



August 14, 2007

Dear Members, Consultants, Speakers and Guests:

Thank you for your willingness to participate in the September 12, 2007 joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee. This meeting will focus upon the safety and efficacy data related to aprotinin injection (Trasylol®, manufactured by Bayer Pharmaceuticals, Inc.) and is, in large part, a follow-up to the Cardiovascular and Renal Drugs Advisory Committee held on September 21, 2006. Trasylol is approved for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion.

Following the 2006 Advisory Committee meeting, FDA was provided with information and data from a large sample size observational study conducted by Bayer Pharmaceuticals. The findings from this study, along with published reports from a few other observational studies have prompted FDA to reconvene the Advisory Committee to reconsider the available information. The nature and extent of the observational data also prompted FDA to pursue a joint meeting of the Cardiovascular and Renal Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee.

In general, FDA anticipates discussions related to the following topics:

- Strengths and limitations of the presented observational clinical data, especially in light of the available controlled clinical data.
- The overall risks and benefits of Trasylol.

The supplied briefing materials consist of:

1. Draft topics for the discussion and an executive summary
2. A copy of the current Trasylol label
3. Copies of relevant publications
4. Copies of FDA review documents from 2006
5. Copies of FDA draft review documents from 2007.

The final questions will be given to you prior to the start of the meeting.

We look forward to your participation and to a productive meeting on September 12, 2007.

Sincerely,

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**FDA Advisory Committee Briefing Document  
 Joint Meeting of the  
 Cardiovascular and Renal Drugs Advisory Committee  
 and the Drug Safety and Risk Management Advisory Committee**

September 12, 2007  
 Prepared by Division of Medical Imaging and Hematology Products,  
 Office of Surveillance and Epidemiology  
 and  
 Office of Biostatistics

Trasylol® (aprotinin injection)  
 NDA # 20-304; Sponsor: Bayer Pharmaceuticals Corporation

**Table of Contents**

	<b>Page</b>
<b><u>Draft topics</u></b>	2
<b><u>Summary</u></b>	3
<b><u>Current Trasylol Label</u></b>	12
<b>2006 FDA Review Documents:</b>	
<i><u>Executive Summary (briefing document) for 2006 Advisory Committee</u></i>	27
<i><u>Summary of Advisory Committee responses to questions</u></i>	39
<i><u>OSE review of 2006 NEJM and Transfusion publications</u></i>	42
<i><u>OSE post-marketing safety review</u></i>	61
<i><u>OSE review of risk minimization action plan</u></i>	83
<b>2007 FDA Draft Review Documents:</b>	
<i><u>OSE review of i3 Drug Safety Report</u></i>	102
<i><u>OSE review of 2007 JAMA publication</u></i>	138
<i><u>Statistical review of the three observational studies: NEJM (JAMA), Transfusion and i3 Drug Safety Study databases</u></i>	160

OSE = FDA Office of Surveillance and Epidemiology  
 NEJM = New England Journal of Medicine  
 JAMA = The Journal of the American Medical Association  
 CV = Cardiovascular

**DRAFT Topics for Questions for Advisory Committee Members:**

1. FDA anticipates discussion of the strengths/limitations of the observational clinical data that assess Trasylol effects, especially to the extent they suggest more safety concerns than from the available controlled clinical data. These observational data consist predominantly of published study reports (NEJM, 2006; Transfusion, 2006; JAMA, 2007) and the supplied statistical datasets as well as the study report from the Bayer-sponsored i3 Drug Safety Study and statistical datasets.
2. Based upon the discussions of the totality of clinical data, FDA anticipates discussion of overall risks and benefits of the drug and potential alterations of the Trasylol product label to address any important safety concerns.

# Summary

## 1. Background

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Trasylol is an intravenously administered proteinase inhibitor drug manufactured from bovine lung. Trasylol has anti-fibrinolytic properties and was initially approved by the FDA in 1993 for use among certain patients undergoing coronary artery bypass grafting (CABG). The drug dosage is stated in terms of kallikrein inhibitor units (KIU). Notable drug labeling supplements to the application were approved in 1994 and 1998.

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

Trasylol was the subject of a Cardiovascular and Renal Drugs Advisory Committee Meeting on September 21, 2006. The purpose of that meeting was to elicit advice in response to reports from two published observational studies (Mangano et al, NEJM, 2006; Karkouti et al, Transfusion; 2006) that suggested Trasylol was associated with an increased risk for various adverse cardiovascular-renal reactions as well as the accumulating post-marketing data pertaining to anaphylactic reactions.

Following presentations to the Committee by the authors of the two publications as well as a summary of data from Bayer and the FDA, the Committee provided the following conclusions and recommendations to the FDA:

- Trasylol increases the risk for renal dysfunction, but the data do not establish an increased risk for renal failure requiring dialysis.
- Hypersensitivity/anaphylactic reactions are known serious complications of the administration of Trasylol and methods should be sought to reduce their frequency and impact.
- Reduction in the frequency and amount of blood transfusion during CABG surgery remains an important benefit of the use of Trasylol.
- The benefit/risk ratio of Trasylol appears to be greatest in patients undergoing complex surgery or who have other risk factors for bleeding.
- The population in which Trasylol is used should be more restrictive than currently approved.

The Committee was asked to comment upon the overall Trasylol safety and efficacy data, as follows: "Does the totality of information support the use of Trasylol as a safe and effective therapy to decrease the frequency and amount of transfusions in certain groups of patients undergoing CABG/cardiopulmonary bypass (CPB)?"

The Committee's vote on this query was 18 in favor ("yes"), none opposed and 1 abstaining.

Following the Committee's recommendations, modifications to the Trasylol label were approved in December, 2006 that importantly:

- Revised the indication statement to note that Trasylol is now indicated for use only in patients *who are at increased risk* for blood loss and blood transfusion in association with CPB/CABG. This modification

changed the indicated population from the *broad* population of CPB/CABG patients to only those judged by physicians to be *at increased risk*.

- Revised the boxed warning to note that Trasyolol should only be administered in the operative setting where cardiopulmonary bypass can be started quickly and to more explicitly describe the risk for anaphylaxis. This modification limited Trasyolol exposure to patients who could rapidly undergo CPB.
- Revised the contraindications section to note that Trasyolol is contraindicated for administration to any patients with known or suspected aprotinin exposure in the past 12 months. This change was based upon data showing that the greatest risk for anaphylaxis occurred within the first 6-12 months after a previous aprotinin exposure.
- Revised the warnings section to describe the risk for renal dysfunction as well as to provide additional information regarding anaphylaxis.

Following the September, 2006 Advisory Committee Meeting, FDA was informed that Bayer had obtained the preliminary findings from an observational clinical study shortly prior to the committee's discussions. The preliminary findings from this study (referred to as the "i3 Drug Safety Study") suggested that Trasyolol increased the risk for death and various cardiovascular-renal complications, when compared to other anti-fibrinolytic agents. The report or the data were not provided to either the FDA or the Advisory Committee members prior to or during the September, 2006 Advisory Committee meeting.

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## **2. Purpose of the Current Committee Meeting**

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This September 12, 2007 Advisory Committee meeting is convened to discuss the details of new information regarding Trasyolol, including the i3 Drug Safety Study as well as a published report (JAMA, 2007) of long term mortality outcomes for patients who had participated in the NEJM ("Mangano") study discussed at the 2006 Advisory Committee.

Of special note, over the past year, FDA statisticians have been supplied with the statistical datasets for all three observational studies (subsequently referred to as the "Mangano" study [NEJM, 2006 and long term follow-up in JAMA, 2007], the "Karkouti" study [Transfusion, 2006] and the i3 Drug Safety Study [submitted to the NDA by Bayer].

The major purpose of this Committee is to provide recommendations to the FDA regarding the overall risk-benefit assessment for Trasyolol, especially when considering the information that was not provided to the 2006 Advisory Committee. During presentations to the Committee, the major findings from the three observational studies will be discussed, including a summary of FDA review findings and a summary of the pre-marketing safety and efficacy data.

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## **3. Overview of Trasyolol Safety and Efficacy Data Supporting NDA and Supplemental Approvals**

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Trasyolol was approved by the FDA in December, 1993 based upon data from two confirmatory clinical studies conducted among patients undergoing CABG along with supportive clinical study data that examined the use of Trasyolol among patients undergoing cardiac valvular surgery. In addition to the Trasyolol regimen referred to as "Regimen A," these studies also used a Trasyolol "Regimen B" which has subsequently been referred to as "half dose" or "low dose" regimen. Regimen B consisted of exactly one-half the dose of Regimen A, following the test dose (ie., 1 million KIU loading dose, 1 million KIU pump prime dose and a constant intra-operative infusion at 250,000 KIU/hr). The studies supporting the original approval are summarized in Table 1.

**Table 1. Studies submitted in support of the original approval**

Study #	Design	Safety n	Regimen	Control	Procedure
D-89-004	R, DB, SC	171	A & B	Placebo	Repeat CABG
D-89-005	R, DB, MC	212	A & B	Placebo	Valvular surgery
D-89-006	R, DB, MC	216	A only	Placebo	Primary and repeat CABG

R = randomized; DB = double blind; SC = single center; MC = multi-center

In the two CABG studies, fewer patients receiving Trasylol required any donor blood when compared to patients receiving placebo. In general, the risk for use of donor blood was reduced by half subsequent to the administration of Trasylol. The major efficacy findings for the groups of subjects undergoing repeat CABG are shown in Table 2.

**Table 2. Major efficacy findings in support of the original approval: comparison of the numbers of patients who required donor blood transfusion**

Study	Regimen A	Regimen B	Placebo
D-89-004	22/53 (42%)*	23/49 (47%)*	40/52 (77%)
D-89-006	7/23 (30%)*	not studied	23/32 (72%)

\*p ≤ 0.002 compared to placebo

Except for renal data, the safety data generally showed similar adverse event rates among the study groups, including mortality rates. The findings were notable for the observation that 3% of patients experienced "kidney failure" following Trasylol administration while "kidney failure" was reported for 1% of placebo patients. The incidence of "renal dysfunction" was also increased among patients receiving Trasylol when compared to placebo (23% vs 12%). However, the available data supported a determination that the renal dysfunction was reversible.

In 1994, the sponsor submitted clinical data from "Study D-92-008" in order to support the inclusion of Regimen B within the label's dosage section. This study was a randomized, double-blinded, placebo-controlled study that examined Trasylol usage among patients undergoing repeat CABG. The safety and efficacy findings for Regimens A and B were similar to those detected in the earlier confirmatory clinical study that examined these dose regimens. Based upon this second confirmatory clinical study's findings, the product label was modified to cite the option of either Regimen A or B as an acceptable Trasylol dosage.

In 1996, the sponsor submitted clinical data from three new confirmatory clinical studies in order to support a change in the product label's indication to cite the use of Trasylol among "patients undergoing cardiopulmonary bypass in the course of CABG surgery." This proposal was to broaden the indication to include all patients undergoing cardiopulmonary bypass for CABG, not solely for use among patients undergoing repeat CABG or patients at high risk for bleeding during primary CABG surgery. Table 3 summarizes the three prospective clinical studies submitted in support of the new indication. The major findings from these studies are also described below.

**Table 3. Studies initially submitted in support of the broader indication**

Study #	Design	Safety, n	Regimen	Control	Procedure
D-91-007	R, DB, SC	99	A & B	Placebo	Primary or repeat CABG
D-92-016	R, DB, MC	704	A, B, pump only	Placebo	Primary CABG
D-92-048	R, DB, MC	873	A	Placebo	Primary CABG

R = randomized; DB = double blind; SC = single center; MC = multi-center

In addition to these prospective studies, the submission included a report from a retrospective study (Study 25504) that reported Trasyolol hypersensitivity findings from a group of 387 patients with at least two Trasyolol exposures.

**Study D-91-007** was a pilot, pharmacodynamic study performed at a single clinical site. Hence, this study was regarded as supportive to the other, more informative clinical studies. The study findings supported the efficacy of Trasyolol in reducing blood transfusion requirements.

**Study D-92-016** randomized patients with a broad risk of bleeding among placebo and three Trasyolol dose regimens. In this study, patients were stratified at randomization based upon the risk for bleeding (high vs low, with predefined risk factors for bleeding) and on the perceived risk for perioperative myocardial infarction (high or low, with predefined criteria). Table 4 shows the major efficacy findings.

**Table 4. Study D-92-016 efficacy**

Variable	Regimen A n = 160	Regimen B n = 168	Pump Prime n = 159	Placebo n = 157
% requiring blood	33%	35%	33%	52%
Blood units, range	0 - 8	0 - 6	0 - 7	0 - 21

A notable Study D-92-016 observation was the finding that, among the 25% of patients at low risk for bleeding, no statistically significant difference was noted among the groups for the percentage of patients requiring blood transfusion.

Study D-92-016 safety findings showed a slight numeric excess in the rates of myocardial infarction, as denoted by the site investigators (Regimen A 5%; Regimen B 3%; pump prime 5% and placebo 2%). A blinded adjudication of the myocardial infarction clinical data found only a numeric excess of infarctions in the pump prime group. The rates of post-operative serum creatinine elevations were similar among the study groups.

**Study D-92-048** was an international study that randomized primary CABG patients with a broad risk for bleeding to either placebo or Trasyolol Regimen A. The study assessed a primary endpoint of saphenous vein graft patency rates as determined by post-CABG coronary arteriography and a secondary endpoint comparison of donor blood transfusion requirements.

The study's primary endpoint result showed more patients with graft closure in the Trasyolol group (15%) than in the placebo group (11%). However, the rates for myocardial infarction were similar (Trasyolol 2.9% and placebo 3.8%) as were the death rates (Trasyolol 1.4% and placebo 1.6%). Exploratory analyses showed the higher rates for graft occlusion were evidenced only at the non-USA sites.

The study showed a statistically favorable effect of Trasyolol upon the need for blood transfusion (38% vs 54%) with the treatment effect evident in the subsets of patients either at high or low risk for bleeding.

Study D-92-048 safety findings revealed similar rates of adverse events between the Trasyolol and placebo study groups, including similar rates of renal dysfunction.

**Study 25504**, the retrospective clinical study, suggested that the risk for anaphylaxis was 5% if the re-exposure occurred within six months of the initial exposure. The anaphylaxis risk was 0.9% per re-exposure if the re-exposure occurred after six months. Multiple re-exposures appeared to incrementally increase the risk for anaphylaxis.

Subsequently, the sponsor highlighted data from two additional clinical studies (Studies SN0406 and SN0407 and submitted an exploratory reanalysis of Study D-92-048 and a proposal to add a black box warning to the product label regarding the risk for anaphylaxis. The additional clinical data included

findings from 152 patients at low risk for bleeding who were undergoing primary CABG. Both studies demonstrated a reduction in the need for blood transfusion among patients receiving Trasylol (only the Regimen A was examined). The exploratory re-analysis of Study D-92-048 focused upon subsets of patients identified according to low risk for bleeding as well as USA versus non-USA sites.

FDA determined that the totality of the clinical data, in combination with the revision of the product label to include a black box warning regarding anaphylaxis was acceptable and the supplement was approved in August, 1998 for the relatively broad population of patients undergoing CABG with CPB. As previously noted, in 2006, FDA and the sponsor changed this indication in order to attempt to limit Trasylol usage to certain patients judged to be *at high risk* for bleeding and the need for blood transfusion.

#### **4. Summary of the "Mangano" Publication (NEJM, 2006) and the "Karkouti" Publication (Transfusion, 2006) and Statistical Considerations**

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Briefly summarized below are the major highlights from the two observational clinical studies published in 2006 and discussed at the 2006 Advisory Committee. The publications are supplied as attachments to this document.

It is important to note that these publications refer to anti-fibrinolytic drugs other than Trasylol. Specifically, the publications refer to the use of tranexamic acid and aminocaproic acid, two drugs with anti-fibrinolytic activity that are not FDA-approved for use during cardiac surgery. The FDA-approved indications for these two drugs are the following:

-Tranexamic acid: for use "in patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction."

-Aminocaproic acid: for "enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, transfusion of appropriate blood products and other emergency measures may be required. Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders, such as amegakaryocytic thrombocytopenia (accompanying aplastic anemia); acute and life-threatening abruptio placenta; hepatic cirrhosis; and neoplastic disease such as carcinoma of the prostate, lung, stomach and cervix."

FDA has not been supplied with clinical data to verify the safety and/or efficacy of tranexamic acid or aminocaproic acid when used in the same manner as Trasylol.

Both the "Mangano" and "Karkouti" publications refer to the use of statistical "propensity" methodology. In considering this methodology the following background items are notable, as they pertain to the differences between randomized studies and observational studies:

- As will be discussed during presentations to the Committee, a clinical study's outcomes predominantly derive either from effects caused by an investigational treatment or from differences in prognosis before administration of the investigational treatment. Randomized, controlled clinical studies provide the most definitive evidence that study outcomes are due to an investigational agent since the randomization process ensures that the only differences in prognosis between the study groups are due to chance. Hence, in a randomized study, a treatment effect is demonstrated when the observed effect is unlikely due to chance alone.
- Since observational clinical studies do not involve random assignment of patients to investigational treatments, the choice of treatment assignment may be related to risk factors and prognosis. Thus, study outcomes may simply reflect the underlying prognosis for the patients chosen to receive the specific treatments.

- Statistical methods may be used in an attempt to adjust for those underlying prognostic factors (the "observed variables") that are recorded in an observational database. However, statistical methods are not capable of adjusting for prognostic factors ("unobserved variables") that are not recorded in the database.
- Propensity adjustment is a statistical method that provides an estimate of the chance for a subject with a set of observed variables to receive a specific treatment rather than an alternative/control treatment.
- Outcomes from observational clinical studies may be partially adjusted for the treatment assignment preferences and decisions through the use of propensity scores—in these analyses, outcomes are compared between patients who have the same propensity scores (ie., the same chance for receiving a specific treatment).
- One of the major limitations of propensity methodology is its inability to fully eliminate underlying differences in treatment groups. Hence, the statistical methodology from an observational study may be thoroughly verified, yet the study findings may or may not accurately reflect the truth.

**"Mangano" NEJM publication:** In January, 2006 Mangano, et.al. published a report of a prospective, multi-center observational clinical study that compared the use of aprotinin to the use of two other drugs with anti-fibrinolytic activities (aminocaproic acid and tranexamic acid) as well the use of no anti-fibrinolytic drug. In this study, 4374 patients undergoing coronary revascularization were assessed following the assignment of each patient to the physician-prescribed anti-fibrinolytic drug regimen. In order to adjust for imbalances in baseline characteristics, the study authors used multivariate logistic regression with and without propensity-adjustment to estimate the important study outcomes among the study groups.

The authors reported that, for patients undergoing "complex" or primary coronary artery surgery, aprotinin administration was associated with a doubling in the risk of renal failure requiring dialysis. Additionally, aprotinin administration to patients undergoing primary coronary artery surgery was associated with a 55 percent increase in the risk of myocardial infarction or heart failure and a 181 percent increase in the risk of stroke or encephalopathy. No increase in these adverse reactions occurred with aminocaproic acid or tranexamic acid. All three anti-fibrinolytic drugs were reported to reduce blood loss.

**"Karkouti" Transfusion publication:** In March, 2006 Karkouti, et.al. published (following an earlier, on-line publication) a report of a retrospective, single center observational clinical study that compared the use of aprotinin to tranexamic acid among high-transfusion risk patients. In this study, patients undergoing cardiac surgery with cardiopulmonary bypass were assessed following the assignment of each patient to the physician-prescribed anti-fibrinolytic drug. Using propensity scores, 449 patients who received aprotinin were matched to 449 patients who received tranexamic acid. The study reported that all adverse events occurred at similar rates, except for renal dysfunction which occurred in 24% aprotinin-exposed patients and 17% tranexamic acid patients.

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## **5. Summary of the Preliminary Report from the i3 Drug Safety Study**

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Bayer has supplied a copy of the preliminary study report and datasets for the study entitled, "Mortality and Cardiovascular and Renal Outcomes in Recipients of Aprotinin, Aminocaproic Acid and Tranexamic Acid during CABG Surgery: Report on Computerized Inpatient Data from the Premier Prospective Comparative Database" (the i3 Drug Safety Study). [The information below pertains to the preliminary study report and database. Bayer supplied the final study report to the FDA shortly prior to the generation of this document. The findings in this report are generally similar to those of the preliminary report, as will be summarized at the September 12, 2007 presentation.]

This cohort study used the Premier Perspective Comparative Database, a large, geographically-representative hospital-based database that provides data from approximately one-sixth of all hospitalizations in the United States. The database was used to identify 66435 patients undergoing CABG surgery who received anti-fibrinolytic therapy during a three-year period starting January 1, 2003. The study considered 43 patient, doctor and hospital characteristics as variables. Outcomes, assessed during the hospital stay following the day of the index CABG surgery, were acute coronary revascularization (indicated by the presence of codes for thrombolysis, percutaneous coronary angioplasty, PTCA, or redo CABG), stroke (excluding hemorrhagic stroke), acute heart failure (indicated by the presence of codes for dobutamine use or left ventricular assist device use), acute renal failure (indicated by the presence of codes for hemodialysis or peritoneal dialysis or hemofiltration) or death.

Relative risks and risk differences were calculated. Multivariable adjustment was accomplished by logistic regression. The odds ratio (OR) derived from the logistic regression coefficient was the primary measure of association and approximates the relative risk (RR).

Forty-four percent of patients received aprotinin and 54% received aminocaproic acid. The few remaining patients who received tranexamic acid were included in the aminocaproic acid recipients for primary analyses of aprotinin versus other anti-fibrinolytics.

**Table 5. Major outcomes from the i3 Drug Safety Study: Relative Risks for Events Comparing Trasylol to other Anti-fibrinolytic Agents Using Logistic Regression**

Outcome	RR	95% CI
Death	1.68	1.53 - 1.84
Acute renal failure	1.70	1.55 - 1.86
Acute heart failure	1.08	1.03 - 1.14
Stroke	1.20	1.07 - 1.35

Selected subset analyses were reported to show similar results and propensity score adjustment were also reported to not change the results. The authors' conclusions from the study were reported to support the hypothesis of a higher risk of death and acute renal failure in aprotinin recipients compared to recipients of other anti-fibrinolytic agents.

The data tabulations and their analyses have been provided by Bayer and FDA analyses generally verify the authors' preliminary results.

## 6. The "Mangano" Long Term Follow-Up Study

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On February 7, 2007, JAMA published a study entitled "Mortality Associated with Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery" (JAMA . 2007;297:471-479). This study was based upon long term follow-up of patients who had previously been reported in the NEJM, 2006.

This study reported long-term all-cause mortality in patients who had received aprotinin, aminocaproic acid, tranexamic acid or no anti-fibrinolytic therapy during CABG surgery. The database comprised a substantial proportion of the database that had been analyzed in the NEJM previous report. The co-variate adjusted hazard ratio for death among patients treated with aprotinin compared to no anti-fibrinolytic therapy was 1.48 (95% CI, 1.19-1.85) whereas the comparable hazard ratios for aminocaproic acid and tranexamic acid were 1.03 (95% CI, 0.80-1.33) and 1.07 (95% CI, 0.80-1.45), respectively. Propensity adjustment did not significantly change the hazard ratio for aprotinin (1.37; 95% CI 1.09-1.73). The authors concluded that, not only were short-term adverse reactions increased with the administration of aprotinin, the frequency of death at five years was increased as well.

Of special note, the authors highlight certain limitations of the data—most notably, that long term follow-up information was not available for 11% of the original cohort of patients and that 13% of analyzed patients were lost to follow-up between six weeks and five years and were censored in the analyses.

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## 7. Additional Relevant Publications

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The "Coleman Study": In June, 2007, the Journal of Thoracic and Cardiovascular Surgery (133:1547-1552) published a report by Coleman, et. al., entitled "Evaluating the Safety Implications of Aprotinin Use: The Retrospective Evaluation of Aprotinin in Cardio Thoracic Surgery (REACTS). In this retrospective, observational, single-institution (Hartford Hospital) study, 362 patients receiving aprotinin during CABG with CPB were compared to 2986 patients that did not receive aprotinin. Patients who received aprotinin were at greater risk for adverse outcomes than patients who did not. After multivariate logistic regression including propensity score adjustment, patients receiving aprotinin had a greater odds ratio of developing renal dysfunction (2.03; 95% CI, 1.37-3.01 for all patients; 1.76; 95% CI, 1.08-2.88 for patients undergoing complex surgery). Patients receiving aprotinin did not have a greater risk of death, myocardial infarction or stroke.

The "BART Study": "The Blood Conservation Using Antifibrinolytics: A Randomized Trial in High-Risk Cardiac Surgery Patients (BART)" is a trial currently active in Canada. The study is a multi-institutional, blinded, randomized controlled trial that seeks to compare the efficacy and safety of the use of aprotinin, aminocaproic acid and tranexamic acid in 3000 high-risk patients (re-operation; CABG + aortic valve replacement; combined valves or valve/CABG) undergoing CABG with CPB. An abstract of the study was presented in 2006 and is appended to this document). Subsequent to the abstract, total enrollment has reportedly risen to 2300 patients. Based on the rate of patient accrual, it is anticipated that the trial will be completed in approximately the middle of 2008, although data analysis will lengthen the time for a final report.

The "Brown Study": In June, 2007, Circulation (115:2801-2813) published a report by Brown et al entitled "Meta-Analysis Comparing the Effectiveness and Adverse Outcomes of Antifibrinolytic Agents in Cardiac Surgery". In this study, published randomized controlled trial data from 138 trials were used to compare eight different outcomes after the administration of aprotinin, aminocaproic acid, tranexamic acid or no antifibrinolytic therapy during cardiac surgery. Most of the trials compared an antifibrinolytic agent with placebo, but 29 of the trials compared one antifibrinolytic therapy to another. The analysis indicated that the only statistically significant increase in adverse reactions was renal dysfunction (defined as a 0.5 mg/dL increase in serum creatinine) which occurred only in association with high dose aprotinin compared to placebo (RR, 1.47; 95%CI, 1.12-1.94). There were no differences in mortality, stroke, myocardial infarction or renal failure with any antifibrinolytic agent compared to placebo. There were no significant differences in adverse reactions among any agents when compared "head-to-head."

The "Shaw Abstract": On October 18, 2007 at the Annual Meeting of the American Society of Anesthesiologists, Shaw et al will present an abstract titled "Long Term Survival Following Aprotinin Therapy in Cardiac Surgery". This is a retrospective review of a 10 year experience (January, 1996 to December, 2005) at a single institution (Duke University) on 10854 patients undergoing cardiac surgery. Propensity score methodology was used to predict the risk of receiving aprotinin as part of intraoperative management. Sufficient data was obtained on 9844 patients of whom 1342 received aprotinin and 8924 received another antifibrinolytic agent or no antifibrinolytic agent. The hazard ratio for survival for aprotinin versus control was 1.25 (95% CI, 1.09, 1.44). The unadjusted Kaplan-Meier mortality estimates (aprotinin vs all others) were 15.5% vs. 6.4% at one year and 36.0% vs 19.7% at five years (Log-Rank p<0.0001). However, overall mortality at 10 years was not significantly different (28.2% vs 26.4%).

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## 8. Major Findings from FDA Statistical Review of the Observational Datasets

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Overall, FDA statisticians have verified the accuracy of the major statistical results described in the "Mangano" and "Karkouti" study publications as well as the preliminary i3 Drug Safety Study preliminary report.

Additionally, FDA statisticians performed analyses that used different propensity adjustment methodology from that described in the "Mangano" and "Karkouti" published reports as well as the i3 Drug Safety Study preliminary study. In general, the analytical findings from FDA were similar to those published or reported. Table 6 summarizes the results of FDA's analyses of the "Mangano", "Karkouti" and i3 Drug Safety studies. In these analyses the relative risk compares the Trasylol outcome to either no therapy ("Mangano") or tranexamic acid ("Karkouti") or tranexamic acid/aminocaproic acid (i3 Drug Safety Study).

**Table 6. Summary of Major Findings from FDA Analyses  
(RR = relative risk)**

<b>Outcome</b>	<b>"Mangano" RR (95% CI)</b>	<b>"Karkouti" RR (95% CI)</b>	<b>i3 Drug Safety RR (95% CI)</b>
Renal failure	2.05 (1.05, 3.99)	1.38 (0.86, 2.23)	1.82 (1.61, 2.06)
Renal dysfunction	1.26 (0.76, 2.11)	1.53 (1.11, 2.12)*	n/a
Renal composite	1.63 (1.03, 2.60)	n/a	n/a
Myocardial infarction	1.10 (0.88, 1.39)	1.42 (0.71, 2.83)	n/a
Heart failure	1.05 (0.75, 1.47)	n/a	1.20 (1.14, 1.26)
Coronary revascularization	n/a	n/a	1.47 (1.02, 2.12)
Stroke	1.36 (0.70, 2.64)	1.72 (0.93, 3.19)	1.24 (1.07, 1.44)
Death (in hospital)	0.91 (0.54, 1.53)	1.18 (0.79, 1.76)	1.54 (1.38, 1.73)

Note: Definitions of the outcomes differed among the studies. See accompanying detailed statistical briefing documents for definitions.

\*Based on analysis of a subset of patients with the necessary data.

The Mangano Study was the only study among the three that evaluated long-term mortality. The re-analysis of the study produced similar statistically significant effects on mortality as found by Mangano. The re-analysis showed an estimated risk ratio for aprotinin versus control at four years of 1.39 (95% CI: 1.05, 1.84) and at five years of 1.26 (95% CI: 0.98, 1.62).

Overall, the totality of the data appears most notable for the renal failure/dysfunction outcomes detected among all three studies and the mortality disadvantage detected in the i3 Drug Safety study. These findings should be interpreted in light of the propensity adjustment limitations previously noted and the consideration that the appropriateness of comparing Trasylol to either aminocaproic acid or tranexamic acid is unclear since the safety and efficacy of these two drugs have not been established in the setting of CABG/CPB. In this table, n/a refers to an outcome that could not be calculated due to dataset limitations (for example, lack of creatinine data in the i3 Drug Safety Study database). "Composite" refers to the composite outcome defined in the applicable publication.

**TRASYLOL®**  
(aprotinin injection)

01298181

11/06

Trasylol® administration may cause fatal anaphylactic or anaphylactoid reactions. Fatal reactions have occurred with an initial (test) dose as well as with any of the components of the dose regimen. Fatal reactions have also occurred in situations where the initial (test) dose was tolerated. The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must be sought prior to Trasylol® administration. The risk for a fatal reaction appears to be greater upon re-exposure within 12 months of the most recent prior aprotinin exposure. Trasylol® should be administered only in operative settings where cardiopulmonary bypass can be rapidly initiated. The benefit of Trasylol® to patients undergoing primary CABG surgery should be weighed against the risk of anaphylaxis associated with any subsequent exposure to aprotinin. (See **CONTRAINDICATIONS, WARNINGS and PRECAUTIONS**).

**DESCRIPTION**

Trasylol® (aprotinin injection), C<sub>284</sub>H<sub>432</sub>N<sub>84</sub>O<sub>79</sub>S<sub>7</sub>, is a natural proteinase inhibitor obtained from bovine lung. Aprotinin (molecular weight of 6512 daltons), consists of 58 amino acid residues that are arranged in a single polypeptide chain, cross-linked by three disulfide bridges. It is supplied as a clear, colorless, sterile isotonic solution for intravenous administration. Each milliliter contains 10,000 KIU (Kallikrein Inhibitor Units) (1.4 mg/mL) and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5-6.5.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action:** Aprotinin is a broad spectrum protease inhibitor which modulates the systemic inflammatory response (SIR) associated with cardiopulmonary bypass (CPB) surgery. SIR results in the interrelated activation of the hemostatic, fibrinolytic, cellular and humoral inflammatory systems. Aprotinin, through its inhibition of multiple mediators [e.g., kallikrein, plasmin] results in the attenuation of inflammatory responses, fibrinolysis, and thrombin generation.

Aprotinin inhibits pro-inflammatory cytokine release and maintains glycoprotein homeostasis. In platelets, aprotinin reduces glycoprotein loss (e.g., GpIb, GpIIb/IIIa), while in granulocytes it prevents the expression of pro-inflammatory adhesive glycoproteins (e.g., CD11b).

The effects of aprotinin use in CPB involves a reduction in inflammatory response which translates into a decreased need for allogeneic blood transfusions, reduced bleeding, and decreased mediastinal re-exploration for bleeding.

**Pharmacokinetics:** The studies comparing the pharmacokinetics of aprotinin in healthy volunteers, cardiac patients undergoing surgery with cardiopulmonary bypass, and women

undergoing hysterectomy suggest linear pharmacokinetics over the dose range of 50,000 KIU to 2 million KIU. After intravenous (IV) injection, rapid distribution of aprotinin occurs into the total extracellular space, leading to a rapid initial decrease in plasma aprotinin concentration. Following this distribution phase, a plasma half-life of about 150 minutes is observed. At later time points, (i.e., beyond 5 hours after dosing) there is a terminal elimination phase with a half-life of about 10 hours.

Average steady state intraoperative plasma concentrations were 137 KIU/mL (n=10) after administration of the following dosage regimen: 1 million KIU IV loading dose, 1 million KIU into the pump prime volume, 250,000 KIU per hour of operation as continuous intravenous infusion (Regimen B). Average steady state intraoperative plasma concentrations were 250 KIU/mL in patients (n=20) treated with aprotinin during cardiac surgery by administration of Regimen A (exactly double Regimen B): 2 million KIU IV loading dose, 2 million KIU into the pump prime volume, 500,000 KIU per hour of operation as continuous intravenous infusion.

Following a single IV dose of radiolabelled aprotinin, approximately 25-40% of the radioactivity is excreted in the urine over 48 hours. After a 30 minute infusion of 1 million KIU, about 2% is excreted as unchanged drug. After a larger dose of 2 million KIU infused over 30 minutes, urinary excretion of unchanged aprotinin accounts for approximately 9% of the dose. Animal studies have shown that aprotinin is accumulated primarily in the kidney. Aprotinin, after being filtered by the glomeruli, is actively reabsorbed by the proximal tubules in which it is stored in phagolysosomes. Aprotinin is slowly degraded by lysosomal enzymes. The physiological renal handling of aprotinin is similar to that of other small proteins, e.g., insulin.

## CLINICAL TRIALS

### **Repeat Coronary Artery Bypass Graft Patients:**

Four placebo-controlled, double-blind studies of Trasylol<sup>®</sup> were conducted in the United States; of 540 randomized patients undergoing repeat coronary artery bypass graft (CABG) surgery, 480 were valid for efficacy analysis. The following treatment regimens were used in the studies:

Trasylol<sup>®</sup> Regimen A (2 million KIU IV loading dose, 2 million KIU into the pump prime volume, and 500,000 KIU per hour of surgery as a continuous intravenous infusion); Trasylol<sup>®</sup> Regimen B (1 million KIU IV loading dose, 1 million KIU into the pump prime volume, and 250,000 KIU per hour of surgery as a continuous intravenous infusion); a pump prime regimen (2 million KIU into the pump prime volume only); and a placebo regimen (normal saline). All patients valid for efficacy in the above studies were pooled by treatment regimen for analyses of efficacy.

In this pooled analysis, fewer patients receiving Trasylol<sup>®</sup>, either Regimen A or Regimen B, required any donor blood compared to the pump prime only or placebo regimens. The number of units of donor blood required by patients, the volume (milliliters) of donor blood transfused, the number of units of donor blood products transfused, the thoracic drainage rate, and the total thoracic drainage volumes were also reduced in patients receiving Trasylol<sup>®</sup> as compared to placebo.

Efficacy Variables: Repeat CABG Patients Mean (S.D.) or % of Patients				
VARIABLE	PLACEBO REGIMEN N=156	Trasylol® PUMP PRIME REGIMEN† N=68	Trasylol® REGIMEN B** N=113	Trasylol® REGIMEN A** N=143
% OF REPEAT CABG PATIENTS WHO REQUIRED DONOR BLOOD	76.3%	72.1%	48.7%	46.9%
UNITS OF DONOR BLOOD TRANSFUSED	3.7 (4.4)	2.5 (2.4)	2.2 (5.0)*	1.6 (2.9)*
mL OF DONOR BLOOD TRANSFUSED	1132 (1443)	756 (807)	723 (1779)*	515 (999)*
PLATELETS TRANSFUSED (Donor Units)	5.0 (10.0)	2.1 (4.6)*	1.3 (4.6)*	0.9 (4.3)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.9 (3.5)	0.0 (0.0)*	0.5 (4.0)	0.1 (0.8)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	1.3 (2.5)	0.5 (1.4)*	0.3 (1.1)*	0.2 (0.9)*
THORACIC DRAINAGE RATE (mL/hr)	89 (77)	73 (69)	66 (244)	40 (36)*
TOTAL THORACIC DRAINAGE VOLUME (mL) <sup>a</sup>	1659 (1226)	1561 (1370)	1103 (2001)*	960 (849)*
REOPERATION FOR DIFFUSE BLEEDING	1.9%	2.9%	0%	0%

† The pump prime regimen was evaluated in only one study in patients undergoing repeat CABG surgery. Note: The pump prime only regimen is not an approved dosage regimen.

\* Significantly different from placebo,  $p < 0.05$

(Transfusion variables analyzed via ANOVA on ranks)

\*\* Differences between Regimen A (high dose) and Regimen B (low dose) in efficacy and safety are not statistically significant.

<sup>a</sup> Excludes patients who required reoperation

#### Primary Coronary Artery Bypass Graft Patients:

Four placebo-controlled, double-blind studies of Trasylol® were conducted in the United States; of 1745 randomized patients undergoing primary CABG surgery, 1599 were valid for

efficacy analysis. The dosage regimens used in these studies were identical to those used in the repeat CABG studies described above (Regimens A, B, pump prime, and placebo). All patients valid for efficacy were pooled by treatment regimen.

In this pooled analysis, fewer patients receiving Trasylol<sup>®</sup> Regimens A, B, and pump prime required any donor blood in comparison to the placebo regimen. The number of units of donor blood required by patients, the volume of donor blood transfused, the number of units of donor blood products transfused, the thoracic drainage rate, and total thoracic drainage volumes were also reduced in patients receiving Trasylol<sup>®</sup> as compared to placebo.

<b>Efficacy Variables: Primary CABG Patients</b>				
<b>Mean (S.D.) or % of Patients</b>				
<b>VARIABLE</b>	<b>PLACEBO REGIMEN N=624</b>	<b>Trasylol<sup>®</sup> PUMP PRIME REGIMEN† N=159</b>	<b>Trasylol<sup>®</sup> REGIMEN B** N=175</b>	<b>Trasylol<sup>®</sup> REGIMEN A** N=641</b>
% OF PRIMARY CABG PATIENTS WHO REQUIRED DONOR BLOOD	53.5%	32.7%*	37.1%*	36.8%*
UNITS OF DONOR BLOOD TRANSFUSED	1.7 (2.4)	0.9 (1.6)*	1.0 (1.6)*	0.9 (1.4)*
mL OF DONOR BLOOD TRANSFUSED	584 (840)	286 (518)*	313 (505)*	295 (503)*
PLATELETS TRANSFUSED (Donor Units)	1.3 (3.7)	0.5 (2.4)*	0.3 (1.6)*	0.3 (1.5)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.5 (2.2)	0.0 (0.0)*	0.1 (0.8)*	0.0 (0.0)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	0.6 (1.7)	0.2 (1.7)*	0.2 (0.8)*	0.2 (0.9)*
THORACIC DRAINAGE RATE (mL/hr)	87 (67)	51 (36)*	45 (31)*	39 (32)*
TOTAL THORACIC DRAINAGE VOLUME (mL)	1232 (711)	852 (653)*	792 (465)*	705 (493)*
REOPERATION FOR DIFFUSE BLEEDING	1.4%	0.6%	0%	0%*

- † The pump prime regimen was evaluated in only one study in patients undergoing primary CABG surgery. Note: The pump prime only regimen is not an approved dosage regimen.
- \* Significantly different from placebo,  $p < 0.05$   
(Transfusion variables analyzed via ANOVA on ranks)
- \*\* Differences between Regimen A (high dose) and Regimen B (low dose) in efficacy and safety are not statistically significant.

Additional subgroup analyses showed no diminution in benefit with increasing age. Male and female patients benefited from Trasylol<sup>®</sup> with a reduction in the average number of units of donor blood transfused. Although male patients did better than female patients in terms of the percentage of patients who required any donor blood transfusions, the number of female patients studied was small.

A double-blind, randomized, Canadian study compared Trasylol<sup>®</sup> Regimen A (n=28) and placebo (n=23) in primary cardiac surgery patients (mainly CABG) requiring cardiopulmonary bypass who were treated with aspirin within 48 hours of surgery. The mean total blood loss (1209.7 mL vs. 2532.3 mL) and the mean number of units of packed red blood cells transfused (1.6 units vs 4.3 units) were significantly less ( $p < 0.008$ ) in the Trasylol<sup>®</sup> group compared to the placebo group.

In a U.S. randomized study of Trasylol<sup>®</sup> Regimen A and Regimen B versus the placebo regimen in 212 patients undergoing primary aortic and/or mitral valve replacement or repair, no benefit was found for Trasylol<sup>®</sup> in terms of the need for transfusion or the number of units of blood required.

#### INDICATIONS AND USAGE

Trasylol<sup>®</sup> is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion.

#### CONTRAINDICATIONS

Hypersensitivity to aprotinin.

Administration of Trasylol<sup>®</sup> to patients with a known or suspected previous aprotinin exposure during the last 12 months is contraindicated. For patients with known or suspected history of exposure to aprotinin greater than 12 months previously, see **WARNINGS**. Aprotinin may also be a component of some fibrin sealant products and the use of these products should be included in the patient history.

#### WARNINGS

**Anaphylactic or anaphylactoid reactions have occurred with Trasylol<sup>®</sup> administration, including fatal reactions in association with the initial (test) dose. The initial (test) dose does not fully predict a patient's risk for a hypersensitivity reaction, including a fatal reaction. Fatal hypersensitivity reactions have occurred among patients who tolerated an initial (test) dose.**

Hypersensitivity reactions often manifest as anaphylactic/anaphylactoid reactions with hypotension the most frequently reported sign of the hypersensitivity reaction. The hypersensitivity reaction can progress to anaphylactic shock with circulatory failure. If a hypersensitivity reaction occurs during injection or infusion of Trasylol<sup>®</sup>, administration should be stopped immediately and emergency treatment should be initiated. Even when a

second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

Trasylol® should be administered only in operative settings where cardiopulmonary bypass can be rapidly initiated. Before initiating treatment with Trasylol®, the recommendations below should be followed to manage a potential hypersensitivity or anaphylactic reaction: 1) Have standard emergency treatments for hypersensitivity or anaphylactic reactions readily available in the operating room (e.g., epinephrine, corticosteroids). 2) Administration of the initial (test) dose and loading dose should be done only when the patient is intubated and when conditions for rapid cannulation and initiation of cardiopulmonary bypass are present. 3) Delay the addition of Trasylol® into the pump prime solution until after the loading dose has been safely administered.

**Re-exposure to aprotinin:** Administration of aprotinin, especially to patients who have received aprotinin in the past, requires a careful risk/benefit assessment because an allergic reaction may occur (see **CONTRAINDICATIONS**). Although the majority of cases of anaphylaxis occur upon re-exposure within the first 12 months, there are also case reports of anaphylaxis occurring upon re-exposure after more than 12 months.

In a retrospective review of 387 European patient records with documented re-exposure to Trasylol®, the incidence of hypersensitivity/anaphylactic reactions was 2.7%. Two patients who experienced hypersensitivity/anaphylactic reactions subsequently died, 24 hours and 5 days after surgery, respectively. The relationship of these 2 deaths to Trasylol® is unclear. This retrospective review also showed that the incidence of a hypersensitivity or anaphylactic reaction following re-exposure is increased when the re-exposure occurs within 6 months of the initial administration (5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months). Other smaller studies have shown that in case of re-exposure, the incidence of hypersensitivity/anaphylactic reactions may reach the five percent level.

An analysis of all spontaneous reports from the Bayer Global database covering a period from 1985 to March 2006 revealed that of 291 possibly associated spontaneous cases of hypersensitivity (fatal: n=52 and non-fatal: n=239), 47% (138/291) of hypersensitivity cases had documented previous exposure to Trasylol®. Of the 138 cases with documented previous exposure, 110 had information on the time of the previous exposure. Ninety-nine of the 110 cases had previous exposure within the prior 12 months.

**Renal Dysfunction:** Trasylol® administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period. This risk may be especially increased for patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function. Data from Bayer's global pool of placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) surgery showed that the incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was statistically higher at 9.0% (185/2047) in the high-dose aprotinin (Regimen A) group compared with 6.6% (129/1957) in the placebo group. In the majority of instances, post-operative renal dysfunction was not severe and was reversible. However, renal dysfunction may progress to renal failure and the incidence of serum creatinine elevations >2.0 mg/dL above baseline was slightly higher in the high-dose aprotinin group (1.1% vs. 0.8%). Careful consideration of the balance of benefits versus potential risks is advised before administering Trasylol® to patients with impaired renal function (creatinine clearance < 60 mL/min).

or those with other risk factors for renal dysfunction (such as perioperative administration of aminoglycoside or products that alter renal function). (See **PRECAUTIONS** and **ADVERSE REACTIONS: Laboratory Findings: Serum Creatinine**.)

### **PRECAUTIONS**

**General: Initial (Test) Dose:** All patients treated with Trasylo<sup>®</sup> should first receive an initial (test) dose to minimize the extent of Trasylo<sup>®</sup> exposure and to help assess the potential for allergic reactions. Initiation of this initial (test) dose should occur only in operative settings where cardiopulmonary bypass can be rapidly initiated. The initial (test) dose of 1 mL Trasylo<sup>®</sup> should be administered intravenously at least 10 minutes prior to the loading dose and the patient should be observed for manifestations of possible hypersensitivity reaction. However, even after the uneventful administration of the 1 mL initial (test) dose, any subsequent dose may cause an anaphylactic reaction. If this happens, the infusion of Trasylo<sup>®</sup> should immediately be stopped and standard emergency treatment for anaphylaxis applied. It should be noted that serious, even fatal, hypersensitivity/anaphylactic reactions can also occur with administration of the initial (test) dose (see **WARNINGS**).

**Allergic Reactions:** Patients with a history of allergic reactions to drugs or other agents may be at greater risk of developing a hypersensitivity or anaphylactic reaction upon exposure to Trasylo<sup>®</sup>. (see **WARNINGS**)

**Loading Dose:** The loading dose of Trasylo<sup>®</sup> should be given intravenously to patients in the supine position over a 20-30 minute period. Rapid intravenous administration of Trasylo<sup>®</sup> can cause a transient fall in blood pressure (see **DOSAGE AND ADMINISTRATION**).

**Renal Dysfunction:** Bayer's global pool of placebo-controlled studies in patients undergoing CABG showed aprotinin administration was associated with elevations of serum creatinine values > 0.5 mg/dL above baseline. Careful consideration of the balance of benefits and risks is advised before administering aprotinin to patients with pre-existing impaired renal function or those with other risk factors for renal dysfunction. Serum creatinine should be monitored regularly following Trasylo<sup>®</sup> administration (see **WARNINGS: Renal Dysfunction**).

**Use of Trasylo<sup>®</sup> in patients undergoing deep hypothermic circulatory arrest:** Two U.S. case control studies have reported contradictory results in patients receiving Trasylo<sup>®</sup> while undergoing deep hypothermic circulatory arrest in connection with surgery of the aortic arch. The first study showed an increase in both renal failure and mortality compared to age-matched historical controls. Similar results were not observed, however, in a second case control study. The strength of this association is uncertain because there are no data from randomized studies to confirm or refute these findings.

**Drug Interactions:** Trasylo<sup>®</sup> is known to have antifibrinolytic activity and, therefore, may inhibit the effects of fibrinolytic agents.

In study of nine patients with untreated hypertension, Trasylo<sup>®</sup> infused intravenously in a dose of 2 million KIU over two hours blocked the acute hypotensive effect of 100mg of captopril.

Trasylol<sup>®</sup>, in the presence of heparin, has been found to prolong the activated clotting time (ACT) as measured by a celite surface activation method. The kaolin activated clotting time appears to be much less affected. However, Trasylol<sup>®</sup> should not be viewed as a heparin sparing agent (see **Laboratory Monitoring of Anticoagulation During Cardiopulmonary Bypass**).

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term animal studies to evaluate the carcinogenic potential of Trasylol<sup>®</sup> or studies to determine the effect of Trasylol<sup>®</sup> on fertility have not been performed.

Results of microbial *in vitro* tests using *Salmonella typhimurium* and *Bacillus subtilis* indicate that Trasylol<sup>®</sup> is not a mutagen.

**Pregnancy: Teratogenic Effects: Pregnancy Category B:** Reproduction studies have been performed in rats at intravenous doses up to 200,000 KIU/kg/day for 11 days, and in rabbits at intravenous doses up to 100,000 KIU/kg/day for 13 days, 2.4 and 1.2 times the human dose on a mg/kg basis and 0.37 and 0.36 times the human mg/m<sup>2</sup> dose. They have revealed no evidence of impaired fertility or harm to the fetus due to Trasylol<sup>®</sup>. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mother:** Not applicable.

**Pediatric Use:** Safety and effectiveness in pediatric patient(s) have not been established.

**Geriatric Use:** Of the total of 3083 subjects in clinical studies of Trasylol<sup>®</sup>, 1100 (35.7 percent) were 65 and over, while 297 (9.6 percent) were 75 and over. Of patients 65 years and older, 479 (43.5 percent) received Regimen A and 237 (21.5 percent) received Regimen B. No overall differences in safety or effectiveness were observed between these subjects and younger subjects for either dose regimen, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

**Laboratory Monitoring of Anticoagulation during Cardiopulmonary Bypass:** Trasylol<sup>®</sup> prolongs whole blood clotting times by a different mechanism than heparin. In the presence of aprotinin, prolongation is dependent on the type of whole blood clotting test employed. If an activated clotting time (ACT) is used to determine the effectiveness of heparin anticoagulation, the prolongation of the ACT by aprotinin may lead to an overestimation of the degree of anticoagulation, thereby leading to inadequate anticoagulation. During extended extracorporeal circulation, patients may require additional heparin, even in the presence of ACT levels that appear adequate.

In patients undergoing CPB with Trasylol<sup>®</sup> therapy, one of the following methods may be employed to maintain adequate anticoagulation:

1) ACT - An ACT is not a standardized coagulation test, and different formulations of the assay are affected differently by the presence of aprotinin. The test is further influenced by variable dilution effects and the temperature experienced during cardiopulmonary bypass. It has been observed that Kaolin-based ACTs are not increased to the same degree by aprotinin as are diatomaceous earth-based (celite) ACTs. While protocols vary, a minimal celite ACT of 750 seconds or kaolin-ACT of 480 seconds, independent of the effects of hemodilution and hypothermia, is recommended in the presence of aprotinin. Consult the manufacturer of the ACT test regarding the interpretation of the assay in the presence of Trasylol<sup>®</sup>.

2) Fixed Heparin Dosing - A standard loading dose of heparin, administered prior to cannulation of the heart, plus the quantity of heparin added to the prime volume of the CPB circuit, should total at least 350 IU/kg. Additional heparin should be administered in a fixed-dose regimen based on patient weight and duration of CPB.

3) Heparin Titration - Protamine titration, a method that is not affected by aprotinin, can be used to measure heparin levels. A heparin dose response, assessed by protamine titration, should be performed prior to administration of aprotinin to determine the heparin loading dose. Additional heparin should be administered on the basis of heparin levels measured by protamine titration. Heparin levels during bypass should not be allowed to drop below 2.7 U/mL (2.0 mg/kg) or below the level indicated by heparin dose response testing performed prior to administration of aprotinin.

Protamine Administration - In patients treated with Trasylo<sup>®</sup>, the amount of protamine administered to reverse heparin activity should be based on the actual amount of heparin administered, and not on the ACT values.

### ADVERSE REACTIONS

Studies of patients undergoing CABG surgery, either primary or repeat, indicate that Trasylo<sup>®</sup> is generally well tolerated. The adverse events reported are frequent sequelae of cardiac surgery and are not necessarily attributable to Trasylo<sup>®</sup> therapy. Adverse events reported, up to the time of hospital discharge, from patients in US placebo-controlled trials are listed in the following table. The table lists only those events that were reported in 2% or more of the Trasylo<sup>®</sup> treated patients without regard to causal relationship.

#### INCIDENCE RATES OF ADVERSE EVENTS (>= 2%) BY BODY SYSTEM AND TREATMENT FOR ALL PATIENTS FROM US PLACEBO-CONTROLLED CLINICAL TRIALS

<u>Adverse Event</u>	<u>Aprotinin (n = 2002) values in %</u>	<u>Placebo (n = 1084) values in %</u>
<b>Any Event</b>	76	77
<b>Body as a Whole</b>		
Fever	15	14
Infection	6	7
Chest Pain	2	2
Asthenia	2	2
<b>Cardiovascular</b>		
Atrial Fibrillation	21	23
Hypotension	8	10
Myocardial Infarct	6	6
Atrial Flutter	6	5
Ventricular Extrasystoles	6	4
Tachycardia	6	7
Ventricular Tachycardia	5	4
Heart Failure	5	4
Pericarditis	5	5
Peripheral Edema	5	5

Hypertension	4	5
Arrhythmia	4	3
Supraventricular Tachycardia	4	3
Atrial Arrhythmia	3	3
<b>Digestive</b>		
Nausea	11	9
Constipation	4	5
Vomiting	3	4
Diarrhea	3	2
Liver Function Tests Abnormal	3	2
<b>Hemic and Lymphatic</b>		
Anemia	2	8
<b>Metabolic &amp; Nutritional</b>		
Creatine Phosphokinase Increased	2	1
<b>Musculoskeletal</b>		
Any Event	2	3
<b>Nervous</b>		
Confusion	4	4
Insomnia	3	4
<b>Respiratory</b>		
Lung Disorder	8	8
Pleural Effusion	7	9
Atelectasis	5	6
Dyspnea	4	4
Pneumothorax	4	4
Asthma	2	3
Hypoxia	2	1
<b>Skin and Appendages</b>		
Rash	2	2
<b>Urogenital</b>		
Kidney Function Abnormal	3	2
Urinary Retention	3	3
Urinary Tract Infection	2	2

In comparison to the placebo group, no increase in mortality in patients treated with Trasylol® was observed. Additional events of particular interest from controlled US trials with an incidence of less than 2%, are listed below:

EVENT	Percentage of patients treated with Trasylol®	Percentage of patients treated with Placebo
	<u>N = 2002</u>	<u>N = 1084</u>
Thrombosis	1.0	0.6
Shock	0.7	0.4
Cerebrovascular Accident	0.7	2.1
Thrombophlebitis	0.2	0.5
Deep Thrombophlebitis	0.7	1.0
Lung Edema	1.3	1.5
Pulmonary Embolus	0.3	0.6
Kidney Failure	1.0	0.6
Acute Kidney Failure	0.5	0.6
Kidney Tubular Necrosis	0.8	0.4

Listed below are additional events, from controlled US trials with an incidence between 1 and 2%, and also from uncontrolled, compassionate use trials and spontaneous post-marketing reports. Estimates of frequency cannot be made for spontaneous post-marketing reports (*italicized*).

**Body as a Whole:** Sepsis, death, multi-system organ failure, immune system disorder, *hemoperitoneum*.

**Cardiovascular:** Ventricular fibrillation, heart arrest, bradycardia, congestive heart failure, hemorrhage, bundle branch block, myocardial ischemia, ventricular tachycardia, heart block, pericardial effusion, ventricular arrhythmia, shock, pulmonary hypertension.

**Digestive:** Dyspepsia, gastrointestinal hemorrhage, jaundice, hepatic failure.

**Hematologic and Lymphatic:** Although thrombosis was not reported more frequently in aprotinin versus placebo-treated patients in controlled trials, it has been reported in uncontrolled trials, compassionate use trials, and spontaneous post-marketing reporting. These reports of thrombosis encompass the following terms: thrombosis, occlusion, arterial thrombosis, *pulmonary thrombosis*, coronary occlusion, embolus, pulmonary embolus, thrombophlebitis, deep thrombophlebitis, cerebrovascular accident, cerebral embolism. Other hematologic events reported include leukocytosis, thrombocytopenia, coagulation disorder (which includes disseminated intravascular coagulation), decreased prothrombin.

**Metabolic and Nutritional:** Hyperglycemia, hypokalemia, hypervolemia, acidosis.

**Musculoskeletal:** Arthralgia.

**Nervous:** Agitation, dizziness, anxiety, convulsion.

**Respiratory:** Pneumonia, apnea, increased cough, lung edema.

**Skin:** *Skin discoloration*.

**Urogenital:** Oliguria, kidney failure, acute kidney failure, kidney tubular necrosis.

**Myocardial Infarction:** In the pooled analysis of all patients undergoing CABG surgery, there was no significant difference in the incidence of investigator-reported myocardial infarction (MI) in Trasylol® treated patients as compared to placebo treated patients. However, because no uniform criteria for the diagnosis of myocardial infarction were utilized by investigators, this issue was addressed prospectively in three later studies (two studies

evaluated Regimen A, Regimen B and Pump Prime Regimen; one study evaluated only Regimen A), in which data were analyzed by a blinded consultant employing an algorithm for possible, probable or definite MI. Utilizing this method, the incidence of definite myocardial infarction was 5.9% in the aprotinin-treated patients versus 4.7% in the placebo treated patients. This difference in the incidence rates was not statistically significant. Data from these three studies are summarized below.

**Incidence of Myocardial Infarctions by Treatment Group Population:  
All CABG Patients Valid for Safety Analysis**

Treatment	Definite MI %	Definite or Probable MI %	Definite, Probable or Possible MI %
<b>Pooled Data from Three Studies that Evaluated Regimen A</b>			
Trasylol® Regimen A n = 646	4.6	10.7	14.1
Placebo n = 661	4.7	11.3	13.4
<b>Pooled Data from Two Studies that Evaluated Regimen B and Pump Prime Regimen</b>			
Trasylol® Regimen B n = 241	8.7	15.9	18.7
Trasylol® Pump Prime Regimen n = 239	6.3	15.7	18.1
Placebo n = 240	6.3	15.1	15.8

**Graft Patency:** In a recently completed multi-center, multi-national study to determine the effects of Trasylol® Regimen A vs. placebo on saphenous vein graft patency in patients undergoing primary CABG surgery, patients were subjected to routine postoperative angiography. Of the 13 study sites, 10 were in the United States and three were non-U.S. centers (Denmark (1), Israel (2)). The results of this study are summarized below.

**Incidence of Graft Closure, Myocardial Infarction and Death by Treatment Group**

	Overall Closure Rates*		Incidence of MI**	Incidence of Death***
	All Centers n = 703 %	U.S. Centers n = 381 %	All Centers n = 831 %	All Centers n = 870 %
Trasyol <sup>®</sup>	15.4	9.4	2.9	1.4
Placebo	10.9	9.5	3.8	1.6
CI for the Difference (%) (Drug - Placebo)	(1.3, 9.6)†	(-3.8, 5.9)†	-3.3 to 1.5‡	-1.9 to 1.4‡

\* Population: all patients with assessable saphenous vein grafts

\*\* Population: all patients assessable by blinded consultant

\*\*\* All patients

† 90%; per protocol

‡ 95%; not specified in protocol

Although there was a statistically significantly increased risk of graft closure for Trasyol<sup>®</sup> treated patients compared to patients who received placebo (p=0.035), further analysis showed a significant treatment by site interaction for one of the non-U.S. sites vs. the U.S. centers. When the analysis of graft closures was repeated for U.S. centers only, there was no statistically significant difference in graft closure rates in patients who received Trasyol<sup>®</sup> vs. placebo. These results are the same whether analyzed as the proportion of patients who experienced at least one graft closure postoperatively or as the proportion of grafts closed. There were no differences between treatment groups in the incidence of myocardial infarction as evaluated by the blinded consultant (2.9% Trasyol<sup>®</sup> vs. 3.8% placebo) or of death (1.4% Trasyol<sup>®</sup> vs. 1.6% placebo) in this study.

**Hypersensitivity and Anaphylaxis: See CONTRAINDICATIONS and WARNINGS.**

Hypersensitivity and anaphylactic reactions during surgery were rarely reported in U.S. controlled clinical studies in patients with no prior exposure to Trasyol<sup>®</sup> (1/1424 patients or <0.1% on Trasyol<sup>®</sup> vs. 1/861 patients or 0.1% on placebo). In case of re-exposure the incidence of hypersensitivity/anaphylactic reactions has been reported to reach the 5% level. A review of 387 European patient records involving re-exposure to Trasyol<sup>®</sup> showed that the incidence of hypersensitivity or anaphylactic reactions was 5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months.

**Laboratory Findings**

**Serum Creatinine:** Trasyol<sup>®</sup> administration is associated with a risk for renal dysfunction (see **WARNINGS: Renal Dysfunction**).

**Serum Transaminases:** Data pooled from all patients undergoing CABG surgery in U.S. placebo-controlled trials showed no evidence of an increase in the incidence of postoperative

hepatic dysfunction in patients treated with Trasylol<sup>®</sup>. The incidence of treatment-emergent increases in ALT (formerly SGPT) > 1.8 times the upper limit of normal was 14% in both the Trasylol<sup>®</sup> and placebo-treated patients (p=0.687), while the incidence of increases > 3 times the upper limit of normal was 5% in both groups (p=0.847).

**Other Laboratory Findings:** The incidence of treatment-emergent elevations in plasma glucose, AST (formerly SGOT), LDH, alkaline phosphatase, and CPK-MB was not notably different between Trasylol<sup>®</sup> and placebo treated patients undergoing CABG surgery. Significant elevations in the partial thromboplastin time (PTT) and celite Activated Clotting Time (celite ACT) are expected in Trasylol<sup>®</sup> treated patients in the hours after surgery due to circulating concentrations of Trasylol<sup>®</sup>, which are known to inhibit activation of the intrinsic clotting system by contact with a foreign material (e.g., celite), a method used in these tests (see **Laboratory Monitoring of Anticoagulation During Cardiopulmonary Bypass**).

### OVERDOSAGE

The maximum amount of Trasylol<sup>®</sup> that can be safely administered in single or multiple doses has not been determined. Doses up to 17.5 million KIU have been administered within a 24 hour period without any apparent toxicity. There is one poorly documented case, however, of a patient who received a large, but not well determined, amount of Trasylol<sup>®</sup> (in excess of 15 million KIU) in 24 hours. The patient, who had pre-existing liver dysfunction, developed hepatic and renal failure postoperatively and died. Autopsy showed hepatic necrosis and extensive renal tubular and glomerular necrosis. The relationship of these findings to Trasylol<sup>®</sup> therapy is unclear.

### DOSAGE AND ADMINISTRATION

Trasylol<sup>®</sup> given prophylactically in both Regimen A and Regimen B (half Regimen A) to patients undergoing CABG surgery significantly reduced the donor blood transfusion requirement relative to placebo treatment. In low risk patients there is no difference in efficacy between regimen A and B. Therefore, the dosage used (A vs. B) is at the discretion of the practitioner.

Trasylol<sup>®</sup> is supplied as a solution containing 10,000 KIU/mL, which is equal to 1.4 mg/mL. All intravenous doses of Trasylol<sup>®</sup> should be administered through a central line. **DO NOT ADMINISTER ANY OTHER DRUG USING THE SAME LINE.** Both regimens include a 1 mL initial (test) dose, a loading dose, a dose to be added while recirculating the priming fluid of the cardiopulmonary bypass circuit ("pump prime" dose), and a constant infusion dose. To avoid physical incompatibility of Trasylol<sup>®</sup> and heparin when adding to the pump prime solution, each agent must be added during recirculation of the pump prime to assure adequate dilution prior to admixture with the other component. Regimens A and B, both incorporating a 1 mL initial (test) dose, are described in the table below:

	INITIAL (TEST) DOSE	LOADING DOSE	"PUMP PRIME" DOSE	CONSTANT INFUSION DOSE
TRASYLOL <sup>®</sup> REGIMEN A	1 mL (1.4 mg, or 10,000 KIU)	200 mL (280 mg, or 2.0 million KIU)	200 mL (280 mg, or 2.0 million KIU)	50 mL/hr (70 mg/hr, or 500,000 KIU/hr)
TRASYLOL <sup>®</sup> REGIMEN B	1 mL (1.4 mg, or 10,000 KIU)	100 mL (140 mg, or 1.0 million KIU)	100 mL (140 mg, or 1.0 million KIU)	25 mL/hr (35 mg/hr, or 250,000 KIU/hr)

The 1 mL initial (test) dose should be administered intravenously at least 10 minutes before the loading dose. With the patient in a supine position, the loading dose is given slowly over 20-30 minutes, after induction of anesthesia but prior to sternotomy. In patients with known previous exposure to Trasylol<sup>®</sup>, the loading dose should be given just prior to cannulation. When the loading dose is complete, it is followed by the constant infusion dose, which is continued until surgery is complete and the patient leaves the operating room. The "pump prime" dose is added to the recirculating priming fluid of the cardiopulmonary bypass circuit, by replacement of an aliquot of the priming fluid, prior to the institution of cardiopulmonary bypass. Total doses of more than 7 million KIU have not been studied in controlled trials.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Discard any unused portion.

**Renal and Hepatic Impairment:** Trasylol<sup>®</sup> administration is associated with a risk for renal dysfunction (see **WARNINGS: Renal Dysfunction**). Changes in aprotinin pharmacokinetics with age or impaired renal function are not great enough to require any dose adjustment. Pharmacokinetic data from patients with pre-existing hepatic disease treated with Trasylol<sup>®</sup> are not available.

#### HOW SUPPLIED

Size	Strength	NDC
100 mL vials	1,000,000 KIU	0026-8196-36
200 mL vials	2,000,000 KIU	0026-8197-63

#### STORAGE

Trasylol<sup>®</sup> should be stored between 2° and 25°C (36° - 77°F).

Protect from freezing.



## Bayer HealthCare

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Made in Germany

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04298184 11/06 ©2006 Bayer Pharmaceuticals Corporation 13116 Printed in USA

**FDA Advisory Committee Briefing Document  
Safety Update  
Prepared by the Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
August 21, 2006**

**Trasylol® (aprotinin injection)  
NDA # 20-304; Sponsor: Bayer Pharmaceuticals Corporation**

**Contents**

	<i>Page</i>
<b>1. Executive Summary</b>	<b>2</b>
<b>2. Appendix: publications</b>	<b>11</b>
<b>3. Topics for committee questions</b>	<b>54</b>
<b>4. Trasylol Package Insert</b>	<b>55</b>

## Executive Summary

### *Introduction*

Trasylol is an intravenously administered proteinase inhibitor drug manufactured from bovine lung. Trasylol has anti-fibrinolytic properties and was initially approved in the United States in 1993 for use among certain patients undergoing coronary artery bypass grafting (CABG). The drug dosage is stated in terms of "KIU" or kallikrein inhibitor units. Notable drug labeling supplements to the application were approved in 1994 and 1998.

Trasylol is approved "for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery."

This Advisory Committee meeting is convened to discuss published clinical data and recently submitted safety information pertaining to the risks and benefits of Trasylol. Specifically, the following topics are the focus of the meeting:

- The findings from two publications of observational clinical studies that assess Trasylol effects.
  - Mangano, D., et. al. The Risk Associated with Aprotinin in Cardiac Surgery. *New England Journal of Medicine*. 354(4):353-65; January, 2006.
  - Karkouti, K., et. al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion*. 46(3): 3:327-38; March, 2006.
- Post-marketing reports of hypersensitivity reactions to Trasylol.

These topics are presented for discussion in order to optimize the usage of Trasylol through potential label modifications or other regulatory mechanisms, including the collection of additional clinical data.

At the Committee meeting, the published clinical data will be presented and discussed by the publication authors. It is important to note that the publication authors assume responsibility for the accuracy, integrity and interpretation of the published clinical data. Hence, the potential strengths and limitations of this type of information should be considered during any evaluation of its usage for regulatory considerations.

The post-marketing reports of hypersensitivity reactions to Trasylol consist of sponsor-verified clinical data submitted to the Trasylol drug application, via submissions consistent with routine post-marketing safety reporting to the FDA.

### *Trasylol Regulatory History*

Summarized below are the most notable aspects of the FDA regulatory actions regarding Trasylol.

#### **1. Original approval: 1993**

FDA approved Trasylol in December, 1993 for the relatively limited indication of:

"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 grafting (CABG) surgery. Trasyolol is also indicated in selected cases of primary coronary bypass graft surgery where the risk of bleeding is especially high (impaired hemostasis, e.g., presence of aspirin or other coagulopathy) or where transfusion is unavailable or unacceptable. This selected use of Trasyolol in primary CABG patients is based on the risk of renal dysfunction and on the risk of anaphylaxis (should a second procedure be needed)."

This approval specifically cited the use of "Regimen A" in the dosage and administration section of the label. Regimen A has subsequently been referred to as "full dose" or the "high dose" regimen. Regimen A consists of a 1 mL test dose (10,000 KIU), a loading dose of 2 million KIU, a "pump prime" dose of 2 million KIU and an intra-operative constant infusion dose of 500,000 KIU/hr.

In support of the original approval, the sponsor submitted clinical data from two confirmatory clinical studies conducted among patients undergoing CABG along with a supportive clinical study that examined the use of Trasyolol among patients undergoing cardiac valvular surgery. In addition to "Regimen A," these studies also used a Trasyolol "Regimen B" which has subsequently been referred to as "half dose" or "low dose" regimen. Regimen B consists of exactly one-half the dose of Regimen A, following the test dose (ie., 1 million KIU loading dose, 1 million KIU pump prime dose and a constant intra-operative infusion at 250,000 KIU/hr).

The studies supporting the original approval are summarized in Table 1.

**Table 1. Studies submitted in support of the original approval**

Study #	Design	Safety n	Regimen	Control	Procedure
D-89-004	R, DB, SC	171	A & B	Placebo	Repeat CABG
D-89-005	R, DB, MC	212	A & B	Placebo	Valvular surgery
D-89-006	R, DB, MC	216	A only	Placebo	Primary and repeat CABG

R = randomized; DB = double blind; SC = single center; MC = multi-center

In the two CABG studies, fewer patients receiving Trasyolol required any donor blood when compared to patients receiving placebo. In general, the risk for use of donor blood was reduced by half subsequent to the administration of Trasyolol. The major efficacy findings for the groups of subjects undergoing repeat CABG are shown in Table 2.

**Table 2. Major efficacy findings in support of the original approval: comparison of the numbers of patients who required donor blood transfusion**

Study	Regimen A	Regimen B	Placebo
D-89-004	22/53 (42%)*	23/49 (47%)*	40/52 (77%)
D-89-006	7/23 (30%)*	not studied	23/32 (72%)

\*p ≤ 0.002 compared to placebo

Except for renal data, the safety data generally showed similar adverse event rates among the study groups, including mortality rates. The findings were notable for the observation that 3% of patients experienced "kidney failure" following Trasyolol administration while "kidney failure" was reported for 1% of placebo patients. The incidence of "renal dysfunction" was also increased among patients receiving Trasyolol when compared to placebo (23% versus 12%). However, the available data supported a determination that the renal dysfunction was reversible.

The original approval findings also included the following observations that were included within the product label:

-An increase in the risk for both renal failure and mortality was detected in a case-controlled clinical study that examined Trasylol use among patients undergoing hypothermic circulatory arrest.

-Trasylol had been found to prolong the activated clotting time (ACT) as measured by the Hemochron method; hence the original review concluded that heparin administration during bypass surgery should be based upon ACT findings from a method that was not altered by the presence of Trasylol in the circulation.

-Although no anaphylactic reactions were reported in the initial confirmatory clinical studies, anaphylactic reactions had been reported in non-USA postmarketing experience for Trasylol.

At the time of the original Trasylol approval in 1993, FDA cited the potential therapeutic advance associated with the use of a drug that decreases the need for blood transfusion, especially in light of considerable concern regarding the infectious risks associated with allogeneic blood. Specifically, the FDA press release noted: "Aprotinin can reduce the risks of bypass surgery for some patients," said FDA Commissioner David A. Kessler, MD. "Fewer transfusions mean a much lower risk of infection or possible adverse reactions to the blood." Notably, donor blood HIV-antibody testing was initiated in 1985; hepatitis C antibody testing in 1990 and HIVp24 antigen testing in 1995.

## **2. Additional Dosage Regimen Supplement Approval: 1994**

In 1994, the sponsor submitted clinical data from Study D-92-008 in order to support the inclusion of Regimen B within the label's dosage section. This study was a randomized, double-blinded, placebo-controlled study that examined Trasylol usage among patients undergoing repeat CABG. Three Trasylol dose regimens were examined: Regimen A, Regimen B and a "pump prime only" regimen that consisted of a dose of 2 million KIU added to the pump-prime only. Overall, 287 patients were enrolled and evaluated for safety. The efficacy evaluation was confined to 254 patients. The safety and efficacy findings for Regimens A and B were similar to those detected in the earlier confirmatory clinical study that examined these dose regimens. The "pump prime" regimen did not demonstrate efficacy. Based upon this second confirmatory clinical study's findings, the product label was modified to cite the option of either Regimen A or B as an acceptable Trasylol dosage.

## **3. Broadened Indication and Additional Clinical Data Supplement Approval: 1998**

In 1996, the sponsor submitted clinical data from three new confirmatory clinical studies in order to support a change in the product label's indication to cite the use of Trasylol among "patients undergoing cardiopulmonary bypass in the course of CABG surgery." This proposal was to broaden the indication to include all patients undergoing cardiopulmonary bypass for CABG, not solely use among patients undergoing repeat CABG or patients at high risk for bleeding during primary CABG surgery. Table 3 summarizes the three prospective clinical studies submitted in support of the new indication.

**Table 3. Studies initially submitted in support of the broader indication**

Study #	Design	safety n	Regimen	Control	Procedure
D-91-007	R, DB, SC	99	A & B	Placebo	Primary or repeat CABG
D-92-016	R, DB, MC	704	A, B, pump only	Placebo	Primary CABG
D-92-048	R, DB, MC	873	A	Placebo	Primary CABG

R = randomized; DB = double blind; SC = single center; MC = multi-center

In addition to these prospective studies, the submission included a report from a retrospective study (Study 25504) that reported Trasylol hypersensitivity findings from a group of 387 patients with at least two Trasylol exposures.

**Study D-91-007** was a pilot, pharmacodynamic study performed at a single clinical site. Hence, this study was regarded as supportive to the other, more informative clinical studies. The study findings supported the efficacy of Trasylol in reducing blood transfusion requirements.

**Study D-92-016** randomized patients with a broad risk of bleeding among placebo and three Trasylol dose regimens. In the study, patients were stratified at randomization based upon the risk for bleeding (high versus low, with predefined risk factors for bleeding) and on the perceived risk for perioperative myocardial infarction (high or low, with predefined criteria). Table 4 shows the major efficacy findings.

**Table 4. Study D-92-016 efficacy**

Variable	Regimen A n = 160	Regimen B n = 168	Pump Prime n = 159	Placebo n = 157
% requiring blood	33%	35%	33%	52%
Blood units, range	0 - 8	0 - 6	0 - 7	0 - 21

A notable Study D-92-016 observation was the finding that, among the 25% of patients at low risk for bleeding, no statistically significant difference was noted among the groups for the percentage of patients requiring blood transfusion.

Study D-92-016 safety findings showed a slight numeric excess in the rates of myocardial infarction, as denoted by the site investigators (Regimen A 5%; Regimen B 3%; Pump prime 5% and placebo 2%). A blinded adjudication of the myocardial infarction clinical data found only a numeric excess of infarctions in the pump prime group. The rates of post-operative serum creatinine elevations were similar among the study groups.

**Study D-92-048** was an international study that randomized primary CABG patients with a broad risk for bleeding to either placebo or Trasylol Regimen A. The study assessed a primary endpoint of saphenous vein graft patency rates as determined by post-CABG coronary arteriography and a secondary endpoint comparison of donor blood transfusion requirements.

The study's primary endpoint result showed more patients with graft closure in the Trasylol group (15%) than in the placebo group (11%). However, the rates for myocardial infarction were similar (Trasylol 2.9% and placebo 3.8%) as were the death rates (Trasylol 1.4% and placebo 1.6%). Exploratory analyses showed the higher rates for graft occlusion were evidenced only at the non-USA sites.

The study showed a statistically favorable effect of Trasylol upon the need for blood transfusion (38% versus 54%) with the treatment effect evident in the subsets of patients either at high or low risk for bleeding.

Study D-92-048 safety findings revealed similar rates of adverse events between the Trasylol and placebo study groups, including similar rates of renal dysfunction.

**Study 25504**, the retrospective clinical study, suggested that the risk for anaphylaxis was 5% if the re-exposure occurred within six months of the initial exposure. The anaphylaxis risk was 0.9% per re-exposure if the re-exposure occurred after six months. Multiple re-exposures appeared to incrementally increase the risk for anaphylaxis.

- - -

Following review of the clinical data from the three prospective clinical studies and the one retrospective clinical study, FDA issued a non-approvable letter for the supplemental application. The basis for this action related to the following observations: inconsistent primary endpoint subset findings in Study D-92-016; concern regarding the risk for anaphylaxis if patients had received Trasylol at primary CABG but subsequently required Trasylol at a repeat CABG; and study of only the Regimen A in Study D-92-048.

Subsequently, the sponsor highlighted data from two additional clinical studies (Studies SN0406 and SN0407 and submitted an exploratory reanalysis of Study D-92-048 and a proposal to add a black box warning to the product label regarding the risk for anaphylaxis. The additional clinical data included findings from 152 patients at low risk for bleeding who were undergoing primary CABG. Both studies demonstrated a reduction in the need for blood transfusion among patients receiving Trasylol (only the Regimen A was examined). The exploratory re-analysis of Study D-92-048 focused upon subsets of patients identified according to low risk for bleeding as well as USA versus non-USA sites.

FDA determined that the totality of the clinical data, in combination with the revision of the product label to include a black box warning regarding anaphylaxis was acceptable and the supplement was approved in August, 1998. This approved indication is the currently marketed indication.

### ***Publications and Updated Safety and Efficacy Information***

#### **1. Publications, including FDA Comments:**

Summarized below are highlights from 2006 publications and FDA public comments. Copies of the publications are provided in the Appendix. Some of these publications cite the use of tranexamic acid and aminocaproic acid, two drugs with anti-fibrinolytic activity. These two drugs are not FDA-approved for use during cardiac surgery. The FDA-approved indications for these two drugs are the following:

-Tranexamic acid: for use "in patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction."

-Aminocaproic acid: for "enhancing hemostasis when fibrinolysis contributes to bleeding."

Also included in the appendix is an abstract publication of an on-going clinical study that compares the usage of aprotinin to aminocaproic acid and tranexamic acid (the BART

study, "Blood conservation using antifibrinolytics: randomized trial in high-risk cardiac surgery"). Only summary (non-comparative) information is available from this study.

**New England Journal of Medicine publication:** In January, 2006 Mangano, et.al. published a report of a multi-center observational clinical study that compared the use of aprotinin to the use of two other drugs with anti-fibrinolytic activities (aminocaproic acid and tranexamic acid) as well the use of no anti-fibrinolytic drug. In this study, 4374 patients undergoing coronary revascularization were assessed following the assignment of each patient to the physician-prescribed anti-fibrinolytic drug regimen (patients were not randomized to the study drugs or the no drug regimen). In order to adjust for imbalances in baseline characteristics, the study authors used propensity-adjustment methodology in multivariable logistic regression analyses of important study outcomes among the study groups. The authors reported that, for patients undergoing "complex" or primary coronary artery surgery, aprotinin administration was associated with a doubling in the risk of renal failure requiring dialysis. Additionally, aprotinin administration to patients undergoing primary coronary artery surgery was associated with a 55 percent increase in the risk of myocardial infarction or heart failure and a 181 percent increase in the risk of stroke or encephalopathy. All three anti-fibrinolytic drugs were reported to reduce blood loss.

**Transfusion publication:** In March, 2006 Karkouti, et.al. published (following an earlier, on-line publication) a report of a single center observational clinical study that compared the use of aprotinin to tranexamic acid among high-transfusion risk patients. In this study, patients undergoing cardiac surgery with cardiopulmonary bypass were assessed following the assignment of each patient to the physician-prescribed anti-fibrinolytic drug (as in the prior publication, patients were not randomized to the study drugs). Using propensity scores, 449 patients who received aprotinin were matched to 449 patients who received tranexamic acid. The study reported that all adverse events occurred at similar rates, except for renal dysfunction which occurred in 24% aprotinin-exposed patients and 17% tranexamic acid patients.

**FDA comments:** In February, 2006 FDA issued a Public Health Advisory regarding Trasylol. In this Advisory, FDA anticipated a public discussion of the publication findings and also recommended that physicians who use Trasylol should:

- carefully monitor patients for the occurrence of toxicity and report important findings to the drug manufacturer and FDA;

- consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

## **2. Updated Safety and Efficacy Information:**

Bayer, the holder of the Trasylol NDA has submitted updated safety and efficacy information pertaining to Trasylol clinical studies and post-marketing reports. This information, submitted over the past few months, includes integrated analyses from the world-wide safety experience in cardiac surgery as well as clinical study experience for the use of Trasylol in the prevention of bleeding associated with non-cardiac surgery. Bayer will summarize these findings at the Advisory Committee meeting and the details are not repeated here. Cited below is a brief summary of the sponsor's findings with a special notation regarding hypersensitivity reactions.

**Integrated safety and efficacy information:** Overall, the sponsor's updated analyses of safety and efficacy findings from the controlled clinical trial experience generally appear consistent with the previously reported findings.

The integrated efficacy analyses continue to show that TrasyloI administration decreases the rate of blood transfusion among patients undergoing CABG with cardiopulmonary bypass.

Notable summary findings from the updated and integrated safety findings of the controlled clinical studies are:

- The studies show similar mortality rates between control patients and patients receiving TrasyloI during CABG (2.9% among 2249 TrasyloI patients and 2.5% among 2164 control patients). In this patient population, congestive heart failure rates are also reported as similar (6.3% among TrasyloI patients and 5.9% among placebo patients).
- Myocardial infarction rates in the clinical studies that rigorously ascertained the events showed similar rates (11% among 642 TrasyloI patients and 11% among 656 placebo patients).
- Analyses indicate no increase in the incidence of serum creatinine elevations with low-dose TrasyloI versus placebo. However, the analyses did show an increased incidence of creatinine elevations with full-dose TrasyloI when administered in the presence of peri-operative aminoglycosides (18% of 111 TrasyloI patients and 9% of 117 placebo patients).
- Analyses disclose very limited controlled clinical study data for patients with baseline serum creatinine values greater than 2 mg/dL (only 9 patients exposed to TrasyloI versus 1 placebo patient).

**Hypersensitivity reactions:** The sponsor has supplied a summary of TrasyloI-related hypersensitivity reports from 1984 through 2005. This analysis found a higher than anticipated reporting rate for reactions during 2005. Using Poisson analysis and estimates of product usage, the sponsor reports that spontaneous reports of hypersensitivity reactions increased from 2004 (21/409,783) to 2005 (54/471,922). This increase was mainly driven by an increase in the reporting rate of possibly associated non-fatal cases from the US. However, the number of reports of fatal hypersensitivity reactions increased from 4 in 2004 to 10 in 2005.

FDA has special concerns regarding the findings from the sponsor's summary of hypersensitivity reactions. These concerns relate specifically to the occurrence of fatal hypersensitivity reactions as well as to concerns regarding the utility of the "test" TrasyloI dose procedure in light of the apparent failure to predict fatal hypersensitivity reactions. Notably, this test dose administration alone was reported to result in 19 deaths (included among a total of 51 deaths associated with TrasyloI hypersensitivity reactions).

In response to the hypersensitivity reports, the sponsor has proposed a risk minimization plan that focuses upon additional physician education and outreach efforts regarding the risk for hypersensitivity reactions, specifically encouraging more in-depth history taking regarding any prior exposure to aprotinin. Additionally, Bayer proposes the development of a blood test for the detection of IgG antibodies to aprotinin. This test is proposed for use as a biomarker to detect patients who had previously been exposed to aprotinin. The blood test is currently in a developmental stage.

Summarized below are major observations regarding Trasylol hypersensitivity findings:

**Incidence:** The sponsor estimates a total exposure of 4.3 million patients to Trasylol from 1984 through 2005. To date, 304 cases of suspected hypersensitivity reactions were identified within the sponsor's global drug safety database. Independent adjudication of these 304 cases estimated that 284 of the cases were hypersensitivity reactions possibly associated with Trasylol (51 were fatal and 233 were non-fatal).

**Risk factors:** Given the limitations of the case reports, the following observations are especially notable:

- 133/284 (47%) cases had documented previous exposure to Trasylol; of the 51 fatalities that were adjudicated and assessed as possibly associated, previous aprotinin exposure could be documented in 28 cases.

- 90/107 (84%) cases in which the time of previous exposure was documented had received the drug in the previous six months.

- 38/139 (27%) cases in which the test dose administration was documented experienced a hypersensitivity reaction despite a negative test dose result.

- the majority of cases in which the surgical procedure was documented were in the setting of procedures other than CABG surgery.

- aprotinin is contained with certain fibrin sealants, including Tisseel®, a product marketed in the US with an indication for "use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligation, and cautery is ineffective or impractical."

A publication that cites a summary of 124 hypersensitivity reactions is included in the appendix. This publication cites several risk factors for hypersensitivity reactions, including ones similar to those the sponsor has identified. The publication authors propose that the risk for a hypersensitivity reaction is greatest within the first several months following an initial aprotinin exposure, as shown in the figure, below. In the figure, the number of hypersensitivity reactions is shown on the vertical axis and the time span between repeated aprotinin injections is shown on the horizontal axis.

The publication also outlines the concepts that suggest the detection of IgG antibodies to aprotinin may serve as a biomarker for prior exposure. The publication notes that the low concentration of IgE, as well as its relatively short half-life, may limit its usefulness in an assay that attempts to detect prior aprotinin exposure.

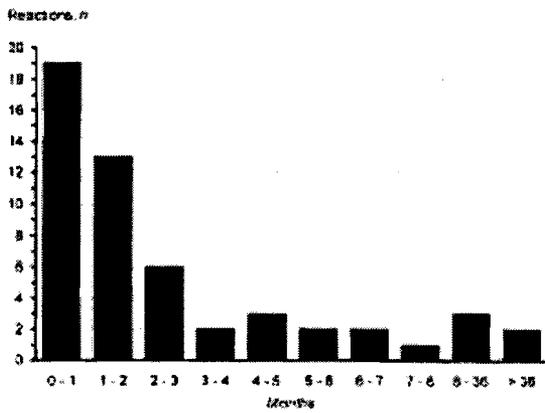


Fig 2. Time spans between repeated apotinin exposures.

**Test dose considerations:** The product label cites the intravenous administration of a 10000 KIU (1 mL) intravenous "test dose" at least 10 minutes prior to the loading dose. The label notes that hypersensitivity reactions can range from skin eruptions, itching, dyspnea, nausea and tachycardia to fatal anaphylactic shock and physicians are to observe patients for the appearance of these signs and symptoms. To date, 19 patients are reported to have died after administration of the test dose alone.

## Appendix: Publications

1. Mangano, D., et.al., The Risk Associated with Aprotinin in Cardiac Surgery. *New England Journal of Medicine*. 354(4):353-65; January, 2006.
2. Karkouti, K., et. al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion*. 46(3): 3:327-38; March, 2006.
3. FDA Public Health Advisory, February, 2006.
4. Beierlein, W. Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Annals of Thoracic Surgery*; 79:741-8; 2005.
5. Fergusson, M., et.al, Incidence of massive bleeding in a blinded randomized controlled trial of antifibrinolytic drugs in high risk cardiac surgery. *Anesth Analg*. 102: SCA1-97; 2006.

## **Topics for Committee Questions**

FDA anticipates posing questions relating to the following major topics:

1. An assessment of the clinical meaningfulness of the findings from the two published observational clinical studies.
2. Perspectives regarding the clinical benefit associated with a reduction in the need for blood transfusion among patients undergoing cardiac bypass grafting, especially in light of current surgical procedures and transfusion practices.
3. Perspectives regarding the occurrence of hypersensitivity reactions and the options to lower the risk for these reactions.
4. Considerations of potential product label alterations, or other options, to address safety and/or efficacy concerns, in light of current surgical and transfusion practices.

## Summary of 2006 Advisory Committee Responses to Questions

### Questions to the Committee:

1. (Safety) Discussion: Published reports (Transfusion 2006; 46:327-38; NEJM 2006; 354:353-65) and an updated Bayer safety review are generally consistent in the detection of an increased risk for renal dysfunction following aprotinin administration. However, the NEJM report described several other serious risks associated with aprotinin.

Please consider the conclusions from the publications and from Bayer's controlled clinical studies and discuss whether Trasylol usage, compared to no hemostatic therapy, is associated with increased risks for the following serious adverse events:

- Renal failure requiring dialysis
- Myocardial infarction
- Heart failure
- Stroke or encephalopathy

In your discussions, please comment upon whether any increased risks apply only to specific subsets of CABG/CPB patients; for example, patients undergoing repeat CABG versus initial CABG.

*The committee agreed that the data are consistent with an association with aprotinin use and renal impairment, specifically for an increasing creatinine, however, most of the committee were not convinced that there was a definite increased risk of renal failure requiring dialysis. The committee also agreed overall that there was no association between aprotinin use and an increased risk of myocardial infarction, heart failure, stroke or encephalopathy. Additionally, the committee commented that these are short-term outcomes and we currently have little or no data on the long-term cardiovascular outcomes in these patients.*

*In terms of subgroup risks, some committee members suggested that the risk-benefit is most favorable in those highest risk patients such as those on anti-platelet therapy or who are undergoing complex surgery. The committee also point out, when discussing increased risks, that these are increased risks compared to no treatment or placebo, and not increased risk compared to other agents. The committee additionally cited the fact that the available data indicate there is no improvement in mortality with aprotinin use.*

*(See transcripts for detailed discussion)*

2. (Safety) Discussion: The identification of patients at high risk for Trasylol hypersensitivity reactions predominantly involves ascertainment of a history of any prior aprotinin exposure and the use of a "test dose" procedure. Bayer has proposed a risk minimization program focused upon healthcare provider education and the possible use of an IgG assay to detect prior aprotinin exposure. Please discuss the strengths and limitations of these procedures. In your discussion, please consider the following questions:

- a. To what extent do you regard these procedures, especially the use of a "test dose," as acceptable measures to identify patients at high risk?

#### *Test Dose:*

*The committee highlighted that nearly half of the reported patients with hypersensitivity reactions had reactions with the test dose alone. Some of the committee found little predictive value in the 'test dose' as a useful screening tool for identifying patients at high risk. Concerns raised included usage in non-cardiac settings such as hip replacement surgery, where CPB is not readily available to resuscitate the patient should a reaction occur. Recommendations were made to rename 'initial dose' as opposed to 'test dose' to alleviate any possible false sense of security in implementing this drug therapy.*

*Many other members of the committee, however, found the test dose of value, cautioning against any decision to abandon the test dose altogether. They emphasized its value, specifically in the surgical setting when given slowly enough to recognize early hypersensitivity signs [hypotension] and where CBP is readily available for rescue/resuscitation.*

*IgG Assay:*

*The committee recognizes that the IgG assay is a work in progress, but many found promise in the Sponsor's RiskMAPP for an IgG assay for identifying high risk patient. The committee applauded the sponsor on their efforts to exclude patients from aprotinin treatment, who would screen positive. An assay with a good negative predictive value would be beneficial as a screening tool, as long as it is coordinated and monitored closely in conjunction with the FDA, (i.e. defining under what clinical situations the assay should be used and how to interpret assay data). The assay should be tested extensively before recommended for routine clinical use.*

*Education:*

*The committee emphasized the need for education on having CPB rescue readily available for resuscitation. Concern was raised, though, in the complete reliance of using the medical history to identify high risk patients for a hypersensitivity reaction, as cases have been cited where such efforts failed to uncover a previous exposure to the drug.*

b. Please discuss whether the risks and consequences of hypersensitivity differ for subsets of patients; for example, patients undergoing repeat CABG versus initial CABG? Are the risks sufficiently high for some subsets of patients such that Trasylol should not be administered? If so, which types of patients?

*The committee had limited comments or recommendations on singling out subgroups that may be at higher risk for hypersensitivity reaction. Those 'redo' CABG patients, especially those within 6 months of originally surgery, were identified as a higher risk of hypersensitivity reaction. An additional suggestion was made for a national registry of patients who have received aprotinin, as a safety measure in identifying patient exposure to the drug.*

*(See transcripts for detailed discussion)*

3. (Efficacy) Discussion: Since Trasylol was originally approved in 1993, allogeneic blood transfusion practices in CABG surgery may have changed due to the wider use of autologous blood and changes in the clinical criteria for transfusion. Please discuss the importance of the Trasylol benefit of reduced perioperative bleeding and the need for blood transfusions, in the context of current cardiovascular surgical, anesthetic and blood transfusion practices.

*A majority of the committee agree that patients that present for surgery today are even sicker than in the past, with proportionally more patients on anti-platelet therapy, re-operations, transplants, etc. The committee agreed that the need for a reduction in perioperative bleeding is as great as or greater than when the drug was first approved. The committee also cited that we have better transfusion practice and safer blood products today than in the past.*

*The committee recognized, though, that there should be caution in not routinely using the drug for everyone but rather, selecting out those patients [high risk] who will benefit the most from it. Recommendations were made for a guideline/consensus paper on the topic for future practice, in addition to the use of databases to pull information.*

*Recommendations were made that, because there is limited current and long-term data, Bayer should be encouraged to sponsor such prospective studies to gather this information. Others encouraged smaller trials and observational datasets to gather additional information about patient populations, drug usage and outcomes.*

*(See transcripts for detailed discussion)*

4. (Safety and Efficacy) Bayer Pharmaceuticals has proposed modification of the Trasylol indication statement to the following: "Trasylol is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at increased risk for blood loss and blood transfusions."

a. Discussion: Please discuss the clinical considerations in identifying patients "who are at increased risk for blood loss and blood transfusion." For example, should this descriptor only apply to patients undergoing repeat CABG?

*A suggestion was made to change the language from 'at increased risk' to 'at high risk' because this raised the question of increased risk compared to who? The majority of the committee cautioned in limiting usage to those patients undergoing repeat CABG. While there was discussion to expand the label to include other forms of cardiac surgery, there were no data to support any changes in the current label in terms of expanding aprotinin use to other forms of surgery.*

b. Vote: Highlights of Bayer's recent safety and efficacy data submissions to the FDA were presented at this meeting along with findings from two publications. FDA review of these data is on-going and may be importantly impacted by further analyses or additional information submitted to the Trasylol NDA. Nevertheless, the Committee's perspectives regarding the highlighted data will form an important component of the on-going FDA review. Based upon the presentations today, do you regard the totality of clinical data as supporting acceptable safety and efficacy for Trasylol usage among certain CABG/CPB patients?

YES: 18

NO: 0

ABSTAINED FROM VOTING: 1

c. Discussion: If your response to "b" is yes, please identify those patients in which the safety and efficacy data sufficiently support Trasylol usage. Specifically, does this population include the proposed CABG/CPB patients "who are at increased risk for blood loss and blood transfusion?"

*Many of the committee members found the label language accurate. Most of committee agreed that there should be limited restriction in the language, for the use of the drug in repeat CABG patients, leaving these clinical decisions to the surgeon.*

*Labeling language was recommended that in addition to an 'increased risk of blood loss/blood transfusion' there should be language such as 'factors that put you at increased risk for the drug.'*

*The committee cited, as examples of those patients who at increased risk of blood loss/blood transfusion, those on anti-platelet therapy; redo CABGs; valve/transplant patients; uremic patients; and patients who are on nephrotoxic drugs.*

*Committee recommendations for package labeling included comments that there was no demonstration that aprotinin improves mortality (i.e. no data on improved outcome). Opinions varied however upon the appropriateness of including this type of "no mortality effect" statement in the product label.*

*Additionally, comments regarding the uncertainty about the value of the 'test dose' should be reflected in the package label (i.e. recommendation that a test dose be given in the complete absence of any data about patient history).*

d. Discussion: If your response to "b" is no, please provide recommendations regarding ways to obtain sufficient safety and efficacy data for Trasylol usage. For example would additional controlled clinical studies in specific CABG patients assist in more thoroughly assessing Trasylol risks and benefits?

*One committee member abstained from voting, citing the limited data available to accurately identify who is at high risk for bleeding, which requires more research, and that a decision analysis regarding treatment versus no treatment is dependant upon that information. None of the committee voted 'No' to this question.*

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PID#** PID# D060185

**DATE:** June 1, 2006

**FROM:** Parivash Nourjah, Ph.D. Epidemiologist  
Division of Drug Risk Evaluation, HFD-430

**THROUGH:** Rosemary Johann-Liang, M.D.  
Deputy Director,  
Division of Drug Risk Evaluation, HFD-430

**TO:** George Mills, M.D., Director  
Division of Medical Imaging and Hematology Products, HFD-160

**SUBJECT:** A critique of study methodology of two recently published observational papers on the safety of aprotinin (Trasylol®) NDA# 20-304

**EXECUTIVE SUMMARY**

Two recently published observational studies, by Mangano et al and by Karkouti et al, reported aprotinin to be associated with risk of renal dysfunction. Mangano et al also found that aprotinin is associated with myocardial infarction and heart failure. Both studies used propensity score modeling to adjust for certain potential confounders. The reliability of the results by Mangano et al can not be assured because the authors failed to provide evidence that:

- (1) the propensity score model balanced covariates among treatment groups,
- (2) there is no effect of geographic region, and
- (3) missing values do not have a substantive impact on treatment effect.

In contrast, the report by Karkouti et al discussed most of the sources of potential biases in their study, although it is not clear what variables were considered in their final propensity model.

Despite these limitations, these independent studies reporting from independent patient populations provide a compelling argument for a primary association between aprotinin and renal dysfunction. This association is further advanced by publication of a meta-analysis of clinical trials. On the other hand, the association between aprotinin and myocardial infarction and/or heart failure remains speculative at this time.

At this time, DDRE recommends HFD-160 consider additions to the approved labeling for aprotinin to highlight the association between aprotinin and renal dysfunction pending results of randomized, double-blinded trials. An analysis of spontaneously reported adverse events with aprotinin and renal dysfunction are underway in our division (review to be provided under a separate cover). Although assessment of this drug-adverse reaction association will be difficult based upon the AERS database alone, the case-review study might provide some insight about these associations.

### **Introduction**

Two recently published studies reported on the risk of aprotinin use among cardiac surgery patients. The first article, entitled *The risk associated with aprotinin in cardiac surgery*<sup>1</sup> was conducted by Mangano et al and was published in **New England Journal of Medicine** on January 26, 2006. In their analysis, Mangano et al, reported that treatment with aprotinin treatment (See relevant current product labeling for aprotinin: Appendix 1) in the setting of primary cardiac surgery was associated with an increased risk for a renal event (odds ratio (OR) = 2.3; 95% CI 1.3 to 4.3) compared to exposure to no antifibrinolytic therapy. The odds ratio for a renal event increased to 2.6 (95% CI 1.4 to 5.0) when stratified to patients undergoing complex cardiac surgery. Mangano et al further reported that treatment with aprotinin in the setting of primary cardiac surgery to be associated with an increased risk relative to no antifibrinolytic therapy treatment for a cardiovascular event (OR=1.4) and a cerebrovascular event (OR=2.2). These point

estimates decreased and lost statistical significance when stratified to patients undergoing complex cardiac surgery.

The second study entitled, *A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery* was conducted by Karkouti et al and published in the March 2006 issue of **Transfusion**. These authors compared treatment with the antifibrinolytic agent tranexamic acid to aprotinin in the setting of cardiac surgery and reported treatment with aprotinin to be associated with a 1.4-fold increase ( $p=0.01$ ) in the risk for renal dysfunction.

In light of these publications, FDA issued the following "Public Health Advisory" on February 8, 2006 (Appendix 2)

This consult follows a request made by the Division of Medical Imaging and Hematology Products to provide a critique of the studies cited above. Below, we provide a brief description of each study's methodology followed by DDEE comments regarding the study methodology and analysis. Please note that this document is limited in its review scope to design and analytical aspect of the study.

#### **Overview of the article by Mangano et al**

##### **Methods**

Mangano and et al studied the risk of thrombosis-related cardiac, cerebral, and renal events associated with antifibrinolytic therapy by using data from 5436 patients scheduled for coronary-artery bypass surgery with cardiopulmonary bypass. After reviewing the medical records of patients, they excluded 1053 patients from study for the following reasons: withdrew from study before surgery (32), died before surgery (2), did not undergo surgery or surgery was rescheduled (97), did not undergo cardiopulmonary bypass (132), were enrolled in another clinical trial (11), had incomplete data (97), received multiple antifibrinolytic agents (226), had no validation of drug type or dose (17), received inadequate dose of antifibrinolytic agents (448). The remaining 4373 patients

were classified into four comparison groups: 1295 patients with exposure to aprotinin, 883 to aminocaproic acid (Appendix 1), 882 to tranexamic acid (Appendix 1), and 1374 to control (patients who did not receive antifibrinolytic treatment). The outcome events in each antifibrinolytic treatment group were then compared to control patients.

The investigator examined four outcomes : (1) *cardiovascular* defined as Myocardial infraction required either new Q waves (Minnesota code 1-1-1 or 1-2-7) or new, persistent ST-segment or T-wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2). Heart failure defined as a cardiac output of less than 2.0 liters per minute associated with a pulmonary-artery occlusion pressure above 15 mm Hg, a central venous pressure above 12 mm Hg, and S gallop, or rales. (2) *Cerebrovascular* included clinically diagnosed stroke, encephalopathy, or coma. (3) *Renal* defined as a postoperative serum creatinine level of at least 177  $\mu$  mole per liter with an increase over preoperative baseline levels of at least 62  $\mu$  mole per liter. Renal failure was defined as dysfunction requiring dialysis or in-hospital death with evidence at autopsy of acute renal failure. (4) *Blood loss* was assessed as chest-tube output during the first 24 hours after surgery.

The investigator used multivariate analyses to assess the risk of each outcome associated with treatment groups by considering 97 preoperative risk factors. Investigators used nonparsimonious logistic modeling to developed propensity scores that distinguish those with exposure to antifibrinolytic treatment from control. Covariates (n=45) were considered into generating propensity scores. The effect of each agent on outcome was assessed by using multivariate logistic regression in which propensity scores as well as other risk factors. In addition, a stratified analyses was planned for patients whose elective surgery involved only coronary-artery revascularization and with no history of cardiac or vascular surgery ("primary surgery" group) versus the remaining patients, who where classified as "complex surgeries." The dose response was assessed among a subgroup of aprotinin group who received either a low-dose regimen (loading dose, 1 million kal-likrein-inhibitor units (KIU); total dose, >2 million KIU) or a high-dose regimen (loading dose, 2 million KIU; total dose, >4 million KIU).

## Results

The investigators reported that patients with exposure to aprotinin group experienced an increased risk for renal events (renal dysfunction or renal failure requiring dialysis) in both patients with primary surgery (odds ratio (OR) = 2.3 and 95% CI 1.3 to 4.3) and with complex surgery (OR=2.6; 95% CI 1.4 to 5.0). Mangano et al further reported that treatment with aprotinin was associated with an increased risk in cardiovascular events (OR=1.14) and cerebrovascular events (OR=2.2) only in patients who underwent primary cardiac surgery. These point estimates decreased and lost statistical significance in patients undergoing complex cardiac surgery. The investigators did not report treatment with either aminocaproic acid or tranexamic acid to be associated with increased renal, cardiac or cerebral events. Major results from the study are shown on the table on the following page which is excerpted from Table 3 from the article and titled, "Table 3. Propensity-adjusted Effect of Treatment on Ischemic Outcome Events."

Table 1

Outcome event comparisons	Patient Undergoing primary surgery (N=3013) <sup>†</sup>		Patients Undergoing Complex surgery (N=1361) <sup>‡</sup>	
	P Value	Odds Ratio (95% CI)*	P-Value	Odds Ratio(95% CI)
<b>Death</b>				
Aprotinin vs. control	0.22	1.59 (0.79-3.34)	0.66	0.86(0.44-1.70)
Aminocaproic acid vs. control	0.65	0.81 (0.33-2.02)	0.01	0.25 (0.09-0.72)
Tranexamic acid vs. control	0.94	1.03 (0.44-2.45)	0.13	0.49 (0.19-1.23)
Propensity score	<0.001	1.22 (1.09-1.36)	0.004	1.18 (1.06-1.32)
<b>Renal event<sup>§</sup></b>				
Aprotinin vs. control	0.006	2.34(1.27-4.31)	0.004	2.59(1.36-4.95)
Aminocaproic acid vs. control	0.86	0.93(0.43-2.02)	0.23	0.56(0.22-1.44)
Tranexamic acid vs. control	0.75	0.88(0.40-1.94)	0.33	1.47(0.68-3.19)
Propensity score	<0.001	1.19(1.08-1.30)	0.58	1.02(0.94-1.11)
<b>Cardiovascular event<sup>¶</sup></b>				
Aprotinin vs. control	0.01	1.42(1.09-1.86)	0.67	1.08(0.75-1.57)
Aminocaproic acid vs. control	0.13	0.78(0.56-1.08)	0.18	0.74(0.48-1.15)
Tranexamic acid vs. control	0.73	0.95(0.70-1.29)	0.93	1.02(0.66-1.57)
Propensity score	<0.001	1.08 (1.03-1.12)	0.16	1.04(0.99-1.09)
<b>Cerebrovascular event<sup>=</sup></b>				
Aprotinin vs. control	0.02	2.15 (1.14-4.06)	0.41	1.29 (0.7-2.35)
Aminocaproic acid vs. control	0.84	0.92(0.42-2.05)	0.07	0.45(0.19-1.06)
Tranexamic acid vs. control	0.21	1.57(0.77-3.19)	0.38	0.70 (0.32-1.55)
Propensity score	<0.001	1.19(1.08-1.30)	0.87	0.99(0.91-1.08)
<b>Composite outcome event<sup>**</sup></b>				
Aprotinin vs. control	0.002	1.49(1.15-1.91)	0.13	1.30(0.93-1.83)
Aminocaproic acid vs. control	0.28	0.85(0.63-1.15)	0.09	0.71(0.47-1.06)
Tranexamic acid vs. control	0.69	0.94(0.71-1.26)	0.44	1.17(0.79-1.73)
Propensity score	<0.001	1.09(1.05-1.14)	0.65	1.01(0.97-1.06)

\* CI denotes confidence interval  
<sup>†</sup> The control group included 1022 patients, and the antifibrinolytic group 1991 patients. Values for the propensity score were missing for 87 patients in the control group and 157 in the antifibrinolytic group.  
<sup>‡</sup> The control group included 352 patients, and the antifibrinolytic group 1009 patients. values for the propensity score were missing for 49 patients in the control group and 114 in the antifibrinolytic group  
<sup>§</sup> A renal event was defined as either renal dysfunction or renal failure requiring dialysis  
<sup>¶</sup> A cardiovascular event was defined as either myocardial infarction or heart failure.  
<sup>=</sup> A cerebrovascular event was defined as stroke, encephalopathy, or coma  
<sup>\*\*</sup> The composite outcome event category included all the other outcome event categories (death, renal event, cardiovascular event, and cerebrovascular event).

## *Comments*

*1. Study data were received from many institutions across the Middle East, Asia, Europe, and North America. The institutions or countries may have different care standards that dictate the administration of these drugs (dose and rate of infusion). In addition, the method of ascertainment of medical information may be different across institution or among countries. There is no evidence in this article that the investigators conducted an analysis based on region of participating institution.*

*2. The investigators stated that 97 variables were considered for use in the analysis. They also mentioned that 45 variables were considered for generation of the propensity score. However, the authors did not provide a list of these 97 variables nor the list of 45 variables that were considered into generating the propensity score. It is also not clear what subset variables from 45 were selected in the final model of propensity score.*

*3. To assess whether propensity scoring adjusted / balanced potential and available confounders between comparison groups, the distribution of confounding variables (covariates) between comparing groups within each propensity score strata should be examined. Mangano et al do not demonstrate or state in their article whether such an assessment was conducted and what the results were. Therefore, it is not possible to assess whether the propensity score used in this study adequately controlled for the effect of covariates on the treatment effect.*

*4. A dose response analysis is performed without consideration for the possibility of bias due to confounding by selection. While high dose may be related to the outcome event, it may also be related to some baseline characteristics of patients, and hence the result may be biased if these confounding variables are ignored. In this article, there is no indication that the investigators examined the possibility of such bias in their dose-response analysis.*

*5. 448 cases were excluded from the study population because they received inadequate dose of antifibrinolytic agents. In the published article, the investigators do not state their*

*definition of “inadequate dose” and their rationale for exclusion of these cases. It would be useful if the authors would have addressed whether these individuals have a different risk pattern than those with an “adequate” dose or if point estimates change with their inclusion, either within the control group or assignment to an exposed group.*

*6. The authors report about 10% of data fields relevant to multivariate analyses were missing. The investigators did not indicate whether they examined the impact of missing values on their results. This would be important to assess the reliability of their results.*

*7. There are some inconsistencies in presentation of the results. For example, within the ABSTRACT section, the authors state, “use of aprotinin was associated with a doubling in risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery.” However, there are no results of multivariate analyses for this outcome in the body of the paper. Another example is the heading of Table 3 - which refers to only one outcome “ischemic outcome events.” In contrast, the table contains multiple outcomes including death, renal event(s), cardiovascular event(s), cerebrovascular event(s), and composite outcomes.*

*8. There is no clear definition of what is considered to be “postoperative” outcome event (i.e. an event which develops within 24 hours of surgery, or within a week after surgery, or some other time interval).*

*9. In this article, the authors displayed the treatment effect for each treatment based on one, common propensity score ( i.e. based on a model that distinguishes probability of being assigned to any type of antifibrinolytic treatment vs. no agent). When there are more than 2 treatment groups, a different propensity score for each pair comparison should be developed. From the text, it is clear that the authors considered different propensity scores for each treatment pair comparison and similar results were found.*

## Overview of the article by Karkouti et al

### Methods

Karkouti et al conducted a matched propensity score study to examine the efficacy and risk of aprotinin in patients who underwent cardiac surgery with cardiopulmonary bypass at a single center from June 1999 to June 2004. From the baseline population of 10949 patients, 79 patients were excluded from the study because they did not receive any antifibrinolytic drugs (19) or participated in an antifibrinolytic drug trial (60). A propensity score was developed based on 586 patients who received aprotinin and 10,284 patients who received tranexamic acid. Multiple covariates were considered in the generation of the propensity score (see Comment #1). The investigators were only able to identify a matched tranexamic acid control for 449 out of the 586 aprotinin patients.

The efficacy of the treatment was addressed by the transfusion outcomes defined as the percent of patients requiring  $\geq 5$  RBC units,  $\geq 5$  FFP units and  $\geq 10$  PLT units. The transfusion outcomes also examined for those were at very high risk for massive hemorrhage: those who had two or more previous sternotomies, those in whom bypass duration was greater than 180 minutes, or those who underwent deep hypothermic circulatory arrest (DHCA) for longer than 15 minutes.

The adverse event outcomes were defined as follows: 1) Stroke defined as any new persistent postoperative neurologic deficit; 2) acute renal failure, defined as a new requirement for dialysis support; 3) acute renal dysfunction, defined as greater than 50 percent increase in creatinine concentration during the first postoperative week to more than 100  $\mu\text{mol per L}$  in men, or a new requirement for dialysis support; 4) myocardial infarction, defined as a new q wave on postoperative electrocardiogram or MB isoenzyme of creatine kinase of greater than 50 U per L, the CK-MB/CK ratio of greater than 5 percent, and new electrocardiogram changes; 5) serious infection, defined as sepsis or deep sternal infection; and 6) in-hospital death.

Results are summarized in the Table 2 (on the following page), which is excerpted from Table 4 of the article. These results suggest exposure to aprotinin to be associated with

1.4-fold increase in the risk for renal dysfunction based on comparison of incidence of 24% in the aprotinin group and 17% in the tranexamic acid groups (p=0.01). No other outcome appeared clinically significant.

Table 2

	Aprotinin (n=449)		Tranexamic acid (n=449)		P_value
	Number	Proportion	Number	Proportion	
Myocardial infarction	12	0.03	10	0.02	0.7
Stroke	15	0.03	13	0.03	0.7
Renal dysfunction	107	0.24	75	0.17	0.01
Renal failure	25	0.056	14	0.031	0.08
Serious infection	21	0.05	21	0.05	1.0
Death	30	0.07	33	0.07	0.7

Since the matching groups were not balanced in respect to recombination factor VIIa (rFVIIa) use, the investigators explored the association of renal events with aprotinin by excluding patients who received rFVIIa. Excluding these patients did not alter the result of association of aprotinin with renal function. They also examined the impact of existing renal dysfunction on the association of aprotinin use with postoperative renal function. These results (shown in Table 3 (below) which is a copy of Table 6 of the article) suggest that aprotinin use seems to be associated with worsening renal function mainly in patients with existing renal dysfunction.

Table 3

	Postoperative renal dysfunction			Postoperative renal failure requiring dialysis		
	Tranexamic acid patients	Aprotinin Patients	P-value	Tranexamic acid patients	Aprotinin Patients	P-value
All patients						
Abnormal preoperative renal function	23/126(0.18)	34/110(0.31)	0.03	8/126(0.06)	14/110(0.13)	0.1
Normal preoperative renal function	52/323(0.16)	73/339(0.22)	0.09	6/323(0.02)	11/339(0.03)	0.3
Excluding patients who received rFVIIa						
Abnormal preoperative renal function	22/124(0.18)	31/104(0.30)	0.04	7/124(0.06)	14/124(0.13)	0.07
Normal preoperative renal function	50/321(0.16)	69/333(0.21)	0.1	5/321(0.02)	10/333(0.03)	0.3

## **Comments**

1. Propensity scores were used to match aprotinin and tranexamic acid groups. No further adjustment for confounding was undertaken. It is not clear how many covariates were original candidates for calculation of the propensity score and how many were included in the final model: the authors mention 20 or 30 covariates ("variables") in different sections of their article. Also, the method by which variables were selected is not stated. For example, it is not clear whether stepwise, backward selection was performed or all variables were forced into the model.

2. Propensity score adjustment is used to reduce bias due to imbalances in covariates within observational studies. The ability of propensity scores to adequately compensate for bias depends on whether every possible and available confounding variable is considered in the analysis (whether at propensity model development or in subsequent analysis). Unobserved covariates, whether their confounding effects are not known or not collected, could still be a source of bias. Karkouti et al note that the possibility of bias due to unmeasured bias may exist in their estimates. The authors also state that several known important confounders were not collected in the course of their study, although the post hoc collection and analysis of some of these variables are shown to have similar distribution in both treatment groups (matched groups) and therefore do not appear to be potentially important confounders.

3. Most of the aprotinin subjects had their surgery during the latter part of study period compared to the matched tranexamic acid group. Since, with advancement of time, the practice of medicine and diagnostic procedure generally improves, the estimate of treatment effect in this study could have been biased if such changes influence outcome events. Karkouti et al believe if any changes have occurred in clinical practice it would most likely favor the aprotinin group. This should result in a decrease in any potential treatment effect attributed to aprotinin. Thus, the 1.4-fold difference in the risk for renal dysfunction could be an underestimate of the actual effect size.

4. 137 aprotinin treated patients could not be matched to patients who tranexamic patients and therefore the results of the study are not generalizable for all aprotinin users.

*As the authors mentioned, this study cannot address the risk or benefit associated with aprotinin among patients with high risk of hemorrhage.*

*5. Unlike Mangano et al who examined the risk profiles of aprotinin, tranexamic acid, and aminocaproic acid with patients who did not received any antifibrinolytic agent, the study by Karkouti et al does not provide any information on the risk of aprotinin compared to patients who were not treated with any antifibrinolytic drugs. There was no negative concurrent control to this study.*

### **Conclusion/Discussion**

The two articles are dense and technical. A hematologist and/or other relevant clinical specialists' review of the clinical components/conclusions would be helpful. This review is limited to an overview of the two articles with emphasis on study designs and analyses. In general, the paper by Mangano et al does not include enough information to assess the reliability of the study, particularly in respect to use of propensity score modeling. In contrast, the paper by Karkouti et al is clearer and offers a better discussion on the limitations of the results.

Despite these limitations and differences in study populations, study outcomes, and designs, both studies report that aprotinin is associated with increase risk of renal function. Karkouti et al report that aprotinin users are 1.4 times more likely to develop renal dysfunction ( $p=0.01$ ). Furthermore, aprotinin recipients were 1.8-times more likely to develop renal failure, although this association was not statistically significant ( $p=0.08$ ). Karkouti et al, however, compared aprotinin risk only with patients who received tranexamic acid treatment (a medication which is not approved by FDA for use in this setting). The study by Mangano et al does offer some insight on the aprotinin risk compared to no treatment. Their study indicated that the odds of renal event (combined renal dysfunction and renal failure requiring dialysis) in aprotinin recipients to be 2.4 times more than the odds of renal events in patients who do not receive any antifibrinolytic agents. However, no statistically different differences in risk for renal

events were reported between aprotinin users compared to recipients of tranexamic acid or aminocaproic acid. Since the multivariate analysis results reported by Mangano et al are limited to the renal composite outcome, it is not clear if aprotinin is associated with renal dysfunction alone, renal failure alone, or with both outcomes.

Individual clinical trials offer inconsistent evidence in support of any association between aprotinin and renal dysfunction. The lack of consistency could be attributed to small sample sizes and patient risk profiles (clinical trials often include lower-risk patients). Brown et al conducted a meta analysis of randomized clinical trials comparing full-dose aprotinin with placebo.<sup>3</sup> They found the combined relative risk to be 1.1 (95% CI: 0.7 to 1.8) for renal failure and 1.5 (95% CI: 1.1 to 1.9) for renal dysfunction. The analysis of the clinical trials included by Brown et al is consistent with the results of these two articles and further provides information in support of a causal association between aprotinin and risk for renal dysfunction.

In summary, two independent observational studies report an association between aprotinin and renal dysfunction. In addition, both studies describe a biological mechanism outlining biologic plausibility for this effect of aprotinin and renal. Taken together, and with further evidence provided by the Brown et al meta-analysis, these data provide a compelling argument in support of an association between aprotinin and renal dysfunction. On the other hand, in regard to cardiovascular and cerebrovascular events, the findings of these two articles are not consistent. Although Mangano et al reported an association between aprotinin and cardiovascular/cerebrovascular events, Karkouti et al did not find these associations. Without replicated and/or supportive evidence, the study by Mangano et al is insufficient at this time to provide a reliable evidence for an association between aprotinin use and cardiovascular/cerebrovascular reactions.

At this time, DDRE recommends HFD-160 consider additions to the approved labeling for aprotinin to highlight the association between aprotinin and renal dysfunction pending results of randomized, double-blinded trials. An analysis of spontaneously reported adverse events with aprotinin and renal dysfunction are underway in our division (review

to be provided under a separate cover). Although assessment of this drug-adverse reaction association will be difficult based upon the AERS database alone, the case-review study might provide some insight about these associations.

## References

1. Mangano DT, Tudor JC, Dietzel C; Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006;354(4):353-65.
2. Karkouti K, Beattie WS, Dattilo KM, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006;46(3):327-38.
3. Brown JR, Birkmeyer NJ, O'Connor GT. Aprotinin in cardiac surgery (letter). *N Engl J Med* 2006;354(18):1954-6; author reply 1954-6.

## Appendix 1

Aprotinin (Trasylol®), a serine protease inhibitor, is the only product approved by FDA for the prevention of peri-operative bleeding and the need for blood transfusion in patients undergoing cardiopulmonary bypass during coronary artery bypass graft surgery. The FDA approval date for aprotinin was Dec 29, 1993.

The most frequent adverse events reported in US clinical trials for aprotinin appeared to be cardiovascular events (atrial fibrillation, hypotension, myocardial infarction, heart failure), fever, nausea and pulmonary events (i.e. lung disorder, pleural effusion). The current product labeling for Trasylol contains a black boxed warning for anaphylactic type reactions, particularly with re-exposure. The Adverse Reactions section of the labeling mentions the following relevant adverse events related to urogenital and cardiovascular body systems (listed in order of appearance):

- Urogenital-kidney function abnormal, urinary retention, urinary tract infection, kidney failure, acute kidney failure, kidney tubular necrosis, oliguria
- Cardiovascular-atrial fibrillation, hypotension, myocardial infarction, atrial flutter, ventricular extrasystoles, tachycardia, ventricular tachycardia, heart failure, pericarditis, peripheral edema, hypertension, arrhythmia, supraventricular tachycardia, atrial arrhythmia, thrombosis, shock, cerebrovascular accident, ventricular fibrillation, heart arrest, bradycardia, congestive heart failure, hemorrhage, bundle branch block, myocardial ischemia, heart block, pericardial effusion, ventricular arrhythmia, pulmonary hypertension

With the exception of encephalopathy, the adverse events described in the Mangano publication are mentioned in the Trasylol (aprotinin) product labeling.

Tranexamic Acid (Cyklokapron® tablets and injection), a synthetic derivative of lysine, is a competitive inhibitor of plasminogen activation indicated in patients with hemophilia for short term use (2-8 days) to reduce or prevent hemorrhage and reduce need for replacement therapy during and following tooth extraction.

The Adverse Reactions section of the labeling mentions the following relevant adverse events related to thromboembolic events:

Worldwide postmarketing Reports: Thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis and central retinal artery and vein obstruction) have been rarely reported in patients receiving tranexamic acid for indications other than hemorrhage prevention in patients hemophilia.

The Precautions section of the labeling mentions that "Venous and arterial thrombosis or thromboembolism has been reported in patients treated with CYKLOKAPRON. In addition, cases of central retinal artery and central retinal vein obstruction have been

reported. Patients with a previous history of thromboembolic disease may be at increased risk for venous or arterial thrombosis.

Aminocaproic acid (Amicar® syrup, tablets and injection), another synthetic lysine derivative with lower potency than tranexamic acid, is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required. Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia, abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix.

The Warnings section of the labeling mentions that in patients with upper urinary tract bleeding, AMICAR administration has been known to cause intrarenal obstruction in the form of glomerular capillary thrombosis or clots in the renal pelvis and ureters. For this reason, AMICAR should not be used in hematuria of upper urinary tract origin, unless the possible benefits outweigh the risk.

Also the Adverse Reactions section mentions that both Cardiovascular events (Bradycardia, hypotension, peripheral ischemia, thrombosis ) and Urogenital (BUN increased, renal failure).

FDA Public Health Advisory  
Aprotinin Injection (marketed as Trasylol)

On January 26, 2006, The New England Journal of Medicine (NEJM) published an article by Mangano et al. reporting an association of Trasylol (aprotinin injection) with serious renal toxicity and ischemic events (myocardial infarction and stroke) in patients undergoing coronary artery bypass grafting surgery (CABG). Another publication (Transfusion, on-line edition, January 20, 2006, Karkouti, et al.) suggests an association between aprotinin administration and renal toxicity among patients undergoing cardiac surgery with cardiopulmonary bypass. FDA is evaluating these studies, along with other studies in the literature and reports submitted to the FDA through the MedWatch program, to determine if labeling changes or other actions are warranted.

While FDA is continuing its evaluation, we are providing the following recommendations to healthcare providers and patients:

Physicians who use Trasylol should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or central nervous system and promptly report adverse event information to Bayer, the drug manufacturer, or to the FDA MedWatch program, as described at the end of this advisory.

Physicians should consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

The study reported in the NEJM was an observational study of patients undergoing CABG who received either Trasylol, one of two other drugs intended to decrease perioperative bleeding (aminocaproic acid or tranexamic acid), or no specific drug treatment.

A limitation of the study was that patients were not assigned at random to receive the treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, patients receiving Trasylol may have been at higher risk to begin with for these serious adverse events compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility prevents a direct assessment of whether Trasylol altered the risk for serious adverse events. The study investigators used statistical procedures (multivariable logistic regression and propensity-score adjustment) to try to adjust for known differences between the treatment groups. Using these procedures, their study concluded that Trasylol was associated with more adverse outcomes. Other findings in the study suggested that patients receiving higher Trasylol dosages were at greater risk than those receiving lower dosages.

The study reported in the on-line edition of Transfusion was also an observational study that used statistical methodology to compare outcomes from patients undergoing CABG. The patients in this study received, at physician direction, either Trasylol or another drug intended to decrease the risk for perioperative bleeding. This study suggested that

## Appendix 2

Trasylol administration increased the risk for renal dysfunction. This study has some of the same limitations as the NEJM publication.

In pre-marketing clinical studies conducted among approximately 3,000 patients undergoing CABG, the risks and benefits of Trasylol were determined in clinical studies that randomized patients to either a placebo or Trasylol. In these studies, the risks for serious renal toxicity and cardiovascular events were determined to be similar between patients receiving Trasylol and those receiving placebo. However, in one study assessing coronary graft patency, Trasylol administration was associated with an increased risk of graft closure. The FDA will work with the authors of the publications and the manufacturer of Trasylol to carefully evaluate the risks and benefits associated with use of Trasylol in CABG. The FDA anticipates the public presentation of the recently reported information and other data at an advisory committee in the near future. The FDA will notify health care providers and patients in a timely fashion as new information becomes available.

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Parivash Nourjah  
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DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang  
6/5/2006 08:56:17 AM  
MEDICAL OFFICER

MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#            D060054

DATE:           July 5, 2006

FROM:           Susan Lu, R.Ph., Safety Evaluator Team Leader  
Division of Drug Risk Evaluation, HFD-430

THROUGH:      Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation, HFD-430

TO:              George Mills, M.D., Director  
Division of Medical Imaging and Hematology Products, HFD-160

SUBJECT:        OSE Postmarketing Safety Review  
Product: Aprotinin (Trasylol®)  
NDA#: 20-304  
Event(s): Renal dysfunction and Overview of AERS reporting

\*This document contains proprietary drug use data which cannot be shared outside of the FDA without clearance from the drug vendors obtained through the Office of Surveillance and Epidemiology.\*

**EXECUTIVE SUMMARY**

This consult follows a request made by the Division of Medical Imaging and Hematology Products to conduct an overview of renal events associated with aprotinin reported to the Adverse Event Reporting System (AERS) database. To contextualize the issues raised in the Mangano<sup>1</sup> and Karkouti<sup>2</sup> published observational studies, AERS crude count analyses of selected renal, cardiovascular and cerebrovascular events associated with aprotinin as compared with those associated with tranexamic acid and aminocaproic acid and an evaluation of reports of renal failure associated with aprotinin is provided.

A total of 503 crude adverse event reports associated with aprotinin were identified in the AERS database, of which 464 reports had a serious outcome including 235 deaths. The majority of reports (80%) were from domestic sources. Gender distribution was balanced with 78% of

<sup>1</sup> Mangano D, Tudor J, Dietzel C. The risk associated with aprotinin in cardiac surgery. NEJM 2006 (354):353-65

<sup>2</sup> Karkouti K, Beattie W, Dattilo K, et al, A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. Transfusion 2006;46(3):327-338

reports occurring in patients  $\geq 50$  years of age. The 20 most frequently reported events were hypotension (97), thrombosis (64), cardiac arrest (58), myocardial infarction (53), post procedural complication (52), anaphylactic reaction (40), renal failure acute (36), shock (33), renal failure (31), procedural complication (29), coagulopathy (28), pulmonary embolism (27), blood pressure decreased (24), blood creatinine increased (21) cardiac failure (20), vascular graft occlusion (20), disseminated intravascular coagulation (19), thrombocytopenia (19) and hemorrhage (18). Most of these events are expected since they are either mentioned in the product labeling or potential complications of cardiac surgery.

A comparison of AERS crude counts of renal failure and impairment (HLT), selected cardiovascular events (myocardial infarction, cardiac failure and cardiogenic shock) and CNS hemorrhages and cerebrovascular accidents (HLT) associated with aprotinin, tranexamic acid and aminocaproic acid was performed. The proportion of renal failure/impairment reports among all adverse event reports associated with each drug was 2 to 3 times higher for aprotinin compared to tranexamic acid and aminocaproic acid. Likewise, the proportion of myocardial infarction and cardiac failure reports among all adverse events reports was higher for aprotinin as well. In contrast, the proportion of cerebrovascular events for tranexamic acid was higher than aprotinin and aminocaproic acid. This comparison of AERS crude counts was performed in lieu of reporting rate comparisons because of 1) lack of accurate drug usage data for products used in surgical settings and 2) differences between these three products in regards to time on market, route of administration and indications for usage.

A data mining analysis of crude report counts in AERS comparing renal failure/impairment events for aprotinin, tranexamic acid and aminocaproic acid showed an elevated signal score for the following events for aprotinin: renal failure, acute renal failure, oliguria, renal tubular necrosis, oliguria and renal impairment. Tranexamic acid and aminocaproic acid did not demonstrate a signal for any of the aforementioned events terms. Data mining quantifies reported drug-event associations by producing a ranked set of scores which indicate varying strengths of reported relationships between drug and events. However, elevated data mining scores do not necessarily indicate causality or increased degree of risk and conversely, non-elevated scores do not preclude an increase in drug related risk.

We reviewed 82 cases of aprotinin associated renal events reported as acute renal failure (31), renal failure (26), renal impairment (12), oliguria (8) anuria (4) and dialysis (1). 80% of cases were reported from the US. The mean age of the patients was 62 years with a range of 1 to 85 years and a female predominance (64%) was observed. Fatal outcomes were reported for 39% of cases. Cases were generally not well documented with information regarding time to onset of event, cumulative aprotinin dose, laboratory data or complete medical history of patient. Patients typically had medical risk factors such as advanced age, complicated post-surgical course and co-morbidities; the most frequently reported were shock/low output syndrome (17), cardiac arrest (12), thrombocytopenic thrombotic purpura (10), thrombosis (10), diabetes (6), disseminated intravascular coagulation (4), underlying renal dysfunction (4), infection (4), cancer (4), heart failure (3) and anaphylaxis (3). Many patients had more than one risk factor for renal dysfunction. The indication for aprotinin usage was cardiac surgery in 79% of cases.

In conclusion, a comparison of crude counts of renal failure and impairment, myocardial infarction, cardiac failure and cardiogenic shock (among all adverse event reports) showed higher proportions for aprotinin when compared to tranexamic acid and aminocaproic acid. A data mining analysis showed an elevated signal score for aprotinin and renal failure, acute renal failure, oliguria, renal tubular necrosis, oliguria and renal impairment. In contrast, tranexamic acid and aminocaproic acid did not demonstrate a signal for these events terms. An analysis of S2 AERS cases of renal failure/impairment showed that many patients had either underlying risk factors or experienced concurrent events which may contribute to renal dysfunction. Admittedly, in many cases it is difficult to make definitive attributions regarding renal dysfunction either due to the complexity of the case or incompleteness of data provided, however the role of aprotinin cannot be excluded. As an association between aprotinin and renal dysfunction is suggested in two independent observational studies<sup>1,2</sup> and analysis of spontaneous reports submitted to AERS. Accordingly, we recommend revisions in labeling for aprotinin to alert healthcare professionals to the potential serious risks of renal dysfunction associated with aprotinin use.

## **BACKGROUND AND PRODUCT LABELING**

An observational study published in the New England Journal of Medicine<sup>1</sup> on January 26, 2006 reported an association between aprotinin and increased risk of renal, cardiovascular and cerebrovascular events as compared to patients who received tranexamic acid, aminocaproic acid or no treatment. Another observational study published March 2006 in Transfusion<sup>2</sup> showed that patients receiving aprotinin had a higher rate of renal dysfunction than those who received tranexamic acid. Both studies utilized propensity scoring to adjust for observed confounders in patient groups. In light of these publications, the agency posted an “Alert for Healthcare Professionals” and a “Public Health Advisory” on the FDA website to provide guidance to healthcare professionals using aprotinin. Bayer has also posted a press statement and letter to health care professionals on its websites. An Advisory committee meeting has been scheduled for September 21, 2006 to discuss this issue.

Aprotinin (Trasylol®), a serine protease inhibitor, is the only product approved by FDA for the prevention of peri-operative bleeding and the need for blood transfusion in patients undergoing cardiopulmonary bypass during coronary artery bypass graft surgery. The FDA approval date for aprotinin was Dec 29, 1993.

The most frequently reported adverse events in US placebo-controlled trials were cardiovascular events (atrial fibrillation, hypotension, myocardial infarction, heart failure), fever, nausea and pulmonary events (i.e. lung disorder, pleural effusion); the labeling states that these reported events are frequent sequelae of cardiac surgery and not necessarily attributable to Trasylol therapy. The Trasylol product labeling contains a black box warning for the risk of anaphylactic type reactions, especially in re-exposure within 6 months. The Adverse Reactions section mentions the following relevant renal and vascular adverse events:

- Urogenital-kidney function abnormal, urinary retention, urinary tract infection, kidney failure, acute kidney failure, kidney tubular necrosis, oliguria

- Cardiovascular-atrial fibrillation, hypotension, myocardial infarction, atrial flutter, ventricular extrasystoles, tachycardia, ventricular tachycardia, heart failure, pericarditis, peripheral edema, hypertension, arrhythmia, supraventricular tachycardia, atrial arrhythmia, thrombosis, shock, cerebrovascular accident, ventricular fibrillation, heart arrest, bradycardia, congestive heart failure, hemorrhage, bundle branch block, myocardial ischemia, heart block, pericardial effusion, ventricular arrhythmia, pulmonary hypertension
- Hematologic and Lymphatic: arterial thrombosis, pulmonary thrombosis, coronary occlusion, embolus, pulmonary embolus, cerebrovascular accident and cerebral embolism.

With the exception of encephalopathy, the adverse events described in the Mangano and Karkouti publications are mentioned in the Trasylol (aprotinin) product labeling.

Tranexamic Acid (Cyklokapron® tablets and injection), a synthetic derivative of lysine, is a competitive inhibitor of plasminogen activation indicated in patients with hemophilia for short term use (2-8 days) to reduce or prevent hemorrhage and reduce need for replacement therapy during and following tooth extraction. The Adverse Reactions section of the Cyklokapron product labeling includes the following information regarding renal and vascular events:

“Hypotension has been observed when intravenous injection is too rapid.... Thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) have been rarely reported in patients receiving tranexamic acid for indications other than hemorrhage prevention in patients with hemophilia.

Aminocaproic acid (Amicar® syrup, tablets and injection), another synthetic lysine derivative with lower potency to inhibit plasminogen activation than tranexamic acid, is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, fresh whole blood transfusions, fibrinogen infusions, and other emergency measures may be required. Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt; hematological disorders such as aplastic anemia, abruptio placentae; hepatic cirrhosis; neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix. The Adverse Reactions section of the Amicar product labeling include the following relevant events: hypotension, thrombosis, stroke, BUN increased, renal failure

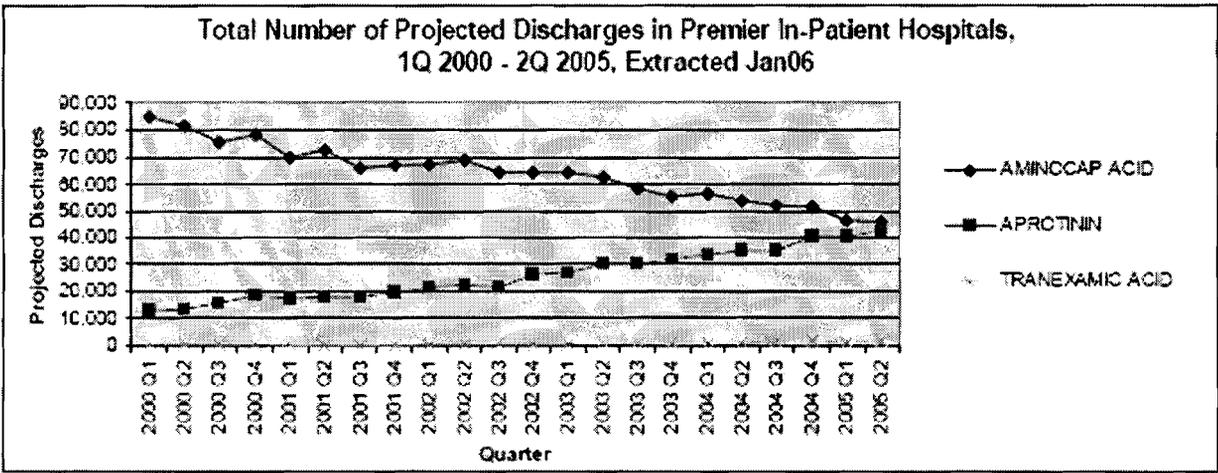
### **USAGE DATA FOR APROTININ, TRANEXAMIC ACID AND AMINOCAPROIC ACID**

Premier's database is a large hospital drug utilization and financial database. The data are derived from over 450 acute care facilities and include approximately 18 million inpatient records. On an annual basis, this constitutes roughly one out of every seven inpatient discharges in the United States. Data are available from January 2000 through the present, but have a lag time of approximately six months.

Hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, bed size, population served, payers and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) appeared to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.

The following table<sup>3</sup> summarizes the total projected inpatient discharges associated with aprotinin, tranexamic acid and aminocaproic acid from the 1<sup>st</sup> quarter of 2000 through the 2<sup>nd</sup> quarter of 2005.

Table 1.



Based on the projected inpatient discharges by year, it appears that the reported usage of aprotinin has increased steadily from 2001 to 2005. During the same time period, the use of aminocaproic acid appears to have declined while the use of tranexamic acid remained constant. Usage data such as these are often used to place a qualitative or quantitative adjustment for exposure on counts of adverse event reports (e.g., MedWatch reports). Quantitative approaches result in *reporting rate* comparisons. Reporting rate calculations are typically based on case counts divided by dispensed prescriptions. Standard reporting rate comparisons require 1) very similar drug products (e.g., time on market, route of delivery, spectrum of indication(s)) and 2) belief that reporting practices are similar for similar drug products over the observed reporting period. Furthermore, standard reporting rate comparisons require an accurate estimate of drug exposure or utilization within the population. Because of multiple indications for use and different available dosage forms for these 3 products, reporting rate comparisons based on estimates of exposure provided by the Premier data may not provide a reliable estimate of exposure. Despite concerns that these products are not similar given disparate indications (e.g.,

<sup>3</sup> Premier Rx Market Advisor, Premier Healthcare Informatics, On-Line. Data extracted 1/25/06. Drug Usage Specialist: Laura Governale

fibrinolytic therapy in the setting of CABG; reduction or prevention of bleeding in patients with hemophilia), this consult will include an analysis that is based on a comparison of the proportions for the event of interest to all adverse event reports for each of the drugs of concern. Such comparisons have been utilized in previous ODS consults and are somewhat analogous to data-mining.

## SEARCH STRATEGY AND RESULTS

### Adverse Event Reporting System

#### *Summary of all events*

The AERS database was searched on February 8, 2006 for all adverse events associated with aprotinin, tranexamic acid and aminocaproic acid. The crude count of reports (all, serious, deaths) by product is shown in Table 2.

<b>Table 2. Crude counts of AERS reports<sup>4</sup> from Marketing Approval Date through 2/8/06</b>				
Drug	Approval Date	All Reports (US)	Serious reports <sup>5</sup>	Death
Aprotinin	12/93	503 (401)	464	235
Tranexamic acid	12/86	220 (12)	202	27
Aminocaproic acid	6/64	199 (192)	118	37

As of February 8, 2006, the AERS database contained a total of 503 *crude* reports for aprotinin. 464 reports had a serious outcome death (235), hospitalization (147), life-threatening (87), disabled (13) and required intervention (42)<sup>6</sup>. There were 307 expedited (15-day), 78 direct, 117 periodic and one RA summary reports. The years of reporting ranged from 1994 to 2006. Most reports (80%) were from domestic sources. Gender distribution was balanced with 78% of reports occurring in patients of  $\geq 50$  years of age. The majority of reports were coded with Preferred terms (PTs) that are classified under the following System Organ Classes (SOCs): Vascular Disorders (235), Cardiac Disorders (200), Investigations (118), Injury, Poisoning and Procedural complications (117), Renal and Urinary Disorders (103) and Respiratory, Thoracic and Mediastinal Disorders (101). The 20 most frequently reported events were hypotension (97), thrombosis (64), cardiac arrest (58), myocardial infarction (53), post procedural complication (52), anaphylactic reaction (40), renal failure acute (36), shock (33), renal failure (31), procedural complication (29), coagulopathy (28), pulmonary embolism (27), blood pressure decreased (24), blood creatinine increased (21) cardiac failure (20), vascular graft occlusion (20), disseminated intravascular coagulation (19), thrombocytopenia (19) and hemorrhage (18). A majority of these events are expected since they are either mentioned in the product labeling or possible sequelae of cardiac surgery.

<sup>4</sup> May contain duplicates

<sup>5</sup> Regulatory definition of serious outcome includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other

<sup>6</sup> A case may report more than one outcome.

There were 220 crude reports associated with tranexamic acid in the AERS database. 202 reports had a serious outcome including death (27), hospitalization (111), life-threatening (34), disabled (22), required intervention (12) and congenital anomaly (1). The years of reporting spanned from 1987 to 2006. Most of the reports originated from foreign sources; United Kingdom (32%), Japan (25%), Denmark (7%) and Sweden (6%) were most often cited. Only 12 reports (5%) originated from domestic sources. The majority of reports were coded with Preferred terms (PTs) that are classified under the following System Organ Classes (SOCs): Nervous System Disorders (77), General Disorders and Administration Site (61), Investigations (51), Respiratory, Thoracic and Mediastinal Disorders (50), Vascular Disorders (50), Skin and Subcutaneous Disorders (29) and Blood and Lymphatic System Disorders (28). The most frequently reported events were pulmonary embolism (18), cerebrovascular accident (13), cerebral infarction (12), pyrexia (12), cardiac arrest (11), depressed level of consciousness (11) dyspnoea (11), renal failure acute (11), shock (9), anaemia (8), blood creatinine increased (8), coagulopathy (8), disseminated intravascular coagulation (8), drug interaction (8), vomiting (8), abdominal pain (7), deep vein thrombosis (7), and malaise (7).

The AERS database contained 199 crude reports for aminocaproic acid. 118 reports had a serious outcome including death (37), hospitalization (51), life-threatening (11), disabled (5), and required intervention (8). There were 65 expedited (15-day), 41 direct and 93 periodic reports. The years of reporting ranged from 1970 to 2006 and 96% of reports were domestic. The majority of reports were coded with Preferred terms (PTs) that are classified under the following System Organ Classes (SOCs): Vascular Disorders (45), Nervous System Disorders (39), General Disorders and Administration Site (30), Investigations (30), Cardiac Disorders (28), Gastrointestinal Disorders (23), Injury, Poisoning and Procedural Complications (20) and Skin and Subcutaneous Tissue Disorders (18). The most frequently reported events were hypotension (17), thrombosis (12), cardiac arrest (10), myopathy (10), dermatitis (9), medication error (7), blood creatinine phosphokinase increased (6), blood creatinine increased (6), cerebrovascular accident (6), coagulopathy (6), vomiting (6), blood pressure decreased (5), bradycardia (5), confusional state (5), convulsion (5), dizziness (5), haemorrhage (5), myocardial infarction (5), and renal failure (5).

#### *Comparison of AERS reports of Renal, Cardiovascular and Central Nervous System Events*

A search of the AERS database was conducted on 2/8/06 to identify all (U.S. and foreign) reports of renal, cardiovascular and central nervous system (CNS) events, specifically reports related to renal failure/impairment, myocardial infarction, heart failure, stroke and encephalopathy. A comparison of crude counts of AERS reporting (foreign and U.S.) with proportions of selected renal, cardiovascular and CNS reports compared to all adverse event reports for each product are provided.

This analysis is similar to comparison of reporting rates. As noted above, comparisons based on a proportion of all reports are used in this analysis as usage data may not provide a reliable estimate of exposure. Therefore, a proportion is calculated with application of all reports as a surrogate for exposure/utilization of the product in the population.

Table 3 contains the counts of renal adverse events in AERS for MedDRA term (HLT) Renal Failure and Impairment<sup>7</sup> and Renal tubular necrosis (PT) with the proportions of selected renal adverse events among all adverse event reports for aprotinin, tranexamic acid and aminocaproic acid.

MedDRA Event Term/Proportion of AE report to all AE reports for drug	Aprotinin	Tranexamic Acid	Aminocaproic acid
All AE reports (domestic and foreign)	503	220	199
Renal Failure & Impairment (HLT) <sup>7</sup>	94	17	10
Proportion of Renal Failure & Impairment (HLT) /all AE reports	18.6%	7.7%	5.0%
Renal Failure Acute (PT)	36	11	4
Proportion of Renal Failure Acute (PT) /all AE reports	7.2%	5.0%	2.0%
Renal Failure (PT)	31	1	5
Proportion of Renal Failure (PT) /all AE reports	6.1%	0.45%	2.5%
Renal Impairment (PT)	15	1	0
Proportion of Renal Impairment (PT) /all AE reports	3.0%	0.45%	Na
Oliguria (PT)	13	3	1
Proportion of Oliguria (PT) /all AE reports	2.6%	1.4%	0.5%
Anuria (PT)	6	5	0
Proportion of Anuria (PT)/all AE reports	1.2%	2.2%	Na
Renal Tubular Necrosis (PT)	4	1	1
Proportion of Renal Tubular Necrosis (PT)/all reports	0.8%	0.45%	0.5%

As shown in Table 3, for the majority of renal related events, the crude report counts and the proportions of renal failure/impairment reports were higher for aprotinin (18.6%) than for tranexamic acid (7.7%) and aminocaproic acid (5%).

Table 4 contains the counts of selected cardiovascular events in AERS for the MedDRA terms, Acute Myocardial Infarction (PT), Myocardial Infarction (PT), and Heart Failures (HLT) and proportion of selected CV adverse events to all adverse event reports. In general, crude report counts and proportion of selected cardiovascular events/all AE reports for aprotinin was greater than for tranexamic acid and aminocaproic acid.

MedDRA Event Term/Proportion of AE report /all AE reports for drug	Aprotinin (n=503)	Tranexamic Acid (n=220)	Aminocaproic Acid (n=199)
Myocardial Infarction (PT)	53	6	5
Proportion of Myocardial Infarction (PT) /all AE reports	10.5%	2.7%	2.5%
Acute Myocardial Infarction (PT)	2	2	0

<sup>7</sup> MedDRA HLT Renal Failure and Impairment consists of following preferred terms (PT): acute renal failure, anuria, Crush syndrome, diabetic end stage renal disease, haemolytic uraemic syndrome, hepatorenal failure, hepatorenal syndrome, nail-patella syndrome, neonatal anuria, oliguria, pancreatorenal syndrome, postoperative renal failure, postrenal failure, renal failure, renal failure acute, renal failure chronic, renal failure neonatal, renal impairment, renal impairment neonatal, scleroderma renal crisis, traumatic anuria

Proportion of Acute Myocardial Infarction (PT)/all AE reports	0.4%	0.9%	NA
Cardiac Failure (PT)	20	1	0
Proportion of Cardiac Failure (PT)/all AE reports	4.0%	0.45%	NA
Cardiac Failure Congestive (PT)	3	0	2
Proportion of Cardiac Failure Congestive (PT)/all AE reports	0.6%	NA	1.0%
Cardiogenic Shock (PT)	8	0	0
Proportion of Cardiogenic Shock (PT)/all AE reports	1.5%	NA	NA

Table 5 contains the counts of selected central nervous system events in AERS for MedDRA terms. Central Nervous System Haemorrhages and Cerebrovascular Accidents (HLT)<sup>3</sup> and Encephalopathy (PT) and the proportion of cerebrovascular events to all adverse event reports.

MedDRA Event Term	Aprotinin (n=503)	Tranexamic Acid (n=220)	Aminocaproic Acid (n=199)
CNS Haemorrhages and Cerebrovascular Accidents (HLT)	28	33	11
Proportion of CNS Haemorrhages and Cerebrovascular (HLT)/all AE reports	5.6%	15%	5.5%
Cerebrovascular Accident (PT)	14	13	6
Proportion of Cerebrovascular Accident (PT) /all AE reports	2.8%	5.9%	3.0%
Cerebral Infarction (PT)	9	12	0
Proportion of Cerebral Infarction (PT)/all AE reports	1.8%	5.5%	NA
Cerebral Artery Thrombosis (PT)	1	6	1
Proportion of Cerebral Artery Thrombosis (PT)/all AE reports	0.2%	0.3%	0.5%
Encephalopathy (PT)	0	1	0
Proportion of Encephalopathy (PT)/all AE reports	NA	0.5%	NA

As shown in Table 5, the proportions of selected cerebrovascular events were generally higher for tranexamic acid than aprotinin and aminocaproic acid.

#### *Summary of AERS Reports of Renal Events for Aprotinin*

For the period through February 8, 2006, the AERS database contained 82 unduplicated cases that were identified by the active ingredient aprotinin or the trade name Trasylol and the MedDRA term "Renal Failure and Impairment" (HLT). Demographic and summary information of these cases are provided in Table 6.

<sup>3</sup> Central Nervous System Haemorrhages and Cerebrovascular Accidents (HLT) consists of 68 MedDRA PT terms including cerebrovascular accident (PT), Cerebral Infarction (PT) and Cerebral Artery Thrombosis (PT).

<b>Table 6. Characteristics of Renal Failure and Impairment case series (n=82)</b>	
<b>AGE (years)</b> (n=64)	mean - 62 median - 68 range - 1 to 85
<b>GENDER</b> (n=72)	male - 26 (36%) female - 46 (64%)
<b>REPORTED RENAL EVENT</b>	Renal failure acute – 31 Renal failure – 26 Renal impairment - 12 Oliguria – 8 Anuria – 4 Dialysis – 1
<b>OUTCOME</b> (a case may have > 1 outcome)	Death – 32 Hospitalization - 21 Life-threatening - 12 Required intervention – 5 Disability – 1
<b>INDICATION FOR USE</b> (n=82)	Cardiac surgery – 65 Spinal surgery – 4 Organ transplant surgery – 3 Vascular surgery – 2 Cerebral hemorrhage – 1 Coagulopathy – 1 Leukemia – 1
<b>REPORTING COUNTRY</b> (n=81)	US – 65 Japan – 8, Taiwan – 1 Great Britain – 2, Germany – 2, Spain -1 , France -1 , Poland -1
<b>TYPE OF REPORT</b>	Expedited – 48 (13 from the medical literature) Direct – 17, Periodic – 17

Eighty-two patients experienced renal failure/impairment reported as acute renal failure (31), renal failure (26), renal impairment (12), oliguria (8), anuria (4) and dialysis (1). The mean age of the patients was 62 years with a range of 1 to 85 years. A female predominance (64%) was observed. Fatal outcomes were reported for 39% of cases. Other serious outcomes included hospitalization (21), life-threatening (12), required intervention (5) and disability (1). Information regarding time to onset of event and cumulative aprotinin dose administered was generally not provided or unclear in the reports. Although most cases did not include information on laboratory results (BUN, creatinine levels), 14 cases noted an increase in blood creatinine levels. Most reports did not provide complete medical history, however, a majority of patients either experienced concurrent events or had underlying medical conditions. The most prevalent events/underlying medical conditions included shock/low output syndrome (17), cardiac arrest (12), thrombocytopenic thrombotic purpura (10), thrombosis (10), diabetes (6), disseminated intravascular coagulation (4), renal dysfunction (4), infection (4), cancer (4), heart failure (3) and

anaphylaxis (3). Many patients had more than one risk factor. Two-thirds of reports lacked information on concomitant medications; in reports documenting information on concomitant medication use, the most frequently reported were heparin (10), protamine (9), digoxin (3), dobutamine (4), norepinephrine bitartrate (3), aspirin (4), furosemide (3), and nitroglycerin (3). Also reported was use of aminoglycosides (4) and ACE inhibitors (3).

The indications for use were reported as cardiac surgery (65), spinal surgery (4), organ transplant surgery (3), vascular surgery (2), cerebral hemorrhage (1), coagulopathy (1) and leukemia (1). In 65 patients where aprotinin was used for cardiac surgery, CABG (31) and mitral/aortic valve replacement (20) were the procedures most frequently cited. Three cases where aprotinin was used for organ transplant surgery were kidney/pancreas, bilateral lung and liver transplant.

Thirty-two cases with a fatal outcome were reported as renal failure (16), acute renal failure (8), anuria (3), renal impairment (2), oliguria (2) and anaphylaxis associated with dialysis (1). Gender was provided in 29 cases with 17 (58%) females and 12 males. Overall, most deaths occurred in patients greater than 60 years of age, however, there were two deaths in pediatric patients; a one-year old child undergoing surgery for multiple congenital cardiac anomalies experienced systemic thrombosis with heparin/protamine reversal and a 14 year old female awaiting a heart transplant experienced renal failure and cardiac arrest following a ventriculoplasty. Most patients were undergoing cardiac surgery, although in 5 cases, the indication was reported as acute promyelocytic leukemia (1), bilateral lung transplant (1), cerebral hemorrhage (1), aorto – subclavian Y prosthesis (1) and thoracoabdominal aortic aneurysm repair (1).

As noted above, most reports did not provide information on time to onset to renal event, laboratory results related to renal function and concomitant medication usage. Furthermore, patients undergoing cardiac surgery are at risk of renal dysfunction. However, there were a few relatively unconfounded cases where aprotinin use was temporal to the development of renal dysfunction. Two representative cases are summarized below.

FDA# 3814926/Mfr# 200110551BWH US Periodic report

67 year-old male with history of diabetes, hypertension, unstable angina, myocardial infarction, but no history of renal disorder, was administered a full dose of aprotinin during CABG surgery. Medications given prior to surgery included metoprolol, cerivastatin, aspirin, nitroglycerin (prn) and benazepril. Pre-operatively, laboratory tests showed BUN 15 and creatinine (0.9) within normal limits. During the post-op period, the patient experienced acute renal failure. Laboratory tests one day after surgery showed BUN 29 and creatinine 2.1 were elevated. 7 days after surgery BUN (36) remained elevated and creatinine (1.2) returned to normal. Dialysis was not needed. The patient recovered and was discharged.

FDA# 5352357 US Direct report

54 year-old female with past history of breast cancer with doxorubicin induced cardiomyopathy and medication allergies, received 5 million units of aprotinin during heart transplant surgery. Pre-transplant continuous therapy included lorazepam, tamoxifen, digoxin, furosemide, heparin, dopamine, dobutamine and multivitamins. One day following surgery (5/15), she developed

acute non-oliguric renal failure attributed either to aprotinin or hypotension during surgery. No nephrotoxic drugs were given during the post-op period. Serum creatinine levels were reported as follows:

5/14	1.3	5/18	7.7	6/12	2.0
5/15	3.3	5/23	6.0	6/26	1.2
5/17	6.7	5/27	3.4		

Renal failure was treated with furosemide and hemodialysis started on 5/18 and continued intermittently until 6/9. Recovery was complicated by surgery for ruptured splenic artery, cardiac arrest and grade 3 rejection. Renal function eventually recovered and patient was discharged from hospital on 6/28.

## DATA MINING ANALYSIS

A data mining analysis of the AERS database was conducted<sup>9</sup> by Joseph Topping M.D., DDRE. The algorithm used for this analysis was the Multi-item Gamma Poisson Shrinker (MGPS),<sup>10,11</sup> which analyzes the records contained in large post-marketing drug safety databases and then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95 respectively.

### *Methodology*

The data mining analysis was conducted using WebVDME software (Ingredient Suspect, Run 323, data current as of April 28, 2006). Drugs were analyzed by ingredient name and included aprotinin, tranexamic acid, and aminocaproic acid. Search terms included *all* Preferred Terms (PTs) in the "Renal Failure and Impairment" High Level Term (HLT) in the MedDRA coding hierarchy. One additional term, renal tubular necrosis, was also included in this analysis. This latter term is in the "renal vascular and ischemic condition" HLT, but was included due to its potential clinical relevance, given the potential pharmacotoxicity of these drugs.

MGPS data mining scores of various terms described above which were reported in conjunction with aprotinin, tranexamic acid, and aminocaproic acid use are presented in the following tables and figures. Data mining scores for aprotinin are presented in Table 7; these same scores are graphically displayed in Figure 1. Data mining scores for tranexamic acid are presented in Table 8 and Figure 2 and scores for aminocaproic acid are presented in Table 9 and Figure 3. Data mining drug-event scores are sorted by descending EBGM value. Frequency of cases (N) and lower and upper confidence limits (EB05, EB95 respectively) are also presented.

9 Data mining analysis of AERS via WebVDME conducted on May 24, 2006.

10 DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data, 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

11 Szarfman A, Machado SG, O'Neil RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

As previously noted, EBGGM scores indicate the strength of the reporting relationship between a particular drug and event. For example, in Table 7, the EBGGM of aprotinin-oliguria = 13.4, indicating that this drug-event combination occurred approximately 13 times more frequently than expected in the AERS database under the assumption of independence (i.e., no association between the drug and the event). A drug-event combination having an EB05  $\geq 2$  indicates 95% confidence that this drug-event combination occurs at least at twice the expected rate when considering all other drugs and events in the database. A drug-event combination having an EB05  $> 1$  indicates 95% confidence that this drug-event combination occurs at least at a higher-than-expected rate considering all other drugs and events in the database.

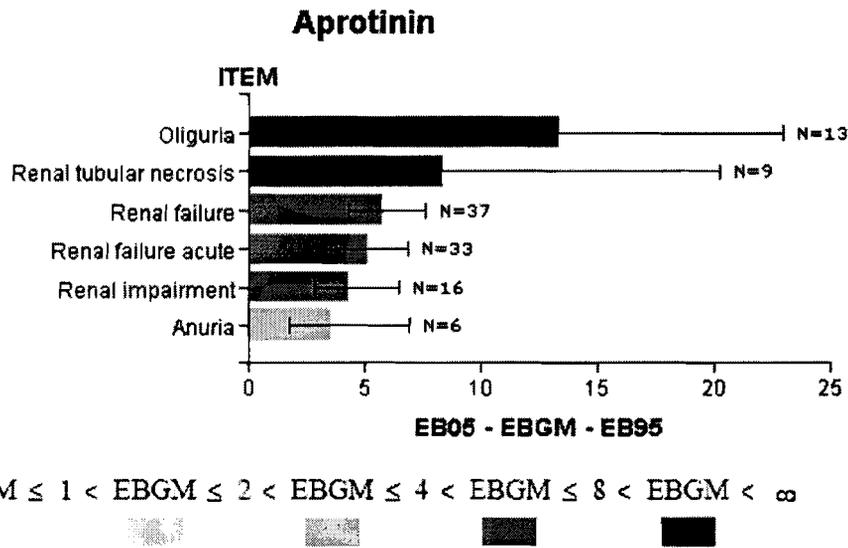
### Results

For this data mining analysis, we defined a “signal” as any drug-event combination having an EB05  $\geq 2$ . In this analysis, aprotinin (Table 7, Figure 1) demonstrated signals for the following PTs: oliguria (EB05 = 6.1); renal tubular necrosis (EB05 = 3.5); renal failure (EB05 = 4.4); renal failure acute (EB05 = 3.8); and renal impairment (EB05 = 2.8). Conversely, tranexamic acid and aminocaproic acid did not display a signal (EB05  $\geq 2$ ) for any of these event terms. Unlike aprotinin, tranexamic acid (Table 8, Figure 2) had no reports for renal tubular necrosis, but did have 2 reports coded with the “renal failure chronic” term. Only 3 terms in the “Renal Failure and Impairment” HLT were reported with aminocaproic acid (Table 9, Figure 3). These terms included renal failure, renal failure acute, and oliguria, none of which had an EB05 score  $\geq 2$ . There was also one case of renal tubular necrosis reported for aminocaproic acid (EB05 = 0.28).

**Table 7. Data Mining Scores for Aprotinin and Renal Events in the “Renal Failure and Impairment” HLT**

MedDRA Preferred Term	N	EB05	EBGM	EB95
Oliguria	13	6.133	13.434	22.951
Renal tubular necrosis*	9	3.475	8.413	20.283
Renal failure	37	4.365	5.798	7.647
Renal failure acute	33	3.842	5.167	6.863
Renal impairment	16	2.847	4.358	6.496
Anuria	6	1.78	3.597	6.967

\*This term is in the “Renal vascular and ischemic condition” HLT



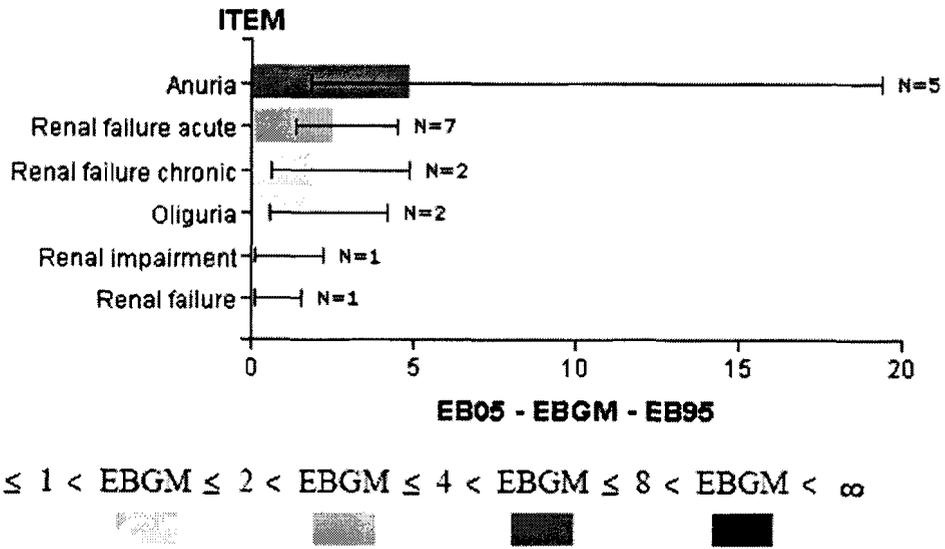
**Figure 1. Data Mining Scores for Aprotinin and Renal Events in the “Renal Failure and Impairment” HLT**

(Note that in all figures, bar length *and* color is determined by the EBGM value for the drug-event. Confidence intervals are depicted by the black lines and number of cases [N] are also listed.)

**Table 8. Data Mining Scores for Tranexamic Acid and Renal Events in the “Renal Failure and Impairment” HLT**

MedDRA Preferred Term	N	EB05	EBGM	EB95
Anuria	5	1.894	4.92	19.446
Renal failure acute	7	1.365	2.566	4.495
Renal failure chronic	2	0.626	1.92	4.872
Oliguria	2	0.556	1.686	4.2
Renal impairment	1	0.177	0.733	2.227
Renal failure	1	0.126	0.524	1.595

## Tranexamic Acid



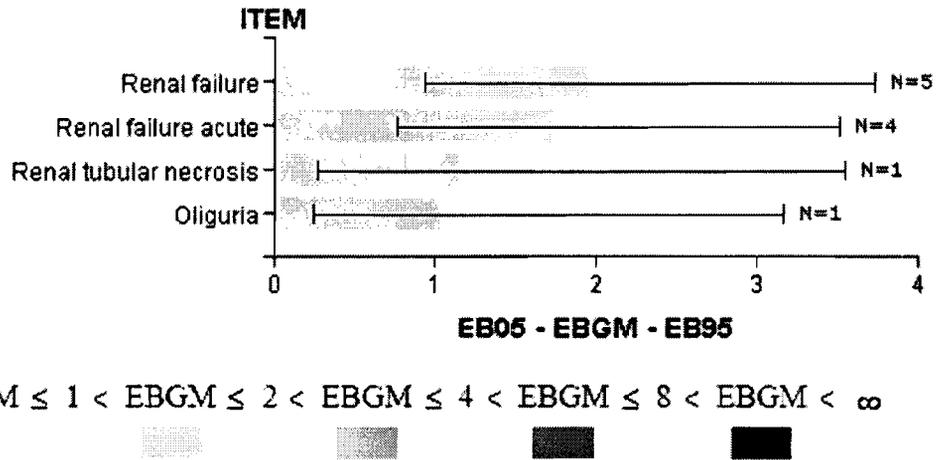
**Figure 2. Data Mining Scores for Tranexamic Acid and Renal Events in the “Renal Failure and Impairment” HLT**

**Table 9. Data Mining Scores for Aminocaproic Acid and Renal Events in the “Renal Failure and Impairment” HLT**

MedDRA Preferred Term	N	EB05	EBGM	EB95
Renal failure	5	0.937	1.965	3.74
Renal failure acute	4	0.764	1.737	3.51
Oliguria	1	0.251	1.04	3.166
Renal tubular necrosis*	1	0.28	1.162	3.549

\*This term is in the “Renal vascular and ischemic condition” HLT

## Aminocaproic Acid



**Figure 3. Data Mining Scores for Aminocaproic Acid and Renal Events in the “Renal Failure and Impairment” HLT**

### *Discussion*

The higher the EBGM score (and accompanying EB05, EB95 confidence intervals) for a particular drug-event, the higher the association between that drug and event, given the database being analyzed. Note that this “association” is a factor of the relative reporting of various events among all drugs in the database. The scores discussed in this section provide an indication of the association of various MedDRA PTs with aprotinin, tranexamic acid, and aminocaproic acid given the data analyzed. However, the causal nature of this association (in all patients exposed to the drug worldwide) cannot be elicited from an MGPS data mining analysis alone, since the association scores (EBGM values) from such an analysis are generated from the AERS database. It is also important for the reader to understand that an elevated EBGM score of association for a particular drug-event combination does not prove causality or an increased relative risk of that drug-event. Similarly, the absence of an elevated EBGM score for a drug-event cannot be interpreted as a definite lack of toxicity for that drug-event. Finally, reporting and detection biases can occur and effects of concomitant illnesses or therapy cannot be controlled for in data mining analyses using MGPS. Because of the spontaneous nature of reporting, the results of this analysis should not be interpreted as a formal comparison of treatment groups or relative risk.

## **DISCUSSION AND CONCLUSION**

A comparison of AERS crude counts of renal failure and impairment (HLT), selected cardiovascular events (myocardial infarction, cardiac failure and cardiogenic shock) and CNS hemorrhages and cerebrovascular accidents (HLT) for aprotinin, tranexamic acid and aminocaproic acid was performed. The proportion of renal failure/impairment reports among all adverse event reports was 2 to 3 times higher for aprotinin compared to tranexamic acid and aminocaproic acid. The proportion of myocardial infarction and cardiac failure reports among all

adverse events reports was several folds higher for aprotinin as well. In contrast the proportion of cerebrovascular events for tranexamic acid was higher than aprotinin and aminocaproic acid.

A data mining analysis comparing renal failure/impairment events for aprotinin, tranexamic acid and aminocaproic acid showed an elevated signal score for the following events for aprotinin: renal failure, acute renal failure, oliguria, renal tubular necrosis, oliguria and renal impairment. Tranexamic acid and aminocaproic acid did not demonstrate a signal for any of the aforementioned events terms. Data mining quantifies reported drug-event associations by producing a ranked set of scores which indicate varying strengths of reported relationships between drug and events. However, elevated data mining scores do not necessarily indicate causality or increased degree of risk and conversely, non-elevated scores do not preclude an increase in drug related risk.

We reviewed 82 cases of renal events reported as acute renal failure (31), renal failure (26), renal impairment (12), oliguria (8) anuria (4) and dialysis (1). Fatal outcomes were reported for 39% of cases. Many cases lacked information regarding time to onset of event, cumulative aprotinin dose, laboratory data, concomitant medications or complete medical history of patient. Most patients experienced concurrent events or had underlying medical conditions which could contribute to renal insufficiency; the most frequently reported were shock/low output syndrome (17), cardiac arrest (12), thrombocytopenic thrombotic purpura (10), thrombosis (10), diabetes (6), disseminated intravascular coagulation (4), underlying renal dysfunction (4), infection (4), cancer (4), heart failure (3) and anaphylaxis (3). Some patients had more than one risk factor. The indication for aprotinin usage was cardiac surgery in 79% of cases.

Although analysis of AERS reports of renal dysfunction, comparison of crude counts of renal dysfunction (among all AE reports) and data mining analysis was suggestive of an association between renal dysfunction and aprotinin, the following should be considered:

- Many studies have demonstrated that renal dysfunction is a potential complication of cardiopulmonary bypass surgery, the setting in which aprotinin is approved for use.<sup>12 13</sup>  
<sup>14</sup> Other adverse events such as myocardial infarction and heart failure which may contribute to renal failure are frequent sequelae of cardiac surgery.
- In clinical practice, the use of aprotinin may be selectively limited to patients with the highest risk of hemorrhage (e.g. complex surgical procedures requiring prolonged CPB support) and likely those of higher risk for postoperative renal dysfunction.<sup>2</sup>
- Aprotinin is the only agent approved to reduce the need for blood transfusion in patients undergoing CABG. The extent to which tranexamic acid and aminocaproic acid are used off label in high risk cardiac surgery is not known.
- In the 82 AERS cases of renal failure and impairment associated with aprotinin, patients typically had medical risk factors such as advanced age, complicated post-surgical course and co-morbidities.

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<sup>12</sup> Chertow GM, Levy EM et al. Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med.* 1998;104:343-8

<sup>13</sup> Conlon PJ et al. Acute renal failure following cardiac surgery. *Nephrol Dial Transplant* 1999 14:1158-1162

<sup>14</sup> Mazzarella V et al. Renal function undergoing cardiopulmonary bypass operations. *J Thorac Cardiovasc Surg* 1992;104:1625-7

In conclusion, a comparison of crude counts of renal failure and impairment, myocardial infarction, cardiac failure and cardiogenic shock (among all adverse event reports) showed higher proportions for aprotinin when compared to tranexamic acid and aminocaproic acid. A data mining analysis showed an elevated signal score for aprotinin and renal failure, acute renal failure, oliguria, renal tubular necrosis, oliguria and renal impairment. In contrast, tranexamic acid and aminocaproic acid did not demonstrate a signal for these events terms. An analysis of 82 AERS cases of renal failure/impairment showed that many patients had either underlying risk factors or experienced concurrent events which may contribute to renal dysfunction. Admittedly, in many cases it is difficult to make definitive attributions regarding renal dysfunction either due to the complexity of the case or incompleteness of data provided, however, the role of aprotinin cannot be excluded. An association between aprotinin and renal dysfunction is suggested in two recent published studies and spontaneous reports submitted to AERS. We recommend revisions in labeling for aprotinin in order to alert healthcare professionals to the potential serious risks of renal dysfunction associated with aprotinin use.

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Attachment A  
Case Summary of Renal Failure/Impairment Cases Reported to AERS

CSENUM	AGE	SEX	MFRCTRL	CNTRY	OUTC1	Risk factors	ALLREACTNS
3032074	34	Female	B98-135 (1)	GB	DE	leukemia	ABDOMINAL PAIN; CEREBRAL INFARCTION; DYSPNOEA; EMBOLISM; OLIGURIA; RENAL CORTICAL NECROSIS; RENAL FAILURE; RESPIRATORY FAILURE
3033435	71	Male	97737	SPAIN	DE	concom med, infection	LEUKOCYTOSIS; PYREXIA; RENAL FAILURE ACUTE; SEPSIS; SHOCK
3145116	77	Female	M98-416 (1)	US	HO	htn, CAD, MI	HAEMODIALYSIS; MENTAL IMPAIRMENT; MICROANGIOPATHIC HAEMOLYTIC ANAEMIA; PYREXIA; RENAL FAILURE; THROMBOTIC THROMBOCYTOPENIC PURPURA
3152998	78	Male	M98-415 (1)	US	HO	htn, CAD, MI, CHF	CARDIAC FUNCTION DISTURBANCE POSTOPERATIVE; HAEMODIALYSIS; HAEMOLYSIS; MENTAL IMPAIRMENT; RENAL FAILURE; THROMBOTIC THROMBOCYTOPENIC PURPURA
3180106	67	Male	BI-990355 (1)	Taiwan	DE	CHF, renal dysfunction	LEFT VENTRICULAR FAILURE; LOW CARDIAC OUTPUT SYNDROME; RENAL FAILURE;
3303872	68	Female	11999/05441	Japan	DE		ANURIA; DISSEMINATED INTRAVASCULAR COAGULATION; MULTI-ORGAN FAILURE; RENAL TUBULAR NECROSIS;
3449970	73	Male	M99-046 (1)	US	DE	htn	HYPOXIA; MULTI-ORGAN FAILURE; RENAL IMPAIRMENT;
3449978	52	Male	M99-159 (1)	US	OT	obesity, diabetes	RENAL FAILURE;
3482136	42	Female		US	DS		RENAL ARTERY THROMBOSIS; RENAL FAILURE ACUTE
3502508		Male	1200007723	France	HO		ANURIA; BLOOD CREATINE PHOSPHOKINASE INCREASED; HAEMODIALYSIS; POST PROCEDURAL COMPLICATION; RENAL FAILURE ACUTE;
3503869		Female	1200007906	Germany	HO		ANURIA; DRUG HYPERSENSITIVITY; HAEMOLYSIS; NUCLEAR MAGNETIC RESONANCE IMAGING ABNORMAL; THROMBOCYTOPENIA;
3586078	51	Female		US	LT		PULMONARY HYPERTENSION; RENAL FAILURE ACUTE; THROMBOTIC THROMBOCYTOPENIC PURPURA;
3623455	81	Female		US	LT	atrial fib	RENAL FAILURE ACUTE;
3624892	67	Male	200110550B/WH	US	DE	diabetes, htn, acute renal insufficiency	CARDIAC ARREST; DIABETES MELLITUS; DIALYSIS; MYOCARDIAL INFARCTION; RENAL FAILURE ACUTE; RESPIRATORY DISTRESS;
3638787	51	Female	200090195B/WH	US	OT		RENAL FAILURE ACUTE;
3639591	64	Female	200090197B/WH	US	OT		RENAL FAILURE ACUTE;
3646339	1	Unk	200110965G/DS	US	DE	multiple congenital cardiac	ACIDOSIS; ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED; ANURIA; AORTIC ANEURYSM; ECHOCARDIOGRAPHY ABNORMAL; ELECTROCARDIOGRAM ST SEGMENT ELEVATION; HAEMORRHAGE INTRACRANIAL; HYPOTENSION; PROTHROMBIN TIME PROLONGED; THROMBOSIS; THROMBOTIC MICROANGIOPATHY;
3810431		Female	200215939B/WH	US	DE		RENAL FAILURE ACUTE; THROMBOTIC THROMBOCYTOPENIC PURPURA;
3810434		Female	200215939B/WH	US	HO		RENAL FAILURE ACUTE; THROMBOTIC THROMBOCYTOPENIC PURPURA;

3810435		Female	200215937BWH	US	HO		RENAL FAILURE ACUTE;THROMBOTIC THROMBOCYTOPENIC
3910438		Female	200215938BWH	US	HO		RENAL FAILURE ACUTE;THROMBOTIC THROMBOCYTOPENIC PURPURA;
3810440		Female	200215929BWH	US	HO		RENAL FAILURE ACUTE;THROMBOTIC THROMBOCYTOPENIC PURPURA;
3810565	33	Female	CTU 171351	US	LT	repeat aortic v replace	RENAL FAILURE ACUTE;thrombotic THROMBOCYTOPENIA purpura
3814813		Unk	200110157BWH	US	HO		RENAL FAILURE;DIALYSIS
3814926	67	Male	200110551BWH	US	HO	diabetes,angina, Mi	RENAL FAILURE ACUTE;
3823066	51	Female	200090195BWH	US	OT		RENAL FAILURE ACUTE;
3868697	21	Female	200226144BWH	US	LT		ACUTE RESPIRATORY DISTRESS SYNDROME;ANAPHYLACTIC REACTION;CATHETER RELATED COMPLICATION;LUNG INJURY;PULMONARY HYPERTENSION;RENAL IMPAIRMENT;SEPSIS;THROMBOSIS;
3945642		Unk	200311313GDS	Poland	OT		RENAL IMPAIRMENT
4028206	65	Female	CTU 205156	US	DE	unstable angina/CAD	ANOXIC ENCEPHALOPATHY;ANTI-PLATELET ANTIBODY POSITIVE;CEREBRAL THROMBOSIS;CORONARY ARTERY THROMBOSIS;DISSEMINATED INTRAVASCULAR COAGULATION;ELECTROCARDIOGRAM ST SEGMENT ABNORMAL;ELECTROENCEPHALOGRAM ABNORMAL;HYPOTENSION;NERVOUS SYSTEM DISORDER;RENAL FAILURE ACUTE;
4037590	44	Male	200328369BWH	US	DE	end stage COPD	CARDIAC ARREST;OLIGURIA;RENAL FAILURE ACUTE;RESPIRATORY FAILURE;RESPIRATORY FAILURE;
4103107	79	Female	200413171BWH	US	DE	cancer	GRAFT THROMBOSIS;POST PROCEDURAL COMPLICATION;PROCEDURAL HYPOTENSION;RENAL FAILURE;
4109791		Unk	200321598BWH	US	OT		RASH GENERALISED;RENAL FAILURE ACUTE;
4109793		Unk	200321598BWH		OT		RASH GENERALISED;RENAL FAILURE ACUTE;
4114674	76	Male	200408973	US	DE	htn	CARDIO-RESPIRATORY ARREST;CIRCULATORY COLLAPSE;GENERAL PHYSICAL HEALTH DETERIORATION;GRAFT THROMBOSIS;HAEMODYNAMIC INSTABILITY;HYPOVOLAEMIA;PHARMACEUTICAL PRODUCT COMPLAINT;POST PROCEDURAL COMPLICATION;RENAL FAILURE;SEPSIS;SHOCK;THROMBOCYTOPENIA;VASODILATATION
4146032	76	Male	200417878BWH	US	DE	redo valve replace/CABG	ACIDOSIS;HYPOPERFUSION;POST PROCEDURAL COMPLICATION;RENAL FAILURE;SHOCK;
5169988	35	Female	M942191	US	HO	redo valve replace	RENAL IMPAIRMENT;
5174567	79	Male		US	DE	Mi	CARDIAC ARREST;MYOCARDIAL INFARCTION;RENAL FAILURE;SHOCK;
5175752	68	Female		US	DE		BLOOD CREATINE PHOSPHOKINASE INCREASED;HYPERGLYCAEMIA;HYPERGLYCAEMIA;RENAL IMPAIRMENT;SHOCK;
5196226	73	Male	M943662	US	DE	RHD, valve surgenes	BLOOD CREATININE INCREASED;BLOOD UREA INCREASED;CEREBRAL INFARCTION;CEREBRAL INFARCTION;RENAL FAILURE ACUTE;

5252033	72	Male		US	HO	HTN	BLOOD CREATININE INCREASED;RENAL IMPAIRMENT;THROMBOCYTOPENIA;acute tubular necrosis?
5274635	63	Male		US	HO	Prior CABG,HTN, smoker	BLOOD CREATINE PHOSPHOKINASE INCREASED,BLOOD CREATININE INCREASED;RENAL FAILURE ACUTE;RENAL TUBULAR NECROSIS,
5275319	71	Female	M943691	US	RI	DM,AF, MVR	BLOOD CREATININE INCREASED;BLOOD UREA INCREASED;OLIGURIA;RENAL FAILURE ACUTE
5279779	63	Male		US	HO	COPD,pacemaker, CAD	LUNG DISORDER;RENAL FAILURE ACUTE;RESPIRATORY DISORDER;SEPSIS;
5296086	64	Male	US	US	HO	DM	BLOOD CREATININE INCREASED;BLOOD UREA INCREASED;RENAL FAILURE ACUTE;RENAL TUBULAR NECROSIS;
5323569	unk	Unk	M951371	US	RI		RENAL FAILURE;
5352357	54	Female		US	RI	breast cancer	BLOOD CREATININE INCREASED;CARDIAC ARREST;HYPOTENSION;RENAL FAILURE ACUTE;
5389901	63	Female	896101003L	US	DE	MI, PVD, RA etc	ANAPHYLACTOID REACTION;CARDIAC FAILURE;HYPOTENSION;RENAL FAILURE;
5397947	83	Male	M952401	US	HO	tolramycin	BLOOD CREATININE INCREASED;RENAL IMPAIRMENT;
5397350	58	Male	M952651	US	OT		BLOOD CREATININE INCREASED;RENAL IMPAIRMENT;
5397954	71	Male	M952661	US	OT		BLOOD CREATININE INCREASED;RENAL IMPAIRMENT;
5454496	14	Female	M962491	US	DE	awaiting heart transpt	CARDIAC FAILURE;PYREXIA;RENAL FAILURE;cardiac arrest
5463646	72	Female	M961611	US	HO		DISSEMINATED INTRAVASCULAR COAGULATION;RENAL FAILURE ACUTE;THROMBOCYTOPENIA;
5466366	76	Female	M963362	US	LT	CHF, MVR	HEPATIC FAILURE;JAUNDICE;OLIGURIA;RENAL FAILURE ACUTE;
5479924	70	Female		US	DE		RENAL FAILURE;THROMBOSIS;
5544292	34	Female	75539	US	DE	promyelocytic leukemia	APNOEA;DYSPTNOEA;RENAL FAILURE;THROMBOSIS;RENAL CORTICAL NECROSIS
5556451	71	Male	BI9701021	Japan	LT		OLIGURIA;LOW OUPUT SYNDROME;
5560650	49	Female	BI9701031	Japan	DE		MYOCARDIAL INFARCTION;OLIGURIA;LOW OUTPUT SYNDROME
5560652	59	Male	BI9701071	Japan	LT		MYOCARDIAL INFARCTION;OLIGURIA;LOW OUTPUT SYNDROME
5560663	74	Female	BI9701261	Japan	LT		MYOCARDIAL INFARCTION;OLIGURIA;LOW OUTPUT SYNDROME
5560667	74	Female	BI9701051	Japan	LT		MYOCARDIAL INFARCTION;OLIGURIA;LOW OUTPUT SYNDROME
5560670	46	Female	BI9701041	Japan	LT		MYOCARDIAL INFARCTION;OLIGURIA; LOW OUTPUT SYNDROME
5560673	70	Male	BI9701031	Japan	DE		MYOCARDIAL INFARCTION;OLIGURIA; LOW OUTPUT SYNDROME
5561350	72	Female	M971321	US	HO	mitral stenosis,aortic regurg	ATELECTASIS;PERITONEAL HAEMORRHAGE;RENAL FAILURE;lung thrombosis
5594073	72	Female	M971701	US	DE	cardiogenic shock	CARDIAC ARREST;PERICARDIAL EFFUSION;RENAL FAILURE;SHOCK;MULTI ORGAN FAILURE
5609129		Unk	M971931	US	DE		CHOLECYSTITIS;HEPATIC FAILURE;RENAL FAILURE;SEPSIS;
5673590		Unk	200420931BWH	US	DE		MULTI-ORGAN FAILURE;POSTOPERATIVE THORACIC PROCEDURE COMPLICATION;RENAL FAILURE;RESPIRATORY FAILURE;THROMBOSIS;

5676041	76	Female	200408973	US	DE	htn, lipidemia	CARDIAC ARREST;CIRCULATORY COLLAPSE;GENERAL PHYSICAL HEALTH DETERIORATION;HAEMODYNAMIC INSTABILITY;HYPOVOLAEMIA;PLATELET COUNT DECREASED;POST PROCEDURAL COMPLICATION;RENAL FAILURE;SEPSIS;VASCULAR GRAFT OCCLUSION
5704216	80	Female	200421152BWH	US	DE		ANGIOPATHY;RENAL FAILURE ACUTE;THROMBOSIS;
5745023	75	Female	200510148BWH	US	DE	mitral/tricuspid regurg	ACIDOSIS;DISSEMINATED INTRAVASCULAR COAGULATION;HEPARIN-INDUCED THROMBOCYTOPENIA;INTRACARDIAC THROMBUS;PLATELET COUNT DECREASED;PYREXIA;RENAL FAILURE;THERAPY NON-RESPONDER;VENTRICULAR DYSFUNCTION;VISUAL DISTURBANCE
5767740		Unk	200510492BWH	US	OT		BLOOD CREATININE INCREASED;DIFFICULT TO WEAN FROM VENTILATOR;RENAL IMPAIRMENT;
5783308		Female	200510360BVD	Germany	DE	glomerulonephritis/renal insufficiency,etc	ANAPHYLACTIC REACTION;BLOOD PRESSURE DECREASED;BRADYCARDIA;CARDIAC ARREST;DIALYSIS;HAEMODYNAMIC INSTABILITY;HAEMOGLOBIN DECREASED;HAEMORRHAGIC DIATHESIS;HAEMOTHORAX;LOCAL SWELLING;
5793171	67	Male	200510610BWH	US	DE	unstable angina	ADHESION;ANURIA;BLOOD BICARBONATE DECREASED;BLOOD GLUCOSE INCREASED;BLOOD POTASSIUM DECREASED;BLOOD PRESSURE DECREASED;CARDIO-RESPIRATORY ARREST;CARDIOMEGALY;DRUG RESISTANCE;HAEMOGLOBIN DECREASED;HAEMOTHORAX;
5795132		Unk	200421191BWH	US	OT		RENAL FAILURE;
5841997	68	Female	200511335BWH	US	DE	none	BLOOD LACTATE DEHYDROGENASE INCREASED;CARDIAC VALVE REPLACEMENT COMPLICATION;DIALYSIS;DISSEMINATED INTRAVASCULAR COAGULATION;GASTROINTESTINAL HAEMORRHAGE;HAEMOLYSIS;INCISION SITE HAEMORRHAGE;RENAL FAILURE;ACUTE RESPIRATORY FAILURE;THROMBOCYTOPENIC PURPURA
5970777	65	Male	200511318BWH	US	DE	CAD,htn,COPD,col on resect	ANAEMIA;BRADYCARDIA;CARDIAC ARREST;CARDIAC FAILURE;CARDIOGENIC SHOCK;CORONARY ARTERY OCCLUSION;ELECTROLYTE IMBALANCE;HYPOTENSION;LUNG DISORDER;MYOCARDIAL INFARCTION;PLEURAL EFFUSION;RENAL FAILURE ACUTE;
5999966	31	Female	200513009GDS	GB	LT	liver transplant	PULMONARY EMBOLISM;ANURIA;BRADYCARDIA;COMPLICATIONS OF TRANSPLANT SURGERY;COMPLICATIONS OF TRANSPLANTED LIVER;DILATATION VENTRICULAR;HEPATIC INFARCTION;HYPERCOAGULATION;HYPOTENSION;METABOLIC ACIDOSIS;METABOLIC DISORDER;OLIGURIA;POOR PERIPHERAL CIRCULATION;
5921661		Female	CTU 262745	US	RI		ANAEMIA;HAEMATURIA;HAEMORRHAGE;RENAL IMPAIRMENT;THROMBOCYTOPENIA;
5939010	52	Female	CTU 264363	US	HO	spinal fusion	HAEMODIALYSIS;HAEMORRHAGE;POST PROCEDURAL COMPLICATION;RENAL FAILURE ACUTE;
5939012	69	Female	CTU 264364	US	HO	spinal fusion	HAEMODIALYSIS;HAEMORRHAGE;POST PROCEDURAL COMPLICATION;RENAL FAILURE;

24

5939020	73	Female	CTU 264362	US	RI	spinal fusion	HAEMODIALYSIS;POST PROCEDURAL COMPLICATION;RENAL FAILURE;
5951900	62	Female	200512759BWH	US	LT	angina, cad	CARDIO-RESPIRATORY ARREST;ECG SIGNS OF MYOCARDIAL ISCHAEMIA;GRAFT THROMBOSIS;HAEMATOCRIT DECREASED;HEPATIC FAILURE;HYPOTENSION;PROCEDURAL COMPLICATION;RENAL FAILURE;VENOUS THROMBOSIS;VENTRICULAR HYPOKINESIA;
5974626	46	Male	200511263BWH	US	HO	cardiomyopathy, diabetes, renal insufficiency	RENAL IMPAIRMENT;haemodialysis

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/s/

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Susan Lu  
7/5/2006 11:57:15 AM  
DRUG SAFETY OFFICE REVIEWER



**MEMORANDUM      DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**DATE:**            November 28, 2006

**TO:**                George Mills, M.D., Director  
                        Division of Medical Imaging & Hematology Products, HFD-160

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
                        Office of Surveillance and Epidemiology, HFD-400

**FROM:**            OSE Trasyolol RiskMAP Review Team

**DRUG:**            Trasyolol (Aprotinin)

**NDA:**              20-304

**SPONSOR:** Bayer Pharmaceuticals

**SUBJECT:** OSE Review of Risk Minimization Action Plan (RiskMAP)

**PID #:**             2006-788

**1 EXECUTIVE SUMMARY**

This consult follows a request by the Division of Medical Imaging & Hematology Products (DMIHP), for the Office of Surveillance and Epidemiology (OSE) to review a risk minimization action plan (RiskMAP) submitted by Bayer Pharmaceuticals to manage the risk of hypersensitivity associated with the use of aprotinin (Trasyolol), a product indicated 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. The RiskMAP proposed by the Sponsor consists of education for prescribers and, potentially, an aprotinin-specific IgG assay (not currently commercially available) to identify patients at highest risk for a hypersensitivity reaction.

We have reviewed an analysis submitted by the Sponsor of hypersensitivity reactions associated with the use of aprotinin contained in the Sponsor's global safety database. Additionally, Susan Lu in the Division of Drug Risk Evaluation (DDRE) reviewed cases of hypersensitivity reactions associated with the use of aprotinin contained in the FDA's

Adverse Event Reporting System (AERS). The Sponsor's analysis of their postmarketing database of hypersensitivity cases and Ms. Lu's review of the AERS cases of anaphylaxis raise concerns about the adequacy of the labeling of Trasylol regarding hypersensitivity and anaphylaxis. The Sponsor proposes to use education reinforcing information in the labeling as the primary tool to manage the risk of hypersensitivity reactions. We do not believe that stressing the information in the current labeling would suffice to manage the risk. We note that the Sponsor currently educates practitioners about the safety information contained in the current labeling. The RiskMAP proposal does not appear to differ substantially from current education, and cases of hypersensitivity, including cases with fatal outcomes, have continued to occur despite this education. Based on the reviews of hypersensitivity reactions undertaken by the Sponsor and Ms. Lu, we have recommendations regarding changes to the Trasylol labeling. If the labeling is enhanced to include the safety messages detailed below, then education may be an appropriate tool to help manage the risk of the product.

The Sponsor's proposed education focuses on cardiothoracic surgeons and cardiothoracic anesthesiologists. While these physicians are the primary Trasylol prescribers, use data provided by Bayer show that non-cardiac surgeries comprise 4% of the use of Trasylol<sup>1</sup>. Similarly, an analysis of use data undertaken by Dr. Laura Governale in the Division of Surveillance, Research and Communication Support (DSRCS) showed that non-cardiac surgeries comprise about 3% of the use of Trasylol.<sup>2</sup> Non-cardiac surgical settings would be unlikely to provide for the capacity either in personnel or in equipment to implement emergent cardiopulmonary bypass (CPB), a strategy recommended to help manage anaphylactic reactions to Trasylol. We recommend that the Sponsor develop a strategy to identify physicians who are using Trasylol in such non-cardiac surgical settings and contact these physicians to educate them on the labeled indication and the requirement to have emergent CPB capability when Trasylol is used.

The Sponsor proposes to conduct a pre- and post-launch survey of hospital records to evaluate compliance with the test dose procedure and to obtain data regarding prior aprotinin exposure. Additionally, the Sponsor proposes to administer a survey to a sample of prescribers to document receipt and application of the key safety messages in the educational program. Additional details should be submitted regarding the survey methodology and the survey instrument. In addition to these steps to evaluate the success of the RiskMAP, we recommend that the Sponsor monitor the non-cardiac use of aprotinin to evaluate the success of the RiskMAP in decreasing the use of aprotinin in settings where emergent CPB is not available.

## 2 BACKGROUND

Trasylol (aprotinin injection) is a natural protease inhibitor obtained from bovine lung. It modulates the systemic inflammatory response (SIR) associated with cardiopulmonary bypass (CPB) surgery by reducing the inflammatory response which translates into a decreased need for allogeneic blood transfusions, reduced bleeding, and decreased

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<sup>1</sup> Bayer submission to NDA 20-304 dated October 6, 2006.

<sup>2</sup> Governale L. Analysis of inpatient use of Trasylol<sup>®</sup> (aprotinin); NDA 20-304. Data extracted October 2006 from *Premier Rx Market Advisor*.

mediastinal re-exploration for bleeding. The FDA approved Trasylol in December, 1993 for 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 grafting (CABG) surgery. Trasylol also was indicated in selected cases of primary coronary bypass graft surgery where the risk of bleeding is especially high (impaired hemostasis, e.g., presence of aspirin or other coagulopathy) or where transfusion is unavailable or unacceptable. This selected use of Trasylol in primary CABG patients was based on the risk of renal dysfunction and on the risk of anaphylaxis (should a second procedure be needed). The original indication was broadened in 1998 for use in patients undergoing primary CABG. Additionally, a “black-box” warning for anaphylaxis was added to the labeling.

Two studies<sup>3</sup> were published earlier this year examining the incidence of serious renal and cardiovascular toxicity following Trasylol administration to patients undergoing coronary artery bypass grafting surgery (CABG). In response to the studies, the Agency issued a *Public Health Advisory*<sup>4</sup>, and the Agency committed to a public discussion of the safety risks associated with aprotinin.

As part of the Sponsor’s safety review following the publication of the studies, the Sponsor conducted a review of hypersensitivity reactions from their global safety database. Hypersensitivity reactions comprise about one-half of the total cases in the Sponsor’s postmarketing safety database for aprotinin. Based on the Sponsor’s review of their safety database, the Sponsor submitted a RiskMAP for hypersensitivity.

The safety of aprotinin was discussed at a September 21, 2006 meeting of the Cardiovascular and Renal Drugs Advisory Committee. The Advisory Committee considered all three safety risks mentioned above, cardiac toxicity, renal function impairment and renal failure, and hypersensitivity<sup>5</sup>. The Advisory Committee did not find the evidence presented to them regarding renal failure requiring dialysis and cardiac toxicity to be persuasive of increased risk for these toxicities. The Advisory Committee believed that the evidence is supportive of a finding that aprotinin is associated with renal function impairment, but the Advisory Committee did not find this to be particularly concerning.<sup>6</sup> The Advisory Committee found anaphylaxis to be the most concerning of the risks considered at the meeting.

Of note, prior to the September 21, 2006 meeting, the Sponsor had received preliminary results from a large observational safety study of patients from a hospital database. The preliminary findings from this new observational study showed that use of Trasylol might increase the chance for death, serious kidney damage, congestive heart failure, and strokes. These data were not considered by the Advisory Committee at the September 21 meeting. FDA is still evaluating these new data and the implication of the data for safe use of the drug.

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<sup>3</sup> Mangano DT, et al. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354: 4: 353-65.  
Karkouti K, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46: 327-38.

<sup>4</sup> Public Health Advisory available at <http://www.fda.gov/cder/drug/advisory/aprotinin.htm>.

<sup>5</sup> The clinical trial data from randomized controlled trials and the observational studies of Mangano et al and Karkouti et al were presented as evidence regarding renal and cardiac toxicity. Postmarketing data from Bayer’s global postmarketing safety database and AERS were presented as evidence regarding hypersensitivity.

<sup>6</sup> Quick minutes; Cardiovascular and Renal Drug Products Advisory Committee; September 21, 2006.

Regarding the Sponsor's proposed RiskMAP for hypersensitivity, the members of the committee endorsed educating physicians about: 1. the risk of hypersensitivity with aprotinin; 2. recognition of hypersensitivity reactions in the OR setting; and 3. resuscitation of patients who experience an anaphylactic reaction. However, the members expressed doubt that education alone would manage the risk. Although the committee agreed that the value of the test dose is questionable, they did not recommend that the practice of giving a test dose be stopped.<sup>7</sup> Members of the committee expressed special concern regarding the use of aprotinin in settings in which emergent CPB is not possible; that is, the use of aprotinin for non-cardiac surgery. While acknowledging that the aprotinin-specific IgG assay is not available to be incorporated into the RiskMAP at this time, and, when available, the assay may have limitations<sup>8</sup> that could impede its effectiveness in preventing hypersensitivity reactions, the committee nevertheless urged the Sponsor to move forward with development of a point-of-use aprotinin-specific IgG assay.

This review is limited to the management of hypersensitivity (notably, anaphylaxis), the risk for which the Sponsor has submitted a RiskMAP. Depending on the evaluation of the additional safety data contained in the observational safety study that was revealed recently, additional risks might be incorporated into the RiskMAP in the future.

### 3 SAFETY RISK—ANAPHYLAXIS

#### 3.1 Assessment of Postmarketing Data

The Sponsor submitted a review of hypersensitivity cases contained in their global postmarketing database for 1984 to 2005. They cite a total of 291 cases of hypersensitivity possibly associated with aprotinin, including 52 cases with fatal outcomes. Notable findings in their review include:

- 138/291 (47%) of the cases documented previous aprotinin exposure;
  - 93/138 (67%) of cases with documentation of the timing of previous exposure reported re-exposure within 6 months;
- A test dose was administered in 139 cases;
  - Hypersensitivity reaction occurred with test dose alone in 81 cases, including 19 fatal cases;
  - The test dose was negative but a reaction occurred with the therapeutic dose in 38 cases, including 9 fatal cases.

Susan Lu in DDRE searched the FDA's AERS database for reports of anaphylaxis with aprotinin. She reviewed 70 reports of anaphylaxis with aprotinin, including 23 cases with

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<sup>7</sup> The value of the test dose was a discussion item, not a voting question for the committee.

<sup>8</sup> Although the idea of an aprotinin-specific IgG assay is attractive, several issues surrounding the assay may limit its effectiveness in preventing hypersensitivity reactions:

- a. the assay has not been proven to be valid and reliable;
- b. the assay is expected to yield false positive results; that is, there will be some patients who will have measurable aprotinin IgG who would not have an anaphylactic reaction if they received aprotinin; and
- c. the assay may yield false negative results; that is, there will be some patients who do not have measurable aprotinin IgG who will have an anaphylactoid reaction if they receive aprotinin.

fatal outcomes. Notable findings in Ms. Lu's review of the AERS cases were similar to the Sponsor's findings from the review of their global postmarketing safety database.

- A test dose was administered in 49 cases
  - In 23 cases, the hypersensitivity reactions occurred after the test dose alone, including 10 fatal reactions
  - In 20 cases, a reaction occurred with the therapeutic dose despite a negative test dose
- In 34 cases, previous exposure to aprotinin was documented, including 29 cases in which the timing of the previous exposure was known (20 cases  $\leq$  6 months; 9 cases  $>$  6 months)
- Where the reason for use was stated, 25% of patients received aprotinin in the course of CABG surgery; the most frequently reported reason for use was valve surgery
- The most frequently observed sign of hypersensitivity observed was hypotension

The data presented by the Sponsor and the AERS data reviewed by Ms. Lu show that the test dose is problematic. The Sponsor stated that hypersensitivity reactions occurred with the test dose alone in 81 cases of the 139 cases in their database that reported the use of a test dose. Nineteen of the reactions to the test dose were fatal. In 38 cases, including 9 cases with fatal outcomes, the test dose was negative but a hypersensitivity reaction occurred with the subsequent therapeutic dose of aprotinin. In the cases in AERS, 23 patients experienced a hypersensitivity reaction with the test dose alone, including 10 cases with fatal outcomes.

Trasylol labeling contains information about the possibility of anaphylactic reactions (both with no prior exposure and with re-exposure) and use of a test dose in the boxed warning, warning, precautions, and adverse reactions sections. The exact language is included in Appendix 1.

### 3.2 Medical Literature

Beierlein et al<sup>9</sup> summarized 124 hypersensitivity reactions reported in the medical literature from 1963 to 2003. The authors concluded the following<sup>10</sup>:

1. the risk for a hypersensitivity reaction upon re-exposure to aprotinin appears to be greatest within the first several months following an initial aprotinin exposure, as shown in the figure reprinted from the article, below.

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<sup>9</sup> Beierlein W, Scheule AM, et al. Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; 79: 741-8.

<sup>10</sup> The publication did not state whether or not any authors had financial ties with Bayer Pharmaceuticals, the Sponsor for Trasylol.

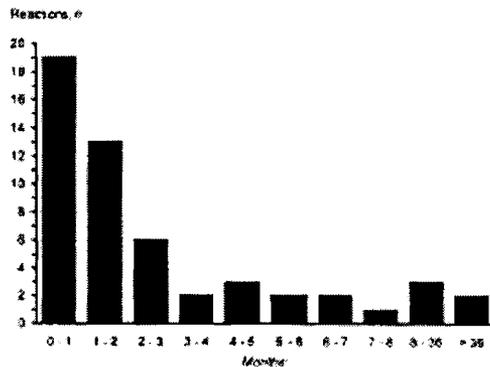


Fig 2. Time spans between repeated aprotinin exposures.

The number of hypersensitivity reactions is shown on the vertical axis and the time span between repeated aprotinin injections is shown on the horizontal axis.

2. the detection of IgG antibodies to aprotinin may serve as a biomarker for prior exposure.

Dietrich et al<sup>11</sup> prospectively studied aprotinin re-exposure in 121 patients at five German medical centers. The patients had a mean re-exposure interval of 1654 days (range, 16-7136 days). Three patients had anaphylaxis with re-exposure. All three patients had re-exposure intervals less than 6 months (22, 25, and 25 days).<sup>12</sup>

## 4 PROPOSED RISKMAP<sup>13</sup>

### 4.1 Goal/Objectives

The Sponsor lists as the goal/objective for the Trasylol RiskMAP:

The RiskMAP will identify those patients most at risk of a hypersensitivity reaction to Trasylol and provide information to reduce these patients from re-exposure to the drug within the period of highest risk of hypersensitivity.

*OSE Comment: The RiskMAP should include an additional goal to decrease the use of aprotinin in settings in which CPB is not available.*

### 4.2 Tools

The tools proposed by the Sponsor are narrowing of the indication for use, healthcare practitioner education on the risk of hypersensitivity, and utilization of a potential aprotinin

<sup>11</sup> Dietrich W, et al. Anaphylactic reactions to aprotinin re-exposure in cardiac surgery. *Anesthesiology* 2001; 95: 64-71.

<sup>12</sup> The authors had financial ties with Bayer Pharmaceuticals.

<sup>13</sup> RiskMAP proposal available in EDR, NDA 20-304, May 17, 2006 submission.

immunoglobulin assay to identify patients at risk for a hypersensitivity reaction. These are described in more detail below.

#### 4.2.1 Narrowing of the Indication for Use

The Sponsor is proposing to narrow the indication for use in patients at higher risk of bleeding. The supplement was submitted in September 2006, prior to the Advisory Committee meeting, and proposes to narrow the indication to patients undergoing primary CABG who are at increased risk for bleeding. The current approved indication and the Sponsor's proposed indication are provided in the table below.

Current approved indication	Proposed indication
prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass the course of coronary artery bypass graft surgery. <sup>14</sup>	prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass the course of coronary artery bypass graft surgery <u>who are at increased risk for blood loss and blood transfusions.</u> <sup>15</sup>

#### 4.2.2 Aprotinin IgG Assay

An aprotinin IgG assay is proposed to predict patients who may experience hypersensitivity. Bayer has stated that Trasylo<sup>l</sup> will be contraindicated in patients who have a positive result<sup>16</sup> to the IgG antibody test. The Sponsor acknowledges that the assay is not commercially available; however, the Sponsor indicated that they are committed to incorporating the assay into the RiskMAP when the assay becomes available.

The danger of the test dose, and the difficulty in diagnosing anaphylactic reactions in the OR setting point to the need to develop another method to detect aprotinin hypersensitivity. Although the idea of an aprotinin-specific IgG assay is attractive, several issues surrounding the assay may limit its effectiveness in preventing hypersensitivity reactions:

- a. the assay is not commercially available, and, according to the Sponsor, the development of a point-of-use assay is even more distant;
- b. the assay has not been proven to be valid and reliable;
- c. the assay is expected to yield false positive results; that is, there will be some patients who will have measurable aprotinin IgG who would not have an anaphylactic reaction if they received aprotinin; and
- d. the assay may yield false negative results; that is, there will be some patients who do not have measurable aprotinin IgG who will have an anaphylactoid reaction if they receive aprotinin.

<sup>14</sup> Approved August 1998; approval letter available at <http://www.fda.gov/cder/foi/applletter/1998/20304s04.pdf>

<sup>15</sup> Bayer submission September 12, 2006.

<sup>16</sup> A positive result would be any measurable antibodies.

While acknowledging these limitations, the Advisory Committee urged the Sponsor to move forward to develop a point-of-use aprotinin-specific IgG assay.

*OSE Comment: We concur with the Advisory Committee.*

### **4.2.3 Healthcare Practitioner Education**

The main component of the RiskMAP is education. The Sponsor proposes educating cardiothoracic surgeons and cardiothoracic anesthesiologists about hypersensitivity reactions with aprotinin.

#### **4.2.3.1 Current educational initiatives**

The submission describes the education initiatives that the Sponsor currently undertakes regarding hypersensitivity reactions. These include:

- τ Sales representatives training includes a discussion of hypersensitivity, and sales staff are directed to engage with the prescriber on this risk;
- τ Full prescribing and warning information are provided with promotional pieces left with the prescriber;
- τ Discussion of information related to hypersensitivity in the Product Information Label via sales representatives and medical science liaisons; and
- τ Incorporation of information on the risk of hypersensitivity into visual aid material and external presentations.

#### **4.2.3.2 Proposed educational initiatives**

##### **Target audience**

The Sponsor has identified the primary target audience for the proposed education as 2,811 cardiothoracic surgeons and 3,473 cardiothoracic anesthesiologists. Patients discharged from the hospital who have been prescribed Trasylol are a secondary target. Finally, healthcare practitioners (HCPs) who report an adverse event with Trasylol to the Sponsor will be targeted to receive safety messages.

*OSE Comment: The Sponsor's proposed education focuses on cardiothoracic surgeons and cardiothoracic anesthesiologists. While these physicians are the primary Trasylol prescribers, use data provided by Bayer and use data generated by DSRCs show that non-cardiac surgeries comprise 3-4% of the use of Trasylol<sup>17</sup>. Non-cardiac surgical settings would be unlikely to provide for the capacity either in personnel or in equipment to implement emergent CPB, a strategy recommended to help manage anaphylactic reactions to Trasylol.*

##### **Educational messages**

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<sup>17</sup> Bayer submission to NDA 20-304 dated October 6, 2006.

Governale L. Analysis of inpatient use of Trasylol<sup>®</sup> (aprotinin): NDA 20-304. Data extracted October 2006 from Premier Rx Market Advisor.

The Sponsor states that the educational program will stress the following messages:

- τ The appropriate indication for use (CABG surgery requiring CPB);
- τ The risk of hypersensitivity is increased with re-exposure within 6 months;
- τ The importance of taking a complete medical history to uncover the use of cross-reacting products;
- τ The correct use of the test dose, including the need to observe the patient for 10 minutes after administration of the test dose;
- τ Encourage readiness for anaphylactic reaction with the test dose and the therapeutic dose;
- τ Information on cross-reacting products; and
- τ Distribution of medical literature regarding hypersensitivity with aprotinin.

#### **Proposed Educational Activities and Materials**

The Sponsor states new educational materials will be produced which will convey and emphasize key safety messages. The new materials include:

1. a safety sheet (not explained);
2. safety messages displayed on the [www.Trasylol.com](http://www.Trasylol.com) website;
3. patient chart labels to be placed in the hospital notes of patients who receive Trasylol to inform the patients' subsequent healthcare providers of Trasylol exposure;
4. a slide educational program to be delivered by the Sponsor's medical science liaisons;
5. educational meeting programs for cardiothoracic anesthesiologists and cardiothoracic surgeons;
6. a rapid interactive e-communication targeted at cardiothoracic anesthesiologists and cardiothoracic surgeons;
7. educational materials intended for distribution by prescribing physicians to patients to inform the patient of exposure to Trasylol and the risk of subsequent exposure; and
8. communication of safety messages to HCPs who report adverse events with Trasylol.

#### *OSE Comment*

- *The sponsor did not describe the basis of the chosen educational tools. For example, what is the rationale for each of the educational activities and materials? How is the setting (where the educational activities will take place) expected to affect the learning process?*
- *A key element of the implementation of the educational plan is the personal contact (outreach) to be made by the Sponsor's staff (Cardiothoracic Sales Specialists and Medical Science Liaisons) with the prescribers. This and other aspects (Trasylol website, scientific programs, etc.) of education are described adequately; however, some educational tools are less well described.*

#### **4.3 Assessment of the Effectiveness of the RiskMAP**

The Sponsor proposes to conduct a pre- and post-launch survey of patient hospital records noting the cases where the test dose was recorded, the history of aprotinin exposure, and previous surgery within 6 months of the current hospital visit<sup>18</sup>. The Sponsor also proposes a structured follow-up questionnaire to be used in a sample of prescribers to document the

<sup>18</sup> Previous surgery within 6 months of the present surgical procedure may suggest previous aprotinin exposure.

receipt and application of the information described in the key safety messages from the educational program.

*OSE Comment:*

- *The Sponsor has not described how they plan to monitor the use of aprotinin in settings that do not offer emergent CPB.*
- *No survey instrument and limited methodology was provided to evaluate the effectiveness of the educational plan in the RMP. For example, who will receive the survey, how will the sample be determined, and what are the selection criteria? What controls will they use to minimize bias? What controls will they use to compensate for the limitations associated with their methodology? How many physicians/patient records will be surveyed? How will the survey be administered? What questions will be posed on the survey instrument?*

## 5 DISCUSSION/CONCLUSION

The RiskMAP proposed by the Sponsor consists of education for prescribers and, potentially, an aprotinin-specific IgG assay (not currently commercially available) to identify patients at highest risk for a hypersensitivity reaction. The Sponsor also plans to narrow the indication for use to patients undergoing CABG (requiring CPB) at higher risk for bleeding. We have the following concerns regarding this RiskMAP proposal.

1. Although we believe that educating about the risk of hypersensitivity is crucial, we have limited evidence that education alone has been successful in managing the significant risks particularly for a product that has been marketed for an extensive period of time. The AC members also felt that education alone may not be sufficient to minimize the risk. The Sponsor also would need to assure the Agency that their educational efforts are rigorous and their plans to evaluate the educational efforts are equally rigorous. The Sponsor should continue to consider additional tools to minimize the risk.
2. The education proposed for prescribers appears to be similar to educational efforts the Sponsor describes as current practice. We note that the education currently being undertaken has not prevented the occurrence of additional cases, including fatal cases. We do not believe that education surrounding the current labeling would be sufficient.
  - The appropriate indication for use (CABG surgery requiring CPB) – the indication has always been for primary or repeat CABG and we assume the company has not promoted its use for other indications, however a significant proportion of patients being treated with aprotinin are for other cardiovascular surgeries. Overall, about 96-97% of use is for cardiac surgery<sup>19</sup>, but CABG surgery comprises only 60% of Trasylol use<sup>20</sup>. The Sponsor hasn't indicated what they will do to prevent its use in non-CABG surgeries

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<sup>19</sup> Bayer submission to NDA 20-304 dated October 6, 2006.

Governale L. Analysis of inpatient use of Trasylol<sup>®</sup> (aprotinin); NDA 20-304. Data extracted October 2006 from *Premier Rx MarketAdvisor*.

<sup>20</sup> Bayer submission to NDA 20-304 dated October 6, 2006.

- The risk of hypersensitivity is increased with re-exposure within 6 months - Although we agree that the 6-month period following exposure to aprotinin is the period of highest risk from re-exposure to aprotinin, postmarketing data support a conclusion that hypersensitivity reactions can occur when re-exposure occurs after six months have elapsed from the previous dose. In fact, an examination of cases of anaphylaxis cases in AERS shows that in one-third of the cases with documented previous exposure to aprotinin, re-exposure occurred longer than 6 months from the previous exposure. For the above reasons, we believe the contraindication for re-exposure with aprotinin should be extended to 12 months.
- The importance of taking a complete medical history to uncover the use of aprotinin and of cross-reacting products<sup>21</sup> - Patients may not know if they have been exposed to aprotinin, and physicians may be unaware of procedures likely to entail exposure to aprotinin-containing products. Even a review of the patients' medical records may not reveal previous exposures to aprotinin or aprotinin-containing products. In Europe, previous exposure to aprotinin is *assumed* for patients with previous cardiac, major orthopedic, or upper abdominal surgery.<sup>22</sup> A similar approach should be included in the U.S. labeling and in their educational plan; that is, previous exposure should be assumed for patients who have had previous surgery in which aprotinin or cross-reacting products are frequently used. The Sponsor should develop a list of procedures that may entail exposure to aprotinin or aprotinin-containing products. This list should be included in the Trasyolol labeling.
- The correct use of the test dose, including the need to observe the patient for 10 minutes after administration of the test dose - The postmarketing data show that the test dose is problematic. The Sponsor stated that hypersensitivity reactions occurred with the test dose alone in 81 cases of the 139 cases in their database that reported the use of a test dose. Nineteen of the reactions to the test dose were fatal. In 38 cases, including 9 cases with fatal outcomes, the test dose was negative but a hypersensitivity reaction occurred with the subsequent therapeutic dose of aprotinin. In the cases in AERS, 23 patients experienced a hypersensitivity reaction with the test dose alone, including 10 cases with fatal outcomes. We encourage the reviewing division to work with the Sponsor to develop a less dangerous method to safely administer the test dose to patients pending the development of an aprotinin-specific IgG assay. Suggestions from the Cardiovascular and Renal Drug Advisory Committee included giving the test dose very slowly and only when emergent cardiopulmonary bypass is available (in *all* cases, not solely in cases with documented history of previous aprotinin exposure), and pre-treating patients with antihistamines and steroids.

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<sup>21</sup> Use of Tisseel, a cross-reacting fibrin glue, has been increasing, with projected exposures of > 110,000 patients in 2005. Governale L. Tisseel use based on hospital discharges with billing charges for Tisseel. Data from Premier Healthcare Informatics.

<sup>22</sup> Beierlein W et al. Forty years of clinical aprotinin use: a review of 124 hypersensitivity reactions. *Ann Thorac Surg* 2005; 79: 741-8.

- Encourage readiness for anaphylactic reaction with the test dose and the therapeutic dose - The labeling lists the signs and symptoms that may signal a hypersensitivity reaction. These include skin eruptions, itching, dyspnea, nausea, tachycardia, and circulatory failure. Ms. Lu's review of the cases in AERS shows that the most frequently reported sign of anaphylaxis is hypotension. Skin eruptions may be hidden by surgical draping, and symptoms that would ordinarily be reported by patients (e.g., dyspnea, nausea, itching) may not present because the patient is anesthetized and mechanically ventilated. Additionally, there are other factors, including other medications used in the OR setting, and the patients' underlying disease, that could account for hypotension, and may delay the diagnosis of hypersensitivity. In fact, in six of the fatal AERS cases, the reporter acknowledged that the medical team did not recognize that the patient was experiencing an anaphylactic reaction at its initial presentation. The labeling should state that the most frequently reported sign of anaphylaxis is hypotension.
3. While, in theory, the IgG assay is a good idea, it is not commercially available, and, according to the Sponsor, the development of a point-of-use assay is even more distant. Moreover, the assay is expected to yield false positive results; that is, there will be some patients who will have measurable aprotinin IgG who would not have an anaphylactic reaction if they received aprotinin; and the assay may yield false negative results; that is, there will be some patients who do not have measurable aprotinin IgG who will have an anaphylactoid reaction if they receive aprotinin. While we encourage the Sponsor to continue to develop this assay, we believe the assay's validity and reliability to predict anaphylactic/ hypersensitivity reactions must be proven. If the assay is a proven predictor of such reactions, the Sponsor will need to consider a practical way for all patients to be tested with the assay.
  4. Recent observational studies raise concerns regarding the safety of aprotinin. In addition to the Mangano and Karkouti studies<sup>23</sup> that raised questions regarding the cardiac and renal safety of aprotinin, two additional observational studies<sup>24</sup> suggest that aprotinin may be associated with increased mortality. These studies must be reviewed for their implications for the safe use of Trasylo<sup>l</sup>. While it is possible that the gathering evidence from the observational studies is the result of the channeling of sicker patients into treatment with aprotinin, it is also possible that aprotinin actually causes increased mortality as compared with the comparator therapies. The data from the observational studies should be analyzed to determine which of these possibilities explains the results of the observational studies. If the answer to this

<sup>23</sup> Mangano DT, et al. The risk associated with aprotinin in cardiac surgery. *N Engl J Med* 2006; 354; 4: 353-65. Karkouti K, et al. A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery. *Transfusion* 2006; 46: 327-38.

<sup>24</sup> Schneeweiss S, et al. Mortality and cardiovascular and renal outcomes in recipients of aprotinin, aminocaproic acid and tranexamic acid during CABG surgery—report on computerized inpatient data from the Premier Perspective comparative database. Initial study report September 13, 2006.

Nesiritide Administered Peri-Anesthesia Study Investigators. Nesiritide shows hint of survival benefit in chronic-HF patients undergoing CABG. Available at URL <http://www.theheart.org/article/741265.do>

question is not clear from this analysis, the Sponsor should conduct a randomized controlled trial to address this question.<sup>25</sup>

## 6 COMMENTS/RECOMMENDATIONS FOR THE DMIHP AND THE SPONSOR

### A. *Labeling Recommendations*

- The Sponsor and the reviewing division should consider contraindicating re-exposure to aprotinin within 12 months.
- Use of aprotinin should be contraindicated for patients who have had a procedure in the previous 12 months in which use of aprotinin is suspected (e.g., heart surgery).
- The labeling should stress that usual symptoms of hypersensitivity may not be present or may be obscured by the OR setting, and that the most frequently observed sign of hypersensitivity is hypotension.
- The labeling should stress the danger of the test dose and the failure of the test dose to predict a hypersensitivity reaction in many cases. The labeling should advise that aprotinin, including the test dose, be administered only when emergent cardiopulmonary bypass is available, and only after pre-treating with antihistamines and steroids.

### B. *RiskMAP Comments and Recommendations*

- Please include as a goal of the RiskMAP to reduce the use of aprotinin in settings in which emergent CPB is not available (i.e., non-cardiac surgery).
- Education and Outreach Plan
  - While cardiothoracic surgeons and cardiothoracic anesthesiologists are the primary Trasyol prescribers, use data provided by Bayer show that non-cardiac surgeries comprise 4% of the use of Trasyol<sup>26</sup>. Non-cardiac surgical settings would be unlikely to provide for the capacity either in personnel or in equipment to implement emergent cardiopulmonary bypass (CPB), a strategy recommended to help manage anaphylactic reactions to Trasyol. We recommend that the Sponsor develop a strategy to identify physicians who are using Trasyol in such non-cardiac surgical settings and contact these physicians to educate them on the labeled indication and the requirement to have emergent CPB capability when Trasyol is used. Because education is the key tool that will be used to minimize the risk of hypersensitivity, the educational efforts must be as effective as possible. To this end, the Sponsor needs to provide additional information to the Agency about their educational efforts:
  - Describe the basis of the chosen educational tools. Explain how any acquired background information shaped the rationale for each of the educational activities and materials, and how the setting (where the educational activities will take place) is expected to affect the learning process.

<sup>25</sup> We note that the Advisory Committee encouraged the Sponsor to conduct such a trial.

<sup>26</sup> Bayer submission to NDA 20-304 dated October 6, 2006.

- Describe to what extent the following elements were considered in developing the educational activities and materials: Characteristics of the targeted CT surgeons and CT anesthesiologists that would be important to their ability to receive and implement the education (such as, but not limited to: demographics, learning preferences, and educational needs)
  - Input from the target audience during educational material development
  - Adaptability of the educational materials to meet the needs of different educational activities or settings
  - Opportunity(ies) for the target audience to demonstrate what they have learned (feedback)
  - Please provide additional information about the implementation of the following educational materials and activities.
    - A list of the educational materials to be supplied by prescribers to patients on discharge from the hospital
    - An explanation of the proposed “rapid interactive e-communication”

C. *Assessment of the Effectiveness of RiskMAP*

The Sponsor proposes to conduct a pre- and post-launch survey of patient hospital records noting the cases where the test dose was recorded, the history of aprotinin exposure, and previous surgery within 6 months of the current hospital visit. The Sponsor also proposes a structured follow-up questionnaire to be used in a sample of prescribers to document the receipt and application of the information described in the key safety messages from the educational program. No survey instrument and limited methodology was provided to evaluate the effectiveness of the educational plan in the RiskMAP.

- Submit all survey methodology including, but not limited to:
  - Who will receive the survey?
  - How will the sample be determined?
  - What are the selection criteria?
  - What controls will they use to minimize bias?
  - What controls will they use to compensate for the limitations associated with their methodology?
  - How many physicians/patient records will be surveyed?
  - How will the survey be administered?
- What questions will be posed on the survey instrument
- Submit the survey instrument that will be used.
- Develop a strategy to monitor the success of decreasing the use of aprotinin in settings in which emergent CBP is available.

*D. Recommendations for further Risk Assessment*

- We recommend the Sponsor ascertain the cause of the death in the I3 Drug Safety Study entitled “Mortality of Cardiovascular and Renal Outcomes in Recipients of Aprotinin, Aminocaproic Acid and Tranexamic Acid during CABG Surgery.”
- Two additional observational studies<sup>27</sup> suggest that aprotinin may be associated with increased mortality. The data from studies must be reviewed for their implications for the safe use of Trasylol. While it is possible that the gathering evidence from the observational studies is the result of the channeling of sicker patients into treatment with aprotinin, it is also possible that aprotinin actually causes increased mortality as compared with the comparator therapies. The data from the observational studies should be analyzed to determine which of these possibilities explains the results of the observational studies. If the answer to this question is not clear from this analysis, the Sponsor should conduct a randomized controlled trial to address this question. We note that the members of the AC encouraged the Sponsor to conduct such a trial.

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<sup>27</sup> Schneeweiss S, et al. Mortality and cardiovascular and renal outcomes in recipients of aprotinin, aminocaproic acid and tranexamic acid during CABG surgery—report on computerized inpatient data from the Premier Perspective comparative database, Initial study report September 13, 2006.

Nesiritide Administered Peri-Anesthesia Study Investigators. Nesiritide shows hint of survival benefit in chronic-HF patients undergoing CABG. Available at URL <http://www.theheart.org/article/741265.do>

## Appendix 1. Trasylol labeling of hypersensitivity/anaphylactic Reactions

The *Boxed Warnings* states the following:

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. (See **WARNINGS** and **PRECAUTIONS**).

The *Warnings* section states the following:

Anaphylactic or anaphylactoid reactions are possible when Trasylol® is administered. Hypersensitivity reactions are rare in patients with no prior exposure to aprotinin. Hypersensitivity reactions can range from skin eruptions, itching, dyspnea, nausea and tachycardia to fatal anaphylactic shock with circulatory failure. If a hypersensitivity reaction occurs during injection or infusion of Trasylol®, administration should be stopped immediately and emergency treatment should be initiated. It should be noted that severe (fatal) hypersensitivity/anaphylactic reactions can also occur in connection with application of the test dose. Even when a second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

**Re-exposure to aprotinin:** In a retrospective review of 387 European patient records with documented re-exposure to Trasylol®, the incidence of hypersensitivity/anaphylactic reactions was 2.7%. Two patients who experienced hypersensitivity/anaphylactic reactions subsequently died, 24 hours and 5 days after surgery, respectively. The relationship of these 2 deaths to Trasylol® is unclear. This retrospective review also showed that the incidence of a hypersensitivity or anaphylactic reaction following re-exposure is increased when the re-exposure occurs within 6 months of the initial administration (5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months). Other smaller studies have shown that in case of re-exposure, the incidence of hypersensitivity/anaphylactic reactions may reach the five percent level.

Before initiating treatment with Trasylol® in a patient with a history of prior exposure to aprotinin or products containing aprotinin, the recommendations below should be followed to manage a potential hypersensitivity or anaphylactic reaction: 1) Have standard emergency treatments for hypersensitivity or anaphylactic reactions readily available in the operating room (e.g., epinephrine, corticosteroids). 2) Administration of the test dose and loading dose should be done only when the conditions for rapid cannulation (if necessary) are present. 3) Delay the addition of Trasylol® into the pump prime solution until after the loading dose has been safely administered. Additionally, administration of H1 and H2 blockers 15 minutes before the test dose may be considered.

The *Precautions* section states the following:

**General:** Test Dose: All patients treated with Trasylol® should first receive a test dose to assess the potential for allergic reactions. The test dose of 1 mL Trasylol® should be administered intravenously at least 10 minutes prior to the loading dose. However, even after the uneventful administration of the initial 1 mL test-dose, the therapeutic dose may cause an anaphylactic reaction. If this happens the infusion of aprotinin should immediately be stopped, and standard emergency treatment for anaphylaxis be applied. It should be noted that hypersensitivity/ anaphylactic reactions can also occur in connection with application of the test-dose. (see **WARNINGS** )

Allergic Reactions: Patients with a history of allergic reactions to drugs or other agents may be at greater risk of developing a hypersensitivity or anaphylactic reaction upon exposure to Trasylol®. (see **WARNINGS** )

Loading Dose: The loading dose of Trasylol® should be given intravenously to patients in the supine position over a 20-30 minute period. Rapid intravenous administration of Trasylol® can cause a transient fall in blood pressure. (see **DOSAGE AND ADMINISTRATION** ).

Use of Trasylol® in patients undergoing deep hypothermic circulatory arrest: Two U.S. case control studies have reported contradictory results in patients receiving Trasylol® while undergoing deep hypothermic circulatory arrest in connection with surgery of the aortic arch.

The first study showed an increase in both renal failure and mortality compared to age-matched historical controls. Similar results were not observed, however, in a second case control study. The strength of this association is uncertain because there are no data from randomized studies to confirm or refute these findings.

The *Adverse Reactions* section of the labeling states the following about hypersensitivity.

**Hypersensitivity and Anaphylaxis:** See **WARNINGS**.

Hypersensitivity and anaphylactic reactions during surgery were rarely reported in U.S. controlled clinical studies in patients with no prior exposure to Trasylol® (1/1424 patients or <0.1% on Trasylol® vs. 1/861 patients or 0.1% on placebo). In case of re-exposure the incidence of hypersensitivity/anaphylactic reactions has been reported to reach the 5% level. A review of 387 European patient records involving re-exposure to Trasylol® showed that the incidence of hypersensitivity or anaphylactic reactions was 5.0% for re-exposure within 6 months and 0.9% for re-exposure greater than 6 months.

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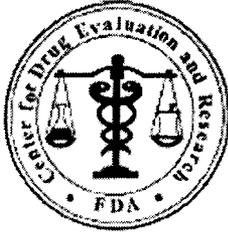
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2007 DRAFT REVIEWS--All SUBSEQUENT REVIEW MATERIALS ARE DRAFT



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: August 10, 2007

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From: Rita Ouellet-Hellstrom, Ph.D., M.P.H., Epidemiologist  
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Subject: Review of 13 Drug Safety Draft Report: *Mortality and Cardiovascular and Renal Outcomes in Recipients of Aprotinin, Aminocaproic Acid and Tranexamic Acid during CABG Surgery: Report on Computerized Inpatient Data from the Premier Perspective Comparative Database. September 13, 2006.*

Drug Name(s): Aprotinin (Trasylol®)

Application Type/Number: NDA: 20-304

Applicant/sponsor: Bayer Pharmaceuticals Division

OSE RCM #: 2007-10

## CONTENTS

EXECUTIVE SUMMARY .....	1
1 BACKGROUND/HISTORY .....	1
2 REVIEW METHODS AND MATERIALS .....	2
3 RESULTS OF REVIEW .....	3
3.1 Objectives .....	3
3.2 Design .....	3
3.3 Informed Consent.....	3
3.4 Data Source(s).....	4
3.5 Study Time Period(s) .....	4
3.6 Population .....	4
3.7 Exposure .....	6
3.8 Disease Outcome of Interest .....	7
3.9 Sample Size.....	9
3.10 Statistical Analyses .....	9
3.11 Results.....	11
3.12 Trends .....	22
4 DISCUSSION .....	24
5 CONCLUSIONS .....	24
6 RECOMMENDATIONS .....	25
7 REFERENCES .....	26
APPENDIX 1: FDA Public Health Advisory, February 8, 2006 .....	27
APPENDIX 2: FDA Public Health Advisory, September 29, 2006.....	29
APPENDIX 3: EBGM Scores by Year .....	31

**TABLES**

Table 1. Characteristics of 66,435 patients undergoing CABG Surgery..... 12

Table 2. Age and sex adjusted relative risk ratio (RR) for cumulative incidence of in-hospital health outcomes among 66,435 patients undergoing CABG surgery..... 12

Table 3. Multivariate logistic regression results for in-hospital outcomes for the full cohort (N = 66,435)..... 13

Table 4. Measured predictors of the study outcome included in the multivariate analyses that show a minimum of 50% increase in risk. .... 14

Table 5. Odds Ratio and 95% confidence intervals (CI) for liver disease as an independent predictor of outcome in the multivariate analysis. .... 14

Table 6. Multivariate logistic regression risk estimates\* of in-hospital outcomes for the full cohort and restricted to medium and high CABG volume hospitals and to medium and high volume physicians. .... 15

Table 7. Multivariate adjusted models showing the association between aprotinin use and of renal failure as a function of increasing covariate information BEFORE CABG surgery. .... 16

Table 8. Multivariate logistic regression risk estimates\* of in-hospital outcomes for the full cohort using traditional modeling, using propensity score analysis, and restricted to patients who stayed at least 2 days after the index CABG surgery. .... 16

Table 9. Risk estimates\* for high-dose aprotinin used during CABG surgery compared to low-dose aprotinin use. .... 17

Table 10. Comparison of risk estimates for death, acute heart failure, stroke and renal failure based on degree of covariate adjustment and limitations (see Table 2 and Table 5). .... 18

Table 11. Empirical Bayesian Geometric Mean Scores (EBGM) and Confidence Intervals for Aprotinin, Aminocaproic Acid, and for Tranexamic Acid for some Selected MedDRA Preferred Terms (PT) Events Observed in Clinical Trials. .... 19

Table 12. Summary of adjusted\* risk estimates for post-operative renal events. .... 20

Table 13. Comparison of odds ratios\* and 95% confidence intervals results\* from multivariate logistic regression models without (MLR) and with (MLR\_PS) propensity score adjustments for patients undergoing primary and complex surgery. Mangano et al 2006.<sup>1</sup> .... 21

Table 14. Incidence Rates of Adverse Events ( $\leq 2\%$ ) By Treatment for all Patients from US Placebo-Controlled clinical trials ..... 21

Table 15. Average length of stay (ALOS) for patients receiving aminocaproic acid, aprotinin, and tranexamic acid by year - limited to cardiovascular operations. .... 23

## EXECUTIVE SUMMARY

Aprotinin (Trasylol<sup>®</sup>) is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass (CPB) in the course of coronary artery bypass graft surgery (CABG) who are at an increased risk for blood loss and blood transfusion.

In 2006, two studies reported on the risk of aprotinin use among cardiac surgery patients. On September 21, 2006 an Advisory Committee (AC) met to discuss clinical and observational data questioning the appropriateness of using prophylactic aprotinin injections 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. This discussion followed the February 8, 2006 FDA Public Health Advisory for the use of aprotinin injection. On September 27, 2006, a few days after the AC meeting, the sponsor told FDA that it had commissioned a safety study. The preliminary results for this study dated September 13, 2006, were not submitted for discussion at the September 21, 2006 AC meeting. The Agency issued another Public Health Advisory on September 29, 2006.

This review provides a description of the i3 Drug Safety study methodology and analysis and comments on the study's preliminary results. The i3 report presents results from a large hospital-based cohort study that used administrative data to assess risk of acute revascularization, acute heart failure, stroke, acute renal failure, and all cause in-hospital death for recipients of aprotinin compared to users of other antifibrinolytics (tranexamic and aminocaproic acid). The strength of this study is its ability to identify and capture information on a large number of patients undergoing CABG surgery. The main limitations are its use of administrative data rather than clinical data from the medical records to identify medical outcome and to ascertain covariates that mitigate patient risks. In addition to multivariate analyses, the investigators conducted sensitivity and limited sub-analyses, to evaluate potential confounding.

Despite the limitations discussed above, the analyses conducted by the i3 Drug Safety Group offer a robust assessment of aprotinin use and also confirm renal effects reported by other studies. Elevated risks for cardiovascular events, and stroke, however, were likely associated with uncontrolled confounding in this study. Elevated risk estimates for death were also reduced when controlling for confounders but remained elevated nonetheless. The risk estimates for death appeared to be highly correlated with the risk estimates for renal events. Risk estimates for renal dysfunction remained stable when analyses were adjusted for confounding and show a high likelihood for an association with aprotinin use. OSE/DDRE recommends that medical records be reviewed to confirm renal failure, to identify the possible cause of in-hospital death, and to assess the possible contribution of liver disease to morbidity and/or mortality after aprotinin use.

If a process is underway to re-analyze data collected by other investigators, OSE supports the Agency's efforts to also obtain and re-analyze the i3 Drug Safety's Premier data in an effort to reproduce and standardize the analysis of all three datasets and to evaluate, in this and other databases, whether liver disease is a possible outcome of aprotinin use. Re-analysis of the Premier data should include a stratified analysis by propensity score deciles or quintiles and should adjust for days-since-surgery.

## 1 BACKGROUND/HISTORY

Aprotinin (Trasylol<sup>®</sup>) is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass (CPB) in the course of coronary artery bypass graft surgery (CABG) who are at an increased risk for blood loss and blood transfusion.

In 2006, two studies reported on the risk of aprotinin use among cardiac surgery patients. The first article<sup>1</sup>, published in New England Journal of Medicine on January 26, 2006 reported that treatment with aprotinin in the setting of primary cardiac surgery was associated with an increased risk for a renal and cardiovascular events compared to treatment with no antifibrinolytic therapy. The risks decreased (renal events) or disappeared (cardiovascular events) when the analysis was limited to patients undergoing complex cardiac surgery.

The second study<sup>2</sup>, published in the March 2006 issue of Transfusion, reported a 40% increase risk for renal dysfunction associated with aprotinin treatment compared to treatment with tranexamic acid in a single setting of cardiac surgery.

The Division of Medical Imaging and Hematology Products requested the Office of Surveillance and Epidemiology requested the Division of Drug Risk Evaluation (OSE/DDRE) to provide a critique of the studies cited above. The critique<sup>3</sup> was completed on June 1, 2006. This document was limited in scope to reviewing the design and analytical aspect of the study.

In light of these publications, FDA issued the following "Public Health Advisory"<sup>4</sup> on February 8, 2006 (Appendix 1). At the same time, the product label was modified to more prominently advise prescribers about the potential risk of adverse renal events when using this product.

On September 21, 2006 an Advisory Committee (AC) met to discuss clinical and observational data questioning the appropriateness of using prophylactic aprotinin injections 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. This discussion followed the February 8, 2006 FDA Public Health Advisory for the use of aprotinin injection.

Prior to the AC meeting, the sponsor had commissioned an observational clinical study to quantify the association between serious cardiovascular and renal outcomes among persons undergoing coronary artery bypass graft (CABG) surgery. This study was based on a proposal prepared by the contract research organization i3 Drug Safety, a division of Ingenix Pharmaceutical Services, Inc. to use the Premier Perspective Comparative Database, an inpatient administrative database. On September 27, 2006, a few days after the AC meeting, the sponsor told FDA that it had commissioned this safety study. The preliminary results for this study dated September 13, 2006, were not submitted for discussion at the September 21, 2006 AC meeting. The Agency issued another Public Health Advisory<sup>5</sup> on September 29, 2006 (Appendix 2).

This review provides a description of the i3 Drug Safety study methodology and analysis and comments on the study's preliminary results.

## 2 REVIEW METHODS AND MATERIALS

The study was evaluated for consistency, completeness and whether the study and analytical methods could achieve the study objectives. The research methods assessed include the study's

- o Design
- o Data Sources
- o Informed Consent
- o Study Time Periods
- o Population Selected
- o Exposure Criteria

<sup>1</sup> <http://www.fda.gov/cder/drug/advison/aprotinin.htm>

<sup>2</sup> <http://www.fda.gov/cder/drug/advison/aprotinin20060919.htm>

- Disease Outcome
- Sample Size
- Analytical Methods

### 3 RESULTS OF REVIEW

#### 3.1 OBJECTIVES

The investigators conducted a cohort study to quantify the association between aprotinin use and serious cardiovascular and renal outcomes and in-hospital death from any cause compared to aminocaproic acid and tranexamic acid use among patients undergoing CABG surgery.

##### OSE Comments on Objectives

The investigators proposed to compare cardiovascular, renal and in-hospital mortality outcomes in CABG patients receiving the antifibrinolytic aprotinin with those receiving aminocaproic acid and tranexamic acid. The objectives stated in this report are consistent with the proposed objectives.

#### 3.2 DESIGN

The investigators used a hospital-based retrospective cohort design to compare the experience of patients undergoing a CABG procedure that required cardiopulmonary bypass and intravenous administration of antifibrinolytics during surgery.

##### OSE Comments on Study Design

Although not specifically stated, because the investigators refer to the study population as a cohort, it is assumed that the study design is that of a retrospective cohort that will assess the incidence in each treatment group and summarized by calculating the relative risks of aprotinin treatment to that of other antifibrinolytic treatments.

Use of a retrospective cohort design is appropriate to evaluate exposure and outcome. Although the Premier data is based on information related to reimbursement, establishing a chronological sequence is relatively straightforward.

#### 3.3 INFORMED CONSENT

The draft review does not mention IRB review/approval and informed consent. The protocol, however, does mention constraints imposed by the Health Insurance Portability and Accountability Act (HIPAA). The protocol also states that medical record review would need to be done under oversight of an appropriate institutional review board (IRB) to use patient identifiable data for linkage to medical records. No medical record abstraction was done for the preliminary study.

##### OSE Comments on Institutional Board Review (IRB) / Informed Consent

Because of the proprietary nature and the database used for the study and the agreements in place between Premier and the hospitals, it is not expected that the investigators could obtain informed consent. It is expected, however, that the investigators submit their protocol for IRB review and approval. Neither the draft report nor the study protocol mentions IRB review and approval. The report does state, however, that Premier provided a de-identified data set for the present analysis, which was fully compliant with the 1996 Health Insurance Portability and Accountability Act (HIPAA).

### 3.4 DATA SOURCE(S)

Data for this study were drawn from the Premier Perspective Comparative Database (PCD), a large hospital-based, service-level comparative database in the United States (US). The PCD provides detailed resource utilization data along with patient primary and secondary diagnoses and procedure codes for approximately one-sixth of all hospitalizations in the US, with broad geographic diversity.

The Premier database has been used for research studies in the past, including ones examining the relation between perioperative drug use and mortality. Detailed service-level information is available for each hospital stay and includes information such as drug utilization by product name and strength, quantity dispensed, and unit cost of drugs, department costs, charge detail as well as surgeon and hospital characteristics. Patient level information includes demographics, principal and secondary diagnoses, principal and secondary procedures, length of stay, cost of care, day-of-stay data, and mode of discharge including death, but not cause of death.

The Premier database was proposed because Premier is able to go back to hospitals for chart reviews for patients of interest under oversight of an appropriate institutional review board (IRB) to use patient identifiable data for linkage to medical records.

#### OSE Comments on Data Sources

Limitations of using claims data for research are well known and acknowledged by the investigators. Limitations that may affect this study include incomplete pre- and post-operative data capture, minimal information on patient's medical and behavioral history, and medical codes that maximize re-imburement rather precisely reflect a patient's health condition.

The data source used is consistent with what was proposed in the original protocol. Medical record review, however, was not initiated nor completed for the preliminary report.

### 3.5 STUDY TIME PERIOD(S)

The study incorporates three years of Premier data beginning April 1, 2003.

#### OSE Comments on the Study Time Period(s)

The Premier analytical database captures information on patients undergoing CABG beginning April 1, 2003. The investigators state that the Premier database captures CABG information for a three year period. Based on this information, it is assumed that the total study period is between April 1, 2003 and March 31, 2006. There is no reference in the report, other than the admission year covariate listed in univariate tables where the complete time period is referenced.

The protocol had originally proposed a longer study period beginning January 2001 and extending through September 2005 but the investigators reported revising the time period when they learned that only after April 1, 2003 were all procedures, test orders, and medication dispensing consistently and reliably coded with information about the day they were administered. According to the investigators, data before April 1, 2003 were excluded from the study. It was later learned, however, that the dataset actually included procedures/admissions starting January 1, 2003.

### 3.6 POPULATION

The study included all patients 18 years or older within the Premier database who underwent a CABG procedure (ICD-9 CM procedure code 36.1x) that required cardiopulmonary bypass and intravenous administration of aprotinin, aminocaproic acid, or tranexamic acid. Patients were followed to the end of their hospitalization.

Patients were excluded if they:

- Received multiple antifibrinolytic agents during surgery;
- Received less than two million units aprotinin (i.e., fewer than two vials), less than 10g of aminocaproic acid (i.e. fewer than two vials), or less than 1 g of tranexamic acid (i.e. less than one full vial);
- Did not receive any antifibrinolytics.

The index day was the date of the CABG procedure. Follow-up time started on the day following the index day for all outcome except ischemic stroke and death which were observed beginning with the day of surgery. Observation for potential study outcomes continued until the end of the hospital stay during which the CABG procedure occurred. Patients transferred to a second facility were followed up until the date of transfer.

The following patient characteristics were included in the analytical database:

Demographic	Age, sex, race, low income status (Medicaid or indigent), marital status (living with partner)
Admission	Year of admission, admission type, day of CABG surgery after admission, emergency admission
CABG Surgery Type	Redo, complex (any other surgery in addition to CABG), number of vessels involved, percutaneous coronary procedure or thrombolysis during index hospitalization but before CABG surgery, use of plasma expander during surgery, use of a cell saver, whole blood, red cells, plasma, or platelet transfusions during surgery, cardiac arrest during or before CABG surgery, and diagnosis related group (DRG) severity coding.
Health History <i>(as recorded in the discharge diagnoses)</i>	Diabetes, hypertension, liver disease, COPD/asthma, cancer, old MI, old stroke, angina, renal failure, heart failure.
Health History <i>(Identified via drug use &amp; procedures)</i>	Warfarin use and arrhythmia before the index day
Hospital characteristics	Teaching status, location (Midwest, Northeast, South, and West, and urban/rural), hospital size (number of beds), CABG volume, hospital aprotinin preference (proportion of all antifibrinolytic use)

About 44% of patients received aprotinin and 54% aminocaproic acid. The few remaining patients received tranexamic acid and were included with the aminocaproic acid recipients for primary analyses of aprotinin versus other antifibrinolytics.

### OSE Comments on the Study Population

Because the original study encompassed a longer time period, the original proposal projected had identified 104,539 discharges that received an antifibrinolytic agent and of these, 73,905 hospitalizations during which CABG was performed. The preliminary study reports on 66,435 qualifying patients.

For this study, investigators used the ICD-9CM's 36.1x code (bypass anastomosis for heart revascularization) to identify CABG patients. Underascertainment of CABG surgery is not likely to be a major concern since the procedure is costly and reimbursement is likely claimed. To identify CABG surgery patients, however, other studies have included the 36.2 (Heart revascularization by arterial implant) ICD-9 CM code as well for post-operative surveillance that have used claims databases<sup>4</sup>. A claim for CABG surgery is not likely to differ by treatment group.

Information on patient demographics and surgery are likely reliable if recorded. Identification of outcome depends on the accuracy of ICD9 codes. Results of laboratory tests and other diagnostic procedures are usually not recorded. Capture of any medical diagnosis depends on the accuracy of the information recorded. These limitations are acknowledged by the investigators. When evaluating relative risks, underascertainment per se is not likely to be a major problem unless data capture of the covariate is unbalanced across treatment groups. Costs<sup>5</sup> of the antifibrinolytics vary significantly with aprotinin being significantly more costly than aminocaproic acid or tranexamic acid. Consequently, information on prior medical history or existing medical complications that would justify use of the more costly aprotinin would more likely be recorded for claims purposes when compared to the lower cost antifibrinolytics and could introduce imbalance in the treatment groups. Unidentified residual confounding remains a concern for this study.

When possible, the sensitivity and positive predicted value of selected diagnostic and procedure codes should be verified by reviewing at least a sample of medical records. The investigators for this study had proposed to review some medical records but had not completed that task for the report under review.

### **3.7 EXPOSURE**

The study included three drug exposure groups on the day of the index CABG procedure:

- Aprotinin intravenous (IV)
- Aminocaproic acid IV and
- Tranexamic acid IV

Because of relatively small number of tranexamic acid users, the primary analysis combined aminocaproic acid and tranexamic acid into one non-protinin antifibrinolytic group. For this study, exposure referred to aprotinin exposure and exposure to non-protinin antifibrinolytics was considered the referent exposure group.

Aprotinin use was further categorized into low dose (2-4 million IV units) and high dose (>4 million IV units) on the day of CABG surgery to evaluate a possible dose response effect. Oral use was sporadic and not considered in the analysis.

### OSE Comments on Exposure

The investigators excluded patients who received multiple antifibrinolytic agents during surgery, those who received less than two million units aprotinin (i.e., fewer than two vials), less than 10g of aminocaproic acid (i.e. fewer than two vials), or less than 1 g of tranexamic acid (i.e. less than

one full vial), and patients who did not receive any antifibrinolytics without providing any justification for doing so. It is understandable why they would exclude patients who received multiple antifibrinolytics since including them would make drug-related outcome difficult to interpret. It is unclear why patients who did not receive any antifibrinolytic were excluded since an important question that remains unanswered is whether use of any antifibrinolytic really improves morbidity and mortality.

### 3.8 DISEASE OUTCOME OF INTEREST

The outcomes in this study were assessed during the hospital stay following the day of the index CABG surgery. The outcomes considered were

- Acute coronary revascularization (indicated by the presence of codes for thrombolysis, percutaneous transluminal coronary angioplasty (PTCA), or redo CABG),
- Stroke (excluding hemorrhagic stroke),
- Acute heart failure (indicated by the presence of codes for dobutamine use or left ventricular assist device use),
- Acute renal failure (indicated by the presence of codes for hemo- or peritoneal dialysis or hemofiltration), and
- In-hospital deaths.

For all outcomes other than stroke, the exposure risk window was from the day after CABG surgery to the end of hospitalization. In addition, it was assumed that the outcome occurred on the day the respective charges were recorded in the database. No narrower timing information (e.g. hour) was available within the Premier database.

#### OSE Comments on Outcome of Interest

According to the protocol, outcome to be measured for this study included myocardial infarction, stroke, heart failure, dialysis, and death. Codes were provided in the protocol for all outcomes except myocardial infarction. Codes were also provided in the protocol for acute revascularization and acute renal failure as well. The study report does not address myocardial infarction at all. The investigators noted that since chronology was critical in this study, they focused on an outcome that could be reliably identified by procedure codes.

Renal insufficiency could not be determined in the absence of laboratory values in the Premier database therefore acute renal failure was defined as "renal failure" or "renal failure requiring dialysis".

OSE/DDRE has several concerns about outcome identification and ascertainment in the study report. These include lack of specificity in using ICD-9 CM codes to identify some outcome as noted by the investigators, differences in length of the observation period to ascertain outcome, and differences in duration of hospital stay.

#### ICD-9 CM Code - Specificity

The sensitivity and specificity of ICD-9 diagnostic and procedural codes vary depending on the seriousness and knowledge of the disease under study. For example medical record review of cases initially identified using only ICD-9 codes in some studies have shown a sensitivity of 67% for code 410 to identify a myocardial infarction (MI) and a specificity of 100%<sup>6</sup>. On the other hand, the sensitivity and specificity for the ICD-9 procedure codes and CPT codes to identify thrombolysis in ischemic stroke were 55% and 98% respectively<sup>7</sup>.

Although, the codes used in this study are, for the most part, specific enough to identify the more serious disease conditions such as post-operative acute myocardial infarction (81%)<sup>8</sup>, acute renal failure and in-hospital death, they may not be specific enough to remove residual confounding associated with the serious conditions lacking more specific ICD-9 codes such as heart failure, stroke, renal dysfunction, and acute revascularization. Consequently, diagnostic and procedural ICD-9-CM codes used to identify the adverse events and covariates need to be verified against information available in the medical records. The investigators proposed medical record review at least for a sample of records but the current report only presents data based on claims.

#### Length of Observation Period (Follow-up)

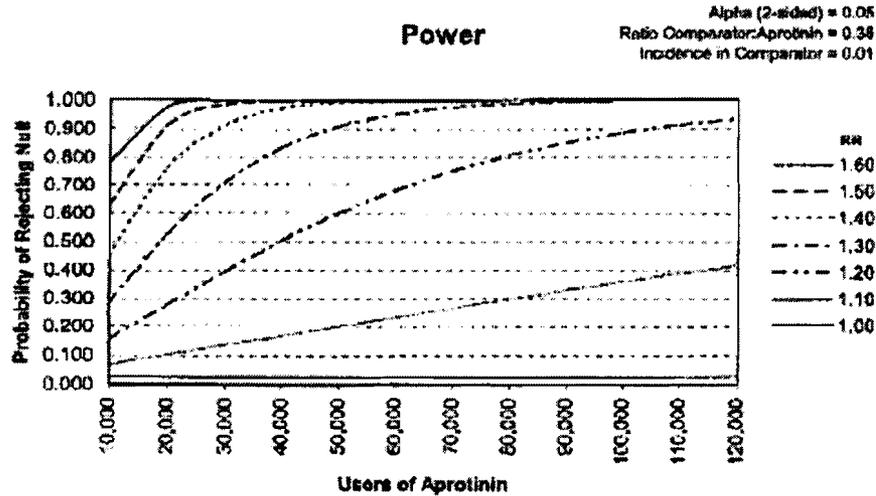
Following CABG surgery, patients remained hospitalized, were transferred to other facilities, or were discharged at different rates. The probability of an outcome to be observed, therefore, differed across patients. What is more of a concern for this study, however, is whether the rate of ascertainment and follow-up differed by treatment group. Since aprotinin is indicated for high risk patients, it is highly likely that aprotinin recipients would need longer hospital stays, have more serious outcome, and consequently be at higher risk of having any outcome observed. The investigators did not provide any information as to whether there differences in the length of observation across treatment groups. In addition, a time-to-event analysis would have been very appropriate to analyze these data to adjust for differences in length-of-observation.

#### Duration of Hospital Stay

The investigators observed prescribing preferences in the Premier data. They could not assess the full impact of these prescribing preferences because the database contained only procedural and diagnostic information codes that related to the hospital stay and contained very limited information on pre-existing medical conditions. The investigators did perform sub-analyses evaluating duration of hospital stay for acute renal failure and death to assess whether the risk estimates were affected when more pre-existing patient medical information was available (See Section 3.10.1.3 and Table 6). According to the authors, these sub-analyses showed that misclassification and under ascertainment differed by the number of days a patient was in the hospital but were non-differential across treatment groups and subsequently would not impact the risk ratios observed. Information on the prevalence of renal failure prior to CABG increases with the number of days in the hospital and, with the exception of patients hospitalized six or more days, the relative risk decreases with increasing information. Can the increase in the prevalence of acute renal failure indicative of more information on pre-existing conditions with increasing hospital stay or is the increase in prevalence more indicative of a group of patients who are sicker and need more hospitalization?

### 3.9 SAMPLE SIZE

An a priori power calculation estimated that there would be at least 90% power to detect relative risks of 1.3 or greater for outcomes occurring in 1 % or more of CABG surgeries under a wide range of assumptions about how many aprotinin users would be available. The calculations assume a ratio of aminocaproic acid to aprotinin of 0.38 observed in the Premier data.



#### OSE Comments on Sample Size

Sample size information in the report was extracted from the Sample Size and Power section of the March 3, 2004/March 3, 2006 proposal. Although these calculations were based on a larger number of potential ( $n=73,905$ ) aprotinin users, the power estimates remain relevant to the actual counts observed in the study.

### 3.10 STATISTICAL ANALYSES

The investigators proposed primary analyses which included univariate and multivariate analyses and secondary analyses that included cohort restrictions and use of propensity scores to adjust for confounding by indication (use of aprotinin). Sensitivity analyses were also done to assess the effect of incomplete medical histories for patients with short hospital stays. Analyses on medical record abstraction were not done since medical abstractions were not completed for this preliminary report.

#### 3.10.1 Primary Analyses

##### 3.10.1.1 Univariate Analyses

Unadjusted risk ratios (RR) and risk differences (RD) for developing study outcomes during hospital stay were estimated by cross-tabulating the primary exposure (aprotinin vs. non-aprotinin antifibrinolytics) with each study outcome (acute revascularization, acute heart failure, stroke, acute renal failure, death) and 95% confidence limits were calculated.

### 3.10.1.2 Multivariate Analyses

Using logistic regression, the investigators estimated age and sex adjusted odds ratios and odds ratios adjusted for all patient and hospital covariates. The protocol stated that a backward selection procedure would be used to reduce the number of covariates adjusted. In the analysis, all identified covariates were used instead. The covariates used in the logistic regression were:

- Age
- Age<sup>2</sup>
- Sex (male)
- Race/ethnicity: White (reference), Black, Other
- Smoking (current, past)
- Admission year (2003, 2004, 2005, 2006(Q1))
- Emergency admission
- Day of CABG
- Low income status
- Marital status(w/partner)
- Redo cardiac surgery
- Additional cardiac surgery
- Number of vessels (1, 2, 3, 4+)
- Pre-existing percutaneous coronary procedures
- Fibrinolytic medications or direct thrombin inhibitors prior or during CABG
- Plasma expander (yes/no)
- Cardiac arrest
- Whole blood or red cells during CABG (post-baseline)
- Platelets or plasma during CABG (post-baseline)
- Use of a cell saver during CABG (post-baseline)
- Hospital CABG volume (0-99, 100-500, >500)
- Hospital size (<400, 400-649, 650+ beds)
- Teaching hospital
- Rural hospital
- Region (Midwest, Northeast, South (reference), West)
- Diabetes (if recorded in the discharge diagnoses)
- Hypertension (if recorded in the discharge diagnoses)
- Liver disease (if recorded in the discharge diagnoses)
- COPD/asthma (if recorded in the discharge diagnoses)
- Cancer (if recorded in the discharge diagnoses)
- Old MI (if recorded in the discharge diagnoses)
- Old stroke (if recorded in the discharge diagnoses)

### 3.10.2 Secondary Analyses

Two secondary analyses were performed: cohort restrictions and adjustments based on propensity scores calculated based on the probability of receiving aprotinin treatment.

#### 3.10.2.1 Cohort Restrictions

The analyses in the primary analyses were repeated for patients with complex surgery and separately for those patients who stayed at least 1, 2, 3, 4, 5, or 6 days in the hospital for the index CABG surgery. With this progressive restriction of the population, an increasing number of days were available to provide information on patient characteristics before the CABG surgery.

The secondary analyses

1. Excluded users of tranexamic acid from the comparison group,
2. Restricted the study population to patients
  - a. Undergoing complex CABG surgeries,
  - b. Treated in high-volume facilities or by high-volume surgeons,
  - c. Having diabetes, and
  - d. Not transferred to other hospitals within the first 2 days post-operation.

### 3.10.2.2 Propensity Scores

Coefficients (propensity scores) were obtained from a logistic regression model that was used to compute predicted probability of aprotinin exposure among study cohort members. The regression used all measured covariates described above as predictors of aprotinin use. The investigators designated the fitted probability for each patient as his/her propensity for aprotinin treatment (propensity score). Were omitted from the analysis members of the aprotinin and comparator groups whose propensity scores did not overlap (i.e. did not fall within the range of scores for the other group). The analyses were repeated for each study outcome, adjusting for quintiles of propensity score.

### 3.10.2.3 Sensitivity Analyses

Because a small proportion of patients may have been transferred to another institution early after CABG surgery so that potential events were not recorded in the database, the investigators conducted a sensitivity analysis excluding patients who left the hospital within 2 days after CABG surgery for any reason other than death.

### 3.10.2.4 Generalized Estimating Equation (GEE) Analysis

The generalized estimating equations (GEE) was used to explore whether adjusting for clustering of patients within hospitals would increase standard errors of the main effects in the regression analyses. In this report the odds ratios were considered to be a good approximation to the relative risk ratio in the case of rare outcomes.

### 3.10.3 OSE Comments on Analyses

Univariate and multivariate analyses are appropriate models to analyze such complex data. Following CABG surgery, patients remained hospitalized, were transferred to other facilities, or were discharged at different rates. Not all patients undergoing CABG were followed for the same length of time and consequently were at different risk of having an outcome observed. It is important that any analysis take into consideration the observed time for each patient while in the hospital. An appropriate survival time (time to event) analysis should have been considered. Any differences observed across treatment groups would be particularly concerning if the observed time period also differed by treatment group.

## 3.11 RESULTS

### 3.11.1 Primary Analyses

Of 162,687 patients undergoing surgery during the study time period, 66,435 patients (40.8%) were included in the study. Of the 162,687 patients initially identified, 77,732 (48%) received no antifibrinolytics, and 18,504 (11%) received inadequate doses or multiple doses and were therefore excluded from the analysis.

### 3.11.1.1 Univariate Analyses

According to first figure in the i3 report, 66,435 patients were included in the analysis and of these, 29,358 (44%) received aprotinin and 37,077 received either aminocaproic acid (n=35,719) or tranexamic acid (n=1,358). Among the 42,596 patients undergoing complex CABG surgery 19,232 (45%) received aprotinin and 23,364 (54%) received either of the other two comparators.

**Table 1. Characteristics of 66,435 patients undergoing CABG Surgery**

Demographic	Aprotinin	%	Other	%
<b>N</b>	<b>29,358</b>		<b>37,077</b>	
Age 65+	17,446	59.4	20,170	54.4
White/Black	24811	84.5	29200	78.8
Smoke*	5,334	18.2	6,391	17.2
Surgery	Aprotinin	%	Other	%
Redo Cardiac*	1,275	4.3	602	2.8
Additional Cardiac*	7,694	26.2	7,176	19.6
Complex CABG*	19,232	65.5	23,364	63.0
Hospital/Region	Aprotinin	%	Other	%
CABG Volume 100-500	12,032	41.0	13,527	36.5
Hospital size beds 650+	9,632	32.5	11,408	30.8
Southern Region	18,170	61.9	20,403	55.0

\* Lower bound of the 95% confidence intervals above 1.0

In summary, according to the univariate analyses (Table 1), patients receiving aprotinin were somewhat older, of white or black race, and were more likely to smoke than patients receiving other antifibrinolytics. Patients receiving aprotinin were also more likely to have redo, complex and/or additional cardiac surgery. Finally in this cohort, more of the aprotinin use occurred in patients at hospitals with 100-500 CABG volume per year in hospitals located in the South, and somewhat more at hospitals with 650 or more beds.

**Table 2. Age and sex adjusted relative risk ratio (RR) for cumulative incidence of in-hospital health outcomes among 66,435 patients undergoing CABG surgery.**

Outcome	Antifibrinolytics		Relative Risk Ratio	95% (CI)*
	Aprotinin	Other		
N	29,358	37,077		
Acute revascularization	88	95	1.17	0.87-1.56
Acute heart failure	4,056	4,480	1.11	1.06-1.17
Stroke	619	574	1.30	1.15-1.45
Acute Renal Failure	1,339	965	1.75	1.61-1.90
In-hospital death	1,365	940	1.75	1.60-1.90

\* CI = Confidence intervals

Relative to patients receiving non-aprotinin antifibrinolytics, patients receiving aprotinin had a 75% higher incidence of developing acute renal failure or dying and less than a 15% increased risk of experiencing a stroke or acute heart failure while in the hospital. These relative risk ratios were based on age- and sex-adjusted cumulative incidence rates (Table 1).

### 3.11.1.2 Multivariate Analyses

With multivariate adjustment (see Section 3.10.1.2 for a list of covariates), the estimated risks were over 50% higher for aprotinin recipients than for recipients of other antifibrinolytics with respect to acute renal failure and in-hospital deaths and 20% higher for stroke (Table 3). Aprotinin recipients had an 8% increase in risk for acute heart failure. Adjusting for other covariates decreased the risk ratios for acute heart failure and stroke but increased the risk ratio for acute revascularization, acute renal failure, and in-hospital deaths.

**Table 3. Multivariate logistic regression results for in-hospital outcomes for the full cohort (N = 66,435)**

Outcome	Relative Risk Ratio (RR)	95% CI
Acute revascularization	1.30	0.96-1.76
Acute heart failure	1.08	1.03-1.14
Stroke	1.20	1.07-1.35
Acute renal failure	1.70	1.55-1.86
In-hospital death	1.68	1.53-1.84

\* CI = Confidence intervals

Results from the multivariate analyses showed that other covariates were important predictors for the study outcomes. Table 4 lists information on covariates that account for an increased risk of at least 50% or more. Region is an important independent predictor of acute vascularization, acute heart failure, and death.

**Table 4. Measured predictors of the study outcome included in the multivariate analyses that show a minimum of 50% increase in risk.**

Acute Revascularization:	Other race, emergency admission, CABG surgery on first day, no additional cardiac surgery, one vessels included in the surgery, use of platelets or plasma during CABG, no cancer, undergoing surgery at a large hospital with fewer than 500 CABG procedures, located in the West (RR 2.1)* and Northeast.
Acute Heart Failure	Additional cardiac surgery, cardiac arrest, platelets or plasma during CABG, diabetes, liver disease (RR 2.9)*, large hospital with low CABG volume in the Midwest.
Stroke	CABG day 6 or more of hospitalization, old stroke, and hospital with high CABG volume.
Acute Renal Failure	<u>Aprotinin</u> , black (RR = 3.1)*, CABG on day 6 or more of hospitalization (RR=2.2)*, platelets or plasma during CABG, diabetes (RR=2.6)*, and liver disease (RR=7.5)**.
Death	<u>Aprotinin</u> , female, more than 1 day in hospital before CABG, redo and additional cardiac surgery, cardiac arrest (RR 5.9)**, platelets or plasma during surgery, diabetes, no hypertension, liver disease (RR7.9)**, hospital in the South.

Liver disease, identified as a code on the discharge summary, could indicate a prior history of liver disease or it could indicate liver complications identified during hospitalization. Liver disease, however, appears to be a very important predictor for most of the outcomes evaluated but is particularly notable for acute renal failure and death (Table 5) suggesting a possible liver-renal involvement that leads to death. Medical record review would be necessary to further define such an association.

**Table 5. Odds Ratio and 95% confidence intervals (CI) for liver disease as an independent predictor of outcome in the multivariate analysis.**

Outcome	Odds Ratio	95% CI
Acute revascularization	0.75	0.19 – 3.07
Acute heart failure	2.92	2.49 – 3.43
Stroke	1.48	0.99 – 2.21
Acute renal failure	7.48	6.20 – 9.02
In-hospital death	7.94	6.59 – 9.56

### 3.11.2 Secondary Analyses

#### 3.11.2.1 Cohort Restrictions

In an effort to identify artifacts arising from possibly inadequate baseline patient information, the investigators examined the associations between aprotinin use with renal failure and death in subsets of the cohort that showed unusual doctors/hospitals or high risk patients (Table 6) and in patients with longer hospital stays (Table 7), allowing for capture of more complete baseline data. There were no appreciable differences in risk estimates observed when comparing the full model

with the limited models for acute heart failure, stroke, and acute renal failure (Table 6). Risk estimates increased for acute revascularization and in-hospital deaths when the analysis was limited to high volume physicians. The risk estimates decreased for in-hospital deaths in the analyses that were limited to high volume hospitals. There were no appreciable differences in risk estimates between the full model and the models limited to patients with at least 2 days of hospital stay after their CABG surgery (Table 8).

**Table 6. Multivariate logistic regression risk estimates\* of in-hospital outcomes for the full cohort and restricted to medium and high CABG volume hospitals and to medium and high volume physicians.**

Outcome	Full Cohort 66,435		Limited to medium & high volume hospital (≥ 100 CABG) 63,672		Limited to medium & high volume physicians (>50 CABG) 55,126	
	RR	95% CI	RR	95% CI	RR	95% CI
Acute revascularization	1.30	0.96-1.76	1.34	0.98-1.83	1.55	1.08-2.23
Acute heart failure	1.08	1.03-1.14	1.08	1.02-1.13	1.06	1.00-1.12
Stroke	1.20	1.07-1.35	1.21	1.07-1.36	1.18	1.04-1.35
Acute renal failure	1.70	1.55-1.86	1.69	1.54-1.86	1.74	1.57-1.93
Death	1.68	1.53-1.84	1.53	1.53-1.85	1.73	1.55-1.91

\* RR = Risk Ratio; 95% CI = 95% Confidence Interval

In addition, the report provides information on the association between aprotinin use and renal failure and in-hospital deaths as a function of increasing covariate information before CABG surgery. Table 7 shows results of a multivariate adjusted model for acute renal failure that include the increasing information on prior treatment for renal failure (dialysis or hemofiltration) and heart failure (medication use) associated with longer hospital stays before the index day. There was no systematic effect of increasing the required pre-surgery days in the adjustment. The relative risk estimates for renal failure decreased from 1.70 (1.55-1.86) to a minimum of 1.36 (1.15-1.61) for patients with at least 3 hospital days prior to the index CABG surgery, but the relative risk estimate was higher for patients with longer stays (RR= 1.54; 95% CI 1.25-1.89). For the death outcome, increasing the number of hospital days required before the index day also did not result in any meaningful or systematic changes in effect estimates.

**Table 7. Multivariate adjusted models showing the association between aprotinin use and of renal failure as a function of increasing covariate information BEFORE CABG surgery.**

	Day of CABG during index hospitalization					
	1+	2-	3-	4+	5-	6-
Study Size	66,435	43,255	29,565	21,710	15,347	10,533
Number of events	2,304	1,753	1,400	1,184	993	808
Effect of aprotinin						
Relative Risk	1.70	1.57	1.45	1.36	1.40	1.54
95% Confidence Interval	1.55-1.86	1.38-1.79	1.25-1.69	1.15-1.61	1.17-1.68	1.25-1.89
Prevalence of renal failure prior to CABG	--	1.8	2.3	2.8	3.4	4.2
Prevalence of heart failure prior to surgery	--	28.1	35.9	40.9	46.9	53.3

The report also states that the associations were present to the same extent in patients undergoing complex CABG surgery, in patients with diabetes, in patients treated at high-volume facilities or by high-volume surgeons, and in patients not transferred to other hospitals within the first two post-operative days. The September 13, 2006 report, however, does not show supporting data.

### 3.11.2.2 Propensity Scores

Propensity score analyses showed similar results (Table 8) compared to traditional modeling of the full cohort for all health outcomes.

**Table 8. Multivariate logistic regression risk estimates\* of in-hospital outcomes for the full cohort using traditional modeling, using propensity score analysis, and restricted to patients who stayed at least 2 days after the index CABG surgery.**

Outcome	Full Cohort (traditional modeling)		Full cohort (propensity score modeling**)		Limited to patients staying for at least 2 days post CABG	
	RR	95% CI	RR	95% CI	RR	95% CI
Acute revascularization	1.30	0.96-1.76	1.34	0.96-1.75	1.30	0.96-1.76
Acute heart failure	1.08	1.03-1.14	1.09	1.04-1.15	1.08	1.03-1.14
Stroke	1.20	1.07-1.35	1.21	1.07-1.36	1.20	1.06-1.35
Acute renal failure	1.70	1.55-1.86	1.67	1.53-1.82	1.69	1.55-1.86
Death	1.68	1.53-1.84	1.64	1.50-1.79	1.67	1.53-1.84

\* RR = Risk Ratio; 95% CI = 95% Confidence Interval

\*\* Using logistic regression adjusting for quintiles of propensity scores after trimming non-overlapping areas of the propensity scores among treated and untreated patients.

### 3.11.2.3 Aprotinin Dose

High-dose aprotinin use was associated with a higher risk of acute revascularization, acute renal failure, and in-hospital death (Table 9).

**Table 9. Risk estimates\* for high-dose aprotinin used during CABG surgery compared to low-dose aprotinin use.**

Outcome	RR	95% CI
Acute revascularization	1.87	1.16-3.00
Acute heart failure	1.06	0.98-1.16
Stroke	1.15	0.96-1.37
Acute renal failure	1.21	1.06-1.38
Death	1.31	1.16-1.42

*RR = Risk Ratio; 95% CI = 95% Confidence Interval*

### 3.11.2.4 Sensitivity Analyses

Sensitivity analyses explored how strong an unmeasured confounder would have to be to explain the findings regarding acute renal failure and death. The results of these analyses showed that if a hypothesized confounder elevated the risk for death seven-fold, it would also need to have a six-fold greater prevalence of aprotinin use to produce sufficient confounding to explain an apparent risk ratio of 1.7.

### 3.11.3 OSE Comments Study Results

This large hospital-based cohort study used administrative data to assess risk of acute revascularization, acute heart failure, stroke, acute renal failure, and all cause in-hospital death for recipients of aprotinin compared to users of other antifibrinolytics (tranexamic and aminocaproic acid). The strength of this study is its ability to identify and capture information on a large number of patients undergoing CABG surgery (n=66,435) compared to the other studies.

The main limitation of this study, acknowledged by the investigators, is its use of administrative data rather than clinical data from the medical records to identify medical outcome and to ascertain covariates that mitigate patient risks. Patients who usually undergo CABG procedures have complex clinical conditions (medical histories) that could affect surgical outcome not all of which may be captured by administrative data unless the claims for these conditions influence reimbursement. The potential bias due to selective assignment of patients to aprotinin based on their clinical profile, therefore, may not be addressed completely without reviewing the patients' medical records.

Although, the codes used in this study are, for the most part, specific enough to identify the more serious disease conditions such as post-operative acute myocardial infarction, acute renal failure and in-hospital death, they may not be specific enough to remove residual confounding associated with the serious conditions lacking more specific ICD-9 codes such as heart failure, stroke, renal dysfunction, and acute revascularization. Consequently, diagnostic and procedural ICD-9-CM codes used to identify the adverse events and covariates need to be verified against information available in the medical records. The investigators proposed medical record review at least for a sample of records but the current report only presents data based on claims. The sponsor claims that medical records cannot be reviewed for these data, the i3 Drug Safety group claim they can, have done so in the past, and they have a contract in ready should they be given the authorization to proceed with this analysis. OSE has knowledge that some medical record review can be done on a limited basis.

Findings for in-hospital death, stroke, and acute heart failure in this study are not as convincing as results for acute renal failure. The investigators acknowledge and demonstrate in their secondary analyses that the risk estimates for in-hospital death, stroke, and acute heart failure decrease with

increasing covariate adjustment (Table 10) suggesting the existence of possible residual or unmeasured confounding. The risk estimates for acute renal failure, however, barely change with increasing adjustments.

**Table 10. Comparison of risk estimates for death, acute heart failure, stroke and renal failure based on degree of covariate adjustment and limitations (see Table 2 and Table 6).**

Outcome	Crude Risk Estimate	Age/Sex Adjustment	Full adjustment	Hospital ( $\geq 100$ CABG)	Physicians ( $\geq 50$ CABG)
Death	1.84	1.75	1.68	1.53	1.73
Acute heart failure	1.14	1.11	1.08	1.08	1.06
Stroke	1.36	1.30	1.20	1.21	1.18
Acute renal failure	1.75	1.75	1.70	1.69	1.74

In addition to multivariate analyses, the investigators conducted sensitivity and limited sub-analyses, to evaluate potential confounding. Despite the study's limitations, the findings showing an increased risk for acute renal failure are compelling for several reasons. The study results are consistent with

1. Spontaneous adverse event reports
2. Results from other reported studies
3. Adverse events occurring at a frequency of  $\geq 2$  % in the clinical trials and noted in the label

### 3.11.3.1 Risk Estimates Consistent with spontaneous Adverse Event Reports

A previous OSE/DDRE review<sup>9</sup> summarized spontaneous reports from the Adverse Event Report System (AERS) database. This review noted that disproportionality analyses identified greater than expected probabilities for cardiovascular and renal events (including renal failure and renal necrosis) for aprotinin but not for aminocaproic acid or tranexamic acid.

Manual review of the cases in this review confirmed the higher proportion of case reports with renal failure and impairment, myocardial infarction, cardiac failure and cardiogenic shock but not for tranexamic acid or aminocaproic acid.

Table 11 presents more recent Empirical Bayesian Geometric Mean (EBGM) scores and confidence limits for aprotinin, aminocaproic acid, and tranexamic acid for most MedRA preferred terms (PT) events identified in the clinical trials as having an adverse event occurrence of 2% or more in the aprotinin treated group compared to placebo. Although the EBGM scores are measures of disproportionality for each drug and should not be directly compared, the results do point to a higher proportion of renal events reported for the aprotinin product. Although not addressed by the i3 Drug Safety analysis, the disproportionality analysis suggests that thrombotic events, although expected in this type of surgery, are more frequently reported for aprotinin. Could an increase frequency of thrombosis in the aprotinin treated group explain an increase in cardiovascular events observed in the observational studies? Visualization of cumulative EBGM scores with a lower bound (EB05) of 2.0 or greater in the confidence intervals is presented by year in Appendix 3 for aprotinin, aminocaproic acid, and tranexamic acid.

**Table 11. Empirical Bayesian Geometric Mean Scores (EBGM) and Confidence Intervals for Aprotinin, Aminocaproic Acid, and for Tranexamic Acid for some Selected MedDRA Preferred Terms (PT) Events Observed in Clinical Trials.**

EVENT	Aprotinin		Aminocaproic Acid		Tranexamic Acid	
	EBGM	90% CI	EBGM	90% CI	EBGM	90% CI
Thrombosis	16.8	13.7-20.4	8.6	3.7-19.5	3.5	1.7-6.7
Shock	8.6	5.8-12.5	0.6	0.1-1.8	4.1	2.2-7.3
Cerebrovascular Accident	2.1	1.6-2.8	1.8	0.9-3.3	3.7	2.3-5.7
Thrombophlebitis	1.9	0.6-4.8	--	--	1.3	0.3-4.0
Pulmonary Embolus	5.4	4.0-7.1	2.0	0.9-4.1	12.2	6.8-18.8
Myocardial Infarction	3.0	2.4-3.6	1.8	1.0-3.0	1.5	0.7-2.7
Renal Failure	7.1	5.7-8.9	1.7	0.8-3.3	0.5	0.1-1.5
Acute Renal Failure	9.9	8.0-12.1	1.9	0.9-3.6	2.7	1.5-4.6
Renal Tubular Necrosis	4.4	3.3-14.8	1.1	0.3-3.5	--	--

### 3.11.3.2 Risk Estimates Consistent with other Reported Studies

Risk estimates for renal adverse events are also consistent with results reported by other investigators (Table 12). Two of these studies have been previously reviewed by OSE/DDRE<sup>3</sup>. Although the definition of renal events differed across studies and the comparator groups selected for each study also differed, the risk estimates are fairly consistent.

Karkouti et al<sup>2</sup> reported that aprotinin users with normal preoperative renal function were 1.4 times more likely to develop renal dysfunction (p=0.09) and 1.5-times more likely to develop renal failure requiring dialysis (p=0.08), although these associations were not statistically significant. The results were statistically significant only for postoperative renal dysfunction among patients with abnormal preoperative renal function. The investigators in this study used propensity scores to match patients receiving aprotinin with patients who received tranexamic acid treatment (Table 12). Propensity scores in this study were calculated based on the probability of receiving aprotinin treatment. Patients who could not be matched were excluded from the analysis.

Mangano et al.<sup>1</sup> also detected and increased risk of renal events (combined renal dysfunction and renal failure requiring dialysis) among patients receiving any antifibrinolytic treatment (aprotinin, aminocaproic acid, and/or tranexamic acid) compared to patients receiving no antifibrinolytic treatment. In this study, aprotinin remained an independent predictor of renal events after adjusting for other covariates.

Table 12. Summary of adjusted\* risk estimates for post-operative renal events.

Study	Design	Comparator Group	Renal Event	Risk Ratio	Significance
i3 Drug Safety	Retrospective Cohort	Aminocaproic acid/tranexamic acid	Acute renal failure	1.7	1.6-1.9
Mangano et al <sup>10**</sup>	Prospective Cohort	No antifibrinolytic	Renal Event <sup>†</sup>	2.6	1.4-5.0
Karkouni et al <sup>10***</sup>	Case Control (matched)	Tranexamic acid	Renal dysfunction <sup>††</sup>	1.4	p=0.09
			Renal failure <sup>††</sup>	1.5	p=0.3
Coleman et al <sup>10***</sup>	Retrospective Cohort	Lack of aprotinin	Renal dysfunction	2.0	1.4-3.0

\* Included adjustments with or matched using propensity scores (PS) and analyzed using PS quintiles/deciles.

\*\* Propensity score (PS) calculated on probability of receiving any antifibrinolytic.

\*\*\* PS calculated based on probability of receiving aprotinin.

† Renal dysfunction and renal failure for patients undergoing complex surgery.

†† Proportion of renal events in aprotinin treated patients to proportion in tranexamic acid treated patients.

Table 13 summarizes Mangano et al's results<sup>1</sup> for each study outcome evaluated. The table shows a decrease in risk estimates with propensity adjustment for all outcome including renal events in the full cohort analyses. For patients undergoing complex surgery, the risk estimate increased for renal events in the main multivariate model without propensity adjustments but the increase disappeared with propensity adjustment. With propensity adjustment, the risk estimates were elevated in patients undergoing complex surgery only for in-hospital deaths.

**Table 13. Comparison of odds ratios\* and 95% confidence intervals results\* from multivariate logistic regression models without (MLR) and with (MLR\_PS) propensity score adjustments for patients undergoing primary and complex surgery, Mangano et al 2006.<sup>1</sup>**

Aprotinin vs. Control (No use)	Outcome	Primary Surgery		Complex Surgery	
		Odds Ratio	95% CI	Odds Ratio	95% CI
Death	MLR	1.6	0.8-3.3	0.9	0.4-1.7
	MLR_PS	1.2	1.1-1.4	1.2	1.1-1.3
Renal Event	MLR	2.3	1.3-4.3	2.6	1.4-5.0
	MLR_PS	1.2	1.1-1.3	1.0	0.9-1.1
Cardiovascular Events	MLR	1.4	1.1-1.9	1.1	0.8-1.6
	MLR_PS	1.1	1.0-1.1	1.0	1.0-1.1
Cerebrovascular Events	MLR	2.2	1.1-4.1	1.3	0.7-2.4
	MLR_PS	1.2	1.1-1.3	1.0	0.9-1.1

\* Rounded to the one decimal places.

### 3.11.3.3 Risk Estimates Consistent with Clinical Trial Data in the Label

The i3 Drug Safety renal results are also consistent with some of the renal risk estimates from the clinical trial adverse event data summarized in the product's label. Although the relative risks observed are stated to be not statistically significant (possibly due to the small number of observations), the ratio of aprotinin incidence rates compared to placebo incidence rates for aprotinin were of the same magnitude as those observed in the observational studies. The relative risk for renal failure was 1.7 and for kidney tubular necrosis it was 2.0 (Table 14). The relative risk for acute renal failure was only 0.8, however.

**Table 14. Incidence Rates of Adverse Events ( $\leq 2\%$ ) By Treatment for all Patients from US Placebo-Controlled clinical trials**

EVENT	Aprotinin (A)	Placebo (P)	Relative Risk A/P
N	2,002	1,084	
Thrombosis	1.0	0.6	1.7
Shock	0.7	0.4	1.8
Cerebrovascular Accident	0.7	2.1	0.3
Thrombophlebitis	0.2	0.5	0.4
Deep Thrombophlebitis	0.7	1.0	0.7
Pulmonary Embolus	0.3	0.6	0.5
Kidney Failure	1.0	0.6	1.7
Acute Kidney Failure	0.5	0.6	0.8
Kidney Tubular Necrosis	0.8	0.4	2.0

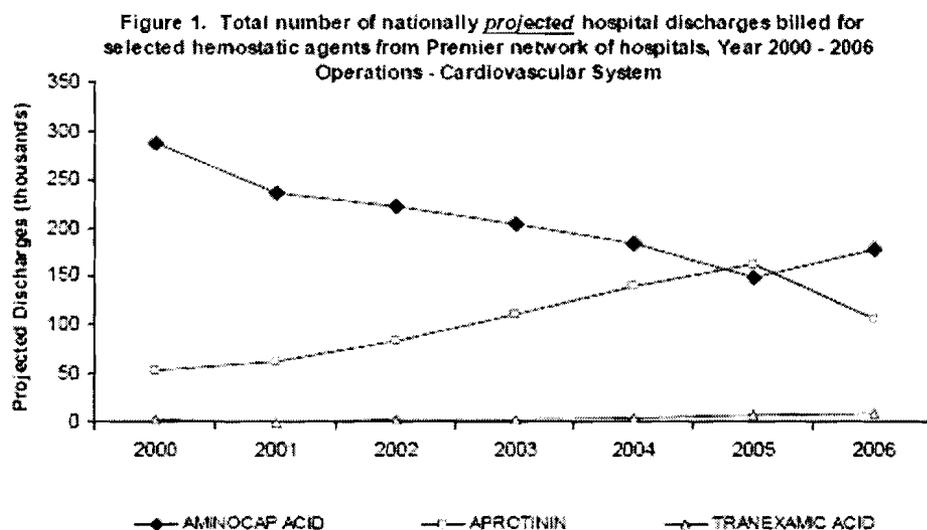
### 3.12 TRENDS<sup>11</sup>

In October 2006, OSE provided an analysis of drug utilization patterns for aprotinin<sup>12</sup>. That review showed that, based on inpatient data from Premier data, use of aprotinin had increased dramatically since 2000 and replaced aminocaproic acid as the most frequent hemostatic agent used beginning in the third quarter of 2005. Greater than 97% of aprotinin use was associated with operations involving the cardiovascular system during 2005.

This review updates the information presented in the previous report. To establish consistency, the trend data are restricted to the *ICD9 Operations –Cardiovascular System* for the three hemostatic agents compared and are presented by year (2000 to 2006) and by quarter (2004 to 2006).

Figure 1 confirms the earlier trends in the Premier<sup>6</sup> database that, for cardiovascular operations, aprotinin use has steadily increased from the year 2000 and surpassed use of aminocaproic acid in 2005. The trend data suggest, however, that use of aprotinin may be decreasing beginning in 2006. Use of tranexamic acid remains very low.

*\*\*The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\**



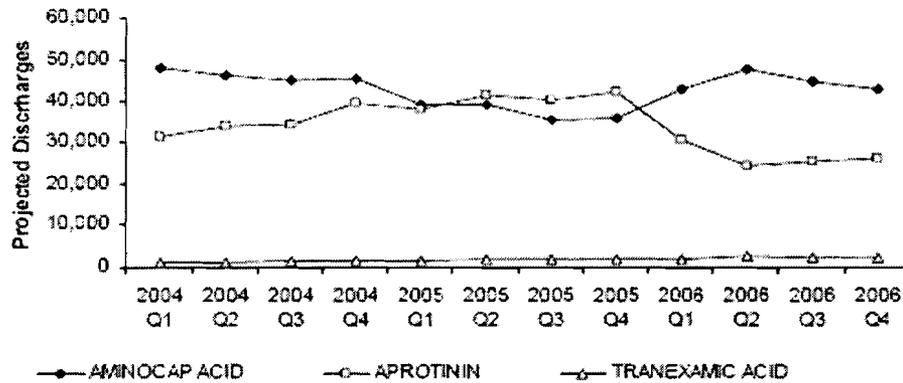
Source: Premier RxMarket Advisor™, Years 2000 - 2006, Extracted July 3, 2007.

Figure 2 shows trend data by quarter beginning in Q1-2004 through Q4-2006. The downward trend in hospital discharges mentioning aprotinin use begins towards the end of 2005 and continues through the second quarter of 2006 then stabilizes. The beginning of the downward

<sup>6</sup> Projected Patient Discharges represent national estimates. Premier Perspective™ contains data from approximately 450 hospitals from January 2000 through present with a lag time of 6 months. The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. These data do not include out-patient treatment in hospital clinics nor emergency departments unless the patient is admitted.

trend coincides with the first published paper (Mangano et al<sup>1</sup>, January 26, 2006) that raised concerns about the risk of aprotinin use and followed by the FDA September 8, 2006 Public Health Advisory (Appendix 1). Use began to stabilize after the publication of the second paper (Karkouti et al<sup>2</sup>, March 2006).

Figure 2. Total number of nationally *projected* hospital discharges billed for selected hemostatic agents from Premier network of hospitals, 1Q2004 - 4Q2006 By Quarter



SOURCE: Premier RxMarket Advisor™, Quarters 1Q2006 - 4Q2006. Extracted July 23, 2007

Table 15 shows that between 2000 and 2005 patients who received aprotinin during their cardiovascular operations were more likely to have longer hospital stays than patients receiving aminocaproic acid or tranexamic acid but the average hospital stay for aminocaproic acid has steadily increased over the years to be nearly comparable (10.2 days) to the average stay for aprotinin (11.6 days) in 2006 suggesting that aminocaproic acid may have been used for more complex surgeries in 2006.

Table 15. Average length of stay (ALOS) for patients receiving aminocaproic acid, aprotinin, and tranexamic acid by year - limited to cardiovascular operations.

	2000	2001	2002	2003	2004	2005	2006	Total
Total	9.7	9.7	9.9	9.9	10.1	10.6	10.7	10.1
Aminocaproic acid	9.3	9.3	9.4	9.5	9.6	9.9	10.2	9.6
Aprotinin	11.4	11.2	11.2	10.8	10.7	11.2	11.6	11.1
Tranexamic acid	9.4	10.6	9.3	8.9	8.8	8.9	9.0	9.0

Source: Premier RxMarket Advisor™, Years 2000 - 2006, Extracted July 3, 2007.

“The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.”

## 4 DISCUSSION

The i3 report presents results from a large hospital-based cohort study that used administrative data to assess risk of acute revascularization, acute heart failure, stroke, acute renal failure, and all cause in-hospital death for recipients of aprotinin compared to users of other antifibrinolytics (tranexamic and aminocaproic acid). The strength of this study is its ability to identify and capture information on a large number of patients undergoing CABG surgery. The main limitation, acknowledged by the investigators, is the use of administrative data rather than clinical data to identify medical outcome and to ascertain covariates that mitigate patient risks. In addition to multivariate analyses, the investigators conducted sensitivity and limited sub-analyses, to evaluate potential confounding.

Despite the study's limitations, the findings showing an increased risk for acute renal failure are compelling because the results are consistent with results from other studies, with labeled adverse events from in the clinical trials, and with reports of spontaneous adverse event. Liver disease as an independent predictor of renal failure and death could suggest a possible hepatic-renal association that results either because aprotinin is used in a vulnerable population (pre-existing liver disease) or because of in-hospital medical complications. Findings for in-hospital death, stroke, and acute heart failure in this study decreased with increasing covariate adjustment suggesting the existence of possible residual or unmeasured confounding.

To confirm findings, the investigators proposed to validate renal and death outcome through medical record verification which the investigators claim is possible whereas the sponsor claims it is not possible. In addition, the investigators have revised the protocol and limited its scope to the renal and death outcomes.

The results of this large study supports the renal associations with aprotinin use seen in the other observational studies whether these studies compared aprotinin use with other antifibrinolytics or with no use. These other studies were smaller in scope but had access to more detailed and specific clinical data. In addition, there is currently in progress a Canadian clinical trial<sup>d</sup> designed to determine if aprotinin use is superior to epsilon-aminocaproic acid and tranexamic acid in decreasing postoperative bleeding, in minimizing exposure to any blood product, and in decreasing both fatal and life-threatening or serious post-operative conclusions.

## 5 CONCLUSIONS

Despite the limitations discussed above, the analyses conducted by the i3 Drug Safety Group offer a robust assessment of aprotinin use and also confirm renal effects reported by other studies. Elevated risks for cardiovascular events, and stroke, however, were likely associated with uncontrolled confounding in this study. Elevated risk estimates for death were also reduced when controlling for confounders but remained elevated nonetheless. The risk estimates for death appeared to be highly correlated with the risk estimates for renal events. Risk estimates for renal dysfunction remained stable when analyses were adjusted for confounding and show a high likelihood for an association with aprotinin use. OSE/DDRE recommends that medical records be reviewed to confirm renal failure, to identify the possible cause of in-hospital death, and to assess the possible contribution of liver disease to morbidity and/or mortality after aprotinin use.

If a process is underway to re-analyze data collected by other investigators, OSE supports the Agency's efforts to also obtain and re-analyze the i3 Drug Safety's Premier data in an effort to

<sup>d</sup> Blood Conservation using Antifibrinolytics: A Randomized Trial in High-Risk Cardiac Surgery Patients (BART).

reproduce and standardize the analysis of all three datasets and to evaluate, in this and other databases, whether liver disease is a possible outcome of aprotinin use. Re-analysis of the Premier data should include a stratified analysis by propensity score deciles or quintiles and should adjust for days-since-surgery.

## **6 RECOMMENDATIONS**

No changes to the aprotinin label are advanced with this review.

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## APPENDIX 1: FDA PUBLIC HEALTH ADVISORY, FEBRUARY 8, 2006

### FDA Public Health Advisory Aprotinin Injection (marketed as Trasylol)

On January 26, 2006, *The New England Journal of Medicine* (NEJM) published an article by Mangano et al. reporting an association of Trasylol (aprotinin injection) with serious renal toxicity and ischemic events (myocardial infarction and stroke) in patients undergoing coronary artery bypass grafting surgery (CABG). Another publication (*Transfusion*, on-line edition, January 20, 2006, Karkouti, et al.) suggests an association between aprotinin administration and renal toxicity among patients undergoing cardiac surgery with cardiopulmonary bypass. FDA is evaluating these studies, along with other studies in the literature and reports submitted to the FDA through the MedWatch program, to determine if labeling changes or other actions are warranted.

While FDA is continuing its evaluation, we are providing the following recommendations to healthcare providers and patients:

- Physicians who use Trasylol should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or central nervous system and promptly report adverse event information to Bayer, the drug manufacturer, or to the FDA MedWatch program, as described at the end of this advisory.
- Physicians should consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

The study reported in the NEJM was an observational study of patients undergoing CABG who received either Trasylol, one of two other drugs intended to decrease peri-operative bleeding (aminocaproic acid or tranexamic acid), or no specific drug treatment.

A limitation of the study was that patients were not assigned at random to receive the treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, patients receiving Trasylol may have been at higher risk to begin with for these serious adverse events compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility prevents a direct assessment of whether Trasylol altered the risk for serious adverse events. The study investigators used statistical procedures (multivariable logistic regression and propensity-score adjustment) to try to adjust for known differences between the treatment groups. Using these procedures, their study concluded that Trasylol was associated with more adverse outcomes. Other findings in the study suggested that patients receiving higher Trasylol dosages were at greater risk than those receiving lower dosages.

The study reported in the on-line edition of *Transfusion* was also an observational study that used statistical methodology to compare outcomes from patients undergoing CABG.

The patients in this study received, at physician direction, either Trasylo1 or another drug intended to decrease the risk for perioperative bleeding. This study suggested that Trasylo1 administration increased the risk for renal dysfunction. This study has some of the same limitations as the NEJM publication.

In pre-marketing clinical studies conducted among approximately 3,000 patients undergoing CABG, the risks and benefits of Trasylo1 were determined in clinical studies that randomized patients to either a placebo or Trasylo1. In these studies, the risks for serious renal toxicity and cardiovascular events were determined to be similar between patients receiving Trasylo1 and those receiving placebo. However, in one study assessing coronary graft patency, Trasylo1 administration was associated with an increased risk of graft closure. The FDA will work with the authors of the publications and the manufacturer of Trasylo1 to carefully evaluate the risks and benefits associated with use of Trasylo1 in CABG. The FDA anticipates the public presentation of the recently reported information and other data at an advisory committee in the near future. The FDA will notify health care providers and patients in a timely fashion as new information becomes available.

## APPENDIX 2: FDA PUBLIC HEALTH ADVISORY, SEPTEMBER 29, 2006

### FDA Public Health Advisory Aprotinin Injection (marketed as Trasylol)

September 29, 2006

Since January, 2006, FDA has been conducting a safety review of Trasylol (aprotinin injection). The review was triggered by the results of two published research studies: one that reported an increase in the chance of kidney failure, heart attack and stroke in patients treated with Trasylol compared to those treated with other similar drugs, and the other that reported an increase in kidney dysfunction compared to another drug. On September 21, 2006, FDA held a public meeting of the Cardiovascular and Renal Drugs Advisory Committee to discuss the safety and overall risk-benefit profile for Trasylol. At that meeting, the committee discussed the findings from the two published observational studies, the Bayer worldwide safety review, and the FDA review of its own post-marketing database.

On September 27, 2006, Bayer Pharmaceuticals told FDA that it had conducted an additional safety study of Trasylol. The preliminary findings from this new observational study of patients from a hospital database reported that use of Trasylol may increase the chance for death, serious kidney damage, congestive heart failure and strokes. FDA was not aware of these new data when it held the September 21, 2006, Advisory Committee meeting on Trasylol safety. FDA is actively evaluating these new data and their implications for appropriate use of the drug.

While FDA conducts its evaluation of this new safety study, we recommend the following to healthcare providers:

- Physicians who use Trasylol should carefully monitor patients for the occurrence of toxicity, particularly to the kidneys, heart, or brain, and promptly report observed adverse event information to Bayer Pharmaceuticals, the drug manufacturer, or to the FDA MedWatch program, by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet at <http://www.fda.gov/medwatch/index.html>.
- Physicians should consider limiting Trasylol use to those situations where the clinical benefit of reduced blood loss is essential to medical management of the patient and outweighs the potential risks.

These recommendations are similar to those provided in a February 8, 2006, FDA Public Health Advisory and information sheets for health care professionals and patients which were based on the published studies mentioned above. See <http://www.fda.gov/cder/drug/infopage/aprotinin/default.htm>.

Trasylol works to slow or prevent bleeding, and is used to reduce blood loss and the need for blood transfusion during some types of heart surgeries. Trasylol is made from the lung tissue of cattle.

In the published studies and the recently supplied Bayer study, patients were not assigned at random to receive various treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, in these safety studies, patients receiving Trasylol may have had a higher chance for serious complications to begin with as compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility complicates the assessment of whether the available studies show that Trasylol treatment, rather than other factors, increased the chance for serious kidney or heart complications.

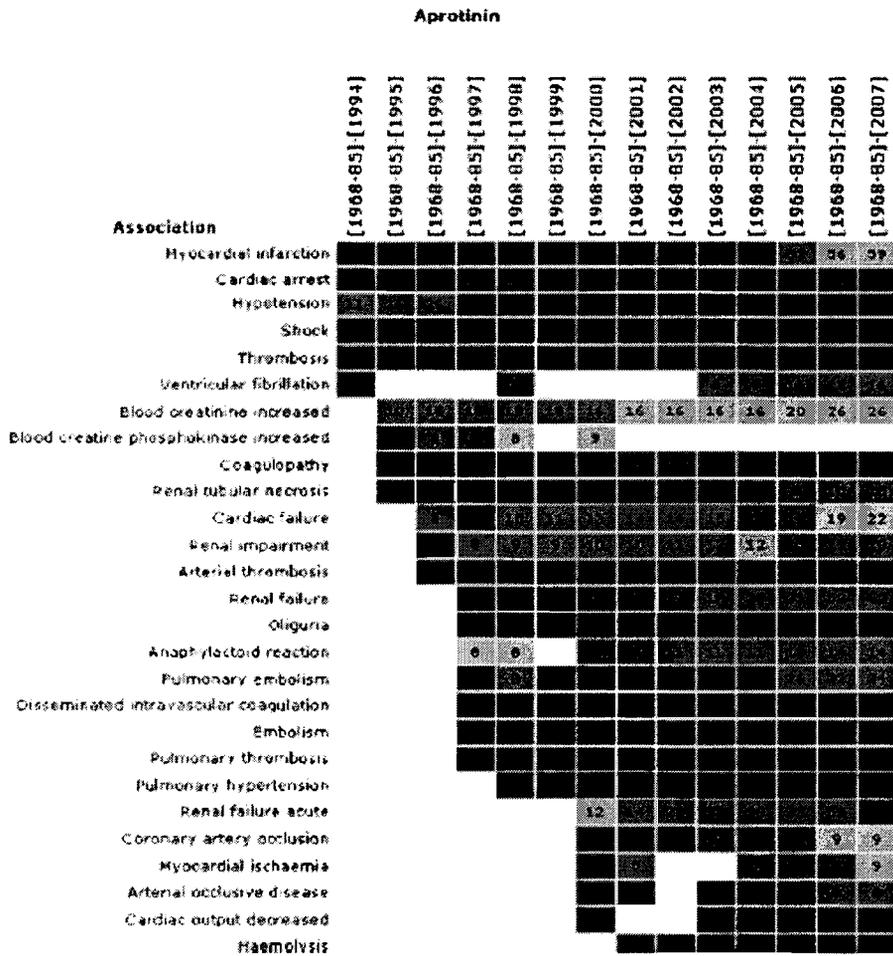
The new study was done for Bayer by a contract research organization. Existing hospital data from 67,000 records of patients undergoing coronary artery bypass graft surgery were examined. 30,000 of the patients were treated with Trasylol and 37,000 were treated with alternate products. Using complex epidemiological and statistical methods, the report suggested that patients receiving Trasylol were at increased risk for death, kidney failure, congestive heart failure and stroke.

Healthcare providers and patients are encouraged to report adverse event information to FDA via the MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by the Internet at <http://www.fda.gov/medwatch/index.html>.

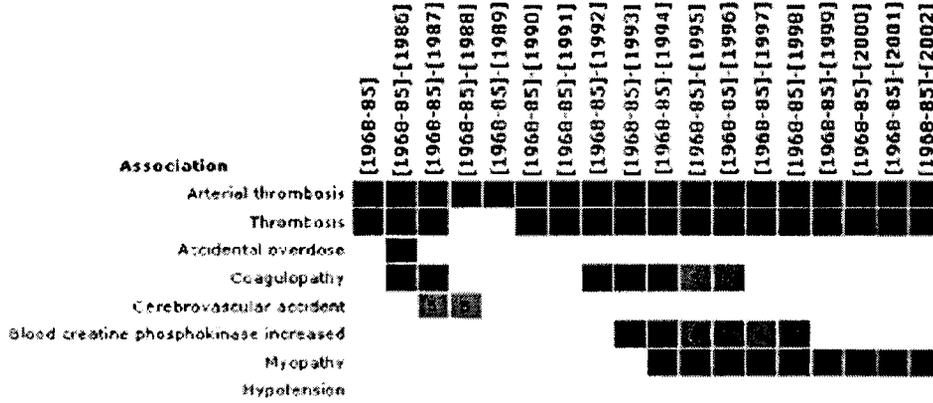
### APPENDIX 3: EBMG SCORES BY YEAR

EBMG scores for aprotinin, aminocaproic acid and tranexamic acid by year.

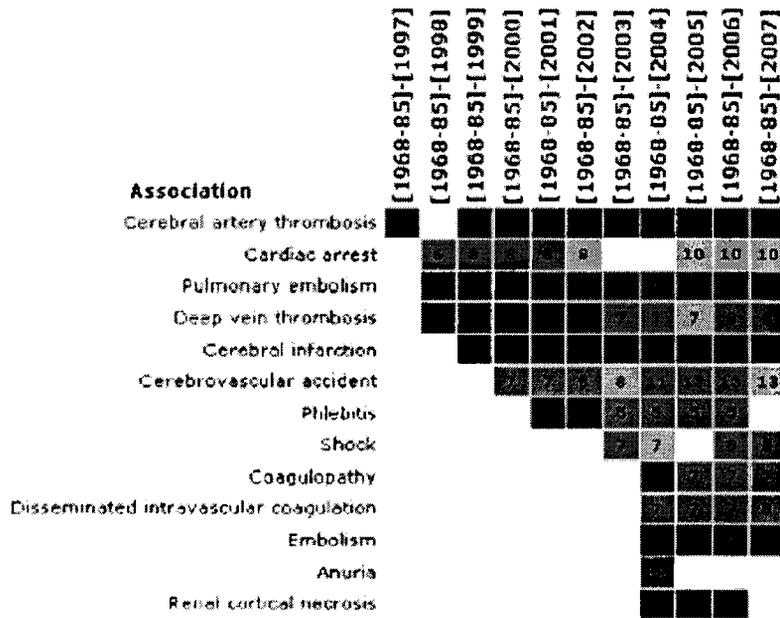
(The number in each box represents the number of reports for the year. The color represents the strength of the disproportionality EBMG signal. Only events with a signal of 2.0 or more lower bound of the confidence interval are presented)



### Aminocaproic Acid



### Tranexamic Acid



0 ≤ EBGH ≤ 1 < EBGH ≤ 2 < EBGH ≤ 4 < EBGH ≤ 8 < EBGH < ∞

### **Empirical Bayes Geometric Mean (EBGM),**

The Bayesian algorithm used for the data mining analysis was the Multi-Item Gamma Poisson Shrinker (MGPS).<sup>13,14</sup> This algorithm analyzes the records contained in large post-marketing drug safety database and then quantifies potential drug-event associations by producing a ranked set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as the Empirical Bayes Geometric Mean (EBGM), provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95 respectively.

An examination of the relative frequency of reports for aprotinin, aminocaproic acid, and tranexamic acid was conducted by applying the MGPS algorithm to FDA's AERS database (WebVDME 6.0)<sup>5</sup> MedDRA preferred terms (PT) were used for the analysis.

<sup>13</sup> DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

<sup>14</sup> Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

<sup>5</sup> *The version of AERS used in this analysis is the CBAERS version. The CBAERS database is a reformatted, integrated (de-normalized) version of the AERS database containing wider tables with more complete data in each table, facilitating systematic retrieval and analyses.*



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: August 10, 2007

To: Rafael Rieves, M.D., Director  
Division of Medical Imaging & Hematology Products (DMIHP)

Thru: Ann McMahon, M.D., Acting Deputy Director, for  
Mark Avigan, M.D., C.M., Director  
Division of Drug Risk Evaluation (DDRE)

From: Rita Ouellet-Hellstrom, Ph.D., M.P.H., Epidemiologist  
Division of Drug Risk Evaluation (DDRE)

Subject: Review of a follow-up observational study: *Mortality Associated with Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery*, JAMA, 2007; 297(5): 471-479

Drug Name(s): Aprotinin (Trasylol®)

Application Type/Number: NDA: 20-304

Applicant/sponsor: Bayer Pharmaceuticals Division

## CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND/HISTORY .....	3
2 REVIEW METHODS AND MATERIALS .....	4
3 RESULTS OF REVIEW .....	4
3.1 Objectives .....	4
3.2 Design .....	4
3.3 Informed Consent .....	6
3.4 Data Source(s) .....	6
3.5 Study Time Period(s) .....	7
3.6 Population .....	7
3.7 Exposure .....	8
3.8 Disease Outcome of Interest .....	8
3.9 Sample Size .....	9
3.10 Analyses and/or Study Results .....	10
4 DISCUSSION .....	14
5 SUMMARY .....	15
6 RECOMMENDATIONS .....	16
7 REFERENCES .....	17
APPENDIX 1 – STUDY CENTERS .....	18
APPENDIX 2 BASELINE POPULATION CHARACTERISTICS .....	20
APPENDIX 3 - COX PROPORTIONAL HAZARD MODELS .....	21
APPENDIX 4 - COVARIATES .....	22

## EXECUTIVE SUMMARY

On June 1, 2006 DDRE reviewed two recently published articles on the risk of antifibrinolytics and aprotinin use among cardiac surgery patients. In February 2007, investigators from the first study published the results of a long-term mortality follow-up of patients who underwent coronary artery bypass graft (CABG) surgery and whose results were reported in the 2006 paper.

The investigators hypothesized that use of blood-sparing therapies in general, either aprotinin (a serine protease inhibitor), or the lysine analogs in patients presenting for coronary artery surgery may be associated with higher long-term all-cause mortality.

This review reports on the long-term mortality follow up study. The results of the analysis provide evidence that 1) patients receiving aprotinin during CABG surgery differed on demographic characteristics and type of surgery (Table 3) from those who receive other antifibrinolytics; 2) aprotinin may be an independent predictor of mortality although the risk estimates are somewhat decreased when introducing propensity adjustments in the analytical models; 3) that calculated propensity scores predict antifibrinolytic rather than aprotinin use and may not sufficiently adjust for the higher risks for which aprotinin is indicated; 4) the increased risk observed for aprotinin may be a surrogate for unmeasured confounding associated with related medical and surgical complexity; and finally, the rate of follow-up is imbalanced across treatment groups in this study. Study participation rates are lower for centers using tranexamic acid and the loss-to-follow-up rate is higher in the no-use and aprotinin group and lowest for the aminocaproic acid group. Results would differ if all or many of the patients who were lost-to-follow-up were deceased. Other researchers' concerns about possible differences across participating centers, missing covariates usually predictive of CABG outcome, and the interpretation of observed results have been addressed with post-hoc analyses and the results of these analyses did not modify the initial study results.

OSE supports the Agency's efforts to obtain and re-analyze the original data provided by Dr Mangano to reproduce and re-analyze the data in an attempt to assess residual confounding. Re-analysis may shed some light on patient's pre-surgical risks and their effects on in-hospital mortality and geographical differences. Re-analysis of the long-term mortality data, however, cannot resolve the possible biases introduced by different rates of follow-up. No changes to the aprotinin label are advanced with this review.

## 1 BACKGROUND/HISTORY

On June 1, 2006, the Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation (OSE/DDRE) reviewed<sup>1</sup> two recently published articles on the risk of antifibrinolytics and aprotinin use among cardiac surgery patients. The first article<sup>2</sup>, published in *New England Journal of Medicine* on January 26, 2006, reported that treatment with aprotinin in the setting of primary cardiac surgery was associated with an increased risk for renal events (odds ratio (OR) = 2.3; 95% CI 1.3 to 4.3), cardiovascular events (OR=1.4; 95% CI 1.1 to 1.9), and cerebrovascular events (OR=2.2; 95% CI 1.1 to 4.1) compared to no exposure to antifibrinolytic therapy. The second article<sup>3</sup>, published in the March 2006 issue of *Transfusion*, a case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery, compared treatment with the antifibrinolytic agent tranexamic acid to aprotinin in the setting of cardiac surgery and reported treatment with aprotinin to be associated with a 1.4-fold increase ( $p=0.01$ ) in the risk for renal dysfunction.

At that time, OSE/DDRE recommended additions to the approved labeling for aprotinin to highlight the association between aprotinin and renal dysfunction pending results of the Canadian

*Blood Conservation using Antifibrinolytics: A Randomized Trial in High-Risk Cardiac Surgery Patients (BART)*, a randomized, double-blinded clinical trial.

Shortly after a September 21, 2006 CardioRenal Advisory Committee meeting on the issue, draft results of another aprotinin study<sup>4</sup>, lead by Dr. Schneeweiss of i3 drug safety, was made available by Bayer Pharmaceuticals, the sponsor.

In February 2007, Mangano et al<sup>5</sup> published the results of the long-term mortality follow-up of patients who underwent coronary artery bypass graft (CABG) surgery and whose results were reported in the 2006 paper.

This review reports on the Mangano et al's<sup>5</sup> 2007 long-term mortality follow-up study.

## **2 REVIEW METHODS AND MATERIALS**

The published study was evaluated for consistency, completeness and whether the study and analytical methods achieved the study objectives. The research methods assessed include the study

- Design
- Data Sources
- Informed Consent
- Study Time Periods
- Population Selected
- Exposure Criteria
- Disease Outcome
- Sample Size
- Analytical Methods

## **3 RESULTS OF REVIEW**

### **3.1 OBJECTIVES**

#### *3.1.1 Study Objective*

The investigators hypothesized that use of blood-sparing therapies in general, either aprotinin (a serine protease inhibitor), or the lysine analogs in patients presenting for coronary artery surgery may be associated with higher long-term all-cause mortality.

Consequently, the investigators proposed to contrast long-term (5-year) all-cause mortality in patients undergoing CABG surgery who received any of two lysine analog antifibrinolytics (aminocaproic acid and tranexamic acid), or serine protease inhibitor aprotinin with CABG patients receiving no antibleeding agent during surgery.

#### *3.1.2 OSE Comments on the Study Objectives*

It is important to note that the objective of this study is to contrast long-term mortality among patients who had any antifibrinolytics during surgery with those that did not receive any blood-sparing therapy.

### **3.2 DESIGN**

#### *3.2.1 Study Design*

The mortality study was a prospective follow-up study designed to evaluate the mortality experience of the 4,374 patients undergoing CABG surgery. Of these, 1,374 received no

antifibrinolytic therapy, 1,295 received aprotinin, 883 received aminocaproic acid, and 822 received tranexamic acid. The results of this study were published elsewhere<sup>2</sup>.

Of the initial 69 participating centers (Table A-1), the investigators stated that 62 sites in North and South America, Europe, and Asia agreed to complete the 5-year long-term study. Seven centers (498 patients) did not participate in the post-discharge phase of the long-term follow-up study.

Investigators interviewed patients and recorded responses on validated instruments at 6 weeks, 6 months, and annually at 1, 2, 3, 4, and 5 years following hospital discharge. All data fields were adjudicated centrally at the Ischemia Research and Education Foundation by blinded investigators. National death registries such as the Social Security Death Registry were used to supplement death information. All patients observed in the long-term follow-up as well as those who died in the hospital were included in the survival analysis. Only patients observed for the long term follow-up were included in the multivariate logistic analysis. Patients observed in the long term follow-up study and subsequently lost-to-follow-up (13%) were included in the analyses until they were censored on the date of last contact.

### 3.2.2 OSE Comments on Study Design

The long-term mortality study design is a simple follow-up of patients who underwent CABG surgery in the original study. The investigators stated that only 62 (90%) of the original 69 centers participated in the mortality study although only 61 centers are listed as participating; and 7 centers participated only in the in-hospital phase (Appendix 1).

The authors state that only 13% of the patients were lost-to-follow-up. With 90% of centers participating in the study and 87% of patients, it is possible to estimate reliable population rates if it can be assumed that the reason for non-participation is random across treatment groups. The loss-to-follow-up rate, however, does not appear to be random in this study, but appears to differ across antifibrinolytics groups (Table 1 and Figure 1).

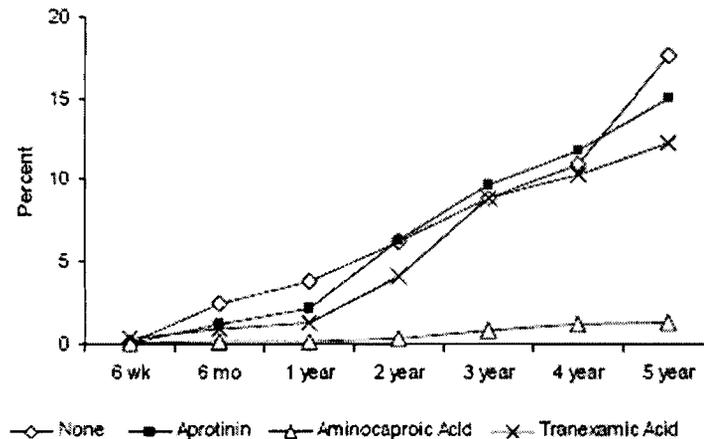
**Table 1: Cumulative Percent of Patients Lost-to-Follow-up by Antifibrinolytic Type at Time of Surgery (Number of Patients Lost-to-Follow-up), Figure 1 in Mangano et al, 2007<sup>2</sup>.**

Follow-up Time	None (1,238)	Aprotinin (1,277)	Aminocaproic	Tranexamic	Total (3,876)
			Acid (849)	Acid (512)	
6 weeks	0.1	0.1	0.1	0.3	1.0
6 months	2.4	1.3	0.2	0.9	2.2
1 year	3.8	2.2	0.2	1.3	3.0
2 years	6.1	6.2	0.4	4.1	5.5
3 years	8.8	9.6	0.9	8.7	8.2
4 years	11.0	11.8	1.2	10.3	9.9
5 years	17.7	15.0	1.4	12.3	13.4

Patients receiving no antifibrinolytics at the time of surgery had the highest overall loss rate (17.7%) compared to the group receiving aminocaproic acid (1.4%). Patients receiving aprotinin (15%) had the next highest loss rate. The loss is higher for the no-use and the aprotinin groups and consistently lowest for the aminocaproic acid group (Figure 1). The losses in the control (no-use) treatment group occur early in the follow-up period compared to losses for aprotinin and tranexamic acid treatment groups. Although the investigators stated that National Social Security

Death Registries were searched, there is a concern that some deaths may have been missed. Since follow-up appears more complete for the aminocaproic acid treatment group and this treatment was used only in North America, it is possible that follow-up was less complete for centers in other countries. The investigators did not specify when and how frequently the National Death Registry searches were completed and what time periods were covered in the search. Because the proportion of losses across groups is not balanced, there is a concern that the mortality rate observed may not reflect the actual mortality rates in the study population.

Figure 1: Percent Loss-to-Follow-up by Treatment Group



### 3.3 INFORMED CONSENT

#### 3.3.1 Informed Consent

The investigators state that the study was initiated following institutional review board approval and written informed consent was obtained. Specific information as to when this informed consent was obtained was not detailed in this publication. The 2006 publication, however, states that informed consent was obtained prior to scheduling surgery.

#### 3.3.2 OSE Comments on Informed Consent

OSE has no specific comments; the investigators appear to have followed acceptable research guidelines involving human subjects.

### 3.4 DATA SOURCE(S)

#### 3.4.1 Data Source(s)

In the original study, which forms the basis for the long-term mortality follow-up, the investigators enrolled patients according a sampling rate of  $N + 50$  where  $N$  was the number of expected myocardial revascularization surgeries expected during a 1-year period at each institution. There were 69 participating institutions in the original study in North America ( $n=40$  or 58%), South America ( $n=2$ ), Europe ( $n=23$  or 33%), the Middle East ( $n=1$ ), and Asia ( $n=3$ ) (Appendix 1). Approximately 63% of the centers were in North America and Europe in the main study. Only 62 stated (61 listed) institutions participated in the long-term mortality follow-up study: 39 in North America, 21 in Europe and 1 in Asia, the majority (97%) from North America

and Europe. Although 7 (8) centers did not participate in the long-term follow-up study, 7 of the 8 did contribute to the in-hospital phase of the mortality study (Table A-1 in the Appendix).

### *3.4.2 OSE Comments on Data Sources*

Although the authors state that 62 of the 69 sites participated in the long-term follow-up study, the listing at the end of the published article lists 8 non-participating sites. In-hospital deaths from the 7 non-participating sites with 498 patients were included in the survival analysis but not in the long-term analysis. Since 97% of the participating sites were located in North America and Europe, non-participating sites may have been excluded due to the difficulties of following patient population over a long period of time and/or the lack of National Death Registries in those countries.

## **3.5 STUDY TIME PERIOD(S)**

### *3.5.1 Study Time Period(s)*

Enrollment commenced on November 11, 1996. The in-hospital phase was completed on June 30, 2000, and the long-term follow-up was completed on January 5, 2006. Patients were interviewed at 6 weeks, 6 months, 1, 2, 3, 4, and 5 years following their surgery.

### *3.5.2 OSE Comments on Study Time Period(s)*

The authors provide dates for the long-term mortality study and the frequency of patient interviews. No time period or dates are provided for the National Death Registry searches although death registries may have a lag of two or more years. Based on the time period provided, it is assumed that patients were enrolled for the CABG surgery study over a 5-year period between November 11, 1996 and June 2000, at least at the North American and European centers.

## **3.6 POPULATION**

### *3.6.1 Study Population*

Although no additional information is provided in this paper on the study population, the eligibility criteria for study enrollment in the initial study required patients to be at least 18 years of age, not enrolled in another study or trial, and able to engage in a pre-operative interview.

### *3.6.2 OSE Comments on the Study Population*

The authors present the demographic and baseline characteristics for all patients undergoing CABG in Table 1<sup>5</sup> of their paper. This information is identical to the information presented in Table 1<sup>2</sup> of the 2006 paper but it also includes information on geographic regions not included in the original paper. A complete copy of the authors' Table A1 can be found in Appendix 2. The geographic characteristics are summarized in Table 2 of this review.

Table 2 shows that, in the original study, aminocaproic acid use occurred mostly in North America (95.8%) and to a lesser extent in South America (4.2%). Thus excluding the centers from the Middle East, South America, and two of the three Asian countries should not seriously impact the observations for this product. In fact, since the majority of the patients were enrolled at North American, European, and Asian centers for apronin (98.6%), aminocaproic acid (96.1%), and no-use (90.1%), exclusion of the Middle East and South American countries should not affect the estimates observed for these products in the mortality study. The non-participating

Asian centers contributed observations to the no-use and tranexamic acid treatment groups. It is unclear, however, how excluding two of the three Asian centers impacted the overall balance. Results for the tranexamic acid (62.3%) are more likely to be impacted by excluding the Asian, Middle East, and South American centers.

**Table 2: Number and proportion of study subjects in the initial study by region and the mortality follow-up study [limited to North America, Europe, and Asia (1)] by antifibrinolytics received.**

	Control		Aprotinin		Aminocaproic Acid		Tranexamic Acid		Any Antifibrinolytics	
	1,374		1,295		883		822		3,000	
Region	N	%	N	%	N	%	N	%	N	%
Europe	790	57.5	899	69.4	0	--	405	49.3	1,304	43.5
North America	328	23.9	377	29.1	846	95.8	240	29.2	1,463	48.8
Asia	227	16.5	0		0	--	21	2.6	21	0.7
Middle East	19	1.4	2	0.2	0	--	64	7.8	66	2.2
South America	10	0.7	17	1.3	37	4.2	92	11.2	146	4.9
Mortality Study (N America, Europe, Asia (1))	1,238	90.1	1,277	98.6	849	96.1	512	62.3	2,638	87.9

### 3.7 EXPOSURE

#### 3.7.1 Exposure

Study subjects undergoing CABG surgery who were enrolled in the initial study were either given antifibrinolytic (aprotinin, aminocaproic acid or tranexamic acid) or no antifibrinolytic therapy at the time of surgery.

#### 3.7.2 OSE Comments on Study Exposure

Exposure classification in the mortality study is straightforward since the study examines the five-year mortality experience of patients enrolled in the initial study. These patients either received or did not receive antifibrinolytic therapy during their CABG surgery. The investigators, however, do not address whether any of these patients were subsequently exposed to the same or different antifibrinolytics during the 5-year observation period and whether they had additional cardiac surgery. Any additional exposure to antifibrinolytics and cardiac surgery could confound the observations. Since follow-up information was obtained by interview and from medical records, it would seem that information on additional exposure would be available.

### 3.8 DISEASE OUTCOME OF INTEREST

#### 3.8.1 Disease Outcome of Interest

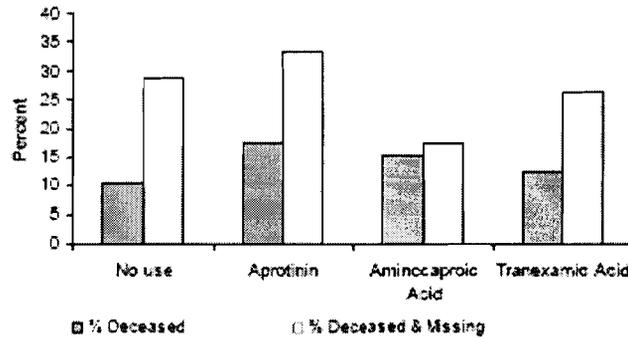
The study examines all-cause mortality.

#### 3.8.2 OSE Comments on Disease Outcome of Interest

Although all-cause mortality is a definitive outcome not subject to issues surrounding case definitions, finding and documenting deaths is more difficult. As was discussed in Section 3.2.2, this study had an imbalance in follow-up rates across treatment groups over five years. The

investigators do not discuss the follow-up methods used other than to mention that Social Security Death Registries were queried. Consequently, it is difficult to assess the quality and completeness of the follow-up and the resulting measured outcome. How many attempts were made to contact patients? Was a relative contacted if direct contact was unsuccessful? When and how frequently were the registries queried?

**Figure 2: Proportion deceased by initial type of antifibrinolytics therapy given: observed deaths compared to observed deaths and patients lost-to-follow-up.**



If it can be assumed that all the patients lost-to-follow-up were deceased (Figure 2), the differences observed between no antifibrinolytic use compared to aprotinin use would be much narrower (16% when including lost to follow-up vs. 69% when only including documented deaths). The aminocaproic acid treatment group is the only antifibrinolytic therapy group where combining the known deceased with those lost-to-follow-up would make very little difference in the proportion of deaths observed.

Geographical and regional differences may be important surrogate confounders for incomplete follow-up which in turn may explain differences in follow-up rates since the quality and completeness of death registries may vary by country.

### 3.9 SAMPLE SIZE

#### 3.9.1 Sample Size

All CABG patients from the 62 (61) participating centers were included in the mortality follow-up study (n=3,876 or 88.6% of the original 4,374 CABG population).

#### 3.9.2 OSE Comments on Study Sample Size

Since this study is designed to assess mortality rates in all patients that have undergone CABG surgery during the initial study period, sample size per se is not so much of a concern. The mortality population under study comprises approximately 89% of the total population and nearly 100% of those from the North American and European centers. Of concern, however, is the imbalance of follow-up across for treatment groups as discussed in Sections 3.7 and 3.8.

### 3.10 ANALYSES AND/OR STUDY RESULTS

#### 3.10.1 Analyses

Three methods were used to assess the mortality impact of antifibrinolytic treatment during CABG surgery:

1. Survival analysis
2. Multivariable logistic regression, and
3. Propensity score adjustment

A Cox Proportional Hazard (Survival) analysis was performed on all 4,374 patients enrolled in the in-hospital study. The Cox Proportional Hazard regression model with covariate-adjusted survival was used for this analysis. The origin time was set as the time and date of surgery and patients were right censored at the time of last contact. All but one center participated in this in-hospital phase of the study. The proportional hazards assumption was evaluated and time-dependent covariates were included in the model. Cumulative mortality was calculated as 1 minus the adjusted survival.

The multiple logistic regression analysis included 97 perioperative risk factors to evaluate the association of drug group with 5-year mortality among patients participating in and completing the 5-year follow-up program. The final model assessed the association of each treatment (aprotinin, aminocaproic acid, or tranexamic acid versus no treatment) with 5-year mortality in the presence of the significant covariates and also included in-hospital outcome events.

Propensity score adjustments were used to assess selection bias not adequately controlled by standard multivariable approaches. Propensity scores were calculated for any antifibrinolytic treatment versus no treatment using a nonparsimonious logistic regression model. The model included 45 treatment selection covariates. The derived propensity scores were then used for multivariable covariate adjustment together with the antifibrinolytic drug indicator variables. Propensity scores were also included in some of the Cox models.

Dose-response secondary analyses for patients who received a low-dose or a high dose-regimen were also performed. These analyses compared the mortality experience of aprotinin patients with that of control patients.

##### 3.10.1.1 OSE/DDRE Comments on Analyses

The investigators selected various methods to analyze their data.

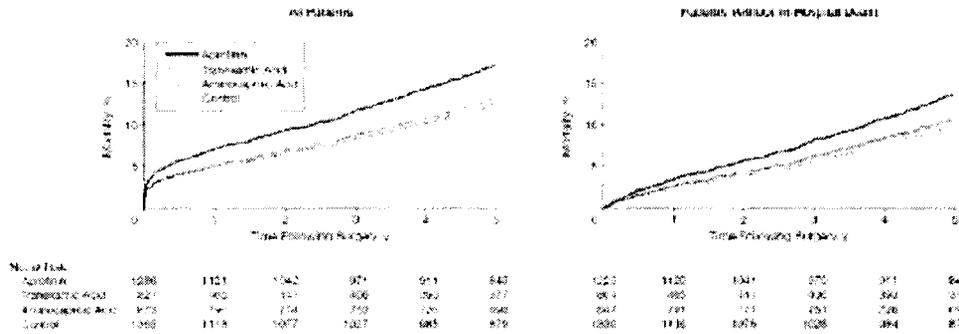
The Cox Proportional Hazard (Survival) model is appropriate to assess long-term follow-up provided the hazard ratio remains constant over time. For this study, the model allows incorporation of the survival experience for all initial 4,374 patients undergoing CABG surgery until the date of last contact. This model was also used by the investigators to evaluate survival for the cohort members (4,249) who survived their index hospitalization at the 62 (61) participating centers. It is unclear, however, whether the variables listed in Tables 2 and 3 in the publication (see Appendix 3) were the only variables included in the model after initial univariate evaluation of the 97 covariates referenced<sup>1</sup> in this publication and listed in Appendix 4 of this review or whether the tables lists only the covariates that independently predicted death. The survival analysis was done both with and without propensity score adjustments. Just like in the 2006 publication, it remains unclear which variables were used to derive the propensity score and which ones were used as covariates in the model.

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<sup>1</sup> [http://www.iref.org/LIFU\\_Death\\_Appendix\\_1.1.html](http://www.iref.org/LIFU_Death_Appendix_1.1.html)

Finally, the Cox proportional hazards model assumes that the hazard for one group is proportional over time to the hazard for the comparator group. The aprotinin cumulative mortality curves in Figure 3 of the published paper appear to be increasing over time faster than that for other treatment groups. Whether this change in slope is sufficient to affect the results of the survival analysis needs to be explored further.

Figure 3: Cumulative mortality curves compared among study groups, Mangano et al, 2007 Figure 2<sup>5</sup>



Left: mortality was calculated from the observed survival distributions as 1 minus the estimated survival among 4145 patients by study group: control (1368 patients), aminocaproic acid (175 patients), tranexamic acid (821 patients), aprotinin (1286 patients). Patients with missing covariates were excluded (n=29). Survival was significantly different between aprotinin and control (P=0.005), but not between aminocaproic acid and control (P=0.83), or between tranexamic acid and control (P=0.46). Survival was adjusted using the propensity score regression method (see Methods). Patients participating in the in-hospital, but not long-term phase were censored at 6 weeks. Right: mortality calculated as 1 minus the observed survival among patients without in-hospital death (n=128): control (1368 patients), aminocaproic acid (821 patients), tranexamic acid (804 patients), aprotinin (1229 patients). Patients with missing covariates were excluded (n=29).

A multivariate logistic regression analysis was performed using the 97 perioperative risk factors to predict long term mortality for only the patients (3,876) enrolled at the 62 (61) centers that participated in the 5-year follow-up study. The investigators used this model to assess the treatment effect for aprotinin, aminocaproic acid, and tranexamic acid separately compared with no treatment over the 5-year follow-up. Although use of propensity adjustments is not mentioned in the methods section, it is assumed that these models were run with and without propensity adjustments because odds ratios for models with and without propensity score adjustments are mentioned in the results section. Results for this analysis are not tabulated. It is unclear why this model was selected to analyze the subset of patients enrolled at participating centers. According to the investigators, the risk estimates obtained by each model were not much different than those obtained by the survival model. It is at least reassuring to note that differences observed were not due to the model selected.

Propensity scores were calculated to obtain a probability of being treated with an antifibrinolytic compared to no antifibrinolytic treatment during surgery. The score captures information on at least 45 treatment selection covariates. There are two issues with the way propensity scores were calculated and used:

- 1) Of the 97 perioperative covariates referenced (Appendix 4), it is unclear which covariates were included in the model used to calculate the propensity score, which ones were used in the analytic models (Cox Proportional Hazard / Multivariate logistic regression) for analysis, and which ones were completely omitted. Both of the analytic models were used with and without propensity adjustments.
- 2) Propensity scores were calculated based on the use of any antifibrinolytic compared to no use. Only one of the three antifibrinolytics used has been approved for the CABG indication in the U.S. and then only for high risk surgeries. Both papers show that the antifibrinolytics differed significantly from the control group but also across groups. Fewer patients who received aprotinin were African American, had some college

education, and had an urgent or emergency surgery than those receiving the other antifibrinolytics. Aprotinin patients, however, were more likely to have had valve, carotid, liver disease, and complex surgery than patients receiving the other antifibrinolytics treatments. Therefore, a combined propensity score for antifibrinolytic treatment may not completely adjust for differences in risk.

**Table 3: Selected imbalances for aprotinin group with other antifibrinolytics groups, Mangano et al., 2007<sup>5</sup>.**

	Aprotinin %	Aminocaproic Acid %	Tranexamic Acid %
African American	4.3	15.7	12.8
Education (some college or more)	21.6	45.1	29.3
Urgent or emergency surgery	14.8	18.9	17.5
Congestive Heart Failure	43.1	27.9	33.7
Complex Surgery	38.2	32.3	26.6
Valve disease	25.4	19.9	15.2
Carotid disease	17.2	12.2	12.3
Liver disease	11.7	7.5	8.0

3) Dose response analyses were done to assess whether mortality increased with increasing dose. Dose-response analyses provide insights into causality assessment when dose information is available.

### 3.10.2 Results

Table 4 summarizes the survival and multivariate estimates reported from the analytical models that compare each antifibrinolytic with no use. Other important predictors of mortality identified by the models are presented publication's tables 2 and 3 and are attached in Appendix 3 of this review.

Risk estimates for aprotinin were consistently predictive of mortality whether all patients were analyzed (survival analyses) or only those in the long-term follow-up and whether adjustments were made with propensity scores. Aminocaproic acid and tranexamic acid were not predictors of in-hospital or long term mortality after adjusting the analytical models with the other covariates.

According to the survival model, the most important ( $p < 0.001$ ) independent predictors of mortality included medical history covariates (congestive heart failure, diabetes mellitus, and peripheral vascular disease), complex surgery, prior warfarin use, creatinine of more than 1.3 mg/dl on admission, and preoperative myocardial infarction. Some of these covariates (complex surgery, congestive heart failure) showed imbalance across antifibrinolytic treatment groups (Table 3).

Aprotinin was also an independent predictor of mortality. When propensity scores were introduced in the survival model, the same covariates independently predicted death. The statistical significance for aprotinin as an independent covariate, however, decreased to a probability of 0.008 instead of  $p < 0.001$ .

Detailed risk estimates obtained from the multivariate logistic regression were not presented in the publication for any other covariates except the antifibrinolytics.

**Table 4: Hazard (HR) and Odds Ratios (OR) with 95% Confidence Intervals (CI) reported for 5-year mortality study, Mangano et al, 2007<sup>5</sup>**

	Aprotinin		Aminocaproic Acid		Tranexamic Acid	
	HR	95% CI	HR	95% CI	HR	95% CI
<b>Cox Proportional Hazard Model</b>						
All patients (n=4,374)	1.48	1.19-1.85	1.03	0.80-1.33	1.07	0.80-1.45
Survivors	1.47	1.14-1.90	1.09	0.82-1.46	1.12	0.79-1.60
All patients with Propensity Score	1.37	1.09-1.73	0.89	0.68-1.17	1.04	0.77-1.41
Survivors with Propensity Score	1.43	1.10-1.88	1.05	0.77-1.41	1.12	0.79-1.60
<b>Multivariate Logistic Regression</b>	<b>OR</b>	<b>95% CI</b>	<b>OR</b>	<b>95% CI</b>	<b>OR</b>	<b>95% CI</b>
Participating Center (n=3,876)	1.51	1.17-1.96				
With propensity score	1.48	1.13-1.93				
With in-hospital non-fatal events as covariates	1.52	1.14-2.02	1.06	0.77-1.45	1.10	0.74-1.62

Table 5 presents the results of the dose response analysis for aprotinin. These results indicate that the risk of death increased with higher doses of aprotinin used. The confidence interval, however, are wider at the higher doses probably due to the small number of patients receiving the higher doses.

**Table 5: Association between aprotinin dose and mortality, Mangano et al, 2007.**

Dose	Odds Ratio	95% Confidence Interval
Control	1.00	Reference
Low dose†	1.58	1.14-2.20
High dose††	2.07	1.08-3.95

† Low dose = loading = 1 million KIU; total = 2 million KIU.

†† High dose = loading = 2 million KIU; total = 4 million KIU.

### 3.10.2.1 OSE/DDRE Comments on Study Results

The risk estimates obtained from the survival analyses and the multivariate analyses are very similar and point to an independent effect for aprotinin on long-term mortality. Although still significant, the effect of aprotinin decreases somewhat when propensity scores are included in the analytical models. Given that, with the exception of age, all other independent predictors of mortality are variables that measure pre-existing medical conditions, or perioperative risk factors that assume increased risk at surgery, it is possible that the independent effect of aprotinin may be a surrogate for unmeasured or residual confounding.

The argument supporting an independent and increased risk associated with the aprotinin is the consistency of the risk estimates observed across all analytical models used and the dose-response association observed with increasing exposure to the product.

The arguments against supporting an independent and increased risk for aprotinin includes the fact that the risk estimates for aprotinin are of the same magnitude as that for medical and/or perioperative predictors as well as the imbalance observed for follow-up across treatment groups. Even the dose-response relationship, usually a good predictor of causality, may fail if the

probability of receiving any dose of aprotinin treatment is directly associated with medical and surgical complexity.

Adjustment for confounding by indication, in this study, would have been more efficient if the propensity scores had been calculated based on the probability of receiving aprotinin rather than the probability of being prescribed any antifibrinolytic.

#### 4 DISCUSSION

This review reports on the long-term mortality follow up study. The results of the analyses provide evidence that patients who receive aprotinin during CABG surgery differed on demographics and type of surgery (Table 3) from those who receive other antifibrinolytics. These differences may be an indication that the covariate labeled ‘aprotinin’ may serve as a surrogate for residual confounding, or the aprotinin may be an independent predictor of mortality. That the risk estimates decrease somewhat when introducing propensity adjustments in the analytical models argues in favor for the existence of residual confounding.

An uneven follow-up across treatment groups also points to a potentially important bias that could affect the results of this long-term mortality study. The loss-to-follow-up rate is higher in the no-use and aprotinin treatment groups and lowest for the aminocaproic acid group. Results would differ if all or many of the patients who were lost-to-follow-up were deceased. Although survival analyses stratified on follow-up time since surgery could provide a better estimate of mortality during the early period of follow-up, the imbalances appear as early as 6 months for aprotinin and the no-use control group. An aggressive follow-up strategy would be the only way to assess the imbalance effect on long-term mortality. Finally, the participation rate is lower (62%) for centers using tranexamic acid compared to centers using aprotinin (98%), aminocaproic acid (96.1%), or no use (90.1%).

The June 13, 2007 Journal of the American Medical Association (JAMA) issue contains four letters to the editor addressing additional concerns about the Mangano et al’s mortality study as well as the investigators’ replies.

Schametzky et al<sup>6</sup> raised concerns about site-level bias suggesting differential enrollment between European and North American centers (also addressed in this review) and suggested additional analyses be done for patients treated in European centers versus those treated in North American centers. The analyses were presented in the reply<sup>7</sup> and showed very little differences which were attributed to small numbers created when stratifying by centers:

Europe	HR = 1.48; 95% CI = 1.10-2.00
North America	HR = 1.39; 95% CI = 0.96-2.00

Coca and Parikh<sup>8</sup> commented on the investigators’ discussion attributing a probable mechanistic role of aprotinin as a mediator of long-term death via coronary thrombosis. Coca and Parikh suggested that chronic kidney disease as defined may be induced by acute kidney injury rather than arterial thrombosis may mediate long-term hazards associated with aprotinin. They suggested that the investigators stratify their analyses by acute injury status using a sensitive definition ( $\geq 25\%$  rise in serum creatinine) to address their hypothesis. Mangano and others in their response presented results of their re-analyses evaluating the association of aprotinin use and acute perioperative renal injury. Their analysis of in-hospital renal events found a significant association with long-term mortality that was similar to that observed for thrombosis-related events and concluded that both acute vascular thrombosis and acute renal toxicity may account in part for the relationship between aprotinin and long-term mortality.

Renal injury related	HR = 1.76; 95% CI = 1.22-2.56
Thrombosis related	HR = 1.37; 95% CI = 1.09-1.72

Shuhaiber<sup>8</sup> questioned whether Mangano and others considered preoperative hemoglobin levels either as covariates in the analytical models or included in calculating propensity scores since hemoglobin levels are correlated with worse CABG outcome. This author also questioned whether institutional policies regarding the mean number of grafts per patient, perioperative blood loss, blood-saving techniques, and the level of hemoglobin resulting in transfusions could introduce bias when pooling results. The investigators responded by stating that covariates capturing information on anemia were included both in the Cox proportional hazard and propensity score-adjusted analyses and found that neither hemoglobin level (admission, pre-operative, bypass, post bypass, intensive care unit, post intensive care unit, and at discharge) nor its temporal change had any independent effect on long-term mortality. In addition, inclusion of surgical variables including conduit-related factors had minimal effects on findings but no results were included to support these statements.

Habib<sup>10</sup> raised the concern that two important determinants of long-term CABG outcomes were not included in the analyses: 1) the extent of coronary disease such as the number of vessels involved and 2) differences in grafting approaches across centers such as completeness of revascularization, use of internal thoracic artery grafting, and arterial versus vein grafting which affect long-term CABG outcomes. The investigators responded by referring to Figure 3 in the original article that show findings by five different risk indices. With respect to differences across sites, the inclusion of internal mammary (thoracic) artery was routine (83%) and radial artery use was uncommon (11.6%). Finally, in the presence of either covariate, the adjusted HR were similar for aprotinin

Thoracic artery conduit HR = 1.42; 95% CI = 1.13-1.77

Radial artery conduit HR = 1.48; 95% CI = 1.18-1.85

Neither aminocaproic nor tranexamic acid were associated with increased mortality in the presence of either conduit covariate.

## 5 SUMMARY

The results of the analysis published by Mangano et al (2007) provide evidence that patients who receive antifibrinolytics differ on demographic, prior medical history, and surgical characteristics from those who do not (Appendix 2). The paper also notes that

- Patients receiving aprotinin during CABG surgery differ from those who receive aminocaproic acid and tranexamic acid (Table 3).
- Risk estimates obtained from survival and multivariate analyses indicate that aprotinin is an independent predictor of mortality although the risk estimates are somewhat decreased when introducing propensity adjustments in the analytical models.
- Propensity scores calculated predict antifibrinolytic rather than aprotinin use and may not sufficiently adjust for the higher risks indicated for aprotinin use and consequently the increased risk observed for aprotinin may be a surrogate for residual or unmeasured confounding and correlated with medical and surgical complexity.
- Study participation rate is lower at centers using tranexamic acid (62% vs.  $\geq 90\%$ ).
- The rate of follow-up is imbalanced across treatment groups in this study. The loss is higher in the no-use and aprotinin treated groups and lowest for the aminocaproic acid treated group (Section 3.2). Results would differ if all or many of the patients who were lost-to-follow-up were actually deceased.
- Other researchers identified concerns about differences across participating centers, missing covariates usually predictive of CABG outcome, and the interpretation of the

observed results although post-hoc analyses in response to these concerns did not modify the study results.

## **6 RECOMMENDATIONS**

OSE supports the Agency's efforts to also obtain and re-analyze the original data provided by Dr Mangano in an effort to reproduce and re-analyze the data in an attempt to assess residual confounding. Re-analysis may shed some light on patient's pre-surgical risks and their effects on in-hospital mortality and geographical differences. Re-analysis of the long-term mortality data, however, cannot resolve the possible biases introduced by differing rates of follow-up.

No changes to the aprotinin label are advanced with this review.

## 7 REFERENCES

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- <sup>4</sup> Schneeweiss . *Mortality and cardiovascular and renal outcomes in recipients of Aprotinin, Aminocaproic acid and tranexamic acid during CABG Surgery.* 2006
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- <sup>6</sup> Schametzky E, Schill W, and Garbe E. 2007. *Long-term mortality associated with aprotinin following coronary artery bypass graft surgery.* Letter, JAMA; 297(22):2475.
- <sup>7</sup> Mangano DT. 2007. *Long-term mortality associated with aprotinin following coronary artery bypass graft surgery.* Reply, JAMA; 297(22):2476
- <sup>8</sup> Coca SG and Parikh CR. 2007. *Long-term mortality associated with aprotinin following coronary artery bypass graft surgery.* Letter, JAMA; 297(22):2475-6.
- <sup>9</sup> Shuhaiber J. 2007. *Long-term mortality associated with aprotinin following coronary artery bypass graft surgery.* Letter, JAMA; 297(22):2476
- <sup>10</sup> Habib RH. 2007. *Long-term mortality associated with aprotinin following coronary artery bypass graft surgery.* Letter, JAMA; 297(22):2477

## APPENDIX 1 – STUDY CENTERS

Table A-1. Centers Participating in the Aprotinin and Coronary Artery Bypass Graft Surgery Observational Studies, Mangano 2006 and 2007

	Country	Center	Investigator
1	United States	*University of Chicago, IL	S. Aronson
2		*Weiss Memorial Hospital	S. Aronson
3		*Beth Israel Deaconess Medical Center, Boston MA	M. Comunale
4		*Massachusetts General Hospital	M. D'Ambra
5		†University of Rochester	M Eaton
6		*Baystate Medical Center	R Engleman
7		*Baylor College of Medicine	J Fitch
8		*Duke Medical Center	K Grichnik
9		*University of Texas Health Science Center at San Antonio Hospital	CB Hantler
10		*Andie L. Murphy Memorial Veterans Hospital	CB Hantler
11		*St Luke's-Roosevelt Hospital	Z Hillel
12		*New York University Medical Center	M Kanchuger & J Ostrowski
13		*Stanford University Medical Center	CM Mangano
14		*Yale University Medical Center	J Mathew, M Fontes, & P Barash
15		*University of Wisconsin	M McSweeney & R Wolman
16		*University of Arkansas for Medical Sciences	CA Napolitano
17		*Discovery Alliance	LA Nesbitt
18		*Veterans Affairs Medical Center, Milwaukee	N Nijhawan
19		*Texas Heart Institute	N Nussmeier
20		*Mercy Medical Center	N Nussmeier
21		*University of Arizona	S Polson
22		*University of Texas Medical School	EG Pivalizza
23		*Emory University Hospital	J Ramsay
24		*Kaiser Foundation Hospital	G Roach
25		*Thomas Jefferson University Hospital	N Schwann
26		*Hahnemann University Hospital	N Schwann
27		*VA Medical Center, Houston	S Shenaq
28		*Maimonides Medical Center	K Shevde
29		*Mt Sinai Medical Center	L Shore-Lesserson & D Bronheim
30		*University of Michigan	J Wahr
31		*University of Washington	B Spiess
32		*VA Medical Center, San Francisco	A Wallace
33	Austria	*University of Graz	H Metzler
34	Canada	*University of British Columbia	D Ansley & JP O'Connor
35		*The Toronto Hospital	D Cheng
36		*Laval Hospital, Québec,	D. Côté
37		*Health Sciences Centre, University of Manitoba	P Duke

**Table A-1. Centers Participating in the Aprotinin and Coronary Artery Bypass Graft Surgery Observational Studies, Mangano 2006 and 2007**

Country	Center	Investigator
38	*University of Ottawa Heart Institute	JY Dupuis & M Hynes
39	*University of Alberta Hospital	B Finnegan
40	*Montreal Heart Institute	R Marineau & P Couture
41	*St Michael's Hospital, University of Toronto	D Mazer
42	††Fundacion Clinico Sano	JC Villalba & ME Colmenares
43	*Centre Hospitalier Régionale Universitaire, Le Bocage	C Girard
44	*Hospital Pasteur	C Isetta
45	*Universität Würzburg	CA Greim & N Roewer
46	*Universität Bonn	A Hoeft
47	*University of Halle	R Loeb & J Radke
48	*Westfälische Wilhelms- Universität Münster	T Mollhoff
49	*Universität Heidelberg	J Motsch & E Martin
50	*Ludwig-Maximilians Universität	E Ott & P Ueberfuhr
51	*Universität Krankenhaus Eppendorf	J Scholz & P Tonner
52	*Georg-August Universität Göttingen	H Sonntag
53	*Orszagos Kardiologiai Intezet	A Szekeley
54	*Escorts Heart Institute	R Juneja
55	††Apollo Hospital	G Mani
56	††Hadassah University Hospital	B Drenger, Y gozi & E Elami
57	††San Raffaele Hospital, Università de Milano	C Tommasino
58	††Instituto Nacional de Cardiologia	P Luna
59	††University Hospital Maastricht	P Roekaerts & S DeLange
60	*Institute of Cardiology	R Pfitzner
61	*Institute of Cardiology	D Filipescu
62	††Siriraj Hospital	U Prakanrattana
63	*Glenfield Hospital	DJR Duthie
64	*St Thomas' Hospital	RO Feneck
65	*The Cardiothoracic Centre, Liverpool	MA Fox
66	*South Cleveland Hospital	JD Park
67	*Southampton General Hospital	D Smith
68	*Manchester Royal Infirmary	A Vohra
69	*Papworth Hospital	A Vuylsteke & RD Latimer

\* Participated in the in-hospital phase and the discharge phase of the long-term mortality study.

† Did not participate in the in-hospital phase and the discharge phase of the long-term mortality study.

†† Participated in the in-hospital phase but not the post-discharge phase of the long-term mortality study.

## APPENDIX 2 BASELINE POPULATION CHARACTERISTICS

**Table 1.** Baseline Characteristics of 4374 Study Patients by Treatment

Characteristic	Control Group (n = 1374)	Antifibrinolytic Group								
		Overall (n = 3007)		Aprotinin (n = 1295)		Aminocaproic Acid (n = 883)		Tranexamic Acid (n = 822)		
		No. (%)	P Value*	No. (%)	P Value*	No. (%)	P Value**	No. (%)	P Value**	
Age, mean (SD), y	63.2 (9.6)	64.6 (9.6)	<.001	64.9 (9.2)	<.001	65.1 (9.8)	<.001	63.4 (9.7)	.64	.72
Male sex	1110 (80.0)	2377 (79.2)	.24	1018 (78.5)	.14	690 (78.1)	.13	671 (81.6)	.53	.83
African American, American Indian, or Hispanic ethnicity	53 (3.9)	80 (2.6)	<.001	55 (4.3)	.24	139 (15.7)	<.001	105 (12.8)	<.001	.24
Education, some college or above	498 (36.1)	918 (30.6)	<.001	280 (21.8)	<.001	309 (35.1)	<.001	240 (29.2)	<.001	.43
Surgery urgent or emergency status	288 (21.0)	506 (16.9)	<.001	192 (14.8)	<.001	167 (18.9)	.34	144 (17.5)	.05	.63
Medical history										
Asthma	1273 (92.6)	2088 (69.4)	.002	1136 (87.6)	<.001	783 (88.9)	.004	736 (90.6)	.49	.53
Hypertension	831 (60.5)	2100 (70.0)	<.001	907 (70.6)	<.001	660 (74.7)	<.001	533 (64.8)	.34	.52
Myocardial infarction	714 (52.0)	1548 (52.2)	.98	684 (52.1)	.04	453 (51.6)	.22	451 (55.1)	.19	.83
Congestive heart failure	461 (33.6)	1078 (36.1)	.12	557 (42.1)	<.001	345 (39.3)	.004	276 (33.7)	.97	.46
Diabetes mellitus	305 (22.2)	806 (26.9)	.20	353 (27.3)	.06	325 (36.8)	<.001	220 (26.9)	.52	.37
Complex surgery	343 (25.0)	990 (33.3)	<.001	493 (38.2)	<.001	285 (32.3)	<.001	219 (26.6)	.38	.43
Egdon fraction $\geq 44\%$	247 (18.0)	508 (16.9)	.40	199 (15.4)	.07	169 (19.1)	.41	140 (17.0)	.57	.88
Pulmonary disease	238 (17.4)	683 (22.6)	<.001	327 (25.3)	<.001	216 (24.6)	<.001	140 (17.1)	.84	.86
Creatinine > 1.2 mg/dL on admission	188 (13.8)	449 (15.0)	.29	195 (15.1)	.24	132 (14.9)	.43	122 (14.8)	.48	.56
Beta disease	183 (13.3)	525 (17.5)	<.001	241 (18.6)	<.001	132 (14.9)	.28	152 (18.5)	.001	.97
Valve disease	169 (12.4)	622 (20.7)	<.001	329 (25.4)	<.001	168 (19.0)	<.001	105 (12.8)	.36	.62
Coronary disease	163 (11.9)	452 (14.9)	.003	223 (17.2)	<.001	106 (12.2)	.43	101 (12.3)	.41	.42
Pericardiacus/transmural coronary aneurysm	138 (10.0)	542 (18.0)	<.001	223 (17.2)	<.001	173 (19.6)	<.001	146 (17.8)	<.001	.71
Liver disease	106 (7.7)	283 (9.5)	.06	151 (11.7)	<.001	66 (7.5)	.86	66 (8.0)	.79	.90
Stroke	89 (6.5)	191 (6.4)	.90	90 (7.0)	.62	64 (7.3)	.46	57 (6.9)	.05	.64
Type 1 diabetes mellitus	78 (5.7)	242 (8.1)	.006	116 (9.0)	.001	80 (9.1)	.002	46 (5.6)	.94	.50
Atrial coronary stand	54 (3.9)	277 (9.2)	<.001	95 (7.3)	<.001	78 (8.8)	<.001	54 (6.6)	.008	.89
Heart block	13 (0.9)	37 (1.2)	.13	19 (1.5)	.07	8 (0.9)	.85	10 (1.2)	.38	.62
Coronary artery bypass grafting	5 (0.4)	19 (0.6)	.26	11 (0.8)	.90	7 (0.8)	.24	7 (0.8)	.62	.99
Geographic region										
Europe	790 (57.5)	1904 (62.2)		899 (69.4)		0		405 (49.3)		
North America	228 (23.9)	1463 (48.4)		377 (29.1)		846 (95.8)		240 (29.2)		
Asia	207 (16.6)	21 (0.7)		0		0		2 (2.6)		
Middle East	13 (1.0)	66 (2.2)		2 (0.2)		0		64 (7.8)		
South America	10 (0.7)	146 (4.8)		17 (1.3)		37 (4.2)		32 (3.9)		

\*P value for trend; the value for a statistic is given; multiply by 10<sup>4</sup>.

\*\*P value compares patients treated with an antifibrinolytic agent and control patients.

†P value calculated after adjustment to propensity score odds in the 4374 study patients.

‡P value of ethnic group determined by principal investigators.

§Missing data for patients with history of atrial fibrillation: 2 in control group, 1 who received aprotinin, and 1 who received aminocaproic acid; for patients with myocardial infarction missing data for 3 in control group, 21 who received aprotinin, 10 who received aminocaproic acid, and 4 who received tranexamic acid; for patients with congestive heart failure missing data for 4 in control group, 3 who received aprotinin, 2 who received aminocaproic acid, and 4 who received tranexamic acid; for patients with pulmonary disease missing data for 5 in control group, 8 who received aprotinin, 4 who received aminocaproic acid, and 3 who received tranexamic acid; for patients with beta disease missing data for 1 in control group; for patients with valve disease missing data for 9 in control group and 2 who received aprotinin; for patients with liver disease missing data for 1 in control group, 7 who received aprotinin, and 5 who received aminocaproic acid; for patients with stroke missing data for 2 in control group, 3 who received aprotinin, and 5 who received aminocaproic acid.

¶Complex surgery was defined as surgery necessary for the following conditions: current surgery for emergency status or urgent status with evidence of congestive heart failure preoperatively; a history of coronary artery bypass grafting, valve surgery, noncoronary aneurysm or aortic dissection, or other cardiac or vascular noncardiac surgery; and combined current heart surgery.



## APPENDIX 4 - COVARIATES

The following are the 97 covariates selected prospectively for multivariable analysis.

### Cardiovascular Variables

History of hypertension  
History of antihypertensive Rx  
History of smoking: regularly smoked  
History of smoking: current  
  
History of diabetes  
History of diabetes (NIDDM)  
History of diabetes (IDDM)  
History of hypercholesterolemia  
History of angina  
History of unstable angina  
Preop: angina/ischemia  
Preop: Left main coronary disease (cardiac catheterization)  
History of myocardial infarction  
History of myocardial infarction within 90 days (prior to surgery)  
History of number of myocardial infarctions > 1  
  
Preop: myocardial infarction  
History of CHF  
History of CHF with hospitalization  
Admission: CHF  
Preop: CHF  
Preop: cardiomegaly (CXR)  
Preop: left ventricular aneurysm (cardiac catheterization)  
Preop: EF (minimum) (cardiac catheterization)  
Preop: EF (normal-mild vs moderate-severe) (cardiac catheterization)  
Preop: IABP  
History of dysrhythmia  
History of tachyarrhythmias  
History of conduction abnormality  
History of heart block  
History of unknown dysrhythmia  
History of valve disease  
History of PTCA  
History of coronary endarterectomy  
History of coronary atherectomy  
History of intracoronary stent  
History of CABG  
History of valve surgery  
History of other cardiac surgery  
History of other noncardiac surgery

### Cerebrovascular Variables

History of carotid disease  
History of transient ischemic attack  
History of syncope  
History of seizures  
History of stroke  
History of head trauma  
History of carotid endarterectomy  
Admission: stroke

### Renal Variables

History of renal disease  
  
Preop: creatinine

### Gastrointestinal Variables

History of gastrointestinal disease  
History of liver disease  
History of alcohol abuse

### Other Organ Variables

History of hematologic disorder  
History of anemia  
Admission: hemoglobin < 10 gm  
History of IV drug use  
History of pulmonary disease  
History of peripheral vascular disease

### Surgical & Demographic Variables

Surgery: emergency  
Surgery: urgent  
Surgery: CABG only  
  
Surgery: CABG + valve (without other cardiac/noncardiac surgery)  
Surgery: other combined surgery  
Surgery: ≥ 3 grafts  
Demo: gender  
Demo: BSA  
Demo: ethnicity-African-American or Hispanic or Am. Indian  
Demo: ethnicity-Asian  
Demo: ethnicity-Caucasian  
Demo: ethnicity-Hispanic  
Demo: age  
Demo: private insurance

### Medication Variables

Preop: Medications-ACE inhibitors  
Intraop: Medications-ACE inhibitors  
Preop: Medications-antiarrhythmics  
Intraop: Medications-antiarrhythmics  
Preop: Medications-anticoagulants  
Intraop: Medications-anticoagulants  
Preop: Medications-beta blockers  
Intraop: Medications-beta blockers  
Preop: Medications-bronchodilators  
Intraop: Medications-bronchodilators  
Preop: Medications-calcium channel blockers  
Intraop: Medications-calcium channel blockers  
  
Admission: Warfarin coumadin (past week)  
Preop: Medications-diuretics  
Intraop: Medications-diuretics  
Preop: Medications-inotropes  
Intraop: Medications-inotropes  
Preop: Medications-nitrates  
Preop: Medications-K<sup>+</sup> channel blockers  
Preop: Medications-platelet inhibitors  
Preop: Medications-peripheral vasodilators  
Intraop: Medications-transfusion: FFP  
Intraop: Medications-transfusion: RBC  
Intraop: Medications-transfusion-platelets  
  
Intraop: Medications-antibiotics

**Statistical Section: Mangano, Karkouti, and i3 Drug Safety  
Observational Studies of Aprotinin**

**Primary Reviewers**

**Mark Levenson, Ph.D. (Mangano & Karkouti Studies)  
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## Table of Contents

<b>LIST OF TABLES .....</b>	<b>4</b>
<b>LIST OF FIGURES .....</b>	<b>5</b>
<b>1.0 EXECUTIVE SUMMARY .....</b>	<b>6</b>
1.1 BACKGROUND AND REVIEW OBJECTIVES .....	6
1.2 REVIEW FINDINGS .....	8
1.2.1 Renal Outcomes .....	8
1.2.2 Cardiovascular Outcomes .....	8
1.2.3 Cerebrovascular Outcomes .....	9
1.2.4 Mortality Outcomes .....	9
<b>2.0 INTRODUCTION.....</b>	<b>9</b>
2.1 BACKGROUND .....	9
2.2 OBJECTIVES .....	10
<b>3.0 STATISTICAL METHODS .....</b>	<b>11</b>
3.1 CHOICE OF RISK FACTORS .....	11
3.2 CHOICE OF STRATA .....	12
3.3 PROPENSITY SCORE MODELING AND EVALUATION OF BALANCE .....	12
3.4 ESTIMATION OF TREATMENT EFFECTS .....	13
3.5 CHOICE OF OUTCOME MEASURES .....	14
<b>4.0 MANGANO STUDY .....</b>	<b>14</b>
4.1 STUDY SUMMARY.....	15
4.1.1 OUTCOMES .....	16
4.1.2 REVIEW ISSUES .....	17
4.2 PATIENT POPULATION AND DISPOSITION.....	18
4.3 MANGANO METHODS EVALUATION .....	21
4.4 TREATMENT EFFECT RE-ANALYSIS .....	26
4.5 SUMMARY AND DISCUSSION.....	36
<b>5.0 KARKOUTI STUDY.....</b>	<b>37</b>
5.1 STUDY SUMMARY.....	37
5.1.1 OUTCOMES .....	38
5.1.2 REVIEW ISSUES .....	39
5.2 PATIENT POPULATION AND DISPOSITION.....	39
5.3 TREATMENT EFFECT RE-ESTIMATION.....	41
5.4 SUMMARY AND DISCUSSION.....	47
<b>6.0 I3 DRUG SAFETY STUDY.....</b>	<b>48</b>
6.1 DATA SOURCE.....	48
6.2 PATIENTS.....	49
6.3 OUTCOMES .....	50

6.4	REVIEW ISSUES.....	51
6.5	PRIMARY ANALYSIS .....	51
6.6	SENSITIVITY ANALYSIS .....	51
6.6.1	ANALYSES TO ADJUST FOR THE LENGTH OF HOSPITAL STAY.....	52
6.6.2	ANALYSES TO ADDRESS THE IMPACT OF BASELINE COVARIATE INFORMATION.....	52
6.6.3	ANALYSES THAT EXCLUDES PATIENTS IN THE 10 <sup>TH</sup> PROPENSITY-SCORE DECILE.....	52
6.7	SUBGROUP ANALYSIS.....	53
6.8	BASELINE CHARACTERISTICS .....	53
6.8.1	PATIENT-LEVEL RISK FACTORS.....	53
6.8.2	HOSPITAL CHARACTERISTICS.....	55
6.8.3	HOSPITAL LENGTH-OF-STAY.....	56
6.9	PROPENSITY SCORE MODELING.....	57
6.10	SELECTION OF STRATA.....	58
6.11	ASSESSMENT OF PROPENSITY SCORE BALANCE .....	59
6.12	PRIMARY ANALYSIS OF OUTCOMES .....	59
6.12.1	DEATH.....	59
6.12.2	STROKE.....	61
6.12.3	ACUTE RENAL FAILURE.....	62
6.12.4	ACUTE HEART FAILURE.....	64
6.12.5	ACUTE CORONARY REVASCULARIZATION.....	65
6.13	SENSITIVITY ANALYSES .....	67
6.14	FINDINGS IN SPECIAL SUBGROUPS/POPULATIONS .....	68
6.15	DISCUSSION.....	69
6.16	SUMMARY AND CONCLUSIONS.....	70
6.16.1	STATISTICAL ISSUES AND COLLECTIVE EVIDENCE.....	70
6.16.2	CONCLUSIONS AND RECOMMENDATIONS.....	70
<b>APPENDIX: FDA RISK FACTORS FOR THE MANGANO AND KARKOUTI STUDIES</b>		
.....		72
<b>REFERENCES.....</b>		<b>75</b>

## LIST OF TABLES

Table 1: Mangano, Karkouti, and i3 Drug Safety Study Summaries.....	7
Table 2: Mangano, Karkouti, and i3 Drug Safety FDA Re-analysis Estimates.....	8
Table 3: Mangano study: Patients by treatment group and geographical region.....	16
Table 4: Mangano study: Outcomes.....	17
Table 5: Mangano study: Patient baseline characteristics.....	19
Table 6: Mangano study: Unadjusted outcome rates.....	20
Table 7: Mangano study: Patient disposition.....	20
Table 8: Mangano study: Risk factor significance after adjusting for propensity score.....	22
Table 9: Mangano study: Re-analysis in-hospital outcome estimates and treatment effects.....	29
Table 10: Mangano study: Re-analysis follow-up mortality and treatment effect estimates.....	31
Table 11: Mangano study: Primary surgery, re-analysis and Mangano NEJM in-hospital outcome and treatment effects estimates.....	34
Table 12: Karkouti study: Safety outcomes.....	39
Table 13: Karkouti study: Patient baseline characteristics.....	40
Table 14: Karkouti study: Unadjusted outcome rates.....	41
Table 15: Karkouti study: Patient baseline characteristics, analysis subgroup.....	43
Table 16: Karkouti study: Re-analysis and matched-patient outcome and treatment effects estimates, analysis subgroup.....	46
Table 17: Study Outcomes and their Definitions and Derivations.....	50
Table 18: Summary of Patient Risk Factors by Treatment Group—All Antifibrinolytic Patients.....	54
Table 19: Summary of Hospital Characteristics.....	56
Table 20: Hospital Length of Stay, Day of CABG Surgery, and Number of Follow-up Days.....	57
Table 21: Propensity Score Model Factors.....	58
Table 22: Strata and Sample Sizes.....	58
Table 23: Crude (Unadjusted) Outcome Rates, Risk Differences, and Risk Ratios.....	59
Table 24: Sensitivity Analysis Risk Differences.....	67
Table 25: Sensitivity Analysis Risk Ratios.....	68
Table 26: Subgroup Analysis Risk ratio Results.....	69
Table 27: Comparison of Crude Results, i3 Drug Safety Results, and FDA Results.....	69

## LIST OF FIGURES

Figure 1: Mangano study: "Surgery: Complex" by treatment group and propensity score stratum	23
Figure 2: Mangano study: North American region by treatment group and propensity score stratum	24
Figure 3: Mangano Study: Propensity scores by treatment group	25
Figure 4: Mangano Study: Propensity scores by treatment group and propensity score stratum	26
Figure 5: Mangano study: "Surgical History: CABG" by treatment group and FDA propensity score stratum	27
Figure 6: Mangano Study: FDA propensity scores by treatment group and FDA propensity score stratum	28
Figure 7: Mangano study: Re-analysis in-hospital outcome estimates	29
Figure 8: Mangano Study: Renal composite outcome by treatment group and FDA propensity score stratum	30
Figure 9: Mangano Study: Myocardial outcome by treatment group and FDA propensity score stratum	31
Figure 10: Mangano study: Re-analysis follow-up mortality and estimates	32
Figure 11: Mangano study: 3-Year Mortality by treatment group and FDA propensity score stratum	33
Figure 12: Mangano Study: Primary surgery, renal composite outcome by treatment group and FDA propensity score stratum	35
Figure 13: Mangano Study: Primary surgery, myocardial infarction by treatment group and propensity score stratum	36
Figure 14: Karkouti Study: FDA propensity scores by treatment group and propensity score stratum	42
Figure 15: Karkouti Study: FDA propensity scores by treatment group and propensity score stratum, analysis subgroup	44
Figure 16: Karkouti study: "Preoperative Factors: MI" by treatment group and FDA propensity score stratum, analysis subgroup	45
Figure 17: Karkouti study: Re-analysis outcome estimates, analysis subgroup	46
Figure 18: Karkouti study: Renal Failure by treatment group and FDA propensity score stratum, analysis subgroup	47
Figure 19: Study Flowchart (source: study report)	49
Figure 20: Risk Differences for Death	60
Figure 21: Risk Ratios for Death	60
Figure 22: Risk Differences for Stroke	61
Figure 23: Risk Ratios for Stroke	62
Figure 24: Risk Differences for Acute Renal Failure	63
Figure 25: Risk Ratios for Acute Renal Failure	63
Figure 26: Risk Differences for Acute Heart Failure	64
Figure 27: Risk Ratios for Acute Heart Failure	65
Figure 28: Risk Differences for Acute Coronary Revascularization	66
Figure 29: Risk Ratios for Acute Coronary Revascularization	66

## 1.0 EXECUTIVE SUMMARY

### 1.1 Background and Review Objectives

*Aprotinin* is currently indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion. Aprotinin is the only product labeled for this indication. Three recent observational studies have provided results that suggest that the use of aprotinin may carry with it increased risks of certain adverse cardiovascular and renal outcomes, including mortality.

Although patients who were administered aminocaproic acid or tranexamic acid were used in the analysis, these products do not have labeling as described for aprotinin.

The label for *aminocaproic acid* states “Aminocaproic acid is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. In life-threatening situations, transfusion of appropriate blood products and other emergency measures may be required. Fibrinolytic bleeding may frequently be associated with surgical complications following heart surgery (with or without cardiac bypass procedures) and portacaval shunt.”

The label for *tranexamic acid* states that it is “indicated in patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.”

In January 2006 a paper by Mangano, et al. published in the *New England Journal of Medicine*<sup>1</sup> reported that the use of aprotinin during coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB) was associated with increased risks of renal, cardiovascular, and cerebrovascular adverse outcomes compared to not using an anti-bleeding agent.

In March 2006 a paper by Karkouti, et al. published in *Transfusion*<sup>2</sup> reported that the use of aprotinin for patients undergoing cardiac surgery with CPB is associated with an increased risk of renal adverse outcomes compared to the use of tranexamic acid. The cardiac surgeries included CABG surgery, as well as valve surgery, and combination surgeries.

In September 2006 a preliminary report conducted by i3 Drug Safety<sup>3</sup> and commissioned by the sponsor of aprotinin was released to FDA. The results suggested that, for patients undergoing CABG surgery with CPB, use of aprotinin is associated with increased risks of renal failure, heart failure, stroke, and in-hospital death compared to the use of aminocaproic acid and tranexamic acid.

In February 2007 a paper by Mangano, et al. in the *Journal of the American Medical Association (JAMA)*<sup>4</sup> reported an increase in long-term mortality associated with aprotinin compared to not using an anti-bleeding agent. The paper was based on long-term follow-up of the patients described in the 2006 NEJM paper.

FDA received patient-level data and supporting documentation for each of the three studies. For the Mangano study, specific protocols for the prospective data collection, and analysis plans

were submitted. For the Karkouti and i3 Drug Safety studies no protocols were provided. Details of study design and conduct were limited to the published article (for Karkouti), the preliminary report (for i3 Drug Safety study), and responses to FDA questions. These materials were the basis of the FDA review of the studies.

The Mangano, Karkouti, and the i3 Drug Safety studies were all based on observational data. The studies employed similar methodology including multivariate regression and propensity score methods to adjust for difference in baseline risk factors among the comparison groups. Table 1 summarizes keys aspects of the three observational studies.

Table 1: Mangano, Karkouti, and i3 Drug Safety Study Summaries.

Study	Reference Group	Patients (N)	Study Reported Statistical Significant Findings
Mangano	No agent	Aprotinin: 1,295 Reference: 1,374	Renal composite event*†‡ Cardiovascular event† Cerebrovascular event† Long-term mortality*
Karkouti*	Tranexamic acid	Aprotinin: 586 Reference: 10,284	Renal dysfunction
i3 Drug Safety	Aminocaproic acid and tranexamic acid	Aprotinin: 29,358 Reference: 37,077	Acute renal failure Acute heart failure Stroke Death (in-hospital)

\* Entire analysis group

† Primary-surgery subgroup

‡ Complex-surgery subgroup

\*Complex-surgery (the population consisted of three types of patients: CABG, CABG + valve, Valve alone, with CPB)

The Mangano study was a multi-center international, prospectively planned observational study. The Karkouti study was a retrospective study at a single Canadian hospital. The i3 Drug Safety study was unique among the three studies in that it was based on an administrative claims database and not on clinical data.

The objective of the statistical review is to evaluate the validity and robustness of the conclusions of the Mangano, Karkouti, and i3 Drug Safety studies. In particular, the review examines the sensitivity of the study conclusions to the statistical methods employed in the studies and implements alternative methods. To the extent possible, the review examines each of the studies with common methods. The methods promote transparency, effective diagnostics, and ease of interpretation.

## 1.2 Review Findings

Table 2 displays the results of the re-analysis of the three studies.

Table 2: Mangano, Karkouti, and i3 Drug Safety FDA Re-analysis Estimates

Outcome	Mangano RR (95% CI)	Karkouti RR (95% CI)	i3 Drug Safety RR (95% CI)
Renal composite	1.63 (1.03, 2.60)		
Renal failure	2.05 (1.05, 3.99)	1.38 (0.86, 2.23)	1.82 (1.61, 2.06)
Renal dysfunction	1.26 (0.76, 2.11)	1.53 (1.11, 2.12)*	
Myocardial infarction	1.10 (0.88, 1.39)	1.42 (0.71, 2.83)	
Heart failure	1.05 (0.75, 1.47)		1.20 (1.14, 1.26)
Coronary revascularization			1.47 (1.02, 2.12)
Stroke	1.36 (0.70, 2.64)	1.72 (0.93, 3.19)	1.24 (1.07, 1.44)
Death (in-hospital)	0.91 (0.54, 1.53)	1.18 (0.79, 1.76)	1.54 (1.38, 1.73)

*Note: Definitions of the outcomes differed among the studies. See relevant sections for definitions.*

*\*Based on analysis of a subset of patients with the necessary data.*

### 1.2.1 Renal Outcomes

The review showed that aprotinin had the clearest effect on renal outcomes. In all three studies, the review showed significant renal effects of aprotinin. In the review of the Mangano study, the renal failure outcome, consisting of new dialysis and renal death, showed the most consistent effect. Karkouti reported a statistically significant effect on a renal dysfunction outcome, consisting of new dialysis or elevated creatinine levels. Data were not available to re-estimate this outcome using the common methods. However, the review did find for this study that although not statistically significant, the effect on the renal failure outcome, consisting of new dialysis, was present in a range of patients. The review of the i3 Drug Safety study showed a statistically significant effect on the renal failure outcome, consisting of new dialysis. For this study, the estimated renal failure effect was the largest among the estimated outcome effects.

### 1.2.2 Cardiovascular Outcomes

The effect of aprotinin on cardiovascular outcomes was less clear. Mangano had found a statistically significant effect on a composite cardiovascular outcome, consisting of myocardial infarction and heart failure, for primary-surgery patients. The review found the effect was nearly

statistically significant for this outcome and subgroup. However, the effect was not consistent across patients. Karkouti did not see an effect on myocardial infarction, the cardiovascular outcome considered in that study. The review did not find this effect either. The i3 Drug Safety study reported a statistically significant effect on heart failure. The review showed a statistically significant effect as well. For both the study reported and the review result, the upper limit of the confidence interval for the estimate was relatively small compared to those of other outcomes.

### 1.2.3 Cerebrovascular Outcomes

Mangano reported a statistically significant effect for a composite cerebrovascular outcome, (consisting of stroke, encephalopathy, and coma) for the primary-surgery patients. The review focused on the stroke outcome and did not show a statistically significant effect on stroke for the full analysis group or for the primary-surgery subgroup. For the Karkouti study, neither Karkouti nor the review showed a significant effect on stroke. For the i3 Drug Safety study, the study and the review showed a statistically significant effect on stroke.

### 1.2.4 Mortality Outcomes

For in-hospital death, neither Mangano nor Karkouti showed a statistically significant effect. The review of these studies did not show an effect either. For this outcome in the i3 Drug Safety, the study and review showed a statistically significant effect.

The Mangano study was the only study among the three that evaluated long-term mortality. The review produced similar statistically significant effects on mortality. The review showed an estimated risk ratio for aprotinin versus control at 4 years was 1.39 (95% CI: 1.05, 1.84) and at 5 years was 1.26 (95% CI: 0.98, 1.62). These were similar in size to the hazard ratio estimate report by Mangano of 1.37 (95% CI: 1.09, 1.73). However, there was an apparent difference in the follow-up between the aprotinin patients and the control patients. For the control patients, 27% had no post-hospital follow up or were lost to follow up compared to 17% for the aprotinin patients.

The current review findings show a long-term mortality effect of aprotinin. Further analysis is being performed to understand the geographical effect and the effect of differential follow up on this outcome.

Further analysis of the i3 Drug Safety study will compare aprotinin patients to patients who received no antifibrinolytic agent and will analyze outcomes using methods to adjust for varying lengths of in-hospital stay. At the time of this review, data to conduct such analyses were requested but not available. As part of this statistical review, the principal results reported by the studies were reproduced by following the same methods employed by the respective studies.

## 2.0 INTRODUCTION

### 2.1 Background

Aprotinin is currently indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood

transfusion. Three observational studies have provided results that suggest that the use of aprotinin may carry with it increased risks of certain adverse outcomes.

In January 2006 a paper by Mangano, et al. published in the *New England Journal of Medicine*<sup>1</sup> reported that the use of aprotinin during coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB) was associated with increased risks of renal, cardiovascular, and cerebrovascular adverse outcomes compared to not using an anti-bleeding agent.

In March 2006 a paper by Karkouti, et al. published in *Transfusion*<sup>2</sup> reported that the use of aprotinin for patients undergoing cardiac surgery with CPB is associated with an increased risk of renal adverse outcomes compared to the use of tranexamic acid. The cardiac surgeries included CABG surgery, as well as valve surgery, and combination surgeries.

In September 2006 a preliminary report conducted by i3 Drug Safety<sup>3</sup> and commissioned by the sponsor of aprotinin was released to FDA. The results suggested that, for patients undergoing CABG surgery with CPB, use of aprotinin is associated with increased risks of renal failure, heart failure, stroke, and in-hospital death compared to the use of aminocaproic acid and tranexamic acid.

In February 2007 a paper by Mangano, et al. in the *Journal of the American Medical Association (JAMA)*<sup>4</sup> reported an increase in long-term mortality associated with aprotinin compared to not using an anti-bleeding agent. The paper was based on long-term follow-up of the patients described in the 2006 NEJM paper.

FDA received patient-level data and supporting documentation for each of the three studies. For the Mangano study, specific protocols for the prospective data collection, and analysis plans were submitted. For the Karkouti and i3 Drug Safety studies no protocols were provided. Details of study design and conduct were limited to the published article (for Karkouti), the preliminary report (for i3 Drug Safety study), and responses to FDA questions. These materials were the basis of the FDA review of the studies.

Although patients who were administered aminocaproic acid or tranexamic acid were used in the analysis, these products do not have labeling as described for aprotinin. The label for aminocaproic acid injection solution indicates that it is useful for enhancing hemostasis when fibrinolysis contributes to bleeding. Tranexamic acid is indicated in patients with hemophilia for short term use (two to eight days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.

## 2.2 Objectives

The objective of the statistical review is to evaluate the validity and robustness of the conclusions of the Mangano, Karkouti, and i3 Drug Safety studies. In particular, the review examines the sensitivity of the study conclusions to the statistical methods employed in the studies and implements alternative methods. To the extent possible, the review examines each of

the studies with common methods. The methods promote transparency, effective diagnostics, and ease of interpretation.

### 3.0 STATISTICAL METHODS

The Mangano, Karkouti, and the i3 Drug Safety studies were all based on observational data. The studies employed similar methodology including multivariate regression and propensity score methods to adjust for difference in baseline risk factors among the comparison groups. Data for each study were obtained by FDA so that the study results could be verified and the data could be re-analyzed for statistical robustness. This section describes the statistical methods used for the reanalysis. In this document the term *re-analysis* refers to the alternative methodology applied by FDA to examine the statistical robustness of the study findings. The term distinguishes the alternative methodology from the methodologies employed by the study investigators and verified by FDA. Issues relating to the original analyses conducted by the investigators can be found in Section 4.1.2 for the Mangano study, Section 5.1.2 for the Karkouti study, and Section 6.4 for the i3 Drug Safety study.

The statistical analysis approach used in the re-analysis was designed to promote transparency, effective diagnostics, and ease of interpretation. The statistical analysis employed propensity score methods. Propensity score methods adjust for differences in baseline risk factors between treatment groups. Propensity scores estimate the probability of assignment for a patient to one of two treatment groups based on patient-level baseline risk factors.

The statistical analysis had three chief components:

1. The choice of clinically relevant and statistically appropriate risk factors.
2. The development of the propensity score model, and the evaluation of treatment group balance.
3. The estimation of treatment group effects.

Component 3 makes use of procedures described in the paper by Rosenbaum and Rubin<sup>5</sup>.

For concreteness, it is assumed in this section that the two treatment groups to be compared are: patients who received a drug (treated group) and patients who did not receive a drug (control group). The methodology applies to the comparison of any two groups of patients. The specific groups to be compared are given in the sections pertaining to each of the three studies.

#### 3.1 Choice of Risk Factors

Medical, epidemiological, and statistical expertise and input from the review team was used to select the risk factors. The criteria for the selection risk factors were:

1. Clinical relevance to adverse events and treatment choice
2. Availability in the data collected in the study and provided to FDA
3. Appropriateness for propensity score model
4. Completeness of information across patients (no large amount of missing information).

Risk factors used in a propensity score model should relate to patient-level treatment assignment based on the baseline risk profile of the patient. Predictors of treatment based on aggregates of

patients, such as hospitals or regions are not suitable for use in the propensity score model. Additionally, patient-level treatment decisions not based on the patient risk are not suitable.

The selected risk factors were divided into two classes. The *primary risk factors* were considered the most important. A second set, the *sensitivity risk factors*, were used for sensitivity analysis. The specific risk factors are described in further detail in the relevant sections for each study.

Continuous risk factors such as age were converted to discrete variables based on the quartiles of the risk factor variable. The quartiles were based on the full analysis group.

### 3.2 Choice of Strata

The re-analysis of the i3 Drug Safety Study employed stratification to control for non-patient-level characteristics. For example, factors such as hospital characteristics can be useful for improving the predictability of a propensity score model. Since a surgeon's propensity to prescribe aprotinin may vary from one hospital to the next, hospital characteristics can be used to create strata for which strata-specific propensity scores are estimated. The large study sample size in the i3 Drug Safety study allowed for multiple hospital characteristics to be chosen for the creation of hospital-level strata.

The goal of the hospital characteristic selection was to choose factors that were influential with regards to aprotinin use and balanced well enough to prevent an inadequately represented treatment group within one of the strata. Thus, a highly influential characteristic that was sparsely represented by one of the treatment groups would not meet the objectives since it could result in small treatment group sample sizes within the strata represented by that characteristic. Details pertaining to the hospital-level strata for the i3 Drug Safety study are provided in Section 6.10.

### 3.3 Propensity Score Modeling and Evaluation of Balance

The propensity score model was developed and evaluated based on the risk factors identified by the review team. No use of the outcome values was used in the propensity score modeling. The propensity model was based on multivariate logistic regression. All the primary risk factors were included in the model. The sensitivity risk factors were considered in a stepwise regression (forward and backward) procedure. Pre-defined levels of significance were used in the stepwise procedure to determine what terms to add or remove. For the i3 Drug Safety study, two-way interactions between the primary risk factors were also considered in the stepwise regression procedure.

For each study, the factors selected from the stepwise procedure for the full analysis group and primary treatment group comparison analysis were used in all propensity models for the study. That is, the selection of non-primary risk factors was performed only once for each study. However, the propensity scores were estimated separately for each subgroup and treatment group comparison. The estimated propensity scores were fixed for each subgroup and treatment comparison and did not vary by outcome.

Patients with missing values for any of the risk factors used in the model were dropped from the analysis. Because risk factors with a large number of missing values were not considered in the propensity model, the numbers of patients dropped from the analyses were not large. The number of patients dropped was summarized.

For each subgroup and treatment group comparison, the effectiveness of the propensity score was evaluated using graphical methods and either ANOVA or logistic regression models. All primary and sensitivity risk factors, including those not in the propensity model, were evaluated. Quantiles of the predicted propensity scores were used to define propensity score strata. Deciles were used for the re-analysis of the Mangano and i3 Drug Safety studies. Quintiles were used for the re-analysis of the Karkouti study because of the smaller study size in that study.

A two-way model was used to test the significance of the treatment group effect on the risk factors adjusting for the propensity score quantile. Risk factors with a statistically significant treatment group effect were graphically analyzed with dotplots to determine the magnitude and direction of the treatment group imbalance.

Boxplots were used to evaluate the overlap of the propensity score distributions between the treatment groups.

### 3.4 Estimation of Treatment Effects

Direct standardization was used to estimate the treatment group estimates and effects<sup>6</sup>. The number of patients in the treated group within each quantile was used as the standardization weight for the quantile. With the use of these weights, the estimates reflect the treated-group patient population.

Propensity strata were defined by the quantile. Within each propensity stratum, the proportion of patients with the outcome event for each treatment group was estimated. For a binary outcome with no censoring, the proportion was equal to the number of patients with events divided by the number of patients. The associated variance was based on the binomial distribution. For a binary outcome with censoring, the Kaplan-Meier estimate was used. The associated variance was based on the Greenwood formula.

The summary measures were the overall estimate for each treatment group, the estimate of the risk ratio between the treatment groups, and the associated 95% confidence intervals. For the i3 Drug Safety study, risk differences were also calculated.

The following formulas were used. Let  $s$  be the number of strata, let  $e_{ij}$  be the outcome estimate for treatment group  $i$  and stratum  $j$ , and  $m_j$  be the number of treated patients in stratum  $j$ , then the overall outcome estimate for the treatment group  $i$  is

$$E_i = \frac{\sum_{j=1}^s m_j e_{ij}}{\sum_{j=1}^s m_j}$$

The variance of the estimate is

$$\text{var}(E_i) = \frac{\sum_{j=1}^i m_j^2 \text{var}(e_{ij})}{\left(\sum_{j=1}^i m_j\right)^2}$$

For the Mangano study,  $s=10$  since deciles were used for the propensity strata. For Karkouti,  $s=5$  since quintiles were used for the propensity strata. For i3 Drug Safety estimates,  $s=10$  for the estimates within each hospital characteristic stratum, since deciles were used within each stratum, and  $s=10*k$  for the overall estimates, where  $k$  represents the number of hospital characteristic strata.

The 95% confidence interval for the estimate is  $E_i \pm 1.96\sqrt{\text{var}(E_i)}$

The estimate of the risk ratio of the treatment groups and its 95% confidence interval are, respectively<sup>6</sup>,

$$\frac{E_1}{E_2} \text{ and } \exp\left(\log\left(\frac{E_1}{E_2}\right) \pm 1.96\sqrt{\frac{\text{var}(E_1)}{E_1^2} + \frac{\text{var}(E_2)}{E_2^2}}\right)$$

The estimate of the difference between treatment group and its 95% confidence interval are, respectively<sup>6</sup>,

$$E_1 - E_2 \text{ and } E_1 - E_2 \pm 1.96\sqrt{\text{var}(E_1) + \text{var}(E_2)}$$

The number of patients in each treatment group and stratum were reviewed to ensure individual stratum did not have too few patients of either treatment group for reliable estimates.

The type I error rate of 0.05 was used to judge statistical significance. No adjustments were made for multiple comparisons.

### 3.5 Choice of Outcome Measures

For the outcome measures, the statistical review primarily used the outcome measures as defined in the studies. In certain cases, which are noted in the relevant sections pertaining to the individual study, minor modifications were made to the outcome definition. No sensitivity analyses were done that looked at alternative definitions of these outcomes. For all studies, renal, cardiovascular, cerebrovascular, and mortality outcomes were available. Outcomes were defined differently between the studies.

## 4.0 MANGANO STUDY

## 4.1 Study Summary

The sources for the evaluation of the Mangano study were the published NEJM<sup>3</sup> and JAMA<sup>4</sup> articles and submissions from Dennis Mangano of the Ischemia Research and Education Foundation.

The Mangano study was based on patients from 69 international centers. Of these, 39 were North American centers. Patients undergoing CABG surgery with CPB were eligible for enrollment. The study had four treatment groups, consisting of patients receiving each of aprotinin, aminocaproic acid, and tranexamic acid, and patients who did not receive one of these anti-bleeding agents. The latter group is referred to as the control group. The data collection was prospectively planned. The choice of treatment was not controlled by study.

Data on patients were collected during the hospital stay including baseline risk factors and renal, cardiovascular, cerebrovascular, and all-cause death outcomes. Follow-up, post-hospital mortality information was collected for 5 years, at 6 weeks, 6 months, 1, 2, 3, 4, and 5 years through surveys and death registries.

Overall, 5,436 patients were enrolled. Among these patients, 371 were not considered because they did not meet the enrollment criteria, such as undergoing CPB. An additional 691 patients were not considered because they received inadequate dose or multiple agents, or there was no validation of drug or dose. The remaining 4,374 patients formed the full analysis group.

The analysis performed by Mangano was based on a pre-specified analysis plan and pre-specified definitions of the risk factors and outcome measures were prospectively planned.

The study used two principal methods to compare outcomes among the treatment groups. The first method was multivariate regression. For the in-hospital outcomes, logistic regression was used. For the follow-up outcomes, a time-to-event analysis was performed with Cox proportional hazards regression. Risk factor covariates were included in the regressions to adjust for differences in baseline risk factors of the patients among the treatment groups. All four treatment groups were included in the regressions.

The second principal method used propensity score methodology. For the principle findings, the propensity score was defined as the probability of a patient of receiving any of three agents versus not receiving an agent. The propensity scores were estimated using the predicted values from a multivariate logistic regression. The deciles of the estimated propensity scores were used as a covariate in the regression models in the estimation of the treatment effects on the outcomes. For some regression estimation of treatment effects, but not all, additional risk factors were included as covariates.

For the in-hospital outcomes, the study analyzed subgroups of primary and complex surgery patients. Primary surgery was defined as elective surgery, involving CABG only, and with no history of cardiac or vascular surgery. Other surgeries were defined as complex. The propensity score for the entire population were used in the subgroup analysis and were not re-estimated for the subgroups.

For the analysis presented in the NEJM paper, patients were removed from the analysis due to missing covariate information. For the JAMA paper analysis, missing covariates were imputed.

Seven of the 69 centers did not participate in the follow-up portion of the study. The time-to-event analysis included the patients from these seven centers. As for any patient in the study, if a patient from one of these centers had an event (a death) in the hospital, the event was counted at the time (relative to surgery) of the event. If they did not have an event, their observation time was censored at their hospital discharge date.

The distribution of the patients among the four treatment groups varied among geographical regions. Table 3 shows that the majorities of the control patients and aprotinin patients were in the European region. Nearly all of the aminocaproic acid patients were in the North American region. The differences in geographical distributions among the four treatment groups have consequences on the treatment group comparisons. Differences in standard of care and patient population may be confounded with treatment exposure.

Table 3: Mangano study: Patients by treatment group and geographical region.

Region	Control N=1374 n (%)	Aprotinin N=1295 n (%)	Aminocaproic N=883 n (%)	Tranexamic N=822 n (%)
Europe	790 (57)	899 (69)	0 (0)	405 (49)
North America	328 (24)	377 (29)	846 (96)	240 (29)
Other	256 (19)	19 (1)	37 (4)	177 (22)

#### 4.1.1 Outcomes

Table 4 shows the outcomes used in the Mangano study.

Table 4: Mangano study: Outcomes.

Outcome	Definition
Renal failure (in-hospital)	Required new dialysis or in-hospital death with evidence at autopsy of acute renal failure
Renal dysfunction (in-hospital)	Required a post-operative serum creatinine level of at least 177 $\mu\text{mol/L}$ with an increase over preoperative baseline levels of at least 62 $\mu\text{mol/L}$
Renal composite (in-hospital)	Renal dysfunction or failure
Myocardial infarction (in-hospital)	Required either new Q waves or new, persistent ST-segment or T-wave changes
Heart failure (in-hospital)	Required output of less than 2.0 liters per minute associated with pulmonary-artery occlusion pressure above 18 mm Hg, a central venous pressure above 12 mm Hg, an S3 gallop, or rales.
Cardiovascular composite (in-hospital)	Myocardial infarction or heart failure
Stroke (in-hospital)	Clinical diagnosed
Cerebrovascular composite (in-hospital)	Clinical diagnosed stroke, or encephalopathy, coma
Death (in-hospital)	
Death: 6 weeks, 6 months, 1, 2, 3, 4, 5 years	Based on surveys and death registries

#### 4.1.2 Review Issues

The review issues for the Mangano study chiefly relate to the propensity score approach used by Mangano.

Mangano used a single set of propensity scores that estimated the probability of the use of any of the three anti-bleeding agents versus the control. When comparing individual agents versus the control, the use of these propensity scores may not achieve proper balance of the risk factors between treatment groups. This balance for individual comparisons has not been adequately demonstrated. Additionally, Mangano used the same propensity scores for comparisons within subgroups. Again, this use of propensity scores may not achieve proper balance.

The use of propensity scores in regression to estimate treatment effects requires the overlap of the treatment group propensity score distributions. The overlap has not been demonstrated.

The regression treatment group effect estimates are not obvious in their underlying influences and their interpretability. It is not clear which subsets of patients influence the estimates.

Additionally, there were geographical differences in the usages of the agents. These differences among the treatment groups may confound medical care and patient population issues with treatment effects. No adjustments for geographical differences were made by Mangano.

Section 4.2 summarizes the patient population and disposition of the Mangano study. Following this summary, Section 4.3 presents the findings related to the review of the propensity score approach used by Mangano. This includes results on the effectiveness of the Mangano approach in achieving balance between the aprotinin and control groups and results on the overlap of the propensity score distributions between the groups. Section 4.4 presents the findings from the re-analysis of the study based on the alternative methods described in Section 3.0. The alternative method specifically addresses the pair-wise comparison between the aprotinin and control groups. Because the alternative approach is based on stratification and direct standardization, the underlying influences and the interpretability of the estimates are clearer. Section 4.5 summarizes the current findings of the review.

As part of the review of the study, the principal results were reproduced based exactly on the methods used by Mangano. For the NEJM paper, these results include the odds ratios and associated confidence intervals and p-values for the renal composite outcome for the full patient group, the renal composite, cardiovascular composite, the cerebrovascular composite, and death outcomes for the primary-surgery and complex surgery-subgroups. For the JAMA paper, these include the hazard ratios and associated confidence intervals and p-values for the mortality outcome.

## **4.2 Patient Population and Disposition**

Table 5 shows the baseline characteristics for the aprotinin patients and control patients. The baseline characteristics are the risk factors identified by the FDA review team (see Appendix). They include all the primary risk factors and the sensitivity risk factors selected in the stepwise procedure. For most of these characteristics, there were statistically significant differences between the two treatment groups with the aprotinin group showing a higher frequency of baseline risk factors.

Table 5: Mangano study: Patient baseline characteristics.

Characteristic		Control N=1374	Aprotinin N=1295	P-Value*
Demo: Age	(mean ± sd)	63.18 ± 9.77	64.93 ± 9.22	<.001
Demo: Male	(%)	80.8	78.5	0.135
Demo: Body surface area	(mean ± sd)	1.89 ± 0.20	1.92 ± 0.19	<.001
Demo: African American or Hispanic	(%)	3.9	4.3	0.542
Medical History: Diabetes	(%)	28.0	27.3	0.685
Medical History: Hematologic disorder	(%)	4.4	7.4	<.001
Medical History: Liver disease	(%)	7.7	11.7	<.001
Medical History: Platelet abnormality	(%)	1.1	1.9	0.101
Medical History: Renal disease	(%)	13.0	18.6	<.001
Medical History: Valve disease	(%)	12.3	25.4	<.001
Medical History: Hypertension	(%)	60.3	70.0	<.001
Medical History: Congestive heart failure	(%)	33.5	42.8	<.001
Medical History: Pulmonary disease	(%)	17.4	25.3	<.001
Medical History: Angina	(%)	92.8	87.8	<.001
Surgical History: Previous sternotomy	(%)	3.3	12.7	<.001
Surgical History: Aortic vascular	(%)	1.1	0.9	0.670
Surgical History: PTCA	(%)	10.1	17.3	<.001
Surgical History: Noncoronary angioplasty	(%)	1.5	3.3	0.002
Preop. Medications: Anti-thrombotics	(%)	55.9	71.6	<.001
Preop. Medications: Aspirin	(%)	58.0	60.2	0.242
Preop. Medications: Heparin	(%)	26.2	29.3	0.077
Preop. Medications: Warfarin	(%)	4.0	7.0	<.001
Preoperative Factors: Angina	(%)	16.7	14.9	0.193
Preoperative Factors: Congestive heart failure	(%)	15.4	19.1	0.013
Preoperative Factors: Creatinine >1.3 mg/dL	(%)	13.8	15.1	0.338
Preoperative Factors: Ejection fraction ≤ 44%	(%)	18.0	15.4	0.071
Preoperative Factors: MI	(%)	15.4	15.6	0.863
Surgical: CABG only	(%)	88.5	80.5	<.001
Surgical: Elective	(%)	21.0	14.8	<.001
Surgical: Number of graphs ≥ 3	(%)	73.1	65.3	<.001
Missing Count†	(n)	67	73	

\*P-values for percentages based on chi-square test. P-values for means based on t-test.

†Number of patients with at least one missing characteristic.

Table 6 shows the unadjusted outcome rates by treatment group. For each outcome except for stroke, the aprotinin group had a statistically significant, higher rate of the outcome.

Table 6: Mangano study: Unadjusted outcome rates.

Outcome	Control N=1374 (%)	Aprotinin N=1295 (%)	P-Value*
Renal Composite	2.7	8.0	<.001
Renal Dialysis	1.2	5.1	<.001
Renal Dysfunction	2.4	5.6	<.001
Cardiovascular Composite	15.7	22.2	<.001
Myocardial Infarction	12.6	16.4	0.005
Congestive Heart Failure	5.2	8.8	<.001
Stroke	1.7	2.7	0.093
Death (all cause, in-hospital)	2.3	4.3	0.004

\*P-values based on chi-square test.

There was an apparent difference in the follow-up between the treatment groups. Table 7 shows the disposition of the patient population by five mutually exclusive categories. Among the control patients, 10% of the patients had no post-hospital follow-up compared to 1% of the aprotinin patients. Overall, for the control patients, 27% had no post-hospital follow-up or were lost to follow-up compared to 17% for the aprotinin patients. Excluding patients who died in the hospital, 27% of the control patients had no post-hospital follow-up or were lost to follow-up compared to 18% of the aprotinin patients.

Table 7: Mangano study: Patient disposition.

	Control N=1374 n (%)	Aprotinin N=1295 n (%)
In-hospital death	32 (2)	56 (4)
Post-hospital death	96 (7)	167 (13)
Completed 5-year follow-up with no death	881 (64)	849 (66)
No post-hospital follow-up	136 (10)	18 (1)
Lost to follow-up in the post- hospital period	229 (17)	205 (16)

### 4.3 Mangano Methods Evaluation

This section presents the evaluation of the statistical methods used by Mangano.

The Mangano propensity scores estimated the probability of receiving any of the three active agents versus not receiving any agent. Table 8 shows the statistical significance of differences in the risk factors between treatment groups after adjusting for the propensity score using the ANOVA method described in Section 2. Two sets of p-values are given. The first set reproduces those given in Table 1 of the JAMA article and gives the statistical significance for comparison between patients who received any agent and the control patients. None of the risk factors were significantly different based on this test.

The second set of p-values gives the statistical significance for comparison between aprotinin patients and control patients based on the same propensity scores. For this test, 7 of the risk factors had statistically significant differences.

Table 8: Mangano study: Risk factor significance after adjusting for propensity score.

Characteristic	Any Agent vs. Control P-Value*	Aprotinin vs. Control P-Value*
Demo: Age	0.715	0.243
Demo: Male	0.828	0.594
Demo: Ethnicity-African American or Hispanic	0.242	<.001
Demo: Some college (at least)	0.433	<.001
Surgery: Emergency or Urgent	0.633	0.680
Hx: Angina (imputation)	0.525	0.529
Hx: Hypertension (imputation)	0.515	0.261
Hx: Myocardial infarction (imputation)	0.804	0.624
Hx: Congestive heart failure (imputation)	0.459	<.001
Hx: Diabetes (imputation)	0.367	0.012
Surgery: Complex	0.432	0.003
Preop: Ejection fraction $\leq$ 44%	0.682	0.761
Hx: Pulmonary disease (imputation)	0.858	0.142
Preop: Creatinine > 1.3 mg/dL	0.558	0.751
Hx: Renal disease (imputation)	0.971	0.705
Hx: Valve disease (imputation)	0.620	0.022
Hx: Carotid disease (imputation)	0.422	0.004
Hx: PTCA (imputation)	0.705	0.337
Hx: Liver disease (imputation)	0.902	0.17
Hx: Stroke (imputation)	0.638	0.159
Hx: Diabetes (IDDM)	0.502	0.216
Hx: Intracoronary stent (imputation)	0.892	0.345
Hx: Heart block (2 or 3 degree)	0.817	0.769
Hx: Coronary atherectomy (imputation)	0.987	0.912

Figure 1 further explores one of the risk factors that had a statistically significant difference- "Surgery: Complex." Above each of the 10 propensity score strata, the fraction of patients with the risk factor for each treatment group is plotted. The figure also contains the number of patients in each treatment group for each stratum. The higher numbered strata correspond to subgroups of patients with higher estimated probability of receiving aprotinin. These patients may be considered higher risk of adverse outcomes, since aprotinin use, as seen in Table 5 was associated with higher frequency of baseline risk factors.

For 4 of the strata, including the 3 highest strata, the aprotinin group had notably higher fractions. It appears that the risk factor was not effectively balanced between the treatment groups.

Figure 1: Mangano study: "Surgery: Complex" by treatment group and propensity score stratum.

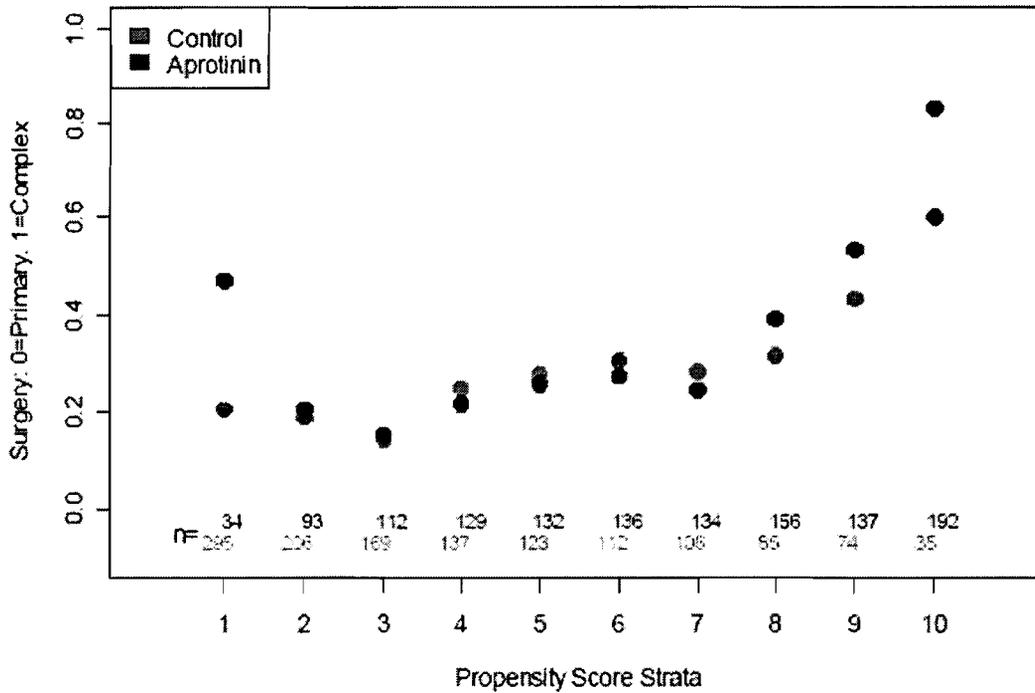


Figure 2 is similar to Figure 1 but compares the fractions of patients who were in the North American region. In 7 of the 10 strata, the control group had higher fractions than the aprotinin group. Note that overall, there was a higher percentage of aprotinin patients in the North American region than of control patients (see Table 3). The difference between the within-stratum and overall results is explained by the different numbers of patients in each stratum for each treatment group.

The difference in percentages within the stratum between the treatment groups represents a lack of balance in the treatment comparison based on propensity score alone.

Figure 2: Mangano study: North American region by treatment group and propensity score stratum.

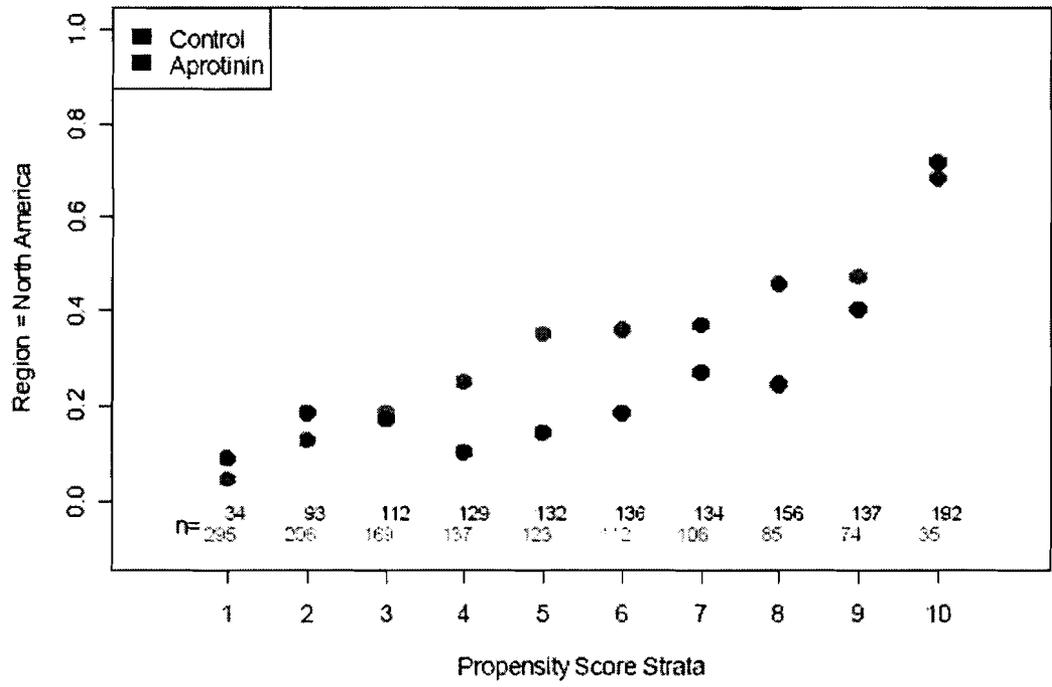


Figure 3 shows the Mangano propensity score distributions by treatment group. As seen in the figure, the two distributions of propensity scores did not entirely overlap. In particular, the control group had propensity scores at a low range that the aprotinin group did not.

Figure 3: Mangano Study: Propensity scores by treatment group.

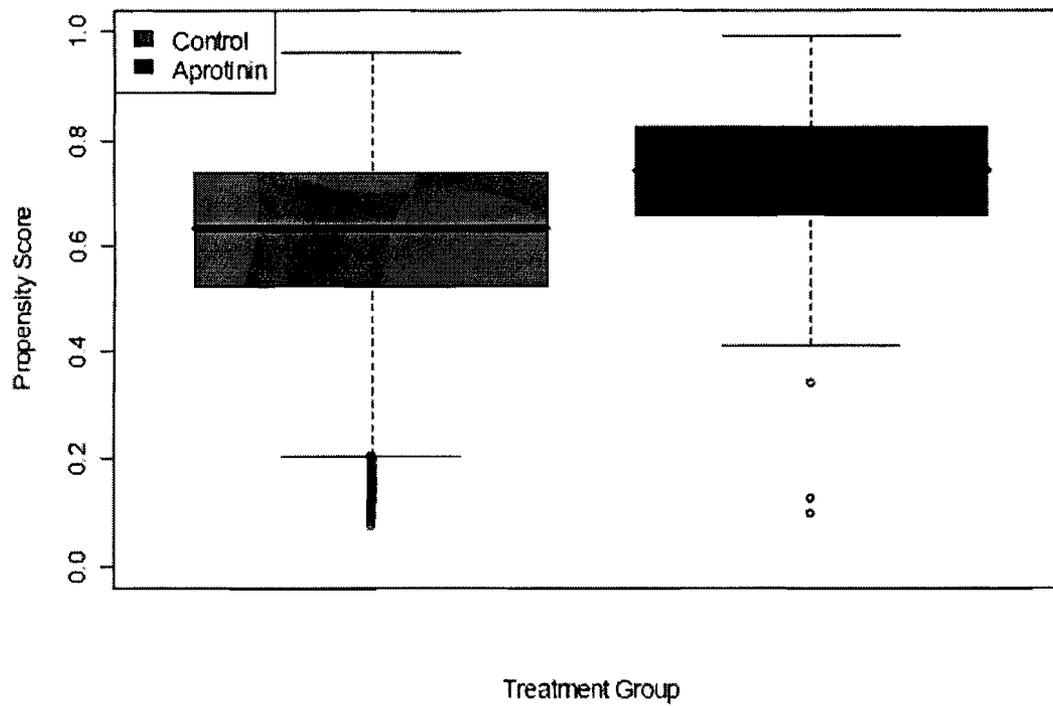
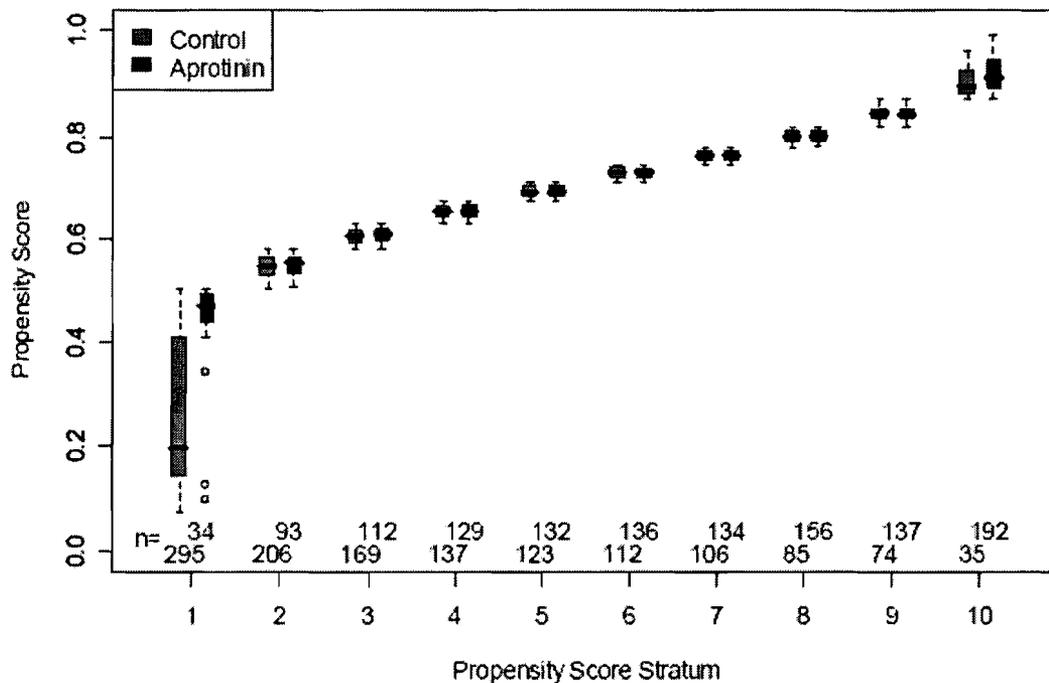


Figure 4 shows the propensity score distributions by treatment group and propensity score stratum. The figure also contains the number of patients in each treatment for each stratum. The lack of overlap in the distributions is apparent in stratum 1.

Figure 4: Mangano Study: Propensity scores by treatment group and propensity score stratum.



#### 4.4 Treatment Effect Re-Analysis

This section presents the results of the re-analysis of the Mangano study using the methods described in Section 3.0.

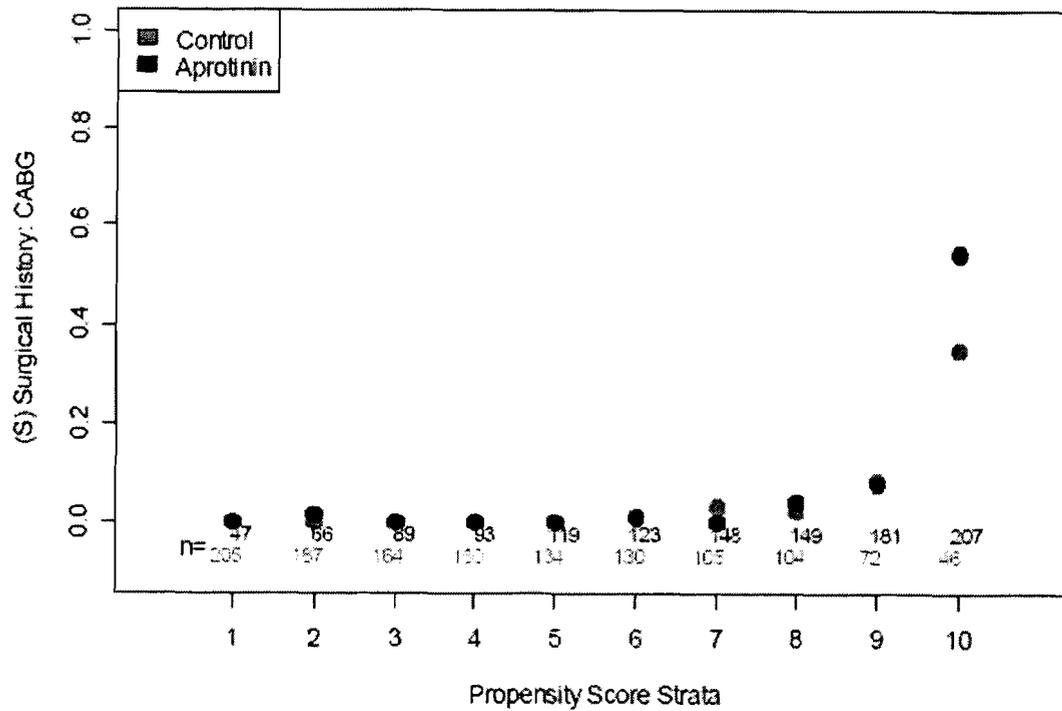
Table A1 in the Appendix gives the primary and sensitivity risk factors selected by the review team for the propensity score model. The risk factors included all those considered in the Mangano JAMA propensity score model with the exception of two risk factors that were not included because of the large number of missing values for these risk factors. These risk factors were "Hx: Carotid disease" and "Hx: Hypercholesterolemia." Table A1 notes the sensitivity risk factors selected by the stepwise regression procedure.

Among the control patients, 67 (4.9%) had missing information for at least one risk factor in the propensity score model and 73 (5.6%) of the aprotinin patients had such missing information.

Two risk factors showed a statistically significant difference between the treatment groups after adjusting for the propensity score. They were "Surgical History: CABG" and "Surgical History: Previous sternotomy." Figure 5 shows the "Surgical History: CABG" risk factor by treatment group and propensity score stratum. The difference in treatment groups appears to be principally

in the highest stratum. The risk factor "Surgical History: Previous sternotomy" had a similar pattern.

Figure 5: Mangano study: "Surgical History: CABG" by treatment group and FDA propensity score stratum.



There was no statistically significant difference in the fractions of patients in the North American region between the treatment groups after adjusting for propensity score.

Figure 6 shows the propensity score distributions by treatment group and propensity score stratum (decile). Overall, there was good overlap between the distributions of the two treatment groups with some differences in the highest stratum.

Figure 6: Mangano Study: FDA propensity scores by treatment group and FDA propensity score stratum.

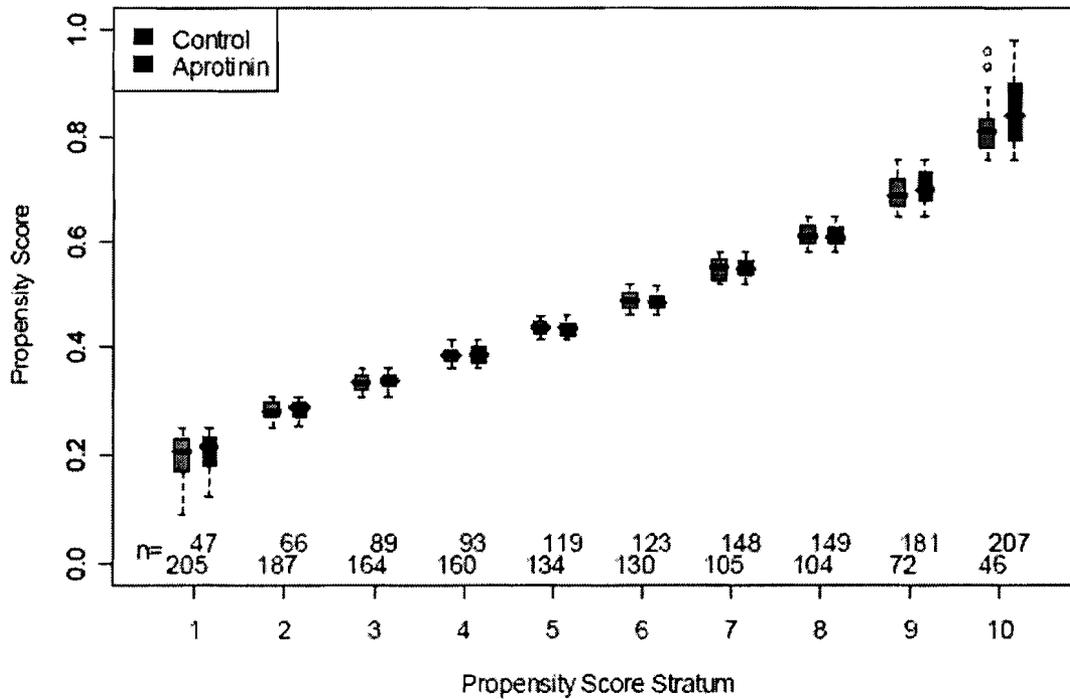


Table 9 gives the re-analysis treatment group and treatment effect estimates for the in-hospital outcomes. Figure 7 plots these outcomes estimates. Among the outcomes, the renal failure and the renal composite outcomes (consisting of renal failure and renal dysfunction) were statistically significant. The renal dysfunction outcome was not statistically significant.

Table 9: Mangano study: Re-analysis in-hospital outcome estimates and treatment effects.

Outcome	Control (%)	Aprotinin (%)	Aprotinin/Control (95% CI)
Renal Composite	4.8	7.8	1.63 (1.03, 2.60)
Renal Failure	2.5	5.1	2.05 (1.05, 3.99)
Renal Dysfunction	4.3	5.4	1.26 (0.76, 2.11)
Cardiovascular Composite	19.5	22.2	1.14 (0.94, 1.38)
Myocardial Infarction	14.8	16.4	1.10 (0.88, 1.39)
Congestive Heart Failure	8.4	8.8	1.05 (0.75, 1.47)
Stroke	2.0	2.8	1.36 (0.70, 2.64)
Death (all-cause in-hospital)	4.6	4.2	0.91 (0.54, 1.53)

Figure 7: Mangano study: Re-analysis in-hospital outcome estimates.

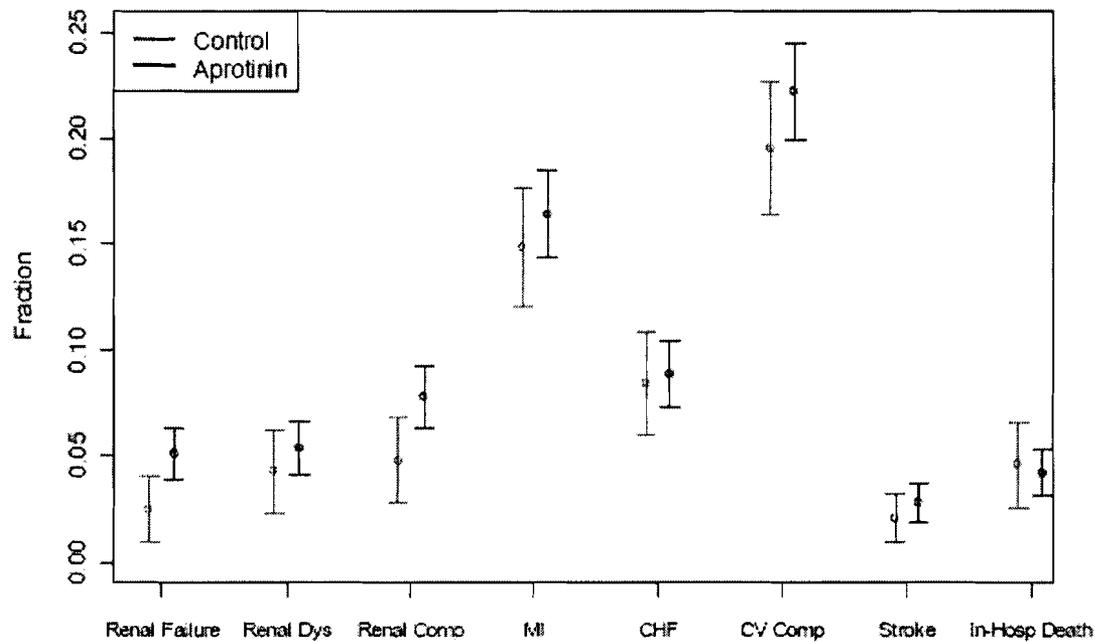


Figure 8 and Figure 9 show the renal composite and myocardial infarction outcomes by treatment group and FDA propensity score stratum. For the renal composite outcome, the

aprotinin group had higher fractions in all but 1 of the 10 strata. For the myocardial infarction outcome, the observed treatment effect was not consisted across strata.

Figure 8: Mangano Study: Renal composite outcome by treatment group and FDA propensity score stratum.

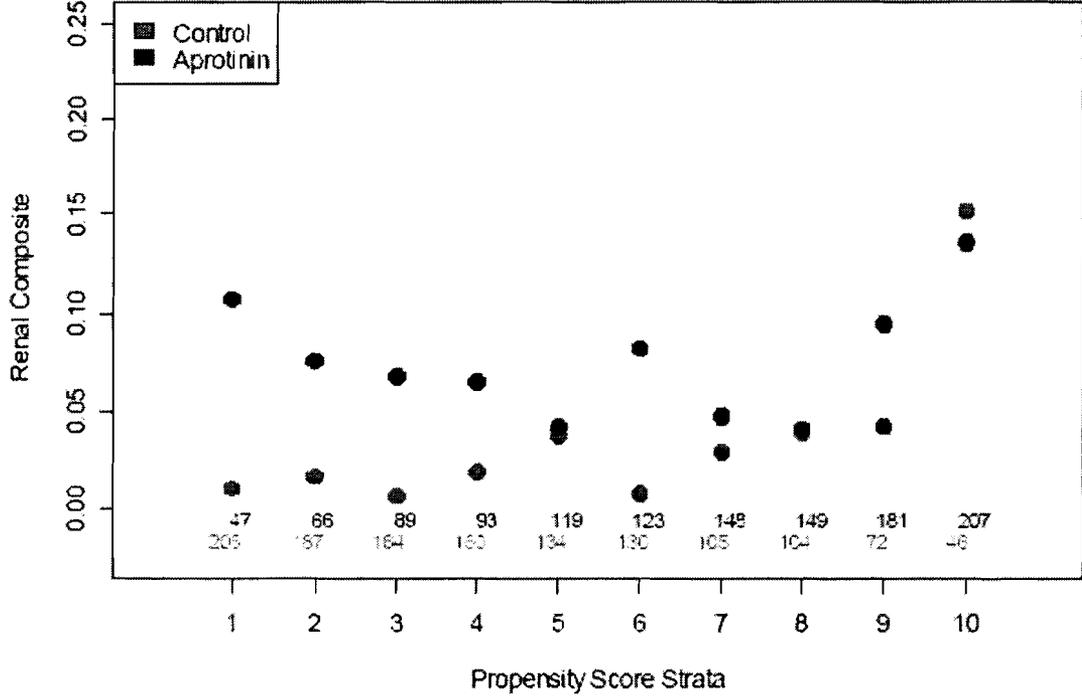


Figure 9: Mangano Study: Myocardial outcome by treatment group and FDA propensity score stratum.

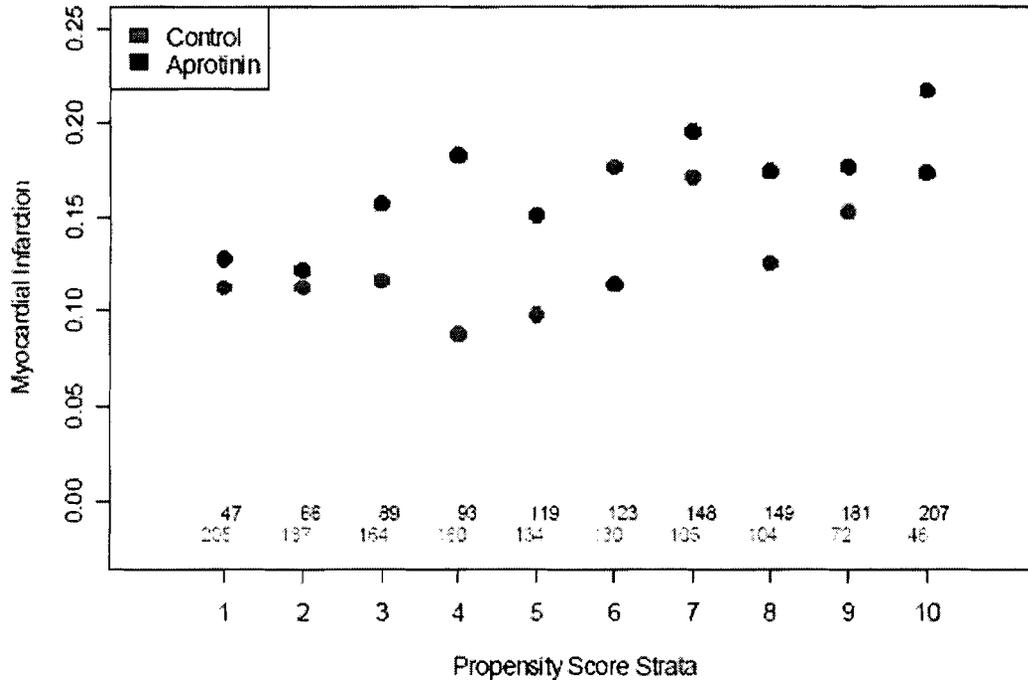


Table 10 gives the re-analysis treatment group and treatment effect estimates for the follow-up mortality outcomes. Figure 10 plots these outcomes estimates. The aprotinin group had higher mortality estimates than the control group, starting at 6 months. As seen in the Table 10, the treatment effect for the years 3 through 5 were statistically or nearly statistically significant.

Table 10: Mangano study: Re-analysis follow-up mortality and treatment effect estimates.

Outcome	Control (%)	Aprotinin (%)	Aprotinin/Control (95% CI)
6 Weeks	5.2	4.8	0.93 (0.57, 1.51)
6 Months	6.4	7.0	1.10 (0.73, 1.68)
1 Year	7.1	8.2	1.16 (0.79, 1.71)
2 Years	8.4	10.7	1.27 (0.90, 1.79)
3 Years	9.7	13.0	1.34 (0.98, 1.83)
4 Years	11.4	15.9	1.39 (1.05, 1.84)
5 Years	14.3	18.1	1.26 (0.98, 1.62)

Figure 10: Mangano study: Re-analysis follow-up mortality and estimates.

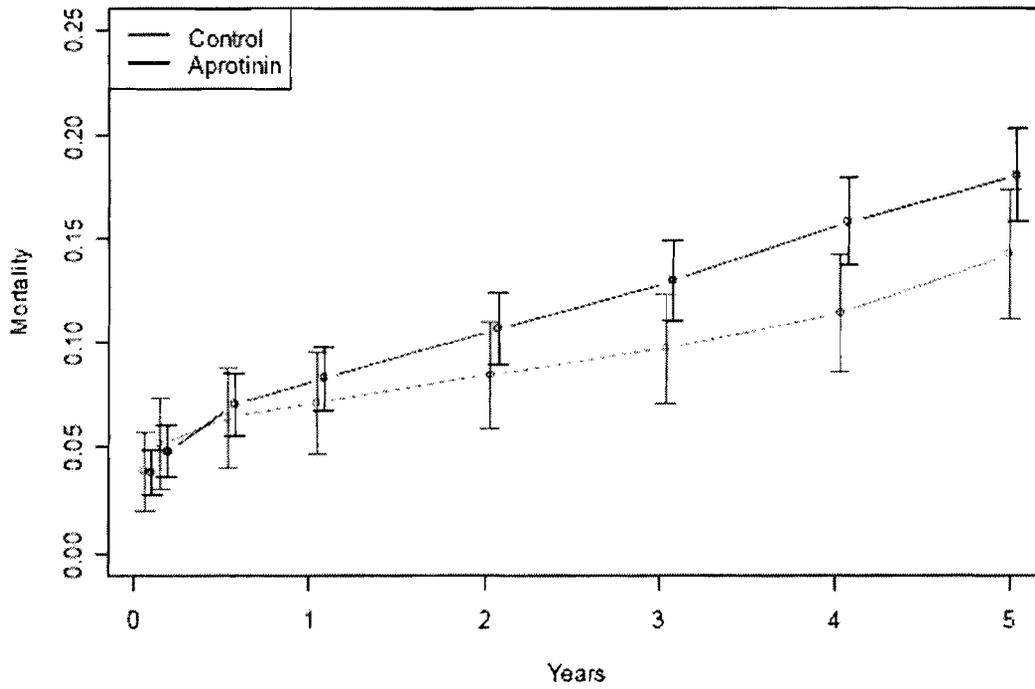
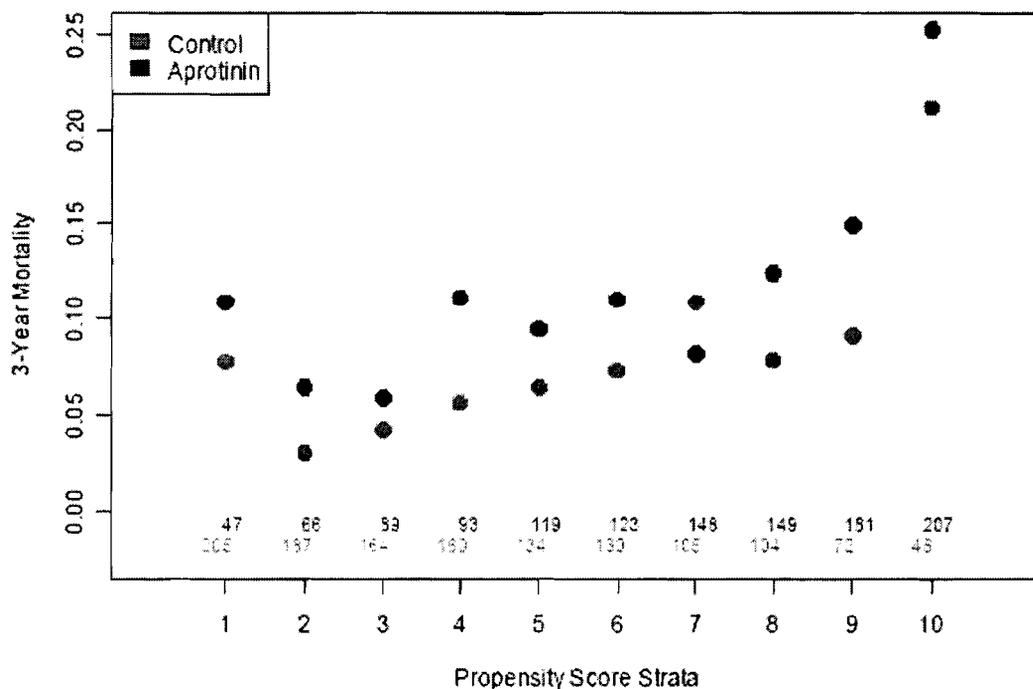


Figure 11 shows the 3-year mortality estimate by treatment group and FDA propensity score stratum. The higher mortality rates for the aprotinin group were seen in 9 out of the 10 strata. Similar patterns hold for years 4 and 5.

Figure 11: Mangano study: 3-Year Mortality by treatment group and FDA propensity score stratum.



The subgroup of patients undergoing primary surgery was analyzed. This subgroup consisted of 1,022 control patients and 796 aprotinin patients. The propensity scores for this subgroup did not show imbalance in the risk factors and there was good overlap in the propensity score distributions between the treatment groups. There was a significant regional difference after adjusting for propensity score. The control group had higher fractions of North American patients.

Table 11 gives the re-analysis in-hospital outcome and treatment effect estimates for this subgroup. Also, included in the table are estimates from the Mangano NEJM paper when available. For this subgroup, the renal failure, myocardial infarction, and cardiovascular composite outcomes were nearly statistically significant.

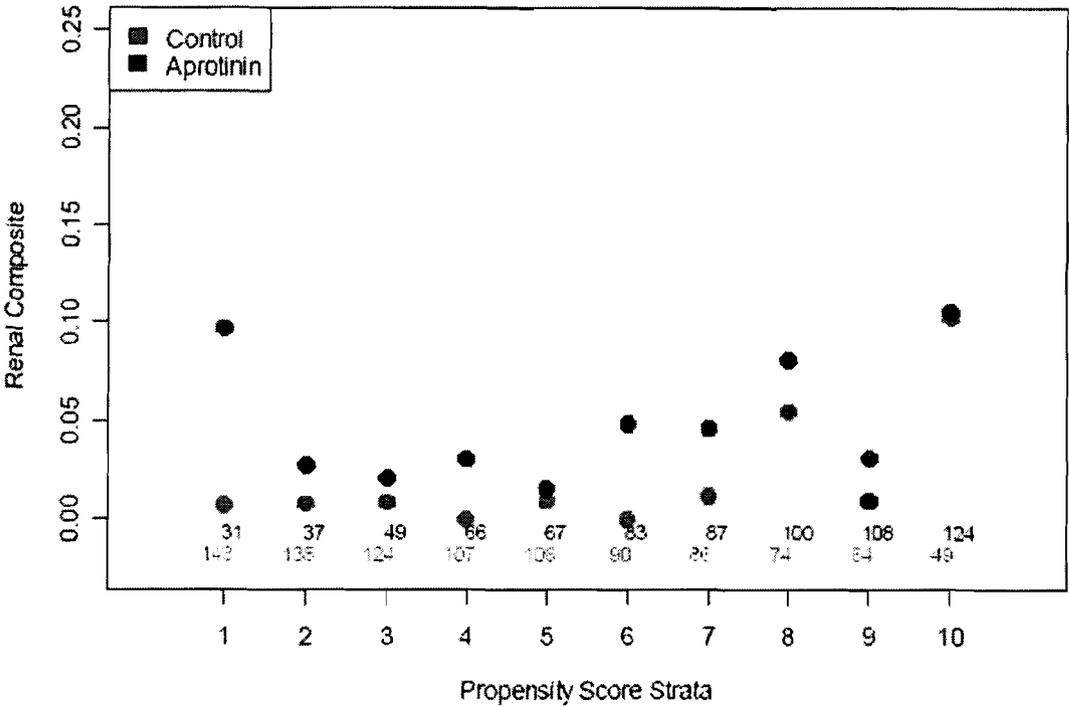
Table 11: Mangano study: Primary surgery, re-analysis and Mangano NEJM in-hospital outcome and treatment effects estimates.

Outcome	Control (%)	Re-Analysis		Mangano NEJM Analysis*
		Aprotinin (%)	Aprotinin/Control RR (95% CI)	Aprotinin/Control OR (95% CI)
Renal Composite	3.2	5.1	1.59 (0.86, 2.94)	2.34 (1.27, 4.31)
Renal Failure	1.7	3.7	2.23 (0.94, 5.31)	
Renal Dysfunction	2.6	3.2	1.22 (0.60, 2.46)	
Cardiovascular Composite	16.2	20.2	1.25 (0.98, 1.58)	1.42 (1.09, 1.86)
Myocardial Infarction	13.0	16.6	1.27 (0.98, 1.66)	
Congestive Heart Failure	4.5	6.4	1.41 (0.87, 2.29)	
Stroke	1.3	1.9	1.48 (0.66, 3.34)	
Death (all cause, in hospital)	2.0	2.5	1.28 (0.57, 2.85)	1.59 (0.76, 3.34)

\* Available only for composite outcomes.

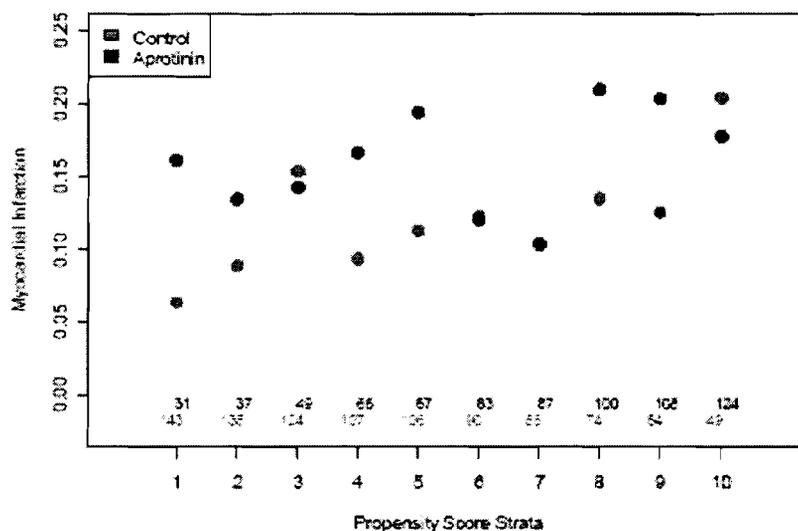
Figure 12 and Figure 13 explore the renal composite and myocardial infarction outcomes by propensity strata. For the renal composite outcome, in 9 of the 10 strata, the aprotinin group had higher fractions. For the myocardial infarction outcome, the pattern was less clear. For this outcome, in the highest stratum, the control group had a higher fraction.

Figure 12: Mangano Study: Primary surgery, renal composite outcome by treatment group and FDA propensity score stratum.



Note: For strata 3 and 5, both groups had zero events.

Figure 13: Mangano Study: Primary surgery, myocardial infarction by treatment group and propensity score stratum.



#### 4.5 Summary and Discussion

The statistical review has addressed several important issues of the Mangano study. These include the effectiveness of the Mangano propensity scores in achieving balanced treatment group comparisons, the use of regression to estimate treatment effects, and the existence of regional differences.

It was found that the Mangano propensity scores did not achieve balance between the aprotinin and control groups for important risk factors. Differences between the treatment groups in these risk factors may lead to biased treatment effect estimates. Additionally, there was a regional difference between the treatment groups that persisted after the propensity adjustment.

It was found that the Mangano propensity score distributions of the aprotinin and control treatment groups did not overlap in the lower range of propensity scores. Without overlap over the whole range of estimated propensity scores, the treatment group effect estimates are sensitive to the form of the regression model.

The Mangano study was re-analyzed with an alternative approach based stratification and direct standardization. The approach promotes transparency, effective diagnostics, and ease of interpretation. Using this approach, the treatment group effects were estimated for the aprotinin patient population.

The treatment comparison considered was between aprotinin patients and control (no agent) patients. In addition to the full group of patients, a subgroup of primary surgery patients was analyzed.

The renal composite (renal failure or dysfunction) outcome was statistically significant for the full group of patients. The renal failure outcome was nearly statistically significant for subgroup of primary surgery patients. The aprotinin patients had consistently higher fractions of the renal composite outcome over a range of patient risk levels, as measured by propensity score.

For both the full group of patients and the subgroup of primary surgery patients, it appears that the renal composite effect was associated with renal failure and not necessarily renal dysfunction. For neither group of patients was the renal dysfunction outcome statistically significant.

For the myocardial infarction outcome, no statistically significant difference between the treatment groups was found in the whole population. For the subgroup of primary surgery patients, the difference was nearly statistically significant.

The effect of aprotinin on the renal composite outcome extends over a range of patient risk level. The effect was seen for both in the full group and primary-surgery subgroup and over a range of propensity scores for both groups.

The effect of aprotinin on the myocardial outcome was not pronounced. The effect was not seen in the full group and was nearly significant for the primary-surgery subgroup. Within the subgroup, the effect was not consistent across patients, as measured by propensity score.

The effects of aprotinin on mortality at the time points 3 through 5 years were statistically or nearly statistically significant. The estimated risk ratio for aprotinin versus control at 4 years was 1.39 (95% CI: 1.05, 1.84) and at 5 years was 1.26 (95% CI: 0.98, 1.62). These were similar in size to the Mangano hazard ratio estimate of 1.37 (95% CI: 1.09, 1.73) (calculated with propensity adjustment).

However, there was an apparent difference in the follow-up between the aprotinin patients and the control patients. For the control patients, 27% had no post-hospital follow-up or were lost to follow-up compared to 17% for the aprotinin patients.

As in any observational study, there exists the potential for unadjusted confounding. Differences in treatment groups may be related to unmeasured risk factors or measured risk factors that are not properly adjusted for.

Work is ongoing on subgroups based on geographical regions and subgroups based on age, sex, and race. Additionally, analysis of the patients with the highest propensity scores may lead to further understanding of the highest risk patients.

## **5.0 KARKOUTI STUDY**

### **5.1 Study Summary**

The sources for the evaluation of the Karkouti study were the published article and data submitted to FDA by Keyvan Karkouti of the University of Toronto

The Karkouti study was a retrospective cohort study of 5 years of surgical data at a single Toronto, Canada hospital. Patients undergoing cardiac surgery with CPB were eligible for the study. The cardiac surgeries included CABG surgery, as well as valve surgery, and combination surgeries. The agents aprotinin and tranexamic acid were compared for safety and efficacy.

The hospital guidelines reserved aprotinin for high-risk patients and tranexamic acid for other patients. According to the paper, aprotinin was reserved for patients with active endocarditis, undergoing complex surgery requiring prolonged CPB, or had at least two previous sternotomies. According to Karkouti, in practice there were deviations from the guidelines, which created the possibility of comparing the agents.

According to the article, there were 10,870 patients available in the study. Of these 586 (5.4%) received aprotinin. The majority of aprotinin patients underwent valve or combination surgeries. In contrast, the majority of tranexamic acid patients underwent only CABG surgery.

Note that there were 33 patients with duplicate records in the tranexamic acid group in the dataset received by FDA. The duplicated records were removed from the FDA analysis.

The study used propensity scores and matching to estimate treatment effects. The propensity scores of receiving aprotinin were estimated using the predicted values from a multivariate logistic regression. Patients receiving aprotinin were matched to those receiving tranexamic acid using a greedy matching procedure based on the estimated propensity scores. Among the aprotinin patients, 449 were matched to a tranexamic acid patient. The study showed that the matched pairs were comparable in terms of the risk factors.

The study assessed safety outcomes with paired comparisons within each match pair using conditional logistic regression.

### 5.1.1 Outcomes

Table 12 gives the safety outcomes used in the Karkouti study. In the Karkouti study, the renal dysfunction outcome was a composite outcome encompassing either a new need for dialysis or elevated creatinine levels. There was no outcome based only on creatinine levels. The renal dysfunction outcome was only available for the 449 matched pairs of patients.

Table 12: Karkouti study: Safety outcomes.

Outcome*	Definition
Renal failure (in-hospital)	New requirement for dialysis support
Renal dysfunction (in-hospital)	50% increase in creatinine concentration during first postoperative week to more than 100 µmol per L in women and 110 µmol per L in men or a new requirement for dialysis support
Myocardial infarction (in-hospital)	New Q wave on postoperative electrocardiogram OR MB isoenzyme of creatine kinase > 50 U per L, the CK-MB/CK ratio > 5% and new electrocardiogram changes
Stroke (in-hospital)	Evidence of a persistent neurological deficit
Death (in-hospital)	

\*There was one additional safety outcome, serious infection, that was not considered in the review.

### 5.1.2 Review Issues

The primary review objective for the Karkouti study was to re-analyze the study using the methods described in Section 3.0. The re-analysis explored the robustness of the study conclusions and allowed for more direct comparisons between the aprotinin studies.

Section 5.2 summarizes the patient population and disposition of the Karkouti study. Section 5.3 presents the findings from the re-analysis of the study. Section 5.4 summarizes the current findings of the review.

As part of the review of the study, the principal results were reproduced based exactly on the methods used Karkouti. These results include the p-values for the treatment group comparisons for the renal dysfunction, renal failure, myocardial infarction, stroke, and death outcomes.

## 5.2 Patient Population and Disposition

Table 13 gives the baseline characteristics for the aprotinin patients and tranexamic patients. The baseline characteristics included in the table are those risk factors identified by the FDA review team (see Appendix). Note that race information was not collected in the study. The characteristics include all the primary risk factors and the particular sensitivity risk factors selected in the stepwise procedure. For most of these characteristics, there were statistically significant differences between the two treatment groups. Risk factors related to the hospital guidelines for the use of aprotinin, e.g., active endocarditis and CABG only surgery, showed that the expected differences between the treatment groups.

Table 13: Karkouti study: Patient baseline characteristics.

Characteristic		Tranexamic Acid N=10251	Aprotinin N=586	P-Value*
Demo: Age	(mean ± sd)	62.59 ± 12.01	55.39 ± 16.61	<.001
Demo: Female	(%)	25.3	34.6	<.001
Medical History: Diabetes	(%)	26.7	11.8	<.001
Preop. Medications: Aspirin	(%)	36.1	17.1	<.001
Preop. Medications: Heparin	(%)	21.2	18.8	0.163
Preoperative Factors: Angina	(%)	43.0	14.3	<.001
Preoperative Factors: Atrial fibrillation	(%)	5.8	18.8	<.001
Preoperative Factors: Congestive heart failure	(%)	20.0	51.4	<.001
Preoperative Factors: Creatinine abnormal	(%)	1.5	4.6	<.001
Preoperative Factors: Ejection fraction < 40%	(%)	20.2	22.7	0.148
Preoperative Factors: Endocarditis	(%)	0.5	8.2	<.001
Preoperative Factors: Hb level	(mean ± sd)	134.30 ± 15.08	127.54 ± 20.72	<.001
Preoperative Factors: INR	(mean ± sd)	1.09 ± 0.19	1.20 ± 0.30	<.001
Preoperative Factors: MI	(%)	16.5	7.2	<.001
Preoperative Factors: PLT count	(mean ± sd)	232.02 ± 69.23	225.43 ± 80.41	0.028
Preoperative Factors: Recent catheterization	(%)	8.9	32.4	<.001
Preoperative Factors: Shock	(%)	1.2	4.1	<.001
Surgical: Urgent	(%)	7.7	18.9	<.001
Surgical History: Previous sternotomy	(%)	5.0	61.1	<.001
Surgical: CABG only	(%)	66.9	10.9	<.001
Surgical: Number of graphs ≥3	(%)	66.3	18.3	<.001
Missing Count†	(n)	45	13	

\*P-values for percentages based on chi-square test. P-values for means based on t-test.

†Number of patients with at least one missing characteristic.

Table 14 gives the unadjusted outcome rates by treatment group. For each outcome except for myocardial infarction, the aprotinin group had a statistically significant, higher rate of the outcome.

Table 14: Karkouti study: Unadjusted outcome rates.

Outcome	Tranexamic Acid N=10251 (%)	Aprotinin N=586 (%)	P-Value*
Renal Failure	1.2	5.8	<.001
Myocardial Infarction	2.3	2.4	0.867
Stroke	1.3	3.6	<.001
Death (all cause, in-hospital)	1.5	7.2	<.001

\*P-values on chi-square test.

### 5.3 Treatment Effect Re-estimation

This section gives the results of the re-analysis of the Karkouti study using the methods described in Section 3.0.

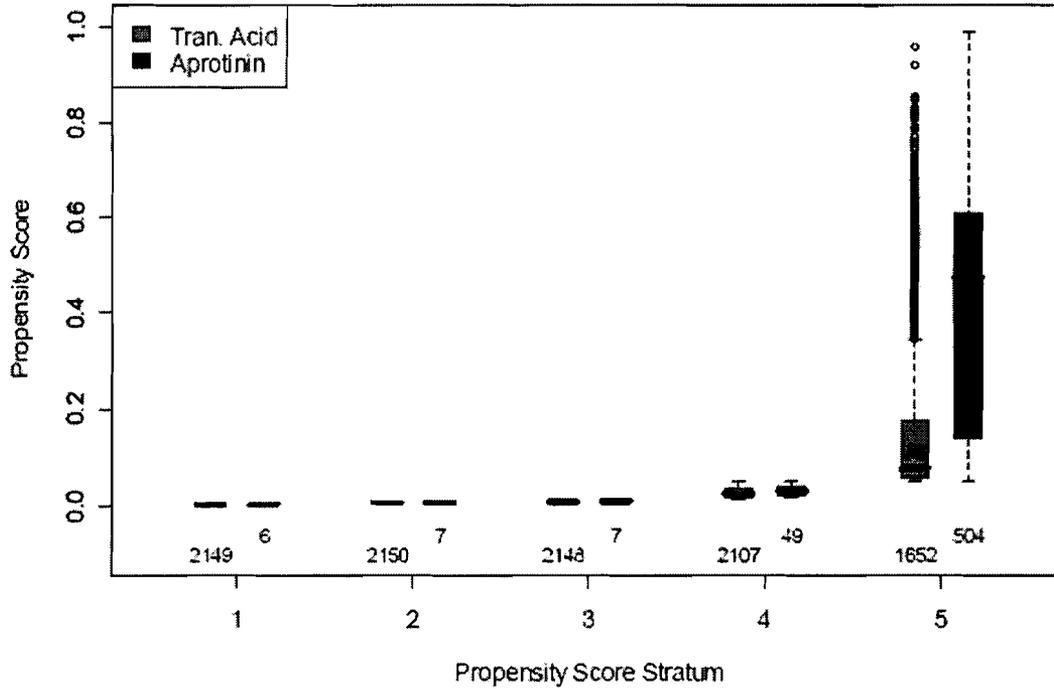
Table A2 in the Appendix gives the primary and sensitivity risk factors selected by the review team for the propensity score model. The risk factors included all those considered in the Karkouti with the exception of two risk factors, cardiac arrest and pump duration. These risk factors were not included in the propensity score modeling, because they are perioperative and may be considered outcomes and not risk factors.

The initial propensity score model estimated the effect receiving aprotinin versus tranexamic acid for the full patient group. Five strata were used for propensity score strata rather than 10 because of the smaller number of aprotinin patients as compared to the other studies.

Among the tranexamic acid patients, 45 (0.4%) had missing information for at least one risk factor in the propensity score model and 13 (0.2%) of the aprotinin patients had such missing information.

Figure 14 shows the propensity score distributions by treatment group and propensity score stratum. Strata 1 through 3 had insufficient aprotinin patients for analysis.

Figure 14: Karkouti Study: FDA propensity scores by treatment group and propensity score stratum.



An analysis subgroup of patients consisting of patients in strata 4 and 5 was defined. The subgroup had 553 of the 586 full-group aprotinin patients (94%). Table 15 gives the baseline characteristics for the subgroup. Comparing Table 15 to Table 13, it is seen that the analysis subgroup has much more similar rates for CABG only surgery between the treatment groups. Only 17.2% of the tranexamic acid patients and 8.0% of the aprotinin patients in the subgroup underwent only CABG surgery.

Table 15: Karkouti study: Patient baseline characteristics, analysis subgroup.

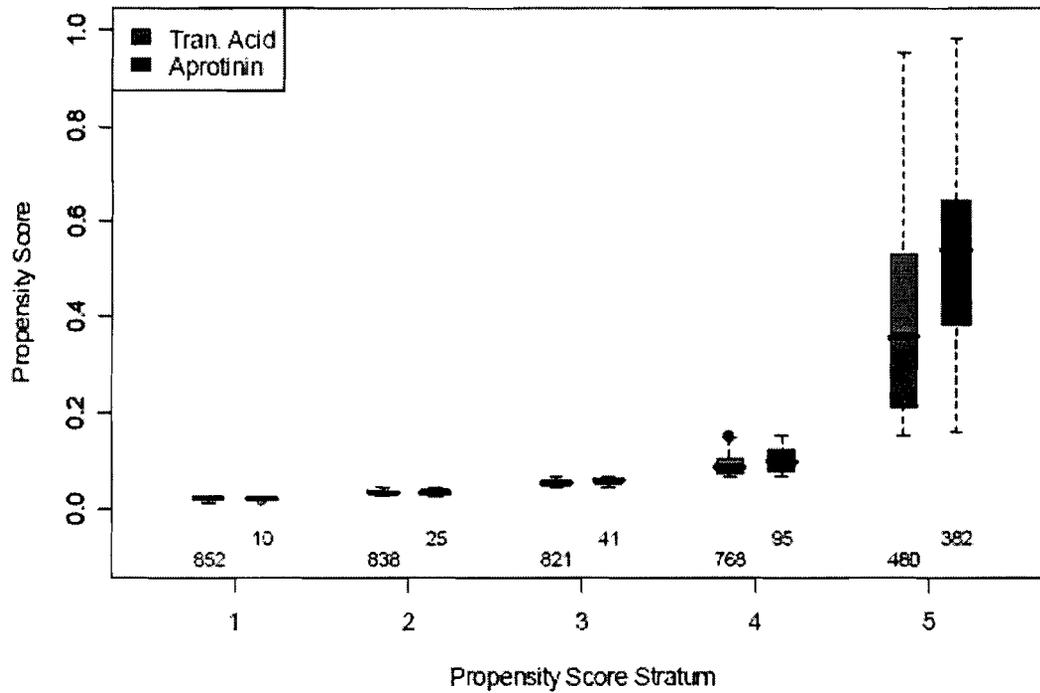
Characteristic		Tranexamic Acid N=3759	Aprotinin N=553	P-Value*
Demo: Age	(mean ± sd)	60.52 ± 14.71	54.79 ± 16.59	<.001
Demo: Female	(%)	33.7	34.9	0.588
Medical History: Diabetes	(%)	16.0	10.8	0.002
Preop. Medications: Aspirin	(%)	22.6	16.3	<.001
Preop. Medications: Heparin	(%)	18.3	19.2	0.635
Preoperative Factors: Angina	(%)	24.0	12.8	<.001
Preoperative Factors: Atrial fibrillation	(%)	11.8	19.5	<.001
Preoperative Factors: Congestive heart failure	(%)	37.2	52.3	<.001
Preoperative Factors: Creatinine abnormal	(%)	2.7	4.7	0.01
Preoperative Factors: Ejection fraction < 40%	(%)	20.6	22.1	0.426
Preoperative Factors: Endocarditis	(%)	1.3	8.5	<.001
Preoperative Factors: Hb level	(mean ± sd)	132.65 ± 16.57	127.33 ± 20.89	<.001
Preoperative Factors: INR	(mean ± sd)	1.12 ± 0.24	1.20 ± 0.29	<.001
Preoperative Factors: MI	(%)	10.8	6.7	0.003
Preoperative Factors: PLT count	(mean ± sd)	225.59 ± 69.02	225.54 ± 81.57	0.987
Preoperative Factors: Recent catheterization	(%)	20.2	32.7	<.001
Preoperative Factors: Shock	(%)	2.4	3.8	0.052
Surgical: Urgent	(%)	15.8	18.3	0.137
Surgical History: Previous sternotomy	(%)	13.6	63.7	<.001
Surgical: CABG only	(%)	17.2	8.0	<.001
Surgical: Number of graphs ≥3	(%)	31.8	15.6	<.001
Missing Count†	(n)	0	0	

\*P-values for percentages based on chi-square test. P-values for means based on t-test.

†Number of patients with at least one missing characteristic.

The propensity score were re-estimated for the analysis subgroup. Figure 15 shows the propensity score distributions by treatment group and propensity score stratum for this subgroup. The overlap in the distributions of the two treatment groups for the strata appeared good.

Figure 15: Karkouti Study: FDA propensity scores by treatment group and propensity score stratum, analysis subgroup.



The only statistically significant difference in risk factors after adjusting for propensity score was the factor "Preoperative Factors: MI." Figure 16 shows that the difference between treatment groups for the risk factor was predominately in stratum 1.

Figure 16: Karkouti study: "Preoperative Factors: MI" by treatment group and FDA propensity score stratum, analysis subgroup.

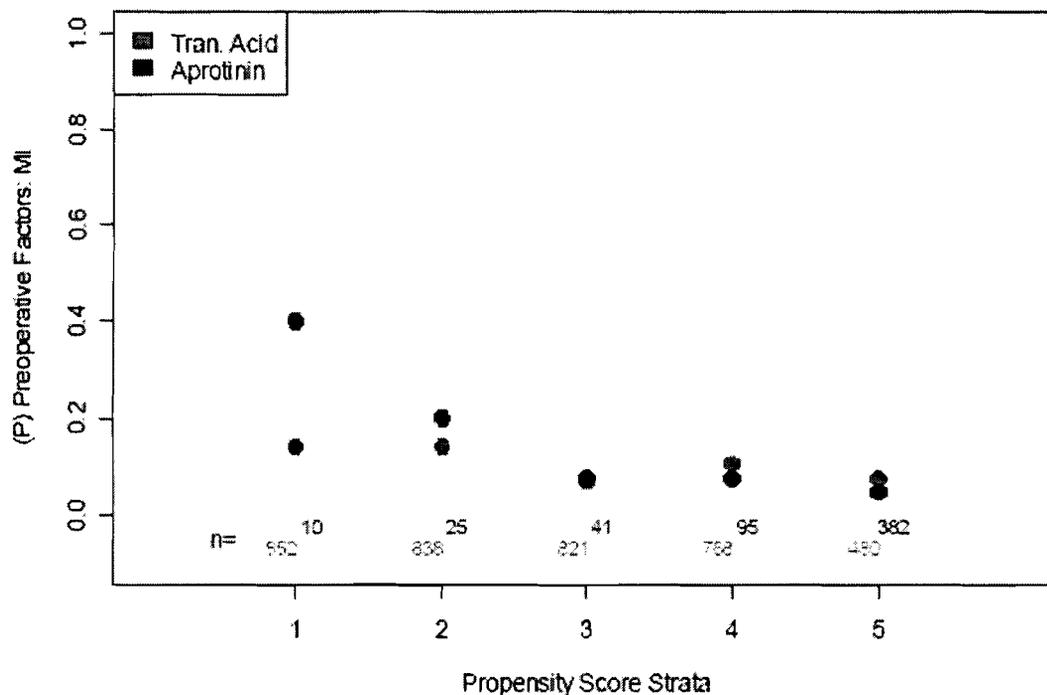


Table 16 gives the re-analysis treatment group and treatment effect estimates. The table includes the treatment effect estimates based on the Karkouti matched patients. The Karkouti article does not include these estimates, but they were calculated using the method stated in the Karkouti article. The renal dysfunction outcome estimates could not be re-analyzed because the outcome was available only for the matched patients. Figure 17 plots the re-analysis treatment group estimates.

For none of the outcomes available for the re-analysis was there a statistically significant treatment group effect. This is in agreement with the matched patient analysis. However, the matched-pair analysis showed a statistically significant renal dysfunction outcome treatment group effect.

Table 16: Karkouti study: Re-analysis and matched-patient outcome and treatment effects estimates, analysis subgroup.

Outcome	Re-Analysis			Matched-Pair Analysis
	Tran. Acid (%)	Aprotinin (%)	Aprotinin/Tran. Acid RR (95% CI)	Aprotinin/Tran. Acid OR (95% CI)
Renal dysfunction*				1.53 (1.11, 2.12)
Renal failure	4.1	5.6	1.38 (0.86, 2.23)	1.85 (0.94, 3.63)
Myocardial Infarction	1.8	2.5	1.42 (0.71, 2.83)	1.22 (0.51, 2.95)
Stroke	2.1	3.6	1.72 (0.93, 3.19)	1.15 (0.55, 2.43)
Death (in-hospital)	6.1	7.2	1.18 (0.79, 1.76)	0.90 (0.54, 1.51)

\* Renal dysfunction outcome was only available for matched patients.

Figure 17: Karkouti study: Re-analysis outcome estimates, analysis subgroup.

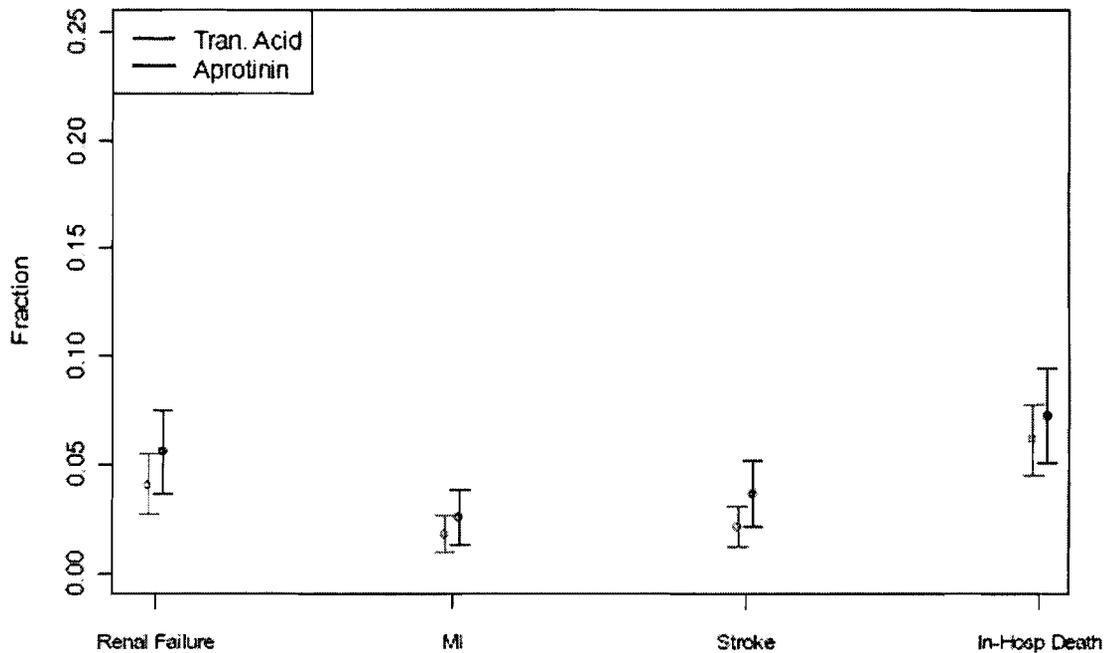
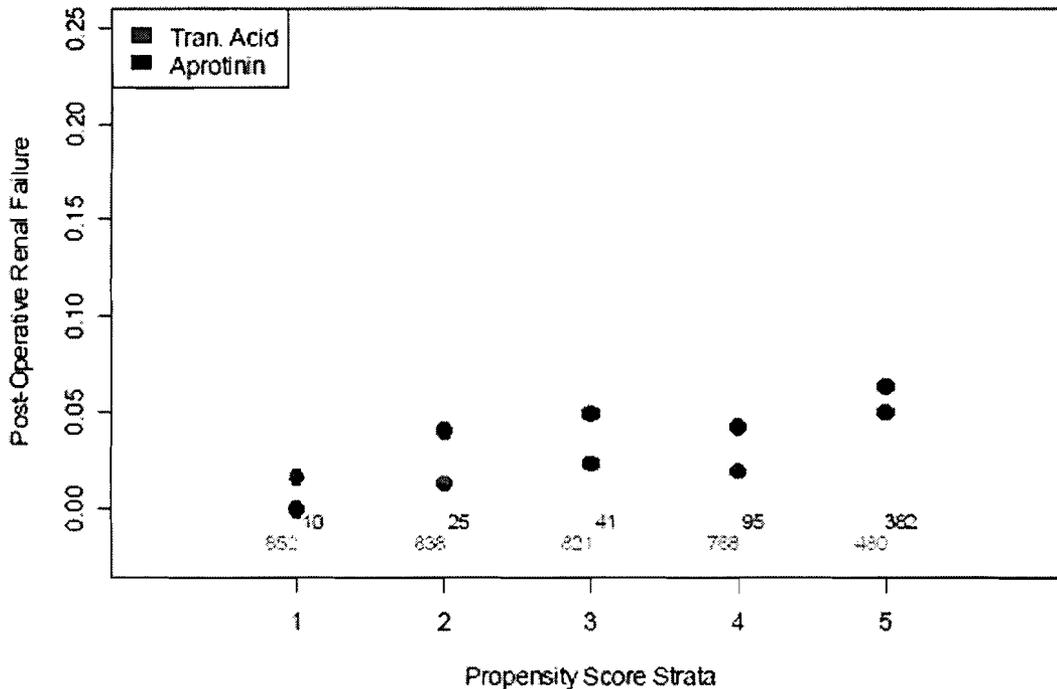


Figure 18 shows the renal failure outcome by treatment group and FDA propensity score stratum. In 4 of the 5 strata, the aprotinin group had a higher fraction for the outcome than the control group.

Figure 18: Karkouti study: Renal Failure by treatment group and FDA propensity score stratum, analysis subgroup.



#### 5.4 Summary and Discussion

The Karkouti study was re-analyzed with an alternative approach based on stratification and direct standardization. The approach promotes transparency, effective diagnostics, and ease of interpretation.

Based on initial propensity score estimates, an analysis subgroup of patients was defined that had sufficient numbers of patients for each treatment group and propensity score stratum. This subgroup contained the vast majority of the initial aprotinin patients (553/586, 94%). The patients in the subgroup were majority valve or combination surgery patients. The propensity scores were re-estimated for the subgroup. The new propensity score estimates effectively balanced the treatment groups with respect to the risk factors. There was good overlap in the propensity score distributions of the two treatment groups.

For the analysis subgroup of patients, the renal failure, myocardial infarction, stroke, and in-hospital death outcome treatment group effects were not statistically significant. Although, the renal failure outcome did not have a statistically significant treatment effect, the aprotinin group had a higher rate of the outcome over a range of patient-risk levels, represented by propensity score.

The results were similar to those reported in the Karkouti study, which used matched-pair analysis. Both the re-analysis approach and the matched-pair analysis provide treatment group effect estimates for the aprotinin patient population.

The Karkouti study also analyzed a renal dysfunction outcome (new dialysis or elevated creatinine levels). The outcome was not available for the entire patient group and could not be re-analyzed.

Based on the matched-pair analysis, aprotinin was associated with higher risk for the renal dysfunction outcome.

As in any observational study, there exists the potential for unadjusted confounding. Differences in treatment groups may be related to unmeasured risk factors or measured risk factors that are not properly adjusted for.

Work is ongoing on subgroups based on age and sex.

## **6.0 I3 DRUG SAFETY STUDY**

### **6.1 Data Source**

An analysis data set provided by the sponsor (supplied by i3 Drug Safety) in a submission dated March 8, 2007 represents the primary source data for this review. This analysis data set was used for the draft version of the study report dated September 13, 2006.

This analysis data were derived from Premier's Perspective Comparative Database (PCD). This is a large hospital-based, service-level comparative claims database. Approximately one-sixth of all hospitals across the United States provide data to the database. Collected patient information includes patient demographics (i.e. age, gender, and admission source), principal and secondary diagnoses, principal and secondary procedures, payor, length of stay, cost of care, drug utilization, department cost and charge detail, day-of-stay, and physician specialty. Detailed service level information is available for each hospital day. This includes medication information (i.e., drug name and strength, quantity dispensed and unit cost). In-hospital mortality information is also obtained.

A limitation of the data is an inability to fully characterize the temporal relationships between events, which are represented by codes. Even though some codes have dates associated with them, the absence of times makes it difficult to determine whether an event occurred before or after other events that occurred on the same day. For example, if a dialysis and a CABG procedure were charged on the same day, one would not know which event occurred first. Other

codes, such as those for certain discharge diagnoses, do not have dates associated with the diagnosis, so one would have to infer whether they represent pre-existing conditions or events that occurred during admission.

## 6.2 Patients

The original data extract from the Premier database identified 162,687 patients who underwent CABG surgery between January 1, 2003 and March 31, 2006 (the draft study report incorrectly states that the start of this time period was April 1, 2003). Of these, 16 patients were excluded for either being <18 years of age or having an unknown gender and 77,732 were excluded because they received no IV antifibrinolytic during CABG. Of the 84,939 patients who received an IV antifibrinolytic during CABG surgery, 3,112 received multiple antifibrinolytic agents and 15,392 received what was considered to be an inadequate dose of an antifibrinolytic agent. An inadequate dose was defined as less than two million units (i.e. fewer than two vials) for aprotinin, less than 10g (i.e. fewer than two vials) for aminocaproic acid, and less than 1g (i.e. fewer than 1 vial) for tranexamic acid. The exclusions left 66,435 patients who were eligible for the study and who represent the full study population. Of these patients, 29,358 received aprotinin, 35,719 received aminocaproic acid and 1,358 received tranexamic acid. Figure 19 provides a patient flowchart that summarizes these results.

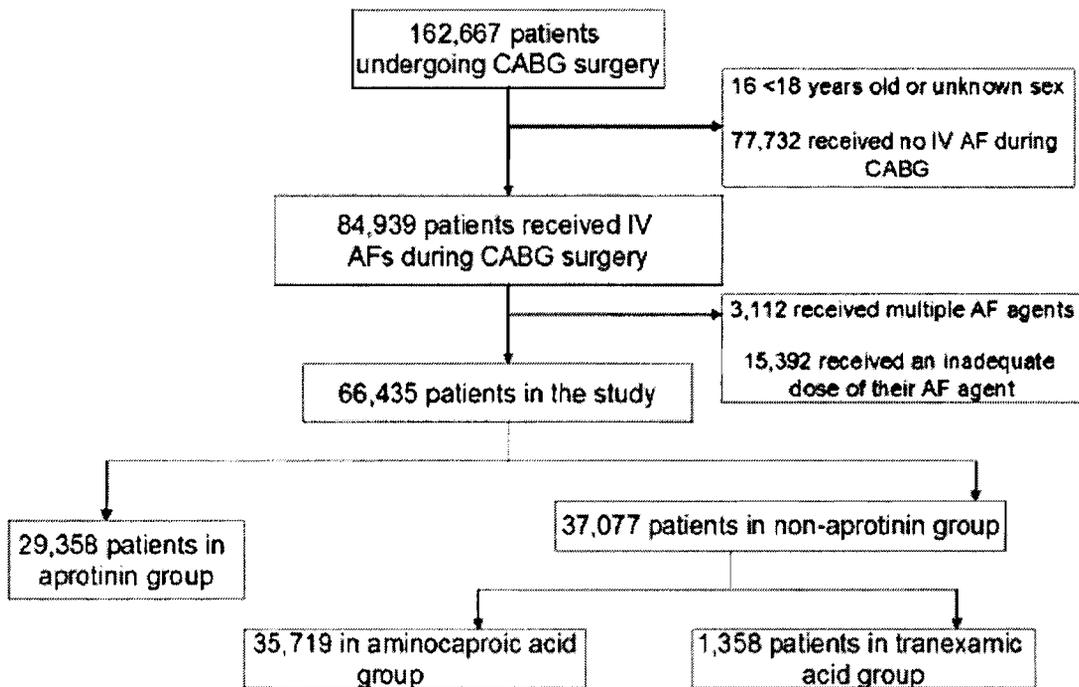


Figure 19: Study Flowchart (source: study report)

Data for the subjects who received no antifibrinolytic agent has been requested so that comparisons between aprotinin patients no treatment patients could be made. However, at the time of this report these data were unavailable.

### 6.3 Outcomes

Study outcomes and their definitions, along with other comments and limitations of their derivations are provided in Table 17. Acute coronary revascularization, stroke, acute heart failure, acute renal failure, and death were outcomes used in the i3 study.

Table 17: Study Outcomes and their Definitions and Derivations

Outcome	Definition	Comments/Limitations
Death	Any patient with a discharge status of "Expired" (UB-29 codes 20-29 and 40-42)	
Stroke	Indicated by the presence of a discharge code for post-operative stroke or ischemic stroke (excluding TIA), or procedure codes for stroke diagnostics and/or therapeutics. Excludes hemorrhagic stroke	<ul style="list-style-type: none"> <li>Assumes that discharge diagnoses of stroke, in the presence of procedure use on the day of or after surgery, were for strokes that occurred after surgery only.</li> </ul>
Acute renal failure <sup>1,2</sup>	Indicated by the presence of codes for hemo- or peritoneal dialysis or hemofiltration	<ul style="list-style-type: none"> <li>Not assessed for patients with pre-existing renal failure and patients with no post-surgery follow-up.</li> <li>Excludes events on the day of surgery.</li> <li>Discharge diagnosis of renal failure not required</li> <li>Not based on lab (creatinine) values</li> </ul>
Acute heart failure <sup>1</sup>	Indicated by the presence of codes for dobutamine use or left ventricular assist device use.	<ul style="list-style-type: none"> <li>Not assessed for patients with no post-surgery follow-up.</li> <li>Excludes events on the day of surgery.</li> <li>Dobutamine use not as severe as left ventricular assist device use.</li> <li>Baseline dobutamine use not accounted for.</li> </ul>
Acute coronary revascularization <sup>1</sup>	Indicated by the presence of codes for thrombolysis, PTCA, or redo CABG	<ul style="list-style-type: none"> <li>Excludes events on the day of surgery.</li> <li>Not assessed for patients with no post-surgery follow-up.</li> </ul>

<sup>1</sup> Three hundred fifty-three (353) patients were discharged on the day of their CABG surgery. For outcomes that could not be assessed on the day of surgery, the implementation by i3 Drug Safety counted patients as not having the outcome for these patients. In this review, outcomes that can not be assessed on the day of surgery are set to missing for these patients.

<sup>2</sup> The implementation by i3 Drug Safety counted post-surgery dialysis as a renal failure outcome when pre-surgery dialysis was present. In this review, this outcome is missing if pre-surgery dialysis codes exist.

Unless footnoted in the table above, the derivations of these outcomes came directly from the i3 Drug Safety analytic data set. Without a medical chart review, the sensitivity and specificity of these outcome definitions is difficult to ascertain.

#### **6.4 Review Issues**

The primary analysis in the i3 Drug Safety report utilized multivariate logistic regression models to estimate risk ratios associated with aprotinin use. With this approach, treatment group effects are adjusted to account for treatment group differences relating to confounding risk factors. One drawback is that the model can fail to adequately create a balance between treatment groups if the factors do not adequately overlap. Without proper investigation, such an occurrence will often go unnoticed.<sup>7</sup> The purpose of propensity score methodologies is to create a balance between treatment groups with respect to the measured confounding risk factors. Proper implementation requires that the balance between groups be checked and verified before going ahead with analysis. In the original i3 study report, the information provided about the balance between treatment groups with respect to risk factors was limited.

A secondary analysis in the i3 report made use of propensity score methods, but there are problems with the implementation. Most notably, many of the covariates used in the propensity score model are invalid propensity scoring covariates because they are either not associated with the outcomes, they are not measured or determined before the decision to administer an antifibrinolytic agent, or they are not patient-level factors. These are discussed in further detail in Section 6.8.

As a result of the methodological deficiencies, the primary focus of this review was on a re-analysis of the data using the same analysis data set used for the i3 report. Unless otherwise noted, the derivations of the covariates and outcomes were not altered. Comparisons between results conducted for this review and results reported in the i3 study report appear in Section 6.15.

Although available in the Premier database, the i3 Drug Safety analysis did not make use of patients who received no antifibrinolytic agent. At the time of this review, data for these patients had been requested, but not yet received.

#### **6.5 Primary Analysis**

Risk ratios between treatment groups were calculated for each of the outcome measures defined in Table 17 for the full study population (defined in Section 6.2). Associated 95% confidence intervals were calculated as described in Section 3.4.

Because of the small number of patients in the tranexamic acid group relative to the aprotinin and aminocaproic acid groups, these two groups were combined to represent the control group.

#### **6.6 Sensitivity Analysis**

Although the Premier database is a large and comprehensive source of information for the research objectives, there are certain limitations (described below) that could present a bias to

overall conclusions. In order to test the impact of these limitations, a series of sensitivity analyses will be performed.

#### **6.6.1 Analyses to Adjust for the Length of Hospital Stay**

In the context of this study, a patient's follow-up period is defined as the number of days in the hospital following CABG surgery. If one group has a longer follow-up period, then the chance of observing events is greater. In order to address this potential cause of bias, two sensitivity analyses were to be conducted. One evaluated outcome rates on a per patient-week basis. For this, the unit of analysis was the total number of events for a particular group divided by the total number of weeks of follow-up for patients in that group. For outcomes that can be ascertained on the day of CABG surgery, the follow-up period includes the day of surgery. For all other outcomes the follow-up period does not include the day of surgery. Patients who were discharged on the day of surgery could not be evaluated for these outcomes.

Another way to handle the issue of differing follow-up times is with time-to-event methodologies. However, the analytic data set used for this report lacked sufficient information to conduct such analyses. This information has been requested and will be used for future analyses.

#### **6.6.2 Analyses to Address the Impact of Baseline Covariate Information**

Another shortcoming relating to claims data is that many of the variables (outcomes and risk factors alike), are not explicitly collected. They are derived from what is observed in the data. Four risk factors used in the propensity score models could only be assessed on the days prior to CABG surgery (renal failure, warfarin use, angina, and anti-arrhythmia drug use). Since 34% of the patients received CABG surgery on the day of their hospital admission, there exists a substantial number of patients for whom the true value of these risk factors is unknown. Many of the remaining risk factors, although ascertainable for patients undergoing surgery on the day of their hospital admission, are more likely to be observed with increasingly long pre-surgery hospital stays.

In order to investigate whether the overall results may change in the presence of increasing covariate information, the propensity score methodology was repeatedly run on patient populations that are restricted to patients who spend  $\geq 1$  and  $\geq 3$  days in the hospital prior to the index CABG surgery. For each set of propensity score models, the c-statistic, a measure of the models' predictive ability, was retained to determine if the approach does result in more accurate propensity scores.

#### **6.6.3 Analyses that Excludes Patients in the 10<sup>th</sup> Propensity-Score Decile**

Preliminary results suggested that propensity score balance was generally very good. However, in a few of the hospital-level strata, box-plots of the 10<sup>th</sup> decile revealed a number of aprotinin patients with high propensity scores that were unmatched in the control group. Such a result may indicate that the aprotinin group still had a higher risk of adverse outcomes.

In order to investigate whether the overall results may be influenced by potential imbalances in the 10<sup>th</sup> deciles, an analysis that excluded all patients in all 10<sup>th</sup> deciles was performed. In order

to determine whether these patients were truly at higher risk, a similar analysis that only *includes* patients in the 10<sup>th</sup> decile was also performed.

## 6.7 Subgroup Analysis

Subgroup analyses were conducted on the following subgroups:

- Males
- Females
- Elderly ( $\geq 65$  years of age)
- Non-elderly ( $< 65$  years of age)
- Whites (Caucasian)
- Non-whites (Blacks and “other”)

For each subgroup, the methods used were identical to those used for the primary analysis with exception that patients were divided into propensity score quintiles instead of deciles. This was to avoid strata sample sizes for the smaller subgroups that may be considered too small to conduct a meaningful analysis.

## 6.8 Baseline Characteristics

### 6.8.1 Patient-level Risk Factors

Many of the factors used in the i3 Drug Safety multivariate logistic regression model and used for their propensity score models were not considered candidate risk factors for the propensity score models in this review. This was either because the factor was not a patient-level factor (such as hospital characteristics and surgeon CABG volume), it was not defined as a strictly pre-operative factor (such as cardiac arrest, fibrinolytic or direct thrombin inhibitor use, plasma expander use, or the transfusion-related factors), or it was not related to the safety outcomes (marital status, year of admission). The factor for complex surgery was not used because it is a composite of three other factors: Redo cardiac surgery, additional cardiac surgery, and previous coronary procedure.

Table 18 summarizes, by treatment group, the patient-level risk factors considered for the propensity score models. Because of the large sample size, the power to detect small treatment group differences is relatively large. As a result, the p-value associated with the treatment group difference is less than 0.05 for most of the risk factors, even when the difference between groups appears small. For example, 71.5% of Control patients are males compared to 70.8% of aprotinin patients. The p-value for this difference is 0.044. The only factors for which the associated p-values are  $> 0.05$  are COPD/asthma ( $p=0.061$ ) and diabetes ( $p=0.628$ ).

Table 18: Summary of Patient Risk Factors by Treatment Group—All Antifibrinolytic Patients

Risk Factor	Treatment Group		p-Value <sup>1</sup>
	Aminocaproic and Tranexamic Acid (N=37,077) n (%)	Aprotinin (N=29,358) n (%)	
<b>Patient age</b>			<0.001#
Mean±SD	65.2 ± 10.82	66.6 ± 10.86	
Median (Range)	66.0 (18.0 - 89.0)	67.0 (19.0 - 89.0)	
<b>Age Quartile</b>			<0.001#
≤58	10444 (28.2)	7109 (24.2)	
59-67	10062 (27.1)	7574 (25.8)	
68-74	8242 (22.2)	6757 (23.0)	
≥75	8329 (22.5)	7918 (27.0)	
<b>Race category</b>			<0.001#
White	27202 (73.4)	22968 (78.2)	
Black	1998 ( 5.4)	1843 ( 6.3)	
Other	7877 (21.2)	4547 (15.5)	
<b>Male</b>	26497 (71.5)	20772 (70.8)	0.044#
<b>Emergency admission</b>	19577 (52.8)	14722 (50.1)	<0.001#
<b>Liver disease</b>	355 ( 1.0)	417 ( 1.4)	<0.001#
<b>Redo cardiac surgery</b>	602 ( 1.6)	1275 ( 4.3)	<0.001#
<b>Additional cardiac surgery</b>	7176 (19.4)	7694 (26.2)	<0.001#
<b>Previous coronary procedure</b>	4715 (12.7)	3920 (13.4)	0.015#
<b>Preexisting renal failure</b>	399 ( 1.1)	490 ( 1.7)	<0.001#
<b>Warfarin drugs</b>	214 ( 0.6)	264 ( 0.9)	<0.001#
<b>Smoking history</b>	6391 (17.2)	5334 (18.2)	0.001#
<b>Low income status</b>	1572 ( 4.2)	1035 ( 3.5)	<0.001#
<b>Hypertension</b>	24356 (65.7)	19022 (64.8)	0.015#
<b>COPD/asthma</b>	9228 (24.9)	7122 (24.3)	0.061
<b>Cancer</b>	3062 ( 8.3)	2699 ( 9.2)	<0.001#

<sup>1</sup> p-Value is from a chi square test for categorical data and a t-test for continuous data

<sup>2</sup> Only assessed on the day prior to surgery, so value is coded as 'unknown' if surgery was on the day of admission

# p<0.05

**Table 18: Summary of Patient Risk Factors by Treatment Group—All Antifibrinolytic Patients (continued)**

Risk Factor	Treatment Group		p-Value <sup>1</sup>
	Aminocaproic and Tranexamic Acid (N=37,077) n (%)	Aprotinin (N=29,358) n (%)	
<b>Antiarrhythmia drugs<sup>2</sup></b>			<0.001#
No	20721 (55.9)	17011 (57.9)	
Yes	3039 ( 8.2)	2484 ( 8.5)	
Unknown	13317 (35.9)	9863 (33.6)	
<b>Angina (use of nitrates)<sup>2</sup></b>			<0.001#
No	10107 (27.3)	8688 (29.6)	
Yes	13653 (36.8)	10807 (36.8)	
Unknown	13317 (35.9)	9863 (33.6)	
<b>Diabetes</b>	26180 (70.6)	20679 (70.4)	0.628
<b>Old MI</b>	5078 (13.7)	4371 (14.9)	<0.001#
<b>Old stroke</b>	1619 ( 4.4)	1526 ( 5.2)	<0.001#
<b>CABG day (relative to hospital admission)</b>			<0.001#
Mean±SD	3.1 ± 2.81	3.3 ± 3.09	
Median (Range)	2.0 (1.0 - 61.0)	2.0 (1.0 - 47.0)	
<b>CABG day category (relative to hospital admission)</b>			<0.001#
1	13317 (35.9)	9863 (33.6)	
2	7701 (20.8)	5989 (20.4)	
3-5	10612 (28.6)	8420 (28.7)	
6+	5447 (14.7)	5086 (17.3)	
<b>Number of vessels affected at CABG</b>			<0.001#
1	6687 (18.0)	6105 (20.8)	
2	12793 (34.5)	9447 (32.2)	
3	11485 (31.0)	8945 (30.5)	
4+	6112 (16.5)	4861 (16.6)	

<sup>1</sup> p-Value is from a chi square test for categorical data and a t-test for continuous data

<sup>2</sup> Only assessed on the day prior to surgery, so value is coded as 'unknown' if surgery was on the day of admission

# p<0.05

Many of the risk factors occur at higher rates in the aprotinin group. The exceptions are with respect to males (rates shown above), emergency admissions (52.8% in the control group vs. 50.1 in the aprotinin group), and hypertension rates (65.7% in the control group vs. 64.8 in the aprotinin group). Such a result demonstrates the need for propensity score adjustments.

### 6.8.2 Hospital Characteristics

Table 19 summarizes the hospital characteristics by treatment group. For all characteristics except rural/urban status, the p-value associated with the treatment group difference is <0.05.

Table 19: Summary of Hospital Characteristics

Risk Factor	Treatment Group		p-Value <sup>1</sup>
	Aminocaproic and Tranexamic Acid (N=37,077) n (%)	Aprotinin (N=29,358) n (%)	
<b>Hospital beds</b>			<0.001#
Mean±SD	535.1 ± 220.28	517.6 ± 227.41	
Median (Range)	463.0 (120.0 - 1836.0)	470.0 (120.0 - 1836.0)	
<b>Bed size category</b>			<0.001#
low (<400)	13667 (36.9)	10629 (36.2)	
Medium (400-649)	12002 (32.4)	9097 (31.0)	
high (650+)	11408 (30.8)	9632 (32.8)	
<b>Hospital CABG volume</b>			<0.001#
Mean±SD	2.5 ± 0.58	2.5 ± 0.57	
Median (Range)	3.0 (1.0 - 3.0)	3.0 (1.0 - 3.0)	
<b>Hospital geographic area</b>			<0.001#
MIDWEST	7364 (19.9)	4873 (16.6)	
NORTHEAST	4415 (11.9)	2526 (8.6)	
SOUTH	20403 (55.0)	18170 (61.9)	
WEST	4895 (13.2)	3789 (12.9)	
<b>Teaching hospital</b>	20819 (56.2)	15674 (53.4)	<0.001#
<b>Rural hospital</b>	2701 (7.3)	2160 (7.4)	0.721

<sup>1</sup> p-Value is from a chi square test for categorical data and a t-test for continuous data  
# p<0.05

### 6.8.3 Hospital Length-of-Stay

Table 20 displays descriptive statistics for the total hospital length of stay, the day of CABG surgery relative to hospital admission, and the number of days between CABG surgery and hospital discharge. The number and percent of patients with zero days of follow-up is also summarized.

Table 20: Hospital Length of Stay, Day of CABG Surgery, and Number of Follow-up Days

Category	Aminocaproic and Tranexamic Acid (N=37,077)	Aprotinin (N=29,358)
<b>Hospital Length of Stay</b>		
Mean $\pm$ SD	9.42 $\pm$ 7.45	10.57 $\pm$ 9.05
Median (Range)	7.0 (1-176)	8.0 (1-206)
<b>Day of CABG Surgery</b>		
Mean $\pm$ SD	3.10 $\pm$ 2.81	3.34 $\pm$ 3.09
Median (Range)	2.0 (1-61)	2.0 (1-47)
<b>Number of Follow-up Days</b>		
Mean $\pm$ SD	7.33 $\pm$ 6.57	8.24 $\pm$ 8.11
Median (Range)	6.0 (0-173)	6.0 (0-204)
<b>Zero Days of Follow-up</b>		
n (%)	116 (0.3)	237 (0.8)

On average, aprotinin patients have lengths-of-stay and follow-up periods that are roughly one day longer than non-protinin patients. The day of the CABG surgery relative to hospital admission is similar between the two groups. More than twice as many aprotinin patients have zero days of follow-up compared to non-protinin patients. Of these patients, all but 6 aprotinin patients and 1 non-protinin patient died on the day of the day of surgery. As mentioned in Section 6.3, patients with zero days of follow-up were dropped from analyses of outcomes that could not be assessed on the day of CABG surgery (acute renal failure, acute heart failure, and acute coronary revascularization).

## 6.9 Propensity Score Modeling

Table 21 lists the 25 model terms selected for all propensity score models. There were 9 primary risk factors selected with input from project statisticians, clinicians, and epidemiologists. They were forced to be included regardless of the statistical significance relative to the other model terms. The remaining model factors were selected by the stepwise selection algorithm as described in Section 3.1. The only candidate risk factors not chosen by the stepwise procedure were hypertension, diabetes, and cancer, leaving 10 terms for model inclusion. Of the 36 possible two-way interactions (9 choose 2), 6 were chosen by the procedure.

Table 21: Propensity Score Model Factors

Primary Risk Factors	Additional Risk Factors	Interaction Terms
Age quartile	Race	Gender by Redo cardiac surgery
Gender	CABG day category	Age quartile by Additional cardiac surgery
Emergency admission	Number of vessels	Additional cardiac surgery by Redo cardiac surgery
Liver disease	Smoking history	Pre-existing renal failure by Age quartile
Redo cardiac surgery	Low income status	Pre-existing renal failure by Previous coronary procedure
Additional cardiac surgery	Asthma	Liver disease by Warfarin use
Previous coronary procedure	Anti-arrhythmic medications	
Pre-existing renal failure	Angina (use of nitrates)	
User of warfarin	Old myocardial infarction	
	Old stroke	

### 6.10 Selection of Strata

As discussed in Section 3.2, hospital characteristic strata were chosen so that stratum-specific propensity scores could be developed with greater predictive ability than non-stratified scores. The chosen hospital factors were south vs. non-south, high CABG volume ( $\geq 650$ ) vs. non-high CABG volume, and teaching vs. non-teaching. This resulted in  $2^3=8$  strata. The number of patients in each treatment group for each of these 8 stratum is shown in Table 22.

Table 22: Strata and Sample Sizes

Stratum	Number of Aminocaproic and Tranexamic Acid Patients	Number of Aprotinin Patients
South, High Volume, Teaching	10,803	6,469
South, High Volume, non-Teaching	3,417	3,776
South, Low Volume, Teaching	869	3,342
South, Low Volume, non-Teaching	5,314	4,583
Non-South, High Volume, Teaching	6,093	3,491
Non-South, High Volume, non-Teaching	1,612	2,452
Non-South, Low Volume, Teaching	3,054	2,372
Non-South, Low Volume, non-Teaching	5,915	2,873
<b>Total</b>	<b>37,077</b>	<b>29,358</b>

Overall, the control group is 26% larger than the aprotinin group. Identifying the strata where this sampling ratio (1:1.26) is noticeably different substantiates the need for stratum-specific propensity score models. Examples are the South, Low Volume, Teaching stratum (ratio=1:0.26) and the Non-South, High Volume, non-Teaching stratum (ratio=1:0.66) where there are considerably more aprotinin patients; and the Non-South, Low Volume, non-Teaching

stratum (ratio=1:2.06) where the number of control patients is more than double the number of aprotinin patients.

### 6.11 Assessment of Propensity Score Balance

Post-adjustment balance was assessed as described in Section 3.3. One diagnostic used was logistic regression models that treated the risk factors as responses and the decile, treatment group, and decile-by-treatment group interaction as model factors. In the investigation, the treatment effect was not found to be significant at the 0.05 level in any case. The treatment-by-decile interaction was significant for the age quartile factor for 2 of the 8 strata. With the possible exception of some of the 10<sup>th</sup> deciles in some of the strata, box-plots revealed very good propensity score balance across the deciles. As a result of the good balance, no patients were dropped from the primary analysis because of inadequate balance.

### 6.12 Primary Analysis of Outcomes

Table 23 displays crude (unadjusted) outcome rates, risk differences (RDs), and risk ratios (RRs) for each of the six outcomes. The sub-sections that follow provide results for each outcome adjusted for hospital characteristic and propensity score decile strata.

Table 23: Crude (Unadjusted) Outcome Rates, Risk Differences, and Risk Ratios

Risk Factor	Treatment Group		Risk Difference (95% CI)	Risk Ratio (95% CI)
	Aminocaproic and Tranexamic Acid (N=37,077) n (%)	Aprotinin (N=29,358) n (%)		
Death	940/37077 (2.5)	1366/29358 (4.7)	0.021 (0.018, 0.024)	1.84 (1.69, 1.99)
Stroke	574/37077 (1.5)	619/29358 (2.1)	0.006 (0.004, 0.008)	1.36 (1.22, 1.52)
Acute Renal Failure <sup>1,2</sup>	609/36567 (1.7)	889/28639 (3.1)	0.014 (0.012, 0.017)	1.86 (1.68, 2.06)
Acute Heart Failure <sup>1</sup>	4480/36961 (12.1)	4056/29121 (13.9)	0.018 (0.013, 0.023)	1.15 (1.10, 1.20)
Acute Coronary Revascularization <sup>1</sup>	95/36961 (0.3)	88/29121 (0.3)	0.000 (-0.000, 0.001)	1.18 (0.88, 1.57)

<sup>1</sup> Only patients with post-surgery follow-up are included in the analysis  
<sup>2</sup> Patients with pre-existing renal failure are excluded from the analysis

#### 6.12.1 Death

Figure 20 and Figure 21 display the RDs and RRs, respectively, by stratum and overall for the outcome of death. Results are consistent across all 8 strata. In all strata, the risk is higher among aprotinin patients. In all but one stratum for the risk difference (the second smallest one) and all but two strata for the risk ratio (the smallest two) the CIs do not overlap the reference point of equality between groups (0 for the RD and 1 for the RR). The overall risk difference estimate of 1.64 indicates that one can expect an additional 1.64 deaths in the aprotinin group compared to the control groups per 100 patients in each group. The overall risk ratio of 1.54 indicates that the risk of death is 54% greater in the aprotinin group compared to the control group.

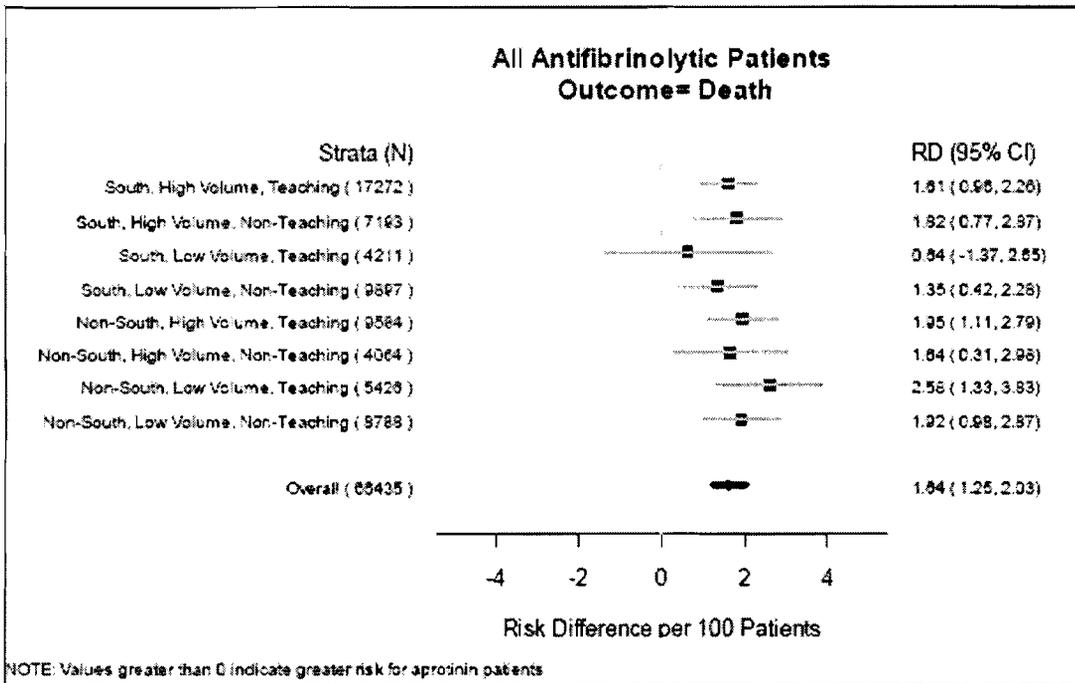


Figure 20: Risk Differences for Death

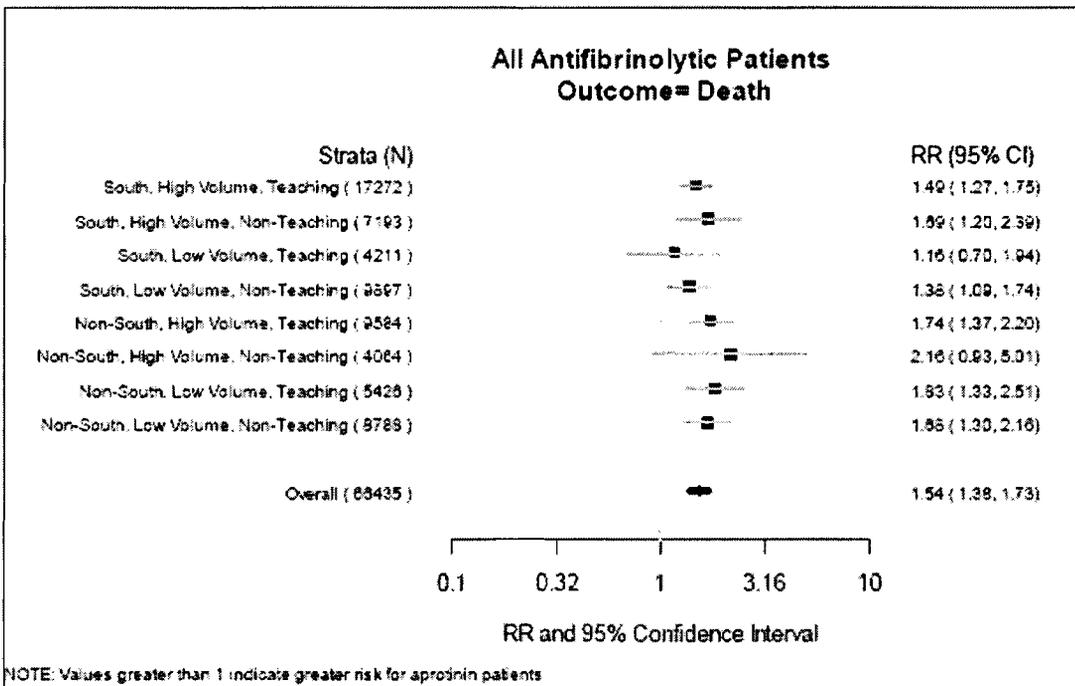


Figure 21: Risk Ratios for Death

### 6.12.2 Stroke

Figure 22 and Figure 23 display the RDs and RRs, respectively, by stratum and overall for the outcome of stroke. Results are relatively consistent across all 8 strata. The risk is higher among aprotinin patients in all but one stratum. The 95% CIs contain the point of equality in all but 2 strata (for both the RD and RR). The overall 95% CI lies above the point of equality for both the RD and RR. The overall RD estimate is 0.41. The overall RR estimate is 1.24.

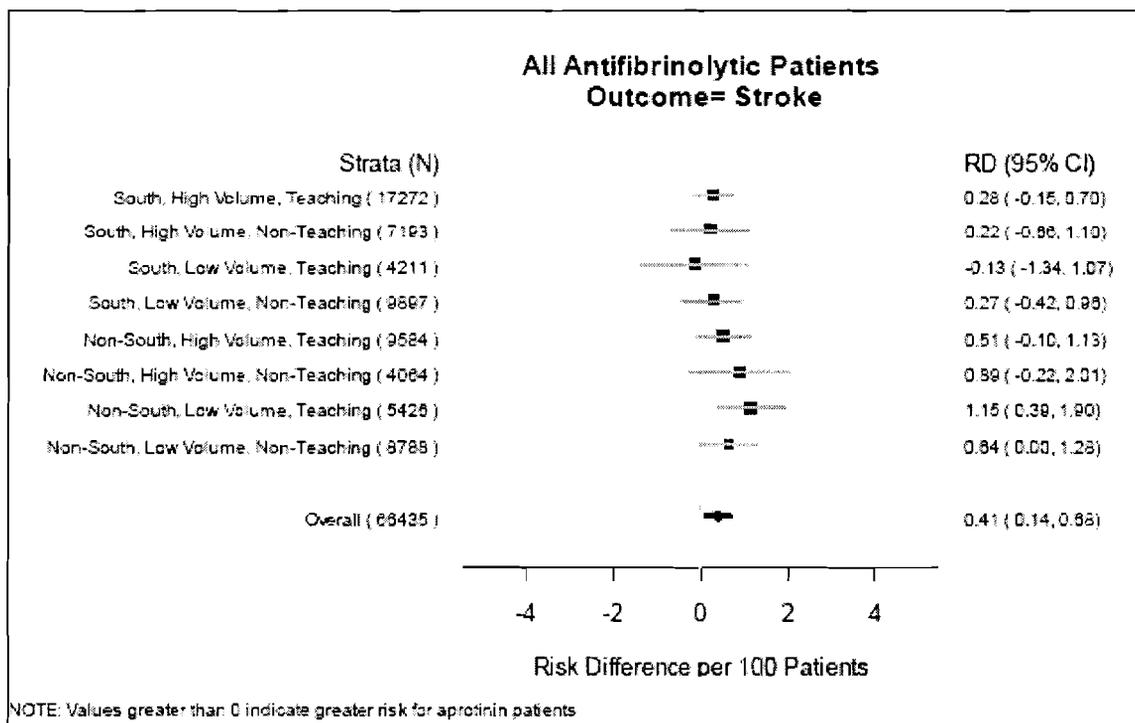


Figure 22: Risk Differences for Stroke

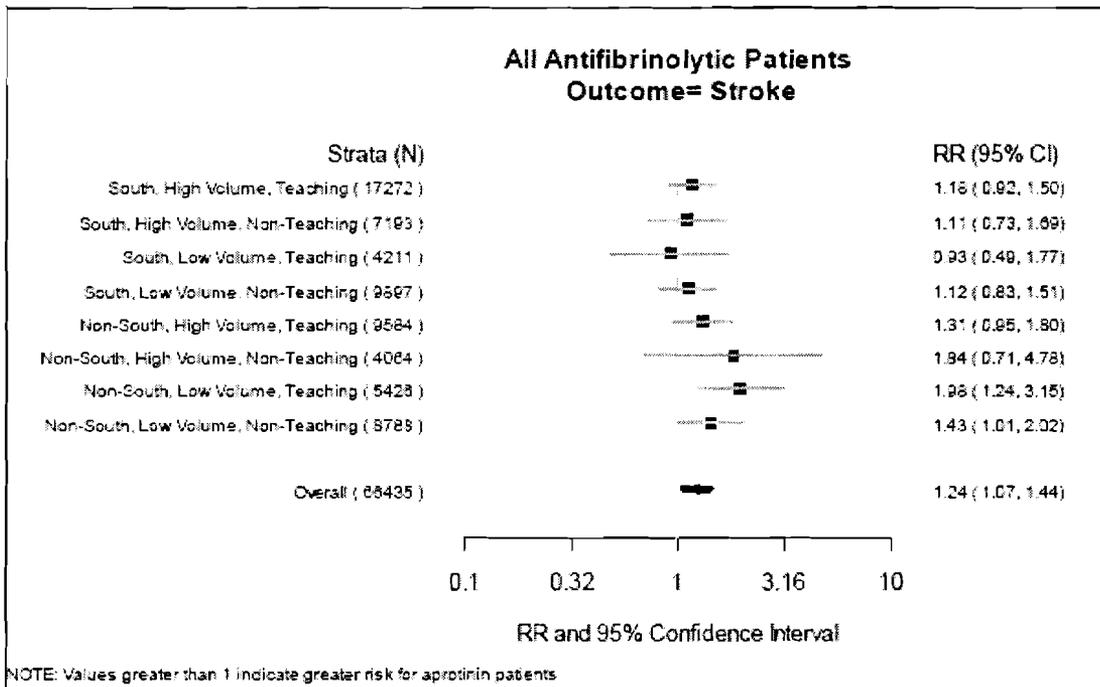


Figure 23: Risk Ratios for Stroke

### 6.12.3 Acute Renal Failure

Figure 24 and Figure 25 display the RDs and RRs, respectively, by stratum and overall for the outcome of acute renal failure. Results are consistent across all 8 strata. For all strata and for the overall result, the risks are higher among aprotinin patients and the 95% CIs do not contain the point of equality for any RD or RR. The overall RD estimate is 1.40. The overall RR estimate is 1.82.

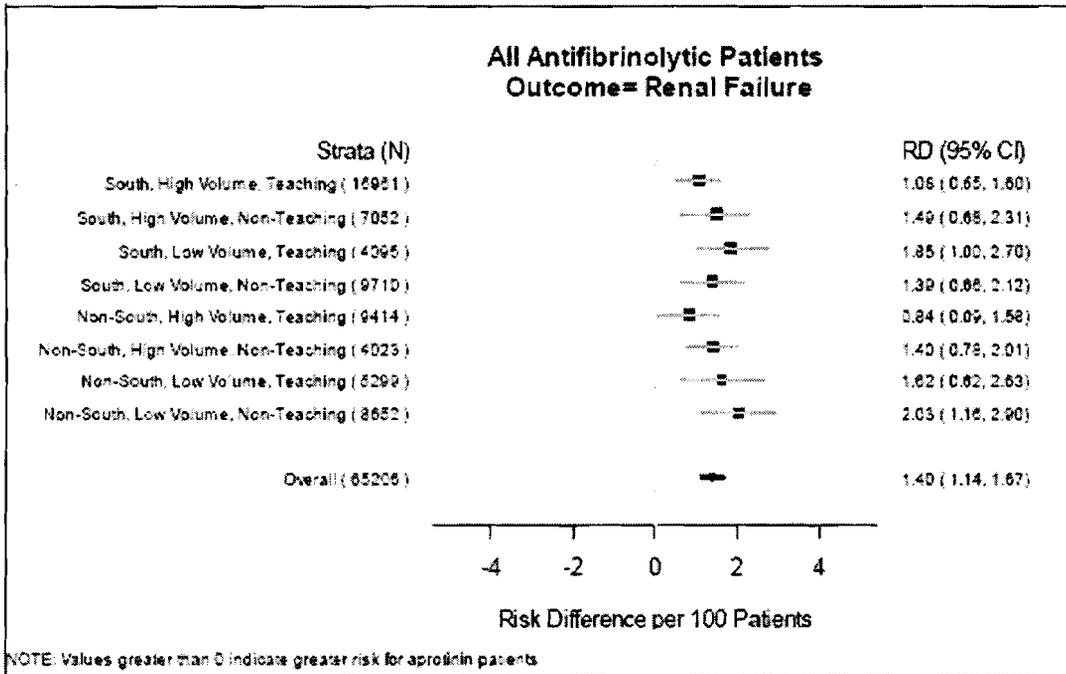


Figure 24: Risk Differences for Acute Renal Failure

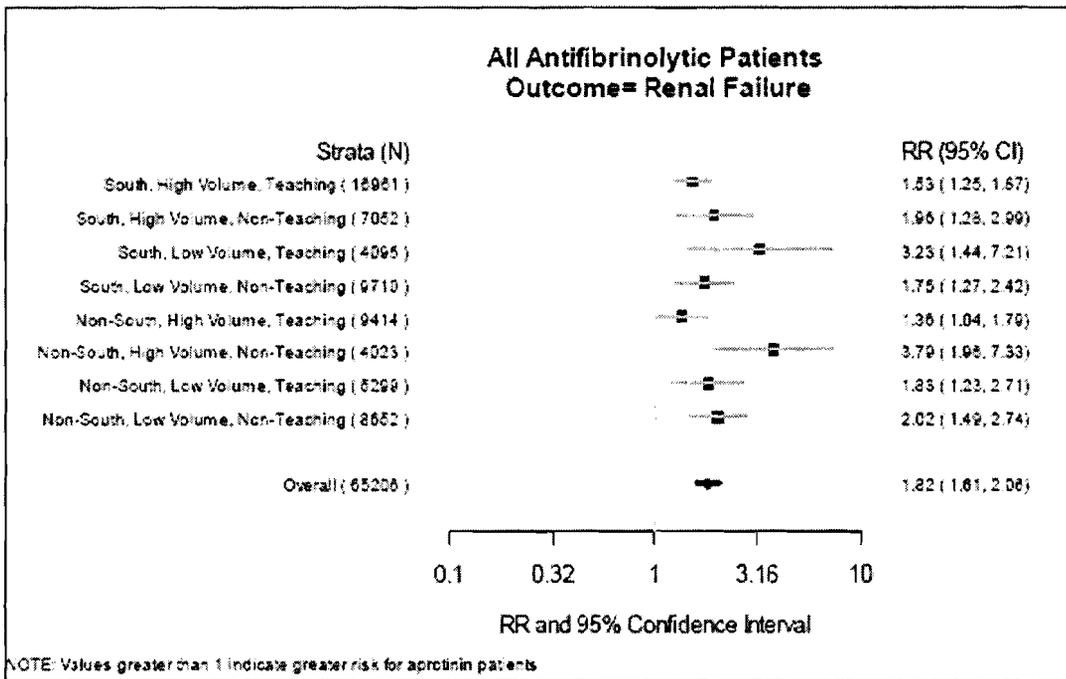


Figure 25: Risk Ratios for Acute Renal Failure

### 6.12.4 Acute Heart Failure

Figure 26 and Figure 27 display the RDs and RRs, respectively, by stratum and overall for the outcome of acute heart failure. Results are relatively inconsistent across the 8 strata, but consistent between RD and RR results. For both the RD and RR, estimates for 6 strata indicate a higher risk among aprotinin patients. For half of those 6 strata, the 95% CI does not contain the point of equality. The overall risk is higher among aprotinin patients and the 95% CIs do not overlap the point of equality. The overall RD estimate is 2.30. The overall RR estimate is 1.20.

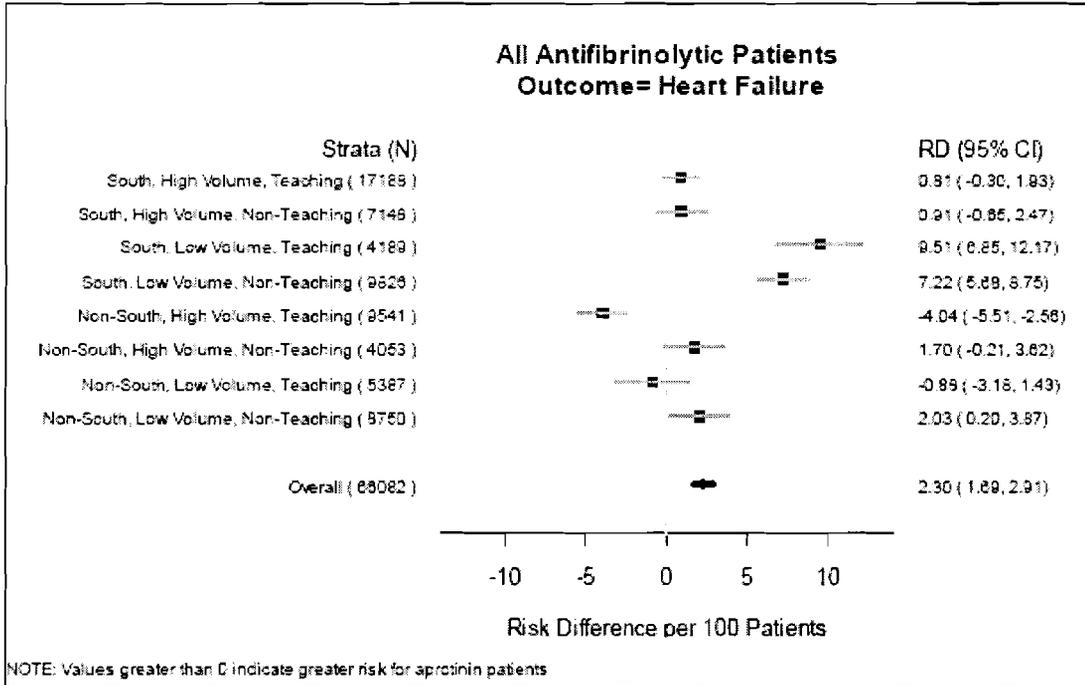
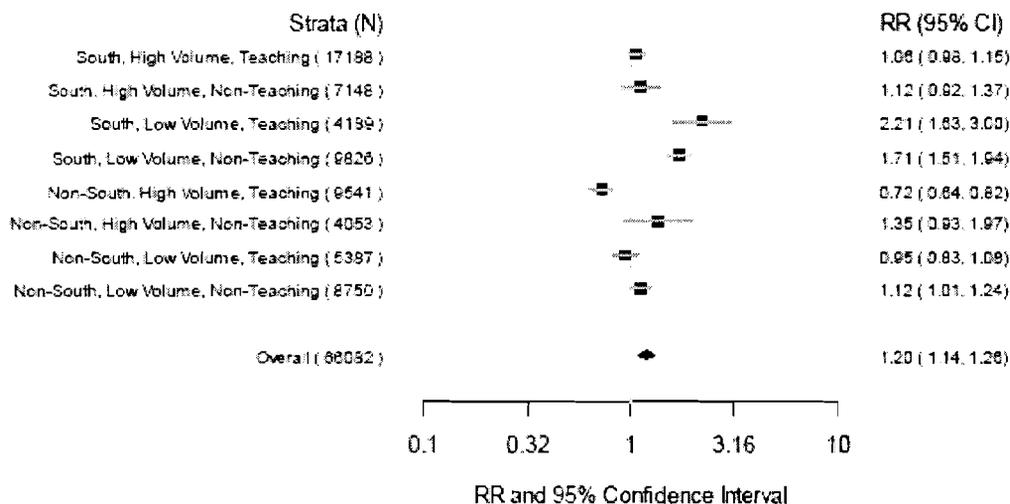


Figure 26: Risk Differences for Acute Heart Failure

**All Antifibrinolytic Patients  
Outcome= Heart Failure**



NOTE: Values greater than 1 indicate greater risk for aprotinin patients

Figure 27: Risk Ratios for Acute Heart Failure

**6.12.5 Acute Coronary Revascularization**

Figure 28 and Figure 29 display the RDs and RRs, respectively, for acute coronary revascularization. Among the 8 strata, results in 6 suggest a higher risk among aprotinin patients, results in 1 suggests a lower risk, and results in 1 suggests no difference. The 95% CIs contain the point of equality for all but one stratum. For the overall estimates, the lower limits of 95% CIs are just above the points of no difference. The overall RD estimate is 0.10 and the overall RR estimate is 1.47.

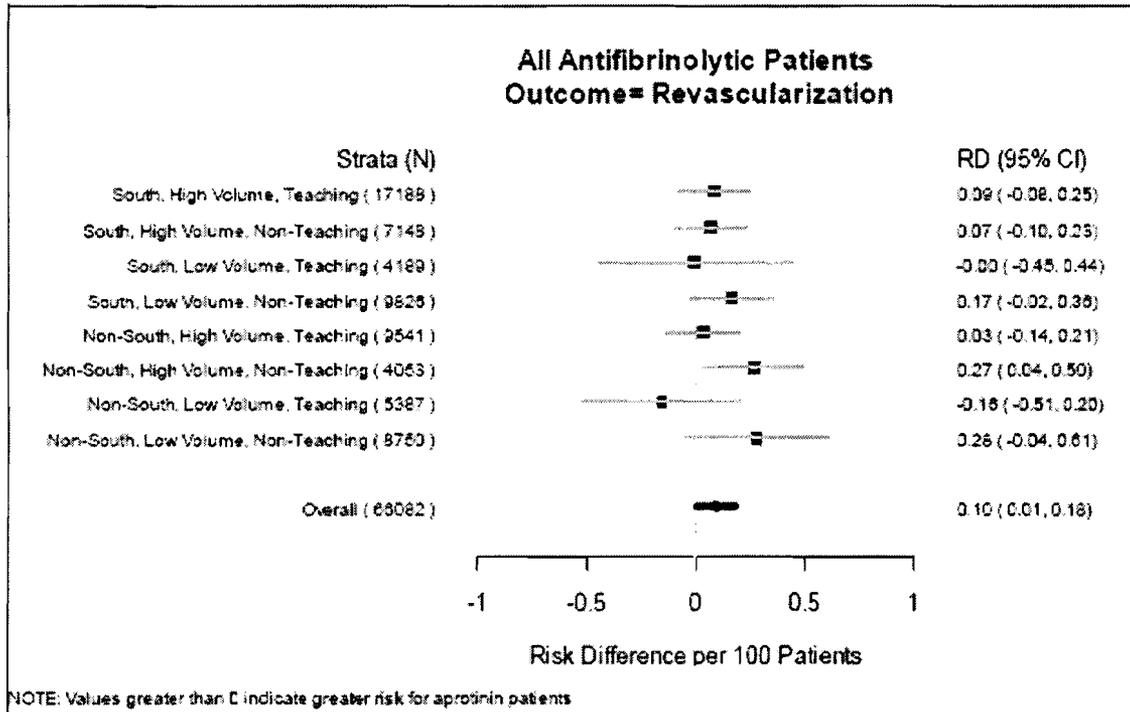


Figure 28: Risk Differences for Acute Coronary Revascularization

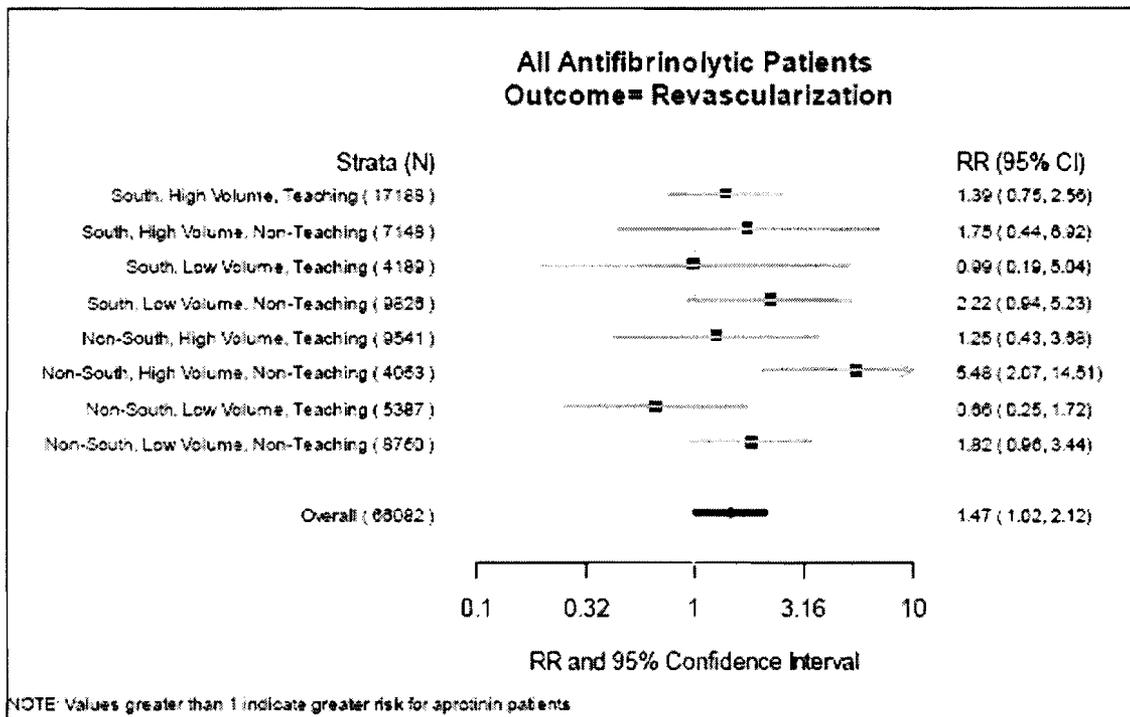


Figure 29: Risk Ratios for Acute Coronary Revascularization

### 6.13 Sensitivity Analyses

Four primary sensitivity analyses were conducted. They as follows:

- Analysis of Patients with  $\geq 1$  Day in the Hospital Prior to CABG Surgery
- Analysis of Patients with  $\geq 3$  Days in the Hospital Prior to CABG Surgery
- Analysis of Patients in Propensity Score Deciles 1-9
- Analysis of Outcomes per Patient Weeks

Details pertaining to these analyses are described in Section 6.6. Table 24 and Table 25 summarize the RDs and RRs, respectively, from each of these analyses. In most cases, conclusions are unchanged from the primary analysis with respect to the direction of the estimate (positive or negative for RDs,  $>1$  or  $<1$  for RRs) and whether or not the confidence intervals contain the point of no difference between groups. Exceptions are as follows:

- All sensitivity analyses of Acute Coronary Revascularization resulted in RD CIs that overlap 0 and RR CIs that overlap 1. The RD point estimates were slightly lower than those from the primary analysis (RD=0.10). The RR point estimate for the analysis of patients in deciles 1-9 was lower than the primary analysis point estimate.
- The sensitivity analysis of Acute Heart Failure for patients with  $\geq 3$  hospital days prior to their CABG surgery resulted in a RD CI that overlaps 0 and a RR CI that overlaps 1.
- The follow-up time-adjusted sensitivity analysis of Stroke resulted in a RD CI that overlaps 0 and a RR CI that overlaps 1.

Table 24: Sensitivity Analysis Risk Differences

Outcome	Risk Difference (95% CI)			
	Patients with $\geq 1$ Pre-surgery Day	Patients with $\geq 3$ Pre-surgery Days	Patients in Deciles 1-9	Follow-up Time Adjusted (Events Per Patient-Weeks)
Death	2.14 (1.61, 2.67)	1.88 (0.84, 2.91)	1.37 (1.01, 1.73)	1.06 (0.74, 1.38)
Stroke	0.46 (0.12, 0.79)	0.61 (0.08, 1.13)	0.39 (0.11, 0.68)	0.22 (-0.00, 0.43)
Acute Renal Failure <sup>1,2</sup>	1.46 (1.13, 1.79)	0.98 (0.16, 1.81)	1.22 (0.95, 1.49)	1.07 (0.84, 1.31)
Acute Heart Failure <sup>1</sup>	1.60 (0.80, 2.40)	0.74 (-0.64, 2.11)	2.02 (1.42, 2.63)	1.14 (0.58, 1.69)
Acute Coronary Revascularization <sup>1</sup>	0.09 (-0.02, 0.19)	0.09 (-0.01, 0.20)	0.08 (-0.02, 0.18)	0.07 (-0.01, 0.15)

<sup>1</sup> Only patients with post-surgery follow-up are included in the analysis

<sup>2</sup> Patients with pre-existing renal failure are excluded from the analysis

Table 25: Sensitivity Analysis Risk Ratios

Outcome	Risk Ratio (95% CI)			Follow-up Time Adjusted (Events Per Patient-Weeks)
	Patients with $\geq 1$ Pre-surgery Day	Patients with $\geq 3$ Pre-surgery Days	Patients in Deciles 1-9	
Death	1.63 (1.42, 1.87)	1.43 (1.14, 1.79)	1.52 (1.35, 1.71)	1.43 (1.27, 1.61)
Stroke	1.25 (1.05, 1.48)	1.30 (1.02, 1.64)	1.24 (1.05, 1.45)	1.16 (0.99, 1.34)
Acute Renal Failure <sup>1, 2</sup>	1.81 (1.57, 2.08)	1.35 (1.02, 1.79)	1.77 (1.56, 2.02)	1.68 (1.49, 1.90)
Acute Heart Failure <sup>1</sup>	1.13 (1.06, 1.20)	1.05 (0.96, 1.15)	1.18 (1.12, 1.25)	1.11 (1.05, 1.16)
Acute Coronary Revascularization <sup>1</sup>	1.47 (0.89, 2.41)	1.76 (0.96, 3.21)	1.36 (0.92, 2.00)	1.37 (0.96, 1.97)

<sup>1</sup> Only patients with post-surgery follow-up are included in the analysis  
<sup>2</sup> Patients with pre-existing renal failure are excluded from the analysis

### 6.14 Findings in Special Subgroups/Populations

Six sets of subgroup analyses were conducted. The subgroups were males, females, non-whites (which includes blacks and patients of “other” race), whites (Caucasians), the elderly (patients  $\geq 65$  years of age), and the non-elderly (patients  $< 65$  years of age). All outcomes were analyzed for each subgroup.

Table 26 provides risk ratios from these analyses. In this table, results from subgroups where patients are considered to be at a higher baseline risk of mortality and cardiovascular and renal outcomes (males, non-whites, and the elderly) are presented beside results from subgroups of patients in the opposite group (females, whites, and the non-elderly, respectively).

Males represent 71% of the total study population, non-whites represent 25% of the total study population, and elderly patients represent 57% of the total patient population. In general, results in individual subgroups are similar to the overall results and similar to results involving patients in the opposite group. For strokes, patients in the higher baseline risk subgroups have lower RRs compared to patients in the opposite groups (RRs=1.17, 1.18, and 1.21 for males, non-whites, and the elderly, respectively, compared to RRs=1.30, 1.25, and 1.26 for females, whites, and the non-elderly, respectively). For all subgroups, the lower limit of the 95% CI for acute coronary revascularization is less than 1.

**Table 26: Subgroup Analysis Risk ratio Results**

Outcome	Characteristic (N w/ characteristic)	Risk Ratio (95% CI)	
		Without Characteristic	With Characteristic
Death	Males (N=47,269)	1.66 (1.37, 2.03)	1.49 (1.29, 1.73)
	Non-whites (N=16,265)	1.61 (1.42, 1.83)	1.54 (1.25, 1.91)
	Elderly <sup>1</sup> (N=37,616)	1.92 (1.56, 2.37)	1.54 (1.36, 1.75)
Stroke	Males (N=47,269)	1.29 (0.93, 1.79)	1.18 (0.98, 1.42)
	Non-whites (N=16,265)	1.29 (1.10, 1.51)	1.33 (0.98, 1.82)
	Elderly <sup>1</sup> (N=37,616)	1.28 (0.96, 1.69)	1.26 (1.06, 1.48)
Acute Renal Failure <sup>2,3</sup>	Males (N=46,537)	1.97 (1.63, 2.38)	1.81 (1.56, 2.11)
	Non-whites (N=15,779)	1.85 (1.60, 2.14)	1.76 (1.35, 2.28)
	Elderly <sup>1</sup> (N=36,914)	1.61 (1.29, 2.01)	1.98 (1.72, 2.28)
Acute Heart Failure <sup>2</sup>	Males (N=47,079)	1.16 (1.08, 1.26)	1.24 (1.16, 1.32)
	Non-whites (N=16,185)	1.18 (1.11, 1.26)	1.18 (1.07, 1.30)
	Elderly <sup>1</sup> (N=37,364)	1.33 (1.22, 1.46)	1.16 (1.09, 1.22)
Acute Coronary Revascularization	Males (N=47,079)	1.29 (0.73, 2.28)	1.27 (0.69, 2.34)
	Non-whites (N=16,185)	1.25 (0.70, 2.22)	1.34 (0.73, 2.45)
	Elderly <sup>1</sup> (N=37,364)	1.53 (0.81, 2.87)	1.43 (0.94, 2.18)

<sup>1</sup> Defined as ≥65 years of age  
<sup>2</sup> Only patients with post-surgery follow-up are included in the analysis  
<sup>3</sup> Patients with pre-existing renal failure are excluded from the analysis

### 6.15 Discussion

Table 27 provides a comparison of crude results, the primary i3 Drug Safety results (from the preliminary report), and results from this review. The i3 Drug Safety results are derived from the treatment effect in a multivariate logistic regression model. Odds ratios are therefore being used to estimate the risk ratio, or relative risk. The results in this review are based on a stratified propensity score analysis. Although the point estimates vary across methods, all results suggest that use of aprotinin carries with it an increased risk of mortality, stroke, acute renal failure, and acute heart failure, as indicated by the CIs that lie above the value of 1. For acute coronary revascularization, the point estimates range from 1.17-1.47, but the CIs include the value of 1 for the crude and i3 Drug Safety results, as well as for all sensitivity analysis results and all subgroup results.

**Table 27: Comparison of Crude Results, i3 Drug Safety Results, and FDA Results**

Outcome	Risk ratio (95% CI)		
	Crude	i3	FDA
Death	1.84 (1.69, 1.99)	1.68 (1.53, 1.84)	1.54 (1.38, 1.73)
Stroke	1.36 (1.22, 1.52)	1.20 (1.07, 1.35)	1.24 (1.07, 1.44)
Acute Renal Failure	1.87 (1.68, 2.06)	1.70 (1.55, 1.86)	1.82 (1.61, 2.06)
Acute Heart Failure	1.15 (1.10, 1.20)	1.08 (1.03, 1.14)	1.20 (1.14, 1.26)
Acute Coronary Revascularization	1.17 (0.88, 1.56)	1.30 (0.96, 1.76)	1.47 (1.02, 2.12)

If the assumption that the aprotinin patients are higher-risk is true, then one would expect the RRs from the i3 Drug Safety and FDA results to be lower than the crude rates. However, this

was not the case for acute heart failure and acute coronary revascularization. For the remaining three original events (death, stroke, and acute renal failure), both the FDA propensity score estimates and the i3 estimates are lower than the crude rates. Of these, only the FDA estimate for death is lower than the i3 estimate. The FDA and i3 CIs for stroke overlap considerably while roughly one-half of the FDA and i3 intervals for acute renal failure overlap.

## 6.16 Summary and Conclusions

### 6.16.1 Statistical Issues and Collective Evidence

The primary analysis used for the i3 Drug Safety report made use of a multivariate logistic regression model. For this review, propensity score methods were used.

A limitation of this study compared to those by Mangano and Karkouti is the non-use of certain factors that were shown in those papers to contribute to the decision to use aprotinin or not. Such factors include creatinine levels, hemoglobin levels, platelet counts, use of aspirin, use of heparin, use of antithrombotics, and previous congestive heart failure.

The outcome of acute renal failure was primarily based on the presence of dialysis procedure codes. Since creatinine clearance would commonly be used for a proper medical diagnosis of renal failure, and since dialysis could be performed for situations other than renal failure, the accuracy of this outcome definition is uncertain. So while any need for dialysis is considered an adverse clinical outcome, by itself it does not constitute a diagnosis of renal failure.

### 6.16.2 Conclusions and Recommendations

For this study, hospital claims data were used to compare safety outcomes among patients who received an antifibrinolytic agent while undergoing CABG surgery between the timeframe of January 1, 2003 and March 31, 2006. Patients receiving aprotinin (N=29,358) were compared to patients receiving either aminocaproic acid (N=35,719) or tranexamic acid (N=1,358). The outcomes that were measured include all-cause in-hospital death, stroke (excluding hemorrhagic stroke), acute renal failure (indicated by the presence of codes for hemo- or peritoneal dialysis or hemofiltration), acute heart failure (indicated by the presence of codes for dobutamine use or left ventricular assist device use), and acute coronary revascularization (indicated by the presence of codes for thrombolysis, PTCA, or redo CABG). After adjusting for baseline risk, the results of this review revealed an increased risk associated with aprotinin for death (RR=1.54; 95% CI 1.38, 1.73), stroke (RR=1.24; 1.07, 1.44), acute renal failure (RR=1.82; 1.61, 2.06), acute heart failure (RR=1.20; 1.14, 1.26), and acute coronary revascularization (RR=1.47; 1.02, 2.12). Results were similar to those from the i3 Drug Safety preliminary report. It should be noted that in many cases the large sample size resulted in very narrow confidence intervals.

One of the sensitivity analyses carried out in this review considered the effect of only analyzing patients with  $\geq 1$  and  $\geq 3$  hospital days prior to surgery, thereby allowing for the possibility that more baseline covariate information could be observed which may impact the propensity score estimation. Another analysis adjusted the rates on a patient-week basis, thereby adjusting for the longer follow-up period seen among aprotinin patients, which was on average approximately one day longer. A final analysis excluded subjects in the 10th propensity

score deciles across strata, which created greater overall balance between comparison groups. None of the results from these analyses resulted in any significant change to the overall results. The overall conclusion from the FDA analysis was similar to those reported in the preliminary report. The review of the final study report is ongoing.

Using this study alone would be inappropriate for drawing any firm conclusion regarding whether the use of aprotinin during CABG surgery can be regarded as safe. Rather, the body of evidence from all studies (including randomized clinical trials, other observational studies, and other post-marketing data) should be considered.

## APPENDIX: FDA RISK FACTORS FOR THE MANGANO AND KARKOUTI STUDIES

Table A1: Mangano Study: FDA primary and sensitivity risk factors.

### Primary Risk Factors

Demo: Age

Demo: Gender

Medical History: Diabetes

Medical History: Hematologic disorder

Medical History: Liver disease

Medical History: Platelet abnormality

Medical History: Renal disease

Surgical History: Previous sternotomy

Preop Medications: Anti-thrombotics

Preop Medications: Aspirin

Preop Medications: Heparin

Preop Medications: Warfarin

Preoperative Factors: Angina

Preoperative Factors: Congestive heart failure

Preoperative Factors: Creatinine

Preoperative Factors: Ejection fraction  $\leq 44\%$

Preoperative Factors: MI

Surgical: CABG only

Surgical: Elective/Urgent

Surgical: Number of graphs  $\geq 3$

### Sensitivity Risk Factors

Demo: Body surface area\*

Medical History: Angina\*

Medical History: Cardiomyopathy

Medical History: Congestive heart failure\*

Medical History: Heart block

Medical History: Hypertension\*

Medical History: MI

Medical History: Peripheral vascular disease

Medical History: Pulmonary disease\*

Medical History: Smoking

Medical History: Stroke

Medical History: Syncope

Medical History: TIA

Medical History: Valve disease

Medical History: Ventricular fibrillation

Surgical History: Abdominal surgery

Surgical History: Aortic vascular\*

Surgical History: CABG

Surgical History: Carotid endarterectomy  
Surgical History: Coronary atherectomy  
Surgical History: Intracoronary stent  
Surgical History: Noncoronary angioplasty/stent\*  
Surgical History: Other vascular surgery  
Surgical History: PTCA\*  
Surgical History: Valve surgery\*  
Preoperative Factors: NYHA Classification  
Preoperative Factors: Stroke  
Preoperative Factors: Valve abnormality  
Surgical: CABG + other than valve  
Surgical: CABG + valve

\* Indicates selected in stepwise regression.

Table A2: Karkouti study: Primary and sensitivity risk factors.

**Primary Risk Factors**

Demo: Age

Demo: Gender

Medical History: Diabetes

Surgical History: Previous sternotomy

Preop Medication:s Heparin

Preop Medications: Aspirin

Preoperative Factors: Angina

Preoperative Factors: Artial fibrillation

Preoperative Factors: Congestive heart failure

Preoperative Factors: Creatinine

Preoperative Factors: Ejection fraction <40%

Preoperative Factors: Endocarditis

Preoperative Factors: Hb level

Preoperative Factors: INR

Preoperative Factors: MI

Preoperative Factors: PLT count

Preoperative Factors: Recent catheterization

Preoperative Factors: Shock

Surgical: CABG only

Surgical: Elective/Urgent

Surgical: Number of graphs  $\geq 3$

**Sensitivity Risk Factors**

Demo: Body surface area

Medical History: Cholesterol

Medical History: Hypertension

Medical History: Peripheral vascular disease

Medical History: Smoking

Medical History: Stroke or TIA

Preoperative Factors: Angina\*

Preoperative Factors: NYHA classification)

Surgical History: Previous sternotomy (count)\*

Surgical: Procedure type

\* Indicates selected in stepwise regression.

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