AFTERNOON SESSION

IN RE:

FOOD AND DRUG ADMINISTRATION
MEETING OF THE CARDIOVASCULAR
AND RENAL DRUGS ADVISORY
COMMITTEE

The above entitled matter was held on September 21, 2006 at 5630 Fishers Lane Rockville, Maryland before Robert A. Shocket, Notary Public.

REPORTED BY: Robert A. Shocket

(Luncheon recess)

DR. LEVY: Thank you. Okay. So, before lunch we heard from Dr. Makuch on statistical considerations of the two observational studies. Now I would like to introduce Dr. Pamela Cyrus of Bayer's US medical organization, who will review the clinical data for aprotinin. Dr. Cyrus?

DR. CYRUS: Good afternoon. I would like to thank the Committee for having Bayer here today to review our clinical trial data. As you heard this morning from Dr. Robie-Suh from the FDA, we have submitted data on an ongoing basis to our NDA as well as with our ongoing pharmacovigilance additional data. With the two recent observational studies we've also conducted a very thorough analysis of our global CABG database and we have submitted that analysis as well as our datasets to the FDA for their review. And that will be the basis of what I am reviewing for you here today.

I would like to start with saying I'm going to show you the six US CABG trials that were also

referred to earlier this morning. Four of those trials included primary CABG patients and four included repeat CABG patients and are the basis for the current U.S. label for Trasylol. I will be reviewing those studies in detail for the efficacy in CABG. Them I will review safety in CABG. When reviewing safety I'm going to review the 45 clinical trials that were conducted globally using the full dose of aprotinin versus placebo. I will be focusing on those interests, safety events of interest here today, myocardial infarction, graft patency, congestive heart failure, stroke, encephalopathy and finally renal function. I will then be reviewing for you our spontaneous report database on hypersensitivity.

To start, there were six U.S. CABG trials that have been conducted with Trasylol. The first two studies, D89-004 and D89-006.

Served as the basis for the initial approval in repeat CABG in 1993. I should note these two studies were supplemented with a cardiac valve study as well as supportive data from no-US data

sources. The third study on the list is D92008. This study served as the basis for the approval of the half dose of aprotinin in 1994.

And, finally, the last three studies, D91007, D92016 and D92048 served as the basis for the expansion of the label to primary CABG. As was noted this morning, there are two approved dosing regimens in the United States. There is the full dose aprotinin and the half dose aprotinin and as reviewed for you by Dr. Robie-Suh, the full dose includes a test dose followed by two million kalikrein-inhibiting units, a loading dose as well as two million KIU in the pump prime regimen and 500,000 KIU per hour as an infusion and the half does is exactly half that with the exception of the test dose.

Now to address efficacy in CABG procedures. The primary endpoint for efficacy in these clinical trials was percent of patients transfused red blood cells. This was the endpoint that was agreed upon with the FDA prior to the initiation of our clinical trials in the United States. First we could say why would we

develop this drug to begin with for cardiac surgery? The number one risk in cardiac surgery -- and I think you've heard Dr. Karkouti mention this in his presentation -- is the risk of bleeding and the need for a subsequent blood transfusion.

There's also risk of infection, stroke, renal failure and reoperation or take-backs to the operating room for diffuse bleeding. This has a huge impact on the patients themselves undergoing CABG surgery. Every patient undergoing open heart surgery according to the American Red Cross on average receives two to six units of packed red blood cells, one to ten units platelets and one to ten units of fresh frozen plasma.

On a societal level this is very important because cardiac surgery utilizes 10 to 20 percent of the U.S. blood supply that is available. With this, there have been very aggressive measures taken on by both the STS and the SCA for blood management programs during cardiac surgery. Bayer convened a consensus panel of independent consultants. This was led by Dr.

Goodnough. And you can see the list of members at the bottom of this slide. And we asked them the question, in your opinion what is the mortality associated with transfusion today for red blood cells and for platelets?

This is the consensus statement that they have come up with just as recently as this month. The transfusion related acute lung injury with red blood cells is ten to twenty deaths per million units of red blood cells transfused with the same rate being reported for platelets. Bacterial contamination as one might expect is more common among platelets and depending on whether it is cultured or uncultured, those rates can also differ. Viral deaths and mortality is much more limited.

Transfusion errors are also on the lower degree but allergic reactions to blood account for five deaths per million units of red blood cells and platelets transfused, bringing the overall mortality per million components of 16 to 27 units per red blood cell and 19 to 100 per unit of platelet transfused. So

as you can see there is a need for blood conservation for the patients especially those undergoing CABG surgery.

Aprotinin is available and helps with that. Aprotinin reduces the transfusion rate in repeat CABG. This is the data from the four U.S. studies that had repeat CABG patients and, as you can see in the orange color, red blood cells were statistically reduced per percent of patients being transfused for both the half and the full dose of aprotinin. This translates into a 38 percent relative reduction in transfusion rate for the full dose of aprotinin relative to placebo.

I have also placed on this slide the percent of patients that required transfusion of platelets. As you can see, 8.4 percent of full-dose aprotinin patients required platelet transfusion compared to 44.9 percent of placebo patients. Not only does aprotinin reduce the percent of patients that are being transfused but it also reduces the number of units transfused in patients as is demonstrated in this slide. You can see, moving up the slide, you have red

blood cells, fresh frozen plasma, platelets and cryoprecipitate.

The full dose of aprotinin reduced the mean number of units transfused of each of these components relative to placebo. For the half dose numerically they were all lower but did not reach statistical significance for cryoprecipitate although it did for reducing mean units of red blood cells, fresh frozen plasma and platelets.

We heard doctor that Dr. Karkouti expressed that those patients that have greater than five units of blood transfused are of concern at his institution. We can see here today that the full dose of aprotinin, 8.4 percent of patients treated with full dose of aprotinin had to receive at least five units of red blood cells compared to 27.6 percent of placebo patients. Furthermore, the need for take-back to the operating room for diffuse bleeding was also reduced with the full and half dose of aprotinin with not a single patient in the valid-for-protocol population requiring a reoperation for diffuse bleeding.

Now turning to the primary CABG studies, which there were four studies that included primary CABG patients, again you can see the consistent effect of reducing the percent of patients requiring transfusion of red blood cells or platelets with both the half and the full dose relative to placebo. Once again, this translates into about a 31 percent relative reduction in red blood cells being transfused for the full dose group relative to placebo.

Just as in the repeat CABG population, aprotinin also reduces the mean number of units transfused in primary CABG. When looking at the blood products again, red blood cells, fresh frozen plasma, platelets and cryoprecipitate, both the full and the half dose reduced the mean number of units transfused in patients undergoing primary CABG. Again for those patients that required greater than five units of red blood cells, you could see that only 2.8 percent of patients receiving full dose aprotinin who underwent a primary CABG procedure received at least five units of red blood cells with the placebo being 10.1 percent,

again being statistically significant. Once again, there was not a single patient who was in the valid-for-protocol analysis who received half dose or full dose aprotinin that required a take-back to the operating room for diffuse bleeding.

I have said a lot about take-backs to the operating room for diffuse bleeding. Those are associated with a significant morbidity and mortality, and Dr. Levy will be reviewing that for you in his presentation on the overall risk-benefit of the drug.

So to summarize the efficacy data from the U.S. clinical trials as it is reflected in our current product information, aprotinin, both the full and half dose, significantly reduced the percent of patients that are transfused red blood cells, the percent of patients that are transfused platelets. It also significantly reduces the mean units of the various blood products that are transfused and it reduces the take-backs to the operating room.

I would now like to review the safety of aprotinin in CABG procedures. As I stated earlier, I'm

going to be focusing on the 45 randomized clinical trials in the Bayer database looking at the full dose of aprotinin compared to placebo. As one might expect with this being randomized clinical trials, the baseline characteristics and demographics were comparable between the two groups. You can see that in the full dose of aprotinin, we have 2,249 patients. In the placebo group it's 2,164. The mean age across both groups is approximately 61, with about 40 percent of the patients being greater than 65 years of age and 60 percent being less than 65 years of age. Male was the most common gender across the studies accounting for 88 percent of all patients and in countries where we were able to record race, keeping in mind due to regulatory limitations, we are not able to collect that in all countries but when we were able to collect it, Caucasian was the most common race.

For surgical procedures, approximately 80, 82 percent of the procedures were primary CABG, with about 12 percent being in repeat CABG. In our clinical trials, by protocol, some only allowed primary CABG,

some only allowed repeat CABG and in some studies where we allowed both, we collected it on the case report form but in other studies we didn't collect that information so we were not able to further categorize those patients. And that accounts for the remainder of the patients that appear in that not categorized.

I should also point out that although we had both primary and repeat CABG about 50 percent of the population in both treatment groups were in isolated CABG procedure. The other 50 percent had CABG plus another cardiac procedure in combination with it.

Looking at some key medical conditions, obviously, this is not an exhaustive list of the medical histories and baseline medical conditions that we collected that may be pertinent to some of the safety events that we're discussing today. When looking at diabetes mellitus, congestive heart failure, a history of a previous myocardial infarction, a history of a previous stroke, a history of hypertension or an estimated glomerular filtration rate defined as less than 60, the groups were quite comparable. And

I'll give you a moment to absorb those rates.

When overviewing the overall safety of the product, I should say that in our database adverse events were collected and defined as any adverse event that was reported that occurred up to seven days after the initiation of studied drug. Mortality data was collected for the entire period of the study. This includes the entire course of hospitalization and the follow-up period.

I should make note that each protocol did differ in what that follow-up period time was. But as you can see for any adverse event it's comparable between groups at 58.2 percent versus 61.3 percent. For serious adverse events, both groups had 13.3 percent in both groups. Serious adverse events were defined in our protocol as being any event that prolonged the hospitalization, was considered an important medical event or potentially life-threatening. The seriousness of this was determined by each individual investigator at their site observing the patient.

Looking at the mortality rates across the randomized clinical trials, you can see that the mortality rate in the perioperative period is 2.9 percent versus 2.5 percent. To put this in perspective if you look at when the bulk of these studies were conducted, which was between 1989 and 1999, for a comparable time period the STS national database reports a mortality rate of 2.9 percent.

Looking then across various meta-analyses, with some limitations in mind, you can imagine that many of these meta-analyses also include Bayer randomized clinical trials that were published and are included in meta-analyses so there are overlaps. There's also overlaps between the various meta-analyses. Having said, there's not a single meta-analyses here that has a hundred percent overlap with either the Bayer clinical trial or the other meta-analyses so I've chosen just to show them all for completeness sake. You can see that for the various meta-analyses that the reported mortality risk that the risk is either neutral or with one exception in the

case of the Levi meta-analyses there was a statistically significant reduction in mortality favoring a reduction in mortality with aprotinin.

Now moving to myocardial infarction as a safety event, before I do that, I would like to take a moment and give you a historical perspective of the development of these studies. The first study conducted in the United States was D89-004 and at the same timeframe study D89-006 was conducted. Study D89-004 was repeat CABG patients only. It was a single-center study. Study D89-006 included repeat and primary CABG patients and was conducted at five centers in the United States. At the end of D89-004, when evaluating the data, the incidence of myocardial infarction was higher in the full-dose aprotinin group than what it was in placebo and although this difference was not statistically significant, Bayer thought that it still warranted further evaluation and consideration before moving forward with development.

When then looking at the results of D8006 and trying to compare those results with D89-004, we

realized it was quite difficult to do because we had not standardized protocols with the collection of CPK, isoenzymes or with the collection of ECGs. We also did not use a standard definition for myocardial infarction so when you were trying to compare across two studies, it was very difficult to have comparable comparisons in rates even when looking at the placebo.

So from that point forward in our clinical development plan we arranged to have a prospective myocardial infarction evaluation with set collection of CPKs and set collection of ECGs. The criteria for that prospective analysis was defined by Dr. Chaitman who is with us today if we want to get into that. Also, retrospectively, we evaluated those two studies that had already been conducted. Doing that, there still remained a difference, albeit not statistically significant, between full-dose aprotinin and placebo in study D89-004.

We evaluated this further and said what else is different between study D89-004 and study D89-006 and it came down to the anticoagulation

protocol that was used for these studies. Anticoagulation protocol that was used for study D89-004 was to maintain activated clotting time greater than 400, to give additional heparin as needed to keep that greater than 400.

In study D89-006 instead of using ACT, the method that was used, centers could either use a fixed-dose heparin regimen or alternatively they could do a direct heparin assay with the Hepcon machine. Why do I mention this? Right after these two studies were conducted, there was a study published by Dr. Wang. In that study it was found that in the presence of heparin that aprotinin artifactually prolongs celite-activated, activated clotting time.

So with this information it became clear that you need to maintain a higher ACT if you are giving aprotinin in the presence of heparin when you are use a celite ACT. Our current product information reflects the information from this study making a difference between celite ACT and kaolin ACT and maintaining that the kaolin ACT should be greater than

480 and the celite greater than 750. From that point forward in our clinical development program not only did we prospectively evaluate myocardial infarction with a set timeline of collecting ECGs and CPKs and having them independently reviewed but we also ensured that the anticoagulation protocol that was followed was direct heparin assay or fixed-dose heparin.

You have to keep this in mind when reviewing the data for myocardial infarction because as one might expect when you look at myocardial infarction and you look across all studies, all CABG rate of myocardial infarction is 6.4 percent versus 5.5 percent. And although that's not statistically significant, you may say let's look at it a little more carefully. If you divide that between primary and repeat CABG, for primary CABG the rates are 5.3 percent both groups with an odds ratio of .99. Remember, the primary CABG studies were the later studies that were done, that were done with the anticoagulation monitoring. For the repeat CABG study the rates are 14.9 percent versus 8.6. That odds ratio is 1.85. It

is statistically significant but 14 out of those 41 events in the aprotinin group are derived from the one study, D89-004.

So, maybe a better way to look at this would be let's look at those studies that prospectively define myocardial infarction and had adequate anticoagulation to try to sort out what this difference is. When you look at those studies and you look at the central blinded evaluator of myocardial infarction, and this is defined as a definite MI, you can see for the all CABG group that the rates are 4.6 versus 4.7 percent. Looking at primary CABG consistent with the global database it's 3.8 versus 3.9 and when looking at the repeat CABG study it was 11.8 versus 11.9. So in those studies where we had very definite collection of CPK isoenzymes, where we had very set ECG measurements and where we had adequate anticoagulation, aprotinin is not associated with an increased risk of myocardial infarction.

Let's step back for a moment and let's look at all the meta-analyses that are out there, again,

knowing that there is overlap between the Bayer studies and between each of these meta-analyses. I should point out that Sedrakyan meta-analyses is the only meta-analyses that includes CABG-only patients. The other meta-analyses are expanded to all cardiac surgery. And as you can see, there is a neutral effect across all of these studies on the risk of myocardial infarction.

Now I would like to shift gears to graft patency. Reflected in our label is the IMAGE study that was referred to this morning. This is study D92048. In this study the primary endpoint was percent of patients with occluded anastomoses. The primary endpoint was to be for all centers. You can see that with that primary endpoint with all centers there is a statistically significant difference between the full-dose aprotinin and placebo with 15.4 versus 10.9 percent graft occlusions. While the study was still blinded, amendment was placed into the study file saying that we would do a by-center evaluation.

The reason for prompting this was there

were two centers in Israel that were having difficulties with the Hepcon machine that was being used. The way they were dosing heparin versus the way they were reviewing it and seeing the results would have underestimated heparinization. Furthermore, they had technical problems with the calibration of the machines and there were also some questions of surgical technique. With discussions with the FDA while the study still remained blinded, upon the FDA's request we looked at U.S. centers only.

When you look at U.S. centers, the rate is no different between the two groups for percent of patients with occluded vessels, 9.4 versus 9.5 percent. The information for both all centers and U.S. centers is reflected in the product information for Trasylol. Let me take it a step further and say within this study we looked at all centers and we said what is the correlation between graft occlusion and perioperative myocardial infarction or mortality and there was no correlation and there were no differences between mortality or myocardial infarction in this study.

To now go more broadly to all the literature that's out there and available on graft patency and in order to compare cross-studies, I'm going to use saphenous vein graft patency because that is the one most commonly reported across these studies, and I'm going to focus on those studies that used the full dose of aprotinin. And as you can see, in five of the six studies when looking at the results for saphenous vein graft there was no statistically significant differences between the groups. Numerically what I want to make note of is the 92 percent patency versus 82 percent in the Lass study. The only study that was statistically significant was the Alderman study, D92048, also known as the IMAGE study, which is the results that I just shared with you and that are reflected in our label.

I would now like to shift gears to congestive heart failure. We've talked a lot about definitions today and how things were defined. In congestive heart failure the way it was defined by Bayer was very simply as reported as an adverse event.

So if the investigator felt that it was congestive heart failure and recorded it as an adverse event, it was looked at in our database and they used whatever criteria they clinically wanted to use at their facility to classify it. This was not prospectively defined in any of our protocols.

When looking in at the incidence of congestive heart failure, you can see the rates are 6.3 percent versus 5.9 percent with an odds ratio of 1.08, suggesting that there's no statistically significant differences between the groups with the incidence of treatment-emergent congestive heart failure. Bayer's summary on cardiac safety is very simple. Aprotinin was not associated with an increased incidence of myocardial infarction, looking across all CABG patients. In five of the six studies, Aprotinin was not associated with an increased risk of graft closure. In the sixth study, the IMAGE study, there was an increased risk of graft closure across all centers but not for the U.S. centers and aprotinin was not associated with an increased incidence of congestive

heart failure.

I would like to move now to cerebrovascular and cerebrovascular safety. Again, the way these terms were defined is that they were recognized as an adverse event by the investigator and recorded in the case report form as an adverse event. There was no prospectively defined definition for stroke. When we looked at the incidence of stroke for all CABG patients, the rates were 1.1 percent for full-dose aprotinin versus 1.6 percent for placebo with an odds ratio of .8.

When looking across primary and repeat CABG, you also see that the rates are less than 1. And, interestingly, with repeat CABG, although it's the smaller sample size of all the subanalyses, the rate is .7 percent for full-dose aprotinin and 3.1 percent for placebo. And these were the patients that you might expect to be at a higher rate and risk for incidence of stroke in the general patients undergoing CABG surgery. The odds ratio there is .23, and does not reach statistical significance although it is approaching it

in favor of aprotinin.

When looking at encephalopathy, again as reported as an adverse event, and our term of encephalopathy that we use in coma would have been included in this. Looking again at the odds ratios and the rates, you can see these events are rare. They're reported with a comparable rate and all the odds ratios are less than 1. Bayer's conclusions on cerebrovascular safety is that aprotinin was not associated with an creased incidence of either stroke or encephalopathy with the term encephalopathy also including coma.

Now moving to renal function, one of the difficulties perhaps when looking across the literature, and as I am sure you are all very aware, is how one defines renal failure and renal dysfunction across the literature and the various definitions that have been used. Bayer focused on using the definition that we used with the original NDA, which was done with the U.S. clinical trial database, which was a .5 milligram per deciliter change over baseline and serum

creatinine. I'm also going to display for you those changes greater than two milligrams above baseline as it was reflected in the original NDA. In your briefing document we've included those terms that are adverse events that are reported which include renal failure and renal dysfunction terms but we felt that it was more objective to use serum creatinine and to use the original definition we had used in the NDA.

When looking across and looking at serum creatinine elevations, looking at the global database, you can see for full-dose aprotinin 9 percent of patients had elevations greater than .5 milligram per deciliter over baseline compared to 6.6 percent of placebo patients. This odds ratio was 1.41. This is statistically significant. In our current product information we provide a cut of this data of .5 milligram per deciliter over baseline but it's for U.S. studies only and it did not reach statistical significance. Bayer has been in discussions with the FDA about making a change to our product information to reflect this current analysis.

I should also mention, though, when looking at the larger change of two milligram per deciliter over baseline, there are no differences between groups. Furthermore, we went through and did an extensive review of the case report forms manually as well as looking at this electronically to make sure we didn't miss any cases of dialysis that were recorded in the case report forms and we found that the incidence of dialysis was the same between both groups at .3 percent. I should also make note, to put this into perspective for you, during this same timeframe that these studies were conducted, the STS database would have reported a dialysis rate of .5 percent in patients undergoing CABG surgery at that time.

In order to look at the time course of these events and the resolution of serum creatinines, I should point out that serum creatinines per protocol did not need to be followed all the way to resolution. Only if the investigator felt that it was a clinically relevant abnormality were they required to follow this up and most of our studies did not go beyond seven days

for follow-up of labs as required per protocol. So, there are some missing data here but when looking at the time and estimating the return to within 20 percent of baseline creatinine for patients that had any abnormal creatinine above the upper limit of normal, you can see that the median time to resolution is nine days for the full dose of aprotinin cared to six days for the placebo group.

Now, to look at serum creatinine elevations by dose, I should point out that in the studies conducted outside of the U.S., that the most common dosing regimen used was the full-dose regimen. This is also known as the Hammersmith regimen which was first described in London at the Hammersmith Hospital and that is the dose that's more adopted in the clinical trials in Europe.

So we didn't have -- most of the data for the half dose does come from U.S. trials and the numbers aren't quite as large as they are for the full dose. And as you can see in those studies that allowed for both the full dose and the half dose as well as

placebo that 11 percent of patients who received .5 milligram per deciliter over baseline a change in serum creatinine was 11 percent for full-dose aprotinin, 7.8 percent for half-dose aprotinin and 7.9 pieces for placebo. Again, the differences between the groups for greater than two milligram per deciliter over baseline and the patients requiring renal dialysis did not differ.

Dr. Hoyle published an article looking at potential risk factors in patients who were receiving aprotinin and may be at risk for renal dysfunction. In that article he describes patients who received perioperative aminoglycosides, patients with baseline renal dysfunction, possibly even due to diabetes, as well as the use of ACE inhibitors. We looked at all of these risk factors across our global database to look at the risk and how it might compare to the overall population.

When we did this analysis and when looking at perioperative aminoglycoside use, you can see for full-dose aprotinin the rate of a serum creatinine

elevation greater than .5 milligram per deciliter over baseline was 23.4 percent for full-dose aprotinin compared to 11.1 percent of placebo. This odds ratio is statistically significant. Also, we looked at patients who had baseline renal impairment. For the purposes of this analysis, we defined it as an estimated GFR less than 60 millimeters per minute and what we found was that rates were 17.7 percent versus 10.6, and this was also statistically significant.

The differences for diabetes mellitus and ACE inhibitors were not different from the overall population. Based on these findings with aminoglycosides and the estimated GFR we have also proposed to the FDA that we would make a label change reflecting this current, most recent analysis.

To summarize then Bayer's position on the renal safety of our randomized clinical trials, there is an increased incidence of serum creatinine elevations greater than 5 milligram per deciliter that was seen with the full dose of aprotinin relative to placebo. The same finding was not observed with the

half dose of aprotinin. There were no clinically relevant differences in the rates of serum creatinine elevations greater than 2 and there were no differences in the rates of dialysis. These elevations were transient with a median time to resolution being nine days for aprotinin versus six days for placebo. The increased incidence was also more noted with aminoglycosides but not with the preoperative use of an ACE inhibitor and there was an increased incidence in patients who had baseline renal dysfunction defined as an estimated GFR less than 60.

Now I would like to move onto hypersensitivity. I will not be showing you the data from the clinical trial database now but I will be focusing on the spontaneous reports given the rare events of hypersensitivity. As was mentioned by Dr. Robie-Suh this morning, historically when Bayer extended its label to primary CABG it does have a boxed warning in its label now. This is highlighted and it reflects that there is an increased risk of hypersensitivity, that that risk is greater if you have

had known pre-exposure and that if you are treating a primary CABG patient you should weigh the benefit of the drug against the potential risk if the patient needs to be re-exposed in the future.

As reflected in our label, the risk of hypersensitivity and the anaphylaxis is related to this exposure history. For patients who have no known prior exposure, the rate is less than .1 percent. For patients who have been re-exposed, the estimate is 2.7 percent across the entire population; however, if you break that down into re-exposure within six months of the prior exposure versus greater than six months, it's 5 percent for less than six months and .9 percent for greater than six months. This information, as I stated and was shared with you this morning by Dr. Robie-Suh is reflected in the product information for Trasylol.

Moving then to the spontaneous reports, to put it in perspective for you these reports are from January 1st, 1985 to March 31st, 2006. It involves 4.38 million exposures. This is a global database so it does include beyond what was shared with you by the

FDA this morning from within the U.S. As noted by Ms. Lu this morning, we do have 311 hypersensitivity cases that we sent to an independent assessor who assessed 291 as being possibly associated with Trasylol. One thing that I should point out with the information that was shared with you this morning, that where the FDA looked at their database, when there was missing data or there was not enough data, they dismissed the case and didn't count it as related to Trasylol. In this analysis we counted it as being associated with a Trasylol if there was lacking data on the spontaneous cases. So of those 291 reports, 52 of them were fatal.

When looking at this across the indications for which the drug is used, you have to bring this into perspective. Outside of the United States, particularly in Europe, the indication is open heart surgery. So, when you see this, this is not, this is the global database, so, please keep that in mind. And, as you can see, the distribution is mostly within the cardiovascular arena where we know it but there are

cases where the indication was unknown or not the reported.

When looking then at the reports within six months of prior exposure to greater than six months of prior exposure, more cases were reported in the less than six months than in other time periods. As one might expect, with having a drug that has the potential risk for hypersensitivity, a test dose was put in place in order to try to minimize the risk to the patient but as we heard this morning there have been 19 fatalities associated with the reaction after the test dose. There have also been cases where the test dose has been negative and a patient has gone on o to have an anaphylactic reaction.

The information about the risk of the test dose having a hypersensitivity reaction associated with it is reflected in the label as well as the risk of having a negative test and going on to develop anaphylaxis and hypersensitivity. What the spontaneous report data doesn't allow us to assess, though, is how many patients did not necessarily go on to get a full

dose of the drug because they did have a reaction to the test dose. But Bayer acknowledges that we should explore other ways to try to minimize the risk of the patient for being at risk for hypersensitivity.

You heard this morning that we have put in a minimization, risk minimization plan to the FDA. This includes prescriber information with a key message. Number one, this drug is indicated for CABG and because it's indicated for reducing perioperative blood loss and subsequent need for transfusion, it should be used in those patients who are at risk for such blood loss and requiring a blood transfusion. Also education includes the increased risk following re-exposure, especially within six months and they're reminded of the boxed warning in our label. Also they're reminded to obtain a complete medical history and that there are other products that contain aprotinin. There are tissue sealants available commercially in the United States that do contain aprotinin so it's not enough to check for a medical history of Trasylol alone but you must also ask for the

tissue sealant history, and to use the test dose and use it correctly and be reminded that the test dose can be negative and that anaphylaxis can still occur and that you can have anaphylaxis with the test dose and that the patient should be monitored carefully and be prepared to potentially intervene.

In addition to that, Bayer is exploring the possibility of having an aprotinin-specific IgG assay that will allow you to better determine who may be at risk for a hypersensitivity reaction. In the near term, we could have available a laboratory-based assay. That doesn't solve everything because a laboratory-based assay, you do have to ship off a blood sample and you have to wait for the results to come back, so Bayer is also actively pursuing a point-of-care assay that will make the results more readily available.

With the development of this assay, both the lab assay and the point-of-care assay, we have a labeling concept that we have discussed with the FDA that when a test should become available that we would

contraindicate Trasylol in patients who have a detectable aprotinin-specific IgG in order to further minimize the risk of hypersensitivity and anaphylaxis.

So to summarize for what I have shared with you today, aprotinin does provide an important clinical benefit for CABG patients. It reduces the percent of patients that receive red blood cells. It reduces the percent of patients that receive platelets. It reduces the mean number of units of all the blood products. It also reduces the number of patients that receive at least five units of red blood cells and it reduces take-backs to the operating room for diffuse bleeding. We have stated that we have discussed with the FDA proposed labeling changes to reflect the recent renal analyses and findings and we're continuing to develop an IgG assay and propose this to be able to further reduce the risk of hypersensitivity. With these measures in place, Bayer remains convinced that the benefits of aprotinin outweigh the risk and that aprotinin, specifically Trasylol, is a valuable component of an armamentarium for the cardiothoracic

surgeon treating the CABG patient. With that, I would like to turn things over to Dr. Jerrold Levy, who is profess of anesthesiology, director of cardiothoracic anesthesiology and deputy chair of research at Emory University and he'll be discussing the risk-benefit assessment.

DR. HIATT: I think we'll take questions after this, then. We'll continue with the next speaker.

DR. LEVY: Yes. Thank you, a privilege to be here to review the risk-benefit assessment of aprotinin. What I would like to do this afternoon is talk about categories of risks considered, discuss hypersensitivity in the context of perioperative anaphylaxis, discuss renal function and other safety considerations raised in recent observational studies, describe what I believe are some of the important beneficial effects of aprotinin, and then summarize with a risk-benefit assessment.

Hypersensitivity in cardiac surgery is of a particular interest. I've spent the past 25 years

studying perioperative anaphylaxis. And you have to understand that test doses of most agents with a potential for anaphylaxis are often administered primarily in the operating room. The idea of a test dose is to make clinicians think about the potential of an impending anaphylactic reaction in some of the complex, critically ill patients that we deal with. As mentioned I think earlier in the presentation, the hallmark of perioperative anaphylaxis is hypotension.

And it's important to understand that mortality is rare when patients in this particular setting are intubated, they're extensively monitored, they have arterial lines, often pulmonary artery catheters, and the clinicians, both the cardiovascular anesthesiologists as well as the cardiac surgeons are experts at resuscitating these patients.

The other important perspective, to remember that in a critical ill patient with a left main equivalent a tight right coronary with aortic stenosis, with mitral stenosis and concomitant coronary disease, these patients are pretty unstable to start

with and that if you look carefully like I have at some of the perioperative hypotensive events, that some of these are related to the effects of anesthetics and other agents on myocardial depression, vasodilation, above and beyond any type of antigenic exposure and anaphylaxis.

In 23 cases of anaphylaxis reported during cardiac surgery, most reactions occurred before the start of cardiopulmonary bypass. This is a study reported out of Australia. And what they noted was that rapid placement onto cardiopulmonary bypass facilitated a good outcome, all but one operation proceeded and there were no intraop or postoperative death in this patient population. Cardiopulmonary bypass is really lifesaving with acute anaphylaxis because of the severe hypotension in cardiovascular compromise. The other important perspective is that the recommendation that currently has been made when re-exposing patients to aprotinin that the ability to institute urgent cardiopulmonary bypass is established with the patient being in the operating room, patient

prepped and draped and the ability to urgently institute cardiopulmonary bypass.

The other important point as we talk about aprotinin anaphylaxis, it's important to understand aprotinin within the context of multiple agents administered in the operating room, that can indeed cause hypersensitivity. This includes antibiotics, not only cephalosporins, vancomycin and other agents, aminoglycoside, blood, in the multiplicity of antigenic thing that blood exposes a patient to from transfusion-related acute lung injury to an incidence of anaphylaxis to 1 in 600 in the IgA-deficient population. Latex, a ubiquitous environmental antigen, can produce anaphylaxis in certain patient population. For instance, healthcare workers, 10 to 12 percent risk of IgE to Latex as well as people undergoing following multiple procedures. The neuromuscular blocking agents in certain patient population may have a high risk of anaphylaxis with an incidence reported as high as 1 in 1500 to 1 in 2500. And then other proteins besides aprotinin which you have heard about, an agent that's

used in practically every cardiac surgical patient, a drug called protamine, isolated from salmon sperm, a complex protein with a similar molecular weight and charge to aprotinin, has an incidence of anaphylaxis in high-risk patients, specifically the diabetics of 1 to 2 percent, and this is from two large prospective studies I published in the eighties, looking okay at 4,700 patients. An even higher incidence Stewart in Circulation reported in 1984 a 27 percent risk of cross-sensitization.

Furthermore, in the FDA database there's 69 deaths associated with protamine and then there are other environmental and other agents that administered in this particular setting. So again it's important to put aprotinin in context to other agents that can indeed cause perioperative anaphylaxis and other causes of acute cardiovascular compromise in this critically ill patient population.

So, regarding hypersensitivity and aprotinin, hypersensitivity including fatal anaphylaxis with aprotinin is known particularly with re-exposure

within six months because of the high titer of ITG antibodies. It's reflected in the label with a boxed warning and recommendations that have been made when re-exposing a standard emergency treatment should be available including when the test dose is administered and the test dose should be administered intraoperatively with the ability to urgently institute cardiopulmonary bypass. Aprotinin-specific IgG antibody test is expected to reduce risk. It compensates for the uncertain history of prior exposure and it may obviate the need for a test toes.

Looking, though, also further on at some of the meta-analyses of the randomized clinical studies, if you look at four important variables, some of which Dr. Cyrus covered, but mortality, myocardial infarction, renal failure and stroke, if you look at the clinical studies of the randomized clinical trials in CABG surgery there is no greater risk of mortality, MI or renal failure and at least from this data there was a reduction in stroke in these patients.

Regarding benefits of aprotinin from a

clinical perspective, if you look at seven different meta-analyses of randomized clinical trials, one of the consistent findings that is reported with aprotinin, aprotinin limits the reoperation that is going back to the OR a second time for re-exploration for bleeding.

One of the important perspectives is that re-exploration has a significant impact on mortality. Patients who go back to the operating room have a significantly increased mortality compared to patients who don't require re-exploration, and bleeding is part of the major cause for re-exploration. The other important perspective , and it was discussed earlier, is the complex changing landscape of our cardiac surgical patients. Clopidogrel, a ubiquitous cardiovascular drug in all of our patients is an increasing issue that I think has serious consequences. Any patient on Clopidogrel increases blood loss -- multiple studies support that -- increases the need for transfusion reoperation and ICU and hospital stay. If you look at the ACC/AHA and STS guideline, it suggested to stop the Clopidogrel five days before CABG surgery,

we still see emergent patients coming for surgery, patients with very tight multivessel disease with unstable angina, who require urgent surgery despite the use of clopidogrel.

One of the important things is that of all the potential things to consider, one of the important perspectives with clopidogrel is there is data with aprotinin, and this is reported by van der Linden in The Circulation last year, that in the patients who are coming to the operating room, receiving clopidogrel, that the use of aprotinin significantly reduced the need for allogeneic blood transfusion and significantly reduced the need for allogeneic transfusions as well as percentages of patients transfused. And these numbers not only are statistically significant but they're clinically relevant because this includes about one unit of phoresed platelets, which is equivalent to about eight units of single-donor platelets from some of the older literature. So, aprotinin reduces bleeding in clopidogrel-treated patients, an increasing problem in our patient population. Regarding stroke,

if you look at four different meta-analyses of studies, one of the things that is, I think, clear is aprotinin does not increase the risk of stroke and in the Sedrakyan analysis there was a significant reduction in stroke.

So, regarding the beneficial effects of aprotinin based on the randomized clinical trials, aprotinin clearly reduces blood loss in transfusion and CABG surgery. It's also effective in aspirin and Clopidogrel treated patients and it's in the 2005 STS guidelines for antiplatelet therapy and recommended in the STS guidelines for reducing blood transfusion with a class one recommendation.

The lysine analogs, both epsilon-aminocaproic acid and tranexamic acid do not do this. Aprotinin also limits reoperation. Reoperation is known to have significant adverse clinical consequences. We showed you the mortality data. There's cost and other issues. And it is recommended in the STS, the Society of Thoracic Surgical Guideline, to limit reoperation with a Class II recommendation.

Again, the lysine analogs, episilon-aminocaproic acid and tranexamic acid do not do this and it may reduce stroke from the data that I showed you.

So, in conclusion regarding risk-benefit consideration, hypersensitivity reaction and creatinine elevations are known safety events. Bayer is pursuing additional measures to reduce the risk of these events. Beyond reducing blood loss and transfusion, aprotinin reduces re-exploration and may reduce stroke from the randomized clinical studies. And aprotinin I believe is an important therapeutic option for the CABG surgery patient with a favorable risk-benefit profile. Thank you.

DR. HIATT: Thank you. We're next going to discuss this and I think use the microphone over here and just to take the prerogative of the Chair, I would like to maybe begin with an overall comment on reviewing the Bayer background information.

DR. ROZYCKI: And I think I would just introduce Dr. Paul McCarthy, who is the head of the U.S. medical organization who will MC the questions in

this period.

DR. HIATT: Okay. I would just like to make some observations. In your background information you made and introduced the concept that blood transfusions might carry risk, including infection, lung injury, hemolysis, release of bad cytokines, increased risk of stroke, and that there was also a study that suggested that a liberal transfusion policy might be associated with excess mortality. And then Dr. Mangano, at least in his background, suggested that antifibrinolytic therapy might be prothrombotic. And I guess a question that comes up in terms of safety is, do we see any prothrombotic signals in this safety database.

And at least when I reviewed these data, in terms of mortality I counted ten excess events with an odds ratio of 1.09, myocardial infarctions -- and these have all been discussed extensively -- been 24 excess events, about the same odds ratio of nonsignificant though in three studies that were adjudicated by an outside panel, there was odds ratios around one and a

half to two and half, increased heart failure events decreased stroke events. And I'm curious because there are two kinds of strokes obviously and my guess is this is probably reducing the risk of hemorrhagic stroke significantly and maybe in neutral and ischemic stroke but I couldn't tell from the data, and maybe it's impossible to tell.

So, my overall comment about it is that it's clearly effective at reducing blood loss and I also think it's effective at preventing what I would call an event, which is reoperation. And I think that that like an event in the heart failure study would be hospitalization, you know, something that is preventable. But the clinical benefit of reducing transfusion and blood loss in my mind was not as obvious at least in terms of some of these other outcomes.

So, that's kind of my overview of what I was reading in terms of the safety information. It probably truly is neutral on these cardiovascular events and outcomes but the point estimates at least go

a little bit in the wrong direction. So, with that I would like to then open up the Committee for comments, questions, or any rebuttal from Bayer.

DR. McCARTHY: I would like to ask Dr. Cyrus from our medical department to comment.

DR. CYRUS: First I would like to speak to, mechanistically -- if I could have the slide on, please -- why aprotinin can be hemostatic and not prothrombotic. You know, during the bypass surgery there's a complex amount of things that happen. The first thing that happens is the, with the contact with the bypass machine, you have thrombin generation, and this is, leads to clotting and obviously this is why heparin is used.

Aprotinin actually inhibits the initiation of the thrombin generation and inhibits its amplification. It also works by a platelet effect where it inhibits the pathological impact of the bypass machine but still allows for the normal hemostatic platelet function. It also inhibits free plasmin but not bound plasmin so basically you are inhibiting the

pathologic but not the physiologic fibrinolysis. So overall what you're doing is you're restoring the normal hemostatic balance that was disrupted by the bypass machine. So mechanistically this is how you could be hemostatic but not prothrombic. If I could I have the next slide, please.

We did a search where we looked arterial or and venous thromboembolic events as reported by the investigator, knowing that, you know, you were pretty close with your hand tabulations, I have to say, but looking at this, if you looked across any arterial or in any venous, the event rate was 7.9 versus 7.6 percent with odds ratio of 1.05. And I should make note this is including all studies including those that may have not have had adequate anticoagulation.

DR. HIATT: Thank you. And, you know, I think these are just issues for consideration around a safety database that wasn't fully adjudicated. The studies weren't decided to test the hypothesis that this drug would reduce short-term mortality or cardiovascular events and that was clearly spelled out

in the background information as well. But I also point out to the Committee that at least in the sponsor's data there were 120 deaths -- it's a reasonable number of events -- 242 myocardial infarctions. So, I think we have a reasonable confidence around these point estimates. So, we'll open up discuss starting down at this end.

DR. PAGANINI: I have a couple questions on various presentations. I guess the first thing would be the definition of dialysis. Is that any intervention or is dialysis there for solute as well as volume? Do you have a clear definition of that? Anytime somebody is hooked up on a machine is dialysis, is that the definition?

DR. McCARTHY: No. It's, the definition was dialysis was undertaken in patients who had clear renal failure with creatinine elevations that were markedly elevated. It wasn't a definition for just fluid removal.

DR. PAGANINI: Thank you. The second question I would have is the cause and effect or a

marker difference. When we use surrogates for outcomes, frequently we will look at how the effect is on the surrogate and assume that if the surrogate gets better, the outcome gets better. Here you've shown an improvement in blood use, a decrease in blood loss and yet -- and a decrease in reoperation, yet there's no improvement in outcome. Could you explain that for me?

DR. HIATT: And that's kind of where I was going, too. I think if the concept of reducing blood exposure should have a lot of clinical benefit, I didn't see it.

DR. McCARTHY: Yeah. I think, you know, the studies that were undertaken were clearly not designed to look at a mortality effect and, you know, the duration of follow-up was basically short-term while they were in hospital, so, and I think also the studies weren't powered to, really to detect or show a mortality difference.

DR. PAGANINI: If I can, Mr. Chairman, and continue here. The third is the encephalopathies and the strokes. Those were primary, those were

investigator defined and not defined initially and yet one of your outcomes is an improvement in stroke. That seems inconsistent if you don't have a clear definition initially and then you have the investigator define what it is and then you use that as an outcome. It's just a comment.

A question I would have is in your slide number C54 you have a difference in your numbers with regards to dialysis versus the rest of the issues, you know, less than five, greater than five or two milligram percent differences. Your denominator here tends to be somewhere between 23 and 33 patient differences. Why is that? Why is it that you have a total group of 335 but when you go to dialysis it's 361, which would in fact decrease the incidence of dialytic intervention when you increase your denominator and that's true across the board. Is that an error or is that just a mis --

DR. CYRUS: No, that's actually true. Not every patient may have had a baseline serum creatinine, so if they didn't have a baseline seater serum

creatinine, there was nothing to compare creatinines to. So for example in the full-dose aprotinin group, 335 had baseline serum creatinines. When looking at dialysis that would include the entire patient population regardless of whether they had baseline serum creatinines and anyone who had an adverse event of renal failure or renal dysfunction would have also had all CRFs, case report forms checked for dialysis. So that's why that denominator does differ.

DR. PAGANINI: Thank you. I'm done.

DR. FLACK: A couple questions. Why was the trial data for hypersensitivity not looked at? Because, one of the things I was actually curious about had to do with, are the anaphylactic reactions after you get a test dose different from that after you get more full-dose therapy?

DR. CYRUS: We did look at the clinical trial data but as one might expect, because this development was done when patient may not have had an opportunity have ever had prior aprotinin exposure, the bulk of these patients obviously had no prior exposure.

What we did is we applied the same criteria that was applied to the spontaneous database for doing a broad search for hypersensitivity. We did that on the clinical trial database across all of the patients. And I should mention that we didn't just do this for CABG because obviously hypersensitivity could be for anything so we did it across the entire open heart surgery database, all studies regardless of whether they were controlled or post-marketing observational studies and all indications including some orthopedic data that we had and across 12,484 patients that are in our overall clinical trial experience, we identified 24 cases that flagged out with hypersensitivity.

We then pulled each of those case report forms to seek out additional information on those cases and clearly some of them occurred while the patient was well out of the OR and even, you know, post-op day two and it clearly wasn't a temporal relationship, where they had a clear alternate explanation assigned by the investigator, such as hypersensitivity to protamine, hypersensitivity to an antibiotic. For those where we

could not exclude a clear alternative explanation and temporally you could not exclude aprotinin, we were left with a rate of .1 percent across the clinical trial, which, that we could not absolutely exclude, which would be consistent with the no prior exposure experience.

DR. FLACK: But, again, the question is, do people who get it after a test dose have, is it a different expression clinically, more serious, less serious, than those who get it after full dosing?

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

DR. LEVY: The test dose basically is still a significant number of molecules and it's really, is there a less of a response to the test dose versus a full dose? Theoretically there may be and that's also potentially some of the idea of a test dose, for instance, ten million versus two million in the full load. So, the idea is one, to remind clinicians and two, a smaller potential antigenic load, although even in skin testing you can still get hypersensitivity.

DR. FLACK: It's fair to say you probably don't really know?

DR. LEVY: Exactly.

DR. FLACK: Okay.

DR. LEVY: Thank you.

DR. FLACK: All right. The other question I had is, when you do get a positive test dose, positive reaction to the test does, is there ever any thought, do people just automatically not use it or do they try to pretreat them with steroids, Benadryl and things like that, they think the risk really warrants it?

DR. LEVY: Good question. First thing, the HIH2 blocker corticosteroids really kind of came into the labeling from Europe where they use a lot of gelatins and other things that have a high risk of hypersensitivity and that's where the concept occurs. Pretreatment for anaphylaxis has never really been established, probably from the contrast media literature which is not, that's not anaphylaxis, not antibody-mediated. The second question, sorry, about

the subsequent --

DR. FLACK: Yeah. Do people ever get a positive test dose-response and then still try to move on with some --

DR. LEVY: If they have a reaction to test dose, then it's stopped. The other thing what also is done is that the dose in the cardiopulmonary bypass reservoir is not put in until after the test dose and the loading dose has been successfully administered because of the resuscitative capability of that.

DR. HARRINGTON: I'm going to try to understand the graft occlusion and the MI a little bit further. So first on the graft occlusion, were these, in these particular studies, what was actually the rate of the angiographic follow-up and was it the same between the treatment groups, between placebo and aprotinin? And then while you're thinking about that one, were all these films read in a core laboratory, an angiographic core laboratory and were they the same core laboratory or are these different core laboratories across the different studies?

DR. McCARTHY: It was the same for the large study that was shown -- it's in our label -- was run out of Dr. Alderman's laboratory in California. So, they were all read centrally.

DR. HARRINGTON: What about the other five studies that comment on graft observations?

DR. CYRUS: These five studies are from the literature. I'll try to remember them off the top of my head. The Havel study with a single-center study so it was done at that institution. The Kalangos was also a single-center. I believe the Bidstrup was as well. The lass study and the Limmer study were, the Ultra-Fast or CT was read centrally as well. And I'm not sure about the last study, the Lass study.

DR. HARRINGTON: But, so it would be a fair statement that the one that showed the difference was the one really that prospectively set out to use a core laboratory, et cetera.

DR. McCARTHY: Yes.

DR. HARRINGTON: On the MI front, the MIs are defined as definite, definite, definite or

probable, definite, probable or possible. Can you help me with, how was MI defined in these and how they ended up in those various categories?

DR. McCARTHY: I would like to call on Dr. Chaitman to respond, who was the central reader.

DR. CHAITMAN: Can you show the slide, please? The three categories -- show the slide. The three categories that we decided on are shown on this slide, definite MI, used ECG criteria or autopsy evidence of myocardial necrosis but not an enzyme marker. It was an electrocardiographic diagnosis. Recall, this is studies that were done 13 years ago. And the second definition, probable, included cardiac enzymes with a CKMB level of 120 units per liter or an abnormal profile where the CKMB exceeded 100 but there was also Q-wave worsening according to the Minnesota Code, and possible MI was an abnormal cardiac enzyme profile where the CKMB exceed 100 unit. If the patient had none of these, then this was absence of these criteria.

And so in the IMAGE trial, which is in your

briefing document, where these data were collected prospectively, we present the data for definite, probable and possible MI and the rates are similar regardless of which definition you use. I should mention also that we used ECG criteria but we didn't use ST or T-wave changes because in a prior publication that we had published looking at the prognostic value of T-wave changes after coronary bypass surgery, about 40 percent of patients have T-wave abnormalities, and the five year prognosis, whether you have them or you don't have them is virtually identical in the absence of enzyme markers. You just have T-wave changes.

DR. HARRINGTON: So Bernie, how did these make it to your attention, did you, did cases get sent to you that the investigators indicate is a possible myocardial infarction or was there some sort of systematic screening of the database looking for abnormalities in either EKGs or enzymes?

DR. CHAITMAN: Yes. The data is going to be shown on this slide. Can we show the slide? The blinded review, we were blinded of course to treatment

assignment so we received the ECG's of all the patients before surgery and then afterwards at three, five and seven days or hospital discharge as well. We had the enzyme data that you see on the slide, case report forms, clinical summary or any other applicable information that would relate to the potential diagnosis of infarction including autopsy reports when they were rarely available. So this was, in this particular series of studies these were prospectively collected.

DR. HARRINGTON: So this information, though, I guess my question is, it was collected but how was it identified, was it, were the enzymes systematic looked at?

DR. McCARTHY: All patients. All patients.

DR. HARRINGTON: You saw every single patient?

DR. CHAITMAN: Yes, absolutely. Yes, absolutely.

DR. PORTMAN: I have a point of clarification. Granted that renal failure based on

creatinine is less than optimal but I think we can all agree that with aprotinin renal failure is certainly a risk factor preoperatively, so are an aminoglycosides, may be contrast agents, though, that we didn't discussed that. But there's some confusion about the use of ACE inhibitors and nothing really mentioned at all about ARBs. And certainty since these studies have been done, their ACE inhibitor use is prevalent and so are ARBs. The study by Gillespie and Kincaid in the briefing documents suggest that ACE inhibitors are a risk factor whereas the global database suggests that it's not. So the question I have is, can you clarify the risk of ACE inhibitors with aprotinin use for renal failure?

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

DR. CYRUS: First the, I guess to answer the question about the angiotensin II, many of those drugs were not approved at the time that these clinical trials were done so we don't have data on that but certainly we have it on the ACE inhibitors. Can I have

the slide, please? And, as you can see, we have about 347 patients in the full-dose aprotinin and 323 patients in placebo that were receiving a preoperative ACE inhibitor use and the rates of serum creatinine elevations greater than .5 were 11.5 percent versus 11.1 percent with an odds ratio of 1.05. So, clearly at least within our database there did not appear to be an increased risk of preoperative ACE inhibitor use in serum creatinine elevations.

DR. PORTMAN: We don't know anything about dosing with those ACE inhibitors?

DR. CYRUS: No. We don't have that information.

DR. PORTMAN: Okay. One last question. It's mentioned in the briefing document that there is a, there may be a competitive inhibition between aprotinin and creatinine for secretion in the proximal tubule which might be responsible in some part for an increase in serum creatinine levels. Is that, is that in fact the case?

DR. McCARTHY: I would like to call on Dr.

Whelton to respond.

DR. WHELTON: Thank you, Dr. McCarthy, Andrew Whelton from just up the road in Baltimore. I guess the fist issue to my mind, does this signal emerge, is to say is this biologically plausible, and it does lead directly into your question because I should share with the Committee that what we now know as solid factual data of the mechanism of toxicity is of course based on preclinical animal data. And if you just bear with me for a moment, following in your mind's eye, a molecule of aprotinin as it goes through the systemic circulation, into the renal circulation, afferent arteriole and then lands at the surface of the capillary loops in the glomerula, the molecular size, about 5,000 DOLT and so it passes quite readily, then of course would enter into the intraluminal space of the proximal tubule.

And, as it is transversing there, it binds to the hairy brush border of the proximal tubular cells. Now, we do know from the animal data that it looks like following binding to the cell wall, it is

engulfed in an endocytotic or pinocytotic vesicle and goes right into the lysosomes. We know physically the lysosomes increase in size. So that appears to be the dominant side of action. So it tells us one, why the drug accumulates within the kidney. It may well be that a small amount will leak out through the destabilized membrane of the lysosome into the cytosole and have additional effects. The gist of it is without ever doing a clinical study, you could then predict, wow, this looks exactly like the mechanism of aminoglycoside toxicity; hence, we should with reasonable assurance see an interaction there and indeed we do.

On the other hand, the ACE inhibitors and the ARBs are going to have an effect dominantly on efferent arteriolar tone. There may be some feedback mechanism for an afferent effect but you would say it is less likely you would have to do the studies. It is interesting as I also looked at the Kincaid data that the numbers are not dissimilar to what are available in the prospective database. And, interestingly in the

Kincaid report, which is very interesting, there's an overlap.

About 60 percent of those who were on ACE may well have had diabetes as the reason for being on it and hence it's unclear if it was underlying diabetic nephropathy. But I think I would go with the prospective data and say that it doesn't look like there is, if there is an interaction, it's got to be small. But other drugs, Cisplatin and amphotericin, I think were we to study them, we would probably see, yes, a mild interaction. And again I'd emphasize this looks like mild, transient and we've got a good explanation for it.

DR. WARNER-STEVENSON: I have two related questions. I'm clinically quite impressed by the serious impact of transfusions and reoperation in the crucial postoperative period. I think the impact of that probably takes quite awhile to see but I am surprised that we don't find some trend towards fewer hospital days, shorter time intubated, something that would relate to these two. That's my first question.

Is there anything that might give us a trend from the data, even if it's not strong, that there is an overall improvement in how people do?

DR. CYRUS: When we collected the data for the clinical trials, we did collect length of hospital stay. Unfortunately it was collected in a very general fashion. It became, it wasn't a primary endpoint and was very difficult to analyze. There was a trend towards decreased hospital stay albeit not statistically significant associated with aprotinin.

DR. WARNER-STEVENSON: And then I have one other related question. I'm interested in the STS guidelines. Certainly in general clinical guidelines represent a lot of thoughtful input that integrates both the trial data and expert clinical opinion. And, I am interested in the guideline which says that it's status 2A for patients who have received aspirin, which makes me assume it's not listed for people who have not received aspirin. And then I am curious about the later guideline from 2006 which indicates it's a level one but that's a guideline for blood conservation. And

I just wondered if any of the surgeons could clarify exactly the status of these recommendations for the general patient or the high-risk patient undergoing surgery.

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

DR. SMITH: She doesn't know, okay. You can put that up. Thank you. This is Peter Smith. I'm chief of thoracic surgery at Duke University and I'm here on behalf of Bayer. The STS guidelines, there are several guidelines that have been promulgated. This one is the one related to aspirin-treated patients citing level A and B evidence that aprotinin limits bleeding in these patients and it has a good safety profile. And it has this 2A recommendation, which means that the preponderance of evidence is on the side of aprotinin being effective in the high-risk patients who are aspirin-treated. The, they caution that this is not extrapolated from the lysine analogs that you can see in 2B recommendation, class 2B evidence rather which is the majority of the information shows that

they're not effective in that, in this setting.

The current state -- I think we have another slide of the STS, the draft ones, yeah. If you could put this one up. The STS has been developing blood conservation guidelines that are now in draft form and have been circulated on the Web site and have been to my understanding approved by SCA, Society of Cardiovascular Anesthesiology as well, with these recommendations. And these recommendations were developed subsequent to the publication in the New England Journal of Medicine that was discussed today. And, the class one recommendation for full-dose aprotinin level A evidence reducing blood transfusion persists; 2B recommendation for half dose and full dose, aprotinin reducing reoperative rate, so that is return to the operating room for bleeding has a 2A recommendation based on the A and B type of evidence. Those guidelines, I expect that they will be published shortly but I am not on the workforce and I have no independent information of their status other than I have seen the guidelines be circulated.

DR. HENNESSY: I had two questions, one in the background material that we got from FDA based on the randomized trials available through 1993, I believe, it was, quotes a rate of renal failure for aprotinin-treated patients at 3 percent versus 1 percent for placebo-treated patients and we haven't seen any data in Bayer's presentation that reflects those numbers and I was wondering what the discrepancy was.

DR. CYRUS: That information is based on adverse event reporting so it would have been renal failure as listed as an investigator term as an adverse event. We chose to present data based on the more subjective creatinine change -- objective, excuse me. The more subjective findings of renal dysfunction and renal failure are in the briefing document as adverse events where we did use broad definitions.

DR. HENNESSY: Thanks. So my second question is although the utility of a test dose seems intuitive and seems obvious, lots of things that seem intuitive and obvious when you study them turn out not

to be. And has the utility of a test dose ever been studied and is there any consideration that that should be done?

DR. McCARTHY: I would like to call on Dr. Adkinson first.

DR. ADKINSON: Good afternoon. My name is Franklin Adkinson. I'm a professor of allergy and immunology up the road at Johns Hopkins and I have spent a good bit of my professional career being interested in doing research in immunologic drug reactions.

I don't know the history in the case of aprotinin but I suspect that the 1-CC challenge dose was adopted by transfer from the practice for radio-contrast media, which for many years included a 1-CC challenge dose or test dose prior to the administration of RCM. We now know that that was a very unhelpful screening device in the sense that the vast majority of contrast media reactions are not predicted by such a test dose. Nevertheless, the test dose I think remains useful in drugs like aprotinin,

where we are administering a known allergen, that is a foreign protein, to patients who can develop and will in a predictable fashion develop some degree of immunologic sensitivity to it if repeatedly exposed to it.

And, it makes sense from an allergic point of view to give a smaller dose rather than a larger dose to someone who may have a hypersensitivity state with regard to that material because contrary to what many textbooks used to say, we now believe that allergic reactions like almost every other biologic reaction are dose-related and higher doses impose significant risks.

So, using a 1-CC challenge dose as an incremental challenge or a way of incrementally introducing a potentially allergenic material to someone who may or may not be sensitive makes sense from the point of view of the mechanism of the reaction that's trying to be prevented and it makes sense from the I think presumed and I believe well established experimental models, dose-response relationship between

exposure and allergic reactions, particularly fatal anaphylaxis. But to answer your question directly, no. As far as I'm aware this was not, this practice was not derived from any direct test or clinical evaluation of the value of the test dose.

DR. HECKBERT: Yes, I have another question about allergic reaction, hypersensitivity reactions. We had in our circulated materials some information about the use of IgG as a test. Can you comment on, what is the extent of knowledge about the use, utility of the IgG level to screen for the risk of hypersensitivity?

DR. McCARTHY: Yeah, I would like to call on Dr. Heller from Bayer to respond.

DR. HELLER: Some of this information, as it happens, I think the panel may have in the review by Beerline, et al, which was in the FDA's briefing document, and, I think a number of salient points. That review recommends, at least my read of that review recommends consideration of IgG as a useful clinical marker. Now, in that review there's a table that

summarizes data which were primarily from two sources. One is a paper by Professor Dietrich, who is actually with us today, which characterizes a series of patients who, all of whom had, were re-exposed, had had prior exposures to aprotinin and were examined for their IgG status, that is, whether or not they had detectable IgG and were then exposed to aprotinin and the outcomes were recorded.

In addition, there's another series in the literature by Shiwala, and I can refer you to the table in that publication. I can, actually I have the slide here which is very similar so let's show that slide since we're talking about numbers. In terms of the publication by Professor Dietrich, 117 patients, 121 exposures, the IgG status was, preoperatively was determined and was positive for 18 out of those 121 exposures. There were among those cases -- and I remind you all of these were re-exposures -- there were three cases of anaphylaxis. The second paper, Shiwala's paper, he looked at 448 cases, preoperative IgG status, and here in both cases we're talking about

detectable IgG, 15 were positive. There was one case of anaphylaxis. And the point that is made, I think in the Beerline review, and we have captured that on that portion of the table on this slide, is that the negative predictability, that is, the confidence interval around the absence of a reaction in the presence of a negative IgG is highlighted in the paper. Now, I think it's probably inescapable to note that in this series there are, the sensitivity was 100 percent, that is, all four cases were recognized but it has to be allowed that that is not a large number. So, I will, I think those are probably the most pertinent data and I will, well, I was going to ask a follow-up question but perhaps Dr. Adkinson should comment further.

DR. ADKINSON: This is obviously not a large dataset on a proposed screening test and I think one has to go to analogous situations with other foreign proteins administered to man and a belief that the large majority of these anaphylactic reactions and particularly those that are fatal have an immunologic

mechanism for which this would be a reasonable surrogate marker. Many of you are aware that anaphylaxis is commonly attributed to IgE antibody rather than IgG antibody and yet IgE antibody is difficult to measure in vitro especially in the presence of larger quantities of IgG. And other studies with foreign proteins in human administration show quite clearly I think that IgE antibody responses do not occur except in the presence of IgG responses. So that all patients who make IgE will make IgG as well and therefore should be detectable by this aprotinin-specific IgG assay.

The important property of this test I think in terms of predicting serious and potentially fatal allergic reactions is the expected very high negative predicted value, that is, insofar as all of these reactions are immunologically mediated, my expectation would be that they would be easily identified by this IgG assay. The price to be paid for that is that some patients, an appreciable number of patients will have clinically false positive results in the sense that

they will have IgG antibody but will not be at risk of the systemic allergic reaction and hence will be denied treatment that they otherwise may benefit from. But given the desire to prevent these fatal reactions, it seems to me that the risk-benefit assessment of those two properties at this point in time with this limited amount of data would favor precluding the use of the product in patients who have made an immunologic response in the past, even at the expense of perhaps denying some patients treatment who otherwise might be able to receive it safely.

DR. HIATT: And just while you're up there, I mean, maybe it's more directed to the sponsor but we do have to wrestle with this issue. And what is Bayer's plan; in other words, what would your algorithm be, screen everybody who has received aprotinin previously and if they have a positive IgG antibody you would exclude them?

DR. McCARTHY: No. Our recommendation, and we are in preliminary discussions with the FDA in this regard, is to screen everybody undergoing CABG surgery

who are prospective candidates for the drug and to contraindicate if the test is positive. And we would like to move forward with the introduction of the test into the marketplace as soon as we can.

DR. HIATT: So your proposal then would be any test positive would be excluded?

DR. McCARTHY: Correct.

DR. HIATT: And what would be the overall population prevalence of a positive test in this population, do you have any idea?

DR. McCARTHY: In this population, I don't know if you want to comment, Alan, but I do know in the re-exposure patients it gets as high as about somewhere between 40 to 50 percent.

DR. HIATT: Okay.

DR. McCARTHY: Yeah, and that's in patients who have previously exposed to aprotinin.

DR. HIATT: Right. And I know that's a clinical risk factor --

DR. McCARTHY: Sorry?

DR. HIATT: We already know that that

re-exposure --

DR. McCARTHY: Yeah.

DR. HIATT: -- is a clinical risk factor --

DR. McCARTHY: Yeah.

DR. HIATT: -- within six months. And then the population, that that, I mean that hasn't been previously exposed?

DR. McCARTHY: Yeah. I call on Dr. Heller to respond to that.

DR. HELLER: Yeah, a quick clarification. In terms of patients who were exposed there is a dataset that suggests that if you look at detectable IgG within six months and six months to one year, you will find detectable IgG in 40 to 50 percent of the cases. It is also clear that, provided there's no additional re-exposure, that the IgG falls and becomes undetectable. And perhaps the best series is a series again by Professor Dietrich, who looked at 80 patients who were known re-exposures after a year and found, reported in his paper one case of positive detectable IgG. So, so that's that, yeah, that's, that shows the

data from Professor Dietrich.

The other relevant data is in a paper by Shiwala who examined several hundred patients who either gave no, well, all of whom in terms of the patients we're talking about, these patients had no history of exposure. Some had a history of surgical procedures but no history of exposure and he found a background incidence in patients for whom there was no documented exposure of approximately 4 percent. Another point that I think is relevant -- and Dr. Adkinson could perhaps respond further on this -- is that to our understanding if you are positive for IgG and with time that IgG becomes no longer detectable, it is as if you had not developed the IgG.

DR. HIATT: All right. So, just to clarify the sponsor's position for the Committee to understand then, that your discussion with the FDA would lead to a screening test in all patients who might be treated with aprotinin and that if there is a positive IgG titer -- and we haven't learned what the definition of positivity is -- that you would exclude them?

DR. McCARTHY: Yeah. Positivity is a detectable IgG.

DR. HIATT: It is detectable?

DR. McCARTHY: Right.

DR. HIATT: All right. And that's your position?

DR. McCARTHY: Correct. Keep in mind, though, that we did talk about two potential assays, the laboratory-based assay and the point-of-care assay. We're further along with the lab-based assay, so, patients who are undergoing emergency surgery wouldn't really have that option until the point-of-care test is, becomes available.

DR. HIATT: So there would have to be other obviously clinical predictors which we're not aware of --

DR. McCARTHY: Correct. Correct.

DR. HIATT: -- that might make them high risk?

DR. McCARTHY: Yeah.

DR. HIATT: Okay. Yes. You're next.

DR. LINCOFF: I wanted to go back to the issue of myocardial infarction. And I understand the limitations in the analysis that was presented but on, so on your slides, C38 and C39, which talk about the incidence of the adjudicated myocardial infarction in the initial trials, 89004 and 89006 and then the subsequent trials where they were prospectively defined, it's reassuring on C39 that the repeat CABG did not show a difference in myocardial infarction rates once there had been the changes in practice with the anticoagulation but you have to recognize that's only 135 patients. And so it seems like the entire database that we have in the reassuring set is very small, whereas in the previous study you had 521 patients, recognizing that that was the group, in which you didn't have the uniform policy for the anticoagulation. That's a nice theory and it does make sense but do you have any sort of supportive data in terms of total heparin doses or anything that would reassure us that patients undergoing repeat bypass, I mean, there is, there is theoretical and

pathophysiologic reason to believe those patients might be more at risk for thrombosis and myocardial infarction.

So, and so those being the group that had the higher rate of infarction in the first set of trials is not completely ameliorated or the concern is not completely ameliorated by the second set of a rather small number. So, do you have any additional data that might help us feel reassured that there isn't an access risk of myocardial in repeat bypass.

DR. CYRUS: I guess it's a two-part question in the way I'm viewing it. The first part as far as the additional data in repeat CABG patients, recall that historically repeat CABG was the initial approval and in Europe the approval did precede the approval in the U.S., so most of the repeat CABG development had already been done. You can say, well, why didn't they see this in Europe but, you know, Dr. Royston is sitting here with us and his policy at his institution was to maintain the ACTs at a higher rate than what they were being maintained in the U.S., so

the interaction with the celite ACT may not have been picked up in the European trials that were part of the early development.

And as to why we believe this was the case for study, D89-004, there is a, despite the fact that the bypass time was the same for both groups and if the bypass type is the same, you might use that as a surrogate for the heparin dose, there was a statistically significant difference between the full and the half dose of aprotinin versus placebo and the total amount of heparin given, with less heparin being given to the aprotinin-treated group as opposed to the placebo-treated group. Then if you look at ACT and you look at the Wang data, which would suggest that where you start running into trouble when you are using the celite ACT is at the 90 minutes of bypass time, and you look at that same correlation with study D89-004, that was at a time when their ACT was still above that 400, which was the cutoff that the site was using for their anticoagulation and there were statistically significant differences in the ACTs, so we're using

that as the marker.

DR. KASKEL: I would like to get back to the measurement of renal function for a minute. Knowing the difficulties using creatinine, serum creatinine and creatinine clearances in estimating kidney function, I wonder if it would be useful to think about a pilot study using some more exact measurements of kidney function. There are other methods available. Iothalamate clearance is being used now in an NIH-funded trial. There are exact measurements that one could possibly do on a small subcohort of patients control and treated group just to see once and for all if you can decipher any effect on kidney function as well as outcome data.

DR. JEEVANANDAM: I have a couple of questions. Referring to your slide, C45, which is incidence of congestive heart failure, if you look at the full dose of the aprotinin group, there is a higher incidence at 14.1 as opposed to 11 with an odds ratio of 1.33. Is that statistically significant? It seems like there are certain numbers --

DR. McCarthy: No.

DR. CYRUS: No.

DR. JEEVANANDAM: They're not significant. The other question I had is, I know aprotinin has been looked at in other randomized blinded trials, specifically valve trials where there was -- and could you comment on other trials other than CABG trials where there might have been an effect on renal function? Because, you know, a lot of the questions we had in our first presentation by Dr. Mangano was perhaps concomitant procedures with higher incidence of renal dysfunction. So, do you have other trials other than just CABG trials looking at renal function?

DR. CYRUS: First the data that I shared with you, about 50 percent of those patients had an isolated CABG procedure. The other 50 percent did have a CABG-plus procedure so there is some of that in there. Probably the most recent study where you could just remove the effect of bypass totally is a study that was just conducted by Bayer in hip surgery. So if you remove, forget the bypass effect on the kidneys and

let's look at a patient population that may not be at increased risk for changes in creatinine and there were no differences between the groups in that patient population. Can we have a slide on? Here's the data for that, that study, just to sort of suggest that in a patient population who was not at risk for renal dysfunction that aprotinin did not have an effect.

DR. JEEVANANDAM: I have another question here. In your IMAGE trial you had an overall higher incidence of graft thrombosis and then if you looked at the U.S. sites that difference went away. You specifically said that there were two sites in Israel that had a higher incidence of graft thrombosis. If you just took out the Israel sites but kept the other foreign sites in, did it make a difference or was it only those two specific sites that were the difference in that study?

DR. CYRUS: Just to be clear, there are only three sites that were outside the U.S. Two were in Israel and one was in Denmark. The analysis has not been done, leaving the Denmark center in.

DR. JEEVANANDAM: And my final question is on anaphylaxis. You know, being a cardiac surgeon we deal with this all the time, so, if we have a reoperative case, I will not have them even give the test dose of aprotinin until I know I have access to being able to go on bypass, whether it's an aortic access or a venous access or both. And when we, if we do have anaphylaxis after the test dose, or usually it occurs during the loading dose, obviously we can go on pump and manage hypotension. I saw some of your more mortality statistics with anaphylaxis. Were those mortalities on patients not going on bypass or, you know, such as hip operations where I think it would be a much more of a problem if somebody had anaphylaxis during a hip and you're not going to plan on going on bypass or the ability to go on bypass, those patients might have a higher fatality rate than patients who have bypass as a --

DR. McCARTHY: Obviously not all the cases were in the setting of cardiac surgery. And we would agree with you and that's part of our risk minimization

plan, is to really get the message out that since the drug can cause anaphylaxis and particularly in, you know, obviously with the test dose that's been seen as well, that it is really important to educate physicians who are using the drug as to how best to manage anaphylaxis should it occur.

I think we have some examples where test dose has been given in the induction room setting and, you know, in discussions with our experts and cardiovascular anesthesiologists, the real emphasis is that the test dose should really open be applied when the patient is intubated and the bypass, can go on bypass in the event of an anaphylactic reaction.

DR. HIATT: I'd just like to remind the Committee we have more ground to cover. We have an open public forum with three speakers and then we have to discuss some things. So, maybe if we take a few more burning questions.

DR. ELLIS: The discussion of the hips raises the question for me, particularly with regard to the hypersensitivity. This morning, we saw an

increased use of the drug in maybe 250,000 uses a year in the U.S., which suggests that, you know, a high percentage of patients receiving cardiac surgery receiving the drug. I'm wondering if you can comment about, if you know about percentage use that's on-label in the U.S., off-label cardiac surgery in the U.S., and noncardiac surgery in the U.S.

DR. McCARTHY: Yeah, approximately between 60 and 65 percent of the use of the drug is in CABG surgery, either CABG surgery alone or CABG surgery with, in combination with, say, a valve. And the others, remaining 30, an additional 30 or 35 percent that then is in, in other types of cardiac surgical procedures and then there's about 5 to 10 percent where it's used in other situations such as pediatrics. It's also used in liver transplant surgery to some extent.

DR. HECKBERT: Yes, I have a question about your global database, clinical trial database. I think it includes something over 4,000 patients. It looks to me like the U.S. studies in that database from your slide C37, most of them are from the early nineties and

they would reflect the kind of patient that would present and might be considered for clinical trial in those days. Is it, do you have -- and you don't have anything beyond the early nineties in the United States in that database. What about from other countries, are we seeing the kind of patients that now go for CABG? Do we have data in your global database from more contemporary types of patients? And the other thing to point out is that at least in the U.S. the more recent trials tended to be primary CABG, so, even less serious.

DR. CYRUS: Yeah, the bulk of our clinical trial experience that I shared with you in the safety database was between the late eighties and late nineties. There were a few studies that went to 2001. We do not have randomized clinical trials beyond 2001 in the database that I shared with you today. I would like to call on Peter Smith to maybe talk about the type of patients he's seen and how this data could be extrapolated.

DR. SMITH: Thank you. I think, I would

like to show you a slide from STS data that I got together actually for some discussions we had recently with CMS, because you've remarked that the incidence of the use of this drug has gone up and why. And the patients are different than the patients who are studied in the randomized trials, of course. Some of those differences have already been pointed out.

But, I can also indicate that since the randomized trials had a pretty high percentage of reoperations in them, there were many patients who were studied in the randomized trials who were every bit as risky for bleeding as we see today. These are data the STS database comparing 1995 to '99 to a more recent period, 2000 to 2003. Isolated coronary patients, you see we're looking at 800,000 patients approximately in the earlier period and 550,000 in the later period. This is showing the characteristics of the patients that are coming to bypass surgery today or recently. You can see the diabetic incidence is high in about the fourth line there.

Peripheral vascular disease,

cerebrovascular disease, all these other markers of diffuse vascular disease and especially other cardiac interventions like PCI are becoming an increasing component of this. If you go a little lower you see that the blood product use actually has gone up in this period of time from 41 percent of the patients to 44. And, a lot of that has to do with the increased incidence or prevalence, I should say, of both aspirin and now even more particularly clopidogrel in our patient population because many, many, many of our patients now have got existing stents with an indeterminate period of time of need of clopidogrel and we often don't have choice as to delaying the surgery for the indicated five days. In those kind of patients it's hard to do that safely and with aprotinin being the only agent that's shown to be effective in treating these patients, platelets are ineffective in clopidogrel-treated patients. It's only a delay that can obviate the bleeding problems. And just going down you can see that all the predictive factors of risk for our patients are increasing and many of these things

align with the risk of transfusion as well. So I hope that comment was germane.

DR. TEERLINK: A quick one. There's the advantage of coming last in the line here. In regards to slide C52 and C54, and what was the timeframe at which dialysis was queried; in other words, did you follow all cases of dialysis within seven days, 30 days, six months, or was it just if the investigator happened to note it?

DR. CYRUS: The way we did the search for dialysis, dialysis wasn't specifically a checkbox on the case report form. So, in order to try to capture the cases we identified any patient who had an adverse event that fell into that renal failure or renal dysfunction and any patient who had changes in their serum creatinine and then we manually reviewed their case report forms looking into the comment fields, looking into the action taken, looking for evidence of dialysis. So, this number could be an underestimate.

DR. TEERLINK: Yeah, so specific queries and that was during the in-hospital time period, I

mean, during the entire hospitalization?

DR. CYRUS: It would be during the study period so it would have been during hospitalization and the follow-up period as allowed for in each study.

DR. KATO: Also, you know, from the cardiovascular surgery standpoint, I guess one of my problems with the STS database, while it's the only database out there it's not audited. I mean, I still think that the 40 percent transfusion rate that was quoted up there from the mid nineties is still a bit high and I guess I'm wondering about, is that percent, if the percentage of transfusions is actually much lower then is there really a big difference between half-dose and full-dose aprotinin? Because, in terms of the reoperation for bleeding rate, you know, open the full dose is probably powered to have a statistical significance. The half dose doesn't show it. But, on the other hand, it's not, the half dose isn't powered to show anything. So, I guess one of my concerns is that as we're seeing it, it looks like there's a greater risk with full dose, can you justify, with all

this data can you actually justify the full dose versus a half dose in getting the same results for primary CABG?

DR. CYRUS: You know, I should point out from a historical perspective how these doses were derived. The -- if I could have the slide on, please. The -- at the Hammersmith hospital they were noticing a lot in the way of a systemic inflammatory response to the bypass machine and they were aware that aprotinin may have an effect in this. They came to Bayer and they were looking for a kalikrein-inhibiting dose that could indeed have an effect on the antiinflammatory effect. It just so happens when they used this in bypass surgery they also noted that it had a blood-sparing effect.

Because of this historical approach, the main development in Europe used the full Hammersmith and that is where the bulk of the experience with the product is with the full dose. Only when the development began in the U.S. did the half-dose regimen become used, which was very late in the development.

But mechanistically if you look at the dose-dependent properties of aprotinin, you can see that on this very simplistic checkbox slide that both the half and the full dose would have your plasmin-inhibiting properties so you would expect to get some reduced blood loss and transfusion. What you lose from going from the half dose to the full dose or you gain, I should say, by going to the full dose is you gain the ability to restore the platelet function that has been disrupted by the bypass machine. You have an effect on the granular-site activation as well as inhibiting the kalikrein pathway and bradykinin and modulating the systemic inflammatory response. So mechanistically the two doses are different.

If I could have the next slide, please. Dr. Royston has looked at this data and he looked across the correlation, looking at hourly blood loss versus aprotinin dose and I should point out that there is a very high correlation with increasing total aprotinin dose and decreasing blood loss. The yellow dot up there refers to the pump prime regimen, which is

not an approved regimen in the U.S.

If I could have the next slide. When looking then across the clinical trials and looking at those patients that required greater than five units of blood, you can also start seeing that you are looking like there's a dose-response although none of these studies, I should point out, were to look for a difference between the half dose and full dose.

If I could have that, the next slide. The only meta-analyses that looked at dosing was the Munez meta-analyses, which did determine that the full dose of aprotinin may have associated with it a higher rate of renal dysfunction. But I think it's fair to take that same meta-analyses and say let's look at it from an efficacy standpoint and I think when you do that it's very clear that the higher doses of aprotinin did, although both were statistically significant, the clinically meaningfulness of the higher dose is more pronounced.

DR. HIATT: Thank you. I think we'd maybe like to wrap this section up. One just really final

quick question. How long does Bayer get to market this drug; it's been approved since the '93?

DR. McCARTHY: Yes.

DR. HIATT: And how long does the patent run?

DR. CYRUS: There is no patent.

DR. HIATT: Got it. Okay. So, we're going to do the open public hearing now. I have to read this statement. Both the Food and Drug Administration and public believe in a transparent process for information-gathering and decision-making. To ensure such transparency, the open public hearing session of the Advisory Committee meeting, FDA believes that it's 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 you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may

include the sponsors paying 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 relationship at the beginning of your statement, it will not preclude you from speaking.

DR. YOUNG: Hi. My name is Stan Young. I am from the National Institute of Statistical Sciences. The work that I'm going to talk about today was done in joint work with Robert Obenchain, a statistician at the Eli Lilly Company. I will say the National Institute of Statistical Sciences is a freestanding, not-for-profit, nongovernmental body in the Research Triangle Park and our charge is to sort of tie up or tie high-powered theoretical statisticians with practical problems of interest. I have no dog in this fight. I'm here just to talk about statistics. How do I advance? How do I advance the slides? Oh, that way. Okay.

The first thing I want to comment on is one of the things that's been commented earlier, the availability of data to people to look at and evaluate important trials. The National Academy of Sciences looked at this problem back in 2003 and for $20 you can download from the Internet a 120-page document which goes into the ins and outs of sharing data.

I'll just read from that the report. More specifically, the act of publishing is a quid pro quo in which authors receive credit and acknowledgment in exchange for disclosure of their scientific findings. An author's obligation is not only to release the data and the materials to enable others to verify or replicate published findings but also to provide them in a form other scientists build on the data without undue work, whatever is necessary to support the major claims of the paper and would enable one skilled in the art to verify and replicate the claims.

Most journals today explicitly or implicitly require authors provide enough detail about their materials and methods to allow a qualified reader

to verify, replicate and refute the findings of the paper. It is unacceptable to require collaboration, coauthorship or intervention by someone else. The person who gets the data should be free to analyze the data and go forward because that requirement can inhibit a scientist from publishing findings that are contrary to provide his published conclusions.

Mangano has made a very serious claim. The association between aprotinin and serious end organ damage indicates that continued use is not prudent. This is serious. I think it's clear to everyone here that the data structure and analysis in his paper is quite complex. I'll just say we as a matter of statisticians looking at complex studies wanted to get into the business of figuring out how to analyze these studies to help clinicians and other people in society make sense of these very complex studies. Requests for the dataset were essentially ignored by us, and you have heard the story of what's going on with the FDA. There is absolutely no reason that Bayer should not receive the data, too. It's a serious claim. It's a

medical claim.

The other point is that there's insufficient analysis details in their analysis results to replicate. Bob Obenchain from Eli Lilly has worked on propensity score analysis for ten years. He's published software and papers in the area. He and I collaborated for about three or four days pouring through this particular paper. We are rocket scientists. We know how to do this stuff. Okay? And, the descriptions in the paper were not sufficient for rocket scientists to do much with it so heaven help you.

Finally, just a comment. It's error only and not truth that shrinks from inquiry. So, serious scientists should give up the dataset. They should give it up to anyone that wants it and it should be in a form that people can build on and understand and further the research that's in the dataset.

I'll turn and make a few comments on the analysis of complex datasets. This is an area that I have worked on for maybe 20 years or so. There, in

these particular datasets scientists tests here responded, commented, there are multiple response questions. So there's not one question here. The point of the human mind is we focus on one thing at a time. But in the sweep through this dataset, lots of questions are being asked. There are fairly standard ways to adjust analysis for asking multiple questions and they should be done. Responses can be combined in numerous ways. Sort of the off-the-wall kind of a comment is attributed to Johnny van Noyman. You give me four parameters and I can fit an elephant. You give me five and I can make him wiggle his trunk. Okay?

So with multiple responses and being able to combine them in multiple ways, it's no trick at all to get P values of .001, no trick at all. Any graduate student given random data and a few hours on the computer can produce results of that sort. P values can be moved many orders of magnitude through analysis, manipulations. In exploratory analysis, P values and risk ratios essentially have no meaning.

I want to comment a little bit about the

patient allocation. I'm not a clinician so I was reading through the paper thinking randomize, randomize, randomize. No. Very clearly the attending physician could put the patient on whatever they wanted to. So, in this particular case roughly 50 percent more patients were put on the aprotinin group than were put on the other two compounds. Just diagrammatically, can I point here? Yeah, I can point.

Just think about sort of how patients present. There's some very high-risk guys, some moderate risk and some low-risk guys. Now, it's very clear in reading the paper and looking at the prevalues that most of the high-risk guys -- the physicians, I mean, they're intelligent people. They put the high-risk guys on aprotinin. They probably put, they put the very high risk and they probably put the high-risk guys there as well.

Now, intermixed in the paper there are really two kinds of analysis going on. One is an unadjusted analysis where risk factors are not taken into account and another is a purported propensity

score analysis where the risk factors are supposed to be taken into account. And the results from these two analyses are scattered through the paper so you have to be very careful as you are reading the paper which parts were risk adjusted and which parts were not. If you leave the red block in, these are the high-risk people that have been moved across this diagram, and then go down that thing, all that, that column tells you is unadjusted analysis. So, the physicians who I presume -- I go to physicians. I hope they're smart. The physicians that know what they're doing are moving the high-risk people into this drug. And then if you do an unadjusted analysis, you've not a preponderance of high-risk people on aprotinin.

I'll comment one other thing on the statistical analysis. All of the results are against control group and the three drugs. Now, all of the questions that I have been hearing people say here is, what's the difference between the three drugs? So, you can have something over here that is not statistically different from these two but is from the control group.

So, it doesn't come across to me as a very pertinent thing to be comparing everything to the control group. The comparison should be made in and amongst the drug treatments.

This is completely external to the particular study. There was a report in JAMA, 2005, 80 percent much highly-cited nonrandomized studies were contraindicated. So this means a nonrandomized study when it was followed up with a clinical trial, 80 percent of the time the results did not replicate. Now, this is in distinction to clinical trials. Clinical trials when they were followed up replicated about 80 percent of the time. So just going into looking at a nonrandomized study, your prior belief system should be that, you know, this thing is not likely to replicate.

Now, I have followed this over the next two years and there have been a series of reports where nonrandomized studies were attempted to replicate in randomized clinical trials and right now my body count is one for fifteen, so, one for fifteen nonrandomized

studies replicating in randomized clinical trials following up.

So, methodologically the people analyzing nonrandomized trials need to go back to the drawing boards and figure out how they are doing their analysis because most of the claims that they're making are not being sustained in randomized clinical trials.

In summary, until the data are made available to others and a proper analysis is computed -- this is the New England Journal of Medicine thing -- essentially these claims should be ignored. The statistical analysis is seriously flawed. I'll say, where were the editors? Where were the referees? Where were the adults when this was going on? This is, you know, why would I take a day out of my time and come up here and talk to you? I was pretty offended by this trial or the analysis of that trial. Thank you.

DR. HIATT: Thank you.

DR. SPIESS: Good afternoon, everybody. My name is Dr. Bruce Spiess. I come from Virginia Commonwealth University. I'm a professor of

anesthesiology, emergency medicine, and director of the VCURES Shock Research Center. I couldn't pay Dr. Karkouti enough to introduce me. He didn't know I happened to be -- we had never been introduced to each other. He didn't know I was sitting right behind him when he presented, when he presented my data about, about platelets. I'm going to read a prepared statement but before that let me just make a remark or two about his and my study. And it pertains to all of what we're talking about here today, which is devils and the details, and site differences are different. His work was done in Canada. Mine was done in United States sites and some European sites but prior to leukoreduction. So that may be one explanation. His data on platelets has patients on clopidogrel; ours did not. That has to do with timing. I have some disagreements on how his data analysis were run but that's not what we're here to discuss today.

Let me read you my statement and then I would be glad to take any questions you have. It's not, for those who know me here it's not usual that I

read something. I do a full lecture without reading. Thank you to the entire advisory panel for your time and the opportunity to address this group. Thank you also to Cathy Groupe for the instructions regarding today's proceedings and for distribution of the materials that I have sent. By way of full disclosure and in complete evident for transparency let it be known that I have received research support from Bayer Pharmaceuticals as well as consulting and honoraria for specific projects. I am here today, however, completely on my own.

Also by way of disclosure and internally in a complete mishmash of conflict, I have been intimately involved in the past with McSPI databases and McSPI research. I've published extensively from their prior databases. Indeed for a number of years I was the director of the hematology subsection, the hematology study group of McSPI, within McSPI, the specific peer-review group who should have been responsible for the manuscripts including this aprotinin paper.

I have three points to address to you

today, first my opinions with regards to the scientific merit. The New England Journal of Medicine article regarding aprotinin are summarized in my editorial published in the newsletter of the Society of Cardiovascular Anesthesiologists, which I believe has been distributed to you.

Physician channeling of more ill patients toward the more effective drug aprotinin and the employed statistical methods utilized for eliminating bias are a major concern to me. The point I wish to stress, also present in my editorial, is the very likely possibility that some covariate -- and others have mentioned this already -- or confounding variable does exist that was not even included in the multivariate statistical analysis but that was also not even captured in the database.

Specifically I'm referring to a potentially serious, unrecognized confounder, the presence of heparin platelet factor four antibodies or the so-called HIT syndrome. Recent research has found not only that full-blown clinical picture of HIT is quite

prothrombotic but that the presence of HPF-4 antibodies alone have serious implications. Without antibodies present the risk of serious adverse events in a study of over 300 CABG patients just recently completed and published was 5 percent. With moderate levels of antibody present, the incidence of death, MI, stroke and other events went to 12.55 percent. However, a high level of antibody was associated with 31.3 percent of patients having serious outcomes. Unfortunately there was no HPF-4 antibody collected in the mix by database but also unfortunate is the fact that there was no even surrogate such as preoperative heparin usage, length of time in the cardiology ICU preoperatively, multidosing of heparins, et cetera, included in either the analysis or within the database itself.

A case report of sudden right and left heart thrombosis has been published in the Canadian literature in which a patient undergoing open heart surgery clotted extensively after heparin was reversed with protamine. This patient had HIT antibodies and,

interestingly, did not receive aprotinin. My point is this, that HIT antibodies may we have occurred more often in the aprotinin-treated patients due to a selection bias by the physicians channeling treatment to more ill patients. Without testing for HIT, collecting data regarding HIT or even examining HIT surrogates, one cannot eliminate that single and now very important biologic cause for severe adverse events. In my editorial I called for an unbiased third party such as the FDA to examine not only the conclusions but the raw data themself, how the analysis was actually performed, and ultimately the conclusions drawn. I commend you for undertaking this monumental task.

My point with regards to HIT is that experts in cardiovascular surgery, anesthesiology, transfusion, hematology, should have had open access to the raw data and so that the incomplete or inaccurate associations are not published, interpreted as cause and effect. I also stressed in my editorial that our patient deserve the correct answer. Already today

patients throughout the world are suffering because of what's happened.

The second point I would like to stress is the effects of blood transfusion upon open outcome after open heart surgery. That particular subject is one in which I feel I am qualified as an expert. Indeed I have lectured more than fifty times on that subject alone in the last year throughout the world. Most physicians view our blood supply today to be the safest it's ever been. And at least with respect to AIDS, hepatitis, and West Nile Virus, that statement is absolutely true but since the viruses have largely been eliminated from our risk radar, research as has been refocused upon immune modulation trolley and ultimately the adverse events with and without transfusion, with and without leukoreduction.

The body of literature showing associations between transfusion and severe events is large and growing. Within the last three months, several important studies have been added in cardiac surgery, some with databases in excess of 12,000 patients.

These database bases have shown that patients who receive more transfusions have a dramatically higher mortality rate, more renal failure, longer hospital stay as well as a number of other severe outcomes. Importantly, two studies, Engorin, et al., and recently Cook, et al., have shown that patients who were transfused more have a higher mortality rate even out to five years after surgery and those that are transfused have a worse quality of life, and that does include their abilities to perform their activities of daily living. These studies were controlled both with multivariate models and propensity analysis with appropriate control for confounders in the association stand.

In January 16th, 2006, I was invited to participate in the Duke University Clinical Research Institute's sponsored meeting entitled Bleeding, Transfusion in cardiovascular disease, a Think-Tank. And it occurred not many miles from here in Arlington, Virginia. In attendance at that time meeting were 41 physicians and industrial leaders for this provocative

discussion of recent data. There were many members present from the FDA, including Ann Ferreter, Acting Branch, Circulatory Support; James Hung, Ph.D., Office of Biostatistics; Donna Lockner, Deputy Director of the Division of Cardiovascular Diseases; Wolf Sapperstein, Associate Director, Senior Medical Officer, Division of Cardiovascular Devices; Norma Stockridge and Bram Zuckerman. From the National Institutes of Health were George Nemo, acting director of blood resources in the NHLBI, and Keith Horvath, in cardiothoracic surgery branch of the NHLBI.

In the opening statement of that program, Dr. Robert Califf, M.D., vice chancellor of clinical research and director of Duke clinical research reviewed the recent data regarding blood transfusions and its associations with increased mortality in patients undergoing PCI, cath lab interventions as well as cardiac surgery and some recent studies in leukoreduction, randomized and leukoreduction. He showed a number of those papers including from Cochrane database and then concluded with the following

statement. "Blood transfusion is the fourth largest killer of patients in the United States." I would urge you to contact his office for a transcript of that meeting if you have any doubts with regards to the risks of transfusion and outcome in heart surgery. I am absolutely outspoken advocate for us to reduce allogenaic transfusions in heart surgery and I believe the data is strongly present to show the transfusion of allogenaic blood is indeed associated with worse outcomes.

In our center, the Virginia Commonwealth University Health Systems, we reduced transfusion rates for all-comers from heart surgery from greater than 70 percent to now 12 percent. In one six-month period for all-comers during their entire hospitalization it hit 8 percent. That was through an aggressive blood conservation program and aprotinin has been a major backbone of that program. Our patients are doing better, with less time on ventilators, less renal dysfunction, and less congestive heart failure than when they are more liberally transfused. The American

Association of Blood Bankers just recently noted in this last year that the so-called TRICK study by Paul Heber, the gentleman who has designed the BART study, is the single most important study in the history of transfusion.

Every member of this advisory board should read that study as it is the only large randomized controlled trial, prospective controlled trial of blood transfusion. It found that patients transfused less always did as well as or better than those patients transfused more. In severely ill medical ICU patients with the best practice the mortality rate was 28.1 percent. They were very ill patients. That was in-hospital mortality. Withholding blood transfusion to a hemoglobin of 7 grams per deciliter improved in-hospital mortality by 25 percent to a rate of 21 percent, which was highly statistically significant. And I will put it to the FDA. When was the last time a drug was approved by the FDA when its nonusage improved outcome by 25 percent.

Transfusion has never undergone safety and

efficacy testing by the FDA. I gave you my editorial from Critical Care Medicine about transfusion and renal failure. Habib's work has shown that low hematocrit on bypass has an association with an increased renal dysfunction but that transfusing either in response to that low hematocrit or particularly as an effort by physicians to prevent a low hematocrit worsens the risk of renal failure and is not just additive but is a multiplier.

Physicians in the United States transfuse based upon lore, convention and belief. The act to transfuse is in the end analysis an emotion-driven prophylactic event. Only today are we beginning to find the astounding associations between transfusion utilization and worse outcome. Truly in the case of cardiac surgery, less is more. The New England Journal of Medicine paper has caused many cardiac surgery programs to change their practice. When I speak at individual hospitals around the world, their lead cardiac surgeons and anesthesiologist talk to me. For example, at Loma Linda University they stopped using

aprotinin after the paper was published but they noticed such a large increase in bleeding and reoperation rate that within several months they began using the drug once again.

Most often when physicians have changed their practice they tell me they don't believe the results of the article but they're so scared by the litigation climate that it has been, that it has created as a result of that article that they're fearful they'll be sued if anything happens to one of their patients. In Europe the New England Journal of Medicine article was largely ignored but it was the act of the FA publishing an official statement, albeit cautionary and noncommittal, that lent validity and caused some to change.

My plea is this. Please realize that blood transfusion is not necessarily lifesaving. It can be deadly. Indeed there's good data to suggest, and perhaps future generations who will do prospective randomized trials when we might find out Rob Caliph's allegations have some merit. Any decision made by this

important deliberative body will affect the lives of many people.

My third and last point has already been covered to some extent but let me just point out, make this Committee aware that there is a document that you may wish to obtain from the Society of Thoracic Surgeons, the Society of Cardiovascular Anesthesiologists. We are about to publish Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery, a practice guideline. Dr. Vic Feraris led a team of eight physicians from the STS and I led seven physicians from the SCA in a joint effort to create these guidelines for practice. This document is an evidence-based review with over 750 references outlining where the societies will steer practice for our future.

I am not authorized by the societies to publicly pass you the document; however, I do know that if you were to ask for it, you would have it in your hands immediately. I can assure this group the question of not only efficacy but also safety of

aprotinin as well as the lysine analogs was completely and carefully considered by the 15 physicians who sat on those deliberate bodies. Both the Karkouti paper and the Mangano papers were evaluated, cited and considered when the guidelines were crafted.

In summary, I thank you are if your time and your consideration in allowing me to speak. I do believe the Mangano article infers cause and effect rather than simple association. That is a dangerous and a scientifically completely unfounded conclusion, especially when some key confounders have neither been collected nor have they been tested. It, the Mangano paper, calls for the use of drugs. They're not FDA-approved for usage and ones that have little or no safety data testing whatsoever.

Furthermore, blood transfusion in itself is a major risk hazard for adverse outcome, particularly renal failure. That's what Habib's article speaks to. The key ingredient in that risk-benefit equation with which you are now struggling, blood transfusion utilization, was not even tested in the Mangano

article. Ignoring that key confounder alone as a hematology expert makes me wonder what peer review, if any, this manuscript had during its inception, analysis and publication.

Lastly and most importantly, whatever is decided here today will definitely affect the survival and the quality of life of a large number of people both within the United States and worldwide. Thank you very much for your attention. You want me to take questions or --

DR. HIATT: I think we have one more speaker so perhaps we'll move on.

DR. SHORE-LESSERSON: Thank you. Good afternoon and thank you very much, Dr. Hiatt and members of the Advisory Committee. Thank you for allowing me this opportunity to speak to you about the aprotinin issues and the New England Journal of Medicine paper that we've discussed extensively today. My name is Linda Shore-Lesserson. I'm an associate professor of anesthesiology and I have practiced cardiac anesthesiology for sixteen years and have

worked with aprotinin for thirteen years. I have actually worked for aprotinin since before its approval by the FDA when I was principal investigator on a compassionate use protocol that we used at Mount Sinai Hospital in New York City for patients undergoing liver transplantation who had extensive problems with hemorrhage. So I have a long history of working with the drug in clinical trials, clinically, as a practicing clinician, and as an investigator as well.

Now, by way of disclosure, I've mentioned to you my extensive history with the drug. I also would mention that Bayer Pharmaceuticals has supported some of my clinical research as well as a number of other companies within the hemostatic arena with which I have conducted many clinical trials. I have been a consultant for number of companies, including Bayer, and I have received honoraria for speaking, additionally.

Also by way of disclosure, I too, am a member of the McSPI organization and I contributed 48 patients to EPI-2 database with which the New England

Journal of Medicine paper was based upon. In fact, I have to disclose to you that I was the principal investigator whose hypothesis is it was to examine the effects of antifibrinolytic agents on bleeding and transfusions in the EPI-2 database. My primary hypothesis as I put forth the IDR was that we would compare -- and I had a subgroup of investigators working with me -- that we would compare the efficacy in reducing bleeding and transfusions of each of the antifibrinolytic agents compared with placebo or no agent and then the efficacy of each of those agents would be compared with each other, a point that was mentioned by our statistician.

In working with the results and when the adverse outcome data were presented and the coauthors of the paper expressed their desire in how to interpret those results, we could not come to an agreement on how to interpret the adverse outcome data. And, because we could not come to an agreement, I had to recuse myself from authorship. And that is why you see the current list of authors as you do, and I'll go into that a

lists bit further in a few moments.

I would like to express to you my opinions clinically why aprotinin is such a valuable drug in cardiac surgery. I would like to express to you that the cardiac surgical patient nowadays is more complex than ever before. We have clinical trials from the nineties, we have literature that does not reflect even today's cardiac surgical patient. Now, the preponderance of the randomized controlled trials do demonstrate that aprotinin reduces bleeding, reoperations, transfusions, and with respect to end organ outcomes is neutral if not perhaps a little beneficial with respect to certain end-organ outcomes. So I will review very briefly, since we have pretty much exhausted that subject, my feelings on that matter.

I will also put forth that I was a member of the Review Committee for the Society of Cardiovascular Anesthesiologists that approved the new STS/SCA guidelines for transfusion that Dr. Duke and Dr. Spiess have alluded to already. So, clinical

experience agrees with the randomized controlled tries. Clinical experience is that we have been extensive educators in the field of cardiac anesthesiology. And speaking at national meetings around the country and around the world, I have also in addition to Dr. Spiess spoken at many of these meetings and I get questioned all of the time.

Whether I speak about aprotinin or not, when I'm finished, because of my known expertise, the audience will ask me, what do you think about the paper in the New England Journal of Medicine? And I will tell you what I the audience but I will also tell you that I then ask them, well, how have you changed your practice?

And again as Dr. Spiess just said -- and I did not, I did not consult with him at all before these discussions so if they seem similar it's because it's really, it's actual practice. The regular routine answer is, we changed our practice for about a week. We couldn't do it. We had so much bleeding that we had to go back to using the drug. We really see a benefit

and we cardiac surgeons who follow our patients until they leave the hospital don't clinically see an increase in renal failure and if we do it's appreciative because they're a higher risk group of patients who have a higher propensity to have renal failure.

So, my suggestion, and that has been suggested and corroborated by many members of the panel and by the rocket scientists in the audience, is that randomized controlled trials are a standard that cannot be, cannot be met by an observational study because there are confounders that are known and unknown, measured and unmeasured that cannot possibly be included into multivariate analyses propensity analyses.

You saw these data already this afternoon. I believe Dr. Levy or one of the Bayer representatives showed you the meta-analyses of the CABG trials published by Sedrakyan. The meta-analyses demonstrates that there's a benefit of transfusion therapy in patients who receive aprotinin. Also I would like to

point to you that the incidence of renal failure showed no difference in favor or against aprotinin in this meta-analyses, and I would had also like to point out for one of the members of the panel who asked a question about outcomes and why is it that we don't see a beneficial effect on length of stay or actual mortality with respect to these studies, well, if you look at the incidence of atrial fibrillation, it's a post hoc analysis but you will notice that the incidence of atrial fibrillation is marginally reduced in the aprotinin patients. And this is a suggestion that atrial fibrillation is an inflammatory process in cardiac surgery. And, with the known antiinflammatory effect of aprotinin, there is a small reduction in the incidence of atrial tachyarrhythmias after cardiac surgery in these patients who were randomized to receive aprotinin.

Now, these studies were not designed to look at atrial fibrillation and the criteria for diagnosing atrial fibrillation were not standardized across the study; however, atrial fibrillation is an

adverse outcome that's very prevalent. Therefore, it doesn't take a lot of patients to see an effect. The incidence is about 30 percent after cardiac surgery. So, you really don't need a very large study to examine a drug's effect on atrial fibrillation. That's just one point I would like to make.

The real place where we need a drug like aprotinin is in patients who have been exposed to antithrombotic agents. This graph shows you the relative proportions of patients that require cardiac revascularization and who have it done by either CABG surgery, shown in green, or percutaneous coronary interventions, shown in red. And in 2002 percutaneous coronary interventions outnumbered CABG surgeries by about three to one, and now in 2005, 2006, they outnumber CABG surgeries by five to one. What does this mean? Well, this means that this many additional patients are having intracoronary stents placed. They're having drug-eluting stents place and they're maintained on antithrombotic drugs for a minimum of a year because that's what the ACC/AHA guidelines

recommend, is aspirin and clopidogrel therapy for a year. So these patients are presenting for events, cardiac surgical events on their clopidogrel and aspirin. And they bleed excessively because of the additive effects of cardiopulmonary bypass and Clopidogrel. And this has been demonstrated in individual studies, not randomized studies because that would be very difficult to accomplish, and the antithrombotic agents are relatively new but this is a meta-analyses of observational studies looking at patients who have taken clopidogrel within seven days of cardiac surgery. And they evaluated blood loss, transfusions and adverse events like prolonged time on the ventilator, length of stay, reoperations for bleeding in 4,000 patients; 3300 of them were control and about 600 of them had clopidogrel treatment.

Now, you might say we've spent the whole afternoon trashing observational studies, so, why would I show you a meta-analyses of observational data? But the fact of the matter is, these are how patients are cared for. These are how we care for these patients.

We transfuse them more. They are hypothermic after surgery because they get transfused so much more. They stay in the ICU for longer, they're not extubated and think come back to the operating room 9 percent of the time, 9 percent of the time when they have been exposed to clopidogrel versus 1 percent, which is the national arching for reoperation for bleeding.

And if you take a look at what this meta-analyses showed, it showed that as I just suggested, blood loss and transfusions, adverse events, length of stay and re-exploration rates and ventilator time are all prolonged or increased. And here are some the numerical data that were presented in the meta-analyses. There's an excess of 323 MLs of chest tube drainage in these clopidogrel-treated patients. They're transfused one and a half unit more blood. Their risk of transfusion is five times higher. But what's most astounding if you read this literature is that their reoperation rate is anywhere from 7 to 10 percent. And that's really a step backwards. For those of you that practice cardiac surgery, that's a

real step backwards in the care of cardiac surgical patients.

So, I tell you this because clopidogrel as an antiplatelet agent has clinically been demonstrated in small randomized trials to have a reduction in blood loss when aprotinin is used in high dose. Now, these data you also saw, I think Dr. Levy showed them to you in his presentation that in a small 70-patient randomized trial in patients who had been exposed to clopidogrel, those that received aprotinin bled less in their chest tube drainage than those that did not and similarly those that received high-dose aprotinin were transfused only 41 percent of the time versus 61 percent of patients.

Then I have another study I would like to introduce to you and that's a randomized study Of patients who had come to the emergency room with an ST or a non-ST elevation event who needed CABG surgery, who had been exposed to clopidogrel but who could wait five days, and what the investigators did was they randomized these patients to stop their clopidogrel for

five days so the platelets could be regenerated and put them on heparin or they kept the clopidogrel going and gave them high-dose aprotinin at surgery time. And that seems like a very strange study design but it's clinical medicine as we practice it. And what these investigators demonstrated in a slide that I didn't bring but I will describe to you, is that aggregometry studies confirmed that the patients who kept their clopidogrel going still had very, very inhibited platelet function. So, by looking at their aggregometry you would have guessed that they would have bled after surgery.

But clinically these are the results. In the clopidogrel patients who got high-dose aprotinin, they had less chest tube drainage, they had a shorter period of time to chest tube removal, which is considered a marker of hemostasis, and they were transfused one-third the number of units of blood. So these patients were able to be cared for in a relatively average manner rather than in an irresponsible manner because we operate on a patient

who has a lot of the antithrombotic therapy onboard. So this is one major reason why I think we need a drug like aprotinin in clinical medicine.

I would like to just point out to you some of the unusual circumstances that surround the New England Journal of Medicine article. And, many of these have already been pointed out but if you read the fine print you will find that the McSPI organization was designed to be a mentorship organization. It was bringing together people from different countries and investigators, some of them young, designed to mentor through clinical research.

And, if you will notice, the author list on the New England Journal of Medicine paper doesn't contain any clinicians. The two M.D.s don't practice medicine and the other author is a statistician. They're all full-time member of the IREF group. This is very unusual for McSPI. If you go through the literature, and I have sampled a couple of articles for you but if you go through the literature from Epi-1 and Epi-2 and find any other paper except for Dr. Mangano's

aspirin paper, which Dr. Spiess also alluded to, you will notice that there are a number of different authors, all of whom are clinicians. This is a study out of Epi-1; this is a study out of Epi-2. These authors are all investigators who contributed patients to the study, who practice clinical medicine, who believe in the results of the study.

I am currently an author on another Epi-2 publication. This is a McSPI publication. Dr. Elizabeth Ott is the primary author. And these data are published in abstract form in the anesthesiology supplement, last, in 2003. The paper is now in review in the Journal of Thoracic and Cardiovascular Surgery. And what this paper attempted to do was look at different timelines. It first set out to look at country differences, knowing that patients wait a long time for cardiac surgery in England and perhaps in other sites in Europe. But what we found was very surprising and what we found was also alluded to by I believe one of the members of the panel if not the Chair, and that is that there were country differences

that were pretty impressive in the Epi-2 database. So these patients that comprise this dataset are many of the same, probably 4,000 of the same patients comprising these dataset.

Note that in Germany -- and I apologize to the Germans in the audience. The Chancellor of Germany was notified of these data so this is no surprise to him. The mortality, the cardiac morbidity, any morbidity or mortality was higher in Germany than any other U.S., UK or Canadian site. Note that the use of aprotinin occurs predominantly in Germany. This is the way medicine is practiced in Germany. They use a lot of aprotinin and they probably use it in a majority of their CABG patients and they also have another practice, according to Dr. Ott. They transfuse fresh frozen plasma empirically at the end of cardiac surgery. Now, someone asked Dr. Mangano if there was any difference in transfusion requirements among the groups that were analyzed. Well, there actually was an increase in transfusion of FFP in the aprotinin-treated patients.

And when you look at that, you think, well, that's really surprising. Aprotinin is supposed to reduce bleeding. Why would those patients get more fresh-frozen plasma? Well, much of that was empiric, much of that was in Germany, and we don't know if it was a response to bleeding or if it was just the way they practice medicine but the fact is that in that subset, that country's subset, fresh-frozen plasma was transfused in excess to the other countries.

And if you look at Dr. Mangano's propensity renal outcomes analysis, I have it from the paper here, and I have circled the odds ratios for aprotinin and I have also circled the odds ratios for the independent predictive value of the transfusion of fresh-frozen plasma on adverse renal outcomes. The odds ratios are the same, 2.5, 2.4, 2.4. Why wasn't this paper incriminating the transfusion of fresh-frozen plasma as causative for renal failure? I don't know. And, in case you couldn't see those data because they were transferred directly from the article, this is that same table that I have copied over showing the odds

ratios of aprotinin, fresh-frozen plasma administration, and these are the propensity-adjusted. And also someone else mentioned ACE inhibitors today. That was also on this list with an odds ratio of about 1.5 or so.

So, I would suggest to you that saying our findings indicate that reconsideration of the safety of aprotinin among patients undergoing cardiac surgery is warranted and indicate replacement of aprotinin with either aminocaproic acid or tranexamic acid is an irresponsible statement. Those latter two drugs, lysine analogs, are not even labeled for use in cardiac surgery nor have there been extensive safety studies looking at those agents.

Also, I would suggest to you that this cause and effect suggestion is quite a leap. In addition to the kidneys, suggesting a generalized pattern of ischemic injury, where are the data that any of this injury is ischemic? There's a supposition that there's thrombosis going on, that there's ischemic injury. There's no data to support this nor any cause

and effect relationship that I can see thus far. So I think these two statements are really quite a leap of faith and the latter a little irresponsible.

So, in summary, I would put forth to you that the cardiac surgery patient is a very complex animal right now. We need to improve hemostasis. Our hemostatic abilities have been improved in small albeit but randomized prospective trials, evaluating the use of aprotinin and clopidogrel treated patients. And we really cling to that clinical practice. Randomized controlled trials and the impressions of clinicians do not support that end-organ outcomes are at all devastated by the clinical use of aprotinin. In fact, some of them suggest that outcomes such as neurologic injury are improved with aprotinin.

Observational studies can't possibly capture the confounders that are either known or unknown in the investigator's choice to use a drug like aprotinin. I agree there's an association. I do not doubt the findings that renal dysfunction is associated with the use of aprotinin. In univariate and

multivariate analyses I see the association. But do I agree that this is any causal relation? I do not. I do not see that right now. And even the best propensity matching can't account for that which we have heard extensively about. The covariates that were not evaluated or if they were evaluated were not revealed to us include country, fresh-frozen plasma transfusion, cardiopulmonary bypass time and aspirin use. Aspirin use is also reduced in Germany -- so they have a, they have a habit of using a lot of aprotinin and very little aspirin -- surgical expertise and regional techniques. So, again, cause and effect relationship I think is a little irresponsible at this point and to suggest cheaper alternatives that are unlabeled this use is also so. Thank you very much for your attention this afternoon.

DR. HIATT: Thank you. So we're going to transition into the deliberations of the questions presented to us. I just want to ask the Committee, with all you've heard this morning and this afternoon, are there any other points of clarification, albeit

briefly, you would like to ask of any of the speakers that you have heard from today? If not, I think we'll move on to the discussion.

Okay. So you should you all have before you -- I think we'll get it up here on the screen -- the questions for the Committee. You'll see most of these are discussion points and towards the end a voting question. All right. And I think the process as we've done previously is we'll go around the room in kind of random order so you don't get to bias your response based on somebody else's response, and just try to capture your thoughts. I think what I heard prior to this meeting is that you would like a little bit of sort of sense of a summary of where these questions around safety and efficacy might take the further deliberations of the FDA which are not complete.

So in that spirit, the first question, to discuss, these two published reports in an updated Bayer safety review are generally consistent in the detection of an increased risk for renal dysfunction

following aprotinin administration, how the New England Journal of Medicine report described several other serious and mostly cardiovascular risks associated with this drug. Please consider the conclusions from the publication from Bayer as controlled clinical studies and discuss whether Trasylol usage compared with no hemostatic therapy is associated with increased risk for the following serious adverse events: Renal failure requiring dialysis, myocardial infarction, heart failure, stroke or encephalopathy. All right. Ron, do you have a question, clarification? All right.

DR. PORTMAN: No.

DR. HIATT: All right. You want to jump in?

DR. HENNESSY: Sure.

DR. HIATT: Go for it.

DR. HENNESSY: Sure. I was going to say that in my view the data are consistent with an association between aprotinin and renal failure. I don't know whether it's renal failure requiring dialysis or not. We saw that in both observational

studies and in the clinical trials database. I don't think that there are strong data that aprotinin is associated with increased risks of MI heart failure or stroke or encephalopathy. I think we, it's also not been demonstrated that aprotinin improves mortality and I think that maybe it would be a good idea to put in the label what we don't know about the drug and that is it's not been demonstrated to improve mortality or to improve survival.

DR. HIATT: And as part of your discussion to everyone, are there any subgroups that you might identify or highlight? And also note that question number three will talk a bit more about efficacy. Why don't we just carry on this way. We're just going down the table, Lynn, if you don't mind, and we'll just maybe work our way around.

DR. WARNER-STEVENSON: I think that there's a strong suggestion that it is associated with an increased creatinine. I don't see data for increasing dialysis and I don't see convincing data for increasing of the other three events. In terms of the risk in

general, I think we would all favor focusing most on the highest-risk patients and so I think I'm most comfortable with the risk-benefit ratio being favorable in those patients who are at increased risk for bleeding either because of use of antiplatelet therapy or because the surgery itself is complex or a redo.

DR. HECKBERT: Yes. My impression from what we have reviewed and heard today is that there is an increased risk of renal impairment but I am not convinced that there's an increased risk of renal failure requiring dialysis. For the other endpoints, MI, heart failure and stroke or encephalopathy, I don't think that the evidence supports increased risk but I would like to emphasize that these are increases or no increased versus no treatment or versus placebo. We're not considering versus other agents. I think that's the question that's being put to us. And I agree with the importance of the fact that there's no, no improvement in mortality, that that, that probably should be noted.

DR. HIATT: Just to clarify, I noted that

you would have anticipated a benefit ultimately on mortality?

DR. WARNER-STEVENSON: I don't believe the trials have really been adequately designed to look at longer term outcomes, I mean, basically looking at decreasing transfusions, which they do.

DR. CHEUNG: I would like to actually address the question why there is no change in mortality and put out a hypothesis case that I guess somebody was asking why do you only see a hint of possibly less hospitalization or a hint of less mortality. I mean, it's a possibility that transfusion, although we haven't heard that, this is really a risk by itself but it also can be a marker of other comorbidity. But another possibility is that the renal failure per se is an important factor. I would like to actually ask the, maybe change it a little bit, is that in the Q&O failure literature even upon five milligram per deciliter rise in serum creatinine is associated with worse outcome. So I'm not sure that we have to be really, really tied to the issue of renal

failure requiring dialysis. So it's potentially possible, just a hypothesis, that a drug can be associated with one, benefits of decreasing bleeding but in fact but leads to more renal failure and those two cancel each other. So I think this is a possibility.

DR. PAGANINI: I'm less convinced with the dialysis relationship. I am very convinced with the renal dysfunction relationship. My concern is that this drug tends to be given to the sicker patient and if we go down risk factors for renal dysfunction, valve surgery, history of congestive heart failure prior to surgery, elderly, COPD, left ventricular end function is less than 35, peripheral vascular disease, increased serum creatinines pre-op, diabetes and gender all tend to have a higher risk of acute renal failure. And that seems to be the database in which this drug is being used.

So, I believe that what we should do is say that there may well be an increased risk in renal dysfunction with this drug but it's clouded by the

group of patients that they're seeing. And I haven't to date seen any subgroup of patients with higher serum creatinines, which is a preoperatively, as a subgroup of patients that are given this drug. So if there was a subgroup of patients, I would be very cautious of, it's the higher creatinine. And I had go, rather than 1.3, I would say anything 1.9 to 2 or greater would have special risk for high, for an increased risk in acute renal failure. And again that may or may not be the fodder for some sort of prospective study that either the company or someone else would like to do.

DR. PORTMAN: Well put. I completely agree with you in what you're saying and the clouding of the issue of renal failure by the selection of patients. I think this is a critical issue because, you know, maybe aside from smoking, chronic kidney disease is a tremendous risk factor for cardiovascular disease. And because dialysis patients, transplant patients are living longer, they're going to be presenting themselves to the cardiovascular team and the surgeons more often. And so they're not just going to come in

with preexisting chronic kidney disease but even kidney failure.

So, how to deal with those patients is really a critical issue that I think needs to be addressed and I'm not convinced by any of the studies I've seen so far that we have a really good answer about aprotinin and renal failure and I think it needs to be studied in much more detail. Maybe the BART study will give us those answers but that's my feeling.

DR. KNAPKA: Okay. The patient, I have haven't seen anything here today that, you know, would make me worry about any of these risk factors. You know, I think time has proven that the traditional studies, we have controls, the control studies, randomized studies given in the United States, some real safe drugs and I would hate us to go to three prospective studies and start to use them as gospel. So, I think, I don't think we should really ignore them but I think we certainly, on the other hand, I don't think we should go hog-wild and take their data as the truth. I think there's an awful hot of work to be done

here. I just, and I think somebody made a comment about that New England article. I read it and I have, although I'm not medical but I am in science and I, too, wondered why did, why was it ever published, what happened to reviewers? There was just to me so many errors in it and so many variables and it's variables that I don't think anybody ever dreamed of. And when you start going through, you know, 69 centers in 19 countries, there's no way you can get all the variables. And so I just, I don't think that study should be ignored but on the other hand I don't think we really should change what we're doing because of it.

DR. FINDLAY: I would echo others' comments on the suspicion, the strong sufficient suspicion about renal failure. I have a concern about that. And, no, on the others.

DR. BALSER: I agree. I, my view would be there aren't data that were presented here to suggest an increased incidence of renal failure, that would, at least in the cardiac critical care community, which is the community I have been a part of, be convincing. I

think that the notion of putting something into the warning label about lack of demonstrated reduction in mortality or long-term mortality, I would just caution that we have a lot of drugs approved or not approved by the FDA where with it is extraordinarily difficult to collect long-term outcome data. The labeling of those drugs has been silent on this issue and I think that's appropriate when we have no idea. So, I would, I wonder why in this situation we would want to go there.

The other comment I had is I do think it might be, given the much, we have a lot more experience with aprotinin now around anaphylaxis issue and I think the cardiac surgeons here made some good comments about, you know, how the test dose should be administered and at what stage in the operation it should be administered, to, such that the patient can be put rapidly on bypass if they do have an antiphylactic reaction. I just wonder if some more explicit instruction in the labeling is warranted given that we have now more experience with the drug and know much more about how to protect patients if that does

occur. Thank you.

DR. DeMETS: Well, this has been a fascinating day and a fascinating discussion. I think the cardiologists and the clinicians here have done most of the heavy lifting even for the statistical side. But I have to say a comment that when I looked at the New England Journal paper I was disturbed by it. As has been alluded earlier, I guess I pretty much dismissed the conclusions that were drawn. But, I have to say the reason it's been fascinating today is because this kind of data I suspect we're going to see more of. That is, in the post-Vioxx era, put it in that term. We're going to have to rely on observational data of this kind to make, to get some further information. We will not have randomized trials of long duration for rare events. But I think today's discussion has demonstrated just how big a challenge that is.

And we've heard over and over again the challenge in the analysis. I mean, "It's in the analysis stupid," is sort of the bottom line and it's

very tricky stuff and it's very hard to do. And so we need as we look at these trials or these kind of data in the future, we're going to have to really drill down on the analysis details a lot more than we do in, say, randomized trials. So that's just sort of a general overview and I think it's been, it's just been a good lesson.

As far as the specific issue, I think I would agree with the previous comments that the issue of creatinine increase seems to be there. I don't think there's enough data to rule in or rule out an issue of dialysis. I mean, there's no evidence to say that it is but it's pretty small numbers and it comes from a pretty wide -- but I would see no basis for making a claim or a comment on that.

DR. TEERLINK: So I would agree with all the previous comments as well. I think we are confronting a number of challenges here, one of which Dave just mentioned in terms of this, that we will increasingly need to rely on observational data. And, this may be an opportunity to really put our heads

together and figure out, maybe not in this forum but in other forums to try to figure out, well, how can we actually effectively do this? Because it's what we're going to be getting in the future. And in that context I think I would reinforce that I think the Epi-2 database is a quite, quite impressive amount of information that could be potentially available that could possibly benefit a great deal, a great many patients given all the caveats that we've said about observational data. So, I would once again reinforce I think what was a common belief that we'd really love to have this data be made available in a useful manner to the FDA with the appropriate protections in place to protect the investigators.

In regards to the specific questions, I think that there is evidence for an increase in creatinine in response to aprotinin use. I don't believe there is any support for the other adverse outcomes. And then it also asks to please comment upon the increased risks applying to these different subsets, and since I don't believe those necessarily

can be ruled in or ruled out, there is still an open question in regards to these issues. And, I think that we are, it's important for us to encourage clinicians to use a risk-benefit analysis in saying that perhaps in patients who are, you know, simple, straightforward cases, if there is such a thing -- not being a cardiac surgeon I have no idea -- but, you know, that may be where the risk-benefit may not be in favor of aprotinin use.

DR. FLACK: I agree with most of what's been said. I think it's been a very interesting day. There's no question in my mind that the creatinine goes up and future studies or maybe even existing datasets ought to be really teased out to really figure out how long does the creatinine stay up, is it persistent, is it a transient rise. I mean, every time the creatinine goes up, it's not necessarily bad. Creatinine goes up when you use ACE inhibitors in patients for hemodynamic reasons in the kidney. On the other hand, I think a pretty good case was made this morning about the physiologic plausibility of going into the kidney,

inhibiting the kalikrein system which you would predict would probably lead to reductions in bloodflow and hypoxia in the kidney. Nevertheless, we need to clarify that. I think it's probably real. I'm not at all convinced about the need for a dialysis or any of the other endpoints.

And I think, observational studies are going to be like randomized clinical trials. They're not all going to have the same weight. I mean, some well done trials are, have a lot more weight than other trials that don't get as well done. And so I think today in part what we saw was that there were some serious issues about the methodologies used to analyze this observational dataset which exacerbated some of the weaknesses of the observational dataset but in no way precludes I think future use of observational datasets when done right to provide insight.

DR. HARRINGTON: So I'll start by saying that we have had a long discussion I think that's nicely pointed out the multiple problems of the particular paper in the New England Journal that I

won't go through. I will, though, comment on two specific things regarding the paper, that I'm very troubled by the lack of data sharing and what that means. And I'm also very troubled by the last speaker's comments regarding the interactions of the study group members over authorship on a particular paper because of disagreements in interpretation. Going into the specific questions, I'm actually less bothered by the long-term outcome associating transfusion in this particular area though I would absolutely like to see it and encourage Bayer to engage in some programs, which is looking at the long-term relationships.

I think now we have a host of observational data from surgery, from percutaneous intervention, from acute coronary syndromes that would all suggest that transfusion is bad, as one of the presenters say. And we have randomized clinical trial data largely led by the surgical trauma and critical care communities that that would suggest including in systematic overviews of these data that a less aggressive transfusion strategy

is better for our patients. I also agree that there is an association with renal dysfunction. I agree with my colleague at the end of the table who said these relationships though are complex, it clearly needs more study, and I'm particularly encouraged by the sponsors looking at the data around aminoglycosides to see, this is at least one step that might be taken. I agree with the previous speakers that dialysis, low frequence event, no association, and I don't see any association of aprotinin with worsening outcomes of any of the cardiovascular outcomes.

DR. KASKEL: I agree with what's been said around the table and I think the fact that we have a dilemma with somewhere between 20 and 30 -- Americans having creatinines over 1.3 presently, this would become a greater problem in the future as patients get sicker. I think that this begs the importance of study, of scientific study. Even though we have observational studies we need a prospective study even if it's on the small number, subcohort study looking at renal function in a scientific manner in these type of

patients to try and discern what's going on.

DR. ELLIS: So as everyone said, elevates creatinine doesn't seem to convincing produce the other complications. Query, I guess I'm still concerned about the lack of long-term follow-up; otherwise, I ask myself the question, well, blood is bad but if you don't show better outcomes with aprotinin are you just substituting blood for something else that has its own set of problems despite the fact that we don't have, you know, good safety data on these small outcomes. As the last speak said, you know, I'm concerned with sort of the moving target of what cardiac surgery is like and hypercoagual states on the one hand and antiplatelet therapy on the other hand and I think that as the target moves we need to revisit these issues.

DR. KATO: I think I'm on now. Okay. I, too, share the comments and feelings of the previous speakers. I have actually been somewhat relieved and encouraged by the fact that the sponsor has come forward with as much data as they have and has made an attempt to be almost -- oh, excuse me -- almost, almost

overly transparent, which I find refreshing in this day and age. I would like to see more, you know, continued ongoing study of this drug as we move forward and despite the fact that cardiovascular surgery and cardiology and coronary artery disease in general is just changing very, very rapidly but I think that's just the nature of our environment now. So, again, I think the appreciation, my appreciation actually goes to the sponsor for being as open and forthcoming as they have been.

DR. JEEVANANDAM: I, too, echo the comments of everybody around the table. You know, it increases creatinine, doesn't seem to increase the need for dialysis, and the other three, I think, it doesn't really increase the incidence of. I think the one thing I would like to see, though, the sponsor do is, you know, is there an association with increasing creatinine and things like aminoglycosides or other drugs such as maybe cyclosporine and things, so, I wonder if there's any interactions that they might have looked mining through the data. In a separate study, I

mean, we presented a paper, we published a paper on this aprotinin in heart transplantation and it took a lot of work but we were able to show better pulmonary function and better outcomes as well in terms of decreased length of ICU stay but, you know, that obviously is an off-label use of this drug.

DR. LINCOFF: Well, being the last one in line here --

DR. HIATT: I'm the last.

DR. LINCOFF: Oh, I'm sorry, second to last. I'll say that briefly that I, you know, virtually all of the opinions I agree with here. I think that there is some signal with creatinine and I don't think that that necessarily means there's no signal ultimately with dialysis. I think a small proportion of patients but it's a very small proportion; it's a signal that we can't really see in the larger randomized trial database and I don't think it clinically outweighs the benefit of the aprotinin.

DR. HIATT: Thanks. I've actually been intrigued around safety issues in drug development and

have published some statistical analyses about how to look at that. And when you look at the Bayer database, my first comment is, I think that there are sufficient numbers of deaths, myocardial infarctions, strokes and heart failure events to draw conclusions. So, that's my first comment. And when you look at that, as we discussed earlier in the day, I was intrigued by the fact that there was numeric excess and what I would call ischemic events in the database.

The question in my mind was did the observational studies support that. And, I think the Karkouti study really is fairly neutral on these events and I was reassured by that. And then the Mangano paper has already been discussed at length. I think that that paper though did suggest significantly increased risk of cardiovascular ischemic events but I think my problem is whether I am yet ready to accept that data. I think that data needs to undergo the proper matching and re- analysis and I think if that were to continue to show the signal, then I might be slightly concerned. But where I stand today is that I

think that this drug is fairly neutral on cardiovascular ischemic event, which was my major concern. I think the renal issue is probably transient. I'm not convinced there's a signal for dialysis nor am I convinced that there are any particular subgroups to be concerned about, with the caveat that these are short-term outcomes and we really don't know the long-term outcomes.

All right. Let's go to question number two. Safety, further discussion. This is about the hypersensitivity. Identification of patients at high risk for Trasylol hypersensitivity reactions predominantly involves ascertainment of a history of any prior exposure and the use of a test dose procedure. Bayer has proposed a risk minimization program focused upon healthcare provider education and the possible of use an IgG assay to detect prior aprotinin exposure. Please discuss the strengths and limitations of these procedures. In your discussion, please consider the following questions: To what extent do you regard the procedures, especially the use

of a test dose as acceptable measures to identify patients at risk and B, please discuss whether the risks and consequences of hypersensitivity differ for subsets of patients, for example those undergoing repeat CABG versus initial, are the risks sufficiently high for some subsets of patients such that's Trasylol should the not be administered; if so, who are those patients? Go back to you, Michael.

DR. LINCOFF: I think with regard to the test dose that it is striking that nearly half of the reported events happened after the test dose or with the test dose. So it doesn't appear, and maybe the severity was less but the same proportion died. So, it doesn't appear that a test dose per se is a very useful screen. You may as well give the full dose and get the benefit since you're going to have to crash them onto cardiopulmonary bypass of whatever it takes to rescue them. But in any case I think that the idea of the IgG assay, a reliable means of having a good negative predictive value is where this really goes. It doesn't sound like the test dose is a real useful issue.

In terms of the education, et cetera, education from the standpoint of providing a reasonable way to rescue patients, that is, having cardiopulmonary bypass available does sound like it's appropriate and also the recognition that this is, in those who may not be as familiar with the drug that this is a possibility and certainly important. It sounds like there's a lot of difficulty, though, in getting an adequate history in that it is used in some gel compounds, et cetera, and that it may be difficult despite best efforts to really identify who has been previously exposed. Clearly the risk of hypersensitivity is higher than patients who have had, who are having repeat surgery as the likelihood of exposure although there are a proportion which sounds like about 20 percent who had it on what may have been primary exposure which may be an anaphylactoid reaction.

And I'm curious whether or not the IgG assay would be useful in those patients. There have been so few patients in whom it has been studied, if rolled out into a larger group there may be still a

larger proportion of patients who are IgG negative who actually develop a primary reaction, if it is an anaphylactoid reaction. And so I guess we should always be concerned and ready to deal with that type reaction even in patients who are IgG negative.

DR. HIATT: We'll go to the right here just because it's a random thing. I'm concerned about this one and I don't think that, it wasn't clear to me that a clear path forward was articulated though I was actually fairly reassured that Bayer is planning to screen people with the IgG assay and exclude people from use of this drug if they test positive. I think it's also interesting that the assay wanes over time parallel with kind of the risk. But I'm not sure that the education program, I'm not sure how effective that will be nor do I know what I would necessarily say in an education program because I think that the risk factors though they seem to be there, haven't been fully fleshed out.

My other comment is that how are you going to know if things are getting better. I mean, these

are very, very low-frequency events and event rates are going to be hard to compare because of the secular trends over time but I do applaud the idea that I think an assay with a good negative predictive value could be promulgated and used and as long as that's coordinated with the FDA, it's probably the best you can do.

DR. HENNESSY: Yeah, I think an assay should be tested before it's recommended for routine clinical use and given that we also don't know what the utility is of the test dose, I think it would be fair to reflect that uncertainty in the package label. The package label recommends that a test dose be given in the complete absence of any data that, that helps.

DR. WARNER-STEVENSON: I also feel that I really don't have enough information on which to judge at this time. I think the company is doing a very responsible job trying to keep on top of what we are learning. Certainly the problems are going to become bigger and not smaller. We're going to have more and more patients who have had previous reoperations so it's going to get even more important. I agree, I'm

not at all convinced that the test dose is the appropriate route to go. I'm not convinced that we know enough about the IgG to do that and I would just have to say this is a work in progress that requires a lot of attention.

DR. HECKBERT: Yeah, I would, comment is that regarding the test dose, from what we have read and heard today it sounds as though that is not an adequate way of screening. And regarding the IgG, it sounds like it has promise. I think if we, if the FDA were to recommend it and to increase the education information, I think ideally it would be good to have the company or someone monitor this to see is it used, is the IgG used and what proportion are positive and in what setting and what's done about it. And I know the events, the hypersensitivity reactions will be very rare. It may be hard to draw conclusions about whether anything was prevented but I think if it's going to be recommended, it should be evaluated.

DR. CHEUNG: Even though I totally agree with the test dose, not very useful scientifically but

I think it does give us physicians some comfort. I don't think it's a very big deal to have, give a test dose as long as the physicians know to interpret correctly and that's why the education part comes in. So, I am actually endorsing both the test dose and the development of the antibody assay.

DR. PAGANINI: I don't think there's enough data to, for the IgG testing as yet. I think it's an interesting concept that needs a much larger patient population before you can sort of suggest this is a good screening technique. I would be very leery of abandoning the test dose. It may catch some low-hanging fruit that have had a positive response. A negative test dose doesn't mean that you're not going to have a reaction; we all understand that. So I think there's, issues here are the exposure load, how much should be given as far as an exposure and when and where to test if you're going to do the test load. And those are issues that still have to be defined.

DR. PORTMAN: I agree the test dose is concerning, doesn't seem like a very good test. Maybe

we should call it an initial dose. But my big worry is the noncardiac use because if you are ready to put a patient on the pump, you know, you can go ahead and give him the dose. They can go right on the pump and you can control it but if you're doing it for a hip, you know, then you're not necessarily going to be ready. You've got a punch of orthopedists standing around. I mean, you know, I'm not sure what, how that's going to help so that worries me somewhat.

Another thought is, is whether or not there's a pretreatment for this that could be evaluated. Granted it's a different immunologic mechanism but when we give OKT3, for example, and we have a cytokine release system, you know, we use it anyway but we have a very aggressive pretreatment regimen to try to minimize that. So that might be something to look into. If you're going to do this electively, is there a desensitization that's possible if we feel the drug is that valuable, is it, is that something that could be done to allow its use?

DR. KNAPKA: Well, in my own mind I don't

know how the test dose really is going to identify the high-risk patients and that's probably my ignorance but I think the idea of a training program and education is really the way to go and should, you know, certainly include the physicians and certainly the patients to a certain point.

DR. FINDLAY: I would revaluate the test dose and study it over time, also study the assay before widespread use but it seems like a logical idea. I applaud Bayer for trying to make use of this drug safer. It's a no-brainer to ascertain prior use. And, if I am interpreting this right, I think another risk-mitigation strategy would be to try to get more patients off aspirin and clopidogrel many days before surgery.

DR. HIATT: Jeff, you're next.

MR. BALSER: I don't have any additional comments.

DR. HIATT: Okay.

DR. DeMETS: I would agree with the issue about the test dose is not good enough, I wouldn't

abandon it but I would think if you're getting a new test that with the number of bypass surgeries done in this country annually that you could design a very simple one-page form to find out whether in fact with all the patients, all patients whether there is it a problem with the new test, does it work.

DR. TEERLINK: In terms of the test dose, I actually will put my nickel down on being a fan. You know, there was a 36 percent fatality with the test dose, 26 percent fatality rate in the non -- of the patients who got through the test dose so there is some differential there. And we don't know how many of those patients who got through the test dose, if they had not had a test dose would be converted from a nonfatal event to a fatal event because of the higher antigen load. So, I am, you know, perhaps concerned about that.

The test dose makes sense. I think there are some other alternatives that you could be done. I agree with the concerns about noncardiac use of this agent. And, this brings up another issue that's come

up in a couple other meetings of the concept of is it possible to actually have a national registry that anytime anybody gets a dose of aprotinin it goes to a national registry where that, you know, somebody has to write a prescription. I know, there's some challenges to this but somebody has to write a prescription for it and that gets put in saying, you know, this patient has had it and that that be queriable database so that we have yet another way to check to see if there is prior exposure. And then the other thing is to actually address the surgical, educate folks on how to use it such as that they are able to go on bypass more rapidly.

DR. FLACK: Certainly looks like people who have, get exposed to aprotinin within six months are definitely higher risk than those after six months. I, I think, though, the assay, unless there's some kind of point in service assay is going to be a logistical nightmare and very hard to implement in clinical practice. I just don't see, even with the education, surgeons and teams really taking this up very rapidly.

I think the sponsor, Bayer, has done a very nice job in going into their dataset, not being defensive about it and not spinning it too much but one thing I do want to chide them a little bit about is this drug's been out on the market forever and your worldwide database has virtually nothing in it with Blacks and Hispanics, two very large minorities in this country. And I would encourage as you go forward and build your database to really pay attention to that because that just shouldn't happen in these days and times.

The information about, I mean, the test dose, I'm not that sold on it. There was no really good indication that the outcomes were that much different if you had a test dose in a reaction and didn't, and, so, I don't really know what to say about the test dose. I'm not really that big on it. I don't know if there are any cross-reactions, anything that people could have been exposed to that may augment your ability to respond to this and maybe that's something that can be looked at in the future, so.

DR. HARRINGTON: I found the description

from our allergist colleague from Hopkins constructive in that it was pretty much a random decision, to give this and not based on a lot of scientific insight or perhaps scientific insight that was only available at the time. But having said that, I am like others reticent to abandon the test dose. I think the comments from Ron down the other end about the relationship between giving the test dose and being ready to go on pump are very important ones and should be ones that are stressed in the education campaign. And I also worry about this issue with hip surgery and not having the ability to get rapidly in a mode where you could save that patient's life.

Like others, I worry about the assay but I commend Bayer for at least trying to be proactive in developing a way to screen these patients and I also commend them for saying we will educate physicians, that if it's positive not to give the drug rarely do you hear people say that they're going to advocate not giving their drug and like others I think that any educational campaign with clinicians is challenging but

I think it needs to be done.

DR. KASKEL: I agree with everything that's been said and would like to add another population to what Dr. Flack mentioned about populations that need to be studied and that would be children. We're mandated to study these medications in children. Children not little adults. They're different.

DR. KATO: As a cardiovascular surgeon I'm a big fan of the test dose. The most dangerous time period in the operating room is actually from the time of incision to the time of canulation. And at that point in time, you know, if anything does happen, the heart fibrillates, the patient becomes hypotensive. You're really up the creek without a paddle. The advantage of doing a test dose at the time when you are heparinized and the canular are in is that the instruction or the order to go on bypass is literally let's go on bypass and circulation is instantaneously restored.

I think that the other advantage of having a test dose is that then you don't have to add the

aprotinin into the pump prime nor do you have to run it during, you know, during the are rest of the procedure. If there's any additional anaphylactic antigenic antibody response, at least you try to minimize continuing damage as you do the operation.

So again I think the problem with the IgG assay would be that, one, I would agree with my colleagues that it would take time to get that assay run and particularly many of these high-risk patients that would need or that could benefit by the aprotinin, you may not have the time to do an IgG assay and therefore you may be reluctantly back to the position of giving a test dose to see whether it works or not. So, that's where I'm kind of at a -- I can't, I can't make a decision about the IgG assay or not.

DR. ELLIS: I would be in favor of continuing the test dose. You know, I think we saw data that the rate of positive IgG G after a year out from exposure was one percent. Depending on how much that test cost, there could be some cost-effectiveness issues if you can clearly document that someone has not

had surgery in the last year. But it certainly sounds promising. I think a lot more needs to be developed.

DR. JEEVANANDAM: I actually may be in a unique situation here because I have used, we need to use aprotinin a bit because we do a lot of ventricular-assist devices and follow it up with a bridge-through transplant. So I have personally had about four patients who had have anaphylactic reactions.

Now, I don't think I've actually reported them so I might be as guilty as everybody else. So I was probably one of the reasons they don't have a lot of them reported. I think we've developed a strategy for it. I mean, clearly none of the patients reacted to the test dose but what we do now is give the loading dose really, really slowly. And if you give a loading dose slowly, they usually will have a reaction within the first 10 to 20 percent of that loading dose. And if you start to see any decrease in blood pressure we stop it right away and support them immediately with epinephrine and steroids.

The last two patients we haven't had to crash on bypass. The first two patients we did not realize that so we just gave them the loading dose like we would normally do and they had a crash on bypass. And I agree with Norman. I mean, you know, even now we will not give the dose, the loading dose of aprotinin till we are sure that we have access to go on pump. I mean, I wouldn't put the cannulas in or give heparin but at least we know that we have arterial and venous access.

The other thing is, you know, most of the time if you're doing a reoperative CABG, it's going to be after a year. Hopefully it's after a year so by that time, you know, their antibodies should have come down to negligible levels. I think there is a subgroup of patients such as bridge-through transplant where you do them within the first three or four months and I think those are the parents that have the highest risk for this anaphylaxis.

I think the other problem, that IgG assay, I agree with everybody at the table. It might become a

logistic problem where unless you have it as a point of use you waiting for the result to come back which may delay some cases. And I must admit even if the data, what that was presented was, you know, it identified patients but it didn't, it wasn't specific enough. So, even if I had a positive IgG, I may be very careful and make sure all the cannulas and everything are ready but I can tell you on a bad explant and a transplant unless you use aprotinin, that patient has a high chance of morbidity just from bleeding. So I actually might even, you know, understanding there are more risks but be prepared to take those risks even with IgG positivity.

DR. HIATT: Okay. Question number three, an efficacy question. Since Trasylol was originally approved in '93, allogeneic blood transfusion practices in CABG surgery may have changed due to a wider use of autologous blood and changes in clinical criteria for transfusion. Please discuss the importance of the Trasylol benefit of reducing perioperative bleeding and the need for transfusion in the context of current

cardiovascular surgical anesthetic and blood transfusion practices. I would probably throw in there the need for reoperation as well. Ron, do you want to start it and come back this way? No, you don't want to start? You have to.

DR. PORTMAN: I have to? Okay. Come back to me.

DR. HIATT: Okay. Lynn, you want to start?

DR. WARNER-STEVENSON: I would anticipate in fact that it's going to become only more urgent as we go on. I think the thing in the, the abstract included in our packet was very illustrative of the interim report from the BART study that suggested so far a 12.2 percent incidence of life-threatening bleeding episodes compared to the anticipated 5 percent. And certainly the patients that we're sending to surgery now are much sicker than they were a few years ago. So, I think it's only going to get worse. The other thing just about the previous question about the test dose, I think we should definitely continue it but I liked the suggestion that came from this end of

the table that we stop calling it the test dose because that may give some people a false sentence of the security. Just call it the initial dose perhaps.

DR. HENNESSY: So aprotinin is given and it clearly reduces the need for transfusion and people make the inference that it probably improves survival. Encanide and flecainide were given to prevent premature ventricular contractions in people who have had heart attacks and the inference was made that it probably improves survival. I think that if in the label for encanide and flecainide we had said that these drugs have not been shown to improve survival that it would have had less uptake than it did and that ultimately when it was shown to have killed people it would have killed fewer people in the interim, I would say that there is an analogous situation and that because people are using it to improve mortality and we don't know that it does, we should make it explicit that we don't know that it does.

DR. HIATT: I think the need for this kind of drug is still there and that in fact probably sicker

patients are coming to bypass surgery than previously. Because I'm not convinced that there's a safety concern, because the data to support the transfusion need is pretty good, but I guess the thing that most convinces me is the reoperation data. I think that's a heart event; whether you need a few less units of blood or not the clinical benefit of that we discussed at length today but I think the need for reoperation is a really heart event. So, I think it continues to be relevant in the efficacy, at least short-term, has still been demonstrated.

DR. LINCOFF: I agree with my colleagues that the efficacy or the indication for the efficacy continues to be there, and in fact is probably magnified. Not only are patients sicker as had been mentioned but we're using more antiplatelet agents in a larger proportion of these patents. Many of these patients or perhaps more of these patients will be reoperations, more complex operations, transplants, et cetera.

So I think that this, that there's nothing

to suggest that the underlying risk of bleeding is any better in patients that are undergoing surgery now than it was at the time the drug was approved. We do have better transfusion practices but in part those reflect the use of drugs such as this as well as the algorithms for more conservative transfusions.

So, and I remain not particularly concerned by the lack of long-term mortality data. I don't believe that there is evidence that there's long-term mortality risk. And many drugs don't have any influence on long-term mortality but still change important morbidity. I think if we had enough patients there probably would be a downstream effect of preventing reoperations and large massive transfusions but if you calculate the numbers of patients that that would likely require to see in a trial, I think we would talking in the multiple 10,000 range and I just don't think that's practical, so.

DR. JEEVANANDAM: I, you know, looking through the data clearly there is a decreased incidence of bleeding and transfusion and having used the drug

and using other agents as well, I think there's no, no question that this is, this improves hemostasis. Now, and there's the question and that comes up of does decreasing transfusion lead to improved long-term survival and I guess none of the studies have empowered to look at that, at least in the immediate postoperative period, and not getting blood transfusions decreases pulmonary vascular resistance makes them a lot more hemodynamically stable and there is a much lower incidence of reoperation. So I think that, you know, the drug is important in terms of decreasing bleeding and decreasing the need for transfusions.

DR. ELLIS: I don't think that the changes in clinical practice have by any means diminished the indications for the drug.

DR. KATO: I'm still concerned about the use of aprotinin in, you know, in primary routine bypass candidate, bypass surgery candidates. I'm not, while no bleeding or no transfusions may be good, the extreme of that, which is you know, thrombosis,

inadvertent thrombosis of whether it's a native coronary artery or the rest of the blood in the body, is also a bad thing. And so finding that, walking that fine line I think is still difficult. Given the, when aprotinin was first, I believe that when aprotinin was first approved the average transfusion was about six units of blood, and, which in the United States even at that time wasn't really relevant because the average transfusion rate was only about two units.

So, I'm still, while I think that aprotinin has its place for decreasing perioperative bleeding and the need for transfusions particularly in high-risk patients, I think there still needs to be caution of not using it routinely in everyone but selecting out those people the best way you can who are going to benefit from it.

DR. KASKEL: I agree with what's been said and maybe one needs to consider guideline paper or a consensus paper on the topic in the future.

DR. HARRINGTON: Clearly when you look at the data that Peter Smith showed from STS, the use of

blood products during cardiac surgery are still very high and has been pointed out, the patients are different. They're more complex. They have more comorbidities. The drugs are different. There's a lot antithromboitc use. Techniques are different. And so I would go back to Bayer and say that there's a knowledge deficit here and that I would encourage people who have access to data, for example, the large STS dataset to actually look at some these transfusion questions within those data sets as a helpful means of advancing the field but I would also put to Bayer -- maybe this follows up on Norm's point -- that because this data originates in the late eighties, early to mid nineties, we don't have contemporary prospective studies and I would encourage Bayer to sponsor such studies. Because, if I'm hearing my surgical colleague right, there is some equipoise in the field about this balance between transfusion and thrombosis, that sounds like clinical trials could be done. And, I would encourage people active in the field to look at what those studies might look like and to engage in them.

DR. FLACK: Not much to add, just say one thing. It would make me feel better if I saw more tangible evidence of benefit. Certainly reducing transfusion appears to be something that's very desirable and in and of itself you might say, well, that's a benefit and if I didn't need blood I wouldn't want to get it, I don't care how sick the blood supply is but if you're also looking at the mortality data and these are sick people and despite the fact you reduce transfusion and reoperation and those things, you see pretty similar mortality, you sort of scratch your head and say, okay, well, you are supposed to, should be reducing it, what's happening? Are we substituting something else? So, I would encourage the company to really look for some sophisticated ways to try to get at clinical benefit short of doing a big randomized trial by doing some very careful analyses of both probably smaller trials and observational datasets.

DR. TEERLINK: I'm comfortable with the degree of efficacy of the agent in terms of reducing blood product usage. If anything, I think the patient

population is getting more and more complex and so would anticipate that it would be more useful at least for that specific endpoint. In terms of the getting at actual outcomes we on this committee have often sat and insisted upon finding these hard outcomes. This agent has already been approved for this indication. I think it would be, I would second Bob's point that using databases to try to find out more information in regards to the outcomes, though I'm not sure we actually do have clinical equipoise from the surgeons in regard to its use and it would be interesting to see whether a real outcomes trial would be possible. I think probing the databases would be useful.

DR. DeMETS: I don't have any additional comments.

DR. BALSER: Just that I, you know, I don't think we have the data to make any changes in recommendations around when to use but I think a lot of us would like to see better stratification of what patients benefit in primary CAB. Some primary CABs, it's certainly appropriate and you wouldn't want to

change the labeling so that was prohibited but there are a lot of centers doing very simple cases where they aren't using this drug and so what is the risk-benefit ratio in those cases and which cases, so, I think that's just something that requires further study but needs to be done.

DR. FINDLAY: Nothing to add.

DR. KNAPKA: I have nothing to add.

DR. PORTMAN: Thank you for allowing me to put my thoughts together.

DR. HIATT: Absolutely.

DR. PORTMAN: As a patient I think if you can't tell me for sure it's going to be a benefit but it's not going to be a detriment, however, I'm going to get less blood exposure, then I'm probably going to be pretty happy and say yes, give me that drug. So I think the other concern is that so much Plavix use and stenting and aspirin, I mean, we don't really know in a control way, you know, what this drug is going to do under those circumstances and that should be studied as well.

DR. PAGANINI: I think it's effective in reducing drug transfusions and re-op. I think that we're seeing, we've heard that the type of patient that might benefit from this is increasing and therefore it's use may reduce the load on the blood banks for cardiac surgery which would in and of itself be something positive. However, I don't see any improvement in these surrogates translating into an overall ultimate improvement in outcome either in short-term or long-term and that's somewhat concerning.

DR. CHEUNG: From what I have seen and heard today, I am very much in favor of its continued use to decrease the bleeding. I think diffuse bleeding reoperation is and the burden on the blood bank is something we all should be very, very concerned of. In terms of the short-term and long-term outcome, the short-term mortality is unchanged.

That's why that we're going to have more and more patients with comorbidity and many of those do have underlying kidney disease associated with all the other comorbidities. I think we should pay more

attention to those because those are going to be the one coming on the table more and more often. So it's kind of a two-way street. On one hand I think those patients can benefit the more. On the other hand, they might be the high-risk population. We really need to sort out what is the kidney, potential kidney risk to these patients.

DR. HECKBERT: Yes, I support the drug remaining available for patients who are at high risk for blood loss and blood transfusions. I would also comment that from the public health point of view, the question isn't just whether it's better than placebo or nothing. I think another question of public health importance would be whether it is equally effective or better or worse than tranexamic acid or aminocaproic acid. And that's a question that would be difficult to study in the U.S. but I think it's an important question.

DR. HIATT: All right. We have one more question. This is a voting question. It's a bit long so I think I'm not going to just read the whole thing.

But, Bayer has proposed modifying the indications statement as following. Trasylol is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusions in patients undergoing bypass and CABG who are at increased risk for blood loss and blood transfusions.

So, discussion. We'll discuss the clinical considerations for identifying patients who are at increased risk for blood loss and transfusions and who should that apply to and then the voting question highlights this safety and efficacy database. And you can see this before you. Based on the presentations today, do you regard the totality of clinical data supporting acceptable safety and efficacy for Trasylol usage among certain CABG/CPB patients? And then you have a discussion of yes or no. All right. Anyone want to start with this one? Lynn, your light's on.

DR. WARNER-STEVENSON oh. Not intentionally but --

DR. HIATT: How do you like that?

DR. WARNER-STEVENSON: Yes, I do think the

totality of clinical data supports this. I actually would say, kind of, I know this wasn't what was asked but I would wonder if within the database at this point you mentioned some small experiences in some valve patients in the randomized parts, if it might be possible to delete the phrase "in the course of coronary bypass graft surgery." For instance, patients who are high risk, who are just having valve surgery, et cetera. I just raise that as a point of discussion but I certainly would support it as it stands but perhaps think slightly more broadly than just the CABG patients since it's certainly being used in a number of other populations.

DR. HECKBERT: Yes, I would support the revised, the revision to the label. I might say it at high risk for high blood loss and blood transfusion because if you say at increased risk, that means, that begs the question compared to who. But, anyway, and in terms of, based on what we heard and read today, I don't think that it would be appropriate to say that this descriptor only applies to patients undergoing

repeat CABG. And let's see. I guess there's B here. And yes, I do regard the totality as supporting acceptable safety and efficacy for certain patients.

DR. HIATT: And as you go through this, can you all maybe help us define who would be the increased-risk patient?

DR. WARNER-STEVENSON: Oh, certainly I think the patients who are on antiplatelet therapy, the patients who are re-dos and then we could debate valve transplant RAD.

DR. HECKBERT: I don't have anything to add to that.

DR. CHEUNG: Being a nephrologist and knowing that uremia -- definitely adds CKD or chronic kidney disease to that list. I think that statement is actually very accurate but whether you can use it beyond the coronary bypass obviously is something that is, I guess not particularly FDA-approved for other purposes although from all the data it sounds like it could be applicable to others as well. But that statement itself I think is conservative and I think

it's quite accurate.

DR. PAGANINI: I also agree that the statement is accurate. I don't know how you would identify high-risk patients of bleeding other than what has already been stated, that is, those that are already on antiplatelet activities and those that are uremic. I would propose that perhaps an additional statement that no data on improved outcome be added as well. And as far as voting on the clinical data, supporting acceptable safety and efficacy of the drug, I think that that has been shown. There are questions about renal dysfunction. I think they will come out but the safety and efficacy of the drug overall in this subgroup of patients seem to be acceptable.

DR. PORTMAN: And as far as whether it should be unlimited to repeat CABG, I would say no. I think we shouldn't take that away from a surgeon. You know, if he feels it's very important in his practice, he should be able to use the medication. As far as high-risk patients are concerned, I think clearly patients with renal failure is a high-risk patient.

Patients who are on nephrotoxins, such as aminoglycosides. The patients who are on antiplatelet therapy and those that have received the drug within six months with a risk of anaphylaxis I think is another group that needs to be attended to but I do support its safety and efficacy.

MR. PAGANINI: Okay.

DR. KNAPKA: I agree with the statement, I vote yes, and for, though, says population, high risk but I think high risk would be an individual, too. I think that there's some people who may be in the population, and I think the physician's, one of the responsibilities is to determine is this individual at high risk. I'm not so sure we can say well, there's this population at high risk because there may be some in there that's not. So, I think there's a little danger. You're trying to group people in groups but we're all individuals and we react differently.

DR. FINDLAY: Yes, I would support the continued use and the proposed restriction and I would hope that Dr. Mangano's raw data would eventually

become available to all for analysis to put that debate to rest.

DR. BALSER: I agree with the restriction and vote yes.

DR. DeMETS: I vote yes and the exposure within six months is a part that would concern me so I support that.

DR. TEERLINK: I would not limit this to only patients undergoing repeat CABG and I would vote yes.

DR. FLACK: I vote yes and I would not limit it.

DR. HARRINGTON: I vote yes. I also think it's a responsible statement because it stresses that we're looking for an increased risk cohort and it's stressing that the benefit as of now is only on blood loss and transfusion and not the other clinical outcomes as been mentioned. Regarding definition of risk, we've heard today that there are consensus documents forthcoming from the professional societies and I would look to those based on empirical data that

would define risk and that I don't think it would be our job to define what those risk characteristics are without seeing more data. And I also would not want to confine it only to redo procedures.

DR. KASKEL: I would vote yes and agree with what's been said.

DR. KATO: I would vote yes but adding on both primary or first-time coronary artery bypass graft surgery as well as redo coronary artery bypass graft surgery. I don't think we have seen enough data for other operations to include that so from an evidence-based perspective, as much as I think that it should be used for complex valve surgery or CABG valve surgery, I don't think we have enough data to make that statement. In terms of adding on a couple of other risk factors for bleeding, elderly, usually in the age group of over 70 or 75, I would also add mechanical-assist devices to this group of high-risk patients.

DR. ELLIS: I vote yes and I'm not in favor of prescription-to-prescriptions on who is at high

risk. I think clinicians generally know who those people are.

DR. JEEVANANDAM: I vote yes and concur with what's been said.

DR. LINCOFF: I vote yes. I would not restrict repeat procedures and I would really like to emphasize that I think the clinician's judgment in identifying high-risk patients on whatever basis, particularly use the guidelines, et cetera, should not be specified in the label but it should be at the clinician's discretion they do a pretty good job of it.

DR. HIATT: I think if the sponsor wants to change the label, obviously you should be thought of about that and I think that there's increased, factors that put you at increased risk for blood loss and factors that might put you at increased risk for the drug. And so we have already enumerated some of these. Antiplatelet therapies might put you at increased risk for blood loss but renal insufficiency might put you at increased risk for drug toxicity.

So, if the sponsor is going to entertain

changing a label, I think I would sort of broaden that a little bit and then the way I would try to get at what that is, is to probe the existing database and try to look at prediction models for what those risk factors might be to thoughtfully change the label. So I support the concept but I'm not sure I would support this language. In terms of the voting question, I think yes, the totality of it is, does support its use and then as I just said earlier, I think that a label change to define patients at increased risk should look at both drug toxicity and bleeding risk.

DR. CHEUNG: Mr. Chairman, I did not know the, procedurally whether it's correct or not. I meant to vote yes but I guess I did not say it explicitly, so.

DR. HIATT: Thank you.

DR. BALSER: Mr. Chairman, the issue of restriction, I think what I was responding to was of the pharmaceutical company's request, as you indicated, to indicate folks who are at increased risk for blood loss or blood transfusions, which I took as a fairly

general comment. I was not suggesting that we should restrict it to only re-dos. So, just wanted to clarify that.

DR. HIATT: Good. Thank you. Thank you for that clarification.

DR. BALSER: And a different general statement is fine with me. I agree that it needs some work.

DR. HIATT: Any other comments from the Committee? I'm sorry.

DR. HENNESSY: So as you pointed out, the question who is at high bleeding request is a research question and I think there are data available to answer that. In terms of what's the threshold for treatment versus not treatment, I think that's an appropriate question that could be answered by a decision analysis. I think that decision analysis would have to make some assumptions between the relationship between bleeding, preventing bleeding and mortality that we don't know about. In terms of my vote, I suspect that there are subgroups in whom there's a survival benefit for the

drug but that hasn't been demonstrated so in the absence of that being demonstrated, I'm going to abstain from the voting question.

DR. HIATT: All right. Before we adjourn, I think that in addition to the specific questions the Committee has been faced with, we saw something a bit more generic which we always have discussed, which is the use of observational data to address safety concerns in a post-marketing fashion. And I think my final comments would be that I think this information has been very interesting but poses unique analytic challenges.

And in the spirit of how this committee has been run in the years I've served, full transparency disclosure is absolutely critical to evaluate any database. And we hold that standard to all sponsors who bring us new data to this committee and we also hold that standard to other published articles that have been recently discussed around new indications for antithrombotic agents.

So, I think in light of that, these

observational studies are really not informative until they have been rigorously evaluated independently by not just FDA but other statisticians and investigators that want to review it. And so I think the Committee strongly advocated approach. I would like to articulate that again and that until we can see the data in that light, I think we're challenged to draw any meaningful conclusions. I would also like to thank the sponsor for the authors of these articles and for this committee's deliberations today. And I believe we're adjourned.

(Meeting adjourned at 4:54 p.m.)

State of Maryland.

Baltimore County, to wit:

I, ROBERT A. SHOCKET, a Notary Public of the State of Maryland, County of Baltimore, do hereby certify that the within-named proceedings personally took place before me at the time and place herein set out.

I further certify that the proceedings were recorded stenographically by me and this transcript is a true record of the proceedings.

I further certify that I am not of counsel to any of the parties, nor in any way interested in the outcome of this action.

As witness my hand and notarial seal this 18th day of October, 2006.

_____

Robert A. Shocket,

Notary Public

My Commission Expires:

November 1, 2006