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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE (CRDAC) IN JOINT SESSION WITH THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSARM)

Wednesday, September 12, 2007

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P A R T I C I P A N T S

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Acting Designated Federal Official, CRDAC

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Keyvan Karkouti, M.Sc., M.D. F.R.C.P.C.
Toronto General Hospital

Dennis T. Mangano, Ph.D., M.D.
Ischemia Research and Education Foundation

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FDA Participants at the Table (Non Voting):

Gerald Dal Pan, M.D.
Mark Levenson, Ph.D.
Richard Pazdur, M.D.
Rafel Dwaine Rieves, M.D.
George Shashaty, M.D.

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P R O C E E D I N G S

DR. PHAN: Before the Chair begins, I need to read some statements regarding the meeting procedure.

For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and an open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that any conversation about today's topic takes place in the open forum of the meeting and not during breaks or lunch.

We are also aware that members of the media are anxious to speak with the FDA about these proceedings. However, like the advisory committee

members, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

For the convenience of the media representative, I would like to identify the FDA press contact, Ms. Riley and Mr. Kelly. If you are present, please stand up.

Thank you. I'm sorry; Ms. Sandy Wash.

Finally, I would like to remind everyone present, please silence your cell phones and pagers if you have not already done so.

We look forward to an interesting and productive meeting. Thank you for your participation and cooperation.

Call to Order

DR. HARRINGTON: Thank you. My name is Bob Harrington. I am a cardiologist at Duke University and I am going to serve as the Chair for this joint advisory panel meeting today of the Cardiorenal Panel and the Drug Safety and Risk Management Advisory Committee.

The first order of business is to have the

Committee introduce yourselves. What I would like the committee to do is to introduce yourself, tell us where you are from and what your area of expertise is.

So why don't we start with Dr. Lincoff.

DR. LINCOFF: Michael Lincoff from the Cleveland Clinic. I am an interventional cardiologist with expertise in clinical trials.

DR. TEERLINK: John Teerlink from San Francisco V.A. Medical Center and University of California, San Francisco. My area of expertise is heart failure and ecocardiography.

DR. CRAWFORD: Good morning. Stephanie Crawford, University of Illinois at Chicago, College of Pharmacy, safe medication systems and risk management.

DR. ELLIS: John Ellis, Department of Anesthesia and Critical Care, the University of Chicago.

DR. FINDLAY: Steve Findlay from Consumers Union. I am the Consumer Representative on the Cardiovascular and Renal Disease Group Panel.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University. Expertise in label comprehension, neurocognitive functioning and risk management.

DR. LEVENSON: Mark Levenson, statistical reviewer, CDER, FDA.

DR. SHASHATY: I am George Shashaty. I am the medical reviewer in the Division of Medical Imaging and Hematology Products.

DR. RIEVES: Hi. I'm Dwaine Rieves, Acting Division Director in Medical Imaging and Hematology Products at FDA.

DR. PAZDUR: Richard Pazdur, Office Director, FDA.

DR. DAL PAN: Gerald Dal Pan, Director of the Office of Surveillance and Epidemiology at FDA.

DR. PAGANINI: Emil Paganini, Cleveland Clinic Foundation, Adult Nephrologist. Expertise in dialysis and acute renal failure.

DR. GILLETT: James Gillett, Professor Emeritus of Toxicity at Cornell University, Ithaca. Patient Representative on behalf of people with

Barrett's esophagus, COPD, various anesthetic and other uses of drugs.

DR. WARNER STEVENSON: Lynn Warner Stevenson, Brigham and Women's Hospital in Boston. I am a cardiologist with a specialty in heart failure and transplantation.

DR. KATO: Norman Kato, private practice, cardiothoracic surgery, Los Angeles, California.

DR. NELSON: Lewis Nelson, emergency medicine from New York University School of Medicine with an expertise in medical toxicity.

DR. CHEUNG: Albert Cheung, practicing and research nephrologist at the University of Utah.

DR. BLACK: I am Henry Black at New York University. I am a clinical trialist and preventive cardiologist.

DR. HECKBERT: Susan Heckbert, University of Washington. I am a general internist and epidemiologist, Department of Epidemiology.

DR. NEATON: Jim Neaton, the University of Minnesota, biostatistician with expertise in clinical trials.

DR. LESAR: Timothy Lesar, Director of Pharmacy, Albany Medical Center in Albany, New York. Expertise in medication safety.

DR. KASKEL: Rick Kaskel, pediatric nephrology, Albert Einstein College of Medicine and expert in clinical trials and progressive renal disease.

DR. PHAN: Mimi Phan, Doctor of Pharmacy, Designated Federal Official.

DR. HARRINGTON: So the first order of business, Mimi, is for you to read the Conflict of Interest Statement.

I'm sorry; go ahead.

DR. JEEVANANDAM: Val Jeevanandam. I am a cardiac surgeon from the University of Chicago. Expertise in transplantation and ventricular-assist devices.

DR. HARRINGTON: Terrific. Mimi is reminding me, I should introduce myself. That is probably a good idea. Bob Harrington from Duke University and I am the Director of the Duke

Clinical Research Institute and a clinical cardiologist.

Conflict of Interest Statement

DR. PHAN: Good morning. This is the conflict of interest statement for the joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Today is September 12, 2007.

The following announcement addresses the issue of conflict of interest and is made as part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential conflict of interest for the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), Dr. Henry Black has been granted a waiver for his unrelated Speaker Bureau activity for a competing

firm. Dr. Black receives less than $10,001 per year. Waiver documents are available at the FDA's dockets web page. Specific instruction as to how to access this webpage are available outside today's meeting room at the FDA information table.

In addition, copies of our waivers can be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

In addition, Dr. Keyvan Karkouti, an FDA-invited speaker, would like to acknowledge that he served as a consultant to Bayer in 2006.

In the event that the discussion involves any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from the discussion and their exclusion to be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment

upon.

We also we like to announce that Dr. Annette Stemhagen, the Industry Representative to the Drug Safety and Risk Management Advisory Committee has canceled her participation very recently. Unfortunately, this did not allow enough time to arrange for a substitution.

Thank you.

DR. HARRINGTON: So, just two housekeeping announcements before we start, the first of which is we have a very busy schedule so if the speakers would respect the time limits and keep to their allotment. Secondly, we also have a very large panel today and, again, if people could raise their hands and I will direct the conversation with the various speakers.

If the red light is on for the panel, your mike is on and your remarks can be heard. So just be aware of that.

The first speaker is Dr. Dal Pan who will provide some opening remarks.

Opening Remarks

DR. DAL PAN: Good morning. My name is Gerald Dal Pan and I am the Director of the Office of Surveillance and Epidemiology in FDA's Center for Drug Evaluation and Research. On behalf of my colleagues in that office and in the Office of New Drugs and in the Office of Biostatistics, I would like to welcome you to today's advisory committee meeting which we have convened to discuss aprotinin which is also known as Trasylol.

Trasylol, which is manufactured by Bayer Pharmaceuticals is approved for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at increased risk for blood loss and blood transfusion.

Today's meeting, which is a joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, is, in large part, a follow up to the Cardiovascular and Renal Drugs Advisory Committee held nearly one year ago on September

21st, 2006.

The main topics of the September, 2006 meeting were renal dysfunction and hypersensitivity associated with the use of aprotinin. Published papers by Dr. Dennis Mangano and Dr. Keyvan Karkouti form the basis for the discussion of the renal dysfunction while an in-depth analysis of postmarketing safety reports by FDA staff were the basis for the discussion of hypersensitivity.

At that meeting, the advisory committee provided input to FDA that led to changes in the label for aprotinin mainly related to strengthening the warnings regarding hypersensitivity and renal dysfunction. Later this morning, you will hear about those label changes in more detail.

About one week after the 2006 Advisory Committee meeting, FDA learned that Bayer had commissioned a large-sample-sized observational study of aprotinin. This study pointed not only the renal adverse effects associated with aprotinin but also suggested that in-hospital mortality was higher in aprotinin-treated patients than in

patients treated with alternative agents.

Finally, an additional analysis published in February, 2007 by Dr. Mangano suggested an increased long-term mortality in aprotinin-treated patients. The findings from these studies have prompted FDA to reconvene an advisory committee to reconsider the available information.

The nature and extent of the observational data also prompted FDA to pursue a joint meeting of the Cardiovascular and Renal Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee.

FDA epidemiologists, biostatisticians and medical officers have reviewed these data in great detail and FDA biostatisticians have reanalyzed much of the primary data. So today you will hear presentations from Bayer and from the FDA on these findings and, after the open public hearing this afternoon, we will ask you to discuss these data and to make recommendations for further action.

Thank you and welcome.

DR. HARRINGTON: Thank you, Dr. Dal Pan.

The next presentation is by Dr. Shashaty who will give us an overview of aprotinin.

Trasylol (aprotinin) NDA 20-304: Overview

DR. SHASHATY: Good morning.

[Slide.]

My name is George Shashaty. I am the medical reviewer for Trasylol NDA 20-304. The purpose of my presentation is to provide the backdrop for the rationale for this meeting. Trasylol is a small-molecular-weight protein derived from bovine lung. It is a serine protease inhibitor that has antifibrinolytic and other pharmacologic activities.

[Slide.]

The current indication for Trasylol is for the prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at increased risk for blood transfusion and blood loss.

It must be noted here that the current

indication is more restrictive than the indication that was extant during the periods in which the studies to be discussed today were performed.

[Slide.]

Trasylol was the subject of a Cardiovascular and Renal Advisory Committee meeting on September 21st, 2006. The purpose of that meeting was twofold. The first was to review observational studies published by Mangano, et al., and Karkouti, et al., that suggested an excess of adverse reactions associated with the use of Trasylol.

The second was to evaluate anaphylactic reactions associated with the use of Trasylol that had been reported to the sponsor and the agency. The topics that were covered at that meeting are provided in the background package beginning on Page 90 of the current FDA background package.

A significant handicap to FDA's evaluation of the Mangano study was that the FDA was not granted access to the data files from that study. Since then, the FDA has received the data files.

[Slide.]

After presentations were made by the sponsor, FDA and the authors of the publication that led to the scheduling of the advisory committee meeting, the following conclusions and recommendations were made.

First, Trasylol is associated with an increased risk of renal dysfunction. Second, the benefits of Trasylol appear to be greatest for patients undergoing complex surgery or who have other risk factors for bleeding. Third, the benefit/risk equation favors Trasylol. Fourth, the treated population should be more restricted.

Fifth, methods should be devised to minimize the frequency and consequences of anaphylaxis. When the committee members were polled on the question, does the totality of information support the continued use of Trasylol for the indication, the vote was 18 in favor, none opposed and one abstention.

[Slide.]

Subsequent to the 2006 advisory committee

meeting, regulatory actions consisted of the following major label revisions. First, warnings for anaphylaxis were enhanced. These included modification of the black box warning. Re-exposure within one year was added as a contraindication. The need for immediately available cardiopulmonary bypass before drug administration was established and the uncertainty of the test dose to predict anaphylaxis was expressly stated.

Second, in the Warnings Section, a statement was added for the increased risk for renal dysfunction and, third, the indication was restricted to patients with an increased risk of bleeding although there was no definition provided as to what constituted an increased risk of bleeding.

[Slide.]

Several days after the date of the advisory committee meeting, the agency was informed of a preliminary report of a Bayer-sponsored study regarding Trasylol. The report had been forwarded to Bayer prior to the advisory committee meeting.

Known as the i3 study, this was an observational study of 66,435 patients undergoing CABG with CPB between 2003 and 2006 and receiving antifibrinolytic therapy, either Trasylol, aminocaproic acid or tranexamic acid.

The conclusions from the study indicated that, with or without propensity-score adjustment, the administration of Trasylol as compared to aminocaproic acid or tranexamic acid during CABG with CPB was associated with significantly greater relative risks for renal failure, death, acute heart failure and stroke but not for myocardial infarction.

The sponsor stated that the rationale for nondisclosure prior to the advisory committee meeting included time restraints for sponsor review and a limited knowledge of the study within the sponsor company. The raw data files from this study have been received by the agency. The analyses and conclusions from the study as well as additional analyses and conclusions performed by FDA will be presented in depth during the FDA's

epidemiology and statistics presentations later this morning.

[Slide.]

I would like to briefly discuss the approved indications for the two antifibrinolytic drugs with which Trasylol has been compared in many of these studies. Both are relatively old drugs and data from randomized controlled trials for their use in CABG and CPB are not available to FDA.

There is, however, a large amount of literature published particularly related to aminocaproic acid. In the United States, the use of aminocaproic acid is vastly greater than that for tranexamic acid.

The labeled indication for aminocaproic acid is long and permits use whenever fibrinolysis contributes to bleeding. Highlighted in here in red is the phrase that relates to its use in cardiac surgery. The labeled indication for tranexamic acid is much more restricted and is for use in patients with hemophilia for short-term use to reduce or prevent hemorrhage and reduce the need

for replacement therapy during and following tooth extraction.

[Slide.]

In February, 2007, Mangano, et al., using the same database that had been used for the initial study on Trasylol reported on longer-term mortality rates in patients receiving or not receiving an antifibrinolytic agent during CABG with CPB.

In this JAMA publication which included most of the centers that had contributed to the database, the reported hazard ratio for death at five years following surgery was significantly greater for patients treated with Trasylol as compared to those who received no antifibrinolytic agent.

Patients treated with aminocaproic acid or tranexamic acid exhibited no increase in the risk of death compared to those who received no antifibrinolytic agent. The raw datafiles have been received by the agency. The analyses and conclusions from the study, as well as additional

analyses and conclusions performed by FDA, will be presented in depth during the FDA's epidemiology and statistics presentations later this morning.

[Slide.]

Since the publication of the original Mangano study, additional information on the use of and adverse reactions related to Trasylol have been reported. Data from a randomized controlled trial referred to as the BART trial comparing the efficacy and safety of Trasylol, aminocaproic acid and tranexamic acid in high-risk cardiac surgery patients have been reported but only in abstract form.

To date, approximately 2,400 of a planned 3,000 patients have been enrolled and, after the latest interim analysis by the Data and Safety Monitoring Board at about 2,000 patients, the trial has been allowed to continue without modification.

As a reflection of the consensus of the primary users of antifibrinolytic drugs during CABG with CPB, the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists

Guideline states that the use of aprotinin during CABG with CPB is a Class I recommendation with A level of evidence.

There is a typo on this slide. That is a 2007 recommendation not a 2006.

A number of other retrospective and metaanalytical studies have been or in in the process of being published. In general, these studies suggest that renal dysfunction is the only adverse reaction that occurs with greater frequency after the use of Trasylol compared to the use of other antifibrinolytic drugs or no antifibrinolytic drug.

A to-be-presented abstract describing an observational study suggests an increased risk of death over the long term associated with use of Trasylol.

[Slide.]

The use of Trasylol for its labeled indication is based on the balance between its benefits and risks. Trasylol has consistently been shown to diminish blood loss and the need for

transfusion when administered during CABG surgery with CPB.

Despite this benefit, Trasylol has never been demonstrated to improve survival which would seem to be its most desired salutary effect. There appear to be definite risks associated with the use of Trasylol the best documented of which are renal dysfunction and the risk of anaphylaxis.

Some of the recent studies also suggest the possibility of increased rates of cardiovascular and cerebrovascular adverse reactions and the risk of death.

In this era, blood transfusions are believed to be relatively safe but accurate data on adverse reactions and death due to transfusions are not readily available. Nonetheless, the continued use of Trasylol should be based on whether the risks associated with its use exceed the risks associated with the transfusion of blood.

[Slide.]

The agency is particularly interested in the committee's discussion of and recommendations

for the following topics. First, based on the totality of available information, should Trasylol continue to be marketed for its labeling indication. Second, if so, should modifications be made to label. If so, what changes are recommended. Third, should the sponsor be required to carry out and submit the results of additional studies to demonstrate the efficacy and safety of the use of Trasylol during CABG with CPB.

DR. HARRINGTON: Thank you, Dr. Shashaty. I will just remind the panel we are going to have time for questions later this morning of all the speakers so we are going to concentrate it in that time period. We will also have the entire afternoon available for questioning and discussion of the relevant speakers.

Because we have a large and diverse panel, not all of whom might be familiar with the issues of bypass surgery, the use of this agent and the need for blood transfusion, we have asked Dr. Corso to give a brief overview of the procedure and some of the issues that a therapy like this might be

desired to address.

So, Dr. Corso.

Coronary Artery Bypass

DR. CORSO: Thank you.

[Slide.]

This morning, as you said, I am here to try to give an overview of what heart surgery is, bleeding, transfusions and what we do to try to stop it. For those who are heart surgeons in the room, I will apologize for showing you a couple of things that you clearly know as well as I do.

[Slide.]

As you know, coronary-bypass surgery started back in about 1946 with Vineberg when he implanted mammary arteries into the heart muscle, itself. There was no heart-lung machine and the progression of experience, techniques, et cetera, increased and progressed over the next several years. There are doctors in there who performed it without the heart-lung machine and, today, we are still doing patients on the heart-lung machine and without. But that is clearly what we are here to

discuss today.

[Slide.]

The classic operation today and for approximately 84, 85 percent of the patients being done in this country is this standard operation, sternotomy, mammary-artery harvest, saphenous-vein removal, cannulation for cardiopulmonary bypass, arrest the heart to protect the heart, anastomosis, weaning from bypass and reverse heparin and stop bleeding.

[Slide.]

Today, we are doing things in a different way. We do an operation for a patient specifically as one operation does not fit all. There is on-pump surgery through a sternotomy I just described, off-pump surgery, meaning no support with cardiopulmonary using sternotomy, small incisions on pump, small incisions off pump.

All of these have specific aims to decrease risk and cost.

[Slide.]

For those not aware of what heart surgery

looks like, this is obviously the heart that is cannulated through the aorta, through the right atrium. This is the heart here. The patient's aorta is being cross-clamped. Cardioplegia solution is being injected to cool the heart so that the heart is arrested and to allow for a very accurate anastomosis.

The off-pump surgery that I particularly subscribe to where I think you can do in about 50 percent of the patients, we do not use any of this and a heart is allowed to beat and support the body which has some advantages we are not going to talk about here.

[Slide.]

This is what it looks like in the operating room when we are doing coronary bypass surgery or any other kind of heart surgery.

This is the heart-lung machine. As you can see blood is going out through tubes, through oxygenators, heaters, coolers and back in which creates its own issues we will talk about in a minute.

[Slide.]

This machine here is a cell saver used to aspirate blood from the pericardial sack to allow for that blood to be washed and retransfused and preserved.

[Slide.]

This is the type of operation you see off pump--

[Slide.]

--or on pump, coronary anastomoses done in various parts of the heart with obvious areas of open blood vessels that need to be closed both technically, chemically and hematologically.

[Slide.]

The main complication of cardiopulmonary bypass, and this particular slide came from a talk that I give on why off-pump surgery is good, but complications of the heart-lung machine are many. Even though the gold standard for coronary bypass valve surgery, et cetera, are with the use of the heart-lung machine, the use of it does have complications, the complications of cannulation,

meaning putting the tubes in the heart.

You can get bleeding from these open holes, dissections of the aorta, embolization of atherosclerotic debris from the aorta itself.

[Slide.]

The actual transfer of blood from the patient's body through tubes, through oxygenators, heaters, coolers, et cetera, creates many cascades all of which can have a negative effect postoperatively. Consumption of coagulation factors, platelet damage, which is important, pyrogen production, leukocyte-mediated endothelial damage, complement-induced increased poracity upon the permeability, bradykinins, et cetera.

[Slide.]

Neurologic is a significant problem with coronary bypass surgery on pump especially. That number varies depending on studies but it is anywhere from 0.8 up to 5 percent depending on age of the individual. But, again, it relates frequently to the use of the heart-lung machine embolization, et cetera.

[Slide.]

The main complications of CABG, in summary, are death, MI, CVA, infection and bleeding. We are going to talk about this bleeding because it is a major problem especially today with our cardiology colleagues now stuffing the patients full of drugs that prevent clotting for their own good but it makes our life absolutely miserable.

70 percent of the complications of coronary bypass grafting have been associated with the use of the heart-lung machine which is why some of us have moved on to using off-pump surgery if possible.

[Slide.]

Bleeding is a problem with heart surgery no matter how good and slick we think we are. There are over 300,000 coronary bypass surgeries done in this country per year. 46 percent of them receive blood or blood products. 2.5 percent of them go back to the operating room for bleeding that needs to be controlled mechanically. This comes from the STS database.

[Slide.]

Blood transfusions are important, although there are many--you can poke holes in many of the studies talking about a unit of blood is not dangerous or it just relates to the risk of cross-match problem. The fact is, the more blood you give, the higher mortality of patients is.

Clearly, people who bleed a lot have other problems as well. However, the use of blood, in itself, can have a significant outcome effect on those patients.

[Slide.]

The Northern New England Cardiovascular Disease Group looked at 8,000 patients and found out that the amount of blood and the hematocrit was an important factor in the low output failure after coronary bypass surgery.

[Slide.]

The adverse effects post-surgery have been demonstrated in multiple studies showing a prolonged need for mechanical ventilation, impaired wound healing, multiple organ-system failure,

prolonged length of stay in the hospital, increased post-operative mortality.

[Slide.]

Another group, 10,000 patients coming from Blackstone's paper out of Cleveland Clinic, looked at 10,289 patients. The blood-transfusion rate was 49 percent. Platelets, fresh-frozen plasma, were seen at 2.5, cryo in 0.5, risk adjusted, increased early hazard at six months and late hazard at ten years. Decreased survival is dose-dependent--i.e., the number of units of blood given.

Unadjusted risk, five-year survival in non-transfused versus transfused patients was 80 percent and 63 percent.

[Slide.]

Further, looking at outcomes of patient survival in numbers of units transfused, the greater number of transfer, the lower the long-term survival was. This is looking at that group of patients looking at three, six months up to nine years.

[Slide.]

Finally, the large-scale study looking to seek isolated CABG relating transfusions and outcomes, each unit of red blood cells transfused is associated with an increased risk of mortality, renal failure, intubation, infection, cardiac, neurologic and overall rates of complications.

So, consequently, blood transfusions and the need for them is not without its own risks. The idea of being able to try to stop that is, obviously, uppermost in our minds.

[Slide.]

What are the predictors of post-operative bleeding, other than the use of the heart-lung machine; advanced age, small body size, meaning that patient who goes on the heart-lung machine, the smaller they are, the more the blood will be diluted, the lower the hematocrit, the more need to transfuse.

Anti-platelet and antithrombolytic drugs; most of us have gotten used to operating with aspirin. Now some of us are being forced to operate in the presence of plavix which is a much

more important factor as far as post-operative bleeding, good for stents, not good for heart surgery.

Prolonged operating time; the longer the operation takes, the more the platelet dysfunction is and coagulation problems develop. Emergency operations are done fast, therefore less time taken to stop bleeding on the way in, more trouble having bleeding on the way out.

Other comorbidities, meaning the sicker the patient, the more likely that that patient will bleed.

[Slide.]

Aspirin has been a problem as far as increasing the risk of bleeding. Most of us have gotten used to it and I believe, right now, it has sort of become the rule. We give aspirin immediately after surgery. We don't stop it preoperatively. Plavix, we would love to stop perioperatively.

[Slide.]

But, in our particular situation, we have

a very large catheterization laboratory doing about 18,000 procedures, so we wind up doing an awful lot of surgery the day or the day after, and the plavix has already been loaded and you are behind the 8-ball.

But, in any effect, aspirin does increase it but I don't think that is going to change because there has been demonstrated improvement in patency of grafts done on patients who are on aspirin so that is not going to change.

[Slide.]

As mentioned by Dr. Shashaty, the STS has come out with various ideas on blood conservation and what to do in patients and what is a real recommendation and not.

[Slide.]

Clearly identify the high-risk patient preoperatively. Obviously the patients who are hemophiliacs and have other blood dyscrasias are a problem. Patients who are on plavix are a higher risk.

But the recommendation is that high-dose

or low-dose aprotinin is beneficial in decreasing bleeding. In our own institution, we use Amicar routinely and aprotinin in very high-risk patients and clearly there is a difference in that regard.

Lysine analogs as mentioned before. The cell saver that I showed you in the picture is very important because you can take the cells, wash them and get rid of some of the debris that causes some of the coagulation difficulties in transfusing those patients.

And then have a blood-transfusion algorithm based on testing of those patients both preoperatively, intraoperatively, in the intensive-care unit, and have a multi-modality approach so that you can have the hematologists involved when you run into problems, the anesthesiologist, the cardiologist who would, hopefully, agree to let you stop of the plavix to get them further out before they go the surgery.

[Slide.]

Class II recommendations; preoperative Epogen. If the patient has got a low crit, you

have time and you want to increase that patient's hemocrit, especially in Jehovah's Witnesses, then I think it is worthwhile to use. Sometimes, you don't have the time to do that.

In centers that have advertised themselves as Jehovah's Witnesses centers, they will take hematocrits up to 16 grams hemoglobin which is something that we don't do but, clearly, it is effective if you have time.

Intervention in patients with thrombocytopenia. That is especially a problem these days when most of these patients are on anti-platelet drugs.

Autologous predonation sounds really good and it works very well when you can, but you have the unstable patient or the patient with critical coronary anatomy, you take one or two units off of blood now, you have an unstable patient with critical anatomy who is anemic, then you have an emergency operation and you wind up using more blood.

Off-pump surgery, I am big proponent of

that. We do approximately 50 percent of our patients, coronary-bypass patients, off pump. We have demonstrated that you can save blood. There is no hemodilution. There are less issues that relate to the heart-lung machine.

Alternatives to blood sampling sounds simple. If you need to take a blood test, and you can take a small tube versus a large tube, maybe a small tube is a good idea.

Total quality management of the whole program will save you blood.

This one is the bane of my existence, discontinue plavix five to seven days pre-op. That works in certain situations and it does work. The patients do bleed less, but when they are taken down to the operating room, you have got to do this patient in the next day, two days. Stopping it for two days does nothing. Stopping it for five to seven days does. So, when possible, I think that is a good idea.

Red blood-cell transformation of less than 6; there has been enough written about that

particular subject to fill this room. What is the mortality of a hemoglobin of 6, 7, 8, 9, 10? What age? What comorbidities? I think you have to individualize on these patients. We do not take it down to 6 unless it is a very young individual.

Blood-component transfusion for clinical bleeding. Obviously, if their coagulation cascade is off, we need to treat them with whatever is necessary for that particular situation.

[Slide.]

The problem that we run into and that you all are going to be debating today is whether aprotinin is safe and equally effective as the other alternatives.

[Slide.]

The work force for the STS says that it does decrease bleeding. We are not talking about renal insufficiency, et cetera. I will submit to you, though, a lot of blood transfusions decreases survivability. So there is a balance there that needs to be made and I think that is what you are here for.

I am going to skip a couple of slides here because I am running out of time.

[Slide.]

But, basically, what we need to do to save blood is pretty straightforward. Preoperative measures, make sure that you have got the patient in as good a condition as possible, stop Coumadin, stop Lovenox, aspirin. We don't stop plavix. We do--the rest of the issues are questionable but potentially possible.

[Slide.]

Intraoperative factors, Trasylol for high-risk patients, a good technique in the operating room.

[Slide.]

Using small circuits for the cardiopulmonary bypass machine that decreases dilution is worthwhile.

[Slide.]

And the best strategy is reduces--using these small circuits does reduce the systemic inflammatory response, decreases dilution and does

allow for less blood transfusion. These small circuits avoid reduced graft patency of off-pump surgery. I will be glad to debate that at any time.

Let's move on.

[Slide.]

Intra-op, you can use various glues, stimulants for clotting, et cetera, and they all work. They all cost a lot of money, too. So I think nothing is as good as a good technique and a patient that can clot. But these things will benefit you there.

[Slide.]

Post-op measures, fairly standard, small tubes instead of big tubes. Make sure your coagulation is working. Explore early if you think that patient has a problem with bleeding because you can stop a lot mechanically after while.

[Slide.]

Conclusions; a multi-modality approach to blood conservation is essential. Guidelines are useful. Aprotinin is an important adjunct to

stopping bleeding especially in these very high-risk patients and avoids the blood transfusion cardiac surgery, decreases cost, morbidity and probably mortality.

Thank you.

DR. HARRINGTON: Thanks, Dr. Corso. That was a very nice overview and I think particularly helpful for people not familiar with the procedure. Thank you.

Next, we are going to hear from two investigators who have performed analyses and written in this field. The first is Dr. Karkouti. Again, I will just remind him that he has ten minutes. He is followed by Dr. Mangano and then we will take a brief break before we hear from the sponsor.

A Propensity Score Comparison of Aprotinin versus Tranexamic Acid: Updated Analysis of a Large, Single Center Cardiac Surgery Database

DR. KARKOUTI: Thank you very much for inviting me to present our study again.

[Slide.]

Just a reminder. Our study was a propensity-score comparison of aprotinin versus tranexamic acid. I am going to take this ten minutes to present an updated analysis of our data. Our study was a large single-center cardiac-surgery database as opposed to the other ones you will hear which were multicenter.

In the analysis, I am going to focus on the effects of confounding when you are assessing the effects of aprotinin and outcomes.

[Slide.]

There was a mistake in the beginning. I was never a consultant for Bayer. All I have, in terms of conflict of interest, is $3,000 that I received during 2005-2006 for various speaking engagements.

[Slide.]

Basically, the way we use aprotinin at our hospital is we use it for the highest-risk patients. Our guidelines specifically state that we use it for those who we expect to be at high risk of massive bleeding or coagulopathy.

Everybody else gets tranexamic acid. That works out to about 10 percent of our cases get aprotinin, about 90 percent get tranexamic acid.

Unfortunately, not every patient who is very high risk gets aprotinin, fortunately for our study purposes, and not every moderate or low-risk patient gets tranexamic acid. So we had an opportunity to compare the patients who had aprotinin with those who had tranexamic acid who had similar risk profiles using statistical means propensity analysis.

Our database is prospectively collected. It is a clinical database. It has been validated. It is used for research often. For this analysis, I used data from 1999 to 2006. For our study, we went up to 2004 so have two more years of data now.

Basically, we have 948 aprotinin patients and about 14,000 tranexamic acid patients in the current analysis I am going to present. What we did was we used propensity-score modeling to match patients who received aprotinin to those who received tranexamic acid matching for the baseline

likelihood of receiving aprotinin.

Now, it is critical when you use propensity analysis--and you will hear a lot more about this when FDA presents its epidemiological reviews--it is critical when you use propensity analysis that you know what goes into the decision to use aprotinin or any drug that you are assessing. You can account for this decision in the propensity-score model.

It is also recommended that this decision should not include any outcomes that you are going to measure so that you can assess the effects objectively.

[Slide.]

Now, this creates a problem because when we use aprotinin, we base it not only on preoperative risk factors but also perioperative risk factors. We base it on the expectation of long pump runs and massive blood transfusion and coagulopathy. These things are not quantifiable when we decide to use aprotinin, but it is quantifiable when we go back to try to assess it or

try to assess the outcomes of aprotinin.

Since the success of propensity matching can only be shown if you have good baseline matching of the patients in terms of prognostic factors, what I am going to do is present to you what happens with propensity analysis when you look at the different sets of confounders.

[Slide.]

So, basically, there are three sets of confounders that go into the decision to give aprotinin. There is the preoperative baseline prognostic factor, age of the patients, urgency of surgery, complexity of surgery. These we know when we decide to use aprotinin.

There are also the pump-related factors that affect outcomes, pump duration and circ arrest, deep hypothermic circulatory arrest, duration, whether or not the patient goes on it. Blood sugar and hematocrit on pump are important in terms of outcome but they don't really go into the decision whether to use aprotinin.

So we take a guess. We guess whether the

pump time is going to be long or whether the patient is going to go on circ arrest and base our decision on that.

There are coagulopathic-related things. Massive blood transfusion is one of the worst complications in cardiac surgery and we base our decision to use aprotinin on how likely we think that patient is going to massive blood transfusion and massive coagulopathy which we have defined here as needing more than four units of FFP.

[Slide.]

So the first one we do have available we can quantify and most of the observational studies are just for the preop ones. We have adjusted for the second and third ones just to see what the effects are when you do different model.

So we did three models. In the first one, we just included preoperative variables. In the second one, we included the preop plus the pump-related variables. In the third one, we included preop plus pump-related plus coagulopathy-related and that we defined as anyone

who gets five or more units of red cells perioperatively or more than four units of FFP perioperatively.

As you can see, each model matched about 750 patients. We had about 500 matched patients in our original study and the model's performances were similar in terms of C-index. I have listed the C-indexes there.

So if you look at the diagnostics in terms of C-index, you don't notice any difference in the models that way.

All models produced very good matches in terms of prognostic factors in terms of patient comorbidity and surgical factors. So the preoperative variables were well matched with all three models.

What about the intra or the perioperative variables. Well, it wasn't so well matched, depending on the models that you look at.

So what I have here is the prematched characteristics of the patients in terms of pump time, circ arrest, whether they went on it or not,

the incidence of more than four units of red blood cells or more than four units of FFP as a measure of coagulopathy.

As you can see, before matching, in the 10,000 patients here, in 950 patients here, there were large differences between the two groups. So, if you don't do any matching, you are comparing a very high-risk group to a relatively low-risk group.

[Slide.]

In the first model, where we did matching, based only on preoperatively known factors, you kind of reduce the differences but still there is a large difference. There is a 20-minute difference in the average pump time between the two groups, aprotinin group, tranexamic acid-matched group, so about 750 patients in each group.

Then, in terms of circ arrest and the coagulopathy, the aprotinin group is 50 percent higher risk, more than 50 percent higher risk, than the tranexamic-acid group. So if you take these matches and look at the outcome, you are

essentially comparing a higher-risk group to a lower-risk group. In my opinion, you are comparing apples to oranges. It is not a fair comparison, but the argument is made that, well, these are really outcomes.

The question is are they outcomes? To my knowledge, there is no evidence, there is no reason, why aprotinin would be prolonging CPB duration compared to the alternatives. So I don't think that is an effect of aprotinin. So, really, it can't be considered an outcome or there is no reason why giving aprotinin would make somebody go on having circ arrest.

There is also no data, as far as I know, that aprotinin is worse than tranexamic acid in terms of efficacy. So there is no reason to expect giving aprotinin should increase massive transfusion or massive coagulopathy.

So, in my opinion, these are variables that we need to adjust for if we are going to get a fair comparison between aprotinin and tranexamic acid.

[Slide.]

What about Model 2 where we put the pump-time variable, which essentially is pump duration and whether the patient went on circ arrest. As you can see, this is Model 1 now, just from the last slide. This is Model 2. As you can see, these differences are gone.

However, the coagulopathy issue is still there with the massive coagulopathy still pretty high relative to the tranexamic-acid group.

[Slide.]

When we do the third model, those differences disappear, too. So here, I think, we would have a fair comparison comparing aprotinin to tranexamic acid which is what we did.

[Slide.]

These are the results of the three models. It is a busy slide but, once I explain it, I think it will make sense. On the X axis, we have the odds ratio of the complications of aprotinin relative to tranexamic acid. So if the odds ratio is over 1.0, aprotinin has higher risk.

On the Y axis, we have the complications. We looked at renal dysfunction which we define as a 50 percent increase in creatinine or dialysis dependence, renal failure, which was basically needing dialysis, stroke, MI and mortality.

The lower lines in each group are the Model 1, where we adjusted for preop variables, Model 2 where we adjusted for pump variable and Model 3 where we adjusted for pump plus coagulopathy.

As you can see with Model 1, we just adjusted for preoperative variables. Almost every complication is statistically significantly higher for aprotinin, renal dysfunction 70 percent higher, renal failure about twofold, stroke about threefold higher, MI about twofold but that didn't reach significance, mortality 30 percent higher but that didn't reach significance.

Also, what you can see after adjusting for the pump variables, all the points move to the left. So there is some confounding in terms of these estimates explained by the pump variables.

Renal dysfunction still stays significant. Renal failure stays significant with the p of 0.45 or something like that, close to being nonsignificant.

Stroke, MI and mortality, in fact, goes the other way, but stroke and MI lose their significance. There is a large drop in stroke and, in fact, pump time is one of the strongest predictors of having a stroke.

In the third model, the renal dysfunction still stays significantly strong so a p of 0.002, I believe. Renal failure is no longer significant. Stroke and MI basically go closer to 1.0 and mortality, again, stays near 1.0.

So the argument here is which one is the real model, which one should be used. My opinion is we should use the third one. A lot of people are going to disagree with that, but, in my opinion, using the first one is not right.

As a caveat, when you do logistic regression, and let's say you are modeling renal failure, no one would argue that you shouldn't put the pump time or massive bleeding into that model.

So I don't see why it should be any different when you do propensity analysis.

In fact, when we do logistic regression, you see the same results except rental failure stays significant in all of our logistic-regression models. Renal dysfunction we can't do because we don't have the data in every patient. But stroke and MI and morality, there is no signal that aprotinin increases those adverse events.

[Slide.]

So, whether you agree or not with my conclusions, I think one conclusion is clear. Except for renal dysfunction and possibly renal failure, adverse outcomes associated with aprotinin use are highly dependent on perioperative confounders. As long as you don't adjust for these, I don't think you are comparing apples to apples anymore.

Existing observational studies may not have accounted for these confounders; hence, prognostic imbalances may explain their findings.

Thank you very much.

DR. HARRINGTON: Thank you, Dr. Karkouti.

The next presenter is Dr. Dennis Mangano who will be giving us a review and an update of his group's analyses that were published, and I believe you have copies, from the New England Journal and JAMA, or at least have the references.

Safety of Aprotinin vs. Epsilon Aminocaproic Acid vs. Tranexamic Acid

DR. MANGANO: Thank you, and thank you for inviting me.

[Slide.]

I have been asked to look at this problem from 20,000 feet so this will not be detailed scientific, but we will look at safety surveillance contrasting aprotinin and two antifibrinolytics and the paradigm is observational study.

[Slide.]

There are conflicts of interest, not by me, personally or by my non-profit IREF, but by some of the investigators. We address here three studies; the January, 2006 New England Journal article, the February, 2007 JAMA article and, more

recently, the May 2007 Journal of Thoracic and Cardiovascular Surgery article contrasting four countries' outcomes.

[Slide.]

With respect to these, the New England Journal article, there were no conflicts to report. None of the investigators or the Foundation has ever had a relationship with any of the sponsors of the three drugs including Bayer.

[Slide.]

With respect to the JAMA article published in February of this year, two investigators from Romania and the United States that are multicenter study investigators did have a relationship between '94 and '99 and in 2002 with Bayer regarding meeting fees and honoraria neither of which had an existing relationship at the time the study was performed, analyzed or published.

[Slide.]

Regarding the Journal of Thoracic and Cardiovascular Surgery article, two investigators from Canada and the United States, as I understand

it, are currently consultants to Bayer Pharmaceuticals, but I cannot comment any further regarding the nature of those relationships.

[Slide.]

To address the issue, I would like to again revisit some of the issues presented in last year's meeting including early development, the graft-occlusion and kidney-toxicity issues, the long-term mortality issues and anticipated questions by the committee with some responses and, finally, my impressions.

[Slide.]

As we know, transfusion was discovered in the 30s in Germany, used in patients in 1959.

[Slide.]

Thereafter, Dr. Royston, who I think is present here, published an article describing 22 patients' experience with aprotinin versus control and indicating blood-sparing properties.

[Slide.]

Cosgrove, in the ATS, published a high-dose, low-dose, versus control randomized

trial with aprotinin indicating blood-sparing properties.

[Slide.]

On the basis of this, in 1993, FDA approved aprotinin for the limited indication of patients undergoing bypass-graft surgery using cardiopulmonary bypass at increased risk for bleeding.

[Slide.]

Thereafter, a series of randomized controlled trials were conducted.

[Slide.]

By 1997, four years after approval, the evidence seemed to indicate that there were substantial blood-sparing effects with aprotinin so it was effective. Nearly all of the randomized controlled trials seemed to indicate that there were no safety concerns with the use of this medication in these patients.

[Slide.]

However, at about the same time, an issue emerged regarding newly implanted graft occlusion

associated with aprotinin.

[Slide.]

That manifested from Cosgrove's original study in 169 patients not only finding effectiveness but also raising concern.

[Slide.]

At autopsy, Dr. Cosgrove concludes, acute vein-graft thrombosis was found in six of 12 vein grafts studied at post mortem examination in patients receiving aprotinin but not in any of the five grafts in patients receiving placebo.

[Slide.]

This is of concern, because these are newly implanted grafts and these are the reasons for patients coming to surgery in the first place.

[Slide.]

That led the FDA to look at this issue, and the FDA did look at the issue, reviewing 1200 patients that were treated with placebo versus 2200 patients treated with aprotinin. They indicated a significant association between aprotinin use in coronary-graft closure, acute closure, was found.

[Slide.]

This led to the image study conducted in approximately 700 patients, a randomized controlled trial.

[Slide.]

This study was conducted between 1993 and 1995. The results were known in 1995 but first published in 1998, three years later. That study included 13 international sites, an equal split in terms of randomization and angiography performed at 11 days after implantation of the graft.

[Slide.]

The prespecified primary endpoint of that study was acute vein-graft occlusion.

[Slide.]

The result indicated a statistically significant increase of 41 percent in acute graft occlusion associated with aprotinin use versus placebo use.

[Slide.]

One inference from that study and the inference that I drew at the time, when applied to

100,000 administrations of the drug compared with placebo or no drug as the caveat, would be that aprotinin would be associated with an increase of 4,500 vein-graft occlusions per 100,000 administrations of the drug raising concern.

[Slide.]

However, the conclusion of that study are foretelling for they stated that, in this study, the probability of early vein-graft occlusion was increased by aprotinin. This is an interesting choice of words. Then, on the basis of subsequent secondary post hoc analyses attempting to understand why the primary endpoint was what it was, it states, the outcome was promoted by multiple risk factors for graft occlusion, so this randomized controlled trial finding, primary finding, was adjusted.

[Slide.]

The regulatory decision on the basis of this data was that there was no substantive change--that is, no black box warning--but the image data and the associated interpretations as

published were added to the package insert and that occurred in May, 1998.

[Slide.]

As well, in 1998, an unrelated but important regulatory action took place.

[Slide.]

The indication was expanded.

[Slide.]

The basis for the expansion was the determination of anti-inflammatory properties associated with aprotinin. And that was clear.

[Slide.]

The indication expanded to now include any patient undergoing bypass graft surgery with the use of cardiopulmonary bypass regardless of risk of bleeding, in effect.

[Slide.]

Parenthetically, this expanded use based on anti-inflammation is a curious one but one understands it at the time. In retrospect, however, our group has been involved in studies of Bextra, pexelizumab and cariporide all of which we

have found to be unsafe in these patients even though they mitigated inflammation in these patients.

[Slide.]

The net effect over the period following this in 1998 to 2005 was a rapid growth in the use of aprotinin--

[Slide.]

--to conservatively more than 350,000 patients receiving aprotinin in the single year of 2005. In January of 2006, the projection was greater than 700,000 patients would receive aprotinin worldwide in the year 2006.

[Slide.]

However, in January of 2006, an issue arose regarding kidney toxicity. This was based on our research involving a study called Epi 2 which enrolled patients from 69 centers in 17 countries. It was prospectively designed. It was not an accumulation of hospital records. It was designed over a period of three years conducted over five years and collected more than 11,000 pieces of data

per patient prospectively.

This observational study investigated the question of aprotinin versus Amicar versus TEA versus no antifibrinolytic control in a substantial number of patients.

[Slide.]

Essentially, the finding, as presented last year, was that we found statistically significant associations between aprotinin use and renal dysfunction compared with no antifibrinolytic use and compared with both Amicar and TEA, neither of which were associated with such renal outcome for dysfunction, dialysis and a composite variable, adjusted odds of 2.41.

[Slide.]

As well, we found an interesting dose-response relationship which indicated a dose response compared with control of low and high dose for these markers of renal dysfunction or renal failure.

[Slide.]

As well, we found indications,

particularly after adjustment, with respect to neurologic--that is stroke and encephalopathy outcome--cardiovascular, heart failure and MI and composite outcome as well as a suggestion with respect to in-hospital death. But that turned out not to be significant in multivariable analyses. But certainly there were signals there as we thought.

[Slide.]

Interestingly, when we look at the blood-sparing effects and contrasted fibrinolytics versus aprotinin, we found that both were equivalent, both classes of drugs, with respect to blood loss, chest-tube output and transfusion of any product; that is, efficacy was comparable.

[Slide.]

The advisory committee met on the 21st of September last year.

[Slide.]

As we heard, no change was recommended based on these findings.

[Slide.]

However, what emerged afterward was the emergence of a study.

[Slide.]

This looks inflammatory but it tells a story and it is the source of the only data that I have regarding this important accumulation of hospital records in which the FDA laid claim to new data--

[Slide.]

--which says that preliminary results of the study demonstrate that use of Trasylol may increase the chance for death, serious kidney damage, heart failure and stroke.

I found this to be a remarkable occurrence, especially after the advisory committee last September and my reactions to that committee. 67,000 patients were included, presumably, in this accumulation of records with 30,000 aprotinin and 37,000 placebo. This is an enormous undertaking to accumulate so many hospital records.

[Slide.]

I found it interesting with respect to the

damages that were associated with aprotinin use--

[Slide.]

--particularly serious kidney damage and our findings which seemed to be, in effect, validated by this study.

[Slide.]

Our findings with respect to in-hospital death, our findings with respect to congestive heart failure.

[Slide.]

And our findings with respect to stroke.

[Slide.]

What emerged during that year as well were a series of other studies some of which, unfortunately, are not presented here--

[Slide.]

--but all of which have indicated an association between aprotinin use and increased risk. Although not being randomized controlled trials, the findings were impressive. Thus about 80,000 patients in this compendium of studies seems to indicate that there may be a problem with

increased risk.

[Slide.]

So, in 2006, aprotinin safety was challenged with respect to kidney toxicity.

[Slide.]

But that is not the first challenge, for, in the press release of aprotinin when it was approved in 1993 by the Food and Drug Administration based on two placebo-controlled trials conducted in the United States that is the basis for approval. The release stated specifically kidney toxicity was also a problem in some patients in these two trial. That is a red flag in yet two rather small studies.

[Slide.]

So, in effect, in 2006, we did not challenge its safety. We rechallenged it based on the original FDA finding and concern regarding toxicity.

[Slide.]

In 2007--

[Slide.]

--a second issue emerged from the same database wherein 51 of the 69 centers had agreed to participate in a long-term--it turns out to be 20-year--survival study of our original cohort.

[Slide.]

There were 3,876 patients for whom we have long-term data collected prospectively and meticulously and at considerable labor, and that allowed us to investigate again these four drugs.

[Slide.]

Here we present now Kaplan-Meier univariate, in effect, curves but cumulative morality curves and we contrast that among study groups finding that, among all patients, aprotinin patients significantly fared worse than either control or the other two drugs with respect to five-year survival.

[Slide.]

If you look at the subgroup of patients who survived initial hospitalization, left the hospital and then investigated the long-term post survival effects, we find similar findings in these

groups of patients, again cumulative or adjusted survival curves.

[Slide.]

The adjustments with respect to a proportional hazard were substantial and, in the face of either propensity adjustment or not, our findings held even taking into account multiple confounders. Again, these data have been looked at fairly carefully.

[Slide.]

In 2007, then, long-term mortality was challenged by our observational findings.

[Slide.]

Last year, a series of questions was posed by the Committee.

[Slide.]

Some of those are answered and some of those, I think, I will address here to pre-empt certain questions and make the process more efficient. Those questions relate to the studies that we have presented in New England Journal and JAMA regarding pre-existing disease, U.S. versus

non-U.S. findings, different definitions and renal findings being transient or inconsequential as well prior study findings regarding the randomized controlled trials and meta-analyses that are performed.

[Slide.]

With respect to pre-existing disease--

[Slide.]

--the comments have been made regarding aprotinin patients being sicker as the rationalization for our findings.

[Slide.]

We have investigated that and we believe our findings survive any differences in disease status as documented by covariate adjustment of point estimates, dose-response validation, logistic regression adjustment, proportional-hazard analysis and propensity adjustment using average of covariate as well as other features, the average of covariate-adjusted survival.

As an example, with respect to these questions, let me present comparisons among

high-risk groups; that is, select the patients at highest risk and what the outcomes are contrasted among study groups for in-hospital events

[Slide.]69

If you select patients, for example, by disease category, older patients and examine the group of older patients and ask the question, of the incidence of renal events among these patients, you find that aprotinin but not tranexamic acid or epsilon aminocaproic acid has a much higher incidence of renal events as well for hypertensives, high-cholesterol women, those with vascular disease, diabetes, et cetera.

This is sort of a linear comparison, a pictorial comparison. Of course, the covariate adjustments done in multivariable regression or Cox proportional hazards are much more sophisticated. But these serve to make the point.

[Slide.]70

If you take the Cleveland Clinic Risk Score, the two types of Euro scores, the STS risk score of the VA risk score, and define a high-risk

population only, and ask the question again, country find consistent findings in the highest risk patients.

[Slide.]71

If you look at those with excessive blood loss, moderate, small or nearly no blood loss, you find, again, even in the highest-risk patients, the same consistent findings for renal events.

[Slide.]72

If you look at five-year mortality using the same paradigm, you find consistency among disease classification as well as risk index.

[Slide.]73

We do not believe that the disease status significantly impacted any of our findings and I do not believe influenced our conclusions.

[Slide.]74

U.S. versus non-U.S. was brought up.

[Slide.]

What we find simply is for all patients, U.S. or non-U.S. patients, the findings survive as well as by country the findings survive.

[Slide.]

In May of 2007--

[Slide.]

--a separate study with a separate design using the same database had been constructed and in review for two years contrasting outcomes in the United Kingdom, Canada, the United States and Germany.

[Slide.]

This was published in the Journal of Thoracic and Cardiovascular Surgery and the United Kingdom had the lowest death and outcome rate, second Canada, third United States and highest was Germany among all four for both death and morbid events. There was an independent effect of country on composite outcome.

The practices that were associated with such adverse outcomes were use of aprotinin, fresh frozen plasma, platelets, non-use of aspirin and heparin. The conclusions were significant between country differences in perioperative outcome exists and appear to be related to hematologic practices

in surgery.

[Slide.]

For example, we find the usual no-aprotinin/aprotinin incidence of composite outcome. What we find, interestingly, is that, in Germany, 7 percent of the patients in our cohort received aprotinin.

As well, with respect to aspirine, from our findings in 2002 in New England Journal, that early use of aspirin within 48 hours mitigates outcome. We find that Germany had the lowest incidence of use of aspirin in this population prevalence.

[Slide.]

Last year, we prospectively defined myocardial infarction in heart failure. We were challenged with respect to the definition. But once prospectively defined by protocol, you are stuck with the definitions. You can post hoc search those definitions for whatever intent but we are stuck. But the question arises, are our findings robust with respect to a range of

definitions of these variables.

[Slide.]

For infarction, our New England Journal definition certainly showed that aprotinin was associated with increased renal events using that definition. If we used ECG alone or the case-report form alone, we would find the same pattern. As well, heart failure, hemodynamic measures of heart failure or use of a balloon pump all showed consistent findings. These are post hoc analyses but demonstrate that the findings are definition independent.

[Slide.]

Renal findings have been labeled over the past year as transient or inconsequential and our renal findings, in fact, were challenged as rises in creatinine and questioned with respect to consequence.

[Slide.]

I don't believe renal findings are inconsequential. On the basis of 45 trials of aprotinin, we found certain renal safety signals

with respect to aprotinin use although no trial was really powered to examine the question.

Microglobulin production depletion, deposition of protein bands within the tubule cells, dose-dependent increases in creatinine, some evidence of dysfunction and platelet-fibrin thrombotic occlusions of arterioles post mortem had been signals that were raised in the earlier studies.

[Slide.]

As well, the adjusted odds found in these 80,000 patients and the issue of serious kidney damage found in the 67,000 patients seemed to indicate that there is a problem here.

[Slide.]

Increases in postoperative creatinine were found in some randomized controlled trials.

[Slide.]

However, such changes are transient and without consequence. Our changes in creatinine postoperatively are without consequences. I reported in response to a question at last year's

meeting that they have serious consequence. When you look at different measures of creatinine change from 0.1 mg/dL post to pre to more than 2 mg/dL to change plus amount greater than 2 mg/dL, you find that survival is impacted; that is, there is an association in adjusted survival.

[Slide.]

As well, among those who survived their index hospitalization, when you look at pre-discharge renal changes and ask the the question among survivors, you find that they portend or are associated with reduced survival.

[Slide.]

Prior studies. Randomized controlled trials are the gold standard in medicine. Randomized controlled trials clearly prove safety of aprotinin.

[Slide.]

I don't believe that randomized controlled trials are the gold standard for safety. They are for efficacy, clearly. But, for safety, we rely on accumulated evidence as the drug is marketed to

populations that are much more sick, older with many more diseases than those in the clinical trials.

We rely on that accumulated evidence by report and occasionally studies are done to accumulates that evidence prospective and not just through garnishing of records.

So I do not agree that randomized controlled trial are the gold standard for safety. I don't think they will be in the future either because of the cost, expense and disincentive from the business standpoint.

[Slide.]

Regarding this question, clearly the earliest studies reviewed by a formal body, the FDA, indicated a problem. So not all randomized controlled trials have indicated safety and certainly the FDA made comment.

[Slide.]

But thereafter it is claimed that all demonstrate safety.

[Slide.]

35 randomized controlled trials were depicted here and I looked at the power of these trials looking at their outcome rate in the placebo group to assess power. Even in the large one, because the outcome rates were low, their power to assess outcomes was not necessarily high.

[Slide.]

But what we see here is, with respect to efficacy--that is, need for transfusion--we see that these trials indicate and were powerful enough to determine that this drug was effective. And it is effective. And the data are reliable.

[Slide.]

But with respect to safety and renal injury, when you look at the inherent power in these trial retrospectively and go back, what you find is that there is very little power in any of these trials even in the larger ones because of the health of patients with respect to renal injury to assume any conclusion.

[Slide.]

Generally, the randomized controlled

trials were small, averaging 63 patients in aprotinin, 48 in control.

[Slide.]

In fact, 18 of the 35 randomized controlled trials performed did not assess renal injury.

[Slide.]

The conclusion from these trials is that there is no significant difference between aprotinin and control with respect to renal injury and therefore it is safe. But that conclusion should be preempted by the fact that there isn't enough power and, therefore, no conclusion should be drawn.

[Slide.]

When you look at death, MI, dialysis and stroke, you find the same issues of underpowered trials.

[Slide.]

What about combinations of these trials.

[Slide.]

There have been meta-analyses in

combinations of trials, particularly over the last year rationalizing that drug is safe. Are these meta-analyses--

DR. HARRINGTON: If you could take just two more minutes.

DR. MANGANO: I know. I only have two more slides--maybe five more slides, but it will take two minutes.

[Slide.]

Are these meta-analyses reliable in terms of heterogeneity. I don't believe so. Of the 4,390 patients in these trials, for example, in patients with increased creatinine, 1371 excluded patients with increased creatinine.

[Slide.]

As you look at patients who are excluded for receiving aspirin or anti-platelet, 25 percent of the trials had such exclusion.

[Slide.]

As you look at the trials and look at the heterogeneity for elective surgery, 65 percent included elective and the other 35 percent did not.

Primary; yes/no. Other procedures, 70 percent included other procedures and 30 percent didn't and there were vessel restrictions. So I believe that these trials were heterogeneous.

[Slide.]

Most important is, when you look at unmeasured or unreported outcomes in these trials, a surprising number of these trials, more than 50 percent, did not measure or report outcomes such as a heart failure, stroke, encephalopathy or renal dysfunction.

[Slide.]

Those are the anticipated questions and response.

[Slide.]

The impressions are as I have written them.

[Slide.]

The association of aprotinin with acute renal injury and with long-term mortality indicates that continued use is not prudent--

[Slide.]

--particularly given that there exists far safer, equally effective and less expensive generic medications, aminocaproic acid and tranexamic acid

[Slide.]

Thank you.

DR. HARRINGTON: Thank you, Dr. Mangano. Thank you, Dr. Karkouti.

Why don't we take a 15-minute break. I will remind the panel that we will have plenty of time for questions and discussion following the sponsor and FDA presentations and this afternoon as well.

DR. PHAN: I also want to remind the Committee members not to discuss the topics today outside of the meeting.

[Break.]

DR. HARRINGTON: Let's move on to the next section which will be the sponsor presentation. Dr. Malik from Bayer will make the introductions and the sponsor has a series of presentations which will occupy the next hour. Followed by that, we will hear from the FDA and their analyses of data .

We will have a short period then, after that, for questions prior to going to lunch.

SPONSOR PRESENTATION

Bayer Introduction

DR. MALIK: Good morning, Dr. Harrington, members of the committee, guests.

[Slide.]

My name is Kemal Malik. I am Head of Global Development and a member of the Board of Management of Bayer Healthcare Pharmaceuticals.

[Slide.]

On behalf of Bayer, I would like to thank the FDA for the opportunity of being here today to discuss tranexamic acid, Trasylol.

[Slide.]

Over the course of the next hour, in addition to me giving a brief overview, you will hear from the following: Dr. Sebastian Schneeweiss, who is Associate Professor in the Department of Epidemiology at Harvard School of Public Health who will give an overview of the i3 drug safety study; Dr. Pamela Cyrus, who is Vice President, U.S.

Medical Affairs, who will give an overview of the Trasylol clinical data particularly focusing on safety events;

Dr. Robert Makush who is Professor of Biostatistics at Yale School of Public Health who will discuss some of the methodological considerations of the recent observational studies with aprotinin; and, finally, Dr. Peter Smith who is Professor and Division Chief of Thoracic and Cardiovascular Surgery at Duke University Medical Center.

We will finish up with an overview from a surgeon's perspective of the use of Trasylol.

As you know, one year ago, there was a meeting of the Cardiovascular and Renal Drug Advisory Committee to discuss the risk-benefit profile of Trasylol. This was prompted particularly by papers from Dr. Mangano and Dr. Karkouti which you heard about earlier today.

At that meeting, we also presented data from our clinical-trial database. Over the past year, several events have taken place which have

required us to meet again here today.

One of these is the i3 drug safety study. This was a retrospective observational study which was commissioned by Bayer and compared aminocaproic acid, tranexamic acid and aprotinin in patients undergoing coronary-artery-bypass graft surgery.

The study was conducted by Dr. Alexander Walker from i3 and it was based from data from the premier administrative claims database.

Unfortunately, shortly after last year's advisory committee, Bayer became aware that two individuals within our organization had received preliminary results of this study prior to the advisory committee. They chose not to share these data more widely within Bayer or with the advisory committee.

On behalf of Bayer, I would like to personally apologize for this error. As was publicly stated when we published the results of an independent investigation conducted by William Taylor, no other individuals other than these two people knew of the results of this study prior to

the advisory committee meeting.

Moreover, I would like to emphasize that those consultants who are with us at the meeting did not know about the existence of these data prior to the advisory committee meeting.

Over the last year, we reviewed all the policies and procedures in our organization covering the governance of observational studies to ensure that this error is not repeated.

Since that time, Bayer has worked with i3 Drug Safety premier external consultants and the FDA to understand the i3 drug safety study further. In this effort, Bayer has become aware of a number of study design and methodology issues in particular related to the database which were not apparent at the time when the study was commissioned. These issues will be discussed further during the course of the presentations today.

In order to assure that discussion is as open and as transparent as possible, we have invited i3 Drug Safety to come to present the

results directly to you.

Bayer, after consulting with experts in the field, disagrees with i3's interpretation of the study results because we believe, in this case, they are based on an unsuitable database and that makes reliable conclusions problematic. You will hear more about this during the course of the presentations.

In closing, we look forward to discussing the data around Trasylol with you. Bayer remains convinced that, when the totality of the data is reviewed, it will demonstrate there continues to be a favorable risk-benefit profile for the use of Trasylol when used according to the label.

[Slide.]

Lastly, I would like to mention that, in addition to the presenters I have mentioned, Bayer has brought a number of external additional experts with us. I won't go through the list in detail in the interest of time, but it is here for you.

So, once again, thank you very much for the opportunity for Bayer to be here today. I

would now like to hand over to Dr. Sebastian Schneeweiss.

Safety of Aprotinin vs. Aminocaproic Acid During CABG Surgery

DR. SCHNEEWEISS: Good morning.

[Slide.]

Ladies and gentlemen, Mr. Chairman, I am here to present the results of a study on the safety of aprotinin compared with aminocaproic acid during CABG surgery. The study was performed by i3 Drug Safety and was commissioned by Bayer.

[Slide.]

In June, 2006, i3 Drug Safety was commissioned by Bayer to conduct a study on the safety of aprotinin. On September 13, 2006 i3 Drug Safety delivered the preliminary report according to the contract. The preliminary report is on the supplementary CD you have received with the printed briefing documents.

Based on comments and suggestions by Bayer and its consultants as well as FDA, i3 submitted a revised study protocol for the final analysis in

December, 2006. Again, this is on the supplementary CD under Schneeweiss, 12-21-2006,.

Changes from the preliminary study included a focus on two of the original five study outcomes that were best addressable in the study's data source; that is renal failure requiring dialysis and in-hospital all-cause mortality.

Patients receiving very low doses of the study drugs were now included. The very few patients receiving tranexamic acid were excluded and a data-dense subgroup of patients was identified to further improve control of confounding. Some covariates for which the temporal sequence with regard to CABG surgery was not entirely clear were dropped and new covariates were added.

In March, 2007, i3 initiated work and, in early August, delivered its final report with results of the database analysis and the final report is on the supplementary CD you have received with your printed documents.

In late August, i3 delivered an addendum

to the final report that was requested by Bayer. This presentation reports results from the final report of the database study as well as the addendum.

[Slide.]

The objective of the study was use the largest in-hospital administrative database in the U.S. to study the safety of aprotinin compared with aminocaproic acid. In short, the premier prospective database is an in-hospital administrative database covering about one-sixth of all U.S. hospitalizations.

The database routinely undergoes multiple validity checks and the premier database is further used by Medicare for a pay-for-performance program that includes MI care as well as CABG surgery.

[Slide.]

In brief, the primary analysis of the full study population of 78,000 patients showed a 60 percent increased risk of renal failure requiring dialysis, the red numbers, and the 64 percent increased risk of mortality, the blue numbers.

[Slide.]

Multiple analytic approaches in different study populations were conducted to evaluate to robustness of the primary findings.

[Slide.]

In a selected data-dense population of 13,000 patients with more pre-surgery information and after propensity score matching, the relative risk decreased. In a tertiary analysis called instrumental verbal analysis, an increased risk was still evident.

[Slide.]

After excluding patients with pre-existing renal failure, the result in the primary analysis remained unchanged while the propensity score matched analysis in a subgroup showed no associations with renal failure in the long term. However, the association persisted for outcomes within seven day of CABG surgery.

[Slide.]

Sensitivity analysis showed that strong unmeasured confounding is necessary to fully

explain the primary study findings and--

[Slide.]

--lastly, a medical-records abstraction study is to be completed by the end of this month.

[Slide.]

To jump right ahead, the following conclusions can be drawn from the study. This is the largest cohort study on the safety of aprotinin today using a complex design and analysis to address existing limitations of administrative in-hospital data.

It needs to be acknowledged that, to answer this research question, nonrandomized studies are likely confounded by patient predictors of unintended outcomes. This study found an association between aprotinin use and renal failure requiring dialysis as well as in-hospital mortality compared with aminocaproic acid that persisted through multiple analytic approaches.

It is possible that these associations are fully explained by confounding but this is not probable. The September 28th report on the trial's

abstraction will address this issue quantitatively.

A secondary analysis excluding pre-existing renal failure suggests that an analysis of short-term outcomes is more valid than the prespecified primary analysis of long-term outcomes.

[Slide.]

Let me now go into more details of the analysis. The premier database is the largest comprehensive in-hospital administrative database in the United States. The database contains information on the lab tests ordered, the medications used, the procedures performed in each hospital day as well as hospital discharge diagnoses, information on admission type and demographic factors of patients. The three-year study period started in April in 2008.

[Slide.]

163,000 patients undergoing CABG surgery were identified during the study period. The study population reduced to the 78,000 patients after patients were excluded because they did not receive