FDA statisticians do any investigation of within-center propensity scores and showing that same rule was used across all centers in North America, for example?

DR. HARRINGTON: Dr. Levenson?

DR. LEVENSON: We did not develop a separate propensity-score model by center. The sample sizes were too small to do that. We used the common model throughout all the centers. We did look at a subset of centers where both agents under consideration were used.

If you just look at those centers alone, the results are very similar.

DR. RUBIN: For example, one thing that you could have done, even if you didn't want to do separate propensity-score estimation within each center because, obviously, that is where the decisions are being made. They are not being made by state policy or something like that.

You could have checked, within each center, for balance of the covariates across the treatment groups using the propensity score that

you had, and I don't believe that was done either.

DR. LEVENSON: For the centers where there are both agents used, yes; we did.

DR. RUBIN: And they were balanced?

DR. LEVENSON: It is a much more variable situation because there are much more small sample sizes. Even centers that did use both sometimes used more of one.

DR. RUBIN: Right. That is why I had unsatisfactory at this time. The dataset was not designed to answer this question. So it is really a struggle to do it right because it was intentionally limited to 50 patients at each center.

If it had been designed to answer this question, it would have been designed to get a lot of people at each center. You are not trying to get a representative answer across many, many centers. That is not the issue here.

The issue would be to get lots of data within each center so you could created balance within the center and the year because also there

are probably changing rules in time. The experience this year is not the same as--2005 is not the same as 2004. So, to say that propensity scores are the same doesn't seem to make much sense.

DR. HARRINGTON: Another comment I want to come back to is when we start talking about the randomized trials, whether or not trials done in the early 90s are applicable today.

But let me go off to Dr. Neaton who has been waiting.

DR. NEATON: Just a comment to follow up on this. I think, quite apart from center, the Mangano study was done over ten years. The secular trends in the use of the drugs as well as the changes in kind of prognosis that people--in the treatments. There is a big issue to consider.

My question is to the sponsor. In your placebo-controlled trials, you found evidence of increased risk of renal dysfunction. That has been corroborated now, same order of magnitude of risk, it looks like, in the epidemiological studies.

What is being done to follow up on that in terms of the long-term adverse consequences of that?

DR. McCARTHY: There are no long-term studies planned at this stage but, you know, based on today's discussions and deliberations, we would certainly welcome advice from the committee in that regard and would certainly follow up depending on the outcome of today's meeting.

DR. HARRINGTON: Dr. Black and then Dr. Lesar and then Dr. Young.

DR. BLACK: Hi. Thanks very much. I want to change the focus just a little bit and address this to my cardiovascular surgical colleagues wherever they are sitting. We have heard a lot and we have to make some risk-benefit calculations here. We have been focusing almost entirely on risk and there has been very little mentioned about benefit except trials that, as you say, are a decade old and a few anecdotal reports, perhaps, I think delivered with lots of passion about what the benefit might be.

So I would like a little more discussion in an era where it looks as if we have safer alternatives based on what is available as to why this is such an important drug because you wouldn't even do a study without it. So there must be some reason why you think this is so valuable.

I would just like that articulated a little better.

DR. HARRINGTON: Go ahead.

DR. JEEVANANDAM: Some of those statistics are deceiving. I think there was one in the Mangano article where the incidence of bleeding is the same among whether they used the antifibrinolytic Amicar or with aprotinin. Clearly, in clinical practice, there is a difference in bleeding. We kind of grade how a surgeon perceives bleeding is going to be in the case and then we will decide on which antifibrinolytic or serum potentially inhibitor to use.

DR. BLACK: But we don't really have a comparative trial as if we are thinking about other

trials to do. It sounds like an active comparator trial might be a good idea.

DR. JEEVANANDAM: Going forward, for a randomized clinical trial, yes, you would have to do--I don't think we would do one with placebo. You would have to do it with another antifibrinolytic whether it be tranexamic or Amicar with aprotinin.

The problem you are going to have with that trial is--you know, a lot of surgeons, now, have established patterns of how you use aprotinin. You would have to break those patterns to be able to do a randomized trial. And you also have the whole law-suit arena where you have lawyers who are coming around aprotinin patients.

So it is going to very hard to enroll into that trial.

DR. HARRINGTON: Although, we had to break the OB-GYN docs of using hormonal therapy in our perimenopausal women, too. So I suspect we can do it with the surgeons, too.

DR. BLACK: But I think, right now, and,

again, I would like some other opinions, not being a real expert in this area, just looking at this data, there is a certain sense of futility I have that we can never really make sense of all that we have seen today, which trends in the same direction, which goes back to the earlier studies. It seems to have the same signal at about the same level.

But those are very old trials and there was no potential alternative.

DR. JEEVANANDAM: I think the biggest problem with all the trials that we have seen today is propensity matching looks at things on paper. What you are completely missing is what the surgeon's determination--the surgeon's judgment in putting somebody on aprotinin.

DR. BLACK: I am not missing that at all.

DR. JEEVANANDAM: Right. You are not missing it. I am saying that is like the unwritten or there is an underlying problem with the propensity matching because no one is determining that.

DR. BLACK: No; I got that. I think we have to require of surgeons and procedure people in general to have the same willingness to have what they do tested the way you give pills get tested. I think that is something we ought to be talking about.

DR. HARRINGTON: So I am just going to ask the panel try to speak one at the time because the transcriber is having a hard time picking us up. No apology needed. Norm, do you want to get in on this discussion?

DR. KATO: I would have to agree that I think that surgeons tend to be fairly passionate people. They are very dedicated to their work. I think one of the problems with bleeding, per se, and perhaps one of the reasons why it becomes this real passionate issue is that we have to deal with the patient going forward.

If you decide, oops, gee, we are bleeding a whole lot now, we should have given this two hours ago or four hours ago, there is no real way to kind of go back in the process.

To be honest, in my renal-failure patients, I just use Amicar and have gotten very good results with no excessive bleeding at all. So I am actually kind of surprised to hear that you use aprotinin all the time.

So I think there is still a lot of variable in how we use this and, to some degree, if you want to call it kind of the mystique or it is just a hunch or it is, gee, our last case worked pretty well doing this, so this is what we do now.

I first starting Amicar in the early 1990s when I finished my training. We just did it because it seemed like a good thing to do. We didn't have anything else to use. And, lo and behold, it took off and it really worked quite well.

But is there any randomized controlled trial saying that it works? No. On the other hand, my blood-uses data I think can match the best published studies.

DR. HARRINGTON: Dr. Lesar.

DR. LESAR: Thinking like Dr. Black is

that, I think, during this whole discussion, one side of the mind is saying is why doesn't the translation of reduction of transfusions appear in the outcome data, that if transfusions produce all these negative outcomes, which is firmly established, why didn't we reduce them even as a percent reduction as was shown during the public comments. Why does this not translate or why haven't we seen these outcomes; that is patient mortality, morbidity, or return to the operating room. Why does that not appear in the studies?

DR. HARRINGTON: That is certainly one of the questions I wrote down. If everyone is up there passionately talking about how bad blood transfusion is and this stuff reduces blood transfusion, why aren't we reducing death. I think that is your question.

Does the Bayer group want to tackle that?

DR. McCARTHY: I would like to call on Dr. Shander to respond to that question.

DR. SHANDER: Thank you. I think that the magnitude of the issue of transfusion is much

bigger than just the outcomes that we have mentioned, whether it is acute renal failure and mortality but also the issue of infection.

There are other issues in terms of--as was already mentioned by some of the people in the public regarding the issues of the cost of making blood safe as well as, as you can see, if the slide is up--

[Slide.]

Going back to 1984 when first HIV was detected in blood, you can see that, in the Bay Area, 1 in 100 units of blood contained HIV virus. Over the years, down to 2007 where we are today, the risk is minimal with enveloped virus except hepatitis B which still remains quite high, if you will, but not a major risk.

The cost of doing this is in the probably tens or hundred million for quality-of-life years saved so that there is an enormous amount of money spent making blood safe and that cost, right now, is being translated to institutions or hospitals where it was hidden from them before.

Because of making blood safer, and if we go to Slide 6, please--

[Slide.]

We have also reduced, in many ways, the donor population. We have restricted the donor population. So, on one hand, we have increased cost of blood which will continue because, as you know, we have potential agents now--Trypanosoma cruzi is one--that has to be tested for and, at this time, we are reducing the donor pool making, again, the whole issue of blood management much more relevant than it ever was. Before it was an option. I think now it is a necessity.

You have heard, also, from before, in terms of the mortality, the overall morbidity and mortality of the associated blood transfusion. I think that there are three major areas where we are concerned. One is acute lung injury, if I could have Slide 31, please--

[Slide.]

Where acute lung injury is now thought to be about 1 in 5,000 components. There is about 1

in 625 recipients, mortality. And this is, again, very conservative mortality because one of the members of the public quoted newer data showing actually that mortality is much higher than that.

But, even if you go up to 20 percent, we have about 4,200 cases annually which are reported. There is a considerable amount of under-reporting of this syndrome. So you see mortality is estimated to be between 210 to 420 cases yearly, again akin to, probably, a jumbo jet over a total number of about 5 million recipients of blood products in this out whereas, as you know, the airline industry boasts probably billions of passengers.

The other big question is the contribution of transfusion-associated circulatory overload on this area.

Now, if you go to the next slide, please--

[Slide.]

You could see there mistransfusion, which, again, the FDA considered to be the number-one risk of allogeneic blood transfusion is about 69 or

close to 70 percent in this description from the British and the Irish Hemovigilance study.

Again, the numbers have changed from 1996 where is was around 50 percent up to 70 percent in 2004 reported. I don't think is because we have had more mistransfusion. I think it is because we are becoming more cognizant of this and reporting is getter better.

Mortality in the United States from this is about 1 in 600,000. So, again, you can add these numbers as we go along.

So, with that last one is actually transfusion-related acute lung injury--I'm sorry; transfusion-related immune modulation which is Slide 118--

[Slide.]

Where--I'm sorry; these are the updated rates, if you will, of transfusion-related acute lung injury. As I mentioned to you, this is the study that was already mentioned with mortality approaching 50 percent in this group.

So, again, if you look at

transfusion-related immune modulation, which is what causes--we think causes the infection in this population, especially in the cardiac population and there is plenty of data suggesting a very strong signal associated between the two.

There is increased mortality. There is also increased, not only of wound infection but pulmonary infections associated with about 50 percent mortality.

If you go to the next slide, please--

[Slide.]

One of the things that has been a strong signal in the cardiac-surgery population has been the reduction of leukocytes in terms of improving survival. Although, in this study, where mortality was associated with transfusion-related immune modulation, once adjusted, there was still an increase of 70 percent in mortality, when leukodepleted blood is used in the cardiac-surgery population, that can be reduced somewhat. But, again, it does not eliminate that.

So the question remains, still, with all

of these signals of transfusion, mortality and morbidity, why isn't it that we are seeing an improvement in survival after use of aprotinin with the reduction of transfusion.

I, again, submit to the committee to possibility is that, with those patients who have shown no difference in mortality in these studies, the possibility is that, without aprotinin, they would have lost much more blood, been exposed to much more transfusion and that mortality could be more than doubled than what we are seeing.

So the fact that it is equated in both groups, I think, has to do, or is due to, probably, a reduction in loss of blood and reduction in allogeneic transfusion.

DR. HARRINGTON: So, are you saying that is an hypothesis or is that--

DR. SHANDER: I am saying that is an hypothesis, a strong hypothesis, because we have so many signals in terms of the outcome associated with transfusion, not only in the cardiac population but also in the non-cardiac surgical

population across the board.

DR. HARRINGTON: Can I maybe push you a little bit that, if--I will buy that blood is bad, that I don't want any if I am having an operation unless it is absolutely necessary, that, therefore, something that reduces blood might be good. But the only way we know that is if we do a randomized controlled trial to test that hypothesis that you elegantly lay out. Would you agree with that?

DR. SHANDER: Well, if we could do that and, again, I think we have to again look at the selection of patients--

DR. HARRINGTON: Sure.

DR. SHANDER: When it comes to transfusion, there is always the issue, the ethical issue, and whether we reach, again, the clinical equipoise. But I think that, yes, a study is warranted.

DR. HARRINGTON: Thank you. I think it was Dr. Cheung and Dr. Ellis.

DR. CHEUNG: I would like to make a response to Dr. Lesar's question. An alternative

explanation is that that aprotinin is doing something good by decreasing transfusion which I acknowledge has all kinds of signals that might be beneficial. But it could very easily be counteracted by something that aprotinin does is bad.

What we keep hearing this morning is that it causes kidney dysfunction, whatever term you would like to use, but that seems to be quite a consistent signal. At least in the nephrology circle, we are pretty much enthusiastic about the concept that chronic kidney disease, even to a relatively mild degree, is an extremely important cause of long-term cardiovascular mortality.

So I am still not convinced that this dysfunction is transient and readily reversible. I think we have very little data on that. Whether it leads to immediate dialysis or not, I think you can debate it some more. And I think that, since the dysfunction of the kidney part of this is so consistent, I think we seriously look at whether that can very, very easily explain the long-term,

possible long-term, mortality.

DR. HARRINGTON: So I am going to go over here to Dr. Ellis and then Dr. Day, Dr. Kaskel, Dr. Warner Stevenson, and then our consumer representative.

DR. ELLIS: Dr. Cheung alluded to some of my questions about whether or not there was something bad. I mean, blood loss is bad. It appears that transfusing blood is bad although aprotinin reduces blood loss. Again, there seems to be a signal in the other direction or, perhaps, a neutrality.

So, again, we are left--and from a statistical perspective, and I am not a statistician, I find myself having difficulty distinguishing between blood loss and the need to give a transfusion and how one separates out those two in terms of blaming the transfusion versus the blood loss that necessitated the transfusion.

Obviously, the decision to transfuse will vary amongst physicians for a given trigger and target. So, listening to all of this, I await, if

anything, to see the randomized trial as I am sure all of us do in the year, year and a half, that will really address these issues.

We have heard that there is not equipoise in the U.S. amongst cardiac surgeons to randomize people to not receive antifibrinolytics. Fortunately, our colleagues north of the border seem to have been able to do that. So I await that.

I still am frustrated, as Dr. Cheung and others, by the lack of ability to show that, by reducing all of this awful blood-product use, that we can find any benefit.

DR. HARRINGTON: Dr. Day.

DR. DAY: I had not requested to speak, but I do have something on my mind.

DR. HARRINGTON: Well, I am glad I called on you, then.

DR. DAY: And many of my questions have been asked by colleagues. But I was wondering if Dr. Mangano would like to comment on some of the evidence presented during the open public comments

especially RBC as a continuous variable and how that might affect the results that he obtained.

DR. MANGANO: Yes. As transfusion and outcome variable or a predictor variable. If you include outcomes in any logistic-regression analysis or any analysis like that, it will trump all the predictors.

The data that were presented emphasizing transfusion unfortunately did not emphasize the timing of transfusion and the timing of the outcome event. Some transfusions occur after renal failure and simply putting transfusion in the model means that the predictor occurred after the outcome.

I find transfusion to be an outcome variable that occurs after the drug is administered, not before, and, therefore, contaminates the discussion.

Regarding transfusion and fresh-frozen plasma as well as red cells and platelets, they were put into our models and our models didn't demonstrate that we ignored transfusion or that aprotinin had a similar effect to fresh-frozen

plasma but did demonstrate that, regardless of the independent effect of transfusion on outcome, aprotinin trumped that in that it preserved that. So, in patients with low transfusion or high, aprotinin was satisfied.

I respectfully disagree completely with Dr. Rubin even though I honored his work earlier and what he has said in his analysis is, if you do a multicenter study and you include a couple of hundred patients per center in a thousand centers, for example, you cannot do propensity analysis because he is demanding it to be done by center.

That is an impossibility today. We studied 100 patients per center to put the mandate that we would independently develop propensity scores by center. It makes no practical sense whatsoever. Therefore, taking your hypothesis, one will discount every multicenter study available that could be done which incorporates less than a thousand patients per center.

So I understand that you are a consultant for Bayer and maybe that has influenced your

actions. I hope not. But I completely disagree with the use of propensity

Thank you.

DR. HARRINGTON: Thank you. Before we go off this topic, Dr. Day brings up something that I wanted to ask Jim's input on. If I think about the pathway of, you know, at the baseline, then something happens, in this case, transfusion, then something else happens in terms of death, in a randomized trial, we would be taught to think of that as a post-randomization variable or a post-baseline variable.

There are analytical ways to handle this. Can you help us out?

DR. NEATON: Well, I actually tend to agree with Dr. Mangano on the public presentation that we heard. I guess--and the reason I asked the first question this morning was I wanted to understand the timing of the decision when you use the drug because that is what is important.

So I think the analysis that we saw earlier would be much improved if, instead, we

worked with what the predictors were, and they seemed to line up pretty well with who was going to need the transfusions in the two groups if those were built in, either to the propensity model or as covariates in the analysis.

So it is an interesting analysis. I think it is fraught with some problems of interpretation. I don't want to totally dismiss it, but I think it does have a problem of chicken-egg.

DR. HARRINGTON: Does Bayer want to respond?

DR. McCARTHY: I would call on Dr. Rubin to comment.

DR. HARRINGTON: We don't want to turn this into an argument about the merits of a propensity score. So keep it brief.

DR. RUBIN: I will. The purpose of doing a propensity-score analysis as close as you can to the decision-maker level is to try to get an answer that mimics that answer you would get from a randomized experiment.

If a dataset has structure so that it

makes it impossible to do such an analysis, then there is very little hope that you can get the same answer you would have there as you would have gotten in a randomized experiment.

With respect to transfusion, I agree with Dr. Mangano that that is an outcome variable and formally should be treated that way. But, when you have results like the one we have seen here, it sort of suggests that there are missing key covariates that are bouncing around that you really should have that, if you adjusted for them, it would make this transfusion result go away.

The only way, I think, you are ever going to unbundle these issues is to do a randomized trial where you probably have two factors running, maybe aprotinin versus AA and another factor which is encouragement to give more or fewer transfusions. I understand there have been randomized experiments done where you do randomize the number of transfusions or encouragement to have more transfusions. I think it was done in Canada if I am not mistaken.

DR. HARRINGTON: It was.

DR. RUBIN: So at least you can get some doctors to agree to participate in such a study.

DR. HARRINGTON: So I have got Dr. Kaskel, then you, Lynn, and then Dr. Gillett next to you.

DR. KASKEL: I wanted to have Dr. Smith's slide 102 shown for a moment just to review

[Slide.]

I think the remarkable thing, looking at this dataset, is how stable the creatinine is. It goes down, as Emil had said, in the ICU and then goes up right afterwards back to a baseline and a slight increase on Day 7 in the treatment group.

But this is a remarkable stability in patients who are undergoing tremendous fluctuations in their cardiovascular and renal status. I use this as an example of how we need to do more. If you are going to be thinking about assessing renal function in the future with a randomized controlled clinical trial.

I think I said this last year. There are other measures of renal failure or renal

dysfunction that can be put into a trial and can be implemented at multiple sites. For instance, not just the serum creatinine but measurements of, or estimates of, creatinine clearance; cystatin is another estimate used today, iohexal clearances or measurements of GFR that are specific.

I think if you are going to go the trouble of an RCT, you need to be very attentive to measurements of renal failure.

Thank you.

DR. HARRINGTON: Good points. We will probably come back to those when we do talk about the trial issues later. Dr. Warner Stevenson.

DR. WARNER STEVENSON: I want to make a couple of comments on the mortality issue. It seems like one of the main things of the mortality comes from the Mangano study from this year. In fact, if you look at that, the mortality curves diverge over time and get more and more apart as you get up to five years.

It is very hard to understand why that would happen from the use of aprotinin whereas it

is very easy to understand if, in fact, what you have done from the beginning is identify two groups at different risk of bad outcomes, which I suggest is what we did.

The next thing, clearly it does decrease transfusions. I would emphasize that we don't have any other drug that is indicated for that in this setting so I am not sure in what detail we can discuss our other options. The data we have, at least for North America, suggests that this drug is being used appropriately in the high-risk patients to decrease their transfusion requirement to make it similar to that in the low-risk patients.

So I am not sure why we would necessarily see a mortality benefit from that use.

But I want to address one particular question to the FDA experts here. Part of our role, I think, is to anticipate the impact of our deliberations on future discussions. Clearly, approved agents are always going to be used in a broader population than a trial population.

In fact, my concern is that as the

inevitable post-approval observational studies come up, I want to make sure that, as we discuss these issues about risk and propensity that the deliberations don't end up actually discouraging the development of therapies for high-risk patients because we may be in exactly the same place with another such therapy in the future.

DR. HARRINGTON: Good comments. Dr. Gillett.

DR. GILLETT: The long-term consequences of transfusion and/or durative surgery, long time on the surgical table, seem to be kind of missing from the endpoints that are looked at by any of these studies. If, indeed, getting people to have shorter surgeries by minimally invasive surgery or have fewer transfusion by the use of agents is desirable, then why aren't we looking at some of the endpoints, neurological, behavioral, memory loss, other endpoints which are admittedly difficult but have been used in quite a number of studies now to define better operative conditions and better surgical management in a way which seems

to give the surgeon and the patient more satisfaction when it is all done.

DR. HARRINGTON: Does someone want to respond specifically to this? Dr. Day, you had your hand up first.

DR. DAY: I had a question in looking at all the briefing documents. I didn't really see data collection on neurocognitive consequences of agents, no agents, and different agents. Was there something presented that I missed or something that someone has collected that hasn't been mentioned.

DR. HARRINGTON: Does Bayer want to respond to that?

DR. CYRUS: As part of the briefing document, there was a reference to Dr. Coleman out of Hartford Hospital. He looked at the database there and he did find a statistically significant decrease in neurologic outcome. This was mostly driven by delirium in that finding.

Then, as far a meta-analysis--

DR. DAY: I'm sorry; a decrease for what condition. I mean, with the agent or without?

DR. CYRUS: With the agent, with aprotinin. It was a decreased association with aprotinin relative what was really a broad cerebrovascular thing. It included, I think, stroke, delirium and encephalopathy and coma. But that effect was mostly driven by delirium.

When looking at other analyses that have been done including a meta-analysis by Dr. Sedrakian, which only looked at CABG surgeries, as well as some publications by Dr. Smith as well as Dr. Levy who are here and the clinical trials where stroke was reported as an adverse event, not looked at from a prospectively defined very set neurological outcome, there did appear to be a statistically significant decrease in the reporting of stroke as an adverse event.

However, large, more detailed, trials have not been done. There have been some small MRI imaging and neurocognitive tests. One was done by Dr. Merkin in Canada and those test failed to show any advantage with aprotinin.

DR. DAY: Had memory tests been included,

or was this like the Mini Mental Status?

DR. CYRUS: Dr. Merkin's study, I don't recall exactly which test he used, but it was not a Mini Mental. He had some tests that looked at frontal-lobe function, a few that looked at memory. And when you looked at collectively and you looked at the variable between the test and the re-test period, there really wasn't anything there.

DR. GILLETT: What prompted this question, basically, was the failure of any of the studies to address the optimization decision-making which Dr. Corso discussed so excellently this morning. I just didn't understand why these data were not being collected or at least being--maybe they are not there in observational studies when you use administrative recommendations. They don't say how long you are the table, how long you are on the machine, how long these things are going on.

DR. CYRUS: I will just make one statement. It wasn't a Bayer-sponsored study but Bayer was going to provide study drug for a large NIH grant that was submitted by Dr. Elliott

Bennett-Guerrero out of Duke who was going to look at neurologic outcomes in CABG surgery.

After Dr. Mangano's publication, it failed to get funding for the very reason of the observational-study publication. He was unable to conduct that.

DR. HARRINGTON: Dr. Gillett, did you have any other question right no? No? Okay. Dr. Ellis? Or Dr. Jeevanandam? You guys decide.

DR. JEEVANANDAM: Looking at the i3 data, if you look at their total cohort, about 50 percent of patients received aprotinin in that study versus if you look at all the other observational studies, the amount of total patients who received aprotinin is much lower than that.

So clearly there is a different pattern of aprotinin usage. So I guess my question--you know, the label is for high-risk patients undergoing CABG surgery. I suspect, obviously, from that 96 percent that you talked about, there are a lot of patients receiving this drug that are outside exactly what is labeled.

So I wonder if you have any idea what percentage of patients are getting this drug that are outside label and, if you look at the BART inclusion/exclusion criteria, that actually probably reflects real-time use much more than these studies do because they are looking at valve patients, or re-operative valve patients. If you look at their preliminary abstract, they had an 11 percent incidence of exsanguinating or massive hemorrhage which is one of the things that we are trying to prevent with aprotinin.

So that trial may actually be very important to see what their results are. But just wondering whether you had any idea about what percentage of patients are actually being used on-label versus what is essentially off-label--

DR. McCARTHY: Dr. Smith, could you respond, please.

DR. SMITH: You ask a very interesting question. I think that the i3 percentage of aprotinin use is more like 25 percent because they start off by excluding about half the patients to

get no antifibrinolytic, and then it is about 50:50 for aprotinin and Amicar, so down around 25 percent.

You know, interestingly, the thing that has been mentioned here is how the drug is used not only in what patients is it used by how is it delivered.

For example, 17,000 patients were excluded when the FDA received the untreated patients because they got post op Amicar or antifibrinolytic which is--no one does that anymore. More than half of the data in the Epi 3 dataset, aprotinin was administered not by a label indication so it couldn't be identified as either a half dose or a full dose.

So when we look at these observational trials, we are seeing exposure of many patients that are off-label, both in terms of the indication and the method of administration which may account for some of the problems. But I was responding specifically to, I think, your concern that half the patients got aprotinin there. It is probably

about 25 percent which is probably reasonable.

DR. HARRINGTON: So let me just clarify that, Peter. Are you saying that, in a typical, large surgical practice, about 25 percent of patients undergoing cardiac surgery will receive an antifibrinolytic agent or specifically aprotinin?

DR. SMITH: Now?

DR. HARRINGTON: Today; yes.

DR. SMITH: Today it is probably about 15 to 20 percent would get aprotinin. At least at our institution, like has been mentioned by your other surgeons, the remainder get Amicar. So it would be standard to give some sort of therapy and it would be 15 to 20 percent. But I would be speculating.

DR. HARRINGTON: I think we have Dr. Ellis and then Dr. Lincoff.

DR. ELLIS: Don't go, sir. A question for the sponsor. We have, in our briefing document, an abstract, the Shaw abstract. I realize it is just an abstract but it is to be presented at the American Society of Anesthesiologists this year that contrasts long-term survival after CABG at

Duke and is adjusted for aprotinin propensity EuroSCORE, age, gender and surgery date that suggests similar long-term results to Mangano.

I wonder if you have any comment about that. That is Question 1. Question 2 is there appears to be a dose-response relationship in some of the studies, particularly with the renal dysfunction between the half dose and the full dose. I wonder any thoughts the sponsor may have about recommendations for full versus half-dose dosing. So two separate questions.

DR. SMITH: I will handle the first question. First I think that you shouldn't assume that since I am from Duke that I know the answer to that question. So Dr. Shaw is our cardiac-anesthesia group and our cardiac-anesthesiology group decided that they wanted to do observational analysis of our own patients.

My role in this was to give them permission to look at the individual surgical data and our outcomes, which I did immediately. They

have published these abstracts without my input. So I know no more than what is published already in abstract form. There are two which have not been peer-reviewed yet.

But I think--maybe we could put the slide up.

[Slide.]

You are referring to this retrospective review of many of my patients where 13 percent receive aprotinins. This may address what Dr. Harrington was talking about. In the end, I think that the main conclusions here were long-term mortality was increased and they used EuroSCORE as one of the risk adjusters.

Obviously, when I get back to Duke I will ask them or maybe they will hear from here whether they looked at our blood-transfusion data because that corrected that in the presentation from the floor for the thing. So they show a Kaplan-Meier curve that shows a separation so it very similar to what was shown from the floor.

The second abstract was a

renal-dysfunction abstract. We may not have a slide of it. Let's show this next slide. Slide on.

[Slide.]

This is the curve from that. That is the Kaplan-Meier survival curve adjusted by EuroSCORE.

Slide off.

Their other abstract is on renal dysfunction. They looked at the same set of patients and they basically showed renal dysfunction by creatinine increase, a delta in creatinine increase. But interestingly, at Duke, the baseline creatinine in the aprotinin-treated patients was significantly higher than the non-aprotinin patients. So it seemed to be a marker for other risk factors and there was no difference in dialysis at Duke between aprotinin- and non-aprotinin-treated patients when corrected by EuroSCORE.

Does that answer your question about Shaw?

DR. ELLIS: Thank you. Do you have a follow up to that, Lynn?

DR. WARNER STEVENSON: I wanted to make a really short comment in relation to the dose-relation issue. We just found here, in fact, in the 2007 STS Guidelines that it is a Level 1 recommendation to use low-dose aprotinin in patients undergoing cardiac procedures. That is without any specific risk. Whereas it is also a recommendation to use high-dose aprotinin in the high risk. So I think we have a reason why there is going to be a dose-related effect. It is because, on some recommendations, they are actually recommending it for regular use which might be something else that Bayer needs to readdress.

DR. McCARTHY: Dr. Harrington, if I could just comment on--we did have a discussion with Dr. Shaw. We spoke to him about two weeks ago to discuss his work. Unfortunately, he couldn't attend the meeting today but he did state to us that there is very significant confounding in his data and I think that, when we see the full data presented at the upcoming meeting, I think that will become evident.

If I could also, perhaps, call on Dr. Makuch to comment on the issue of long-term mortality as well, too, if he may.

DR. HARRINGTON: Briefly.

DR. McCARTHY: Yes.

DR. MAKUCH: I will speak almost as quickly as I did for my talk. C-71, if I could have that up.

[Slide.]

Basically--and I won't talk about propensity, either. Number one, I just want to point out that there really is differential lost-to-follow-up--it is the fourth bullet--27 percent of the control versus 18 percent of the aprotinin patients. I really think that that has to be considered when looking at the survival data.

The second point I want to emphasize is the second bullet. We talk about confounding. Is it really important? It really is important. There is confounding between treatment and geographic region. It is not only confounding. It is total confounding.

Let me just flip the page just for a second and just say what would you do if you were doing a multinational RCT and, in Asia and in the Middle East, only one of the treatments was used and the other treatment arm in your RCT was never used in those areas of the world and, also, in other, in other areas of the world, the randomization allocation between the two treatments was, let's say, 8 to 1 or 9 to 1.

Certainly, I know that if I was doing a clinical trial and that happened, I would probably be taken on the carpet. But I think the next issue, though, is that, given that if that ever did occur, and I hope it would never occur in anything I was involved in, what would I do with those data. You can ask yourself what you would do with those data but I know what I would do and that would be, if I have no patients in one treatment within any center or any, let's say, region of the world, I would discard those patients from the comparison because, otherwise, I have no idea whether it is the center effect or the treatment effect that is

causing anything.

Certainly, I would not defer to regression modeling to somehow smooth over such major imbalances in terms of the treatment allocation.

Then C-78 and then I will be done.

[Slide.]

And so this really then relates to something that Dr. Rubin was saying but the second bullet, which I didn't get to this morning, is that the treatment-selection criteria vary across centers which confounds the treatment and outcome relationship.

So, in addition to Bullet 1, which is saying the treatment is confounded with patient risk and we don't know whether it is treatment or the patient risk factors independent of treatment that are causing this association, it gets much more complicated in administrative or observational databases where we have the second bullet operating.

Generally, I think that is the case. And the point is that I don't think any of the analyses

I have seen today have taken into account the second layer of confounding as represented in Bullet 2. The analyses have attempted, as I have seen today, to address the confounding issue in Bullet 1.

However, there is a publication by DeLong in the article noted in which she points out, the fourth bullet, that all of these standard methods are inadequate in these situations in which we have not only the first but also the second layer of confounding and that there is a proper treatment of these issues, but it does require more complex models than I have seen here today to appropriately take into account the confounding.

Then the last sentence to add is that when--and she uses and STS database for a different reason--she showed that when these more complex models were used that included appropriate accounting for confounding that the treatment effect was reduced by 35 to 40 percent using these more complex models than when compared to the more simple logistic-regression models that were

presented here today.

DR. HARRINGTON: Thank you. We have got Dr. Lincoff and then Dr. Heckbert.

DR. LINCOFF: It is clear we are going over from different directions, the bottom line being that we have a lot of observational studies which are pointing, with a similar signal of increased mortality and increased renal dysfunction or renal failure, and a number of reasons why those studies may or may not be valid for reasons of confounding, et cetera.

There is no way--although, even if we could do the ultimate analysis that would adjust for every confounder, even those that aren't observed, we may or may not see a difference and, in the end, there is no way--there is not going to be a way to sort this out with the existing dataset.

We have got a signal that is concerning. It may be invalid but how to deal with it, and we have to deal with it. So, as we move into the latter part of the discussions which are going to

involve randomized trials, in preparation for that, I would like to ask, to my knowledge, BART is the only sizeable study that is randomized that is undergoing. But, with 3,000 patients and what seems to be a mortality rate now around 5 percent, and there was no discussion about what the observed renal-failure rate of this interim analysis is, has anyone done, either on the sponsor's side or, perhaps, in our own group, even a back-of-the-envelope calculation of what sort of power we would have to detect, with this trial structure, what we would consider an acceptable difference in mortality or renal dysfunction.

My gut instinct is it is going to be very low and that, essentially, for that question, this is not going to be a useful study.

DR. HARRINGTON: Dr. Levenson, has the FDA--or Dr. Shashaty, has the FDA looked at this?

DR. SHASHATY: Well, I think the information about the BART study that we have, and I have discussed this with Dr. Ebert who is, I guess, the prime investigator for the study, the

information from last week was that there were approximately 2,400 patients who had been enrolled.

There has been, for some reason, a decreasing number of persons being enrolled. I sort of sense from him that there was some resistance to patients becoming incorporated into the trial and all that he could provide for me was the information that, at the last interim analysis, there did not appear to be a reason for the Data Monitoring Safety Board to recommend a change in the conduct of the trial.

Now, as we pointed out, the frequency of large-measure blood loss is about 11 of 11.5 percent. We know that mortality is 5 percent. I believe that those still are extant as the trial has continued. Basically, he told me there were no new figures that would be useful in our discussions.

Was there some other issue that you--

DR. LINCOFF: Yes, because I don't think anybody is challenging that aprotinin will probably have a beneficial effect on the primary endpoint.

It may not. That is the point of the trial.

But the massive bleeding is not the question. The question here is patients dying or having renal failure. I am concerned with 3,000 patients as the target, even if they reach their target, with a death event rate of 5 percent, the interim analyses are never going to see a reason to stop the trial. Even when the trial is done, and we say, well, we now finally have a contemporary, a modern, randomized trial, we are not going to have an answer for this anyhow.

And if that is the case, if we can predict that ahead of time, then we have to make our decisions today on the basis of there is currently no dataset to be expected that will ever answer this question beyond the observational data that we have been debating all day today and either move forward with plans to do something about it or make a decision based upon this admittedly flawed dataset. But, nevertheless, it is all we have got.

DR. SHASHATY: Can I make a comment, please.

DR. HARRINGTON: Absolutely.

DR. SHASHATY: If one takes the pooled analysis of deaths in patients, in the randomized trials performed by the sponsor, as you know from the background package, the rate of death was 2.9 percent in the aprotinin-treated patients and 2.5 percent in the control population which was the placebo-administered population.

This is not statistically different. The number of patients were about 2,100 in each arm.

As an old-time guy, I am interested in knowing, does the patient live or die? Well, the best information we have from randomized controlled trials from the sponsor is no, there is no difference in the rate of death.

Okay. if there is no difference in the rate of death, again, as an old-time guy, I fall back to, well, what was the benefit that we gained from your intervention, whatever it is. As best we can determine, and I think this has been demonstrated over and over and over again, is that there is a decreased need for the transfusion of

blood on a percentage basis and the number of units of blood transfused per patient is reduced.

So that says to me, is that the only benefit that we know. As far as I can tell, I know that Bayer says that the frequency of resurgical procedures is reduced. The percentage there is about 1.5 percent in the control and they say 0 percent in the aprotinin.

But the studies are not that enormous. But it seems to be a relatively small one. So then you are really falling back on what is the problem of the use of blood? If you look at Page 25 of the sponsor's background package, you see that there is a consensus conference from 2006, and I believe this is what the sponsor is stating is the risk of blood transfusion.

If you do a couple of calculations--that is, it is stated that 14 million units of blood are transfused in 2001, 10 to 20 percent of the blood is used for cardiac surgery; therefore, the number of units of blood used in cardiac surgery is 1.4 to 2.8 million units.

It says that the death per million units of red blood cells, if we could exclude platelets for the time being, is 16 to 27. Therefore, the number of deaths in cardiac surgery due to red-blood-cell transfusions, if you multiply the two lower numbers, you get 22 dead people.

If you multiply the two higher numbers, you get 75 dead people. If you take the mid-point, there are about 54 deaths--I would assume, unless my figures are way off--there 54 deaths that are due to blood transfusions in association with cardiac surgery. I mean, that is the best figures I can come up with.

So what one has to consider is if the primary thing that you are avoiding by transfusing blood is 54 deaths, and with a range of 25 to 75 or approximately that, what is the risk, if any, of death of the use of Trasylol.

The information about the risk of renal dysfunction, we have thousands of drugs that induce renal dysfunction temporarily. We use them because they have a benefit. I am not certain--and, if we

found there were a benefit, I would accept the risk of renal dysfunction--dialysis is a different story--renal dysfunction to achieve that benefit.

But I would ask you to look at the relative benefits that are being associated with the use of this drug.

DR. HARRINGTON: Go ahead, Dr. Lincoff, Dr. Heckbert and then Dr. Neaton.

DR. LINCOFF: I certainly don't disagree with any of that, but I think--certainly, every trial of every agent can't be powered for mortality. But, once there is a serious enough question, and I think this is a serious question. It may be wrong. It may be confounded. But I think there is a serious enough question about mortality and about important renal failure, not just a rise in creatinine but, at least in some studies, a need for dialysis.

Then the obligation, I think, is to have data to support it one way or the other. Certainly, 2,000 patients per arm is not enough in these old trials anyhow to answer the question of

mortality.

So the fact that there was no difference is the classic no difference observed, it is just an underpowered observation. So we are left with the real question of whether or not there is an adverse effect on mortality.

All these calculations of lived saved per transfusion prevented bring up the question that was brought up earlier, then why aren't we seeing the mortality benefit. Maybe it is because it corrects back to normal but then these are all correct mortality rates that we are looking at anyhow, or are adjusted.

So, in the end, we just don't know. I think we are still left with the conclusion that our dataset is insufficient now to make any comments regarding these important questions.

It is not enough just to say there are lots of reasons why the observational data may not be real, may not be giving us the truth. At this point, I think there is enough doubt that we need to answer the question. Again, I think, with the

calculations--I mean, I am not a statistician but I would imagine, with 3,000 patients, we are not going to have the statistical power to do so with the one existing randomized trial.

DR. HARRINGTON: So we are going to come back to that discussion, Mike. Let me go to Dr. Heckbert, Dr. Neaton and then down to Emil.

DR. HECKBERT: Actually my comments are, again, on clinical trials, what do we have, what can we expect out of the results from BART and where should we go from here.

It seems to me, as I mentioned earlier, that the observational studies in this instance may not provide us with the kind of information we need because of the intractable confounding. I guess I just wanted to make one comment about the BART study.

I didn't do power analyses myself but I noticed that in the abstract, their original--as was mentioned earlier, their main endpoint was massive bleeding. They were expecting a rate of percent. What they have to date was 11 percent.

They say, in their abstract, that the trial was about 3,000 subjects so 1,000 in each arm, was powered to detect a 3 percent absolute difference between groups in the primary outcome. So I am assuming that is like 5 percent versus 8 percent or 4 percent versus 7 percent, something like that. So it is a big difference.

We would like to be able to detect smaller differences than that. Assuming their calculations are correct, which I do, that is what we will be able to do once we have the BART data. They are saying that their mortality is 5 percent right now so, assuming all is correct and stays that way, that is what we will be able to do.

One thought I had was I was favorably impressed with the Brown meta-analysis. Most of the data in the Brown meta-analysis is versus placebo, aprotinin versus placebo. But they did do the analyses of the more sparse data on head-to-head comparisons.

The data from the BART trial can be added into the meta-analysis material that is in the

Brown study. So we will have an increment there that can be analyzed by meta-analysis.

I think what our group needs to decide is is that going to be adequate or do we need to go beyond that in terms of trial data.

DR. HARRINGTON: So, Jim?

DR. NEATON: I just wanted to kind of make certain when we talk about mortality, we are talking about the same thing. So I understood the BART study is looking at in-hospital mortality. And all the data we have seen in the terms of the placebo-controlled trials are in-hospital mortality of 5 percent.

That is a very different situation, in my mind, in terms of a trial that might look at longer-term mortality to understand the consequences of some adverse effects that occur as a result of the drug early on.

DR. HARRINGTON: Good point. Go ahead.

DR. SHASHATY: If I might answer, I think that there is a mortality at 30 days as well.

DR. HARRINGTON: As one of their measured

endpoints. Okay. Emil.

DR. PAGANINI: Children, children, children. I can say that because I am also old, George. One of the issues that we have got to find out is, over time, there are differences--if you look at acute renal, there are four published papers now that show acute renal failure and mortality in post-open-heart surgical patients over time. It is improved from ten years ago to now.

So there are a lot of variables that are happening in the ICUs and in care of patients that are outside of just pure acute renal failure.

The other issue the definitions. There are no clear definitions for acute renal failure from changing creatinine to doubling creatinine to reaching some specific point to whatever. So that is a variable.

However, small changes in serum creatinine have been associated with rather dramatic changes in mortality. Indeed, in our own database of over 45,000 patients, we will see folks that have acute kidney injury but not requiring dialysis having a

mortality of around 23 percent.

Those folks that have acute kidney injury requiring dialysis has a mortality of somewhere in the range of 50 percent. Also, in both of these subgroups, that don't require dialysis and those that do require dialysis, both subgroups have a marked increase in infections both in kidney failure with infections or kidney failure on dialysis with infections, the latter probably associated with interventions, the former an effect of just kidney dysfunction.

So, therefore, the mere fact of having kidney dysfunction is a major issue for outcome, a major issue. Not transient. A major issue. So any drug that increases the risk of acute kidney injury has to be balanced to a rather significant benefit.

So I would agree that the benefit-risk ratio, which is what we are asking here, is going to have to be proven. I don't see it in observational studies.

DR. HARRINGTON: Good comment. Are there

any other--because we are going to enter the question phase next. Do any of the panel members have questions that they particularly want to ask of the sponsor or of the FDA or any of the previous speakers?

If not, why don't we take a break for why don't we say until just a couple minutes before 3:30 and then we will come back and do the three questions that have been asked of us.

[Break.]

Questions to the CRDAC/DSaRM

DR. HARRINGTON: This is the question period. There has been a little bit of a change. Actually, Mimi handed me this. It is effective July 26, 2007, for the way the questions are posed to the committee that require a vote.

We have three questions today that require a vote. I will read the question into the record. We will then have discussion. I will make sure that we go around the table and that everybody has had a chance to address or provide comments so that everybody's perspective has been included.

At that point, we will then call for a vote. I will ask you--first, we will ask members voting yes to raise their hands. While your hand is raised, and please be patient with us, we will go around the room and ask you to state your vote for the record along with your full name so that it can be recorded into the record.

We will then go ahead and ask the same for no. And, finally, do the abstentions. We will then, on conclusion of the vote, Mimi will read the final count of yes, no and abstain into the meeting record. So a little bit of change for those of you who have been on these panels previously to try to keep things a bit more organized.

So let me start with the first question. This is a voting question. And the question reads as follows: The Trasylol product label was modified in 2006--it will also be on the screen--to change its indicated population from the relatively broad population of patients undergoing CABG with cardiopulmonary bypass to CABG CPB patients who "are at increased risk for blood loss and blood

transfusion."

Modifications were made to the label regarding warnings for anaphylaxis and renal dysfunction and also to contraindicate Trasylol use in patients with known or suspected use in the last 12 months.

Here is the question: Based upon Trasylol risks and benefits evidences in Bayer's controlled clinical studies and the panel's consideration of the presented observational study data, do you recommend continued marketing authorization for Trasylol.

If your answer is yes, please describe any necessary product labeling modifications or restriction, and then we will proceed to Questions 2 and 3.

So I will open up the discussion to the panel. If there is no discussion, we will proceed right to the vote. But if people have comments, we will take them now. Dr. Lincoff.

DR. LINCOFF: I have a question for the FDA and it relates to the subsequent questions. If

a drug is approved, is there an actual mechanism to enforce the requirement to do a subsequent randomized trial or can that only take the form of a recommendation if you continue to maintain authorization for a drug to be sold.

DR. RIEVES: We can work out a postmarketing commitment. Again, it is somewhat of a negotiation arrangement. That requirement aspect there is, perhaps, not as rigid as you might be conceptualizing it. We generally work towards a negotiation of a postmarket commitment.

DR. HARRINGTON: Go ahead.

DR. FINDLAY: Can I clarify that further. Can continued marketing be contingent upon the completion of a study within a certain amount of time?

DR. RIEVES: Again, this would fall into that category of postmarketing commitment. We would have to work with the sponsors to get agreement, if you will, on time lines for enrollment, completion. Those are good-faith agreements that we would do our best to work out

with the sponsor. Again, they are somewhat negotiable-type arrangements.

DR. HARRINGTON: Go ahead, John, and then we will go over to Norm.

DR. TEERLINK: If I could follow up on that. Is, then, the only other option to say that we recommend pulling it off the market until--and stop and then say the only way you get back on the market is to do this study?

We have heard a lot about how postmarketing studies never get done. And I think, if we were to recommend a study, if there is this sense that this is important and really needs to get done, are you saying that the only mechanism we have to guarantee it getting done is to pull it off the market for now and then say the only chance you have on getting back on the market is doing this study?

DR. RIEVES: I may ask for some of my chiefs to weigh in on this also. This arrangement is heavily a negotiation paradigm, if you will, the agreement with the company. And, hopefully, we

could work that agreement out.

Candidly, it is more difficult, actually, with the product on the market and sometimes the more draconian approach, as you are outlining, is about the only insurance, if you will. We work in good faith with the company as we expect the company to do also in terms of sticking with the time lines for enrollment and completion of these studies. But, again, this is a negotiation, a somewhat voluntary agreement, if you will.

DR. HARRINGTON: Dr. Pazdur.

DR. PAZDUR: The question you have for a yes and no answer, can we require, in this situation, the answer is no. The issue is one that--I think it it is a misrepresentation--somebody said that companies never do these postmarketing studies. I think that is somewhat of a very broad incorrect generalization here.

I think there is a spotlight here and public interest in getting this trial done. I think that I would have confidence that Bayer has a

public and really a necessary commitment to do these trials.

So to say, well, the only way we can get the company to do the trial is to take the drug off the market, the correct word, that would really be a draconian move here.

DR. HARRINGTON: Dr. Kato and then Dr. Lincoff.

DR. KATO: But, again, just a follow up. In point of fact, there is no--you cannot force the company in any legal or contractual manner to do a study, number one, and, number two, I guess I am just curious--you mentioned that postmarket studies are done all the time. I am kind of curious what percentage of drugs or devices that have been recommended for postmarket surveillance actually have had those studies done.

DR. PAZDUR: I can't give you the exact number here. I would be happy to get back to the committee on that. But the issue is they are done on a routine basis by most companies.

The issue here is we cannot require it at

this time to be done. Obviously, people that follow paper, et cetera, there is obviously discussion in Congress looking at this whole issue of postmarketing commitments and, perhaps, this is stimulating some of this conversation here.

But, at the present time, I cannot say that you must do this trial. It has to be a negotiated effort, as Dr. Rieves has pointed out.

DR. HARRINGTON: Dr. Lincoff.

DR. LINCOFF: Actually, I don't think anyone had said that they never do this. I think the concern here is that sponsors often do but there is often not the same drive or commitment in terms of enough money, et cetera, to really move enrollment along quickly when there is not the NDA or an expansion of indication at risk here.

That is important because, if, in the end, it is done, and it does show that there is excess risk and then the drug is removed from the market, we will have lost however many years it takes to get this data.

So, in this first question, what we are

really being asked here is, do we think that we have enough uncertainty in the existing dataset to risk the next couple of years of however many excess events might happen or might not. I think if we are going to vote to say yes, we are willing to take that risk, we would like to know that this is going to be done with the same sort of rapidity and the amount of money it takes and the drive that it would if this was to get this drug approved in the first place for marketing.

DR. PAZDUR: Perhaps the company wants to bear in on this and what their commitment is. One of the other alternatives that we do have, and we have done this, for example, in the oncology drugs where we have a significant amount of accelerated approvals where this is really a mandated postmarketing commitment is revisit this issue at subsequent committees and look at accrual, problems with accrual, et cetera. And we could make plans to revisit this issue on a periodic basis.

DR. HARRINGTON: So, to adhere to the timeliness of the request. Dr. Malik?

DR. MALIK: Kemal Malik, Global Development with Bayer. I think a couple of things to say, and I think Dr. Rieves and Dr. Pazdur would agree with this, Bayer has always endeavored to fulfill its postmarketing commitments historically. So there has never been a doubt about that.

Secondly, we do stand behind the risk-benefit of Trasylol, as I indicated earlier. However, we do welcome the input from advisory committee and, if the input from the advisory committee is that a subsequent randomized controlled trial is appropriate, we will immediately and absolutely start working with the agency defining what the appropriate study would be.

I would acknowledge, and I think some of the discussions took place earlier, that this is not without challenges. I mean, we have discussed it internally, obviously. That would be contingent upon us saying earlier that the highest form of standard, the gold standard, is a randomized controlled clinical trial.

So while all this maelstrom of observational studies, was going on, we have obviously considered what can you do in terms of a randomized controlled clinical trial. It has problems. Can you run a placebo controlled study? People we have spoken to have said, no, you can't. And I think that was confirmed by your comment earlier. Can you run a study versus Amicar? Amicar is an unapproved drug for this indication. We would need the agreement of the FDA to allow us to do that.

The study design, what patients you would consider, what should be the endpoints. You talked about the sample size. Potentially, you are talking about a study of 7,000, 8,000, 9,000 patients. Who knows what sort of undertaking we are talking about.

There are more discrete things that could be done. I think this all talks to a joint commitment that, if it is felt appropriate by the committee, that we undertake such an exercise. We will commit to work with the agency defining what

is an appropriate thing to do and reach agreement with the agency and then move forward.

DR. HARRINGTON: Dr. Day, did you have a comment?

DR. DAY: If a drug is withdrawn from the market, that does put in jeopardy any trials that are ongoing at present and can jeopardize the execution of any that might be done in the future. So that is one point.

Another point is there have been a number of drugs that have been withdrawn and have come back on the market. Can someone from FDA or somewhere tell us anything, any data, about these, how many, say, in the past 10, 20 years have been withdrawn and come back and it was contingent upon other trials and any relevant information about how that impacted time to completion.

DR. HARRINGTON: Dr. Dal Pan.

DR. DAL PAN: I can mention two drugs that were withdrawn and then came back to the market. The first is alosetron. It went by the name Lotronex. It was a drug for GI disease and had a

risk of ischemic colitis. It came back with a restricted distribution program, much different from the more liberal prescribing when it was initially brought to market. I don't know a lot about what happened in the interim because I wasn't involved in that.

Another drug for which we had an advisory committee about a year ago was natalizumab or Tysabri. Tysabri is a monoclonal antibody indicated for multiple sclerosis. Shortly after its entry to market, two or three cases of progressive multifocal leukoencephalopathy were observed. The product was withdrawn immediately from the market.

In that case, the company was able to go back and look at how many cases really had occurred and get some estimate. Then we had an advisory committee, both to bring that back as well as to expand the indication--expand is probably the wrong word. They had additional data to support the indication and so it was brought back. That also has a restricted distribution program.

I am not aware of any other examples like that.

DR. DAY: I just wanted to thank you for that. I was actually on both of those committees when they were coming back. But what I didn't know in the interim of how that slowed down any additional work that was done. So that would be harder to get. But thank you very much.

DR. HARRINGTON: Dr. Warner Stevenson.

DR. WARNER STEVENSON: I just wanted to clarify; are we discussing the possibility of taking this drug of the market and essentially leaving the only drug that we use one that is not approved that will then take its place? I just wanted to clarify if that is really what we are discussing.

DR. RIEVES: That is correct. This is a marketing question. That is exactly right. So this is a fairly--

DR. HARRINGTON: So, Lynn, I was hoping somebody would bring that up because that is the question. It says, do you recommend continued

marketing authorization. So do you want to speak to your comment? I am reading into your implied remarks, but there is an uneasiness in your remark about what the practitioner would be left with.

DR. WARNER STEVENSON: Well, I think we have a substantial body of data here from which we are debating the degree of magnitude of certain risks. It seems a bit foolhardy to me to throw the baby out with the bath and say, because we are not exactly sure about the magnitude of these, we would rather take something that is completely unapproved for this indication. It seems, as I say, a bit foolhardy.

DR. PAZDUR: I think it is also very important--we are concentrating on risk here and any regulatory decision has to be based on a risk-benefit decision and what is the benefit of this drug must be weighed against any uncertainty in the risk here. That would always have to be discussed in any type of situation that we are discussing here.

Remember, it is a risk-benefit, and taking

a drug off the market, obviously, denies benefit, whatever that might be, to a population.

DR. WARNER STEVENSON: If I could just make one more comment. As soon as we get into benefit-risk for an individual patient, I would urge us to move past the relative-risk considerations which gives us a lot of p-values and zeros. As I see the data, when we are talking about a risk of an increasing creatinine by 0.5 from an absolute risk from about 6.5 to 9 percent, so that would be affecting about 2.5 patients per 100, if we look at the data on the re-do CABG or on the patients who have had plavix, we would be talking about preventing transplant in about 25 out of 100 patients.

So we are looking at 2.5 risk versus 25 benefit. I haven't really heard any debate about the benefit of decreasing transfusions. So, as soon as we do risk-benefit, we have to move away from the relative risk and the p-values and into the absolute risk in the patients.

DR. HARRINGTON: Let me just get the order

here. It is Dr. Ellis, Dr. Teerlink, Dr. Gillett.

DR. ELLIS: I think, in some ways, jumping ahead as we talk about risk-benefit, that speaks, then, also to the possibility of changing indications which I think has two potential benefits, possibly limiting the drug in patients to whom at least some would think it is most beneficial.

There was, at least in the Mangano study, the sense that the signal for harm was less in complex procedures. How you go about operationalizing a more stringent definition of complex procedures, I am not sure. I think that may decrease exposure for patients who potentially have less to benefit and perhaps also have an impetus for sponsors to do studies to seek to rebroaden the indication..

DR. TEERLINK: I have two points. One is I am a bit confused where we are tying--that aminocaproic acid isn't approved for the use in surgery. My reading is that it actually says fibrinolytic bleeding may frequently be associated

with surgical complications following heart surgery with or without cardiac bypass procedures suggesting that, in fact, Amicar is approved for heart surgery.

Is that a misreading of the label?

DR. RIEVES: That is not a misreading of the label. That is correct.

DR. TEERLINK: So if we were to remove aprotinin from the market, there is, actually, an approved agent that is available and it is the agent against which, in many of these studies, aprotinin has been compared and, on a relative-risk basis, found to be, perhaps--or, perhaps not, depending on our interpretation of the data--wanting.

So that is the first point. So it is not actually leaving people high and dry, although you may be worried that the use of the agents are not equivalent in terms of practice patterns, which we have heard a bit earlier.

The second issue, and this is a question as well for the regulatory folks in terms of is it

possible to require a restricted-use program such that we can ensure that this is, in fact, used for patients to reduce transfusions such that you could say, well, we require that there be a voice-recognition system or something that says you have to go through a list and say, yes, yes, yes, using whatever predictive model is agreed upon to say that we predict that this patient will have a high risk of bleeding and the only way the patient actually can get that drug is by having the physician check off all of those things and actually it be verified that it is a high-risk patient.

DR. HARRINGTON: Dr. Rieves.

DR. RIEVES: That is a consideration. It would need some thought in terms of logistics because, so often, the timeliness for using antifibrinolytics is such that that process for our restricting distribution would have to take the timeliness into consideration. It might represent some special challenges.

But it is an option.

DR. TEERLINK: And most of those factors are, in fact, known fairly well preoperatively. Obviously, it would be different in emergent surgery but, as we saw from the data, this isn't an agent that is selected that often, or as often, in emergent surgery anyway. So most of these are variables that are known well before time of surgery.

DR. HARRINGTON: Let me go through. Dr. Gillett, I think it was Dr. Findlay and then Emil.

DR. GILLETT: Just a quick question. Does this only include the material presented by Bayer and by FDA? Does it include the public comments that were presented from other studies some of which were published and some of which are not, some of which are in abstract, et cetera?

DR. HARRINGTON: In terms of you making your decision and considering things, you should consider everything you have heard today including the public hearing. That is one of the reasons that that piece is held, so that you may consider those remarks.

DR. GILLETT: Okay. Thank you.

DR. HARRINGTON: Dr. Findlay.

DR. FINDLAY: Following up on the question of Dr. Teerlink's before, so that would sort of a formal risk-mitigation program. Can you just give us a little bit on how many drugs now on the market like Accutane and others have such a program and is that--again, that is negotiated with the companies? And, under--well, let's leave it at that for now.

DR. DAL PAN: Just by way of background, lots of drugs have risk-management plans. All drugs have risk management to the extent that they have prescriptions and a label and things like that. A lot of companies supplement that with some other kind of education. Some call that a risk-management plan. Others don't.

When you get into the realm of--so you can get into two other realms. One is you have something that is not quite a restricted distribution but you may have something like a patient-physician agreement or something like that. There are some of those, not many.

And then we have the restricted distribution program. So those would be things like natalizumab or Tysabri, alosetron, Lotronex, Revlemid, thalidomide, the isotretinoin products. I can't name them all, but there is not a long, long list of them. But there are certainly those drugs that do have them.

DR. HARRINGTON: We are going to go to Emil. Then we will come to Dr. Day. Steve, did that answer your question?

DR. FINDLAY: Yes.

DR. HARRINGTON: Okay. Emil.

DR. PAGANINI: Just one quick question, again for FDA. In those restricted patterns, is there any off-label use or the only way you can get the drug is to have a specific issue? Because we have all, on this panel, I would gather, used drugs off-label at one time or another for something.

So, having a drug out there and available can, in fact, make it available for off-label use. We have heard from their own data that there is a significant amount of off-label use. So, by making

it available off-label use for those that are going to be using it anyway probably increases the risk for the person that is using it off-label. And that is the consequence. Is that the deal?

DR. PAZDUR: If it is a lawfully marketed drug, basically, off-label use is a practice of medicine which we don't regulate. So it could be used off-label.

DR. HARRINGTON: Dr. Day and then Dr. Teerlink.

DR. DAY: I just wanted to comment that the is a very wide range in the types of risk-management programs that you were referring to. So, on the one hand, the isotretinoin products, Accutane et al., it is huge. It is millions of dollars a year to operate. The doctor has to attest to things. The patient does. The female patients have to get tested for pregnancy. I mean, it is a huge thing that is administered.

I think that that is on the one hand to things that are more simple. I think what you were suggesting is just a physician answering some

questions that are then tracked in some ways and then can go forward.

If you could just clarify that it would be a very simple kind of thing and not a gigantic--because, the patients can't register for this, usually.

DR. TEERLINK: So I was not making any specific recommendation. I was actually trying to see what our options are. One way to envision it, and I think this is how things like Bozentan and isotretinoin, these other agents work, you can't get it unless the certain forms or certain questions are answered in a certain way. It is not available otherwise.

So it would be possible to have aprotinin still available for high-risk patients who are truly at high risk for bleeding through a system where it could be made, I believe, available only to those patients through a system.

DR. PAZDUR: So that means having some physician attestation program.

DR. TEERLINK: Physician attestation and

things like that. It is a considerable--I am not proposing it without recognizing that it is a considerable barrier. However, my guess is that Bayer has demonstrated this willingness to work very hard to ensure that patient safety is followed, and I respect that.

I think that, if that were the recommendation, they would be able to make this work.

DR. DAY: There is another component to this, and that is distribution. There is a whole wing of the isotretinoin program about distribution centers and so on. Here we are talking about a hospital situation where often a patient comes in and, within a couple of days, has this kind of surgery.

So it is pretty complex to think about and it would be different--are there any cases of in-hospital medications where there is a registry or physician attestation program as a model?

DR. DAL PAN: I am not, offhand, aware of any in-hospital things.

DR. TEERLINK: How about every clinical trial we do?

DR. DAL PAN: I was just told that Trovan is a drug like that although I don't have many of those details. I don't know the details of how that program works. Clearly, for something like this product, a high-risk patient might need it within a few hours of coming to the hospital so that truly restricted distribution in the sense of the isotretinoin products or something like that would have to be very different.

DR. HARRINGTON: So let me try to move this along because we have got other questions we want to get to. I respect John's perspective that perhaps one option would be some sort of risk-management program. I also respect Dr. Day's perspective that perhaps people other than this panel should figure out the details of that, people who have more expertise in that topic.

Are there other--I'm sorry. Dr. Black.

DR. BLACK: I would say the same thing. I think that we are talking about details and that is

not appropriate for this discussion right now. We may want to have a straw vote or formal vote about whether we think that is necessary and then leave it to the sponsor and, perhaps, the FDA to figure out how to do it.

DR. PAZDUR: The basic question here that we are asking is one of should this have continued life and then the specifics I think we have heard concerns about and is something that we would want to work out.

DR. HARRINGTON: I agree with you. Anything burning? So I am going to read the question officially for the record and then ask people--I am going to vote yes first, no second, abstentions third. Leave your hands raised so that Mimi can get the count. Leave your hands raised so that Mimi can get the count.

So, based upon the Trasylol risks and benefits evidenced in Bayer's controlled clinical studies, in your consideration of the presented observational study data, do you recommend continued marketing authorization for Trasylol.

I would like the yeses to raise their hand.

[Show of hands.]

I am going to start with you, Steve, if you could say your full name and yes.

DR. FINDLAY: Steven Findlay. Yes.

DR. ELLIS: John Ellis. Yes.

DR. JEEVANANDAM: Val Jeevanandam. Yes.

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. TEERLINK: John Teerlink. Yes.

DR. LINCOFF: Michael Lincoff. Yes.

DR. HARRINGTON: Robert Harrington. Yes.

DR. KASKEL: Rick Kaskel. Yes.

DR. LESAR: Timothy Lesar. Yes.

DR. NEATON: Jim Neaton. Yes.

DR. HECKBERT: Susan Heckbert. Yes.

DR. BLACK: Henry Black. Yes.

DR. CHEUNG: Albert Cheung. Yes.

DR. KATO: Yes.

DR. WARNER STEVENSON: Lynn Stevenson. Yes.

DR. GILLETT: Jim Gillett. Yes.

DR. PAGANINI: Emil Paganini. No.

DR. HARRINGTON: We are going to do the no's next. I know you are anxious down there, Emil.

So next is the no's. Please everyone voting no to this question raise their hand.

[One hand raised.]

DR. HARRINGTON: So we will start with you, Emil. Does that count as two no's or just one?

DR. PAGANINI: Emil Paganini. No.

DR. HARRINGTON: Abstaining?

[One hand raised.]

DR. DAY: Ruth Day. Abstain.

DR. HARRINGTON: So did you count them up?

DR. PHAN: We have 16 yes, one no and one abstain.

DR. HARRINGTON: Now, I would like to have a few minutes discussion before we go to Question 2 because, if yes, which is the majority vote, the FDA has asked us to describe any necessary product label modification or restrictions on Trasylol's

distribution. So this gets to some of the risk-management discussions we have had.

So let me go to, I think, Lynn and then Dr. Crawford.

DR. WARNER STEVENSON: I would like to propose that we come up with a specific definition of high risk and this will probably be something that will be done in connection with the STS.

DR. HARRINGTON: Dr. Crawford.

DR. CRAWFORD: Thank you. I echo the last comment. I was going to make the same suggestion on top of this. I would feel a lot better about the "yes" vote I just made if Bayer could come up with a stronger physician education plan and other health professionals than just "Dear Doctor" letters.

DR. HARRINGTON: Dr. Heckbert.

DR. HECKBERT: I was just requesting a clarification. The next thing we are going to vote on is whether the mortality issue should be specifically labeled. Is that part of this discussion, too? These seem to blend into each

other.

DR. HARRINGTON: You can start blending.

DR. HECKBERT: Yes; I agree with the previous comments that some discussion of this would be very helpful parameters.

DR. HARRINGTON: Dr. Cheung.

DR. CHEUNG: By voting yes, I still have a lot of unease, I have to say. I think the language of the kidney dysfunction is really way too soft. I think that there should be, although I don't know the details of how to do it at this point, to implement something similar to what was previously discussed, not only the labeling but now to control distribution.

But more than that is what I was alluding to this morning is that we need to have Bayer come up with a definition more clearly and do analysis, a benefit-risk analysis, even though I understand that these observational studies you can argue for another one week on the merit of confounding adjustment and so on and so forth.

But, based on that definition, have some

pre-specified statistical method to see what the existing data would tell us about the risk-benefit ratio on those groups of patients.

DR. HARRINGTON: Let me ask--I want to get a clarification from you. When you say "definition of the renal issue," do you mean as a prerequisite for avoiding the drug up front or do you mean as a definition as to the endpoint event?

DR. CHEUNG: I mean put in the label more strongly that these are not necessarily reversible, they are not necessarily trivial, but also do the statistical analysis on whatever they think should be used, those groups of patients that it should be used on, what do the existing data tell us, the renal dysfunctions, the stroke, and so on, because all we are predicting upon here is that there is a benefit to those high-risk patients, those patients with high-risk for bleeding.

I would like to see the data on that even with existing data, do analysis of that.

DR. HARRINGTON: Next I think was Dr. Ellis and then Dr. Teerlink.

DR. ELLIS: We haven't talked much today about hypersensitivity but I would like to see, perhaps in the black box, it made explicit about non-cardiac surgery not being an indication.

It says here, when cardiopulmonary bypass--it should only be administered in operative settings where CPB can be rapidly administered. I think that needs to be clearer that this should only be cardiac surgery, that having the CPB machine down the hall when you are doing a hip is not appropriate. It is only 4 percent, but I think it should be addressed.

DR. HARRINGTON: Fair enough. John.

DR. TEERLINK: So my yes vote is contingent upon a restricted-use program. And I think the only benefit we can see from this agent is reducing transfusions purportedly. So it has to be--I would suggest that it only be available to patients where there is a high probability of requiring a significant blood transfusion.

DR. HARRINGTON: Norm, and then Dr. Gillett.

DR. KATO: I guess I will go back to, in addition to the restriction, the product label modification has to be more explicit. Right now, it really is focused around anaphylaxis and it really has to include the other complications we have spoken about today, the possibility of renal dysfunction or renal failure, the possibility of myocardial infarction, stroke and death.

DR. HARRINGTON: Dr. Gillett and then Dr. Lesar.

DR. GILLETT: I voted yes mainly because I am concerned about issues such as we had with pesticides where, as soon as you banned a pesticide, it was replaced by a less effective, more dangerous compound that had passed a low threshold of behavior when there was a cheap, good alternative that turned out to be useless.

So we found ourselves having to respond to increased worker mortality and other issues. So that is not an issue here, but the point is that you are always going to go down to the next lowest. And what is our next lowest? Our next lowest is a

bunch of compounds which haven't met any of the standards of RCTs that we would like for this purpose. And I think that is really scary as far as I am concerned.

So I would like to see us take advantage of this opportunity to avoid that. At same time, am not happy we negotiated with PhRMA on OxyContin, a risk-management program which is real questionable, as far as I am concerned, as it has turned out. I am not sure whether FDA can enforce risk-management programs adequately.

This is not as serious as oxycodone but it is certainly the type of problem, the difficulty of getting a pharmaceutical house to get its ducks in a row.

DR. HARRINGTON: Next is Dr. Lesar.

DR. LESAR: I would just like to suggest a potential change in the labeling. I would add a statement, such as, to the Indications, that, "aprotinin has not been demonstrated to reduce morbidity and mortality. An overall positive benefit-to-risk ratio has not been demonstrated

despite reduction in transfusion needs. Some observational studies have suggested no benefit or harm."

DR. HARRINGTON: Steven, did you have a--

DR. FINDLAY: Yes. I would like to propose that the observational study results be added to the label in some way that is appropriate, to be worked out, with appropriate discussion of the unresolved statistical issues.

DR. HARRINGTON: Henry, were you going to say something? No? Okay.

Let me see if I can summarize the committee's view on the first question. We had a majority vote yes to continued market authorization. But then a number of points were brought up to qualify those yeses.

I think, most importantly, several of us alluded to the fact that we needed a better definition of high risk. I certainly agree with that. I don't think just saying patients at high risk is enough. It leads to wider-spread use than for, perhaps, was intended.

I think several people brought up a physician-education program and I also would agree that that is an important caveat.

The third thing is that at least one member, perhaps two, has raised questions about a more restricted-use policy and I think the agency might take that into consideration.

Several have brought up a change in the actual labeling to highlight some of the insufficiencies of the data that exist to date and particularly pointing out, in the noncardiac-surgery population, that the drug is not currently indicated and making that very apparent.

Have I captured the tenor of the committee's concerns? Okay.

So lets move to Question 2. We have begun this discussion but let's continue it. I will read the question and then we can have some discussion and then we'll vote.

The i3 Drug Safety Report and a published report in JAMA have suggested mortality disadvantages to the use of Trasylol when compared

to the use of no antifibrinolytic drugs. Should these study findings, one or both, be described in the product labeling.

If yes, describe the conclusions to be drawn from the studies and provide suggestions regarding the emphasis or prominence for display of the information.

So this is asking us, I think, a really important question is that, to what extent do you take observational data with all its flaws that we have discussed today and include it in the label and how prominently do you do that. So this is a very important discussion.

Anybody want to start it? Go ahead, Henry.

DR. BLACK: I would think no, it should not be included in the label. I think it is just not reliable enough right now and, as I think, as you know, you talked about the Women's Health Initiative and so much would have been included in the prominence of estrogens and progestins that turned out to be wrong when we did the right study.

So I don't think we should get in there.

DR. HARRINGTON: Do you feel, Henry, that there is a difference between benefit and risk when you are having this discussion about observational studies? In other words, would be wiser to err on the side of inclusion in a situation like this where we are talking about risk as opposed to the Women's Health studies where we may have been talking about benefits?

DR. BLACK: I think you could take it at either level. You could just take--I think you could take the position that this data is just not reliable enough, whichever direction it goes in, which is where I would be. Or you could say, when it comes to risk, it belongs there. But I can easily see a slippery slope where the same sort of inadequate data is used to promote benefits, too.

DR. HARRINGTON: Dr. Neaton.

DR. NEATON: I share Henry's point of view. The major kind of signal in these data came through renal failure which is already in the label. The new data that I guess is most

concerning to me is the long-term mortality data.

The analysis by the FDA kind of weakened that. Also, that is the area where there is the most concern about the follow-up experience of the patients in the study. So I actually like some of the language that was mentioned earlier and that might get us back into more discussion of 3.

But I would be kind of hesitant to put these data as we saw today in the label because there would have to be too many caveats put around them for anybody to really appreciate and understand.

DR. HARRINGTON: Let me go to Dr. Findlay, Dr. Lincoff, Teerlink, Lesar.

DR. FINDLAY: I disagree. I think, in the world of prescription drugs today, there is a megatrend and that megatrend is towards transparency, towards consumers, towards doctors, towards--in every way. The FDA, itself, is moving in that direction and I think labeling and the kind of thing we are talking about now ought to move in that direction, too.

Granted, it is tricky to present this stuff and the companies hate it. I think we have to move in that direction.

DR. HARRINGTON: Dr. Lincoff.

DR. LINCOFF: I agree with that statement. I mean, the whole point of this discussion here is that we at least have some concern. Now, again, the weaknesses and the strengths of the data have been discussed but particularly if we are proposing that a clinical trial be done to look at these issues in the interim, there is this doubt.

To have the warnings in the label without some description of the studies, I agree it will be difficult to make it understandable but it should not be impossible to write this in a way that expresses what the findings are and also expresses what the limitations of these type of data are.

We have all seen them in guidelines. We have all seen them in a lot of places. I think you need to provide the information that backs up the warnings.

DR. HARRINGTON: Dr. Teerlink, Dr. Lesar,

Dr. Stevenson.

DR. TEERLINK: I agree and don't need to say more.

DR. HARRINGTON: Tim, did you have another comment?

DR. LESAR: No. I just wanted to reiterate my statement, my previous statement. Specifically, I just want to refer to it. I think there should be a fairly strongly stated summary in the Indications but it could be summarized in the Warnings Section as to where it would as a total of the studies that we heard about today.

DR. HARRINGTON: Lynn.

DR. WARNER STEVENSON: I have some concerns about including this in there. If we think of any therapy developed for the high-risk subgroup of the population, when we then, in an observational way, apply that and look at a whole population, it is going to look as though it increases mortality. And I am not really sure how we could ever get around that.

So, again, I do have concerns about