

fold higher, so it's 1 percent, not 0.01 percent. So, then, you can just use the sort of statistical logic of how many events do I need to exclude a certain amount of risk.

So, if you expose 10,000 patients to the contrast agent in total, that is, 5,000 placebo, 5,000 contrast agent, and you accumulated 100 events, you could exclude a certain amount of risk, and the amount of risk excluded would be maybe as much as a 75 percent increase in events. And those are all numbers that have been previously generated.

So, I don't think it's a hopeless task here. I really would like the committee to deliberate the possibility of placebo-controlled trials to define safety for this class of agents.

DR. LINCOFF: Again, I think the issue is not one of the desirability of the control but whether or not you think you could randomize control because I think randomization changes the whole paradigm.

I think it is practically impossible to get multiple thousands for anything other than trials in very unusual conditions and, even if you do, you don't get all the high-risk patients that you want because I mean trial

after trial has shown that when you compare it to clinical practice, the trials in general enroll patients who are not high risk.

So, the key is how to get a comparator that is relevant and it may be placebo, and it may be the other contrast agent, whatever it is.

I think the best approach is to try to do it prospectively, to say that I am going to do a registry, I am going to collect this data, and I am going to collect this data on all the patients that by clinical practice get the new agent.

I am also going to try to take it that the same institutions are comparable institutions or whatever, patients who don't get the agent, and collect exactly the same data and identify what data you think is important and then you might have enough information to try to do some sort of propensity models to match and multivariate risk adjusted models to try to match the patients, because we know that the therapy is going to be preferentially used, and so they may be high risk or low risk patients, and that will make it difficult.

The second best approach is to use a historical

control. But then the problem is what did you collect. Did you collect the data that you need--and I think that makes it much more difficult to adjust. Without randomization, you have to adjust. We always know that adjustment is never perfect, it is probably never good, but I think it's the best we have.

DR. HIATT: Part of my strategy today is to potentially lead you through every possible scenario, and so you would argue that placebo-controlled studies to define the safety of these agents, not the efficacy, but the safety are impossible, and the reason you cited is that we couldn't put high-risk patients into a study like that, correct?

DR. LINCOFF: No, not only that, not that we couldn't, but you wouldn't have the representation you want, but also I think the smaller studies that will establish the efficacy will tell you about frequent side effects.

So, if you see those, it won't get approved. It's like drug-eluting stents. It's like a lot of different therapies that we find out later may have an event that happens very rarely.

The therapy is approved on the basis of studies that are adequately sized for efficacy and provide some

safety database, but then you are wondering about or you find out about very bad events that occur very rarely. And I don't think it's practical to expect to enroll patients in randomized trials that have multiple thousands of patients except for unusual situations like acute myocardial infarction or situations where mortality is the only endpoint that you can choose anyhow.

DR. WARNER STEVENSON: I am still trying to clarify your question. So, we are assuming now that pre-approval we had a randomized trial that showed efficacy or whatever, and it showed there wasn't anything too terrible that happened in a whole lot of people, and now we have approved this agent and we are moving to how are we going to get a feel for if there is some safety issues that are not of vast magnitude, and we are trying to decide how to do that after approval. Is that correct?

DR. HIATT: Well, I didn't pose the question as pre- or post-approval. I would imagine that in this situation that might be a Phase IV commitment. It might, in fact, be impractical in the Phase III arena.

But the way you stated it, Lynne, so I have studied 1,000 patients and I have got great images, and I

have met the structural criteria the FDA has put before me and, in my population, I have 10 deaths, and that's it--and that is not unlike the situations that we have heard before.

I would just--I absolutely have to state that with 10 events, you have learned nothing about the safety of the agent. You just don't know, so you need to acquire more events to understand the safety.

I think what I would like to cover in this question is all the different possible ways to acquire those events, you know, whether it's just exposing everybody to the agent and seeing who is dead at the end, whether it's observational studies with proper adjustment, which I think is a great idea which we need to talk about a bit further. But the other thing on the table is can you do that in the context of randomized controlled trials, and I don't think we have fully explored that option.

DR. HENNESSY: So, with randomized trials, once the product has been approved, the only people that you can do randomized trials in are those in whom there is clinical equipoise.

DR. HIATT: Correct.

DR. HENNESSY: And there has got to be equipoise

by the people administering the therapy or the diagnostic. It has been approved based on structural grounds, and everybody thinks that this class of patients needs to get it regardless, then, you are not going to be able to randomize those people.

We also know that for other kinds of diagnostics, we have higher standards in terms of demonstrating health outcomes rather than prettier pictures, for lack of a better term. So, we might be able to kill two birds with one stone, and in the pre-approval process, get evidence both for clinical benefit and have enough people to have a safety assessment with adequate statistical power.

If you don't do that pre-approval, I think what you are left with post-approval if you want to do it in a randomized way. It's Agent A versus Agent B to do comparative safety or comparative effectiveness but, if the people who are using the therapy are convinced that there is not equipoise, then you can't do a randomized trial versus no treatment or versus placebo.

DR. HIATT: The ethical mandate for equipoise has to be maintained. I would agree with that. But the problem with your suggestion is that I need a few hundred patients

to demonstrate diagnostic efficacy of my product, and I need tens of thousands to exclude a safety concern.

DR. HENNESSY: Maybe somewhere in the middle, so I don't know how many patients you would need to demonstrate a health benefit, and we talked about this. So, if you are using echo without contrast versus echo with contrast, how many patients do you need to randomize to show a health benefit, and that is going to be more than a couple of hundred.

DR. HIATT: But maybe less than 10,000, and I think that is a salient comment, that another approach to this is not just to look at a risk of death at 1 in 10,000 or 100,000, but to ask that question, because if you actually spare a lot of people needless procedures or fix lesions that appropriately are fixed that would have been missed because you didn't use the contrast agent, that might not take a lot of patients to show that health outcome benefit.

DR. HENNESSY: Right. It if improves mortality, then, it improves mortality, and if it has got a 1 in 10,000 risk, at that point it doesn't matter, because it improves mortality.

DR. HIATT: Exactly. So, we were told that the guidance talks about the structural indication that the sponsors were held to. I would like the committee to wrestle with whether that is enough or not going forward for that very reason.

DR. FOGEL: I think we are all dancing around one particular issue, and we all know that every drug that we ever produced has some kind of side effect, and the question here really is, before we release the drug or the imaging agent on the public, the question is what side effects will we tolerate and at what frequency. And I don't think anybody here has really come out, or at least I haven't heard really anybody come out, with a lower limit, a lower bound of would it be 1 in 10,000, 1 in 100,000, 1 in half a million side effects, and is that enough to protect the public, and which side effects do we protect.

I mean, of course, obviously, death is a bad one, but would we do it for the other extreme like a headache or diarrhea. I mean we are all dancing around that one issue, and if we knew what we would all come to a consensus on as to what would be the frequency and the side effects that we would tolerate before we release it to the public, then, I

think we can then have an upper bound of how many patients we would need to exclude something like that.

DR. HIATT: Your thinking is good, and, in fact, that is a salient issue. If you can't define the risk, you can't form a risk-benefit equation.

Now, I think the data we heard, particularly this observational study in press, suggests that they had enough events to have fairly narrow confidence intervals around the risk, and the upper boundary fell below 1, you know, so that gets closer to my mandate for defining the risk.

Now, we don't know the benefit clinically. We know the benefit structurally, but you are absolutely right.

It is not that a drug or a test agent is without risk. It is that I need to understand the risk. If the confidence intervals are huge, Dr. Main's first study, where there were 75 events, probably had very broad confidence intervals that would make me nervous. But his follow-up study had very tight confidence intervals around that safety concern, and that is much more reassuring.

So, it is simply a matter of defining the risk-benefit, and it appears to me that they have come close to doing that with the observational data. But let's not draw

any conclusions quite yet, because I don't want to dismiss the possibility that these risks should be defined in the context of randomized trials.

DR. WARNER STEVENSON: I don't see how you can exclude a risk of 1 in 10,000 prior to approval, it just can't be done. So, I think the question is can you exclude a larger risk beforehand and then supplement that information after approval. As Dr. Hennessy said, I don't think you can do anything randomized to exclude a risk of 1 in 10,000. You will never randomize the patients.

DR. HIATT: Wait a minute. So, if you just play with their event rate numbers 1 percent, and you want 100 events in your safety database, you need to give 10,000 people the agent or some control.

Is that an impossible hurdle to overcome?

DR. WARNER STEVENSON: I think so.

DR. HIATT: I want to just get that out there, because when I run those numbers in my head, that is where I come to. I want 100 to 150 events in my safety database, 100 deaths or 100 really bad irreversible harm events, and if you are telling me that you can't get that with a placebo control, then, that is something that we need a bit of a

consensus on here, so that we can perhaps move past that point. But I don't want to let that go, because that is the ultimate way to do that.

We have had lots of example on this committee where observational studies pointed the way towards signals.

But they weren't defined until the randomized safety trials were ultimate done and published, and we have some very recent evidence of that.

So, I want to be very cautious. The Committee is moving quickly beyond this is an impossible thing to do. I would propose that it is not necessarily that high a hurdle, but I just want to get a bit more of a consensus about this. I am making the sponsor nervous.

Go ahead.

DR. HENNESSY: So, the degree of risk that will be tolerated obviously has to do with the amount of benefit conferred by the agent, and we have anecdotal evidence of its benefit. We don't have clinical trial data showing clinical benefit so it's difficult to say what the acceptable risk is without having a quantified benefit.

DR. NEATON: I would like to second that. That is the problem I think we have here is that we have heard, not

to be kind of derogatory, the term pseudocomplications. But we have heard a lot of pseudobenefit as well, because we have seen nice pictures and claims that there is fewer diagnostic procedures, and that is going to lead to kind of less costs and that is going to lead to a better benefit that we haven't seen the data.

So, I think down the pike, for new agents, I think you want to have probably some type of intermediate size trial. I think a 10,000 patient trial with 100 deaths, you know, maybe is over the top. But maybe an event short of death that could establish that these agents really do improve patient outcomes and can measure in a randomized trial at least the mild to moderate, if not the serious adverse events and deaths reliably, it would be very important.

Then, you can go into your post-approval and do the database on the survival and the other serious events.

DR. FOGEL: I am sorry, I have to disagree about the risk-benefit, because there are some cases where you will have a risk that is totally outweighed by the benefit even with small numbers. So if you have every single patient in a five-patient study die, it doesn't matter what the

benefit is. I mean they are going to be dead, or if they are going to be comatose or anything like that.

So, I think it matters the degree of what the side effect you are willing to tolerate again.

DR. NEATON: Based upon the data we have where it looks like the risk is relatively low for serious events. I am thinking about an agent for the future.

DR. TEERLINK: What we are hearing is that there is clearly an inverse relationship between, you know, the higher bar you set for efficacy, the more tolerance there will be for this fuzziness around the side effect and adverse effect profile, so the sponsors can work out their own calculus in terms of where they want to invest their time and efforts in terms of reaching those necessary events and giving us security about the ultimate outcomes.

I think from my standpoint, if you do, in your early 2000ish, whatever patient studies you have, you aren't seeing huge numbers of signals and a huge number of events, that is cautiously reassuring to me, because there may be more or less, but you know that--it sets an upper limit that it still isn't kind of entirely satisfactory, but sets an upper limit to how dangerous these substances can be.

So, for example, in these cases, we have seen a lot of the earlier data had some potential early signals, but weren't confirmed later on as we went to larger studies, and then with the Definity program, where we had 3,000 or 4,000 patients, I think there is a number of patient exposure where we can be a little more comfortable saying yes, it's fine with postmarketing commitments to look more carefully at these smaller 1 in 10,000. but I think it is unreasonable to expect to rule out those 1 in 10,000 in the pre-approval.

DR. HIATT: Let me do some reality testing here. Does the committee really think that a 1 percent mortality risk in a day is like really, really a rare thing? Are you serious? That is the numbers from this unpublished multi-center and safety outcomes database, mortality rate at one day is 1.08 percent for non-contrast and 1.06 for Definity.

DR. LINCOFF: But the difference is 0.002.

DR. HIATT: I understand there is no difference, but I am asking you if that event rate matters.

DR. LINCOFF: But your ability to discriminate a change in that event rate is still going to require a large number of patients.

DR. HIATT: Correct.

DR. KAUL: The 1 in 100 is in very sick people.

That study is done in intensive care unit, so that is very different, because otherwise, there isn't--there is hardly a signal outside of that. So, that is what you are to come to, and in terms of imaging agents, it is very hard to show clinical benefit of an imaging technique, because, for example, I do an echo and find a thrombus in the LV cavity.

The patient is given anticoagulation. That is the benefit I did to the patient. The benefit way down, 10 years down the road, that he or she did not have a stroke will be given to the anticoagulation, and not to my reading.

So, it is a very hard thing to do clinically what you are suggesting. It was very easy to do with a drug, but it is very hard to do with where you have made a diagnosis to implicate the diagnosis with nothing else happening, because once you have made a diagnosis, things start happening, and there the noise and reverberations are much larger.

DR. NEATON: I appreciate that comment. However, there have been many other diagnostic tests that have been evaluated in randomized trials. That is the beauty of doing

a randomized study. I have heard the argument here from several people today that as a consequence of the imaging, I am able to do diagnostic tests, make faster diagnoses of illnesses, which will improve the patient's health.

Let's see it. So, I mean you can do that potentially in a randomized trial or maybe a variation of a strategic trial where a group gets kind of the initial contrast media versus standard, and that the standard kind of requires a redo or something, they get the imaging on the second time.

There ought to be ways of addressing that.

DR. KAUL: I agree with you. For example, we can show that we can identify high risk versus low risk. Now, whether the high risk gets the bypass and lives longer is beyond me, you see, but I can identify high risk.

DR. HIATT: We get your point.

DR. KAUL: I can identify risk stratified, that is very important, but I think what Lynne said was a very good idea about the type of design she said earlier. I think something like that would be very good for imaging, because something like that would show that whether it's beneficial or not.

DR. HIATT: Thank you very much.

DR. FLACK: I understand both sides of this argument as a physician and an epidemiologist, and Jim Neaton is actually one of my mentors, so I don't want to contradict him, but, as a physician, I mean I understand that cardiologists are using these tests and these tests have been approved and they are making decisions, and anecdotally, they believe that they are getting benefit.

I am willing to--have to literally accept the fact that we do stuff all the time in clinical medicine without randomized trial data, and getting the better picture of something that you don't have a good picture of, I accept that as benefit.

I think you want to have that benefit, though, with a reasonable amount of safety and certainly some kind relative safety to compare to what is out there on the market.

I guess for me, it would force me to sort of throw out there that the best way to probably do that without an ungodly number of patients is to do high-risk groups of people before these drugs come to market where you can test then without having to study thousands of people per se who

are at low risk because it doesn't make a lot of sense to study them.

I am actually moved by the prettier pictures because if you have fuzzier pictures you are probably going to make worse calls, and that is something we have to accept in clinical medicine.

But I do understand the desire, and it sounds like the approval quite honestly--I may get whacked by the FDA for saying this--is relatively low. We are just proving you have a pretty picture and study a few hundred people.

DR. HIATT: John, I think the point you also made that--I was trying to drive home by the event rate--is you do want to study sick people, because they do have events and that is the best way to learn something, and once again, the observational data actually aren't bad in terms of excluding risk.

DR. WARNER STEVENSON: May I just clarify something in my own mind? Clearly, the high risk patients have more events, there is no question. But it is not necessarily clear to me that if what we are looking for is an event specifically related to this diagnostic, that I am going to end up with a proportionately larger delta between

the two arms just because I had a high risk group.

I will have more events, but I am not sure that my sensitivity to pick up an increase in events with the intervention is going to be that much--and it might be if it's a cardiovascular collapse.

But if it's something else I am not sure that that is a correct assumption that the high risk patients necessarily give me a bigger distinction in events.

DR. TEERLINK: If it's idiosyncratic, then, it may be anybody is at risk for that, but I think we may be referring to, at least what I was saying, I was actually referring to high risk for each side effect that you believe may happen. You may not know all the things that are going into that.

DR. WARNER STEVENSON: But by definition, the unexpected, which is what we need the big group for, we didn't know who was going to get that.

DR. TEERLINK: What I am saying is once again we are differentiating between an efficacy trial and the safety trial, and some of the population, you may have a population that will have a greater benefit in terms of efficacy and that is what you study for efficacy. But you may have

another population that you think may be at greater risk for safety complications, and that that is a high risk from a safety standpoint group of patients that you would want to study.

DR. WARNER STEVENSON: I just don't know who those are, though.

DR. TEERLINK: Well, you can guess based on--and it's a guess--you have animal data, you have your Phase I/Phase II studies, and then you have to do an--it is what we do with drug development, it is what we do with device development, it is what you for all these developments, you try to see based on the previous information, you make an informed choice in terms of where you think the greater safety risk is going to be, and look at it.

DR. HIATT: That actually segues nicely to is there a comparator group of interest here. If these agents overall have the same hemodynamic properties, if they carry the, quote "same risk," is it fair to learn something about safety if you compare one agent to the next, or would you need saline or something like that.

What would be an appropriate comparator group here?

DR. HENNESSY: I think that prior to approval, an appropriate comparator group would be no contrast agent with the outcome being some clinically important outcome like mortality. Once it's approved, then, figuring out what an appropriate control group is going to be difficult.

DR. HIATT: Sure, and we are still stuck with the issue that the event rate may be so low that we will be unable to put any competence around a mortality signal pre-approval.

DR. HENNESSY: Unless you study high risk people. You study your ICU people who you get lousy images without contrast. It shouldn't take very many of those people to demonstrate a clinical benefit of contrast.

DR. HIATT: We just played with the numbers, and so they told us that the highest risk group was studied in this observational database, and that rate is 1 percent.

So, if your outpatient echo patient, the event rate is 0.1 or 0.01 percent, it really is the background reported rate, then, we will be challenged to see that.

I realize I am dancing a little bit on both sides of the issue. I am trying to set up these arguments intentionally to make the committee--to force you to ask how

far you would go to define the safety signals.

DR. NEATON: Why would you make 24-hour mortality the endpoint?

DR. HIATT: You wouldn't. It is a very short-term exposure. We don't know what the other end of the curve is, but one would maybe extend that past 24 hours.

DR. NEATON: It might be 5 percent within 30 days.

DR. LINCOFF: It will be 100 percent in 10 years, but that doesn't help you. I don't think you can give a general answer that is specific, because it is what the standard of care is.

I mean if you do a study five years from now with a new agent, and if five years from now, everybody is getting contrast, you won't be able to do a placebo-controlled.

DR. HIATT: That is, by definition, always the case.

DR. LINCOFF: Right.

DR. HIATT: And if background therapies are established, then, you have to do comparator trials.

DR. LINCOFF: So, the question is what is a comparator. An appropriate comparator is what we think is

the gold standard of safety and effectiveness. Right now, because we are having this discussion, there is still the question of should we be using contrast agents.

So, if you were to do a study now, I think the appropriate comparator would be not using the contrast agent. But, obviously, these change and so that changes the comparator.

DR. HIATT: What bothers me is that if there is sort of this shift going on and background therapies that are accepted, and for which the safety is never established, ever, then, you start comparing potentially one unsafe agent to another, and, of course, you will never distinguish that risk either.

DR. TEERLINK: I think for these agents--and if we were voting, obviously, I couldn't say this, but I think it is impossible to do. I don't think we can give future sponsors any advice to say that they have to do a placebo-controlled trial in this area now because I think it would be almost impossible to enroll, given the standard of care now in most of these settings. I mean by definition if you can't see a good image on echo--we give contrast, and that is what we do. That's standard of care.

To try to enroll a study where you don't do that, won't happen. So, I think then you get into the more complicated, okay, we have already got agents approved in this area, now, we are going to non-inferiority approaches and doing other things that say or equivalency, whatever type of phrase you want to look at, to say this is as good as what we currently have.

The safety data will have to be something separate, in a separate issue. But I think it is going to be very difficult for anybody realistically to do a placebo-controlled trial in this area unless they can slice off a very small segment that may or may not be relevant.

DR. HIATT: So, the goal in a few minutes is to draw the committee back to try to come to a focused resolution on what would be a reasonable request to define safety.

DR. FOGEL: If you don't see the heart well on echo, you don't necessarily have to give contrast. You can try an alternative imaging modality whether that be MRI, whether that be CT, or other imaging modalities, so it is not impossible to do that.

DR. HIATT: That is Lynne's strategy approach,

which is a very thoughtful way to look at this question for both safety and efficacy, because you can look at outcomes.

DR. TATUM: Can we address a question to the FDA, as well?

DR. HIATT: Sure.

DR. TATUM: So the conundrum that we have got here is what we got as an approval based on an anatomical basis, and that has led to a very diverse population with both high risk and low risk patients, so we have got an issue, number one, based on that for benefit, and number two, an issue with safety.

My understanding going forward is that that would be a very rare approval these days, that the intent of the FDA is for applications, and if we were dealing with a specific application, let's say, simple screening in an outpatient, it would be different. If we were dealing with, in fact, those patients only in the intensive care unit, we would have a defined population, efficacy could be defined much more easily than we have with this broad open application or approval as it is.

Is that true, and is that something we should be actually encouraging to be sure that we do deal with

specific applications where we can assess safety very closely and also efficacy at the same time, and make that risk-benefit ratio make sense?

From what I am hearing here, that is the problem we are dealing with.

DR. RIEVES: To speak in fairly broad generalizations, most of the imminent applications that are coming forward, we are probably looking towards anatomical improved visualization, if you will, that has generally been the precedent in the past and that has been the most recent development program.

There has been, in general again, very little interest in actually showing clinical diagnostic efficacy, it's anatomical in general.

DR. HIATT: Does the inability to mask or blind the study support the use of single arm designs. For example, does the open label nature of the study negate the advantages of a randomized comparator group?

DR. LINCOFF: Can I just ask, do you have any right to say that we won't accept that? I mean as an extreme, let's say somebody was proposing I am going to put a needle in your carotid artery and inject something there

to visualize your brain, and I am going to say it makes your brain a better picture of your brain, do you have to accept that as the standard of efficacy?

DR. RIEVES: It will ultimately come down to the risk-benefit assessment, and it is somewhat getting back to where we were a little bit earlier. It's the challenge of diagnostic agents. No, we do not have to accept that, because it's the risk-benefit ratio there, of course.

However, interpreting that ratio gets into a lot of judgment for diagnostic agents and, as you see here, we anticipate bringing some of these types applications to this committee over the next many months.

It is going to be challenge. We do not have to accept it even though it's in our guidance as a reasonable goal. But, again, having that relatively low threshold for anatomical delineation with presumptive evidence of diagnostic benefit also presumes and gets into how much we actually need demonstrated sufficient safety to support that.

So, it's a balancing act probably even much more so for diagnostic agents than for therapeutic, which is part of the challenge we have.

DR. HIATT: This committee might be a little uncomfortable with that thinking in that we might actually like to see some outcome data that might support the diagnostic modality.

DR. WEISS: I think as Dr. Rieves was trying to say, too, it's the whole idea of the implied benefits of showing something, and you heard a lot of compelling information earlier today from people who were very passionate about the benefits of showing something in the heart, the thrombus or the abnormal wall motion, et cetera, et cetera.

To answer your question, if there isn't really any utility, if there is just for the heck of it to stick something in somebody's carotid to show something without really any attempt to really look further beyond that, to say that there is some reason to do that, we certainly have the prerogative of not accepting that.

But when you go through the hierarchy of what kinds of claims sponsors would be able to make and what they need to show, it really gets into a lot of these very difficult questions about if you want this type of claim, what is the hurdle, what kinds of data, what kinds of safety

information do you need versus something that has maybe more downstream clinical outcome information, to some extent is like what we wrestle with when looking at surrogate outcomes.

You don't actually have the actual clinical benefit. And so you have to make risk-benefit decisions on sort of less than full information, but we readily admit that these questions, particularly in the abstract, are very, very difficult to try to address, and we really appreciate your struggles with it, because we struggle a lot with that, as well.

DR. HOLMBOE: I actually think this is the fundamental issue. I mean we have known for a long time that just because you get increased sensitivity of a diagnostic test doesn't necessarily means it leads to all good things.

I mean there is a down side to that. So, if it is only limited that I can see things better, it is more sensitive to pick it up, then, I think we are one step short and I wonder if the paradigm is just out of date now, that it really gets back to what Lynne talked about earlier, that we are really trying to get at what is the decision-making

process that comes out of this increased sensitivity or improved test.

To me, it is really hard to interpret safety signal without knowing what that is, because again, we know that there also is harm that can be induced by overtesting, you know, overly sensitive tests. I mean that has been written about for a long time. It is called the cascade effect, and I know people have written about this.

So, I really worry that we are sitting here struggling in this conversation, and we are working with the wrong paradigm.

DR. ZANETTI: As a patient and a cardiac patient, I think the benefit of a test, enhanced ultrasound, is not prettier pictures, but the fact that it can give me answers without having to have a more risky test. I have had four cardiac cath. What I have heard today is if the boys want to do it again, we are doing an enhanced ultrasound.

DR. GEVA: I would like to second Eric's comments and to add to it. I think that, in fact, we can measure some of these potential benefits or presumed benefits are measurable, and I think that goes back to the issue of randomized trials, and it depends a lot on the trial design

and what the outcomes are.

In many of the imaging studies, especially non-invasive imaging studies, mortality may not be the ideal endpoint, but use of alternative imaging modalities, the comparison of complications between various imaging modalities, and those can be used as measures of outcome, and their use should be encouraged when considering benefits of diagnostic tests.

DR. WARNER STEVENSON: I just wanted to clarify this issue that we talked about earlier, which is that I am not so sure that I would necessarily want to see the downstream effect of the whole decision tree. I think those are very complicated. We are talking about multiple different diagnoses.

What I would suggest is that we may want to separate in our mind why we are doing the enhanced ultrasound. For instance, I don't care if the EF is 20 or 26, frankly. I care if there is left ventricular thrombus, yes or no. I care if there is a pseudoaneurysm yes or no.

So, I do think we need to distinguish between why we do it and I would also suggest that for any new agent being approved that it may be important to very carefully

collect the information from the echo before the contrast and after the contrast, so that we can see, in fact, what we really did learn from having the contrast in that rather than just having it be assumed.

DR. HIATT: We have covered (c), but just to make sure if there are any other comments on this, does the inability to blind these studies support the use of single arm designs? Does the open label nature of the studies negate the advantages of randomization in comparator groups?

DR. HENNESSY: They are really different issues, so when you can randomize it better than non-randomize, control group is better than not control group, and generally speaking, blinded is better than no blinding although in the situation of the diagnostic, I am not sure that that is relevant.

So, just because you can't have the perfect doesn't mean that you should immediately jump to an uncontrolled case series essentially.

DR. HIATT: Agree.

DR. NEATON: Why is this question worded this way? This precludes the use of a blinded study and why is that?

DR. HIATT: I think we could go with the sentiment

of the literal nature of it.

DR. NEATON: It might be two contrasts that are being compared. There may be some situations where blinding can be accomplished.

DR. HIATT: That is true.

DR. HENNESSY: For example, blinding of outcome ascertainment, but not blinding by the health care team.

DR. LINCOFF: And in part, we have been just saying we would like to see more in the way of outcomes rather than just it's as pretty picture, so if you want outcomes, you have to allow the operator to act on the basis of the information they got.

If all you want is do I get a better picture, you can send it to a blinded core lab and leave the operator out of it. But, if you want to have some downstream information, then it become difficult although in some cases not impossible to blind.

DR. HIATT: This is probably the hardest question in terms of what would you actually recommend to sponsors and how would you all think about approving new agents?

I think the committee has wrestled with some realities and I think we have to put our recommendations in

the context of what we have seen.

In this context, we have seen observational data that don't suggest a signal of concern. We have said that these event rates in the broader population are probably quite low, and therefore, to ascertain at least a mortality risk in Phase III may be very challenging.

We haven't spent a lot of time on it, but I think today, a properly designed observational or prospective studies could be incorporated into the development program with appropriate propensity and other statistical controls, that they might, in fact, be quite informative.

Now, I wouldn't stop there, because remember if an observational study detects a signal of concern, that does not define cause and effect. And so, if you are going forward and you do see signals emerging that you hadn't expected, and which we wouldn't necessarily expect today, that might force you back into randomized trial design to definitely answer those questions.

But I would say--and I just want the committee to react to these statements--from what we have seen today, and we sort of tried to float a variety of arguments, some of which weren't received real well, that one might pursue, and

obviously, the best way to go here is a 10,000-patient randomized placebo-controlled study to define the safety of these agents.

But if that is not practical, then, observational studies would probably be a viable option, and you can decide where along the development strategy those need to be done.

I guess I would invite the committee to react to that summary statement, if you all agree with that or not, so we get some sense of the consensus.

DR. WARNER STEVENSON: One of the things about such a large observational database, which I would caution the sponsors about, is one would want to avoid a tendency to have preferential use of your agent in the highest risk patients because frankly, it is my conviction that it is not possible, with propensity analysis, if the reason that you choose a new therapy is because the patient is at high risk of a bad outcome, I don't think it is fully possible with propensity analysis to adjust that out.

So, you would want to make sure after your drug is available that there isn't a preferential use of it in the highest risk patients if in some way one could try to

modulate that.

DR. HIATT: That is really an appropriate comment, Lynne, and I would assume that as these methods move forward, that appropriate statistical adjustments would be applied.

What you are stating there, there may be an inherent bias in ascertainment of patients in an observational study that may be impossible to overcome, and the sponsor would be need to recognize that.

I would also add to these statements that there is a strong sentiment on the committee that some level of outcome assessment is needed to best inform the risk-benefit analysis, and that just structural imaging I think this committee is saying it is really not sufficient to inform those decisions.

I think the idea of a strategy approach where there could be some at least proximate, not, as you say, Lynne, you can't play it out to the nth degree here, but there could be some easily measured outcomes that could be very informative because, if the biases we heard earlier today are true, patients should do a real lot better, because they got the contrast as opposed to an uncontrasted

ultrasound test. And, if that is true, then, those outcomes should be readily apparent and the risks are very low, so the risk-benefit would be very easy to ascertain in that context.

DR. TATUM: Could I just clarify? Are we recommending, if I understand this correctly, outcome data for an anatomical application? Is that what I am understanding?

DR. HIATT: That is what I think a number of people on the committee have recommended, that a pure structural endpoint, that is consistent with the guidance, is not adequate.

DR. TATUM: This is a fundamental difference. This is very fundamental different approach in the way we are doing things, is that correct.

DR. RIEVES: That is correct. We do have a guidance that actually this has been under critical thought for probably close to 20 years, I suspect now, that actually went into that.

We can revisit it in the future, and I think we will have the opportunity to revisit in the future, but the sentiment is appreciated, and we understand.

DR. HIATT: Remember Cardiorenal focuses at outcomes, I mean that is the nature of this committee.

DR. WARNER STEVENSON: I would like to modulate that a little bit. I am not sure that the outcome would have to be something like mortality. It might be how many thrombi did you pick up that you would have otherwise missed. I mean it is some outcome, but it isn't necessarily a direct mortality outcome, but it is something other than just they are pretty.

DR. HIATT: That is absolutely right, and I really do think that the advisors and the sponsors could be smart enough to figure that out, because it seems to have so much face validity here that those outcomes ought to be at that level. It shouldn't be a mortality outcome, but it should be something that is clinically relevant rather than a better image. It is like I changed my number of some test.

DR. HENNESSY: With aprotinin, I certainly would have liked to have seen mortality trials.

DR. HIATT: Me, too.

DR. HENNESSY: So, if we ask for something less than mortality, we might get a surrogate endpoint that ends up not accurately predicting what it is we want to prevent.

DR. HIATT: We are comparing apples and oranges here. Aprotinin is an intervention designed to do something and that is not the purview of today's discussion. This is a diagnostic test. I really do think the outcomes of interest are different, but the committee is saying outcomes matter, and image is not necessarily an outcome.

Do you want to say something?

DR. GRAYBURN: If you don't mind, I would just like to respectfully disagree on the basis of equipoise.

I think it depends on what the population is you are talking about, but if I have a patient, as we had recently, with a hemopericardium, no blood pressure, doing a code, and you see a pericardial effusion on there, we put bubbles in, it's in the pericardium.

Now, I know the guy needs to go to surgery. I can't randomize that patient to any study. It would be unethical. I totally agree with doing randomized trials when there is clinical equipoise, but in many of these situations in the ICU where a patient is dying, and there is no time to get an MRI, you know, not the same as an outpatient stress echo, there is equipoise--I mean you can't randomize those patients, it is unethical.

DR. HIATT: Let me suggest that we are not going to design the trials today or design the inclusion/exclusion criteria for such trials, but what we are simply saying is that outcomes would be important in the consideration of risk and benefit.

DR. GRAYBURN: But there are no outcomes data for the use of radiopaque contrast to do coronary angiography of standard angiography. There are no outcomes data for the use of gadolinium contrast and MRI or for --

DR. TEERLINK: Just because we got it wrong before doesn't mean we need to do it again.

DR. HIATT: We appreciate your comments. Thank you.

DR. FOX: Can I just add a comment about I agree with a lot of the ideas that have been put forward around observational studies, and it allows you potentially to access large numbers of patients and look for less dramatic outcomes than dying in the next five minutes, but maybe faster diagnosis, less health care costs, and et cetera.

But just the point to be made that those kinds of studies I can't think of a feasible way to do those pre-approval.

DR. HIATT: To try to summarize again, I think we are saying that what we have seen appears on an absolute level, very low risk, that it has been somewhat defined already for the class perhaps, and that going forward that there may be observational prospective ways to look at that risk and there may be strategies to look at intermediate outcomes of interest in appropriate patients.

Do you have any comments on this question?

All right. The third question is --

DR. WEISS: Just, Mr. Chair, I was just wondering if, in response to comments made earlier by Dr. Day about risk management strategies, given the fact that we spent a lot of time already talking about clinical program and clinical development, would it be appropriate to see if we can interject some commentary about a risk management program which are necessarily things that are done postmarketing once a product is approved, that this might be a good segue into that, and then come back and address Question 3? Would that be something that you are comfortable with?

DR. HIATT: Of course. We have members of the committee that maybe could just start that commentary about

a risk management program.

DR. DAY: At the risk of shortchanging Question No. 3, which is official, one of the major problems is what are the risks and we focused a lot today on the serious ones and how are we looking at the ones that are more moderate, and so on, so in order to know what a risk management plan should be, we need to know for what risks.

I would like to mention one thing at this point that is very unusual about this situation, is that these agents were approved and then contraindications were added, and then other things happened and contraindications were removed.

So, I think right now is a critical time to consider risk communication strategies. For example, the sales force in the companies going out and also in the press and general communication to the physicians who will be using these agents.

We need to be very careful about talking about removal, so we have heard a lot today. There is removal of contraindications, and as some of you have said, and put into the warnings. But just the idea of removal of contraindications, people could come away with this, oh, all

these concerns have gone away and now there is extension of these agents to many other things--liver, et cetera, et cetera.

I think that appropriate risk communication strategies within the companies especially with respect to the sales force is really important at this time. I would like to hear from other colleagues from the Drug Safety Risk Management Advisory point of view.

DR. HENNESSY: As best we can tell, the risks associated with this drug were based on anecdotal evidence and from both controlled epidemiologic studies, those potential risks were not borne out.

A risk management plan assumes that there are risks and it assumes that the people in whom those risks are present can be identified, so one, I am not sure that there is an increased risk, the data seem to point otherwise, and if there is an increased risk, the data have pointed to a group that is at higher risk in whom the contrast agent should be avoided in, and whom don't get an increased benefit from the contrast agent.

So, I am not sure that a risk management plan makes sense in this setting.

DR. HOLMBOE: I am going to take a slightly different perspective, a little bit from the patient's view, and also point out that I am struck by the sequence of events with these agents where I think, as Ruth pointed out, they were out, they were then a signal through the spontaneous reporting system was generated.

It then led to a lot of retrospective analysis and then they were removed. To me, I think the fundamental issue the FDA is going to have to face is what are they going to do prospectively with regard to surveillance of new agents as they go out or new diagnostic tests.

We sat on a number of different panels, and this keeps coming up, and I think that is going to have to be a fundamental shift, that the spontaneous reporting system, important as it is, to me is just insufficient.

I think this may be an example of where, in this case, although it was important to get a signal, it may turn out that it gave an erroneous signal. It may be a prospective approach and using a registry or other types of longitudinal databases could have been helpful, and we certainly have enough experience with registries in this country now that I really think that needs to be part of the

conversation for new drug approval.

I think it is particularly important from a patient point of view, because as you have heard very passionately today, these drugs were used in, quote, "lifesaving situations." Well, in those situations, you are not going to be able to have a shared decision-making conversation with your patient.

You are not going to be able to spend 10 minutes talking about the risk and benefits of contrast. You are just not going to be able to do that, and so I think that, to me, actually heightens the moral obligation to make sure that when we put these agents out, that we do follow them forward, because patients are not going to be able many times to participate in a risk-benefit conversation even though we may think the risk-benefit equation is okay for us.

So, to me, that is another issue I think again moving forward and think about risk management that really needs to be taken into consideration.

DR. HIATT: So, you are saying that, or the two of you are saying that, a specific RiskMAP program may not be as critical as initiating the appropriate observational

studies as early as possible in the development program to provide a more clear signal, is that what you are saying?

DR. HOLMBOE: Yes, I think that is what I am emphasizing in this particular case. In other medications obviously, you really do need a risk management plan. There is a lot of patient communication that has to be part of it.

In this case, like I said, the patient communication part is a little bit more tricky, because for a lot of these really ill patients, you are not going to be having those conversations. So, I think that heightens the need for again these prospective observational databases to pick up signals earlier instead of waiting for something to happen.

DR. HIATT: So, just so we understand this understand this clearly, and link this to the previous conversation, so what we are not saying is that every new agent needs a 10,000-patient exposure safety database pre-approval, that uses a randomized control.

What we are saying, though, is that as efficacy is being demonstrated in controlled studies, that safety assessments are initiated early in the observational context using appropriate methods, that that would be the

requirement for the safety database.

Is that what we are saying?

DR. HOLMBOE: That is certainly one of my recommendations.

DR. WARNER STEVENSON: I would like to very strongly agree with that. I think we will be much less vulnerable to these spontaneous erratic reports that get everybody excited that we have to respond to if, at the same time, we can say we already have ongoing a prospective registry that we started. As soon as it was approved, we have got 15,000 patients in it. We can look at it immediately and see if this spontaneous report in fact has any validity, and I think it will decrease a lot of the entropy that has been created.

DR. HIATT: Just to continue that. I, too, think that that is the best recommendation going forward, remembering that in actual practice, the event rates are probably a lot less than what were reported.

More comments on the RiskMAP?

DR. RIEVES: This is great feedback and it is interesting how the dynamics have changed in the last seven years or so since Definity was approved, for example,

because you can tell from the history there, the review team felt as if they needed some sort of prospective study, but at that time, our science of observational studies was somewhat in its infancy, as well as a regulatory aspect. That was an agreed upon PMC. Either the sponsor could do it or they didn't do it. The company sells the product.

We get into this sort of situation, but moving forward now, thankful for the science improving as well as the recent FDA law, as we did with these recent studies. These can be postmarketing requirements meaning we have more regulatory authority in the future, so your points are well taken.

DR. KASKEL: I just came from a meeting yesterday of the Clinical Translational Science Awards, and I just want to bring that up because there was a discussion about how this new network for clinical translational investigation around the country could interact with industry, and even FDA. This was brought up in a smaller meeting.

Although early, it is only two years that it has been around, there is about 38 centers, and there will be another 30 or so funded, this potentially in the future can

be a mechanism to have the specific registry set up to send out an announcement, an alert from industry via the FDA, four centers that are interested to come to the table with specific criteria set up for all the studies that you would want to do with making sure the regulations are met.

It is just thinking to think about for the future, but the role of the Clinical Translational Science Award, one of them specifically talked about longitudinal studies to provide the road map to get the clinical material for translational investigation.

DR. HIATT: That is an excellent suggestion. I would take it to heart because the CTSA environment has an informatics core within each of the recipients, and these informatics cores will be linked. And there is, as part of the CTSA mandate--and it is sort of an academic industry outcome partnership, so I think that, too, provides another infrastructure to do really well-controlled observational studies.

More comments on the RiskMAP program? Is it clear?

DR. DAY: There are a lot of terms being used. It was risk management plan, then it went to RiskMAP, and it is

changing, and so on, and so forth. Just talking about the general category does not presume that there has to be a risk map. There was applause before when somebody said we don't need a risk map right now, and everybody is all excited or some people were.

But the whole idea about risk assessment, continued assessment, and mitigation, whatever you want to call it, management, and so on, it doesn't have to marshal a huge plan that is going to cost a lot, et cetera, but the idea of the registries and going forward is part of this whole arena of risk assessment, communication management, et cetera.

DR. HIATT: So you would agree if a sponsor said I have got to set up a registry, that was part of that plan?

DR. DAY: Sounds good.

DR. HIATT: Good.

Shall we move on to the third question, which I don't think we will agonize too much on?

This is the safety risks for one member of a "class" of drugs may represent risks for all members of the drug class, given similarities. What are the important considerations in determining "class" safety risks for these

agents, especially for serious but uncommon risks that are not likely detectable in the premarket clinical studies?

I think we have gone through quite a bit already, but does anyone, just on that sort of primary question, have any other comments to make?

DR. HENNESSY: If somebody wanted to be conservative, you could say if there is a risk identified for one agent. Then, in the absence of data, you would assume that it's present for other agents, although you would certainly be open to be proven wrong. And, similarly, if you wanted to be conservative, just because one agent shows a particular benefit doesn't mean that all of the other ones do, and you would require evidence to show that it does.

So, in some sense, is this a double standard for evidence of risk versus evidence of benefit? But I think that that can often be appropriate.

DR. HIATT: There are other examples in cardiovascular medicine where class risks, say PD-3 inhibitors, carried forward throughout the class, and the standards might be different than for other classes, so it probably is informative.

Let's go through the specific questions then.

In addition to any other items, comment on the limitations or importance of the physical or chemical nature of the products or the microbubbles, and I would also suggest that we think about the energy being delivered with the ultrasound.

Do anyone want to comment on the actual microbubbles themselves? Does anyone want to comment on the ultrasound energy that is deployed? Do you think that that matters? Does that change the risk profile? Does it matter if the energy is high enough to destroy the bubbles?

DR. LINCOFF: It seems like there was some data that was sort of cited and referred to although it wasn't explained, that the energy doesn't predict the risk of premature ventricular contractions, but downstream implications of that don't seem much.

They have not been able to show any signs of microvascular damage although I don't know if they have looked at real high levels of energy.

DR. WARNER STEVENSON: I think just in a general sense that we would have some interest in making sure that additive therapies are evaluated together, additive

therapies perhaps being the high acoustic energy plus the microbubbles. I think using the word "destroying" the microbubbles in the coronary circulation certainly caused a response from those of us sitting up here, and perhaps that is totally benign. But I think that is something that one would want at least a modicum of comfort with rather than just assuming that that would be as safe as the microbubbles alone.

DR. HENNESSY: That would be an area where I would think that we can learn a fair amount from animal studies. I assume the studies have been done applying high amounts of energy to animals, and we ought to know something about it from that. I just don't know what that is.

DR. WARNER STEVENSON: Once again I would emphasize that that may be a particular model in which animals would be just the beginning because the abnormal circulation could perhaps be much more vulnerable with plaques, et cetera, to these effects than a healthy pig.

DR. PAGANINI: Would it not be important to know what is in the bubble? I mean we only have two fillers right now.

DR. HIATT: So, you are saying --

DR. PAGANINI: If somebody else came up with another gas, wouldn't that be important to know, and how that compared with whatever has already been approved?

DR. HIATT: You bet.

What about the mechanism of diagnostic action, echogenic contrast? I am not sure what you are asking.

DR. RIEVES: It ties into (a) to a large extent, the assumption that they are all used as echo contrast, can we make broad generalization regardless of the gas, regardless of the shell with respect to the serious cardiopulmonary reactions specifically. They are bubbles and used in echo.

DR. HIATT: I am not sure anyone is going to say to you that they all would share the same risk.

DR. PAGANINI: Again, I am sorry to belabor these, but diagnostic action, would we say that these are used just to get pictures or can they be used for physiology as well? Flow, we have heard of this morning. Other reasons for doing this beyond just the picture stuff?

DR. HIATT: Well, we heard today that the indications for these agents are going to expand tremendously and they are going to go into peripheral

circulation, identify vascular lesions and organs.

I would certainly think that--and we saw some evidence that they could be very interesting uses for defining changes in physiology from rest to exercise, for example, and I guess the issue with that is that the population broadens, are the risks exactly the same across these populations.

I mean they might have started with the highest risk population, you know, sick patients with cardiovascular disease, or it could work the other way around. Obviously, these are just issues that need to be out on the table as you consider new indications for these agents.

Effects in animals. For example, similar hemodynamic responses in pigs.

DR. RIEVES: What this gets into, for example, our friends at Bracco have shown us the porcine data that show all these contrast agents generally produce similar effects in the animals. On the other hand, if you look at the postmarketing reports, they are predominantly coming from Definity, if you will.

We have had questions raised that is there differential safety between these agents, Optison versus

Definity, for example. Given what we know about the porcine study results, does that impact your decision as to differential safety potentially, or based on what we know now, even though they have been more reported for Definity, based on the porcine data, we have to conclude the risks are probably the same.

DR. HIATT: Yes. I mean the obvious explanation there is that they just did better studies.

Does anybody else share any different opinion about that?

I would think that you would think about the same kinds of issues, approached in the same kind of way for existing and new agents.

DR. PAGANINI: But if you had a mandatory registry, anyone who was using this form of diagnostics, wouldn't that help you in differentiating perhaps, looking at one particular market versus another product? Not to make the definitive statement but to at least raise a flag.

DR. HIATT: It would level the playing field. If every new agent had the same kind of observational database as part of their development, presumably they would have the same ability to detect the same signals. So, as long as the

recommendation is kind of consistent, then, you would hope, and then you might be able to compare across agents if the rates appear to be markedly different.

DR. RIEVES: Right. We would probably get some idea there. It teeters into differential marketing claims also. So, we are sort of getting into another area, but your point is well taken.

DR. TATUM: You are asking a question about class effect. Do you really believe that with different shells on these bubbles and future different ones, that you truly have one class?

DR. RIEVES: That is actually our question to you all. We don't bring the easy questions. We have a variety of opinions. Tell me, share yours.

DR. TATUM: Going back to just some knowledge of nanostructures, obviously, as you change the shells, you get difference in bar distributions, you get different reactivities, you activate different cells, you get different coding characteristics if it stays in the bloodstream for long enough, so it is very hard for me to believe that an albumin versus liposome versus something else is going to be identical. And I don't know the

mechanisms related to what we are concerned about, whether it is purely a physical effect or whether something else is going on to say this is truly all one class.

I think that is a question I would have a hard time saying I would accept that as it stands right now.

DR. KREFTING: Look at the porcine study where you had two different ultrasound contrast agents, different shells, yet, the reactivity and outcome in many of the pigs was the same.

DR. HIATT: I think we are absolutely saying that you can't make any assumptions as these agents' physical properties go from one development program to the next.

If we all thought that they were the same, one really well done observational study might answer your safety concerns forever, but because we are recommending that every new development program have a safety study embedded in it. Then that implication of that recommendation is that they may not be the same and that you would have to have the ability to detect safety signals unique to each development program. Right?

DR. TATUM: Right, and I think the question came up about the renal. We don't know what is going on there,

and, of course, a change right there could change the distribution considerably and potential toxicity.

DR. KASKEL: That was exactly what we were talking about before, about the albumin, how much of this has been studied in preclinical studies to see what fraction of that albumin would reach the renal circulation where clearly it is going to be very important to determine that in some fashion, and that can change, a host of factors in the glomeruli and the tubules that are deleterious .

DR. PAGANINI: I just want to underline the fact that the renal cortex is, in fact, the higher cortex.

DR. HIATT: Do we have other comments on these questions or do you all have any comments?

DR. RIEVES: Well, folks may walk away thinking you haven't accomplished much here because even though we have had a lot of hot air, it has been very productive hot air in the sense that the visibility, very critical thinking, and that is what we were looking for.

So, your thoughts and especially this idea of post marketing observational studies, your concepts, and even your comment about differential effects, those points are well taken here, so we much appreciate it.

DR. HIATT: With that, I think we are close to wrapping up just a few minutes ahead of time. I really do thank all the sponsors and the public for their comments and the Committee's deliberations. I think that we have tried to wrestle with the issues of safety here, and recommended some well-defined paths forward to elucidate those signals, and also to emphasize the importance of broadening the claims to include some intermediate outcomes of benefit.

Any other comments? If not, thank you, all. We are adjourned.

[Whereupon, at 4:50 p.m., the meeting was adjourned.]