't know who I'm asking because I wasn't part of this in 2008.

DR. PACKER: Can I make a suggestion? Hold that thought for the discussion later.

MS. PATRICK-LAKE: Okay.

DR. PACKER: Hold that thought for the discussion later.

Mark?

DR. WOODS: I'd like to go to slide 60 in Dr. Filice's presentation, and I guess earlier today we heard about the chilling effect of the

black box warning. But when I look at this data either way you cut it, it looks like it's thawing out.

DR. PACKER: It's global warming.

[Laughter.]

DR. WOODS: Yes. So either way you interpret it, it would appear that use is very much on the rise.

DR. FILICE: I think it speaks for itself, but it does seem, by sales, that that's the case, yes.

DR. PACKER: Okay. Judy?

DR. HOCHMAN: So the design of the two studies using the Premier database are clearly very different, and we've identified a lot of them. One is survivor bias. The other is -- they're just very different patients.

So I was intrigued by the Optison presentation where they actually did the Definity analysis by their methodology and vice versa -- it's C35 -- and come up with very similar odds ratios.

Did you confirm that? And also, I only see here same-day mortality. I'm wondering if they did that for the 48-hour and the in-hospital, whether they have that data.

DR. CHARLES: The analyses that you're referring to that were presented in Optison, those were not confirmed by the agency.

DR. PACKER: Okay.

DR. HOCHMAN: Do they have the 48 hour? Can we ask?

DR. PACKER: Yes, you can ask.

DR. HOCHMAN: Do you have these data for the 48-hour mortality and the in-hospital total mortality?

DR. BHAT: We do have that based on our study, and I'm not able to confirm. I understand the data that GE used, so we cannot say that we can match.

DR. PACKER: Okay. Elaine?

DR. MORRATO: My question is for Dr. Charles.

Were there data in the dataset that you

could identify what institution these patients were coming from? In other words, we might expect different utilization patterns in the products, and we know that there are differences in mortality rates between hospitals, and that might wash out effects or cause effects.

DR. CHARLES: Agreed. However, the data did not contain the specific institution that patients were hospitalized in.

DR. PACKER: Michael and Brian.

DR. PROSCHAN: You mentioned earlier the question about class effects versus individual drugs. And one thing that was in the briefing document, I think in the FDA's portion, was the fact that Optison uses larger microbubbles. And hypothesis was that larger bubble maybe help you see things more clearly, but they're also more dangerous, possibly. And I don't know if anyone has any comments about that possibility.

DR. PACKER: It's certainly something to keep in the back of our mind because we don't know.

Brian?

DR. STROM: This is just a follow-up to Dr. Charles. First, great presentation and a extremely clear presentation of a confusing subject.

The GE presentation had what seemed to be a very key analysis where they changed the matching, and the results from the two products became the same. To me, that's key, and you expressed that you didn't validate that. That's key both because that throws question into the whole design using matching and propensity score analysis. It also is key to interpreting is there really a difference between the two groups.

I think one sort of answer to the committee in some of the questions that are coming up is you can't in propensity scores directly compare the two groups because now you have a three-group analysis. And, actually, one of my trainees just developed methods for that. It's not published yet. So right now, that's not doable using propensity scores.

I note in your presentation, though, that

you ignored that. Is that simply sort of a formality given you didn't know about it in advance or was that a deliberate decision?

DR. CHARLES: You're correct. Today was the first time I noticed in the presentation those results.

DR. PACKER: Okay. Yes.

DR. PAPADEMETRIOU: Looking at the comparison of the two studies, there were a lot of patients in both, but the difference was mostly in the controls, not in the active treatments.

Can you comment on that?

DR. CHARLES: Yes. As I noted, in the Definity study, the background risk estimate was higher in comparison to the noncontrast in the Optison study. It may be due to the variables that were collected. I mean, I can't speak to patient populations that were studied, but there are some underlying differences in it, too, is what I would assume, based on those different risks.

DR. FILICE: Without being a statistical expert by any means, I think it's a good point, and

we noticed that it is true that if you look at -- with all the caveats, that they're different designs and different analyses, that the -- as you said, the control groups have different mortality rates, and the contrast groups have relatively similar mortality rates. So it could be that that control group was accounting for that difference in the odds ratio, but I will defer to other statistical experts on that point.

DR. PACKER: Okay. Sanjay?

DR. SANJAY KAUL: In the briefing document, the FDA provided estimates for in-hospital mortality in the Optison observational registry, point estimate 1.31, lower 95 percent limit 1.1, upper 1.5.

How do you interpret that? I mean, since there was no going in hypothesis, which doesn't really matter whether it's a primary endpoint or a secondary endpoint -- we're not talking about multiplicity or alpha error.

How do you interpret that all-cause mortality, in-hospital all-cause mortality

excluding risk ratio or odds ratio of 1?

DR. PACKER: You can pass if you want.

[No audible response.]

DR. PACKER: Okay. That's fine. No problem.

One question just methodologically that I just want to understand. The propensity score balances the groups for the test procedure but not for the outcome variable; is that correct?

DR. CHARLES: That's correct.

DR. PACKER: Now, in order to then go to the next step, you do either a conditional or unconditional logistic regression, and then you put in as confounders those that determine the outcome variable independent of whether they got contrast or not; is that right?

DR. CHARLES: That's correct.

DR. PACKER: But the outcome variable here is all-cause mortality. The determinants of all-cause mortality are infinite.

How do you determine what confounders to include in the unconditional logistic regression?

DR. CHARLES: So what was done previously before including variables into the multivariable logistic regression model, univariate tests were done to see whether there was an association between mortality, treatment and particular confounding variables prior to including them into the model.

DR. PACKER: But most of the mortality is going to be determined by variables that you don't measure.

DR. CHARLES: Correct.

DR. PACKER: And so there's such an emphasis on the propensity score and not a lot of emphasis on the impossibility of identifying confounders when you do the next step of the analysis.

Am I wrong here, Ralph?

DR. D'AGOSTINO: Well, the ideal situation with the propensity score, once you've done the propensity matching, you're like a clinical trial.

DR. PACKER: Right.

DR. D'AGOSTINO: In a clinical trial, you don't necessarily have to bring in covariates.

DR. PACKER: Right.

DR. D'AGOSTINO: And so the pure analysis would be that sort of conditional logistic. Then you can sit back and say, well, maybe I should try to understand what's going on with the mortality and get rid of the confounders, and that's where you get to the point you're talking about.

But, ideally, if you've done the propensity score well -- and Brian's mentioned a number of times how you can go wrong -- you have like -- you're almost in this clinical trial setting. And one of the problems I'm having with what they've done, they've done all this propensity score matching, then they don't use it in the analysis. And you don't know what effect that could have. And then your comment about the certain measured confounders, you don't know what effects you could have.

DR. PACKER: So let me just make sure I understand. When they do their second step, the step that actually, quote, "generates the odds ratio," they're not using the propensity score,

they're just identifying the patients from the propensity score?

DR. D'AGOSTINO: But they have two groups of individuals which are identical on the propensity score. That doesn't guarantee that they're identical on the different variables that were used in the propensity score –

DR. PACKER: Right.

DR. D'AGOSTINO: And that doesn't guarantee that you're going to actually have a sort of valid analysis.

DR. PACKER: Well, especially since the variables that caused the balance and propensity score were those that determined the outcome variable of the test as opposed to the outcome variable of death, and those are not going to be the same. Those are going to be dramatically different.

So did you -- you adjusted for confounders in the outcome of death?

DR. CHARLES: Correct.

DR. PACKER: And what could you possibly put

in?

DR. CHARLES: Well, the variables that were put in were, again, those that were identified as baseline. We did, however, do a sensitivity analysis to look at the effect of conditioning in the logistic regression model for outcome; that is conditioning on the matched pair design for the Definity study as well as the matching in the Optison study.

If I can have backup slide 37? So to your left here, it shows you the results presented in the talk and to the right are those obtained from the conditional model that takes into account the matched pairs design. The overall conclusions, that is, confidence intervals, still excluded the null value of 1 here. However, we noted that the risk estimates were slightly lower in the condition and logistic regression.

Similar method was done for Optison, and the results didn't suggest any difference in conclusions.

If I can have backup slide 44? Again just

showing you the comparison of the --

DR. PACKER: I totally understand, but that either means that there wasn't a major influence of confounders or that you didn't include the right confounders.

DR. D'AGOSTINO: This doesn't necessarily include confounders, does it? This is conditions on the matching.

DR. CHARLES: This is conditions on the matching, including confounders.

DR. D'AGOSTINO: You're including confounders.

DR. CHARLES: Yes.

DR. D'AGOSTINO: The other thing that I was raising with my question is that the upper limit on the confidence interval was .9, and with the other concerns that we have about the real baseline and so forth and the timing of the contrast, it's very, very easy for me to think that you would just run right over the 1.

DR. PACKER: Brian, I'll get to you in one second.

Jim?

DR. NEATON: This is kind of reassuring that you're getting -- at least my recollection of the literature on this is that if you ignore the matching, it should bias a little bit toward the null, and that's been true in both studies here. But I just want to be sure, in the conditional logistic, you included the other covariates as well?

DR. CHARLES: Yes, additional covariates were included into that model.

DR. NEATON: So what's just the straight matched analysis, what Michael mentioned before, the two-by-two table; the simplest analysis that one could look at? I mean, going back to what you were saying, in terms of just to add to what Ralph was saying, typically, you'd match, and you would kind of look for predictors and a propensity score that were associated with the outcome of interest. I mean, you're interested in balancing covariates for your two treatment groups that are related to the outcome.

DR. PROSCHAN: Right. I mean, I just wanted to -- yes. I just wanted to look at those pairs and basically throw out the pairs that are concordant where both members died or neither member died, just look where they're different and see how much of a difference there is there.

DR. PACKER: Brian?

DR. STROM: Let me see if this helps clarify, because I think we're mixing up two or three different things, and it's part of the confusion.

One is what propensity scores do is you model exposure. Based on the model of exposure -- not outcome, but exposure -- in whatever variables you a priori choose, you get a propensity score, which is a number which is the probability of exposure. That's what you're controlling for. And so you're reducing the 29 or 35 or whatever number of variables to one variable, and that why it has an advantage when you have a lot of confounders and only one -- and very few outcomes. This situation is different because

you've got plenty of outcomes, but that's when it's mostly useful. So you're reducing it to one exposure.

You then can add other variables -- then you model the outcome with the exposure in the model and the propensity score in the model, and you can add variables in the model as well. Then what this did is you can control for the propensity score analytically by stratification or modeling, or by matching -- with this here, they did matching, and then this is analysis paying attention to or ignoring that matching. And, again, it didn't make much of a difference, as you'd expect.

But all of it goes back to your primary question, which is propensity scores are just another way of controlling for confounding, and if you haven't measured the right variables, you haven't controlled for the confounding.

DR. PACKER: Okay. Thank you very, very much. We'll move forward. By the way, I really recommend everyone who does this, I would not run a dating service because the math -- never mind. I'm

really glad I'm not on the record for that. I'm on the unmatched -- yes, I would be an outlier, for sure.

Open Public Hearing

DR. PACKER: We're going to go to the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes 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 might have with the sponsor, its product, or, 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 this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in 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 this 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.

Our first speaker in the open public hearing

is Dr. Barry Goldberg.

DR. GOLDBERG: As I see who I am, I have no financial involvement. Nobody's paying for me. I own no stock in companies. Are we working with essentially all the agents under grants, NCI grants and other grants, my whole group? The answer is yes.

What I want to talk about, maybe a little refreshing, is not cardiac, but I think that's an important aspect of where ultrasound contrast agents are going. They're being used around the world. Right now, unfortunately, the United States, we only have CT, which is, by the way, ionizing radiation and MR, which can cause some kidney problems. It's being used, and this is something we want to discuss.

What is it being used for? This list, I'm sure isn't complete: tumor detection, characterization of disease staging, treatment guidance, serum monitoring, et cetera. Right now, this is what we have. We have MR and CT. We can compare and make diagnoses by injecting a contrast

agent, by the way, quite large volumes of contrast agent if you're talking about the iodine agents. And as a radiologist, we deal with reactions in these areas, unfortunately, all the time.

With contrast ultrasound, there are guidelines established, and the I think exciting thing that we have an advantage just like arteriography, it's real-time agent. And I just wanted to show you what we do in our research studies and in clinical studies around the world. This shows contrast. You can hardly see a mass here, and here with contrast, you can see that mass very clearly.

So there are established guidelines. We can distinguish, just like CT and MR, hemangiomas with certain characteristics. I'm not going to teach you this now. Focal and nodular hyperplasias, so benign lesions have characteristics. And, in fact, if you note the characteristics of CT and MR, you are already are 90 percent of the way making diagnosis with ultrasound; with hepatocellular carcinoma, typical patterns that can be seen.

Without contrast, just like without CT with MR contrast, you really don't have the important information. With ultrasound, you can do it at the bedside. You can do it in the emergency room, and it can be done quite rapidly as outpatient or inpatient. And this is what is happening in many parts of the world. When I say many of the world, from China to Europe to Canada to Latin America and so on.

It isn't just liver masses. This looks like two cysts in the kidney. When we gave contrast and contrast appears as white, these are all abnormal vascularity, and this was a tumor.

This was another case of breast cancer, and, again, we're using it under grant situations, and it's being clinically around the world. They show a mass here, and these are all tumor vessels. So you can quite easily confirm and actually see effects of treatment.

Guidance. This is something that has being used to guide needles into lesions but then to monitor the effectiveness. With CT and MR, you

need to do it not at the time. We can go into the operating room and quite easily do it. And here's an example actually looking at a tumor. Contrast is given. You see all this contrast. It's all viable tissue. You start treating, but we left part of the tumor here. And here it is completely gone.

So rapidity of treatment, even things that -- we just completed a grant, NIH grant, looking at lymph nodes five years, and we can show lymph nodes around tumors, in this case melanoma, in animal models, about 20 percent more accurate than the radioactive iodine. And if you have a lot of tumor, the tumor destroys the normal nodes, nodes as small as a few millimeters.

Even simple things, looking at areas of alteration in plaque -- the white, remember, is the contrast -- or here was a graft, but these arrows are pointing to leakage of contrast in the aneurysm, a very quick diagnosis.

In fact, I started doing ultrasound in 1970 after I read the first article in 1968 by Ray

Gramiak, a radiologist here in the United States, and Dr. Pandya, a cardiologist, and have been looking at all these things. And, of course, these things are accepted here. In Latin America, we see the pancreas, so looking at organ transplants. And you can actually look at time intensity curves and see perfusion.

Why is that important? Well, here is a case where we look at inflammatory bowel disease. We see thick bowel under normal circumstances, but here we can see the vessels and the increased contrast. Right now, you have to have essentially invasive procedures to make these diagnoses. But this is being done in Canada. Here's a thick wall bowel, and here's -- all this is contrast, so you can easily diagnose and see the effect of treatment noninvasively.

So when you talk about complications and death rates, you have to look at what are the complications and death rates from doing endoscopic, of course, using iodine with its reactions and then the effect of radiation long-

term in cancer, even thing as trauma, trauma from the emergency room, on the battlefield, wherever.

Here, very quickly, there is an area of irregularity, but you can't make a diagnosis. Contrast, this is the area of the hematoma, easily diagnosed within seconds. Remember, this is a blood pool agent, circulates even here.

Splenic trauma. Here's what it looks like on CT, beautiful. Here's what it looks like on ultrasound. This was done in a few minutes at the bedside. Here, the patient had to be moved, and in many cases, it can be difficult and delay diagnosis and treatment; perhaps hinted at in these earlier studies where we've seen statistically improved results when you know the results of the contrast.

Where are we going? There's a lot of work being done in the future on dissolving clot, on putting antibodies or other agents into tumors, and that's an exciting new area. So ultrasound contrasts right now are only approved for cardiac indication in the United States. They're approved for multiple indications in numerous other

countries. In fact, some of my friends around the world make fun of me and the United States as a third-world country when it comes to contrast. You cite examples of cases of people's lives being affected in a positive way or saved. And it's just a little bit depressing, certainly from a radiologist's point of view, to look at all these things that are being done -- by the way, at minimal, less cost than an MR and CT, no ionizing radiation, no long-term effects on kidneys because, as we heard, it's evaporated through the lungs.

What we're hoping for are contrast agents as an alternative to imaging modalities, safety concerns, renal toxicity, and cost containment. I know the FDA has been asked to try to reduce the amount of radiation exposure to the public. And I was at an FDA meeting in the past a number of times, and the question was, is ultrasound ionizing? It's nonionizing.

So from a non-cardiologist, although Ray Gramiak once told me for a radiologist, I'm not such a bad guy, and so did Harvey Feigenbaum, for

those who know Harvey. And I think from the AIUM, our national ultrasound society, the American College of Radiology representing radiologists here in this country, that we are strongly supportive of what is going on with the cardiology results, and we're looking forward to having a chance to use this and having an effect on patients' outcome.

I believe I kept to my time, leaving time hopefully for some questions, or maybe I answered everything. Thank you.

DR. PACKER: Thank you very, very much.

We'll go on to the next presentation, and that's Dr. Paul Grayburn.

DR. GRAYBURN: Thank you, Dr. Packer.

I'm here today to kind of, if I can, get the focus back to the main question of the day, which is it justified to have a black box warning on ultrasound contrast agents in the United States. And I'm here to represent ICUS, which is the International Contrast Ultrasound Society.

This is me. I'm an ICUS board member. I have a lot of activities that involve me in

peer-reviewed studies, and so I'm interested in all of your comments about the studies today. But I want to really get back more to the clinical question because ICUS is really a clinically-based organization. It's a multidisciplinary medical society that was founded when the black box warning came out, and it was grassroots group of physicians who got together and said this is not right, this is hurting our patients. And we came to the FDA. They were wonderfully responsive to us and modified the black box warning. And so we really maintained that patient care focus in this organization.

Now, you've kind of heard much of this already. After the black box warning came out in 2007, a number of studies have been done that you've seen showing that these agents are safe. They improve the accuracy of diagnosis, and they change patient management. There's an overall positive risk-benefit ratio. The boxed warnings chill the use of these agents and negatively impact the care of our patients.

The ACC, AHA and ASE guidelines for echo in

2003 pointed out that echo agents may improve the diagnosis of free wall rupture and identifying intracardiac thrombus.

You've already seen cases of this. This is a thrombus which on the left looks like a mural thrombus; on the right, it's hanging by a stalk. And the doctors that wrote this case report in circulation a couple of years ago elected not to put this patient on anticoagulants fearing it would dissolve the stalk and cause an embolization. Instead, they sent them to surgery and had this removed. It's a big change in management.

You've already seen a couple of cases of LV pseudoaneurysm today. This is a life-threatening disease, not apparent on the left, obvious on the right by the arrow. And this points out something that we haven't really talked about today, and that is that there is a risk to not using ultrasound contrast agents. This patient's life was saved by going to urgent surgery. This patient likely would have died had the diagnosis not been made and he continued to sit in an ICU with an unrecognized

rupture of his free wall.

Now, just to carry that story a little bit further, according to the ACC, AHA guidelines, there's a half a million STEMIs every year in the United States. One to 6 percent have rupture. They may die immediately, or they may form a pseudoaneurysm. And if they do, treatment is immediate surgery. We know that 2-D echo without contrast only picks up 26 percent of those. Contrast is diagnostic.

So really, if there's only 5,000 patients a year that have a pseudoaneurysm and we pick up three-fourths of those with contrast, that's 3750 patients whose lives could be saved every year. Now, compare that to 1 out of a million patients who died temporally after an Optison administration, and you can see that the risk-benefit ratio is obvious here. There's no clinical equipoise. We don't need to do a randomized trial.

ICAL, which is the commission that accredits echo labs, has come out now and said that contrast

is mandatory. It is standard of care for doing modern echocardiography. And so now we have a kind of conflict between agencies that accredit and say you have to do this and agencies that are saying, well, you have to have a black box warning on these agents.

You've already seen this paper from Kurt, so I don't want to spend too much time on it. But as you have already seen in the SICU, two-thirds of patients either had a procedure canceled, a procedure that could be dangerous to the patient, or had medications changed. So these agents do impact management. And further on in this study, there was a cost savings basically tied to the elimination of downstream testing.

You've seen this slide from Khawaja that Bill Roberts and I published in the American Journal of Cardiology, showing that overall in the meta-analysis there is a tendency, a strong tendency, for these agents to reduce mortality. This is 5 million patients. This is real-world experience, 5 million patients getting an echo,

211,000 of them having contrast. If there were a signal here that contrast agents were so unsafe that we have to put a black box warning on them, that signal would show up.

In the same study, you see that the incidence of allergic or anaphylactoid reactions is there. It's small, 1 in 10,000. It is there, and we're prepared to deal with those. We have epi pen kits on our echo machines, and all of our sonographers are trained and know what to do.

This is the ASE registry that you've also seen showing no signal here. Again, Kevin Wei published this paper and said, "The incidence of severe adverse reactions to ultrasound contrast agents is lower than or similar to that reported for other contrast agents used for other cardiac imaging tests."

I'm one of the few echo people in the world who is an interventionalist and does cath all the time, and I inject contrast agents down the coronary arteries of my patients, and there is no black box warnings on those agents, even though

they have similar risk profiles.

We know about these risks of allergic reactions, as I've said, so I'm going to skip that, and I want to just close with two slides here.

This is the MMR vaccine, measles, mumps, rubella, that our children are mandated to have. It carries substantial mild risks, fever in 1 out of 6 people. But look down at the bottom. It can cause deafness, long-term seizures, coma or lowered consciousness, or permanent brain damage in children. There's no black box warning on this. I'm not saying there should be. I'm just pointing out the obvious disparity between ultrasound contrast agents and vaccines.

Look at this statement which comes off the CDC website. Down at the bottom of that, near to the last paragraph, it says, "This happens so rarely. Experts cannot be sure whether they are caused by the vaccine or not." And that's the case with these contrast agents. We're looking at events that occur in one out of a million patients. And even if we say let's use a logarithmic scale

and make it out one of 100,000 to one out of a million, there are rare events, and we're not going to be able to study them adequately, as you guys know better than I do, being clinical trialists and statisticians.

This is the use of agents. In the purple bar, you see stress, and the green bar is rest. And then the total, 2005, 2006, and then it dropped off like a rock after the black box warning came out. You've already heard from Dr. Goldberg about some of these exciting applications that are available, some unfortunately in other countries, which is a disservice to American patients. Myocardial perfusion imaging works well. I'm not going to go into that. But I would like to summarize ICUS' position on this controversy.

These ultrasound contrast agents are safe. The black box warning is not justified by the data or by clinical experience. These agents benefit patients by improving the accuracy of diagnosis. Failure to use contrast in appropriate patients increases the risk and expense of a misdiagnosis or

alternative testing that is done that doesn't have to be done.

The FDA black box warning decreased the use of contrast, despite the guidelines and accreditation standards saying that this is standard of care to use it. And so we believe that the FDA should remove the black box warning in the interest of the public health and the interest of our patients that we serve every day.

Thank you very much for your attention.

DR. PACKER: Thank you very much.

The final comment is from Dr. James Thomas, who will have only five minutes because he signed up past the deadline.

DR. THOMAS: And I will speak quickly. Thank you very much for the opportunity.

As president-elect of the American Society of Echo, or ASE, I'm pleased to have the opportunity to provide the comments to the advisory committees regarding the safety and clinical utility of these contrast agents. I have no financial interest with any of the companies and

neither my time nor travel was supported by any of them.

ASE is an organization of approximately 14,000 physicians, cardiac sonographers and other professions committed to excellence in cardiovascular ultrasound and its application to patient care. ASE supports its mission through education, advocacy, research, innovation and service to our members and the public.

ASE strongly supports the use of ultrasound contrast agents in clinical practice for several reasons. These agents assist physicians in maximizing the accuracy of information obtained from echocardiograms and thus optimizing patient care. Several studies have shown the clinical utility of contrast administration in improving the accuracy of echocardiographic studies in technically difficult patients, as you've heard today.

In addition, the appropriate use of contrast is cost effective since the improved accuracy in difficult-to-image patients impacts their

management and decreases downstream utilization of more invasive and more costly procedures. As you've seen, the impact of contrast on patient management has been shown recently to be highest in critically ill patients.

ASE believes that while these agents are generally safe and well tolerated, it is important for the clinical community to remain vigilant in monitoring and documenting any unexpected reactions. Any pattern of unanticipated reaction should be carefully studied on a prospective basis.

However, as we have previously relayed to the FDA, we felt that the safety profile of these agents did not justify the initial black box warning that was imposed on these agents in October 2007. In this regard, the black box warning affected in large measure populations in whom administration of contrast is especially useful for patient management such as critically ill patients in ICUs. For these reasons, we very much appreciate your willingness to reverse some of the warnings in May 2008.

Unfortunately, the negative effects of the black box warning still linger. Several institutions have decided to stop using contrast altogether, a situation that has persisted despite the new label, resulting in non-diagnostic echoes and the need for additional more invasive and expensive testing. However, additional evidence about the safety of contrast has subsequently become available, and I must say, I have been very reassured by what I have heard today from the various trials reported.

We urge the community and industry to collect the safety data necessary for FDA's review to further limit and hopefully eliminate the remaining warnings pertaining to pulmonary hypertension and unstable cardiopulmonary conditions.

We also urge the agency to look not only to the past but also to the future in assessing ultrasound contrast agents. Practicing physicians use ultrasound contrast agents for a number of indications beyond those currently approved by the

FDA, including, among others, stress echo, vascular imaging and myocardial perfusion imaging. The administration of contrast for these and other indications is supported by numerous studies, and ASE believes that echocardic contrast agents have broad applications beyond those currently approved.

We encourage the companies that manufacture these agents to perform adequate and well controlled clinical trials to seek the agency's approval for additional applications expeditiously. Moreover, scientists who are affiliated with ASE and others are performing research on additional applications of echo contrast agents that could have major impact on patient management in the future. These include molecular imaging, gene and drug delivery, and sonothrombolysis, among others.

The society encourages these scientists and any company interested in developing these applications commercially to seek advice from the FDA early in the product development process to facilitate the transition from the benchtop research laboratory into the bedside clinical

practice.

Finally, the ASE appreciates the opportunity to have an open dialogue with the FDA regarding the safety and clinical utility of ultrasound contrast agents. We are grateful to be provided the opportunity to offer these comments and hope that both the agency and industry will call open us as consideration is given to further narrowing the current contraindications for these agents and as new and exciting applications for these products are explored in the future. We look forward to ongoing discussions, both formal and informal, with the agency, industry stakeholders and others to bring the clinical benefits of ultrasound contrast agents to full fruition.

Thank you very much.

Questions to the Committee

DR. PACKER: Thank you very much, Dr. Thomas.

The open public hearing portion of this meeting is now concluded. We will no longer take comments from the audience. The committee will now

turn its attention to address the task at hand, which is the careful consideration of the data before the committee as well as the public comments.

I'll ask the committee to turn to the questions which have been distributed from FDA to us. I'm not going to read the prologue. Everyone can do that for themselves. The most important part of this is that the FDA is not seeking advice on the approval of these drugs. That is not the question at hand. The question at hand is what the new studies mean, how they should be interpreted, whether or not they should be incorporated into labeling. There will be no voting. So this is a labeling discussion based on the new data that we heard about today.

I'm going to take the questions in the following order. Let me just remind everyone that we have discussed many of these questions already in great detail. There is no need for anyone on this committee to necessarily reiterate what they have said. Remember, the FDA has been listening

the whole day. They don't just start listening at the beginning of the discussion period. And, therefore, everything that you have said before is going to be incorporated into their thinking.

I want to begin with question number 3. The Definity and Optison retrospective observational cohort studies were similar in design and different in other ways. However, unlike the Optison study, the Definity study suggested that patients receiving contrast had a lower mortality. Discuss the appropriateness of the study design, including the time period studied in relationship to the time of approval of safety labeling changes discussed above. Discuss the apparent lack of consistency in the results between the studies. Does this inconsistency raise questions about the robustness and clinical meaningfulness of the study results?

As we talk about this point, I am going to ask the committee to consider question number 1 as well because, remember, question number 1 relates to when the FDA sees something going on in spontaneous adverse event reporting, the FDA feels

that there is a need for clarification because the spontaneous adverse event reports are very hard to interpret. There's no control group. The background rate is unknown. Very often, these happen in patients with tremendous number of comorbid conditions, which may or may not contribute to the rates that are observed. The reporting rates can be stimulated by noise in the community, public interest. So, frequently, they go to the sponsor, and they say please provide us with more data.

The options available to a sponsor are, in fact, not infinite. In general, sponsors will try to obtain more data by doing some kind of observational study, cohort study, case control study, something that can generate an adequate control group which was missing in the analysis of the spontaneous adverse event reports; so that the FDA frequently gets protocols, not all of that dissimilar to the protocols that you saw that the sponsor presented to FDA, and the FDA and the sponsor sit down and they discuss them in good

faith. And they think, well, okay, at least this will move the process forward.

Now you see that -- fast forward two years, three years. We get to enjoy a whole day looking at the results of these studies. And we want to find out whether the ball has really moved forward as a result of these observational studies. The FDA and the sponsor said absolutely, we'll get you some more data, and they got more data.

Ralph, what do we make from all of these data that we have heard today?

DR. D'AGOSTINO: Starting off with the idea of observational studies, I don't see how we can exclude observational studies for the safety issue. You have an approved product. You can say put a clinical trial together, and even that would turn out to be an observational study because the products are out there.

So I think observational studies are extremely important, and I think the retrospective aspect, the retrospective studies in some sense were sometimes better than the registries because

the registries are culling out only the ones who are developing things, and they're done in vacuum. So this mixture of cohort studies and retrospective studies, I think is a reasonable way to go.

I think the difficulties that I'm facing with the material that was presented before us is the study designs really aren't laid out for us. So we don't know really how the studies were put together. We have this matching. We have the propensity scores which I kind of think is a reasonable thing to do. My son's written papers on it, not me, so I'm not being attacked if you dislike propensity scores.

But propensity scores are a sensible way to try to address the problem. The difficulty that comes up in the particulars of this dataset is we're not really sure what is being measured. The time period overlaps with the black box warning, so we don't know if things are changed. The baseline data, we don't know what that really means. The timing of the contrast exam, we don't know how that affects the outcome variable. So we have a whole

series -- and I'm not going to reiterate anymore. We have a whole series of questions which makes our interpretation of this dataset very hard and cumbersome and not clear. And it's very easy to imagine manipulating or thinking about some of the faults, and we find that the Definity study doesn't look as good as it seems to be. The other study is showing us there's a possibility that there still is a risk.

So we're left, I think, with two studies that don't give us clear indications. They give us lots of data, and if there was some broad, broad signal, maybe we would definitely see it. But we have lots of data, and trying to say here's a definitive answer on the Definity study, I just don't think we can do it. But, again, back to the role of observational studies, I think it's very important, and the question is you need clearer designs.

Now, Jim keeps talking about maybe that data's there and we can get more out of the data, but it sounds like as we talk more that it's a lost

cause. We don't know how -- we'll never retrieve the baseline. We'll never retrieve timing. And so we just have these data analyses that are leaving us, I think, with an uncomfortable feeling.

I tried to rush that. Do you want me to say more? I can say more and more.

DR. PACKER: Well, we may ask you to do that, Ralph, but you can at least catch your breath.

I don't think that there's anybody on the committee that thinks that we should vote to abolish observational studies. That's not going to happen. And in this domain, they're the only way to get information that can move the process forward. And the issue about what the differences are between an observational study and a randomized trial, we don't have to review because everyone knows there are differences.

The question is to what degree these observational studies, done the way they were in the manner that they actually helped to move the process forward -- and there is -- everyone has

already said all of the concerns that they have about this. The question is, are these concerns sufficiently great that we are left with a lot of precision but not a lot of interpretability? In other words, we have a precise but not necessarily unbiased estimate.

DR. D'AGOSTINO: Let me just add my two cents to that. As I think with the Definity study, we cannot make a conclusion that the contrast has, in fact, improved survival. And I just don't think there's any way that you can pull that out. Whether or not it's carrying a big burden, I don't think the data indicates that it's carrying a big excess burden.

With the other study, I think what we're left with is that we don't know if there's a burden being there. We found confidence intervals that cover one, but that upper limit of the confidence interval is large enough to keep our concern going.

DR. PACKER: There's a principle in epidemiology, particularly when it comes to observational studies. In contrast to randomized

trials, it's not so unusual when you live in the world of randomized trials and you have a unbelievably large and well done randomized trial to make a decision based on one trial. But in the world of observational studies, in general, no one makes a decision based on one observational study. You do a whole host of observational studies. They're done differently in different populations doing different methods, by different investigators, and you're looking for consistency and replicability of a finding in observational studies.

The thing that's so weird about this one is that we've got two, and they sort of go in opposite directions. And if you believe the confidence intervals, they don't overlap. And the last thing we have here is consistency between the two.

So, Brian?

DR. STROM: Yes, a bunch of comments. First, let me respond to what you just said, Ralph, and then add a couple.

There aren't two studies here. There's one

database. There are two approaches to the same database, and, in fact, there were two different analyses that gave different answers even of the first product. So I think it's important to clarify.

Also, just again in response to your comment, I would argue for clinical trials. You also don't want to go with just one. I think the difference between clinical trials in non-experimental studies is the issue of the size of the effect. When you're dealing with what epidemiologists consider a weak association, a relative risk of less than 2, it's easy to have it be created by subtle bias or confounding. It's not necessarily real, and certainly we're dealing with effects here that are of that size. So studies that are too big, you can have a very precise measurement of a wrong answer, and size doesn't make up for those issues.

Turning to Ralph's comments, I agree with almost everything he said, with two exceptions. One is I think these studies could have been done

better. I think the issues, for example, of baseline and timing could be addressed because --

DR. D'AGOSTINO: I said that.

DR. STROM: I thought you said that you didn't think baseline and timing could be addressed.

DR. D'AGOSTINO: No. I didn't think with the data we have and the presentation we have --

DR. STROM: Oh, got it. I misunderstood. Yes, with the data and presentation we have, we can't. But they easily, for example, could exclude the first day's data, the first day in the ICU, first day whatever, use that as baseline and then only look at the data from the second day onward for follow-up.

The other place I sort of disagree with Ralph a little bit in terms of focus is propensity scores, which I also agree are useful. I just don't agree they're useful for this and for here. And I think this is actually a classic demonstration of them being used wrongly, for a few ways.

Classic teaching in epidemiology is the only purpose of the modeling is to control for confounding. The only way you know whether you controlled for confounding is you look at the unadjusted versus adjusted results, which is what I kept asking about. And then if it differs, then you say what was the confounding variable, what was the change. You can't do that in propensity scores.

So when you do hypothesis testing, in general, propensity scores, which clearly have their place, is an inferior approach. It also has a statistical problem except when you have lots of variables per outcome, lots of confounders per outcome. And here there were plenty of outcomes.

The trouble with propensity scores, it's sort of a black box. It doesn't let you understand your data and understand your findings and do the post hoc analyses to really understand it. A lot of what we're all grappling with is what does this mean given the absent results -- given the discordant results and could it be differences in

the confounders and so on.

The other thing you can't do with propensity scores here is compare the two products and a control, especially controlling for year, calendar year, with the changes of care over year because you're -- again, you could add year to the model, but is it important, isn't it?

So what they should do is -- I do think there's something doable that we haven't seen, which is going back to the raw data here from Premier and doing a straightforward unadjusted/adjusted analysis with three study groups, each of the two exposures and the unexposed group, where there isn't an issue of the control group changing in the two analyses because of the same control group, and you adjust for it using logistic regression in the classic ways. And you'd have an answer. It would never, though, address the questions of is there a selection bias here, that the people who are getting the contrast agent are different from the people who don't get a contrast agent.

DR. PACKER: Ralph?

DR. D'AGOSTINO: Just a quick –

DR. STROM: There's no rebuttal here.

[Laughter.]

DR. D'AGOSTINO: No, no. Just a quick response. I think we were again saying, a number of us, what is the unconditional type result? What would you get if you just looked at this data, I think we were saying, and I agree 100 percent.

Usually, in my experience and a lot of experience, when we do that, we see differences, but then we say, "My God, the populations are so different," and the propensity score starts honing in on the differences. And there's a lot of theory, the difficulties you get, which is the sort of covariate adjustment.

So I think the thing that we were just hearing, if we went back to the original database, did some kind of unadjusted analysis but ultimately getting into how do you look at these three groups, that is the real key that we're missing completely and how do you bring in the time and then the

questions that we were bringing around the table here. And we just don't have any way of looking at this database and sorting out what has happened with this more careful analysis.

DR. PACKER: Michael?

DR. PROSCHAN: Yes, it's interesting because there was discussion about wanting to have observational studies that are consistent, and this meta-analysis came up several times, this meta-analysis of observational studies. And I think that's the picture of inconsistency in the sense that -- I mean, the largest trial -- if you look at that, the largest trial is showing virtually no effect. And yet it's not getting a big percentage of the weight, and that's because it's a random effects analysis.

So I think sort of this meta-analysis is a microcosm of what we're dealing with in terms of inconsistency. And I think that -- I also think that it's highly likely that this meta-analysis was not done correctly because it's very difficult to do a random effects meta-analysis correctly when

you only have a few studies. The standard method is based on more studies than that. So I think it's quite likely that this isn't done correctly.

DR. PACKER: Okay. Jim, I'm going to ask you to chime in because we're overweight in terms of statisticians and epidemiologists here and underweight on this side. So we might as well complete the --

DR. NEATON: Get it over with.

DR. PACKER: Might as well get it over with, right.

DR. NEATON: Well, the comments I think have all kind of hit the nail on the head. To me, I think it would be very interesting to go back to the same database and in comparable populations to compare both products. And so we have a difference, it appears, that I worry about could be due to the populations.

So if I'm going into an ICU where already the underlying risk of the population is high, it may be harder to detect a signal than if I go into another population where the risk is lower and a

modest toxic effect could manifest itself. That's kind of what I worry about.

So I think going back to this database was a good idea. Hopefully, when it goes back again, you write a protocol, and we can have some of the discussion and the answers to the questions we had here today. But why not do a kind of parallel analysis with both agents?

DR. PACKER: It's like the two companies should probably cooperate on this, maybe?

DR. NEATON: I think an ideal situation would be that a third party works with Premier and designs a study comparing both agents and perhaps a couple different populations with a kind of breadth of risk.

DR. PACKER: Ralph?

DR. D'AGOSTINO: They should pay for the study, but it should be done completely independent of them, obviously.

DR. PACKER: Okay. Let me ask a question in the following way. Brian corrected me, and it was a very important correction. There aren't two

different studies here. There's one database. There are two companies that went in and used different approaches. No one says the database is perfect, and no one says the approaches are perfect. The two companies went in, used two different approaches, and got two different non-overlapping results.

Does anybody in the committee think that the risk, if any, of these two agents is different from each other?

DR. PROSCHAN: I don't think we can tell.

DR. PACKER: No, no, it's fine.

DR. PROSCHAN: I mean, it's possible that they are.

DR. PACKER: That was actually my question. I'm perfectly okay with we can't tell, but I don't see anyone who thinks that the data that they have, the two approaches that they have, got an answer sufficiently unbiased and unconfounded that anyone can rely on the point estimates and the confidence intervals to suggest that the two agents are different.

Is that good enough?

DR. PROSCHAN: Agreed.

DR. PACKER: Okay.

DR. STROM: Again, it's not the confounding; it's the issue, different designs.

DR. PACKER: It's different designs, different approaches, even different bias of the survivor effect because of the populations that were studied. So it sounds to me -- I just want to make sure -- that because neither design -- no one is saying that one approach was better than the other approach; that neither approach was adequate to yield a point estimate and confidence intervals that one can feel comfortable represents the effect of the agent in this population on all-cause mortality. I think that's the consensus. Okay?

[Affirmative nods.]

DR. PACKER: Good.

We're going to just move this forward.

Mike? No? Mike Weber? No? Okay.

Peter?

DR. KABOLI: Thank you. So I'm going to

predicate my comments with the fact that I'm a clinician. I see patients as a hospitalist. But I'm also a researcher who does observational studies, and I understand the limitations of both. I understand that there are no definitives, and I would love to have a definitive answer. But I've found that I once even thought a patient was dead, and they weren't dead yet. And so even death is not always definitive.

DR. PACKER: That's a classification issue, not a design issue, right?

[Laughter.]

DR. KABOLI: Yes, it was an observer bias issue.

DR. PACKER: Yes, it's observer bias, very common.

DR. KABOLI: But I think the point is, is that it went through a process here that was decided on in 2008 using the data that was available, plus using a registry, plus using other sources, and said, "Well, what is really the signal here?" And I don't get a sense that the signal

here is showing that there is definitive harm to patients consistently.

DR. PACKER: That's a very important point, but keep on going because what we have to do is now sort of go back -- the observational studies don't help us very much, but you say you can still learn something from them?

DR. KABOLI: I can. I mean, we can lock the statisticians in a room for a week, and then in the end, I don't think they're going to agree as to whether this was an adequate design with the data that they had. I think the people that did the analyses -- at least all the analyses I've ever done, you don't look at it just one single way. I'm sure these people that did this looked at it multiple ways to try come up with what was the best answer.

I find the results are actually reassuring, that if there's a signal here, I'm not too -- I don't feel like they missed it. Plus I think the issue of -- as I read all the materials ahead of time, the thing that kept coming to me is that I

think there's an underlying risk of anaphylaxis as there is with most drugs that we give to people. The thing about the risk of anaphylaxis is that you can't account for that in any sort of propensity model because it's unpredictable. You cannot come up with variables that are going to predict who's going to have anaphylaxis. So you can do all the propensity matching you want, and I don't think we'll ever come up as to whether that factor can be put into the model, and that the rate --

I mean, the rate is probably somewhere between 1 in 10,000 and 1 in 50,000 from consistently what people have been saying. And as I look at other drugs that we don't have black box warnings on, they'll have that rate or even higher, and we don't have a black box warning that says there's an anaphylaxis risk and, therefore, it should have a black box warning.

So I sort of feel like they did the studies, the FDA did them independently, and I'm really failing to see a great risk here that warrants this sort of restriction. And I know we're not quite to

that question yet.

DR. PACKER: But we're getting there.

DR. KABOLI: But nobody else has not put in their opinion, so I threw my opinion in there.

DR. PACKER: And we're moving that forward.

Sanjay?

DR. SANJAY KAUL: At the risk of sounding like a statistician, all models are wrong and some may be more useful. And it's not clear to me if the propensity score model utilized by the sponsors or the FDA was useful in adding greater clarity or confusion.

If you have results that are sensitive to your differences in design and differences in the way you approach them, it speaks to the weakness of the evidence. The evidence is not sufficient enough to inform any judgment, whether it's adverse or beneficial, both in terms of the quality as well as the quantity of evidence, even if you look at the point estimates. And from observational datasets, odds ratio of 1.5 to 2, I don't know how to interpret them. I mean, can we draw any

reliable inferences from that?

You talked about unpredictable adverse events. That's the situation where I think observational trials have a greater role to play because the confounding by indication, which is a critical limitation for assessment of efficacy, is the Achilles heel. And that's why we do the randomization studies, but that is because the treatment effect is known and predictable. But when you have an unknown, unpredictable adverse event, I think observational trials are quite useful.

DR. PACKER: By the way, they're observational studies. It's a small point. It's hard to do an observation trial. Trial sort of implies something, so observational trials randomized --

DR. SANJAY KAUL: Right. So in regards to that, I think it would have been critical -- at least to me, it would have been interesting to see what the impact would have been of pre-warning and post-warning. Pre-warning observational datasets,

this was totally unexpected and not predictable. And post-warning, this was somewhat predictable and see what would have been the impact.

I would also have liked to see more objective information on utilization and whether the reduced utilization, if we believe that, led to adverse treatment decisions.

So I think this should have been an online effort to collect the data, and there's no reason why it cannot be done now.

DR. PACKER: Hold on. One second. I just want to make sure that we're doing this in an organized way.

Henry?

DR. BLACK: I also want to talk as someone who's not a statistician, would never pretend to be one, but is a clinician and not an echocardiographer. I think the question is really whether the black box warning was justified.

DR. PACKER: That's not what we're discussing now.

DR. BLACK: Well, that's what I want to talk

about.

DR. PACKER: Well, then hold that.

DR. BLACK: And I have another question that's a corollary to that, which you can get to later on, is whether or not taking it away would change anything. And I think we have seen lots of information from our outsiders on how much they think it's affected things, and I wonder whether other people think it as well.

DR. PACKER: Can you hold that one second?

Stu?

DR. RICH: Again, these are comments, but I want to dovetail it to what Peter said, because as a clinical cardiologist, I want to raise a couple other sensitivities.

I think our decision is a risk-benefit, not just risk alone, and no one is taking about benefit. The benefit --

DR. PACKER: No, no. Our decision has -- a risk-benefit is a decision based on approval. Okay? That's risk-benefit.

DR. RICH: Yes, but --

DR. PACKER: Let me clarify.

DR. RICH: Okay?

DR. PACKER: Okay? The efficacy of these agents is not in doubt and not under discussion. The future looks unbelievably promising. The advocacy enthusiasm of those who use it and rely on it is clear and very sincere. That is not the point. The point really is whether there is a problem here that people ought to know -- ought to be aware of and how that should be reflected in the labeling, period.

You can have ACE inhibitors that reduce mortality but they still cause angioedema. You still put a black box in the ACE inhibitor label because it causes angioedema. That has nothing to do with risk-benefit.

DR. RICH: Well, I do think that the potential benefit does impact our judgment here. If there was no value to these agents at all, then no risk is even acceptable.

DR. PACKER: But then we wouldn't be having this discussion. It would be pulled, and we could

have spent the day at home.

DR. RICH: But the benefit side has been limited to storytelling. We've not seen any hard data, so it's going to be really hard to know about that.

The other thing I just want to point out is that the use of this is very different than a physician prescribing a drug. I think typically -- and I'm not an echocardiographer -- there is a physician order given to echo labs that the technician can often make the judgment to use it when the image is poor. And it's often a hospital decision through hospital risk management to say we don't care, we're not using it anymore, forget clinical judgment, forget patient situations, forget how it can help because of the liability issues.

So it makes this a little different than if this were a drug which we're talking about a black box warning because I think the impact here -- I use contrast agents with black box warnings because I know what the indication is, I know what the risk

is, and I know what the benefit is, and I know what I'm doing here.

But I think this does fall a little bit in a unique kind of situation as to the forces that affect its use, and it may be very important in the observational studies as well because who knows which institutions were impacted by a hospital decision as opposed to a physician decision over its use?

DR. PACKER: Mike, you look like you had a comment.

DR. WEBER: No. I just wanted to add to Stuart's comment that, in fact, there really is -- we really are talking about a risk-benefit, not of the drug or the treatment, but of the black box. And the big question we're going to ask, is the black box doing more harm than good, right? Will removing the black box --

DR. RICH: He doesn't agree.

DR. WEBER: Oh, I think it -- don't say he doesn't agree. Milt agrees with everything that is reasonable.

The point is, what we're going to be talking about in a minute and what Henry wanted to bring up, when we do discuss the black box, we're going to ask if we remove the black box, will it allow more people to get access to a treatment that is going to improve their outcome. So we will be discussing that.

DR. PACKER: Let me see if I can understand this. There's a kid in ninth grade who is taking an English class. The teacher wants him to complete an English assignment that illustrates his knowledge of the subject. They really want to make sure that the composition that this kid hands in actually shows that he read the material, could interpret it, analyze it, and create a robust presentation in a composition.

The kid doesn't do any of that, but he hands in a composition which falls short of all of the endpoints and all of the metrics and really doesn't result in a composition which is interpretable. But, boy, he worked really hard on it and really worked for hours and days. And, you know, he's a

really good kid from a really good family.

So what grade should this kid get? Didn't yield an interpretable composition, but he's such -- he tried so hard, and he's such a good kid.

What do you think? Do you say go back and do it again? Do you say it's good enough for government work?

[Laughter.]

DR. PACKER: Do you say --

DR. WEBER: No. You say at any given moment, you have to make the best possible decision based on what you have much as you wish you had a great deal more upon which to base your decision. And that's the situation we're in this afternoon, right?

DR. PACKER: That's the situation we face every moment of every day.

DR. WEBER: So it's not the kid, whether we should give him an A or a D or whatever he might --

DR. PACKER: No. That is exactly the question. That analogy is precisely the situation

that we're in because we've gotten the sense that these data are not terribly interpretable.

DR. WEBER: Agreed.

DR. PACKER: And we've also gotten the message that this is a really useful thing to do, it's a really helpful diagnostic tool. But these observational studies don't help us very much in assessing the safety of it. So the analogy with the kid in eighth grade is an appropriate one. And I said eighth grade. He was in seventh grade, I guess he got promoted.

DR. WEBER: You said ninth grade.

DR. PACKER: Ninth?

DR. WEBER: But in the end, Milt, we have to make some sort of a -- when we get to question 5, we're going to have to make a decision, bad and incomplete and inconclusive as these data are.

DR. PACKER: You absolutely do, and then you have to tell the FDA what the basis of that recommendation is, and we'll get there.

DR. WEBER: Okay. We will.

DR. PACKER: Okay.

Bray?

MS. PATRICK-LAKE: So going back to your ninth-grade analogy, I just wanted to say, to be fair to the companies, didn't they have meetings with the agency and didn't we know what we were going to get from them? Didn't somebody agree on a study design? So I'm confused as to why we're sitting here going, well, we can't interpret what we asked for.

DR. PACKER: Oh, Bray, what a great question.

Shaw, I'm going to -- can I put you on the spot?

DR. CHEN: I'll try to answer that.

You are right. You cannot vote the observational study out today. I was told by my superior that there would be a workshop, probably a conference on how to handle observational data, how to handle a positive signal and so on, I think, so we'll know better.

So the question today is how good is the observation data we have now. I heard there's some

problem with the design, but is that the best you can get practically? And if you improve those designs, how much more precise or improvement in data you get to help our decision? Are you going to get it from negative to positive? Is that possible?

So I think that's the practical issue we have to deal with.

DR. PACKER: Bray, let me, if I could, just try to address your question. Both sides went into this process in extraordinarily good faith. They both wanted to do the best thing they could to answer the question, but it isn't unusual, even though both sides go in -- it wasn't just the FDA that went in, in good faith, but all the sponsors went in, in good faith. No one went forward with the intent of creating a biased study design. So that's off the table.

But that doesn't mean that what is present is interpretable because there's a lot of times when you just are working with a database that can't give you the answers that you're looking for,

and you didn't know that before you began the process. So the relationship between the company and the FDA isn't a contractual relationship. It's a good faith, we'll go in, we'll see what we can learn. And, not infrequently -- they walk away with this sense of, well, despite the fact that we all did the best thing, and, of course, there are all these other recommendations as to what they could have done -- you still don't get interpretable data.

DR. FOX: Thanks, Mr. Chairman. Just a couple of comments. I'd like to go back to your earlier comment that the options available to sponsors are actually quite limited. And thank you for that because it's true, or at least I think it's true. And to me, the problem that we're grappling with here is about strength of evidence.

You made some -- and others have made some -- good observations about spontaneous reporting. There is no denominator other than sales numbers, which, as we know, are also open to interpretation.

As you also mentioned, spontaneous adverse event reports are influenced by the media in some cases, or by the activities of both proponents and opponents of a particular product or class of products. So we all love double-blind randomized-control trials, but if your events rates are very low, where as Dr. Kaul pointed out, the anticipated treatment effect or intervention effect, if you want to call it that, on a background event rate is itself very small, those clinical trials are undoable. They're just undoable.

So what's in the middle ground? In the middle ground are observational studies where at least you have a denominator. You can say, okay, in this database or that database, we've got 100,000 people or a million people or 5 million people or 10 million people.

The problem there is, especially with claims data, ICD-9 or ICD-10 codes, you don't have any clinical detail. You don't have any abstraction of charts to find out were those so-called events -- do they actually represent events,

clinical events. They represent somebody asked for payment for a clinical service delivered. It's not a clinical event. So it's an approximation of an observation of the truth.

So when I look at -- and then, of course, you've got the methodological issues we've been debating all day about one company designed their observational study one way and another company designed it a different way, on the same database, as people have pointed out, and got slightly different answers.

DR. PACKER: Not slightly.

DR. FOX: Well, I would call them slightly. And the reason why I say that is because it's a pseudo precision. Because these are ICD-9 claims data, I call that pseudo precision; they're not real events. And depending on how you want to dive into that database, you can pull out an answer.

So to Sanjay's point, if we don't know whether it's 1.1 or .7 or 1.5 relative risk, does that actually tell us anything? Probably not anything different from seeing 1.000, but if it

were 2.5 or 3.9 or .1, then you might have something.

So I'm just encouraging the committee not to put too much weight on the so-called precision of the point estimates and so forth that we saw but rather give the companies credit because you're not going to get a randomized clinical trial, ever, to tell us the truth about this.

DR. PACKER: No one is expecting or proposing a randomized trial.

DR. FOX: But that difficulty itself, I think, tells us some useful information, which is we are talking about very rare events even if they are quite serious or even fatal in their impact compared to the utility of the products we're talking about -- I think the comments of some of the other panel members are --

DR. PACKER: Let me see if I can get everyone to now move this out of the realm of their concerns about the validity of the observational studies and to their thought process about labeling. Why don't we do that?

Yes, of course?

DR. TATUM: I think Dr. Fox hit on something very important, and that is we're using databases that are based on billing, billing and utilization and not on the data that you need to actually do this. I don't know if the Medicare database is a better one, but I have used it in the past, and I find that there's more detail in there than there is in others, and there are other systems in the government that basically don't use billing data. But as long as it's billing data and ICD-9s, you're going to have a terrible time with observational data, picking out rare events.

One other small comment. The last one I was in that was interesting because it was actually a gadolinium safety question, and we saw in one of the studies that all the events were clustered. Now, that may not be true in this case, but in other cases, we need to be very observant of genetic, pharmacogenomic effects that actually cluster data. And they can be a real problem if you're trying to put together large observational

studies.

DR. PACKER: Brian?

DR. STROM: Let me just answer the question. Medicare is claims data; it's exactly the same. I think what's important to realize, though, is to the degree that you're looking at imprecise data, possibly invalid data, which is very much -- I very much share Jonathan's concern -- it will tend to bias toward the null. When you use these databases, you get increasingly valid -- you look at inpatient diagnoses instead of outpatient, you look at medical record diagnoses and so on, the associations go away from the null.

So that I think the issues here, yes, there are absolutely issues about validation of the data and using codes and so on, absolutely. But there's also weird design issues that it was done with a propensity score with matching and you change the matching and you get different answers. So it's not robust, and the trouble with the propensity score approach is you can't explore that robustness.

The beauty we had here, which was wonderful, is we had two different studies approaching it, so you could see that it wasn't robust. Normally, you wouldn't even see that in the propensity score study because you wouldn't have the second study getting different answers.

DR. PACKER: Okay. We'll do Ralph, Allan, Vandana and --

DR. D'AGOSTINO: I just wanted to make a couple of comments on things we've been saying. When I was mentioning, Peter, when Milt asked me to make my comments on the observational studies, I did say something very similar to yours, that if there was a big signal, there was something big going on, wouldn't we have seen it and so forth. And the more I think about it, maybe we wouldn't have seen it because we get rushed into a propensity score analysis that may have lost all of that in some sort of feel for the data. We don't have a feel for the raw data, so it's hard to make that judgment.

But I think it's a very important point,

that the data -- we're not seeing a big signal coming out of this here, and when we start culling it down, what are we actually looking for?

I wanted to make a mention of what Milt was saying about his grade school student.

DR. PACKER: Ninth grade.

DR. D'AGOSTINO: I always tell my students, my experience was, here's a question. Well, I can't answer this question. I'm not able to answer this question, but I'm really capable of answering this other question. And I think what we're doing is we're answering other questions, and I applaud you wanting to focus.

The other thing about the last comment, my experience with what the FDA says and what have you, there was a former director of cardio renal, which I won't mention his name, and we were in a similar circumstance. And he says, "Well, just because I made a mistake doesn't mean I'm going to live by it."

We have the data before us, and there are serious problems with it. So I think the way we're

looking at it is perfectly right.

DR. PACKER: Allan.

MR. COUKELL: Thank you. So spontaneous adverse event reporting is always unsatisfactory. On the other hand, these are reactions that seem to be closely temporally related to the administration of the drug, which is always given under highly supervised conditions, so it gives us some confidence that these things might be real.

How common are they? We don't know. We don't have the denominator, so you do observational studies to try and get at that. The observational studies have all the problems that we've spent time discussing today. Were these events much, much more common, even a badly designed observational study may have been able to come up with it more easily.

So one hypothesis is these reactions don't occur at all. The other is that they occur fairly rarely, and then you're stuck discussing what is it that clinicians should know and how should we tell them that, which I think gets you to where you want

to go, which is how should we tell them that.

It does seem that there was a dip in use after the black box warning. It's come back up. It also seems clear that these agents are going to be used in ever expanding settings by more and more people using them for the first time. It seems to me that you want them to know that there's this rare but potentially a very serious event.

DR. PACKER: Okay. Yes, please.

DR. SACHDEV: I'd like to put your analogy in a slightly different context. There are many students in the ninth grade class, and sometimes the assessment is based on a curve compared to other students. So when we get to question 5, I think we need to think about the other diagnostic contrast agents and look at the data that we have even though it's imprecise. We need to compare that to the other agents.

So we send someone for a cardiac cath, we're giving them contrast. What's the risk of anaphylaxis, what's the risk of other adverse events, and do we put black box warnings on those?

DR. PACKER: I have no idea whether iodinated agents have a black box warning.

Does anyone know?

DR. KRANTZ: Basically, when I looked it up, hypaque and visipaque, it doesn't seem like they have anything other than intrathecal use. So to me, it doesn't look like --

DR. PACKER: It doesn't look like that.

Okay. Let me just make a comment. This committee cannot be charged with -- nor can any division within FDA be charged with the responsibility for parity because can you imagine how we would drive ourselves crazy if we actually wanted to make sure that everything was fairly labeled and that you would -- I mean, we would spend the rest of our remaining days trying to do that with, by the way, no authority to do it whatsoever.

So the inequalities that exist in the labeling shouldn't bother you because that is a part of the history of drug development, and we can't fix it today. We can't.

MR. COUKELL: Could I make one quick follow-up that I forgot to make before?

DR. PACKER: Yes.

MR. COUKELL: You said before that we can't think about benefit, but as I read the FDA guidance on when to use a black box warning, it fairly specifically says an adverse reaction so serious in proportion to the potential benefit. So it does seem like you have to think about that, and were that not the case, every antineoplastic would have a black box warning.

DR. PACKER: Well, but ACE inhibitors have a black box warning, and they're a way to save lives in heart failure. I don't understand how to interpret that.

DR. PROSCHAN: Milt, as a point of order, are we discussing question 5 now?

DR. PACKER: No, we're not yet, but we will in one second.

Michael?

DR. PROSCHAN: I would maintain that when we look at this data that we're looking at, we are

looking at risk benefit because any benefit from using the contrast echo is going to be reflected in these event rates, presumably. So, in fact, we are looking at that when we look at echo with and without contrast.

The other thing that is kind of interesting, the temporal association question is really intriguing, but it's very difficult to do a formal analysis, and that's why we didn't see that.

One idea is to try and -- if you could assume that these events are sort of uniformly spread over a certain time period like zero to two days or four days or whatever, then you could say are there a whole lot more events really close to the time of the contrast. But that assumption that they're sort of uniformly spread out is not necessarily true anyway even without any contrast.

DR. PACKER: Okay. Here's what I want to do. I want the committee to consider two remaining questions going forward, and they're actually embodied in questions 4 and 5. And I want you to consider those questions separately.

Question 4 basically says do you have enough confidence in the observational data that a summary of the observational data should be incorporated into labeling. Presumably, the summary of the Definity study would be incorporated into the Definity labeling and the summary of the Optison study would be incorporated into the Optison labeling.

Hold on. One second.

I want you to take that and consider that separately from question number 5, which is, what you would do with a boxed warning, because those are -- your thinking process for 4 and your thinking process for 5 might be quite different.

So, Peter, I think that gets directly to your point.

Don't worry about number 2. Number 4, is there --

Yes, Ralph.

DR. D'AGOSTINO: I do not feel comfortable enough with the Definity trial to say that should be incorporated into the label.

DR. PACKER: Okay. Brian?

DR. STROM: I don't feel comfortable with either of the studies given the way they're done to incorporate it. And I wonder, to short circuit things, if everybody else feels the same way.

DR. HOCHMAN: We said it.

UNIDENTIFIED SPEAKER: Yes, absolutely.

DR. STROM: It would be very different if redone the way we're all talking about.

DR. PACKER: Okay. Do I get a consensus from the committee that the way that these studies have been designed and the uncertainties of how they were carried out and analyzed would lead one to conclude that a paragraph on their design and results should not -- are not appropriate for labeling? Is everyone --

DR. HOCHMAN: The Premier database?

DR. PACKER: Premier; Premier.

DR. HOCHMAN: Because they each did three studies.

DR. PACKER: The Premier retrospective observational data, I think that there's a uniform

yes around the room. Okay.

DR. PAPADEMETRIOU: As now done.

DR. PACKER: As now done with all of the possibilities of going back and doing something terrific and having that terrific thing incorporated into labeling.

Okay. Next question, which is a separate question, independent of how you voted for 4, what do you think of 5?

Mike?

DR. WEBER: Could you put a slide of the current black box up on the screen?

DR. KREFTING: That's one currently in effect, and associated with that is the contraindications section, which would be slide 22.

DR. PACKER: Why don't we forget about the contraindications? Let's go to the boxed warning.

Mike, do you have a comment?

DR. WEBER: Well, I think no one has suggested at any point, not even the sponsors, that the words would go away. The question is would the line around them go away, the box. And I think we

all want to keep those words there.

DR. PACKER: The only remaining question for the committee is a formatting question.

DR. WEBER: Exactly. And based on what I've heard today, my feeling is that we don't have enough evidence to really feel comfortable about any sort of decision like this. I am not totally persuaded that having a black box has mitigated against the use of what may be a very beneficial procedure.

Stuart argued before, and he's closer to it than I am, that in hospitals and institutions where they do these procedures, often they follow the rules of the road more closely than physicians like you or me who prescribe ACE inhibitors or other things with black box warnings. And so this could have a negative impact and could dissuade people from having a test they really ought to get.

If that really is the case, then I would favor removing the black box.

DR. PACKER: Okay. Can we have a -- Sidney?

DR. WOLFE: I believe that the main thing

driving the original black box, which I think many people agree was a little too strong, it was modified, and it's resulted now in this use on a patient basis coming back, were really spontaneous reports of unknown dimension. And Brian said about five hours ago that there are a number of reasons why the range of 1 out of 10, 1 of 100 get reported are so. I think we have an additional reason here, which is that there's a huge bias on the part of the echocardiographers to attribute adverse events to everything other than the drug, and they are a major source of reports. There is yet another reason.

So I think what we're back to is do we know anything different now about the occurrence of, if not the rate of, spontaneous adverse reaction reports of this kind that would warrant us to reduce the warnings to people, particularly at a time when there's an increasing amount of off-label use for indications that sound tantalizing but which have not been subjected to really any kind of study.

So, if anything, we're in an expanding universe of use. And if you read the box warning, it's hard to disagree with anything there. The first bullet, serious, have been seen. And the temporal relationship, when you look at whatever, slide number 52, almost all these are clustered temporally in association with the drug.

So the first is true. You should assess all patients for contraindications. You should monitor them. I mean, what in here should we get away with? And we know that the box does increase the amount of attention, particularly to a group of people that are expanding in number and the previous experience and so forth.

So I can't imagine why we'd want to decrease from what there is now. I think that what happened before is the people who thought the previous black box warning was too strong got their way. It was weakened, I don't think inappropriately. I think we're left with some very fundamental things which I just don't see the justification or a public health safety of reducing by taking the box off.

DR. PACKER: You're saying this sounds like motherhood and apple pie, and it's hard to be against motherhood and apple pie?

DR. WOLFE: I'm just saying most of the black box warnings are not based on randomized-controlled trials. We have things, Vioxx, whatever, whatever. It's based on what Virchow a hundred-plus years ago said. We have an event. There isn't any other explanation for it. Its contiguity and time is very close. There are plausible biological mechanisms, and I think there's clearly an underreporting of it. So we can't guess on what the actual rate is. It's high enough to warn people in the way that this boxed warning does.

DR. FILICE: Dr. Packer?

DR. PACKER: Hold on one second.

Sanjay?

DR. SANJAY KAUL: I didn't find the Definity data exculpatory, and neither did I find the Optison data incriminating. So the question I had is, why did we go on this expedition to find

exculpatory evidence to begin with? I don't think we can get away from that.

DR. PACKER: Judy?

DR. HOCHMAN: So I'm trying to figure out sort of the downside of the black box because it does read sort of reasonable. It says to monitor. Clearly, there's an idiosyncratic reaction. There's anaphylaxis. We don't know the real incidence. I don't think we know the incidence. But there's a separate sort of cardiopulmonary rest that's not allergic. I don't know. Some of these sort of read like that, but it's impossible to know.

So I would turn to the data presented about the vials, number of vials sold, and it seems like we've recovered pretty much to the pre-chill of the black box, so that sort of education issue.

I would also make the point in regard to the issue of iodinated contrast agents in the alternative. Those are always given in very well controlled settings, hospitals or radiology suites. Echo is used in like every cardiologist's office,

and that's a very big difference.

So I think that they have to be alert. There could be an anaphylactic reaction. They need resuscitation equipment. These are the cautions they should monitor. It's comparing apples and oranges to compare coronary angiography, or anything, an x-ray procedure, with iodinated contrast, to the potential use in sort of every doctor's office because all cardiologists have ultrasound.

So I guess the only other thing is we didn't really talk about the other alternative which is sort of MRI. And, clearly, there's a cost issue there. But I don't know, in fact, that the rate of anaphylaxis is anywhere near this.

So I come out -- I think there's an education that's needed, and these studies should all be published so the hospitals that have said we can't use this at all, which is ridiculous, maybe get some more education. We have a lot of black box warnings. For clopidogrel, it says be aware of polymorphisms, and people may not respond, and I

don't think it's changed practice at all in terms of prescribing clopidogrel. So -- well, I guess enough said. I've made my point.

DR. FILICE: Dr. Packer, could I just make one comment, please?

DR. PACKER: Oh, of course.

DR. FILICE: I'm sorry. To just help, we actually would like a little more specific attention to number 2, and especially --

DR. PACKER: Yes, we will. We will definitely go there.

DR. FILICE: -- just especially in light of this fourth bullet, the focus on the monitoring in terms of pulmonary hypertension. So we would like that to be addressed. Thank you.

DR. PACKER: No problem.

Let me, just for the sake of addressing bullet number 2 -- because I think there is a consensus that whatever changes we're seeing in the pulmonary artery pressures or pulmonary vascular resistance are small. And, frankly speaking, I don't know what the significance of those changes

are. And you can say that, small and uncertain clinical significance.

Does that seem reasonable?

DR. KAUL: Or say reasonable assurance given the small sample size.

DR. FILICE: And then I guess the follow-up would be how would that influence any of the language of the boxed warning or would it?

DR. PACKER: I don't think so one way or another. And the reason is because the hemodynamic studies were small. They were done in stable patients. It's not terribly -- I don't know. It's not helpful in terms of at least -- the problem, I think, Ross, is that the committee is expressing opinions that are no longer what I would consider to be data dependent but more dependent on their view of the universe, their view either as clinicians, their view of the political environment of how hospitals make decisions. It's a little bit hard for us to play politicians.

I think that if we were to go around -- and we're not supposed to take a vote, so I'm not

taking a vote -- you would see a diversity of views as to whether the black box warning should remain in place or not. And there are going to be people who are going to say everything in the black box warning seems totally appropriate, and they don't see a problem with keeping it. A lot of people think that even if you have it, the prescriptions have recovered. Some people will say, well, if there are any physicians who are going to be discouraged by the black box warning, then it should be taken away.

Can we be more helpful than that?

DR. FILICE: I mean, obviously, any answer the committee gives is fine. I just wanted to make sure that was addressed because I know that's something that we were interested in the committee's opinion.

DR. RICH: Milt?

DR. PACKER: Yes.

DR. RICH: As long as we're focusing on data, I wasn't part of the judgment in 2008 when this warning came up, but as I read bullet point 4,

it's not just to tell you that be careful. It says, "Monitor vital sign measurements." I think that's reasonable, anyone who's unstable with cardiopulmonary condition, even pulmonary hypertension.

Electrocardiography now requires another procedure, a technician, a machine, and an interpretation, a physician to interpret. It doesn't even tell me how frequently I need to get this. Cutaneous oxygen saturation is another purchase of another machine during and for at least 30 minutes. I've not seen a shred of data saying that 30 minutes is a cut point. We're talking about two days following doing this.

So this, to me, makes no sense. I would say either make it right or get rid of it, but this I think just sends a message. It's a description of an acute cardiopulmonary collapse that will or will not occur within 30 minutes, and, therefore -- and that's nothing at all that we've heard all in this data. So I'm really confused.

DR. PACKER: Well, interestingly enough, I

think what we heard the sponsors say was that they're perfectly okay with keeping all of this, illogical as it may seem, as long as it doesn't have dark lines around it.

DR. FOX: That's right.

DR. RICH: Well, fine, but I'm just saying that if we're going to talk about the data we've seen and how to make an appropriate warning, this doesn't fit.

DR. PACKER: I understand.

Elaine, you look like -- we need wisdom.

DR. MORRATO: I think the first sponsor did want to have that language removed. And the second sponsor was, I think, acceptable with the language if we didn't have the box. And I would agree that none of the studies really addressed the 30 window nor the monitoring, et cetera, other than indirectly, that one study occurred in an ICU-type setting in which people are getting monitored, presumably.

If you're looking for language, it may be wise to stick with description of what is known,

which is the 30 minutes relate to the cases, that the events are occurring in a certain period of time. As always, you should have equipment and trained personnel to deal with it as opposed to being prescriptive in a monitoring over a certain period of time. That might be a compromise that gets the point across that these things occur early and quickly as opposed to not saying anything.

DR. PACKER: Jim?

DR. TATUM: I was going to say that it's clear that it says unstable cardiopulmonary conditions, and in that scenario, the monitoring we're talking about is not going to be that unusual. So we're not talking about a stress test. We're not talking about an outpatient facility as such. So it's fairly clearly defined to that particular population.

But I did want to come back to a pro and a con on this. One is as compared to gadolinium black box. In that case, it serves a very definite purpose because we know what the GFR is going to be. We know which class of ones we want to avoid.

And so it gives instructions basically as to what the risks are, how to mitigate those risk and what the risk you're taking when you do use it for certain circumstances.

So I think this is very dissimilar. We don't have that kind of data, those kind of monitoring points, those times to cutoff, you know, the flip sense. So that would be, I'd say take the box off.

But the other piece that we keep talking about here is that this has been used on a cover prescription by the technical staff, and I think that kind of changes the paradigm. It's much like contrast is used, actually, in the same way. If a physician was going to be the one responsible every time for this, I have no problem with moving the black box and putting it to the middle of it. But if it's basically the tech that's going to pick it up, maybe in an outpatient or other things, I think having something that says, oh, by the way, this is not just a simple test, and you need to know it, and maybe you need to ask the doc about it.

So that's the flip coin here, and it's the same problem we had with gadolinium because we had too many cases where people just -- you go into the room, put it in the MR injector and you go off and call the doc later. So it's a similar type of thing there.

DR. PACKER: Vandana?

DR. SACHDEV: I still think we need to consider what level of risk warrants a black box above and beyond the warnings and contraindications. So we have a lot more data that we just heard compared to what was present in 2008, so --

DR. PACKER: Most of which we've discounted.

DR. SACHDEV: Right. So does that mean that we have the same information and we still believe that the level of risk is high enough that we need the boxed warning after the warnings and contraindications? That's not clear to me at all.

DR. PACKER: I'm asking a question.

Peter, we're going to go around. I promise we're going to finish in five minutes.

DR. KABOLI: Okay. I'll be brief.

I agree with what Sid was saying, and it sort of reminded me of the discussions we have about withdrawal of intubation in patients and whether you're making a decision to intubate someone or take something out, and whether this is the same analogous sort of situation. And when I read the materials ahead of time, I said to myself, well, I got the -- I guess it's only a draft, not for implementation, but when to use a boxed warning. And I read this, and I said, well I could see the only one that applies is the first bullet that says there is an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug. The other two don't apply, in my opinion, as I read these.

So it's really are we saying is this so serious, based on the data that we have now, to continue the decision that was made in 2008 or do we change the decision? So that's -- I guess I

don't feel like we have that.

DR. PACKER: Okay.

Brian and then down. Right.

DR. STROM: So let me just give sort of a summary of my sense. One is the most positive thing I've heard today is the impact of the black box warning, that it actually worked, that it did something, maybe, which is unusual compared to drugs. But it's important to keep in mind that black box warnings do not prohibit use. Black box warnings are simply a way to convey -- to clarify the risk-benefit balance, to convey that accordingly.

We're also in a climate now where more and more black box warnings are being added. There's no science of when do you include it and when don't you include it. But, clearly, if you look now compared to five years ago, there's a lot more of them. To take it away now sends a clear message that we've seen data that changes the risk benefit from what it was before we saw this data, and we haven't. We're all very clear on that. So if we

haven't seen anything that changed it, it would send a really bad message of this stuff is safer than what we thought.

True anecdotes are awful. I'm the first person -- it's my field. I'm the first person who pans pharmacovigilance. Our standard line is the "plural of anecdote is not data." But those anecdotes are awfully convincing that it's real, and we haven't seen -- that was what was present a few years ago, that's what present now, and we haven't seen anything to change that. So especially in a climate where black boxes are being deflated instead -- or inflated, whatever you call it, that their impact is less, it takes less to get a black box, why would you take it away?

DR. PAPADEMETRIOU: Speaking as a clinician, I see that these black box warning can work as a deterrent, and I think, if anything, the language should be modified and be softened. I think it can work as a deterrent not to do studies in patients that need them and patients can benefit and that can help their care, improve their care. And I

think that leaving the way it is, it may, at the institution level, deter some of the administrations to make the media available, and the studies may not be available in that institution.

From that point of view, I think it's worth modifying the language, making it softer to reflect less intimidation to the technicians who do the studies or to the physicians who are going to use the media so the test is available to those patients that need it and can benefit from it.

DR. FOX: I'd like to go back to strength of evidence. I don't think that the strength of evidence was there to justify the boxed warning in the first place. I don't think that the strength of evidence is there today to justify keeping it. I think that many of the admonitions that are contained in the boxed warning are, as many people have pointed out, located elsewhere already in the label in the warnings precautions and contraindications. Nobody is arguing that those should go away. And as far as pulmonary

hypertension, unstable cardiopulmonary and all the rest of that other stuff, that's very vague language, and clinicians are going to interpret that one way, P&T committees and risk management committees are going to interpret that a different way. And the personal injury law community will interpret it yet a third way.

DR. D'AGOSTINO: I haven't seen any data that actually addresses this in terms of being able to change it. We have a lot of data, but it doesn't necessarily address these particular items. And I don't know what the arguments were two or three years ago, but I don't see anything that's overwhelming in the data we have that sort of addresses these and says now we can surrender them.

DR. PACKER: Henry.

DR. BLACK: I want to just repeat what Jonathan said; I was going to say that. I'm not sure what the justification was for putting it in, in the first place, and I don't see it. From what you heard then, it's like inflation creep or grade creep. That's why there's more and more black box

warnings and why their impact becomes less and less because they're not used appropriately.

I wasn't at the 2008 meeting or what happened before. It's already been softened. There isn't anything here. And I think there is an impact on it, based on what we saw, and I think it's likely to happen again. I don't think it's going to affect things very much except in the legal environment we're in where risk management, to hospitals at least, is so important that they're not going to go against this for obvious reasons, that I think we ought to take it away.

DR. SUNDARAM: Having read the entire 2008 minutes, even though I wasn't here, I think I do agree with Dr. Fox, and I do not see any evidence, for the reason for the box warning as mentioned in the statute. Having said that, I do not believe on the other hand going forward, at least having worked in the hospital setting, that it will have a huge impact in terms of the usage of either one of these contrast agents.

DR. PACKER: Vandana?

DR. SACHDEV: So as an echocardiographer, there are implications to the black box warning. And when we go in and tell someone that they have a suboptimal echocardiogram, and they need an IV, and they need a contrast agent, we're supposed to explain the risks and benefits, and we do tell them there's a black box warning. And can you imagine trying to explain to a patient what that means when we don't have any agreement about what it means?

DR. PACKER: You would have to do that whether there was a line around it or not.

DR. SACHDEV: Exactly. So there are implications, though, apart from just the precautions and the warnings themselves. The black box warning itself scares people. And coming from a research hospital, it does act as a deterrent to being used for patients that are in clinical trials, people that are starting new studies. IRBs have questions. There's a lot of confusion about this.

DR. PACKER: I'm sorry. I don't understand. You still have to explain risk-benefit whether

there's a line around it or not.

DR. SACHDEV: Right, so I'm saying there's an extra implication to the box itself. I agree with all the --

DR. PACKER: You tell the patient that there's a line around this?

DR. SACHDEV: The IRBs oftentimes say you should tell patients that it's a black box warning on the label, and that scares people.

DR. PACKER: Okay. Let me just -- I just want -- I'm going to end this in two seconds. I just want to -- I think what the FDA has heard is a diversity of opinions. I want to know whether the diversity that you've heard is helpful, and one other thing that we could do is not vote officially but just by a hand raising tell you whether we believe there should be a black box without saying what should be in it. In other words, people might not like what's in it but still think that there should be a black box, or do you want us not to raise our hands at all?

DR. FILICE: I think we don't need to do the

raising of hands. There will be a couple things that hopefully we can get a little more clarification on. I promise to make this as brief as possible. But regarding the Premier database, there was a lot of talk about how to potentially reanalyze that and a better method. Let me just tell you what I've heard and ask if there are any further clarification that you might want to offer.

We've heard that maybe going back to reanalyze the raw data from Premier using unadjusted and adjusted analyses; using three groups, Definity, Optison and a noncontrast; comparing it year by year so you get a sense for what's happened over the years and as the labeling changes have occurred and maybe with other populations other than just ICU populations.

If there's anything additional, you might want to comment on.

DR. PACKER: I think that the individual comments as to how one should approach the analyses, there are four experts here who would be delighted to talk to you about that. And, frankly,

they're the right people to talk about this.

DR. FILICE: Great.

DR. HOCHMAN: Did we ever address whether the other two studies should be included in the label now? We only discussed the Premier and agreed that it should not. I don't know that we came back -- I would think that the other two studies could be included in the labeling. They are what they are, a thousand prospective patients, and the PA pressure measurement I think adds information. And they did it, and I think it should go into the labeling.

DR. PACKER: Just by a quick show of hands, how many believe you can take this black box, take anything out of it that you want, including everything that's in red, or -- remember, this is going to appear someplace in the label. Just as a sense, how many of you would want to see a black box retained in this, just by a show of hands.

[Show of hands.]

DR. PACKER: And how many should not?

[Show of hands.]

DR. PACKER: And we're not counting because there's no vote, but now you get a sense.

DR. VESELY: We need to get some kind of (off microphone) in the transcript.

Adjournment

DR. PACKER: Okay. Thank you very much to everyone, and we are adjourned.

(Whereupon, at 4:15 p.m., the meeting was adjourned.)