Trasylol® (Aprotinin Injection) Briefing Document

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1. Background

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 who are at increased risk for blood loss and blood transfusion (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.(1) 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.

In this briefing document, Bayer will present data from the analysis of the Bayer global randomized controlled database (which includes 2,249 full-dose aprotinin-treated and 2,164 placebo-treated patients). Bayer will also review recent observational studies of aprotinin and discuss the methodological limitations of these studies.

1.1 Review of key regulatory activities prior to Jan 2006

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 was 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.

On 12 Oct 1994, an NDA supplement was approved to add the Trasylol half-dose regimen.

On 02 May 1997 Bayer submitted additional safety information. 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. This supplement was approved on 08 Aug 1997.

On 30 Sep 1997, an NDA supplement was approved to update the adverse event tables.

An NDA 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.

1.2 Review of key activities from Jan 2006 to 21 Sep 2006

Two retrospective observational studies published in early 2006 reported safety events possibly associated with aprotinin use during cardiac surgery. Mangano et al(2) proposed that, in comparison to patients who received no treatment, aprotinin use was associated with an increased incidence of cardiovascular events (myocardial infarction and/or congestive heart failure), cerebrovascular events (stroke, encephalopathy and/or coma), and renal events (renal dysfunction and/or renal failure requiring dialysis) in patients undergoing elective coronary-artery revascularization with no history of cardiac surgery, vascular surgery or angioplasty, and with an increased incidence of renal events in patients undergoing "complex coronary-artery surgery." The study by Karkouti et al(3), which used propensity score matching to compare high transfusion risk cardiac surgery patients who received aprotinin to those who were treated with tranexamic acid, reported that

"While the true difference in adverse events between the two drugs should best be addressed by prospective randomized control trials, our results suggest that aprotinin use may be associated with worsening renal function in patients with existing renal dysfunction." (See Section 9 for a detailed discussion of these studies.)

Subsequent to the publication of these 2 observational studies, the FDA released a public health advisory and Bayer sent letters to over 110,000 physicians and health care providers and posted a notice on the internet to notify the public and health care community about potential risks.

In addition, Bayer prepared and submitted 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) in the setting of CABG surgery. The Bayer randomized controlled trial database in CABG surgery patients includes 2,249 full-dose aprotinin-treated and 2,164 placebo-treated patients. As part of its evaluation of aprotinin, Bayer also reviewed all spontaneous reports received by the company. The most frequently reported event was hypersensitivity. On 17 May 2006, Bayer submitted to the FDA a risk minimization plan to specifically address the risk of hypersensitivity. (See Section 7.6 for details of the risk minimization plan.)

The two observational studies published in 2006(2, 3) and the analysis of data from the Bayer randomized controlled database in CABG surgery were the focus of the FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting that reviewed Trasylol on 21 Sep 2006.(4) In the first study [Mangano 2006] Mangano et al concluded that use of aprotinin compared to no hemostatic treatment was associated with an increased risk for an in-hospital cardiovascular event (myocardial infarction and/or congestive heart failure), a cerebrovascular event (stroke, encephalopathy, and/or coma), and a renal event (postoperative elevation of serum creatinine and/or renal failure requiring dialysis) in patients undergoing "primary" CABG surgery, and with an increased risk of an in-hospital renal event in patients undergoing "complex" CABG surgery.(2) The authors also asserted in the abstract

and discussion to that paper, though not supported by the reported results,(5) that among patients undergoing complex or primary CABG surgery "use of aprotinin was associated with a doubling of the risk of renal failure requiring dialysis."(2) The authors further reported that the risk of in-hospital mortality for patients who received aprotinin compared to no treatment was not statistically different in either the "primary" or the "complex" surgery group.(2) In the second study [Karkouti 2006], Karkouti et al reported that aprotinin compared to tranexamic acid 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).(3) Karkouti et al reported no increased risk of cardiac or cerebrovascular events among patients receiving aprotinin, and no difference in in-hospital mortality. (For a detailed review of these observational studies, see Section 9.)

FDA's Cardiovascular and Renal Drugs Advisory Committee at its meeting on 21 Sep 2006(4) reviewed the reported results from these two observational studies(2, 3) as well as data from Bayer's randomized, controlled clinical trials in CABG surgery.(6, 7) Following its review, the Advisory Committee agreed that the data were consistent with an association between aprotinin use and renal impairment, specifically an increase in serum creatinine; however, most of the committee was not convinced that there was a definite increased risk of renal failure requiring dialysis. The committee also "agreed overall that there was no association between aprotinin use and an increased risk of myocardial infarction, heart failure, stroke or encephalopathy."(4)

1.3 Review of key activities since 21 Sep 2006

As a consequence of the 2006 publications of the observational studies by Mangano et al.(2) and Karkouti et al.(3) Bayer contacted i3 Drug Safety in February 2006 regarding the possibility of performing a study then contracted i3 Drug Safety in June 2006 to conduct a retrospective observational study of the effects of aprotinin, tranexamic acid and aminocaproic acid in patients undergoing CABG surgery. The

observational study, which was drawn from an administrative database (Premier Prospective Comparative Database) involving patients who underwent CABG surgery, was conducted by Dr. Alexander Walker, an employee of i3 Drug Safety. In September 2006 two individuals from Bayer's Global Drug Safety Group received from i3 Drug Safety a preliminary report,(8) dated 13 Sep 2006, entitled "Mortality and Cardiovascular and Renal outcomes in recipients of aprotinin, aminocaproic acid and tranexamic acid during CABG surgery: Report on Computerized Inpatient Data from the Premier Perspective Comparative Database." This preliminary report was based exclusively on the electronic data from the Premier Database, and it was preliminary to any medical record review.(8) At that time the authors reported their preliminary result that with "multivariate adjustment, the estimated risks were higher for aprotinin recipients than for recipients of other antifibrinolytics with respect to acute renal failure (RR=1.70; 95% CI 1.55-1.86), death (RR=1.68; 95% CI 1.53-1.84), acute heart failure (RR=1.08; 95% CI 1.03-1.14), and stroke (RR=1.20; 95% CI 1.07-1.35)."(8) The authors concluded that findings of their analysis "support the hypothesis that there is a higher risk of death and acute renal failure in aprotinin recipients."(8) The preliminary findings raised such significant questions on the study population, outcomes and methodology used by i3 Drug Safety that the two members of Bayer's Global Drug Safety Group who were responsible for monitoring the study progress and to whom the preliminary findings had been circulated by i3 Drug Safety chose to initiate further discussions with i3 Drug Safety in an effort to address their questions and criticisms. Other than the two individuals from Bayer's Global Drug Safety Group, no other Bayer employees were aware of the preliminary study report prior to 21 Sep 2006. Regrettably, the findings in the preliminary study report were not disclosed to the FDA prior to the 21 Sep 2006 Advisory Committee meeting.

On 27 Sep 2006 Bayer submitted to the FDA a copy of the preliminary report, the draft study protocol and Dr. Walker's answers to questions posed by Bayer. Bayer also briefed other relevant regulatory authorities and informed them of this matter. With respect to the results reported by i3 Drug Safety, Bayer believes that

limitations of the administrative database that was used render it unsuitable for addressing the comparative safety of hemostatic agents in the complex clinical setting of CABG surgery. Bayer also notes that the statistical methodology in this study is inappropriate as well. (See Section 11 for a detailed discussion of the i3 Drug Safety Study.)

Additionally, on 29 Sep 2006, the FDA posted a public health advisory on its website related to Trasylol. Referring to the Preliminary Report, FDA in a Public Health Advisory issued 29 Sep 2006(9) stated "The preliminary findings from this new observational study of patients from a hospital database reported that use of Trasylol [aprotinin] may increase the chance for death, serious kidney damage, congestive heart failure and strokes."(9) FDA stated further(9):

"In the published studies and in the recently supplied Bayer study, patients were not assigned at random to receive various treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, in these safety studies [referring also the observational clinical studies published earlier in 2006 by Mangano et al(2) and Karkouti et al(3)] patients receiving Trasylol may have had a higher chance for serious complications to begin with as compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility complicates the assessment of whether the available studies show that Trasylol treatment, rather than other factors, increased the chance for serious kidney or heart complications."(9)

FDA also indicated that it was "actively evaluating these new data and their implications for appropriate use of the drug."(9)

On 15 Dec 2006, Bayer announced Trasylol label changes. Of note, Bayer had submitted to the FDA draft labeling concepts on 12 Sep 2006 in advance of the Advisory Committee meeting held on 21 Sep 2006. Based upon these concepts and input from the Advisory Committee, the Trasylol US product information was

revised on 15 Dec 2006 with respect to renal dysfunction and hypersensitivity as follows:

- Limit Trasylol use to patients who are at an increased risk for blood loss and blood transfusion in the setting of coronary artery bypass graft surgery with cardiopulmonary bypass.

- Contraindicate the administration of Trasylol to any patients with a known or suspected prior exposure to Trasylol or other aprotinin-containing products within the previous 12 months.

- Provide additional information on the management and prevention of anaphylactic reactions, including the administration of Trasylol only in an operative setting where cardiopulmonary bypass may be rapidly initiated.

- In addition, the 1 mL "test dose" was renamed the "initial (test) dose" so as not to convey unrealistic expectations about that dose to predict subsequent hypersensitivity reactions.

- Highlight the risk for kidney dysfunction.

The complete text of the revised US product information is included in Appendix 1.

The change to the US label was accompanied by the dissemination of another Dear Healthcare Provider Letter (DHCP), and the new and current US PI for Trasylol, in order to further raise awareness of the potential risks of all adverse events possibly associated with Trasylol, including hypersensitivity, listed in the Product Information including the boxed warning. A copy of the Dear Health Care Provider Letter is included in Appendix 2.

As part of the ongoing risk minimization efforts, in the US, the company sales, marketing and medical affairs personnel continued to perform educational activities for and with prescribers. (See Section 7.6 for details of the risk minimization plan.)

As discussed above, recent revisions to the Trasylol labeling included a recommendation regarding management of possible anaphylactic reactions, ie Trasylol should be administered only in surgical settings where cardiopulmonary bypass (CPB) can be rapidly initiated. Because the use of CPB is not practical in non-cardiac surgical settings, Bayer decided to end all development efforts for aprotinin in non-cardiac surgical settings. Specifically, Bayer decided not to pursue an indication in hip surgery (the results of the study had been submitted to the FDA in April 2006), and on 15 Jan 2007, Bayer announced that it had decided to terminate three ongoing clinical studies investigating the safety and efficacy of Trasylol on transfusion requirements and blood loss in adults: elective spinal fusion surgery, pneumonectomy or esophagectomy for cancer and radical or total cystectomy in bladder cancer. It is important to emphasize that Bayer's decision to end these clinical trials was not related to safety findings in those studies. Bayer is currently finalizing medical research reports for these three trials and will submit the reports to the FDA as soon as they are available.

In February, 2007 Mangano et al(10) reported in the *Journal of the American Medical Association* [Mangano 2007] that aprotinin treatment in patients undergoing coronary artery bypass graft (CABG) surgery was associated with significantly increased 5-year mortality compared with control (no treatment). Mangano 2007 comprises the authors' analysis of the 5-year mortality data available for a subset of the same set of 4,374 CABG patients described in the report published in January 2006 in the *New England Journal of Medicine* [Mangano 2006](2) and reviewed at the September 2006 Advisory Committee. With respect to Mangano 2007 Bayer believes that inappropriate statistical methodology and other methodological flaws raise doubts as to the validity of the authors' conclusions. (See Section 10 for a detailed discussion.)

In June 2007, Brown et al published a meta-analysis of antifibrinolytic agents used in cardiac surgery.(11) Aprotinin (high and low dose) was demonstrated to reduce blood loss and reduce transfusion. The high dose significantly reduced the rate of

re-exploration. There was no significant risk of mortality, stroke, myocardial infarction, or renal failure. The high dose of aprotinin was associated with an increased incidence of renal dysfunction (defined as elevation of creatinine above 0.5 mg/dL above pre-treatment levels). The low dose was not associated with an increased incidence of renal dysfunction.

In June 2007, Coleman et al reported an observational study on all patients undergoing cardiothoracic surgery (CTS; i.e. patients had to have undergone CABG surgery [either alone or with valve or other surgery] and utilized a CPB pump) at one institution between 01 Jan 2000 and 31 Dec 2005.(12) Overall, 3,348 patients were included in this evaluation, of which 362 (10.8%) patients received aprotinin during surgery (250 of the patients receiving aprotinin had complex surgeries) and 2,986 patients did not. Patients receiving aprotinin were older, more likely to be undergoing complex surgery, and were sicker as evidenced by a more significant history of left main disease, chronic obstructive pulmonary disease, hypertension, cerebrovascular disease, aortic stenosis, and preoperative renal dysfunction and an increased need for urgent or emergency surgery ($P < 0.05$ for all). After multivariate logistic regression including propensity score adjustment, the authors found that patients receiving aprotinin were nearly twice as likely to experience postoperative renal dysfunction ($P < 0.001$) but nearly one third less likely to experience a neurologic complication compared with control ($P = 0.01$), although the decrease in neurologic complications with aprotinin was mainly a result in decreased delirium. In this study, renal dysfunction was defined as acute or worsening renal failure resulting in 1 or more of the following: 1. an increase in serum creatinine to >2.0 mg/dL and twice the baseline creatinine level or 2. a new requirement for dialysis. No additional differences in myocardial infarction or mortality were noted between aprotinin and control ($P > 0.53$ for all comparisons). This study is limited due to the small number of patients who received aprotinin.

1.4 Organization of briefing document

This briefing document is prepared for the FDA Advisory Committee Meeting to be held on 12 Sep 2007. Following a review of the factors influencing morbidity and mortality in CABG surgery (Section 2) and an overview of transfusion in cardiac surgery (Section 3), aprotinin clinical data is reviewed. The mechanism of action of aprotinin is reviewed in Section 4. Section 5 summarizes the dosing of aprotinin. The efficacy of aprotinin is reviewed in Section 6. Section 7 summarizes the safety of aprotinin with a focus on mortality, thromboembolic events, renal findings, and hypersensitivity. The focus of Section 7 is the Bayer randomized clinical trial database (which includes 2,249 full-dose aprotinin-treated and 2,164 placebo-treated CABG surgery patients) and the various meta-analyses of controlled trials. Section 8 provides an overview of the evaluation of observational studies in general. In addition to a review of the two observational studies discussed at FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting of 21 Sep 2006 (Section 9), this briefing document reviews the Mangano et al 2007 publication (Section 10) as well as the i3 Drug Safety study findings (Section 11).

2. CABG: Factors Influencing Morbidity and Mortality

Coronary artery bypass grafting (CABG) has a high incidence of cardiac and surgical procedure-related adverse events. The underlying atherosclerotic cardiovascular disease is often associated with metabolic disease, diabetes mellitus, and hypertension, which are among its main risk factors.(13) These may secondarily lead to renal and hepatic dysfunction and thromboembolic complications with consequential end organ damage. Hence, patients who are scheduled for CABG surgery are often polymorbid with multiple organ functional deficits and limited compensatory potential that make them particularly vulnerable to the development of complications. A meta-analysis of 176 studies with 205,717 patients undergoing CABG showed that the major surgery-related adverse events occurring in-hospital was death (1.7%); non-fatal myocardial infarction (2.4%); non-fatal stroke (1.3%); gastrointestinal bleeding (1.5%); and renal failure (0.8%).(13) Thirty-day mortality was 2.1%. Risk factors for unfavorable outcome

were advancing age, female sex, low ejection fraction, history of stroke, myocardial infarction or heart surgery, and presence of diabetes or hypertension that are all associated with increased 30-day mortality and morbidity after CABG.(13)

According to the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database of 503,478 CABG procedures, CABG has a mortality rate of 3.05% and a major complication rate of 13.40%.(14) Major complications include stroke (1.63%), renal failure (3.53%), re-exploration for bleeding (5.17%), prolonged ventilation (5.96%), and sternal infection (0.63%).(14)

Data from the literature indicate that 5.5-21% of all CABGs are repeat operations.(15-17) Repeat cardiac surgery is inherently more technically demanding than primary surgery, as sternal re-entry, pericardial adhesions, in situ arterial grafts, and patent atherosclerotic vein grafts increase the complexity of the procedure.(17) Further, patients undergoing re-operative surgery are older, exhibit a higher pre-operative risk profile regarding both cardiac and non-cardiac comorbidities, and more often need an urgent or emergent operation in comparison with those undergoing primary CABG.(16, 17) Repeat CABG is associated with significantly increased morbidity and mortality relative to primary CABG surgery(13-17) such as myocardial infarction(13), stroke(18, 19), and renal failure.(20) In a meta-analysis of general CABG patients(13), the mean incidence (±SE) of myocardial infarction patients with no prior CABG was calculated at 4.72 (±1.18)% while it was 9.04 (±2.71)% in studies with "some patients with prior CABG." What can be concluded from these data is that the incidence of myocardial infarction in repeat CABG patients is higher compared with that in primary CABG surgery patients.

Not all surgeries are routinely scheduled, as data from the STS National Adult Cardiac Surgery Database of 503,478 CABG procedures shows 6.6% of patients require an emergent or salvage procedure and 31.1% require an urgent procedure.(14) Non-elective CABG surgery is associated with increased morbidity and mortality.(14, 21, 22)

In comparison to cardiac valve surgery alone, procedures combining CABG and valve surgery have a clearly increased risk of myocardial infarction(23), stroke(24, 25), and renal failure.(26, 27) The increased cardiopulmonary bypass time associated with this complex surgery may be the underlying cause since increased CPB time itself has a significant effect on the incidence of myocardial infarction(13), stroke(24, 28), and renal failure.(27, 29, 30) The increased generation and transport of particulate emboli may be a common pathogenic factor that contributes to the increased risk.(31)

The individual surgeon and hospital may also be a substantial source of variability, even in high-standard countries such as the US, justifying a close look for center effects, particularly in imbalanced observational studies. Significant variability in institutional transfusion practice in CABG surgery has been documented, with transfusion rates for red blood cells ranging 27-92% of patients and for platelets ranging 0-36% of patients.(32) In CABG surgery, surgeon has been identified as a predictor of transfusion(33), as well as increased risk of death.(34)

In May 2007, another observational study was published in the Journal of Thoracic and Cardiovascular Surgery (JTCVS) by Ott et al., looking at "Coronary Artery Bypass Graft Surgery – Care Globalization: The impact of National Care on Fatal and Nonfatal Outcome."(35) This database was a subset of the database of 4,374 CABG patients described in the report published in January 2006 in the New England Journal of Medicine.(2) In-hospital mortality was 1.5% (9/619) in the United Kingdom, 2.0% (9/444) in Canada, 2.7% (34/1283) in the United States, and 3.8% (32/834) in Germany ($P = 0.03$). The rates of the composite outcome (morbidity and mortality) were 12% in the United Kingdom, 16% in Canada, 18% in the United States, and 24% in Germany ($P < 0.001$). After adjustment for difference in case-mix (using the European System for Cardiac Operative Risk Evaluation) and practice, country was not an independent predictor for mortality. However, there was an independent effect of country on composite outcome. Practices that were associated with adverse outcomes included the intraoperative use

of aprotinin and transfusion of fresh-frozen plasma or platelets, and the use of heparin or lack of administration of aspirin during the early postoperative period. The association between blood product transfusion, aprotinin use, or aspirin administration and adverse outcome in this study suggests that the complex interaction of factors affecting blood coagulation and hemostasis may play an important role in clinical outcome.

The multitude of individual and procedural risk factors renders the between-group balancing of variables a challenging task. The incidence of major adverse events in patients after CABG varies widely across studies and patient populations, and it was concluded that this heterogeneity must be controlled when using the literature to benchmark safety.(13) Particularly, high variability was seen in multicenter, multinational studies.(13) Not only between-trial heterogeneity but also between-group imbalances of risk factors within a single study may affect the conclusions that can be drawn from the data. Control for this heterogeneity can be better accomplished in large multi-center or smaller single center placebo-controlled trials than in observational studies.

2.1 Risk models for morbidity and mortality

As there have been changes in patient characteristics/profiles over time in patients undergoing CABG, crude mortality rates based on surgical procedure alone are probably not adequate for assessing peri-operative risks.(36) Roques et al conducted a multivariate analysis for 20,014 patients undergoing cardiac surgery from 132 centers in Europe. The variables determined to be risk factors for mortality are summarized in Table 2-1.

Table 2-1: Roques: Predictors of Peri-Operative Mortality in 20,014 Patients Undergoing Cardiac Surgery

Variable	Odds Ratio	Standard Error	P Value
Age (continuous)	1.1	0.007	0.001
Female	1.4	0.128	0.001
Serum creatinine >200 mmol/L	1.9	0.256	0.001
Extracardiac arteriopathy	1.9	0.376	0.001
Pulmonary disease	1.6	0.284	0.006
Neurological dysfunction	2.3	0.584	0.001
Previous cardiac surgery	2.6	0.324	0.001
Recent myocardial infarct	1.6	0.208	0.001
LVEF 30-50%	1.5	0.138	0.001
LVEF <30%	2.5	0.340	0.001
Chronic congestive heart failure	1.5	0.179	0.001
Systolic pulmonary pressure >60 mmHg	2	0.423	0.001
Active endocarditis	2.5	0.678	0.001
Unstable angina	1.5	0.202	0.001
Urgent operation	1.6	0.173	0.001
Emergency operation	2.8	0.440	0.001
Critical preoperative state	2.2	0.319	0.001
Ventricular septal rupture	3.8	1.735	0.002
Non-coronary surgery	1.6	0.170	0.001
Thoracic aortic surgery	3.2	0.650	0.001

Source: Table 5 in Roques et al.(36)

This data support the need to consider multiple baseline variables to accurately assess the risk of peri-operative mortality. Therefore, this database was used to define a EuroSCORE to predict peri-operative mortality.(37) The EuroSCORE risk factors and weights are summarized in Table 2-2.

Table 2-2: EuroSCORE Risk Factors, Definitions and Weights

	Definition	Score
Patient-related factors		
Age	Per 5 years or part thereof over 60 years	1
Sex	Female	1
Chronic pulmonary disease	Long term use of bronchodilators or steroids for lung disease	1
Extracardiac arteriopathy	Any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta, limb arteries or carotids	2
Neurological dysfunction	Disease severely affecting ambulation or day-to-day functioning	2
Previous cardiac surgery	Requiring opening of the pericardium	3
Serum creatinine	>200 μmol/l preoperatively	2
Active endocarditis	Patient still under antibiotic treatment for endocarditis at the time of surgery	3
Critical preoperative state	Any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria <10 ml/h)	3
Cardiac-related factors		
Unstable angina	Rest angina requiring i.v. nitrates until arrival in the anaesthetic room	2
LV dysfunction	Moderate or LVEF 30-50%	1
	Poor or LVEF <30%	3
Recent myocardial infarct	(<90 days)	2
Pulmonary hypertension	Systolic PA pressure >60 mmHg	2
Operation-related factors		
Emergency	Carried out on referral before the beginning of the next working day	2
Other than isolated CABG	Major cardiac procedure other than or in addition to CABG	2
Surgery on thoracic aorta	For disorder of ascending, arch or descending aorta	3
Postinfarct septal rupture		4

Source: Table 2 in Nashef et al.(37)

Based on the scoring system, mortality could be predicted based on the multiple baseline risk factors (see Table 2-3).

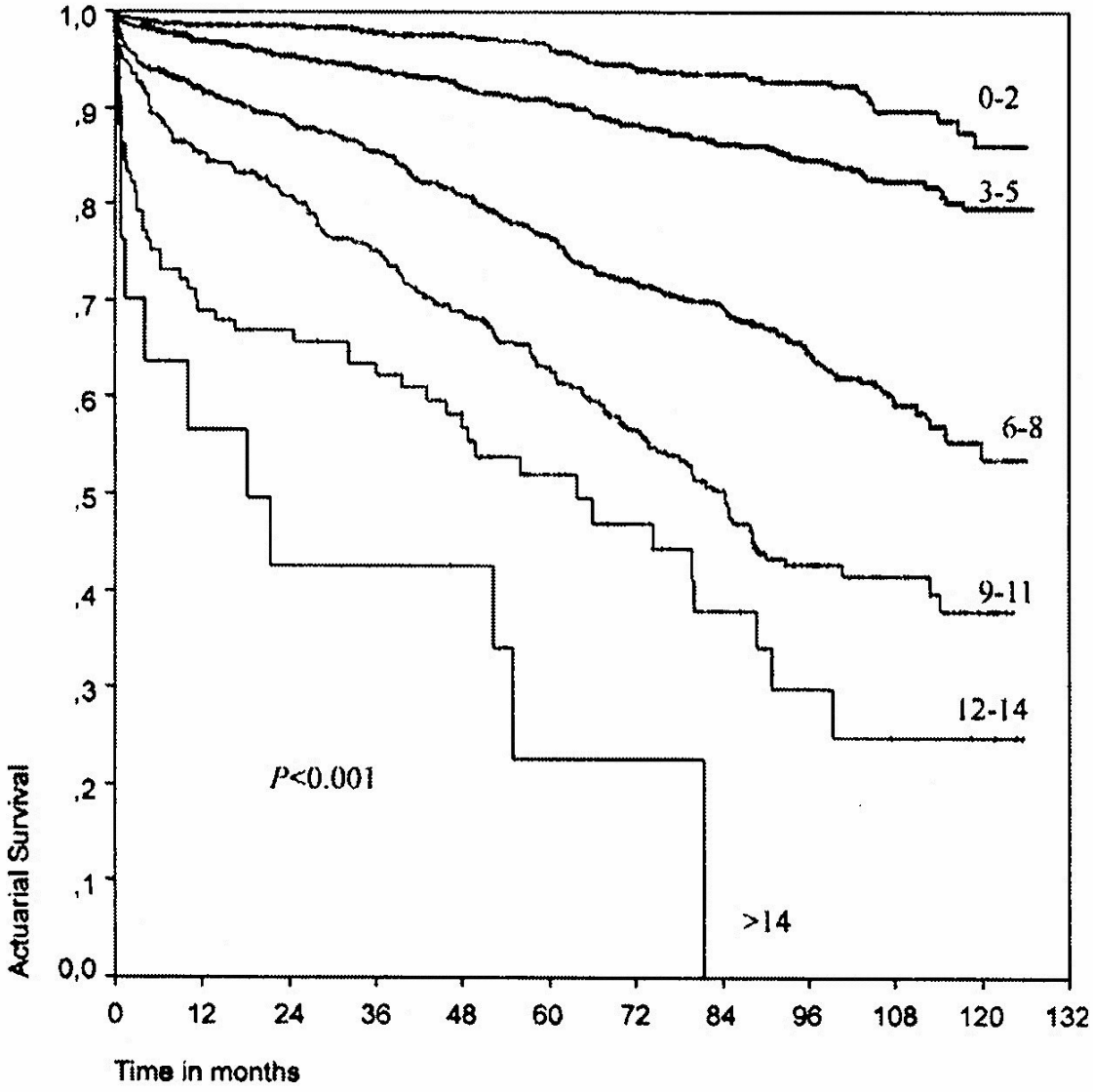
Table 2-3: EuroSCORE Predictor of Peri-Operative Mortality

EuroSCORE	Observed Mortality Rate	95% CI for Expected Outcome
0-2 (low risk)	0.8% (36/4529)	1.27 – 1.29
3-5 (medium risk)	3.0% (182/5977)	2.90 – 2.94
6 plus (high risk)	11.2% (480/4293)	10.93 – 11.54

Source: Table 3 in Nashef et al.(37)

Toumpoulis et al evaluated the predictive value of the EuroSCORE on long-term survival in patients with CABG. Figure 2-1 displays the survival curves by standard EuroSCORE. The standard EuroSCORE appeared to be predictive of long-term mortality. These data support that when predicting long-term mortality, multiple baseline variables should be considered.

Figure 2-1: Long-Term Survival by EuroSCORE



Patients at risk.

Months	0	12	24	36	48	60	72	84	96	108
0-2	610	554	526	479	440	412	356	287	220	145
3-5	1479	1298	1205	1097	990	880	726	564	375	213
6-8	1099	913	842	760	663	552	409	310	192	109
9-11	452	349	314	271	231	174	129	92	50	30
12-14	103	67	60	54	38	24	18	11	7	4
>14	17	8	6	6	5	1	1	0	0	0

Source: Figure 1 in Toumpoulis et al.(38)

Morbidity and mortality risk models have also been developed based on the STS database.(14) The publication reports on 7 risk models with the odds ratios and 95% confidence intervals for these 7 outcomes (mortality, stroke, renal, prolonged ventilation, deep sternal infection, re-exploration and composite outcome). The odds ratios for mortality and renal outcomes for the CABG-only risk model (reflecting 403,325 CABG-only records) are summarized in Table 2-4. As demonstrated in this table, the outcomes of mortality and renal failure are affected by multiple baseline variables.

Table 2-4: STS CABG-Only Risk Model for Mortality and Renal Outcomes

Variable	Mortality OR (95% CI)	Renal OR (95% CI)
Age (years)	1.05 (1.05, 1.05)	1.05 (1.05, 1.06)
Aortic stenosis	1.40 (1.21, 1.61)	1.27 (1.11, 1.46)
Black	1.34 (1.23, 1.45)	1.41 (1.31, 1.52)
Body surface area[a]	0.91 (0.89, 0.93)	1.04 (1.02, 1.05)
Congestive heart failure		1.18 (1.11, 1.25)
Chronic lung disease	1.41 (1.35, 1.48)	1.31 (1.26, 1.37)
Cerebrovascular accident	1.10 (1.04, 1.17)	
Diabetes, oral treatment	1.15 (1.09, 1.21)	1.35 (1.29, 1.42)
Ejection fraction <50%	0.98 (0.98, 0.98)	0.99 (0.99, 0.99)
First re-operation	2.76 (2.62, 2.91)	1.55 (1.46, 1.64)
Hispanic	1.04 (0.92, 1.17)	1.11 (1.00, 1.24)
Hypercholesterolemia	0.82 (0.79, 0.86)	
Hypertension	1.12 (1.08, 1.17)	1.45 (1.39, 1.51)
Intra-aortic balloon pump	1.46 (1.37, 1.55)	1.54 (1.45, 1.64)
Immunosuppressive therapy	1.75 (1.57, 1.95)	1.48 (1.33, 1.64)
Insulin	1.50 (1.42, 1.58)	2.26 (2.16, 2.37)
Left main artery ≥50% stenosis	1.18 (1.14, 1.24)	1.06 (1.02, 1.10)
Male	0.84 (0.80, 0.89)	1.06 (1.00, 1.12)
Mitral insufficiency	1.22 (1.17, 1.28)	1.29 (1.24, 1.35)
Multiple re-operations	4.19 (3.61, 4.86)	1.60 (1.33, 1.92)
NYHA functional class IV level	1.15 (1.10, 1.20)	1.16 (1.11, 1.20)
Other race	1.12 (1.01, 1.25)	1.22 (1.11, 1.35)
Prior myocardial infarction	1.18 (1.16, 1.21)	1.10 (1.08, 1.12)
PTCA <6 hrs	1.32 (1.18, 1.48)	1.46 (1.29, 1.66)
PVD/CVD	1.29 (1.25, 1.34)	1.30 (1.27, 1.34)
Renal failure/dialysis	1.88 (1.80, 1.96)	4.30 (4.09, 4.52)
Shock	2.04 (1.90, 2.19)	1.60 (1.48, 1.72)
Smoker		1.05 (1.03, 1.08)
Status (urgent or emergent)	1.96 (1.88, 2.05)	1.38 (1.31, 1.45)
Triple-vessel disease	1.21 (1.17, 1.26)	1.19 (1.14, 1.23)

a Odds ratio is based on a 0.1 unit change in body surface area (BSA).

Number of records = 403,325 CABG-only records (learning data set). For odds ratio (OR) only statistically significant risk factors are noted for each model with 95% confidence interval (CI) listed.

NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; PVD/CVD = peripheral vascular disease or cerebrovascular disease or both.

Source: Table 3 in Shroyer et al.(14)

In a retrospective study, Mora-Mangano et al also used univariate and multivariate analyses to assess the risk for renal dysfunction in 2,222 patients undergoing CABG surgery.(39) The final risk model is displayed in Table 2-5. Once again, the complexity of baseline conditions have been demonstrated to affect the renal outcome.

Table 2-5: Mora-Mangano: Risk Model for Renal Dysfunction in Patients Undergoing CABG

Risk Factor	Adjusted Relative Risk (95% CI)[a]	Adjusted 95% CI[b]
Preoperative		
Age		
70-79 years	1.6 (1.1-2.3)	1.1-2.4
80-95 years	3.5 (1.9-6.3)	1.8-6.7
Congestive heart failure[c]	1.8 (1.3-2.6)	1.3-2.4
Previous coronary artery bypass graft surgery	1.8 (1.2-2.7)	1.3-2.5
Preoperative creatinine level 124 to 177 μmol/L	2.3 (1.6-3.4)	1.7-3.2
Diabetes		
Type 1 diabetes	1.8 (1.1-3.0)	1.1-2.9
Glucose level >16.6 mmol/L	3.7 (1.7-7.8)	1.9-7.2
Intraoperative and postoperative		
Cardiopulmonary bypass lasting ≥3 hours	2.8 (1.9-7.2)	1.6-4.9
Low output state[d]		
Severe	4.5 (2.9-7.2)	2.5-9.1
Moderate	3.1 (1.9-4.9)	1.9-5.8
Mild	4.3 (2.2 8.5)	2.6-7.9

a Relative risks and 95% CIs estimated by odds ratio derived from a multiple logistic regression model, adjusted for each variable in the table.

b 95% CIs derived from generalized estimation equation model, adjusted for each variable in the table and within-center clustered sample correlation.

c New York Heart Association class III or IV.

d Severe: intraaortic balloon pump insertion; moderate: 1) cardiac index <1.5 L/min per m^2 body surface area for at least 30 consecutive minutes or administration of at least three inotropic drugs, 2) congestive heart failure confirmed with cardiac index <1.5 L/min per m^2, 3) pulmonary artery occlusion pressure >18 mm Hg, or 4) central venous pressure >12 mm Hg; mild: congestive heart failure confirmed with rales, S3 murmur, chest radiographic findings, or jugular venous distention.

Source: Table 3 in Mora-Mangano et al.(39)

Aronson et al reported a risk index for perioperative renal dysfunction/failure based on multivariate analysis from a cohort of 4801 patients undergoing CABG surgery.(40) Increased pulse pressure was the most significant risk predictor. Table 2-6 displays the results.

Table 2-6: Aronson: Predictors of Post-Operative Renal Dysfunction/Renal Failure

Predictor	OR (95% CI)[a]	*P*
Without PP[b]		
Age >75 y	2.27 (1.38-3.72)	0.001
Medical history		
Congestive heart failure	2.39 (1.56-3.66)	<0.001
Myocardial infarction	1.59 (0.99-2.55)	0.058
Renal disease	3.89 (2.54-5.97)	<0.001
Intraoperative factor		
Inotropes[c]	2.52 (1.62-3.92)	<0.001
Intra-aortic balloon pump	4.04 (2.04-8.00)	<0.001
CPB time ≥122 min	1.88 (1.22-2.89)	0.004
With PP[d]		
Age >75 y	2.04 (1.23-3.37)	0.006
Pulse pressure, mm Hg		
≥40	1.49 (1.17-1.89)[e]	0.001
>40-60		
>60-80		
>80-100		
>100		
Medical history		
Congestive heart failure	2.38 (1.55-3.64)	<0.001
Myocardial infarction	1.75 (1.08-2.83)	0.023
Renal disease	3.71 (2.41-5.70)	<0.001
Intraoperative factor		
Inotropes[c]	2.75 (1.75-4.31)	<0.001
Intra-aortic balloon pump	4.41 (2.21-8.80)	<0.001
CPB time ≥122 minutes	1.78 (1.15-2.74)	0.010

a Among the 2,381 patients in the derivation cohort, 47 patients were excluded with missing values for at least 1 of the predictors in the model, including the covariates. The Hosmer-Lemeshow goodness-of-fit χ^2 test statistic was 5.5 (P = 0.599). The C index for the model was 0.833.

b The ORs are adjusted for the factors included in the final model and presented in this table.

c More than 2 intraoperative inotropes treatment.

d Among the 2,381 patients in the derivation cohort, 47 patients were excluded with missing values for at least 1 of the predictors in the model, including the covariates. The Hosmer-Lemeshow goodness-of-fit χ^2 test statistic was 4.1 (P=0.844). The C index for the model was 0.839.

e The OR is for 20-mm Hg increment in PP.

Source: Table 3 from Aronson et al.(40)

A multitude of individual and procedural risk factors have been demonstrated to affect outcomes following CABG surgery. Control for these risk factors can be better accomplished in large multi-center, randomized, controlled trials than in observational studies. In observational studies, it is critical to consider if known

risk factors were available and reliably recorded and appropriately handled in the statistical analysis. (See Section 8 for a detailed discussion.)

3. Overview of Transfusion in Cardiac Surgery

In the US, approximately 4.9 million patients received nearly 14 million units of whole blood and red blood cells in 2001.(41) 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.(32) Although blood and blood products are important and potentially life-saving therapeutic agents, numerous infectious(42-46) and noninfectious risks(47-61) are inherently associated with transfusion and it is unlikely that transfusion will ever be without any risk.

Bayer convened an independent expert panel to prepare an updated summary on the mortality risk associated with blood transfusion. Table 3-1 displays the consensus of the panel regarding that mortality risk.

Table 3-1: Consensus Panel Summary: Mortality Due to Transfusion

	Deaths Per Million Units RBC	Deaths Per Million Units Platelets
Transfusion-related acute lung injury	10-20	10-20
Bacterial contamination	0.1	15-75 (uncultured) 4-15 (cultured)
Lipid-enveloped viruses	<1.0	-
Transfusion errors	~1-2	-
Allergic reactions	5	5
Total mortality per million components	16-27	19-100

Consensus Panel on the risks of blood transfusion, September 2006: Lawrence T. Goodnough (chair), Neil Blumberg, Mark Brecher, George Despotis, Victor Ferraris, Steven Kleinman, Paul Ness, Aryeh Shander.

Cardiac surgery continues to place a large demand on available blood supply. Overall, 10 to 20% of transfusions are utilized for cardiac surgical procedures.(32) Although the extent of blood loss and the need for donor blood transfusions may

have decreased somewhat in recent years, a need for further reduction remains. 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.(62)

3.1 Patients at increased risk for bleeding and transfusion

The transfusion pattern in CABG surgery suggests that 10-20% of patients consume about 80% of the transfused blood products.(63) 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.(32, 64) Stover et al demonstrated that the hospital and the physician were independent predictors for transfusion.(32)

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.(65)

Repeat cardiac surgery procedures are predictors of increased transfusion requirements.(66-71) Performance of urgent or emergent cardiac procedures was also a risk factor for transfusion.(69-72) There appears to be an increased risk of transfusion in CABG surgery with revascularization of 3 or more grafts.(73-75) 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.(76) Furthermore, combined CABG and valve surgery,(77, 78) as well as prolonged cardiopulmonary bypass time(67, 70, 72, 79, 80) are also independent risk predictors for transfusion.

3.2 Anti-platelet therapy

Many patients undergoing CABG surgery are on anti-platelet therapy, and these agents may increase the need for transfusion in patients having CABG.(81-83)

Aspirin has been demonstrated to prolong event-free survival after myocardial infarction.(84) Therefore, not unexpectedly, the majority of patients (at least 60%) who require a CABG procedure have received aspirin within 24 hours of the surgical procedure.(33) Approximately 80% had received aspirin in the 5-day period preceding CABG surgery in one large observational study.(85)

The use of aspirin results in impaired platelet aggregation and clot formation. After cessation of aspirin use, it takes 4-5 days to regain only about 50% of the platelets and 7-10 days to replace all platelets.(86, 87)

Some 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 did not receive aspirin.(33, 88-92) Other studies have not demonstrated this finding.(93-95) In one study, transfusion requirements (for red blood cells and platelets) were increased by 15% for patients taking aspirin.(83)

Clopidogrel is used to treat patients with coronary artery disease and unstable angina.(96, 97) Audited hospital data from 2006 show 42.6% of patients

undergoing CABG received clopidogrel during their hospital stay. Approximately 12% to 26% of patients undergoing CABG surgery are receiving clopidogrel at the time of the surgery.(81, 82)

The clopidogrel-induced platelet inhibitory effect is irreversible for the life-span of the platelet. Current treatment guidelines recommend that clopidogrel be held for 5 days prior to CABG.(98) However, data suggest that as many as 5% of patients receiving clopidogrel require urgent or emergent CABG.(81) Among patients with non-ST-segment elevation acute coronary syndromes admitted to CABG-capable hospitals and undergoing CABG, 30% (852/3977) received clopidogrel within 24 hours of admission: 739 (87%) underwent CABG <5 days of their last dose of clopidogrel, while 113 (13%) underwent CABG surgery ≥5 days after discontinuing clopidogrel.(99)

Several studies have demonstrated that clopidogrel therapy within 5 days of CABG was associated with increased rates for bleeding, blood product transfusions, massive transfusion, re-operation for bleeding, prolonged stay in intensive care units and prolonged length of stay in the hospital.(81-83, 99-104)

The effects of aspirin and clopidogrel are synergistic. Audited hospital data from 2006 show 39.2% of patients undergoing CABG received both aspirin and clopidogrel during their hospital stay. Transfusion requirements (for red blood cells and platelets) were increased 15% for patients taking aspirin and 51% for those taking both aspirin and clopidogrel.(83) The re-exploration (for bleeding) rate in patients undergoing CABG increased from 2.3% on aspirin alone to 10.4% in patients on aspirin and clopidogrel.(83)

Several reports have demonstrated severe, intractable bleeding with use of either the direct thrombin inhibitors for anticoagulation during cardiopulmonary bypass(105-108) or with pre-operative use of clopidogrel.(81-83, 100-103, 109-113) 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.(81-83, 100-103, 109-113) 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.(109)

3.3 Blood management

Over the years, various treatment modalities, including mechanical measures and pharmacological agents such as aprotinin and the lysine analogues, 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.(114-118) 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.(114-118)

The need for blood management in cardiac surgery was recently addressed in 2007 by the Society of Thoracic Surgeons (STS) and The Society of Cardiovascular Anesthesiologists (SCA) Practice Guideline Series titled Peri-operative Blood Transfusion & Blood Conservation in Cardiac Surgery. According to the guidelines, evidence suggests that, "high and low dose aprotinin, epilson aminocaproic acid and tranexamic acid are all effective at significantly reducing total blood loss and the need for packed red blood cell transfusion. Only high-dose aprotinin has been shown to significantly reduce the risk for re-exploration. None of the agents reduces mortality, myocardial infarction, thrombosis, or renal failure or renal dysfunction. Among only the isolated CABG patients, a significant reduction in stroke was observed in aprotinin treated patients. High-dose aprotinin has been associated with increased risk of renal dysfunction, but not renal failure.

There is limited head-to-head evidence to support the use of one agent over the other."(65)

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.(119) 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.

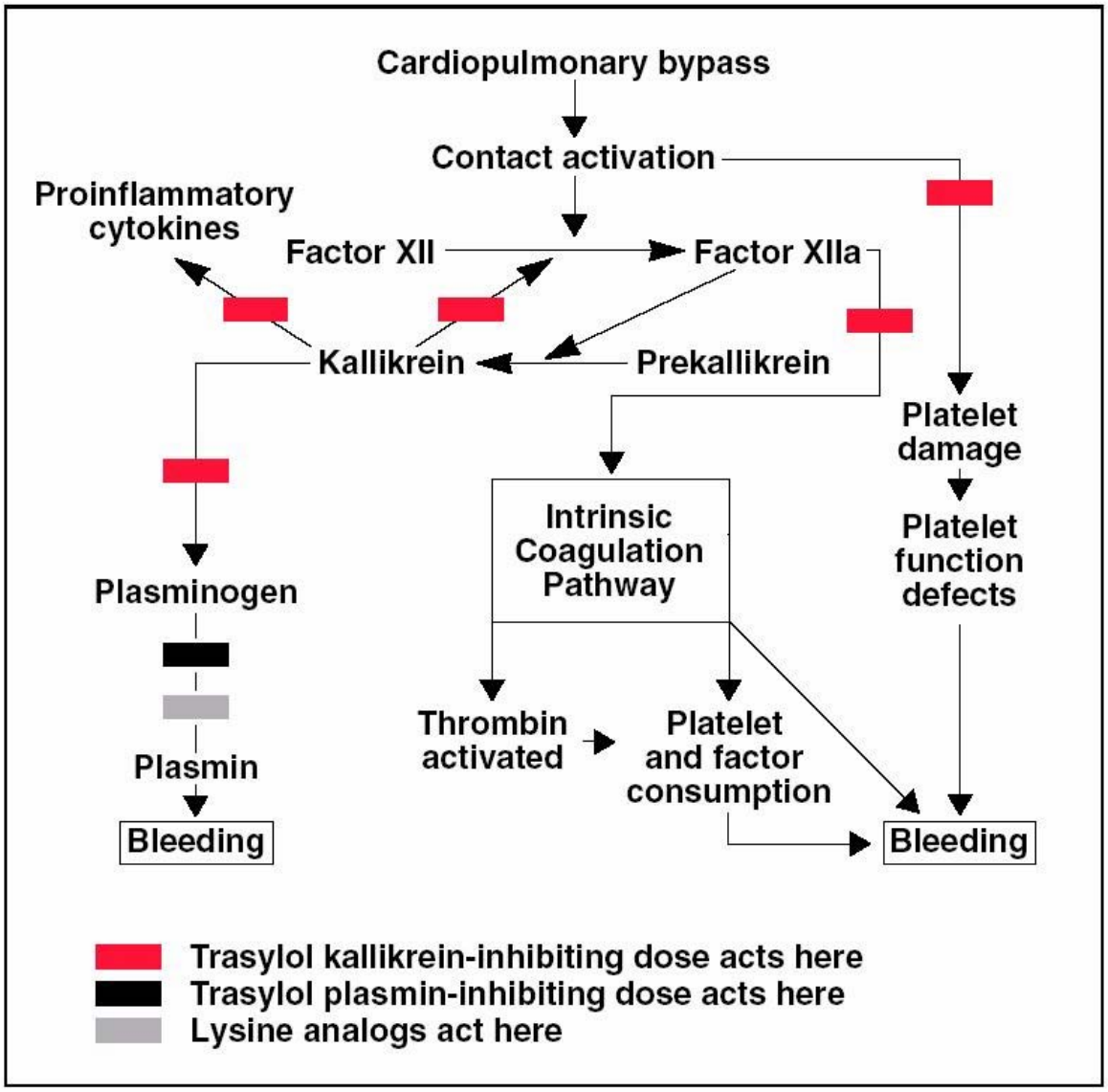
4. Mechanism of Action of Aprotinin

CABG surgery with cardiopulmonary bypass activates and amplifies intersecting plasma protease-based processes. 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.(120)

Robust generation of the procoagulant and inflammatory mediator thrombin occurs during CABG surgery with cardiopulmonary bypass. The surgical team uses heparin during the operative period to limit clot formation, as heparin irreversibly complexes with endogenous anticoagulant antithrombin and accelerates its inhibition of thrombin. Upon closure of the surgical site, the anticoagulant effect of heparin is reversed with administration of protamine. As consumption and dilution of coagulation factors and platelets and inflammatory-mediated activation of fibrinolysis occurs peri-operatively, additional therapeutic interventions are necessary to mitigate inflammation and fibrinolysis which contribute to intra- and post-operative bleeding and organ injury.(121)

The overall mechanism of action of aprotinin is summarized in Figure 4-1.

Figure 4-1: Overall Mechanism of Action of Aprotinin



Adapted from Dietrich W.

4.1 Thrombin platelet interaction and coagulation

During cardiopulmonary bypass, kallikrein amplifies activation of coagulation. This results in intra-operative thrombin generation and the consumption of clotting factors(122), resulting in the intra-operative pathologic activation of platelets via the platelet thrombin protease activated receptor-1.(123, 124) Kallikrein-mediated

plasmin-generation results in the exhaustion of platelet glycoprotein receptors and loss of appropriate platelet function.(125) Aprotinin reduces intra-operative kallikrein and thrombin generation thus sparing the availability of clotting factors for post-operative hemostasis.(126-130). Plasma levels of aprotinin achieved clinically with the full-dose aprotinin regimen inhibit plasma kallikrein, factor XI, and to a lesser extent factor XII.(122) Aprotinin limits plasmin-mediated defects in glycoprotein Ib and glycoprotein IIb/IIIa receptors.(131, 132) and prevents pathologic thrombin-mediated platelet activation by interfering with the activity of the platelet protease activated receptor-1.(124, 133) As a result, aprotinin preserves platelet function during cardiopulmonary bypass without preventing formation of hemostatic plugs at wound and suture sites where collagen is likely to be exposed.(133, 134)

4.2 Fibrinolysis

Cardiopulmonary bypass surgery causes hyperfibrinolysis as a result of kallikrein-induced generation of free plasmin through urokinase-plasminogen activator.(127, 135-137) Unlike localized tissue-plasminogen activator generated plasmin, free plasmin results in a systemic fibrinolysis rapidly inactivating fibrinogen and fibrin, 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.(122, 138, 139) In contrast, lysine analogues bind to plasminogen, limiting the ability of clot-bound plasmin to bind to fibrin.(138) These antifibrinolytic mechanisms help to explain why aprotinin can be beneficial in inhibiting free plasmin mediated peri-operative bleeding without affecting physiologic clot fibrinolysis.(140)

4.3 Inflammation

Clinical manifestations of systemic inflammation from cardiac surgery with cardiopulmonary bypass are respiratory compromise, renal failure, neurological dysfunction, and myocardial dysfunction.(120, 121, 141) Kallikrein and bradykinin

are generated augmenting vascular permeability, generating edema and activating neutrophils.(142, 143) 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.(144-146) Complement generated during surgery affects vascular tone leading to reduced tissue perfusion and indirect negative effects on tissues through chemoattractant and activation effects on neutrophils(147) further propagating the inflammatory response and tissue injury.(140, 148, 149)

Aprotinin inhibits kallikrein, in a dose-dependent manner, in vitro, in animal models(120, 122, 135) and in the clinical cardiopulmonary bypass setting.(150, 151) Although lower concentrations of aprotinin 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.(120) Aprotinin reduces generation of inflammatory cytokines and complement formation in the course of CABG surgery with cardiopulmonary bypass.(120, 121, 130, 141, 152, 153) Patients and animal models undergoing cardiopulmonary bypass have shown a reduction in edema with aprotinin administration.(154, 155) 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 clinically.(156-161) Modulation of systemic inflammatory response by aprotinin has been postulated(120) to be associated with improved myocardial, pulmonary and cerebrovascular outcomes.(162)

5. Dosing

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

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 dose 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 regimen 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, an initial (test) dose of 10,000 KIU (1 mL or 1.4 mg) is infused at least 10 minutes before the loading dose.

6. 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 describing the effects of aprotinin in reducing blood loss and transfusions among patients receiving concomitant medications such as clopidogrel have been published.

6.1 Overview of literature: meta-analyses

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-exploration due to bleeding. 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, considerable overlap exists in the trials included in each meta-analysis. Sedrakyan et al limited their meta-analysis to trials examining patients undergoing CABG surgery; this was the only meta-analysis that included only CABG patients.(163) 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.(163) 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 1,966 aprotinin-treated patients required a transfusion compared to 936 of 1,464 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 6 meta-analyses.(11, 164-168) In addition, 3 meta-analyses have shown that aprotinin reduces the mean number of units transfused,(165-167) 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.(167) However, it should be noted that these meta-analyses included numerous cardiac surgery trials and were not limited to CABG only.

6.2 Repeat CABG (Bayer US trials): blood loss and transfusion requirements

The current US prescribing information for the effectiveness of Trasylol in patients undergoing repeat CABG surgery was based on data from 4 US trials. Table 6-1 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 and data from the pump-prime dosing regimen are not further discussed.

Table 6-1: 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)(169)	Repeat CABG	154	52	49	53
D89-006 (448;Lemmer)(170)	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)(171)	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 6-2 summarizes the key efficacy outcomes for the pooled analysis for patients undergoing repeat CABG surgery.

Table 6-2: 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 red blood cells	76.3%	48.7%[b]	46.9%[b]
% of patients who required 5 or more units of red blood cells	27.6%	12.4%[b]	8.4%[b]
% patients who required donor platelets	44.9%	14.2%[b]	8.4%[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	1,132 (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]	1,659 (1226)	1,103 (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.

6.3 Primary CABG (Bayer US trials): blood loss and transfusion requirements

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 D89-006 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 6-3 summarizes these US trials.

Table 6-3: 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)(170)	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)(172)	Primary CABG	644[b]	157	168	160
D92-048 (472; Alderman)(173)	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 6-4 summarizes the key efficacy outcomes for the pooled analyses in patients undergoing primary CABG surgery.

Table 6-4: 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 red blood cells	53.5%	37.1%[b]	36.8%[b]
% patients who required 5 or more units of red blood cells	10.1%	5.7%[b]	2.8%[b]
% patients who required donor platelets	17.6%	5.7%[b]	4.1%[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]	1,232 (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.

6.4 Re-exploration for 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.(174-177) More importantly, re-exploration appears to be

associated with increased morbidity. Three of these large (n = 6,015, n = 8,586, and n = 2,221, respectively) database analyses revealed a consistent and dramatic increase (3 to 4-fold) in mortality (from patients not requiring re-exploration from bleeding compared to those requiring re-exploration for bleeding), from 1.2% to 4.8%,(176) from 3.3% to 9.5%,(174) and from 5.5% to 22%,(177) 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 1,500 to 2,000 mL within 24 hours, there is an exponential increase in percentage of patients who develop adverse outcomes and an increase in mortality (12.1% in patients with >2,000 mL versus 4.3% in patients with <2,000 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.

In the US clinical trials that enrolled patients undergoing repeat CABG surgery, re-exploration (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-explorations 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-explorations (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-explorations 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.(178) This meta-analysis examined 1,808 placebo-treated and 1,818 full-dose aprotinin-treated patients undergoing CABG surgery. The risk of re-exploration 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-explorations. For surgical bleeding, the re-exploration rates were 3.6% and 2.0% for placebo-treated and aprotinin-treated patients, respectively. For diffuse bleeding, the re-exploration rates were 1.4% and 0.2% for placebo-treated and aprotinin-treated patients, respectively.

The results from the Bayer database are supported by 6 meta-analyses that have evaluated the impact of aprotinin on re-exploration for bleeding.(11, 164-168) The first meta-analysis examined 45 randomized trials.(166) The risk of re-exploration 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-explorations (p <0.001). In this same meta-analysis, the re-exploration 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.

The Cochrane Collaboration reviewed 29 trials (n = 2,900) for the risk of re-exploration.(165) The use of aprotinin significantly reduced re-explorations 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-explorations 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-explorations was not analyzed because this drug did not significantly reduce the need for transfusion.

In the Brown meta-analysis, high-dose aprotinin reduced the rate of re-exploration by 51% (relative risk = 0.49; 95% confidence interval 0.33; 0.73).(11) Low-dose aprotinin, aminocaproic acid and tranexamic acid did not reduce the rate of re-exploration compared to placebo.

Similar reductions in the need for subsequent re-explorations in patients receiving aprotinin were reported in the 3 other meta-analyses.(164, 167, 168)

6.5 Efficacy and use of anti-platelet agents

6.5.1 Aspirin

Table 6-5 summarizes the efficacy of aprotinin among aspirin-treated patients undergoing repeat CABG surgery in the Bayer US clinical trial database. 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 6-5: 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 6-6 summarizes the efficacy of aprotinin among aspirin-treated patients undergoing primary CABG surgery in the Bayer US clinical trial database. 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 6-6: 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.(179) Twenty-eight patients were randomized to receive full-dose aprotinin and 23 patients to receive placebo. The total blood loss was only 1,209.7 mL in the aprotinin group compared to 2,532.2 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.(163) Levi et al demonstrated a significant decrease in re-operations among cardiac surgical patients receiving aspirin.(167)

6.5.2 Clopidogrel

Three studies published in 2005 demonstrate that full-dose aprotinin use during CABG surgery reduces bleeding and the need for transfusion among patients receiving clopidogrel.(180-182)

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.(180) 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.(182) 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 1,200 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 review of 33 patients who underwent CABG surgery within 5 days of clopidogrel exposure.(181) 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).

A recent observational study was reported by Ouattara et al.(183) The study was designed to compare the effect of preoperative use of aspirin with or without clopidogrel on postoperative bleeding and transfusion requirement in patients undergoing first-time CABG surgery and in whom low dose aprotinin was systematically used. All patients (n = 217 patients; pretreated during a period of 5 days prior surgery by either aspirin alone [n = 157] or combined with clopidogrel [n = 60]) undergoing isolated first-time CABG between November 2003 and May 2004 were enrolled. Aprotinin was systematically used in all these patients considered as high risk for bleeding. No significant difference between both groups concerning the preoperative characteristics except for unstable angina (33 vs 19%, P = 0.02) and left main coronary artery stenosis (27 vs 13%, P = 0.02), which were more frequent in patients receiving clopidogrel. The median chest tube output was similar in both groups 24 hours postoperatively at 350 mL (95% CI 150–850) vs 375 (95% CI 175–875), and the difference between groups (7%, 95% CI 29 to 22) did not encompass the predetermined margins of equivalence (25%). No significant difference was found on blood transfusion use (38 vs 38%, P = 0.99). The conclusion of the study is that, in patients undergoing first-time CABG surgery and intra-operatively treated by a half-dose aprotinin regimen, aspirin combined with clopidogrel may be continued up to the day of surgery without increasing postoperative bleeding and transfusion rates.

6.6 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. Furthermore, full-dose aprotinin use during CABG surgery has been shown to reduce bleeding and the need for transfusion among patients receiving clopidogrel.

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.

7. Safety

7.1 Bayer global CABG randomized controlled trial database: demographic and baseline characteristics

Based on early studies that demonstrated significant decreases in blood loss and transfusion requirements among patients undergoing CABG surgery with the use of aprotinin(1, 149), 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. Overall, 2,249 patients received full-dose aprotinin and 2,164 patients received placebo.

The global CABG safety database as presented in this section includes 45 studies with 2,249 patients receiving full-dose aprotinin and 2,164 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 7-1 summarizes demographic characteristics for the CABG trials. In general, the demographic characteristics were similar between the treatment groups.

Table 7-1: 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 = 2,249	Placebo N = 2,164
Age (years)		
Mean ± standard deviation	61.1 ± 9.0	61.3 ± 9.0
<65 years; n (%)	1,381 (61.4)	1,290 (59.6)
≥65 years; n (%)	868 (38.6)	871 (40.2)
Missing, n (%)	0 (0.0)	3 (0.1)
Sex, n (%)		
Male	1,993 (88.6)	1,911 (88.3)
Female	255 (11.3)	253 (11.7)
Missing	1 (<0.1)	0 (0.0)
Race, n (%)		
White	1,579 (70.2)	1,500 (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	1,819 (80.9)	1,785 (82.5)
Repeat CABG	276 (12.3)	255 (11.8)
Not Categorized	154 (6.8)	124 (5.7)
CABG only	1,151 (51.2)	1,067 (49.3)
CABG plus other[a]	1,098 (48.8)	1,097 (50.7)

a Includes one patient in each group who had pediatric surgery procedures.

Key medical conditions at baseline were also similar between groups (see Table 7-2).

Table 7-2: Key Baseline Medical Conditions
(Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Baseline Medical Conditions	Full-Dose Aprotinin N = 2,249	Placebo N = 2,164
Diabetes mellitus, n (%)	394 (17.5)	422 (19.5)
Congestive heart failure, n (%)	116 (5.2)	102 (4.7)
Prior myocardial infarction, n (%)	879 (39.1)	820 (37.9)
Cerebrovascular accident, n (%)	72 (3.2)	66 (3.0)
Hypertension, n (%)	908 (40.4)	882 (40.8)
Estimated GFR <60 mL/min, n/N (%)	435/2,046 (21.3)	404/1,953 (20.7)

7.2 Mortality

7.2.1 Peri-operative mortality

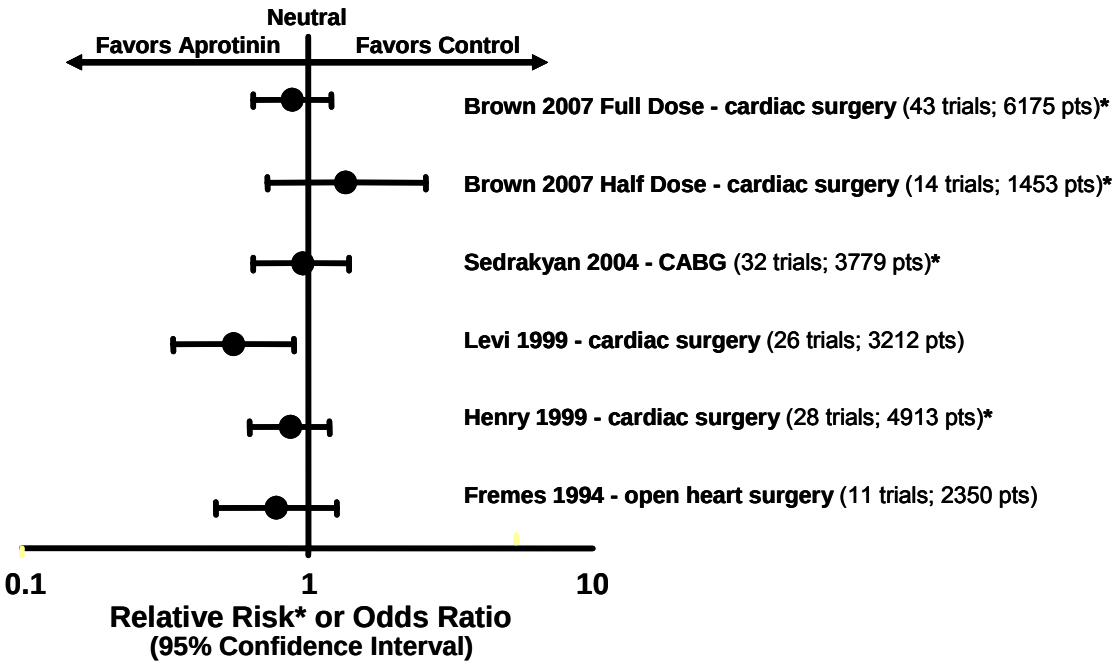
A randomized controlled trial with peri-operative mortality as the primary endpoint has not been conducted by Bayer or reported in the literature.

Overall, in the Bayer Global Randomized Controlled trial database, 2.9% (65/2249) of full-dose aprotinin patients and 2.5% (55/2,164) 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.(13, 184, 185) 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%.(184)

The perioperative mortality rates reported in meta-analyses(11, 163-165, 167) show no increased risk in the aprotinin group (see Figure 7-1).

Figure 7-1: Mortality Risk: Aprotinin vs Control per Meta-Analysis of RCTs



7.2.2 Long-term mortality

In February 2007, Mangano et al reported an observational study. The authors concluded that "Aprotinin treatment (223 deaths among 1,072 patients [20.8% 5-year mortality]) was associated with significantly increased mortality compared with control (128 deaths among 1,009 patients [12.7%]; covariate adjusted hazard ratio for death, 1.48; 95% confidence interval, 1.19-1.85)…" This database was a subset of the same set of 4,374 CABG patients described in the report published in January 2006 in the New England Journal of Medicine.(2) The limitations of this study are discussed in Section 10. The inappropriate statistical methodology raise serious doubts as to the validity of the author's conclusions. Bayer believes that the reported results of this study are not reliable and should not serve as a basis for affecting the use of aprotinin in clinical practice.

A comprehensive randomized controlled trial with long-term outcome of mortality has not been conducted. However, after completion of Study D92-048 (IMAGE Study), a trial evaluating the effect of aprotinin on graft patency, a survey was

performed to assess mortality during a follow-up period among patients surviving the study period. Post-trial outcomes were captured via physician contact by telephone, from national death registry (for one center), or from the patient's medical records. Cause of death was also obtained and categorized as either cardiac or non-cardiac related. These classifications occurred through a review of all deaths, without patient identifiers or treatment information, by two Bayer physicians. Deaths that could not be ascribed to a non-cardiovascular etiology were assumed to be cardiac related. The overall response rate to the survey was approximately 75%. The median follow-up time periods were 3.99 years for aprotinin-treated patients and 4.01 years for placebo-treated patients (p = 0.518).

The mortality data is displayed in Table 7-3. Overall, across all sites, the cardiac mortality was 7.5% in the aprotinin-treated group and 7.1% for the placebo group. These mortality rates are lower than those noted among patients with stable angina treated with bypass surgery during long-term follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery.(186)

Table 7-3: Study D92-048: Mortality Rates for the Study Period and in 4-Year Follow-Up by Site

	Full-Dose Aprotinin		Placebo			Relative Risk
	n/N	%	n/N	%	P Value	(95% CI)
Cardiac Mortality						
US sites only	10/173	5.8	12/173	6.9	0.875	0.8 (0.5, 2.5)
Non-US sites only	14/146	9.6	11/153	7.2	0.454	1.3 (0.6, 2.8)
All sites	24/319	7.5	23/326	7.1	0.810	1.1 (0.6, 1.9)
All Cause Mortality						
US sites only	16/179	8.9	13/174	7.5	0.616	1.2 (0.6, 2.4)
Non-US sites only	18/150	12.0	13/155	8.4	0.297	1.4 (0.7, 2.8)
All sites	34/329	10.3	26/329	7.9	0.273	1.3 (0.8, 2.1)

Overall, 13 deaths were assessed as related to non-cardiac causes (10 aprotinin-treated patients and 3 placebo-treated patients). Most non-cardiac deaths were related to malignancies. The non-cardiac causes of death for aprotinin-treated patients were throat cancer, lung cancer, metastatic colon cancer and small bowel

obstruction, non-small cell lung cancer, squamous cell lung cancer, multiple myeloma, gastric carcinoma, sepsis, burns and suicide. The causes for placebo-treated patients were cancer and flu complications, chronic renal failure (requiring hemodialysis), and lymphoma.

7.3 Thromboembolic events

At the Cardiovascular and Renal Drugs Advisory Committee meeting on 21 Sep 2006, the committee agreed overall that there was no association between aprotinin use and an increased risk of myocardial infarction or stroke.(4) Table 7-4 summarizes the incidence of thromboembolic events. Arterial thromboembolic events included stroke and myocardial infarction. Venous thromboembolic events included deep vein thrombosis and pulmonary embolism.

Table 7-4: Incidence of Arterial or Venous Thromboembolic Events as Reported by Investigator

	Full-Dose Aprotinin N=2,249		Placebo N=2,164		
Event	**n**	**%**	**n**	**%**	**Odds Ratio (95% CI)**
Any Arterial or Venous Thromboembolic Event	178	7.9	165	7.6	1.05 (0.84, 1.31)
Any Arterial Event	174	7.7	161	7.4	1.05 (0.84, 1.31)
Any Venous Event	5	0.2	4	0.2	1.00 (0.58, 1.74)

7.4 Renal safety

7.4.1 Overview of meta-analysis

Of note, when reviewing the literature, various definitions of renal dysfunction and renal failure are used. In this section, the terms are used as cited in the publication.

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.(165) Data on renal failure or dysfunction were available on 3,776 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 2,210 (3.2%) aprotinin-treated patients and 37 of 1,566 (2.4%) patients in the control groups. Authors concluded that 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.(163) Data on renal failure were available on 3,003 patients from 17 studies. Approximately 65% of the aprotinin-treated patients received the full-dose regimen. Renal failure developed in 26 of 1,755 (1.5%) patients treated with aprotinin and 16 of 1,248 (1.3%) patients receiving placebo.(163) 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 2,283 patients undergoing coronary artery bypass surgery.(187) 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).(187) 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.(168)

Data on renal dysfunction were available from 8 placebo-controlled studies. Higher and lower doses of aprotinin were given to 1,344 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).(168) 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/renal failure.

Brown et al reported a meta-analysis in patients undergoing cardiac surgery (reported as an update to the Munoz meta-analysis). Aprotinin was not demonstrated to increase significantly the risk of renal failure requiring dialysis. However, high-dose aprotinin resulted in an increased risk of renal dysfunction (relative risk 1.47, 95% confidence interval 1.12, 1.94). Renal dysfunction was defined as a 0.5 mg/dL increase in creatinine from baseline. The low-dose aprotinin was not associated with an increased risk of renal dysfunction (relative risk 1.01, 95% confidence interval 0.69, 1.49).

7.4.2 Mechanisms of potential renal dysfunction developing during the clinical use of aprotinin

Bayer consulted with Dr. Andrew Whelton (nephrologist, Johns Hopkins University School of Medicine) to evaluate the potential mechanism of renal dysfunction associated with aprotinin. This section was prepared based upon his review.

The sum of renal functional effects, linked to the administration of aprotinin, represents a combination of systemic and intra-renal hemodynamic modifications together with intracellular metabolic disturbances, as particularly noted within renal proximal tubular cells. In the vast majority of patients who receive therapeutic

doses of aprotinin no adverse clinical renal effects are noted. However, in a minority of patients who receive the drug, a transient and reversible form of renal impairment may be encountered. The mechanism of the latter toxicity may be summarized by combining the findings derived from auto-radiographic, immunochemical and electron microscopic studies of the kidney together with clinical renal functional studies and the results of prospective randomized trials.(188-200)

Two separate categories of aprotinin effects upon renal function need to be examined and these are; A) the acute intrarenal hemodynamic and clinical renal function consequences and; B) the renal tubular functional effects of the compound.

7.4.2.1 Summary of intra-renal hemodynamic effects of aprotinin administration in man

The intra-renal hemodynamic effects of the administration of aprotinin represent a cascade of events that are largely offsetting and result in little detectable disturbance of renal function. Aprotinin inhibits the renal release of kallikrein, the primary enzyme in the kinin-generating pathway.(199, 201, 202) The latter kinins trigger the release of vasodilators such as the prostaglandin prostacyclin and nitric oxide from renal tubular and interstitial cells and from the vascular endothelium.(201-203) In counter balance, aprotinin delays the degradation of atrial natiuretic peptide and increased concentrations of the latter peptide appear to promote diuresis and renal vasodilatation.(199, 204) Several other intra-renal hemodynamic minor consequences of aprotinin exposure have been assessed in various animal models.(159, 160, 203-208) However, the foregoing renal hemodynamic and functional effects appear to be the dominant features and findings in man.

7.4.2.2 Summary of the renal tubular biochemical and functional effects of aprotinin administration in man

Following systemic administration and delivery of aprotinin into the renal circulation, aprotinin molecules, which are relatively small (6,512 Daltons) and possess a cationic charge, are readily filtered through anionically charged

glomerular basement membranes. Subsequent to glomerular filtration, as aprotinin molecules transit through the lumen of the first part of the renal proximal tubule (S-1 segment), virtually all the drug is electrostatically bound to receptors on the vast surface area of the brush border cells which line the lumen of the proximal tubule and only a small fraction of filtered drug transits through to the distal portion of the renal tubule where it is subsequently incorporated into the basal portion of collecting duct cells.(192, 196, 198, 200) The electrostatically bound molecules of aprotinin are rapidly engulfed or pinocytozed by the cell surface membranes (within 30 minutes) and the resulting endosomes enter the cell cytoplasm and are then phagositozed by the abundant number of lysosomes contained within proximal tubular cells.(200) The latter process becomes apparent within hours.(200) Once contained within the lysosomes the tissue half-life of aprotinin is markedly extended (several days) compared to the 5-7 hour systemic half-life of aprotinin.(209) This prolonged retention of aprotinin within lysosomes results in renal biochemical, morphologic and tubulo-glomerular dysfunction that varies from no apparent damage through to spotty tubular necrotic cells and transient but reversible reductions of glomerular filtration. The biochemical changes that occur within renal proximal tubular cells are clinically reflected by the excretion of increased concentrations of tubular function markers such as the inhibition of tubular reabsorption of the glomerular filtered protein α-1 microglobulin and tubular cell enzymes such as β-glucosaminidase.(190, 191)

Since the basement membrane of the proximal tubule remains intact new tubular epithelial cells replace the drug damaged or dysfunctional cells. Hence, there is no evidence for an irreversible form of damage to the kidney but rather a minor reversible form of renal impairment. In prospective randomized clinical trials, wherein evidence of renal dysfunction was encountered, the mean time for return of renal function to baseline values as compared with placebo, was an extension of approximately 4-5 days.(188)

7.4.2.3 Pre-existing renal functional impairment

In the clinical setting of pre-existing renal impairment, an increase in aprotinin-related renal adverse effects has been observed in the RCT database.(188) This clinical finding may be related to a more prolonged systemic delivery of aprotinin to proximal tubular lysosomes, as a consequence of the extended intravascular half-life of the drug.(188, 209) The resultant potential lysosomal aprotinin overload may be the contributing mechanism to the observed increase in renal adverse events. The study of Rustom and colleagues, performed in adult individuals with pre-existing mild renal impairment (a mean glomerular filtration rate (GFR) = 40 ± 5.4 mL/min), solidifies this hypothesis since these investigators identified that the cumulative kidney uptake of radiolabelled aprotinin at 24 hours, corrected per mL of GFR, was increased to 0.67 ± 0.14% of the dose/mL of GFR as compared with 0.32 ± 0.03% of the dose/mL of GFR ($p < 0.005$) in patients with normal renal function.(195, 196) In essence, this is a doubling of renal proximal tubular uptake of aprotinin at 24 hours and further investigations will be needed to define the elution rate of the drug from the kidney and its relationship to the rate of return of an elevation of serum creatinine to baseline values in patients with known pre-existing renal impairment.

7.4.2.4 Mechanisms whereby concurrent drug administration may enhance aprotinin induced renal dysfunction

Aminoglycoside antibiotics also exert their potential for nephrotoxicity by accumulating within and disrupting renal proximal tubular lysosomal function.(210) Hence, it is not surprising that the extant prospective randomized clinical data demonstrate an enhancement of potential nephrotoxic effects during the concurrent administration of aminoglycosides and aprotinin.(188, 193) Other drugs that potentially impact upon tubulo-glomerular function, such as angiotensin converting enzyme inhibitors, may also upon occasion enhance the nephrotoxic potential of aprotinin.

7.4.3 Bayer global randomized controlled trial database

7.4.3.1 Serum creatinine and renal dysfunction

Mean serum creatinine values over time from the global clinical trial database trials are summarized in Table 7-5.

Table 7-5: 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	2,100	1,512	1,508	931	931	2,051
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	2,013	1,417	1,450	879	866	1,960
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 7-6 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).

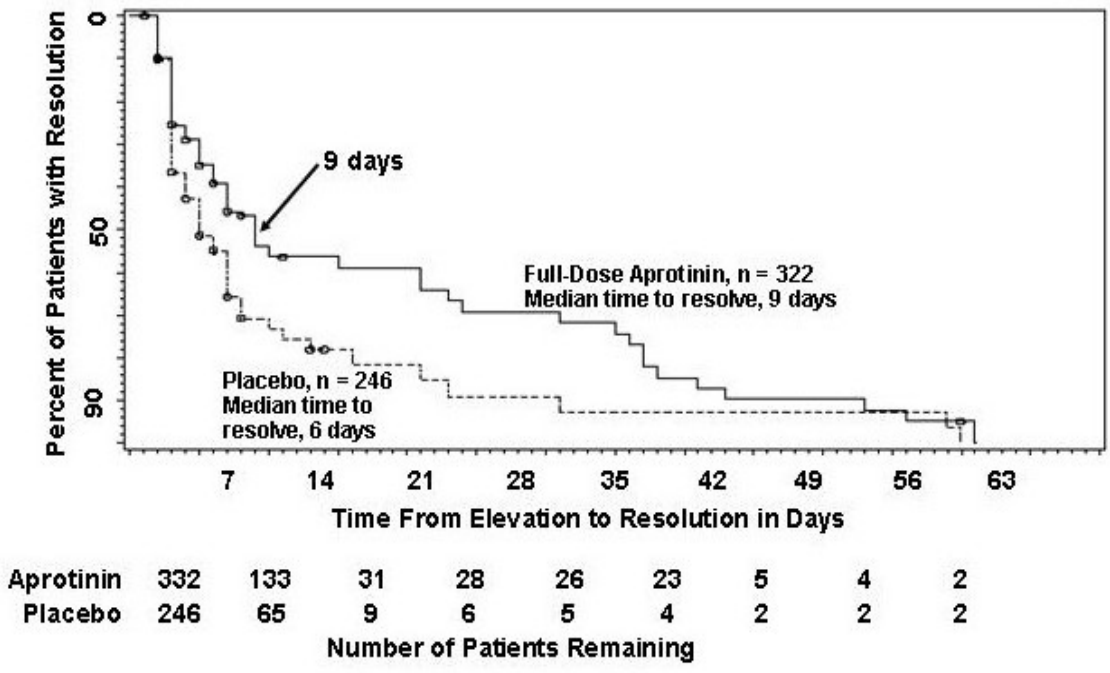
Table 7-6: Incidences of Serum Creatinine Elevations in CABG Patients (Population: Bayer Global Randomized Controlled Trials: CABG Patients Valid for Safety)

Creatinine Change	Full-Dose Aprotinin n/N	%	Placebo n/N	%	Odds Ratio (95% CI)
> upper limit of normal[a]	332/1,825	18.2	246/1,724	14.3	1.35 (1.12, 1.62)
>0.5 mg/dL over baseline	185/2,047	9.0	129/1,957	6.6	1.41 (1.12, 1.79)
>0.5 mg/dL over baseline and a value of >2.0 mg/dL	88/2,047	4.3	62/1,957	3.2	1.33 (0.97, 1.81)
>2.0 mg/dL over baseline	23/2,047	1.1	16/1,957	0.8	1.16 (0.73, 1.85)

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

The majority of these baseline creatinine elevations were transient (see Figure 7-2). The median time to resolution was 9 days in the aprotinin group and 6 days in the placebo group.

Figure 7-2: Kaplan-Meier Estimates for Median Time[a] to Resolution in Days



a Estimated time to return to within 20% of baseline creatinine for patients with treatment-emergent increases above upper limit of normal.
Source: Bayer Global CABG Randomized Clinical Trial Database.

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. Among patients treated with full-dose aprotinin, the peri-operative use of aminoglycosides and impaired creatinine clearances at baseline were associated with an increased risk of post-operative serum creatinine elevations (see Table 7-7).

Table 7-7: 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)

	Full-Dose Aprotinin		Placebo		Odds Ratio
Subgroup	**n/N**	**%**	**n/N**	**%**	**(95% CI)**
Overall	185/2,047	9.0	129/1,957	6.6	1.41 (1.12, 1.79)
Baseline creatinine					
<1.4 mg/dL	135/1,750	7.7	95/1,650	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	83/1,026	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 peri-operative aminoglycoside use					
No	142/1,863	7.6	107/1,759	6.1	1.25 (0.96, 1.61)
Yes	43/184	23.4	22/198	11.1	2.63 (1.49, 4.65)

CI = confidence interval.

7.4.3.2 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 7-8. 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 7-8: 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 = 2,249		Placebo N = 2,164	
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

7.4.3.3 Renal dialysis

Renal dialysis was performed on or recommended for 0.3% (6/2,249) of patients receiving full-dose aprotinin and 0.3% (7/2,164) 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).

7.4.4 Dose-response relationship

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

Table 7-9: Incidences of Creatinine Elevations or Dialysis 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
Dialysis	1/361	0.3	3/366	0.8	3/365	0.8

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

In contrast to the Bayer clinical trial database, Dietrich et al did not find that higher doses of aprotinin were associated with adverse renal outcomes. Dietrich et al conducted an analysis of 8,281 adult patients undergoing cardiac surgery on CPB who were treated with aprotinin, including 4,762 patients undergoing CABG surgery.(211) The results of a multivariate regression analysis demonstrated that higher aprotinin doses were not associated with adverse renal outcomes. Furthermore, as the aprotinin dose increased, blood loss decreased.

7.4.5 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.(189, 190, 199, 212) Meta-analyses by Sedrakyan et al, the Cochrane Collaboration and Brown et al also report no increased risk of renal failure associated with aprotinin therapy.(11, 163, 165) However, Brown et al did report an increased risk of renal dysfunction (serum creatinine change of >0.5 mg/dL over baseline) associated with high-dose aprotinin but this finding was not observed with low-dose aprotinin.(11)

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 0.3% 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.

On 15 Dec 2006, the Trasylol US product information was revised to reflect the following:

- "Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period."
- "This risk may be especially increased for patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function."
- The incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was statistically higher in the high-dose aprotinin group (9.0%) compared with placebo (6.6%).
- "In the majority of instances, post-operative renal dysfunction was not severe and was reversible."

- Renal dysfunction may progress to renal failure and the incidence of serum creatinine elevations >2 mg/dL above baseline was slightly higher in the high-dose aprotinin group compared to placebo (1.1% vs 0.8%).

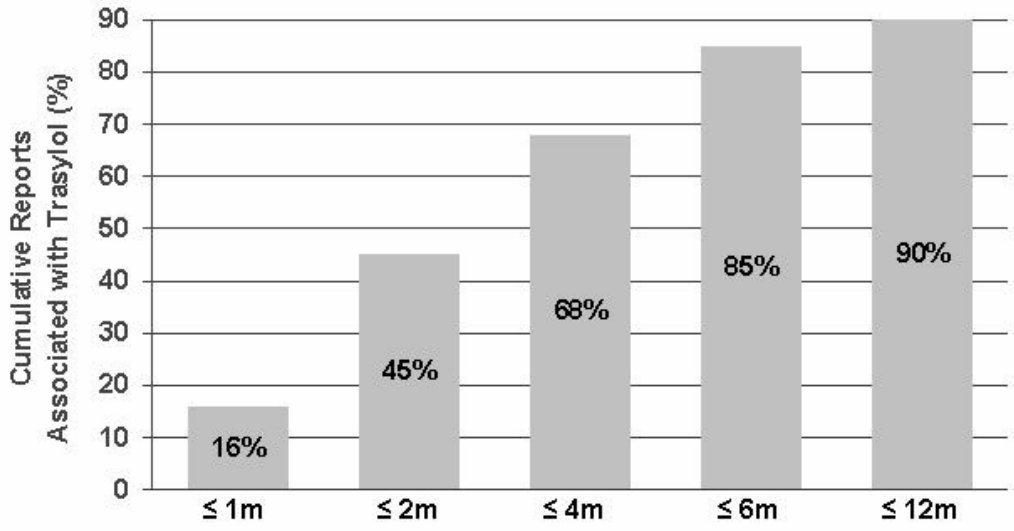
- Careful consideration of the balance of benefits versus potential risks is advised before administering Trasylol to patients with impaired renal function (creatinine clearance <60 mL/min) or those with other risk factors for renal dysfunction (such as peri-operative administration of aminoglycoside or products that alter renal function).

7.5 Hypersensitivity

The risk of hypersensitivity reactions to aprotinin is primarily related to exposure history. 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).

As reported at the 21 Sep 2006, FDA Cardiovascular and Renal Drugs Advisory Committee Meeting, 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 tissue sealants 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 received Trasylol within the previous 12 months. (See Figure 7-3)

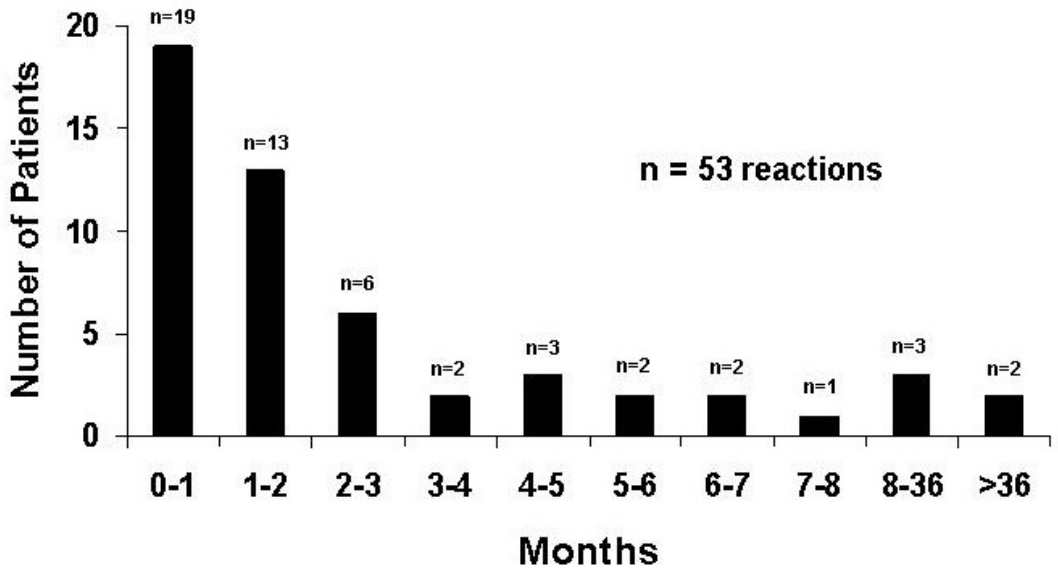
Figure 7-3: Temporal Relationship of Re-exposure to Spontaneous Reports of Hypersensitivity Reactions*



*** Patients with known time of previous Trasylol exposure reported 1/1/1985 to 3/31/06, (n=110). Data on file, Bayer Pharmaceuticals Corp.**

These data are consistent with a review by Beierlein(213) which reported that 90.6% of all cases of anaphylaxis from re-exposure occurred when the re-exposure took place within the first 8 months of the previous exposure (see Figure 7-4).

Figure 7-4: Beierlein: Time Interval to Aprotinin Re-exposure Hypersensitivity Reaction



The spontaneous adverse events also reported that fatal reactions have occurred with the initial (test) dose, and that both fatal and non-fatal reactions have occurred in situations where the initial (test) dose was tolerated.

Based on these findings, Bayer revised the Trasylol US product information in December 2006. Information concerning the potential for hypersensitivity reactions was expanded:

- Trasylol administration may cause fatal anaphylactic or anaphylactoid reactions.
- "The risk for anaphylactic or anaphylactoid reactions is increased among patients with prior aprotinin exposure and a history of any prior aprotinin exposure must be sought prior to Trasylol administration."
- "Although the majority of cases of anaphylaxis occur upon re-exposure with the first 12 months, there are also case reports of anaphylaxis occurring upon re-exposure after more than 12 months."

- Trasylol is contraindicated in patients with a known or suspected aprotinin exposure during the last 12 months. Aprotinin may also be a component of some fibrin sealant products.

- The initial (test) dose does not fully predict a patient's risk for a hypersensitivity reaction, including a fatal reaction. Fatal reactions have occurred with an initial (test) dose as well as with any of the components of the dose regimen, and have also occurred in situations where the initial (test) dose was tolerated.

- Trasylol should be administered only in operative settings where cardiopulmonary bypass can be rapidly initiated.

An updated review of the company's spontaneous report database revealed that there were 916 spontaneous adverse events of any type received by Bayer Global Pharmacovigilance from 1985 to 30 Jun 2007. Of these reports, 374 were reports of suspected hypersensitivity and were subsequently adjudicated. Five of the 374 cases were associated with the administration of tissue sealants containing aprotinin, and these were excluded from further analysis. Of the remaining 369 reports, 291 non-fatal and 60 fatal reports were assessed as possibly associated with Trasylol administration in a total exposure of 4.77 million. For the majority of the 291 non-fatal reports the outcome was reported as "recovered" or "improved." Further analysis of all possibly associated cases of hypersensitivity revealed that 89.1% of patients had received Trasylol within the previous 12 months.

7.6 Risk minimization plan

Based on the spontaneous report findings, Bayer initiated a risk minimization plan for hypersensitivity in May 2006.

As part of a risk minimization plan, sales representatives and Medical Science Liaisons (MSLs) training included a discussion of hypersensitivity incidence. Sales staff were directed to engage with prescribers to directly reinforce the risk of hypersensitivity, while MSLs were directed to contact key opinion leaders.

- A targeted campaign was launched from Jun to Jul 2006 through field representatives who disseminated safety information, emphasizing hypersensitivity to 2,811 practicing Cardio-Thoracic (CT) surgeons and 3,473 practicing CT anesthesiologists in 1,122 CT surgical institutions that conducted 310,755 surgical procedures that included CABG surgery (estimated to be greater than 95% of total procedures) annually in the US (Data source: audited data from 2005, Solucient, LLC).

- Additionally from June to December 2006, external key opinion leader speakers delivered 127 educational programs to 4,430 attendees; MSLs delivered 129 educational programs to 1,598 attendees. Information on hypersensitivity was emphasized in all of these educational programs.

As part of the ongoing risk minimization plan, the revisions to the US product information (December 2006) were accompanied by the dissemination of a Dear HealthCare Provider (DHCP) Letter, accompanied by the new and current US PI for Trasylol, in order to increase awareness of the potential risks of all adverse events possibly associated with Trasylol, including hypersensitivity, listed in the US Product Information and the Box warning. This letter reminded physicians to assess the benefit-risk ratio for each patient for all adverse events that may possibly occur with administration of Trasylol. Mailing of this letter totaled 152,289, mailed to 42,884 hospital pharmacists, 38,000 nurse anesthetists, 36,648 anesthesiologists, 25,692 orthopedic surgeons, 3,199 Chairs or Directors of Pharmacy and Therapeutics Committees, 2,956 cardiothoracic surgeons, 1,755 perfusionists, 762 pediatric surgeons, and 393 transplant surgeons.

In particular, the following statements were placed in the DHCP Letter of 15 Dec 2006:

> "Trasylol® is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary

bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion."

- "Limit Trasylol use to patients who are at an increased risk for blood loss and blood transfusion in the setting of coronary bypass graft surgery with cardiopulmonary bypass.

- Contraindicate the administration of Trasylol to any patients with a known or suspected prior exposure to Trasylol or aprotinin-containing products within the previous 12 months."

- Provide additional information on the management and prevention of anaphylactic reactions, including the administration of Trasylol only in the operative setting where cardiopulmonary bypass may be rapidly initiated.

As discussed above, recent revisions to the Trasylol US product information included a recommendation regarding management of possible anaphylactic reactions, i.e. Trasylol should be administered only in surgical settings where cardiopulmonary bypass (CPB) can be rapidly initiated. Because the use of CPB is not practical in non-cardiac settings, Bayer decided in January 2007 to end three ongoing clinical studies investigating the safety and efficacy of Trasylol on transfusion requirements and blood loss in adults undergoing: elective spinal fusion surgery, pneumonectomy or esophagectomy for cancer, and radical or total cystectomy in bladder cancer.

- Information on the risk of hypersensitivity into visual aid materials, including wall charts, and external presentations were incorporated. From January to June 2007, external key opinion leader speakers delivered 136 educational programs to 4,141 attendees; MSLs delivered 158 educational programs to 2,405 attendees (to cardiothoracic surgeons and anesthesiologists). Key messages were:

- Use only for CABG patients at increased risk for blood loss and blood transfusions
- Increased risk following re-exposure within 12 months (boxed warning)
- Contraindication in patients who have had exposure in past 12 months
- Obtain complete medical history
- Other products may contain aprotinin
- Correct use of initial (test) dose
- Be prepared to treat a potential reaction

- Key safety messages are displayed on the front page (upon a user entering the site) on the Trasylol.com website (www.Trasylol.com). Reviews what Trasylol is, indication, and how to administer Trasylol with attention toward managing hypersensitivity risks as per the US Label. The website has had 44,571 hits from August 2006 to June 2007.

8. Evaluation of Observational Studies

Observational studies can serve to generate hypotheses and raise questions for further study. However, the design and analysis of observational studies may be complex, and "the results often depend crucially on the type of analysis used to generate them."(214) Ioannidis(215) has reviewed highly cited nonrandomized studies, noting that many were subsequently contradicted by randomized trials examining the same questions. Prominent examples are the effects of hormone replacement therapy as reported in the Nurses Health Study and the effect of vitamin E as reported in the Health Professionals Follow-Up study and the Nurses Health Study.(215) Thus, it is important to evaluate nonrandomized studies with a thorough understanding of methods employed.

This section outlines a structured approach for reviewing observational studies and evaluating the reliability of their conclusions. This structured approach will provide a common framework for review of the observational studies (Mangano 2006 and Karkouti 2006) discussed at FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting of 21 Sep 2006 (Section 9), and for review of the 2007 publication by Mangano et al (Section 10) and the administrative database analyses reported by i3 Drug Safety (Section 11).

In general, observational studies can be evaluated with respect to whether the selected data source is suitable to the question under investigation and whether the study design and analysis are appropriate. Selection of a suitable data source is a necessary requirement because even the most optimal design and analysis is of no avail if the available data are inadequate.

This section begins by reviewing the design features of observational studies of treatment effect as compared with randomized trials (Subsection 8.1) and the importance of demonstrating comparability between treatment groups in non-randomized studies as well as in randomized studies (Subsection 8.2). Suitability of the selected data source is discussed in Subsection 8.3. Subsection 8.4 concludes this section with a structured approach to the review and evaluation of observational studies of treatment effect that will be applied to the studies reviewed in Sections 9, 10, and 11 of this briefing document.

A central theme in Subsections 8.2 and 8.3 is the recognition that in a nonrandomized study of treatment effect, where treatment is decided by the treating clinician, there may be extreme imbalances in baseline risk factors between treated and control patients (if, for example, the test treatment is generally reserved for patients at higher risk or for patients undergoing more difficult or complex surgeries). The resulting imbalance in risk factors is termed *channeling bias* or "confounding by indication." Statisticians refer to these imbalances as the result of a "non-ignorable assignment mechanism" of treatment. There are statistical methods for dealing appropriately with these imbalances. However, these statistical

methods require that the study database contain the important patient risk factors. If important risk factors are not available in the database or if they are inaccurately recorded, it is almost always impossible to account for them in the analysis, and the results in this case are predictably biased against the drug or treatment that was given to patients perceived to be at higher risk.

8.1 Characteristics of randomized clinical trials (experiments) compared with observational studies

The accepted scientific standard for determining effects of drug treatment is "adequate and well-controlled" studies. Typically, "adequate and well-controlled" studies, according to 21 CFR 314.126, are prospective, double-blind, randomized clinical trials.(216)

Table 8-1 summarizes characteristics typical of well-designed randomized clinical trials (experiments) as compared to observational studies. Randomized treatment assignment and double-blind design are, of course, not features of observational studies. However, other design features, such as standardized methods of data collection, well-defined outcomes, standardization of clinical practices associated with the studied outcomes, selection of patients who have the condition under study and appropriate attention to patients excluded from analysis may or may not be incorporated in the design of observational studies. It is useful to consider these features in the evaluation of observational studies.

Table 8-1: Characteristics of Randomized Clinical Trials Compared with Observational Studies

	Randomized Clinical Trials		Observational Studies	
Design Feature	**Characteristic**	**Expectation**	**Characteristic**	**Expectation**
Treatment Assignment	Randomized treatment; May be stratified	Expected balance between treatments on baseline characteristics (measured and unmeasured)	Treatment not randomized; Treatment assignment may depend on patient baseline characteristics	Patient baseline characteristics often unbalanced ("channeling bias, confounding by indication")
Blinding	Double-blind design	Minimizes bias of subjects, observers, and analysts	Generally un-blinded	Results subject to bias of subjects, observers, and analysts
Data Collection Design	Pre-specified and data largely complete	Missing data are identified as missing	Data collection methods may not be pre-specified. Data may be incomplete; (especially baseline characteristics)	May be impossible to establish or demonstrate balance for baseline characteristics
Clinical practices	Clinical practices often pre-specified and standardized	Clinical practices are independent of treatment under study	Clinical practices are variable, and may be associated with treatment under study	Clinical practices that are associated with outcome may be confounded with treatment under study
Selection of patients	Appropriate selection of patients	Patients have the condition under study	Whether patients have the condition under study may be uncertain	Patients may be unrepresentative of the intended study population
Patients excluded from analysis	Intent-to-Treat analysis	Ensures patients are not excluded from analysis based on outcome	Eligible patients may be excluded from analysis based on outcome	Biased estimate of treatment effect; "Selection bias"
Outcomes	Outcomes pre-specified and collected prospectively	Outcomes well-defined and reliable	Outcomes may be defined only by available surrogate outcomes	Outcomes may be missing or misclassified

Table 8-2 summarizes additional characteristics that are typical of well-designed multi-center randomized clinical trials. Randomized treatment assignment by block

within center is, of course, not a feature of multi-center observational studies. However, standardized methods of data collection across centers and a standardized approach to clinical practices affecting the studied outcomes can, in principle, be incorporated in the design of observational studies. It is useful to consider these features in the evaluation of multi-center observational studies.

Table 8-2: Special Characteristics of Randomized Multi-Center Trials Compared with Multi-Center Observational Studies

Randomized Clinical Trials		Observational Studies	
Characteristic	**Expectation**	**Characteristic**	**Expectation**
Patients randomized to treatment in blocks within center	Expected balance between treatments for contributing centers	Use of treatment under study may vary by center; criteria for treatment choice (based on patient characteristics) may vary by center	Confounding of center and test treatment
Data collection methods standardized across centers	Data extent and quality uniform across centers	Data extent and quality may vary across centers	Data extent and quality may be confounded with center
Clinical practices often prespecified and standardized	Clinical practices uniform across centers	Clinical practices may differ across centers and may be associated with center and/or test treatment	Clinical practices that are associated with outcome may be confounded with center and/or test treatment

8.2 Coping with the absence of randomization

8.2.1 The problem of channeling bias

One of the requirements of randomized clinical trials is that "the analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables."(216) Assessment of comparability is required in randomized trials because lack of comparability calls into question whether observed effects are the effect of treatment or the effect of other influences. The same requirement for assessment of comparability holds for observational studies.

A critical advantage of randomized controlled trials compared with non-randomized studies is that the random allocation ensures expected balance with respect to

baseline characteristics (both measured and unmeasured) of treated and control patients. In nonrandomized studies, however, the treating clinician typically chooses for a given patient one treatment over another based on prognostic factors. Accordingly, in a nonrandomized study, there may be extreme imbalances in background characteristics between treated and control patients (if, for example, one treatment is generally reserved for perceived to be at higher risk or for patients undergoing more difficult or complex surgeries). The resulting imbalance in baseline characteristics (or lack of comparability) between the test treatment and control groups is termed *channeling bias*. Other terms sometimes applied are "confounding by indication," "treatment selection bias," or simply "selection bias."[1]

In observational studies of treatment effects, it is sometimes (but not always) possible to identify treated and control patient subgroups that are comparable on observed baseline characteristics using propensity score methods.(217-219) Ideally, these subgroups of treated and control patients are as balanced with respect to known background characteristics as would have been achieved by randomization. This effort is undertaken to avoid confounding due to imbalances in background characteristics between the treatment groups leading to incorrect inferences that observed outcomes are causally related to the treatment received.

Professor Donald Rubin, co-inventor of propensity score methodology, has suggested that "observational studies can and should be designed to approximate randomized experiments as closely as possible. In particular, observational studies should be designed using only background (baseline) information to create subgroups of similar treated and control units," and "this activity should be conducted without any access to any outcome data, thereby assuring the objectivity of the design."(218) D'Agostino and D'Agostino, in their January 2007 paper published in *Journal of the American Medical Association,* advocate exactly this approach stating that "the statistical methods in observational studies need first to be

[1] The term *selection bias* as used in classic epidemiology has a different meaning and generally refers to the exclusion of patients for whom the relationship between treatment and outcome is different than for patients who are not excluded.

judged based on their performance in creating a balance on background characteristics between treated and control groups, and the impact of outcome data should play no role in this assessment."(217)

8.2.2 The propensity score

Because use of propensity scores for dealing with channeling bias was reported in the observational studies by Mangano et al,(2, 10) Karkouti et al,(3) and in the study by i3 Drug Safety(8) it is helpful to explain the basic concept of propensity score methodology and to address common misconceptions.

Propensity score methodology is based on the concept that the clinician's decision to prescribe treatment A versus treatment B to a given patient can be modeled mathematically, yielding a probability (the propensity score) that a patient with a given set of known baseline characteristics will receive treatment A rather than B. If one then considers a subgroup of patients with similar propensity scores, some of whom actually received treatment A and some of whom actually received treatment B, these treated and control patients can be compared as if the treatment decision had been randomized since all of the patients in the subgroup were equally likely to have received treatment A. Alternatively, in theory, if one considers a pair of patients (one patient who received treatment A and one patient who received treatment B) matched with similar propensity scores, the treated and control patients can be compared as if the treatment had been randomized.

One of the inherent properties of the propensity score approach is that to the extent that the propensity score model truly describes the treatment choice (and with sufficiently large samples), it can be shown that within subgroups of patients with similar propensity scores, there is balance between treatment groups for all of the known baseline factors included in the propensity model. *Note, however, that there is no assurance whatsoever of balance for unknown or unmeasured baseline factors (unless these are known to be closely associated with factors included in the propensity model).*

Another critical characteristic of propensity score methods is that the propensity model can be developed based only on knowledge of patient baseline characteristics and the treatment received. Knowledge of the outcomes is not required, and development of the propensity model without knowledge of the outcome ensures objectivity in the analysis. The treatment effect can then be estimated as a weighted average of the treatment effects within subgroups of patients that are defined by similar propensity scores, avoiding to some extent the model-based assumptions made in directly modeling the outcome by logistic regression.(220)

The sole criterion for evaluating the success of a propensity model is whether baseline characteristics in a subgroup of patients with similar propensity scores are balanced. The propensity score is iteratively developed until balance is achieved.(220) Further, the examination of balance of baseline characteristics within subgroups (strata) of propensity score (termed propensity score *diagnostics*) is essential for determining whether the propensity model was or was not successful in achieving balance.(221, 222) If balance cannot be achieved in all subgroups, the analysis must be restricted to the subgroups where balance is achieved. Diagnostics are also essential for determining whether balance is even achievable, because in some datasets with severe channeling bias, analysis with propensity score methods will reveal that the treatment groups are so different in baseline characteristics that a reasonable comparison is not possible.(219) In this case the database is not suitable to address to question at hand.

It is a common misunderstanding that the discriminatory power of the propensity score model (ability of the model to determine correctly the treatment actually received) characterized by the c-score is the measure of a successful propensity model. If the model is successful in achieving balance, the c-score reflects only the distribution of propensity score between treatments, which is simply a characteristic of the data set.

It is helpful to summarize these points and some other stipulations for the meaningful use of propensity score methods:

- The sole criterion for evaluating a propensity model is the demonstration of balance of baseline characteristics in subgroups of patients with similar propensity scores. Successful application of propensity score methods requires that balance be demonstrated.(221, 222)

- The propensity score is iteratively developed until balance is achieved.(220) The use of interaction terms (e.g., considering baseline characteristics in combination) and other nonlinear terms in the propensity model may be necessary to achieve balance.

- A separate propensity score must be estimated for each pair of treatments compared. Propensity models for comparing multiple treatments are experimental and generally inappropriate, although in special situations they can be helpful.(223)

- The propensity score model is intended to model the treatment decision at the treatment decision point.(221, 222) Use of the model assumes that a consistent set of criteria are applied at the treatment decision point. If available data suggest, for example, that different treatment decision criteria are used across centers, a single propensity model intended to apply across centers is generally not meaningful or helpful. Under these conditions, a single propensity model, otherwise adequately developed, cannot account for different types of channeling bias within centers.

- Note that use of the propensity score as an additional covariate or as a simple indicator variable in an analysis of outcomes by logistic regression is not reliable.(218) Under conditions of imbalance of baseline characteristics, regression models, unless coupled with the correct application of propensity technology through matching and/or subclassification, cannot be expected to give reliable results.(219)

8.3 Selection of a suitable database

Section 8.1 notes that design features usually found in well-designed clinical trials may be present or absent in observational studies. In evaluating the data set used for an observational study, it should be determined whether data collection methods for baseline characteristics (covariates) and outcomes were prespecified and standardized; the extent to which clinical practices associated with outcome were prespecified and standardized; whether recorded outcomes are well-defined and reliable; and whether treatment assignment and baseline patient characteristics are recorded and reliable.

Section 8.2 notes that demonstration of comparability between treatment groups, as required for randomized trials,(216) can and should be investigated in observational studies. Thus, whether key patient baseline characteristics (known risk factors) are available in the database and reliably recorded is critically important.

As an example of the effect of missing risk factors, consider an observational comparison of aprotinin and control treatment in CABG surgery in which the aprotinin patients have a higher prevalence of multiple cardiac re-operations, a higher prevalence of shock at the time of surgery, a higher prevalence of emergency vs elective surgery, a higher prevalence of insulin-dependent diabetes, and a higher prevalence of pre-existing aortic stenosis. All of these characteristics are well-established and statistically significant risk factors for mortality after CABG surgery.(14) Consider now the effect on the results of such a study if none of these risk factors is recorded in the database. The lack of comparability between the treatment groups cannot be "adjusted for" in a regression model because these important risk factors are not available and, therefore, cannot be included in the model. Even an objective and appropriate analysis by propensity score methods demonstrating balance on all the *available* risk factors would not address channeling bias in this circumstance because the demonstration of comparability between treatment groups for the *available* risk factors says nothing about comparability for the risk factors that were not recorded.

The problem of missing or misclassified risk factors in administrative data sources has been addressed by Shahian et al in the context of CABG surgery.(224) In a comparison of clinical and administrative data sources, Shahian et al showed substantial variability in CABG outcomes assessed from the different data sources and found that CABG combined with other surgical procedures misclassified in the administrative data as isolated CABG was a predominant contributing factor.(224) Shahian et al hypothesized that the performance of high volume, tertiary centers is misjudged when isolated CABG volumes and mortality rates from administrative databases are "inflated by the inclusion of combined procedures that are inherently higher risk."(224) Shahian et al concluded that "cardiac surgery report cards using administrative data are problematic compared with those derived from audited and validated clinical data, primarily because of case misclassification and nonstandardized end points."(224) Others have also highlighted the limitations of administrative data in outcomes research related to CABG surgery(225-227) or ischemic heart disease.(228)

8.4 Criteria for evaluation of observational studies

In summary, the evaluation of an observational study must consider whether the data source is suitable and whether the design and analysis are appropriate. Selection of a suitable data source is critical because no analytic technique can compensate for an inadequate database.

When evaluating the database selected for an observational study the following should be determined:

- Whether data collection methods were prespecified and standardized.
- Extent to which clinical practices associated with outcome were prespecified and standardized.
- Whether recorded outcomes are well-defined and reliable.

- Whether treatment assignment and baseline patient characteristics are recorded and reliable.

Whether patient baseline characteristics (known risk factors and factors involved in treatment choice) are available in the database. Whether patient baseline characteristics (known risk factors) are available in the database and reliably recorded is critically important because it is impossible to investigate or demonstrate comparability of treatment groups if known risk factors are unavailable and omitted from the analysis. Note that patient risk factors, in the context of investigating outcomes after CABG surgery, include not only the baseline medical condition of the patient but also characteristics of the operating surgeon, e.g., case mix and experience.

When evaluating the design and analysis, the "the statistical methods in observational studies need first to be judged based on their performance in creating a balance on background characteristics between treated and control groups…"(217) In other words, do the investigators demonstrate comparability of patient baseline characteristics between treatment groups? Comparability must be investigated by displays of balance of patient characteristics for subgroups, classified, for example, by the propensity score (Section 8.2.2).

Note two caveats with respect to the display of balance of baseline characteristics between treated and control subgroups identified by forming subgroups (subclasses) on the propensity score or by matching on the propensity score:

1. If the available data indicate that different treatment decision criteria were used across participating centers, a single propensity model, intended to apply across centers is inappropriate. In this case the propensity model may produce balance of covariates for subgroups of the population overall, but the model will not account for channeling bias within centers. In this situation it is generally the case that *within center,* covariates for subgroups or matched pairs with similar propensity scores are *not* balanced between

treatments. The source of the problem (Subsection 8.2.2) is that the propensity model failed to model the treatment decision at the correct treatment-decision point.

2. If multiple baseline characteristics that are known risk factors are unavailable in the data set (Subsection 8.2.3), demonstration of balance of observed patient characteristics between treated and control subgroups (e.g., using subclassification or matching on propensity score) provides evidence of balance between treatment groups only for the available baseline factors examined, and provides no assurance whatsoever of balance for the unavailable risk factors.

In addition to investigation of baseline comparability of the treatment groups, other considerations in the analysis are issues of excluded patients (Table 8-1) and the potential for confounding of the test treatment[2] with clinical practices that are associated with outcome (Table 8-1). Multi-center observational studies may present other issues that must be addressed in the analysis (Table 8-2). These include circumstances in which treatment is confounded with center, treatment and/or center is confounded with clinical practices associated with outcome, or center-specific treatment-selection criteria vary with respect to patient risk.(220) Whether these circumstances apply must be explored and addressed in the analysis. Ideally, balance between treatment groups should be demonstrated with respect to contributing centers and with respect to clinical practices, including, in the context of CABG surgery, the contributing surgeons.

Table 8-3 compares the databases used in observational studies by Mangano et al,(2, 10) Karkouti et al,(3) and i3 Drug Safety(8) that are discussed in this briefing document. Table 8-4 compares the statistical analyses applied in the reports of Mangano et al, 2006(2); Mangano et al, 2007(10); Karkouti et al, 2006(3); the i3 Drug Safety Preliminary Report(8) and the i3 Drug Safety Final report.(229)

[2] The term *test treatment* refers to the treatment intervention under investigation, i.e., aprotinin or control.

Table 8-3: Comparison of Three Data Sources Selected for Observational Studies

	Mangano 2006 and 2007[a]	Karkouti 2006[b]	i3 Drug Safety Study[c]
Data Source	Clinical Database	Clinical Database	Administrative Claims Database
Data collection largely complete for key covariates	Generally, Yes	Generally Yes	No Multiple key covariates missing; Available covariates misclassified
Outcome measures prespecified, clearly defined and reliable	Generally, Yes	Yes	No Outcomes other than death defined by surrogate outcomes
Data set reliably identifies test treatment and dose	Generally, Yes Treatment order for patients receiving multiple hemostatic agents unknown	Yes Patients did not receive multiple hemostatic agents	Generally, Yes Exact dose unknown; Treatment order for patients receiving multiple hemostatic agents unknown
Database identifies patients with the condition of interest	Yes CABG Surgery on CPB with or without other surgical procedures	Yes Cardiac surgery on CPB	Generally, Yes CABG surgery (both on-CPB and off-CBP) with or without other surgical procedures
Database allows identification of patients who experienced study outcomes prior to the test treatment	Generally, Yes	Generally, Yes	No Generally uncertain whether patients experienced the study outcomes (other than death) prior to test treatment
Test Treatment[d] confounded with center	Test Treatment confounded with center	No Single Center	Test Treatment confounded with center
Data collection methods standardized (across centers)	Yes	Yes Single Center	No Extent of data collection varies with center

Table 8-3: Comparison of Three Data Sources Selected for Observational Studies

	Mangano 2006 and 2007[a]	Karkouti 2006[b]	i3 Drug Safety Study[c]
Clinical practices associated with outcome are standardized (across centers)	No Clinical Practices associated with outcome are known to be confounded with center	Generally, Yes CPB management and transfusion policy directed by clinical guidelines	No Clinical Practices associated with outcome are likely to be confounded with center

a Section 9 and 10
b Section 9
c Section 11
d *Test treatment* refers to hemostatic treatment, i.e., aprotinin or control.

Table 8-4: Statistical Analysis in the Observational Studies by Mangano et al, 2006;(2) Mangano et al 2007;(10) Karkouti et al, 2006;(3) and the Analyses by i3 Drug Safety(8, 229)

	Mangano 2006[a]	Mangano 2007[b]	Karkouti 2006[c]	i3 Drug Safety, First Analysis[d]	i3 Drug Safety, Second Analysis[d]
Method for dealing with channeling bias	”Propensity-adjusted multivariable logistic regression”	“Propensity-adjusted multivariable regression”	One-to-one matching on propensity score	Multivariable logistic regression with secondary analysis using propensity score as an indicator variable	Multivariable logistic regression with secondary analyses using propensity matching and instrumental variable analysis
Propensity estimation models the treatment decision at the treatment decision point	No	No	Yes[e]	No	No
Balance demonstrated after correct application of propensity score methods at the treatment decision point	No	No	Yes	No	No
Propensity score methods appropriately applied	No	No	Generally, yes	No	No
Confounding of test treatment and center addressed in the analysis	No	No	Yes, Single Center	No	No

Table 8-4: Statistical Analysis in the Observational Studies by Mangano et al, 2006;(2) Mangano et al 2007;(10) Karkouti et al, 2006;(3) and the Analyses by i3 Drug Safety(8, 229)

	Mangano 2006[a]	Mangano 2007[b]	Karkouti 2006[c]	i3 Drug Safety, First Analysis[d]	i3 Drug Safety, Second Analysis[d]
Confounding of clinical practices and center addressed in the analysis	No	No	Not applicable	Unknown if clinical practices are confounded with center	Unknown if clinical practices are confounded with center
Center-specific treatment selection criteria addressed in the analysis	No	No	Not applicable	No	No
Patients included in the primary analysis	4374	4374 (3357 completed 5-year follow-up)	898	66,365	78,199
Eligible patients excluded from analysis based on outcome, or excluded for reasons associated with outcome	Yes 255 patients (Subsection 10.3.4)	Yes 1146 patients (Subsection 10.3.4)	No	Yes 3112 patients (Subsection 11.2.4)	Yes 2,839 patients (Subsection 11.2.4)

a Sections 9 and 10
b Section 10
c Section 9
d Section 11
e Karkouti et al modeled propensity at the hospital level. Treatment choice was guided by hospital policy. Surgeons generally followed similar treatment decision criteria as evidenced by demonstrated balance of contributing surgeons between treatment groups.

9. Observational Studies Reviewed at the Cardiovascular and Renal Advisory Committee September, 2006 (Mangano, 2006 and Karkouti 2006)

FDA's Cardiovascular and Renal Drugs Advisory Committee at its meeting on 21 Sep 2006(4) reviewed the observational study by Mangano et al published January 2006 in the *New England Journal of Medicine* [Mangano 2006](2), and the observational study by Karkouti et al published March 2006 in *Transfusion* [Karkouti 2006](3) as well as data from Bayer's randomized, controlled clinical trials in CABG surgery.(6, 7) The authors of both observational studies reported the use of propensity score methodology.

In his assessment of the two observational studies before the Advisory Committee, Dr. Robert Makuch, Professor of Biostatistics at the Yale School of Epidemiology and Public Health, and consultant to Bayer, emphasized the importance of evaluating baseline comparability between treatment groups to "assure any treatment group differences are likely due to treatment as opposed to other predictive factors independent of treatment."(230)

Karkouti 2006(3) was a single-center observational comparison of aprotinin and tranexamic acid in high-risk cardiac surgery. Data were available for 586 patients treated with aprotinin and 10,284 patients treated with tranexamic acid. Because aprotinin was given only to high-risk patients there were profound imbalances in baseline risk factors. Dr. Makuch pointed out that the issue of major imbalances was properly addressed in the design stage of the study by propensity score matching, resulting in 449 patients in each treatment group. Because the patients treated with aprotinin were so different from the patients treated with tranexamic acid (i.e., at higher risk because of many more risk factors), there were 137 aprotinin patients who could not be matched. Importantly, Karkouti et al demonstrated that among the matched patients there was balance for all of the measured baseline risk factors, and this allowed a more straightforward analysis. Dr. Makuch also noted that the association between aprotinin exposure and post-treatment serum creatinine

elevations reported by Karkouti et al was not inconsistent with the results of randomized, controlled trials.(230)

Mangano 2006(2) was an international, multi-center observational comparison of the hemostatic agents aprotinin, aminocaproic acid, and tranexamic acid versus no hemostatic treatment in CABG surgery. The study included 4,374 patients, with 1,295 treated with aprotinin. In the Mangano data, as well, there were highly statistically significant imbalances between the aprotinin cohort and the no treatment cohort, indicating that aprotinin was given preferentially to high-risk patients. The authors of the Mangano study, however, in contrast to Karkouti et al, did not employ matching in the design stage; thus, they had to rely on "generally inappropriate complex statistical modeling" to address baseline imbalances. Dr. Makuch noted that a careful review of the statistical analysis in Mangano 2006 was therefore mandatory. Moreover, in the absence of an appropriate analysis of the underlying data, it is unknown whether any reliable conclusions comparing aprotinin to other treatments can be drawn from these data.(230)

Dr. Makuch made the following observations regarding the statistical analysis in Mangano 2006:

- Estimated propensity score was used as a variable in covariate adjustment, rather than the correct use to create matches or subclasses.
- No diagnostic displays or analyses were provided to support the claimed balance of covariates achieved by propensity scores.
- No diagnostic displays or analyses were provided to support the claimed balance of covariates for each pair of treatment groups compared.
- 410 patients (9% of patients) had missing covariates for propensity scores for the renal outcome analysis.
- 407 patients had missing propensity scores for the ischemic outcome analysis.

- Analyses including outcome variables were used to help decide which covariates to include in the regression model. This introduces bias at least in the significance levels.

- With significant between-treatment imbalances in numerous baseline risk factors regression modeling is known to be unreliable.

- Crude data were sometimes used in the report where adjusted data should have been used.

Dr. Makuch concluded that "analytic methods to correct for baseline imbalances in the Karkouti study were generally appropriately applied," while "[a]nalytic methods to correct for numerous and highly significant baseline imbalances in the Mangano 2006 study were incorrectly applied." "Additional issues also were raised such as subgroup analyses, leading to questionable validity of the findings. In summary, the Mangano study results should not be considered reliable at this time." (Table 9-1)

Table 9-1: Comparison of Data Sources

	Multiple RCTs	Karkouti 2006(3)	Mangano 2006(2)
Randomized	Yes	No, Matched	No
Baseline Comparability	Yes	Yes (on observed covariates through matching)	Major imbalances
Patients Excluded	No	Yes, through matching	Yes, 691 patients
Sample Size	4,413	898	4,374
Aprotinin exposed patients	2,200	449	1,295
Outcome Definitions	Prespecified	Prespecified	Prespecified, Different from previous studies of the same database
Analysis	Standard	Propensity matching	"Propensity-adjusted multivariable logistic regression"

Table adapted from the presentation by Professor Makuch at FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting on 21 Sep 2006.(231)

Dr. S. Stanley Young of the National Institute of Statistical Sciences (an independent research institute), speaking in the Public Hearing section of the same meeting, stated that "the statistical analysis is seriously flawed."(232)

The Advisory Committee agreed. Dr. David DeMets, Professor and Chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin and member of the Advisory Committee, commented in the afternoon Advisory Committee discussion "when I looked at the New England Journal paper I was disturbed by it. As has been alluded earlier, I guess I pretty much dismissed the conclusions that were drawn."(233) Speaking on the future prospects for regulatory reliance on observational data, Dr. DeMets went on to say "And so we need as we look at these trials or these kind of data in the future, we're going to have to really drill down on the analysis details a lot more than we do in, say, randomized trials."(233)

The criticisms of the analysis reported in Mangano 2006 did not include the further observation that the propensity estimation by Mangano et al(2) did not model the treatment decision at the treatment decision point. Design characteristics of the studies by Karkouti et al(3) and the study reported in Mangano 2006 are summarized in Section 8, Table 8-3 and Table 8-4.

10. Review of Mangano et al, JAMA 2007

10.1 Synopsis

Mangano et al, reporting an observational study (10) published in Feb 2007 in the *Journal of the American Medical Association* (Mangano 2007), concluded that aprotinin treatment in patients undergoing coronary artery bypass graft (CABG) surgery was associated with significantly increased 5-year mortality compared with control (no treatment). Mangano 2007 comprises the authors' analysis of the 5-year mortality data available for a subset of the same set of 4,374 CABG patients described in the earlier report published in January 2006 in the *New England Journal of Medicine*(Mangano 2006).(2)

10.2 Suitability of the database

10.2.1 Data source and quality

Mangano 2007 is based on a subset of the same population derived from the Multicenter Study of Perioperative Ischemia, Epidemiology II (McSPI – EPI II) database that was described earlier in Mangano 2006. The McSPI – EPI II database is an international multi-center clinical database collected between November 1996 and June 2000. Patients in the database were selected from among patients at least 18 years old scheduled for CABG surgery with cardiopulmonary bypass at approximately 70 centers in 17 countries in North America, Europe, Asia, South America, and the Middle East.(2, 10) A total of 5,436 patients were enrolled with 5,065 patients considered suitable for evaluation. Patients undergoing surgical procedures concomitant with CABG (such as carotid endarterectomy or valve surgery) were not excluded from the database,(2, 234-236) and were not excluded from Mangano 2007.(10) The in-hospital portion of the McSPI EPI-II database, which comprises the in-hospital portion of the data forming the basis of the Mangano 2007 report, was locked 15 Oct 2001.(237)

The McSPI EPI-II database has been the basis of multiple publications(2, 35, 234-239) and abstracts.(240-242) on a variety of topics and was not collected for the purpose of evaluating the effects of hemostatic therapies. Data were prospectively collected during the course of the index hospitalization for coronary artery surgery using a case report form that included demographic, historical, clinical, laboratory, electrocardiographic information, as well as resource use and adverse outcomes.(235, 236) Published papers do not describe quality assurance procedures except to state that data were adjudicated centrally(237) and “examined for completeness and accuracy before the database was closed.”(235, 237) Whether data collected in the case report form were systematically monitored against source documents is not reported.

10.2.2 Availability of key covariates

The McSPI – EPI-II database is a prospectively collected clinical database with many covariates generally available in the database.(243)

10.2.3 Outcome measures

Five-year mortality was assessed prospectively by the investigators. National death registries, such as the Social Security Death Registry, were used to supplement information.(10)

10.2.4 Availability of test treatment and dose

Hemostatic treatment was available in the database; however, it appears that when multiple hemostatic agents were given, the order of the treatment is unavailable in the database. In the case of patients who received more than one hemostatic agent during surgery, it is possible that the second agent was given because of lack of efficacy of the first agent or an emerging poor outcome. However, the treatment that was given first (presumably the intended treatment) cannot be distinguished. Thus, the exclusion of patients who received multiple agents could be an exclusion based on events after administration of the test treatment.

10.2.5 Confounding of test treatment and center

To date, none of the publications based on the McSPI – EPI II database(2, 10, 35, 234-242) reports enrollment of the 5,065 evaluable patients by treatment and by country. However, among the 4,374 patients described in Mangano 2007, none of the 248 patients in Asia received either aprotinin or aminocaproic acid; none of the 2,094 patients in Europe received aminocaproic acid; and none of the 85 patients in the Middle East received aminocaproic acid.(10) These profound and statistically significant differences in the use of hemostatic agents across geographical regions (Table 10-1) indicate that hemostatic treatment is confounded with center. The confounding between selection of hemostatic agents and center in the McSPI EPI-II database is a serious limitation to the use of the McSPI EPI-II database for the study of the effects of hemostatic treatment. Importantly, the high degree of confounding of hemostatic treatment with center must be accounted for in the analysis. Failure

to account for confounding of treatment and center in the analysis can result in an entirely erroneous assessment of treatment effects.(220)

Table 10-1: Mangano 2007: Test Treatment is Confounded with Geographic Region

	Treatment Cohort							
	No Treatment (N = 1,374)		Aprotinin (N = 1,295)		Aminocaproic Acid (N = 883)		Tranexamic Acid (N = 822)	
	N	%	N	%	N	%	N	%
Europe	790	57.5	899	69.4	0	0	405	49.3
North America	328	23.9	377	29.1	846	95.8	240	29.2
Asia	227	16.5	0	0	0	0	21	2.6
Middle East	19	1.4	2	0.2	0	0	64	7.8
South America	10	0.7	17	1.3	37	4.2	92	11.2
P value[a]			<0.0001		<0.0001		<0.0001	

Profound and statistically significant imbalances in geographic region among treatments indicates that test treatment is confounded with center.

a P values are for the comparison between each treatment cohort and the no treatment cohort. P values calculated by Bayer.

Adapted from Table 1, Page 472 of Mangano 2007(10)

10.2.6 Confounding of clinical practice and center

Clinical practices associated with outcome such as use of fresh frozen plasma, heparin, aspirin, and transfusion policies were not standardized across participating centers in the McSPI EPI-II database, and this is another limitation of the database for the study of the effects of hemostatic treatment. A 2007 publication based on the McSPI – EPI II database(35) describe statistically significant between-country differences in the use of aprotinin, significant between-country differences in the use of fresh frozen plasma, heparin, and aspirin, and significant between country differences in outcome. Another publication based on the McSPI – EPI II database(241) 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% across countries, and transfusion of fresh frozen plasma from 0 to 98% across countries.(241) Thus, *clinical practices that are associated with outcome* are confounded with center. Importantly, the observation that *clinical practices associated with outcome* are confounded with

center, and that center, in turn, is confounded with hemostatic treatment must be accounted for in the analysis.

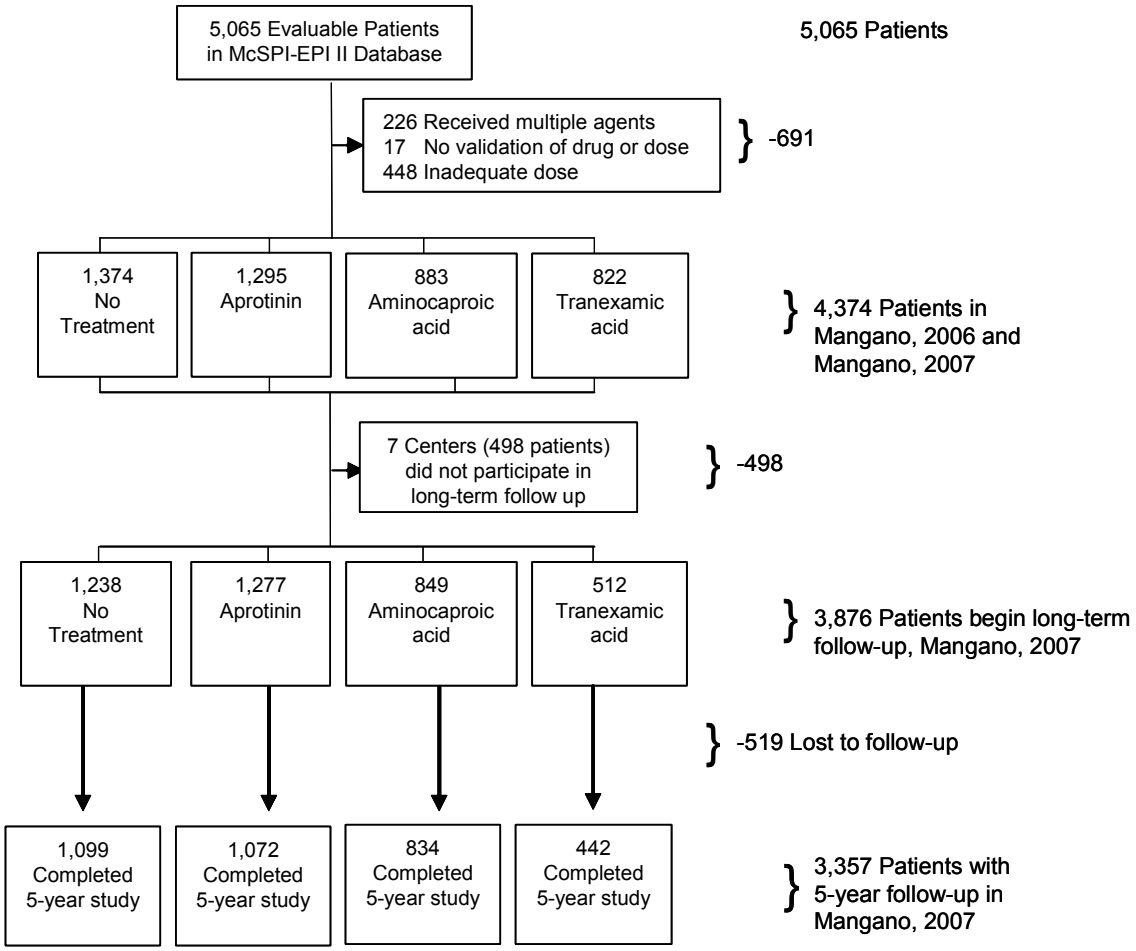
10.2.7 Method of patient sampling

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.(2, 234-237) This method of patient selection employed in creating the observational McSPI-EPI II database does nothing to ensure expected balance among treatment groups with respect to patient baseline characteristics within centers. Further, this selection method has the effect of over-representing patients from low-volume centers compared to the sample population.

The overall distribution of patients is summarized in Figure 10-1.

A total of 691 evaluable patients who received hemostatic treatment were excluded from the analysis comprising 226 patients who received multiple agents at surgery and 17 patients who had missing data for hemostatic treatment or dose. An additional 448 treated patients were excluded based on pre-specified criteria for "inadequate dose"(2) (Figure 10-1).

Figure 10-1: Patient Enrollment in Mangano 2007



Though not stated in the Mangano 2007 report,(10) Mangano et al excluded in the Mangano 2006 study(2) 691 of the 5,065 McSPI – EPI II evaluable patients arriving at the 4,374 patients described in Mangano 2007.

10.2.8 Investigation of baseline comparability (channeling-bias)

The importance of investigating balance of baseline characteristics between treatment and control groups (baseline comparability at the treatment decision point) in the design and analysis of observational studies is emphasized in Section 8. The authors of Mangano 2007 provide in their Table 1, page 472(10) selected baseline characteristics for the identical in-hospital population (N = 4,374) described in the Mangano 2006 in-hospital study.(2) Thus, the authors' Table 1 in Mangano 2007 includes the 498 patients treated in- hospital at the seven sites that did not

participate in the post-discharge phase in the Mangano 2007 study. Information on baseline comparability for the subset (N = 3,876) of patients who participated in the post-discharge phase, and for the subset (N = 3,357) who completed five-year follow-up is not provided.

The authors of Mangano 2007 include in their Table 1, page 472(10) only some of the baseline characteristics that are known risk factors for adverse outcomes. For example, the authors do not provide information for risk factors previously reported in the same McSPI – EPI II database by Mangano and collaborators(2, 234, 237, 238) as important, independent predictors of mortality, e.g., perioperative aspirin treatment,(2) and perioperative statin treatment,(238) or important, independent predictors of adverse outcomes, e.g. pulse-pressure hypertension,(234) intraoperative use of fresh frozen plasma,(2) and intraoperative red cell transfusion.(2) Nevertheless, it is clear from the baseline characteristics that are reported in the authors' Table 1, page 472(10) that there are profound and statistically significant imbalances between treatment groups. Patients at higher risk for adverse outcomes, including mortality, were given aprotinin in preference to no treatment, and given aprotinin in preference to the other agents (aminocaproic acid and tranexamic acid).

Table 10-2 below, adapted from the authors' Table 1, page 472 of Mangano 2007(10) shows for illustration those baseline characteristics that were statistically significantly imbalanced between the aprotinin and the no treatment cohort.

Table 10-2: Mangano 2007: Significant Imbalances in Baseline Characteristics

	No Treatment Cohort (N = 1,374)		Aprotinin Cohort (N = 1,295)		
	N	%	N	%	P value[a]
Age, mean (SD), y	63.2 (9.8)		64.9 (9.2)		<.001
Education: some college or above	496	36.1	280	21.6	<.001
Surgery: urgent or emergency status	288	21.0	192	14.8	<.001
Medical history					
Angina	1,273	92.8	1136	87.8	<.001
Hypertension	831	60.5	907	70.0	<.001
Congestive heart failure	461	33.6	557	43.1	<.001
Complex surgery	343	25.0	495	38.2	<.001
Pulmonary disease	238	17.4	327	25.3	<.001
Renal disease	183	13.3	241	18.6	<.001
Valve disease	169	12.4	329	25.4	<.001
Carotid disease	153	11.1	223	17.2	<.001
Percutaneous transluminal coronary angioplasty	138	10.0	223	17.2	<.001
Liver disease	106	7.7	151	11.7	<.001
Type 1 diabetes mellitus	78	5.7	116	9.0	.001
Intracoronary stent	54	3.9	95	7.3	<.001

a P values are for the comparison between the aprotinin cohort and the no treatment cohort.
Adapted from Table 1, Page 472 of Mangano 2007(10)

The authors' Table 1 on page 472 of the Mangano 2007 report appears to describe the identical locked patient population database (N = 4,374) as described in the authors' Table 1, page 356-7 of the Mangano 2006 report;(2) however, some of the values reported in Table 1, page 472 of the Mangano 2007 report(10) differ from the corresponding values reported in Table 1, page 356-7 of the Mangano 2006 report.(2) The most prominent inconsistency is "history of heart block," reported in Table 1, page 356-7 in Mangano 2006(2) to affect 224 of the 1,295 aprotinin patients, but reported in Table 1, page 472 of the Mangano 2007 report(10) to affect 19 of the 1,295 aprotinin patients. The authors give no explanation for these inconsistencies in the two publications, both reporting baseline data for the identical set of patients residing in the same database locked years earlier.

10.3 Statistical analysis

10.3.1 Method for dealing with lack of baseline comparability (channeling bias)

The authors state that "three methods were used to assess drug associations with outcome: survival analysis, multivariable logistic regression, and propensity score adjustment".(10) The survival analysis was performed "on all 4,374 patients enrolled in the in-hospital study using Cox regression, illustrated using covariate-adjusted survival,"(10) and "multivariable logistic regression" was performed "to further evaluate the association of drug group with 5-year mortality among patients participating in and completing the 5-year follow-up program."(10) Similar to the approach taken in Mangano 2006, the analysis examined paired comparisons of each of the three active treatment cohorts with the no treatment cohort. In contrast to the approach taken in Mangano 2006, the authors of Mangano 2007 did not stratify patients according to "primary" or "complex" surgery.

The authors state on page 474, "To assess (treatment) selection bias not adequately controlled by standard multivariable approaches, we used propensity score adjustment methods" as a method of statistical adjustment for the acknowledged, highly significant imbalances in risk factors that are known to affect mortality.

The authors attempt to apply propensity score methods to take baseline imbalances into account, but do not follow the principles of propensity score methods as outlined in Subsection 8.3 of this briefing document. Some of principal concerns with the analysis are listed below:

1. It appears that distinct propensity scores were not estimated for each pair of treatment groups compared.(223)

2. The propensity score model does not model the treatment decision at the treatment decision point, in this case, at the level of the surgical team or at the level of the hospital (assuming surgical teams with similar decision criteria).(221, 222) Because of the profound differences in choice of treatment across geographical regions (Table 10-1), it is readily apparent that

the criteria determining treatment decision are not uniform across the contributing centers.

3. 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 472.

4. It appears that the estimated propensity score was used as a variable in a covariate adjustment and not used to create subgroups or to match patients.(222)

5. The goodness of fit statistic (the C-statistic) is of limited relevance for propensity score estimation; covariate balance is critical, not the predictive ability of the propensity score.(221, 222)

Importantly, in the presence of baseline imbalances between treatments, the application of regression methods (i.e., Cox regression with covariate adjustment or multivariable logistic regression) without the correct application of propensity technology through matching and/or creation of subgroups of similar propensity score, cannot be expected to give reliable results. This fact has been repeatedly documented by analysis and by simulation in hypothetical situations(244, 245), and the critical importance of this fact in the regulatory evaluation of nonrandomized studies is recognized, e.g. Yue, 2007.(219)

10.3.2 Method of dealing with confounding of test treatment and center

Table 10-1 indicates that there was profound confounding of test treatment and center. This degree of confounding requires an analysis of treatment effect by country or by center. This is not provided. Failure to consider treatment effect by center can result in completely erroneous conclusions if, for example, the results for the study population overall are driven by a few countries or by one or two large centers.(220)

10.3.3 Method of dealing with confounding of clinical practices and center

It was observed in Subsection 10.2.6 that clinical practices known to be associated with outcome such as transfusion, use of fresh frozen plasma, and peri-operative aspirin are demonstrably confounded with country (and center) in the McSPI EPI-II database. Center, in turn, is confounded with test treatment. Thus, for example, if centers in a given country used more fresh frozen plasma (FFP) (associated with adverse outcomes) and these same centers used more aprotinin, it would be impossible to separate the effects of FFP from the effects of aprotinin in the absence of an appropriate analysis. These circumstances require at least an analysis by center that investigates and establishes balance with respect to the confounding clinical practices. Such an analysis is not attempted and may be impossible because of the limited number of patients per center.

10.3.4 Patients excluded from analysis

Of the 5,065 evaluable patients in the McSPI-EPI II database, a total of 3,357 patients (approximately 66%) completed the 5-year follow-up. A total of 1,243 patients were excluded from the 5-year follow-up analysis based on events subsequent to administration of the test treatment or based on factors (e.g., center) that may be associated with outcome: 226 patients were excluded because of treatment with multiple agents; 498 patients were excluded because of non-participation in the long-term follow-up portion of the study (all are from 7 centers); 519 patients (all from 9 centers) were lost to follow-up (Figure 10-1). Note that 465 patients were excluded because of missing data (17 patients) and pre-specified dose requirements (448 patients) (Figure 10-1). Thus 4,600 patients (5,065–465) were otherwise eligible for inclusion in the 5-year follow-up analysis. The exclusion of 1,243 patients, nearly 27% of the 4,600 otherwise eligible patients, based on outcome or based on center (associated with outcome) raises concern for selection bias, i.e. the relationship between treatment and outcome in the excluded patients may be different from the patients who were included.

Further, non-participation in the post-discharge phase was associated with test treatment as well as center (Table 10-3). The authors' assertion that the exclusion of these patients had "little effect because the *in-hospital* mortality by study group was similarly distributed among the 62 centers participating in this study vs the 7 centers that did not (data available from authors upon request)"(10) does not adequately address concern for selection bias.

Additionally, the authors acknowledge that 13% of patients in the post-discharge phase (all patients from nine unspecified centers) were lost to follow-up, and state that the "distribution of these patients among the study groups, however, was similar."(10) In fact, a total of 205 of 1,277 participating aprotinin patients (16%) were lost to follow-up, whereas 15 of 849 participating aminocaproic acid patients (2%) were lost to follow-up (Table 10-3).

Table 10-3: Patient Participation was Unequally Distributed Across Centers and Treatments

Treatment Group	N	Number/Percent not Included in Post-Discharge Phase (All from Seven Non-Participating Centers)	Number/Percent of Post-Discharge Participants Lost to Follow-up (All from Nine Centers)	Number/Percent of Patients With 5-year Follow-Up Available
No agent	1,374	136 (10%)	229 (18%)	1,009 (73%)
Aprotinin	1,295	18 (1.4%)	205 (16%)	1,072 (83%)
Aminocaproic acid	883	34 (4%)	15 (2%)	834 (94%)
Tranexamic Acid	822	310 (38%)	70 (14%)	442 (54%)
Total (All treatment cohorts)	4,374	498 (11%)	519 (13%)	3,357 (77%)
p value[a]		<0.0001	<0.0001	<0.0001

a p values calculated by Bayer.

Data from Mangano et al, 2007.(10) Note that the 4,374 patients described in Mangano 2007 are those remaining after the exclusion of 691 of the 5,065 evaluable patients in the McSPI – EPI II database.(2)

10.4 Summary

10.4.1 Database selection

The international, multi-center database selected for this study is a prospectively collected clinical database relatively rich in covariates (baseline risk factors).

Treatment assignment is generally clear from the database. In the study population overall, there are profound and high statistically significant imbalances among and between the treatment groups (channeling bias) consistent with other studies indicating that aprotinin compared with other agents(3, 12) or with no treatment(12)is prescribed to riskier patients and/or to patients undergoing more complex surgical procedures.

A serious limitation of the selected database is the profound confounding between country (center) and test treatment and the absence of any standardized treatment guidelines (e.g., for transfusion, fresh frozen plasma, use of aspirin) across centers allowing serious confounding between these clinical practices and center. Center, in turn, is associated with treatment.

The method of patient selection in the McSPI-EPI II database, designed to enroll 50 patients per center per year is also not well-suited to the investigation. This method limits the number of patients per center per year, an impediment to a more suitable analysis. If there were a sufficient number of patients in each center, a more suitable analysis would develop a propensity model within each center (where criteria for treatment choice may be more uniform) and seek to establish balance of baseline characteristics within center.

Further, the method of patient selection in the McSPI – EPI II database, which over-represented the lower volume centers, would affect the generalizability of any properly derived results.

Characteristics of the McSPI – EPI II database, the data source for this study, are summarized in Section 8, Table 8-3.

10.4.2 Statistical analysis

The statistical methods used in this study are inappropriate.

1. The authors attempt to deal with the profound and statistically significant imbalances in baseline factors with the use of propensity score methods, but

apply these methods incorrectly. Use of a single propensity model across all centers does not model the treatment decision at the treatment decision point. There is no creation of subgroups or matched pairs and no demonstration of the balance achieved by the use of propensity scores. Under conditions of significant baseline imbalances, analysis by regression models, unless coupled with appropriate use of propensity score methods, is known to be unreliable as described in Section 8.2.2.

2. The authors make no attempt to deal with the serious confounding of test treatment with center and the serious confounding of clinical practices (that are known to be associated with outcome) with center.

3. Nearly a third of the 5,065 evaluable patients in the McSPI EPI-II database did not complete the five-year follow-up. A total of 1,243 evaluable patients (nearly a quarter of 4,600 patients who were otherwise eligible) are excluded from the five-year follow-up analysis on the basis of outcome (e.g., use of multiple hemostatic agents) or on the basis of center and/or loss to follow-up (associated with outcome). The exclusion from analysis of nearly a quarter of otherwise eligible patients raises concerns of selection bias.

Elements of the statistical analysis are summarized in Section 8, Table 8-4.

10.5 Conclusion

Some of the limitations affecting the validity of this study demonstrated in this briefing document are cited by Ferguson in his accompanying editorial to its publication.(246) Dr. Ferguson notes that "aprotinin use in cardiac surgery has never been uniformly standardized, but generally has been reserved for patients in whom the surgical team anticipated a higher risk for intraoperative blood loss. This anticipation was driven by the surgical team's perception of increased technical complexity, increased risk of adverse outcome, or both for the patient in question." The authors' incorrect propensity analysis as discussed in Section 10.3.1 (i.e., failure to model treatment choice at the level of the surgical team or, at least, at the

level of the surgical center) does not create balance for the factors that affect choice of treatment. As Dr. Ferguson states with respect to observational datasets, "the reason patients receive the drug/device therapy must be determinable"(246) and taken into account in the analysis. Dr. Ferguson also notes that the "use of antifibrinolytics varied widely across surgeons, sites, and countries,"(246) i.e., the problem of confounding of center and treatment, and concludes that "The mechanism for this late mortality difference is not clear and causality cannot be inferred from this dataset analysis."(246)

It is noteworthy that Mangano 2006, which describes the in-hospital outcomes in the same database, did not report an association between aprotinin and in-hospital mortality for either the primary surgery or the complex surgery groups.(2)

In summary, the profound baseline differences between treatment groups and the authors' inappropriate statistical methodology used to address these imbalances make the authors' conclusions unreliable. In addition, serious confounding of treatment with center and confounding of clinical practices with center are not addressed. Thus, no causal assessment of the relationship between aprotinin and 5-year mortality is possible.

Based on this review Bayer believes that the reported conclusions are neither valid nor reliable and should not serve as a basis for affecting the use of aprotinin in clinical practice.

11. Review of the Analyses by i3 Drug Safety

Given Bayer's receipt of i3 Drug Safety's final report on 07 Aug 2007 as well as the new approach that i3 Drug Safety has taken in its revised analysis, Bayer is continuing its review of the final report from i3 Drug Safety and may have additional comments to provide to the FDA between the time of this submission of the briefing document (09 Aug 2007) and the Advisory Committee Meeting.

11.1 Background

In February 2006 Bayer contacted the contract research organization i3 Drug Safety, a division of Ingenix Pharmaceutical Services, Inc. to explore the possibility of an observational study with aprotinin. In June 2006 Bayer commissioned an observational administrative database study based on a written proposal (Study Proposal)(247) prepared by i3 Drug Safety. i3 Drug Safety proposed to use the Premier Perspective Comparative Database (Premier Database), an inpatient administrative database, "to conduct a study of serious cardiovascular and renal outcomes among persons undergoing CABG (coronary artery bypass graft) surgery to quantify the association between aprotinin use and the occurrence of the specified outcomes."(247) The outcomes specified were myocardial infarction, stroke, heart failure, dialysis, and death occurring after CABG surgery through the end of hospitalization.(247) According to the contractual agreement between Bayer Healthcare AG and i3 Drug Safety, i3 Drug Safety was to deliver a preliminary report based exclusively on electronic data from Premier followed thereafter by a final report "with supplemental data provided by medical record review and sensitivity analyses."(247)

The Study Proposal(247) stated that i3 Drug Safety would work with Premier to obtain the necessary institutional approvals to conduct medical record abstraction for a sample of 100 patients who have had study outcomes, and an additional 100 patients at random. The medical record review would describe the correspondence of codes for study outcomes (within the Premier data set) to a clinical definition of study outcomes (as determined from the medical record). In addition, the medical record review would compare patient characteristics (clinical covariates) as determined by codes (within the Premier data set) to clinical covariates as determined from the medical records. The information obtained from medical record review would "inform a sensitivity analysis that will estimate the robustness of the study effect estimate to variations in assumptions about the completeness of data in the Premier database."(247)

In September 2006 Bayer received from i3 Drug Safety a preliminary report,(8) dated 13 Sep 2006, entitled "Mortality and Cardiovascular and Renal outcomes in recipients of aprotinin, aminocaproic acid and tranexamic acid during CABG surgery: Report on Computerized Inpatient Data from the Premier Perspective Comparative Database." This preliminary report was based exclusively on the electronic data from the Premier Database.(8) At that time the authors reported their preliminary result that with "multivariate adjustment, the estimated risks were higher for aprotinin recipients than for recipients of other antifibrinolytics with respect to acute renal failure (RR = 1.70; 95% CI 1.55-1.86), death (RR = 1.68; 95% CI 1.53-1.84), acute heart failure (RR = 1.08; 95% CI 1.03-1.14), and stroke (RR = 1.20; 95% CI 1.07-1.35)." The authors concluded that findings of their analysis "support the hypothesis that there is a higher risk of death and acute renal failure in aprotinin recipients."(8)

Referring to the Preliminary Report, FDA in a Public Health Advisory issued 29 Sep 2006(9) stated "The preliminary findings from this new observational study of patients from a hospital database reported that use of Trasylol may increase the chance for death, serious kidney damage, congestive heart failure and strokes."(9) FDA stated further(9):

> "In the … recently supplied Bayer study, patients were not assigned at random to receive various treatments, but rather had their treatment chosen by their physician as part of their standard medical care. Consequently, in these safety studies [referring also the observational clinical studies published earlier in 2006 by Mangano et al(2) and Karkouti et al(3)] patients receiving Trasylol may have had a higher chance for serious complications to begin with as compared to patients receiving no treatment or treatment with another drug intended to decrease bleeding. This possibility complicates the assessment of whether the available studies show that Trasylol treatment, rather than other factors, increased the chance for serious kidney or heart complications."(9)

FDA also indicated that it was “actively evaluating these new data and their implications for appropriate use of the drug.”(9)

Following receipt of the Preliminary Report, Bayer initiated a meeting with i3 Drug Safety,(248) with participation of FDA,(249) on 18 Oct 2006 and a subsequent meeting with i3 Drug Safety and representatives of the Premier Database on 29 Nov 2006.(250) Bayer also sought from i3 Drug Safety more thorough information on the study methods and the method of statistical analysis, (251) and forwarded to i3 Drug Safety on 27 Oct 2006 questions from FDA(252) regarding the database, data collection methods and the statistical analysis. Bayer received from i3 Drug Safety a partial response to its questions on 3 Nov 2006(253), and a partial response to FDA’s questions on 16 Nov 2006.(254)

On 22 Dec 2006 Bayer received from i3 Drug Safety a draft “revised study protocol” including a revised statistical analysis plan which according to i3 Drug Safety “will provide as clear a result as the available data are likely to hold.”(255) The proposed revised analysis was substantially different from the analysis in the Preliminary Report, and sought to investigate only the outcomes acute renal failure requiring dialysis and in-hospital mortality. The revised study protocol did not include a provision for medical record review.(255)

Bayer forwarded i3 Drug Safety’s revised study protocol to FDA and responded to i3 Drug Safety with Bayer’s position that a thorough understanding of the preliminary analysis as reported in the Preliminary Report was pre-requisite to consideration of a revised analysis plan.(256)

Also, at the request of FDA, Bayer requested from i3 Drug Safety the analytic data set corresponding to the statistical analysis in the Preliminary Report and the corresponding raw data obtained from Premier. These materials were provided to FDA for their review during the month of March 2007.

On 03 Apr 2007, Bayer provided FDA and i3 Drug Safety with a detailed review of i3 Drug Safety’s Preliminary Report.(257) Bayer concluded that the Premier

Database is unsuitable for addressing the relative safety of hemostatic agents in the complex milieu of cardiac surgery and that conclusions on the relative safety of hemostatic agents in cardiac surgery based on the Premier Database are unreliable.

On 27 July 2007, i3 Drug Safety informed Bayer that it had implemented its "revised analytic protocol" and did not plan to produce a final report based on the analysis as described in its Preliminary Report. Rather, i3 Drug Safety indicated its intention to produce a final report based on its revised study protocol dated 21 Dec 2006. i3 Drug Safety intended to issue this report in two parts, the first part on 07 Aug 2007, and the second part, including the results of medical record review, some weeks later.

This section summarizes Bayer's review of the preliminary analysis conducted by i3 Drug Safety as described in i3 Drug Safety's preliminary report dated 13 Sep 2006 (Preliminary Report)(8) and provides an initial review of the revised analysis conducted by i3 Drug Safety as described in its report of 07 Aug 2007.(229) Suitability of the Premier Database is discussed in Subsection 11.2. Subsection 11.3 provides a summary of Bayer's review of the preliminary analysis. Subsection 11.4 provides Bayer's initial review of the revised analysis described in the report of 07 Aug 2007.

This review is based on the Study Proposal,(247) the Preliminary Report,(8) the report of 07 Aug 2007(229), meetings with i3 Drug Safety,(248) including FDA,(249) and including representatives of the Premier Database,(250) and written communications from i3 Drug Safety.(253-255, 258-264) Bayer has also had an opportunity to review the analytic data set corresponding to the analysis in the Preliminary Report and the corresponding raw data, which was received from i3 Drug Safety in March 2007. As of the time of submitting this briefing document (09 Aug 2007) Bayer has not yet received the analytic dataset corresponding to the revised analysis described in the report of 07 Aug 2007(229).

Based on information gathered as a result of the efforts and analysis the company has taken over the nearly 11 months that have passed since receiving the Preliminary Report, Bayer believes that limitations of the Premier Database render it unsuitable as a vehicle for addressing the comparative safety of hemostatic agents in the complex clinical setting of CABG surgery. These limitations are the absence of medical history or clinical diagnoses at baseline (other than the admission diagnosis giving the reason for admission), the absence of laboratory data and the absence of timing of clinical diagnoses that emerge during the course of hospitalization. It will be shown that because of these limitations key covariates (risk factors) are missing from the analysis; relevant covariates are misclassified, outcomes cannot be identified as treatment-emergent, and it is impossible to ascertain reliably non-fatal outcomes that emerge on the day of surgery. The limitations of administrative data in outcomes research related to CABG surgery have been highlighted by others.(224-227)

11.2 Suitability of the database

11.2.1 Data source and quality

Data were drawn from the Premier Perspective Comparative Database, an administrative claims database and incorporated three years of Premier data starting 01 Apr 2003.(8) Despite the use of the Premier database by the Centers for Medicare and Medicaid Services Hospital Quality Incentive Demonstration Project, the FDA, and a variety of pharmaceutical manufacturers and research organizations, this database has limitations that render it unsuitable as a vehicle for addressing the comparative safety of hemostatic agents in the complex clinical setting of CABG surgery. These limitations include the absence of any medical history or clinical diagnoses at hospital admission (other than the admission diagnosis giving the reason for admission), no recording of laboratory data, and no recording of clinical diagnoses that emerge during the course of hospitalization (other than the primary and secondary diagnoses recorded at the end of hospitalization). There is no standardized requirement for the extent of data that hospitals provide for fields such as *secondary diagnoses* that are not “required fields.” Consequently, there is

variability across contributing hospitals with respect to the number of "secondary diagnoses" at discharge.(250) (Figure 11-1)

Further, there is no standardized mechanism (other than edit checks for internal consistency) for ensuring that data entered into the Premier Database by participating hospitals are an accurate reflection of clinical data recorded in the hospital medical record. This is the responsibility of the contributing hospitals.(250)

Figure 11-1 Average Number of Discharge Diagnoses Per Hospital Among 137 Contributing Hospitals with More Than 50 CABG Procedures During the Study Period (Preliminary Analysis)

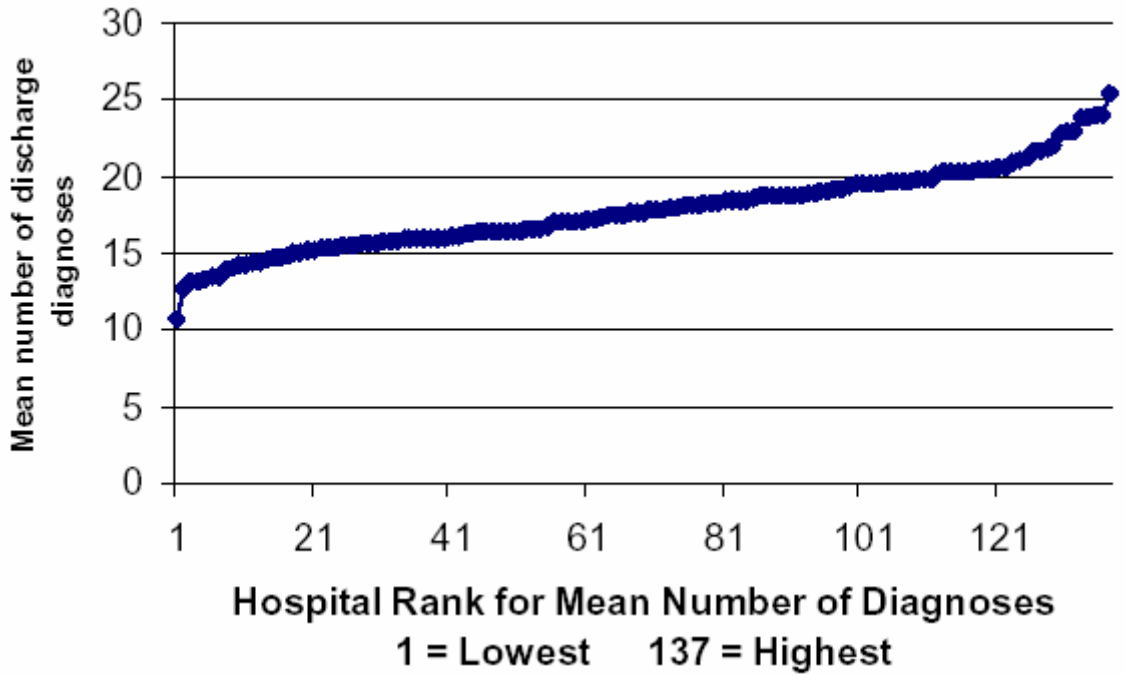


Figure adapted from i3 Drug Safety(264)

The analytic dataset corresponding to i3 Drug Safety's preliminary analysis described in the Preliminary Report comprised patients (N = 66,435) who underwent CABG surgery and who received intravenous (IV) antifibrinolytic therapy (aprotinin, aminocaproic acid, or tranexamic acid) on the day of index

surgery, for hospitalizations that began during the study-period and for which drugs and procedures were "date-stamped". (For all hospitalizations on or after 01 Apr 2003, drugs and procedures were date-stamped. Some hospitals initiated this convention earlier.) Patients were considered eligible if they received at least two million units aprotinin (i.e. two vials), at least 10 g of aminocaproic acid (i.e. two vials), or at least 1 g of tranexamic acid (i.e. one full vial). The analytic dataset corresponding to i3 Drug Safety's revised analysis described in the report dated 07 Aug 2007 (N = 78,199) included only patients within the same time period who received aprotinin or aminocaproic acid on the day of index surgery.(229) Eligible patients had exposure coded along with covariates and outcomes based on administrative records in the Premier raw dataset. Eligible patients were reportedly drawn from all Premier affiliated hospitals across the United States where CABGs were performed.(264). Patients with additional surgical procedures at the time of CABG were not excluded.

11.2.2 Availability of key covariates

Many of the key risk factors for mortality and morbidity following CABG surgery are not available in the Premier Database. A majority of the independent risk factors comprising the Society for Thoracic Surgeons (STS) validated risk models for mortality and morbidity in isolated CABG surgery(14) are not available. These include cardiovascular re-operation beyond the first re-operation, time interval <6 hours since previous cardiac intervention, cardiogenic shock at the time of surgery, NYHA classification, triple vessel disease, left main coronary artery disease, ejection fraction, presence of aortic stenosis, presence of mitral insufficiency, urgent versus elective surgery, and body surface area(14) (Table 11-1). Other independent risk factors that are nominally available such as cardiac re-operation, heart failure, hypertension, and diabetes cannot be definitively determined from data in the Premier Database. (Table 11-1).

Table 11-1: Risk Factors in the Society for Thoracic Surgeons (STS) Validated Risk Models[a] for CABG-Only Surgery(14) Compared With Risk Factors Included in Analyses and Whether Available in the Premier Database

STS Variable	STS Definition	i3 Definition	Generally Available in the Premier Database	STS Mortality Odds Ratio (95% CI)	STS Renal Failure Odds Ratio (95% CI)
Age (years)	Age (years)	Age (years)	Yes	1.05 (1.05, 1.05)	1.05 (1.05, 1.06)
Aortic stenosis	By history of catheterization result	Not included	No	1.40 (1.21, 1.61)	1.27 (1.11, 1.46)
Black	By history	By history	Yes	1.34 (1.23, 1.45)	1.41 (1.31, 1.52)
Body surface area[b]	From height and weight	Not included	No	0.91 (0.89, 0.93)	1.04 (1.02, 1.05)
Congestive heart failure	By physician history	By medications	Surrogate only[c]		1.18 (1.11, 1.25)
Chronic lung disease	By physician history	By secondary discharge diagnosis	Variable[d]	1.41 (1.35, 1.48)	1.31 (1.26, 1.37)
Cerebrovascular accident	By physician history	By secondary discharge diagnosis	Variable[d]	1.10 (1.04, 1.17)	
Diabetes, oral treatment	(Diabetes control prior to hospitalization); By physician history	By secondary discharge diagnosis or anti-diabetic therapy	Variable[d]	1.15 (1.09, 1.21)	1.35 (1.29, 1.42)
Ejection fraction <50%	By physician history based on determination	Not included	No	0.98 (0.98, 0.98)	0.99 (0.99, 0.99)
First re-operation	By physician history	By charge code	Frequently misclassified[e]	2.76 (2.62, 2.91)	1.55 (1.46, 1.64)
Hispanic	By history	Race “other” by history	No	1.04 (0.92, 1.17)	1.11 (1.00, 1.24)
Hypercholesterolemia	By physician history	Not included	Variable[d]	0.82 (0.79, 0.86)	

Table 11-1: Risk Factors in the Society for Thoracic Surgeons (STS) Validated Risk Models[a] for CABG-Only Surgery(14) Compared With Risk Factors Included in Analyses and Whether Available in the Premier Database

STS Variable	STS Definition	i3 Definition	Generally Available in the Premier Database	STS Mortality Odds Ratio (95% CI)	STS Renal Failure Odds Ratio (95% CI)
	based on lab determination				
Hypertension	By physician history based on measurement or active treatment	By secondary discharge diagnosis	Variable[d]	1.12 (1.08, 1.17)	1.45 (1.39, 1.51)
Intra-aortic balloon pump	(At the time of surgery) By physician history	Not included	Yes (may be available by charge code)	1.46 (1.37, 1.55)	1.54 (1.45, 1.64)
Immunosuppresive therapy	Prior to surgery - By physician history	Not included	Yes (may be available by charge code)	1.75 (1.57, 1.95)	1.48 (1.33, 1.64)
Insulin-dependent diabetes (DM)	(Diabetes control prior to hospitalization); By physician history	Charge codes for insulin not specific for DM	No	1.50 (1.42, 1.58)	2.26 (2.16, 2.37)
Left main artery ≤50% stenosis	By physician history based on catheterization	Not included	No	1.18 (1.14, 1.24)	1.06 (1.02, 1.10)
Male	By history	By history	Yes	0.84 (0.80, 0.89)	1.06 (1.00, 1.12)
Mitral insufficiency	Physician history based on catheterization	Not included	No	1.22 (1.17, 1.28)	1.29 (1.24, 1.35)
Mutiple re-operations	Physician history	Not included	No	4.19 (3.61, 4.86)	1.60 (1.33, 1.92)
NYHA functional class IV level	Physician history	Not included	No	1.15 (1.10, 1.20)	1.16 (1.11, 1.20)

Table 11-1: Risk Factors in the Society for Thoracic Surgeons (STS) Validated Risk Models[a] for CABG-Only Surgery(14) Compared With Risk Factors Included in Analyses and Whether Available in the Premier Database

STS Variable	STS Definition	i3 Definition	Generally Available in the Premier Database	STS Mortality Odds Ratio (95% CI)	STS Renal Failure Odds Ratio (95% CI)
Other race	By history	By history	Yes	1.12 (1.01, 1.25)	1.22 (1.11, 1.35)
Prior myocardial infarction	By physician history	By secondary discharge diagnosis	Variable[d]	1.18 (1.16, 1.21)	1.10 (1.08, 1.12)
PTCA <6h	By physician history	Not included	No	1.32 (1.18, 1.48)	1.46 (1.29, 1.66)
PVD/CVD	By physician history	By secondary discharge diagnosis	Variable[d]	1.29 (1.25, 1.34)	1.30 (1.27, 1.34)
Renal failure/dialysis	By physician history	Charge code for hemodialysis or filtration	Variable[d]	1.88 (1.80, 1.96)	4.30 (4.09, 4.52)
Shock	(At the time of surgery); By physician history	Not included	No	2.04 (1.90, 2.19)	1.60 (1.48, 1.72)
Smoker	(Present smoker); By physician history	By secondary discharge diagnosis	Variable[d]		1.05 (1.03, 1.08)
Status (emergent vs elective surgery)	(Emergency vs. elective surgery); By physician history	Not included[f]	No	1.96 (1.88, 2.05)	1.38 (1.31, 1.45)
Triple vessel disease	By physician history based on catheterization	Number of vessels bypassed at surgery included	No	1.21 (1.17, 1.26)	1.19 (1.14, 1.23)

a Risk factors for outcomes mortality, renal failure, stroke, prolonged mechanical ventilation, deep sternal infection, and re-operation.(14)
b Odds ratio is based on a 0.1 unit change in body surface area (BSA).
c Operational definition(255, 260) } is based on medication and/or procedure proxies and may not correctly reflect the clinical diagnosis.
d Secondary discharge diagnosis codes are variably recorded in the Premier Database and may not correctly reflect the risk factor.

Table 11-1: Risk Factors in the Society for Thoracic Surgeons (STS) Validated Risk Models[a] for CABG-Only Surgery(14) Compared With Risk Factors Included in Analyses and Whether Available in the Premier Database

STS Variable	STS Definition	i3 Definition	Generally Available in the Premier Database	STS Mortality Odds Ratio (95% CI)	STS Renal Failure Odds Ratio (95% CI)

e Re-do surgery is frequently misclassified as first-time surgery in the Premier Database. (Subsection 11.3.2)

f The i3 Drug Safety covariate *emergency admission* corresponds to admission from the emergency room and does not refer to emergency vs elective CABG surgery.

Studies have consistently demonstrated that many of the key risk factors for adverse outcomes are more commonly present in patients treated with aprotinin as compared with other agents or no therapy.(2, 3, 10, 12)

Because multiple key risk factors are not available or not reliably recorded in the database, it is impossible to adjust for the missing risk factors in the analysis, impossible to establish comparability of the treatment groups, and impossible to determine whether the treatment groups are sufficiently similar to permit any statistical comparison.(219) This is a major limitation of the Premier Database for the investigation of hemostatic therapy in the complex clinical setting of CABG surgery. Importantly, medical record review, even broad-based with proper sampling methods, cannot address this problem as it would be necessary to extract the missing covariates from thousands of medical records.

11.2.3 Outcome measures

The outcome definitions used by i3 Drug Safety in their preliminary analysis (Preliminary Report) are shown in Table 11-2.

Table 11-2: Definition of Outcome Events in the Preliminary Analysis[a]

Outcome Event	Definition
Acute coronary revascularization	ICD procedure codes for thrombolysis, PTCA, or redo CABG
Stroke	ICD codes for the diagnosis of stroke OR ischemic stroke OR charge codes for stroke diagnostics/therapeutics
Acute heart failure	ICD procedure codes for left ventricular assist device OR codes for use of dobutamine
Acute renal failure	ICD procedure codes relating to hemo- or peritoneal dialysis OR Premier-specific charge codes for dialysis or hemofiltration
Death	Death

a From Preliminary Report(8) and Table of outcome definitions provided by i3 Drug Safety(258) and the Implementation Document for the preliminary analysis.(260)

Table 11-2 shows that definitions for all outcomes in the preliminary analysis(8) (other than death) were based on medication and procedure proxies and/or the secondary discharge diagnosis codes recorded in the Premier Database. Note that absence in the database of medication and procedure proxies for these outcomes prior to treatment does not prove that the condition was absent. Thus, it is impossible to verify (for outcomes other than death) that any of these outcomes are treatment-emergent. Further, because the timing of events other than death on the day of surgery (whether before or after treatment) cannot be determined in the Premier Database, it is impossible to distinguish for certain whether events on the day of surgery are outcomes or pre-existing conditions.(253) FDA, recognizing this limitation, requested in October 2006 that i3 Drug Safety provide a listing of outcomes on the day of surgery by treatment group.(252).

The revised protocol and revised analysis by i3 Drug Safety limited the studied outcomes to renal failure requiring dialysis and in-hospital mortality.(255) The outcome *renal failure requiring dialysis* was defined by the presence of charge codes for dialysis/hemofiltration with follow-up beginning *the day after surgery*. Since hemofiltration is frequently used in the setting of CABG surgery for fluid removal, this definition is not specific for renal failure. Also this definition cannot be relied upon to identify specifically treatment-emergent dialysis and cannot determine the outcome for patients who require new dialysis on the day of surgery.

11.2.4 Availability of test treatment and dose

Hemostatic treatment is available in the database with dose estimated based on the medication charge (e.g., number of vials charged). When multiple hemostatic agents were given, the order of the treatment is unavailable in the Premier database.

Patient enrollment in the preliminary analysis and the revised analysis is described in Figure 11-2 and Figure 11-3.

Figure 11-2: Patient Enrollment (April 2003 – March 2006) in the Preliminary Analysis by i3 Drug Safety Study [Figure Adapted From the Preliminary Report(8)]

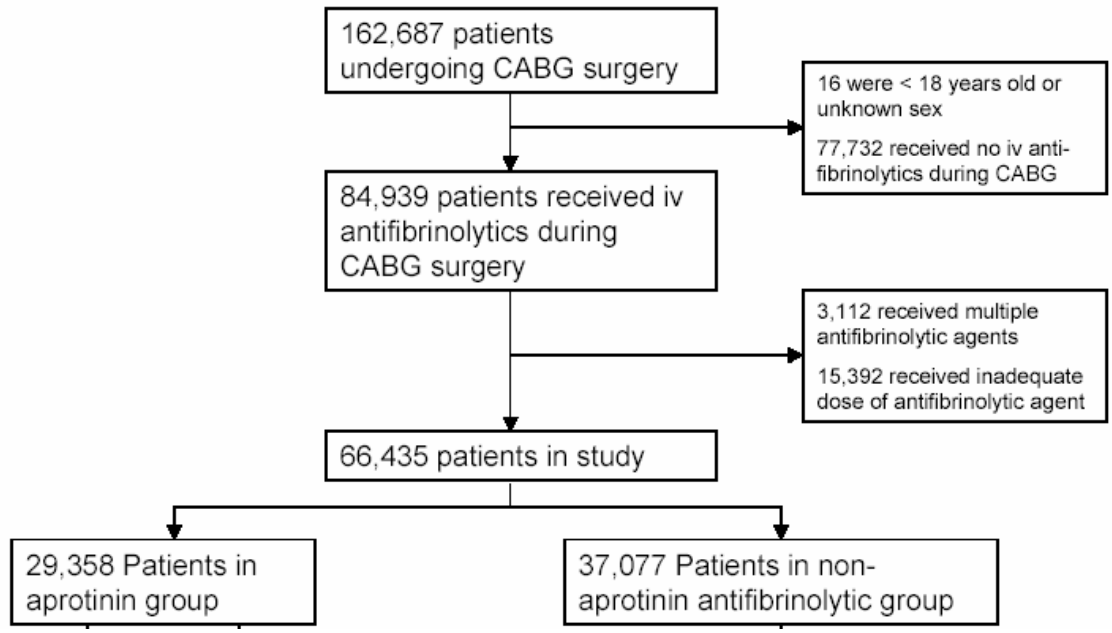
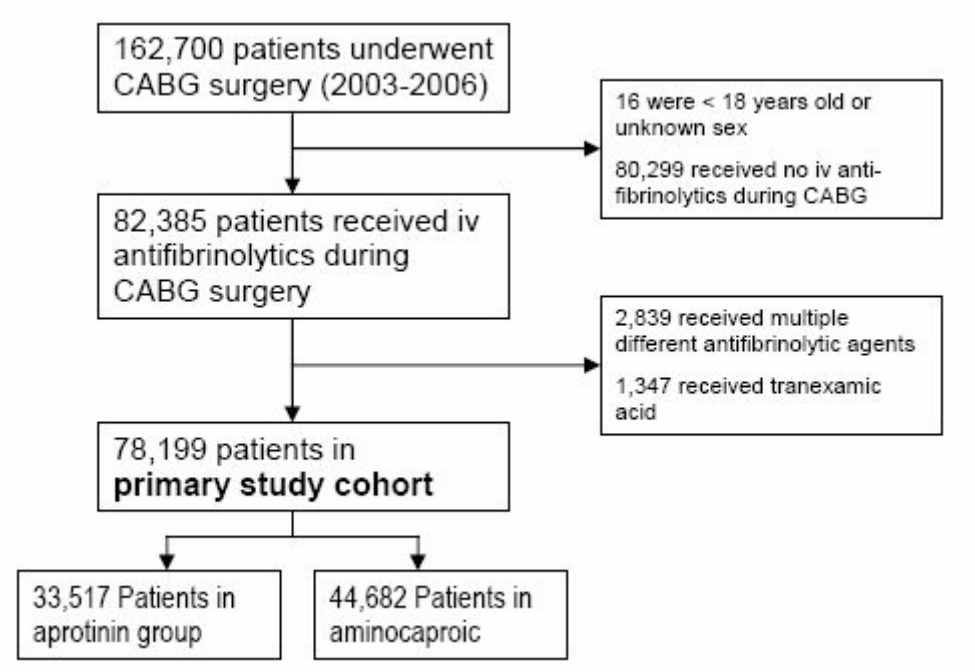


Figure 11-3: Patient Enrollment (April 2003 – March 2006) in the Revised Analysis by i3 Drug Safety Study (Figure Adapted From the Final Report of 07 Aug 2007)(229)



11.2.5 Confounding of test treatment and center

The 66,435 patients comprising the data set used in the i3 Drug Safety preliminary analysis(8) were drawn from 204 Premier hospitals that perform CABG surgery. Though patient enrollment by treatment and center is not reported, Table 1a in the Preliminary Report(8) indicates that there were statistically significant differences in the choice of hemostatic agents across geographical regions.(8) (Table 11-3)

Table 11-3: Imbalances in Geographic Region Between Treatments. (Adapted From Table 1a, Page 16 of the Preliminary Report(8)

	Treatment Cohort			
	Aprotinin (N = 29,358)		Aminocaproic and Tranexamic Acid (N = 37,077)	
	N	%	N	%
Midwest	4,873	16.6	7,364	19.9
Northeast	2,526	8.6	4,415	11.9
South	18,170	61.9	20,403	55
West	3,789	12.9	4,895	13.2

The comparison between the aprotinin cohort and the control cohort was statistically significant, $p < 0.0001$. P value calculated by Bayer.

Further, the Preliminary Report indicates that the use of aprotinin in this population varied from 0 to 100% across contributing hospitals.(8) In approximately 25 of the 204 participating hospitals the choice of hemostatic treatment was never aprotinin, whereas in approximately 25 other participating hospitals, the choice was always aprotinin. Confounding of treatment and hospital can create difficulties in separating the effect of hospital from the effect of treatment on the outcomes. This must be taken into account in the statistical analysis.

11.2.6 Confounding of test treatment and surgeon

Figure 3a of the Preliminary Report(8) indicates that among 1,510 contributing surgeons (all of whom used hemostatic agents), approximately 550 used no aprotinin, while approximately 360 surgeons used only aprotinin.(8) Thus, among the 1,510 surgeons, 910 surgeons (approximately 60% of the surgeons) used one or the other treatment exclusively. Confounding of treatment and surgeon can create

difficulties in separating the effect of surgeon from the effect of treatment on the outcomes. This must be taken into account in the statistical analysis.

11.2.7 Confounding of clinical practices and center

Clinical practices associated with outcome such as use of heparin, aspirin, and transfusion policies were not standardized across participating centers. The potential for confounding of clinical practices with center is another limitation of this multicenter database for the study of the effects of hemostatic treatment. This is a serious limitation given the evidence that center is also confounded with the test treatment.

11.2.8 Investigation of baseline comparability

11.2.8.1 Dataset used in the Preliminary Analysis

It is noted in Subsection 11.2.2 that many baseline characteristics (covariates) known to be associated with the choice of aprotinin treatment vs other agents(2, 3, 10, 12) and known to be predictive of the studied outcomes are not included among the covariates in the analyses because they are not available in the Premier database. Nevertheless, there were statistically significant imbalances between the aprotinin and control cohorts even among the clinical baseline characteristics reported in the 66, 435 patients in the preliminary analysis as shown in Table 11-4. Among these are the statistically significant higher prevalence in the aprotinin cohort of known risk factors(14) such as redo CABG surgery, additional surgery, age 65 or greater, old stroke, old MI, smoking, and female gender (lower prevalence of male gender) as compared with the control cohort. These data indicate that patients at higher risk for adverse outcomes, including mortality, were given aprotinin in preference to the control agents (aminocaproic acid and tranexamic acid).

Table 11-4: Imbalances in Patient Baseline Characteristics. Adapted From Table 1a, Page 16 of the Preliminary Report.(8)

	Aprotinin Cohort (N = 29,358)		Aminocaproic and Tranexamic Acid Cohort (N = 37,077)[c]		Odds Ratio[a]	P value[b]
	N	%	N	%		
Age ≥65	17,446	59.4	20,170	54.4	1.23	≤0.0001
Male	20,772	70.8	26,497	71.5	0.97	≤0.0001
Smoking	5,334	18.2	6,391	17.2	1.07	0.0018
Emergency admission	14,722	50.2	19,577	52.8	0.90	≤0.0001
Low income status	1,035	3.5	1,572	4.2	0.83	≤0.0001
Marital status (with partner)	18,275	62.3	23,316	62.9	0.97	≤0.0001
Re-do cardiac surgery	1,275	4.3	602	1.6	2.75	≤0.0001
Additional cardiac surgery	7,694	26.2	7,176	19.4	1.48	≤0.0001
Pre-existing percutaneous coronary procedures	3,920	13.4	4,715	12.7	1.06	0.0155
Cardiac arrest	550	1.9	551	1.5	1.27	≤0.0001
Diabetes	20,679	70.4	26,180	70.6	1.00	0.6282
Hypertension	19,022	64.8	24,356	65.7	0.99	0.0159
Liver disease	417	1.4	355	1.0	1.48	≤0.0001
COPD, asthma	7,122	24.3	9,228	24.9	0.97	0.0614
Cancer	2,699	9.2	3,062	8.3	1.11	≤0.0001
Old MI	4,371	14.9	5,078	13.7	1.09	≤0.0001
Old Stroke	1,526	5.2	1,619	4.4	1.20	≤0.0001

a Odds ratio for aprotinin vs other treatment.
b P values are for the comparison between the aprotinin and the control cohort. P values calculated by Bayer.
c The majority of the control cohort in the preliminary analysis were treated with aminocaproic acid (N = 35,719).(8)

11.2.8.2 Dataset used in the Revised Analysis

Table 11-5 indicates that there were statistically significant imbalances between the aprotinin and aminocaproic acid cohorts within the 78,199 patients in the primary study cohort. Among these are the statistically significant higher prevalence in the aprotinin cohort of known risk factors(14) such as redo CABG surgery, additional surgery, old stroke, old MI, and peripheral artery disease, as compared with the aminocaproic acid cohort. These findings are consistent with other reports(2, 3, 10, 12) and indicate that patients at higher risk for adverse outcomes, including mortality, were given aprotinin in preference to aminocaproic acid.

Table 11-5: Imbalances in Patient Baseline Characteristics. Adapted From Table 1 of the Report of 07 Aug 2007(229)

	Aprotinin Cohort (N = 33,517)		Aminocaproic and (N = 44,682)		Odds Ratio[a]	P value[b]
	N	%	N	%		
Age ≥65	19,824	59.1	24,607	55.	1.18	<0.0001
Male	23,637	70.5	31,906	71.4	0.96	0.00698
Emergency admission	16,540	49.4	23,721	53.1	0.86	<0.0001
Low income status	1,211	3.6	1,979	4.4	0.81	<0.0001
Marital status (with partner)	21,008	62.7	28,384	63.5	0.96	0.02
Re-do cardiac surgery	1,347	4.0	744	1.7	2.47	<0.0001
Additional cardiac surgery	8,516	25.4	8,197	18.4	1.52	<0.0001
Complex CABG procedure	21,562	64.3	28,084	62.9	1.07	<0.0001
Pre-existing percutaneous coronary procedures	4,448	13.3	5,677	12.7	1.05	0.02
Diabetes	14,565	43.5	19,275	43.1	1.01	0.38
Hypertension	21,835	65.2	29,369	65.7	0.97	0.09
Liver disease	474	1.4	422	0.9	1.50	<0.0001
COPD, asthma	7,976	23.8	10,992	24.6	0.96	0.01
Cancer	3,064	9.1	3,785	8.5	1.09	0.001
Old MI	5,051	15.1	6,278	14.1	1.09	<0.0001
Old Stroke	1,758	5.3	1,945	4.4	1.22	<0.0001
Endocarditis	171	0.5	83	0.2	2.76	<0.0001
Peripheral artery disease	3,257	9.7	3,840	8.6	1.14	<0.0001
Chronic kidney disease	714	2.1	622	1.4	1.54	<0.0001
Hemostatic disorder	124	0.4	111	0.3	1.49	0.002
Renal failure requiring dialysis	570	1.7	469	1.1	1.63	<0.0001

a Odds ratio for aprotinin vs aminocaproic acid.
b P values are for the comparison between the aprotinin and the control cohort. Odds ratios calculated by Bayer.

11.3 Summary of Bayer's review of the Preliminary Report

11.3.1 Bayer's findings from review of the database

Bayer has had an opportunity to review the raw data and the analytic database that form the basis of the preliminary analysis. Review of the analytic database together with the raw data raises to date concerns with the preliminary analysis:

1. Sixty-one records in the analytic database correspond to a second admission of the same individual to the same hospital (though treated in the analysis as independent patients). In this sample of patients with *known* re-operation, the known re-operation appeared in the Premier Database (raw data) at the second admission as primary (first-time) surgery in over half the cases. This

observation raises the serious concern that re-operation, a key risk factor for adverse outcomes, is broadly misclassified in the Premier database. Other covariates, i.e., surrogates for chronic conditions not expected to change with time such as hypertension, diabetes, COPD, old MI, were inconsistently classified between the two admissions.

2. Outcomes identifiable as not treatment emergent were included in the analytic database in the preliminary analysis. Over 600 subjects with the reported outcome *renal failure* met the definition for *renal failure* before surgery.

3. Over one hundred subjects in the analytic database, assigned to the aprotinin group, had evidence of other anti-fibrinolytics (oral) on the day of surgery; hundreds more received another anti-fibrinolytic (other than the assigned treatment category) over the course of hospitalization.

11.3.2 Bayer's findings from review of the preliminary analysis

In addition to Bayer's concerns about the suitability of the selected database, Bayer identified significant issues with the study design and analysis:

1. The propensity score model did not model the treatment decision at the treatment decision point, in this case, at the level of the surgical team or at the level of the hospital (assuming surgical teams with similar decision criteria).(221, 222) Because of the profound differences in choice of treatment across hospitals and surgeons (Subsections 11.2.5 and 11.2.6), it is apparent that the criteria determining treatment decision are not uniform across the contributing centers. Use of a single "overall" propensity model across multiple centers and surgeons cannot estimate treatment effect when criteria for treatment choice vary across centers and surgeons.(229)

2. Displays of covariate balance within decile of estimated propensity score(261) demonstrated that adequate balance of covariates was not achieved by propensity score methods.

3. The estimated propensity score was used as an indicator variable in regression models of the outcome and not used in accordance with the principle of propensity score methods to create subgroups or to match patients.

4. In the presence of imbalances of baseline characteristics, analysis by regression alone is unreliable. Analysis without application of propensity technology through matching and/or subclassification cannot be expected to give reliable results.(217-219)

5. The authors' regression models for the studied outcomes were inconsistent with validated CABG risk models based on clinical databases.

11.4 Revised analysis

The authors' revised analysis differs from the preliminary analysis in that:

- Aprotinin treatment is compared with aminocaproic acid treatment. Patients receiving tranexamic acid are excluded.(229)

- Patients excluded in the preliminary analysis because of inadequate dose are now included in the primary study cohort.

- The studied outcomes are limited to in-hospital renal failure requiring dialysis and in-hospital death.(229)

- The renal failure outcome analysis now excludes patients with pre-existing chronic kidney disease, as evidenced by a discharge diagnosis for chronic kidney disease(229) however, patients with renal failure requiring dialysis prior to CABG are not excluded from the renal failure analysis.

- The authors provide additional secondary analyses as described below. (The primary analysis, similar to the preliminary analysis, is by multivariable logistic regression including all patients.)

11.4.1 Secondary analysis using propensity matching in the "Data-Dense" study population

A second study population was derived by applying multiple restrictions selected to isolate patients with clearer exposure histories and fuller characterization of baseline health, patients who moreover had the surgery performed by surgeons known to have performed numerous CABG surgeries and surgeons who demonstrated a willingness to use either study drug.(229)

This "data-dense" study cohort was derived by eliminating from the primary study cohort: 1. patients who had surgery before the third hospital day; 2. patients who received less than 2 million units aprotinin or fewer than 2 vials; 3. patients who received less than 10 g of aminocaproic acid; 4. patients treated by surgeons who performed fewer than 50 CABG procedures during the study period; and 5. patients treated by surgeons who always used the same antifibrinolytic agent. (Figure 11-3)

A "data-dense" study cohort was derived by eliminating from the primary study cohort: 1. patients who had surgery before the third hospital day; 2. patients who received less than 2 million units aprotinin or fewer than 2 vials; 3. patients who received less than 10 g of aminocaproic acid 4. patients treated by surgeons who performed fewer than 50 CABG procedures during the study period; and 5. patients treated by surgeons who always used the same antifbrinolytic agent. (Figure 11-3)

Propensity score was estimated in the data-dense population N = 13,345 patients (6,387 treated with aprotinin group and 6,958 patients treated with aminocaproic acid) using 51 covariates. Aprotinin patients were then matched to aminocaproic acid patients using a "greedy" matching algorithm, that matched 4,799 aprotinin patients to aminocaproic acid patients with the closest propensity score. This analytic approach is discussed in Subsection 11.4.3.

11.4.2 Instrumental variable analysis

As another secondary analysis, the authors did an instrumental variable analysis to possibly address unmeasured patient characteristics using surgeons with strong

preference for or against aprotinin as the instrument. The population selected was the 3,643 patients who were otherwise qualified for the "data-dense" cohort with the exception that they were treated by surgeons where 100% of their patients received either aprotinin or aminocaproic exclusively. Outcomes were compared using regression with adjustment for all measured covariates. In a second analysis, surgeons who prescribed aprotinin to 90% or more of their patients were classified as aprotinin-preferring, and surgeons who prescribed aprotinin to 10% or fewer as aprotinin-avoiding. Two-stage linear regression was used to calculate risk difference estimates with full covariate adjustment. This analytic approach is discussed in Subsection 11.4.3.

11.4.3 Method for dealing with lack of baseline comparability (channeling bias)

Table 11-5 indicates that there were statistically significant imbalances between the aprotinin and aminocaproic acid cohorts within the 78,199 patients in the primary study cohort. Among these are the statistically significant higher prevalence in the aprotinin cohort of known risk factors(14) such as redo CABG surgery, additional surgery, old stroke, old MI, and peripheral artery disease, as compared with the aminocaproic acid cohort. These findings are consistent with other reports(2, 3, 10, 12) and indicate that patients at higher risk for adverse outcomes, including mortality, were given aprotinin in preference to aminocaproic acid.

Section 8 of this briefing document emphasizes that the statistical methods in observational studies need first to be judged based on their performance in creating a balance on background characteristics between treated and control groups.(217) The authors attempt to use propensity score methods to create balance. However, the propensity score model does not model the treatment decision at the treatment decision point, in this case, at the level of the surgeon or at the level of the hospital (assuming surgical teams with similar decision criteria).(221, 222) Because of the profound differences in choice of treatment across the medium-and-high volume surgeons as illustrated in the authors' Figure 4 of the final report (even excluding those who use a single treatment exclusively), it is apparent that the criteria

determining treatment decision are not uniform across the contributing surgeons. In this case the propensity model may produce balance of covariates for subgroups of the population *overall*, as suggested in the authors Table 1, but the model will not account for different types of channeling bias within surgeons. Further, it would be expected that *within surgeon,* the covariates for matched pairs with similar propensity scores, as developed by the authors, are *not* balanced between treatments.

The authors also attempt to create balance using an instrumental variable analysis. Instrumental variable analysis has been used in variety of applications including measurement of drug effectiveness.(265-268) An instrumental variable is a factor that is related to treatment, but unrelated to observed and unobserved patient risk factors and also unrelated to the outcome, other than through its relationship to treatment.(269) In the authors' analysis, physician preference for use of aprotinin is the instrument, and the concept is that physician preference is largely independent of patient characteristics. A basic underlying assumption of the method is that the instrument must not be correlated with patient risk factors. This can be tested for the observed risk factors.

The authors' Table 1 indicates significant imbalances between the cohorts treated by the aprotinin-preferring surgeons as compared with the aminocaproic acid preferring surgeons, e.g. ethnicity, smoking, number of vessels at surgery, hospital size, and rural vs teaching hospital. In several instances, these imbalances are greater than for the primary study population. These observations suggest that the inherent assumptions of the instrumental variable analysis are not well met, and the instrumental variable analysis does not offer any benefit in reducing bias from known or unknown confounders.

11.4.4 Dose-dependency

The authors refer to "dose-dependency of the present findings;"(229) however, the authors' Table 3 does not demonstate statistically significant differences among the doses of aprotinin for either outcome. Further, the authors do not report any display of balance of baseline characterstics between the dose groups compared.

11.4.5 Method of dealing with confounding of test treatment and surgeon

The confounding between test treatment and surgeon requires appropriate attention in the analysis. The authors' supplementary regression analysis conditioning on surgeon is not sufficient because it assumes that the relationship between outcome and covariates is identical for all surgeons.

11.4.6 Claims based on the c-score

The authors state that they "assessed the quality of our covariate assessment by computing the covariates' predictive ability for both study outcomes independent of antifibrinolytic drug use category. The prediction of all-cause in-hospital death and renal failure in our multivariable models is as good as or better than that of widely accepted risk prediction models for patients with CABG surgery," citing the validated risk models based on clinical databases (the authors' Table 4) (229). This argument is misleading because it relies on the false implication that the authors' calculated c-score >0.79 for their all cause in-hospital mortality regression model is a measure of its *predictive* power. In fact, there are no data to suggest that the authors did anything to assess the *predictive* power of their all-cause mortality model because no test of predictive power (e.g., assessment of c-score using an independent validation data set) is reported. Furthermore, given the fact that the authors' regression models assert that *hypertension, old MI, and cancer* confer a statistically significant benefit for mortality and for renal failure[3] as shown in Table 3 of their report,(229) it is unlikely that the authors' regression model would demonstrate any useful predictive power if it were applied to an independent data set.

In fact, Shahian has observed that "[a]s a consequence of failing to differentiate complications from comorbidities, the performance of risk models based on administrative data may be exaggerated. This results from including predictors in the risk model that are actually late-hospitalization, preterminal events and thus highly predictive of subsequent mortality."(224) Shahian has also noted that in

[3] .For example, for *hypertension* the odds ratio was 0.47; 95% CI 0.43 -0.51 for mortality, and 0.15; 95% CI 0.13-0.16 for renal failure requiring dialysis.

complex hospitalizations there is a tendency in administrative data to undercode chronic or asymptomatic comorbidites with the result that these may be paradoxically protective.(224) Such undercoding may explain the authors' paradoxical findings for hypertension, but the observed undercoding raises doubts as to the validity of all of the chronic disease covariates obtained from this administrative database.

11.4.7 Sensitivity analysis

The authors provide a sensitivity analysis to "explore how strong an unmeasured confounder would have to be" to explain their findings and state their belief that there is "no plausible candidate for such a confounder." The sensitivity analysis is flawed by the inherent assumption that it characterizes the prevalence and association of a *single* unmeasured confounder. This sensitivity analysis would be reasonable in a situation where balance between treatment groups was demonstrated on all of the known confounders, but it is inappropriate in the present setting where *multiple* baseline risk factors known to affect the studied outcomes (in-hospital death and renal failure requiring dialysis) are demonstrably missing from the analysis.

11.5 Summary

11.5.1 Database selection

The administrative claims database selected for this study is unsuitable as a vehicle for addressing the comparative safety of hemostatic agents in the complex clinical setting of CABG surgery. Limitations are the absence of any recorded medical history or clinical diagnoses at baseline (other than the admission diagnosis giving the reason for admission), the absence of recorded laboratory data, and the absence of timing of clinical diagnoses that emerge during the course of hospitalization. As a consequence key covariates are missing from the design and analysis; relevant covariates included in the analysis are misclassified, outcomes cannot be identified as treatment-emergent, and it is impossible to ascertain non-fatal outcomes on the day of surgery.

This conclusion is consistent with the conclusion of others, who have highlighted the limitations of administrative data in outcomes research related to CABG surgery.(224-227) noting that much of the predictive value of surgical risk models is derived from a limited number of critical clinical variables not typically included in administrative databases.(224) Other problems with the use of administrative databases to investigate outcomes in CABG surgery include misclassification of covariates, misclassification of outcomes, and difficulty distinguishing pre-existing conditions from outcomes(224) as observed in this study.

Characteristics of the data source for this study are summarized in Section 8, Table 8-3.

11.5.2 Statistical analysis

It must first be noted that key risk factors (covariates) known to predict in-hospital mortality and acute renal failure are missing from the analysis. In the absence of comprehensive information for the missing covariates, no method of analysis can compensate for this deficiency.

Additionally, there are a number of flaws in the analysis. Principle among these are:

1. The authors attempt to deal with the statistically significant imbalances in the *observed* baseline risk factors with the use of propensity score methods, but apply propensity score methods inappropriately.(221, 222)

2. Under conditions of imbalance of baseline characteristics, regression models, unless coupled with the correct application of propensity technology through matching and/or subclassification, cannot be expected to give reliable results.(219)

3. Given the substantial and statistically significant differences between the populations by the value of the instrument, the essential assumptions needed for an instrumental variable analysis are not likely to hold.

4. The authors' sensitivity analysis is inappropriate because it seeks to identify a *single* confounder in a setting where *multiple* baseline risk factors known to affect the studied outcomes are demonstrably missing from the analysis.

Elements of the statistical analysis are summarized in Section 8, Table 8-4.

11.6 Conclusion

The Premier administrative claims database selected for this study is unsuitable as a vehicle for addressing the comparative safety of hemostatic agents in the complex clinical setting of CABG surgery. Key covariates are missing, relevant covariates that are available are misclassified, outcomes cannot be identified as treatment-emergent, and it is impossible to ascertain non-fatal outcomes on the day of surgery. This is a fundamental flaw that cannot be addressed by any statistical analysis.

Observational studies are difficult to design and difficult to analyze. This is particularly true of efforts to compare treatment effects of aprotinin with other agents or no hemostatic treatment, given the consistent evidence that aprotinin is typically administered to patients who are perceived to be at higher risk for bleeding and other complications. A proper design and analysis seeks to establish balance for known risk factors, and, ideally for risk factors that are unknown or unmeasured.

12. Overall Conclusions

Based on the Bayer clinical trial data, as well as the literature, aprotinin has been consistently demonstrated to reduce the risk of blood transfusion. 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. Furthermore, full-dose aprotinin use during CABG surgery has been shown to reduce bleeding and the need for transfusion among patients receiving clopidogrel.

Based on the Bayer global clinical trial database, as well as the literature, aprotinin appears to be associated with renal dysfunction. The association of aprotinin therapy with renal failure (requiring dialysis) is not as definitive. 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 0.3% 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. Based on these data, on 15 Dec 2006, the Trasylol US product information was revised.

Hypersensitivity to Trasylol (a bovine product) has been a known risk of the product. Since 28 Aug 1998, the warning section of the Trasylol US product information has included a box warning for the increased risk of hypersensitivity

and anaphylactic reactions upon re-exposure to aprotinin. In May 2006, Bayer initiated an ongoing risk minimization plan for hypersensitivity. On 15 Dec 2006, the Trasylol US product information was revised to include a contraindication for administering Trasylol to any patient with known or suspected prior exposure to Trasylol or aprotinin-containing products within the previous 12 months. The revisions also provided additional information on the management and prevention of anaphylactic reactions, including the administration of Trasylol only in the operative setting where cardiopulmonary bypass could be rapidly initiated. Furthermore, Bayer decided not to pursue an indication or development of aprotinin in non-cardiac indications.

Data from the Bayer global clinical database, as well as the meta-analysis of randomized controlled trials, do not indicate a mortality risk associated with aprotinin. As addressed in this briefing document, based on the limitations of the observational studies (i3 Drug Safety, Mangano 2007), Bayer believes that the reported conclusions are neither valid nor reliable and should not serve as a basis for affecting the use of aprotinin in clinical practice.

A non-Bayer sponsored randomized, controlled trial is ongoing in Canada titled "Blood Conservation Using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population" (BART).(270) This study is a randomized, multicenter, controlled trial of 2,970 high-risk cardiac surgery patients. Surgical procedures include re-operation for CABG or aortic valve replacement, combined CABG/valve procedures, or multiple valve procedures. Treatment arms include full-dose aprotinin, tranexamic acid, and epsilon aminocaproic acid. The primary endpoint is massive post-operative bleeding. Secondary endpoints include 30-day all-cause mortality, myocardial infarction, stroke, renal failure, prolonged ventilation, and prolonged low cardiac output.(270) The study remains ongoing (and is expected to end in March 2008).(270) This study should provide important additional safety data on aprotinin compared to the lysine analogs.

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 2,249 full-dose aprotinin-treated and 2,164 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 who are at increased risk of bleeding.

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Appendix 1: US Product Information

TRASYLOL®
(aprotinin injection)

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

DESCRIPTION

Trasylol® (aprotinin injection), $C_{284}H_{432}N_{84}O_{79}S_7$, 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 who are at an increased risk for blood loss and blood transfusion.

CONTRAINDICATIONS

Hypersensitivity to aprotinin.

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

WARNINGS

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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 than 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
Acute Kidney Failure	0.5	0.6
Kidney Tubular Necrosis	0.8	0.4

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

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

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

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

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

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

Musculoskeletal: Arthralgia.

Nervous: Agitation, dizziness, anxiety, convulsion.

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

Skin: *Skin discoloration*.

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

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

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

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

Treatment	Definite MI %	Definite or Probable MI %	Definite, Probable or Possible MI %
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 postoperative angiography. Of the 13 study sites, 10 were in the United States and three were non-U.S. centers (Denmark (1), Israel (2)). The results of this study are summarized below.

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

	Overall Closure Rates*		Incidence of MI**	Incidence of Death***
	All Centers n = 703 %	U.S. Centers n = 381 %	All Centers n = 831 %	All Centers n = 870 %
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 **CONTRAINDICATIONS** and **WARNINGS**. Hypersensitivity and anaphylactic reactions during surgery were rarely reported in U.S. controlled clinical studies in patients with no prior exposure to 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: Trasylol® administration is associated with a risk for renal dysfunction (see **WARNINGS: Renal Dysfunction**).

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

hepatic dysfunction in patients treated with Trasylol®. 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 initial (test) dose, a loading dose, a dose to be added while **recirculating** the priming fluid of the cardiopulmonary bypass circuit ("pump prime" dose), and a constant infusion dose. To avoid physical incompatibility of Trasylol® and heparin when adding to the pump prime solution, each agent must be added **during recirculation** of the pump prime to assure adequate dilution prior to admixture with the other component. Regimens A and B, both incorporating a 1 mL initial (test) dose, are described in the table below:

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

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

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

HOW SUPPLIED

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

STORAGE

Trasylol® 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

Rx Only

~~01298181~~ 12/06 13121 Printed in USA

Appendix 2: Dear Health Care Provider Letter from Dec 2006

Bayer HealthCare

IMPORTANT DRUG WARNING
Regarding Trasylol® (aprotinin injection)

December 2006

Dear U.S. Healthcare Professional:

Bayer Pharmaceuticals Corporation (Bayer) would like to inform you of important new safety information regarding Trasylol (aprotinin injection) and new prescribing information. Specifically, Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period. Other Trasylol safety concerns include the risk for anaphylactic reactions, including fatal reactions. These safety concerns have resulted in an important revision of the prescribing information to:

- Limit Trasylol use to patients who are at an **increased risk for blood loss and blood transfusion** in the setting of coronary bypass graft surgery with cardiopulmonary bypass,
- Contraindicate the administration of Trasylol to any patients with a known or suspected prior exposure to Trasylol or other aprotinin-containing products within the previous 12 months,
- Provide additional information on the management and prevention of anaphylactic reactions, including the administration of Trasylol only in an operative setting where cardiopulmonary bypass may be rapidly initiated,
- Highlight the risk for kidney dysfunction.

Additional details regarding the changes to the Trasylol prescribing information are described below.

Bayer and the U.S. Food and Drug Administration (FDA) are continuing to review information pertaining to the use of Trasylol, and this review may result in other actions, including additional changes to the prescribing information. Consequently, physicians and healthcare providers should closely monitor patients following Trasylol administration and should report any serious adverse events.

The information currently under review at Bayer includes preliminary findings from an observational clinical study that was reported to the FDA following a public discussion of Trasylol safety at a September 21, 2006 FDA Advisory Committee meeting. This study used complex statistical and epidemiological methods, and the association of Trasylol with the safety problems described in this study is the subject of the on-going review by Bayer. A preliminary report of this study has been submitted to the FDA; any further updates to the report will be submitted to FDA for review.

Changes to the Trasylol Prescribing Information

These changes mainly include revised text with respect to anaphylactic reactions and renal dysfunction in the **BOXED WARNING; CONTRAINDICATIONS; WARNINGS; WARNINGS—Re-exposure to aprotinin; WARNINGS—Renal dysfunction**; and **PRECAUTIONS—General** sections of the U.S. product label. In addition, the **INDICATIONS and USAGE** section has been revised to limit the use.

Changes to the label are in italics text:

Revised **BOXED WARNING**:

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

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Revised **CONTRAINDICATIONS** section:

Hypersensitivity to aprotinin.

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

Revised **WARNINGS** section:

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

Hypersensitivity reactions often manifest as anaphylactic/anaphylactoid reactions with hypotension the most frequently reported sign of the hypersensitivity reaction. The hypersensitivity reaction can progress to anaphylactic shock with circulatory failure. If a hypersensitivity reaction occurs during injection or infusion of Trasylol®, administration should be stopped immediately and emergency treatment should be initiated. Even when a second exposure to aprotinin has been tolerated without symptoms, a subsequent administration may result in severe hypersensitivity/anaphylactic reactions.

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

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

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

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

Renal Dysfunction: *Trasylol® administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period. This risk may be especially increased for patients with pre-existing renal impairment or those who receive aminoglycoside antibiotics or drugs that alter renal function. Data from Bayer's global pool of placebo-controlled studies in patients undergoing coronary artery bypass graft (CABG) surgery showed that the incidence of serum creatinine elevations >0.5 mg/dL above pre-treatment levels was statistically higher at 9.0% (185/2047) in the high-dose aprotinin (Regimen A) group compared with 6.6% (129/1957) in the placebo group.*

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In the majority of instances, post-operative renal dysfunction was not severe and was reversible. However, renal dysfunction may progress to renal failure and the incidence of serum creatinine elevations >2.0 mg/dL above baseline was slightly higher in the high-dose aprotinin group (1.1% vs. 0.8%). Careful consideration of the balance of benefits versus potential risks is advised before administering Trasylol® to patients with impaired renal function (creatinine clearance < 60 mL/min) or those with other risk factors for renal dysfunction (such as peri-operative administration of aminoglycosides or products that alter renal function). (See ***PRECAUTIONS*** *and* ***ADVERSE REACTIONS: Laboratory Findings: Serum Creatinine****).*

Revised **PRECAUTIONS** Section:

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

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**).

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

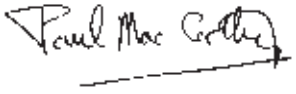
Revised **INDICATIONS AND USAGE** section:

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

Based on the new label language, the U.S. Food and Drug Administration has posted a press release and a public health advisory to their website (www.fda.gov). Additionally, on September 29, 2006 the FDA posted a Public Health Advisory on their website related to Trasylol.

For more information, a copy of the complete revised label is attached. Additionally, 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 Mac Carthy, MD, FRCPI
Vice President, Medical Affairs
Bayer Pharmaceuticals Corporation

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Bayer HealthCare

IMPORTANT DRUG WARNING
Regarding Trasylol® (aprotinin injection)

December 2006

Dear U.S. Healthcare Professional,

Bayer would like to inform you of developments related to Trasylol® (aprotinin injection) including: recent changes to the U.S. prescribing information, including a change in indication and the need to have cardiopulmonary bypass equipment available during surgery.

U.S. Label Modifications
Bayer has been in ongoing discussions with the Food and Drug Administration (FDA) regarding prescribing information on Trasylol. On December 15, 2006 agreement was reached with the agency and is being communicated through a "Dear Healthcare Professional" letter, a copy of which is attached.

This letter includes the following language:

Revised **INDICATIONS AND USAGE** section:

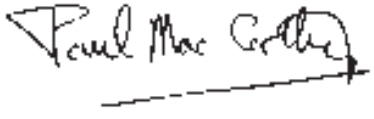
- Trasylol® is indicated for prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery ***who are at an increased risk for blood loss and blood transfusion.***

"Trasylol administration increases the risk for renal dysfunction and may increase the need for dialysis in the perioperative period." Other Trasylol safety issues include the risk for serious hypersensitivity reactions, including fatal reactions. These safety issues have resulted in an important revision of the prescribing information to:

- Contraindicate the "administration of Trasylol to any patients with a known or suspected prior exposure to Trasylol or other aprotinin-containing products within the previous 12 months,"
- Provide additional information on the management and prevention of hypersensitivity reactions, including the administration of Trasylol "**only in an operative setting where cardiopulmonary bypass may be rapidly initiated**,"
- Highlight the "risk for kidney dysfunction."

For more information, a copy of the complete revised label is attached. Additionally, 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,



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