

with renal cell carcinoma. Patients were considered good responders or bad responders based on the results, so here you can see contrast here and here.

This obviously in terms of effectiveness, the vascularity is not seen, and let's see if we can make this work. Well, not in real-time, but the idea is this is contrast, it is colored green. After good responders and then the question, the treatment here showing effectiveness, the tumor has become necrotic, and here the vascularity is the same.

There are also investigational uses, and we heard a lot about them and, of course, more and more are being used. We saw plaque characterization, trauma, detection of sentinel lymph nodes, therapeutic uses, treatments, and so on.

Here is a case in which there was trauma to the spleen and this is the ultrasound, and this dark area with contrast shows where the trauma was.

Now, if I go back, let's see if we can get that slide, well, anyhow there was showing not seeing any signs before and now we can see an area of hematoma, no flow within that dark area.

What else are we doing? We are doing research actually here, and looking at sentinel lymph nodes, contrast agents you inject around tumors, and actually, you can see the lymphatic channels. Here is a lymphatic channel going to several sentinel lymph nodes.

So, one can look at that and then you can actually--if there is any significant tumor, the contrast is reflective, is again around tumor, just like you do with your blue dye or your red activity. About the only difference is you can actually see the whole node, and if there is tumor, the tumor replaces, so the dark areas are tumor and the white is not.

In conclusion, ultrasound contrast agents we believe have a proven safety profile. And you have heard a lot this morning, detection and characterization of lesions with ultrasound is a significant improvement over conventional ultrasound and has been proven to be comparable to contrast-enhanced CT and MRI.

Remember there are some cases where they provided more information. It is diagnostically effective for a variety of applications including indeterminate, patients with renal insufficiency.

Just to end, it is our considered opinion that the lack of availability of ultrasound contrast for non-cardiac imaging in the United States hinders the delivery of optimal diagnostic imaging services to our patients.

As a result, the United States lags behind the rest of the world in the appropriate and proven application of ultrasound contrast agents.

The ultrasound community believes that this is having an adverse impact on clinical care in the United States, and these are statements put together by discussions and representing the American College of Radiology, the American Institute of Ultrasound in Medicine, and the Society of Radiologists in Ultrasound.

I thank you for your attention and I leave time for questions.

DR. HIATT: I suppose if the Committee has any quick questions, what I would like to do after these series of presentations is come back to clarifying questions for everything you have heard this morning and earlier this afternoon.

Any clarifications anyone wants to make or should we move on to the next speaker? Thank you. We will perhaps

call you back in a little bit.

Would the second speaker come and identify yourself, please.

DR. ZOGHBI: Good afternoon. I am Bill Zoghbi from Houston, Texas. I direct the Cardiovascular Imaging Center. I am here today as a representative of the American Society of Echocardiography, as their president, to share with you some comments, and I really appreciate the opportunity to provide these comments to the Committee.

Just a brief word about the American Society of Echocardiography or ASE. It is an organization of approximately 14,000 physicians, cardiac sonographers, and other professionals committed to excellence in cardiovascular ultrasound and its applications to patient care.

ASE supports this mission through education, advocacy research, innovation, and importantly, service to our members and the public.

To share with you, one is that ASE strongly supports the use of ultrasound contrast agents in clinical practice. As you heard today, there are several reasons for this stance. One, that these agents assist physicians in

maximizing the accuracy of information obtained from echocardiograms and in optimizing patient care.

Several studies that you have seen have shown the clinical utility of contrast administration and improving the accuracy of echocardiographic studies in technically difficult patients.

In addition, the appropriate use of contrast is extremely cost effective since the improved accuracy of echocardiographic studies in difficult to image patients impacts patient management and decreases downstream utilization of more invasive, more risky and more costly procedures.

The impact of contrast on patient management--and I know that has been alluded to this morning--has been shown recently and presented at the American College of Cardiology to be highest in critically ill patients and ranges between 35 and 65 percent impact on the management of these patients.

ASE also 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 reactions should be carefully studied on a prospective basis.

However, as we previously related to the FDA, we strongly object to the initial box warning that was imposed on echocardiography contrast agents in October 2007. Not expectedly the Agency's reactions provoked a justifiable outcry from our members on behalf of their patients.

In this regard, it is especially unfortunate that the black box warning affected in large measure populations in whom the administration of contrast is especially useful for patient management particularly the critically ill patient.

We are aware of the relative scarcity of safety data that served as a backdrop to the FDA's decision to impose the box warning and we very much appreciate the FDA's decision to reverse some of the contraindications in May 2008 after more data on safety were available.

However, we strongly believe that further action is necessary. The negative effects of the black box warning on the appropriate utilization of contrast still linger. Unfortunately, the box warning has had significant deterrent effect on the appropriate use of contrast.

Several institutions have decided to stop using contrast all together, thus negatively affecting patient outcome. The end result is nondiagnostic echocardiograms followed by more procedures at greater risk to the patient and cost to the health care system.

We urge the FDA and industry to collect the safety data necessary to eliminate or further limit the remaining contraindications pertaining to pulmonary disease and shunting including the lengthy monitoring period.

In assessing the need to retain the current safety precautions, we urge the Agency to consider that in many cases, the administration of contrast poses a substantially lower risk to the patient as was shown this morning than the performance of alternative diagnostic testing, such as transesophageal echocardiography, cardiac CT scans, or cardiac catheterization.

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 that you have seen also this morning.

These include, among others, stress echocardiography for LD opacification, vascular imaging, and myocardial perfusion imaging.

In parenthesis, for LV opacification during stress, it has been recently shown as published in JACC Imaging that the impact on accuracy is 30 percent in technically difficult study patients.

The administration of contrast for these and other indications is supported by numerous studies. ASE believes that echocardiography contrast agents have broad applications beyond that currently approved.

We encourage the companies that manufacture these agents to seek Agency approval for additional applications expeditiously as supporting data become available.

Moreover, scientists who are affiliated with ASE and other scientists are performing research on additional applications of echocardiography contrast agents that could have a 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 research laboratory into 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 appreciate the opportunity to offer these comments and hope that both the Agency and industry will call upon 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 in the care of our patients as expeditiously as possible.

Thank you very much for the opportunity.

DR. HIATT: Thank you. Any clarifying questions for Dr. Zoghbi? If not, I am sure we will come up with some later.

Would the third speaker please come and introduce yourself.

DR. GRAYBURN: I am Paul Grayburn. I am a cardiologist at Baylor University Medical Center in Dallas. I appreciate the opportunity to be here today.

Let me say that I paid my own way. I have done research over the past 12 years with contrast agents, so I have done clinical trials, many of the clinical trials and pre-clinical trial data that you saw this morning was done at least partly in my laboratory.

I have been a blinded reader for some of these studies. I do not own any equity positions in any of the companies, and I am not currently receiving any money from them either as research grants or otherwise.

Let's have the first slide up, please.

I am here along with Mike Main, Steve Feinstein, and Jonathan Goldman, and we actually are just four people who represent a much larger grass-roots organization, cardiologists and other professionals involved in imaging including radiology, vascular medicine, sonographers, physicists, et cetera, in 14 different countries.

All of us have experience with these agents and we got together and submitted a letter in response to the black box warning that came out last fall. I would like to say

that although the four of us here today represent this grass-roots movement, we really represent our patients and that is why we are here on our own penny.

We are here to stand up in defense of our patients and their right to live and receive proper medical therapy. As you are aware, there was a letter that we sent to the FDA Medical Imaging Division on November 10th. They were gracious and agreed to meet with us on December 11th.

At their request, we signed confidentiality agreements with the sponsors, which is the reason why Drs. Feinstein and Main presented today, that we were requested by the FDA to meet with the sponsors to get access to data that we did not have so that we could move forward with trying to assess the safety of these agents.

This is the letter that we sent and I just want to highlight one comment in it, which is that this was in November. We do not believe that these new black box warnings reflect the proven efficacy of ultrasound contrast agents, their established safety record, the potential risks of alternative procedures, and the likely confounding effects of pseudocomplication.

Now, we published an article, an editorial in JACC

where we highlighted our opinion that these safety events that brought about the black box warning were, in fact, pseudocomplications.

Now, it turns out that there have been some interesting quotes from FDA officials that have been made public at meetings. This is one. Nobody needs to die from a diagnostic test. That is actually an absurd comment, but we will get to that.

The threshold for approval and persistence needs to be 100 percent safety. Well, no cardiovascular test except possibly the stethoscope meets this criteria so ,if that criteria is going to stand, we can't cath anybody, we can't put a stent, we can't do bypass surgery, we can't, you know, we can't do anything. That's ridiculous.

If you look at the diagnostic tests and for coronary angiography--this is diagnostic angiography, it is not interventional cardiology--the death rate is 1 in 1,000. For exercise treadmill testing, 1 in 2,500, and that is according to the guideline statements of the American College of Cardiology and American Heart Association.

Radionuclide exams, as Dr. Goldberg has said, or even CT scans, have a risk associated with them, a longer

term risk due to potentially inducing a malignancy, and contrast echo, somewhere in the 1 to 500,000 risk of death.

So, if by not doing a contrast echo forced my patient to undergo coronary angiography, over the long haul, I am going to wind up killing more patients by doing that than I would if I did the contrast echo.

As a doctor, who actually has a practice and takes care of patients, that is unacceptable.

Now, after the black box warning came out, these were the lists of contraindications to ultrasound contrast agents. Since the revision of the labeling, you will notice that these highlighted in yellow have been removed from contraindications to warnings and that is worsening or clinically unstable heart failure, acute coronary syndromes, ventricular arrhythmias, respiratory failure, or severe emphysema.

Again, going back to these tests, if we don't do contrast and instead we do a cath or a stress test, we are actually going to put more patients at risk by doing that than we would by giving them a contrast agent, and anyone can readily see that that is unacceptable.

Now, what is the list of absolute

contraindications to cardiac catheterization, which as we have shown you has a 1 in 1,000 risk of death? Well, according to Grossman's Textbook, which is the textbook of cardiac catheterization, the only absolute contraindication is refusal of a mentally competent patient to consent to the procedure, so we obviously have a different standard for the use of ultrasound contrast agents and an invasive procedure like cardiac catheterization.

I would submit to you that in the 21st century, that is unacceptable.

These are the American College of Cardiology, American Heart Association, American Society of Echocardiography 2003 guidelines for the clinical application of echocardiography, and this is specifically for use in myocardial ischemic syndromes.

I don't expect you to be able to read this from the back of the room, and I apologize for that, but just to highlight this, it is a Class I indication meaning it needs to be done to assess mechanical complications of MI and mural thrombus. And, down at the bottom, you see the transesophageal echo would be indicated if the transthoracic echo can't be done meaning if we can't give contrast now to

make an assessment of mechanical complication of MI or thrombus, we would do a TEE.

Well, this is a TEE procedure. The patient is lying on their left side to prevent aspiration pneumonia. They are sedated usually with Versed and fentanyl, which carries a risk of respiratory compromise and necessity for intubation, and then this tube is placed down their throat which carries a risk of esophageal perforation or laryngospasm. This is Mayo Clinic data showing the risk of transesophageal echocardiography. The death risk is 1 in 10,000. The other risks are listed for you.

This is a German multi-center study that was published over 10 years ago in Circulation, multi-center survey of over 10,000 examinations by TEE. There was one death. It was a patient who had an esophageal perforation and bled to death.

So, the mortality rate of TEE is 1 in 10,000, which is several orders of magnitude less than the mortality rate of giving an ultrasound contrast agent.

These are the guidelines again for clinical application of echocardiography in the setting of acute myocardial infarction, and it is talking about the ability

to assess infarct expansion, LV remodeling, and in particular, free wall rupture and thrombus.

So, the statement is made in the guidelines that echocardiographic contrast agents may improve diagnosis and free wall rupture and in identifying intracardiac thrombus. So this isn't my statement or Dr. Main's statement, this is the American College of Cardiology, American Heart Association, ASE guidelines, a whole panel of experts.

Another statement that has been made is that the risk-benefit analysis is different for diagnostic testing than it is for life saving drugs. This is patently absurd. It is mind boggling anybody could say that. Accurate diagnosis and appropriate treatment are inextricably linked.

Failure to make the correct diagnosis leads to administration of the wrong therapy or withholding the correct therapy. In patients with cardiovascular disease, this can be fatal. So, it is nonsense to say that diagnosis is not as important as therapy.

One cannot give therapy unless you have the proper diagnosis. We all know that.

Let me show you some movies if they will play. Thank you. Oftentimes if patients are obese or on

mechanical ventilators lying supine in an ICU setting, this is the echo that we get. It is not very good. This is a post-MI patient.

One is hard pressed to see the left ventricular cavity, so we can't really tell you whether the left ventricular function is normal, mildly depressed, severely depressed, whatnot.

This is the same patient--let's see if that will play--after contrast. One sees this black hole up at the top there, this black hole right here, there is a large apical mural thrombus. Now, patients with apical mural thrombus after an anterior MI have a high risk of stroke and need to be treated with anticoagulation.

So, in this case, the administration of the contrast made a dramatic change in the therapy of the patient.

Here is another example. This is a patient of Dr. Main's. This is a lady who had breast cancer, subsequently had an MRI and has impaired left ventricular function. There is a question about mural thrombus in the apex. You can see the wall motion abnormality here, but you can't see very well the actual apex.

I think I skipped ahead. Let me show you this. This is really important. It looks really funny the way it is playing, but what you see in the contrast come into the right ventricle here, and now it is going to fill the left ventricle and what you will see--I apologize for the fact the movie is not playing well--but it is leaking into the pericardium here.

This is actually a patient of Dr. Feinstein's partners, who has a left ventricular pseudoaneurysm from rupture of the myocardium. This is a surgical emergency. I am going to stop that before somebody has a seizure.

The patient went to surgery and had life-saving and indicated correction of this free wall rupture of the heart.

Now, just to show you a slide that I put together here, according to the ACC-AHA guidelines for the management of acute myocardial infarction, there are half a million ST-segment elevation MIs per year in the U.S. One to 6 percent of those have LV rupture.

We don't have more precise numbers for that because many of these die immediately before they get to the hospital or they don't get an autopsy to confirm the

diagnosis. So, the estimate is 1 to 6 percent of these have LV rupture.

If the LV rupture causes immediate death, they may not make it to the hospital, however, the pericardium can wall this off, and they have what is known as a pseudoaneurysm where the rupture or the leakage of blood out of the left ventricle is contained by the pericardium.

This has a very high risk of death and the treatment is immediate surgery as in the case I just showed you. Now, a large series by Frances et al., published in JACC in 1998, showed that echocardiography without contrast--in those days contrast wasn't available, so it was pretty much all without contrast--it was only 26 percent sensitive in diagnosing proven LV pseudoaneurysms so three-fourths of them will be missed by doing an echo. And yet contrast is absolutely diagnostic, because you see the leakage of the microbubbles out into the pericardial space that makes the diagnosis.

Now, if we just take the low number, 1 percent of these MIs have an LV pseudoaneurysm, that is 5,000 patients per year, contrast could potentially identify 3,750 or 75 percent of them, and if they went to surgery, and all of

them survived, which isn't going to happen, at least you could potentially save 3,750 lives per year.

Now, there were four deaths with Definity reported over a six-year period and now it seems like there are seven according to recent addition. But the contraindication of Definity in acute MI would mean to prevent these four or seven deaths, you would be willing to execute 22,500 Americans for pseudoaneurysm that you don't diagnose. That is absurd.

I will say to the credit of the Imaging Division of the FDA, when we showed them this data, which no one had ever shown them before, and they weren't aware of this, they took off the contraindication appropriately, so we really appreciate the responsiveness that the FDA has had in looking at this data and appreciating the fact that contrast saves people's lives.

I work in an ICU setting. I see this happen on a weekly basis. I see all kind of interesting cases, patients on inotropes and Lasix for presumed systolic heart failure when it turns out they have hypertrophic cardiomyopathy picked up with contrast. They are taken off the inotropes, put on beta blockers, taken off the Lasix, given volume,

they come off the ventilator, their renal failure improves, and they survive.

Contrast is not just making a prettier picture, it saves lives. There is no question about this.

There is a current, in 2007, a list of risk factors for cardiovascular collapse in patients receiving contrast agents resulted in those new contraindications, and I don't fault the FDA for doing that.

I think when those things happen, there was a concern that maybe there is a safety signal from these contrast agents. But let me remind you that that was an anecdotal safety signal, and as we have come forth with data that you have seen already, it appears that it really was anecdotal and we are trying to now move from putting a black box warning based not on science, but on anecdote, to removing the block box warning, so that our patients can get the benefit they deserve.

Again, I am here standing in the gap for my patients. I am not here, I don't care about the sponsors, I don't care about their profit, I care about my patients.

So, this approach equates association with causation and it is not valid, and everybody in this room

knows that. Complications occurring after any medical procedures can be attributed to the procedure or the progression of the underlying disease. That is called a pseudocomplication, and we think that that is what may be going on here.

This is Hildner's paper that was published many years ago looking at patients in the 24 hours up to a cath versus 72 hours after the cath, looking at serious adverse events and death, and there is no difference.

So, it appears that serious adverse events occurring before a cath and after a cath are due to the underlying disease, and not the procedure itself, hence, the term "pseudocomplication" and something we all are aware of, which is serious adverse events are relatively common in patients who are sick enough to warrant invasive testing.

What do we need to know in order to try to determine the adverse event rates of a medical procedure or, in this case, the diagnostic contrast agent?

We need to know the number of patients undergoing the procedure, we need to know the number of adverse events, and we need to know the ambient rate of adverse events in patients with that same disease state who are not undergoing

the procedure.

Now, as Dr. Hiatt mentioned in a question earlier, it is true that the best way to get this information is a randomized, controlled trial, there is no doubt about that, but with an event rate as low as 1 in 10,000, that is not going to ever happen.

This was Mike Main's study he showed you earlier, it is retrospective, but it is much better than anecdote, and that is, 18,671 patients, over 12,000 did not -- they just got an echo, no contrast agent, 6,000 got Definity, and what we saw in that study again was that really although the Definity patients were sicker, and that is shown in this table, that there was no difference in mortality between the patients who got just a plain echo and the patients who got Definity.

The implication there is that these patients are sick, that is why we are doing echos on them. They are in my intensive care unit dying. I need to know why they are dying, so I can fix it and save their life, so I am going to get an echo. Some of them are still going to die because of their underlying disease.

Again, this is the study Dr. Main presented

earlier, 4 million patients from the Premier database. If you look in this slide again, there is a lot of data on it. You will have to look in the handouts for this, but if you look at worsening heart failure, it is more common in the Definity patients, 42 percent versus the non-contrast echo, 31 percent, same for acute MI, same for ventricular arrhythmias, respiratory failure, much sicker patients get Definity.

Again, if you look at the one-day mortality rate Definity has a lower mortality rate than non-contrast echo. Why is that? Well, I don't know, but I would hypothesize that the reason is, is because we made an accurate diagnosis here and instituted life-saving therapy, which I would postulate is the reason for this gap and the reason that this bar isn't right here.

Let me just conclude by saying that ultrasound contrast agents improve diagnostic accuracy and enable proper therapeutic intervention.

The question came up earlier this morning about efficacy. Let me just say that this panel was convened about safety. There is a safety concern. These agents were approved for efficacy years ago. There has never been a

question about efficacy.

I can tell you, I have shown you some case example, but I can tell you the efficacy, which is seeing the heart better, translates into life-saving therapy, and it does so on a common basis.

Pseudocomplication is likely responsible for many of the adverse events, but I say that with a caveat that we really don't know much about these adverse events, and we need to learn more about them.

Known risks of alternative testing are much greater than the perceived risk of contrast. [End of allotted time.]

DR. HIATT: Thank you very much.

Any clarifying questions? I might just comment that event rates are important when we have these deliberations. The spontaneously reported event rate of mortality appears to be 1 in 10,000, but the observed event rate that your group has shown us is 1 in 100, so we should just distinguish that.

DR. GRAYBURN: As was mentioned before, there is always a concern that these self-report events are underreported, so we are putting an estimate of what we

think the risk is on those reported deaths.

DR. HIATT: If you have comments, please come to the microphone and just identify yourself.

DR. KAUL: I am Sanjiv Kaul. I spoke earlier this morning. I agree with you, but it's a different patient subset. These are very, very sick people, and it's 1 in 100, but in the general population, which is mostly outpatients, the risk is much smaller.

DR. HIATT: What I would like to do now, before we go to the FDA questions is ask the members of this Committee to clarify any issues that have been presented thus far to any of the presenters, just to go around the room and make sure we understand what we have heard, maybe any concerns about things we haven't heard. Michael.

Clarifying Questions to the Presenters

DR. LINCOFF: There is clearly some interest in looking ahead at the questions and the various animal models and the applicability to the human situation.

I don't know if there is anybody who can answer this, who has the proper expertise, but is there any data regarding these pulmonary intravascular macrophages and whether or not they are induced in humans in certain disease

states.

At least my read on this data is that in virtually all patients, there is not a safety issue. But there do appear to be some patients who have events that sound like they were related to the contrast, and we can debate the statistics, et cetera, but the number is always going to be very small.

So, mechanistically, is there a potential explanation for a similar phenomenon that is occurring in the pigs, or is that model just completely irrelevant? I don't know if anyone has that information.

DR. ROBINSON: Yes, there is I believe some literature reports on pulmonary migration from the liver to the lung. It usually occurs in hepatic dysfunction, surgical removal, or cirrhosis situations, which I don't think are common to what we have seen in these situations, so I think it is unlikely, but we can look a little bit more on this.

DR. DENARO: It is correct, so we have analyzed in our patient population, because again the majority of our patient examination for liver disease, so some of these patients certainly has macrophage at the line level.

Our idea is that in reality, it is not sufficient that most likely the patient has to have some triggering, and only when the macrophage are activated, then, they can be releasing mediator if they are stimulated by particulates.

So, it is much more complicated, and again we have analyzed the pig model, not because we believe the pig model is the model, we don't know which is the model, because I am sorry, we don't know the mechanism, and a lot of hypothesis.

The question is that if you look at the pig, the image of the pig, from a pathophysiological point of view, it is reasonable to believe that this is what is happening in humans. Now, how the activation happen is very complicated and again is rare event, but that is what most likely happened.

The fact that in pig and rats and dog, you can prevent that by giving aspirin or other, that tell you it is the activation that most likely is important in that reaction. But, again, I don't think the fact that there are macrophages that line level alone is sufficient to trigger the mechanism.

DR. HIATT: Just to clarify that comment, and

let's complete this question, Dr. Lincoff, do you know if any of these spontaneous reported deaths that occurred temporally in association with the agent were in patients who were receiving aspirin or other nonsteroidals that could have blocked that mechanism?

DR. DENARO: This is a very interesting question which we did look at. Generally, these are patients which if receive aspirin, they receive low dose aspirin, so it's a different mechanism.

Here, when you use in pigs, you have to pretreat with high dose of aspirin, because you need to eliminate the cascade of levotrine and all the other thromboxanes, and so on. So, if you don't have high level of aspirin, you do not prevent that.

Let me clarify. We find that, as we said, one is clearly not related because it's 9 hours after--the patient was very sick. They gave morphine and then the lady died. I think it is very difficult to believe that there is a correlation with the agent.

Another is a clear case of anaphylactic shock, so the patient got severe allergic reaction to the SonoVue and unfortunately, they were not able to rescue, but this

happened. It happened with any medication, it happened very often that you have an alleged shock, you may not be able to rescue.

The other three are very complicated cardiovascular patient, one which we think with this group there is a concomitant reaction, one we don't have any element, and one more, we believe that most likely this could have been a patient that gone to hypotension due to the agent, and in a very severe cardiovascular patient, if you get severe hypotension, you get the high probability of that.

DR. FLACK: I would actually like to follow up on that. I am not sure that the question was really answered, is there a really good look at data related to aspirin use in the datasets that you have.

You can speculate that many of the people may be on low dose aspirin, but that may not be true. The data would actually tell you that. So, has there been any careful look because the data in at least the animal models would suggest that that is probably a potential benefit.

In reality, in a unselected population, these complications are like a needle in a haystack, and about the

only way you are going to get a collection of these events is really study higher risk people as opposed to excluding them.

Again, do the datasets that are out there have any specific looks at aspirin irrespective of dose or across doses?

DR. HIBBERD: That's a good question. I am Mark Hibberd. Today, we don't have that information, but I think it's something that could potentially be looked at in the large outcomes databases that exist, and it might be possible then to pair it up with the mortality reports that we made earlier today and see if that leads to some form of explanation of who may die and who may not. So, thank you for that thought.

DR. HIATT: I would like to ask Bracco or any of the sponsors, the clarification on some of the animal findings. Consistent across the compounds, I think is the observation and perhaps particularly in pigs that with acute administration, there is an increase in pulmonary pressure and concomitant decrease in systemic pressure or systolic blood pressure.

My question is if you have identified the

mechanism, is this all 100 percent explained by a decrease in cardiac output due to pulmonary vasoconstriction, and that the fall in systemic pressure is a reflection of that, or is there additional vasodilating mechanism on the systemic side that account for the hypotension?

DR. ERIKSEN: I may divert the question. We have no measure probably. I am not able to answer.

DR. HIATT: Do any of the other sponsors take that on? What I am trying to understand is if there is one thing that came out of the animal models, there was a lot of nothing, but if there was something, there appeared to be an acute hemodynamic effect which could be deleterious in patients with underlying coronary disease.

I am just trying to get a better handle of the mechanism particularly of the systemic hypotension.

DR. ERIKSEN: I am Morten Eriksen from GE Healthcare. I am a physiologist and worked with circulation physiology and cardiodynamics for many years. I think that the systemic hypotension can be fully explained in these animals by the findings of the pulmonary vasoconstriction.

However, to further investigate the mechanisms, it would have been very nice, for example, to have some

pressure measurements, let's say, in the left atrium or something to see if there is a pressure drop there or not.

The most likely explanation is that there is an isolated effect caused by the pulmonary vasoconstriction.

Also, if you block the pulmonary vasoconstriction by drugs, it is a local effect in the lungs that we then block, then, we also lose the effects on the arterial side, which further indicates that this is not an effect on the arterial side. It is a pulmonary effect.

DR. HIATT: That was my speculation and I appreciate the clarification.

DR. PAGANINI: Sitting as a nephrologist on the board, I was underwhelmed with the amount of renal data that was presented either in underlying renal dysfunction and their presentation of those type of patients to this type of stuff, or renal dysfunction created or not created by the drug beyond the 8-hour and 24-hour period since renal dysfunction tends to not reflect itself until 24 to 36 to 48 to 72 hours following creatinines.

The other issue that I would like to ask is drug-drug interactions. Does anybody have any drug-drug interactions beyond positive with aspirin, but even negative

ACE, ARBs, things of that nature? Would that set a patient up for perhaps worse outcome versus non-worse outcome?

Finally, any type of work with CKD patients, patients with creatinines that are in the range of 2, 1.92, or greater receiving any of these medications?

Has this confounded or given you any type of issues with more complications, recognizing that off-label use, especially those that were presented today have a much larger population of CKD underlying a lot of these patients that are going for this off-label use and it would be important for us to understand whether or not the renal dysfunction enhances or doesn't enhance.

A fourth question. These are all just very 40,000 feet questions that are just thrown out there. Our experience with gadolinium makes us very concerned about long-term outcome and renal dysfunction overall.

Are there any plans anywhere in looking at that long-term outcome with patients with chronic renal disease that might potentially be in somebody's database over a longer period of time?

DR. HIBBERD: This is Mark Hibberd again. Just a quick question on the renal issue. That is another patient

subset that would be interesting to look at in some of the outcomes databases, but from a Definity point of view at least, the kidneys are not motive primary excretion, so we wouldn't expect it to be an issue.

DR. PAGANINI: Can I just follow up a little bit? Actually, of all of the databases that were presented here, Definity had the largest number of what was called urogenital dysfunction in their database, but the others didn't seem to have that in their database.

I am just wondering why that is. Two, whether it is excreted or not excreted by the kidney, it can still be acute kidney injury can be affected by a lot of different things, not just a direct toxicity against the tubules.

It can be affected by hemodynamic changes, it can be affected by inflammation somewhere else. It can be affected by a whole series of things that may or may not have something to do with just excreting the agent through the kidney.

The issue that I guess I am trying to go in the back way is that the circulation that has been shown as a fairly typical circulation is an isolated muscle circulation with an arterial, capillary, venule.

In the kidney, that is not generally what happens. It is an arterial, capillary, arterial, venule later on, and that second rate of arterial, capillary, venules, may have some effect on proximal tubular cells or other tubular cells that are affected with acute kidney injury.

I am just wondering if anyone has sort of thought of that, or is looking at that, or if any database is set up for that, or if we should be looking at that, Mr. Chairman, in all of these classes.

I think renal has not been served well here and yet we know that acute kidney injury is a problem with a lot of dyes that are used in cardiac casts and other things.

DR. HIATT: I think those are excellent points, and I don't know if they are going to be answered today, unless someone from the sponsor can come up with some renal toxicity data, that may be something that the Committee should note, that is, information that was not presented.

DR. ROBINSON: The short answer is not of kidney relevance, I just want to try to put some context to it. The administration of Definity is about equivalent in terms of the number of bubbles administered in blood, the number of bubbles, the massive material that is administered is

about 0.75 milligrams, two of which are endogenous lipids. Then, you have got some gas which is cleared by the lungs.

So, the comparison with CT, with x-ray contrast agents where you are giving grams of material or MR contrast agent where you are giving grams of material and the potential for osmotic effects, et cetera, I just want to be clear that the potential there is, in my view, in a different realm. But I don't disagree with you. It is obviously something that should be looked at in more detail.

DR. FOUILLET: Interesting question.

DR. HIATT: Please identify yourself.

DR. FOUILLET: Xavier Fouillet from Bracco Research, Geneva. We have performed rapid dose studies in rat and monkeys for one month with SonoVue at very high dose of 5 mL/kg, and we did not find any adverse finding in the kidneys, in histopathology, in clinical test and in biochemistry. So, I hope it help the question.

DR. FOGEL: Mark Fogel from Children's Hospital.

As a pediatric cardiologist, I am very sensitive to the issue of intracardiac shunts and I know that there is actually a contraindication to these agents with intracardiac shunts, and we also know through numerous

pathology studies that there are small intra-atrial communications throughout adulthood even into 80s and 90s.

I guess I was wondering, in the patients either in the Premier database or in the spontaneous reports of fatalities, whether or not there was any evidence for any right-to-left shunts at the atrial level.

I guess I was also wondering, in adults, before you use the contrast agents, how do you ensure that there aren't any intra-atrial communications because like I said, there are numerous pathology studies to show that even octogenarians and people in their 90s can have small, sometimes even large, intra-atrial shunts, and especially if you using this in a setting where you can't see the heart very well in the first place, how do you ensure that?

I know at least when we do it in pediatrics, a lot of times what we will do is we will use agitated saline and inject, and we will see any right to left shunting across the intra-atrial septum at that level.

I was wondering how this all works.

DR. HIATT: That is a great question and just to clarify, then, if that remains as part of the box warning, how can you be compliant with the box warning if you don't

know about the shunting before you give the test agent.

DR. MAIN: In response to that question regarding the Premier database, no, we do not have any data on whether patients had intrapulmonary or intracardiac shunts, hospital billing data only, so we don't have that level of diagnosis, in our own database, I do not have that level of data either. We could certainly probably look at that.

Just one comment. I mean every day in the echocardiography laboratory, we perform agitated contrast saline injections with 9 cc of saline, 1 cc of air. We oftentimes add a little blood to that from the patient.

We agitate that, create very large bubbles and then try to force that across the atrial septum to prove presence of a PFO. Obviously, these are much larger bubbles with much greater standard deviation in terms of the size.

This is a study that is performed every day. We do this without any fear, and this has proven to be a very safe technique over time. You can certainly say the persistence of these air-filled bubbles is much less duration, nonetheless, it is a study that is done every day.

What we do in clinical practice? The product insert is unclear as to what constitutes an intracardiac

shunt. I would say that almost all clinicians do not view the 26 percent of patients with a PFO as having a clinically relevant intracardiac shunt.

The way this is interpreted in clinical practice is patients who have a clinically significant shunt, in other words, a large atrial septal defect. Obviously, we shy away from contrast injection in those patients, but it is not a common practice to exclude a patent foramen ovale prior to using an ultrasound contrast agent.

DR. FEINSTEIN: It is a good question on shunting. I think Michael mentioned the use of agitated saline, which is routine in our practice. In fact, every single transesophageal echo, particularly those that are sent to us for diagnosis of right-to-left shunts, we use agitated saline.

We put 1 cc of free air into 9 cc of saline and rapidly agitate it. The microbubbles looked under a microscope around 200 microns. When they pass through, they do go throughout the body. This is routinely done. This is an approved technique today, probably since 1985.

Historically, I got interested in this also because as I mentioned, macroaggregated albumin, which is

used as Pulmolite today, over 700,000 procedures are performed with particle-size up to 150 microns, whereas, the capillaries are 8 to 10 microns, and the microspheres are under 4.

These macroaggregated clumps of albumin are designed to get blocked in the lung and record with label of nuclear medicine techniques where the clots are forming, so it is a pulmonary artery blocking mechanism to detect PEs.

There are several studies back in the early '80s showing that when you take a gamma camera and place it over the brain and the kidney in these patients who are critically ill with pulmonary emboli, a certain amount of these large particles shunt through the brain and into the kidney, well established.

In some literature, if you want to determine the shunt through the heart, you give macroaggregated albumin, put a scanner over the brain or the kidney. So, there is literature on the effect of macroparticles.

There are daily effects of using agitated saline with macrobubbles, so I guess one would say if you are going to use anything, I would prefer to use the commercial ultrasound contrast agents for these patients. They are

smaller, they dissipate quicker, and they generally don't trap in the lung.

DR. TATUM: Jim Tatum, NIH. A question to anybody who has the nonclinical data. I was wondering about studies that have been done with repeated doses and you have had longer durations in animals, and if there is any signal in the pulmonary vasculature or in the lungs, period, as you get out, longer doses, longer times.

My rationale for asking the question, we already know with some nanostructures in preclinical settings that we are looking at some histology changes in the lungs with repeated dosing including macrophage increases.

DR. FOUILLET: I can speak for some of you. We have studies only up to one-month study, 28-day study, in both rats and monkeys, and we did not find histopathology findings in the lung. But I can at least speak for that.

DR. ROBINSON: With respect to Definity, in the primate, there have been repeat doses out to a month with high doses, and no lung lesions have been seen. In rats, we have seen some lung lesions with some eosinophil infiltration with repeat dosing. That is not seen after single administration.

DR. WARNER STEVENSON: I think we have certainly had very eloquent discussions from our clinical echocardiographers and certainly we would not want to deny an important diagnostic and therapeutic approach without which we might hurt many for a theoretical risk of perhaps hurting a very small number.

However, it has not been clear from any of these presentations. Again, when we do consider risk and benefit, are we considering using this routinely in all patients who have an echo, which was mentioned by one of these physicians, or is this something which we are recommending using when there is poor image quality, or for certain indications, such as post-MI or looking for intracardiac masses?

I wonder if we could have some clarification of any difference in these groups in whom we might be considering using the contrast media.

DR. GRAYBURN: It's a great question. I don't think anybody really seriously advocates using this in everybody. Most patients make good quality echos and don't need this. It is in stress echo, and I think Sanjiv mentioned this in his talk, that is a little bit of a

different story.

Stress echo is subjective, it is difficult to interpret, and unless they make a really perfect picture, it is beneficial, but in my experience, we use it about 10 percent of the time and heavily weighted toward the ICU where the patient makes crummy images because they are supine, on a ventilator, you know, can't roll over.

To get a good echo, you often have to roll the patient completely on their left side, have them blow all their air out and hold it. So, outpatient echos in our office practice are beautiful, we never need contrast.

In the hospital setting, particularly the ICU setting, we need it all the time although we don't really advocate using it routinely.

Another thing that I would just like to mention in response to your question is we would all really like to see proper adjudication of these described deaths.

You know, we have asked for that, and these come from different places, and if we are going to try to figure out is there a subset of people that are at risk, we really need to have expert adjudicators look very carefully at these charts and try to figure out did the contrast agent

have nothing to do with this or is there something about these patients that may relate to that. We need to get to that information.

DR. KAUL: Sanjiv Kaul. I would like to respond to Lynne also. Lynne, as we are using it more and more, and recognizing the utility, the indications grow.

For example, every suspected patient with LV thrombus we do it, but we never used to do it before. We thought we saw a thrombus, and would treat them, and now we know there is no thrombus there after giving contrast. In fact, it rule out thrombus more than it rules in, in the practical situation when you start using it in everybody.

You know, it started with LV cavity, you don't see two segments. Then, if you really want to do an ejection fraction, and you take end-diastolic and end-systolic, no matter how good your images are, you can't see the edges.

You can see them when you are moving, you can sort of interpolate with your eyes, but when you have just an end-systolic and end-diastolic, and you want to do an ejection fraction, accurate measurement, not eyeballing, the contrast helps a lot.

The more one learns, the more the indications, and

the indications are also afforded by the peers. The peers see something, the surgeons see something. They want that to be used. So, it is very hard to draw a line, you know, it is very dynamic, as you know, the practice of cardiology.

So, there some clear-cut image, lovely glass window, probably not, but there are so many other indications. Myocardial perfusion will use it for everybody because there is no other way to measure myocardial perfusion if contrast agents become approved for it.

Carotids, intima-medial thickness, like Steve said, intima-medial thickness is very hard to measure. But when you have that clear-cut edge with contrast, it becomes easier to measure. So, it is a moving target.

DR. HIATT: Before we go on to more comments, I would like to follow up on that and a question Lynne raised earlier. That is, that we get the impression that the indications for contrast agents is going to grow as more studies are done outside of particularly the coronary or the cardiac indications to carotid and liver and kidney.

The question I think that raises is does the accuracy of this test, which is better than uncontrasted, lead to additional testing, that if that is necessary and

appropriate, would be associated with reduced risk and better outcomes, or could it lead to needless procedures, which then trigger the harms associated with those procedures, such as the risk of a cardiac cath, and that that would then, in fact, enhance the safety signal.

The reason I am bringing that up is the charge before the Committee is to really wrestle with safety of these agents, but what we haven't heard today, and I would ask the Committee if you can comment on this, as well, do we really know if those assumptions are true or not.

To further clarify that, can these contrast agents lead to procedures that in and of themselves could cause additional harm, and therefore, the risk-benefit that we are trying to wrestle with has not been fully disclosed.

DR. KAUL: Very important question, but that is a question for anything. I mean any diagnostic agent or anything we do, will it be abused, will it be overused, where will it fit into the clinical picture.

It is very hard. You know, I mean, for example, you do nuclear, you do echo, you do this, you do that, and then we come up finally after some experience that maybe for this echo is better. Maybe for this nuclear is better.

Maybe for this--so I think that is how it was, and then the CT comes along with coronary angiography around the block, non-invasive, things change.

But it is very hard to know whether--unless you have enormous experience--whether you are going to answer the questions you are raising.

DR. HIATT: I am going to turn this question back to the Committee, and you don't have to answer right now, but we are going to come to this, because I think it is something that we have to wrestle with - what is the fair game here in terms of what are the long-term safety consequences of a diagnostic test.

DR. NEATON: I think that is actually an excellent question. That gets back to what I was asking before lunch about the benefit part, the presumed benefit, and what you are suggesting is that some of the presumed benefit may not be the case, because there may be diagnostic tests that are ordered that cause harm.

So, I guess two questions. In the Premier database, which I think is an excellent start in terms of looking at the safety issues, do you have data on the percentage of patients that went to other diagnostic

procedures?

Can you do some risk stratification according to kind of the nature of the contrast echo that was done?

DR. FEINSTEIN: Let me just answer that one directly. Leslie Shaw from Duke published I believe in 1998, in the Journal of Managed Care, the cost effectiveness of using contrast ultrasound to improve the efficacy and reduce downstream costs. It was really a cost effective study.

So, other than that one back in '98, when we were simply looking at LVO, left ventricular opacification, Leslie determined it was a cost effective mechanism to reduce downstream costs. So, I am going to stay on published literature on that one.

DR. NEATON: I am not familiar with the study, but was that based on presumed benefit downstream and estimated cost, or actual benefit?

DR. FEINSTEIN: At that time, '98, based on standard of ultrasound imaging as it is today, which lacks clarity in probably 15 to 20 percent. Extrapolating those to additional tests, which would be a transesophageal echo or nuclear study.

So, if you get an answer directly for LVO or ejection fraction, you don't proceed. So, it was simply limited to ejection fraction, which is the main call for us.

Now, if I could just answer to Dr. Stevenson's point, the ASE guidelines, which Sharon Mulvagh was the senior author, and she is here, in the year 2000, it was very clear to guide the clinician what to use and when to use contrast. Two out of 6 regions, as I showed, greater than that, of course you use it, less than that, no.

So, those are the standard guidelines that we follow today in our echo lab, and those are taught to our sonographers, and those we represent.

The issue of efficacy, when we came here, we were all very clearly focused on safety and looking for a safety signal, which quite honestly after hundreds of hours of work and release of data to us, we didn't find.

Efficacy, we believe these agents are efficacious. That is what they were approved for by the FDA. So, I have to stand by that. The ASE guidelines are based on efficacy, so that necessarily wasn't our point unless others would like to speak to that.

DR. NEATON: I understand that. I mean your

definition and the way the agents were approved is different from my definition of efficacy. I am not interested in kind of whether the measurement of ejection fraction or the ability to see the image. I am looking at down the road implications of doing the contrast.

DR. FEINSTEIN: That is called effectiveness I think.

DR. NEATON: Maybe we will call it effectiveness, but if I could ask the folks from Bracco for the study that was published by Jeetley.

DR. FEINSTEIN: Do you have the data there for 12 to 15 months of what the differences were in terms of mortality for the two randomized groups that you studied?

DR. SENIOR: I was the senior author in that paper.

In that particular study, we compared stress echocardiography with contrast with exercise ECG, so there are two different tests which are done in a randomized fashion.

The purpose of that study was to look at exactly what you have asked, to look at cost to diagnosis, and we looked at outcome, too. But the study was not powered

really to look at outcome as much as to cost to diagnosis.

So, when we looked at cost to diagnosis meaning if we do an exercise ECG versus a stress echo with contrast, what happened regarding the downstream cost, we found that, although exercise ECG was cheaper to start with, it was about 70 or 60 pounds, and stress echocardiography with contrast was costlier, at 130 or 140 pounds. But the downstream investigations were much more in the exercise ECG arm, because we couldn't come to a diagnosis.

So, these patients underwent cath and many of the cathes were normal, normal coronary angiography, or they underwent another investigation because they were considered too high risk to have catheter at that time, and then they proceeded to cath.

So they had more investigation. Therefore, it became more costly. While, with stress echo, very few patients underwent cath who were negative, and those who were positive, when they underwent cath, they had revascularization, so meaning it was accurate in determining that these patients should undergo catheterization with revascularization.

In those terms, it was more cost effective. Now,

when we looked at the outcome data, meaning those in whom we discharged, saying that they were fine, in the low risk group there was no difference in outcome in terms of exercise ECG.

Both were equally good in predicting that the patient is fine, but the number of patients that we could discharge was much higher with stress echo because we could come to a diagnosis very quickly compared to the exercise ECG.

DR. NEATON: So, in other words, you are not powered to really look at long-term outcomes in the two randomized groups. And there were more procedures, more diagnostic procedures that were costly done in the exercise.

DR. SENIOR: That's right.

DR. NEATON: It just seems that as you broaden this indication, that you have got to begin looking at longer term data than 24-hour mortality in terms of understanding kind of the benefits and the relative safety of the product.

DR. HIATT: Before we continue here, Dr. Rieves has a comment, and I also want to note that we are in kind of an open question discussion phase. We are going to be

transitioning to the questions to the panel, and we are going to want to do that here in a minute.

But, Dr. Rieves, do you want to make any comment about process right now?

DR. RIEVES: I will try to be brief. It is a challenge here, and dealing with isolated perceptions of safety it is very uncommon to weigh. We usually look at risk-benefit. I do think we have to consider that for the diagnostic agents. They are somewhat unique in that we have a very specific guidance from the FDA and, when we do have a product that we are bringing to the Committee for risk-benefit assessment, we will need to review our guidance on efficacy demonstrations because there are different levels of efficacy.

It hinges very, very heavily on what the company proposes as a marketing claim, and that level of claim can vary almost from the trivial, meaning I can make the picture better--and that may be sufficient--all the way to actually demonstrating a diagnostic clinical benefit, which some would perceive as the highest hurdle where we actually have a demonstrable diagnostic benefit.

For the marketed ultrasound contrast agents, I

would like to emphasize that the approved FDA claim that is made is a structural claim. It is not a claim of diagnostic benefit. It is a claim that we can see the left ventricular chamber and the endocardial border better, that is not a marketing claim for a diagnostic benefit.

But as you can see here, as illustrated, once these products are approved, they are out on the market and perhaps reasonably so, we understand that, they are used in much broader indications. And, as you can see, last year, we were in the dilemma of having a very constrained premarket database as well as largely relying on testimonials of presumed benefits to try to assess.

So, we appreciate the conversation, but with respect to diagnostic efficacy, I want the Committee to understand that what we are dealing with in terms of demonstrated, approved by FDA, is among the lowest level meaning a structural claim for the companies in terms of FDA approval.

DR. TEERLINK: I actually was going to address partly that point, myself, as well, in terms of I think, at the risk of having Dr. Grayburn think I am patently absurd, that there is a perhaps shift in kind of how we are looking

at risk-benefit in the diagnostic testing.

One of the issues for the sponsor is going to be as there is an increase in push for saying that these agents do more and more. I mean a lot of these presentations have been predicated on the fact that there is clinical benefit, and the clinical benefit so clearly outweighs any potential risk. Yet, we haven't really seen any of that, nor was that actually the purpose of this meeting.

One of the challenges is going to be we are now kind of moving--and this is in the devices. You know, I had the honor of sitting in a lot of different settings, and it is happening in the devices, as well, where we are moving from these diagnostic tools, these devices as tools, saying, you know, it just does this thing and approve it just for this thing, to saying it has to make the patient feel better, live longer, and how do you show that.

In the area of diagnostics, it is particularly difficult because your diagnostic tests may or may not have anything--you can control your diagnostic test, but it is very difficult to control what physicians do with that information.

Nonetheless, our duty and our charge is to protect

the public health, and if what the physicians do with that information is bad for patients, even though your tests may do exactly what it says it does, if there is a suggestion that it might hurt other people later on down the line, it would be incumbent upon us to look at that type data or demand that type of data.

It does not apply to this current situation, but I think it is, as we look forward to how to look at other diagnostic tests, needs to be brought into some perspective.

In addition, one of the things I was also going to ask about was there was a postmarketing commitment previously for Definity, I believe, that remained unfulfilled I guess was what you had termed before, and then there is now a risk management plan.

I think it would be interesting to hear what that postmarketing commitment was, what the obstacles were to completing that, and what the risk management plan is that is in place.

DR. DAY: I had a comment about that, as well, and I noticed that the risk management plan had updates of the label, health care provider education, and two types of studies. I did a search through the briefing materials from

all the companies on the health care education component and didn't find much.

Lantheus had some in there, but it would be good to hear about this especially because when we segue into the questions, there are now three questions, whereas, in the draft questions sent to the committee there were 4, and the last one was about risk management plans, the current, and if any were needed in the future. That question now no longer is before us today.

So, any comments about things that are going on now would be helpful, and I would like to ask the Chair if there is time towards the end of the afternoon, that we could address Question 4, which is no longer existing, whether that would be possible.

DR. HIATT: I guess I would turn that question over to the FDA.

DR. RIEVES: Yes. Our intent with our own questions was to generate a productive discussion. Those questions can be engineered if you see that it will lead to really moving the field forward, which is all our goal.

DR. DAY: And I just wanted to comment that you have several people here on the panel with expertise in risk

assessment and management plans.

DR. HIBBERD: Would you like me to respond to the question about the risk management plan?

DR. HIATT: Yes.

DR. HIBBERD: Mike Hibberd, Lantheus Medical Imaging. I would just like to make the point that the new company Lantheus is fully committed to executing the various parts of that risk management plan which have been put in place.

I think it is fair to say that the original sponsor of the NDA was slow to execute some of the postmarketing studies although an ongoing dialogue with the FDA did exist.

However, in a forward looking fashion, Lantheus has already begun a very large prospective registry for safety, which looks at adverse events and a variety of other hemodynamic parameters, as well as the impact of the monitoring that was requested for certain conditions under the former label, so that study is underway.

We have also committed to do a small prospective study in patients with and without pulmonary hypertension later this year in all likelihood to try and get further

information on the potential safety or lack of safety in that conceivably at-risk group.

In addition, there are some other commitments, but we have a headstart on that already in the sense that the Premier analysis that was presented today and other ongoing analyses were already started at that time and so we are providing some of that information in advance of the commitment made to the FDA in that respect.

So, looking forward, Lantheus in particular is very committed to making sure that this data is accumulated, reported publicly, as well as to regulatory authorities.

DR. HIATT: Thank you for that.

We can go just a few more minutes. I think we are going to have time for these questions, but relatively soon, I would like to transition to the questions.

Michael, please, and we will kind of wrap up here in a few minutes.

DR. LINCOFF: I will try to keep it quick. I would like to sort of maybe take an alternative approach to John Teerlink's assertion in terms of what we need to balance in terms of downstream consequences.

I think the goal of any sort of regulatory

approval is to decide if a test, a diagnostic test has an advantage over other diagnostic tests that have similar or worse safety, and to try to balance the safety of a diagnostic test that we are looking at against the other tests that may be replaced or made unnecessary by a new test.

I think whether or not the results of such a test are abused or used inappropriately by clinicians thereafter to lead to downstream events is not really the purview of a regulatory agency, but more the professional agencies. It is guidelines in terms of use.

Now, that is different from saying that I am worried about a drug that we approved for one indication, that people might use for another, and that is a higher risk indication, and the risk-benefit may change in that indication. That, I think is valid, and we have certainly done that at other times in the past.

But if you don't believe that a test is going to be used in a population that may expose that population to a much higher risk than the population that you are comfortable with the safety data, if you think that it will be broadly applied, that you have enough safety data in that

group, then, I think that is the question.

So, in my mind at least, I think what we should be focusing on is whether we believe the safety data that we have seen provides a reasonable level of confidence and what additional steps need to be taken to broaden that confidence perhaps to the other patients that might be included in a study for other indications.

DR. KASKEL: I would like to echo my colleague Emil's comments about the lack of renal data. Those are provocative slides showing a renal transplant and the ability to discern acute rejection. This has tremendous clinical application in the field of transplant medicine, and I would urge the industry to devise appropriate preclinical testing, knowing that these agents have vasoactive effects.

A kidney after transplant has high thromboxane levels. All the drugs we use stimulate some of the vasoconstrictors in the kidney, so clearly, that needs to be evaluated in preclinical studies, and also in terms of testing to make sure there are no short-term and long-term outcomes.

We need to use some of the more sensitive

biomarkers that exist, and in the kidney, unfortunately, besides proteinuria, we have some new ones now on the way that could be looked at in preclinical studies and in clinical studies, such as NGAL and Kim1. There are biomarkers. The NIH just had a meeting a few weeks ago here about the use of biomarkers in immune disease, so I would encourage research, both preclinical and clinical in the area.

DR. FLACK: Is there any knowledge about the effects of these agents in patients with pulmonary hypertension? Pulmonary hypertension is actually relatively common clinically, given all the lung disease, HIV, obesity, and cardiac disease that we see.

Earlier, it was pretty localized or pretty clear that the effect on the systemic hemodynamics was being mediated through change in the pulmonary circulation.

Again, this is not critical if you don't know, but this is really trying to ask, one, do you know about anything specifically with patients with pulmonary hypertension, and, two, going forward, would you be prepared to examine those patients, because it seems to me that trying to find a needle in a haystack with these

complications, what you are really looking for are easily identified markers of patients who might be at heightened risk to have more than a minuscule chance of complications.

DR. HIATT: Maybe if the sponsors wrestle with that, perhaps that will be our last question for this part of the discussion.

DR. FEINSTEIN: Thank you. Yes, Dr. Flack, this morning when I presented some of the data from 1995-96, the sponsors at that time were asked to segregate out high risk patients, respiratory patients.

They did that. When I reviewed the data, even with three and four times the dose of Optison which we currently use, those patients had fewer AEs than the non-impaired. So, impaired pulmonary COPD, bronchiectasis had fewer events than the non-impaired and fewer than the overall group. Those were about 199 patients studied.

The study that actually the FDA brought to our attention, Ira did, was the Erb study, these patient undergoing cardiac bypass surgery performed in 2001, 35 patients, uninterrupted anesthesia, sick patient. Their ejection fraction on the average was 40.

Now, PA pressures--and I went back to look--were

all over 30, 35, and that was the average. So, these are sick patients with elevated pulmonary artery pressures receiving direct central venous bolus injections serially of Optison in the OR with continuous monitoring.

So, based on the Optison data I saw from 1995-96 with the impaired pulmonary patients, absolutely no effect on pulmonary saturations, based on the Erb paper zero change in the pulmonary, and that is at least historic data.

DR. SENIOR: We have published the data, which I think you do have the paper, it was published in 2001, where we looked at patients with reduced ejection fraction and Class II to III heart failure. Many of them were actually in Class III heart failure. The mean ejection fraction was 30 percent and all of them had increased pulmonary artery pressure. The mean pulmonary artery pressure was 25 mm, the normal is 15 to 16. That is, we took the systolic and the diastolic and meaned it.

There, we gave SonoVue in 13 patients and 6 we gave saline, and these were randomized controlled trial, and no difference was noted in terms of pulmonary hemodynamics, mean capillary wedge pressure, cardiac output, and oxygen saturation.

So, it's a small study, but we didn't find any difference in hemodynamics.

DR. HIATT: Thank you very much.

What I am going to do at this point in time is call for about a 10-minute break. We are then going to present the questions and spend the rest of the afternoon discussing the questions.

[Break.]

DR. HIATT: As people are coming in, this phase of the discussion primarily focuses within the committee, what the committee has heard and how they reacted to the presentations, the backgrounders we reviewed, the questions before us, and a word to the sponsors and the interested members of the public, that we would like to be able to call on you to clarify questions that we might have, but we are not going to be looking for an extensive back-and-forth discussion. This will be more areas of clarification.

If you feel passionately that something is misrepresented, certainly, let us know and we can try to hear that concern.

What we would like to do now is transition to the Questions for the Committee and focus our discussions mostly

to those questions.

With that, we are going to get an overview of the questions.

FDA Introduction to Questions

DR. KREFTING: Good afternoon, everybody.

[Slide.]

I am Ira Krefting. I am a medical officer in the Division of Medical Imaging and Hematology Products. As you might have noticed, I also joined the ranks of the hairless presenters today. However, as far as I can tell, even though I only use accept-assignment doctors, I believe I never got Definity.

[Slide.]

What I am going to do in this discussion today is perhaps restate the obvious to you. Our expectations as the Division, our interests in calling this Advisory Committee, our hopes in calling it is to get answers to some questions we are going to propose.

First, to reiterate, as you heard earlier from Dwaine, why is this Advisory Committee different from all others. Well, here, this is an Advisory Committee where we have engendered discussions. The discussions so far have

been so good, it seems that you have stole a bit of my thunder and already mentioned some of the questions coming down the road.

As you have all noticed, we are not discussing one specific agent here. We are not asking the Committee to vote on approval or disapproval of a specific application before them. This is a discussion. It has been so lively so far, to heighten awareness of these agents and talk about some of the very important points that have already been brought up as the day has worn on.

What we are seeking guidance on is three areas, and to introduce the questions to you, given that there are three broad areas, we will have three major questions to present. The first of those questions will revolve around the preclinical trials. You have heard so much discussion already.

Our next group of questions will concern clinical trial design and, finally, making up the trilogy will be questions concerning class labeling or class issues for these agents.

Of course, we are honored to have all of you folks here and the brilliance of some of the points that have been

put forth, if we have time and inclination, there is no crime in moving forth to a fourth question if we want to discuss it.

[Slide.]

To start, our first question is: Please discuss the relevance of the hemodynamic alterations in animals to the reports of serious events in patients, particularly the data from studies in pigs.

As it has been reiterated multiple times here, the reactions in pigs are suggestive of similar but very uncommon events in adults.

[Slide.]

Point (a) of that is: To what extent are the animal data useful in estimating risks for patients with serious underlying conditions such as acute respiratory failure? For example, are the findings in pigs more applicable to these patients, compared to the findings in less "sensitive" animals?

Implied in this question is our concern in that the sick individuals who get these studies, particularly individuals with respiratory compromise, is their histology, is their lung pathohistology more suggestive of what is

going on in the pig.

We heard partial discussion about that a little while ago.

[Slide.]

Part (b) to that question is: Are the animal hemodynamic data useful to estimate share human hemodynamic risks among the ultrasound contrast agents?

For example, if all ultrasound contrast agents produce very similar hemodynamic responses in animals, to what extent does this information suggest that the ultrasound contrast agents will have similar hemodynamic risks in humans?

I am going to move along to all the questions and I will turn the podium back to the Chairman at the end for his skillful discussion with all of the members, but I just wanted to give this overview.

[Slide.]

Moving on to our second question: Please discuss optimal ways to establish clinical safety and efficacy of investigational ultrasound contrast agents.

[Slide.]

Part (a) of that is: To what extent can a single

arm study design in patients with serious comorbidities
identify ultrasound contrast agents-related adverse events?

Part (b): What are the potential comparator
groups for randomized studies of investigational ultrasound
contrast agent safety?

[Slide.]

A further part to that question, Part (c): Does
the inability to mask or to blind ultrasound contrast agent
studies support the use of a single arm design? For
example, does the "open label" nature of the studies negate
the advantages of a randomized comparator group?

[Slide.]

Finally, the third question section is: Safety
risks for one member of a "class" of drugs may represent
risks for all members of the drug class, given similarities
among the products. What are the important considerations
in determining "class" safety risks for ultrasound contrast
agents, especially for serious but very uncommon risks that
are not likely detectable in the premarket clinical studies?

[Slide.]

In addition to any other items, can the Committee
comment on the limitations or importance of:

- a. Physical or chemical nature of the products, the microbubbles we have been talking about over today;
- b. Mechanism of diagnostic action (echogenic contrast)
- c. Effects in animals, the similar hemodynamic responses that have occurred in pigs and perhaps in human beings.

With this brief introduction I will turn the podium back to the Chairman to further discuss the issues and questions and perhaps if we could bring the slides back to the first, that would be great.

Thank you all very much.

Discussion of Questions to Committee

DR. HIATT: Thank you very much.

Let's try to focus through these questions and then we will get to the risk management issues, as well. I think there should also be time to discuss any other broader related topics to this one, because we are talking about not a particular agent and we are also looking forward in what might be required in the future.

Does anyone want to lead off on the first question? The relevance of hemodynamic alterations in

animals, the serious events in patients, particular in pigs.

DR. HENNESSY: Usually, we rely on animal data when we don't have human data. That's the most important time to rely on, and once you have human data, like we have on these contrast agents, I think that the animal data become less important, and to state the obvious, sometimes animal data are generalizable to humans and sometimes they aren't, and I don't know of any good rule of thumb to figure out when they are and when they aren't other than figuring that out.

Also, to state the obvious, some of us are more like pigs than others.

[Laughter.]

DR. HIATT: Thanks for that comment.

Just as we go around on this one, I think everyone here would recognize significant limitations to any animal model particularly in understanding safety as opposed to mechanisms of action or efficacy side of the equation but that, as one of the other presenters pointed out, there may be opportunity to discern signals and also there appeared to be a relatively consistent hemodynamic response which was further clarified as what I think was said is pulmonary

vasoconstriction leading to decreased cardiac output and systemic hypotension rather than a specific myocardial depressor effect or effects on systemic vascular resistance.

So, that signal might, in fact, be of interest to the Committee.

Michael.

DR. LINCOFF: I think the key point, first of all, is that we are not only looking backward at the agents that exist, but there is also a question here as new agents come along, so what is the potential efficacy of animal models.

I think, Bill, that you have really pointed out the main issue is that these models can sometimes help illustrate mechanism although we don't know if the mechanism is the same.

The manifestations may be similar, that is, a rise in pulmonary artery pressure and drop in cardiac output in this case, but it is very difficult to say is it because of the same basic pathophysiologic mechanism, but nevertheless, it may give us some insights and it may also give us some insights into potential ways to prevent it.

I think what is very clear is that animal models are not at all predictive of the rate or the risk or the

incidence of an event in a human, and whether or not they help clarify whether there is a class effect. They might if there seems to be a consistency with different agents and newer agents showing the same effect. You might expect the same effect once you accumulate enough patients to have a safety signal.

DR. TATUM: One of my colleagues keeps saying that the only relevant species is Homo sapiens. We talk about nonclinical data here instead of preclinical, and I think that is reasonable. But, in the preclinical setting, my understanding of why you do the testing is to actually develop signals that you really don't expect, or you don't have a great idea about, and the ones that you will then actually be investigating or looking into as you go into Phase I and Phase II.

I think the danger you are running into here is we are taking a signal that was developed, then, was monitored, and now we are now we are looking back on it and say oh, gee, it was more significant than we thought, and that is really a dangerous piece. I think we have to go forward with the clinical data and particularly when we are talking about an imaging drug.

This imaging drug is a little different because it does have a potential physiologic effect, but in most cases, in imaging drugs, it is not like therapeutics, we are looking at toxicity profiles and other things, so we have a very different way that we have to begin to look at these.

So, there are two things. One is the efficacy issue, and I think the models that we are looking at here weren't really designed for looking at efficacy necessarily, but that is really important in the imaging as we look into other imaging modalities and other tumors, and those types of things, and then to look also what the potential is for the toxicities related toward the effects.

The idea of the exploratory I&D has been a great one, where we are able to actually use microdosing in small doses, what you do in therapeutics to actually get some of that human experience right upfront and begin to start at it.

The other thing in this discussion we keep going back and forth about is we are talking about diffusion of the technique broadly. And we are concentrating on actually what we believe might have been side effects in the highest risk population and the diffusion is not likely to go into a

higher risk but into a lower risk population at the same time.

I don't have a problem with using a very sensitive model, but that is only because you are trying to look for the lowest signal. But then, after that, I think you have to go to the nonclinical to actually understand the mechanistic studies in the back side of it, and they override what we saw in those first three clinical models.

DR. HIATT: I think we would all agree that the clinical trumps the preclinical. But the absence of a safety signal in an animal model does not make you feel better certainly when you look at humans.

But the presence of a consistent signal in an animal model that has a hemodynamic profile that might lead you to concern particularly because the class of drugs was initially developed for cardiac imaging is one that I think is noteworthy.

Then, the other signal might be the anaphylactic reactions to the drug, so that there may be some signals here that are noteworthy and then as we think--well, I don't know if we have heard this or not--that there may be subpopulations, say, pulmonary hypertension where further

hemodynamic measurements might be warranted.

If the signal is excluded in that population, then, that would also be informative. But that sequence of events as a pig model that might be hypersensitive is, to me, not a bad thing, because it points the way to look for something that your responsibility is then to refute that that signal is present.

DR. TATUM: Absolutely on the same page.

DR. TEERLINK: Along those same lines, I think the idea of the preclinical data is to give you some idea of whether the things that you anticipate are going to happen or not.

So, in terms of going forward for these types of agents, you know, if you look at the kind of broad categories, what you are mostly worried about, there is capillary compromise, and this is either through mechanical format--there are either vasoactive type substances or there is going to be actually endothelial damage.

Each of those different models should attach each of those kind of different problems. Then, there is the immunologic group of damages, which includes the hypersensitivity reactions and whether you, in fact, do

develop some kind of antibodies to it or things like that longer term, which in this case obviously you didn't.

Then, those can be translated in the process of looking at those, looking for the idiosyncratic reactions that pop up as further signals for your clinical program.

So, I view the preclinical studies as ways to kind of put to rest at least in an animal level the big risk that you think might be there and then also observe for possibility of syncratic reactions that might emerge.

DR. HIATT: And to your point, too, we superficially see these as transient risks, so we are not talking about chronic oral drug therapy where the risks may be maintained throughout the course of the therapy, but rather transient risk.

But that still doesn't prevent the possibility of the cascade of events that might lead to risks that are perhaps a bit more long term than one hour post exposure.

DR. WARNER STEVENSON: I think we need to distinguish between the risks that we would expect in an otherwise healthy population, to which the animal data may be most relevant, and the risks in a patient who has a long sequence of chronic conditions which are almost impossible

to duplicate in animals.

DR. HIATT: So, sticking on the animal model issue, can the inform us, because you mentioned earlier that, in fact, the risks are on an absolute basis in humans very low. There may be subgroups for whom that risk may be higher.

Perhaps the example where the ultrasound energy is turned up and the bubbles are destroyed intentionally, is that a potential subgroup at risk that could be studied in an animal model.

I mean obviously, animal models of diseases are challenging particularly in the context of a contrast agent, but can the Committee think of other questions that might be appropriately addressed at this level?

DR. FLACK: I think one of the potentially important findings in the animal models--and I agree that actually if you are going to study the animals it is probably good to study those that are a bit sensitive, because studying a bunch of animals where you will not find anything is not going to help you--it is to actually look at mechanisms and then basically take that information and look at people who have either a pharmacologic agonist or

antagonist at potentially these targets or genetic predispositions, maybe have abnormalities or non-physiologic abnormalities in these systems and try to assess whether that is telling you anything about risk and really putting people above these sort of needle in a haystack sort of a risk that you have, because these agents appear pretty safe except when you get in certain groups of people and there it is hard to sort out from the disease itself.

So, that is how I would use the animal data.

DR. HIATT: John, I think you triggered another thought that we didn't hear much about concomitant medications in drug-drug interactions, and so that is an opportunity. The other interaction that wasn't really discussed at length was the ultrasound energy as one variable versus the contrast agent as the second variable, and the interaction between those two variables was discussed a bit, but we don't know. There is a flat dose-response across all ultrasound energies that were delivered and once again an animal model might be useful for that.

DR. FLACK: And also, too, this whole notion of how you administer the agents, whether it is more continuous or more bolus, it seems like it is important based on some

of the data that I heard.

Perhaps in some of these datasets that needs to be examined as a predictor variable as far as risk because it is easy to get your hand on.

DR. TATUM: Dr. Kaul had brought that up. I wonder if he has anything more to say about that, because he was saying that he used a continuous infusion instead of a bolus, and I know that is true for nanostructures again where boluses can be problematic.

DR. HIATT: So, the approach is just to focus on the particular question.

DR. KAUL: Yes, I will focus on that, but I have to give you a little bit of context. The context is that the reaction we see is very similar to liposomes. If you look at liposomes, they have very similar reactions even in humans.

It is almost all complement-mediated. I mean you are talking about pulmonary macrophages and all that, but we have no evidence that in humans it raises pulmonary artery pressure. We know it causes hypotension, but we don't know if it raises pulmonary artery pressures simultaneously.

So, it may simply be complement-mediated, and I

think if that is the truth, then, obviously, a very dilute, longer duration of administration will cut down the chances of complement activation and the amplitude of complement activation.

DR. HIATT: That comment perhaps further illustrates that maybe the mechanism of what struck me in the preclinical was the pulmonary pressure increases, the systemic vascular resistance decrease. Maybe that is not fully worked out, because to get back to that earlier point, it might matter if everything that is occurring systemically is derived from pulmonary vasoconstriction versus an inhibition of cardiac function versus peripheral vasodilation.

That might be a mechanism that is worth exploring further because there may be patient populations for whom those different mechanisms might be relevant in terms of safety.

DR. FOX: I heard a couple people now mention the potential for drug-drug interactions, and clearly that is a very important area for drug development in general, usually predicated on findings in the preclinical investigation around the routes metabolism for the active drug product

itself or one or more of the excipients through cytochrome p450, et cetera.

I think the sponsors for this class of agents have done a good job in showing that the components of the products are either in inert gas that is excreted unchanged at the lungs or are endogenous components that are cleared through sort of either reticular endothelial mechanisms or lipid metabolism.

I guess before we encourage the sponsors to go down a route of additional investigation looking for drug-drug interactions, I would like to hear maybe what the basis for some of those might be.

DR. HIATT: Well, some drugs might be pulmonary vasodilators, others not. I mean at least in the cardiovascular disease population we know what the background medicines look like.

We talked earlier today about aspirin and perhaps a dose of aspirin might be protective if it's thromboxane mediated. You know, some background medications may predispose to protect you if there is an endothelial component such as statins or ACE inhibitors.

So, I am just speculating here, but it does sound

like if there is a drug-drug interaction that might lead you to a subgroup at risk, that that hasn't been ascertained in the safety database thus far.

There is a second part to this animal question. I think we have kind of hit on this a fair amount already. It has to do with hemodynamic changes that were demonstrated. Does the animal hemodynamic data, is it useful to estimating the human hemodynamic risks of ultrasound contrast agents, that is, if every drug in this class has a similar hemodynamic profile in animals, would that extrapolate to similar hemodynamic risks in humans.

Could we discuss that a little bit further? Is anyone concerned with--you saw the background or the data presented in animals--

DR. WARNER STEVENSON: I think, in general, as we have said, if there is some profound effect in animals, it may trigger us to look for it in humans. On the other hand, I think we have to be careful not to be looking at a human model for porcine disease instead of a porcine model for human disease.

One of the things, as well, I think we didn't didn't discuss very much this morning, is that, in order to

do these elaborate hemodynamic studies in animals, they are anesthetized and restrained such that one could certainly miss many things that would happen in an awake animal I think. So, if we see it, it is interesting. If we don't, I am not sure what we can conclude from that.

DR. KASKEL: You know, there are genetic animal models of vascular reactivity, and it may be worth looking into preclinical studies using some of these transgenics that would allow you to test pulmonary and/or renal vascular reactivity to these agents.

That would be something that they could consider, as well. Also, I think we need to think about the genetic variability in the host-response to these agents. That hasn't really been addressed. We didn't see any demographic breakdown in the clinical information presented this morning, but could certain groups have different responses than others, I don't know, but it is worth considering.

DR. HIATT: Other responses to the first question? I guess I would like to try to summarize a few things and see if you agree, that the question before us in essence, are these animal models helpful particularly the pig.

You heard varying opinions about that from the

sponsors' research, that maybe it was not representative of humans, i.e., they were overreactive. Others felt that, gee, that's a good thing because that maybe give you a signal of concern that an underreacting species might not.

I think the consensus is that, at least from the data we have seen, that it has been helpful, that there are a couple of things that have been identified, animals that appear to be something that would carry you forward in terms of selecting a population of patients who might be at risk, those with pulmonary disease in particular.

I don't think we are pushing anyone to go further into an animal-based exploration to understand these rare safety events in humans.

Is that a fair consensus? Does anyone want to disagree? All right.

I don't want to race through these. This is the best part of the day.

The next one actually perhaps should generate a bit more discussion. Discuss optimal ways to establish the clinical safety and efficacy of investigational ultrasound contrast agents. This is now what you have seen today and the signals of concern, and many statements that were

proclaimed by many of the presenters that there is an inherent good, more accuracy in these agents leading to presumed better outcomes. Then, there are three components to this question.

To what extent can a single arm study design in patients with serious comorbidities identify ultrasound contrast agent-related adverse events?

Let's discuss for a moment now. You are trying to establish the safety database of some kind. You saw that it doesn't take a lot of patience to demonstrate efficacy, and this is often the case in these situations, as is the case for symptomatic medications for cardiovascular indications where a small number of patients is adequate to demonstrate efficacy, but the exposures are so low that safety is left undefined.

I think that these questions should open us up a little bit. In addition to just the focus of that question, what are the potential design considerations before the FDA advising new sponsors for the sponsors to consider in understanding these safety signals.

The first question is about a single arm study, which to me means no placebo or no comparator. Let's start

with that.

DR. WARNER STEVENSON: Once again, as you point out, it is difficult to test a diagnostic agent versus a therapeutic agent, and what we are really doing is testing a strategy more than just the substance.

I would wonder about what could almost be like a dose ranging study in which in one arm everybody gets the contrast agent. In the other arm, you don't give the contrast agent until you have done the initial study and you have decided that you don't have good resolution, in which case, if the first arm does better, then, perhaps you should be using it more; if the second arm does better, you should be using it less.

It doesn't necessarily answer the absolute benefit, but it does help answer the strategy question of how one might use it. This is presuming you have passed your Phase II level in which you have decided that there is no obvious immediate severe toxicity.

DR. HIATT: Lynne, that is a really excellent comment. In my mind, it might address safety and efficacy particularly in the broader context. We need to go there.

Let's talk for a moment about the safety side of

the equation. What can we learn from single arm studies in terms of safety?

DR. LINCOFF: Well, single arm studies clearly have the potential to accrue the most patients in the shortest period of time, because, in general, these are registry experiences, often postmarketing, but not necessarily but because of the absence of randomization and often their entry criteria could be broad, which is exactly what you want because what you want is to focus on potentially the higher risk patients.

Any kind of randomized design will often mean that you will be taking out the patients in whom you are actually most concerned about, either because you feel like they can't do without the test under evaluation.

So, the difficulty, of course, is that you don't know how to compare that to a reference. You can obtain a point estimate for the complications that you are concerned about and the confidence interval. You can also identify idiosyncratic things that you never expected on the basis of a single arm study.

I mean they are certainly useful. You can also-- and this may be tromping on to b, but it's a little bit of a

related issue--you can also take a contemporary comparison group with if you collect enough data with the attempt to do propensity analyses to try to take out the factors that contributed to the non-randomized assignment to one therapy or the other, although those are clearly limited. But certainly they are better to do those prospectively than try to look back retrospectively when you haven't collected much data.

So, I think these are clearly, you know, the best way to identify these infrequent events although it is difficult to say whether or not they are more frequent than they would be with the other therapy.

DR. HIATT: Thanks for that introduction. I think Dr. Main and others made the statement that I agree with, that the risk of an event, whether it's mortality or an ischemic event or an allergic event, maybe the latter is not the best example, that the risk of these cardiovascular events is driven more by the underlying disease than it is driven by the therapy or the diagnostic agent.

There is always going to be a background event rate, and that event rate will vary based on populations and their risk factors, their age, their other comorbidities.

Therefore, in a single arm study, you will never obviously be able to distinguish the background risk of an event versus that induced by the agent although I would concede that you might pick up completely unexpected reactions that were not associated with the underlying disease.

DR. NEATON: I would agree. I would stay away from a single arm study in the broadest definition. I mean you want some control, preferably randomized, but if not randomized, you know, kind of a concurrent control or historical control as was suggested.

I wonder, I mean I actually thought in the material that we were given to read, that some of the studies that were done--we saw some presented today on the mild to moderate adverse events. That is where you really need to have preferably a placebo controlled or randomized controlled.

I think there I would encourage those kind of studies still to be done, and I would like to see them powered to look at a broader efficacy outcome than what was done in the earlier studies that we discussed earlier, at least indications or diagnostic tests down the road.

For the more serious events, I think that is being done now in the Premier database may be the only route you are going to get there with it, because of the rarity of the events. And so I think some plans to make certain that there is a prospective follow-up of a large number of people with concurrent controls in a database like that would be very important to supplement a randomized study to look at kind of mild or moderate events, things that could be done in a few hundred people as opposed to 10,000 or 20,000 people.

DR. HIATT: Absolutely, and we will need to discuss at length the nature of observational studies whether they are retrospective or prospective.

One other comment, though, on this question. We tend to focus on what is necessary to prove a drug or an agent is effective, it works, it answers a specific hypothesis. But I think developing safety databases is a different activity sometimes, and in that case, exposure in events is what matters.

We shouldn't necessarily confuse our thinking about what you would ask us a sponsor to do to prove that the therapy or the diagnostic test works versus what you

might ask them to show you that it doesn't cause untoward side effects or harms.

DR. FLACK: I think the randomized studies are probably going to have to be tilted toward high risk groups of people. One of the things that I worry about is that some of these events are probably so infrequent in lower risk groups of people, that you may study several hundred people and easily miss something that is important.

On the other hand, you get a certain type of certainty about your observations that you don't get from a single arm study. But I think that, if it were me, I would fully try to focus on higher risk groups of people and actively look at these strategies compared to other diagnostic modalities.

The other thing I would say is that probably years ago, I probably wouldn't have thought that these databases were clean enough, that I do believe that they serve a purpose that is complementary to the randomized studies.

You can stratify the data, you can adjust and propensity score match and get reasonable comparisons, and you can get large groups of people that you are never going to be able to study in a randomized trial. So they don't

necessarily replace it, but I think they are very important and ought to be undertaken.

I would encourage the look for risk beyond the short term, immediate hours after being exposed to these agents. I think that there really does need to be a look at risk beyond the immediate time of exposure.

You can talk all you want about these drugs or they are cleared and the gas is gone, and this, that, and the other, but some of the toxicities may still show up at a later point in time, as well as potentially if we are lucky benefits.

DR. HIATT: What you are referring to, which I think we need to get to, is the nature of observational studies, which in my mind are never single arm. They are really observing different treatment decisions, treatment strategies for which you try to use statistical methods to adjust for imbalances in the groups.

DR. FLACK: Well, you are not randomizing, you are going to end up stratifying your data and artificially creating arms, so I think we are talking about the same thing.

DR. HIATT: We are. What I would like to do

perhaps is make a statement and see if the Committee agrees.

I don't think you can learn anything from a single arm study. So, I would discourage the FDA or any sponsor from conducting the classic open label, expose everybody to an agent, and pretend that you could learn something, because you can never distinguish the background event rate from the test agent event rate.

Michael, the only thing I would concede is that if something really weird happened in an open label, single arm exposure kind of thing, that might be informative but, in general, I think that is a bad idea.

DR. PAGANINI: I disagree with you.

DR. HIATT: Good.

DR. PAGANINI: You have got to start somewhere. You can't start with a prospective randomized controlled, stratified stuff to look at things that have a very small signal because you are starting to talk about large populations.

I see the value of a single arm study as first foray into the use of the drug in the clinical side with either historical controls or stratified controls. I see that when you get into prospective randomized controlled

studies, you get into those groups that have a higher risk, the subgroups that have a higher risk like CKD patients and things of that nature.

I would use the single arm as an initial foray into its clinical use with some sort of look at, either retrospectively, and I will tell you why that is important. I think it will be important because you would look at two things. You would not only look at safety, which may or may not rear its head but, more importantly, it would look at efficacy.

I think the efficacy, looking at a known diagnostic entity to see if it does it better than whatever has been out there, or to look at unknown diagnostic entities that you have missed, that you haven't realized you have missed in the past in this single arm. You are picking up all these other things that you didn't know you had.

Those are all pieces of information that can then be rolled into a very well-designed, well-defined, clearly randomized and stratified prospective, which then could give you a hell of a lot more data.

DR. HIATT: I don't disagree. Let's clarify the definition of these terms. Single arm, in my mind, I use

that definition in a limited fashion to refer to everyone gets exposed to the drug or the agent, and there is no inherent comparison to anything except maybe historical background event rates.

What you were implying in your statements is that there were inherent contrasts buried in there and I think what we need to talk about in a moment is the nature of either retrospective or prospective observational studies where patients are being exposed to the agent, for whom there are robust ways to make comparisons between groups, and that is different from just exposing everybody to an agent and assuming you can learn something.

DR. HOLMBOE: Bill, are you referring to this as kind of a pre/post study, the single arm where you simply compare to where they were and where they end up? I am having a hard time getting into the definition here versus-- in other words, a pre/post is you have that population, looked where they were, where they end up, and that's the end of it.

I think Emil is actually talking about there is some opportunity for controls, single arm, giving it to drug, you would at some point either compare them with some

other group. I think that is what we are getting hung up on here is what do we mean by this term a single arm.

To me, the way you are describing it, it's a pre/post. I don't take the drug, I get the drug and see what happens, that's it.

DR. HIATT: Yes, and we are going to talk about comparator groups here in just a moment.

DR. TEERLINK: We have had a lot of opportunity to deal with observational data on this committee. And I think one of the things that has been very impressive to me is the ability of physicians to choose patients in a way to get either therapy or diagnostic modality or something that way outstrips any of our supposed robust statistical measures to accommodate that.

You know, we have been able to see physician selectively use certain therapies and certain groups in patients with certain characteristics that kind of tilt things in a way that it is difficult to adjust for and perhaps even impossible to ultimately adjust for.

One of the encouraging things parenthetically about this whole group and the analyses we have seen so far is unlike many of our other cases where we have sat around

this table where we said, well, gee, you know, the active whatever it was looked worse, but that was because the patients were sicker.

Here, we actually have something that may have looked better and the patients looked sicker, and that is encouraging. But I think you can only get to that point and start exposing that number of patients after you have done first the randomized controlled trials to get a sense of, in those sicker populations, what the risks are.

DR. HIATT: And let's just interweave our thinking about the Part (b), which is what would be the comparator groups. I would like to throw this concept out to the committee, that--let's go back to the event rates, because if you are trying to build a safety database now, then, the event rates matter.

We were told that the spontaneous reporting, these event rates was maybe 1 in 10,000, and that makes it sound like it would be kind of a hopeless endeavor to pick these up in a randomized-controlled, placebo-controlled trial, right?

But if you look at the retrospective studies that we saw, the two of them, those event rates are actually 100-