DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

# CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE

Thursday, September 21, 2006

8:00 a.m.

**MORNING SESSION ONLY**

CDER Advisors and Consultants Staff Conference Room
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Rockville, Maryland

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C O N T E N T S

C O N T E N T S (Continued)

**Bayer Pharmaceuticals Presentations** (Continued)

P R O C E E D I N G S

**Call to Order and Introductions**

DR. HIATT: We will convene the meeting of the Cardio-Renal Advisory Committee. I am Dr. William Hiatt from the University of Colorado. I would like to welcome you all today.

Today, we are going to discuss an approved medication, aprotinin or Trasylol, which is used to prevent blood loss during cardiac surgery and cardiopulmonary bypass. A number of issues have been raised around safety and I think that will be the major focus of our deliberations today, but I would like to begin by going around the room.

We have a number of guest consultants here today in addition to the standing members of the committee, so I think if we could go around the room and introduce yourselves and tell us where you are from and your discipline or specialty and begin over here.

DR. KNAPKA: I am Joe Knapka. I am a Ph.D. nutritionist and I am here as a Patient Representative. I have had heart surgery and I am facing some more, so I can represent the patients well, I hope. Thank you.

DR. BALSER: I am Jeffrey Balser. I am an

anesthesiologist and Vice Chancellor for Research at Vanderbilt University.

DR. DeMETS: Dave DeMets, biostatistician, University of Wisconsin, a member of the advisory panel.

DR. TEERLINK: John Teerlink, University of California, San Francisco, and San Francisco VA, cardiologist, member of the advisory panel.

DR. FLACK: John Flack. I am an internist, a hypertension specialist, cardiovascular epidemiologist and I am Chair of the Department of Medicine and Chief of Translational Research and Clinical Epidemiology at Wayne State.

DR. HARRINGTON: I am Bob Harrington. I am an interventional cardiologist at Duke University and I am a member of the advisory panel.

DR. KASKEL: Rick Kaskel, pediatric nephrologist at Albert Einstein. I am a member of the advisory panel.

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

DR. ELLIS: John Ellis, anesthesiologist, University of Chicago, a special adviser.

DR. JEEVANANDAM: Valluvan Jeevanandam, University of Chicago, cardiothoracic surgeon, a special adviser.

DR. LINCOFF: Mike Lincoff. I am an interventional cardiologist at the Cleveland Clinic and I am a member of the Cardio-Renal Advisory Committee.

DR. HIATT: Again, I am William Hiatt, specialty is vascular medicine, University of Colorado School of Medicine.

LCDR GROUPE: Cathy Groupe, Executive Secretary for the committee.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I am a pharmacoepidemiologist at the University of Pennsylvania and I am a consultant.

DR. WARNER-STEVENSON: Lynn Warner-Stevenson. I am a cardiologist, Director of the Heart Failure Program at Brigham and Women's Hospital in Boston and a member of the panel.

DR. HECKBERT: Hello. I am Susan Heckbert, University of Washington. I am a cardiovascular epidemiologist and general internist and I am a consultant.

DR. CHEUNG: Alfred Cheung, adult nephrologist and dialysis director at the University of Utah. I am a consultant.

DR. PAGANINI: Emil Paganini. I am a nephrologist, adult nephrologist, ICU nephrology specialist, Cleveland Clinic Foundation, Cleveland, Ohio.

DR. PORTMAN: Ron Portman, pediatric nephrologist, University of Texas in Houston, member of the panel.

DR. AVIGAN: I am Mark Avigan, Director of Drug Risk Evaluation Division in the Office of Surveillance and Epidemiology at the FDA.

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

DR. RIEVES: Hi there. Dwaine Rieves. I am a deputy within the Division of Medical Imaging and Hematology Products at the FDA.

DR. ROBIE-SUH: Kathy Robie-Suh. I am a medical team leader in the Division of Medical Imaging and Hematology Drug Products, FDA.

MS. LU: Susan Lu. I am a safety evaluator team leader in the Office of Surveillance and Epidemiology, FDA.

DR. HIATT: I think next on the agenda is the Conflict of Interest Statement.

**Conflict of Interest Statement**

LCDR GROUPE: The following announcement addresses the issue of conflict of interest and is made a 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 the committee participants, it has been

determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the following participants. Please note that all of the consulting and speaking activities waived are unrelated to aprotinin injection and its competing products.

Dr. David DeMets for his Data Safety Monitoring Board activities for a competitor for which he received less than $10,001 per year; Dr. John Flack for his speaking bureau activity for a competitor for which he received from $10,001 to $50,000 per year, also, for his consulting for a competitor for which he received less than $10,001 per year; Dr. John Ellis for his participation in a continuing medical program that is partially funded by a competitor. The firm contributes less than $5,001 per year.

In addition, in accordance with 21 U.S.C. 355(n)(4), an amendment of the Food and Drug Administration Modernization Act, Dr. Ellis has been granted a waiver for ownership of stock in a competitor valued at less than $5,001. This deminimis

financial interest is covered by a regulatory waiver under 18 U.S.C. 208(b)(2).

Waiver documents are available at the FDA's Dockets web site. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table. In addition, copies of all the 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 the event that the discussions involve 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 such involvement and their exclusion will 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 wish to comment upon.

Thank you.

DR. HIATT: Thank you.

Next, we are going to get an FDA background for the issues we are going to discuss today.

Dr. Rieves will begin that discussion.

**Trasylol (aprotinin for Injection)**

**Bayer Pharmaceuticals**

**FDA Presentations**

**Opening Remarks**

DR. RIEVES: Good morning. My name is Dwaine Rieves. I am a deputy within FDA's Division of Medical Imaging and Hematology Products. We thank you for your attendance and participation in this meeting.

Today, we are just discussing Trasylol or aprotinin injection, a drug approved several years ago by the FDA for use in cardiovascular surgery to reduce the need for blood transfusion.

This meeting was prompted largely by safety information published earlier this year, hence, we have entitled this meeting a "Safety Update," however, as you will see, we hope to obtain perspectives regarding the efficacy of the drug in the context of advances in surgical, anesthesia, and blood transfusion practices.

Also, we highlight the Update aspect of the title to emphasize that the FDA review of safety information is ongoing and opinions from this meeting are important to completion of

this review.

[Slide.]

The background for our meeting is highlighted here. Most notably, two publications appeared early this year that raised important questions regarding Trasylol's safety. These publications, one in the New England Journal of Medicine and the other in the Journal of Transfusion, suggested that Trasylol usage in clinical practice may be associated with more cardiovascular and/or renal risk than had been detected in premarketing studies.

In response to these publications, FDA issued a Public Health Advisory that, among other items, recommended physicians consider limiting Trasylol usage to those situations where the clinical benefit of reduced blood loss is essential and this benefit outweighs Trasylol risk.

The Health Advisory also noted that these two publications used relatively complex statistical methodology and that FDA anticipated the discussion of this methodology, as well as other aspects of the studies at an advisory committee, hence, today's meeting.

Following the appearance of these publications, Bayer Pharmaceuticals initiated a review of the cumulative Trasylol

safety and efficacy data. This process has resulted in the submission of considerable amounts of safety and efficacy data to the FDA over the past few months.

FDA is currently in discussions with Bayer regarding the findings and proposed actions. Advice from this committee will form an integral part of this review and action process. Following completion of this process, FDA and Bayer anticipate certain regulatory actions as will be reflected in the questions we have developed for the committee.

[Slide.]

So, to clarify, the purpose of our meeting today is to obtain perspectives and advice that will help FDA complete two activities. Most importantly, these perspectives will assist in the completion of the review process.

In that regard, our discussion topics are centered around review of the published data, review of the spontaneous post-marketing reports, as well as the results from Bayer's recently submitted comprehensive clinical study data report. This review activity forms the basis for the subsequent process involving regulatory actions.

[Slide.]

This slide highlights two important aspects of today's

topics, that is, FDA perspectives regarding the use of published clinical reports and the off-label use of marketed drugs.

Firstly, FDA regards published data as an important source of drug usage information and we also recognize that the information contained within a published report is, by necessity, limited due to the need for succinctness, clarity and focus.

Two, we are all aware of the publication bias that inherently underlies the publication of a new or novel observation as opposed to a less newsworthy finding.

Nevertheless, published reports serve as an important source of both safety and efficacy information.

One aspect of the published data that is especially pertinent to today's discussion is that even though we are discussing published data today at an FDA advisory committee, FDA, nor the committee, assumes the role of arbiter or validator of a publication's findings. Instead, we recognize that the author and publisher assume the responsibility for data integrity, conclusions and any opinions expressed in the manuscript.

The second major bullet on this slide highlights the

fact that some of the publications cite the usage of marketed drugs for purposes other than those cited in the drug's label.

Specifically, the publications note that two drugs with hemostatic properties, tranexamic acid and aminocaproic acid, are sometimes used in cardiovascular surgery even though these drugs do not have this usage cited in their product label.

In this regard, FDA recognizes that good medical practice and the best interest of patients often require that physicians use legally available drugs including the use of what we commonly refer to as the "off-label" use of drugs.

This decision is a medical practice based decision in which the physician chooses to use a drug based on an appreciation of the medical evidence, professional experience and appreciation of a patient's unique needs.

Consequently, FDA regards these types of off-label drug usages as physician-based decisions in the practice of medicine, a practice different from marketing claims of safety and efficacy for the off-label usage.

Given this perspective, it is important to note that the data supporting an off-label usage may be extensive or very limited and the available data may not have undergone FDA review.

Given these caveats, I would like to briefly highlight the two publications that prompted this meeting. We are fortunate to have Dr. Keyvan Karkouti to present one of these publications and we are awaiting Dr. Dennis Mangano, who hopefully can join us shortly.

[Slide.]

The New England Journal of Medicine publication was entitled, "The Risk Associated with Aprotinin in Cardiac Surgery." This study was a multi-center observational study gathering data from patients undergoing CABG with cardiopulmonary bypass.

The study compared outcomes from four groups of patients, those receiving the hemostatic drugs aprotinin, aminocaproic acid and tranexamic acid, as well as a group of patients receiving no hemostatic drug.

The study's analytic methodology included certain propensity adjustment methods in an attempt to adjust for imbalances in baseline characteristics among the patients in the study groups.

[Slide.]

The major findings from the study, as cited in the study abstract, were the observations that aprotinin use was

associated with an increased risk for several serious adverse events among some patients including an increased risk for renal failure requiring dialysis, myocardial infarction or heart failure and stroke or encephalopathy.

We should note that these observations relate to potential safety risks that are not described in the current Trasylol product label.

[Slide.]

The next publication was entitled, "A Propensity Score Case-Control Comparison of Aprotinin and Tranexamic Acid in High Transfusion Risk Cardiac Surgery."

This study was a single-center observational study that obtained data from certain high transfusion risk patients undergoing cardiac surgery with cardiopulmonary bypass.

The study also used propensity adjustment methodology to adjust for imbalances in patient's baseline characteristics.

The major findings from this study was that patients receiving aprotinin were at an increased risk for perioperative renal dysfunction. A risk for renal dysfunction is not described in the current Trasylol product label.

[Slide.]

As noted on this slide, our presentations and

subsequent questions today may be grouped into two categories. Firstly, the bulk of our discussion today will relate to what may be called "unlabeled" risk, that is, safety risks not currently described in the Trasylol product label including possible renal or cardiovascular risk.

We will have presentations regarding both the published observational studies, as well as Bayer's controlled clinical studies and, at the end of the day, discuss the extent to which these data provide evidence of new safety risk that may necessitate a product label revision.

Secondly, we will discuss a known safety risk that is highlighted within the current Trasylol product label, that is, the risk for serious hypersensitivity reactions including fatal anaphylaxis, a labeled risk.

This discussion will relate to a summary of the cumulative reports of hypersensitivity reactions over the past many years from both the sponsor's post-marketing database, as well as information from the FDA's Adverse Event Reporting System.

Importantly, this reporting system is most useful for the detection of rare, serious and unexpected adverse events, such as anaphylaxis.

This reporting system does not provide useful information regarding renal and cardiovascular risk due to the inability to distinguish the occurrence of these events from the background rate of the events in the patient population. Hence, the summary of the FDA Adverse Event Reporting System findings will relate only to serious hypersensitivity reactions.

[Slide.]

Before moving to the bulk of our discussions today regarding any unlabeled Trasylol risk, we would like to set the stage for the discussion by briefly describing the labeled risk.

In this context, we have a presentation by Dr. Kathy Robie-Suh from our Office of New Drugs regarding the current Trasylol label and the regulatory background and a presentation from Ms. Susan Lu from our Office of Surveillance and Epidemiology, regarding the labeled risk for serious hypersensitivity reactions.

DR. HIATT: Thank you, Dr. Rieves.

Any clarifications that need to be made at this stage?

[No response.]

DR. HIATT: Thanks.

**FDA Regulatory Overview**

DR. ROBIE-SUH: Good morning. My name is Kathy Robie-Suh. I am a medical team leader in the Division of Medical Imaging and Hematology Drug Products and I will present an overview of the Trasylol regulatory history.

[Slide.]

To set the stage for the subsequent discussion of the New England Journal of Medicine and Transfusion publications, I will briefly describe three major areas.

First, I will review certain important aspects of the current Trasylol product label. Then, I will highlight major events in the regulatory history that led up to this label. Finally, I will briefly comment on recent information submitted to the NDA.

[Slide.]

Trasylol is a protease inhibitor derived from bovine lung tissue. The product is currently approved for use with the following indication: "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."

[Slide.]

Before moving to certain efficacy and safety highlights from the label, it is relevant to note the Trasylol dose and administration procedures. The current Trasylol label cites the option for use of two dosage regimens as outlined in this slide.

Regimen A is referred to as the "full dose" regimen and Regimen B is described as the "half-dose" regimen.

Trasylol administration consists of four components as shown in the columns here. There is a test dose of 10,000 units administered intravenously at least 10 minutes before the loading dose, a loading dose administered intravenously over 20 minutes, a "pump prime" dose and a constant infusion dose administered intravenously through a central line to the end of surgery.

As you can see, except for the test dose, the "half-dose" regimen is exactly half that of the "full dose" regimen.

[Slide.]

The major efficacy findings are highlighted on this slide. In general, the label indicates that in pooled U.S. randomized, double-blind, placebo-controlled trials, four studies in primary coronary artery bypass graft surgery and

four in repeat coronary artery bypass graft surgery, Trasylol administration decreased the rate of blood transfusion and perioperative bleeding in repeat and primary CABG surgery.

This table summarizes the extent of blood transfusion usage in the major clinical studies for regimens A and B in both primary and repeat CABG surgery.

With 412 patients evaluated in repeat CABG surgery, 76 percent of patients receiving a placebo received at least 1 blood transfusion, while only 47 and 49 percent of patients receiving the Trasylol regimens A and B respectively received transfusions.

In four studies evaluating 1,440 patients undergoing primary coronary artery bypass graft surgery, 37 percent of patients in both regimen A and regimen B groups required donor blood as compared to 54 percent of patients who received placebo. Both regimens also showed improvement in secondary efficacy measures, such as thoracic drainage volume and units of blood transfused.

[Slide.]

With regard to labeling of safety information, we note as highlighted here that the top of the label carries what is commonly referred to as a "black box warning." This warning is

especially pertinent to today's discussion.

It reads, Anaphylactic or anaphylactoid reactions are possible when Trasylol is administered. Hypersensitivity reactions are rare in patients with no prior exposure to aprotinin. The risk of anaphylaxis is increased in patients who are re-exposed to aprotinin-containing products.

The benefit of Trasylol to patients undergoing primary CABG surgery should be weighed against the risk of anaphylaxis should a second exposure to aprotinin be required.

This safety consideration will be discussed in greater detail subsequently. The box also refers the physician to the more detailed information in the Warnings and Precautions sections of the label.

These next two slides summarize the most notable safety information contained within the Warnings, Precautions and Adverse Reaction sections of the labeling.

The risk for hypersensitivity reactions is generally the most prominent and extensively discussed safety consideration within the label. Certain label text citations regarding hypersensitivity reactions are highlighted here. In general, four statements are especially notable.

[Slide.]

Hypersensitivity reactions are rare in patients with no prior exposure. The risk is greatest if re-exposure occurs within six months of initial exposure.

Reactions range from skin eruptions, itching, to dyspnea, nausea, tachycardia to fatal shock. Finally, severe, including fatal, reactions can occur with the test dose alone.

[Slide.]

The Adverse Reactions section of the current label also provides supplemental information regarding some areas of particular interest including myocardial infarction, certain renal findings and coronary artery bypass graft patency.

This section contains tables from U.S. placebo-controlled studies summarizing the rates of various adverse events including the observations as highlighted here.

The studies showed a myocardial infarction rate of 6 percent for both Trasylol and placebo-treated patients. Rate of renal dysfunction in these studies was 3 percent in the Trasylol-treated patients and 2 percent in the placebo-treated patients.

The label also notes a finding of a higher graft closure rate in one clinical study of over 700 patients but no difference in the rate of myocardial infarction in that study.

As will be discussed later today, based upon a recent cumulative integrated analysis of controlled clinical studies, the sponsor has proposed modifications to the label to update the renal dysfunctions findings.

In the next two slides, I will present important aspects of the regulatory history of Trasylol.

[Slide.]

There were two major events in the Trasylol regulatory history. The first major event was the original approval of Trasylol in 1993 for limited indication in high-risk patients based on efficacy data from four randomized, double-blind, placebo-controlled clinical trials.

[Slide.]

The 1993 approval contained the indication statement cited here. Specifically, Trasylol was indicated for the prophylactic use to reduce perioperative blood loss and the need for transfusion in patients undergoing cardiopulmonary bypass in the course of repeat coronary artery bypass graft surgery.

Trasylol is also indicated in selected cases of primary coronary artery bypass graft surgery where the risk of bleeding is especially high, impaired hemostasis, such as presence of

aspirin or other coagulopathy, or where transfusion is unavailable or unacceptable.

Hence, this indication limited the patient population to patients undergoing repeat coronary artery bypass graft (CABG) surgery, or those at high risk of bleeding.

The Indications section also included a statement citing the reasons for limitation as being concerns for renal dysfunction and anaphylaxis.

I will mention here that the initial approval was only for the "full dose" regimen. That's regimen A. The "half-dose" regimen, regimen B, was added a year later based on an additional confirmatory study.

[Slide.]

The second major event in the regulatory history was the approval in 1998 of a supplement, which included expansion of the indication statement to the present use, which is contained within the current label, namely, an indication that is applicable to the broad population of patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass.

Also, as previously noted, this expansion of the indication was accompanied by the addition to the label of a

black box warning regarding hypersensitivity.

[Slide.]

This slide, titled "New Developments," highlights the ongoing nature of the Trasylol safety review. Over the past few months and as recently as the past few days, the sponsor has submitted additional information to the NDA.

The sponsor will describe and discuss the extent of this information subsequently. As highlighted here, the sponsor has performed a comprehensive review of the controlled clinical study experience with Trasylol and observed an increased risk for renal dysfunction.

Consequently, the sponsor has proposed modifications to the product label, as well as other plans, including a risk minimization plan that focuses upon education and the potential use of an immunoassay to help detect prior aprotinin exposure.

As additional background to the sponsor's presentation, Ms. Susan Lu from the FDA Office of Surveillance and Epidemiology will now provide additional information regarding the post-marketing experience with Trasylol.

Thank you.

**FDA OSE/Postmarket Reports**

MS. LU: Good morning. I will provide an overview of

post-marketing reporting of hypersensitivity reactions associated with Trasylol.

[Slide.]

My talk will consist of three parts. First, I will briefly describe the FDA Adverse Event Reporting System, or what we commonly refer to as "AERS."

Second, I will summarize the hypersensitivity finding from the review of the sponsor's data submitted to the NDA, as well as the information submitted to the FDA AERS database through MedWatch.

Finally, I will discuss risk management of Trasylol-associated hypersensitivity.

[Slide.]

AERS is a computerized database that consists of over 3 million reports of adverse events.

Reports are voluntarily submitted to FDA from health care professionals and consumers. Pharmaceutical manufacturers are required to report adverse events of which they become aware.

As the last bullet notes, one of the major strengths of the AERS database is the detection of rare but serious adverse events, such as anaphylactic reactions. Another utility is in

developing a case series to describe the spectrum and natural history of an adverse event.

[Slide.]

It is important, however, to note some limitations of spontaneous reporting. As Dr. Rieves noted earlier, AERS is of lower utility for evaluating expected events in an at-risk population. For example, in drugs used primarily in the older population, cardiac events may be expected, so it is difficult to say whether it was the drug or not.

Likewise, renal failure and cardiac events in a post-surgical setting may be a complication of surgery and, therefore, AERS is of limited usefulness in evaluating these events for Trasylol.

Additional limitations of spontaneous reporting include underreporting, biases in reporting and variable quality of the reports themselves.

Other considerations specific to reporting for Trasylol are that AERS does not include reports prior to U.S. approval in 1993 and foreign reports of labeled events, both categories of which are in the sponsor's database.

The totality of these limitations emphasize the role of the sponsor for estimating renal and cardiac adverse event

rates. Consequently, I will focus on hypersensitivity reactions and, prior to a summary of the AERS reporting for hypersensitivity, I will summarize the data from the NDA.

[Slide.]

Information submitted to the NDA estimates that Trasylol patient exposure from the date of approval in 1993 to 2005 has steadily increased over the past several years, especially since 1998, the year in which FDA approved a broader indication. So, for 2005, about 250,000 patients received Trasylol in the U.S.

[Slide.]

Now, I am going to briefly summarize Bayer's findings on post-marketing reporting of hypersensitivity reactions.

[Slide.]

Information submitted to the NDA indicate that hypersensitivity is the most frequently reported spontaneous adverse event associated with Trasylol, accounting for 41 percent of reports in Bayer's worldwide database; 85 percent of these reports were coded as anaphylactic reaction or anaphylactic shock.

The sponsor's independently adjudicated review of hypersensitivity types of reactions identified 291 reports that

were classified as possibly associated with Trasylol; 52 of these reports had a fatal outcome.

[Slide.]

As noted on this slide, approximately half, or 47 percent, of the patients of hypersensitivity reactions had a history of prior Trasylol exposure, or two-thirds of exposure in the past 6 months.

[Slide.]

The sponsor has also noted the receipt of 81 case reports where the hypersensitivity reaction occurred following administration of the test dose alone, including 19 fatal cases.

Furthermore, 38 reports indicated that the patient had a negative test dose result but experienced a hypersensitivity reaction with the therapeutic dose administration; 9 of these patients had a fatal outcome.

[Slide.]

In summary, the major points from the sponsor's review of spontaneously reported data shows that hypersensitivity is the most frequently reported event.

Of 291 cases with a possible association with Trasylol, about 1/6th of these were fatal. Approximately half of the 291

cases occurred among patients who had a history of prior aprotinin exposure mainly within 6 months.

The test dose administration alone is associated with reactions including 19 fatalities. Despite a negative test dose result, 27 percent of patients experienced a hypersensitivity reaction with the therapeutic dose.

Lastly, most of the hypersensitivity reactions occurred when Trasylol was administered to patients undergoing surgeries other than CABG.

[Slide.]

The next few slides will summarize findings from a similar analysis of reports of anaphylactic reactions in the FDA AERS database. As mentioned earlier, AERS does not contain reports prior to the U.S. approval of Trasylol or many foreign reports, both of which are in the sponsor's database, and largely reflects the U.S. post-marketing experience.

[Slide.]

In conducting our review, we searched the database for all reports of anaphylactic/anaphylactoid and hypersensitivity reactions.

Following identification of these cases, each report was examined for important clinical features and we excluded

reports where the reaction was most likely due to an alternate cause or there is inadequate information provided for assessment.

[Slide.]

Using the criteria for inclusion, 70 reports of anaphylaxis were identified associated with Trasylol administration; 23 reports had a fatal outcome.

In terms of demographics, there are no obvious differences in reporting by gender and most occurred in adult population although a few cases reported in the pediatric patients. Fifty-eight reports were from the U.S., with only 12 reports from foreign sources.

[Slide.]

As you recall, the test dose is administered before a loading dose and continuous infusion. Among the 49 cases where the time to onset of anaphylaxis was known, almost half reported an onset during or shortly after the test dose. The remainder of cases had a reported onset of anaphylaxis during administration of either the loading dose or the continuous infusion.

[Slide.]

We evaluated the reports for information regarding test

dose administration. Twenty-three out of 49 patients experienced a reaction after the test dose alone including 10 patients who had a fatal outcome. Another subset of 20 patients reportedly had a negative test dose result but developed anaphylaxis of administration of the therapeutic dose.

So, we see here that the test dose itself is associated with severe reactions and is frequently not predictive of an allergic response.

[Slide.]

Among the case reports containing some information regarding prior aprotinin exposure, approximately half the reports noted that the patients had a history of prior exposure, 29 cases had information relating to the timing of this exposure, and most prior exposure had occurred within the past 6 months. However, 10 percent of reports did state that the patient had no history of prior exposure.

The exposure history information was not provided in 41 percent of reports. In some of these cases, it possibly may have been unknown to the reporter, however, 18 out of 29 cases mentioned that the patient had previous surgery, so there may have been previous exposure in some of these patients, as well.

[Slide.]

A majority of reports of hypersensitivity reaction, when accompanied with indication information, related to non-CABG uses of Trasylol. The most frequently reported use was for valve surgery.

[Slide.]

This slide describes some of the clinical features of the case reports. A description of anaphylaxis signs was available in 57 cases. Most of the signs were related to cardiovascular events with a predominance of hypotension. Typically, the first and, in some cases, the only sign reported was hypotension, and, in some cases, resulted in cardiac arrest or cardiovascular collapse.

Other less frequently reported manifestations included respiratory events and dermatologic events.

In the cases where treatment for anaphylaxis was described, the use of vasopressors in most cases is especially notable. So, from the clinical presentation of the cases, hypotension and cardiovascular collapse are predominant signs. One concern is that because the patients are anesthetized, the initial signs of anaphylaxis may go unrecognized.

Next, I will be describing two case reports of

anaphylaxis, one from the AERS database and a second from the published literature.

[Slide.]

The first case is the anaphylactic reaction with a negative test dose result in a patient who had previous exposure to aprotinin but where the exposure history was unknown to physicians.

This occurred in a female who had a history of mitral valve replacement and CABG 7 weeks prior and who was admitted for a redo of mitral valve replacement. Before the operation, review of the records of her prior surgery obtained from another hospital showed that she had no prior aprotinin exposure.

During her surgery, after induction of general anesthesia, a test dose of Trasylol was given but no reaction was observed, so the loading dose was initiated. During the loading dose, progressive hypotension developed following by bradycardia that was unresponsive to the administration of vasopressors.

CPR was started with gradual return of blood pressure and heart rate. The surgery was cancelled and the patient was sent to the ICU. The other institution was again contacted

because the physicians did have a high suspicion of an aprotinin reaction and the anesthetic records from the previous surgery revealed that the patient indeed had prior exposure to aprotinin.

Apparently, this patient had two surgical procedures just a day apart at that institution and the anesthetic record of the surgery where aprotinin was not used was sent.

This case illustrates both the questionable utility of the test dose and the difficulty in obtaining complete Trasylol exposure history.

[Slide.]

Our second case is a near fatal anaphylactic reaction to test dose administration in a patient with primary aprotinin exposure. This patient received a test dose of aprotinin after induction of anesthesia and intubation and immediately, the systemic blood pressure became undetectable with an associated sudden increase in peak airway pressures.

Despite 45 minutes of CPR, repeated administration of vasopressors, as well as steroids and antihistamines, there was no recovery of cardiac function. Cardiopulmonary bypass was instituted, which continued for an hour during which time the patient gradually recovered.

He was transferred to the ICU where he was intubated with infusions of epinephrine and nitroprusside and recovered. Specimens of the patient's blood showed highly elevated IgG response to aprotinin.

This case illustrates that severe anaphylactic reactions can be associated with primary exposure to aprotinin and with a test dose administration alone.

[Slide.]

In general, the major findings from review of 70 AERS reports of anaphylaxis are similar to those from the sponsor's reports and include the following observations.

In relation to the test dose, nearly half of the fatal cases were associated with test dose administration alone and nearly half of the patients who were documented to have received the test dose experienced anaphylaxis despite a negative test dose result.

Looking at previous exposure, nearly half the patients had a previous exposure to aprotinin, mostly within 6 months, however, 10 percent of patients were documented to have no previous exposure to aprotinin.

In terms of the severity of the clinical presentation, cardiovascular events, such as hypotension and cardiac arrest,

were reported predominantly. Lastly, 25 percent of patients received Trasylol for the approved indication of CABG surgery.

[Slide.]

I would like to mention that Bayer has proposed a Minimization Action Plan to minimize the hypersensitivity risk and this plan is currently under review.

The sponsor's stated goal for the RiskMAP is to identify those patients most at risk of a hypersensitivity reaction to Trasylol and to provide information to reduce these patients from re-exposure to the drug within the period of highest risk of hypersensitivity.

[Slide.]

The tools the sponsor proposes to use consists of the development of an aprotinin IgG assay to identify patients who have been previously exposed to aprotinin and education. The education will be targeted at physicians and will focus on the appropriate indication for use, the risk of hypersensitivity with re-exposure particularly within 6 months, the importance of taking a complete medical history to uncover previous exposure, the appropriate use of the test dose, readiness for handling hypersensitivity reactions and information on cross-reacting products.

[Slide.]

We do have some thoughts about the approach to the RiskMAP. First, the clinical utility of the aprotinin IgG assay is unknown at this time.

Second, what is the effectiveness of the educational message to mitigate the risk?

For example, the education was stress to test dose but it appears that the test dose is frequently not predictive. Also, the test dose itself can cause serious reactions.

Regarding the emphasis on taking a complete medical history, patients may not realize that they have been exposed to aprotinin and even a review of medical records may not provide this information.

We also have concerns that the hypersensitivity reactions may not be easily recognized. Patients are anesthetized, cannot report symptoms such as skin reactions, nausea, or shortness of breath, so non-cardiovascular signs may not be detected. The first recognizable sign could be a cardiovascular collapse.

These points do emphasize some of the challenges in managing the risk of anaphylaxis and we would appreciate the committee's feedback on some of these points.

[Slide.]

Lastly, I would like to acknowledge the following colleagues for their valuable contributions to the ongoing Trasylol safety update project.

This concludes my presentation. I thank you for your attention.

**FDA Topics of Discussion**

DR. RIEVES: Since we anticipate that most of our discussions today will center around any unlabeled risk associated with Trasylol, we return to the findings highlighted by the two recent publications in Bayer's recently completed data review.

[Slide.]

Both publications, as well as Bayer's recent findings, pertain to certain risk not currently described in the Trasylol product label.

We are especially appreciative to our guest presenters today, Dr. Dennis Mangano and Dr. Keyvan Karkouti, who will provide summaries of their work. Subsequently, Bayer Pharmaceuticals will provide a summary of their clinical experience with Trasylol.

All presentations are aligned for this morning, such

that we dedicate the afternoon to the public speakers and reserve two to three hours for discussion and response to our questions.

[Slide.]

At the end of the day, FDA is posing four major topics for discussion. The initial safety topic concerns the two published observational studies that cite more Trasylol safety concerns than were detected in randomized, controlled clinical studies, that is, potential safety risks that are not described in the current product label.

We will specifically request that the committee consider the two published reports in the context of the randomized, controlled clinical study findings and that the committee offer an opinion regarding the extent of Trasylol safety risk.

The next safety topic focuses upon the risks for hypersensitivity reactions and procedures to lessen this risk. Subsequently, we will request the committee's perspective regarding Trasylol efficacy data, in light of current surgical, anesthesia and blood transfusion practices that may importantly differ from those at the time of the original Trasylol product approval.

Finally, we will request a discussion and a vote regarding an interpretation of the totality of the presented data, as well as a possible alteration of the product label indication statement.

We would like to emphasize that we request this vote regarding the overall Trasylol risk and benefit profile in the context of obtaining a general sense of the committee's perspective regarding the presented data.

Again, we note that FDA's review is ongoing and subsequent analyses and data submissions to the NDA may importantly impact the final review outcome. Nevertheless, the highlights of the submitted data are presented today and the committee's perspective regarding this information is an important part of the review process.

Again, we thank you for your participation and look forward to a productive discussion.

Thank you, Mr. Chairman.

DR. HIATT: Before you sit down, we are just going to take a moment for transition and perhaps if the committee would like to clarify anything that has been presented thus far.

I would like to just clarify a point of process as we get started. The major topic we are going to turn to now are

two published observational studies, as you described, that raise significant safety concerns.

The process the committee is used to deliberating these kinds of data are that either the sponsor or the publication is presented and then, typically, there is an FDA independent review of that data, so that we have contrasting analyses to go over as a committee.

I want to clarify today that we are simply going to focus on what is in the published literature. Could you clarify that?

DR. RIEVES: Yes, sir, that's exactly right. We are going to focus upon the publications as they are available for us all to read.

In that context, we do have some statisticians, epidemiologists here who can comment, but we also note that Bayer, the pharmaceutical company, is going to address some of the statistical aspects of those studies.

We also have some statisticians who can offer some commentary but, at the end of the day, the bottom line we think is obtaining opinions regarding the value of observational clinical data that shows fairly striking differences in outcomes versus what we obtained from randomized, controlled

clinical data.

So, our question really goes beyond the details, the nuances of the statistical methodology and gets at interpretation of the value of observational clinical data versus the randomized, controlled type studies, which we are traditionally used to.

DR. HIATT: So, just to clarify, we won't have an independent FDA review of either publication.

DR. RIEVES: That is correct, not a formal presentation.

DR. HIATT: I would like to go around the committee.

Dr. Harrington.

DR. HARRINGTON: I just want to pursue that last point a little bit. You are absolutely right, that part of the focus today will be to talk about how one views and uses observational data in the context of looking at treatments, which we are used to looking at in the context of randomized trials. But observational data, as you well know, how one views it is largely determined by how one analyzes it.

It bothers me some that we are relying upon published data without having had an independent party have complete access to those data to perform other analyses.

You made an interesting statement when you started this morning. You said that you are looking for the committee to discuss the topic of how one views published data, and so I am curious as to does FDA have a perspective going forward about was there an attempt specifically to get this data for complete independent review, and, number two, is FDA formulating any policy going forward as to whether or not you will try to obtain full data on observational reports that you would like the committee to evaluate.

DR. RIEVES: Regarding that second question, regarding policy, I think it is wise that I defer to some of my chiefs on that aspect of it. Regarding the ability to obtain source data, if you will, for one of the publications, yes, we have obtained source data. We have carried on dialogues, attempts to obtain source data for the other publication, but that has not been successful at the present time.

It is important to consider, though, even when we do obtain source data, if you will, a database, a SAS database, the expectations that go into that. For example, with our sponsor's clinical studies, we not only obtain the database but we usually inspect the clinical sites to make sure the integrity of the database is there.

We are talking about considerable resource allocation to that type of verification, which we commonly do for formal submissions to the NDA. It is important to note that publications are not submissions to the FDA. So, there are a lot of regulatory nuances, and, as you rightly point out, this gets into a number of policy areas.

Mr. Chairman, perhaps some of my chiefs can comment upon the role of publications in safety and/or efficacy.

DR. PAZDUR: Clearly, we would like to get the primary data and look at it and do our own analysis of these studies. I think that is obvious from wherever a data source would come from, whether it's a company submission of a primary randomized study or observational data, we would like to get that material.

DR. HIATT: Other points to clarify before we go to the presentations of the two published reports?

DR. WARNER-STEVENSON: I just wanted to ask, I believe Dr. Lu, you commented at the end on the issue of the sensitivity, that 25 percent of the patients, in fact, were receiving it for approved indications.

Is that because a fair number came in before the indications were broadened in 1998, or are we seeing patients

who were receiving this for other than bypass surgery?

MS. LU: Yes, the majority of reports, 75 percent of the reports were for indications other than CABG surgery. We haven't really looked to see pre-1998 versus after the expanded indication. I am sorry but I can't answer that question.

DR. HIATT: Any other thoughts?

[No response.]

DR. HIATT: I think we will move on then.

Dr. Mangano, you have got the stage.

**Guest Speaker Presentations**

**Dennis Mangano, M.D., Ph.D.**

DR. MANGANO: Thank you. Good morning.

[Slide.]

This morning I am going to present the results which have been published in January of this year regarding post-marketing safety surveillance of a serine protease inhibitor and two antifibrinolytics compared with a control group and what is presented as an observational paradigm which I happen to believe is a paradigm for the future.

I want to thank everyone here for their attention and their gracious attention over the next 45 minutes. I am going to try to present a series of concepts, first, an introduction,

then, some perspectives, temporally and clinically, the study itself, and some final impressions or biases as you will.

[Slide.]

Potential conflicts of interest, I guess I don't need this. I am involved with several nonprofits. I do not consult with pharmaceutical companies and never have. I don't receive honoraria, I am not on speakers' panel, I don't own any stock, nor do the nonprofits. I do have some intellectual property that I do own, which will not impact on any of this.

[Slide.]

In terms of my biases, I think they will become clear during the questions and answers.

[Slide.]

I would like to give a perspective from my point of view at least, from 1959 to 2010. Trasylol was first used in 1959 in Germany for various indications. In 1987, an important report by Royston in Lancet pointed out that it may have important blood-sparing activity.

In 1992, Cosgrove published a report in which he highlighted that there may be problems with coronary vein graft thrombosis.

[Slide.]

In that report, if you read it says, Acute vein graft thrombosis--and he underlined--was found in 6 of 12 patients, vein grafts studied at postmortem examination receiving aprotinin and none in 5 in others. Of course, this is a small report but highlighted what I believe is an important problem.

[Slide.]

In 1993, the drug was approved for a limited population who are especially at risk for bleeding and, very pertinent at that time was the statement produced by the FDA on December 30th, 1993, that kidney toxicity was also a problem in some patients in the trials, and there were only a few trials at that time.

[Slide.]

Why? Unlike epsilon-aminocaproic acid and tranexamic acid, aprotinin has a high affinity for the kidney. It passes freely through the glomerulus and is selectively bound to the brush border of the proximal tubular membrane, enters the cytoplasm, accumulates for 24 hours and inhibits tubule proteases, as well as prostaglandin and renin synthesis and bradykinin release.

Under normal conditions, you get some impairment of salt and free water excretion. Under normal thermic ischemia,

hypothermia, or other high kallikrein activity states, the untoward tubular effects are magnified and complicated further by dose-dependent renal afferent vasoconstriction, impairing deep cortical and medullary perfusion and its autoregulation and, finally, resulting in some models focal tubular necrosis.

Aprotinin, because of its interference with endothelial cell nitric acid synthesis and release, may instigate macro- or microvascular thrombosis in some models.

The lysine analogues, in contrast, are excreted nearly intact within 24 hours of intravenous administration with renal clearance approximating creatinine clearance and few reports documenting association of aminocaproic acid or tranexamic acid with renal dysfunction. That is a safety profile as we will see was validated by our results.

[Slide.]

Now, despite the early warning by the FDA and this evidence, only a minority of the 45 aprotinin surgery trials even commented on renal dysfunction and none was powered to discern renal failure.

Albeit they were randomized, controlled trials, they were insensitive with a third of the trials reporting on renal failure. That is an important limitation in our discussion.

However, a number of safety signals exist in the literature since 1993. Alpha 1-microglobulin production association, deposition of protein bands within tubule cells accompanied by proteinuria, dose-dependent increases in postoperative creatinine, reports of renal dysfunction and platelet fibrin thrombotic occlusions of the renal arterioles postmortem, so signals existed.

[Slide.]

In 1994, the FDA raised questions regarding graft thrombosis and they looked at 1,267 placebo-treated and 2,204 aprotinin-treated patients and they found a significant association between aprotinin using coronary graft closure, albeit retrospective, but leading to the IMAGE trial, which I am sure all of you are aware of.

[Slide.]

That trial was conducted in '95 and reported three years later. In the interim, Lemmer, Levy and D'Ambro issued reports, which we might address later, but are pertinent.

The IMAGE trial finally was published by Alderman including, for the coronary vein graft analysis, 703 patients, 363 aprotinin, 340 control.

[Slide.]

What the IMAGE trial found, if you could read it, essentially is the primary study endpoint was coronary vein closure within about 10 days after surgery and they found a 40 percent increase associated with aprotinin compared with control, 15.4 percent versus 10.9 percent.

That 4.5 percent absolute increase is important, I believe. The study went on to analyze groups of centers, which was not part of the primary endpoint and factors leading to such but the primary result was one which validated the FDA safety concerns regarding coronary vein graft closure, one of the reasons these patients come to surgery.

IMA closure arithmetically was increased from 1 percent to 1.8 percent, not inconsistent.

[Slide.]

If you apply these statistics conservatively worldwide, you realize that there are an additional 800 IMA occlusions per year if you believe that arithmetic finding and 4,500 vein graft occlusions per year occurring in patients because of aprotinin use.

Whether tranexamic acid or epsilon-aminocaproic acid also would occlude vessels is not clearly known. But what is known is that it carries a burden at least with respect to vein

graft occlusion.

[Slide.]

Several months later, the FDA issued an expanded indication for the drug regarding it being an anti-inflammatory.

[Slide.]

The word of caution here is we performed a series of studies, first with Bextra and the first of these studies was published in 2003. Then, with pex, which is a monoclonal antibody to C5a-9, and then Cariporide, all of which are potent anti-inflammatory agents used in this setting, with the idea that we could reduce injury by suppressing inflammation, none of them worked and all of them had unsafe properties.

So, use of the indication for anti-inflammatory is called to question here.

[Slide.]

Finally, we presented an observational study that had been prospectively designed, which we will talk about, and Dr. Karkouti also presented a study in about 900 patients, which he will talk about and we sit here today with the advisory.

The only other thing on the horizon is the so-called BART study from Canada. We don't know how many patients, we

await its findings, however, that study will only address 14 percent of the patients undergoing bypass surgery, because of inclusion and exclusion, and will have little to no bearing on the patients and the findings in our study.

It addresses a much more isolated population, which is at much higher risk and not the general population. So waiting for that study and relying on it has its limitations.

[Slide.]

Let me give you a few clinical perspectives if you allow me that with respect to thrombosis.

[Slide.]

Clearly, thrombosis plays a dominant role in the pathology of ischemic vascular disease--we all know that--and it affects infarction failure, stroke, even renal dysfunction and, in surgical patients, this is especially important with myocardial infarction occurring between 6 and 24 percent, serious heart failure between 3 and 7 percent, focal stroke 2 to 7 percent and renal failure between 1 and 7 percent depending on population.

So, atherosclerosis and associated thrombosis I believe manifests in these patients and plays a role.

[Slide.]

Antithrombotic therapy, such as antiplatelet and anti-clotting factor, including TPA, which is a serine protease agonist, opposite aprotinin effectively, have been the mainstays of treatment for ischemic vascular disease for both MI and stroke, as you know, in this population.

[Slide.]

Cardiac surgery patients are maintained on antithrombotic therapy, I believe to their advantage, acute reversal, I believe is quite detrimental.

Antithrombotic therapy, specifically, antiplatelet aspirin therapy, is the only proven therapy that reduces CABG morbidity and mortality.

[Slide.]

This is a study which we published in 2002 in Negium [ph] and we see that the use of aspirin early and aggressively reduces morbidity, leading us to the concept that platelet aggregates and microthrombi in the vessels may play an important role, thereby gives rise to the salutary effects of aspirin in this setting. Again, thrombosis in this setting presenting a problem.

[Slide.]

Hemorrhage. Hemorrhage comes in small, medium and

large doses in surgery. All hemorrhage is not equal.

[Slide.]

Hemorrhage depends on whether or not the procedure is a single bypass procedure or combined, for example, with a valve procedure and, whether or not there is a re-operation, single primary versus re-operation combined has a spectrum of bleeding associated with it.

[Slide.]

Large hemorrhage requiring re-operation is associated with increased morbidity and mortality.

[Slide.]

This slide is taken from one of the investigators prominent in this field. Re-exploration for bleeding was found in about 4 percent of these three studies and there were a series of risk factors which I won't belabor that cause it.

More importantly, adverse outcomes are increased in those patients who get re-explored for bleeding as one might expect.

[Slide.]

However, I think only very large hemorrhage is associated with increased morbidity and mortality and not mild to moderate.

[Slide.]

The reason I say this is if you look at the database on which we base the aprotinin article, and look at blood loss among three groups, all patients, control patients, or any one of the three antifibrinolytics, you find that only when we get to quite large blood losses of beyond 1,000 ml, that we see increases in mortality and below that we don't see increases for one reason or another.

I believe our heightened awareness should be to this segment of the population, an extreme risk for bleeding and not in this segment of the population necessarily.

[Slide.]

Hemorrhage prophylaxis appears reasonable for large hemorrhage but not otherwise. The hemorrhage prophylaxis agents available are essentially crude, because they affect many biochemical pathways.

[Slide.]

Hemorrhage thrombosis, as you know, is a simple yet elegant system, carefully controlled and orchestrated.

[Slide.]

Surgery and bypass induce multiple derangements and the balance between hemorrhage and thrombosis, including

hemodilution activation and consumption. It is a complex area bypass with complex effects on hemorrhage and thrombosis that are not at all straightforward.

[Slide.]

Drugs that reduce hemorrhage may increase thrombosis. That's a bias, but I think reasonable.

The last concept is TPA versus anti-TPA or serine protease agonist versus antagonist. At least the patients with STEMI, use of anti-TPA therapy is counterintuitive since use of serine protein agonist TPA is effective, so I believe that use of this therapy should be expected to bear outcome.

[Slide.]

With STEMI, as you see here, with coagulation necrosis in someone who has undergone bypass, TPA may be used in one setting and serine protease, an antagonist, the opposite and yet another.

If the patient is taken to the CCU at least up until four or five years ago, would be treated with TPA, if exactly the same patient is taken to the OR, then, the first major drug that is given beyond the anesthetic is a serine protease antagonist and wouldn't one expect that if, in fact, such an agent were given in the CCU, instead of the agonist, that there

would be detrimental effect.

It appears logical to me and it has always bothered me about aprotinin.

[Slide.]

So, those are concepts I trust I didn't go through too quickly. Most of these are fairly obvious.

[Slide.]

Let's get to the study.

[Slide.]

The rationale between '88 and 2006, in terms of thrombosis, acute inhibition of fibrinolysis or acute inhibition of serine protease activity produces thrombosis-related events. That's a hypothesis of the study, a rationale for it. It appears somewhat intuitive to me.

The safety for thrombosis-related events, as well, was caution with reports of coronary vein graft thrombosis, which we talked about, thrombosis of pulmonary and hepatic arteries, peripheral veins and diffuse vasculature.

So, in terms of thrombosis, the rationale applied is summarized by these two findings. With respect to kidney toxicity, in terms of the rationale for the study, the initial caution of the FDA, as well as the association with creatinine

elevation and the in vitro and in vivo studies, form the basis for the rationale for investigating that endpoint.

Now, at the same time we have to recognize that there were a large number of other analyses and secondary analyses nearly always concluding drug safety albeit randomized, controlled trials are believed to be the gold standard, when they don't assess the appropriate outcome, certainly are not.

The randomized, controlled trial for efficacy is the gold standard, for safety it is not and it is not used as such commonly.

[Slide.]

The body of safety evidence that exhibited itself when I reviewed it had three important limitations; inadequate power for safety assessment--generally, the trials were small, 25 to 75 patients per arm--and not use of sensitive detection for safety events occurring with an incidence of less than 20 percent.

The comparison with less costly medications was not done commonly and, in fact, done rarely. Both aminocaproic acid and tranexamic acid showed blood-sparing capabilities equal to aprotinin in general. Yet, head-to-head comparisons were few and far between despite the enormous difference in

cost between these agents with aprotinin between $500 and $1,200 a patient and the others, less than $50 a patient.

There was an inherent bias, I believe, in the literature, because nearly all trials were pharmaceutical company sponsored, as one would expect, we are all human.

[Slide.]

The design, EPI II. EPI II was a study of 69 international medical centers. There was 5,065 patients. It took five years to design, it was specified and we admitted patients with primary and complex bypass surgery.

At each center, we took every nth patient admitted for bypass to allow 100 patients per center to be enrolled over a two-year period. The design occurred between '93 and '96. The collection for the in-hospital study between '96 and 2000, over five years--the data quality assurance started in 1997 and was completed on October 12th of 2001, which was five years. The database was locked on October 15th, 2001, two periods, perioperative and long term, and the long-term study is ongoing.

We collected more than 7,500 clinical data fields per patient. That contrasts with several hundred in most randomized trials or observational studies. The clinical data

fields accumulated was close to 44 million entries for these patients.

Blood sampling and storage was done for a series of analyses with 65,000 samples collected and stored. We are doing a series of analyses with it.

[Slide.]

In summary, we collected approximately 143 million pieces of data in this patient population. This is not a typical observational study and certainly not a registry, on average, close to 30,000 fields per patient.

This has been an entirely consuming effort of my life for the last 15 years.

[Slide.]

The specific aims was to compare the relative safety between the three agents, which are used commonly to reduce blood loss during bypass, during CABG with bypass versus no agent. Safety was assessed by individual organ, heart, brain, kidney, GI tract and overall.

The secondary aim was to assess the relative safety between the three agents on blood loss as assessed by total chest tube output over 24 hours, which is traditional.

The tertiary aims were if a finding was positive, then,

we would contrast the findings by dose.

[Slide.]

EPI II inclusion criteria was scheduled to undergo bypass, CABG with bypass, able to complete the interview, and gave informed consent and that's it. Exclusion was enrolled in another study or trials. It was a simple, powerful study.

The drug groups were aprotinin, aminocaproic acid and tranexamic acid in the doses shown and dose-response was created as shown, which I think is consistent with the literature.

[Slide.]

Outcomes, of course, were pre-specified, defined by protocol and classified as cardiovascular events, which included myocardial infarction, heart failure; cerebrovascular events, which included stroke, encephalopathy, or coma; renal events, which included dysfunction triggered by creatinine change and renal failure requiring dialysis, or autopsy evidence of acute renal failure, GI events and GI ischemia detected by abdominal pain with associated bowel ischemia or detected at surgery and GI infarction requiring resection of the bowel at surgery or diagnosed at autopsy. Blood loss was output over 24 hours.

[Slide.]

Multivariable logistic regression was straightforward. We chose 97 preoperative risk factors, we performed standard regression analysis and looked for associations all prospectively. This was not a needle in the haystack or cherry picking.

[Slide.]

The preoperative risk factors, the univariates that were selected were post hoc, after the publication perturbed and we investigated approximately 1,000 risk factors and the analysis and the results are unchanged.

The univariates cannot be read but, for those interested, will probably be published in some form as a result of this meeting.

[Slide.]

The propensity analyses, as we know, were described in the study. We performed propensity by picking 45 variables and those variables were chosen on the basis of a preceding database, EPI I, which we had conducted in the late eighties, early nineties, 2,400 patients. We looked for the predictors of bleeding in that independent database and used those as the basis for the propensity covariates.

[Slide.]

We chose propensity to treat by an antifibrinolytic. We split into two populations and we considered two variations in those populations. We performed propensity analysis in a number of fashions, post hoc after publication. All of the results are consistent.

As well, we took the 45 propensity variables and expanded them to a group of over 250 variables, randomly selecting groups, building propensity scores and find the results to be the same.

[Slide.]

Propensity covariates are the 45 that were prospectively defined are shown here and include a series of standard variables.

[Slide.]

Results. You have seen the results, I won't belabor them. The study enrolled 4,346 patients. Some were withdrawn at the beginning and, essentially, 4,374 patients entered the study with approximately 1,300 in control and aprotinin and 800 to 900 in aminocaproic and tranexamic acid.

[Slide.]

Baseline characteristics, there are some differences,

but I think that is much ado about nothing. There has been a lot of talk about aprotinin patients being sicker, not borne out in a series of multivariable propensity and disease-specific analyses.

[Slide.]

The essential result was this. The renal dialysis was significantly increased in the aprotinin-treated patients versus control and that neither epsilon- aminocaproic acid or tranexamic acid were associated with increased risk of renal dialysis, renal dysfunction, or renal composite.

Critical, I think to the entire discussion at least to me and from a public health perspective are the findings with respect to aminocaproic acid and tranexamic acid and the safety. We might isolate the discussion of aprotinin versus control but I don't think that is fair, nor fair to the public.

[Slide.]

With respect to composite events, we also found significant differences for series of composite events, which hint at questions of thrombosis of the heart and the brain. I won't belabor that.

[Slide.]

There are a number of ways of looking at differences

between populations and certainly the most powerful is appropriate multivariable regression especially when you are collecting 7,500 fields per patient and analyzing them.

You can also look at it in a more simplistic way of looking at patients with high cholesterol or unstable angina or women or patients over the age of 75, et cetera, and seeing whether or not, in a simplistic, unilateral, univariable way whether or not the results hold.

What you see here is control, aminocaproic acid, tranexamic and aprotinin. For each of these subgroups we find a consistent finding with respect to the incidence of renal events. But again more powerful are the other analyses, as well, so I am not concerned about differences between the groups.

[Slide.]

As well, if you look at blood loss in quartiles in these populations and ask if the renal results hold for low bleeders versus high bleeders and, in fact, they do, as well. Those are unpublished.

[Slide.]

Published is the multivariable logistic regression model for renal composite outcome. What you see is aprotinin

versus control has an odds of 2 1/2, with neither epsilon-aminocaproic acid or tranexamic acid associated with renal composite.

[Slide.]

And if you look at primary surgery versus complex surgery, what you find are associations that are significant for renal, cardiovascular, cerebrovascular for composite and renal for complex.

[Slide.]

Powerful is the dose-response and we selected doses that were pure for the dose-response analysis in order to fit the standard, clinically accepted doses for low and high. What we find is a significant increase by dose from control to low dose to high dose with respect to renal outcomes, cardiovascular outcomes and composite outcomes. That was not significant arithmetically, at least interesting.

[Slide.]

Blood loss, efficacy, no difference. We can look at minimum, maximum, quartiles, means, medians, costs, we cannot find a difference in blood loss in these patients even when you adjust for variables that are likely associated with blood loss.

[Slide.]

Health implications, we hinted at them, and, if you extrapolate conservatively, what we see is if you replace aprotinin with aminocaproic acid in primary surgery, you could save about 4,800 dialyses a year and, in complex, 6,000 for worldwide statistics, making assumptions with respect to use.

[Slide.]

We believe those are important for public health.

The limitations. Each of the blood loss sparing therapies has been marketed for 15 years. Practices are embedded and formalized practice pattern prescription. Whenever you get a drug marketed for a long period of time, it is virtually impossible to do an unbiased with respect to inclusion/exclusion, randomized, controlled trial. You are not going to get it.

Patients, who surgeons or anesthesiologists believe would benefit by the drug and they are assigned to the control group, may not be included in the trial. As well, physicians who fear, for example, that the drug may have safety problems, may not enroll certain patients. I think it is more or less an impossible problem to solve once a drug is marketed and entrenched.

Even in Canada, in the BART trial, they are having trouble enrolling patients because certain physicians do not want to enroll them in those studies for fear of safety, so there are serious questions with respect to inclusion/exclusion criteria for randomized, controlled trial evidence after a drug is marketed and, certainly, combining randomized, controlled trials is fraught with biases and limitations, as well.

The weakest link, the weakest trial will limit the interpretation of those findings. Certainly, a combined randomized, controlled trial does not equal a randomized, controlled trial.

Post-approval safety assessment using unbiased study entry in the framework of a randomized trial, including sufficiently sized populations, has not been performed during these 15 years and is difficult, if not likely impossible to conduct as I said.

There is an inherent bias in the selection. There is necessary withholding of salutary blood-sparing therapies. There is reluctance to include the sickest patients, which is absolutely critical in this setting given the trends in off-label use and that is an advantage of observational study.

The required sample size and cost to detect less

frequent events will increase safety randomized, controlled trials by factors of 4 to 16, so the detection of these events and, if you believe the statistics, that will wind up costing 3 or $4 billion dollars at least to conduct a properly formed set of trials given that it takes 800 million to get the drug to that level.

So, you are talking about hundreds of millions of dollars to conduct these studies. There is a reluctance, we are human, a disincentive of sponsors to carefully discern safety risk of a marketed drug, especially if you are middle management. We have to face that. It is part of the picture.

Given that, I believe an observational study for safety, when sufficiently comprehensive and large, when sufficiently comprehensive and large, may offer critical insights even in light of limitations.

We assessed safety among high-risk and extraordinary high-risk patients. It's a comprehensive trial. We included more than 800 patients per group and looked at hundreds of variates and perturbations among those variates using parsimonious propensity analysis, as well as very robust multivariable corrections.

We believe our findings with respect to renal failure

are real, true, clinically important and a public health concern. They are substantive for effect size, for consistency among primary and complex surgery, for dose-response, for consistency with early in vivo/in vitro animal studies and suggestive reports in patients and for consistency with a 1993 FDA admonition regarding the observation of kidney toxicity in some aprotinin-treated patients.

Finally, our specific comparative analyses involving epsilon-aminocaproic acid and tranexamic acid, we believe are on point for they allow us to mitigate bleeding, less costly with safer drugs and our comparisons show that this was true.

If we compare the three groups, then, selection bias for an antifibrinolytic could be eliminated and the results hold, as well.

[Slide.]

The conclusions. The association between aprotinin and serious end organ damage indicates that continued use is not proved in this population especially given the less expensive generics, which are we believe safe.

[Slide.]

My final impressions--and I will be done in two minutes.

In terms of efficacy, I don't believe the blood-sparing abilities of these three agents are different, I believe they are all equally effective.

In terms of inflammation, it has questionable benefit. It is an anti-inflammatory, but the anti-inflammatories tested do not achieve effectiveness and, in fact, raise questions regarding safety. I question whether or not that should even be an indication.

Regarding safety, thrombosis is a problem for aprotinin, may be a problem for the other two, but it appears that it is clearly a problem with aprotinin both in vein grafts, as well as in other vessels and the recent reports that have emerged are highlighting that and will continue to do so.

In terms of kidney toxicity, I think it is a serious problem for aprotinin but not the other two.

[Slide.]

The findings contrasted, the 1,300 patients in the aprotinin-treated versus control, give credence to the earlier studies.

[Slide.]

In terms of cost, we know from a public health perspective that the generics are far less expensive. The

future, BART, we should not fool ourselves that BART is going to answer the question, because it won't for more than 80 percent of the patients undergoing bypass.

Look at the inclusion and exclusion criteria, apply those statistics internationally. It only addresses the question as an extreme population. Only 13 percent of BART patients match our patients, so we should not wait for that study to resolve the issue. It won't.

Randomized, controlled trials are too expensive, the patients are too healthy and inclusion/exclusion biases exist. Observational studies, they are very comprehensive and independent and I believe offer hope for the future. But they are expensive. The EPI II study costs over $100 million to conduct. But I believe that the observational study is the future paradigm if done appropriately in the setting of a drug which has become entrenched in practice.

[Slide.]

Once again, I want to thank you for your attention and I guess I will answer questions later.

Thank you.

**Questions from the Committee**

DR. HIATT: Thank you very much. Please stay, Dr.

Mangano. We have actually put a significant time to discuss each of these studies, so we actually have until 10 o'clock for the committee to go over this.

I think we would like to, first, really understand the data you have presented and then later on deliberate the value of observational versus randomized trials, in making these kinds of safety observations.

Let me begin. This is clearly a huge effort and you just mentioned it was a very expensive study. Could you give us a little bit more information on how this study was actually managed? Was there a steering committee? Were the sites monitored? Was there an independent events committee that adjudicated the events that were prospectively defined?

DR. MANGANO: Yes, yes and yes.

DR. HIATT: Could you speak a little bit more to just the actual kind of nuts and bolts of how this study was conducted?

DR. MANGANO: The study was designed on the basis of EPI I. EPI I was designed in the mid-eighties, was conducted at 24 centers in the United States, collected about 3,000 fields per patient, a smaller study.

Every nth patient was sampled as we know. The centers

were chosen because they were the best, the leading cardiac surgery centers in the country. EPI I is expanded into EPI II on the basis of that experience. EPI II was designed over a four-year period. The case report forms are meticulous.

We had about 40 or 50 people designing the EPI II study. The data were collected at each site. Every single field was quality assured and checked by a group of 23 individuals working for 18 months to check the database.

Between the last patient enrolled and the database locking was 17 months. All fields were checked, all quality controlled communication with centers coordinated, et cetera.

I have been involved in randomized, controlled trials and this was conducted better than any trial I have ever been involved with, so I think it's meticulous and would bear up under any regulatory assessment.

DR. HIATT: Just clarify that. I appreciate that, but was there an independent events committee that adjudicated the events?

DR. MANGANO: Yes, every event was adjudicated by an independent events committee for cardiac, cerebral and renal events.

DR. HIATT: And they were blinded to this group?

DR. MANGANO: Of course, they were. I mean I wouldn't even present that. I hate to answer that way, but absolutely blinded to the events.

DR. HIATT: And then in terms of managing--this is an international trial--so managing the sites, gathering data at the sites, were there monitoring staff that would go to these sites, or did the sites prepare the data--

DR. MANGANO: Each site was preselected. Each site was put through a procedure of collecting the data, of, for example, NIH Stroke Scale, the standard NIH instruments used for collection of stroke scale, falcine tests, other testing was all done at each site. Transesophageal echocardiography was standardized by view and--

DR. HIATT: So, if there were questions that would come up on a case report form that was being entered into a database--

DR. MANGANO: There are always questions on those forms.

DR. HIATT: So, there was an independent monitoring staff that would work with the sites, overseeing the primary collection of data, as you do in a typical monitoring study?

DR. MANGANO: Yes, once the data for a series of

patients came back, for one patient, then it was reviewed by a QA staff, double data entry, et cetera.

DR. HIATT: So QA centrally.

DR. MANGANO: Yes, all QA was central.

DR. HIATT: I am going to turn, run now through the committee, but let's first just begin with understanding some of these data.

DR. BALSER: Dennis, one of the issues in the data that I am having trouble understanding is the high rate of congestive heart failure in the study groups, or specifically in the aprotinin group relative to the controls or the ACA group, it is about 35 percent higher.

What do you think happened there?

DR. MANGANO: Do you want me to guess? First of all, it happened. I think that the ischemic injury after cardiac surgery manifests in many, many different ways and the transient ischemic response and even some of the lesser infarcts don't manifest necessarily into heart failure.

The best evidence of ischemic injury, we believe now is LV dysfunction and not infarction in this patient population. Only when there is implication of muscle do we believe that the ischemic injury that is experienced really is manifest.

We questioned whether or not, therefore, that the congestive heart failure findings implicate a thrombosis-like event or series of events that occur. My gut feeling is that there is more microvascular thrombosis with this agent than with the others but I have absolutely nothing to back that up in the literature.

I believe that failure events are consistent with graft thrombosis, serious graft thrombosis, if it did occur, and with infarction.

DR. BALSER: But I am talking about Table 1, which I thought was pre-existing heart failure.

DR. MANGANO: Oh, you are talking about pre-existing.

DR. BALSER: Yes, which was 30 percent, 35 percent higher in the aprotinin group.

DR. MANGANO: Let's go back. Well, it was higher in the aprotinin group. Why? When you look at all patients with heart failure, and you look at the renal events in that group with heart failure, you get the same pattern as you do here.

DR. BALSER: But if every nth patient selected, and the numbers here are incredibly large, what is the statistical likelihood that you would end up with 35 percent higher rate of pre-existing heart failure in the aprotinin group than in any

other group?

DR. MANGANO: If you looked at 100 variables that way, probably 3 or 4 of them will be higher in one group versus another.

DR. HIATT: So, just incredibly bad luck.

DR. MANGANO: I don't know if it's bad luck, because you just--you account for that. There are other variables that occur more frequently in the other groups than in the aprotinin group and it may be bad luck for them, as well.

So, in an observational study, that is the way it landed and all you can do is look at covariate impact and multivariable analysis and propensity adjustment with multivariable analysis and by looking at each of the critical risk factors and seeing whether or not, for those patients with LV dysfunction or heart failure pre-existing, whether or not the same pattern exists and whether or not it is significant and whether or not there is a dose-response for those patients, in fact.

DR. HIATT: There are some comments down here about that point.

DR. CHEUNG: Actually, a continuation in that theme there. Is your propensity adjustment--I am sure there will be

a lot more questions about that--I think you said that is primarily for bleeding, right? For example, when you are targeting the renal outcome, you are not--

DR. MANGANO: The propensity adjustment is for likelihood or the covariates associated with likelihood of use of an antifibrinolytic. The basis for that decision is the clinician's impression that the patient would likely suffer larger blood loss, so when your propensity adjusts, you are saying, well, what are the factors that will go into the choice of using aprotinin versus control, or one of the others versus control.

It is the clinician's impression of all the factors clinically that they may use in making that decision. Bu,t beyond that, you go back to an independent database and then you find the factors that are likely associated with large blood loss and you place those in the propensity model, as well.

DR. CHEUNG: Right. That is what I mean. You are targeting bleeding. But you are not targeting, for example, what factors was disposing to renal dysfunction and then go back and do a propensity that way, or--

DR. MANGANO: Oh, we did it, yes, we did that--

DR. CHEUNG: --or was CHF, the predisposing to CHF--

DR. MANGANO: Yes, we did those analyses. They were not--they were done after the fact and not part of the primary analysis. But we did that with the factors that were including in the propensity analysis, renal variates, heart failure variates and the factors likely to occur with each of those five outcomes.

It turns out the 45 factors initially chosen contain about 90 percent of the risk factors for renal outcome, 90 percent of the risk factors for an infarction, 90 percent of the risk factors for a cerebral event.

DR. CHEUNG: And those, you have not presented them in the paper or here so far, is that true?

DR. MANGANO: The 45 risks, the 45 covariates, the propensity covariates, if you look at the risk factors for the individual outcomes, then, among the 45, about 90 percent of the factors reported in the literature or from separately analyzed databases are included in the propensity analysis.

When we include other risk factors in the literature that weren't in the analysis and go back and even perform the propensity more parsimoniously, then, we get similar results.

DR. HIATT: I think there is going to be a lot of

questions. Perhaps just for due process, we could go around the room this way because there have been several hands up and if you could try to keep focused, because we do have a lot to discuss.

David, you are next on the list.

DR. DeMETS: Yes, I think I appreciate your comment that the observational data, the paradigm you present, will be important in the future as we try to assess safety. But, as part of that, the analysis I think is critical, as you have partly outlined.

But I am wondering if, for the benefit of my colleagues, I want to ask a little bit more about the use of propensity score, could you define for the panel briefly what the propensity score does and specifically, walk through more slowly exactly how you did it and then I have a couple of follow-up questions to that.

We need to understand the methodology. It is briefly described, we don't have a lot of details, so I think that is critical to this whole presentation.

DR. MANGANO: Dr. Karkouti is going to go through a more elaborate description of propensity and, perhaps after he does his, we both could address--because the same questions are

going to come up with his. But we both can address those at the same time.

DR. DeMETS: Then, can I ask, you mentioned having a lot of variables, hundreds, for the use of the propensity score and the multivariate. What did you do about missing data, for example? You must have had some missing data.

DR. MANGANO: We had missing data. It was about 2 percent in general if you look at a field and among these patients it was not a lot. The data were very, very clean.

DR. DeMETS: So, how many, in your typical propensity score development, how many patients did you lose? If it's 2 percent per variable, that adds up over a number of variables.

DR. MANGANO: Probably 3 or 4 percent of patients.

DR. DeMETS: Only 3 or 4 percent missing data.

DR. MANGANO: Yes, yes, yes.

DR. DeMETS: That's amazing.

DR. MANGANO: Don't forget these 45 variables is a propensity score on major variables. I mean you would have to look at the case report form, look at the variables and look at how they were aggressively--that is not unusual for some of the studies that we conduct in this setting.

DR. DeMETS: I will have some follow-up questions

later.

DR. HIATT: John. I have a series of questions, so if we can try to keep it pretty brief.

DR. TEERLINK: EPI II was clearly designed, it addressed multiple different hypotheses. I mean you did the aspirin stuff, you have done a lot of stuff from EPI II, which provides some very useful information.

In some of those studies, you used one set of definitions for endpoints. In another set of studies, you seemed to use a different set of definitions. So, if there is an endpoint committee that is saying what heart failure is and, at one time they are expected to say that heart failure equals balloon pump or LVAD for one study but then, for this study, they had cardiac output, wedge pressure and rales, were they asked to adjudicate for one study in one way and another study in another way?

And the same thing for MI, you know, first of all, how did the endpoint committee adjudicate them, secondly, why the very different definitions of endpoints for this version versus your previous studies?

DR. MANGANO: Each of the investigators is allowed to submit an IDR, which is a 40- or 50-page document, which

addresses a hypothesis, a study question, background, statistics, et cetera. They develop this over about a year.

We funded 24 of those IDRs. In those IDRs that are reviewed, all outcomes are not exactly the same but generally the same. I don't think there are huge outcome differences.

DR. TEERLINK: I mean in MI, you got rid of the enzymatic criteria.

DR. MANGANO: What do you mean got rid of it?

DR. TEERLINK: There were no--at least according to your--

DR. MANGANO: Right, yeah.

DR. TEERLINK: So, MI was merely an E change.

DR. MANGANO: The definition of the outcome by the investigator is prespecified by the investigator. The fields within the case report form themselves that they use in those definitions are all prespecified.

DR. TEERLINK: So, you had a separate endpoint committee for this specific study.

DR. MANGANO: Yes.

DR. TEERLINK: Okay. Then, I saw there is no age information or center information or things such as that in your publication.

Given that you previously published an abstract that said that among the most important things to determine, you know, what the outcomes were in CABG patients using the EPI II database were age, were study site and were aspirin use, none of which are included in this manuscript, I am assuming those were included as covariates.

DR. MANGANO: Yes, they were.

DR. TEERLINK: So, study sites in all of your other studies were important but weren't important in this one, or how did that sort out?

DR. MANGANO: Study site was important but did not affect the finding. There are countries in which aprotinin has greater use versus lesser use, tranexamic acid greater use versus lesser use, but they did not affect the--

DR. TEERLINK: So, there was no difference in mortality in this analysis by country.

DR. MANGANO: There is a difference in mortality by country. There is a difference in aprotinin usage by country. There is a difference in composite by country. All those differences exist and there is a spectrum of differences by center, as well.

When you put those variables in and ask whether or not

the association holds with site, with country, with continent, with region, with insurance and all of those factors, with age, the association between aprotinin and renal failure and the lack of association with the other two drugs in renal failure holds when you perturb those multivariable analysis. All of those were looked at.

DR. FLACK: I certainly appreciate the scrutiny, the careful way you collected data and I do think that observational data is clearly complementary to randomized trials, that they will always answer the same questions and is valuable.

I am impressed, though, and somewhat surprised, by your steadfast sort of conviction that this data is unassailable. We work with this kind of data all the time and I have never had that kind of conviction working with observational data, because there is too many problems that you can run into even with the best analytical techniques.

I think what is going to come out later in discussion here is that there are serious questions about the analytical techniques, so I am going to just cut right to the chase.

That is, if you are this confident in the data and you want a body like this to render an opinion about how it should

affect labeling in this, that and the other, then, when are you going to be prepared to make the data available to the scientists at least at the FDA?

I can understand why you wouldn't want to make it available to Bayer, make it available to the scientists at the FDA to provide independent validation, as well as some alternative techniques, because you know and I know that data, I don't care how well collected, is highly sensitive to the analytic techniques applied to it.

In certain of observational data where there is a lot more noise in the data, and there is a lot of bias, and I do not dismiss the fact that these patients were a lot different at baseline with heart failure and all, are you prepared now to basically let the FDA scientists analyze the data and go from there, because otherwise, I have serious reservations about what you are putting through here.

DR. MANGANO: Regarding your first comment that it is unassailable, I think the facts speak for itself, it is being assailed right now. I am not saying it's unassailable. I am saying that we put in--let me finish--let me respond.

DR. FLACK: Why don't you just answer the most important question--

DR. MANGANO: I will, just let me respond to the first one.

DR. FLACK: --okay, because I think you are filibustering.

DR. MANGANO: Okay. I offered the FDA the first week of February this database and I brought a CD and wanted to give it to them. I prepared CDs for the FDA to look at every single field in this database.

The FDA then wanted to combine this data with Bayer's data. Bayer also wanted my data. I purchased the computer with the entire database on it, brought it to the FDA and said, here, the only constraint is I want to be present when you are analyzing it and I want the data, because I am the custodian of the data, intellectual property, et cetera. You may not like that. I purchased the computer, I put the database on the computer, I gave it to the FDA.

DR. FLACK: That's not the way we do science.

DR. MANGANO: What?

DR. FLACK: That's not the way we do science. We do share data. Data is made available from the studies that the government funds and people are not necessarily there.

DR. MANGANO: Well, isn't your question did I offer the

FDA the database? I did. I would give it to them tomorrow.

DR. FLACK: Okay. There seems to be a difference in opinion, I guess--

DR. MANGANO: I will show you the correspondence, I will show you the CDs prepared. I will bring the computer that I purchased and I will bring four people who came with me to the FDA at our expense to do that.

DR. FLACK: Well, I think the FDA is here and I think they can respond to this.

DR. MANGANO: Okay, but, you know, that's--that's what it is.

DR. HIATT: Any response?

DR. RIEVES: We appreciate the comments there and that is correct. We were offered limited access to the data. There was this qualifying expectation that our examination be chaperoned or supervised, if you will.

Our statisticians did not feel comfortable with that limitation and, considering we have had fairly lengthy negotiations throughout the spring and early summer, our attorneys with other attorneys, that sort of thing, to try to obtain the data for, quote "somewhat of an independent," at least exploration of the mathematics.

I am sorry, you may not have missed--you may have missed that, but what I was saying was that, as you have heard, we were offered a chaperoned exposure to the data sets.

Our statisticians felt uncomfortable having a supervised access to that data in the sense that we would not have the ability to explore the data and at least verify the mathematics and the statistical aspects.

So, after a lot of negotiations during the spring, as well as during the summer, we decided that these were not going to be productive, meaning essentially that we were not going to have independent access or unsupervised access to the data set.

DR. MANGANO: Well, in terms of the supervision, I would like to make a comment that all I required was that I be physically present within the FDA when you were analyzing the data. There is--I am sorry--there are patient confidentialities here that are important, that I respect.

DR. FLACK: This data, number one, is large. Two, it should be de-identified where nobody can link that data to a patient and, three, I don't understand, what do you think being present in the building is going to accomplish in regards to safeguarding the integrity of the science or confidentiality. That escapes me.

DR. MANGANO: You have an opinion and it has obviously been weighted to some degree before this meeting.

DR. FLACK: No, I do science all the time.

DR. MANGANO: All I can say is I am happy to share the data.

DR. HIATT: Perhaps we won't debate that further maybe. Dr. Harrington.

DR. MANGANO: I am sorry, you know, you are ticked off about it.

DR. FLACK: There is nothing to be sorry about, just answer the question.

DR. HARRINGTON: I will echo John's comment, too, that I encourage you to share the data in an unfettered fashion. I won't debate it now, but I do have a series of questions about the methods.

I am trying to understand, Dennis, the whole definition of the events, the ascertainment issue and the adjudication issue, let's go one by one.

The definition of myocardial infarction, Q wave and ST segment changes, not a standard definition of MI put forward by the WHO, the ACCHA, EFC, STS, et cetera, who decided that that would be the definition of the study?

DR. MANGANO: I did in the protocol that was written.

DR. HARRINGTON: And why was that particular definition chosen at odds sort of with other things that were going on around 1996, 2000?

DR. MANGANO: Well, I don't know if it's at odds. Are you talking about non-ST elevation MI?

DR. HARRINGTON: I am talking about just standard definitions of myocardial infarction. Post-bypass surgery typically include Q waves but also include enzymatic criteria--

DR. MANGANO: Right.

DR. HARRINGTON: --wall motion abnormalities, et cetera.

DR. MANGANO: The enzymatic data is still being analyzed with respect to CK and troponin release. That costs another $10 million for analysis and was not included in any of the manuscripts.

DR. HARRINGTON: The second question has to do with the ascertainment to which I think John was getting at a bit. If EKG was the primary measure of MI, did you have 100 percent ascertainment of EKG, or give us a sense of what the ascertainment was.

DR. MANGANO: We collected EKGs before surgery and for

three periods after surgery.

DR. HARRINGTON: What were they?

DR. MANGANO: It was on ICU entry, on the first day, the third day and the seventh day.

DR. HARRINGTON: Give me a flavor of the data in terms of the completeness of each of those time points.

DR. MANGANO: I can't quote that right now.

DR. HARRINGTON: I will take rough.

DR. MANGANO: I think it's--I don't want to sound defensive about the data--but it's over 90 percent for each of those periods.

DR. HARRINGTON: At each of those time points.

DR. MANGANO: Yes.

DR. HARRINGTON: And when those data were then--I am assuming that the source EKG, the way you have said it, was then provided to an independent body to review for the presence of Q waves and/or ST segment changes. Is that--

DR. MANGANO: Yes, each EKG went to two cardiologists separately in panels and Minnesota coded each of them. The codes were then crossed over by a third cardiologist and, if there were discrepancies, it went to a panel of five.

DR. HARRINGTON: And so the MI definition was solely

based on the EKG criteria and the adjudicators, if you will, did not have access to the other clinical data.

DR. MANGANO: No, no. They did that for all the ECGs in the database.

DR. HARRINGTON: And then I just have a couple sort of yes/no things.

Do you have transfusion data in the data set?

DR. MANGANO: Yes.

DR. HARRINGTON: But you have not presented it.

DR. MANGANO: No. There is no difference in transfusion parameters between the groups.

DR. HARRINGTON: Do you have the long-term follow-up data available?

DR. MANGANO: Not today, not for this meeting.

DR. HARRINGTON: But it has not been presented publicly or anything like that?

DR. MANGANO: It has not been presented publicly yet.

DR. HARRINGTON: My final question is, is that with 100 percent source document verification of all of these variables, you indicated $100 million is what this study cost. Who paid for all of that?

DR. MANGANO: The Foundation paid about $45 million for

the study. The general study cost, as assessed, was assessed by the investigators' sweat equity, as well, what the equivalent value would be for collecting such data.

DR. HARRINGTON: Where did the 45 million come from?

DR. MANGANO: From the endowment and the Foundation.

DR. HARRINGTON: But the source of that, is that philanthropy, is that--

DR. MANGANO: Some of it is philanthropy, a lot of it was clinical trials that we had performed in the early 1990s and a lot of it has been growth and management.

DR. HARRINGTON: Industry-sponsored clinical trials that you took the margin of and reinvested into this Foundation?

DR. MANGANO: That's correct.

DR. HIATT: I would like to be able to go and complete this discussion around the room. So, we are a little bit over, but if we could maybe just sort of charge ahead here.

DR. KASKEL: I am not speaking for my colleagues in nephrology. It is only because I come with my name at this point that I get a first shot at some of the nephrologic issues. But the definition of renal disease is varied.

I think we should have access to see what these

patients came in with, if they had a pre-existing condition, was there proteinuria, how were the measurements of kidney dysfunction measured. These are important criteria for us to look at.

Also, the concomitant use of ACE inhibitors, ARBs, I know you do have some data on angiotensin-converting enzyme inhibitors. We need to know if they were exposed to other nephrotoxins, aminoglycosides, effects of anesthesia, also, the measurement of creatinine can be affected by apoprotinin after it is processed in the proximal tubule possibly, that we need to address how that has been dissected here.

Also, there is a lot of functional hemodynamic changes in patients like this with high vasoactive substances coming in with cardiac problems.

Clearly, a functional change in GFR from the use of this agent needs to be considered, what happens over time. You can follow them for seven days, what happens in two weeks, three weeks, to measurements of renal function, is it permanent or reversible.

The indications for dialysis will vary from site to site. So, these are some of the things that I certainly would like to look at down the line here.

DR. MANGANO: Certainly.

DR. KATO: From a technical perspective, I noticed that cardiopulmonary bypass time was not included, is that correct, in the baseline data?

DR. MANGANO: Was it included? That's one of the variates, but we did include it in the analysis, of course.

DR. KATO: And it didn't show anything?

DR. MANGANO: No.

DR. KATO: Okay. And what about--

DR. MANGANO: It did not alter the relationship between aprotinin and renal failure and the other two drugs and renal failure and cardiopulmonary bypass time is a variable in one or more outcomes in terms of its being associated with one of those outcomes.

DR. KATO: Sure. Another event that was occurring right around this time was the use of either the change in technique from a side butting cross clamp to a simple cross-clamp application on the aorta, which makes a big difference in terms of stroke, perioperative stroke. Was that looked at?

DR. MANGANO: Yes.

DR. KATO: And no difference?

DR. MANGANO: On?

DR. KATO: That variable also fell out in terms of your analysis?

DR. MANGANO: Yes.

DR. KATO: But that wasn't included in your document?

DR. MANGANO: No.

DR. KATO: Thank you.

DR. MANGANO: The document, the methods by themselves have a limited space to describe those. I guess what I should have done is put all the variates on line, let people look at them. That would have been a smart thing to do. That wasn't suggested by the New England Journal, so we didn't do that. But all those variates were looked at.

DR. ELLIS: Two brief questions. One, I was confused in reading the manuscript about the inclusion of patients undergoing coronary artery revascularization or angioplasty.

Can you comment on why patients undergoing angioplasty would be included in the study? That is what the manuscript says.

DR. MANGANO: Prior angioplasty.

DR. ELLIS: Okay. It is not clear reading that.

The second, could you comment on the use of antiplatelet medications in this patient population?

DR. MANGANO: Pre-op?

DR. ELLIS: Pre-op, yes.

DR. MANGANO: Very low incidence of Plavix use, less than 5 percent. Aspirin use was defined in the aspirin manuscript, which was not insignificant, 50, 60 percent of patients pre-op. For vein grafts, aspirin at exit, which doesn't impact this data, it might impact long term, for vein graft protection in the final week after bypass was used fairly consistently among centers.

DR. JEEVANANDAM: Just looking through this data, I think we need to be careful. It's not randomized and this is observational. That has a lot to do with when the surgeon or an anesthesiologist, or a combination, decide to use this drug.

DR. MANGANO: Yes.

DR. JEEVANANDAM: Being a surgeon, I use this drug, you know, intermittently or depending on our patients. You know, clearly in my own use, I use aprotinin when we have a higher risk patient, a re-operation patient, somebody who has heart failure, somebody who is coming in for a high-risk mitral valve repair, et cetera and, clearly, that is borne out by this data where, you know, if you look at it, not propensity match, but just raw data, the patients who got aprotinin were clearly a

much sicker group of patients.

A lot of times, we would just--it's a gut instinct on whether we are going to use aprotinin or whether we use Amicar. I think that is the type of thing that isn't borne out by this data.

You know, propensity matching may only go so far but there are a lot of subtle reasons why drugs are used and, if it is not a randomized trial, or it is not blinded, I think there is an inherent flaw.

DR. MANGANO: There is no question that it is and you try to identify those by using non-parsimonious propensity and you try to identify as many of those factors--as in your practice, there are practices around the world that we have here, such as in India, which doesn't use aprotinin, or in Austria or Germany, which uses a lot, or in Canada, which use more, certain countries in Europe which use more Amicar or tranexamic acid than aprotinin in their high-risk patients.

So, there is an international use pattern for these agents. But I think consistently, among patients who are most likely to bleed, by the surgeon or the anesthesiologist, whoever is making the decision, they will use one or the other of those drugs prophylactically in those patients.

DR. LINCOFF: I have three questions if time allows. The first is that in your abstract, or actually, the first line of the results in the abstract, you say that the use of aprotinin in the multivariate propensity-adjusted model doubled the risk of renal failure requiring dialysis and yet nowhere in the text do I see addressing renal failure requiring dialysis.

You talk about the composite renal event with the odds ratios but the only place I see the direct reference to the renal failure requiring dialysis, which is the real endpoint of concern, is in the univariate graph, which is not multivariate adjusted.

DR. MANGANO: Right.

DR. LINCOFF: I think that it is pretty clear that these patients are different and so the data for not adjusted is irrelevant. That what we are really interested in--and then there is, of course, a lot of discussion whether that is even valid given different techniques--

DR. MANGANO: I don't know if it's irrelevant. It is relevant to the people who develop a 5 percent, it is relevant to the public who develops renal failure.

DR. LINCOFF: Of course it is. But it is not relevant to comparing different groups, since the groups are different.

So there is an underlying rate at which a group that is at higher risk will develop renal failure and what we are interested here is how much of that is contributed to by the aprotinin. So, the unadjusted don't give us that information, the multivariable does.

DR. MANGANO: Right. That's a good point. What we did for that is we had a publication from EPI I defining the risks with respect to renal failure. Firstoff, in the Annals of Internal Medicine, we took those factors for renal failure and put them into the model, as well, for propensity and multivariable adjusted.

DR. LINCOFF: No, I understand that, I am not challenging that, because I know there is going to be a lot of discussion about how this propensity analysis performed.

My question is, you highlight the first line of your results is that you doubled, the aprotinin doubled the risk of renal failure requiring dialysis and yet I don't see that anywhere in the text of the paper.

So, is that, in fact, true, or is that a--

DR. MANGANO: You mean the univariate?

DR. LINCOFF: No, it says in a propensity-adjusted, multivariable logistic regression, use of aprotinin was

associated with a doubling in the risk of renal failure requiring dialysis.

DR. MANGANO: Yes, that's true.

DR. LINCOFF: That is a very strong statement.

DR. MANGANO: That's true.

DR. LINCOFF: In the paper, all that you talk about is your renal composite--

DR. MANGANO: Composite, right.

DR. LINCOFF: --which includes rise in creatinine.

DR. MANGANO: Right.

DR. LINCOFF: So, it may just be an error in the abstract, but--

DR. MANGANO: No, it is not an error.

DR. LINCOFF: So, you are asserting that dialysis risk was doubled.

DR. MANGANO: Yes.

DR. LINCOFF: And do you have that data anywhere?

DR. MANGANO: Not with me, but I can provide it to you.

DR. LINCOFF: All right. The second question I have regards Dr. DeMets had asked you a dropout rate or the rate at which you couldn't include in the propensity analysis or some of the multivariable analyses because fields weren't available.

I realize you didn't have the details of this, but I will point out that in your Table 2, you exclude 410 patients, that is out of 4,374 for that renal adjustment, so that is more like a 10 percent rate rather than--

DR. MANGANO: For which, for which variable are you talking about?

DR. LINCOFF: Results of multivariable logistic regression for the renal composite outcome.

DR. MANGANO: The renal, right.

DR. LINCOFF: Excluded were 410 patients with missing values for at least one of the cohorts of propensity scores--

DR. MANGANO: Right, for renal. He was asking for all outcomes.

DR. LINCOFF: All right. So, there are dropout rates that are perhaps higher than 2 percent.

DR. MANGANO: Yes.

DR. LINCOFF: The third is can you just talk briefly--

DR. MANGANO: For individual--well, we can go into that, it is not necessary.

DR. LINCOFF: The third is can you talk just briefly about the structure of the organization, the Ischemia Research and Education Foundation specifically, because, you know, you

talked about the 31 different projects that have been approved and I am still sort of stuck on this endpoint, the differences between studies.

Did these patients, these 4,300 patients--were these patients used, the same patients used, for different studies, different publications, different analyses and, if so, did you truly actually convene different endpoint committees for each of these studies, taking the same patients and defining endpoints differently from study to study?

DR. MANGANO: No.

DR. LINCOFF: So, then, how do you create endpoints that are different from study to study, from the same adjudication?

DR. MANGANO: The definition of the endpoint is specified. It is specified by the field within the case report form. I want to choose, for one reason or the other, I am interested in non-ST elevation MI for looking at cardioplegia.

So, that investigator says the most pertinent type of infarction for cardioplegia, for whatever reason, is non-ST elevation MI. I am defining non-ST elevation MI by fields, 7.1, 11.1, or 7.3, 12.2, or 6.3, 7.8.

Those three fields have been quality assured and

checked and that is used generally in the definition.

DR. LINCOFF: Okay. So, then the clinical events committee refined or checked those figures.

DR. MANGANO: That's correct.

DR. LINCOFF: And then used a computer or whatever to actually define the other ones.

DR. MANGANO: That is correct, that is right. I am sorry for the misunderstanding.

DR. HIATT: Propensity was used to adjust the data but, to clarify, not to match different groups. So in the other study we are going to review next, after propensity adjustment, the group baseline differences became very similar.

DR. MANGANO: Yes.

DR. HIATT: I didn't see that here. So, one question about it is--

DR. MANGANO: It's in a big table that I presented. I think it is one of the tables in the publication. It is the propensity adjusted and unadjusted.

DR. HIATT: Yeah, where things didn't change much.

DR. MANGANO: That's correct.

DR. HIATT: And that is one of the criticisms. But it would have been nice to have seen patient baseline demographics

where there are fairly significant differences, particularly in pre-op risk factors, suddenly become more common between groups, whether that adjustment is between the control group--

DR. MANGANO: Right.

DR. HIATT: --or between different drug groups, which might, in fact, be more relevant. But I didn't see that and it wasn't clear to me.

DR. MANGANO: I think that is in the table, if I am not mistaken. I can point it out during the break.

DR. HIATT: So, did you match subjects and then look for the outcomes, or did you use propensity simply to make adjustment?

DR. MANGANO: Used the propensity scores of covariate and multivariable model as an example.

DR. HIATT: Okay, but that didn't--

DR. MANGANO: Each patient is assigned a score.

DR. HIATT: I think we will get a little bit more to understanding this analysis after the second paper, but I wanted to clarify. Let's keep going around the room.

DR. WARNER-STEVENSON: I think we have heard a number of questions related to how endpoints were adjudicated and I am just going to take another endpoint as an example, because

heart failure was also significantly more with aprotinin.

In your discussion of the criteria for that, it's a cardiac output of less than 2 associated with a wedge pressure over 18, a central CVP above 12, an S3 gallop or rales.

Did they have to have all of those, some of those, two of those?

DR. MANGANO: Or.

DR. WARNER-STEVENSON: I am sorry?

DR. MANGANO: Or.

DR. WARNER-STEVENSON: Well, or. So, rales alone would have been enough?

DR. MANGANO: No. Let me get to the definition. I am still operating on California time here.

DR. WARNER-STEVENSON: I have it here.

DR. MANGANO: Yeah, but it's hard for me to hear you.

DR. WARNER-STEVENSON: Cardiac output of less than 2, associated with a pulmonary occlusion--

DR. MANGANO: Right, a cardiac output of less than 2, associated with any of the other factors.

DR. WARNER-STEVENSON: So, S3 gallop was routinely assessed in postoperative patients? That would surprise me.

DR. MANGANO: No, it is not routinely assessed.

DR. WARNER-STEVENSON: But if they happen to notice it.

DR. MANGANO: But when it's marked, it is a field and when it is there, you know, it is specific but insensitive.

DR. WARNER-STEVENSON: So, I think I would have some concerns on that.

DR. MANGANO: Yeah.

DR. WARNER-STEVENSON: On how that is adjudicated.

DR. MANGANO: Right.

DR. WARNER-STEVENSON: Actually, to summarize again, I think we all have concerns that these patients are significantly sicker and a quick review of that is heart failure, carotid disease, liver disease, history of bypass, history of valve disease and, currently, a concomitant valve surgery.

I guess further debate will be on whether we can really neutralize that by any propensity scoring or multivariate analysis.

Can you mention for a moment the 691 patients excluded, because the mortality was highest in those patients and the use of fibrinolytics was somewhat different in those?

DR. MANGANO: Well, they had multiple--the reasons for exclusion are there.

DR. WARNER-STEVENSON: Some of them had multiple fibrinolytic agents, some of them had what you considered an inadequate dose and then there was something else.

DR. MANGANO: Right. The reasons are listed. Do you want me to go to that?

DR. WARNER-STEVENSON: No, I understand the reasons. Was that prospectively defined that you--

DR. MANGANO: Yes.

DR. WARNER-STEVENSON: --that those were the reasons for which patients would be excluded?

DR. MANGANO: Yes.

DR. WARNER-STEVENSON: I would also applaud the effort to provide a counterweight to industry incentives for trials. I think we need this effort. We also need this effort to be transparent and, certainly, I think there is an incentive to prove our hypotheses regardless of what the sponsorship is.

DR. MANGANO: I am all for transparency. But this is an unusual setting where you take the first observational database, the first call you get from the sponsor to get your data. The second call, a few minutes later from the FDA to get your data. There is a heightened awareness and a concern and people are human.

We went through great lengths in terms of the ethics of the problem, and, athough you could blind, et cetera--to leave the data in any one repository would demand that we go back to each center and say is this within your country's guidelines, do you give us permission, it is going to be used for regulatory, it will be totally unblinded, and we just don't--we have a very strict data control committee and the data has never gone out of the Foundation ever, even to an investigator.

So, we have been fairly meticulous. We offered to work with the FDA and it didn't happen. We will offer to work with them again. But we--you know, this is a new paradigm in terms of independent data being shared and contrasted.

So, there was also a question of whether or not this data would be combined with other data and a mosaic of all data would be included and watered down.

So, the question is, one of the major questions that came up is if you are going to do a meta-analysis of everything and put everything into a pot, what is the design of that study, what are your endpoints, what are your questions, because you could pull out anything you want.

One concern I had was lumping this data in with other data without having the design of exactly how it was going to

be analyzed raises concern with me in terms of prospective nature.

You could take this data and pull anything you want out of it. You could say the drug is safe and don't ever worry about it again, but if the FDA is going to perform a series of analyses, we believe it important to get the design for those analyses presented to us in written form, so we know what the prospective question is, because don't forget, the FDA is under some pressure right here, which is that they have a drug that is marketed 13 years.

So, I am happy to cooperate. I would like the design to be prospective and we will work with the FDA if they want to do that.

DR. HIATT: I think in the next just remaining couple of minutes, we are about a half an hour late to the break, can we just finish up with the last few questions?

DR. HECKBERT: Okay, great. Yes, I had a question. I did find the description of the statistical analysis quite difficult to follow and that is why I have a few questions there.

Were these propensity scores developed for use of any antifibrinolytic drugs versus none?

DR. MANGANO: Yes.

DR. HECKBERT: Or were they developed independently for the propensity to use each of the antifibrinolytic drugs?

DR. MANGANO: Any.

DR. HECKBERT: Any.

DR. MANGANO: Yes.

DR. HECKBERT: All right. That could be a problem.

Also, I noticed in this presentation and also in your abstract, you seem to have been focusing on the unadjusted results. In fact, that was a question over here was that the first sentence of the abstract presents a result that is unadjusted for covariates even though it is not in the paper.

Do you feel that the unadjusted results are the ones that are the main results of the paper?

DR. MANGANO: No.

DR. HECKBERT: Because that is what is presented in the abstract and that is what made me wonder.

DR. MANGANO: What does the first sentence read?

DR. HECKBERT: It says it's propensity-adjusted, multivariable--

DR. MANGANO: So, that is adjusted, that is the adjusted result.

DR. HECKBERT: But then in response to the question over here, you said that was an unadjusted result.

DR. MANGANO: No, I didn't. I said we did the adjusted results and they do show a doubling.

DR. HECKBERT: I see; and they just weren't presented in the paper.

DR. MANGANO: Yes.

DR. HECKBERT: I see. Okay. Finally, why was the particular definition of MI that has been described already used in this paper, why did you choose that, why did you feel that--

DR. MANGANO: Because we had the ECGs on everyone and we took a simple definition of infarction in the study. We had four ECGs. They were meticulously read and we could identify--it was a very specific definition and we believe we can get very high quality data from that.

DR. HECKBERT: So, it was to avoid a missing data problem.

DR. MANGANO: To avoid enzymatic definition of infarction, which in these patients was a huge burden.

DR. HECKBERT: Because of missing data.

DR. MANGANO: No, we have 65,000 blood samples, we

didn't analyze them to CKs and troponins. It wasn't missing data.

DR. WARNER-STEVENSON: Thank you.

DR. MANGANO: There is a real bias on this committee.

DR. CHEUNG: Since the renal failure seems to be a big emphasis that you in the other paper--I want to just ask about the endpoints very carefully. One is in the abstract, it says requiring dialysis but in, the Methods section, is the composite of requiring dialysis and autopsy finding or autopsy finding.

Is the autopsy finding, is it a big chunk of that composite outcome?

DR. MANGANO: No.

DR. CHEUNG: And are they adjudicated on the slide, or is this is whoever reports it--

DR. MANGANO: No.

DR. CHEUNG: --if it happens to have it, you have it?

DR. MANGANO: We got the autopsy evidence.

DR. CHEUNG: But I mean is it asked specifically to look for it, or just if it happens to be an autopsy report, you answer it, if not, so be it?

DR. MANGANO: If there is autopsy evidence provided.

If there is no autopsy evidence provided, if we don't have the pathology report, we can't just say that there is autopsy evidence.

We gleaned whether or not there was autopsy evidence from the pathology report.

DR. CHEUNG: In just creatinine definition, why the particular definition?

DR. MANGANO: It was based on the Annals of Internal Medicine definition that we previously published in the first database.

DR. PAGANINI: Dr. Mangano, let me, first of all, congratulate you on trying to do something different and I don't mean that disparagingly. I mean that.

DR. MANGANO: Thank you. I appreciate that.

DR. PAGANINI: I would also like to congratulate you on what you have done before in identifying intraoperative issues and their response with renal failure.

I assume that many of those issues that you have already reported many years ago, pump time, cross-clamp time, et cetera, were used in variables here.

DR. MANGANO: Yes, they were.

DR. PAGANINI: And your EPI I variables were used as

variables here.

DR. MANGANO: Yes, they were.

DR. PAGANINI: Did you use any variables that surfaced in analysis of the EPI II data to be used here, or did you rely on EPI I and previous data?

The rationale behind this--let me finish the question--is that when you start to use different databases for their indicators, then, you are perhaps using indicators in a database that never generated it and they may or may not become meaningful.

My concern is that multiple indicators from several other databases not generated from perhaps, for example, half of this database generating with bootstrap techniques, some sort of indicator, and then applied to the other half, may have been a stronger way of going rather than using already established from other areas.

The biggest issue that I have with this--and I am sorry, I don't mean to lecture--but the biggest issue I have with this is a chronological issue.

In the eighties, the open heart surgical patient is markedly different than in the year 2000 and what the patient brings to the table in the year 2000, prior to open heart

surgery, is a definitely different patient than what we have brought to the table in the eighties and, therefore, indicators may vary.

Would you mind commenting a little bit on that?

DR. MANGANO: Yes, indicators do vary. The EPI I data collection was between 1991 and 1993. The majority of those variables survive analyses that are gleaned from the literature. They are pretty consistent findings with respect to renal failure and the associative factors.

We did not use EPI II to define the predictors that would then again be used in the same analysis as covariates in this study.

We tried to be inclusive with respect to the covariates used in the multivariable analyses, both from the EPI I experience and from the literature, but not relying on the EPI II experience with the data.

We took the '97 covariates and performed the analyses because that is the way we prespecified them. Then then we went back and looked at several hundred other covariates and all the ones that I could possibly think of in this database that might be even casually associated with renal failure and placed those in, in post-hoc analysis, to see if the findings

were robust, and we found consistent findings.

DR. PORTMAN: A few quick questions. Was there any kind of uniform criteria for dialysis?

DR. MANGANO: No.

DR. PORTMAN: Because as we all know, oftentimes patients are dialyzed due to pump failure, heart pump failure rather than to renal dysfunction.

DR. MANGANO: Well, dialysis, as you know, carries very substantial risks especially after heart surgery. The clinical decision, as surgeons may tell you, or intensivists may tell you, is a very serious one.

So, I believe that the patients undergoing dialysis, that definition of dialysis is highly specific and meaningful. In separate analyses, we looked at dialysis as reported on long-term outcome and, though it is not published as of yet, the dialysis variable that we have is very prognostic for long-term mortality, as are each of the other variables that I have mentioned that we have chosen here including the ECG. We did validate those by a long-term mortality analysis, which isn't published yet.

DR. PORTMAN: Well, I might take exception with you there, but to move on. Creatinine is a poor measure of renal

function really.

Did you look at a more standardized formula like the MDRD formula to calculate out a GFR for these patients rather than relying on a creatinine since body size I am sure varies tremendously?

DR. MANGANO: No, not for this analysis.

DR. PORTMAN: Is that being planned?

DR. MANGANO: We have done that post hoc.

DR. PORTMAN: And you have those data?

DR. MANGANO: Not with me, but we have the findings.

DR. PORTMAN: Finally, related to renal dysfunction, we have a definition of postoperative renal dysfunction. Do we have any long-term data on the patients with dysfunction? Is this a transient elevation in creatinine that normalizes with long-term follow up, or is this a permanent problem?

DR. MANGANO: A 65 increase in five-year mortality is associated with this definition of renal dysfunction without dialysis.

DR. PORTMAN: But if it's a matter of five or six or seven days, I am concerned that the importance of that is not what you just stated.

DR. MANGANO: I will show you the data.

DR. PORTMAN: That would be great.

DR. HIATT: I think we are really close to taking a break here. I think we will just go ahead and maybe do 10 minutes or so.

DR. MANGANO: Thank you for your comments and especially your skepticism.

DR. HIATT: We appreciate the time you spent clarifying things, too. Thank you.

[Break.]

DR. HIATT: We will begin with the next presentation.

**Keyvan Karkouti, M.D.**

DR. KARKOUTI: Thank you very much. Thank you for asking me to come and help explain our study, hopefully not as extensively, but defend it after the presentation is over.

Our objectives were quite different than Dr. Mangano's study. We, our hospital, it was a single-center study. I will get into that in a minute. But basically, our use of antifibrinolytics is completely off label. Everybody gets one. Ninety percent get tranexamic acid, the high-risk group get aprotinin. I will explain how we were able to match patients and hopefully come up with a relatively unbiased analysis.

[Slide.]

Firstoff, I have received some speaker's fees from Bayer, less than 3,000--actually, 3,000 Canadian in total, so less than 3,000.

[Slide.]

What I am going to do, my conclusions are on my overview slide, so that if anybody falls asleep during the next half an hour, you won't miss much.

First, I will talk about propensity analysis, a few slides on how we did it and why we did it the way we did it. Then, as I said, our hypothesis was that aprotinin was superior to tranexamic acid and we disproved that. So our conclusion was that aprotinin was not superior to tranexamic acid.

I will spend some time addressing two major criticisms. One was, as Dr. Weiskopf kindly put in his recent letter to the Editor in Journal of Thrombosis and Hemostasis, that the "results are irredeemably biased," so I am going to address that point to see if they are, in fact, irredeemably biased.

Then, the second criticism that we have often heard, and has been published a lot, is that this doesn't gibe with the evidence out there, so how can it be right, so it is probably wrong if the RCTs aren't showing the same thing.

Finally, my conclusion is going to be that there is no

convincing evidence that aprotinin is better or worse than the alternatives.

[Slide.]

So, propensity analysis primers, I am not a statistician. I am a clinical epidemiologist. I am an anesthesiologist and my expertise is in clinical studies, so I don't understand the theory behind propensity analysis. But I do know how to use it, and a couple of good references in terms of clinical use of propensity analysis I have listed there, and that is basically what I have come up with when I compare logistic regression with propensity analysis.

[Slide.]

I think everyone is familiar with logistic regression by now. It has been used numerous times in many studies and the objective of both are the same. We know in observational studies, patients aren't randomized to one group or the other.

For example, at our hospitals, the ones who get aprotinin for the most part are higher risk than the ones who get tranexamic acid, so the objective of these two techniques is to adjust for this bias by measuring and adjusting for the different confounders.

They do it differently, though. Logistic regression

models for the outcome, for example, if you run it until they get transfusion, the outcome would be transfusion and the confounders we would adjust for would be things like baseline hemoglobin, pump time and, in that, you would have the variable we are interested in, which would be aprotinin versus alternatives or versus placebo.

In that way, you get an adjusted association of the variable you are interested in with the outcome you are measuring.

Propensity is different. Propensity analysis, what you do is you model for the likelihood of getting the intervention that you are trying to analyze. In this case, we are going to model for the likelihood of somebody getting aprotinin versus tranexamic acid in our hospital.

In that model, you can put as many covariates as you want unlike logistic regression which I will explain later. Once you do that, you get a score for each patient, that Patient X had an 80 percent chance of getting aprotinin and that patient either got aprotinin or tranexamic acid.

So, then you can go and match Patient X, who had an 80 percent chance of getting aprotinin and actually got aprotinin, to Patient Y, who had 80 percent chance of getting aprotinin

but got tranexamic acid.

Based on that, once you do that, the two matched groups are theoretically or almost unbiased assessment, because theoretically, not only have you matched for all the confounders you put into the model but probably also for the variables you didn't put in the model. But I don't think that has been proven beyond a doubt.

In any case, in both cases, in logistic regression, you get an odds ratio of the outcome for the exposure and, in propensity analysis, you do matching based on treatment or no treatment and see how the outcomes differ.

[Slide.]

What are the advantages, why do propensity analysis as opposed to logistic regression? Mainly because logistic regression has certain assumptions that have to be met, that propensity analysis doesn't.

Logistic regression can't adjust for confounders where there is large difference in distribution between the treatment groups. It assumes a linear relationship between the confounder and the outcome. You are limited by the number of outcomes and the number of events for the confounder that you can put into the model.

So, you can't do rare covariate analysis, you can't do very large sample sizes to do rare outcome analysis. You don't have the same limitations with propensity analysis.

There are no underlying assumptions and you can put as many covariates as you want in the model because you are not modeling for the outcome, you are just modeling for the intervention.

[Slide.]

So, what makes for a good propensity analysis, propensity score analysis? Well, I think, as opposed to just a logistic regression paper, I think you have got to exploit its advantages over logistic regression and use it appropriately.

[Slide.]

I have an example here where in this study, it is not important what they did. But basically, what they were trying to do is see the relationship between propensity analysis and logistic regression.

Initially, they did logistic regression to see the effect of high level of care afterwards with some covariates. The outcome was the composite outcome of mortality and complications and, when they did logistic regression, they found that the risk of adverse events was reduced if they went

to a higher level of care center.

Then, they did propensity analysis, much like Dr. Mangano did, and then they put that in the model to see what the effect of met odds ratio is and what they found is that if you just do the propensity score in the model and the outcome, the odds ratio changes.

But once you start adding the covariates in the model, basically, it is as if you didn't do a propensity analysis--and you might not bother, because by the time you get to the number of covariates--you had 9 initially--by the time you get to 4 covariates, the odds ratio is exactly the same as it was without the propensity score and the propensity score itself is no longer significant. It is not playing any role in the logistic regression. So, essentially, you are doing logistic regression.

[Slide.]

Then, what you have got to do is, okay, so using that reason, I agree. But, once you do matching, I think it is important to confirm that you have succeeded in matching patients, so you have to demonstrate that it is adequately balanced, that the confounders have been well matched.

Then, when you make conclusions, you have to realize

that it has limitations and it does not match for unmeasured confounders and it is only theoretical I think at this point that you do match for unmeasured confounders.

So, going to our study, it was a single-center study, Toronto General Hospital. We do 2- to 3,000 cases of cardiac surgery per year including transplants, LVADs, all sorts of surgery, adult congenital. It's an adult hospital.

As I said, aprotinin is used in high-risk patients. But we realize that a lot of times somebody who had--and our indications for aprotinin use are pretty strict--they have to be multiple reduced, complex surgery expecting 2 1/2- to 3-hour pump time, active endocarditis, Jehovah's Witness and I think that is about it.

But in any case--but there were some cases that started off as simple and got complex, so those guys got tranexamic acid. Maybe it was a mitral valve repair, that they had to do it three, four times and, by the end of the case, it was complex and there were some complex cases who got tranexamic acid, so realized there would be an opportunity here to match patients who were relatively with the same risk profile.

The database we used is a prospectively collected clinical database. We combined two different databases. One

is a database that is used by the Cardiac Care Network in Ontario to make decisions on the allocation of care and how each hospital is doing.

That data is collected prospectively in terms of perioperative variables and entered in the computer. The outcomes are collected by a single, one or two full-time nurses whose only job is to collect the outcomes from the databases and they have specific definitions of what the outcomes are.

This data, as I said, it's a clinical database, so there was no question of what we were going to use this data for when it was collected, so anyway they are blinded to the outcomes that we are studying here.

Then, what we did is, as I said, we did propensity score matching, so we ended up with about 11,000 consecutive patients with pretty complete data.

When the data wasn't complete, we went back to the medical records to complete it and, if we couldn't find the data from medical records, then, we just deleted that patient from the analysis, and there were very few deletions. So, the database was pretty good and after cleaning it up, it was even better.

[Slide.]

This is what happened when we did propensity analysis. As I said, we had about 11,000 patients, 10,284 who received tranexamic acid and only 586 over the 4 1/2 year course of the study that received aprotinin.

What happens when you do the propensity score and you apply it back to these groups, you will see that the propensity score, the average propensity score in the aprotinin group was 0.4, so on average, the aprotinin group had a 40 percent chance of getting aprotinin and the tranexamic acid group was 0.03, so over the 10,000 patients, on average, they had a very low likelihood of getting aprotinin.

But once we matched, when we ran the program--and the matching program is a macro for SAS, there is absolutely no manual controls in terms of who you can put in the model and who you can't put in the model.

You run the macro and it comes up with a matched group. We matched 449 patients and, as you can see, the average propensity score in both groups was exactly equal.

In the 137 patients that we didn't match, the average propensity score was markedly higher, which is one of the main limitations. We cannot extrapolate the results of this study to the really high risk group and really can't extrapolate it

to the really low risk group.

What we have here in the group that we matched is the moderate-high risk group. Once I show the patient characteristics, I think it will be obvious.

[Slide.]

This table is basically what the patients were like before matching. It is not important to know what the variables were. I have highlighted some of them, but what is important is that as you can see, they were different in almost every case and these are important covariates.

So, as I said, we gave aprotinin to the higher risk populations and the aprotinin patients were higher risk. Some important variables we have in there, for example, abnormal renal function, which we defined basically as what is called abnormal by our lab, which is a creatinine level of greater than 100 micromoles per liter in women and more than 110 in men, or if the patient was on dialysis.

In that, for example, 26 percent of the aprotinin group had abnormal renal function versus 19 percent of the tranexamic acid group and everything is basically like that. It was higher risk in the aprotinin group.

[Slide.]

But in the matched group now, we have 449 in each group. As you can see, all those p values are nonsignificant. Some of them are in favor of aprotinin, some other important ones are in favor of tranexamic acid. But, overall, I think the balance seems to suggest that our matching was able to give us two groups of patients with equal underlying risk of outcomes.

Now, there were some variables that were important that we didn't have in the database, that then we went back and looked at in the matched patients specifically, for example, total heparin administered, total protamine and total Pentaspan, which is a medium molecular weight hydroxyethylstarch, the only thing we have in Canada in terms of starches, and we found that the groups were actually pretty well matched for these covariates, again suggesting that the match is probably consistent for the confounders that we didn't measure.

Important things like ACE inhibitors, for example, were not in the database. We did not go back and look at those mainly because it is impossible to know which patients had ACE inhibitors in the morning and which ones didn't, so it is really hard to match for that.

[Slide.]

Our primary outcome was efficacy transfusions and our hypothesis was that we would see a marked superiority with aprotinin mainly because that was the clinical impression and it still is at probably most places across Canada. But what we found was that there was really no difference in the transfusion rates.

We have the RBC transfusion rates up there. The black line is tranexamic acid, the white bar is aprotinin, different groupings. No matter how you look at the transfusion outcome, it was more or less the same. There was no significant difference in terms of RBC transfusions, platelet transfusions and FFP transfusions between the two groups.

So, our primary hypotheses we rejected, the aprotinin is not superior to tranexamic acid in this moderate high-risk group in terms of transfusion rates. These are in-hospital transfusion rates.

[Slide.]

What about the other outcomes? We were really interested in massive blood loss, massive blood transfusion. We think that is really where the morbidity and mortality comes into play in cardiac surgery. So, we looked at different

thresholds of transfusion. Again, we didn't find much of a difference.

Then, we looked at outcomes that may be related to transfusion. The reason we included these outcomes is because they are related to transfusion, not because we were trying to find out if aprotinin had a worse renal failure rate or renal dysfunction rate. But we do know that the risk of MI, stroke, renal failure and infection and death are directly related to the amount of blood loss.

So, our hypothesis was, that if aprotinin is better, it should show a reduction in these outcomes. We didn't find any reduction of these adverse events with aprotinin use. We did find a renal dysfunction increase with aprotinin and a significant [?] and a trend toward increased renal failure.

Renal failure was defined as dialysis dependent and we only--almost as Dr. Mangano said, in my opinion, renal dialysis dependent is a pretty good indication of renal failure, although rarely it might be used for other indications.

Renal dysfunction was defined as a 50 percent increase in creatinine within the first week of surgery, so we went and looked at the highest creatinine in that one week and if that was more than 50 percent from the baseline, or the patient

needed new dialysis, that was called renal failure, renal dysfunction.

Based on feedback from FDA, we went back and looked at different definitions including measuring creatinine clearance, looking at 100 percent increase or halving of the creatinine clearance and the pattern is the same. The p value is different but, for the most part, it is all 0.05 or below. Obviously, we are getting into multiple looks but, in terms of hypothesis generating, I think it's valuable.

There were no difference in terms of outcomes, in terms of duration of stay, or in ICU or hospitalization. As you can see, mortality was exactly the same, more or less the same, infection and strokes, they were all the same.

[Slide.]

So, we went back and looked at renal dysfunction in more detail once we picked that up and so we divided patients into those who had pre-existing renal dysfunction based on a lab value of more than 100 or 110 creatinine, or the ones who didn't have, who had normal renal function and it seemed to be, although the pattern was similar in both groups, it seemed to be that the patients with abnormal renal function had more pronounced worsening as opposed to the ones who didn't have it.

Then, the same thing with renal dialysis, again not statistically significant but a trend toward significance. We also excluded patients who had factor VIIa, because more of them had aprotinin relative to the timeline of our study.

We started using factor VII near the latter parts of the study. More patients got aprotinin near the latter parts of the four-year time period. So, once we excluded those, we still found the same results, that there was really no change in the overall analysis.

[Slide.]

This is just to demonstrate that the ones we didn't match were different than the ones we did match. The aprotinin group, the 137 group, were higher risk. These are the really high-risk groups, which we really can't comment on. They have longer pump runs, more severe, more extensive surgery, more anemic, endocarditis, things like that.

[Slide.]

So, our conclusion was pretty simple. Our hypothesis was that aprotinin is superior to tranexamic acid, therefore, it should be associated with reduced transfusions and improved outcomes. We did not find that, so we rejected the hypothesis.

[Slide.]

What about the two major criticisms? The first one is that it is not randomized, therefore, "results are irredeemably biased" because of confounding by indication.

There is no question that aprotinin was higher risk than the tranexamic acid group and the people who argue this point say that no amount of statistical analysis can adjust for that risk difference.

Therefore, aprotinin is actually, if you follow that logic, aprotinin is actually more effective because when we compared it to a lower risk group, our transfusion rates were the same. So, if they are really higher risk, they did better, because they should have had more blood loss and aprotinin was not more harmful but, in fact, was safer because again the complication rates were similar when you are comparing the higher risk group to a lower risk group.

[Slide.]

I just wanted to point out again, this is the same slide you saw, that the patients were pretty well matched in terms of a lot of confounders and also in terms of the three confounders here that we did not initially adjust for, or we did not adjust for, period. But then we went back and got the data.

[Slide.]

Just a little about observational studies and their value in terms of measuring the efficacy and harm. This is from a very good editorial in the Canadian Medical Association Journal in 2006, which comments on this point and specifically, the conclusion is pretty simple.

If are looking at efficacy, there is no question that you need RCTs to look at efficacy except for the caveat being that low quality RCTs may overestimate benefits of therapy. By "low quality," I mean any unblinded study that aprotinin has less than 200, 300 patients.

By that definition, most aprotinin or antifibrinolytic studies are low quality RCTs.

The best evidence of harm, on the other hand, often comes from large, properly analyzed nonrandomized studies, because RCTs aren't ideal for identifying adverse events.

Just look at the antiphylaxis reaction of aprotinin, for example. There is no way an RCT could address that and, basically, renal failure falls in the same category. It is as rare, 1 to 2 percent, and could happen in the longer follow-up periods, and needed large sample sizes, about 3,000 to 4,000 patients to pick up a 40 percent reduction in renal failure.

[Slide.]

Now, observational studies are valid when you look at the harm if the adverse effects are not linked to the treatment indications. We don't give aprotinin because we think someone has got high risk of renal dysfunction or not renal dysfunction.

So, in a way, it is completely not related to the indication of the intervention. On the other hand, though, blood loss is related to renal failure, so it is not completely independent. There is some dependence, therefore, it could introduce some bias.

[Slide.]

In the same--in this study in that journal, they compared observational NRCTs when there were different studies with more than 40,000 patients in these studies and they looked at to see how they fared in terms of the assessment of harm, the observational studies compared to the RCTs.

[Slide.]

It is not important to actually read this table. What is important is they found 15 different interventions that they could assess where there was large observational studies and large RCTs. What they foundwas that, in every single case, the

risk estimate with observational studies was the same or similar, on the same side as the randomized, controlled trials.

In fact, the observational studies were more conservative than the RCTs in terms of picking up the adverse events. There were two exceptions. One was the ICH, here, where there was a big difference but again on the same side.

One was lap chole studies here and the reasons for that, you could explain where the weaknesses of RCTs or the strengths, depending on how you look at it. But, for example, when you look at anti-ICH, for example, in terms of hemorrhage studies, a lot of the studies exclude the sicker patients. But once you get into clinical practice, you might include sicker patients, therefore, observational studies are more likely to find a higher risk.

For lap chole, the RCTs would, for example, include only surgeons who were well trained in lap choles, whereas, in observational studies, they might have surgeons who were not as good, therefore, theirs would be higher. But, in every other case, the risks were pretty consistent.

[Slide.]

So, the authors concluded that it may be unfair to invoke bias and confounding to discredit observational studies

as a source of evidence on harms, the caveats being they have to be large, there has to be appropriate adjustment for baseline differences and they have to be transparent, because the outcome is highly dependent on how you assess the case.

[Slide.]

I have an example here, if I may. This is a study that came out by Dr. Spiess's group in Transfusion in 2004, that was accompanied by an editorial that said, "Be careful reading this study. You are comparing apples to oranges here."

Despite that, it is getting more and more citations. I think since it has been published, it has got about 30 citations all arguing that platelets are harmful.

The way they did the study was they used data from Phase III RCT aprotinin studies. They took patients who had platelets and the patients who didn't have platelets and they tried to look at the outcomes of the ones who had platelets compared to the ones who didn't have platelets.

They used logistic regression and propensity analysis matching and they adjusted for a lot of variables, as you can see here, including RBC transfusions yes/no and a whole bunch of other ones, but a long list of all the major confounders you could think about.

[Slide.]

What they found was that aprotinin was associated with increased risk of stroke--I am sorry, platelets-- increased risk of stroke and increased risk of death, so they concluded that platelets are harmful, platelet transfusion in cardiac surgery are harmful.

Now, this is data from randomized, controlled trials but used in an observational study manner. So, we thought that's pretty interesting, so let's see if we can reproduce the same results.

[Slide.]

So, we looked at our database, the same database I presented for the aprotinin study. In this database, we had 2,174 patients who had platelets and 9,285 patients who didn't have platelets, so a much larger observational study.

We did logistic regression and propensity analysis just like they did and, when we adjusted for the same confounders as they did, we found that platelets were associated with increased low output syndrome risk, renal failure and death.

But then we did something else, we just took three additional important confounders that we thought they should have adjusted for. One was baseline platelet count, because we

know that is related to platelet transfusions and sicker patients have lower platelets preoperatively.

The other one was difficulty weaning from CPB, because we know if you have problems coming off pump, you are probably going to do worse. You wouldn't have had platelets until that point anyway, so it is a good thing to match for and massive blood loss, because we know if you have massive blood loss, you are a lot more likely to die and a lot more likely to receive platelets.

[Slide.]

So, these are important confounders that we adjusted for and, once we did that, we found absolutely no difference. We matched 924 platelets with 924 no platelets and we found absolutely no differences in any of the outcomes we looked at, as you can see by those p values.

So, I think this demonstrates it is important to be transparent and to make sure that important confounders are adjusted for.

[Slide.]

Just a few quick slides in terms of how our study fits in with the--just to answer this criticism. We agree that neither our study or the study by Dr. Mangano again is

conclusive because of the inherent intentions of the original studies and the fact that they haven't really been reproduced yet.

In fact, we were just analyzing a multi-center study on 3,500 patients across 7 sites in Canada and we are finding a large impact on how you assess the site and which sites you put it in, and the matching or not matching, and it seems to make a big difference in terms of the outcomes. That hasn't been finalized yet but I think it is important to accept the role that unmeasured confounders might have.

[Slide.]

What about consistency with what is out there in terms of placebo-controlled RCTs?

[Slide.]

Well, there is no question that compared to placebo, both aprotinin and tranexamic acid reduced blood loss and, as I said, most of the data is in lower risk surgery. But even in lower risk surgery, they reduced blood loss and, through that mechanism, I believe they reduced mortality and other adverse event rate. S,if the question is give an antifibrinolytic or not give an antifibrinolytic, we are in the camp that yes, patients should receive one. If the question is which one they

should receive, I think that is a separate question.

This is a meta-analysis from Dr. Levi, who basically shows that aprotinin compared to placebo reduces transfusion rates by about 30 percent and the lysine analogues reduce transfusion rates by about the same amount, also 30 percent.

So, in fact, the placebo-controlled studies are consistent with our findings that there is no relative difference between the two groups.

[Slide.]

What about adverse events? This is a meta-analysis that was published in the New England Journal of Medicine in the discussion that resulted from Dr. Mangano's paper and here they have the RCT meta-analysis of renal dysfunction. In terms of renal dysfunction, there is a trend towards worsening renal function or increased creatinine levels with aprotinin, while with renal failure, there was no difference.

What is important to know is the number of patients who had dialysis-dependent renal failure was extremely small even when you put all RCTs together, 35 versus 31 dialysis, so there is no way we can make any comments on renal failure based on the RCTs that are out there.

[Slide.]

What about head-to-head RCTs? Well, this is even worse. There is only 2,400 patients that are out there. Most of them are horrible studies. One of them was 1,000 patients unblinded, and that is like basically half the population right there. Almost all of them had lower risk surgery, primary CABG, I guess, because it's the indication, but really not what we are really interested in clinically anymore.

People brought up the difference between 1980s and 2000. I think in 2006, we are seeing the risks of massive blood loss a lot more than we appreciated back then.

[Slide.]

So, with all those caveats, what do they show us? Well, they show us there is a slight improvement in terms of blood loss with aprotinin, 106 cc on average, but that did not translate into transfusion differences between aprotinin and tranexamic acid.

[Slide.]

So, head-to-head RCTs also are in line with our findings.

[Slide.]

What about the other outcomes? We know dysfunction, renal failure, re-exploration, nothing else. You cannot make

any informative comments based on the head-to-head studies that are out there in terms of RCT studies.

[Slide.]

So, we think that our results are consistent with the totality of existing evidence, so we kind of brushed that criticism aside, too.

[Slide.]

So, in conclusion, there is as yet no conclusive evidence that aprotinin is better than tranexamic acid in our opinion. There is as lot of evidence that it is better than placebo and our study was not designed to address that.

In fact, if you look at RCTs, if you look at the meta-analysis, placebo-controlled studies have been done to the point of redundancy. There seems to be no argument in that sense, that it reduces blood loss and through that mechanism, probably reduces mortality.

But there is a glaring lack of high-quality data in high-risk patients that we actually need to decide whether to use aprotinin or tranexamic acid, which is what is actually I think the clinically important decision in Canada anyway.

The BART study, we resolved part of that. The BART study, for those of you who are not aware, it is a randomized,

controlled trial of 3,000 patients, who is randomizing patients to aprotinin, tranexamic acid, or Amicar and no placebo group, because when the study was being designed by Dr. Hebert, and all the advice he had, placebo use was considered unethical in cardiac surgery at this point based on the avenues that are out there.

So, there is no placebo arm in this study. There are going to be three arms, as I said, each one about 1,000 patients and it will be able to judge, once and for all, I think, whether or not aprotinin is more efficacious than tranexamic acid or their alternatives in the moderately high risk group. These are not the very high risk group, these are the groups that we probably match for.

It will also probably address the renal dysfunction, maybe the renal failure issue, because I think in their interim analysis, they found something like a 20 percent incidence of a composite or renal dysfunction, so I think it will be powered to address that issue, too.

So, I think it will be useful to study and it is not going to answer every question. But I think it will answer some of our questions.

That's all I have to say. Thank you very much

DR. HIATT: Thank you. If you will just stay at the podium for a minute, so we can take some questions. I appreciate the comments about randomized trials, which inevitably, when you are looking at blood loss as an endpoint, you are underpowered to look at safety events and it's accumulation of events that matters.

Questions? Please.

**Questions from the Committee**

DR. LINCOFF: Just a relatively minor point. You had compared your study to Dr. Bruce Spiess's on the use of platelets as an example of randomized versus nonrandomized?

DR. KARKOUTI: No, as observational versus observational.

DR. LINCOFF: Okay, because even though it was a randomized trial, it wasn't randomized to the use of platelet transfusion.

DR. KARKOUTI: No. I just wanted to add, I think, pertinence of confounder adjustment in observational study.

DR. LINCOFF: I agree. That speaks for the quality of the analysis being very important with what you do with a nonrandomized study.

DR. TEERLINK: Actually, I think you are to be

congratulated on doing these kind of rigorous analyses. One of the things that was actually concerning to me about your platelet analysis is that, in fact, it proves our underlying concern, that is, that if you miss a couple confounders, you can change a study from being positive to negative.

So, if anything, I interpret this study, which is very interesting, is actually proving or at least suggesting that we really are on unchartered territory here with these observational studies, because if you just happen to miss one or two important ones that you didn't think of, you can take a study from being harmful to having no effect.

So, where would you go with that?

DR. KARKOUTI: I absolutely agree, but the same can apply, the same criticism applies to a lot of the RCTs that are out there. You can just make subtle changes in small RCTs. I am not talking about 3- or 4,000 definitive RCTs that are out there, but 100 patients, 200 patients, 50 patients, they are probably not as good as RCT, not as good as a large, properly analyzed observational study.

Let me tell you how we put all the data together and what conclusions we have come up with at Toronto General Hospital, is that we haven't changed our practice one bit. We

are still using tranexamic acid for the 90 percent of our patients who are not the really high risk and we are still using aprotinin for the 10 percent who are really high risk based on two things.

One is the clinical impression is still strongly there that aprotinin for the high-risk patients is better. It hasn't been proven, but we don't think there is enough evidence for us to say, to expose those patients to increased risk of bleeding by saying no, the efficacy stuff isn't there, so therefore, you should use tranexamic acid for every patient.

We think if aprotinin is more effective in the really high-risk group, and the renal dysfunction issue is real, the benefit of avoiding massive blood loss outweighs that increased creatinine risk.

So, I think, I mean you are right, every study has limitations. You have to put everything together and it is important not to reach too far based on the available evidence.

DR. HARRINGTON: I, too, want to congratulate you on the care with which you went through all of this. I have a couple of questions, first, around the quality of the data. You said that the nurses are collecting this and that is their full-time job.

So, how complete is the data particularly with looking at variables like renal function, like CK-MB elevation, because you did use enzymatic criteria to define myocardial infarction and then how were these events finally defined? Were there a group of clinicians who looked at the data and said yeah, that's myocardial infarction, was there a separate panel that did this? Help me understand that.

DR. KARKOUTI: No. The solid data, for example, renal function is on everybody. Everybody has creatinine while they are in hospital and nobody goes home before six, seven days and whatever was missing, it's a computerized system at our hospital, so it was very easy to complete the lab data, so I am pretty confident about that. So, renal dysfunction as an outcome I am happy with.

MI, not so much, because we don't have, it's not an RCT, so the nurse goes and looks at the clinical notes, looks at the lab results and says this patient had an infarct. It shouldn't impose a bias in the study because it's done for both groups and there was no idea that this study would be analyzed for this.

DR. HARRINGTON: But it's the nurses looking at the data, following the definition.

DR. KARKOUTI: Exactly, but they are full time, they are nurses whose full-time job is to complete this data.

DR. HARRINGTON: One other question. In the paper, you bring up the possible confounding of a differential use of recombinant factor VII. Can you just explain that to me again?

DR. KARKOUTI: Sure. Actually, there is two confounders, three confounders we try to explain that were not in the model. One was the surgeon. There is no question that surgeons have different bleeding and complication rates, so we wanted to make sure--I mean you couldn't put that in the model, because matching for the surgeon would have reduced our matched group a lot.

So, the way we looked to see if that is a confounder, we looked at which surgeon, the percentage of surgeons, for each surgeon, how much of them got aprotinin and tranexamic acid in the matched group and whether or not that correlated with the transfusion and complication rates, and there was none that we could find.

The second issue was timing. Aprotinin was instituted in 1999 at our hospital and since then, the use has gone up mainly because we are doing more and more high-risk cases, or that fit the criteria.

So, in 1999, hardly any patients got aprotinin, whereas, in 2004, the study period, I don't remember how many, but a lot more had aprotinin. So, when you look at the year of the matching, of the matched groups, more of them had surgery in the latter parts of the year who had aprotinin and more of the tranexamic acid group had surgery in the earlier parts of the study.

We didn't match for the year, because when you do that, again, our numbers would have found a lot. Whether or not that introduces a bias, hard to tell.

You could argue that the patients are getting more and more sicker, therefore, they are getting more and more aprotinin and, therefore, they are more and more high risk, but if you argue that, then, it's a moot point since you are basically saying we didn't match for risk factors. If you accept the fact that we probably did a good job matching for risk factors, that shouldn't be a bias.

Second, the factor VII issue, starting in 2002, we started using factor VII for refractory bleeding in cardiac surgery. So, if they had antifibrinolytics, aprotinin, or tranexamic acid and have received massive blood transfusions, and have ongoing blood loss and have gone back to surgery and

there is no surgical source, then, they get factor VIIa.

That happened to increase over the years, too. Now, we are using about 50 or 60 doses of factor VIIa per year, so again we wanted to make sure that wasn't a bias and that is why we did that.

DR. ELLIS: Just coming back to the issue of surgeon. With all due respect, we know that different surgeons have different blood loss and it looked like one surgeon did about 30 percent of the cases and tended to have less bleeding than the other surgeons.

You said you couldn't put that, it would reduce your ability to match patients. Is there any post hoc way to look at those surgeon-specific factors in terms of affecting outcome?

DR. KARKOUTI: I mean we could. The study would be severely underpowered to make any conclusions, but if you look at that surgeon, for example, that surgeon had an equal number of matched aprotinin and tranexamic acid patients, but that surgeon also has the best outcomes.

So if, for example, a lot of that surgeon's matched patients had tranexamic acid and few had aprotinin, you could argue that now you are no longer doing an unbiased match. But

again whether or not we have proven that we have excluded the surgeon effect, probably not, but it probably like plays a smaller role.

All of these are more relevant to the renal dysfunction issue. In terms of the efficacy issue, I am confident that in the group that we matched, there was no difference, the caveat again being that--somebody mentioned earlier that you choose aprotinin I think based on your gut feeling of whether the patient is high risk or not high risk and you can adjust for gut feeling.

If you believe that--if you gave aprotinin to somebody and that patient in your mind now is high risk, because of giving aprotinin to, of high risk of massive bleeding, you are more likely to give blood products when you come off pump.

So, there is a potential that the ones who received aprotinin, receive more blood products unnecessarily in terms of FFP and platelets. RBC, we could check pretty well, because we had the lowest hematocrit, we have discharge hemoglobin, we have post-pump hemoglobin and there was no difference. But, for platelets and plasma, there could be a bias against aprotinin in the study.

DR. ELLIS: What was your criteria for--it seemed like

your use of platelets and fresh frozen was pretty high relative to your packed red cell transfusion, although, you know, again your red cell transfusion rates seemed to be a little bit high, too--what were your criteria for transfusing each one of those?

DR. KARKOUTI: In the paper, don't forget this is not a high-risk group, so when you look at our overall transfusion rates, they are going to be much different than this matched group.

But the criteria were, for example, we did allow for prophylactic or for a platelet use, for example, if it was a three-hour pump run, a lot of clinicians would come off pump and give the protamine and give platelets, for example.

So, for platelet dysfunction, there are guidelines suggested that you could use platelets without having the platelet counts, but our counts and triggers were pretty much standard.

Hematocrit on pump was about 20 percent transfusion was our trigger, platelets was 80 to 100 post-pump, or high risk of platelet dysfunction, INR 1.5 for FFP, so usual stuff, but we are high blood product users compared to some other sites, I agree with that.

DR. HIATT: Maybe we could go down this way.

DR. PAGANINI: Can I actually make one little quick statement? Clinical use and relating that to whether or not studies are relevant. I will point you to the use of dopamine and protection for acute renal failure, multiple times shown not to be effective, yet is still rampant in most postoperative care. So, I probably wouldn't go down that route.

The road that I would like to ask about in the renal area is creatinine. I would like to remind the committee that creatinine is a physiological marker, not a biomarker and, therefore, very variable.

In the application of the MDRD, which was generated in a chronic renal failure population to acute renal failure prediction or to analyze or try to equalize the effects by way of body surface area, whatever, has been fraught with a lot of discussion and concern, because it is really using a method or a marker in an aberrant way, not from where it was generated, which is chronic renal failure population. So, I would be careful about going down that route.

Finally, the third thing directed, in your propensity score, in the listing of all the things that were there in the propensity, I didn't see renal function in that list at all, preoperative renal function. I didn't see it. Was it on there,

did I miss that somewhere? I didn't see it. Can you point it out for me?

DR. CHEUNG: Under endocarditis, right there.

DR. PAGANINI: Okay, it's just my eyesight, thank you.

DR. KARKOUTI: We did put all the risk factors that we know for renal dysfunction in the model including diabetes, peripheral vascular disease, pre-existing renal dysfunction, lowest hematocrit on pump, which is directly related. We have shown that the more anemic you get, the higher the risk of renal dysfunction post-pump, so all of those reports.

DR. PAGANINI: The issue is with renal dysfunction following open heart surgery, there are three areas. There is the area that the patient brings to the table, which is stuff that we have been looking at.

There is the area that the surgeon brings to the table, which is intraoperatively, and then there is the area post-table, which happens in the ICU for a whole bunch of different things.

There are so many variables that acute renal failure following open heart surgery is very muddy and, as you yourself have shown, if you miss one or two variables, it could really muddy up the water, to show things to be much more effective,

much less effective, or no effect at all.

DR. KARKOUTI: Absolutely, but on the other hand, we know pretty--like all the studies that have looked at predictors of renal failure after cardiac surgery, have all come up with the same predictors over and over again and they explain a lot of the variability.

The same goes for mortality in cardiac surgery. The possibility of all of the studies over the years missing an important confounder is small in terms of renal failure or transfusion, for that matter.

DR. PAGANINI: Understand, but we must also be cognizant of the fact that there is a changing population that is going under the knife and that 20 years ago was a totally different population than we are seeing today having open heart surgery.

Many of the people today who are undergoing surgery would not have ended up on the table at all.

DR. KARKOUTI: Yet the risk factors remain the same more or less, which again goes to the strength of the risk factors.

The question here is you have discovered a new risk--I mean you could look at it and say we have discovered a new risk

factor for renal dysfunction, does it deserve to be investigated or not? The answer is obviously yes and that is what basically we concluded.

We are not saying aprotinin causes renal failure. We are saying aprotinin may cause renal failure and it should be looked at.

DR. PAGANINI: Again, this type of data can't-- cause and effect, it can only see association, so what you are saying is there is an association and perhaps there is a cause and effect.

DR. KARKOUTI: Exactly, the same way we are looking at lowers hematocrit on pump. There is a lot of studies now that say if your hematocrit drops below 20 percent on pump, you are at higher risk.

There is no proof, but based on that alone, a lot of people are maintaining higher hematocrits, for good or bad I can't tell you, but we are doing studies to address the question.

DR. WARNER-STEVENSON: I would like to commend you again for a very thoughtful, hopeful, overall program of research, because we must challenge our current practice particularly have to challenge marketed therapy.

I do want to get back to this issue of the year of surgery, because I am very struck by that. At least from your Figure 1, over half the patients with aprotinin were done in the last two years of your study, whereas, only a quarter of the patients with the other agent.

I think we are all struck, as you said, by the dramatically different patients going to surgery, partly because the easy ones are now going to the cath lab.

Is it possible to take your propensity-matched results and adjust post hoc just for the important variables that came up that you wouldn't match for, like year, for instance, can you just adjust for year and see what happens?

DR. KARKOUTI: We could have matched for year early on, but again you are not--

DR. WARNER-STEVENSON: Not matching, no. I am saying after you have matched--

DR. KARKOUTI: Right, oh, to adjust for the year of surgery.

DR. WARNER-STEVENSON: --then, just to adjust for the year, because that is one variable that really stands out.

DR. KARKOUTI: We looked at that differently. We looked, said okay, if, for example, renal dysfunction rate went

up from year to year, then, that would be an important bias, or other adverse events, or transfusion. In fact, there was no difference in terms of our outcomes from one year to the year.

It was just looking at the annual complication rate and our complication rates from 1999 to 2004 haven't changed. So it is unlikely that that would be, in that sense, we tried to rule out in that sense.

In terms of putting the year in the model and see if it becomes a predictor, that's a good idea. I don't think we did that. You mean do a logistic regression now with the matched, within the matched group, and put the year in it.

DR. WARNER-STEVENSON: Right.

DR. KARKOUTI: Did you guys do that with the data? I don't think we did that, no.

DR. HECKBERT: I wanted to congratulate you on a very clear description of the methods and for addressing an important question. I had a couple of additional clarifications that maybe if they were in there, I missed them.

Do you have information on how long the renal dysfunction lasted in all patients or in one group or the other?

DR. KARKOUTI: No, we only looked at the first week

post-op and took the highest creatinine level.

DR. HECKBERT: Then, was there information on what proportion of the patients had their agent started during surgery because things were not going well versus it was planned as part of the--

DR. KARKOUTI: No, every patient gets antifibrinolytics. Tranexamic acid, they get 50 to 100 milligrams per kilogram right after induction of anesthesia and aprotinin, we use the high dose, so test dose 2 million before the pump run, 2 million in pump and 50,000--

DR. HECKBERT: Thank you.

DR. HIATT: Maybe to wrap up, one point of clarification. I will ask this question and then go to David. Did you give your data to the FDA for independent review?

DR. KARKOUTI: They only asked for the matched group and they have the matched data. They don't have the 10,000 patient database, but they do have the 1,000 patient matched.

DR. HIATT: So, you gave them what they asked for?

DR. KARKOUTI: Yes.

DR. HIATT: Have you all verified these analyses?

DR. RIEVES: We have vetted it within our OSE group and they are comfortable with it. They have no additional

questions to Dr. Karkouti.

DR. HIATT: David, and then I will have one other question.

DR. DeMETS: Thanks for a nice presentation. I had a couple of questions of the things you said.

One is as you were describing the comparisons of logistic regression, propensity scores, you sort of implied that propensity scores have no restrictions, no assumptions. I question that, because, in fact, at least in my understanding and experience, you often use logistic regression to create propensity scores. So, somewhere I mean there are assumptions. It is not a free lunch and some of those assumptions can be quite important.

I just want to either clarify or challenge you on that.

DR. KARKOUTI: I think there are experts that are much more knowledgeable in propensity analysis than me, so I am going to leave that question. The specific points I raised, they don't have this linearity assumption, for example, that you do in terms of with the outcome. They don't have to be linear and the number restrictions, you don't have anymore, you can put as many as you want.

More complex and detailed than that, no, I would rather

not comment.

DR. DeMETS: The second assertion you made is that if you balance on measured covariates, you could probably assume that the unmeasured covariates are balanced. I would challenge you on that, because there is a number of examples, which my colleagues around the table could add to, where we have balance in all the measured covariates and yet we have differences we cannot explain in things like survival and morbidity. So, I don't think it is an assumption that at least I am willing to buy.

DR. KARKOUTI: No. As I said, it hasn't been proven and, again, it depends on how good your underlying propensity analysis is and how much of the variability you are able to accept things, you cannot predict too well.

Whereas, in cardiac surgery, our prediction rules are extremely--like our ability to predict the likelihood of getting aprotinin, the C-index of that model was 0.94, I believe, so we could predict with 94 percent accuracy who would get aprotinin and who would get tranexamic acid.

The same goes for massive blood loss, we can predict with 90 percent accuracy who is going to have massive blood loss based on the peri-op variables. I would say that in some

cases, you are probably right. As I said, it is an assumption that you are matching unmeasured confounders. I wouldn't hang my hat on that, but it's an assumption.

DR. HIATT: One final question.

DR. CHEUNG: I really want to emphasize the point, what variable to put in. It is underlying the importance of the clinician working with biostatisticians.

I mean I also cannot imagine, it is great that you put in platelet count in your variable, I mean that is why it is so important to target what outcome that you are really interested in. Somebody starting with a low platelet count most likely would, are more likely to require the transfusion.

What I want to ask you to comment upon, you made some quick comments about you think that the low bleeders also have high mortality and I think Dr. Mangano showed one slide that sort of contradicts that.

Also, is it your overall take, at least your overall opinion that you are not so much debating on certain population whether it justifies the use of antifibrinolytic, but which one to use? Can you just clarify that a little bit?

DR. KARKOUTI: The first comment in terms of bleeding and adverse event rates, we know that if you don't get any

blood transfusions during cardiac surgery, you are not going to die. The mortality rate of patients who don't get any blood transfusions is zero, they don't die.

As soon as you get one unit of blood transfusion, so you have lost enough blood to require one unit of blood, now, whether it is the blood or the blood loss, I don't know. In my mind, it is irrelevant, you lose blood, you need blood. Your mortality goes up to 2 to 3 percent.

By the time you get to five units transfusion, your mortality now is about 10 to 15 percent, which is probably as much or more than stroke. Actually, it is a little less than stroke and renal failure.

So, we have published that data in Transfusion, I think in 2004. But I think blood loss is an important outcome that we have ignored more or less a lot. I mean if you look at the number of papers that are out there on massive transfusion, there are very few as opposed to renal failure, for example.

So, I think the bigger issue is transfusion and blood loss here and I think you can't argue with those placebo-controlled studies that show a reduction in transfusion and a reduction in mortality. That is quite significant.

We are not so good at predicting who is going to want

to be at 300, who is going to be the liter and a half, so until we can do that 100 percent, I mean the choice is not whether or not, the choice is which one in terms of antifibrinolytics.

The second part of the question was? Sorry.

DR. CHEUNG: You are not arguing about you would use it, not use it in the population, it is just which one?

DR. KARKOUTI: There is recent, new arguments with thromboelastography, for example, the maker of thromboelastogram, which is basically a new way of looking at the clot formation and clot dissociation, says that a lot of patients having heart surgery don't get hyperfibrinolysis, which is our underlying assumption, that if you are having heart surgery, part of your blood loss is because of hyperfibrinolysis.

Now, we may be able to, for the first time, it hasn't been validated, it hasn't been tested that extensively at all, to begin with, but you may be able to tell who is getting fibrinolysis and then treat them.

So, that is down the road. In the future, we may be in a position to say okay, we know exactly, we have a point of care test that tells me who needs antifibrinolytics, but we are not at that point yet.

DR. HIATT: Thank you very much.

We are getting close to noon, but I think the plan will be to begin with the Bayer presentations. We can push the open public hearing back a little bit. There are three speakers slated for that, which begins at 1 o'clock.

So, perhaps if the Bayer speakers don't mind coming to the podium, we can begin and try to get ourselves up to around the noon hour and then sort of resume and complete your presentations after lunch. Would that be okay? Okay.

DR. ROZYCKI: The expectation is we will go through our main presentation and then we would defer the questions until the end of all the subsections?

DR. HIATT: How long are your formal presentations?

DR. ROZYCKI: Sixty minutes.

DR. HIATT: That would put us up close to 1:00. Would it be all right to maybe split it?

DR. ROZYCKI: We have the first part of the presentation is about 10 to 15 minutes and then we have a section that is about 35 minutes and then we have a section that is about another 10 to 15 minutes.

We could do the first part. It would probably take us to about noon.

DR. HIATT: Do you want to do that and then it would take us to about noon and then we will take a break?

DR. ROZYCKI: Yes.

DR. HIATT: Okay.

**Bayer Pharmaceutical Presentation**

**Introduction and Overview**

DR. ROZYCKI: Good morning, Dr. Hiatt, and members of the committee, guests of the committee.

My name is Mike Rozycki. I am Director of U.S. Regulatory Affairs at Bayer. I want to take a few minutes just now to provide an overview of what we are going to be presenting today.

[Slide.]

I would like to start out by saying, first, that Bayer believes firmly in the importance of the clinical benefits associated with aprotinin. We are very happy to be given the opportunity to be here to discuss aprotinin in an open scientific setting.

What we would like to do today is, first, discuss methodological considerations of the two recently published observational studies that we have just heard descriptions of.

Then, we would like to discuss the clinical data that

we have, as well as that's available in the literature, as well as the risk-benefit of aprotinin in coronary artery bypass graft surgery, or CABG, and Bayer's conclusion is that the clinical data and the post-marketing experience support a favorable risk-benefit profile of aprotinin when used according to the label.

[Slide.]

We have already heard a very complete regulatory history of the approval of Trasylol earlier this morning, so I won't repeat that. I did want to just remind the committee of a couple of dates. The initial approval of the NDA for Trasylol was in 1993. That was for repeat CABG, as well as certain patients undergoing primary CABG who are at risk for a high degree of blood loss.

Then, as was discussed earlier this morning, NDA Supplement 004, in 1998, expanded the indication to primary and repeat CABG and also added the boxed warning for hypersensitivity.

It is also worthy to note that both the initial NDA and Supplement 4 were approved along with post-marketing commitments, all of which have been fulfilled.

[Slide.]

I also wanted to take note of the fact that the clinical trial efficacy and safety data that we will be discussing this morning are derived from 45 global Bayer randomized, controlled CABG trials that were conducted in 4,413 patients receiving either full dose aprotinin or placebo.

I also wanted to take note of some of the actions of Bayer took place in response to the publication of articles on the observational studies that appeared earlier in 2006. We immediately, when we found out about the articles, we immediately communicated those articles to the FDA, as well as global regulatory authorities.

We also worked with the FDA and global regulatory authorities to notify health care providers by means of Dear Health Care Provider letter and information on our web site.

We immediately began a comprehensive review of all the data that we had in CABG surgery for aprotinin. This was conducted in very close association and under the guidance of the FDA. All that information has been submitted and is under review by the FDA.

At the same time, we revised our investigative brochure and informed consent materials for our ongoing clinical trials and, finally, we undertook and provided to regulatory agencies

evaluations of the publication methodologies for the observational studies.

[Slide.]

Our presentation this morning will consist of, first, a discussion by Dr. Robert Makuch of Yale School of Public Health. He will discuss the methodological considerations of randomized, controlled trials and two recent observational studies of aprotinin.

Then, Dr. Pamela Cyrus, of Bayer's U.S. Medical Affairs organization, will review the clinical data that Bayer has and that is in the literature for aprotinin.

Finally, Dr. Jerry Levy, of Emory University Hospital, will provide a risk-benefit summary for aprotinin.

[Slide.]

In addition to these presenters, Bayer has brought a number of additional expert consultants who are available with us in the audience today. I won't read through every name on the list now in the interests of time. We did bring a number of handouts that are available at the front desk, that provide the detailed affiliation information for all of these consultants.

[Slide.]

I will move to the next slide that contains more names of consultants.

[Slide.]

Now, at this point, I think I would like to introduce Dr. Makuch. Dr. Makuch is a Professor of Biostatistics at the Yale School of Public Health. He will discuss methodological considerations of randomized, controlled clinical trials and the two recent observational studies of aprotinin.

Dr. Makuch.

**Methodological Considerations on the Two Recent Observational Studies of Aprotinin**

[Slide.]

DR. MAKUCH: I will plan to do this in 12 minutes.

Good morning and thanks for giving me the opportunity to share some thoughts with you this morning.

[Slide.]

First, I will just give you some general thoughts and considerations in evaluating clinical data. In general, there is a hierarchy of evidence. We do have randomized, clinical trials in which the randomization does provide balance, not only with respect to known, but also unknown confounders.

Then, we have the class of nonrandomized clinical

studies that include cohort, case control, observational and case series. The second list of studies does require generally more complex statistical methods to overcome difficulties associated with these designs, such as selection bias, channeling bias and confounding. Nevertheless, I certainly do not wish to in any way imply that there is a dichotomy between these types of studies and that either one or the other really is strongly preferred.

I think that there is really instead just a relative strength of evidence and both these kinds of general study types provide very valuable information and insights.

With respect to some criteria that I have for looking at and evaluating data, they do include baseline comparability. Of course, we want the comparability to assure any treatment group differences are likely due to treatment as opposed to other predictive factors independent of treatment.

With respect to patient population, we generally like to look at the full study population and not selected subgroups to address primary hypotheses.

With respect to outcome definitions, of course, we want them to be consistent across studies and valid. Analytic methods and interpretation, we wish to be properly applied and,

then, for these proper applications of these analyses, to be interpreted appropriately.

We do have also consistency of reports that sometimes we can look at based on the same data in repeated publications. Also, replication of findings using different data.

For an RCT, problems with one or more of these issues reduces its validity. For example, with significant and numerous imbalances between treatments in predictive baseline factors, subsequent reliance then on complex statistical modeling to adjust for these imbalances and subgroup analyses, it has been my experience that the RCT then would be viewed as having little, if any, utility.

Of course, with these same problems, but within the context of a nonrandomized study, this would reduce even further the study's validity.

[Slide.]

With those general criteria in mind, I would like to then just proceed and walk through a brief review of the randomized clinical trials which you will be hearing about from Dr. Cyrus later this afternoon, as well as the two studies that we have heard from the authors this morning.

First of all, the randomized, clinical trials are

randomized. Both the Karkouti study and the Mangano study are nonrandomized studies. One of them is matched, the Karkouti study. The other is not matched. For Dr. Mangano, this study was used, a systematic sampling scheme and nonrandomized treatment assignment.

Regarding baseline comparability in the RCTs, it is assured through the process of randomization. In the Karkouti study, there was baseline comparability, but achieved on observed covariates through the process of matching that you have already heard.

In the Mangano study, there are major imbalances, so baseline comparability was not performed at that time. This is an important distinction between these two observational studies when looking and judging, then, the results later on. Patients excluded, there were not patients excluded in the reports of the RCTs to be provided.

In the Karkouti study, yes, patients were excluded, but through the process of matching. In the Mangano study, also, patients were excluded. We have already heard referred to earlier this morning the 691 patients who were excluded with possibly a different prognosis. Importantly, no data were provided on baseline characteristics or outcomes of these

excluded subjects.

Regarding sample size, this is a somewhat unique example where unlike the standard case of looking at adverse event data, we must heavily rely on observational data, because the numbers of patients are so many orders of magnitude larger than in the RCT database.

Here, that isn't the case. As you can see from the sample size, there is roughly 4,000 subjects in the multiple RCTs, roughly 4,000 in the Mangano study and roughly 900 in the Karkouti study.

And the aprotinin-exposed subjects, there were in excess of 2,200 in the RCT data versus 1,295 in the Mangano study and roughly 450 in the Karkouti study.

[Slide.]

Also, for the outcome definitions, they were prespecified in the RCT data, prespecified as best as I could tell in the Karkouti study and also prespecified as best I could tell in the Mangano study, even though they do differ from previous studies of the same database.

Regarding the analysis, one of the advantages of RCTs is that the analysis can be relatively straightforward. The Karkouti study used propensity matching and the Mangano study

used propensity-adjusted multivariable logistic regression, a requirement really because of the major imbalances at baseline.

[Slide.]

Briefly, the Karkouti study was a single-center, observational comparison of aprotinin and tranexamic acid in high transfusion risk cardiac surgery. Aprotinin was given only to high transfusion risk patients.

There were profound imbalances in pre-existing risk factors, which were properly addressed by propensity score matching, resulting in 449 in each of the treatment groups. Creatinine clearance elevations or creatinine elevations due to aprotinin were not inconsistent with results of RCTs.

I think an important point to make with respect to the Karkouti study is that the issue of major imbalances at baseline was addressed at the design stage through propensity score matching, which then, as you have seen, led to comparable groups at baseline, which then allowed more straightforward analysis.

[Slide.]

But also, as you saw this morning, in the Mangano study, there were a number of significant imbalances in baseline characteristics. The first impression provided by the

slide is simply the large number of highly statistically significant imbalances between the no-treatment cohort and the aprotinin cohort. Perhaps aspirin and age would and could, and perhaps should, have been here, as well, but they did not appear in the publication.

There are 20 factors in this table and the overwhelming majority place the no-treatment cohort in the more favorable prognostic category. For example, 60 percent of the control subjects have hypertension at baseline versus 70 percent for the aprotinin cohort.

For renal disease, the values are 13 percent for the control versus 19 percent for the aprotinin group. Dr. Mangano said he was not concerned by these imbalances, but I respectfully disagree.

Unlike the Karkouti study, in which matching occurred at the design stage to achieve baseline balance, the Mangano study required complete reliance on statistical modeling. Thus, a careful review of the statistical analysis is mandatory.

[Slide.]

First, the estimated propensity score was used as a variable in covariate adjustment, as you have heard this

morning, rather than the correct use to create matches or subclass bins, also, that you have seen this morning.

Secondly, no diagnostic displays or analyses were present to support claim balance of covariates achieved by the use of propensity scores.

Thirdly, no diagnostic displays or analyses to support claim balance of covariates achieved by propensity scores for each pair of treatment groups was compared.

Fourth, despite the massive effort that Dr. Mangano emphasized this morning about data cleanup over a multi-year period, nevertheless, in the Mangano study, there were 410 subjects, again pointed out earlier, that had missing covariate or propensity scores for renal outcome analysis, which is roughly 9 percent of the patient population analyzed. Also, 407 subjects had missing propensity scores for the ischemic outcome analysis, as seen in Table 3.

I think these exclusions become especially important because when dealing with rare event outcomes, the exclusion of even a few relatively high-risk subjects, then, they significantly alter the results that were, in fact, reported. So, 9 percent actually is a very big number for exclusion especially when looking at rare events.

[Slide.]

Also, the outcome variables were used to decide which covariates to include in the regression model. This introduces bias at least in the significance levels. Also, it was significant between treatment imbalances in numerous baseline factors, regression modeling alone is known to be unreliable.

Finally, crude data were sometimes used in the report where adjusted data should have been used. For example, the dose-response assessment of aprotinin was based on crude data that, in fact, excluded 54 percent of the aprotinin subjects.

Again, this perhaps goes to at least a question I have regarding the quality assurance techniques for the data, because it seems to me difficult to appreciate how 54 percent of the doses could have been for some reason missing.

[Slide.]

Another one of the criteria that I mentioned at the beginning of the talk was with respect to outcome definitions and we have the luxury with this particular database that has been locked in 2001 to look at subsequent publications over a period of time.

So, one example is the inconsistent outcome definitions, for example, for heart failure. As you can see

here, in the 2002, 2004 and 2005 papers using the same locked database, the same definition was used, but in the 2006 current paper, the definition used for heart failure is substantially different.

[Slide.]

If we look at the rates of MI in the same locked database for the same publications, we see a two- to four-fold increase in the reported rates for the most recent Mangano study. Whether this is due to different definitions for MI in these four publications or other factors is unclear. What is clear, though is that the earlier publications did include enzyme levels in part of defining an MI.

[Slide.]

Also, another criterion was to look at the consistency of the reported results within a given publication. Again, I think this was perhaps mentioned earlier this morning, but for clarity, in the Mangano study, in the abstract on page 353, it was reported that the use of aprotinin was associated with a doubling in the risk of renal failure, requiring dialysis among patients undergoing complex coronary artery surgery or primary surgery and the odds ratios and confidence intervals are reported.

When one looks at the same paper on Table 3 on page 360, we do see the same odds ratios and confidence intervals and, with the outcome event there being defined as a renal event--and there, a renal event was defined as either renal dysfunction or renal failure requiring dialysis. So, unless there were no subjects who had renal dysfunction, the two definitions and the implications of these analyses clearly differ.

[Slide.]

So, these two publications that you have seen presented this morning, and the RCT data yet to be presented, are important efforts that deserve careful scrutiny. The totality of evidence derived from RCT and observational studies must be assessed, but keeping in mind, though, the relative strength of evidence associated with each kind of study.

Here, the total sample size from RCTs was larger than that from observational studies. Randomized, well-controlled trials are the gold standard for assessing true treatment effects.

Second, analytic methods to correct for baseline imbalances in the Karkouti study were generally appropriately applied.

Third, analytic methods to correct for numerous and highly significant baseline imbalances in the Mangano study were incorrectly applied. Additional issues also were raised, such as subgroup analyses, leading to questionable validity of the findings.

In summary, the Mangano study results should not be considered reliable at this time. Wnd we have heard some discussions about further analysis and access independently to look at that and I certainly would endorse that recommendation, as well.

Thank you.

DR. HIATT: Thank you very much.

This is a question I actually had earlier and didn't ask, but I think it is obvious now, but the Karkouti study actually used propensity scores to match patients and the baseline characteristics became equal. Mangano did not and so that we don't see a matched score. You used the propensity in that study to do adjustment and not for direct matching, is that your interpretation?

DR. MAKUCH: That is my interpretation. It really is an important distinction. After the matching is done using propensity scores, Dr. Karkouti then demonstrates in one of the

tables--I think it was Table 2--that indeed then there is comparability with respect to the groups in terms of these important factors.

So, at the design stage, I think steps were taken to ensure balance at baseline. On the other hand, the other observational study, the Mangano study, there, it was not done, philosophically, very different and so the significant baseline imbalances remained.

Therefore, he placed a reliance on then statistical modeling and also then looking at logistic regression models with or without the propensity scores as an adjustment factor embedded within the logistic regression, so the question then becomes in one's mind can modeling with or without propensity scores somehow arrange to take away those 20 factors that were statistically significantly imbalanced, most of them at less than .0001 between the treatment groups in the Mangano study.

I think every one can draw their own conclusion whether or not that is the case. I conclude, though, that it was not an appropriate use of the propensity score to include it as a covariate as opposed to using it as a matching to look at the bins and to, then. get baseline comparability and, then, to proceed in a more straightforward way with the analysis.

So, I don't have a high degree of confidence and I think we have heard some comments why statistical modeling alone could somehow eliminate all those imbalances.

DR. HIATT: Before you step down and before we take a lunch break, are there any other questions to clarify that you would like to make at this time?

[No response.]

DR. HIATT: Actually, this is a nice transition time. Thank you very much.

We will resume at 1 o'clock. We will continue on with your presentations and then we will go to the open public hearing.

[Luncheon recess taken at 12:00 p.m.]

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

1:00 p.m.

DR. ROZYCKI: Before lunch, we heard from Dr. Makuch on the statistical considerations of the two observation studies. Now I would like to introduce Dr. Pamela Cyrus of Bayer's U.S. Medical organization, who will review the clinical data for aprotinin.

Dr. Cyrus.

**Review of Clinical Data**

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 have also conducted a very thorough analysis of our global CABG data base. We have submitted that analysis, as well as our data sets, to the FDA for their review. That will be the basis of what I am reviewing for you here today.

[Slide.]

I would like to start with saying I am going to show you the six U.S. CABG trials that were also referred to earlier

this morning. Four of those trials included primary CABG patients and four included repeated 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. Then, I will review safety in CABG. When reviewing safety, I am going to review the 45 clinical trials that were conducted globally using the full dose of aprotinin versus placebo.

I will be focusing on the 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.

[Slide.]

To start, there were six U.S. CABG trials that have been conducted with Trasylol. The first two studies, the 89-004 and D89-006 served as the basis for the initial approval in repeat CABG in 1993. I should note that these two studies were supplemented with a cardiac valve study, as well as supportive data from non-U.S. data sources.

The third study on the list is D92-008. This study

served as the basis for the approval of the half-dose of aprotinin in 1994 and, finally, the last three studies, D91-007, D92-016 and D92-048 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 2 million kallikrein inhibiting units loading dose, as well as 2 million KIU in the pump-prime regimen, and 500,000 KIU per hour as an infusion and the half-dose is exactly half that with the exception of the test dose.

[Slide.]

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.

[Slide.]

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 heard Dr. Karkouti mention this in his

presentation--is the risk of bleeding and the need for a subsequent blood transfusion.

There is also risk of infection, stroke, renal failure and re-operation, or takebacks 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 2 to 6 units of packed red blood cells, 1 to 10 units of platelets and 1 to 10 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 has been very aggressive measures taken on by both the STS and the FCA for blood management programs during cardiac surgery.

[Slide.]

Bayer convened a consensus panel of independent consultants. This was led by Dr. Goodnough. You can see the list of members at the bottom of this slide. We asked them the question, "In your opinion, what is the mortality associated with transfusion today for red blood cells and for platelets," and 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 10 to 20 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 5 deaths per million units of red blood cells and platelets transfused, bringing the overall mortality per million components of 16 to 27 units for red blood cells 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.

[Slide.]

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 for 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.

[Slide.]

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 today that Dr. Karkouti expressed that those patients that have greater than 5 units of blood transfused are

of concern in 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 5 units of red blood cells compared to 27.6 percent of placebo patients.

Furthermore, the need for takeback to the operating room for diffuse bleeding was also reduced with the full and half-dose of aprotinin, but not a single patient in the [?] protocol population requiring a re-operation for diffuse bleeding.

[Slide.]

Now turning to the primary CABG studies, of 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.

[Slide.]

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 5 units of red blood cells, you can see that only 2.8 percent of patients receiving full dose aprotinin, who underwent a primary CABG procedure, received at least 5 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 [?] protocol analysis who received half-dose or full dose aprotinin that required a takeback to the operating room for diffuse bleeding.

I have said a lot about takebacks 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.

[Slide.]

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 the 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 takebacks to the operating room.

I would now like to review the safety of aprotinin and CABG procedures. As I stated earlier, I am going to be focusing on the 45 randomized clinical trials in the Bayer database, looking at the full dose of aprotinin compared to placebo.

[Slide.]

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 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 and 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 an isolated CABG procedure. The other 50 percent had CABG plus another cardiac procedure in combination with it.

[Slide.]

Looking at some key medical conditions, obviously, this is not an exhaustive list of the medical histories and baseline

medical conditions that we collected, but may be pertinent to some of the safety events that we are 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. I will give you a moment to absorb those rates.

[Slide.]

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 7 days after the initiation of study 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 of time was.

But as you can see for any adverse event, it is 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.

[Slide.]

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.

[Slide.]

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 is also overlaps between the various meta-analyses.

Having said that, there is not a single meta-analysis here that has 100 percent overlap with either the Bayer clinical trials or the other meta-analyses, so I have chosen

just to show them all for completeness sake.

You can see that for the various meta-analyses that reported mortality risk, that the risk is either neutral or, with one exception, in the case of the Levy meta-analysis, there was a statistically significant reduction in mortality favoring a reduction in mortality with aprotinin.

[Slide.]

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 time frame, 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. 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 D89-006 and trying to compare those results with D89-004, we realized it was quite difficult to do, because we had not standardized protocols with a collection of CPK isoenzymes or with a 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 it 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.

The 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 a Hepcom 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 using 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.

Although that is 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 for both groups with an odds ratio of 0.99. Remember, the primary CABG studies were the later studies that were done, that were done with the adequate anticoagulation monitoring.

For the repeat CABG study, the rates are 14.9 percent versus 8.6, the 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 of look at this would be let's look at those studies that prospectively defined 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 ECT measurements, and where we had adequate anticoagulation, aprotinin is not associated with an increased risk of myocardial infarction.

[Slide.]

Let's step back for a moment and let's look at all the meta-analysis that are out there. Again, knowing that there is overlap between the Bayer studies and between each of these meta-analysis, I should point out that the Sedrakyan meta-analysis is the only meta-analysis that includes CABG-only patients. The other meta-analyses are expanded to all cardiac surgery.

As you can see, there is a neutral effect across all of these studies on the risk of myocardial infarction.

[Slide.]

Now, I would like to shift gears to graft patency.

[Slide.]

Reflected in our label is the IMAGE study that was referred to this morning. This is Study D92-048. 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, an 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 Hepcom 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 machine 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. There was no correlation and there were no differences between mortality or myocardial infarction in this study.

[Slide.]

I will now go more broadly to all the literature that is out there and available on graft patency and, in order to compare across studies, I am going to use saphenous vein graft patency, because that is the one most commonly reported across these studies, and I am going to focus on those studies that use the full dose of aprotinin.

As you can see, in five of the six studies, when looking at results per saphenous vein graft, there was no statistically significant differences between the groups.

Numerically, the one 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 D92-048, also known as the IMAGE study, which are the results that I just shared with you and that are reflected in our label.

[Slide.]

I would now like to shift gears to congestive heart failure. We have 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 reported 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.

[Slide.]

When looking 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 is no statistically significant differences between the groups with the incidence of treatment emergent congestive heart failure.

[Slide.]

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.

[Slide.]

I would like to move now to cerebrovascular events and cerebrovascular safety.

[Slide.]

Again, the way these terms were defined, as 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 0.8.

When looking across primary and repeat CABG, you also see that the rates are less than 1 and, interestingly, with repeat CABG, although it is the smaller sample size of all the subanalyses, the rate is 0.7 percent for full dose aprotinin and 3.1 percent for placebo and these are 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 0.23 and does not reach statistical significance although it is a protein in favor of aprotinin.

[Slide.]

When looking at encephalopathy it again is reported as an adverse event. Our term of encephalopathy that we used, coma would have been included in this. Looking again at the odds ratios and the rates, you can see that these events are rare, they are reported with a comparable rate, and all the odds ratios are less than 1.

[Slide.]

Bayer's conclusions on cerebrovascular safety is that

aprotinin was not associated with an increased incidence of either stroke or encephalopathy with encephalopathy also including coma.

[Slide.]

Now moving to renal function, one of the difficulties perhaps when looking across the literature, 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 0.5 mg/dl change over baseline in serum creatinine. I am also going to display for you those changes greater than 2 mg above baseline as it was reflected in the original NDA.

In your briefing document, we have 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.

[Slide.]

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 0.5 mg/dl 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 0.5 mg/dl over baseline, but it is 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 that when looking at the larger change of 2 mg/dl 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.

We found that the incidence of dialysis was the same between both groups at 0.3 percent. I should also make note to put this into perspective for you. During the same time frame that these studies were conducted, the STS database would have reported the dialysis rate of 0.5 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 creatinine, I should point out that serum creatinine 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 7 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 9 days for the full dose of aprotinin compared to 6 days for the placebo group.

[Slide.]

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 is more adopted in the clinical trials in Europe. So 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.

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 0.5 mg/dl over baseline, had a change in serum creatinine, was 11 percent for full dose aprotinin, 7.8 percent for half-dose aprotinin and 7.9 percent for placebo.

Again, the differences between the groups were greater than 2 mg/dl over baseline and the patients requiring renal dialysis did not differ.

[Slide.]

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 0.5 mg/dl 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 16 ml/minute and what we found was that the 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.

[Slide.]

To summarize then Bayer's position on the renal safety of our randomized clinical trials, there is an increased incident of serum creatinine elevations greater than 5 mg/dl

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 9 days for aprotinin versus 6 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.

[Slide.]

Now, I would like to move on to 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 event of hypersensitivity.

[Slide.]

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 anaphylaxis is related to this exposure history. For patients who have no known prior exposure, the rate is less than 0.1 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 6 months of the prior exposure versus greater than 6 months, it is 5 percent for less than 6 months and 0.9 percent for greater than 6 months.

This information, as I stated, and as was shared with you this morning by Dr. Robie-Suh, is reflected in the product information for Trasylol.

[Slide.]

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 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 Trasylol if there was lacking data on the spontaneous cases. So, of those 291 reports, 52 of them were fatal.

[Slide.]

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 the global database, so please keep that in mind.

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 reported.

[Slide.]

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.

[Slide.]

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 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.

[Slide.]

You heard this morning that we have put in a 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.

Education includes the increased risk following re-exposure especially within six months and they are reminded of the boxed warning in our label.

Also, they are 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 is not enough to check for a medical history of Trasylol alone. But you must also ask for the tissue sealant history, to use the test dose and use it correctly, 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 patients should be monitored carefully and be prepared to potentially intervene.

[Slide.]

In addition to that, Bayer is exploring the possibility of having 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, 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.

[Slide.]

To summarize 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 who 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 5 units of red blood cells and it reduces takebacks 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 are 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.

[Slide.]

With that, I would like to turn things over to Dr. Jerrold Levy, who is Professor of Anesthesiology, Director of Cardiothoracic Anesthesiology and Deputy Chair of Research at Emory University. He will be discussing the risk-benefit

assessment.

DR. HIATT: We will take questions after this then.

**Risk-Benefit Assessment**

DR. LEVY: Thank you. I am privileged to be here to review the risk-benefit assessment of aprotinin.

[Slide.]

What I would like to do this afternoon is talk about categories of risk 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.

[Slide.]

Hypersensitivity in cardiac surgery is of particular interest. I have 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. It is important to understand that mortality is rare when patients in this particular setting are intubated, they are 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 is that in a critically ill patient with a left main equivalent and a tight right coronary with tight 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, basal dilation 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. What they noted was that rapid placement under cardiopulmonary bypass facilitated a good outcome.

All but one operation proceeded and there were no intra-op or postoperative deaths in this patient population.

Cardiopulmonary bypass is really lifesaving with acute anaphylaxis because of the severe hypotension and 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, the patient prepped and draped, and the ability to urgently institute cardiopulmonary bypass.

The other important point, as we talk about aprotinin anaphylaxis, it is 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, aminoglycosides, blood and a multiplicity of antigenic, things that are blood exposed to the patient from transfusion-related acute lung injury to an incidence of anaphylaxis to 1 in 600 in the IgA-deficient patient population.

Latex, a ubiquitous environmental antigen, can produce

anaphylaxis in certain patient populations. For instance, health care 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 populations, we have a high risk of anaphylaxis with incidents reported as high as 1 in 1,500 to 1 in 2,500.

Then, other proteins besides aprotinin, which you have heard about, an agent that is 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. This is from two large prospective studies I published in the eighties looking 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 are 69 deaths associated with protamine. Then there are other environmental and other agents that are administered in this particular setting.

So, again it is 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.

[Slide.]

So, regarding hypersensitivity in aprotinin, hypersensitivity including fatal anaphylaxis with aprotinin is known particularly with re-exposure within six months, because of the high titer of IgG antibodies.

It is 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 dose.

[Slide.]

Looking, though, also further on at some of the meta-analysis of the randomized clinical studies, if you look at four important variables, some of which Dr. Cyrus covered, that mortality, myocardial infarction, renal failure, 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.

[Slide.]

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

[Slide.]

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.

[Slide.]

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, re-operation and ICU and hospital stay.

If you look at the ACC/AHA and STS Guideline, it suggests to stop clopidogrel five days before CABG surgery, but we still see emergent patients coming for surgery, patients with very tight, multi-vessel disease with unstable angina who require urgent surgery despite the use of clopidogrel.

[Slide.]

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 was reported by van der Linden in Circulation last year--that in the patients 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.

These numbers not only are statistically significant, but they are clinically relevant, because this includes about 1 unit of pheresed platelets, which is equivalent to about 8

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.

[Slide.]

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

[Slide.]

So, regarding the beneficial effects of aprotinin based on the randomized clinical trials, aprotinin clearly reduces blood loss in transfusion and CABG surgery. It is also effective in aspirin and clopidogrel-treated patients and it is in the 2005 STS Guidelines for antiplatelet therapy and recommended in the STS Guidelines for reducing blood transfusions with a Class I recommendation. The lysine analogues, both epsilon-aminocaproic acid and tranexamic acid do not do this.

Aprotinin also limits re-operation. Re-operation is known to have significant adverse clinical consequences. We

showed you the mortality data, there is cost and other issues and it is recommended in the STS, the Society of Thoracic Surgical Guideline, to limit re-operation with a Class II recommendation.

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

[Slide.]

So, in conclusion, regarding risk-benefit considerations, hypersensitivity reactions 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.

**Questions from the Committee**

DR. HIATT: We are next going to discuss this and I think use the microphone over here. I will just take the prerogative of the Chair. I would like to maybe begin with an

overall comment on reviewing the Bayer background information.

SPONSOR: I think I would just introduce Dr. Paul McCarthy, who is the head of the U.S. Medical organization, who will emcee the questions in this period.

DR. HIATT: I would just like to make some observations. In your background information, you 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 are also studies that suggested that a liberal transfusion policy might be associated with excess mortality.

Then, Dr. Mangano, at least in his background, suggested that antifibrinolytic therapy might be prothrombotic. I guess a question that comes up in terms of safety is do we see any prothrombotic signals in this safety database.

At least when I review these data, in terms of mortality, I counted 10 excess events with an odds ratio of 1.09, myocardial infarctions. These have all been discussed extensively, but 24 excess events, about the same odds ratio of nonsignificant, although in 3 studies that were adjudicated by an outside panel, there was odds ratios around 1 1/2 to 2 1/2, increased heart failure events and decreased stroke events.

I am curious because there are two kinds of strokes, obviously, and my guess is that this is probably reducing the risk of hemorrhagic stroke significantly and maybe neutral in ischemic stroke, but I couldn't tell from the data and maybe it is impossible to tell.

So, my overall comment about it is that it is clearly effective at reducing blood loss and I also think it is effective at preventing at what I would call an event, which is re-operation.

I think that that, like an event in a heart failure study, would be hospitalization, 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 is 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 mechanistically, if I could have the slide on, please, why aprotinin could be hemostatic and not prothrombotic.

[Slide.]

During the bypass surgery, there is a complex amount of things that happen. The first thing that happens is with the contact with the bypass machine, you have thrombin generation and this leads to clotting 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 are doing is you are 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 have the next slide, please.

[Slide.]

We did a search where we looked at arterial 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 an odds ratio of 1.05. I should make note this is including all studies including those that may not have had adequate anticoagulation.

DR. HIATT: Thank you. I think these are just issues for consideration around safety debates that wasn't fully adjudicated, the studies weren't designed 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.

We will open up discussion 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 solu as well as volume? Do you have a clear definition of that? Anytime somebody is hooked up onto a machine is dialysis, is that the definition?

DR. McCARTHY: No, 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 marked 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 have shown an improvement in blood use, a decrease in blood loss, and a decrease in re-operation. Yet, there is no improvement in outcome. Could you explain that for me?

DR. HIATT: That is 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: I think the studies that were undertaken were clearly not designed to look at the mortality effect and

the duration of follow-up was basically short term while they are in the hospital.

I think also the studies weren't powered really to detect or show a mortality difference.

DR. PAGANINI: If I can, Mr. Chairman, to continue.

The third is the encephalopathies and the strokes. 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 use that as an outcome. It is just a comment

A question I would have is in your Slide No. C-54, you have a difference in your numbers with regards to dialysis versus the rest of the issues, you know, greater than 5 or 2 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, there is 361, which would, in fact, decrease the incidence of dialytic intervention when you increase your denominator and that is true across the board.

Is that an error or is that just an omission?

DR. CYRUS: No, that is actually true. Not every patient may have had a baseline serum creatinine, so if they didn't have a baseline serum creatinine, there was nothing to compare creatinines to.

So, for example, in the full-dose aprotinin group, 335 had baseline serum creatinine. 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 is why that denominator does differ.

DR. PAGANINI: Thank you. I am done.

DR. FLACK: A couple of 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 there.

DR. CYRUS: We did look at that, the clinical trial data, but as one might expect, because this development was done when patients may not have had an opportunity to 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 for the spontaneous database for doing a broad search for hypersensitivity.

We did that on the clinical trial database across all of the patients. 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.

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 post-op date and it clearly was in a temporal relationship or they had a clear alternative 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 0.1 percent across the clinical trial, that we could not absolutely exclude, which would be consistent with the no prior exposure experience.

DR. FLACK: But again, the question is people who get it after a test dose, 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 is really is there less of a response to the test dose versus a full dose. Theoretically, there may be, and that is also potentially some of the ideas of the test dose, for instance, 10 million versus 2 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 is fair to say you probably don't really know.

DR. LEVY: Exactly.

DR. FLACK: Okay.

DR. LEVY: Thank you.

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

DR. LEVY: Good question. The first thing, the H1H2 blocker cortical steroids 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 is where the concept occurs.

Pretreatment for anaphylaxis has never really been established, probably from the contrast media literature, which is not anaphylactic, it is not antibody mediated.

The second question, sorry, about the subsequent?

DR. FLACK: 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 the test dose, then, it is stopped. The other thing is what is 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 want to try to understand the graft occlusion and the MI a little bit further. So, first, on the graft occlusion, 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 are 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 as 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 the graft observations?

DR. CYRUS: These five studies are from the literature. I will try to remember them off the top of my head. The Havel study was a single-center study, so it was done at that institution. The Kalangos was also a center, a single center. I believe the Bidstrup was, as well. The Lass study and the Lemmer study, the ultrafast or CT was read centrally, as well, and I am not sure about the Lass study.

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

DR. McCARTHY: Right.

DR. HARRINGTON: On the MI front, the MIs are defined as definite, definite or probable, definite, probable, or possible. Can you help me with how is 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.

DR. CHAITMAN: Show the slide, please.

[Slide.]

The three categories that we decided on are shown on this slide. "Definite" MI used the 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.

The second definition "probable" included cardiac enzymes with a CK-MB level of 120 units per liter or an abnormal profile where the CK-MB exceeded 100, but there was also a Q-wave worsening according to the Minnesota Code.

"Possible" MI was an abnormal cardiac enzyme profile

where the CK-MB exceeded 100 units.

If the patient had none of these, then, there was absence of these criteria, 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: How did these make it to your attention, did cases get sent to you that the investigators indicate as 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.

[Slide.]

The blinded review, we were blinded, of course, to treatment assignments, so we received the ECGs 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 available.

So, 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, were the enzymes systematically looked at?

DR. McCARTHY: All patients.

DR. HARRINGTON: You saw every single patient?

DR. CHAITMAN: 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 aminoglycosides, maybe contrast agents, although we didn't

discuss that.

But there is some confusion about the use of ACE inhibitors and nothing really mentioned at all about ARBs Certainly since these studies have been done, the ACE inhibitor use is prevalent, and so are ARBs.

The study by Gillespie and Kincaid in the briefing document suggests that ACE inhibitors are a risk factor, whereas, the global database suggests that it is 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 Dr. Cyrus to respond to that.

DR. CYRUS: First, I guess to answer the question about the angiotensin, 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.

Could I have the slide, please.

[Slide.]

As you can see, we have about 347 patients in the full-dose aprotinin and 323 patients in placebo that were receiving preoperative ACE inhibitor use and the rates of serum creatinine elevations greater than 0.5 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 is mentioned in the briefing document that 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, in fact, the case?

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

DR. WHELTON: Thank you, Dr. McCarthy. Andrew Whelton from just up the road in Baltimore.

I guess the first issue to my mind as this signal emerged 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.

If you will just bear with me for a moment, following in your mind's eye, a molecule of aprotinin as it goes to the systemic circulation into the renal circulation afferent arterial and then lands at the surface of the capillary loops in the glomeruli, the molecular size is about 5,000 dalton, so it passes quite readily. Then, of course, would enter into the intraluminal space of the proximal tubule.

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 lysosomes.

We know physically, the lysosomes increase in size, so that appears to be the dominant site 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 cytosol 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. Interestingly, in the Kincaid report, which is very interesting, there is an overlap. About 60 percent of those who are on ACE may well have had diabetes as the reason for being on it and, hence, it is 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 has got to be small.

But other drugs, cisplatinum, amphotericin, I think were we to study them, we would probably see, yes, a mild interaction. Again, I would emphasize this looks like mild, transient, and we have got a good explanation for it.

DR. WARNER-STEVENSON: I have two related questions. I am clinically quite impressed by the serious impact of

transfusions and re-operation in the crucial postoperative period.

I think the impact of that probably takes quite a while 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 is 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 wasn't a primary endpoint and it was very difficult to analyze.

There was a trend towards decreased hospital stay albeit not statistically significant associated with aprotinin.

DR. WARNER-STEVENSON: Thank you. I have one other related question. I am 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.

I am interested in the guideline which says that it's Status IIa for patients who have received aspirin, which makes

me assume it is 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 1, but that's a guideline for blood conservation.

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: This is Peter Smith. I am Chief of Thoracic Surgery at Duke University. I am here on behalf of Bayer.

[Slide.]

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.

It has this IIa 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.

They caution that this is not extrapolated to the

lysine analogues that you can see a IIb recommendation-- Class IIb evidence rather which is the majority of the information shows that they are not effective in this setting.

The current state--I think we have another slide of the STS, the draft ones, if you could put this one up--

[Slide.]

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 the SCA, Society of Cardiovascular Anesthesiology, as well, with these recommendations.

These recommendations were developed subsequent to the publication in the New England Journal of Medicine that was discussed today. The Class I recommendation for full-dose aprotinin level A evidence, reducing blood transfusion persists. IIb recommendation is for half-dose and full-dose aprotinin reducing reoperative rates, so that is return to the operating room for bleeding, has a IIa 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 have two questions, one in the background material that we got from FDA based on the randomized trials available through 1993, I believe it was.

It 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 a 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. The second question is although the utility of the test dose seems intuitive and seems obvious, lots of things that seem intuitive and obvious when you study them turn out not to be.

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. Atkinson first.

DR. ATKINSON: Good afternoon. My name is Franklin Atkinson. I am 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.

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 risk.

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 is trying to be prevented, and it makes sense, from I think presumed, and I believe well established in experimental models, dose-response relationship between exposure and allergic reactions, particularly fatal anaphylaxis.

But to answer your question directly, no, as far as I am aware, this practice was not derived from any direct test or clinical evaluation of the value of the test dose.

DR. HECKBERT: I have another question about allergic reaction, hypersensitivity reaction. 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 utility of the IgG level to screen for the risk--

DR. McCARTHY: 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 Beierlein, et al., which was in the FDA's briefing document and I think the 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 is a table that summarizes data, which are primarily from two sources.

One is a paper by Professor Dietrich, who is actually with us today, which characterizes a series of patients, all of whom were re-exposed, had had prior exposures to aprotinin, 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 is another series in the literature by Scheuler, and I can refer you to the table in that publication. Actually, I have the slide here which is very similar, so let's show that slide since they are talking about numbers.

[Slide.]

In terms of the publication by Professor Dietrich, 117 patients, 121 exposures, the IgG status preoperatively was determined and was positive for 18 out of those 121 exposures among those cases. I would remind you all that these were re-exposures. There were 3 cases of anaphylaxis.

The second paper, Scheuler's paper, he looked at 448 cases, preoperative IgG status. Here, in both cases, we are talking about detectable IgG, 15 were positive, there was 1 case of anaphylaxis. The point that I think is made in the Beierlein review, and we have captured 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 is probably inescapable to note that in this series, the sensitivity was 100 percent, that is, all 4 cases were recognized, but it has to be allowed that that is not a large number.

I think those are probably the most pertinent data. I was going to ask for a follow-up question, but perhaps Dr. Atkinson should comment further.

DR. ATKINSON: This is obviously not a large data set

on a proposed screening test and I think one has to go to analogous situations with other foreign proteins administered to man, and I believe 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. Other studies with foreign proteins and 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 predictive 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 don't have IgG antibody, but will not be at risk of a 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 limit to the amount of data, would favor precluding the use of the product in patients who have made an immunological response in the past, even at the expense perhaps of denying some patients treatment who otherwise might be able to receive it safely.

DR. HIATT: Just while you are up there, or 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 it 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 introductions 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: What would be the overall population prevalence of the positive test in this population, do you have any idea?

DR. McCARTHY: In this population, I don't know if you want to comment on it, but I do know in the re-exposure patients it gets as high as about somewhere between 40 to 50 percent. That is in patients who have been previously exposed to aprotinin.

DR. HIATT: Right; and we already know that is a clinical risk factor.

DR. McCARTHY: Sorry?

DR. HIATT: We already know that that re-exposure is a clinical risk factor within six months and then the population that hasn't been previously exposed.

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

DR. HELLER: A quick clarification. In terms of

patients who are exposed, there is a data set that suggests that if you look at detectable IgG, within six months, 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 is no additional re-exposure, that the IgG falls and becomes undetectable. 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 reported in his paper one case of positive detectable IgG.

So, yes, that shows the data from Professor Dietrich.

The other relevant data is in a paper by Scheuler, who examined several hundred patients, all of whom, in terms of the patients we are 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. Atkinson 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: Just to clarify the sponsor's position for the committee to understand, then, your discussion with the FDA would lead to a screening test on 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--you would exclude them.

DR. McCARTHY: Positivity is detectable IgG.

DR. HIATT: Is detectable.

DR. McCARTHY: Correct.

DR. HIATT: And that is 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 are 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 becomes available.

DR. HIATT: So, there would have to be other obviously clinical predictors, which you are not aware of--

DR. McCARTHY: Correct.

DR. HIATT: That might make them high risk.

DR. McCARTHY: Yes.

DR. LINCOFF: I wanted to go back to the issue of myocardial infarction. I understand the limitations of the analysis that was presented, but so on your Slide C-38 and C-39, which talk about the incidence of the adjudicated myocardial infarction, in the initial trials 89-004 and 89-006 and then the subsequent trials where they were prospectively defined, it is reassuring on C-39 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 is only 135 patients. 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 is 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 theoretical and pathophysiologic reason to believe those patients might be more at risk for thrombosis and myocardial infarction, 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 excess risk of myocardial infarction and renal bypass?

DR. CYRUS: I guess it's a two-part question in the way I am viewing it. The first part, as far as the additional data in repeat CABG patients, recall that historically, repeat CABG was the initial approval.

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 in 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.

As to why we believe this was the case for Study D89-004, despite the fact that the bypass time was the same for both groups and, if the bypass time is the same, you might use that as the 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 was statistically significant differences in the ACT. We are 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. Iothalmate 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 C-45, which is incidence of Congestive Heart Failure, if you look at the full-dose aprotinin group, there is a higher incidence at 14.1 as opposed to 11 with odds ratio of 1.33.

Is that statistically significant? It seems like there are certain numbers. So, they are not significant.

I guess the other question I had is I know aprotinin has been looked at in other randomized, blinded trials, specifically, valve trials.

Could you comment on other trials other than CABG trials where there might have been an effect on renal function, because 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 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.

[Slide.]

Here is the data for that study. This sort of suggests 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. 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 were 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: My final question is on anaphylaxis. Being a cardiac surgeon, we deal with this all the time, so if we have a re-operative 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 venous access, or both.

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 mortality statistics with anaphylaxis.

Were those mortalities on patients not going on bypass? You know, such as hip operations where I would think it would be much more of a problem if somebody had anaphylaxis during a hip, and you are 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--

DR. McCARTHY: You obviously know all the cases were in the setting of cardiac surgery and we would agree with you, and that is part of our risk minimization plan is to really get the

message out that since the drug can cause anaphylaxis. Obviously, with the test dose it has 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 a 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 only be applied when the patient is intubated and can go on bypass in the event of an anaphylactic reaction.

DR. HIATT: I would like just to remind the committee that 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 take a few more burning questions.

DR. ELLIS: The discussion of the hips raises a 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 a high percentage of patients receiving cardiac surgery receiving the drug.

I am wondering if you can comment if you know about percentages that are on label in the U.S., off label cardiac

surgery in the U.S. and non-cardiac surgery in the U.S.

DR. McCARTHY: Approximately, between 60 and 65 percent of the use of the drug is in CABG surgery, either CABG surgery alone or CABG surgery in combination with, say, a valve, and an additional 30 or 35 percent is in other types of cardiac surgical procedures. Then there is about 5 to 10 percent where it is used in other situations, such as pediatrics.

It is also used in liver transplant surgery to some extent.

DR. HECKBERT: I have a quick 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 C-37, most of them are from the early nineties and they would reflect the kind of patient that would present and might be considered for a clinical trial in those days.

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?

The other thing to point out is at least in the U.S.,

the more recent trials tended to be primary CABG, so even less serious.

DR. CYRUS: 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 patient that he is seeing and how this data could be extrapolated.

DR. SMITH: 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 have remarked that the incidence and use of this drug has gone up and why and the patients are different than the patients who were 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 re-operations in them, there were many patients that were studied in the randomized trials that were every bit as risky for bleeding as we see today.

[Slide.]

These are data from the STS database comparing 1995 to '99, a more recent period 2000 to 2003, isolated coronary patients. We are 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, cerebral vascular 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. A lot of that has to do with the increased incidence or prevalence, I should say, of both aspirin and, even more particularly, clopidogrel, in our patient population.

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 is hard to do that safely.

With aprotinin being the only agent that is shown to be effective in treating these patients, platelets are ineffective in clopidogrel-treated patients. It is only delay that can obviate the bleeding problems.

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.

I hope that comment was germane.

DR. TEERLINK: A quick one, which is the advantage of coming last in the line here. In regards to Slide C-52 and C-54, what was the time frame at which dialysis was queried? In other words, did you follow all the cases of dialysis within 7 days, 30 days, 6 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 check box 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.

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: So, specific queries, and that was during the entire hospital time period?

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, from the cardiovascular standpoint, I guess one of my problems with the STS database, while it is the only database out there, it is 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 am wondering about 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 re-operation for bleeding rate, you know, only the full dose is probably powered to have a statistical significance.

The half-dose doesn't show it, but on the other hand, the half-dose isn't powered to show anything. I guess one of my concerns is that as we are seeing, it looks like there is a greater risk with a full dose.

Can you justify--with all this data, can you actually justify the full dose versus a half-dose and getting the same results for primary CABG?

DR. CYRUS: I should point out from a historical perspective how these doses were derived. If I could have the slide on, please.

[Slide.]

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 were looking for a kallikrein inhibiting dose that could indeed have an effect on the anti-inflammatory effect.

It just so happens when they use 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. 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 check box 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 in 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 granulocyte activation, as well as inhibiting the kallikrein pathway and bradykinin and modulating the systemic inflammatory response.

So, mechanistically, the two doses are different.

If I could have the next slide, please.

[Slide.]

Dr. Royston has looked at this data and he looked across the correlation looking at hourly blood loss versus aprotinin dose. 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.

[Slide.]

When looking, then, across the clinical trials and looking at those patients that required greater than 5 units of

blood, you can also start seeing that you are looking like there is 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.

The only meta-analysis that looked at dosing was the Munox meta-analysis, which I did determine that the full dose of aprotinin may have associated with it a higher rate of renal dysfunction, but I think it is fair to take that same meta-analysis and say let's look at it from an efficacy standpoint.

I think when you do that, it is very clear that the higher doses of aprotinin, although both were statistically significant, the clinically meaningfulness of the higher dose is more pronounced.

DR. HIATT: Thank you. I think we maybe would like to wrap this section up.

One just really final quick question. How long does Bayer get to market this drug? It has been approved since '93? How long does the patent run?

DR. CYRUS: There is no patent.

DR. HIATT: Got it.

[End of Questions from the Committee session.]