Trasylol® (Aprotinin Injection) Briefing Document

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1. Executive Summary

Trasylol® (aprotinin injection) is indicated for prophylactic use to reduce peri-operative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery (see US prescribing information in Appendix 1). Aprotinin has been studied and used in Europe for almost 50 years in a variety of clinical conditions. For nearly two decades, it has been used in cardiac surgery to reduce blood loss and the need for transfusion. Extensive data from Bayer and published studies, including randomized clinical trials, meta-analyses, and observational studies, have in general documented the effectiveness and safety of aprotinin.

Two retrospective observational studies published in 2006 reported that aprotinin use during cardiac surgery was associated with an increased risk of cardiac and cerebral adverse events (1) as well as renal dysfunction.(1, 2) In the first study published by Mangano et al (see Appendix 2), aprotinin compared to no hemostatic therapy among some CABG patients was reported to be associated with an increased risk for a cardiovascular event (myocardial infarction or heart failure), cerebrovascular event (stroke or encephalopathy), or renal event (post-operative elevation of serum creatinine or renal failure).(1) In the second study, Karkouti et al (see Appendix 3) reported that aprotinin use compared to tranexamic acid use among a cohort of very high-risk patients undergoing cardiac surgery was associated with an increased risk of renal dysfunction (post-operative serum creatinine elevations or new need for dialysis).(2) Karkouti et al reported no increased risk of cardiac or cerebrovascular events among patients receiving aprotinin.

In contrast to randomized controlled trials, in observational studies the selection of specific treatments as well as the subsequent development of adverse events can be influenced by the patient's demographic and medical conditions.(3) Strategies used to minimize confounding, which are not always easy to apply appropriately, include

techniques such as matching patients according to potential confounders or creating subclasses in which these potential confounders are balanced.(3, 4) However, one can only control for known and measured factors. In addition, the selection of the specific treatment as well as the evaluation of its efficacy and safety may still be biased because the treatment assignment is known.(5) Furthermore, based on the information provided in the paper, the study by Mangano et al has methodological flaws that limit the ability to interpret the results. These include misapplication of propensity scores in an attempt to adjust for underlying imbalances in risk factors, excluding patients from the analyses without apparent justification, and use of non-standard outcome definitions. In addition, although Mangano et al state that the three treatments studied (aprotinin, aminocaproic acid, and tranexamic acid) are equally effective at limiting blood loss or transfusion requirements, no analysis is provided to support this conclusion.

The safety conclusions drawn by Mangano et al are not consistent with those from the Bayer database of prospective, randomized, double-blind, placebo-controlled trials or from numerous other clinical trials, meta-analyses, and observational studies that have been published over many years. These results are outlined in this briefing document. The renal safety conclusions published by Karkouti et al cannot necessarily be applied to general clinical practice because the study included only very high-risk patients undergoing cardiac surgery. However, the results with respect to serum creatinine elevations are consistent with data from Bayer's database and from other published studies.

Subsequent to the publication of the studies by Mangano et al and Karkouti et al, the FDA has scheduled a meeting of the Cardiology and Renal Drugs Advisory Committee for 21 Sep 2006, to review the efficacy, safety, and benefit-risk analysis for the use of aprotinin among patients undergoing CABG surgery.

In general, the results from Bayer studies and from other published trials, meta-analyses, and observational studies demonstrate the efficacy and safety of aprotinin when used among patients undergoing CABG surgery utilizing cardiopulmonary

bypass. Aprotinin consistently reduces blood loss, transfusion requirements, and the need for re-operations for diffuse post-operative bleeding.

Although blood and blood products are important therapeutic agents, there is evidence that stored blood does not function as well as fresh blood and numerous infectious (including viral and bacterial infections) and noninfectious complications (such as transfusion-related acute lung injury and hemolytic transfusion reactions), some which can result in death, are associated with transfusion. In addition, blood supplies can be limited, and cardiac surgery places a large demand on the available blood supply. Patients undergoing cardiopulmonary bypass (that is, extracorporeal circulation) during cardiac surgery are at increased risk of excessive peri-operative blood loss and often require transfusions of donor blood and blood products.(6-8) Overall, 10 to 20% of the transfusions in the US occur during cardiac surgery.(9)

The results from the Bayer US randomized clinical trial database demonstrated that the full-dose aprotinin regimen reduced blood loss and need for transfusion among patients undergoing primary (no prior cardiac surgery) and repeat (history of prior cardiac surgery) CABG surgery. Patients receiving full-dose aprotinin required the transfusion of significantly fewer RBC units, platelet units, fresh frozen plasma units, and cryoprecipitate units.

The half-dose aprotinin regimen reduced blood loss and need for transfusion among patients undergoing primary and repeat CABG surgery. Patients undergoing primary CABG surgery who received this regimen required the transfusion of fewer RBC units, platelet units, fresh frozen plasma units, and cryoprecipitate units. Patients undergoing repeat CABG surgery required the transfusion of significantly fewer RBC units, platelet units, and fresh frozen plasma units.

Among patients undergoing primary or repeat CABG surgery who were receiving aspirin, both the full-dose and half-dose regimens of aprotinin reduced the need for transfusion. Furthermore, full-dose aprotinin reduced the need for re-operations for diffuse bleeding among patients undergoing primary CABG surgery.

It can be expected that the marked reduction in the number of blood or blood product units transfused among patients receiving aprotinin would lead to fewer transfusion-related complications. Similarly, the need for fewer re-operations due to diffuse bleeding should lead to fewer complications associated with these procedures. However, none of the aprotinin studies were specifically designed to evaluate the effect of aprotinin on complications associated with transfusions or with subsequent surgeries, and the FDA never requested such endpoints.

Other non-Bayer studies have shown that patients treated with aprotinin may have decreased risk of stroke or cognitive dysfunction as well as benefits associated with the anti-inflammatory effects of full-dose aprotinin. The decline in the incidence of stroke after CABG surgery that has been associated with aprotinin therapy should translate into clinical benefit for these patients. Again, however, the studies were not designed or sized to evaluate the effect of aprotinin on complications associated with post-operative strokes.

Furthermore, studies have shown that full-dose aprotinin use among patients undergoing CABG surgery who were receiving clopidogrel decreased bleeding and need for transfusion.

The global Bayer database shows that aprotinin was generally well tolerated among patients undergoing primary or repeat CABG surgery. The adverse events reported were frequent sequelae of cardiac surgery and not necessarily attributable to aprotinin.

During the initial clinical development of aprotinin, adverse event reports suggested an increased risk of myocardial infarction among aprotinin-treated patients undergoing repeat CABG surgery in Study D89-004. Possible explanations for the increased incidence of myocardial infarction in this study include inadequate heparinization among patients in the aprotinin group because of the effect of aprotinin on celite-activated clotting times, variability in the definition and reporting of myocardial infarctions, and a higher risk patient population.

Aprotinin, in the presence of heparin, prolongs celite-based activated clotting times. In the presence of an artificially prolonged activated clotting time, it would be easy to inadvertently under-heparinize patients receiving aprotinin. In Study D89-004, patients were anticoagulated using local monitoring procedures (300 units of heparin per kilogram body weight initially followed by additional doses if the activated clotting time fell below 400 seconds) and not the protocol-specified method (fixed-heparin dose). The Trasylol prescribing information recommends specific methods to monitor anticoagulation to ensure adequate heparinization during cardiopulmonary bypass.

Subsequent analyses and clinical trials demonstrated that with adequate monitoring of anticoagulation and use of a standardized myocardial infarction definition and data collection methods, aprotinin was not associated with an increased risk of myocardial infarction.

Seven studies prospectively evaluated graft patency. Although one international multicenter trial (Study D92-048) showed significant differences in graft patency overall, the rates were similar for aprotinin-treated patients and placebo-treated patients enrolled at US sites. In addition, there were no differences in the number of deaths or myocardial infarctions between aprotinin-treated and placebo-treated patients at US and non-US sites in this study. These data are presented in the Trasylol prescribing information.

Numerous, but not all, published controlled studies have demonstrated transient changes in renal function but no enhanced risk of renal failure associated with aprotinin therapy. In the Bayer global database of randomized controlled trials, the incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was 9.0% in full-dose aprotinin-treated patients and 6.6% in placebo-treated patients (odds ratio 1.41; 95% confidence interval 1.12, 1.79). The incidence of more clinically significant elevations of >2.0 mg/dL above baseline was 1.1% and 0.8% for these treatment groups, respectively (odds ratio 1.16; 95% confidence interval 0.73, 1.85). Overall, 1.9% of full-dose aprotinin-treated patients and 1.7% of

placebo-treated patients had renal failure as recorded by the investigator (odds ratio 1.09; 95% confidence interval 0.74, 1.60), and 0.3% of aprotinin-treated patients and 0.4% of placebo-treated patients had dialysis performed or recommended.

Among patients treated with full-dose aprotinin, the peri-operative use of an aminoglycoside and impaired baseline creatinine clearances increased the risk of post-operative serum creatinine elevations.

No increased risk of stroke or encephalopathy was observed among aprotinin-treated compared to placebo-treated patients in the Bayer global database of randomized controlled trials.

The risk of hypersensitivity reactions to aprotinin is related to exposure history. In a retrospective review, the incidence of hypersensitivity/anaphylactic reaction was 5.0% for re-exposure to aprotinin within 6 months and 0.9% for re-exposure after 6 months, while hypersensitivity/anaphylactic reactions in patients with no prior exposure to aprotinin were rare (less than 0.1% in the US controlled clinical studies). The prescribing information for Trasylol contains a boxed warning regarding anaphylaxis and recommends that physicians consider a history of exposure to aprotinin when assessing the risk of hypersensitivity and anaphylaxis.

The Society of Thoracic Surgeons Practice Guidelines published in 2005 make a class IIa recommendation (based on level A and B evidence) for the use of aprotinin to limit bleeding among high risk patients who have taken aspirin shortly before undergoing CABG surgery. The Society of Thoracic Surgeons draft guidelines from 2006 on blood conservation note that full-dose aprotinin significantly reduces blood transfusions (class I recommendation based on level A evidence) and need for re-operations (class IIa recommendation based on level A and B evidence). The guidelines also note that half-dose aprotinin reduces the number of patients needing blood transfusions (class IIb recommendation based on level B evidence).

In summary, aprotinin is an important part of blood conservation programs during CABG surgery. When used in accordance with approved labeling, the Bayer US

and global randomized controlled clinical trial database (which includes 2249 full-dose aprotinin-treated and 2164 placebo-treated patients) together with other published studies and more than 10 years of post-marketing experience, supports a favorable benefit-risk profile for the prophylactic use of aprotinin to reduce peri-operative blood loss and the need for blood transfusions among patients undergoing CABG surgery utilizing cardiopulmonary bypass.

2. Introduction

Trasylol® (aprotinin injection) is indicated for prophylactic use to reduce peri-operative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft (CABG) surgery.

Two retrospective observational studies published in 2006 reported that aprotinin use during cardiac surgery was associated with an increased risk of cardiac and cerebral adverse events (1) as well as renal dysfunction.(1, 2) With observational studies, however, the selection of specific treatments as well as the subsequent development of adverse events can be influenced by the patient's demographic and medical conditions.(3) Strategies used to minimize confounding include matching patients according to potential confounders, as in case-control studies, and examining the data with techniques such as regression analysis and stratification.(3, 4) However, one can only control for known and measured factors. In addition, the selection of the specific treatment as well as the evaluation of its efficacy and safety may still be biased because the treatment assignment is known.(5) Furthermore, the study by Mangano et al has methodological flaws that limit the ability to interpret the results.

Subsequent to the publication of these 2 observational studies, the FDA released a public health advisory (see Appendix 4) and Bayer sent letters to physicians and health care providers (see Appendix 5) and posted a notice on the internet to notify the public and health care community about these potential risks. In addition, Bayer has sent to the FDA an extensive review and summary of the clinical efficacy and

safety data available for aprotinin (based on both Bayer and non-Bayer data), and the FDA has scheduled a meeting of the Cardiology and Renal Drugs Advisory Committee for 21 Sep 2006, to review the efficacy, safety, and benefit-risk analysis for the use of aprotinin among patients undergoing CABG surgery.

The following briefing document reviews and critiques these 2 observational studies (Section 3), and gives a brief overview of transfusion in cardiac surgery (Section 4). This document also reviews the mechanism of action (Section 5), clinical pharmacology (Section 6), and the regulatory history of aprotinin (Section 7), as well as the available efficacy (Section 8) and safety data (Section 9) for aprotinin. The reviewed efficacy and safety data includes that obtained from published non-Bayer studies as well as from Bayer's databases, including randomized clinical trials and post-marketing surveillance data.

3. Recent Observational Studies

Two observational studies published in early 2006 sought to investigate possible associations between administration of aprotinin to patients undergoing cardiac surgery and subsequent adverse events. Because observational studies are by definition not randomized, the conclusions cannot be accepted without careful examination of the study design and the analysis of the resulting data.

Mangano et al in an observational study published in the New England Journal of Medicine(1), concluded that use of aprotinin was associated in a subset of CABG patients with increased risk for a cardiovascular event (myocardial infarction or heart failure), a cerebrovascular event (stroke, encephalopathy, or coma) or a renal event (postoperative elevation of serum creatinine or renal failure) compared to no hemostatic treatment. Karkouti et al in an observational study published in Transfusion(2), concluded that use of aprotinin in a cohort of very high-risk cardiac surgery patients (a population not restricted to CABG) was associated with an increased risk of postoperative elevation of serum creatinine or renal failure compared to patients treated with tranexamic acid. Tranexamic acid is not FDA-

approved in the management of patients undergoing cardiopulmonary bypass in the course of CABG surgery.

The conclusions of Mangano et al regarding the safety of aprotinin in CABG surgery are inconsistent with the results of prospective, randomized, double-blind, placebo-controlled trials reported by Bayer and by others. These randomized clinical trials, balanced with respect to background characteristics of treated and control patients, (as well as comprising in the aggregate a significantly larger patient population than the population studied by Mangano et al) demonstrate that the risk of cardiovascular, cerebrovascular, and serious renal events is not increased in patients receiving aprotinin compared to placebo. Additionally, although Mangano et al conclude that the three studied treatments (aprotinin, aminocaproic acid, and tranexamic acid) were equally effective(1), no analysis comparing efficacy among the active treatments is presented in the paper.

An examination of the report by Mangano et al considered together with results reported in prior publications based on the same database, raises significant concerns. It will be shown in Section 3.1.1.4 that the authors apply propensity score methodology in a manner that is inconsistent with its appropriate application as described by the inventors of propensity score technology(10-16), while application of linear regression alone is unreliable.(13, 17) The inappropriate statistical methodology as well as other methodological flaws, documented in Section 3.1.1.3, raise serious doubts as to the validity of the conclusions and provide a likely explanation for the discrepancy between the authors' conclusions and the results of prospective, randomized clinical trials.

Karkouti et al conclude that aprotinin compared to tranexamic acid may be associated with postoperative increases in serum creatinine or renal failure in very high-risk cardiac surgery patients. This conclusion is not inconsistent with the results of the Bayer randomized placebo-controlled trials that demonstrate transient increases in serum creatinine in association with the full-dose regimen of aprotinin as discussed in Section 9.6 of this document. These trials do not demonstrate an

association between aprotinin and the need for dialysis. Karkouti et al also conclude that there is no statistical difference between aprotinin and tranexamic acid with respect to transfused blood products in these high-risk patients, a conclusion that is not supported by the body of published literature that reports experience with these agents in cardiac surgery as reviewed in the recently published Practice Guidelines for Preoperative Blood Transfusion and Adjuvant Therapies from the American Society of Anesthesiologists Task Force.(18) While the propensity-based statistical analysis by Karkouti et al is generally appropriate, it is suggested in Section 3.2.5 that an improved propensity analysis to achieve better balance of baseline characteristics between the treatment cohorts together with sensitivity analyses would produce more informative conclusions. Ultimately, the most reliable approach for comparing the safety and efficacy of treatments is by means of prospective, double-blind, randomized clinical trials.

3.1 Mangano et al: The risk associated with aprotinin in cardiac surgery (N Eng J Med 2006; 354:353-65)

Mangano et al report an observational study comprising an analysis of the international database (5065 evaluable patients) collected in the Multicenter Study of Perioperative Ischemia, Epidemiology II [McSPI – EPI II] between November 1996 and June 2000.(19-21) The McSPI – EPI-II database has been the subject of multiple analyses as reported in three previously published papers(19-21) and four previously published abstracts.(22-25)

3.1.1 Study design

3.1.1.1 Patient population and method of selection

Subjects were selected from among patients scheduled for CABG surgery with cardiopulmonary bypass at 69 centers in 16 countries in North America, Europe, Asia, South America, and the Middle East.(1) To date, none of the publications based on the McSPI – EPI II database(1, 19-25) reports enrollment of the 5065 evaluable patients by center or by country.

Patients were required to be at least 18 years old, not enrolled in another clinical trial, and able to engage in a pre-operative interview.(1, 19, 20) Patient selection employed a systematic sampling method (enrollment of every Rth patient where R is expected number of cases annually/50) intended to yield a target enrollment of 50 patients per year from each study center independent of the volume of CABG surgery performed at the center.(1, 19-21) This method over-represented patients from low-volume centers. This point is discussed further in Section 3.1.5.

3.1.1.2 Patients excluded from analysis and assessment

Of 5436 patients enrolled in McSPI – EPI II, 371 enrolled patients were classified as unevaluable because they did not undergo CABG with cardiopulmonary bypass, were enrolled in another clinical trial, or data were considered inadequate.(1, 19-21) Thus, the McSPI – EPI II database, locked on 15 Oct 2001,(19) comprises 5065 patients considered suitable for evaluation.(1, 19-21) Patients undergoing surgical procedures concomitant with CABG (such as carotid endarterectomy or valve surgery) were not excluded from the database(1, 20, 21), and were not excluded from the present study.(1)

Of the 5065 evaluable patients, Mangano et al excluded 691 patients treated with antifibrinolytics on the grounds that they "received multiple antifibrinolytic agents" (226 patients), an "inadequate dose of antifibrinolytic agent" (448 patients), or "had no validation of drug type or dose" (17 patients).(1) No information on characteristics, treatment, or outcome is provided for the excluded patients. In a study intended to evaluate safety, it is important to understand the reason for the exclusion of 654 treated patients for whom data are presumably available. Bias introduced from exclusion of these patients is of particular concern because it will be shown in Section 3.1.3.1 that these excluded patients (all treated with antifibrinolytics) were significantly different ($p < 0.0001$) from the treated patients who were not excluded with respect to characteristics related to the studied outcomes.

3.1.1.3 Treatment cohorts

With 691 treated patients excluded, 4374 patients were categorized into one of four treatment cohorts: no treatment (1374 patients), aprotinin (1295 patients), aminocaproic acid (883 patients), and tranexamic acid (822 patients) according to the treatment received before the end of cardiac surgery as recorded in the McSPI – EPI II database.(1) While an earlier publication(19), reports that at least 61 patients received desmopressin as a hemostatic agent, there is no indication of how these patients were categorized in the present study.(1)

3.1.1.4 Method of analysis

The authors give information in Table 1 page 356-7(1) for only a fraction of the baseline medical risk factors that they state are available, and provide no information to allow for the assessment of non-linear relationships, though they state on page 357(1) that covariate interactions were not necessary. Important baseline characteristics possibly predictive of the studied outcomes such as age, body mass, perioperative aspirin treatment, and cardiopulmonary bypass time are not provided. Table 1 alone, however, demonstrates that patients at higher risk for adverse outcomes were given aprotinin in preference to no treatment, and given aprotinin in preference to the other agents (aminocaproic acid and tranexamic acid). The authors state that they applied analysis by "multivariable logistic regression and propensity-score adjustment"(1) as a method of statistical adjustment for the acknowledged, highly significant imbalances in risk factors that are known to affect the outcomes under study. The analysis is unreliable because it does not follow principles for the correct analysis of observational studies. The principal concerns with the analysis are listed below:

1. The choice of covariates was apparently done explicitly using the outcome variable in a stepwise regression, thereby violating a fundamental principle of design in both randomized experiments and observational studies.(14) Generally, this leads to exaggerated significance levels, which are invalid, even assuming the collection of the original covariates was appropriate.

2. The estimated propensity score was used as a variable in a covariate adjustment and not used to create bins or to match units. This violates another rule of propensity score technology.(14)

3. It appears that distinct propensity scores were not estimated for each pair of treatment groups compared, which generally violates another rule of propensity score technology.(15)

4. There are no displays or analyses supporting the claimed balance of covariates achieved by the use of propensity scores, despite the authors' claim of balance on page 358.(1)

5. The goodness of fit statistic (the C-statistic) is of limited relevance for propensity score estimation; covariate balance is critical, not fit of the underlying regression used to create the propensity score.(12, 14)

6. It appears that patients with missing data in covariates were excluded from the analyses. As a result it is not possible to assess the relevance of the analyses reported in Tables 2 and 3 of the paper.

It must be recognized that the application of linear regression alone with inadequate application of propensity technology through matching and/or subclassification, cannot be expected to give reliable results. This fact has been repeatedly documented by analysis and by simulation in hypothetical situations.(13, 17) The unreliability of linear modeling without adding application of propensity score matching and/or subclassification has also been documented by comparing results of actual randomized trials to the conclusions obtained from corresponding observational studies designed to address the same questions. An example is Deheija and Whaba's re-analysis of the data from Lalonde.(26, 27) There are two fundamental reasons for this: First, no real-world relationships are exactly linear; and second, under conditions of significant covariate imbalances between treatment groups (as in the present study), linear modeling is based on extrapolation that is totally unreliable.

3.1.1.5 Outcome events

The analysis is mostly applied to *composite* outcomes such as *cardiovascular event* (the combined incidence of myocardial infarction or heart failure). Except for the outcome *death*, the authors do not present any analysis to assess the risk of individual events of clinical interest such as myocardial infarction, stroke, or renal failure. The outcome events are defined in Table 3-1.

Table 3-1: Definition of Outcome Events in Mangano et al, 2006

Outcome Event	Definition
Death	Death during the index hospitalization[a]
Renal event	"Either renal dysfunction (postoperative serum creatinine level of at least 177 μmol per liter [2.0 mg/dL] with an increase over preoperative baseline levels of at least 62 μmol per liter [0.7 mg/dL])" or "renal failure requiring dialysis."
Renal composite outcome event	The term *renal composite outcome event* used in Figure 2 and Table 2 of the paper is not defined. *Renal composite outcome event* is assumed here to be equivalent to *renal event* as defined above.
Cardiovascular event	"Either myocardial infarction ("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]") or heart failure ("cardiac output of less than 2.0 liters per minute associated with a pulmonary-artery occlusion pressure above 18 mmHg, a central venous pressure above 12 mmHg, an S_3 gallop, or rales.)"
Cerebrovascular event	"Clinically diagnosed stroke, encephalopathy, or coma".
Composite outcome event	Includes "all the other outcome event categories (death, renal event, cardiovascular event, and cerebrovascular event)"

a Death is not defined in the paper. Death was defined as death during the index hospitalization in previous papers based on the McSPI-EPI II database.

3.1.2 Results

3.1.2.1 Primary analysis – stratified by primary and complex surgery

Patients were classified as undergoing Primary Surgery if the index surgery was elective and involved only coronary artery revascularization (with no history of cardiac or vascular surgery or angioplasty) (3013 patients) or Complex Surgery – all others (N = 1361).

The authors' primary analysis [Table 3 page 360(1)]is stratified by primary and complex surgery and comprises within each stratum comparisons between each of the three exposed cohorts (aprotinin cohort, aminocaproic acid cohort, and tranexamic acid cohort) and the untreated cohort with respect to the incidence of five outcome events during the index hospitalization, for a total of 30 comparisons. There is no statistical adjustment for multiple comparisons.

3.1.2.2 Analysis for the renal composite outcome event in all patients

The analysis for the *renal composite outcome event* in all patients [Table 2 page 359(1)], comprises comparisons between each of the three exposed cohorts (aprotinin cohort, aminocaproic acid cohort, and tranexamic acid cohort) and the untreated cohort. Odds ratios are reported after multivariable logistic regression "in the presence of covariates with propensity adjustment" based on *treatment with any antifibrinolytic* versus no treatment.

Given the multiple significant baseline imbalances for risk factors predicting renal dysfunction between the aprotinin and no treatment cohorts as shown in Table 1, pages 356-7(1), it would be expected that the odds ratio for the *composite renal event* after "multivariable regression and propensity adjustment" would be different from the corresponding odds ratio based on crude data. It is noteworthy that the reported odds ratio of 2.41 for the *composite renal event* for aprotinin versus no treatment derived after "multivariable regression and propensity adjustment" is not very different from the odds ratio for the *renal composite outcome event* of 2.81 for aprotinin versus no treatment that can be derived from the crude data given in Figure 2 on page 358.(1) Note that it is not possible to make the analogous comparison for the authors' stratified analysis in Table 3 because the crude data within each stratum are not provided in the paper.

3.1.3 Limitations

The fundamental defining characteristic of observational studies is that patients are not randomized to treatment. A critical advantage of randomized controlled trials compared with observational cohort studies is that the random allocation ensures

expected balance with respect to background characteristics of treated and control patients and avoids channeling bias (patients "channeled" to a given treatment based on prognostic factors). Although statistical methods, properly applied, may reduce bias in observational trials, there may be residual confounding from confounders that are unknown or unmeasured. In this paper the statistical methods for dealing with the observed baseline imbalances among and between the treatment groups (that is, aprotinin was given to the sicker patients) are incorrectly applied (Section 3.1.1.4), and this observation alone invalidates the conclusions.

In addition to the application of inappropriate statistical methods to deal with baseline imbalances, there are other methodological flaws as demonstrated below. Among these are the exclusion of 691 treated patients; the apparent absence of any attempt to adjust for known country effects; and the use of non-standard definitions for outcome variables. These flaws are fully apparent only from careful review of the previously published papers based on the McSPI – EPI II database. It will also be shown that the dose-response assessment is invalid.

3.1.3.1 Patients excluded from analysis and assessment

The authors excluded 691 patients treated with antifibrinolytics who "received multiple antifibrinolytic agents" (226 patients), "inadequate dose of antifibrinolytic agent" (448 patients), or "had no validation of drug type or dose" (17 patients).(1) No information on the baseline, characteristics, treatment, or outcome is provided for the excluded patients.

Based on the known total of 164 in-hospital deaths in the McSPI – EPI II database(19), and based on the approximate number of deaths by treatment cohort in the present study as derived from Figure 2, page 358(1), there were approximately 51 deaths among the 691 treated patients excluded (mortality approximately 7.4%) compared with approximately 86 deaths (mortality approximately 2.9 %) among the 3000 treated patients who were included in the study ($p < 0.0001$). Also, based on a previously published analysis of the McSPI – EPI II database stating that at least 1258 patients were treated with aminocaproic

acid (given as monotherapy to at least 1069 patients)(19), patients who received aminocaproic acid were disproportionately excluded among the 691 excluded patients ($p < 0.0001$).

Table 3-2: The 691 Excluded Patients (All Treated with Antifibrinolytics) Had Significantly Higher Mortality, and Significantly More Treatment with Aminocaproic Acid Than Did the 3000 Treated Patients Who Were Not Excluded

	Treated Patients Included N=3000	Treated Patients Excluded N=691	Treated Patients Excluded on Monotherapy N=448	p Value
Deaths (%)	~86 (2.9%)	~51 (7.4%)		p <0.0001
Number treated with aminocaproic acid (%)	883 (29.4%)	>375 (>54.3%)		p <0.0001
Number treated with aminocaproic acid as monotherapy (%)	883 (29.4%)		>186 (>41.5%)	p <0.0001

The authors excluded 691 patients treated with antifibrinolytics who "received multiple antifibrinolytic agents" (226 patients), "inadequate dose of antifibrinolytic agent" (448 patients), or "had no validation of drug type or dose" (17 patients). (p values calculated by Bayer.)

The exclusion of 691 treated patients, shown above to contribute 37% of the deaths among the treated patients in the McSPI-EPI II database (together with the associated adverse events), is a serious methodological flaw. This flaw is compounded further by the concomitant disproportionate exclusion of patients treated with aminocaproic acid.

3.1.3.2 No apparent adjustment for center or country effects

A prior publication based on the McSPI – EPI II database(23) describes statistically significant between-country differences associated with the use of aprotinin, fresh frozen plasma, heparin, and aspirin, as well as significant between-country differences in outcome. The patients described(23) overlap substantially with the primary surgery patients in the present paper. Another prior publication reports dramatic differences in transfusion practices observed across 16 countries

represented in the McSPI – EPI II database; intraoperative RBC transfusion varied from 9% to 100% and transfusion of fresh frozen plasma from 0 to 98%.(24)

Table 3-3: Mortality, Morbidity, Use of Aprotinin and Use of Fresh Frozen Plasma in Patients Undergoing Simple CABG in the Four Highest Enrolling Countries in the McSPI – EPI II Database. Data from Ott et al.(23)

Country	N	Death, MI, Cardiac Failure	Use of Aprotinin	Use of Fresh frozen plasma
Germany	834	18.5%	69%	11%
USA	1283	13.6%	20%	8%
Canada	444	12.4%	6%	1.4%
UK	619	9.2%	23%	2.4%
p value		<0.001	<0.001	<0.001

MI = myocardial infarction.

Given these known differences across countries, the apparent absence of an analysis by country, or controlling in some way for the differences among countries, is a serious omission. It is unknown whether even the crude results that are presented are driven by results from one or two countries. Moreover, there is no evidence that there was any statistical adjustment for the significant differences in both treatment and outcome across the major contributing countries to the McSPI – EPI II database.

3.1.3.3 Non-standard definitions for outcome events

The outcome definitions for *myocardial infarction* and for *heart failure* utilized in the present paper are distinctly different from the definitions for these outcomes used in earlier published papers based on the McSPI – EPI II database (see Table 3-4).(19-21) The definition of *myocardial infarction* in the present paper, in contrast to the earlier McSPI – EPI II publications(19-21) classifies new, persistent ST-segment or T-wave changes as myocardial infarction, independent of cardiac enzyme determinations. Such changes are common in coronary bypass patients, and to consider such changes diagnostic of myocardial infarction is contrary to accepted medical practice. This overbroad definition would be expected to yield a higher number of events of myocardial infarction reported by the authors of the present study as compared with the earlier papers based on the same database.(19-21) It is noteworthy that the incidence of myocardial infarction derived from data in the

present paper is apparently about 13.7% compared with values of approximately 6.2%(20) and 7.5%(21) derived from data reported in previously published papers based on the same database. Definitions for cerebrovascular outcome variables in the present paper are also different from the corresponding definitions in the three other published papers based on the same database; and definitions of the renal outcomes are not identical.(19-21)

Table 3-4: Definition of Myocardial Infarction and Heart Failure in Mangano et al, 2006(1) compared with Corresponding Definitions Used in Previously Published Papers Based on the McSPI-EPI II Database (Mangano, 2002(19); Mathew, 2004(20); Nussmeier, 2005(21)

Definition	Mangano, 2006(1)	Mangano, 2002(19)	Mathew et al, 2004(20)	Nussmeier et al, 2005(21)
Myocardial Infarction	"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)" [page 354]	"either new Q waves (Minnesota code 1-1-1 to 1-2-7); new persistent ST segment or T wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2), and elevated values for the MB isozyme of creatine kinase; or evidence of acute myocardial infarction on autopsy [page 1310]	"either new Q waves (Minnesota code 1-1-1 to 1-2-7), new persistent ST segment or T wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2) and elevated values for the myocardial band isozyme of creatine kinase; or evidence of acute myocardial infarction on autopsy [page 1721]	"If there were new Q waves (Minnesota code 1-1-1 to 1-2-7), new persistent ST segment or T wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2), elevated values for the myocardial band isozyme of creatine kinase (according to each institution's guidelines), or evidence of acute MI on autopsy" [page 508]
Heart Failure	"required a cardiac output of less than 2.0 liters per minute associated with a pulmonary-artery occlusion pressure above 18 mm Hg, a central venous pressure above 12 mm Hg, an S3 gallop, or rales". [page 354-5]	"If a ventricular assist device was used; if continuous inotropic support was required for at least 24 hours; or if there was evidence of heart failure on autopsy" [page 1310]	"If a ventricular assist device was used; if continuous inotropic support required for at least 24 hours; or if there was evidence of heart failure on autopsy" [page 1721]	"If a ventricular assist device was used; if continuous inotropic support was required for at least 24 hours, or if there was evidence of heart failure on autopsy" [page 508]

3.1.3.4 Dose-response assessment

The "dose-response assessment" excludes 699 of 1295 patients treated with aprotinin for whom dose information is presumably available. Exclusion of more than half the patients from the dose assessment analysis is sufficient reason alone to invalidate the analysis.

The use of crude data without statistical adjustment is a second, independent reason to invalidate this analysis. The authors acknowledge that aprotinin was given to higher risk patients but ignore the baseline imbalances in risk factors between the aprotinin cohort and no treatment cohort. Thus, the comparisons between the aprotinin dose cohorts and the no-treatment cohort are not valid for assessing risk. Further, the authors provide no information on the balance of risk factors between the two aprotinin dose categories (for example, it is unknown whether higher doses were given to higher-risk patients). Thus, the comparison of crude data between the aprotinin dose cohorts cannot be considered valid because the critical information to allow for assessment of balance of baseline characteristics is not provided.

3.1.4 Statements that are inconsistent with the reported results

There are a number of statements within the paper that are inconsistent with the reported results. Two such statements, in particular, have confused readers and commentators, and therefore warrant clarification in this review. The first of these appears in the abstract:

In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio 2.34; 95 percent confidence interval, 1.27 to 4.31).

The odds ratios cited in the abstract (taken from Table 3 of the paper) do not refer to *renal failure requiring dialysis*, but rather to the authors' composite outcome *renal event,* defined (Section 3.1.1.5) as postoperative elevation in serum creatinine or

renal failure requiring dialysis. In fact, the paper does not report any statistical analysis for the risk of either renal failure or renal failure requiring dialysis. The unfounded statement appearing in the paper that aprotinin "doubles the risk of renal failure requiring dialysis" has been repeated in commentaries on the present paper(28, 29), in an internet-based continuing medical education (CME) program(30), and continues to appear as a "fact sheet" among press releases posted by the Ischemia Research and Education Foundation on its web site.(31) Also, it can be shown (detail beyond the scope of this review) that both of the risk ratios given in the abstract (for cardiovascular and cerebrovascular events in primary surgery patients) appear to be mathematically inconsistent with the odds ratios given in the authors' Table 3, which reports the analysis by "multivariable linear regression with propensity adjustment."

A second statement, also apparently inconsistent with the reported results, has also served to confuse readers and commentators.(30, 32) This statement appears in the conclusions:

Unlike the serine protease inhibitors, analysis of the less costly lysine analogs aminocaproic acid and tranexamic acid demonstrated no such safety concerns, although these two agents were equally effective in reducing blood loss." (page 361, (1))

In fact, there is no efficacy analysis reported in the paper. An appropriate analysis for blood loss by treatment would require an appropriate statistical assessment of baseline imbalances (considering that patients treated with aprotinin were at higher risk for blood loss compared to the no treatment cohort, and compared to patients treated with the other antifibrinolytics) and an appropriate adjustment, if possible, using for example propensity score subclassification and perhaps model-based adjustment as well. A more useful efficacy analysis would also examine the use of blood products. Use of red blood cell (RBC) products, fresh frozen plasma, and platelets, was collected in the McSPI – EPI II database(21), but these data are not reported in the present paper.

3.1.5 Limited relevance to U.S. clinical practice

Data were collected between 1996 and 2000 from 69 centers in 16 countries. The number of patients contributed by country is not reported. Clinical practice was highly variable across the countries that contributed to the McSPI EPI-II database(23, 24) (Section 3.1.3.2) and not necessarily applicable to the US. The method of patient selection (enrollment of every Rth patient where R is expected number of cases annually/50) over-represented patients from low-volume centers, where experience with cardiac surgery may have been less extensive than high-volume centers. Information in the paper indicates that fewer than half the patients (46% at most) could have received aprotinin according to approved US prescribing information. These considerations seriously limit the extent to which the results from the McSPI EPI-II database, even if correctly analyzed, can be applied to the use of aprotinin in clinical practice in the US, and the analyses here are completely inadequate.

3.1.6 Conclusions: Mangano et al, 2006

The authors' inappropriate statistical methodology, as detailed in Section 3.1.1.4, makes the authors' conclusions entirely unreliable. In addition, detailed review in the context of prior publications based on the McSPI – EPI II database demonstrates significant opportunities for statistical bias introduced by the authors' methodology. Chief among these, and cited by others(33-35) are i) exclusion of 691 treated patients who were significantly different from the treated patients included in the study with respect to both outcome and treatment(33-35), ii) absence of consideration of country differences in the analysis despite the fact that large, statistically significant differences among countries are reported in the same database(33-35), and iii) the use in this study of non-standard outcome definitions (for example, definition of myocardial infarction inconsistent with standard medical practice) different from those used in previously published analyses of the same database.(33) This review also demonstrates that the reported aprotinin dose-response assessment is not valid because of no attempt to adjust for expected baseline differences between the dose groups.

It is also clear that the profound differences in clinical practices among the countries contributing to the McSPI EPI II database, the fact that apparently fewer than half the aprotinin patients (46% at most) could have received aprotinin according to FDA-approved prescribing information, and the non-representative patient selection process (over-representation of low-volume centers), limit the extent to which results can be generalized to apply to the clinical use of aprotinin in the US.

Many of the limitations affecting the validity of this study demonstrated in this review have been cited by others.(33-38)

In summary, Mangano et al attempt to apply propensity score methodology, but do so in a manner that is incorrect and inconsistent with its appropriate application as described by the inventors of propensity score technology(10-16), while application of linear regression alone is unreliable.(13, 17) The inappropriate statistical methodology as well as other methodological flaws raise serious doubts as to the validity of any of the authors' conclusions and provide a likely explanation for the discrepancy between the authors' conclusions and the results of prospective, randomized clinical trials. Based on this detailed review, Bayer concludes that the results of this study are neither reliable nor valid and cannot serve as any basis for affecting the use of aprotinin in clinical practice.

3.2 Karkouti 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)

Karkouti et al reported a propensity-matched, observational cohort comparison of aprotinin and tranexamic acid in very high risk patients who underwent cardiac surgery with cardiopulmonary bypass at the Toronto General Hospital between June 1999 and June 2004.(2) It is not stated what proportion of the studied patients received aprotinin for its approved indication of CABG surgery.

3.2.1 Study design

3.2.1.1 Patient population and method of selection

Eligible patients were adults undergoing cardiac surgery with cardiopulmonary bypass at Toronto General Hospital consecutively entered into two databases between June 1999 and June 2004. Of 10,949 consecutive patients, 79 were excluded because of participation in another trial or because they did not receive any antifibrinolytic drug. Among the 10,870 patients available for analysis, approximately 5% (586 patients) were treated with aprotinin and 95% (10,284 patients) were treated with tranexamic acid. The far greater use of tranexamic acid compared to aprotinin was attributed to institutional guidelines, which recommended that aprotinin be "reserved for patients who had active endocarditis, were undergoing complex procedures requiring prolonged cardiopulmonary bypass support, or had at least two previous sternotomies."

A total of 449 patients treated with aprotinin were one-to-one matched by propensity score with 449 patients treated with tranexamic acid (Section 4.1.3). Of the 586 patients who were treated with aprotinin, 137 could not be matched because their propensity scores were too extreme, and were therefore excluded from the subsequent analysis. The authors provide baseline characteristics and mean propensity score for the treatment cohorts before matching (aprotinin, N = 586 patients and tranexamic acid, N = 10284 patients), for the 137 aprotinin patients who were not matched, and for the matched cohorts (aprotinin, N = 449; tranexamic acid, N = 449).

3.2.1.2 Treatment cohorts and analysis

Patients were categorized into one of two treatment cohorts (aprotinin or tranexamic acid) based on the treatment received.

The propensity score derivation model was constructed with multivariable logistic regression, with antifibrinolytic therapy as the binomial dependent variable and all measured covariates that could be related to aprotinin use or perioperative

hemorrhage (30 variables), as well as important two-way interaction terms, included as predictor variables. "Surgeon" was not included as a covariate in the propensity score derivation model. Distributions of surgeons and their RBC transfusion rates in the matched patients were examined to detect any systematic surgeon-specific between-group differences that could bias the results.

The propensity score derivation model was used to calculate propensity scores for each patient, and based on this score, each patient who received aprotinin was matched to a unique control patient, using a "greedy" matching technique (page 329(2)). Measured covariates and outcomes in the matched group were compared between treatment cohorts with paired t test or Wilcoxon signed-rank for continuous variables and conditional logistic regression for categorical variables. Although the authors intended to examine 12 outcome variables, the authors stipulated that differences between treatments would be considered significant if the p-value for the comparison was less than 0.05.

While the application of propensity score methodology is generally sound, the matching is not ideal (Section 3.2.2.3), and there are other related limitations, for example, the authors' method for the handling of missing data for continuous variables (page 329(2)) is not appropriate.

3.2.1.3 Outcome variables

The outcome variables and definitions are listed below:

Outcome Variables Related to Blood Transfusion

- Received at least 1 RBC unit
- Received at least 5 RBC units
- Received at least 10 RBC units
- Received at least 5 platelet units

- Received at least 1 fresh frozen plasma unit

Outcome Variables Related to Adverse Outcomes

Definitions of the "adverse postoperative events" given below are verbatim from pages 329-330(2):

- Surgical re-exploration.
- Stroke - "defined as any new persistent postoperative neurologic deficit."
- Acute renal failure – "defined as a new requirement for dialysis support."
- Acute renal dysfunction – "defined as a greater than 50% increase in creatinine concentration during the first postoperative week to more than 100 μmol per L (equivalent to 1.13 mg/dL) in women and greater (sic) 110 μmol per L (equivalent to 1.24 mg/dL) in men or a new requirement for dialysis support."
- Myocardial Infarction – "defined as a new Q wave on postoperative electrocardiogram or MB isozyme of creatine kinase of greater than 50 U per L, the CK-MB/CK ratio greater than 5%, and new electrocardiogram changes."
- Serious Infection – "defined as sepsis or deep sternal infection."
- "In hospital death"

3.2.2 Results

3.2.2.1 Use of antifibrinolytic drugs during the study period

The authors noted that the use of aprotinin increased over the 5-year study period, with a consequent imbalance in the matched treatment groups with respect to the year of surgery. This is a potential source of bias that is addressed in Section 3.2.3.

3.2.2.2 Propensity score derivation

The propensity score derivation model included 20 variables, 6 of which were interaction variables. The model included in order of importance: 1. Number of previous sternotomies (0, 1, >1); 2. Type of procedure: Isolated CABG or single-valve surgery versus complex; 3. Endocarditis; 4. Cardiopulmonary bypass duration; 5. Deep hypothermic circulatory arrest; 6. Preoperative hemoglobin concentration; and 7. Urgency of procedure (elective versus non-elective).

3.2.2.3 Comparison of baseline characteristics before and after matching

The authors' Table 2, Treatment Group Comparisons after matching (page 332(2)) indicates that the marked imbalances of measured covariates between the treatments were dramatically improved after matching, with no statistically significant differences between the matched cohorts. However, it is the magnitude of the imbalance, and not its statistical significance that is also relevant in determining the effects of imbalances.(39) The imbalances in risk factors between the aprotinin cohort and the tranexamic cohort that remained after matching might have triggered re-estimation of the propensity score and re-matching. These imbalances include higher representation in the aprotinin cohort for atrial fibrillation, congestive heart failure, recent myocardial infarction, and endocarditis; and higher representation in the tranexamic acid group for diabetes mellitus, peripheral vascular disease, and abnormal baseline renal function (Table 3-5). These characteristics have been associated with an increased risk of renal dysfunction.(20, 40, 41)

Table 3-5: Comparisons (for Some Measured Covariates) After Matching: Comparison of the Aprotinin Cohort and the Tranexamic Acid Cohort (Data from the Authors' Table 2, page 332(2))

Characteristic	Aprotinin Cohort N = 449 n	%	Tranexamic Acid Cohort N = 449 n	%	p Value	Odds Ratio[a]
Diabetes Mellitus	53	12	70	16	0.2	0.72
Peripheral Vascular Disease	43	10	52	12	0.3	0.81
Atrial Fibrillation	79	18	68	15	0.3	1.24
Left ventricular ejection fraction <40%	101	22	90	20	0.4	1.16
Congestive Heart Failure	224	50	207	46	0.3	1.17
Recent Myocardial Infarction	36	8.0	30	6.7	0.4	1.21
Recent cardiac catheterization	117	26	128	29	0.4	0.88
Endocarditis	26	5.8	20	4.5	0.4	1.31
Abnormal renal function	110	24	126	28	0.2	0.83
Recent anti-platelet use	82	18.3	70	16	0.3	1.21
On heparin before surgery	71	16	89	20	0.1	0.76

a The odds ratios aprotinin vs. tranexamic acid were calculated from the data.

Information on other relevant covariates such as insulin-dependent diabetes, concomitant therapy with aminoglycosides, concomitant therapy with angiotension-converting enzyme inhibitors or angiotension II receptor antagonists is not provided, and it is not stated whether these variables were included in the propensity score estimation.

3.2.2.4 Primary analysis – outcomes in the matched patients

Table 4 page 333(2) in the paper compares the matched treatment cohorts for the 12 outcome variables. Consistent with the exploratory nature of the study, statistical significance in the analysis is not corrected for multiple comparisons.

Among the outcome variables examined, only the comparison for the *renal dysfunction* variable ($p = 0.01$) gave a nominal p value less than 0.05. There were 107 patients (24%) in the aprotinin cohort with the outcome *renal dysfunction* as compared with 75 patients (17%) in the tranexamic acid cohort (equivalent to a calculated odds ratio, aprotinin versus tranexamic acid of 1.56; 95% confidence interval 1.12, 2.17).

The analysis for the outcome variables related to transfusion of blood products showed no significant difference between the treatment cohorts.

3.2.2.5 Analysis for renal dysfunction stratified by preoperative renal function

The analysis shown in Table 5 of the paper compared the incidence of *renal dysfunction* and *renal failure* across the matched treatment cohorts with stratification by preoperative renal function. Table 5 indicates (after stratification) a statistical difference ($p < 0.05$) in the incidence of *renal dysfunction* between aprotinin and tranexamic acid in the stratum with abnormal preoperative renal function ($p = 0.03$), but not in the stratum with normal preoperative renal function ($p = 0.09$).

Although the authors suggest that "aprotinin may be associated with worsening renal function in patients with existing renal dysfunction" [page 336(2)], the results do *not* provide statistical evidence that the aprotinin vs. tranexamic acid odds of *renal dysfunction* was higher in patients with pre-existing abnormal preoperative renal function as compared to patients with normal preexisting renal function as the test for this interaction is not statistically significant ($p = 0.36$).

3.2.3 Limitations

Limitations in interpreting the reported results, as cited by the authors, include unmeasured risk factors, the possibility that use of aprotinin itself may encourage transfusion, changes in practice with time over the course of the study, and the absence of a placebo control.(2) Additionally, propensity matching was not ideal, as noted above.

3.2.3.1 Possible confounding

The results may have been affected by confounding despite the use of propensity matching. Potential sources of confounding relevant to the renal dysfunction finding, in addition to the known imbalances in the matched cohorts noted in Section 3.2.2.3, are any differences between the matched groups with respect to potential confounders for which information on balance is not provided. These

include, for example, insulin-dependent diabetes, perioperative hyperglycemia, peri-operative use of aminoglycosides, angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs, and serum creatinine at baseline. It is not stated whether these covariates were included in the propensity score estimation.

The imbalance between the matched cohorts with respect to the year of surgery is a limitation noted by the authors. Given that there were no patients treated with aprotinin in the first year of the study, it would be preferable to exclude the patients who had surgery in the first year and to include the year of surgery in the propensity score.

3.2.3.2 Comparison of efficacy

The absence of a demonstrated difference in the measured transfusion parameters between aprotinin and tranexamic acid may be a result of confounding inherent to the observational study design. It is possible, as suggested by the authors, that "antifibrinolytic drug choice itself may affect transfusion practice if the decision to use aprotinin, by reinforcing the impression that the patient has a very high risk of postoperative hemorrhage, results in a more liberal administration of blood products," [Page 336 (2)]. The authors also note that there was no set of rules (other than clinical guidelines) to guide transfusion practice. It is also possible that the matched cohorts differed in baseline covariates related to transfusion that were not included in the propensity score. It should be noted that it is not stated whether the matched cohorts were balanced with respect to whether they underwent CABG surgery, the FDA-approved indication for aprotinin. It is not clear whether CABG surgery was included in the propensity score estimation.

3.2.4 Do the results apply to general clinical practice?

The described characteristics of the matched patients indicate that the studied patients were at very high risk for blood loss and for adverse events. Approximately 70% of the matched patients underwent procedures other than isolated CABG or single valve surgery; approximately 50% had congestive heart failure; 15 to 18% had atrial fibrillation; 16 to 17% had non-elective surgery; and 26 to 29% had

cardiac catheterization within two days of surgery. Importantly, there is no information in the paper to indicate what fraction of the studied patients underwent CABG surgery, and what fraction of the studied aprotinin cohort received aprotinin for the approved indication of CABG requiring cardiopulmonary bypass. The authors acknowledge that the studied patients are not representative of typical cardiac surgery patients on cardiopulmonary bypass.

3.2.5 Conclusions: Karkouti et al, 2006

This observational study compares aprotinin with tranexamic acid in a group of very high-risk cardiac surgery patients with respect to adverse outcomes and transfusion of blood products. Propensity matching has been used as a method for dealing with the profound difference (as directed by institutional guidelines) between patients treated with aprotinin and patients treated with tranexamic acid. Because of these differences the matched cohorts represent a group of patients at very high risk for bleeding and for adverse outcomes. The use of propensity score methodology is generally sound, but matching between the studied cohorts is not ideal, suggesting that re-estimation of the propensity score might have resulted in better balance. It is clear that the cohorts were not balanced with respect to year of surgery. Balance between the cohorts with respect to CABG surgery (the FDA-approved indication for aprotinin) is not known. Also, there is no information in the paper to indicate what fraction of the studied patients underwent CABG surgery, and what fraction of the studied patients received aprotinin for the approved indication of CABG requiring cardiopulmonary bypass.

The finding of an association of aprotinin with a higher incidence of *renal dysfunction,* as defined by the authors, as compared to tranexamic acid is of interest. Post-operative increases in serum creatinine have been observed in association with aprotinin in randomized, placebo-controlled clinical trials, and this is noted in the prescribing information.

The absence of a demonstrated difference in measured transfusion parameters between aprotinin and tranexamic acid as observed in the present study may be a

result of confounding related to the non-randomized, unblinded design inherent to observational studies. It is also possible that this result is related to the fact that the study was confined to very high risk cardiac surgery patients and/or the fact that aprotinin was used for other than its labeled indication of CABG surgery. As stated in the Practice Guidelines for Preoperative Blood Transfusion and Adjuvant Therapies by the American Society of Anesthesiologists Task Force (2006), "The literature supports the use of aprotinin in reducing blood loss and in reducing the number of patients transfused in major surgical procedures (for example, selected cardiac and orthopedic procedures.) In addition, the literature is supportive of the use of epsilon-aminocaproic acid and tranexamic acid in reducing blood loss; however, the impact of these drugs on reducing the number of patients transfused is equivocal."(18)

Bayer would recommend that the authors investigate whether the analysis is affected by adjustment for year of surgery (exclusion of patients with surgery in the first year of the study and inclusion of year of surgery in the propensity score) with balance examined for year of surgery. It would also be useful to examine results for the subset of matched patients who underwent CABG surgery, as consistent with the FDA approved labeling for aprotinin or, ideally to include whether the patient underwent CABG surgery in the propensity score estimation and to match patients on this variable. Finally, a sensitivity analysis along the lines of Cornfield et al(42) or Rosenbaum and Rubin(43) as illustrated in Connors et al 1996(44) should be undertaken. Ultimately, the most reliable approach for comparing the safety and efficacy of these treatments is by means of prospective, double-blind, randomized clinical trials.

4. Overview of Transfusion in Cardiac Surgery

4.1 Transfusion risk

In the US, approximately 4.9 million patients received nearly 14 million units of whole blood and red blood cells in 2001.(45) The total number of units of all blood products transfused was 29 million. Overall, 10 to 20% of the transfusions in the

US occur during cardiac surgery.(9) Although blood and blood products are important and potentially life-saving therapeutic agents, numerous infectious and noninfectious risks are inherently associated with transfusion and it is unlikely that transfusion will ever be without any risk.

4.1.1 Infection

Although the risk of viral infections such as human immunodeficiency virus, hepatitis B, and hepatitis C, from the transfusion of contaminated blood has declined due to implementation of a number of donor testing strategies, the risk of bacterial infections associated with transfusion has become recognized as a significant cause of morbidity and mortality.(6, 46, 47)

RBC units are typically available 3 to 4 days after donation and can be stored for up to 42 days.(48) The risk of bacterial infection from contaminated blood is directly related to the length of storage but has been reported for blood stored as few as 7 to 14 days.(49) The organisms contaminating blood as a result of donor bacteremia include *Yersinia enterocolitica* and other Gram negative bacteria.(46, 49, 50)

The risk of platelet-related bacterial infection is greater with transfusion of pooled platelet concentrates from multiple donors than with platelets obtained by apheresis from a single donor.(51) Due to an increased risk of bacterial growth within a contaminated unit, platelet storage is limited to 5 days.(49) The most common contaminating organisms within platelet units are *Staphylococcus aureus, Klebsiella pneumoniae, Serratia marcescens* and *Staphylococcus epidermidis*.(51)

Bacterial infections are associated with approximately 11 to 18% of transfusion-related fatalities as reported to the FDA.(47) Based on data from the US, the estimates for aggregate risk of transfusion-related infections are 1 in 60,000 per RBC unit transfused and 1 in 69,000 per cryoprecipitate or fresh frozen plasma unit transfused.(52) The aggregate risk of transfusion-related infections is higher for platelets, 1 in 17,000 per unit transfused.(52) Statistical modeling suggests that the

risk of death is 0.1 to 0.25 deaths per 1 million RBC units transfused and 21 deaths per 1 million platelet units transfused.(49)

4.1.2 Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is a serious pulmonary syndrome that, if not recognized and appropriately treated, can lead to death. This syndrome has been well-characterized, with a constellation of symptoms including dyspnea and severe hypoxemia, hypotension, and fever, and needs aggressive and prompt interventions. Criteria for diagnosis include: symptoms usually beginning 1 to 2 hours after transfusion and fully manifest within 1 to 6 hours; bilateral pulmonary infiltrates on radiography that are consistent with non-cardiogenic pulmonary edema, with no evidence of cardiac compromise or fluid overload; and hypoxia defined as a PaO_2 to FiO_2 ratio of 300 mmHg or less or an oxygen saturation below 90% by pulse oximetry.(53)

Blood products implicated in causing TRALI include whole blood, packed RBCs, fresh frozen plasma, cryoprecipitate, platelet concentrates, and platelets collected by apheresis.(54)

A prospective, epidemiologic study identified two patient groups at increased risk for developing TRALI: patients with a hematological malignancy and patients undergoing cardiopulmonary bypass.(55)

The pathophysiology of TRALI has been postulated to involve the presence of anti-HLA and anti-granulocyte antibodies (found in 15 to 26% of cases) within the plasma derived from multiparous females or blood donors and/or the presence of lipid products within blood components that activate recipient neutrophils and/or pulmonary endothelium(56). Although TRALI does not occur exclusively after the transfusion of blood from donors with anti-HLA or anti-granulocyte antibodies, the presence of one or both of these antibodies has been reported in 89% of TRALI cases. Unlike the antibodies associated with allergic or anaphylactic-type transfusion reactions, the antibodies implicated in causing TRALI appear to be of

donor origin. Once these antibodies are administered to the recipient, they may cause pulmonary endothelial activation as well as complement activation with resultant neutrophilic influx into the lungs and damage to the pulmonary microvasculature via this neutrophil degrannulation and/or complement activation.(6, 50, 54)

In North America, the reported incidence of TRALI varies from 1 in 5,000 to 1 in 1,323 transfusions(55-57) while the reported incidence in Europe is lower at 1 in 7,980 transfusions, but this may be attributed to underreporting due to the lack of a standard definition.(58)

TRALI was the cause of 16.3% of the 265 transfusion-related fatalities reported to the FDA between 2001 and 2003.(47, 59) The majority of deaths from TRALI are associated with the administration of fresh frozen plasma, followed by RBC units and apheresis collected platelets. Although the number of deaths associated with TRALI has been estimated to be 10.3 per million RBC units transfused(60 and personal communication with the author), based on a 25% mortality rate and the wide range of reported frequency (1 in 400 to 1 in 500,000), death rates can range from 1 to 500 deaths per million units transfused.

4.1.3 Hemolytic transfusion reactions

Hemolytic transfusion reactions are most often caused by ABO incompatibility between the patient and donor during RBC transfusion. These reactions may result in death. The risk of acute hemolytic reaction is estimated at 1.1 to 7.9 per 1,000 units transfused (61, 62), and such reactions are estimated to cause 0.6 deaths per million units transfused.(49, 60)

4.1.4 Storage defects

Several studies have demonstrated an association between the length of blood storage and reduced ability of the blood to deliver oxygen.(63-66) Stored red cells undergo important biochemical changes, including the depletion of 2,3-diphosphoglycerate. This results in a shift in the oxyhemoglobin dissociation curve,

so that 28-day old blood can only initially (that is, within the first 12 to 24 hours after transfusion) deliver 6% of its carried oxygen compared to fresh whole blood that can deliver 23%.(67, 68) Stored blood was associated with a substantial decrease in oxygen delivery to tissues in an animal model.(66) In a study of patients who underwent cardiac surgery, mechanically ventilated patients were randomized to receive either 1 RBC unit or 2 RBC units along with 40% oxygen or 100% oxygen and no blood for 3 hours after a transfusion trigger of 8 g/dL hemoglobin was reached.(64) Oxygen delivery increased significantly with transfusion and 100% oxygen ventilation but oxygen consumption was unchanged. Ventilation with 100% oxygen, but not transfusion, increased skeletal muscle oxygen tension. Thus, transfusion was effective in improving only systemic oxygen delivery while 100% oxygen ventilation improved both systemic oxygen transport and skeletal muscle oxygen tension, resulting in an improved oxygenation status.

Structural changes in stored red cells appear to increase their aggregability. As red cells age, each cell elongates and loses flexibility.(63) Aging cells can have cellular fragments and spicules on the surface.(69) Depending on the storage duration, these stored red cells have the potential to aggregate, posing a circulatory risk as related to micro-circulatory occlusion and inadequate oxygenation. Thus, transfusion of stored blood, particularly in the second half of the approved storage period, may contribute to blood flow disorders and negative outcomes.

Prolonged storage of platelets has been associated with decreased adhesive capacities and enhanced procoagulant activity.(70) Chemokines found in platelets can be due to either white blood cell contamination or platelet activation or lysis during preparation or storage.(71)

4.1.5 Transfusion-related immunomodulation

Stored blood has increased cytokine levels.(71, 72) Although many studies have demonstrated that patients who were transfused have a higher incidence of post-operative infections,(73-81) this is a topic of considerable debate.

The risk of infection tends to increase with the number of units transfused.(82) For patients undergoing CABG surgery who did not receive a transfusion, 2.6% developed an infection compared to 3.1% for those receiving 1 unit, 6.7% for those receiving 2 units, and 7.7% for those receiving 3 units. For patients transfused 6 or more units, 22.2% developed an infection. Another study suggests that there is a 5% increased risk of bacterial pneumonia per unit transfused and a 6% increased risk of wound infection per unit transfused.(83)

Leukocytes in allogenic blood are postulated to be the cause of immunomodulatory effects, which are predominately related to the infusion of large amounts of foreign antigen which modulates the recipient immune system and may include the following specific alterations: increased alloimmunization, reduced CD8 suppressor T cell number and function, reduced CD4 T helper number, reduced NK cell number and function, reduced macrophage number and function, reduced MLC response and response to mitogen, and cell-mediated cytotoxicity.(84)

However, two randomized, controlled trials in cardiac surgery have been inconclusive with respect to the post-operative infection rate and the effect of leukocyte removal from transfusions.(85, 86) A third study demonstrated that transfusion of leukocyte-depleted blood resulted in a lower infection rate but had no effect on 90-day mortality.(87)

4.1.6 Other adverse outcomes associated with transfusion

A publication by Kleinman et al summarized the overall risks of transfusion of blood products in Canada.(88) The risk for any transfusion-related reaction was estimated to be 643 in 100,000 RBC units transfused, and the risk of potentially severe reactions was estimated to be 43.2 in 100,000 RBC units transfused. For platelets, the risk of any reaction was 10,926 in 100,000 units transfused, and the risk of potentially severe reactions was estimated to be 126 in 100,000 units transfused. In a 1997 US Government Accounting Office report, the risk for potentially severe reactions in the US was 80 in 100,000 units transfused.(89)

4.1.7 Effects of transfusion on short-term survival (within 3 months of surgery)

There may be other, incompletely characterized mechanisms related to the number of white cells within the unit or the age of the unit that may account for increased mortality as related to transfusion of red cells in high-risk cardiac surgical patients. The reduced safety of red cells in high-risk populations is highlighted by several studies which demonstrate an increase in either complications or mortality with increased transfusion of red cell units.(85-87, 90, 91) In the first randomized study that evaluated the clinical impact of liberal versus conservative transfusion strategies in a large series of 713 critically ill intensive care unit patients, Hebert et al demonstrated a higher complication rate (myocardial infarction, pulmonary edema and acute lung injury) in patients who received a greater number of red cell units as directed by a liberal transfusion strategy.(90) Although an observed 20% reduction in short-term mortality was not shown to be statistically significant, the lack of significance may have been related to a type II statistical error (that is, an additional 1700 patients would have to be enrolled to adequately evaluate the potential for a 0% reduction). A similar study was completed by Bracey et al and evaluated the effect of reducing the red cell transfusion trigger from 9 g/dL to 8 g/dL of hemoglobin in a series of 428 cardiac surgical patients.(91) This study demonstrated that sustaining a lower hemoglobin and administration of less red cell units (0.9 ± 1.5 units for the treatment group versus 1.4 ± 1.8 units for the control group, $p = 0.005$) did not adversely effect patient outcome (that is, no statistical difference in morbidity or mortality). Although an observed reduction in mortality by 50% was not statistically different ($p = 0.321$) between the treatment group (1.4%) and the control group (2.7%), this may reflect a type II statistical error since 5300 patients would have been required to adequately power a study to detect a 50% reduction in mortality.

The adverse consequences related to administration of red cell units in cardiac surgical patients is also indirectly supported by the reduced mortality observed when patients receive leukoreduced units during or after cardiac surgery in three

prospective, randomized studies.(85-87, 90, 91) Bilgen et al(87) observed a 50% reduction (from 10.1% to 5.5%) in-hospital mortality and van de Watering et al(85) observed a 50% reduction (from 7.8% to 3.5%) in 60-day mortality. Although Wallis et al(86) observed an 80% reduction (from 3.2% to 0.5%) in three-month mortality, this was not statistically significant; however, this study may have been underpowered to adequately address this issue and may reflect a type II statistical error (1174 patients would have to be enrolled to detect an 80% decrease in mortality from a baseline of 3.2%). These findings were also supported by Habib et al who observed a higher mortality in patients who were anemic but also received red cell units during cardiopulmonary bypass.(79) By far, this may be the most significant risk related to red cell transfusion in cardiac surgical patients since the findings from these studies would translate into a white cell-mediated mortality of 22,000 to 46,000 deaths per million red cell units. Although one recent study does not support these findings, the study by Fung et al was not randomized and used a historical control group,(92) unlike the previously cited randomized, prospective studies.

Results from one recent study identified the age of transfused red cell units as an independent risk factor for hospital length of stay, adverse renal outcomes and in-hospital mortality.(48) Age of transfused red cells may be more relevant to high risk populations like cardiac surgical patients who may be predisposed to end-organ damage or multi-organ system failure.

Several recent studies have demonstrated that transfusion of non-leukoreduced units may potentially increase the incidence of multi-organ system failure in the perioperative setting.(93-95) Although the exact mechanisms of the effect of transfusion on the incidence of this complication have not been clearly elucidated, it is postulated that in patients who are at high-risk (for example, trauma and long cardiopulmonary bypass intervals) for developing endothelial dysfunction, either white cell lytic enzymes or other cellular debris cause additional damage to the already dysfunctional endothelium. Support for this mechanism is provided by the

findings of van der Watering et al who demonstrated that non-cardiac (that is, as related to other causes like multi-organ system failure) mortality was reduced by 90% when patients undergoing cardiac surgery received leukoreduced packed RBC units.(85)

A review of data on 16,184 patients undergoing CABG surgery, found a 6-fold increased risk of peri-operative stroke associated with high transfusion requirements (that is, > one liter of transfused red cells).(96)

Platelet transfusion is also potentially associated with mortality after CABG surgery. An observational study found that platelet transfusion was associated with increased mortality among 5016 patients undergoing CABG surgery.(19) However, another observational study reported that leukocyte-reduced platelet transfusions were not associated with an increased risk of morbidity or mortality.(97) A propensity-adjusted analysis of 1,720 patients from the Bayer database undergoing CABG surgery reported an association between platelet transfusions and an increased risk of stroke and death.(98)

Habib et al performed a retrospective database analysis of 1,760 patients using both multivariate analysis and propensity adjustment.(79) The authors found an association between hematocrit values less than 24% and renal dysfunction. However, the study also found an independent association between transfusion and increased renal dysfunction. Another smaller study showed an association of anemia and increased serum creatinine values.(99)

4.1.8 Effects of transfusion on long-term survival

In a retrospective review of 1,195 patients who underwent primary CABG surgery, patients with transfusions were compared to patients who had not had transfusions, adjusting for confounding variables.(100) Kaplan-Meier survival curves demonstrated an increased risk of mortality up to 60 months from the time of surgery in patients who were transfused (risk ratio 1.7; 95% confidence interval 1.4, 2.0; $p < 0.001$). In a study of 1136 critical care patients, transfusion was also

directly correlated with mortality.(101) In a retrospective review of 24,112 patients with acute coronary syndrome in which 10% of patients received a transfusion, a multivariate analysis demonstrated that transfusion was associated with higher 30-day mortality among patients with a hematocrit above 25% at the time of transfusion.(102)

The US Social Security Death Index was used to determine long-term survival among 10,289 patients who underwent CABG surgery between 1995 and 2002 at the Cleveland Clinic Foundation.(103) There was a risk-adjusted reduction in survival among those patients who received a peri-operative transfusion compared to those who did not, both within the first 6 months post-operatively and up to 10 years post-operatively.

4.2 Transfusion triggers

Given the potential risks associated with transfusion, blood and blood products should only be administered when appropriate. The American Society of Anesthesiology has published guidelines for the transfusion of RBC units during the peri-operative period.(104) Transfusion is recommended for patients on cardiopulmonary bypass with hemoglobin values of 6.0 g/dL or less; patients greater than 65 years of age with chronic cardiovascular or respiratory disease and hemoglobin values of 7.0 g/dL or less; patients with rapid and uncontrolled blood loss; and patients with acute blood loss over 1500 mL. The benefit of transfusion for stable patients with hemoglobin values over 7.0 g/dL is not clear.

4.3 Blood supply

The National Blood Data Resource Center reports a decreasing margin between blood supply and demand.(105) Specifically, a nearly 50% decrease in the difference between number of units collected versus transfused for the years 1987 (13.7 million units collected versus 11.5 million units transfused for a surplus of 2.2 million units or 16%) and 1999 (13.2 million units collected versus 12 million units transfused for a surplus of 1.2 million units or 9%) has been observed and illustrated in a figure supplied on the National Blood Data Resource Center website. Shortages

become more evident when considering supply by blood type (especially type O), regional variations, and seasonal differences (especially in the summer and the Christmas and New Year holidays), and as demonstrated by frequent and urgent local, regional, and national communications to the public to consider donation.(106) Although blood supplies are usually sufficient, reports have been published that surgery has been postponed or cancelled because platelets were not available.(107) With increased screening for blood-bourne pathogens and regulation, the blood supply is safer but at the cost of fewer donors, who may not meet screening questionnaire criteria, are burdened by the intrusiveness or length of the questionnaire, or have a false positive test result.(106) Therefore, the need to conserve donor blood is important to ensure that an adequate supply is available for those patients who need it.

4.4 Blood management programs in cardiac surgery

Cardiac surgery continues to place a large demand on available blood supply. Overall, 10 to 20% of transfusions are utilized for cardiac surgical procedures.(9) Although the extent of blood loss and the need for donor blood transfusions may have decreased somewhat in recent years, there is still a need for further reduction. The average number of units required by adult patients undergoing open-heart surgery is estimated to be 2 to 6 RBC units, 2 to 4 fresh frozen plasma units, and 1 to 10 platelet units.(99)

The transfusion pattern in CABG surgery suggests that 10-20% of patients consume about 80% of the transfused blood products.(108) Identification of patients at higher risk for transfusion can facilitate optimal management of these patients pre-operatively and peri-operatively by decreasing their transfusion needs, lowering their risk of developing potential complications associated with transfusions, and conserving blood resources.

One of the greatest influences on transfusion is the individual treating physician or the hospital. Enormous variability exists in transfusion practices. In some practices, up to 80% of patients undergoing cardiac surgery are transfused while in

other practices, as few as 10% receive blood transfusions.(9, 109) Stover et al demonstrated that the hospital and the physician were independent predictors for transfusion.(9)

Based upon a review of multivariate and observational studies, The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists have published a list of risk factors associated with increased transfusion of blood or blood products during cardiac surgery. These risk factors include: advanced age, pre-operative anemia, female gender, body size, pre-operative anti-thrombotic therapy, pre-operative coagulopathy, cardiogenic shock, congestive heart failure, poor left ventricular function, renal insufficiency, insulin-dependent adult onset diabetes mellitus, peripheral vascular disease, pre-operative sepsis, liver failure, hypoalbuminemia, prolonged cardiopulmonary bypass time, need for re-operation, aortic surgery, complex surgery, combined valve and CABG surgery, valve surgery, and internal mammary artery grafting.(110)

Repeat cardiac surgery procedures are predictors of increased transfusion requirements.(111-116) Performance of urgent or emergent cardiac procedures was also a risk factor for transfusion.(114-117) There appears to be an increased risk of transfusion in CABG surgery with revascularization of 3 or more grafts.(118-120) The use of bilateral internal mammary artery grafts results in a greater risk for postoperative blood loss than saphenous vein grafts or unilateral internal mammary artery grafts.(121) Furthermore, combined CABG and valve surgery.(122, 123) as well as prolonged cardiopulmonary bypass time(112, 115, 117, 124, 125) are also independent risk predictors for transfusion.

Although employment of several pharmacologic (such as aprotinin) and non-pharmacologic strategies (such as normovolemic hemodilution and cell salvage) has reduced bleeding and transfusion, use of new anticoagulant agents is offsetting some of the beneficial effects of blood conservation strategies. Anti-platelet agents may increase the risk for transfusion during cardiac surgery. Several studies have demonstrated that aspirin-treated patients who undergo cardiac surgery are more

prone to bleeding and require more transfusions (especially platelets) than those patients who do not receive aspirin.(126-129) Although, the exact association between other more potent agents and either the severity of bleeding or transfusion requirements in patients undergoing cardiac surgical procedures is currently being defined, several reports have demonstrated severe, intractable bleeding with use of either the direct thrombin inhibitors for anticoagulation during cardiopulmonary bypass(130-133) or with pre-operative use of clopidogrel.(134-145) In fact, all twelve studies that evaluated the effect of clopidogrel in the cardiac surgical setting demonstrated a consistent 2- to 8-fold increase in both blood loss and transfusion when patients were receiving this agent pre-operatively. Many of these studies suggest that clopidogrel use is also associated with increased duration of mechanical ventilation, re-operation for bleeding, prolonged stay in intensive care units, and prolonged length of hospital stay. In addition, one of the twelve studies demonstrated an increased in-hospital mortality rate when patients received clopidogrel pre-operatively.(145)

Over the years, various treatment modalities, including mechanical measures and pharmacological agents such as aprotinin, have been employed during cardiac surgery in an attempt to reduce the need for transfusions of donor blood and blood products. Mechanical measures have been of modest benefit.(146-150) Such measures include the use of non-blood priming of the extracorporeal circulation oxygenator system, transfusion of stored autologous donor blood, intra-operative hemodilution, off-pump CABG procedures, re-infusion of blood salvaged from the operative field, and re-infusion of mediastinal blood shed post-operatively.(146-150)

4.5 Transfusion conclusions

Although blood and blood products are important therapeutic agents, there is evidence that stored blood does not function as well as fresh blood. In addition, numerous infectious (such as viral and bacterial infections) and noninfectious (such as TRALI and hemolytic transfusion reactions) complications, some which can

result in death, are associated with transfusion. Measures to reduce the exposure to donor blood or blood products are important in reducing the risk of these complications. Furthermore, there is a decreasing margin between blood supply and demand.

5. Mechanism of Action of Aprotinin

The perturbation of CABG surgery with cardiopulmonary bypass activates and amplifies intersecting plasma protease-based processes. These must be proactively managed by the surgical team to limit associated coagulopathies, surgical complications, and organ injury. Contact activation, initiated upon contact of blood with surgical instrumentation and the extensive surface area of the cardiopulmonary bypass circuit, results in activation of the kallikrein-kinin system, the coagulation-fibrinolysis cascade, and the complement system.(151)

Robust generation of the procoagulant and inflammatory mediator thrombin occurs during CABG surgery with cardiopulmonary bypass. The surgical team specifically uses heparin during the operative period to limit clot formation, as heparin irreversibly complexes with endogenous anticoagulant antithrombin and accelerates its inhibition of thrombin. Full anticoagulant doses of heparin are essential during the period of surgical contact activation to limit thrombin-mediated fibrin clot formation and pathologic thrombosis. Upon closure of the surgical site, when the pathologic stimulus for thrombin generation is removed and the goal is to limit post-operative bleeding from sutures and injured microvasculature, the anticoagulant effect of heparin is reversed with administration of protamine.

The post-operative course, including bleeding, is also impacted by the consumption and dilution of coagulation factors and platelets which occurs peri-operatively, as well as the inflammatory-mediated activation of fibrinolysis. Hence, while maintaining intensive heparin therapy is critical during the operative period to prevent thrombosis, additional therapeutic interventions are necessary to mitigate inflammation and fibrinolysis which contribute to intra- and post-operative bleeding and organ injury.(152)

5.1 Thrombin platelet interaction and coagulation

During cardiopulmonary bypass, kallikrein amplifies activation of coagulation resulting in intra-operative thrombin generation and the consumption of clotting factors.(153) Kallikrein mediated thrombin generation results in the intra-operative pathologic activation of platelets via the platelet thrombin protease activated receptor-1.(154, 155) Further kallikrein-mediated plasmin-generation results in the exhaustion of platelet glycoprotein receptors and loss of platelet function leaving platelets unable to clot.(156) Aprotinin reduces intra-operative kallikrein and thrombin generation thus sparing the availability of clotting factors for post-operative hemostasis.(157-161) Aprotinin has been shown to inhibit the contact activated coagulation pathway by inhibition of plasma kallikrein, factor XI, and to a lesser extent factor XII at plasma levels clinically achieved with the full-dose regimen.(153) Disruption of factors XI and XII in mice prevents the formation of occlusive thrombi and protects against stroke without increasing the bleeding risk.(162) Aprotinin limits plasmin-mediated defects in glycoprotein Ib and glycoprotein IIb/IIIa receptors that are necessary for platelet adherence to endothelium and normal fibrinogen-mediated aggregation and physiologic clot formation postoperatively.(163, 164) Aprotinin directly prevents pathologic thrombin-mediated platelet activation by interfering with the activity of the platelet protease activated receptor-1 without affecting platelet responses from adenosine diphosphate and collagen.(155, 165) This preserves platelet function during cardiopulmonary bypass without preventing the formation of hemostatic plugs at wound and suture sites where collagen is likely to be exposed.(165, 166)

5.2 Fibrinolysis

Cardiopulmonary bypass surgery causes hyperfibrinolysis as a result of kallikrein-induced generation of free plasmin through urokinase-plasminogen activator.(158, 167-169) Unlike tissue-plasminogen activator generated plasmin which is localized to resolve formed clot, free plasmin results in a systemic fibrinolysis rapidly inactivating fibrinogen and fibrin, thus limiting formation of physiologic clot and contributing to diffuse bleeding. At clinically relevant concentrations, full-dose

aprotinin inhibits kallikrein and is a potent reversible inhibitor of free plasmin without directly affecting clot-bound plasmin.(153, 170, 171) This mechanism is in contrast to the mode of action of lysine analogs which bind to plasminogen and limit the ability of clot-bound plasmin to bind to fibrin.(170) These antifibrinolytic mechanisms help to explain why aprotinin can be beneficial in inhibiting free plasmin mediated peri-operative bleeding without affecting physiologic clot fibrinolysis.(172)

5.3 Inflammation

Cardiac surgery with cardiopulmonary bypass elicits a systemic inflammatory response and ischemia-reperfusion injury. The clinical manifestations of systemic inflammation are respiratory compromise, renal failure, neurological dysfunction, and myocardial dysfunction.(151, 152, 173) Kallikrein activation occurs almost instantaneously at the start of cardiopulmonary bypass.(174) The major product of the kinin-kallikrein cascade is the potent vasodilator bradykinin. Bradykinin augments vascular permeability, facilitating movement of plasma proteins and activated neutrophils into tissue resulting in organ edema and inflammation.(175) Proinflammatory cytokines (such as IL-6, IL-8, and TNFα) are elevated during cardiac surgery with cardiopulmonary bypass and are associated with cardiac and pulmonary dysfunction following cardiopulmonary bypass.(176-178) During cardiopulmonary bypass, kallikrein activates the complement system both directly and through the generation of plasmin.(179) Complement generation during surgery affects vascular tone leading to reduced tissue perfusion and has indirect negative effects on tissues through chemoattractant and activation effects on neutrophils(179) to further propagate the inflammatory response and tissue injury.(172, 180, 181)

Aprotinin inhibits kallikrein, in a dose-dependent manner, in vitro, in animal models(151, 153, 167) and in the clinical cardiopulmonary bypass setting.(182, 183) Although lower concentrations achieved with the half-dose aprotinin regimen (approximately 137 KIU/mL) have antifibrinolytic effects via inhibition of plasmin,

the higher concentrations achieved with the full-dose regimen (approximately 250 KIU/mL) also modulate the systemic inflammatory response via kallikrein inhibition.(151) Aprotinin reduces the generation of inflammatory cytokines in animal models and in the course of CABG surgery with cardiopulmonary bypass.(151, 152, 173) Animal models and patients undergoing cardiopulmonary bypass have shown a reduction in edema with aprotinin administration.(184, 185) Aprotinin through inhibition of kallikrein and plasmin reduces complement formation.(161, 186, 187) The inhibition of activation and transmigration of neutrophils into tissues by aprotinin has been observed in animal models of lung, renal, and heart injury as well as the clinical cardiopulmonary bypass setting.(188-193) Modulation of systemic inflammatory response by aprotinin has been postulated(151) to be associated with improved myocardial, pulmonary and cerebrovascular outcomes.(194)

6. Clinical Pharmacology

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 500,000 to 2 million kallikrein inhibiting units (KIU).

After intravenous injection, rapid distribution of aprotinin occurs into the total extracellular space, leading to a rapid initial decrease in plasma aprotinin concentration.

Average steady state intra-operative plasma concentrations were 137 KIU/mL (n = 10) after administration of the following aprotinin regimen (the half-dose regimen described in Section 7.1): 1 million KIU intravenous loading dose, 1 million KIU into the pump prime volume, 250,000 KIU/h of operation as a continuous intravenous infusion.

Average steady state intra-operative plasma concentrations were 250 KIU/mL (n = 20) after administration of the following aprotinin regimen (the full-dose

regimen described in Section 7.1): 2 million KIU intravenous loading dose, 2 million KIU into the pump prime volume, 500,000 KIU/h of operation as a continuous intravenous infusion.

Aprotinin is rapidly excreted from the body. In humans, a biphasic elimination pattern with an initial half-life of 0.3 to 0.7 hours and a terminal half-life of 5 to 10 hours is observed.

Following a single intravenous dose of radiolabeled 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.

In patients with chronic renal failure, the aprotinin clearance and metabolic clearance are reduced in parallel with glomerular filtration rate.(195, 196) Tubular uptake and metabolism are also reduced but not in proportion to glomerular filtration rate.(196) Although a substantial decrease in aprotinin clearance is noted, renal impairment does not affect the maximum concentration or distribution half-life of the drug.(197) However, in 1 patient who underwent CABG surgery and had end-stage renal disease treated with peritoneal dialysis, plasma concentrations at 24 and 32 hours were approximately 4-fold higher than for 1 control patient. In addition, aprotinin clearance was reduced by almost 50% and the peak concentration was higher.(198)

7. Clinical Development

7.1 Historical overview

Aprotinin has been studied and used in Europe for almost 50 years in a variety of clinical conditions, including acute pancreatitis.(199) For nearly two decades, it has been used in cardiac surgery to reduce blood loss and the need for transfusion.

Two dosing regimens for Trasylol are approved in the US, the full-Hammersmith and the half-Hammersmith regimens.

The full-Hammersmith regimen consists of a loading dose of 2 million KIU (200 mL or 280 mg) infused over 20 to 30 minutes after the induction of anesthesia followed by a constant infusion of 500,000 KIU/hr (50 mL/h or 70 mg/h) during the procedure. A pump prime of 2 million KIU (200 mL or 280 mg) is added to the re-circulating priming volume of the cardiopulmonary bypass circuit. This regimen is also known as the high-dose, full-dose, and full-dose Hammersmith regimens as well as the kallikrein-inhibiting dose. This regimen is called regimen A in the US prescribing information and will be called the full-dose regimen in this document.

The half-Hammersmith regimen consists of a loading dose of 1 million KIU (100 mL or 140 mg) infused over 20 to 30 minutes after the induction of anesthesia followed by a constant infusion of 250,000 KIU/hr (25 mL/h or 35 mg/h) during the procedure. A pump prime of 1 million KIU (100 mL or 140 mg) is added to the re-circulating priming volume of the cardiopulmonary bypass circuit. This regimen is also known as the low-dose, half-dose, and half-dose Hammersmith regimens as well as the plasmin-inhibiting dose. This regimen is called regimen B in the US prescribing information and will be called the half-dose regimen in this document.

For both regimens, a test dose of 10,000 KIU (1 mL or 1.4 mg) is infused at least 10 minutes before the loading dose.

An additional dosing regimen for Trasylol, the pump-prime regimen, is not approved in the US. The pump-prime regimen consists of 2 million KIU (200 mL or 280 mg) added to the re-circulating priming volume of the cardiopulmonary bypass circuit. A test dose of 10,000 KIU (1 mL or 1.4 mg) is infused prior to priming the pump.

7.2 Bayer clinical development overview

Based on early studies that demonstrated significant decreases in blood loss and transfusion requirements among patients undergoing CABG surgery(181, 200)

Bayer pursued a clinical development program for the use of aprotinin during CABG surgery. Overall, 49 Phase II/III controlled trials investigating the use of aprotinin during CABG surgery were conducted from 1987 to 2001, although the majority were conducted between 1987 and 1995. Eight trials were conducted in the US and 41 were conducted outside the US. One of the 8 trials, Study D90-013, was cancelled after only 7 patients were enrolled because of technical difficulties

Forty-eight of the 49 studies were randomized, double-blind, and placebo-controlled trials. The one exception was a randomized, open-label and placebo-controlled trial (Study 1477). The majority of trials enrolled patients undergoing primary CABG surgery, although a substantial number of patients in the 49 studies underwent repeat CABG surgery as well as valve repair or replacement surgery. The full-dose aprotinin regimen was used in 45 trials and the half-dose regimen in 8 trials. Other regimens, including a pump-prime regimen, were used in 10 trials. Some studies included more than one dosing regimen.

7.3 Regulatory history

Bayer AG introduced Trasylol into clinical use in 1953 in Germany for the treatment of acute pancreatitis. The first reports on the use of aprotinin to reduce blood loss during and after open heart surgery were published in the 1960s and 1970s, and generally consisted of uncontrolled studies and case reports. The first controlled studies reported marked reduction in bleeding and reduced need for donor blood transfusion in patients receiving aprotinin. The US IND for the use of aprotinin to reduce blood loss and transfusion requirements in open heart surgery requiring cardiopulmonary bypass was filed on 05 May 1989. Bayer proposed to study both the full-dose and half-dose regimens. The subsequent pivotal studies confirmed the earlier efficacy findings. At the time of submission of the US NDA in 1992, aprotinin was marketed in 33 countries for various indications to prevent blood loss.

7.3.1 Initial NDA submission and approval

The initial NDA for Trasylol was submitted on 23 Nov 1992 and included 26 studies that evaluated the efficacy and safety of aprotinin, among which were 2 pivotal efficacy studies that were carried out in the US, Study D89-004 and Study D89-006. Study D89-004 was a single center study performed in patients undergoing repeat CABG surgery in which patients were stratified on the basis of prior aspirin therapy. Study D89-006 was a multicenter trial in patients undergoing primary or repeat CABG surgery; patients were stratified on the basis of CABG procedure (primary versus repeat) and prior aspirin therapy. Study D89-005 was a third US trial performed in patients undergoing primary cardiac valve replacement surgery.

The NDA for the full-dose regimen of Trasylol was approved on 28 Dec 1993 for prophylactic use to reduce peri-operative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of repeat CABG surgery. Trasylol was also indicated in selected cases of primary CABG surgery where the risk of bleeding is especially high (such as impaired hemostasis, presence of aspirin use, or other coagulopathy) or where transfusion is unavailable or unacceptable. Concerns regarding the risk of myocardial infarction, renal dysfunction, and graft closure among Trasylol-treated patients were addressed in the initial US prescribing information. Both Bayer and the FDA agreed that additional studies were needed to assess the risk of myocardial infarction and graft closure.

7.3.2 Noteworthy NDA supplements

7.3.2.1 Supplement 002

On 28 Jan 1994 Bayer submitted Supplement 002 (S-002) to support the use of the half-dose Trasylol regimen. This submission relied on data from the previously submitted Study D89-004 and an additional trial, Study D92-008. Supplement 002 was approved on 12 Oct 1994.

7.3.2.2 Supplement 004

On 29 Oct 1996 Bayer submitted Supplement 004 (S-004) to support expanding the Trasylol indication to include patients undergoing primary CABG surgery. This supplement was supported by efficacy data from 3 studies. Study D91-007 was a pilot study to assess the role of aprotinin on preventing platelet dysfunction during cardiopulmonary bypass. Study D92-016 was a multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of aprotinin in reducing blood loss and transfusion requirement among patients undergoing primary CABG surgery. Study D92-048 was a multicenter, randomized, double-blind, placebo-controlled study to investigate the effect of aprotinin on graft patency among patients undergoing primary CABG surgery.

This supplement also proposed updating the safety information in the US prescribing information. These proposed updates included incorporating additional adverse event data from patients who underwent primary and repeat CABG surgery, excluding adverse event data from patients who underwent other types of surgery, adding subsections describing myocardial infarction and graft patency data, and expanding the warnings on hypersensitivity reactions.

This supplement was approved on 28 Aug 1998, and the indication was expanded to include primary CABG surgery. In addition, the warning section was expanded to include a box warning for the increased risk of hypersensitivity and anaphylactic reactions upon re-exposure to aprotinin. Other safety information originally submitted in S-004 was approved separately in Supplement 005 (see Section 7.3.2.3).

7.3.2.3 Supplement 005

On 02 May 1997 Bayer resubmitted the safety information from S-004 in a new supplement, S-005. The revisions to the prescribing information included changes to explain prolongation of whole blood clotting tests and to provide multiple methods for monitoring adequate anticoagulation, to add myocardial infarction and graft patency subsections, and to include additional data on the risk of

hypersensitivity on re-exposure to aprotinin based on retrospective review of 387 European cases. There was no update to the number of patients in the adverse events section from the original approval in this supplement. This supplement was approved as submitted on 08 Aug 1997.

7.3.2.4 Supplement 006

On 12 Sep 1997, Bayer submitted Supplement 006, which updated the adverse events tables to include 2002 aprotinin-treated patients and 1084 placebo-treated patients from Studies D89-004, D89-005, D89-006, D91-007, D92-008, D92-016, D92-022, D92-048, and D95-006. In addition to the above studies, events from U92-001, D94-026, and post-marketing surveillance were added to the section of adverse reactions. Studies U92-001 and D92-022 were open-label, compassionate use and double-blind, placebo-controlled, compassionate use protocols, respectively. Study D95-006 examined the efficacy and safety of aprotinin therapy among patients undergoing hip replacement surgeries. Study D94-026 was an open-label study that examined the effect of aprotinin on wheal and flare responses and mast cell degranulation. This supplement was approved 30 Sep 1997.

8. Efficacy Results

In general, the results from Bayer studies and from other published trials, meta-analyses, and observational studies demonstrate the efficacy of aprotinin for reducing blood loss, transfusion requirements, and the need for re-operations among patients undergoing CABG surgery utilizing cardiopulmonary bypass. In addition, studies showing the efficacy of aprotinin in preventing stroke and cognitive dysfunction in the setting of CABG surgery as well as for reducing blood loss and transfusions among patients receiving concomitant medications such as clopidogrel have been published.

8.1 Overview of literature

Numerous meta-analyses have been published that demonstrate the efficacy of aprotinin for reducing the need for transfusion, the mean number of units transfused, and the need for re-operation. These meta-analyses have included numerous trials

that were designed to study the efficacy of aprotinin during a variety of cardiac surgeries, including CABG surgery. In general, there is considerable overlap in the trials included in each meta-analysis, although Sedrakyan et al limited their meta-analysis to trials examining patients undergoing CABG surgery.(201) In addition, numerous Bayer studies are included in the different meta-analyses.

The meta-analysis published by Sedrakyan et al was designed to evaluate clinical outcomes associated with aprotinin use among patients undergoing CABG surgery.(201) Included were trials that used random allocation of treatments, used a placebo group, and used pre-operative and continuous intra-operative aprotinin regimens. Excluded were studies that only added aprotinin to the priming volume of the heart-lung machine or only administered the drug post-operatively. Analysis of the results from 25 trials that reported transfusion data showed that aprotinin significantly reduced the need for blood transfusion associated with CABG surgery (relative risk 0.61; 95% confidence interval 0.58, 0.66). Overall, 793 of 1966 aprotinin-treated patients required a transfusion compared to 936 of 1464 placebo-treated patients. Similar reductions in the need for blood transfusion were noted for aprotinin-treated patients who were aspirin users (relative risk 0.67; 95% confidence interval 0.61, 0.72) or non-users (relative risk 0.53; 95% confidence interval 0.47, 0.60).

Similar reductions in the need for transfusions as well as in the need for subsequent re-operations have been reported in 5 meta-analyses. (202-206) In addition, 3 meta-analyses have shown that aprotinin reduces the mean number of units transfused,(203-205) and 1 meta-analysis showed that the full-dose aprotinin regimen was more effective than the half-dose regimen and that aprotinin was more effective than lysine analogues in reducing the need for transfusion.(205)

The Society of Thoracic Surgeons Practice Guidelines published in 2005 report that there are level A and B evidence (see below for definition) that aprotinin significantly limits bleeding in high-risk patients who have taken aspirin shortly

before undergoing CABG surgery.(207) Thus, the guidelines make a class IIa recommendation for the use of aprotinin for this patient population.

The Society of Thoracic Surgeons draft guidelines on blood conservation presented at the International Conference of the American Thoracic Society in 2006 recognize that full-dose aprotinin significantly reduces blood transfusions (class I recommendation based on level A evidence).(110) The guidelines also note that half-dose aprotinin reduces the number of patients needing blood transfusions (class IIb recommendation based on level B evidence) and that full-dose aprotinin reduces re-operations (class IIa recommendation based on level A and B evidence).

Level A evidence consists of data from well-designed placebo-controlled, blinded, randomized clinical trials or meta-analyses.(207) Level B evidence consists of data from a single well done randomized trial or from non-randomized, analytical observational studies. Level C evidence consists of consensus opinion or data from descriptive studies or informative case reports. Class I recommendations are based on evidence or general agreement that a given procedure or intervention is useful or effective. Class II recommendations are based on conflicting evidence about the usefulness of an intervention or procedure, with class IIa recommendations indicating that the weight of evidence favors the intervention or procedure and class IIb recommendations indicating that the usefulness of the intervention or procedure is less well established but consensus favors acceptance of the intervention or procedure. Class III recommendations are based on evidence that an intervention or procedure is not useful or is possibly harmful.

8.2 Blood loss and transfusion requirements: repeat CABG

8.2.1 Bayer US trials

The current US prescribing information for the use of Trasylol in patients undergoing repeat CABG surgery was based on data from 4 US trials. Table 8-1 summarizes these US trials. All 4 studies were prospective, randomized, double-blind, placebo-controlled trials. Two studies were multicenter; Study D89-006 had

5 sites and Study D92-008 had 11 sites. In these trials, 3 aprotinin dosing regimens were used, although not all studies necessarily had all 3 treatment regimens. Study D89-006 randomized patients to receive full-dose aprotinin or placebo. Study D89-004 and D91-007 randomized patients to receive full-dose aprotinin, half-dose aprotinin, or placebo. Study D92-008 randomized patients to receive full-dose aprotinin, half-dose aprotinin, a pump-prime aprotinin regimen, or placebo. The pump-prime regimen consists of only 2 million KIU of aprotinin added to the priming volume of the cardiopulmonary bypass circuit. This regimen is not approved in the US.

Table 8-1: US Randomized, Double-Blind, Placebo-Controlled Trials in Repeat CABG

		Number of Patients Evaluated for Efficacy			
Study # (International #; Principal Investigator)	**Surgical Procedure**	**Total**	**Placebo**	**Half-Dose Aprotinin**	**Full-Dose Aprotinin**
D89-004 (447;Cosgrove)(208)	Repeat CABG	154	52	49	53
D89-006 (448;Lemmer)(209)	Primary CABG	141	67	NA	74
	Repeat CABG	55	32	NA	23
D91-007 (457;Levy)	Primary OHS	54	17	18	19
	Primary CABG[a]	18	5	7	6
	Repeat OHS	38	12	14	12
	Repeat CABG[a]	17	7	4	6
D92-008 (466;Levy)(210)	Repeat CABG	254[b]	65	60	61

a This group is a subset of the overall population.
b This study was the only repeat CABG study to also include the pump-prime dose regimen with 68 patients valid for efficacy.
CABG = coronary artery bypass graft; NA = not applicable; OHS = open heart surgery.

In the pooled analysis, fewer patients receiving aprotinin (either the full-dose or half-dose regimen) required any donor blood compared to patients receiving placebo. The number of donor blood units required, the volume of donor blood transfused, the number of platelet units transfused, the number of fresh frozen plasma units transfused, and the total thoracic drainage volume were also reduced in patients receiving either full-dose and half-dose aprotinin as compared to placebo. The thoracic drainage rate and units of cryoprecipitate transfused were only

significantly reduced in patients receiving full-dose aprotinin. Table 8-2 summarizes the key efficacy outcomes for the pooled analysis for patients undergoing repeat CABG surgery.

Table 8-2: Key Efficacy Variables in the US Repeat CABG Patient Pool (Population: Repeat CABG Patients Valid for Efficacy)

Variable	Placebo N = 156	Aprotinin Half-Dose[a] N = 113	Aprotinin Full-Dose N = 143
% of patients who required donor blood	76.3%	48.7%[b]	46.9%[b]
Mean (SD) units of donor blood transfused	3.7 (4.4)	2.2 (5.0)[b]	1.6 (2.9)[b]
Mean (SD) mL of donor blood transfused	1132 (1443)	723 (1779)[b]	515 (999)[b]
Mean (SD) platelets transfused (donor units)	5.0 (10.0)	1.3 (4.6)[b]	0.9 (4.3)[b]
Mean (SD) cryoprecipitate transfused (donor units)	0.9 (3.5)	0.5 (4.0)	0.1 (0.8)[b]
Mean (SD) fresh-frozen plasma transfused (donor units)	1.3 (2.5)	0.3 (1.1)[b]	0.2 (0.9)[b]
Mean (SD) thoracic drainage rate (mL/hr)	89 (77)	66 (244)	40 (36)[b]
Mean (SD) total thoracic drainage volume (mL)[c]	1659 (1226)	1103 (2001)\[b]	960 (849)[b]
% of patients requiring re-operation for diffuse bleeding	1.9%	0%	0%

a Differences between the full-dose and half-dose regimens are not statistically significant.
b Significantly different from placebo, $p<0.05$ (transfusion variables analyzed via ANOVA on ranks).
c Excludes patients who required re-operation.
SD = standard deviation.

8.2.1.1 Red blood cells transfused

Table 8-3 summarizes the number and percent of patients undergoing repeat CABG surgery who required donor blood transfusion by study and in a pooled analysis. In the pooled analysis, 46.9% of full-dose aprotinin-treated patients and 48.7% of half-dose aprotinin-treated patients required a transfusion compared to 76.3% of placebo

patients. The full-dose aprotinin regimen had a significant 38.5% relative reduction in transfusion rate. The half-dose aprotinin regimen had a significant 36.2% relative reduction in transfusion rate.

Table 8-3: US Trials: Repeat CABG: Number and Percentage of Patients Requiring Donor Transfusion
(Population: Repeat CABG Patients Valid for Efficacy)

Study	Placebo % (n/N)	Half-Dose Aprotinin		Full-Dose Aprotinin	
		% (n/N)	p-value[a]	% (n/N)	p-value[a]
D89-004	77 (40/52)	47 (23/49)	0.002	42 (22/53)	<0.001
D89-006	72 (23/32)	NA	NA	30 (7/23)	0.001
D91-007	100 (7/7)	100 (4/4)	NR	83 (5/6)	NR
D92-008	75 (49/65)	47 (28/60)	0.001	54 (33/61)	0.007
US Pool	76.3 (119/156)	48.7 (55/113)	<0.001	46.9 (67/143)	<0.001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

Table 8-4 summarizes the number of blood units transfused in patients undergoing repeat CABG surgery. Overall, both the full-dose and half-dose regimens of aprotinin significantly reduced the number of units of blood transfused.

Table 8-4: US Trials: Repeat CABG: Mean Number of Units of Blood Transfused
(Population: Repeat CABG Patients Valid for Efficacy)

Study	Placebo N = 156	Half-Dose Aprotinin N = 113	p-value[a]	Full-Dose Aprotinin N = 143	p-value[a]
D89-004	3.5	2.0	0.0042	1.8	0.0003
D89-006	3.3	NA	NA	0.4	0.0001
D91-007	7.1	2.5	NR	3.0	NR
D92-008	3.4	2.3	<0.001	1.6	0.001
US Pool	3.7	2.2	0.0001	1.6	0.0001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

In the repeat CABG studies, the distribution of patients in each treatment group who required increasing numbers of RBC units is summarized in Table 8-5. Overall, 23.7%, 51.3%, and 53.1% of patients receiving placebo, half-dose aprotinin, and full-dose aprotinin, respectively, did not receive a transfusion. Furthermore, 8.4% of patients receiving full-dose aprotinin ($p < 0.0001$ versus placebo) were transfused

5 or more units compared to 12.4% of half-dose aprotinin-treated patients (p = 0.0166 versus placebo) and 27.6% of placebo patients.

Table 8-5: US Trials: Repeat CABG: Distribution of RBC Units Transfused (Population: Repeat CABG Patients Valid for Efficacy)

	Placebo N = 156		Half-Dose Aprotinin N = 113		Full-Dose Aprotinin N = 143	
# Units Transfused	n	%	n	%	n	%
0	37	23.7	58	51.3	76	53.1
1	12	7.7	11	9.7	13	9.1
2	24	15.4	14	12.4	16	11.2
3	22	14.1	8	7.1	13	9.1
4	18	11.5	8	7.1	13	9.1
≥5	43	27.6	14	12.4	12	8.4

8.2.1.2 Platelets transfused

Table 8-6 displays the mean number of platelet units transfused in patients undergoing repeat CABG surgery. Overall, aprotinin therapy was associated with a statistically significant reduction in the number of donor units of platelets transfused compared to placebo.

Table 8-6: US Trials: Repeat CABG: Mean Donor Units of Platelets Transfused (Population: Primary CABG Patients Valid for Efficacy)

	Placebo	Half-Dose Aprotinin		Full-Dose Aprotinin	
Study	N = 156	N = 113	p-value[a]	N = 143	p-value[a]
D89-004	5.6	0.9	0.0160	1.3	0.0264
D89-006	4.1	NA	NA	0.4	0.0171
D91-007	3.0	0.25	NR	0.0	NR
D92-008	4.8	1.7	<0.001	0.5	<0.001
US Pool	5.0	1.3	0.0001	0.9	0.0001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

For the repeat CABG studies, the distribution of patients in each treatment group requiring increasing numbers of platelet units is summarized in Table 8-7. Overall, 55.1%, 85.8%, and 91.6% of patients receiving placebo, half-dose aprotinin (p <0.0001 versus placebo), and full-dose aprotinin (p <0.0001 versus placebo), respectively, did not receive platelets. Furthermore, 35.3% of placebo patients

received 5 or more donor units of platelets compared to 9.7% and 7.0% of patients receiving half-dose ($p < 0.0001$ versus placebo) and full-dose aprotinin therapy ($p < 0.0001$ versus placebo), respectively.

Table 8-7: US Trials: Repeat CABG: Distribution of Donor Units of Platelets Transfused
(Population: Repeat CABG Patients Valid for Efficacy)

# Units Transfused	Placebo N = 156		Half-Dose Aprotinin N = 113		Full-Dose Aprotinin N = 143	
	n	%	n	%	n	%
0	86	55.1	97	85.8	131	91.6
1	5	3.2	5	4.4	2	1.4
2	6	3.8	0	0.0	0	0.0
3	2	1.3	0	0.0	0	0.0
4	2	1.3	0	0.0	0	0.0
5	0	0.0	0	0.0	0	0.0
≥6	55	35.3	11	9.7	10	7.0

8.2.1.3 Total blood and blood products transfused

Table 8-8 displays the units of blood and blood products transfused in patients undergoing repeat CABG surgery. Overall, there were significant 75.2% and 60.6% relative reductions in blood and blood product units transfused in patients receiving the full-dose and half-dose aprotinin regimens, respectively, compared to placebo.

In the pooled analysis, therapy with the half-dose of aprotinin did not significantly reduce the number of units of cryoprecipitate transfused ($p = 0.1348$ versus placebo) while the full-dose of aprotinin was associated with a statistically significant reduction ($p = 0.0013$ versus placebo).

In the pooled analysis, there was a statistically significant reduction in the number of fresh frozen plasma units transfused with both half-dose ($p = 0.0001$) and high-dose ($p = 0.0001$) aprotinin therapy compared to placebo.

Table 8-8: US Trials: Repeat CABG: Mean Units of Blood and Blood Products Transfused
(Population: Repeat CABG Patients Valid for Efficacy)

Study	Placebo N = 156	Half-Dose Aprotinin N = 113	p-value[a]	Full-Dose Aprotinin N = 143	p-value[a]
D89-004	10.0	3.0	0.0014	3.4	0.0001
D89-006	10.7	NA	NA	0.3	0.0003
D91-007	12.6	3.3	NR	3.0	NR
D92-008	10.3	5.5	<0.001	2.2	<0.001
US Pool	10.9	4.3	0.0001	2.7	0.0001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

For these repeat CABG studies, the distribution of patients in each treatment group requiring increasing numbers of blood and blood product units is summarized in Table 8-9. Overall, 18.6%, 47.8%, and 52.4% of patients receiving placebo, half-dose aprotinin ($p < 0.0001$ versus placebo), and full-dose aprotinin ($p < 0.0001$ versus placebo), respectively, were not transfused with blood or blood products while 49.4% of placebo-treated patients received at least 5 units compared to 18.7% and 13.3% of half-dose aprotinin-treated ($p < 0.0001$ versus placebo) and full-dose aprotinin-treated patients ($p < 0.0001$ versus placebo), respectively. Furthermore, 37.2% of placebo-treated patients compared to 9.7% and 5.6% of patients receiving half-dose ($p < 0.0001$ versus placebo) and full-dose aprotinin ($p < 0.0001$ versus placebo), respectively, were transfused at least 10 units.

Overall, 6.4%, 2.7% and 0.7% of placebo-treated, half-dose aprotinin-treated ($p = 0.5037$ versus placebo), and full-dose aprotinin-treated patients ($p = 0.0111$ versus placebo), respectively, received at least 5 cryoprecipitate units. Overall, 6.4%, 1.8%, and 0.7% of placebo-treated, half-dose aprotinin-treated ($p = 0.1057$ versus placebo), and full-dose aprotinin-treated patients ($p = 0.0038$ versus placebo), respectively, received at least 5 units of fresh frozen plasma.

Table 8-9: US Trials: Repeat CABG: Distribution of Units of Blood and Blood Products Transfused
(Population: Repeat CABG Patients Valid for Efficacy)

	Placebo N = 156		Half-Dose Aprotinin N = 113		Full-Dose Aprotinin N = 143	
# Units Transfused	n	%	n	%	n	%
0	29	18.6	54	47.8	75	52.4
1	10	6.4	11	9.7	12	8.4
2	19	12.2	15	13.3	17	11.9
3	14	9.0	8	7.1	10	7.0
4	7	4.5	4	3.5	10	7.0
5	4	2.6	3	2.7	7	4.9
6	10	6.4	3	2.7	2	1.4
7	0	0.0	1	0.9	1	0.7
8	3	1.9	2	1.8	1	0.7
9	2	1.3	1	0.9	0	0.0
≥10	58	37.2	11	9.7	8	5.6

8.2.2 Bayer Non-US studies in repeat CABG

Six non-US clinical trials of aprotinin reported transfusion rates in patients undergoing repeat CABG surgery. These studies ranged in sample size from 9 to 60 patients per treatment group. Three trials demonstrated statistically significant reductions in transfusion rates associated with aprotinin therapy. Two studies had numerical reductions in transfusion rates with aprotinin, albeit not statistically significant. One study showed the same rate of transfusion for aprotinin-treated and placebo-treated patients. Overall in the non-US studies, 112/253 (44.3%) of patients treated with aprotinin compared to 157/220 (71.4%) of placebo patients required a transfusion. Compared to placebo, therapy with aprotinin was associated with a 38% relative reduction in transfusion rates. These results are consistent with the results observed in the US trials and support the effectiveness of aprotinin therapy in patients undergoing repeat CABG surgery.

8.3 Blood loss and transfusion requirements: primary CABG

8.3.1 Bayer US trials

The current US prescribing information for the use of Trasylol for patients undergoing primary CABG surgery was based on data from 4 US trials. All 4 of these trials were prospective, randomized, double-blind and placebo-controlled

trials. Three were multicenter; Study D89-004 had 5 US sites, Study D92-016 had 21 US sites, and D92-048 had 13 sites (1 site was in Denmark, 2 sites were in Israel, and 10 sites in the US). All valid CABG patients from US and non-US sites were included in the analysis. In these trials, 3 aprotinin dosing regimens were used, although not all studies necessarily had all 3 treatment regimens. Study D89-006 and Study D92-048 randomized patients to receive full-dose aprotinin or placebo. Study D91-007 randomized patients to receive full-dose aprotinin, half-dose aprotinin, or placebo. Study D92-016 randomized patients to receive full-dose aprotinin, half-dose aprotinin, the pump-prime aprotinin regimen, or placebo. Table 8-10 summarizes these US trials.

Table 8-10: US Randomized, Double-Blind, Placebo-Controlled Trials in Primary CABG

		Number of Patients Evaluated for Efficacy			
Study # (International #; Principal Investigator)	**Surgical Procedure**	**Total**	**Placebo**	**Half-Dose Aprotinin**	**Full-Dose Aprotinin**
D89-006 (448; Lemmer)(209)	Primary CABG	141	67	NA	74
	Repeat CABG	55	32	NA	23
D91-007 (457; Levy)	Primary OHS	54	17	18	19
	Primary CABG[a]	18	5	7	6
	Repeat OHS	38	12	14	12
	Repeat CABG[a]	17	7	4	6
D92-016 (471; Lemmer)(211)	Primary CABG	644[b]	157	168	160
D92-048 (472; Alderman)(212)	Primary CABG	796	395	NA	401

a This group is a subset of the overall study population.
b This study was the only study to include the pump-prime dose regimen with 159 patients valid for efficacy.
CABG = coronary artery bypass graft; NA = not applicable; OHS = open heart surgery.

In the pooled analysis, fewer patients receiving the full-dose or half-dose aprotinin regimen required any donor blood in comparison to the placebo regimen. The number of units of donor blood required, the volume of donor blood transfused, the number of units of donor blood products transfused, the number of cryoprecipitate units transfused, the number of fresh frozen plasma units transfused, the thoracic drainage rate, total thoracic drainage volume, and the percentage of patients

requiring re-operation for diffuse bleeding were also reduced in patients receiving the full-dose and half-dose aprotinin regimens as compared to placebo. Table 8-11 summarizes the key efficacy outcomes for the pooled analyses in patients undergoing primary CABG surgery.

Table 8-11: Efficacy Variables in the US Primary CABG Patient Pool

Variable	Placebo N = 624	Aprotinin Half-Dose[a] N = 175	Aprotinin Full-Dose[a] N = 641
% of patients who required donor blood	53.5%	37.1%[b]	36.8%[b]
Mean (SD) units of donor blood transfused	1.7 (2.4)	1.0 (1.6)[b]	0.9 (1.4)[b]
Mean (SD) mL of donor blood transfused	584 (840)	313 (505)[b]	295 (503)[b]
Mean (SD) platelets transfused (donor units)	1.3 (3.7)	0.3 (1.6)[b]	0.3 (1.5)[b]
Mean (SD) cryoprecipitate transfused (donor units)	0.5 (2.2)	0.1 (0.8)[b]	0.0 (0.0)[b]
Mean (SD) fresh frozen plasma transfused (donor units)	0.6 (1.7)	0.2 (0.8)[b]	0.2 (0.9)[b]
Mean (SD) thoracic drainage rate (mL/h)	87 (67)	45 (31)[b]	39 (32)[b]
Mean (SD) total thoracic drainage volume (mL)[c]	1232 (711)	792 (465)[b]	705 (493)[b]
% of patients requiring re-operation for diffuse bleeding	1.4%	0%[b]	0%[b]

a Differences between full-dose aprotinin and half-dose aprotinin in efficacy are not statistically significant.
b Significantly different from placebo, $p<0.05$ (transfusion variables analyzed via ANOVA on ranks).
c Excludes patients who required re-operation.
SD = standard deviation.

8.3.1.1 Red blood cells transfused

Table 8-12 summarizes the number and percent of patients undergoing primary CABG surgery who were transfused donor blood by study and in a pooled analysis. In a pooled analysis, 36.8% and 37.1% of patients receiving full-dose and half-dose aprotinin, respectively, compared to 53.5% of placebo patients, required transfusion. Overall, the full-dose aprotinin regimen was associated with a significant 31.2%

relative reduction in transfusion rates while the half-dose aprotinin regimen had a significant 30.7% relative reduction.

Table 8-12: US Trials: Primary CABG: Number and Percentage of Patients Requiring Donor Transfusion
(Population: Primary CABG Patients Valid for Efficacy)

Study	Placebo % (n/N)	Half-Dose Aprotinin % (n/N)	Half-Dose Aprotinin p-value[a]	Full-Dose Aprotinin % (n/N)	Full-Dose Aprotinin p-value[a]
D89-006	52 (35/67)	NA	NA	38 (28/74)	0.052
D91-007	80 (4/5)	86 (6/7)	NR	67 (4/6)	NR
D92-016	52 (82/157)	35 (59/168)	<0.001	33 (53/160)	0.001
D92-048	54 (213/395)	NA	NA	38 (151/401)	<0.001
US Pool	53.5 (334/624)	37.1 (65/175)	0.002	36.8 (236/641)	<0.001

NA = not applicable; NR = not reported in study report due to the small sample size.
a Compared to placebo.

Table 8-13 summarizes the number of blood units transfused in patients undergoing primary CABG surgery. Overall, both the full-dose and half-dose regimens of aprotinin significantly reduced the number of blood units transfused compared to placebo.

Table 8-13: US Trials: Primary CABG: Mean Number of Units of Blood Transfused
(Population: Primary CABG Patients Valid for Efficacy)

Study	Placebo N = 624	Half-Dose Aprotinin N = 175	Half-Dose Aprotinin p-value[a]	High-Dose Aprotinin N = 641	High-Dose Aprotinin p-value[a]
D89-006	2.1	NA	NA	1.1	0.0246
D91-007	3.8	2.0	NR	2.3	NR
D92-016	1.8	0.9	<0.001	0.8	<0.001
D92-048	1.6	NA	NA	0.8	<0.001
US Pool	1.7	1.0	<0.001	0.9	<0.001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

In the pooled analysis, the distribution of patients in each treatment group who required increasing numbers of RBC units is summarized in Table 8-14. Overall, 46.5% , 62.9%, and 63.2% of placebo-treated, half-dose aprotinin-treated ($p = 0.002$ versus placebo), and full-dose aprotinin-treated patients ($p < 0.001$ versus placebo), respectively, did not receive a transfusion. Furthermore, 2.8% of patients receiving full-dose aprotinin ($p < 0.0001$ versus placebo) were transfused 5 or more units

compared to 5.7% of patients receiving half-dose aprotinin (p = 0.0286 versus placebo) and 10.1% of placebo patients.

Table 8-14: US Trials: Primary CABG: Distribution of RBC Units Transfused (Population: Primary CABG Patients Valid for Efficacy)

	Placebo N = 624		Half-Dose Aprotinin N = 175		Full-Dose Aprotinin N = 641	
# Units of Transfused	n	%	n	%	n	%
0	290	46.5	110	62.9	405	63.2
1	57	9.1	16	9.1	74	11.5
2	118	18.9	22	12.6	85	13.3
3	49	7.9	9	5.1	35	5.5
4	47	7.5	8	4.6	24	3.7
≥5	63	10.1	10	5.7	18	2.8

8.3.1.2 Platelets transfused

Table 8-15 displays the mean donor units of platelets transfused in patients undergoing primary CABG surgery. Overall, both the full-dose and half-dose of aprotinin significantly reduced the number of donor units of platelets transfused.

Table 8-15: US Trials: Primary CABG: Mean Donor Units of Platelets Transfused (Population: Primary CABG Patients Valid for Efficacy)

	Placebo	Half-Dose Aprotinin		Full-Dose Aprotinin	
Study	N = 624	N = 175	p-value[a]	N = 641	p-value[a]
D89-006	1.9	NA	NA	0.8	0.0439
D91-007	3.2	0.0	NR	0.0	NR
D92-016	1.2	0.3	<0.001	0.4	0.001
D92-048	1.2	NA	NA	0.1	< 0.001
US Pool	1.3	0.3	0.0001	0.3	0.0001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

In the pooled analysis, the distribution of patients in each treatment group who required increasing numbers of platelet units is summarized in Table 8-16. Overall, 82.4%, 94.3%, and 95.9% of placebo-treated, half-dose aprotinin-treated (p = 0.0005 versus placebo), and full-dose aprotinin-treated patients (p <0.0001 versus placebo), respectively, did not receive platelets. Furthermore, 2.9% and 3.3% of patients receiving half-dose (p = 0.004 versus placebo) and full-dose

aprotinin (p <0.0001 versus placebo), respectively, received 5 or more donor units of platelets compared to 11.5% of placebo patients.

Table 8-16: US Trials: Primary CABG: Distribution of Donor Units of Platelets Transfused
(Population: Primary CABG Patients Valid for Efficacy)

	Placebo N = 624		Half-Dose Aprotinin N = 175		Full-Dose Aprotinin N = 641	
# Units Transfused	**n**	**%**	**n**	**%**	**n**	**%**
0	514	82.4	165	94.3	615	95.9
1	21	3.4	4	2.3	5	0.8
2	8	1.3	1	0.6	0	0.0
3	2	0.3	0	0.0	0	0.0
4	7	1.1	0	0.0	0	0.0
≥5	72	11.5	5	2.9	21	3.3

8.3.1.3 Total blood and blood products transfused

Table 8-17 summarizes the units of blood and blood products transfused in patients undergoing primary CABG surgery. Overall, significant relative reductions in total blood and blood products transfused of 68.3% and 61.0% for patients receiving the full-dose aprotinin and half-dose aprotinin regimens, respectively, were noted.

In the pooled analysis, both the full-dose (p = 0.0001) and half-dose aprotinin regimens (p = 0.0107) significantly reduced the cryoprecipitate units transfused compared to placebo.

In the pooled analysis, both the full-dose (p = 0.0001) and half-dose aprotinin regimens (p = 0.0001) significantly reduced the fresh frozen plasma units transfused compared to placebo.

Table 8-17: US Trials: Primary CABG: Mean Units of Blood and Blood Products Transfused
(Population: Primary CABG Patients Valid for Efficacy)

Study	Placebo N = 624	Half-Dose Aprotinin N = 175	p-value[a]	Full-Dose Aprotinin N = 641	p-value[a]
D89-006	5.7	NA	NA	2.2	0.0100
D91-007	8.2	2	NR	2.7	NR
D92-016	4.1	1.6	<0.001	1.5	<0.001
D92-048	3.8	NA	NA	1.1	< 0.001
US Pool	4.1	1.6	0.0001	1.3	0.0001

a Compared to placebo.
NA = not applicable; NR = not reported in study report due to the small sample size.

In the pooled analysis, the distribution of patients in each treatment group who required increasing numbers of units of blood or blood products is summarized in Table 8-18. Overall, 42.6%, 61.1%, and 61.0% of patients receiving placebo, half-dose aprotinin ($p = 0.0011$ versus placebo), and full-dose aprotinin ($p < 0.0001$ versus placebo), respectively, were not transfused with blood or blood products. In addition, 22.4% of placebo-treated patients received at least 5 units compared to 10.8% and 7.3% of patients treated with half-dose ($p = 0.0013$) and full-dose aprotinin ($p < 0.0001$), respectively. Furthermore, 13.1% of placebo patients compared to 5.1% and 3.6% of patients receiving half-dose ($p = 0.0076$) and full-dose aprotinin ($p = 0.0011$), respectively, were transfused at least 10 units.

No patient treated with full-dose aprotinin and only 1 patient treated with half-dose aprotinin required cryoprecipitate. Among patients treated with placebo, 5.0% required cryoprecipitate and 4% required at least 5 units. Overall, 3.4%, 0.0%, and 1.1% of placebo-treated, half-dose aprotinin-treated ($p = 0.0012$ versus placebo), and full-dose aprotinin-treated patients ($p = 0.0080$ versus placebo), respectively, received at least 5 units of fresh frozen plasma.

Table 8-18: US Trials: Primary CABG: Distribution of Units of Blood and Blood Products Transfused
(Population: Primary CABG Patients Valid for Efficacy)

	Placebo N = 624		Half-Dose Aprotinin N = 175		Full-Dose Aprotinin N = 641	
# Units Transfused	N	%	n	%	n	%
0	266	42.6	107	61.1	391	61.0
1	48	7.7	16	9.1	70	10.9
2	94	15.1	19	10.9	77	12.0
3	46	7.4	9	5.1	35	5.5
4	30	4.8	5	2.9	21	3.3
5	21	3.4	6	3.4	11	1.7
6	16	2.6	1	0.6	8	1.2
7	8	1.3	1	0.6	3	0.5
8	9	1.4	2	1.1	2	0.3
9	4	0.6	0	0.0	0	0.0
≥10	82	13.1	9	5.1	23	3.6

8.3.2 Bayer Non-US studies in primary CABG

Thirty-seven non-US clinical trials reported transfusion rates for patients undergoing primary CABG surgery. These studies ranged in sample size from 7 to 77 patients per treatment group. Twenty-one studies demonstrated that aprotinin significantly reduced the transfusion rates compared to placebo. Twelve studies had a numerical reduction in transfusion rates associated with aprotinin therapy, but the rates did not differ statistically from placebo. For the remaining 4 studies, 2 showed the same rate of transfusion for aprotinin-treated and placebo-treated patients while 2 showed a small and non-significant increase in the rate of transfusion for aprotinin-treated patients. Overall in the non-US studies, 566/1417 (39.9%) of aprotinin-treated patients compared to 836/1304 (64.1%) of placebo patients required a transfusion. Compared to placebo, aprotinin was associated with a 38% relative reduction in transfusion rates. These results are consistent with the results observed in the US trials and support the effectiveness of aprotinin therapy in patients undergoing primary CABG surgery.

8.4 Re-operation for diffuse bleeding

Excessive microvascular bleeding can also result in re-exploration, which has been shown to be associated with a variety of negative outcomes such as renal failure,

sepsis, atrial arrhythmias, prolonged requirement for mechanical ventilatory support and longer length of stay.(213-216) More importantly, three of these large (n = 6015, n = 8586, and n = 2221, respectively) database analyses revealed a consistent and dramatic increase (3 to 4-fold) in mortality, from 1.2% to 4.8%,(213) from 3.3% to 9.5%,(214) and from 5.5% to 22%,(215) respectively. It is not the re-exploration, but more importantly the degree of bleeding that usually necessitates re-exploration which probably results in a negative outcome. This is illustrated by the analysis by Moulton et al which revealed that when patients bleed more than 1500 to 2000 mL within 24 hours, there is an exponential increase in percentage of patient who develop adverse outcomes and an increase in mortlity (12.1% in patients with > 2000 mL versus 4.3% in patients with < 2000 mL blood loss). In these analyses, only approximately 50% of patients who have excessive bleeding requiring re-exploration have a surgical source of bleeding, which demonstrates the important role of acquired hemostatic abnormalities that result in diffuse, microvascular bleeding and that can be attenuated by pharmacologic therapy.

Re-operations may be due to surgical bleeding or diffuse bleeding. Surgical bleeding is often due to inadequate hemostasis associated with vessel sutures. Surgical bleeding may be reduced if there is better visibility in the surgical field. Diffuse bleeding may be secondary to an inflammatory process or coagulopathy from contact activation.(217-219) Aprotinin attenuates the inflammatory process by inhibiting kallikrein inhibition and protein C.(220, 221) Aprotinin also reduces bleeding by inhibiting fibrinolysis, and contributes to better visibility in the surgical field.(222)

In the US clinical trials that enrolled patients undergoing repeat CABG surgery, re-operations (including those for diffuse or surgical bleeding) were required for 4.8% of full-dose aprotinin-treated patients (p = 0.6852 versus placebo), 6.2% of half-dose aprotinin-treated patients (p = 0.7619 versus placebo), and 6.7% of placebo-treated patients. None of the patients treated with full-dose (p = 0.2489) or

half-dose aprotinin (p = 0.2484) required re-operations for diffuse bleeding compared to 3 (1.9%) patients treated with placebo.

In the US clinical trials that enrolled patients undergoing primary CABG surgery, re-operations (including those for diffuse or surgical bleeding) were required for 3.5% of full-dose aprotinin-treated patients (p = 0.0069 versus placebo), 1.1% of half-dose aprotinin-treated patients (p = 0.0005 versus placebo), and 6.7% of placebo-treated patients. None of the patients treated with full-dose (p = 0.0017) or half-dose aprotinin (p = 0.0248) required re-operations for diffuse bleeding compared to 9 (1.4%) patients treated with placebo.

Similar results were published from a meta-analysis of 33 trials in the Bayer global randomized clinical trial database.(223) This meta-analysis examined 1808 placebo-treated and 1818 full-dose aprotinin-treated patients undergoing CABG surgery. The risk of re-operation for surgical or diffuse bleeding was significantly reduced with aprotinin therapy (relative risk 0.51; 95% confidence interval 0.37, 0.72), with 5.8% of placebo-treated and 2.9% of aprotinin-treated patients requiring re-operations. For surgical bleeding, the re-operation rates were 3.6% and 2.0% for placebo-treated and aprotinin-treated patients, respectively. For diffuse bleeding, the re-operation rates were 1.4% and 0.2% for placebo-treated and aprotinin-treated patients, respectively.

The results from the Bayer database are supported by 5 meta-analyses that have evaluated the impact of aprotinin on re-operation for bleeding.(202-206) The first meta-analysis examined 45 randomized trials.(204) The risk of re-operation was significantly reduced with aprotinin therapy (relative risk 0.44; 95% confidence interval 0.27, 0.73), with 5.2% of placebo-treated and 1.8% of aprotinin-treated patients requiring re-operations (p <0.001). In this same meta-analysis, the re-operation rates for bleeding were 2.9% for patients in the control group and 2.4% for patients treated with tranexamic acid (p = 0.84) among a total of 882 patients enrolled in 12 trials. Lysine analogues are discussed in Section 8.8.

The Cochrane Collaboration reviewed 29 trials (n = 2900) for the risk of re-operation.(203) The use of aprotinin significantly reduced re-operations for bleeding by 60% (relative risk = 0.40; 95% confidence interval 0.25, 0.66). In this same meta-analysis, the use of tranexamic acid did not significantly reduce re-operations for bleeding (relative risk 0.72; 95% confidence interval 0.29, 1.79) among a total of 774 patients enrolled in 9 trials. The effect of aminocaproic acid on the rate of re-operations was not analyzed because this drug did not significantly reduce the need for transfusion. Lysine analogues are further discussed in Section 8.8.

Similar reductions in the need for subsequent re-operations were reported in the 3 other meta-analyses.(202, 205, 206)

8.5 Stroke and cognitive outcomes

In the brain, ischemia-reperfusion may contribute to secondary injury.(224) In animal models of ischemia-reperfusion injury, increased permeability of the blood-brain barrier allows extravasation of small molecules and blood proteins into brain tissue.(225) Leukocytes accumulate and adhere in cerebral arterioles and venules,(226) and leukocyte-mediated cerebral ischemia-reperfusion injury may contribute to damage to blood vessels and surrounding brain cells.(226-228) Protease-activated receptor 1 activation contributes to neurodegeneration. In one study, inhibition of protease-activated receptor 1 was shown to reduce cerebral infarct volume following ischemia-reperfusion injury.(229, 230)

In animal models, aprotinin modulates the systemic inflammatory response and ischemia-reperfusion injury. Aprotinin interrupts the protease-mediated inflammatory cascade, inhibits neutrophil activation and transmigration, as well as release of cytotoxins, and inhibits ischemia-reperfusion activated proteases that contribute to neuronal cell death.(231, 232) Aprotinin also inhibits protease-activated receptor 1 activation.(155) Aprotinin inhibition of endothelial activation by protease-activated receptor 1 reduces disruption of the blood-brain barrier in dogs.(233)

In addition to plasmin inhibition, the effects of aprotinin use in cardiopulmonary bypass involve a reduction in the systemic inflammatory response. The aprotinin-associated reduction in bleeding and the need for re-operations for bleeding decreases the need for allogeneic blood transfusions. These effects upon systemic inflammatory response may help attenuate some of the central nervous system complications associated with cardiopulmonary bypass.

An association between aprotinin therapy and a reduction in the incidence of stroke following cardiopulmonary bypass has been recognized. In a randomized, placebo-controlled trial (Study D92-008), Levy et al examined the effects of full-dose aprotinin, half-dose aprotinin, a pump-prime dose of aprotinin, or placebo upon blood loss and transfusion requirements in 287 patients undergoing repeat CABG surgery.(210) Of the six study patients (2.1%) who suffered a stroke, 5 were in the placebo group and one was in the pump-prime aprotinin group. No stroke was reported in patients receiving full-dose or half-dose aprotinin (overall $p = 0.01$).

Smith et al reported an analysis designed to evaluate clinical outcomes associated with the use of different aprotinin doses among 2283 patients undergoing CABG surgery.(234) Data from 4 published studies (including D92-008) and from 2 unpublished trials (1 was subsequently published) obtained from Bayer were included in the analysis. For the pooled analysis, patients received either the full-dose aprotinin regimen ($n = 860$), the half-dose aprotinin regimen ($n = 317$), aprotinin only added to the priming volume of the heart-lung machine ($n = 245$), or placebo ($n = 861$). This analysis demonstrated a significant reduction in the incidence of stroke in patients receiving full-dose aprotinin (1.0%) compared to placebo (2.4%; $p = 0.027$).

Bayer subsequently conducted 2 studies designed to evaluate the impact of aprotinin on post-operative central nervous system dysfunction among patients undergoing CABG surgery. The first trial (Study 489) was a randomized, double-blind, placebo-controlled pilot study that evaluated the impact of aprotinin on post-operative central nervous system dysfunction, defined as the onset of new

neurological signs or neuropsychological decline. Patients were randomized to receive full-dose aprotinin (n = 75) or placebo (n = 71). No statistical difference in central nervous system dysfunction was noted between aprotinin-treated and placebo-treated patients.

The second trial (Study 490) was a randomized, double-blind, placebo-controlled exploratory study to assess the effect of aprotinin on cerebral edema among patients undergoing CABG surgery. Patients were randomized to receive full-dose aprotinin (n = 27) or placebo (n = 29). No reduction in the severity of cerebral edema or other central nervous system structural abnormalities was apparent among aprotinin-treated compared to placebo-treated patients.

Although not demonstrated by the Bayer trials, other studies have shown a reduction in cognitive dysfunction associated with aprotinin therapy among patients undergoing cardiac surgery using cardiopulmonary bypass.(235-238)

A retrospective analysis of cardiac surgery patients from 1 institution who were at high risk for post-operative stroke was conducted by Frumento et al.(239) The study showed that the use of full-dose aprotinin was associated with a reduced incidence of stroke. Of the 1,524 patients screened, 149 met all the predefined criteria for increased risk of stroke; pre-operative stroke risk values were similar among patients in each study group. Post-operative stroke in this study was defined as a new cerebral infarct confirmed by computed tomography or magnetic resonance imaging. Overall, 16% (24/149) of patients at high risk for post-operative stroke had a stroke. The incidence of stroke was 0% (0/26) in patients who received full-dose aprotinin, 22% (15/67) in patients who received half-dose aprotinin, and 16% (9/56) in patients receiving no aprotinin ($p < 0.05$).

A prospective cohort study compared the incidence of adverse neurological outcomes in 77 cardiac surgical patients treated with full-dose or half-dose aprotinin.(240) Mean stroke risk indices were similar in both groups; however, the incidence of a Type I outcome was 12% (5/38 patients) in the half-dose group and

0% (0/39 patients) in the full-dose group (p = 0.05). Type I neurological outcomes were defined as death due to stroke or hypoxic encephalopathy, non-fatal stroke or transient ischemic attack, or stupor or coma at time of discharge. Type II neurological outcomes were defined as new deterioration in intellectual function, confusion, agitation, disorientation, memory deficit, or seizure without evidence of focal injury. Type II outcomes were similar between groups.

Sedrakyan et al performed a meta-analysis of 35 published, randomized controlled trials (n = 3,879) that evaluated the impact of aprotinin on clinical outcomes, including stroke, among patients undergoing CABG surgery.(201) The risk of stroke was evaluated in 18 trials (n = 2,976). Aprotinin therapy was associated with a significant reduction in the risk of stroke (relative risk 0.53; 95% confidence interval 0.31, 0.90).

Two additional meta-analyses showed non-significant reductions in the risk of stroke among patients undergoing cardiac surgery.(203, 206)

In summary, an association between aprotinin therapy and reduction in the incidence of stroke following cardiopulmonary bypass has been recognized. Aprotinin may reduce or eliminate the need for platelet transfusion, cardiotomy suction, and the salvaging of blood losses that may translate into a reduced risk for both stroke and the development of microemboli-associated postoperative neuropsychologic deficits. In addition, modulation of the systemic inflammatory response and inhibition of the platelet protease-activated receptor 1 have also been suggested as mechanisms by which aprotinin may attenuate some of the central nervous system complications associated with cardiopulmonary bypass.(151, 152, 155, 233)

8.6 Efficacy and use of anti-platelet agents

Anti-platelet agents may increase the need for transfusion in patients having CABG surgery.(134, 135, 141) Approximately 12% to 26% of patients undergoing CABG surgery are receiving clopidogrel,(135, 141) and approximately 80% had received

aspirin in the 5-day period preceding CABG surgery in one large observational study.(241) Transfusion requirements for red cells and platelets were increased by 15% for patients taking aspirin and by 51% for those taking both aspirin and clopidogrel.(134) Another study suggested that clopidogrel use was associated with increased transfusion requirements, chest drainage, and duration of mechanical ventilation.(141)

The Society of Thoracic Surgeons Practice Guidelines published in 2005 cite level A and B evidence that aprotinin limits bleeding in aspirin-treated patients undergoing CABG surgery.(207) Thus, the guidelines make a class IIa recommendation for the use of aprotinin in aspirin-treated patients undergoing CABG surgery who fall into a high-risk category.

8.6.1 Aspirin

Table 8-19 summarizes the efficacy of aprotinin among aspirin-treated patients undergoing repeat CABG surgery. Among those receiving aspirin, significant relative reductions in transfusion rates of 35.4% for half-dose aprotinin-treated patients and 46.7% for full-dose aprotinin-treated patients were noted.

Table 8-19: US Trials: Repeat CABG: Efficacy and Aspirin Use (Population: Repeat CABG Patients Valid for Efficacy)

Outcome Variable	Aspirin Use	Placebo % (n/N)	Half-Dose Aprotinin % (n/N)	Half-Dose Aprotinin p-value[a]	Full-Dose Aprotinin % (n/N)	Full-Dose Aprotinin p-value[a]
% receiving blood transfusion	No	67.4 (58/86)	43.1 (28/65)	0.0019	47.3 (35/74)	0.0079
	Yes	87.1 (61/70)	56.3 (27/48)	<0.0008	46.4 (32/69)	<0.0001
% receiving blood or blood product	No	74.4 (64/86)	43.1 (28/65)	0.0002	48.6 (36/74)	0.0006
	Yes	90.0 (63/70)	64.6 (31/48)	0.0020	46.4 (32/69)	<0.0001
Re-operation for diffuse bleeding	No	0.0 (0/86)	0 (0/65)	1.0000	0.0 (0/74)	1.0000
	Yes	4.3 (3/70)	0 (0/48)	0.2444	0.0 (0/69)	0.2446

a Compared to placebo.

Table 8-20 summarizes the efficacy of aprotinin among aspirin-treated patients undergoing repeat CABG surgery. Among those receiving aspirin, significant

relative reductions in transfusion rates of 29.7% for half-dose aprotinin-treated patients and 31.0% for full-dose aprotinin-treated patients were noted.

Table 8-20: US Trials: Primary CABG: Efficacy by Aspirin Use (Population: Primary CABG Patients Valid for Efficacy)

Outcome Variable	Aspirin Use	Placebo % (n/N)	Half-Dose Aprotinin % (n/N)	p-value	Full-Dose Aprotinin % (n/N)	p-value
% receiving blood transfusion	No	52.3 (145/277)	33.3 (14/42)	0.0962	35.7 (96/269)	<0.0001
	Yes	54.5 (189/347)	38.3 (51/133)	0.0093	37.6 (140/372)	<0.0001
% receiving blood or blood product	No	56.7 (157/277)	38.1 (16/42)	0.1658	39.4 (106/269)	<0.0001
	Yes	57.9 (201/347)	39.1 (52/133)	0.0026	38.7 (144/372)	<0.0001
Re-operation for diffuse bleeding	No	1.8 (5/277)	0.0 (0/42)	0.4941	0.0 (0/269)	0.0615
	Yes	1.2 (4/347)	0.0 (0/133)	0.2444	0.0 (0/372)	0.0538

Bayer Study 435, a non-US trial, evaluated the effect of aprotinin on reducing total perioperative blood loss among 55 high-risk patients taking aspirin within 48 hours prior to undergoing CABG, valve replacement, or combined CABG and valve replacement surgery.(242) Twenty-eight patients were randomized to receive full-dose aprotinin and 23 patients to receive placebo. The total blood loss was only 1209.7 mL in the aprotinin group compared to 2532.2 mL in the placebo group ($p = 0.0001$). The use of aprotinin also resulted in a significantly smaller number of patients requiring the transfusion of any blood product. Only 59% of patients in the aprotinin group received blood products while 88% of placebo-treated patients received blood products ($p = 0.016$). The mean number of blood units transfused was significantly less ($p < 0.008$) in the aprotinin group (1.6 units) compared to the placebo group (4.3 units). In addition, patients who received aprotinin had generally shorter operative procedures, which may have resulted from the surgeon being able to work more efficiently in a drier surgical field. Aprotinin-treated patients also spent less time in the intensive care unit and in the hospital. This study demonstrated that aprotinin can produce significant reductions in perioperative blood loss and packed red cell transfusion requirements among patients taking aspirin who undergo open heart surgery. The results of this study are included in the US prescribing information for Trasylol.

Two meta-analyses confirm the effectiveness of aprotinin among cardiac surgical patients receiving aspirin. Sedrakyan et al demonstrated a significant reduction in the risk for transfusions among patients undergoing CABG surgery while receiving aspirin.(201) Levi et al demonstrated a significant decrease in re-operations among cardiac surgical patients receiving aspirin.(205)

8.6.2 Clopidogrel

Three studies published in 2005 demonstrate that aprotinin use during CABG surgery reduces bleeding and the need for transfusion among patients receiving clopidogrel.(243-245)

In the first study, patients in the placebo group were taken off aspirin and clopidogrel 5 days prior to surgery while patients in the full-dose aprotinin group remained on aspirin and clopidogrel until surgery.(243) In this randomized comparison of 50 patients, full-dose aprotinin significantly reduced post-operative blood loss (446 mL in the aprotinin group versus 702 mL in the placebo group; $p = 0.004$) and the number of units of blood transfused (0.3 units in the aprotinin group versus 1.0 unit in the placebo group; $p = 0.03$).

The second study was a double-blind, placebo-controlled trial of 73 patients (38 receiving placebo and 35 receiving full-dose aprotinin) with unstable angina undergoing CABG surgery.(245) All patients were treated with clopidogrel less than 5 days prior to surgery. Patients in the full-dose aprotinin group had a reduction in mean thoracic drainage (770 mL versus 1200 mL; $p <0.001$), reduced mean number of RBC units transfused (1.24 units versus 2.84 units; $p = 0.03$), and reduced mean number of platelets units transfused (0.15 units versus 0.89 units; $p = 0.003$).

The third study was a retrospective review of 33 patients who underwent CABG surgery within 5 days of clopidogrel exposure.(244) Eighteen patients received full-dose aprotinin and 15 patients were in the control group. The mean post-operative blood loss was 710 mL in the aprotinin group and 1210 mL in the control group

(p = 0.004). The aprotinin group received fewer transfusions of packed red cells (0.9 units versus 2.7 units; p = 0.01), platelets (0.1 units versus 0.6 units; p = 0.02) and blood products (1.1 units versus 3.7 units; p = 0.002). Three patients in the control group required re-operations for bleeding compared with none in the aprotinin group (p = 0.05).

8.7 Dose-response relationship for efficacy

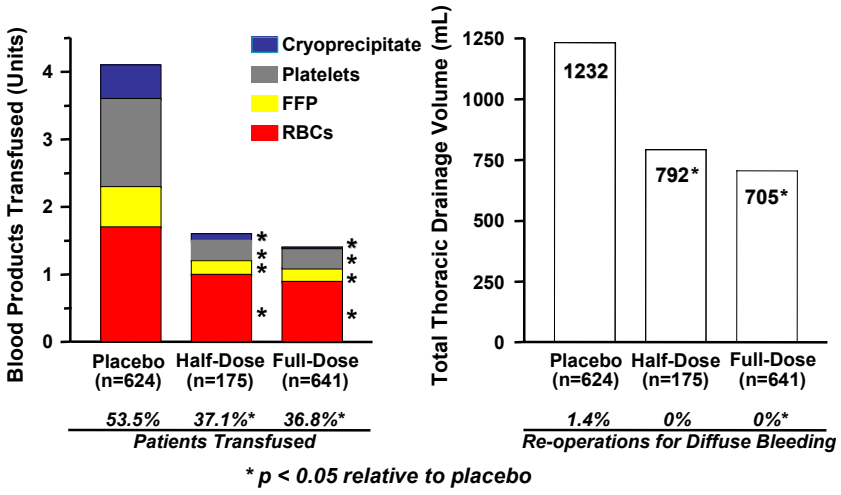
Considerably more patients received the full-dose regimen of aprotinin than the half-dose regimen during the clinical development program. Four US placebo-controlled trials (Studies D89-004, D91-007, D92-008 and D92-016) and 2 non-US placebo-controlled trials (Studies 462 and 478) evaluated the full-dose and half-dose aprotinin regimens. For each outcome variable, the effect of full-dose aprotinin regimen was generally of a greater magnitude than the half-dose regimen, albeit not statistically different. However, none of the studies were designed to test for differences between the aprotinin regimens.

Furthermore, an additional pump-prime dosing regimen was studied in 3 US trials (Studies D92-008 and D92-016 as well as Study D92-022, a compassionate use protocol) and 4 non-US trials (Studies 420, 445, 465, and 467). Among patients undergoing repeat CABG surgery, the pump-prime regimen did not decrease the number of patients transfused (72.1%) compared to placebo (76.3%) as well as blood loss as assessed by total thoracic drainage (1561 mL) compared to placebo (1659 mL). Among patients undergoing primary CABG surgery, the pump-prime regimen did significantly decrease the number of patients transfused (32.7%) compared to placebo (53.5%) and total thoracic drainage (852 mL) compared to placebo (1232 mL). This regimen is not approved in the US.

In a pooled analysis of data from the US trials that evaluated the efficacy of aprotinin among patients undergoing primary CABG surgery, patients receiving the full-dose regimen had a 31.2% relative reduction in transfusion rate while those receiving the half-dose regimen had a 30.7% relative reduction in transfusion rate compared to those receiving placebo. Compared to placebo, both doses of aprotinin

significantly reduced the number of RBC units, platelet units, fresh frozen plasma units, and cryoprecipitate transfused in patients. The full-dose aprotinin also significantly reduced the need for re-operations for diffuse bleeding. Overall, 22.4% of placebo-treated patients received at least 5 units of blood and blood products compared to 10.9% and 7.3% of half-dose and full-dose aprotinin-treated patients, respectively. Furthermore, 13.1% of placebo-treated patients compared to 5.1% and 3.6% of half-dose and full-dose aprotinin-treated patients, respectively, were transfused at least 10 units. The full-dose and half-dose aprotinin regimens were associated with 42.8% and 35.7% relative reductions in thoracic drainage, respectively, compared to placebo. Figure 8-1 graphically displays the key efficacy results for patients undergoing primary CABG surgery.

Figure 8-1: Aprotinin Use in Primary CABG Surgery

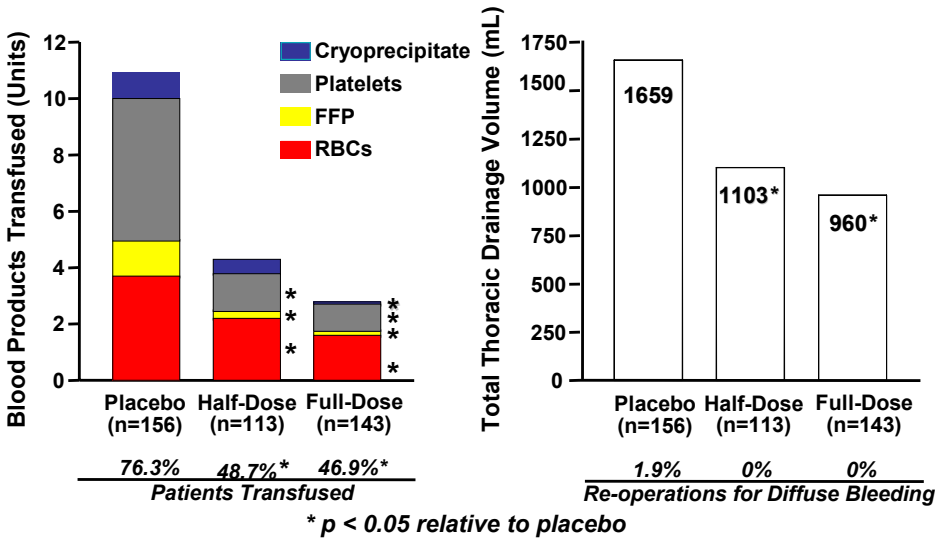


FFP = fresh frozen plasma; RBC = red blood cells.

In a pooled analysis of data from the US trials that evaluated the efficacy of aprotinin regimens among patients undergoing repeat CABG surgery, patients receiving the full-dose regimen had a 38.5% relative reduction in transfusion rate while those receiving the half-dose regimen had a 36.2% relative reduction in transfusion rate compared to those receiving placebo. Patients receiving both doses of aprotinin had significant reductions in the number of RBC units, platelet units,

and fresh frozen plasma units transfused compared to placebo. Patients receiving the full-dose regimen also had reductions in the number of cryoprecipitate units transfused. Overall, 49.4% of placebo-treated patients received at least 5 units of blood and blood products compared to 18.6% and 13.3% of half-dose and full-dose aprotinin-treated patients, respectively. Furthermore, 37.2% of placebo-treated patients compared to 9.7% and 5.6% of half-dose and full-dose aprotinin-treated patients, respectively, were transfused at least 10 units. Although no full-dose treated-patient or half-dose treated-patient required re-operations for diffuse bleeding, the rates did not differ from that noted for placebo-treated patients. Figure 8-2 graphically displays the key efficacy results for patients undergoing repeat CABG surgery.

Figure 8-2: Aprotinin Use in Repeat CABG



FFP = fresh frozen plasma; RBC = red blood cells.

As determined in randomized, double-blind, clinical trials, both the full-dose and half-dose aprotinin regimens have been shown to be effective for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing CABG surgery utilizing cardiopulmonary bypass. In addition to

plasmin inhibition, evidence suggests that the effects of full-dose aprotinin on blood loss and the inflammatory response triggered by cardiopulmonary bypass are the result of both its dose-dependent inhibition of kallikrein and effects on platelet and neutrophil function.(234, 246-249) As described in the Trasylol prescribing information, dose-dependent numerical reductions, albeit not statistically significant, in thoracic drainage and volume of donor blood transfused were noted in clinical trials. While effective in reducing bleeding as a result of plasmin inhibition, half-dose aprotinin does not appear to have significant effects upon the systemic inflammatory response.(234, 246, 247) In addition, the dose-dependent anti-inflammatory actions of aprotinin appear to occur without any relevant differences in the incidence of adverse events between the kallikrein-inhibiting dose (full-dose regimen) and the plasmin-inhibiting dose (half-dose regimen).(210, 234, 246, 247)

An association between aprotinin therapy and a reduction in the incidence of stroke following cardiopulmonary bypass has been recognized. As noted in the Trasylol prescribing information, a pooled analysis of data from controlled clinical trials in the US revealed that the incidence of cerebrovascular accident was 0.7% among patients treated with aprotinin (n = 2002) and 2.1% among those treated with placebo (n = 1084). In addition, the use of aprotinin was associated with a reduced incidence of stroke in three clinical studies, with fewer strokes reported in patients receiving the full-dose aprotinin regimen.(210, 239, 240)

In conclusion, although the full-dose and half-dose aprotinin regimens have efficacy for reducing blood loss and the need for transfusion, the full-dose regimen decreased the need for re-operations for diffuse bleeding and there was a trend for full-dose aprotinin-treated patients to receive fewer units of blood compared to half-dose aprotinin-treated patients. However, none of the studies were designed to compare directly the full-dose and half-dose aprotinin regimens.

8.8 Lysine analogues

Tranexamic acid and epsilon-aminocaproic acid are lysine analogs which have been used during CABG surgery to reduce blood loss and need for transfusion. However,

neither drug is approved by the FDA for this indication. The effectiveness of these agents to reduce bleeding, transfusion and re-exploration has been variable, unlike the consistent findings with aprotinin, and the safety of these agents has not been adequately evaluated. Unlike the prospective, randomized studies that have been performed with aprotinin to examine both safety and efficacy, the majority of the studies that have been performed with tranexamic acid and epsilon-aminocaproic acid are either retrospective or prospective with comparison to historical control groups.

Overall, 5 meta-analysis evaluated the effectiveness of aprotinin, tranexamic acid, or aminocaproic acid compared to control in cardiac surgery.(202-206) Aprotinin significantly reduced the number of transfused patients compared to placebo or no treatment in all 5 meta-analyses that examined this outcome.(202-206) Compared to placebo or no treatment, tranexamic acid significantly reduced the number of transfused patients in both meta-analyses that examined this outcome(203, 204) while aminocaproic acid only reduced the number of transfused patients in 1(206) of 3 meta-analyses.(203, 204, 206) Two meta-analyses(202, 205) evaluated tranexamic acid and aminocaproic acid together as a lysine analog cohort. Only one of those analysis demonstrated that lysine analogs reduced the number of transfused patients.(205)

Aprotinin significantly reduced the need for re-operations for bleeding compared to placebo or no treatment in 4 of 5 meta-analyses that examined this outcome.(202-206) Compared to placebo or no treatment, tranexamic acid(203, 204) as well as aminocaproic acid(203, 206) did not significantly reduce the need for re-operations for bleeding in both meta-analyses that examined this outcome. In the two meta-analysis that combined the lysine analogs(202, 205), only one showed a reduction in the need for re-operation for bleeding.(205)

In the 3 meta-analyses that compared the transfusion outcome, there were no significant differences in the number of transfused patients among those receiving aprotinin and those receiving tranexamic acid.(203, 204, 250) There was no

significant difference in the number of patients needing re-operations for bleeding in the 1 meta-analysis that examined this comparison.(250) However, there were trends for aprotinin being more efficacious in these analyses.

There was no significant difference in the number of transfused patients among those receiving aprotinin and those receiving aminocaproic acid in the 1 meta-analysis that examined this comparison.(250) Again, there was a trend for aprotinin being more efficacious. There was insufficient data to compare the re-operation rates for aprotinin-treated and aminocaproic acid-treated patients in this meta-analysis.

The Society of Thoracic Surgeons draft guidelines from 2006 on blood conservation recognize that the lysine analogues reduce the need for blood transfusion (class IIb recommendation based on level B evidence) but were not indicated for reducing the need of re-operations for bleeding (class III based on level B evidence).(110)

The Society of Thoracic Surgeons Practice Guidelines on aspirin use during cardiac surgery published in 2005 note that many surgeons have safely used epsilon-aminocaproic acid and tranexamic acid for their antifibrinolytic activity despite the lack of definitive evidence of benefit.(207) Thus, the guidelines suggest that other lysine analogues can be used to limit bleeding but that they are not the best option (class IIb recommendation based on level B and C evidence).

8.9 Efficacy conclusions

The results from the Bayer randomized clinical trial database have demonstrated that the full-dose aprotinin regimen reduced blood loss and need for transfusion among patients undergoing primary or repeat CABG surgery utilizing cardiopulmonary bypass. Patients receiving full-dose aprotinin required the transfusion of fewer RBC units, platelet units, fresh frozen plasma units, and cryoprecipitate units. Among patients undergoing primary CABG surgery, full-dose aprotinin reduced the need for re-operations for diffuse bleeding.

The half-dose aprotinin regimen reduced blood loss and need for transfusion among patients undergoing primary and repeat CABG surgery. Patients undergoing primary CABG surgery who received the half-dose aprotinin regimen required the transfusion of fewer RBC units, platelet units, fresh frozen plasma units, and cryoprecipitate units. While patients undergoing repeat CABG surgery required the transfusion of fewer RBC units, platelet units, and fresh frozen plasma units.

Among patients undergoing primary or repeat CABG surgery who were receiving aspirin, both aprotinin regimens reduced the need for transfusion.

It can be expected that the marked reduction in the number of blood or blood product units transfused among patients receiving aprotinin should lead to fewer transfusion-related complications. Similarly, the need for fewer re-operations due to diffuse bleeding should lead to fewer complications associated with these procedures. However, none of the Bayer studies were specifically designed to evaluate the effect of aprotinin on complications associated with transfusions or with subsequent surgeries.

In general, data from other published trials, meta-analyses, and observational studies are consistent with the results noted in the Bayer database. In addition, patients treated with aprotinin may have a decreased risk of stroke and may have other benefits associated with the anti-inflammatory effects of full-dose aprotinin. The decline in the incidence of strokes after CABG surgery that has been associated with aprotinin therapy should translate into clinical benefit for these patients. Again, however, the studies were not designed to evaluate the effect of aprotinin on complications associated with post-operative strokes. Furthermore, full-dose aprotinin use during CABG surgery has been shown to reduce bleeding and the need for transfusion among patients receiving clopidogrel. Trials examining the concomitant use of aprotinin and clopidogrel among patients undergoing CABG surgery have only used the full-dose aprotinin regimen.

Although the studies were not designed to compare the full-dose and half-dose aprotinin regimens, there was a trend among patients receiving full-dose aprotinin compared to those receiving half-dose aprotinin to require fewer units of blood or blood products. In addition, the decreased risk of stroke and the anti-inflammatory effects of aprotinin have been typically associated with the full-dose regimen. These data suggest that the full-dose aprotinin regimen may have clinical benefits over the half-dose regimen.

9. Safety

9.1 Non-clinical toxicology

A variety of toxicological investigations have demonstrated that aprotinin does not have a toxicological effect on the cardiovascular or cerebrovascular system.

Animal studies have shown that aprotinin accumulates primarily in the kidney. Aprotinin, after being filtered by the glomeruli, is reabsorbed by the proximal tubules, taken up by phagolysosomes, and degraded slowly by lysosomal enzymes. The physiological renal handling of aprotinin is similar to that of other small proteins, such as insulin.

In one study, dogs received single intravenous infusions of aprotinin ranging from 340,000 KIU/day over 4 hours to 1,360,000 KIU/kg over 8 hours. The doses correspond to 3 to 10 times the highest recommended doses of aprotinin in humans. Abnormalities observed were pseudoallergic reactions and slight to moderate hyaline transformation of the cytoplasm of renal tubular epithelial cells (hyaline droplets). The hyaline droplets have been shown to represent aprotinin deposits at different stages of degradation. The morphological renal changes, which had no accompanying glomerular alterations, were not totally reversed within a 10-day recovery period.

In rats, daily intraperitoneal administration of aprotinin in doses ranging from 10,000 to 300,000 KIU/day for 13 weeks caused reduced body weight gain in the high-dose animals without any impairment of renal function parameters. At

necropsy the relative weights of the kidneys were found to be increased. In the renal tubules, hyaline droplets and hyaline casts were observed in the two highest dose groups (150,000 and 300,000 KIU/kg). None of the tubular changes were considered permanent and there were no glomerular alterations seen.

In another rat study, after a 35-day recovery period, all pathological findings in clinical chemistry as well as macroscopic and microscopic kidney changes were no longer evident, with the exception that the relative kidney weights in male and female high-dose animals remained elevated. It was concluded that all functional and morphological effects on the renal tubules were generally reversible within 35 days after termination of aprotinin treatment.

In dogs, numerous parenteral studies with aprotinin doses ranging from 5,000 to 500,000 KIU/day were conducted using the intravenous or the intraperitoneal route, for periods of up to 16 weeks. The most pronounced area of observed toxicity in the dog, as in the rat studies, was the tubular epithelium of the kidneys. The reversibility of all morphological and functional renal effects was demonstrated in a recovery period.

9.2 Bayer global CABG randomized controlled trial database

9.2.1 Demographic and baseline characteristics

The global CABG database includes 45 studies with 2249 patients receiving full-dose aprotinin and 2164 patients receiving placebo. All studies incorporated the full-dose aprotinin regimen, and 7 studies incorporated both the full-dose and lower doses. The database includes patients undergoing primary and repeat CABG surgery.

Table 9-1 summarizes demographic characteristics for the CABG trials. In general, the demographic characteristics were similar between the treatment groups.

Table 9-1: Demographic Profile and Baseline Characteristics of CABG Patients (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Demographic Variable	Full Dose Aprotinin N = 2249	Placebo N[b] = 2164
Age (years)		
Mean ± standard deviation	61.1 ± 9.0	61.3 ± 9.0
<65 years; n (%)	1381 (61.4)	1290 (59.6)
≥65 years; n (%)	868 (38.6)	871 (40.2)
Missing, n (%)	0 (0.0)	3 (0.1)
Sex, n (%)		
Male	1993 (88.6)	1911 (88.3)
Female	255 (11.3)	253 (11.7)
Missing	1 (<0.1)	0 (0.0)
Race, n (%)		
White	1579 (70.2)	1500 (69.3)
Black	40 (1.8)	29 (1.3)
Hispanic	35 (1.6)	46 (2.1)
Asian or Oriental	5 (0.2)	15 (0.7)
American Indian	5 (0.2)	3 (0.1)
Uncodable	31 (1.4)	28 (1.3)
Missing	554 (24.6)	543 (25.1)
Weight (in kg)		
Mean ± standard deviation	79.6 ± 13.0	80.2 ± 13.2
Type of Surgery, n (%)		
Primary CABG	1819 (80.9)	1785 (82.5)
Repeat CABG	276 (12.3)	255 (11.8)
Not Categorized	154 (6.8)	124 (5.7)
CABG only	1151 (51.2)	1067 (49.3)
CABG plus other	1097 (48.8)	1096 (50.6)
Pediatric surgery	1 (<0.1)	1 (<0.1)

9.2.2 General safety

Table 9-2 provides an overview of various safety-related events in the CABG studies. Incidence rates for adverse events are reported for events that occurred within 7 days of study drug administration. Deaths are included for any time in the study.

Overall, 2.9% of full-dose aprotinin patients and 2.5% of placebo patients died (regardless of time interval after dosing). Not unexpectedly, most deaths were

attributed to cardiac conditions in both groups. The difference in death rates was not statistically significant (odds ratio 1.09; 95% confidence interval 0.78, 1.52).

The mortality rates from the Bayer clinical database are consistent with those reported in the literature.(251-253) The peri-operative mortality rates for the decade of 1984 to 1993 (when the majority of the Bayer trials were conducted) from the Society of Thoracic Surgeons National Cardiac Database was reported as 2.9%.(251)

Table 9-2: Overview of Safety Events in CABG Patients (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full Dose Aprotinin N = 2249		Placebo N = 2164	
	n	%	n	%
Deaths	65	2.9	55	2.5
Any Adverse Event	1309	58.2	1327	61.3
Any Drug-Related Adverse Event	261	11.6	231	10.7
Any Serious Adverse Event	298	13.3	287	13.3
Discontinuation Due to Adverse Event	59	2.6	39	1.8

Studies of patients undergoing either primary or repeat CABG surgery indicate that aprotinin is generally well tolerated. The adverse events reported are frequent sequelae of cardiac surgery and are not necessarily attributable to aprotinin therapy. Table 9-3 summarizes the adverse events (within 7 days of dosing) that occurred in at least 2% of patients in either treatment group. The events are summarized without regard to relationship to study drug. Overall, 58.2% of full-dose aprotinin-treated patients and 61.3% of placebo-treated patients reported an adverse event. Most adverse events were reported with a similar frequency (<0.5% difference between treatment groups).

Table 9-3: All Treatment-Emergent Adverse Events Occurring in at Least 2% of CABG Patients in Either Treatment Group
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any event	1309	58.2	1327	61.3
Cardiac disorders				
Atrial fibrillation	360	16.0	350	16.2
Atrial flutter	65	2.9	58	2.7
Myocardial infarction	133	5.9	109	5.0
Sinus tachycardia	76	3.4	76	3.5
Supraventricular extrasystoles	45	2.0	47	2.2
Ventricular extrasystoles	95	4.2	104	4.8
Ventricular tachycardia	58	2.6	47	2.2
Pericardial rub	71	3.2	44	2.0
Gastrointestinal disorders				
Constipation	45	2.0	41	1.9
Nausea	138	6.1	130	6.0
Vomiting	49	2.2	59	2.7
General disorders and administration site conditions				
Edema peripheral	75	3.3	79	3.7
Pyrexia	111	4.9	134	6.2
Unevaluable event	60	2.7	63	2.9
Injury, poisoning and procedural complications				
Post-procedural hemorrhage	8	0.4	54	2.5
Investigations				
Body temperature increased	56	2.5	58	2.7
Breath sounds abnormal	61	2.7	53	2.4
Psychiatric disorders				
Confusional state	38	1.7	52	2.4
Respiratory, thoracic and mediastinal disorders				
Atelectasis	177	7.9	177	8.2
Pleural effusion	170	7.6	175	8.1
Pneumothorax	62	2.8	65	3.0
Vascular disorders				
Hypertension	60	2.7	58	2.7
Hypotension	99	4.4	118	5.5
Hemorrhage	25	1.1	58	2.7

9.2.3 Dose-response relationship

The global CABG safety database was evaluated for a dose response. Only those studies that included the half-dose aprotinin, full-dose aprotinin and placebo treatment arms were included in this analysis. The dose-response database includes 7 studies, with 361 patients receiving full-dose aprotinin, 366 patients receiving half-dose aprotinin and 365 patients receiving placebo. Studies 457 and 469 included patients undergoing primary and repeat CABG surgery, Studies 447 and 466 included patients undergoing only repeat CABG surgery, and Studies 471, 478 and 486 included patients undergoing only primary CABG surgery.

Table 9-4 provides an overview of various safety-related events in the global CABG safety database of dose-response studies. Overall, 3.3% of full-dose aprotinin-treated, 4.9% of half-dose aprotinin-treated patients and 3.3% of placebo-treated patients died. Not unexpectedly, most deaths were attributed to cardiac conditions in all groups.

Table 9-4: Overview of Safety Events in CABG Patients in the Dose-Response Studies
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in Dose-Response Studies)

	Full-Dose Aprotinin N = 361		Half-Dose Aprotinin N = 366		Placebo N = 365	
	n	%	n	%	n	%
Deaths	12	3.3	18	4.9	12	3.3
Any adverse event	292	80.9	300	82.0	304	83.3
Any drug-related adverse event	50	13.9	42	11.5	45	12.3

Table 9-5 summarizes the adverse events that occurred in at least 2% of patients in either treatment group. The events are summarized without regard to relationship to study drug. Those events that appear to have a dose-response relationship (with rates in the full-dose aprotinin group exceeding those in the half-dose aprotinin group that exceeds those in the placebo group) were myocardial infarction, diarrhea, dyspnea and lung disorder. The difference in rates of myocardial infarction in the

full-dose aprotinin group compared to the placebo group was predominantly driven by events reported in Study D89-004, as discussed in Section 9.4.3.

Table 9-5: All Treatment-Emergent Adverse Events Occurring in at Least 2% of CABG Patients in Any Treatment Group in the Dose-Response Studies (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in Dose-Response Studies)

	Full-Dose Aprotinin N = 361		Half-Dose Aprotinin N = 366		Placebo N = 365	
	n	%	n	%	n	%
Any event	292	80.9	300	82.0	304	83.3
Blood and lymphatic system disorders						
Anemia	6	1.7	6	1.6	9	2.5
Coagulopathy	1	0.3	4	1.1	18	4.9
Cardiac disorders						
Arrhythmia	2	0.6	3	0.8	8	2.2
Atrial fibrillation	96	26.6	77	21.0	103	28.2
Atrial flutter	29	8.0	17	4.6	27	7.4
Cardiac failure congestive	8	2.2	3	0.8	8	2.2
Low cardiac output syndrome	5	1.4	9	2.5	10	2.7
Myocardial infarction	37	10.2	26	7.1	22	6.0
Nodal rhythm	8	2.2	5	1.4	7	1.9
Pericarditis	18	5.0	7	1.9	8	2.2
Sinus bradycardia	4	1.1	8	2.2	2	0.5
Sinus tachycardia	25	6.9	26	7.1	29	7.9
Supraventricular extrasystoles	9	2.5	14	3.8	14	3.8
Supraventricular tachycardia	13	3.6	20	5.5	18	4.9
Tachycardia	7	1.9	10	2.7	12	3.3
Ventricular extrasystoles	20	5.5	31	8.5	23	6.3
Ventricular fibrillation	8	2.2	8	2.2	9	2.5
Ventricular tachycardia	17	4.7	23	6.3	19	5.2
Pericardial rub	35	9.7	37	10.1	18	4.9
Ventricular dysfunction	8	2.2	8	2.2	9	2.5
Gastrointestinal disorders						
Constipation	12	3.3	9	2.5	17	4.7
Diarrhea	9	2.5	8	2.2	5	1.4
Nausea	32	8.9	37	10.1	37	10.1
Vomiting	9	2.5	12	3.3	15	4.1
General disorders and administration site conditions						
Chest pain	5	1.4	11	3.0	9	2.5
Crepitations	17	4.7	17	4.6	20	5.5
Edema peripheral	28	7.8	23	6.3	24	6.6
Pyrexia	36	10.0	34	9.3	42	11.5
Unevaluable event	14	3.9	23	6.3	18	4.9
Investigations						
Blood creatine phosphokinase Increased	4	1.1	11	3.0	5	1.4

Table 9-5: All Treatment-Emergent Adverse Events Occurring in at Least 2% of CABG Patients in Any Treatment Group in the Dose-Response Studies (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in Dose-Response Studies)

	Full-Dose Aprotinin N = 361		Half-Dose Aprotinin N = 366		Placebo N = 365	
	n	%	n	%	n	%
Blood creatine phosphokinase MB increased	9	2.5	9	2.5	3	0.8
Blood creatinine increased	8	2.2	3	0.8	5	1.4
Body temperature increased	22	6.1	21	5.7	25	6.8
Oxygen saturation decreased	3	0.8	10	2.7	1	0.3
White blood cell count increased	10	2.8	14	3.8	13	3.6
Urine output decreased	8	2.2	8	2.2	9	2.5
Breath sounds abnormal	29	8.0	34	9.3	23	6.3
Psychiatric disorders						
Agitation	5	1.4	8	2.2	14	3.8
Confusional state	11	3.0	13	3.6	24	6.6
Renal and urinary disorders						
Renal failure	8	2.2	6	1.6	7	1.9
Respiratory, thoracic and mediastinal disorders						
Atelectasis	27	7.5	22	6.0	23	6.3
Dyspnea	12	3.3	11	3.0	10	2.7
Hypoxia	9	2.5	5	1.4	8	2.2
Lung disorder	10	2.8	8	2.2	7	1.9
Pleural effusion	23	6.4	23	6.3	31	8.5
Pneumothorax	14	3.9	17	4.6	18	4.9
Rales	20	5.5	15	4.1	17	4.7
Rhonchi	11	3.0	20	5.5	19	5.2
Wheezing	12	3.3	10	2.7	19	5.2
Crackles lung	14	3.9	8	2.2	9	2.5
Vascular disorders						
Hypertension	19	5.3	11	3.0	14	3.8
Hypotension	16	4.4	26	7.1	26	7.1

9.3 Aprotinin and heparinization

Aprotinin, in the presence of heparin, has been demonstrated to prolong celite-based activated clotting time assays.(254-259) Thus, in the presence of an artificially prolonged activated clotting time, it would be easy to inadvertently under-heparinize patients in the aprotinin group. While protocols vary, a minimal celite-activated

clotting time of 750 seconds or a kaolin-activated clotting time of 480 seconds, independent of the effects of hemodilution and hypothermia, is recommended in the presence of aprotinin to ensure adequate heparinization during cardiopulmonary bypass. This information is included in the prescribing information for Trasylol.

9.4 Cardiac safety

9.4.1 Overview of literature

Karkouti et al used propensity scores to evaluate the safety of 449 patients receiving aprotinin and 449 matched patients receiving tranexamic acid who had cardiac surgery at a single Canadian center.(2) The rate of myocardial infarction was 3% (12/449) in aprotinin-treated patients compared to 2% (10/449) in tranexamic acid treated patients ($p = 0.7$).

Mangano et al reported an observational analysis involving 4374 patients undergoing cardiac revascularization, including 1295 patients treated with aprotinin.(1) Their analysis, using multivariate and propensity methods, yielded for aprotinin versus no treatment an odds ratio for myocardial infarction or heart failure of 1.42 (95% confidence interval 1.09, 1.86) for patients undergoing primary surgery, but no effect in patients undergoing complex surgery (including re-operation, emergency surgery, or surgery with additional procedures). There was no significant propensity-adjusted effect of aprotinin treatment on mortality in either primary or complex surgery patients. The use of propensity scores to avoid confounding in non-randomized studies does not account for potential confounding factors that may not have been measured.(3)

A meta-analysis conducted by Levi et al reviewed the occurrence of myocardial infarction among 1995 patients in 18 trials.(205) The odds ratio of a myocardial infarction relative to placebo was 1.13 (95% confidence interval 0.76, 1.67). In an analysis of 666 patients in 7 trials that used “conventional” aprotinin regimens and lower dose regimens, patients taking the conventional regimen had a higher incidence of myocardial infarction (8.1%) than those receiving one of the lower

dose regimens (3.9%). Data on mortality were available from 26 trials that enrolled 3212 patients. Aprotinin was associated with a significant two-fold decrease in mortality (1.5% versus 2.8%); the odds ratio was 0.55 (95% confidence interval 0.34, 0.90).

A meta-analysis by Munoz et al included 37 trials that used higher doses of aprotinin and 17 trials that used lower doses of aprotinin.(206) Data on myocardial infarction were reported in 17 trials (n = 1710) that used higher doses. The rates of myocardial infarction were 6.0% for patients receiving the higher doses of aprotinin and 4.9% for those in the control groups (p = 0.316). Data on myocardial infarctions were available from 10 trials (n = 1125) that used lower doses. The rates of myocardial infarction were 4.1% for patients receiving the lower doses of aprotinin group and 5.0% for those in the control groups (p = 0.470).

Another meta-analysis of 35 randomized controlled trials that enrolled 3879 patients undergoing CABG surgery demonstrated that use of aprotinin was not associated with an increased risk of myocardial infarction or death.(201) In 28 trials (n = 3555), 4.7% (96/2024) of aprotinin-treated patients developed a myocardial infarction compared to 5.0% (77/1531) of placebo-treated patients (relative risk 0.85, 95% confidence interval 0.63, 1.14). In 32 trials (n = 3779), 2.5% (53/2149) of aprotinin-treated patients died compared to 2.4% (39/1630) of placebo-treated patients (relative risk 0.96, 95% confidence interval 0.65, 1.40). Among patients not taking aspirin, myocardial infarction was reported in 1.4% (6/440) of aprotinin-treated and 3.9% (13/336) of placebo-treated patients (relative risk 0.40, 95% confidence interval 0.17, 0.92). This reduction in risk was not observed among patients taking aspirin.

The Cochrane Collaboration published an evidence-based review of randomized controlled trials in adults scheduled for non-urgent surgery that assessed the efficacy and safety of aprotinin, aminocaproic acid, and tranexamic acid.(203) Of the 89 trials included in the analysis, 61 evaluated aprotinin. Fifty-five of these trials enrolled patients undergoing cardiac surgery; 3814 patients were randomized to

receive aprotinin and 2755 patients were randomized to a control group. An additional 7 trials enrolled patients undergoing non-cardiac surgeries, including orthopedic, liver resection, liver transplant and vascular surgery. These trials included an additional 241 patients randomized to receive aprotinin and 217 patients randomized to a control group. In 28 studies that reported data on mortality, there was a non-significant relative risk reduction of 13% (relative risk 0.87; 95% confidence interval 0.63, 1.19) among those patients treated with aprotinin (n = 2828) compared to those in a control group (n = 2085). In 20 trials that reported data on non-fatal myocardial infarction, the risk of sustaining a non-fatal myocardial infarction among those patients treated with aprotinin (n = 1871) compared to those in a control group (n = 1117) was not statistically significant (relative risk 0.97; 95% confidence interval 0.69, 1.36).

9.4.2 Bayer global randomized control trial database

The results of a search for terms suggestive of congestive heart failure are displayed in Table 9-6. The events are summarized without regard to relationship to study drug. Patients could have had more than one event. Overall, 6.3% of full-dose aprotinin-treated patients and 5.9% of placebo-treated patients in the global CABG database had an event suggestive of congestive heart failure. The difference in rates was not statistically significant (odds ratio 1.08; 95% confidence interval 0.84, 1.38).

Table 9-6: All Treatment-Emergent Adverse Events Suggestive of Congestive Heart Failure in CABG Patients
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any Event	142	6.3	127	5.9
Acute pulmonary edema	0	0.0	2	< 0.1
Cardiac failure	28	1.2	26	1.2
Cardiac failure acute	2	< 0.1	0	0.0
Cardiac failure congestive	18	0.8	19	0.9
Cardiogenic shock	13	0.6	5	0.2
Fluid overload	6	0.3	9	0.4
Hepatic congestion	1	< 0.1	0	0.0
Left ventricular failure	7	0.3	4	0.2
Low cardiac output syndrome	23	1.0	26	1.2
Pulmonary congestion	18	0.8	8	0.4
Pulmonary edema	40	1.8	38	1.8
Right ventricular failure	2	< 0.1	2	< 0.1

In order to evaluate whether the use of aprotinin would increase the risk of a cardiac event in a patient population already at a high risk for such an event, additional subset analyses of the global database were conducted. The effect of full-dose aprotinin on the incidence of an event suggestive of congestive heart failure was evaluated by gender, age, prior history of hypertension, prior myocardial infarction, prior congestive heart failure, diabetes mellitus, and type of CABG surgery (primary or repeat). The results are shown in Table 9-7. No statistically significant differences were observed in the event rates between full-dose aprotinin-treated and placebo-treated patients.

Table 9-7: Congestive Heart Failure Event by Subgroup Analysis (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Subgroup	Full-Dose Aprotinin n/N	%	Placebo n/N	%	Odds Ratio (95% CI)
Overall	142/2249	6.3	127/2164	5.9	1.08 (0.84, 1.38)
Gender					
Male	115/1993	5.8	108/1911	5.7	1.01 (0.77, 1.32)
Female	27/255	10.6	19/253	7.5	1.34 (0.79, 2.28)
Age					
<65 years	75/1381	5.4	57/1290	4.4	1.13 (0.81, 1.59)
≥65 years	67/868	7.7	70/871	8.0	0.99 (0.71, 1.37)
History of hypertension					
No	73/1341	5.4	63/1282	4.9	1.04 (0.75, 1.46)
Yes	69/908	7.6	64/882	7.3	1.06 (0.76, 1.48)
Prior myocardial infarction					
No	51/1370	3.7	57/1344	4.2	0.93 (0.65, 1.31)
Yes	91/879	10.4	70/820	8.5	1.19 (0.85, 1.65)
History of diabetes mellitus					
No	108/1855	5.8	95/1742	5.5	1.03 (0.78, 1.36)
Yes	34/394	8.6	32/422	7.6	1.21 (0.78, 1.87)
History of congestive heart failure					
No	117/2133	5.5	106/2062	5.1	1.09 (0.83, 1.43)
Yes	25/116	21.6	21/102	20.6	0.92 (0.51, 1.65)
Type of surgery					
Primary CABG	81/1819	4.5	82/1785	4.6	0.97 (0.71, 1.33)
Repeat CABG	39/276	14.1	28/255	11.0	1.33 (0.79, 2.24)

CI = confidence interval.

The results of a search for adverse events suggestive of a myocardial infarction is summarized in Table 9-8. The events are summarized without regard to relationship to study drug. Patients could have had more than one event. Overall, 6.4% of full-dose aprotinin-treated patients and 5.5% of placebo-treated patients had an investigator-reported event suggestive of myocardial infarction. The difference in rates was not statistically significant (odds ratio 1.18; 95% confidence interval 0.92, 1.50).

Table 9-8: All Treatment-Emergent Adverse Events Suggestive of Myocardial Infarction in CABG Patients
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any event	144	6.4	118	5.5
Acute myocardial infarction	14	0.6	11	0.5
Coronary artery occlusion	1	< 0.1	0	0.0
Myocardial infarction	133	5.9	109	5.0

In order to evaluate whether the use of aprotinin would increase the risk of a cardiac event in a patient population already at a high risk for such an event, additional subset analyses of the global database were conducted. The effect of full-dose aprotinin on the incidence of an event suggestive of a myocardial infarction was evaluated by gender, age, prior history of hypertension, prior myocardial infarction, prior congestive heart failure, diabetes mellitus, and the type of surgery. The results are shown in Table 9-9. Patients treated with full-dose aprotinin with a prior history of myocardial infarction, a prior history of congestive heart failure or undergoing a repeat CABG surgery had an increased risk of a myocardial infarction.

Table 9-9: Myocardial Infarction Events by Subgroup Analysis (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full-Dose Aprotinin		Placebo		Odds Ratio
Subgroup	**n/N**	**%**	**n/N**	**%**	**(95% CI)**
Overall	144/2249	6.4	118/2164	5.5	1.18 (0.92, 1.50)
Gender					
Male	124/1993	6.2	96/1911	5.0	1.23 (0.94, 1.60)
Female	20/255	7.8	22/253	8.7	0.91 (0.54, 1.55)
Age					
<65 years	81/1381	5.9	66/1290	5.1	1.18 (0.86, 1.61)
≥65 years	63/868	7.3	52/871	6.0	1.15 (0.81, 1.63)
History of hypertension					
No	82/1341	6.1	72/1282	5.6	1.10 (0.80, 1.50)
Yes	62/908	6.8	46/882	5.2	1.28 (0.89, 1.82)
Prior myocardial infarction					
No	66/1370	4.8	70/1344	5.2	0.91 (0.66, 1.26)
Yes	78/879	8.9	48/820	5.9	1.46 (1.03, 2.08)
History of diabetes mellitus					
No	115/1855	6.2	96/1742	5.5	1.10 (0.84, 1.45)
Yes	29/394	7.4	22/422	5.2	1.34 (0.85, 2.11)
History of congestive heart failure					
No	126/2133	5.9	116/2062	5.6	1.06 (0.82, 1.36)
Yes	18/116	15.5	2/102	2.0	2.03 (1.01, 4.10)
Type of surgery					
Primary CABG	96/1819	5.3	95/1785	5.3	0.99 (0.74, 1.33)
Repeat CABG	41/276	14.9	22/255	8.6	1.85 (1.07, 3.20)

CI = confidence interval.

9.4.3 Dose-response relationship

The events suggestive of myocardial infarction and congestive heart failure in the dose-response studies are summarized in Table 9-10. The events are summarized without regard to study drug relationship. Patients could have had more than one event. Overall, 10.2% of full-dose aprotinin patients, 7.1% of half-dose aprotinin-treated patients and 6.0% of placebo-treated patients had an event suggestive of myocardial infarction. The difference in rates of myocardial infarction was predominantly driven by events reported in Study D89-004. As discussed in Section 9.4.4, possible explanations for the increased incidence of myocardial

infarction in this study include inadequate heparinization among patients in the aprotinin group, variability in the definition and reporting of myocardial infarctions, and a higher risk patient population.

Table 9-10: All Treatment-Emergent Adverse Events Suggestive of Myocardial Infarction or Congestive Heart Failure in CABG Patients in the Dose-Response Studies in Global Development
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in the Dose-Response Studies)

	Full-Dose Aprotinin N = 361		Half-Dose Aprotinin N = 366		Placebo N = 365	
Event	**n**	**%**	**n**	**%**	**n**	**%**
Myocardial infarction	37	10.2	26	7.1	22	6.0
Congestive heart failure	22	6.1	30	8.2	35	9.6

9.4.4 Myocardial infarction in the US database as determined by independent review

9.4.4.1 Early US clinical development

Study D89-004 indicated that aprotinin may be associated with an increased risk of myocardial infarction among patients undergoing repeat CABG. In the early US Clinical Development Program, which included Studies D89-004 and D89-006, there was no protocol requirement to specifically capture ECG and cardiac enzyme data for all patients at set postoperative timepoints. In addition, no protocol-specified definition for a perioperative myocardial infarction was provided. Thus, myocardial infarction was reported as an adverse event at the discretion of the investigator at each study site; and the criteria used to make this judgment were not necessarily consistent from site to site. The lack of a uniform definition led to variability between sites and between studies in the rates of myocardial infarction, and impacted the ability to combine data across the early studies.

Because of these issues, data from the 2 early US CABG trials (D89-004, D89-006) were submitted in a blinded fashion retrospectively to the Core ECG Laboratory at St. Louis University (headed by Bernard Chaitman, MD) for an objective assessment using a standardized definition of myocardial infarction. For these

studies, data were only sent to the laboratory on patients with the COSTART coded investigator reported treatment-emergent adverse events of myocardial infraction, myocardial ischemia, and increases in CPK (creatine phosphokinase). The data submitted included all ECG tracings; all serum glutamic-oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), CPK, and CPK MB isoenzyme values; a copy of the patient's case report form; a clinical summary; and other relevant documents such as operative notes, discharge summaries, expiration summaries and autopsy reports. All references to the assigned treatment group were deleted if needed.

Based on the data, the Core ECG Laboratory assessed a patient as having a definite myocardial infarction; a definite or probable myocardial infarction; or a definite, probable or possible myocardial infarction (or no myocardial infarction if no criteria were met). The assessments provided by the Core ECG Laboratory were entered into the Bayer database and merged with the random code, after which the incidences of myocardial infarction in the various treatment groups were calculated.

The subsequent 3 trials (Study D92-008, Study D92-016, and D92-048) were designed to collect data on postoperative cardiac events prospectively. In addition, in an effort to obtain a more consistent and unbiased assessment across all of the study sites, laboratory (including serum SGOT, LDH, CPK, and CPK MB isoenzyme values), ECG, and clinical data (including discharge summaries and post-mortem reports) were analyzed by an outside consultant who remained blinded to treatment group assignment. The consultant applied an algorithm similar to the process used during the retrospective analyses of the data from the 2 early US CABG clinical studies. For the later 3 studies, ECG and laboratory data obtained prospectively from all patients were evaluated. In contrast to the retrospective review performed on the earlier 2 studies, this process allowed for a more sensitive, systematic, and unbiased identification and evaluation of potential myocardial infarction events.

Because of the differences in methodology, the data on myocardial infarctions from the 2 early and the 3 later CABG studies are reported separately when appropriate.

Table 9-11 compares the incidences of myocardial infarction as determined by independent review to the incidences of myocardial infarction as determined by the investigators for the earlier trials, Studies D89-004 and D89-006. The incidence of myocardial infarction as defined by independent review among placebo-treated patients undergoing repeat CABG surgery was higher in Study D89-004 than in D89-006, suggesting a higher risk patient population was enrolled in Study D89-004. Furthermore, twice as many placebo-treated patients who underwent primary CABG surgery in Study D89-006 were assessed as having had a myocardial infarction by the independent review compared to the investigators. This suggests a possible bias in reporting myocardial infarctions by the investigators, and that the independent review may provide a more objective assessment.

In Study D89-004, a myocardial infarction occurred in 28.8% (17/59) of patients treated with full-dose aprotinin and in 14.2% (8/56) of placebo-treated patients as assessed by the independent review ($p = 0.167$). Patients were anticoagulated using local procedures and not the protocol-specified methods. Patients were initially given 300 units of heparin per kilogram body weight, with additional heparin given if the activated clotting time fell below 400 seconds. The protocol stated that patients were initially to be given 300 units of heparin per kilogram body weight, with an additional dose of 150 units of heparin per kilogram after 90 minutes of cardiopulmonary bypass. Because a minimal celite-activated clotting time of 750 seconds (compared to a minimal kaolin-activated clotting time of 480 seconds) is recommended with aprotinin therapy to ensure adequate heparinization during cardiopulmonary bypass, inadequate heparinization may be a possible explanation for the elevated myocardial infarction rate among the aprotinin-treated patients compared to the placebo-treated patients. However, the authors noted that the absence of clot formation in the heart-lung bypass machine circuit or other

thromboembolic complications in the study was not consistent with this explanation.(208)

In Study D89-006, activated clotting time was not used to monitor anticoagulation during cardiopulmonary bypass. Instead, blood heparin concentrations were used as a basis for heparin dosing or heparin dosed at fixed intervals was used to maintain adequate anticoagulation. In Study D89-006, the rates of myocardial infarction as determined by the independent review did not differ substantially between the patients treated with full-dose aprotinin and those treated with placebo.

Table 9-11: Incidence of Myocardial Infarction as Determined by Independent Review and by the Investigator
(Population: CABG Patients Valid for Safety Analysis in Studies D89-004 and D89-006)

	Full-Dose Aprotinin		Placebo		p-value or
Study/Method	**n/N**	**%**	**n/N**	**%**	**Odds Ratio (95% CI)**
D89-004 Repeat CABG					
Independent Review Definite or Probable MI	17/59	28.8	8/56	14.3	p = 0.167
MI per Investigator	14/59	23.7	7/56	12.5	OR = 2.18 (0.81, 5.88)
D89-006 Repeat CABG					
Independent Review Definite or Probable MI	3/29	10.3	3/36	8.3	p = 1.0
MI per Investigator	4/29	13.8	3/36	8.3	OR = 1.76 (0.36, 8.58)
D89-006 Primary CABG					
Independent Review Definite or Probable MI	7/79	8.9	6/72	8.3	p = 0.908
MI per Investigator	7/79	8.9	3/72	4.2	OR = 2.24 (0.56, 9.00)

CI = confidence interval; MI = myocardial infarction; OR = odds ratio.

9.4.4.2 Later US clinical development

Data on peri-operative myocardial infarctions were collected prospectively in the 3 later studies in the US Clinical Development Program (Studies D92-008, D92-016, and D92-048). For these studies, relevant data were analyzed in a blinded manner by a consultant using an algorithm similar to that employed for the 2 earlier CABG studies.

Across all 3 studies, the incidences of a definite or probable myocardial infarction were 10.7% and 11.3% among patients treated with full-dose aprotinin and those treated with placebo, respectively (see Table 9-12). The difference in the rates was not statistically significant (odds ratio 0.93; 95% confidence interval 0.65, 1.32).

Among those patients undergoing primary CABG surgery, the incidences of a definite or probable myocardial infarction were 8.6% and 9.3% among patients treated with full-dose aprotinin and placebo, respectively. The difference in the rates was not statistically significant (odds ratio 0.91; 95% confidence interval 0.61, 1.37).

Among patients undergoing repeat CABG surgery, the incidences of a definite or probable myocardial infarction were 28.6% and 29.2% among patients treated with full-dose aprotinin and placebo, respectively. The difference in the rates was not statistically significant (odds ratio 0.97; 95% confidence interval 0.46, 2.04). These findings are in contrast to those noted for patients undergoing repeat CABG surgery in Study D89-004 and Study D89-006.

Table 9-12: Incidence of Prospectively Defined Definite or Probable Myocardial Infarction in CABG Trials
(Population: CABG Patients Valid for Safety Analysis in Studies D92-008, D92-016, and D92-048)

	Full-Dose Aprotinin		Placebo		Odds Ratio
	n/N	%	n/N	%	(95% CI)
All CABG	69/642	10.7	74/656	11.3	0.93 (0.65, 1.32)
Primary CABG	49/572	8.6	55/591	9.3	0.91 (0.61, 1.37)
Repeat CABG	20/70	28.6	19/65	29.2	0.97 (0.46, 2.04)
Study D92-008	20/70	28.6	19/65	29.2	0.97 (0.46, 2.04)
Study D92-016	14/165	8.5	17/173	9.8	0.85 (0.41, 1.79)
Study D92-048	35/407	8.6	38/418	9.1	0.94 (0.58, 1.52)

CI = confidence interval.

Table 9-13 shows the incidences across the 3 later studies of developing a definite myocardial infarction, a definite or probable myocardial infarction, or a definite, probable or possible myocardial infarction. The data in Table 9-13 are described in the current US prescribing information for Trasylol.

Table 9-13: Incidence of Prospectively Defined Myocardial Infarction by Treatment Group
(Population: CABG Patients Valid for Safety Analysis in Studies D92-008, D92-016, and D92-048)

Treatment	Definite Myocardial Infarction %	Definite or Probable Myocardial Infarction %	Definite, Probable or Possible Myocardial Infarction %
Study D92-008 (repeat CABG)			
Full-dose aprotinin	11.8	28.6	32.4
Half-dose aprotinin	14.7	29.9	32.0
Placebo	11.9	29.2	31.3
Study D92-016 (primary CABG)			
Full-dose aprotinin	6.0	8.5	11.0
Half-dose aprotinin	6.4	10.5	13.4
Placebo	4.1	9.8	9.8
Study D92-048 (primary CABG)			
Full-dose aprotinin	2.9	8.6	12.3
Placebo	3.8	9.1	12.0
Pooled Data from Three Studies that Evaluated the Full-Dose Regimen			
Full-dose aprotinin	4.6	10.7	14.1
Placebo	4.7	11.3	13.4
Pooled Data from Two Studies that Evaluated the Half-Dose and Pump Prime Regimens			
Half-dose aprotinin	8.7	15.9	18.7
Pump prime aprotinin	6.3	15.7	18.1
Placebo	6.3	15.1	15.8

9.4.4.3 Cardiac safety in subgroup populations

In order to evaluate whether the use of aprotinin would increase the risk of a cardiac event in a patient population already at a high risk for such an event, additional subset analyses of the data from these 3 later trials (Studies D92-008, D92-016 and D92-048) were conducted. Data from these three later studies were utilized because in these studies steps were taken to ensure adequate heparinization and to use a standardized definition of myocardial infarction as determined prospectively by a blinded independent reviewer. The effect of aprotinin on the incidence of definite or probable myocardial infarction was evaluated by gender, age, prior history of hypertension, prior myocardial infarction, prior congestive heart failure, diabetes

mellitus, and type of CABG surgery. The results are shown in Table 9-14. No statistically significant treatment differences were observed. However, of note, the odds ratios for definite or probable myocardial infarction exceeded 2 for patients with a history of congestive heart failure who underwent primary or repeat CABG surgery. However, the number of patients with a history of prior congestive heart failure was small.

Table 9-14: Definite or Probable Myocardial Infarction as Defined Prospectively by Independent Assessment in CABG Patients (Population: CABG Patients Valid for Safety in Studies D92-008, D92-016, and D92-048)

Subgroup	Full-Dose Aprotinin n/N	Full-Dose Aprotinin %	Placebo n/N	Placebo %	Odds Ratio (95% CI)
Male	55/556	9.9	64/570	11.2	0.85 (0.58, 1.26)
Primary CABG	39/496	7.9	50/512	9.8	0.79 (0.51, 1.22)
Repeat CABG	16/60	26.7	14/58	24.1	1.14 (0.50, 2.62)
Female	14/86	16.3	10/86	11.6	1.35 (0.53, 3.41)
Primary CABG	10/76	13.2	5/79	6.3	2.24 (0.73, 6.90)
Repeat CABG	4/10	40.0	5/7	71.4	0.27 (0.03, 2.12)
Age < 65 years	35/365	9.6	34/347	9.8	1.01 (0.61, 1.69)
Primary CABG	26/335	7.8	23/314	7.3	1.06 (0.59, 1.91)
Repeat CABG	9/30	30.0	11/33	33.3	0.86 (0.30, 2.49)
Age ≥ 65 years	34/277	12.3	40/306	13.1	0.88 (0.53, 1.44)
Primary CABG	23/237	9.7	32/274	11.7	0.81 (0.46, 1.43)
Repeat CABG	11/40	27.5	8/32	25.0	1.14 (0.39, 3.28)
No history of hypertension	19/268	7.1	27/266	10.2	0.67 (0.36,1.23)
Primary CABG	16/244	6.6	18/243	7.4	0.88 (0.44, 1.76)
Repeat CABG	3/24	12.5	9/23	39.1	0.22 (0.05, 0.97)
History of hypertension	50/374	13.4	47/390	12.1	1.10 (0.71, 1.70)
Primary CABG	33/328	10.1	37/348	10.6	0.94 (0.57, 1.54)
Repeat CABG	17/46	37.0	10/42	23.8	1.88 (0.74, 4.75)
No prior myocardial infarction	19/272	7.0	34/294	11.6	0.56 (0.31, 1.02)
Primary CABG	14/251	5.6	27/272	9.9	0.54 (0.27, 1.05)
Repeat CABG	5/21	23.8	7/22	31.8	0.67 (0.17, 2.57)
Prior myocardial infarction	50/370	13.5	40/362	11.0	1.24 (0.79, 1.95)
Primary CABG	35/321	10.9	28/319	8.8	1.27 (0.75, 2.15)
Repeat CABG	15/49	30.6	12/43	27.9	1.14 (0.46, 2.81)
No history of CHF	59/595	9.9	69/603	11.4	0.83 (0.57, 1.21)
Primary CABG	43/534	8.1	52/546	9.5	0.83 (0.55, 1.27)
Repeat CABG	16/61	26.2	17/57	29.8	0.84 (0.37, 1.87)
History of CHF	10/47	21.3	5/53	9.4	2.55 (0.77, 8.41)
Primary CABG	6/38	15.8	3/45	6.7	2.63 (0.61, 11.31)
Repeat CABG	4/9	44.4	2/8	25.0	2.40 (0.30, 19.04)
No history of diabetes mellitus	49/473	10.4	56/473	11.8	0.82 (0.54, 1.24)
Primary CABG	36/421	8.6	41/430	9.5	0.89 (0.55, 1.42)
Repeat CABG	13/52	25.0	15/43	34.9	0.62 (0.26, 1.51)
History of diabetes mellitus	20/169	11.8	18/183	9.8	1.27 (0.64, 2.52)
Primary CABG	13/151	8.6	14/161	8.7	0.99 (0.45, 2.18)
Repeat CABG	7/18	38.9	4/22	18.2	2.86 (0.68, 12.08)

CHF = congestive heart failure; CI = confidence interval.

9.4.5 Graft patency

Based on a literature review and review of Bayer's database, seven studies were identified as having been prospectively designed to evaluate the effect of aprotinin on graft patency. Bayer conducted 4 of these trials, Studies 414 (Bidstrup), D89-006 (Lemmer), 9967 (Lass), and D92-048 (Alderman). Table 9-15 displays the graft patency rates for these studies. Neither of the studies that used non-invasive techniques to evaluate patency (Bidstrup and Lemmer) nor 4 of 5 studies that used angiography (Kalangos, Havel, Lass, Hayashida) demonstrated a statistically significant difference in graft occlusion between patients receiving aprotinin and those receiving placebo. Study D92-048 used angiography to assess graft patency, and this study did show a statistically significant difference between treatment groups. However, this difference was no longer noted when US centers were evaluated alone (as per FDA recommendation).

Table 9-15: Overview of Graft Patency Results

Author	Procedure	Variable	Graft Patency Full-Dose Aprotinin n/N	%	Other Doses of Aprotinin n/N	%	Placebo n/N	%
Bidstrup(260)	MRI scan	Per Patient	38/43	88	NA	NA	43/47	92
Study 414		Per SVG	126/131	96	NA	NA	134/138	97
Kalangos(261)	Angiography	Per SVG	140/142	99	128/128[a]	100	138/139	99
Havel(262)	Angiography	Per SVG	NA	94	NA	95[b]	NA	93
Hayashida(263)	Angiography	Per Patient	NA	NA	36/41[c] 40/41[d]	88 98	34/38	89
		Per SVG	NA	NA	60/65[c] 65/66[d]	92 98	61/65	94
Lemmer(209)	Ultrafast CT	Per Patient	70/83	84	NA	NA	74/81	91
Study D89-006	scan	Per SVG	162/176	92	NA	NA	155/163	95
Lass(264)	Angiography	Per Patient	37/44	84	NA	NA	25/35	71
Study 9967		Per SVG	89/97	92	NA	NA	61/74	82
Alderman(212) IMAGE Study Study D92-048	Angiography	Per Patient (All Centers)	307/363	85	NA	NA	303/340	89
		Per Patient (US Centers)	183/202	91	NA	NA	162/179	91

a Aprotinin 25,000 KIU/kg in the pump-prime solution only.
b Aprotinin 2.0 million KIU in the pump-prime solution only.
c Aprotinin 30,000 KIU/kg in the pump-prime solution and 7,500 KIU/hr during surgery (referred to as "half-dose").
d Aprotinin 1.0 million KIU in the pump-prime solution only (referred to as "minimal-dose").
CT = computed tomography; MRI = magnetic resonance imaging; NA = not applicable or not available; SVG = Saphenous vein graft.

The IMAGE Study (Study D92-048) was a multicenter, multinational, randomized, double-blind, placebo controlled study.(212) Of the 13 study sites, 10 were US centers and 3 were non-US centers (1 site was in Denmark and 2 were in Israel). All patients underwent primary CABG surgery. Patients received either full-dose aprotinin or placebo. Patients were stratified on whether the patient was receiving aspirin or a non-steroidal anti-inflammatory drug prior to surgery. Coronary artery bypass graft patency was assessed by angiography a mean of 10.8 days after surgery. Graft patency could be assessed in 703 patients among the 870 valid for safety.

The study was conducted from April 1993 to May 1995. Early in enrollment, Centers 2 and 3 (non-US sites) experienced problems using the Hepcon machines for measuring anticoagulation. In addition, 2 US sites and the 3 non-US sites used blood from the aortic cannulation site for flushing and preserving the harvested vein graft. Thus, the harvested veins were stored in aprotinin-laced blood prior to grafting for patients treated with aprotinin. The 3 non-US sites enrolled 46% of the study patients while the 2 US sites that followed the above procedure for storage of harvested vein grafts enrolled only 9% of the patients. At the remaining 7 US sites, non-blood containing perfusate was used for storing the harvested grafts. These 7 sites enrolled 45% of the study patients. The problems using the Hepcon machines and storing the grafts were corrected when noted.

During and soon after closure of enrollment into the study, preliminary angiography results were supplied to the FDA at their request in a blinded manner, along with the sealed randomization codes. Prior to unblinding of study results by Bayer, a preliminary statistical analysis plan was provided to the FDA in July 1995, and a preliminary analysis of the angiography data was sent in October 1995. After reviewing the data, the FDA requested, in December 1995, analyses of covariates that supported the suggestion of a treatment by country interaction (based on heparin usage), and recommended analyses be performed excluding non-US centers.

Table 9-16 shows the percent of patients with graft occlusion and myocardial infarction as well as the percent of patients who died.

Table 9-16: Study D92-048: Incidence of Graft Closure, Myocardial Infarction and Death by Treatment Group

	Overall Closure Rates[a]		Incidence of MI[b]	Incidence of Death[c]
	All Centers n = 703 %	US Centers n = 381 %	All Centers n = 831 %	All Centers n = 870 %
Aprotinin	15.4	9.4	2.9	1.4
Placebo	10.9	9.5	3.8	1.6
CI for the difference (%) (aprotinin – placebo)	1.3, 9.6[d]	–3.8, 5.9[d]	–3.3 to 1.5[e]	–1.9 to 1.4[e]

a Population: all patients with assessable saphenous vein grafts.
b Population: all patients assessable by blinded consultant.
c All patients.
d 90% CI; per protocol.
e 95% CI; not specified in protocol.
CI = confidence interval.

As seen in Table 9-16, there was an increased risk of graft closure among aprotinin-treated patients (15.4%) compared to placebo-treated patients (10.9%; p = 0.035). However, further analysis showed a significant treatment by site interaction for 1 Israel site compared to the US centers. When graft closure was analyzed for the US centers only, there was no difference between treatment groups. The results are the same whether analyzed as the percentage of patients who had at least one saphenous vein graft closure postoperatively (per-patient analysis) or as the percentage of grafts occluded (per-graft analysis). It is noteworthy that at all centers, there were no significant differences between treatment groups in the incidences of myocardial infarction (2.9% of aprotinin-treated patients versus 3.8% of placebo-treated patients) or of death (1.4% versus 1.6%). The data in Table 9-16 are presented in the Trasylol prescribing information.

At the Danish and Israeli sites, saphenous vein graft occlusion occurred in 23.0% of aprotinin-treated compared to 12.4% of placebo-treated patients (odds ratio 2.1; 90% confidence interval 1.3, 2.9; see Table 9-17). At the US sites, saphenous vein graft occlusion rates were comparable, with 9.4% of aprotinin-treated and 9.5% for placebo-treated patients having an occluded graft (odds ratio 1.0; 90% confidence interval 0.5, 1.8). Consistent with the correction of the problems measuring

anticoagulation and stopping the storage of harvested veins in aprotinin-containing blood, the saphenous vein graft occlusion rates at the Danish and Israeli sites in both the aprotinin and placebo groups improved from the initial enrollment tercile (34.5% of aprotinin-treated patients and 15.7% of placebo-treated patients) to subsequent terciles (17.0% and 10.9%). At 1 Israeli site, the saphenous vein graft occlusion rate improved markedly from the initial tercile (73% aprotinin-treated patients and 14% of placebo-treated patients) to the subsequent terciles (11% and 3%).

Table 9-17: Study D92-048: Analysis of Graft Occlusion

	Full-Dose Aprotinin % (N)	Placebo % (N)	Odds Ratio (90% CI)	p Value
Any occluded saphneous vein graft				
All sites				
All patients	15.4 (363)	10.9 (340)	1.5 (1.1, 2.1)	0.03
US sites				
All patients	9.4 (202)	9.5 (179)	1.0 (0.5, 1.8)	0.72
Surgery in 1st entry tercile	7.8 (64)	12.1 (66)	0.6 (0.0, 1.7)	0.60
Surgery in 2nd and 3rd entry tercile	10.1 (138)	8.0 (113)	1.3 (0.6, 2.6)	0.35
Israeli and Danish sites				
All patients	23.0 (161)	12.4 (161)	2.1 (1.3, 2.9)	0.01
Surgery in 1st entry tercile	34.5 (55)	15.7 (51)	2.8 (2.1, 6.4)	0.002
Surgery in 2nd and 3rd entry tercile	17.0 (106)	10.9 (110)	1.7 (0.8, 2.6)	0.25
Occluded distal saphenous vein insertions				
All sites				
All saphenous vein graft insertions	7.5 (897)	4.8 (837)	1.7 (1.2, 2.1)	0.02
Single saphenous vein grafts	9.2 (677)	5.9 (656)	1.6 (1.1, 2.1)	0.03
Sequential saphenous vein grafts	2.3 (220)	0.6 (181)	4.2 (0.0, 5.8)	0.49
Occluded internal thoracic artery grafts (single grafts only)				
All sites				
All patients	1.8 (326)	1.0 (304)	1.9 (0.3, 3.8)	0.32

CI = confidence interval.
Source: Adapted from Table IV in Alderman et al. J Thorac Cardiovasc Surg 1998; 116: 716 – 730.(212)

Stepwise logistic regression analysis found that many patient- and graft-related variables interacted with treatment group assignment to predict subsequent saphenous vein graft occlusion in the presence of aprotinin therapy. These variables included smaller distal vessel size, lower total protamine dose, smaller graft size, older age, lower cardiac ejection fraction, female gender, no aspirin within the 2

days prior to surgery, and lower quality distal vessels. These adverse predictors of graft occlusion were consistently more prevalent in the patients enrolled at the Danish and Israeli sites compared to those enrolled at the US sites. As previously noted (see Table 9-16), there were no significant differences between treatment groups (US and non-US sites combined) in the incidences of myocardial infarction (2.9% of aprotinin-treated patients versus 3.8% of placebo-treated patients) or of death (1.4% versus 1.6%).

9.4.6 Post-marketing experience

Two post-marketing observational studies (Study 426 and Study 4001) enrolled patients undergoing CABG surgery. The results of these studies did not reveal any unexpected findings. In Study 426, the rate of myocardial infarction was 5.1% (29/567) and of congestive heart failure was 5.5% (31/567). In Study 4001, the rate of myocardial infarction was 0.8% (10/1180) and of congestive heart failure was 1.7% (20/1180). It is likely that the patients in Study 426 were at higher risk for complications because this was a named patient study that enrolled high risk patients in the United Kingdom conducted prior to approval.

There have been 745 spontaneous adverse events of any type reported to Bayer Global Drug Safety from 1985 to 31 Mar 2006. Of these 745 cases, 67 cardiovascular events (48 were fatal) were reported in a total exposure of 4.38 million. Twenty-nine of these cases were myocardial infarctions (18 were fatal) and 43 cases were congestive heart failure (35 were fatal).

9.4.7 Cardiac safety conclusions

During the initial clinical development of aprotinin, treatment-emergent adverse event reports suggested an increase in the rate of myocardial infarction among patients undergoing repeat CABG surgery who were treated with aprotinin compared to placebo. Further evaluation revealed that these differences may have been attributable to inadequate heparinization as well as the lack of a standardized definition of myocardial infarction and a protocol requirement to capture

systematically the necessary objective data to evaluate if a myocardial infarction had occurred.

No treatment-associated difference was observed in the rates of myocardial infarction in the primary CABG randomized controlled trial database.

The difference in rates of myocardial infarction in the pooled analysis (including a possible dose-response) of patients undergoing repeat CABG surgery was predominantly driven by the events reported in Study D89-004. Possible explanations for the increased incidence of myocardial infarction in this study include inadequate heparinization among patients in the aprotinin group because of the effect of aprotinin on celite-activated clotting times, variability in the definition and reporting of myocardial infarctions, and a higher risk patient population. In Study D92-008, which also enrolled patients undergoing repeat CABG surgery, the rates for myocardial infarction were lower.

Seven studies prospectively designed to evaluate graft patency were reviewed, 5 of which used angiography to evaluate patency. Although significant differences in graft patency were observed in Study D92-048, the rates of saphenous vein graft closure, whether evaluated on a per-patients or per-graft basis, were similar for aprotinin-treated and placebo-treated patients enrolled at US sites.

No treatment-associated differences were noted in the rates of congestive heart failure in the primary and repeat CABG randomized controlled trial database.

As stated in the precautions section of the prescribing information for Trasylol, one of several methods may be used to maintain adequate anticoagulation, despite the aprotinin-associated prolongation of some activated clotting times.

Although Mangano et al reported an increased risk for a combined event consisting of myocardial infarction or congestive heart failure among patients undergoing primary CABG surgery, no increase was noted among patients undergoing complex cardiac surgeries.(1) No explanation or discussion of possible confounding factors

is given for these unexpected findings. These results are not consistent with those obtained from analysis of the Bayer database. In addition, meta-analyses by Sedrakyan et al and the Cochrane Collaboration did not suggest an increased risk of myocardial infarction associated with aprotinin use.(201, 203) Furthermore, the observational study by Karkouti et al also did not reveal an increased risk of myocardial infarction associated with aprotinin use among very high risk patients undergoing cardiac surgery.(2)

With adequate monitoring of anticoagulation, aprotinin does not appear to be associated with an increased risk of cardiovascular events such as myocardial infarction and congestive heart failure.

9.5 Cerebrovascular safety

9.5.1 Overview of literature

As discussed in Section 8.5, numerous studies and meta-analyses have found an association between aprotinin therapy and reduction in the rate of stroke following cardiopulmonary bypass.(201-206, 234, 239, 240, 265)

9.5.2 Bayer global randomized controlled trials

The events suggestive of stroke from the global database and reported from at least 1 patient undergoing CABG surgery are summarized in Table 9-18. The events are summarized without regard to study drug relationship. Patients could have had more than one event. Overall, 1.1% of full-dose aprotinin-treated patients and 1.6% of placebo-treated patients had an event suggestive of stroke. The difference in rates was not statistically significant (odds ratio 0.80; 95% confidence interval 0.53, 1.21).

Table 9-18: Treatment-Emergent Adverse Events Suggestive of Stroke in CABG Patients
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full-Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any stroke event	25	1.1	34	1.6
Cerebellar infarction	0	0.0	3	0.1
Cerebral artery embolism	2	<0.1	0	0.0
Cerebral infarction	1	<0.1	6	0.3
Cerebral ischaemia	1	<0.1	1	<0.1
Cerebrovascular accident	18	0.8	23	1.1
Hemiparesis	5	0.2	5	0.2
Hemiplegia	2	<0.1	1	<0.1
Lacunar infarction	0	0.0	1	<0.1
Ischaemic cerebral infarction	1	<0.1	0	0.0

In order to determine if the use of aprotinin would increase the risk of a cerebrovascular event in a patient population already at high risk for such an event, additional subset analyses of the global CABG database were conducted. For each sub-population, the incidence of any event suggestive of stroke was evaluated by gender, age, history of hypertension, history of myocardial infarction, history of diabetes mellitus, prior stroke, and by type of CABG surgery. The results are shown in Table 9-19. Most odds ratios were less than one with the exception of patients with no prior history of myocardial infarction (odds ratio 1.06). However, in patients with a prior history of myocardial infarction, the odds ratio was 0.55 (95% confidence interval 0.31, 0.98). No other statistically significant treatment differences were observed.

Table 9-19: Stroke Events by Subgroup Analysis (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Subgroup	Full-Dose Aprotinin n/N	%	Placebo n/N	%	Odds Ratio (95% CI)
Overall	25/2249	1.1	34/2164	1.6	0.80 (0.53, 1.21)
Gender					
Male	20/1993	1.0	25/1911	1.3	0.85 (0.55, 1.32)
Female	5/255	2.0	9/253	3.6	0.82 (0.44, 1.54)
Age					
<65 years	11/1381	0.8	12/1290	0.9	0.91 (0.55, 1.50)
≥65 years	14/868	1.6	22/871	2.5	0.80 (0.50, 1.28)
History of hypertension					
No	10/1341	0.8	10/1282	0.8	0.94 (0.57, 1.56)
Yes	15/908	1.7	24/882	2.7	0.78 (0.49, 1.26)
Prior myocardial infarction					
No	18/1370	1.3	16/1344	1.2	1.06 (0.67, 1.68)
Yes	7/879	0.8	18/820	2.2	0.55 (0.31, 0.98)
History of diabetes mellitus					
No	16/1855	0.9	20/1742	1.1	0.82 (0.52, 1.30)
Yes	9/394	2.3	14/422	3.3	0.90 (0.52, 1.54)
Prior Stroke					
No	23/2177	1.1	30/2098	1.4	0.83 (0.55, 1.26)
Yes	2/72	2.8	4/66	6.1	0.83 (0.38, 1.80)
Type of surgery					
Primary CABG	20/1819	1.1	24/1785	1.3	0.82 (0.45, 1.48)
Repeat CABG	2/276	0.7	8/255	3.1	0.23 (0.05, 1.07)

CI = confidence interval.

The events suggestive of encephalopathy and reported from at least 1 patient undergoing CABG surgery are displayed in Table 9-20. The events are summarized without regard to study drug relationship. Patients could have had more than one event. Overall, 0.2% and 0.3% of full-dose aprotinin-treated and placebo-treated patients, respectively, had an event suggestive of encephalopathy. The difference in rates was not statistically significant (odds ratio 0.94; 95% confidence interval 0.55, 1.60).

Table 9-20: Treatment-Emergent Adverse Events Suggestive of Encephalopathy in CABG Patients
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full-Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any encephalopathy event	5	0.2	6	0.3
Coma	3	0.1	4	0.2
Encephalopathy	1	< 0.1	0	0.0
Hypoxic encephalopathy	0	0.0	1	< 0.1
Anoxic encephalopathy	1	< 0.1	0	0.0
Metabolic encephalopathy	0	0.0	1	< 0.1

In order to determine if the use of aprotinin would increase the risk of a cerebrovascular event in a patient population already at high risk for such an event, additional subset analyses of the global CABG database were conducted. For each sub-population, the incidence of any event suggestive of encephalopathy was evaluated by gender, age, history of hypertension, history of myocardial infarction, history of diabetes mellitus, prior stroke, and type of CABG surgery. The results are shown in Table 9-21. No statistically significant treatment differences were observed.

Table 9-21: Encephalopathy Event by Subgroup Analysis (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Subgroup	Full-Dose Aprotinin n/N	%	Placebo n/N	%	Odds Ratio (95% CI)
Overall	5/2249	0.2	6/2164	0.3	0.94 (0.55, 1.60)
Gender					
Male	4/1993	0.2	3/1911	0.2	1.01 (0.58, 1.75)
Female	1/255	0.4	3/253	1.2	0.84 (0.42, 1.70)
Age					
<65 years	2/1381	0.1	1/1290	0.1	0.99 (0.56, 1.76)
≥65 years	3/868	0.4	5/871	0.6	0.91 (0.52, 1.59)
History of hypertension					
No	0/1341	0.0	3/1282	0.2	0.84 (0.47, 1.50)
Yes	5/908	0.6	3/882	0.3	1.10 (0.61, 1.96)
Prior myocardial infarction					
No	2/1370	0.1	3/1344	0.2	0.96 (0.55, 1.69)
Yes	3/879	0.3	3/820	0.4	0.83 (0.42, 1.63)
History of diabetes mellitus					
No	3/1855	0.2	4/1742	0.2	0.89 (0.51, 1.54)
Yes	2/394	0.5	2/422	0.5	1.08 (0.57, 2.04)
Prior stroke					
No	4/2177	0.2	5/2098	0.2	0.93 (0.54, 1.61)
Yes	1/72	1.4	1/66	1.5	0.97 (0.43, 2.17)
Type of surgery					
Primary CABG	3/1819	0.2	3/1785	0.2	0.98 (0.20, 4.87)
Repeat CABG	0/276	0.0	3/255	1.2	0.13 (0.01, 2.54)

CI = confidence interval.

9.5.3 Dose-response relationship

The events suggestive of stroke and encephalopathy in the dose-response studies are summarized in Table 9-22. The events are summarized without regard to study drug relationship. Patients could have had more than one event.

Table 9-22: All Treatment-Emergent Adverse Events Suggestive of Stroke or Encephalopathy in CABG Patients in the Dose-Response Studies in Global Development
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in the Dose-Response Studies)

	Full-Dose Aprotinin N = 361		Half-Dose Aprotinin N = 366		Placebo N = 365	
Event	**n**	**%**	**n**	**%**	**n**	**%**
Stroke	4	1.1	2	0.5	11	3.0
Encephalopathy	1	0.3	1	0.3	3	0.8

9.5.4 Post-marketing experience

Two post-marketing observational studies (Study 426 and Study 4001) that enrolled CABG patients were conducted at Bayer. In Study 426, stroke was reported in 0.5% (3/567) of patients. In Study 4001, the incidence of stroke was 0.3% (3/1180). No cases of encephalopathy were reported in either study.

There have been 745 spontaneous adverse events of any type reported to Bayer Global Drug Safety from 1985 to 31 Mar 2006. Of these cases, 25 cerebrovascular events (14 were fatal) were reported in a total exposure of 4.38 million. Of these 25 cases, 4 were cases of encephalopathy (3 were fatal) and 22 cases were cerebrovascular accidents or strokes (11 were fatal).

9.5.5 Cerebrovascular safety conclusions

The randomized, controlled trial database did not suggest an increased risk of stroke or encephalopathy associated with aprotinin. To the contrary, the literature as well as a meta-analysis support that aprotinin use may be associated with a reduced risk of stroke.

9.6 Renal safety

9.6.1 Overview of literature

The Cochrane Collaboration published a meta-analysis designed to evaluate the efficacy and safety of aprotinin, tranexamic acid, and aminocaproic acid among adult patients undergoing elective cardiac surgery.(203) Data on renal failure or

dysfunction were available on 3776 patients from 13 studies. Approximately 60% of patients received the full-dose aprotinin regimen. The studies enrolled patients undergoing cardiac surgery, including CABG and valve replacement or repair, as well as aortic surgery using deep hypothermic cardiac arrest. Renal failure or dysfunction developed in 71 of 2210 (3.2%) aprotinin-treated patients and 37 of 1566 (2.4%) patients in the control groups. There was no significant risk for developing renal failure or dysfunction among the aprotinin-treated patients (relative risk 1.19; 95% confidence interval 0.79, 1.79).

Sedrakyan et al reported a meta-analysis designed to evaluate clinical outcomes associated with aprotinin use among patients undergoing CABG surgery.(201) Data on renal failure were available on 3003 patients from 17 studies. Approximately 65% of the aprotinin-treated patients received the full-dose regimen. Renal failure developed in 26 of 1755 (1.5%) patients treated with aprotinin and 16 of 1248 (1.3%) patients receiving placebo.(201) There was no significant risk of developing renal failure among the patients treated with aprotinin (relative risk 1.01; 95% confidence interval 0.55, 1.83). Although the results do not indicate an enhanced risk of renal failure associated with aprotinin use, the authors noted that the risk cannot be definitively excluded because of the wide confidence intervals.

Smith et al reported an analysis designed to evaluate clinical outcomes associated with the use of different aprotinin doses among 2283 patients undergoing coronary artery bypass surgery.(234) Data from 4 published studies and from 2 unpublished (1 was subsequently published) trials obtained from Bayer were included in the analysis. For the pooled analysis, patients received either the full-dose aprotinin regimen (n = 860), the half-dose aprotinin regimen (n = 317), aprotinin only added to the priming volume of the heart-lung machine (n = 245), or placebo (n = 861).(234) The incidences of increases in post-operative serum creatinine levels of more than 0.5 mg/dL or to values greater than 2 mg/dL were approximately 8 to 10% in all four treatment groups. The authors noted no

clinically or statistically significant differences in renal findings among the dosing groups studied.

However, one meta-analysis by Munoz et al showed a non-significant increased risk of renal dysfunction among patients treated with a high dose of aprotinin.(206) Data on renal dysfunction were available from 8 placebo-controlled studies. Higher and lower doses of aprotinin were given to 1344 and 412 patients respectively. Most patients receiving a higher dose of aprotinin were administered the full-dose regimen. The lower dose regimens of aprotinin were much more varied but included the half-dose regimen in some patients. The studies enrolled patients undergoing cardiac surgery, including CABG and valve replacement or repair. There was no significant risk of renal dysfunction among patients treated with higher doses of aprotinin (odds ratio 1.46; 95% confidence interval 0.92, 2.33; $p = 0.11$) or among those treated with lower doses (odds ratio 1.01; 95% confidence interval 0.65, 1.57).(206) The authors noted that their ability to examine the rate of this adverse event was severely limited because the trials used variable definitions for renal impairment.

An update of the Munoz meta-analysis(206) was reported by Brown et al in a May 2006 letter to the editor in the New England Journal of Medicine.(266) Brown et al updated the meta-analysis from 1999 to incorporate new trials that used the higher dose of aprotinin. The authors do not explain how they overcame the acknowledged limitation of the original meta-analysis, namely that the trials used different definitions of renal impairment. The updated relative risk for renal failure was 1.09 (95% confidence interval 0.68, 1.76) and for renal dysfunction was 1.47 (95% confidence interval 1.12, 1.94) for the patients treated with the higher doses of aprotinin.

Numerous observational studies, including case-control and cohort studies that were designed to assess the impact of aprotinin on renal dysfunction and failure have been published. Six relatively large case-control or observational studies examined the risk of renal dysfunction or renal failure associated with aprotinin therapy. In a

retrospective study, Gillespie et al matched 219 aprotinin-treated patients to 219 control patients using propensity scores.(267) Although aprotinin doses were not specified, most patients received a half dose of aprotinin. Renal failure developed in 31 of 219 (14.2%) aprotinin-treated patients and in 22 of 219 (10.0%) control patients (odds ratio 1.48; 95% confidence interval 0.83, 2.64). In a retrospective study to assess the impact of aprotinin and angiotensin converting enzyme inhibitor therapy on renal function, Kincaid et al found that more patients treated with aprotinin (31 of 420; 7.4%) than aminocaproic acid (11 of 789; 1.4%) developed renal failure in the setting of cardiac surgery.(268) In a multivariate analysis, concomitant aprotinin and angiotensin converting enzyme inhibitor therapy did predict renal failure ($p < 0.0001$) while the use of aprotinin alone or an angiotensin converting enzyme inhibitor alone did not.

In a retrospective study using univariate and multivariate analyses to assess the risk for renal dysfunction, Mora-Mangano et al found that aprotinin use was not associated with an increased risk for renal dysfunction ($p = 0.951$) among 183 patients undergoing aortic surgery using deep hypothermic circulatory arrest.(269) In a prospective observational study that used univariate and multivariate analyses to define risk factors for renal dysfunction, Provenchère et al found no association between aprotinin therapy and renal impairment among 649 patients undergoing cardiac surgery.(41)

Two observational studies by Karkouti et al and Mangano et al recently reported an association between aprotinin use and renal dysfunction or failure. In a case-control study of very high risk patients that used propensity scores to match 449 patients who received aprotinin to 449 patients who received tranexamic acid during cardiac surgery, Karkouti et al reported that renal dysfunction developed in 107 of 449 (23.8%) aprotinin-treated and 75 of 449 (16.7%) tranexamic acid-treated patients ($p = 0.01$).(2) Among patients with normal baseline renal function, dysfunction occurred in 73 of 339 (21.5%) and 52 of 323 (16.1%) aprotinin- and tranexamic acid-treated patients, respectively ($p = 0.09$). Renal failure requiring dialysis

developed in 25 of 449 (5.6%) aprotinin-treated and 14 of 449 (3.1%) tranexamic acid-treated patients (p = 0.08). Among patients with normal baseline renal function, renal failure occurred in 11 of 339 (3.2%) and 6 of 323 (1.9%) aprotinin- and tranexamic acid-treated patients, respectively (p = 0.3).

In an observational study, Mangano et al reported that aprotinin use compared to no antifibrinolytic therapy increased the risk for a renal composite event.(1) In this study, 1295 patients received aprotinin, 883 received aminocaproic acid, 822 received tranexamic acid, and 1374 received no antifibrinolytic therapy.

A retrospective case study of 2235 patients (1387 patients received aprotinin and 848 received no aprotinin) with renal dysfunction (defined as a post-operative creatinine >2 mg/dL and at least two times the pre-operative value) was conducted by Palykonda et al.(270) No statistically significant differences in renal dysfunction were observed.

Dietrich et al conducted an analysis of 5866 patients undergoing CABG surgery who were treated with aprotinin.(271) The results of a multivariate regression analysis demonstrated that aprotinin dose was not associated with adverse renal outcomes.

As listed by Hörl, potential risk factors for renal dysfunction associated with aprotinin therapy include: concomitant therapy with nephrotoxic drugs, concomitant therapy with afferent renovasoconstrictors, concomitant therapy with angiotension converting enzyme inhibitors or angiotension II receptor antagonists, pre-existing renal disease such as diabetic nephropathy, and pre-existing renal dysfunction.(272) In an open-label, controlled, randomized trial, Mercieri et al showed that mean post-operative serum creatinine values were significantly increased on post-operative days 6 and 7 for patients treated with the combination of vancomycin, gentamicin and aprotinin.(273) Significant increases were not noted for patients treated with 3 other regimens: vancomycin and gentamicin; cefamandole; or cefamandole and aprotinin. Kincaid et al found in a multivariate

analysis that concomitant aprotinin and angiotensin converting enzyme inhibitor therapy was associated with significantly more acute renal failure (defined as serum creatinine >2.0 mg/dL within 72 hours after surgery; p <0.0001).(268) However, the use of either drug alone was not significantly associated with the development of renal failure.

In a case-control study that used propensity scores to match 449 patients who received aprotinin to 449 patients who received tranexamic acid during cardiac surgery, Karkouti et al noted that renal dysfunction developed in 34 of 110 (30.9%) aprotinin-treated patients with abnormal pre-operative renal function and in 73 of 339 (21.5%) aprotinin-treated patients with normal pre-operative renal function.(1) Renal failure developed in 14 of 110 (12.7%) aprotinin-treated patients with abnormal pre-operative renal function and in 11 of 339 (3.2%) aprotinin-treated patients with normal pre-operative renal function.

In a double-blind, placebo-controlled, randomized trial, Lemmer et al found that the rate for post-operative increases in serum creatinine tended to be higher for diabetic patients treated with aprotinin (8 of 34; 23.5%) than for diabetic patients who received placebo (4 of 30; 13.3%; *P* = 0.186).(274)

9.6.2 Bayer global randomized controlled trial database:

9.6.2.1 Serum creatinine and renal dysfunction

Mean serum creatinine values over time from the global clinical database trials are summarized in Table 9-23.

Table 9-23: Mean Serum Creatinine Values Over Time in CABG Patients (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Pre-Op	Day of Surgery	Post-Op Day 1	Post-Op Day 3	Post-Op Day 5	Last Value
Full-dose aprotinin						
n	2100	1512	1508	931	931	2051
Mean, mg/dL (± standard deviation)	1.14 (0.29)	1.00 (0.30)	1.15 (0.42)	1.22 (0.58)	1.24 (0.52)	1.23 (0.52)
Placebo						
n	2013	1417	1450	879	866	1960
Mean, mg/dL (± standard deviation)	1.13 (0.24)	1.01 (0.25)	1.17 (0.40)	1.15 (0.42)	1.14 (0.37)	1.16 (0.41)

Last value can include values obtained prior to or after post-operative day 5.

The incidences of serum creatinine elevations from baseline through postoperative Day 7 are summarized in Table 9-24 for the global database. The incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was 9.0% in the full-dose aprotinin group compared to 6.6% in placebo patients. The difference in rates was statistically significant (odds ratio 1.41; 95% confidence interval 1.12; 1.79).

Table 9-24: Incidences of Serum Creatinine Elevations in CABG Patients (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full-Dose Aprotinin		Placebo		Odds Ratio
Creatinine Change	n/N	%	n/N	%	(95% CI)
> upper limit of normal[a]	332/1825	18.2	246/1724	14.3	1.35 (1.12, 1.62)
>0.5 mg/dL over baseline	185/2047	9.0	129/1957	6.6	1.41 (1.12, 1.79)
>0.5 mg/dL over baseline and a value of >2.0 mg/dL	88/2047	4.3	62/1957	3.2	1.33 (0.97, 1.81)
>2.0 mg/dL over baseline	23/2047	1.1	16/1957	0.8	1.16 (0.73, 1.85)

a only patients with normal baseline serum creatinine values were included.
CI = confidence interval.

In order to determine if the use of aprotinin would increase the risk of a renal event in a patient population already at high risk for such an event, additional subset

analyses of the Bayer global aprotinin CABG database were performed. The incidences of postoperative serum creatinine elevations >0.5 mg/dL above baseline were evaluated by gender, age, history of congestive heart failure or diabetes mellitus, baseline serum creatinine, baseline calculated creatinine clearance, pre-operative use of an angiotensin converting enzyme inhibitor, peri-operative use of aminogylcosides, and type of CABG surgery. The results are shown in Table 9-25. Among patients treated with full-dose aprotinin, the peri-operative use of aminoglycosides and impaired creatinine clearances increased the risk of post-operative serum creatinine elevations.

In general, the differences in the incidences of serum creatinine elevations >0.5 mg/dL above baseline between treatment groups were similar in the subpopulations examined. Similar odds ratios were noted for subgroups within a given subpopulation but often only one of the differences in rates between treatment groups were statistically significant. The differences that were statistically significant most likely reflect larger sample sizes. Examples include the significant differences for males, patients <65 years of age, patients with baseline serum creatinine values <1.4 mg/dL, and patients undergoing primary CABG surgery as well as for patients without a history of diabetes mellitus and congestive heart failure. The lack of an increased risk for serum creatinin elevations among aprotinin-treated diabetic patients is in contrast to published reports.(274) The greater risk for serum creatinine elevations >0.5 mg/dL above baseline among patients with no pre-operative angiotensin-converting enzyme inhibitor use (odds ratio 1.54; 95% confidence interval 1.18, 2.00) compared to those who did use such medications (odds ratio 1.05; 95% confidence interval 0.67, 1.65) was in contrast to the results obtained in a retrospective regression analysis published by Kincaid et al.(268) In the analysis by Kincaid et al, aprotinin tended to be used for patients undergoing re-operations or combined procedures and for patients assessed to be at higher risk of bleeding.

Table 9-25: Serum Creatinine Increase of at Least 0.5 mg/dL Above Baseline by Subgroup Analysis
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Subgroup	Full-Dose Aprotinin n/N	%	Placebo n/N	%	Odds Ratio (95% CI)
Overall	185/2047	9.0	129/1957	6.6	1.41 (1.12, 1.79)
Gender					
Male	161/1802	8.9	114/1721	6.6	1.41 (1.10, 1.80)
Female	24/244	9.8	15/236	6.4	1.16 (0.66, 2.05)
Age					
<65 years	83/1245	6.7	52/1141	4.6	1.40 (0.99, 1.96)
≥65 years	102/802	12.7	77/813	9.5	1.35 (1.00, 1.83)
Baseline creatinine					
<1.4 mg/dL	135/1750	7.7	95/1650	5.8	1.34 (1.03, 1.75)
1.4 to 2.0 mg/dL	42/283	14.8	33/302	10.9	1.31 (0.85, 2.01)
>2.0 mg/dL	8/14	57.1	1/5	20.0	1.41 (0.38, 5.28)
Baseline creatinine clearance					
≥90 mL/min	25/585	4.3	29/569	5.1	0.91 (0.58, 1.41)
60 to <90 mL/min	83/1026	8.1	57/980	5.8	1.37 (0.98, 1.91)
30 to <60 mL/min	73/425	17.2	43/400	10.8	1.55 (1.07, 2.24)
<30 mL/min	4/10	40.0	0/4	0.0	1.31 (0.34, 5.00)
History of diabetes mellitus					
No	138/1678	8.2	93/1571	5.9	1.42 (1.08, 1.85)
Yes	47/369	12.7	36/386	9.3	1.32 (0.87, 2.02)
History of congestive heart failure					
No	167/1937	8.6	120/1860	6.5	1.37 (1.08, 1.75)
Yes	18/110	16.4	9/97	9.3	1.26 (0.63, 2.54)
History of pre-operative ACE inhibitor use					
No	145/1700	8.5	93/1634	5.7	1.54 (1.18, 2.00)
Yes	40/347	11.5	36/323	11.1	1.05 (0.67, 1.65)
History of peri-operative aminoglycoside use					
No	142/1863	7.6	107/1759	6.1	1.25 (0.96, 1.61)
Yes	43/184	23.4	22/198	11.1	2.63 (1.49, 4.65)
Type of surgery					
Primary CABG	144/1658	8.7	105/1620	6.5	1.37 (1.06, 1.78)
Repeat CABG	36/256	14.1	23/237	9.7	1.52 (0.87, 2.65)

ACE = angiotensin-converting enzyme; CI = confidence interval.

The adverse events suggestive of renal dysfunction and reported from at least 1 CABG patient in the Bayer datapool are displayed in Table 9-26. These events are summarized without regard to relationship to study drug. Patients could have had more than one event. Overall, 4.9% and 4.1% of full-dose aprotinin- and placebo-treated patients, respectively, had any event suggestive of renal dysfunction. This difference was not statistically significant (odds ratio 1.21; 95% confidence interval 0.92, 1.59).

Table 9-26: Treatment-Emergent Adverse Events Suggestive of Renal Dysfunction in CABG Patients
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full-Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any renal dysfunction event	111	4.9	88	4.1
Acute prerenal failure	1	<0.1	0	0.0
Anuria	3	0.1	3	0.1
Azotemia	3	0.1	2	<0.1
Blood creatinine increased	22	1.0	18	0.8
Blood urea increased	12	0.5	5	0.2
Oliguria	8	0.4	11	0.5
Proteinuria	1	<0.1	0	0.0
Renal failure	35	1.6	26	1.2
Renal failure acute	7	0.3	8	0.4
Renal tubular necrosis	4	0.2	1	<0.1
Postoperative renal failure	2	<0.1	2	<0.1
Urine output decreased	19	0.8	25	1.2
Renal function test abnormal	1	<0.1	1	<0.1
Renal impairment	9	0.4	1	<0.1

9.6.2.2 Renal failure

The adverse events suggestive of renal failure and reported from at least 1 CABG patient in the Bayer datapool are summarized in Table 9-27. These events are summarized without regard to relationship to study drug. Patients could have had more than one event. Overall, 1.9% and 1.7% of full-dose aprotinin- and placebo-treated patients, respectively, had an event suggestive of renal failure. The difference in rates was not statistically significant (odds ratio 1.09; 95% confidence interval 0.74, 1.60).

Table 9-27: Treatment-Emergent Adverse Events Suggestive of Renal Failure in CABG Patients
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

	Full-Dose Aprotinin N = 2249		Placebo N = 2164	
Term	**n**	**%**	**n**	**%**
Any renal failure event	43	1.9	36	1.7
Acute prerenal failure	1	<0.1	0	0.0
Renal failure	35	1.6	26	1.2
Renal failure acute	7	0.3	8	0.4
Postoperative renal failure	2	<0.1	2	<0.1

9.6.2.3 Renal dialysis

Renal dialysis was performed on or recommended for 0.3% (6/2249) of patients receiving full-dose aprotinin and 0.4% (8/2164) of patients treated with placebo. The Society of Thoracic Surgeons National Database reports a 1.64% dialysis rate among 136,935 patients who underwent CABG surgery from 2005 to 2006 (personal communication with Dr. Peter Smith).

9.6.3 Dose-response relationship

The events suggestive of renal failure and renal dysfunction in the dose-response studies are summarized in Table 9-28. The events are summarized without regard to study drug relationship. Patients could have had more than one event.

Table 9-28: All Treatment-Emergent Adverse Events Suggestive of Renal Failure or Dysfunction in CABG Patients in the Dose-Response Studies in Global Development
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in the Dose-Response Studies)

	Full-Dose Aprotinin N = 361		Half-Dose Aprotinin N = 366		Placebo N = 365	
Event	**n**	**%**	**n**	**%**	**n**	**%**
Renal failure	9	2.5	11	3.0	11	3.0
Renal dysfunction	32	8.9	26	7.1	26	7.1

Mean serum creatinine values over time by aprotinin dose for the 7 dose-response trials are shown in Table 9-29.

Table 9-29: Mean Serum Creatinine Values Over Time in CABG Patients by Aprotinin Dose (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in the Dose-Ranging Studies)

	Pre-Op	Day of Surgery	Post-Op Day 1	Post-Op Day 3	Post-Op Day 5	Last Value
Full-dose aprotinin						
n	337	311	315	290	230	335
Mean, mg/dL (± standard deviation)	1.22 (0.44)	1.03 (0.45)	1.20 (0.51)	1.28 (0.70)	1.26 (0.59)	1.26 (0.62)
Half-dose aprotinin						
N	338	307	312	289	220	333
Mean, mg/dL (± standard deviation)	1.17 (0.28)	1.01 (0.26)	1.18 (0.33)	1.17 (0.44)	1.19 (0.41)	1.20 (0.51)
Placebo						
n	343	307	315	300	225	342
Mean, mg/dL (± standard deviation)	1.20 (0.28)	1.03 (0.26)	1.22 (0.35)	1.18 (0.42)	1.16 (0.39)	1.20 (0.41)

Last value can include values obtained prior to or after post-operative day 5.

Specified elevations in serum creatinine through post-operative day 7 are shown in Table 9-30.

Table 9-30: Incidences of Creatinine Elevations in CABG Patients by Aprotinin Dose (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety in the Dose-Response Studies)

	Full-Dose Aprotinin		Half-Dose Aprotinin		Placebo	
Creatinine Change	n/N	%	n/N	%	n/N	%
>upper limit of normal[a]	58/278	20.9	53/294	18.0	57/287	19.9
>0.5 mg/dL over baseline	37/335	11.0	26/333	7.8	27/342	7.9
>0.5 over baseline and a value >2.0 mg/dL	19/335	5.7	14/333	4.2	15/342	4.4
>2 mg/dL over baseline	6/335	1.8	4/333	1.2	4/342	1.2

a only patients with normal baseline serum creatinine values were included.

Renal dialysis was performed on or recommended for 0.3% (1/361) of patients receiving full-dose aprotinin, 0.8% (3/366) of patients receiving half-dose aprotinin, and 0.8% (3/365) of patients receiving placebo.

9.6.4 Post-marketing experience

Two post-marketing observational studies that enrolled patients undergoing CABG surgery were conducted. The results of these studies did not reveal any unexpected findings. Renal failure was reported in 1.8% (10/567) of patients in Study 426 and 1.1% (13/1180) of patients in Study 4001. One patient in Study 426 was reported to have had dialysis. Renal dysfunction was reported in 2.3% (13/567) of patients in Study 426 and 1.2% (14/1180) of patients in Study 4001.

There were 745 spontaneous adverse events of any type reported to Bayer Global Drug Safety from 1985 to 31 Mar 2006. Of these cases, 81 cases of renal dysfunction (26 were fatal) were reported. Fifty-six of these cases developed acute renal failure (20 were fatal). Two patients required dialysis (both cases were non-fatal).

9.6.5 Renal safety conclusions

In the literature, controlled studies have demonstrated transient changes in renal function but no enhanced risk of renal failure associated with aprotinin therapy.(275-278) Meta-analyses by Sedrakyan et al and the Cochrane Collaboration also report no increased risk of renal failure associated with aprotinin therapy.(201, 203)

In the Bayer global clinical trial datapool, the incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was 9.0% in full-dose aprotinin-treated as compared to 6.6% in placebo-treated patients (odds ratio 1.41; 95% confidence interval 1.12, 1.79). The incidence of the more clinically significant elevations of >2.0 mg/dL above baseline was 1.1% and 0.8% for these treatment groups, respectively (odds ratio 1.16; 95% confidence interval 0.73, 1.85). Overall, 1.9% of full-dose aprotinin-treated patients and 1.7% of placebo-treated patients had

renal failure (odds ratio 1.09; 95% confidence interval 0.74, 1.60), and 0.3% of aprotinin-treated patients and 0.4% of placebo-treated patients had dialysis performed or recommended. The incidences of serum creatinine elevations >0.5 mg/dL, >2.0 mg/dL and renal failure did not differ for patients receiving half-dose aprotinin and placebo.

The peri-operative use of an aminoglycoside or a low baseline creatinine clearance increased the risk of postoperative serum creatinine elevations in CABG patients treated with aprotinin in these CABG studies.

Renal adverse events and treatment-emergent serum creatinine elevations are described in the Trasylol prescribing information.

9.7 Hypersensitivity

The risk of hypersensitivity reactions to aprotinin is related to exposure history. The current prescribing information for Trasylol recommends that the physician consider exposure history in assessing the risk of hypersensitivity and anaphylaxis. In a retrospective review, the incidence of hypersensitivity or anaphylactic reaction was 5.0% for re-exposure within 6 months and 0.9% for re-exposure after 6 months, while the incidence of hypersensitivity and anaphylactic reaction in patients with no prior exposure to Trasylol was rare (less than 0.1% in US controlled clinical studies).

There were 745 spontaneous adverse events of any type reported to Bayer Global Drug Safety from 1985 to 31 Mar 2006. Of these cases, 311 were cases of suspected hypersensitivity and were subsequently adjudicated by an external consultant. Five of the 311 cases were associated with the administration of fibrin glue containing aprotinin, and these were excluded from further analysis. Of the remaining 306 cases, 291 (52 were fatal) were assessed as possibly associated with Trasylol administration in a total exposure of 4.38 million. For the majority of the anaphylactic reactions the outcome was listed as “recovered” or “improved”. Further analysis of all possibly associated cases of hypersensitivity revealed that a

majority had Trasylol within the previous 6 months, and some experienced a hypersensitivity reaction despite a negative result from the test dose.

In conclusion, the risk of hypersensitivity reactions to aprotinin is related to exposure history, and the prescribing information for Trasylol contains a boxed warning regarding anaphylaxis and recommends that physicians consider exposure history to aprotinin when assessing the risk of hypersensitivity and anaphylaxis.

10. Overall Conclusions

In summary, aprotinin is an important part of blood conservation programs during CABG surgery. When used in accordance with the approved Trasylol prescribing information, the Bayer US and global randomized controlled clinical trial database (which includes 2249 full-dose aprotinin-treated and 2164 placebo-treated patients) together with other published studies and more than 10 years of post-marketing experience supports a favorable benefit-risk profile for the prophylactic use of aprotinin to reduce peri-operative blood loss and the need for blood transfusions among patients undergoing CABG surgery utilizing cardiopulmonary bypass.

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TRASYLOL®
(aprotinin injection)

01298181 12/03

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).

DESCRIPTION

Trasylol® (aprotinin injection), $C_{284}H_{432}N_{84}O_{79}S_7$, 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® 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® 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® 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®, 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® 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)[a]	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.

[a] 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® 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® as compared to placebo.

Efficacy Variables: Primary CABG Patients
Mean (S.D.) or % of Patients

VARIABLE	PLACEBO REGIMEN N=624	Trasylol® PUMP PRIME REGIMEN† N=159	Trasylol® REGIMEN B** N=175	Trasylol® REGIMEN A** N=641
% 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® 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® 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® group compared to the placebo group.

In a U.S. randomized study of Trasylol® 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® in terms of the need for transfusion or the number of units of blood required.

INDICATIONS AND USAGE

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.

CONTRAINDICATIONS

Hypersensitivity to aprotinin.

WARNINGS

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.

PRECAUTIONS

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 con-

tradictory 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.

Drug Interactions: Trasylol® is known to have antifibrinolytic activity and, therefore, may inhibit the effects of fibrinolytic agents. In study of nine patients with untreated hypertension, Trasylol® infused intravenously in a dose of 2 million KIU over two hours blocked the acute hypotensive effect of 100mg of captopril.

Trasylol®, 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® 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® or studies to determine the effect of Trasylol® on fertility have not been performed.

Results of microbial *in vitro* tests using *Salmonella typhimurium* and *Bacillus subtilis* indicate that Trasylol® 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^2 dose. They have revealed no evidence of impaired fertility or harm to the fetus due to Trasylol®. 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®, 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® 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® 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®.

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 Trasylol®, 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 Trasylol® is generally well tolerated. The adverse events reported are frequent sequelae of cardiac surgery and are not necessarily attributable to Trasylol® 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 Trasylol® 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

Adverse Event	Aprotinin (n = 2002) values in %	Placebo (n = 1084) values in %
Any Event	76	77
Body as a Whole		
Fever	15	14
Infection	6	7
Chest Pain	2	2
Asthenia	2	2
Cardiovascular		
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
Digestive		
Nausea	11	9
Constipation	4	5
Vomiting	3	4
Diarrhea	3	2
Liver Function Tests Abnormal	3	2
Hemic and Lymphatic		
Anemia	2	8
Metabolic & Nutritional		
Creatine Phosphokinase Increased	2	1
Musculoskeletal		
Any Event	2	3
Nervous		
Confusion	4	4
Insomnia	3	4
Respiratory		
Lung Disorder	8	8
Pleural Effusion	7	9
Atelectasis	5	6
Dyspnea	4	4
Pneumothorax	4	4
Asthma	2	3
Hypoxia	2	1
Skin and Appendages		
Rash	2	2
Urogenital		
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 that 2%, are listed below:

EVENT	Percentage of patients treated with Trasylol N = 2002	Percentage of patients treated with Placebo N = 1084
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

EVENT	Percentage of patients treated with Trasylol N = 2002	Percentage of patients treated with Placebo N = 1084
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 prothombin.

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 Anaylsis

Treatment	Definite MI %	Definite or Probable MI %	Definite, Probable or Possible MI %
Pooled Data from Three Studies that Evaluated Regimen A			
Trasylol® Regimen A n = 646	4.6	10.7	14.1
Placebo n = 661	4.7	11.3	13.4
Pooled Data from Two Studies that Evaluated Regimen B and Pump Prime Regimen			
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 post-operative 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 %
Trasylol®	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 Trasylol® 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 Trasylol® 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% Trasylol® vs. 3.8% placebo) or of death (1.4% Trasylol® vs. 1.6% placebo) in this study.

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.

Laboratory Findings

Serum Creatinine: Data pooled from all patients undergoing CABG surgery in U.S. placebo-controlled trials showed no statistically or clinically significant increase in the incidence of postoperative renal dysfunction in patients treated with Trasylol®. The incidence of serum creatinine elevations > 0.5 mg/dL above pre-treatment levels was 9% in the Trasylol® group vs. 8% in the placebo group (p=0.248), while the incidence of elevations >2.0 mg/dL above baseline was only 1% in each group (p=0.883). In the majority of instances, postoperative renal dysfunction was not severe and was reversible. Patients with baseline elevations in serum creatinine were not at increased risk of developing postoperative renal dysfunction following Trasylol® treatment.

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 post-operative hepatic dysfunction in patients treated with Trasylol®. The incidence of treatment-emergent increases in ALT (formerly SGPT) > 1.8 times the upper limit of normal was 14% in both the Trasylol® 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® 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® treated patients in the hours after surgery due to circulating concentrations of Trasylol®, 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® 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® (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® therapy is unclear.

DOSAGE AND ADMINISTRATION

Trasylol® 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® is supplied as a solution containing 10,000 KIU/mL, which is equal to 1.4 mg/mL. All intravenous doses of Trasylol® should be administered through a central line. **DO NOT ADMINISTER ANY OTHER DRUG USING THE SAME LINE.** Both regimens include a 1 mL 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® 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 test dose) are described in the table below:

	TEST DOSE	LOADING DOSE	"PUMP PRIME" DOSE	CONSTANT INFUSION DOSE
TRASYLOL® 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® 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 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®, 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: No formal studies of the pharmacokinetics of aprotinin in patients with pre-existing renal insufficiency have been conducted. However, in the placebo-controlled clinical trials conducted in the United States, patients with mildly elevated pretreatment serum creatinine levels did not have a notably higher incidence of clinically significant post-treatment elevations in serum creatinine following either Trasylol® Regimen A or Regimen B compared to administration of the placebo regimen. Changes in aprotinin pharmacokinetics with age or impaired renal function are not great enough to require any dose adjustment. No pharmacokinetic data from patients with pre-existing hepatic disease treated with Trasylol® are 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® should be stored between 2° and 25°C (36° - 77°F).
Protect from freezing.

Bayer HealthCare

Bayer Pharmaceuticals Corporation
400 Morgan Lane
West Haven, CT 06516
Made in Germany

℞ **Only**

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Appendix 2: Publication

Mangano, D., et. al. The Risk Associated with Aprotinin in Cardiac Surgery. *New England Journal of Medicine.* 354(4):353-65; January 2006.

Appendix 3: Publication

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.

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 Trasylol or another drug intended to decrease the risk for perioperative bleeding. This study suggested that 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.

The FDA urges health care providers and patients 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.

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Date created: February 8, 2006

Bayer HealthCare
Pharmaceuticals

IMPORTANT Trasylol Safety Information

February, 2006

Dear U.S. Healthcare Professional:

Bayer Pharmaceuticals Corporation (Bayer) would like to inform you that Bayer and the U.S. Food and Drug Administration (FDA) are evaluating recent reports published in the medical literature concerning Trasylol® (aprotinin injection)) and the occurrence of serious adverse events among patients undergoing cardiac surgery.

A study entitled, "The Risk Associated with Aprotinin in Cardiac Surgery" by Mangano et al., was published in the *New England Journal of Medicine*, (Mangano D, Tudor J, Dietzel C. N Eng J Med, 2006 (354) :353-65. www.nejm.com). The publication describes the findings from an observational study of 4,374 patients (1,295 treated with aprotinin) scheduled for coronary artery bypass graft (CABG) surgery in multiple centers in multiple countries. Patients received either no therapy for blood loss, or a drug therapy intended to reduce blood loss (aprotinin, aminocaproic acid, tranexamic acid).

The *NEJM* publication reported an association of aprotinin with increased risk of cardiovascular events (myocardial infarction or heart failure), cerebrovascular events such as stroke, encephalopathy or coma, and renal dysfunction or failure in patients undergoing CABG surgery. Patients were not randomized to these treatments. Instead, choice of study drug (or no treatment) was at physician discretion. Patients receiving aprotinin may have been at a higher risk to begin with for developing renal failure, myocardial infarction, heart failure or stroke compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility prevents a direct assessment of whether aprotinin altered the risk for serious adverse events. To try to adjust for known differences between the treatment groups, the study authors used statistical procedures (multivariable logistic regression and propensity score adjustments).

A study entitled, "A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery" by Karkouti et al. has been published in the journal *Transfusion* (Karkouti K, Beattie W, Dattilo K, McCluskey S, Ghannam M, Hamdy A, et al., Transfusion, on-line edition, 1/20/06. www.blackwellpublishing.com/journal.asp?ref=0041-1132). This was also an observational study that used statistical methodology to compare outcomes from patients undergoing CABG. Like the NEJM study, the patients in this study received, at physician discretion, either Trasylol or another drug intended to decrease the risk for perioperative bleeding.

The study in *Transfusion* has some of the same limitations as the NEJM publication. The study suggested that Trasylol administration increased the risk for renal dysfunction or

failure. Renal dysfunction and renal failure have previously been reported in patients receiving Trasylol and are reflected in the current FDA approved labeling for Trasylol. The study by Karkouti et al. did not find an increased rate of cardiovascular or cerebrovascular events in Trasylol-treated patients and reported comparable mortality rates between the control treatment group and the Trasylol group.

The FDA will review the NEJM and Transfusion reports, data supplied by Bayer and the authors of the studies, other reports in the literature as well as reports submitted to the FDA through the MedWatch program, to determine if any actions are warranted. Bayer welcomes this evaluation and the FDA's accompanying guidance to physicians and patients.

While the evaluation of these published reports and other relevant data continues, the FDA has provided guidance for physicians and patients in the form of an Alert for Healthcare Professionals and a Public Health Advisory concerning Trasylol. These documents and questions and answers related to this issue are posted on the FDA's website at www.fda.gov.

The FDA's guidance includes a recommendation that physicians carefully monitor patients receiving Trasylol for the occurrence of adverse events particularly related to the kidneys, heart, or central nervous system and promptly report any events to Bayer or the FDA's MedWatch program. The FDA also suggests that while the evaluation continues, physicians should consider limiting Trasylol use to situations where the clinical benefit of reduced blood loss is essential for medical management of the patient and outweighs potential risks.

Bayer supports these actions by the FDA. We have been working and will continue to work closely with the FDA and other regulatory authorities in countries where Trasylol is marketed to address questions regarding product safety. We share the company's data on Trasylol with regulatory authorities on an ongoing basis and welcome their evaluation of these published reports. Bayer believes that Trasylol is a safe and effective treatment when used in accordance with the product labeling.

The current U.S. Prescribing Information for Trasylol is available on www.trasylol.com. If you wish to request further information, please contact Bayer Pharmaceuticals Corporation Clinical Communications at 1-800-288-8371.

Sincerely,

Paul MacCarthy, MD, FRCPI
Vice President, Medical Affairs
Bayer Pharmaceuticals Corporation