same definition as the outcome of renal failure, itself, were also excluded from analysis.

[Slide.]

I will now present the results.

[Slide.]

Patient demographics are shown here. The majority of all patients were white, were males and had no history of smoking. The aprotinin patients were slightly older, on average, and a slightly greater percent of aprotinin patients were white compared to the other groups.

[Slide.]

A summary of some of the baseline risk factors is shown here. With respect to re-do cardiac surgery, additional cardiac surgery and stroke, the aprotinin group can be considered more severe than the comparison groups. For nonelective surgery, however, which includes admissions coded as urgent and emergency, the percent of aprotinin patients was less, or smaller, compared to the other groups.

[Slide.]

Now, I would like to show the unadjusted outcome rates across the treatment groups. This is just to give you an idea of the frequency with which these events occurred.

You can see here that the rates among the no-treatment group and the group of patients who received the other agents are rather similar and smaller in all cases than the rates seen in the aprotinin group. But these are, again, rates that have not been adjusted through the propensity-score methodology.

[Slide.]

Now I would like to show the results from the comparison between aprotinin to the other I.V. antifibrinolytics and the comparison between those results and the results from the i3 drug safety preliminary report.

[Slide.]

The risk ratios for the outcomes are shown on this slide. Values greater than 1.0 indicate a greater risk associated with aprotinin. As you can see, the largest risk is with respect to renal

failure and the point estimate of 1.82 indicates that aprotinin patients have an 82 percent greater risk of renal failure.

The next biggest estimate is for death with a value of 1.54 and for all estimates the lower bound of the 95 percent confidence interval exceeds the value of 1.0.

[Slide.]

Now, I will compare the results from the FDA analysis to those from the i3 drug safety study and to the unadjusted risk ratios. Now, the risk ratios from the FDA analyses that we just saw appear here in the last column.

For each of these outcomes, both the i3 and FDA analyses suggest an increased risk associated with aprotinin which is demonstrated by the lower bound of the 95 percent confidence intervals that lie above the value of 1.0,

I will also point out that, if the assumption that the aprotinin patients are at higher risk of these outcomes is true, then one would expect the point estimates from the adjusted

analyses to be lower than those from the unadjusted analyses.

This was the case for all results with the exception of the FDA point estimate for heart failure which is 1.2 and slightly higher than the unadjusted estimate of 1.15.

[Slide.]

Now, I will go over the results from the comparison of aprotinin patients to patients who received no treatment and I will spend some more time on these results since they are new and they were not covered in the briefing package.

[Slide.]

I will start off by showing the strata that we used for analysis. They were based on two hospital characteristics, the geographic region, South and non-South, and whether or not the hospital was a teaching hospital.

You can see here that, overall, 76 percent more patients are in the no-treatment group. But this ratio changes quite a bit across the four strata. For example, here in the non-South

teaching stratum, roughly three times as many patients in the no-treatment group are represented in that stratum. But in the non-South, non-teaching stratum, the distribution between the groups is much more similar.

These results help to demonstrate the need for taking these characteristics into consideration.

[Slide.]

So the propensity scores were estimated separately for each stratum and then patients were divided into propensity-score deciles within each stratum. The overlap between the treatment groups across the deciles was assessed as was the balance with respect to the various covariates.

Overlap was good and the analysis showed good balance between treatment groups with respect to most risk factors.

[Slide.]

This slide helps to demonstrate the overlap between treatment groups across the deciles. This is for one of the four strata, the

non-South teaching hospitals, shown here. The no-treatment group is in red and the aprotinin patients are in blue.

[Slide.]

If you look at 9th decile, just as an example, the overlap between the groups is very good and, across all deciles, you can see that the overlap is good. Results for the other three strata were similar.

[Slide.]

Now with respect to the risk-factor balance after making propensity-score adjustments, getting back to the selected risk factors shown earlier, you can see here that, even though the post-adjustment percentages are much closer, imbalances still exist for re-do cardiac surgery and additional cardiac surgery.

The estimated rates, however, are much closer together. These were the only factors, of all the ones evaluated, that showed a significant imbalance and, in looking at the data, most of the imbalance here was in the 10th decile from each

stratum.

So the sensitivity analysis that looks at only the first nine deciles will address the impact of this imbalance.

[Slide.]

The risk ratios for each of the outcomes are shown on this slide. As you can see, the largest risk ratio is with respect to death with a point estimate of 1.55 indicating that aprotinin patients have a 55 percent greater risk of death.

The next biggest estimate is for renal failure with a value of 1.50. For all estimates, the lower bound of the 95 percent confidence interval is greater than 1.0, although, for stroke, the value is just above 1.0.

[Slide.]

This is a similar plot except here we are showing the risk difference. The risk differences here tell us how many additional or fewer events one can expect in one group versus another per 100 patients in each group.

So the value here of 1.65 for death

indicates that you can expect an additional 1.65 deaths per 100 aprotinin patients compared to 100 patients who received no treatment.

The results here are similar to those from the previous slide with the risk being increased for aprotinin patients for all of the outcomes and the lower bound of the 95 percent confidence intervals falling above 0 for all outcomes.

[Slide.]

Here I am showing the risk ratios for death across the four strata. As you can see, the results are consistent across the four strata despite propensity to use aprotinin being different, as we saw in the earlier slide.

[Slide.]

Here is a similar plot for renal failure. Again, the results are consistent across each of the four strata.

[Slide.]

This slide summarizes the sensitivity-analysis results. The first column here shows the overall results that we just saw.

As you can see, going across the first row for death, results are consistent, pretty consistent, throughout for stroke. What I have highlighted in yellow are the cases where the lower bound of the confidence interval dipped below the value of 1.0.

As you can see, this happened twice for the outcome of stroke but the lower bound from the CI for the overall analysis was at 1.0 to begin with. So the actual values did not change substantially.

For renal failure, the results are, again, consistent throughout and for heart failure, the results are, again, pretty consistent throughout with the possible exception of the results for the events per patient weeks where the point estimate is just above the value of 1.0 and the lower bound of the confidence interval is down to 0.92.

[Slide.]

So now I will provide a brief summary.

[Slide.]

Compared to other I.V. antifibrinolytics and no-treatment, aprotinin is associated with

increased risks of death, renal failure, heart failure and stroke, but there are some study limitations that merit consideration.

There is the issue of unavailable confounders for which no adjustments have been made. The accuracy of the derivations for both the covariates and the outcomes has not been evaluated and there has been, to date, no proper medical-chart review.

[Slide.]

Lastly, I would like to acknowledge the following people for the valuable input that helped shape this review.

Thank you.

DR. HARRINGTON: Thank you. It has certainly been a full morning.

Questions to the Presenters

DR. HARRINGTON: We have about fifteen minutes for questions from the panel. I have been told that Dr. Corso, the surgeon who gave us the overview of bypass and bleeding, needs to leave for the afternoon. So if there are questions for him

specifically, if people could ask those now. But I will otherwise open it up to the panel.

I'm sorry; Mimi wants to make a comment first. No? Okay. Go ahead, Jim.

DR. NEATON: Maybe just it could help me a little bit in terms of Dr. Corso, the timing of when the drug is typically given. When do you begin the I.V. kind of use of the drug?

DR. HARRINGTON: I think Dr. Corso has already left.

DR. NEATON: He has already gone. Okay.

DR. HARRINGTON: We have several surgeons.

DR. NEATON: Somebody else. One of the other surgeons.

DR. HARRINGTON: We have several surgeons on the panel so maybe one of them could help out.

DR. JEEVANANDAM: For a primary case, we give the test dose before we give the heparin. So, actually, ideally, you want to do that even before the skin incision is made. So if you have a decision to start the aprotinin, you will give the test dose and have the bolus load of the aprotinin

go in before you make skin incision.

If you do a re-operation because of the potential for anaphylactic reactions, my preference is not to give the aprotinin until you have access to bypass which, on a re-op either means you have the femoral access or you have the central access.

So, in re-operations, it usually ends up, after you do the sternotomy, do some of the dissections, you are comfortable you can go on bypass if you need to, and then you can give the aprotinin at that time.

But you do not give aprotinin after the procedure.

DR. NEATON: So all the assessments of risk of bleeding, et cetera, are made before you kind of begin the surgery.

DR. JEEVANANDAM: That's correct.

DR. HARRINGTON: Other questions from the panel? Go ahead, Henry.

DR. BLACK: I would like to ask Dr. Cyrus a question, or a clarification.

DR. CYRUS: Go ahead.

DR. BLACK: I just want to go to Slide 53. You were questioning hypertension as not being what you would consider consistent. Were you comparing the 2003 time period with now?

DR. CYRUS: I think the STS model is being updated. But this is what is published.

DR. BLACK: Up to 2003.

DR. CYRUS: Right.

DR. BLACK: Because there is a lot happened in that field. More people are getting ACEs and ARBs and beta blockers and that may affect your answer. So I am not sure--

DR. CYRUS: Unfortunately, the STS risk model hasn't been published and updated. My understanding, and, I don't know, Dr. Smith may want to elaborate because he knows more about the STS database, but my understanding is that they are updating these risk models but the last published one is from 2003.

DR. BLACK: No, no. I understand. But you are saying that you can't pay too much attention to it because it doesn't fit what you

would expect. Yet I think we can explain the hypertension not fitting with--except by changes in care.

DR. HARRINGTON: Dr. Black, could you speak in the mike. I'm sorry.

DR. BLACK: I'm sorry. Yes. I think we can explain why hypertension didn't fit by changes in care in the last few years compared to 2003.

DR. HARRINGTON: Dr. Ellis.

DR. ELLIS: As a clinician, to this point as a clinician, who had done administrative database review, very often hypertension is a diagnosis to attempt to collect when nothing else is available. So I look at that as a marker of relative health. But that is a personal observation.

I want to commend the investigators, Karkouti and Mangano, for providing their data to the FDA for analysis and for our ability to look at that.

I have a question that relates some to Dr. Smith's comment about the greatly increased

propensity for bleeding with clopidogrel. It is not clear to me if, in the various analyses, if clopidogrel did not make it into the multivariable calculations for propensity matching and the like.

So that is a general comment for all of these datasets if that was included.

DR. HARRINGTON: So, perhaps the FDA could help us with that since you had taken a look, Dr. Levenson, or--so the question, I think, Dr. Ellis, is was clopidogrel, as a baseline medication, included in the propensity scores.

DR. ELLIS: Correct. Or at least examined for--if it should be included; yes.

DR. LEVENSON: I am checking the list of variables right now. No, I don't--I can see for the Mangano and the Karkouti review, that was not a preoperative medicine.

DR. ELLIS: It was not included.

DR. LINCOFF: It was not.

DR. HARRINGTON: Let me go to Dr. Lincoff, Dr. Cheung, Dr. Neaton. Dr. Mangano, I will come to you if there is time after the panel asks.

DR. LINCOFF: I would like to address this to the representative from Bayer. I find it a bit disingenuous that you are disavowing the results of the i3 study after you have commissioned it. So what I would like to understand is what were the terms or the situation in which this was commissioned and your input into the statistical analysis plan.

It seems to me that i3 investigators have made much effort in terms of adapting in response to the many questions that were listed and the materials that were sent to us. And there must have been recognition from the very beginning about the limitations of the administrative database study. And yet this was commissioned.

It was carried out. It was modified on the basis of criticisms and questions and yet it is still regarded as disavowed. So if you could, perhaps, give some input into how this study came about.

DR. McCARTHY: Good morning. My name is Paul McCarthy, Head of Medical Affairs for Bayer in

the U.S. I would like to ask Dr. Malik, who is the Head of Worldwide Development, to respond to that question.

DR. MALIK: Thank you for that question. I think when we set out to the i3 drug safety study, it was in the background of the papers from Dr. Mangano and Dr. Karkouti. I think the desire was to try and run an observational study that, perhaps, didn't have some of the deficiencies that were discussed at the last advisory committee and were identified by us as well.

One of the things that wasn't apparent, as I said in my introduction, when we commissioned the study were the drawbacks in the administrative database and that clearly was an error on our behalf. I think we weren't fully aware that the database wouldn't fully answer the questions that we had hoped to identify.

DR. LINCOFF: So was there a statistical-analysis plan prospectively, because I can't find it in the materials you sent us.

DR. MALIK: There wasn't a prospective

statistical-analysis plan.

DR. LINCOFF: So there was no written document that described what variables would be looked at, what was available in the database.

DR. HARRINGTON: Could we ask maybe the i3 investigators to weigh in on this? Please introduce yourself.

DR. WALKER: I am Alec Walker from i3 drug safety. I was involved in the design of the study. The proposal for the analysis from us to Bayer--we were requested to propose something--did contain a fairly extensive description of what was going to be done.

It wasn't a formal statistical-analysis plan. There was, because of delays in contracting and wanting to have this ready for the last advisory committee meeting, we went straight to what we call specifications document which did, in fact, lay out all the analyses that we were going to do. So this was June of 2006.

DR. LINCOFF: This was provided before the decision was made to contract and accept that--in

other words, you didn't present that at the time you presented the data. This was before you started the study; correct?

DR. WALKER: So the proposal described the analysis in fairly rigorous terms. It wasn't specific, step-by-step. And then the first step afterwards, and this is when Dr. Schneeweiss joined the team, was to create the specifications document which we did then follow along.

DR. HARRINGTON: Before you sit down, I have just one quick question. What are your publication rights by contract with this data?

DR. WALKER: We have two important rights in our contract. One is final say over the content and wording of any publication. The other is over a right to disclose to data if we feel that it is of public-health importance.

DR. HARRINGTON: Dr. Cheung, do you have a question for him as well? Okay.

DR. CHEUNG: Although I kind of gather that from the paperwork that we were distributed ahead of time, I want to clarify that there were no

creatinine values post-hospitalization; is that correct?

DR. WALKER: Correct.

DR. CHEUNG: And there are no long-term mortality data yes; is that correct?

DR. WALKER: Correct.

DR. CHEUNG: Then even though you put into the propensity score, but are there no stratification--a specific subgroup analysis on various high group patients?

DR. WALKER: Yes. In the preliminary report, we did a number of analyses on various subgroups mostly looking to the question of whether central groups in the analysis reflected the overall result and we found that they did.

You have a preliminary report in the disc that you were given. I think it is Schneeweiss 2006.

DR. CHEUNG: Specifically in the high group--high-risk patients--that is currently in the label for indication for use?

DR WALKER: I should give that to Dr.

Schneeweiss. So the question is was there a high-risk group in one of the subanalyses that corresponded to what is currently in the label.

DR. SCHNEEWEISS: One of the high-risk subgroups were patients with diabetes. And that is reflected in the preliminary report.

DR. HARRINGTON: Dr. Cheung, does that answer your question?

DR. CHEUNG: Does it mean that the other--although I understand that this may be difficult to define what are the exact high-risk groups, but, nonetheless, is there any subgroup done on all patients that is--attempted to do on all patients that is on the cover of the label, current label.

DR. HARRINGTON: So I think what he is asking is have you done an analysis of on- versus off-label use using these data.

DR. CHEUNG: The most current--right.

DR. SCHNEEWEISS: We have done a subgroup analysis in patients with diabetes and in what we defined as complex CABG surgery patients.

DR. HARRINGTON: Dr. Neaton, do you have a question?

DR. NEATON: Just a follow up on one of the questions about the confounding. I thought the analysis that was presented on the renal outcomes showing the results across deciles of the propensity score was really nice. It cleared up a few things and other questions that I had.

But, has a similar analysis been done for the Mangano study for the mortality outcome? But then maybe just another question is that all these studies enrolled patients over several years and was there any attempt in any of these analyses to consider the time of enrollment when patients came into the--were treated?

DR. LEVENSON: The first question about the plot, whether the effect was consistent over propensity-score strata when we were looking at mortality outcomes, or at least the long-term mortality outcomes, they were. So the effects that were shown to be statistically significant or nearly statistically significant were seen across

all the propensity-score strata. So it had very similar appearance to the plot that was shown for the renal outcome.

In terms of looking at the time of enrollment, no; it was not looked at.

DR. HARRINGTON: Emil?

DR. PAGANINI: This is for actually all folks including FDA. There are at least three separate robust predictive models for post-operative acute renal failure following coronary bypass surgery. And they would predict acute renal failure which requires dialysis.

Have any of those models been used to identify preoperatively or intraoperatively the risk factors that are shown in those models to then bucket those patients into aprotinin and non or aprotinin and others.

I guess what I am trying to get at in a long-winded way, and I am sorry about that, is we already have some pretty good predictive models for acute renal failure requiring dialysis after open-heart surgery. Have any of the groups used

that to categorize their patients and then apply whether or not they receive the drug or not?

DR. LEVENSON: In my review of the two studies, I did not make use of any models, published models, of renal failure. But, of course, there were many preoperative risk factors that would probably be included in such a model but I don't know if all of them would have been.

DR. PAGANINI: The question I would have for any of the others, have Dr. Mangano or anybody else included any of those pretty well-established predictive models for acute renal failure following open-heart surgery into the analysis of any of their papers?

DR. MANGANO: Do you want me to--

DR. HARRINGTON: If you want to answer the specific question, yes, please.

DR. MANGANO: We did stratify by four risk models--one is my wife's, so I was mandated to do that--for renal failure after surgery and did investigate that much in the same way that we presented. We found that the results held with

each of the four models as we defined renal risk by quartile in each of those models. So that was done and the results did hold.

DR. HARRINGTON: I am going to take two more questions, Lynn and then Susan and then we will wrap up for lunch.

DR. WARNER STEVENSON: I want to thank Dr. Karkouti, Schneeweiss, Mangano and a very thoughtful FDA team for trying to address this very difficult issue of making sense of observational data.

As an enthusiast of propensity scoring, I am becoming increasingly disappointed and maybe you can help me. It seems to me that the main conclusion we can draw from the propensity scoring is that, if the outcome differences between therapies are diminished by propensity scoring, then the allocation of therapies is being influenced by the same factors that influence outcomes, particularly if we look at the highest propensity strata. That is where the highest mortality is, also where the highest discrepancy

is, between the therapies.

So it seems what we can conclude is that, I guess we would hope, that the therapy chosen for patients is reflecting some intelligent design. There is no reason to assume that all the factors that influence that can be included, particularly a combination of factors that may influence clinicians and that would include probably most specifically frailty and a rate of clinical decline.

So maybe you can help me. Can we conclude anything other than there is an influence and that we are making decisions in a reasonable way?

DR. HARRINGTON: Maybe FDA could help us with Dr. Levenson and then the sponsor would like to chime in on this one as well.

DR. LEVENSON: I guess I generally agree with what you are saying to the extent that there are factors that are not measured, are not available, that influence treatment decision and outcome results.

The propensity-score models will not be

able to account for that and there will be residual bias in the estimates. So, as you said, the propensity-score adjustment may reduce an unadjusted effect by taking account of known confounders. But there might be additional ones that might bring it down further, or possibly the other way. It may raise it up higher.

DR. HARRINGTON: Did the sponsor want to add to this?

DR. McCARTHY: Yes. We have in the audience Dr. Don Rubin who is a co-inventor of propensity methodology and I think it would be useful to have some comments from Dr. Rubin.

DR. HARRINGTON: That would be very useful, I think.

DR. RUBIN: I think that is a great question and is highly appropriate. The critical thing when using propensity scores is what you are trying to do is you are trying to mimic a randomized experience. In a sense, when you did a randomized experiment, you know the decision to use aprotinin, AA, for example, was decided by a coin

toss at some level.

The idea of propensity scores--not all propensity scores are equal. What you try to do is try to reproduce the decision-maker's rule of why the decision-maker decides to use one thing or the other.

So evaluating a dataset, an observational dataset, you have to first decide what are the variables, what are the covariates, the background variables, that were used to make that decision. Dr. Karkouti was very explicit about that in his presentation. He actually talked--the variables that are examined by the decision maker. Then you try to model that decision to use one treatment versus the other treatment.

I think FDA was also quite good at describing that process. If you don't have the covariates, the background variables or very good surrogates for them that are used to make the decision, so you can mimic this coin toss that has a certain probability of being one treatment versus the other, then propensity-score adjustment just

can't do it.

So people talked about these unmeasured confounders that might be out there, but it is important to realize that also the analysis, the propensity-score analysis, has to be done at the level of the decision-maker.

So if you have centers, medical centers, all over the world, you can't just estimate one propensity score. It makes no sense unless all the centers are using the exact same rule. Obviously, that make no sense. Ideally, you would maybe do a propensity-score analysis at the surgical-team level because they are making the decisions or at the medical center because they are making the decisions and, ideally, you would do it differently in time because the rules may be changing in time.

But you have to try to mimic what that decision-maker is actually doing. And that is when the propensity-score method works well. Otherwise, you are going to have these problems of residual bias, as you mentioned. It is going be confounded by indication.

DR. HARRINGTON: Susan, go ahead.

DR. HECKBERT: Given the problems we have been talking about with observational studies, I have two questions I would like to ask about randomized controlled trials that are either under way or might be thought about for the future.

The first question I have is for representatives, I think, from the FDA who may be in the best position to answer this, regarding the BART study which is a Canadian study. I don't know much about it. All I know, pretty much, is what I have on Page 53 in the briefing documents which is an abstract regarding that study.

I wondered if anyone from FDA or others can comment specifically on are there any issues with that study that make you feel that it will or will not--the results will or will not be useful with regard to the United States practice? And, in particular, do we know whether clopidogrel or other platelet-inhibitor use is being assessed in that study? That is first question.

DR. SHASHATY: Could you put Slide 12 up

for me, please, my Slide 12. This is a sort of summary of the BART trial which is going on in Canada right now. I believe there are 16 centers, and, incidentally, Dr. Karkouti is very well aware of this study and may be able to add additional information.

It was presented in an abstract form in 2006. I believe at that time there were approximately 1200 patients who had been enrolled in the trial. The primary endpoint is what is referred to as massive post-operative bleeding and there were, I believe, four criteria for massive post-operative bleeding.

There is a certain rate of thoracotomy drainage. There is a requirement for your operation. There is death in which bleeding is a predominant symptom and there is one additional definition for massive bleeding.

The rates of massive bleeding in the trial across all patients--if you can go to my No. 12. It is not in my talk, but it is in the additional slides I gave you.

I'm sorry. There are supposed to be 2,970 patients to be enrolled in this trial and they are seeking to demonstrate a 3 percent difference in the rate of massive blood loss following surgery. They had calculated that there would be a rate of about 6 percent.

But what has been found is that the rate is about 11.5 percent. For mortality in the trial to the time of the abstract, it was 5 percent.

One thing that one has to remember is that this is a study in patients who are believed to be at high risk. And the definition for high risk, there are several such as re-do operative procedures, CABG plus some other surgical procedure, et cetera.

As far as I know, and I could be wrong--it is the one before this. Ah.

[Slide.]

This is what it consists of. It is a blinded study, 18 Canadian centers. It is to compares aprotinin, aminocaproic acid and tranexamic acid, and there are a number of

secondary endpoints. The interim analysis at 1210 patients, there was a massive bleed rate of 11.2 percent which was quite a bit higher than was expected at an overall mortality of 5 percent.

I do not think that clopidigrel was included as one of the risk factors.

DR. HECKBERT: I think it was.

DR. SHASHATY: Okay. Dr. Karkouti says he believes that it is.

DR. HARRINGTON: Is your second question, Susan, a quick one?

DR. HECKBERT: Yes. I will make it quick. This is a question for any of the cardiothoracic surgeons that we have here. If we were to--if the Committee or someone or the FDA were to suggest that a randomized controlled trial is needed in the United States, on top of the data that will be available from the BART study, first would it be feasible in the United States to do a trial where aprotinin is compared with on antifibrinolytic? I am a little skeptical that surgeons would be willing to do that.

DR. HARRINGTON: I thought you said this was a quick one. This will be all afternoon.

DR. HECKBERT: It is a yes/no.

DR. HARRINGTON: Maybe I will ask my surgical colleagues, I know there are several, to give a quick answer. We are going to undoubtedly come back to this this afternoon.

DR. JEEVANANDAM: If you are going to compare aprotinin to no fibrinolytic, that would be no. You are not going to enroll any patients. We use at least Amicar on all our patients and then we augment it with aprotinin if we need to.

DR. HARRINGTON: Norm?

DR. KATO: I would agree. I would say no also. Amicar is pretty much the standard baseline antifibrinolytic, at least in our use, too.

DR. HECKBERT: I am impressed in Canada that they are able to randomize between these three. I know this is a longer, more difficult answer, but is the answer no for randomizing between Amicar and aprotinin in the U.S.? Would that be possibly feasible? Or is that like a no?

DR. JEEVANANDAM: That is going to be a longer answer, but it is going to depend on which patient population you select.

DR. HARRINGTON: Let's hold that until this afternoon because there is a specific question for the panel. Fred, you get the last one here.

DR. KASKEL: This goes along with Dr. Paganini's question about acute kidney injury. These patients must have a lot of imaging studies right around the perioperative period. There has been a recent report about the risk of acute kidney injurt associated with gadolinium.

Again, I didn't see any data today in any of the reports showing what patients may have had an imaging study somewhere close to this assessment of renal function. In the acute kidney-injury world, there are markers of risk and I would urge the sponsors and investigators to think about this in the next assessment.

DR. HARRINGTON: That is a good point. We can maybe come back to that this afternoon, get people's input. Let's come back at 1 o'clock so

that we can start right on time with the public hearing.

DR. PHAN: Please refrain from discussing today's meeting at lunch. Enjoy your lunch.

[At 12:00 p.m., the meeting was recessed, to be resumed at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. HARRINGTON: We have the open public hearing for the next hour or shorter, depending on how long this takes. Then we will go into Committee Discussion and take a break. Then we will come back for Committee Discussion and the Questions asked by the FDA.

Before we begin, I have been asked to read the following statement. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if

known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the Open Public Hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this Open Public Hearing to be conducted in a fair, open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

So we could start with the first speaker.

Open Public Hearing

DR. AD: Good afternoon, Mr. Chairman, ladies and gentlemen. At ANOVA Heart and Vascular Institute, we are performing about 1500 cases a year. Our case mix is such that we have many high-risk patients.

Before the first few papers appeared in the literature, we were high-volume users of aprotinin and when the initial results came out, it actually was a big shock for all of us. Over 80 percent of our patients were given aprotinin before the publications.

I have nothing to disclose with regard to finance. However, I want to mention that about a year ago, we presented an abstract at the American Heart Association Meeting suggesting that aprotinin is related to higher perioperative complications.

Meanwhile, in between then and now, we

reanalyzed our data focusing on the group of patients back in 2001 and 2002, CABG only, on pump only with no prior history of renal failure or dialysis.

We performed a few statistical analyses including the propensity-score match with a C-statistic of about 0.43 for about 1100 patients. The nature of the nature was as such as to A, try to see and analyze whether aprotinin has any impact whatsoever on perioperative outcome as well as long-term results.

As you can see by this initial slide, and this is pretty much a middle data of what we had this morning, the patients in the aprotinin group did carry a significantly higher risk as opposed to no-aprotinin group with regard to age, non-elective cases, New York Heart Association and so on and so forth.

So, at the get-go, we were pretty familiar with the fact that aprotinin is a good marker for the high-risk patients.

We performed a few perioperative analyses

based on the STS database and our own analyses as you have seen in the following slide. What we can see, based on the risk adjustment and the STS data, that aprotinin may be related to perioperative complications such as mediastinitis, renal failure and prolonged ventilation.

However, it is not clear that aprotinin, itself, has a major impact that stands when compared to the nonaprotinin group.

We further looked into this data by analyzing the perioperative for variables for unadjusted model and adjusted model, adjusted for the variables you see below to control the risk as much as we can.

As you can see, they adjusted the column on the right-hand side. Nothing stood up as a significant impact of aprotinin on the bad outcomes of patients.

Then we were looking into the latest follow up in order to find out whether the aprotinin patients did not as good as expected in the years following surgery. We have a special

database that we have 100 percent follow up of our patients regarding their late outcome. Due to our relationship with the NDI, the National Death Index, which is a federal agency, all our patients with their Social Security numbers are transferred and we get the death whenever it occurs every quarter and their database is continuously updated.

As you can see for all patients, without any matching, and so on and so forth, it is clearly shown that aprotinin patients do die more than the nonaprotinin group. However, I must remind you that the aprotinin patients were sicker based on the demographic that we showed early.

So then we ran a couple of propensity matches analyses. The first propensity match analysis was between aprotinin and no-aprotinin. As you can see, even after the matching, the aprotinin group did have a higher mortality, the range for five or so years after surgery.

However, when we further divided the group of patients into four different groups saying that we have two no-aprotinin group of patients, meaning

no aprotinin, no blood products/no aprotinin, yes blood products, aprotinin with blood products and aprotinin without blood products, you can clearly see that the black line which represents the aprotinin with blood products group of patients did less good than the other three groups of patients.

So then we matched--we had another propensity match analysis within the aprotinin group of patients saying that we took only the aprotinin patients and we matched propensity and asked the question whether blood products were used or not.

We had about 600 patients in this matching, 301 in each group. As you can see, within the aprotinin group, the patients that got blood products did much less good than the ones who didn't get blood products.

So, in order to further analyze the data and try to control for perioperative risk, we used the EuroSCORE system in order to be able to stratify patients by risk groups. We didn't use the STS scoring simply because the STS scoring

would not give you a low, medium and high-risk group of patients.

For the EuroSCORE, for those who are not familiar with the scoring system, 0 to 2 is a low risk, 3 to 5 is a medium risk, and 6 or over is the high-risk group. As you can clearly see, for the aprotinin/no-aprotinin group of patients, the blood products had a major impact on outcome, especially or only in the group of patients that are considered to be high-risk perioperatively. This is based on the first propensity match analysis.

Then we went to the second propensity match analysis within the aprotinin patients only. As you can see, the low-risk of patients, actually, we had zero mortality in long-term, both in the blood products in the non-blood products group within the aprotinin group of patients.

This is for the medium risk, pretty much the same curves. This is for the high-risk patients within the aprotinin. Again, patients that got aprotinin and however got also blood products around surgery did much less good than

those who didn't get blood products.

So, in order for us to really summarize what we just said, we, again, divided the patient population. We had by no-aprotinin and aprotinin and again by EuroSCORE and the fact that they got or didn't get blood products.

As you can see for the lowest patient, there occurs almost identical, both in the aprotinin and the no-aprotinin group regardless of the fact that patient got blood. For the medium-risk group of patients, again same type of curves for late mortality on the right and the left side. However, when we look at the highest group of patients, regardless of the fact that the patients got aprotinin, the patients with blood products did much less good than the patients who didn't get blood products in both groups.

This is kind of leading us to the conclusion that blood products may play a major role, especially in the high-risk group of patients and aprotinin might be only the marker for a high-risk group of patients.

So we conclude this small study by saying that aprotinin patients present with higher case acuity and, in our case at least, after adjustment for potential confounders, aprotinin failed to increase the risk for postoperative complications. We think that, independent of aprotinin, blood products increase the increased risk of late mortality and EuroSCORE and blood products might be more related to increased risk of late mortality rather than aprotinin use, itself.

Thank you.

DR. HARRINGTON: Thank you. If we could have the next speaker.

DR. FURNARY: Hi. My name is Tony Furnary. I am a cardiac surgeon and researcher from Portland, Oregon.

So, the question that we asked is does aprotinin increase the risk of renal failure in cardiac surgery cardiac surgery patients. I must tell you that these data were presented last year at the American Heart Association Annual Scientific Sessions at an Oral Presentation. These data were

under embargo until Monday at 4 o'clock p.m.--that's two days ago--because there were published yesterday in Circulation and I have made a copy of that paper available to all the panel members.

So I was not allowed to disclose this or not allowed to talk about this for the last year and now I am.

My co-authors and I have absolutely nothing to disclose in a positive or negative fashion; that is, I have not accepted so much as a pen from Bayer and I have nothing against Bayer. So this is really for the patients.

As you all know, and you have heard, aprotinin is frequently used in high-risk surgery patients to decrease bleeding complications and transfusions of packed red cells. A recent, highly publicized report by Dr. Mangano in the New England Journal of Medicine implicated aprotinin as a causal factor for postoperative renal failure.

As you know, this non-randomized retrospective study from 66 center involving 4,300

patients in which the use of aprotinin was based solely on surgical judgment concluded that continued use of aprotinin was not prudent.

Now, in this study, although it was 4,300 patients, there were about 2,500 patients who either got aprotinin or got nothing.

Now, there was a second study by Dr. Karkouti that you have heard of today that also looked at this in propensity analysis and you have heard from that this morning. This was about 900 patients in the literature

Their study concluded that there was an increased incidence of dialysis-dependent renal failure but not an increased incidence of mortality or stroke.

So what we did is we looked at the common finding. We wanted to corroborate the common finding that aprotinin was associated with dialysis-dependent renal failure. So we hypothesized that aprotinin is an independent risk factor for new-onset dialysis-dependent renal failure either acute or chronic, temporary or

permanent, following open-heart surgery.

Now, a recently published risk model, and I was pleased from the question of the panel this morning, a recently published risk model for predicting acute dialysis-dependent renal failure following cardiac surgery was used in our data to calculate a baseline risk score for all patients. This risk model which emanated from the Cleveland Clinic utilizes the variables shown here.

Now, when I present risk data to you during the rest of this presentation, I am going to put all the risk data in blue. So you understand the risk data are in blue.

Now, we used the Merged Cardiac Registry and this was used to identify and this was used to identify 23,000 patients who were operated on between January of 2001 and February of 2006. These 23,000 patients had validated aprotinin usage data.

8,000 patients were excluded for incomplete risk-score data--that is, Cleveland Clinic Risk Score data. And additional 4,000

patients were excluded for lack of any available transfusion data. The remaining 11,198 patients were used for risk-adjusted assessment of renal failure in relation to aprotinin use.

25 percent, or 2,700 of these patients, were selected to receive aprotinin at the discretion of their surgeon. There data will be presented throughout this presentation in yellow.

The 8,500 patients who did not receive aprotinin will be represented in green through out this presentation. The overall procedural distribution is shown here.

Now, we first sought to validate the Cleveland Clinic risk models. You have heard earlier today you have to externally validate a risk model. So we first sought to validate this risk model with the 15,000 patients who we had all those variables for.

Now, a ROC analysis revealed that predictability of the Cleveland Clinic's risk model for renal failure on our data was excellent with a C-index of nearly 82 percent.

Now, what about renal failure? So, the incidence of new-onset postoperative renal failure was 1.3 percent in the non-aprotinin group and was twice as high in the aprotinin subset. This was a very significant difference.

However, demographic comparison showed that patients who were selected to receive aprotinin were at a significantly higher preoperative risk for renal failure, and this included a higher incidence of complex operation and re-do operation, congestive heart failure and low ejection fraction, severe lung disease in female gender and a higher overall preoperative creatinine in the aprotinin subset.

Thus, the risk model predicts a significantly higher incidence of renal failure in the aprotinin population as compared to the non-aprotinin group which is what we saw. The observed to expected ratio of the non-aprotinin group at 1.06 is what was expected but the actual incidence of renal failure was significantly higher than expected in the aprotinin group at 1.22. This

is a significantly higher incidence.

So then we took the composite Cleveland Risk Score, which represents the 12 variables that I showed you, and we entered it into a multivariable analysis. This would be a risk-adjusted analysis of renal failure. We entered that along with aprotinin trying to mimic what had been done in Dr. Mangano's study.

Our model suggests, as did Mangano's, that aprotinin independently increases renal failure by a factor of 1.5 times and slightly increases the predictability of the Cleveland Clinic model.

However, we must all understand that aprotinin is not the only perioperative variable capable of inducing renal failure. As you all heard this morning over and over, there are potentially missing confounding variables. This was brought up several times.

Honestly, I was really disappointed to see this morning that, in none of these studies was the single most important confounding variable associated with postoperative renal failure. It

wasn't discussed at all. It was not discussed by Dennis' group. It wasn't discussed by Dr. Karkouti. It wasn't even mentioned by i3.

Unfortunately, because the FDA only had those datasets to work with, it was not mentioned and not evaluated by the FDA. Because of that, I believe the next slide is the single most important slide that you as a panel will see today because this next slide shows what this important confounding variable is and it shows the missing confounding variable, like this is the missing link; right?

This is the missing confounding variable for all these studies and, to me, this is the most important slide. Our data show, as does that of others, that the number of packed red cells transfused in the perioperative period significantly increases the incidence of new-onset renal failure.

Now, I want you all to note that this is not a dichotomous variable; that is, this is not a yes or no variable. It is not, did you get a

transfusion or not. There is a continuous increase as you increase from 1 to 2 to 3 to 4. This is a direct and significant increasing relationship between increasing number of transfusions and increasing percentage of incidence of renal failure.

It is not dichotomous. It is not yes or no. This is not greater than 4 units or less than 4 units. This is a continuous variable and a continuous variable should be used as such.

So, what does this mean for us? Well, the number of packed red cells transfused in the aprotinin group per patient was significantly higher than that in the non-aprotinin group. Again, that is not unusual because, if we look at the predicted transfusion requirements for these two groups, we can see that the aprotinin group, the predicted transfusion, of the surgeon-selected aprotinin group, was predictably and appropriately higher than that of the non-aprotinin group. So this indicates appropriate utilization of this drug.

Now, although there were no differences in the percent of patients transfused down here, in fact, the aprotinin patients received significantly less packed blood cells than predicted by the model and that is reflected in the difference in the observed to expected rates of transfusion.

So this validates the fact that aprotinin--the usefulness of aprotinin, as a drug.

Now, further risk adjustment, then, with the addition of the highly significant numerical transfusion data--that is the continuous numerical transfusion data, number of packed cells transfused, shows that transfusion adds significantly to this equation. When that is done, this completely attenuates--completely attenuates, negates, attenuates, whatever word you want to use--the independent effect of aprotinin on renal failure.

It also increases the predictability of this model to 91 percent from 82 percent.

So, finally, to confirm this somewhat unusual finding, we repeated these same analyses on

the group of patients who were not transfused. So we repeat on the non-transfused subset in which there were equal proportions of patients in both the non-aprotinin and aprotinin not transfused.

The predicted risk of renal failure was a touch higher in the non-transfused aprotinin group. However, the actual rates of renal failure were significantly lower than predicted in both non-transfused groups. But there was no significant difference in the risk-adjusted incidence of renal failure between the two groups.

So, once again, multivariable testing was done and multivariable testing in the non-transfused subgroup confirms that aprotinin has no independent effect of renal failure with a p-value of 0.6.

So, as you all know, exclusion of any important prognostic predictors or confounding variables, exclusion of those variables, would hamper any statistical analysis causing it to render the wrong conclusion.

So this is demonstrated with a sequential

analysis of our own data. What I am showing you here are the odds ratio, the 95 percent confidence intervals and odds ratios, for each of the patient subsets that I just went over starting with the entire group, the Cleveland Clinic aprotinin model, the Cleveland Clinic packed-red-cell model and the non-transfusion model.

Now, the univariate risk of aprotinin--the univariate risks of aprotinin that is before any risk adjustment, are represented in red right here. You can see there is no significant difference between any of these univariate risks for aprotinin in regards to renal failure and it is essentially saying that these populations, in terms of renal failure, are exactly the same.

Now, the blue bars represent the multivariable odds ratios from the first model that I showed you which is similar to Dr. Mangano's model, and the model containing transfusions and the model with no transfusions.

You can see that the first model, without regard to the number of transfusions, indicates

that aprotinin impacts renal failure significantly. But once the highly significant continuous variable of transfusions is added, aprotinin become non-significant. If you look at the non-transfusion patient population, aprotinin remains non-significant.

So it is only with the addition of this important prognostic predictor--that is, the continuous variable of number of transfusions--that aprotinin is seen not to be a true risk factor for renal failure.

So, to summarize this data, aprotinin does not independently increase the risk of postoperative renal failure following cardiac surgery. Rather, increasing transfusions, as indicated by the number of packed cells transfused to our patients in the perioperative period, are independently related to increased risk of postoperative renal failure.

We also confirmed that aprotinin lowers predited transfusion requirements and, in addition, we validated that the Cleveland Clinic risk model

for renal failure is a good model. But the numerical transfusion data are so powerful that postoperative renal failure risk assessment was further enhanced, as a matter of fact enhanced by 10 percent of the addition of numerical transfusion data--that is, continuous variable transfusion data--to this model.

That is how powerful the transfusion data is. It enhances an already validated risk model.

So I would conclude, and my coauthors and I would conclude, and I want to mention that two of my coauthors are highly respected statisticians one of whom has worked within the FDA, the cardiovascular portion of the FDA for a number of years and worked with them, and that is Gary Grunkemeir.

We all believe that the implication that aprotinin is a causal factor for postoperative renal failure was incorrect and premature and that the previously published results were likely faulty due to the absence of numerical transfusion data in the Mangano and the Karkouti studies and in the i3

studies and in the FDA reanalysis of all those data because those data were not present in those datasets for the FDA to analyze them and it is truly the numerical transfusion data that matter here.

We believe that all efforts to minimize packed-red-cell transfusion should be undertaken to prevent even higher occurrences of renal failure in this population and then, importantly, all subsequent analyses of postoperative renal failure should adjust for packed cell uses in a continuous fashion, in a continuous variable fashion, as this is a highly significant risk factor for the subsequent development of acute renal failure.

I would implore the FDA to go back to Mangano, to go back to Karkouti, reanalyze those data with the packed-cell transfusion, the actual transfusion requirements of each of those patients.

And I would ask Dr. Mangano how that transfusion was calculated because I do not believe it was actually collected. I believe it was estimated.

Finally, based on these data which are appropriately risk adjusted, we believe that FDA should consider withdrawal of a permanent five-year warning based on these data.

Thank you.

DR. HARRINGTON: Thank you very much. Could we have the next speaker.

DR. SPEISS: Good afternoon, ladies and gentlemen. Mr. Chairman, ladies and gentlemen, one year ago I addressed this committee in a public forum. A great deal has occurred in the ensuing year. The Ad Com has copies of my talk. I do not have slides.

By way of full disclosure, I have been retained as a consultant to Bayer Pharmaceuticals, receive research funding a speaking honorarium from them as well. For a number years, I was the Chair of the Hematology Subgroup of McSPI and have published extensively within the organization. Although my disclosure notes conflicts on both sides, I am today making my own comments. No one has seen, previewed or contributed to these

statements. They are entirely my own.

One year ago, I spoke of unrecognized confounders as well as strong associations between transfusion for long ventilation, lung dysfunction, perioperative infection, renal failure and death after heart surgery. Today, the data are even stronger.

There is new sobering evidence regarding blood transfusion and adverse outcomes. Indeed, some of the new manuscripts are directly from the Epi-2 McSPI database. Under-investigated confounding variables can radically change conclusions from observational research.

The methodology for investigating transfusion's relation to outcome creates it both as a confounding variable as well as its own independent adverse outcome.

First, the potential existence of a prothrombotic covariate, let me discuss, that I warned of that last year that it was neither collected nor analyzed within the McSPI database and that is heparin-induced thrombocytopenia. That

possibility is, I believe, even stronger today. The under-investigated or uninvestigated covariate HiTT may be a haunting specter of error in both Mangano's aprotinin articles.

I would point out HiTT is not even capable of being investigated in the i3 database. I call this committee's attention to Pages 124 to 145 of your FDA advisory committee briefing document of August 21, 2007.

A summary consult by Dr. Susan Lu reports on the Adverse Event Reporting System to the FDA regarding aprotinin in 82 patients with renal events. Closely scrutinize that data on those pages and it deals with renal failure, impairment, oliguria, anuria and dialysis.

In 19 of the 82 spontaneous reports or 23 percent, thrombocytopenia was spontaneously reported and thrombocytopenia with thrombosis after heart surgery is HiTT until proven otherwise. Yet, in neither of the Mangano articles nor the i3 databases are there an surrogates for HiTT. There is no data on heparin usage preoperatively.

Overlooked or uncaptured covariates are real. They are important. The overlooked covariate can completely change the conclusions of an observational analysis. The FDA has one, thrombocytopenia with thrombosis, probably HiTT, right within your own database.

That needs to be respected, analyzed and used as a sentinel warning with regards to the issues at hand.

Second, with regard to the issues of uninvestigated confounder, let me brief this committee on a very telling, potentially sad lesson. In 2001, DeFoe, et al., published a study in Annals of Thoracic Surgery from the Northern New England Cardiovascular Database. 7,000 patients were reported in that database and lowest hematocrit values on cardiopulmonary bypass were trisected into bins. Those patients with a hematocrit below 24 percent had a doubling or greater of balloon placement, heart failure, inability to wean from bypass.

In 2003, Habib, et al., published in

Journal of Cardiovascular and Thoracic Surgery. They also segmented patients into different silos of hematocrit and they found that anemia was related to increased stroke, MI, low cardiac output, failure, et cetera.

These two studies caused many within cardiac surgery and anesthesiology to liberalize their transfusion practices. But what was missing from the publications was the key covariate, transfusion; i.e., the physician response to anemia.

Surgenor, DeFoe, Fillinger, et al., the same group as authored the 2001 paper, in December of 2006, after my last briefing to this organization, published a landmark and, I believe, courageous manuscript in Circulation.

In 8000 patients that were never in the original--or that were partially in the original database, this time they loaded in red-cell transfusion and, they said, "In this study, we observed that exposure to both hemodilutional anemia and red-blood-cell transfusion during

surgery are associate with increased risk of low-output heart failure."

To further quote, "The risk of low-output heart failure is greater among patients exposed to intraoperative red-blood-cell usage versus anemia alone." These are more recent findings and represent, therefore, a diametrically opposite opinion than what they published in 2001. Of note, Habib and Goren and others have had similar publications showing reversal of their opinions as well.

In the Mangano Renal Outcome paper, transfusion was evaluated only as a dichotomous variable, yes or no, and the results were ignored. In his mortality paper, there is no evidence of it even being considered.

In 2006, in the New England Journal article, red-cell transfusion had an odds ratio for renal composite outcome of 1.71, FFP usage at 2.4 and aprotinin at 2.4.

Since the last ad com meeting, Koch, et alcohol, published in the Annals of Thoracic

Surgery. They had a 12,500 database from the Cleveland Clinic and looked at activity index and discharge from the hospital and found that those patients transfused had much worse activity index.

Koch's work also found out a dose-dependent association between red-cell utilization and long-term mortality. Even one unit of blood had a 5 percent increase in mortality. Dealing with transfusion as a dichotomous variable in the McSPI database is patently inadequate. Transfusion's importance may have simply been understressed in the McSPI articles.

But was it?

On July 31, 2007, Kullier, et al., with Mangano as the senior author published regarding preoperative anemia. In 4,800 of those patients, 28 percent males and 36 percent females, were anemic. Of importance, Kullier and Mangano found that there was a significant increase in a risk of cardiac and noncardiac events including renal dysfunction, failure, stroke, et cetera. And the adverse events and mortality in relation to

perioperative anemia.

I quote; "The effect of low preoperative hemoglobin on noncardiac outcomes was greatest for postoperative renal events." They went on to say, and again I quote, "Multivariate logistic regression demonstrated that the number of units of intraoperative red-cell transfusion was independently associated with an increased risk of both cardiac and noncardiac failure.

"Patients with low preoperative hemoglobin had a higher rate of postoperative events but, at the same hemoglobin level, the risk of suffering postoperative complication increased significantly with the transfusion of red cells." Again quote.

Indeed, that is a similar finding to what Surgenor, Habib and others have found with renal failure.

In December, 2006, an abstract published in Blood was offered by Moehnle from McSPI, again with Mangano as the senior author. In this publication, the authors looked at a subset of 940 patients who had a postoperative hemoglobin of

10 grams or higher who went on to have an unnecessary transfusion.

Transfusion was highly associated with myocardial infraction at an odds ratio of 1.89, renal dysfunction at an odds ratio of 3.35, renal failure requiring dialysis at 4.0 and wound infection at 5.45. There was no investigation of antifibrinolytics or aprotinin in that analysis.

This series of five papers from the same dataset, all with Mangano as the senior author, have dramatically different public messages regarding the risks of renal failure. Three of the five found transfusion to be highly associated with adverse outcomes. Two did not investigate transfusion at all.

In 2006, the New England Journal article regarding aprotinin and cardiac surgery found FFP to have exactly the same odds ratio as aprotinin and red cells was not statistical different but focused the cause, in that entire article, only upon aprotinin.

The paper by Ott and Mangano as senior

author directly contradicts their own findings of the aprotinin paper. When analyzed for overall, short-term 48 hours or long-term adverse events, aprotinin was absent from the overall data and from the long-term but only present in the short-term.

So who has responsibility to analyze not only correctly but completely the data within the McSPI database? And I firmly believe that our patients are not served by this selective analysis technique with investigation in piecemeal.

Over the last year, new data regarding transfusion-related acute lung infection has been forthcoming. Two major papers by Rana and Khan have been published. In the Rana paper, 19,000 patients at the Mayo Clinic were prospectively monitored for TRALI. They found TRALI in 1 in 1,271 units of FFP but, because most patients got multiple units of FFP, the per-patient risk was 1 in 73 to 1 in 193.

Dramatically, the mortality for TRALI was 50 percent. And TRALI and TACO, transfusion-related acute lung overload, are

dose-dependent and, remember, the FFP was the same as the aprotinin use. Once again a dichotomous variable wherein transfusion is lumped cannot possibly explain these facts.

These newly revealed facts are particularly important vis a vis the discussion regarding the Mangano papers and that FFP had the same association with adverse outcome as did aprotinin.

That finding, regarding FFP and its association with adverse outcome was pointed out at the last ad com meeting. However, nobody at that last ad committee meeting had the sensitivity or the insight into what we now about FFP and TRALI. However, from the McSPI database, Dr. Ott and Dr. Mangano published a paper examining difference in practice pyramides. There is a dramatic difference, greater than a ten-fold difference.

In Germany, 69 percent of patients got FFP versus 5.7 percent in Canada and likewise a greater than tenfold use--I'm sorry; that was aprotinin, a ten-fold use greater difference and FFP exactly the

same. Also noted were large differences in red-cell uses, platelets, et cetera.

So, indeed, the fact that they have the same odds ratio seems to strongly suggest that there is, indeed, a confounding effect.

At the end of the day, the question to be deliberated by this advisory board comes down to the following, and that is, are the risks of adverse events alleged to be caused by aprotinin less or more than the risks of adverse events from transfusion.

Using McSPI's own data from their already published papers, the associations between renal failure, dysfunction and transfusion are at least as strong or stronger than the odds ratios for aprotinin. The potential for under-explored, ignored, noncaptured or statistically incompletely analyzed confounders of both HiTT and transfusion leave me unconvinced of a cause-and-effect relationship.

As I stated last year, our patients deserve the correct answer. A preliminary analysis

of the STS database shows an unprecedented dramatic, trend-reversing, 14 percent sudden increase in blood transfusion and an 8 percent sudden increase in reoperation rate for patients in 2006 after the publication of the New England Journal article.

That represents an estimated 350,000 more units of blood transfused in the United States at a cost of between $70 million to $700 million worth of medical-care costs when we have a profound shortage of blood in the United States.

Who is responsible to our patients who have been transfused, may now have renal failure, dysfunction, MI, infection or died in association with this increased bleeding because of that message? Who is responsible to our nation for an increased blood shortage, increased healthcare costs and a new public-health hazard, I believe.

Lastly, there do exist some data with regards to change in practice; i.e., the switch of the use of Amicar over previously utilized aprotinin.

Attached to my public remarks is an abstract to be presented at the Society of Critical Care Medicine from Wake Forest University cardiac surgery and I have their expressed permission to present this.

In their data, 211 patients, they noted a dramatic increase in red-cell usage and platelet transfusions rather than a decrease, a doubling. They further had a dramatic doubling increase in renal failure as would actually be suggested by Mangano's articles that you would be expect it to be the other way around. But they had an increase that would be suggested by Habib, Surgenor and other people who have published on transfusion.

Also, although not statistically powered to find this, there was a troubling trend for almost doubled mortality. I am told there are other hospitals about to report the same kinds of things nationally. I am told that the surgeons at Wake Forest have returned to the use of aprotinin for the safety of their patients.

Thank you for your kind attention and your

careful deliberations, gentlemen.

DR. HARRINGTON: Thank you. There is an additional speaker who has asked to have two minutes to update remarks that he gave last year, Dr. Stan Young.

DR. YOUNG: I am Stan Young. I am from the National Institute of Statistical Sciences and I have, as I said last year, no dog in this fight other than to see good statistical methods practiced.

I will make just a few comments. Once a claim is made, really, you should be powerfully addressing that particular claim. The time for exploratory data analysis is over. Unfortunately, as I have looked at analyses today, I see lots of analyses this way, that, and so forth and so on.

This would never stand in an FDA trial where you are trying to make a claim for the effectiveness of a product. You need to have a fixed analysis, fixed questions, a very limited number of questions, and all this bounding around, asking lots of questions and lots of directions

could be fine for an exploratory data analysis but it is not really appropriate for a confirmatory data analysis.

I analyze large complex datasets as a living. Quite often, I will divide the dataset into two halves. I will do crazy, exploratory data analysis of one half and then I will turn to the other half with the claims that came from the exploratory analysis and do a definitive analysis of the remaining part of the dataset.

The FDA requires two well-controlled studies. Should we do less for these side-effect kinds of studies?

Interestingly, the Justice Department commissioned a large study on how science should be used in legal proceedings. It is about 600 or 700 pages. 100 pages is devoted to statistics and about 70 pages are devoted to epidemiology studies.

They are very clear. They say that, unless the risk ratio is over 2, the evidence is essentially not admissible.

DR. HARRINGTON: Dr. Young, if you could

just wrap your remarks quickly because you had asked for two minutes.

DR. YOUNG: Okay. I will wrap up and say specifically in the Justice Department document, they said you have to use a higher-level risk ratio of 2 because of potential unmeasured confounding variables. We have been listening all day to unmeasured confounding variables and so this whole enterprise actually has gone forward based on risk ratios less than 2 and we are now moving to the place where, as people find all the additional risk ratios, the risk of aprotinin appears to be approaching 1.

Thank you.

DR. HARRINGTON: Thank you. That brings us to the end of the Open Public Hearing. Those were the three registered and the one additional speaker.

I am now asked to read the following, that the Open Public Hearing portion of this meeting is now concluded and we will no longer take comments from the audience.

DR. HARRINGTON: The committee will now turn its attention to address the task at hand which is the careful consideration of the data before the committee as well as the public comments. Thank you.

Committee Discussion

DR. HARRINGTON: So, from a committee business perspective, we now have approximately an hour and 45 minutes before break to make sure that members of the committee have all their questions answered, that we have a full discussion. Most, if not all, of the speakers from this morning are still here so please feel free to bring them up to the microphone if you have a question that you would like clarification on.

After the break, we will come back and go through the three questions. Each of the questions is a voting question and I will go over the new procedure for voting with you before we start that session.

Then, from a housekeeping perspective, Mimi will keep track of the order in which people

would like to speak so please get her attention by tapping your microphone or just waving at her, and she will try to keep us in line. We don't want to ignore anyone's comments so try to be patient with us as we try to identify you.

So I will open the floor here to--Dr. Crawford is the first committee member that wants to ask a question or speak.

DR. CRAWFORD: Thank you, Mr. Chairman. Most of my comments will be addressed toward the representatives from Bayer. If I might say, if FDA were to do a stratification on the backgrounds of most members of this panel, I think most of us are from the U.S. South, because I am sure you use South as a reference point, and we are going to be pronouncing it "Bay-er" from now on. So, with those apologies.

I have two sets of questions. The first one is going to be the longer one and is with respect to the indicated uses for aprotinin. Dr. Cyrus, on Slide C-65, briefly noted the sponsor's risk-minimization plan which included an

unspecified, at least to this point, physician education. Dr. Peter Smith, in Slide C-98, noted that aprotinin characteristically is used for high-risk patients as his slide said because they are high risk.

Right before lunch, Dr. Shashaty provided examples of such high-risk groups by definition from the BART trial. I apologize if I am mispronouncing it, Dr. Ouelette-Hellstrom's Slide 7 from the Premier data show very high use of aprotinin from the Premier dataset, at least other than last year, 2006, the slight downward blip. But the use of aprotinin seems very comparable to the use of aminocaproic acid.

So my main question is is this level of use appropriate. We don't know--I am unsure as to whether it is or not. So my question is, what evidence, if any, is available regarding the off-label use of aprotinin and specifically any evidence about the effectiveness and safety of such off-label use in the absence of any such data.

I asked the sponsor how would the

physician education aspects or your risk-minimization plan address this and/or do you have plans for additional studies that might examine these issues is the first question.

DR. HARRINGTON: Let's start with that one.

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

DR. CYRUS: You had many points to your question so if I don't address them all, please come back to me. If you look at the use pattern of Trasylol from what we have from market-research data, about 96 percent of the use is in the cardiac arena and then the other 4 percent is outside of the cardiac arena.

So let me start with that 4 percent, if I may. In that 4 percent, it is divided among different procedures. It is used in transplant surgery not only heart and lung transplant but also liver transplant. It is also used in that 4 percent in orthopedic procedures and, on occasion, in oncology procedures as well. It is a

splattering, if you will, across those procedures.

To address any data we have on those, I think it is safe to say that Bayer does not have large randomized controlled trials for those areas with the exception of orthopedics. Bayer has conducted hip studies in the past. We had also conducted a hip study that we reported on last year at the Advisory Committee that did suggest that, within that study, the drug appeared to be safe and effective.

However, since then, Bayer had trials ongoing at this time last year that we discontinued in January of 2007. Those studies were trying to get additional information about the safety and efficacy and other indications and that included a spine study as well as well as a cystectomy study for bladder cancer and a pneumonectomy esophagectomy study.

When, in December of 2006, there was a revised label suggesting that you needed to have cardiopulmonary bypass readily available, Bayer discontinued all clinical trials that were not in

the a cardiac arena. With that, we instructed all of our investigators as to why we had done that.

We had been in the process. We had an active FDAMA review in orthopedic surgery. We sent out a mailing to all those individuals notifying them of the decision and the label change and that cardiopulmonary bypass should be readily available.

In addition to that, when we did the label revision in December of 2006, we did do a mass mailing of a "Dear Healthcare Provider." That went to over 150,000 physicians in the United States and that was sent to not only cardiothoracic surgeons, it was sent to anesthesiologists, hospital pharmacies, directors of PNT committees, orthopedic surgery. In the orthopedic surgery, we made sure it went to everyone who had received our FDAMA.

It went to transplant surgeons and it went to pediatric cardiac surgeons as well. So those were the efforts that we have implemented for the off-label use.

DR. HARRINGTON: Can I follow up on that, though, before Dr. Crawford asks her second

question. I am curious about the on- and off-label use in terms of the 96 percent of patients who you said get it for cardiac usage.

But the indication currently says that it is for patients who are at high risk. So could you give us a sense or maybe Dr. Smith could help from the STS data, what is the breakdown of actual use by what is the labeled indication and how exactly are you defining high risk when you do your provider education?

DR. CYRUS: Within the cardiac arena and high risk, you are absolutely correct. I did say cardiac surgery and the indication is CABG at increased risk for bleeding and blood transfusion. With that mailing that went out to all of these physicians, the change in indication was emphasized.

As far as who is at increased risk, we do have a very aggressive educational program that is done by our medical-science liaisons as well as invited speakers at the request of different institutions when they demonstrate a need.

One of the most sought-after programs that we do are our blood-management programs. In the past year with the availability of the STS guidelines on blood management, they went through extensively--slide on.

[Slide.]

And looked at factors for bleeding and transfusion. This is an exhaustive list. This morning, we saw Dr. Corso speak about the big six which is a way of summarizing this, and Dr. Ferraris, when he speaks, does speak of the big six.

[Slide.]

This is a similar slide to what you saw this morning from Dr. Corso. I have got a feeling we got it from the same source which is Dr. Ferraris. But Dr. Ferraris, when he speaks, he will talk about advancing age, small body size, preoperative antithrombotic and reoperative and complex procedures, emergency operations in the non-cardiac.

We don't specifically say to physicians,

this is the category of increased risk. We leave it to their discretion but we do emphasize to these individuals that there is a change in label and in our blood-management program and we emphasize the STS guidelines, allow them to make a decision.

At the end of those, we also characterize the risk of hypersensitivity including our boxed warning to make sure they are aware that, if they use it in this patient this time, that it may make the drug unavailable for future procedures.

DR. HARRINGTON: But somebody must have done the analysis where you have taken these six and you have looked to see how many people are getting the drug that have one of these indications versus everybody else that is getting the drug. I mean, that doesn't seem very hard to do with all the STS data, et cetera.

DR. CYRUS: Well, the STS data, I don't believe, collects use of medications. But I will allow Dr. Smith to elaborate.

DR. SMITH: That's correct. The STS database doesn't collect antifibrinolytic usage so

that we have no idea in that dataset whether aprotinin was used or Amicar or any others.

DR. HARRINGTON: So if it is so important, Peter, why wouldn't you collect it?

DR. SMITH: That decision was made at the time the database was implemented, more than a decade ago. A number of people wanted to collect that data and a number of people didn't, as you know. Developing a database by consensus amongst 100 surgeons is difficult. It could have been as bit as a telephone book.

DR. HARRINGTON: But you have made it a Class I indication from the same professional society so, if it is a Class I indication, it seems almost inconceivable that you wouldn't collect it. But you don't.

DR. SMITH: I can't explain it but it is not collected. So knowing exactly what kind of patients the drug is used in becomes a much more difficult program to solve.

DR. CHEUNG: Can I follow up?

DR. HARRINGTON: Please. Do you want Dr.

Smith before he sits down.

DR. CHEUNG: Just a question about the renal failure. It is one of the big six because these are high-risk patients. But, on the other hand, in the label, at least the Precaution, is that renal failure also maybe disposes the patient to renal failure at post op. So are risk or not risk? Maybe I should ask Bayer to comment on that.

DR. HARRINGTON: While Bayer is getting ready, I think one of our colleagues would like--

DR. JEEVANANDAM: I can answer that in kind of clinical practice. If somebody is on dialysis, they have an increased risk of bleeding. But, if they are already on dialysis, we use aprotinin all the time because you can't make them worse.

So dialysis, I think, with renal failure is a higher incidence of bleeding but those patients we use aprotinin on as well.

DR. CHEUNG: So, if they have, say, advanced kidney disease, would they be risk or not risk? I mean, obviously, those patients also have

bleeding risk.

DR. JEEVANANDAM: I would say that anybody who has renal disease is at increased risk for bleeding. If somebody is not on dialysis and they have elevated creatinine, at least in our practice, we are very reluctant to use aprotinin.

But if they are already on dialysis and they have been on chronic dialysis, then we can use aprotinin without any increased risk of renal dysfunction.

DR. CHEUNG: But I think there is a big chunk of the patients who are not on dialysis. So would they be also predisposed to more advanced kidney disease, renal failure on the one hand and, on the other hand, are they also have predisposed them to bleeding.

DR. JEEVANANDAM: You are right. They would have increased incidence of bleeding and I guess you have a choice. Either you can take the bleeding or you could take the renal dysfunction. It is the surgeon's preference. We prefer to--we can always handle bleeding in the operating room

instead of throwing them into dialysis. So we would prefer not to put them on aprotinin.

DR. CHEUNG: So I guess that would be the choice of your institution. But I wonder, because this is what is in the Insert, I would like to hear what is the official standard, how it educates the practitioner.

DR. McCARTHY: I would like to call on Dr. Smith to respond to that, too.

DR. SMITH: First, I will have to tell you, I am updated and the next version of the STS database will collect aprotinin I have been told by Dr. Peterson.

DR. HARRINGTON: Probably a good decision.

DR. SMITH: I think that came about when the Level 1 recommendation was made. It was more or less automatic. I mean, in regard to renal dysfunction, obviously, it is to be used in caution in patients with pre-existing renal dysfunction. There is limited randomized-controlled-trial data on patients who have pre-existing renal dysfunction because they were excluded from many of the earlier

trials.

So patients with creatinines of 2 or greater are not well represented. They are not well represented in the patients we operate on either. It is about 3.5 percent of the patients who are operated on in the U.S. have creatinines greater than 2.

So a judgment is called for by the surgeon in that instance as to the risk of bleeding. Transfusion-related renal dysfunction that might occur if you don't use the drug versus some potential adverse effect of the drug and whether that is permanent or not, there are multiple pathways to go to dialysis from intermediate renal dysfunction.

Tamponade bleeding in return for bleeding is one way, too. But that is a grey area and I believe the label just says, Use caution in pre-existing renal dysfunction or when gentamicin is used.

DR. HARRINGTON: Dr. Crawford, I am going to come for your second question, but I know--Emil,

did you want to weigh in on the kidney issues from the nephrology perspective?

DR. PAGANINI: Yes, if I could. There is a whole series of things that I think are real problematic in the overview of everything that we are discussing. The first is that we are basing everything on serum creatinine. Serum creatinine, per se, is what we equate to renal failure. That probably is not as accurate as it could be but, unfortunately, in renal disease, that is all we have to work with.

You have seen the data that even going through bypass surgery, the creatinine decreases. Does that mean that open-heart surgery improves renal function just by the fact of going on to bypass surgery?

We are saying the same thing on the opposite side. When the creatinine goes up, does the creatinine go up for a whole bunch of different reasons, and that is the only marker that we have.

The second is that dialysis is a decision that is very subjective. It is very different

across institutions. It is very different across nephrologists and it is very different across countries.

There are a whole series of different studies looking at the use of dialytic intervention in immediate post op periods in the operating room or after they have been out for a day or two. That variability has not been addressed by any of the studies that we have seen.

Also, some of the databases that we have seen about post-operative dialysis did not exclude preoperative dialysis patients. Well, Christ; if they were on it before, they are going to be on it afterwards. So it is not a big deal.

The very limited use of predictive modeling for acute renal failure is a pre-empt to look at subgroups of patients that would have, in fact, enhanced acute renal failure with the use of aprotinin.

So that is a big loss there. There is only one study that I have heard that really did look at that with a model that was fairly robust

and found that, gee whiz, when you look at that, it looks like those that were predicted to have renal dysfunction are going to have renal dysfunction.

But there, again, another variable was introduced and that is not what we are supposed to be discussing. We are just discussing--so the variable, therefore, of transfusion inclusions, the type of blood products that are being used and infused, have not been involved or haven't been addressed at all.

So I see a series of questions, a really series of problems, that are going to limit our interpretation of any of these databases and I would think I am going to have to look at some sort of an answer in a prospective manner.

I won't get into answering some of the questions that we have here but, to me, all of this is really problematic.

DR. HARRINGTON: Thank you. I think the whole issue of transfusion we are going to spend a lot of time on this afternoon. The public speaker, I think, brought up some interesting points but

there are some methodologic issues as to how one considers that in those analyses, too. But we will come back to that.

Let me go to Dr. Crawford and then over here to Dr. Neaton, Black.

DR. CRAWFORD: Thank you. This one is very quick. Also to Bayer. We know that Dr. Mangano's presentation and the FDA analysis found evidence of a long-term mortality effect. As I looked at the conclusions from each of the Bayer presentations, it was silent on that.

So I ask if you acknowledge that the current evidence would suggest or not--and, if not, let us know why--a long-term mortality effect of an increased risk at least aprotinin.

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

DR. RUBIN: An excellent question, again. One thing that has to be distinguished among these data sources, these observational studies, is the quality of the data source, itself, and the quality of the analysis. Slide up.

[Slide.]

This is a depiction of the quality of the data source on the horizontal axis from poor data sources, case reports, administrative claims data, observational studies based on clinical data. To the right are the very best sources of data, randomized controlled trials.

But then there is also another dimension which is the quality of the analysis. I have put the various data sources and reanalyses in blue boxes. I consider, and I think generally we feel, that the i3 data source is just completely unsatisfactory. So the claims data source with an extremely large number of unreported covariates that are known to be predictive.

As I said this morning, when I was asked a related question, this propensity-score methodology can only work with a dataset when it is applied at the decision-maker level to model what would be done in a randomized experiment by modeling the probability of choosing Treatment A versus Treatment B as a function of covariates that are

used to make the decision.

If you are missing all the covariates, if they are not observed, it is pretty much hopeless to do propensity-score analysis. And, if you are doing the propensity-score analysis at the wrong level, like across centers or in a country when the decisions are being made at medical centers and not by national policy, it is not going to work.

The only hope is to get a data source that has the correct covariates and then you do the model propensity scores correctly and do the diagnostics to show that you create a balance. It could be matched pairs, the way Karkouti did, or in subclasses the way FDA did in some analyses.

So what I regard as unsatisfactory are all the i3 data sources and the analyses can't fix it up. I don't regard, even though the FDA analyses are sitting up there on the upper left, which sort of suggests that the data analysis is satisfactory. It is certainly better than the i3 analysis, but it is not doing it at the decision-maker level. So your propensity-score analyses there can't really

work unless everyone is using the same decision and then it is missing the covariates in any case.

At the lower right, I have the two Mangano datasets saying that the data sources may be okay. They may not be okay because they are limited to 50 patients from each center each year and, therefore, the ability to model the propensity to get one of four potential treatments, from a total of 50 patients, is very limited unless many centers are using the same decision rule in which case you might be able to do something.

So that is why the two Mangano datasets are down there saying it is unsatisfactory at this time because it is possible that a better analysis, a really appropriate analysis, could bring that up to be satisfactory. I just don't know.

But at least the dataset has some potential. The randomized trials are up there in the satisfactory quadrant because, by design, as long as there is follow up and not huge amounts of dropout, they are going to be satisfactory. And the Karkouti one is up there as being satisfactory

because it was done in one center.

You heard this morning how he described the very careful thought that went into why some patients get aprotinin, why some patients get AA. So they thought very carefully about what the background covariates are and they modeled the propensity to get one or the other, and they demonstrated balance in the two groups.

And they had to throw out lots and lots of patients in order to get it, but, in the subgroup that they finally got where they matched the patients, they have demonstrated balance and they have also thought very hard about the covariates that are necessary and modeled them at the decision-maker's level.

So I regard that as a satisfactory data source. But the other data source, the i3 data source, is unsatisfactory, I think. And the Mangano analyses that have been done so far are unsatisfactory. So that is why, at least to my mind, we sort of blow off those results. They are unsatisfactory.

DR. HARRINGTON: Dr. Rubin, before you sit down, specifically, we are following up on Dr. Crawford's question on the mortality finding. So the FDA--would you agree that the FDA, using the Mangano data, had done more appropriate analyses of those data.

DR. RUBIN: Oh, absolutely more appropriate. That is why it sits above--the FDA-Mangano reanalysis ongoing sits above Mangano, which I regard as a totally inappropriate--

DR. HARRINGTON: So, specifically regarding the mortality finding from the Mangano study which the FDA corroborates in their analysis of the data, tell me what specifically it is about the Mangano data that leads you to still treat that particular analysis as unsatisfactory?

DR. RUBIN: Well, because I don't believe that there was any analysis done which could be regarded at the decision-making level. The decision-making level probably is within the center or surgical team. So was there any investigation by--maybe I should ask that as a question. Did the