Antifibrinolytics
The evidence

April 2008

Drugs

- **Aprotinin** (Trasylol) a monomeric (single-chain) globular polypeptide derived from bovine lung consists of 16 different amino acids.
  - Inhibits several serine proteases, specifically trypsin, chymotrypsin and plasmin at a concentration of about 125,000 IU/ml, and kallikrein at 300,000 IU/ml. Its action on kallikrein leads to the inhibition of the formation of factor XIIa. As a result, both the intrinsic pathway of coagulation and fibrinolysis are inhibited. Its action on plasmin independently slows fibrinolysis. Ortho, liver suspended
- **Tranexamic acid** (Cyklokapron).It competitively inhibits the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. It has roughly 8 times the antifibrinolytic activity of an older analogue, ε-aminoacaproic acid. Menstrual, ortho, haemophilia.
- **Epsilon-aminocaproic acid** (Amicar) is a derivative and analogue of the amino acid lysine, which makes it an effective inhibitor for enzymes which bind that particular residue. Such enzymes include proteolytic enzymes including plasminogen, the enzyme responsible for fibrinolysis.

Indication for use

- **About Trasylol®**
- **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.**

Aprotinin

- Aprotinin is one of the most extensively studied drugs in the history of cardiac surgery.
- Through multiple RCTs, aprotinin has been shown to be safe in terms of mortality, effective in terms of reducing bleeding, effective in possibly reducing the incidence of adverse neurologic outcomes.
- It has been shown, in randomized trials, to create a slight increase in creatinine in the perioperative period, which returns to normal by about 7 days, but other than that, has never been shown to increase mortality in randomized trials, never been shown to increase stroke, never been shown to increase renal failure.

Until 2006

- Publication of a large observational study from Dennis Mangano and his group.
- The Risk Associated with Aprotinin in Cardiac Surgery
- Dennis T. Mangano, Ph.D., M.D., Iulia C. Tudor, Ph.D., and Cynthia Dietzel, M.D., for the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation*
- N Engl J Med 2006;354:353-65.

The Risk Associated with Aprotinin in Cardiac Surgery

- This was a retrospective worldwide multicenter observational study in which aprotinin use was selected by the surgeon and was not randomized.
- It was a highly publicized study, it hit *The New York Times*, it hit the nightly news.
- Caused the cardiac surgery community to further investigate the issue.

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Control Group (N=1374)	Antifibrinolytic Group									
		Overall (N=3000)			Aprotinin (N=1295)		Aminocaproic Acid (N=883)		Tranexamic Acid (N=822)	
	no. (%)	no. (%)	P value†	P value‡	P value§	no. (%)	P value†	no. (%)	P value†	no. (%)	P value†
Male sex	1110 (80.8)	2377 (79.2)	0.24	0.59	0.79	1016 (78.5)	0.13	690 (78.1)	0.13	671 (81.6)	0.62
Black, American Indian, or Hispanic race or ethnic group¶	53 (3.9)	300 (10.0)	<0.001	0.88	0.66	56 (4.3)	0.54	139 (15.7)	<0.001	105 (12.8)	<0.001
Education: some college or above	496 (36.1)	918 (30.6)	<0.001	0.14	0.34	280 (21.6)	<0.001	398 (45.1)	<0.001	240 (29.2)	<0.001
Surgery: urgent or emergency status	288 (21.0)	503 (16.8)	<0.001	0.38	0.28	192 (14.8)	<0.001	167 (18.9)	0.24	144 (17.5)	0.05
History of diabetes mellitus	384 (28.0)	898 (30.0)	0.18	0.39	0.11	353 (27.3)	0.68	325 (36.8)	<0.001	220 (26.8)	0.56
History of insulin-dependent diabetes	78 (5.7)	242 (8.1)	0.005	0.72	0.68	116 (9.0)	0.001	80 (9.1)	0.002	46 (5.6)	0.94
History of hypertension	824 (60.3)	2091 (69.9)	<0.001	0.76	0.14	905 (70.0)	<0.001	657 (74.7)	<0.001	529 (64.7)	0.042
History of angina	1272 (92.8)	2688 (89.8)	0.002	0.83	0.67	1136 (87.8)	<0.001	783 (89.3)	0.004	769 (93.6)	0.49
History of congestive heart failure	457 (33.5)	1065 (35.8)	0.13	0.22	0.76	551 (42.8)	<0.001	243 (27.7)	0.004	271 (33.3)	0.95
History of myocardial infarction	714 (52.3)	1548 (52.2)	0.97	0.87	0.15	664 (52.1)	0.94	433 (49.6)	0.22	451 (55.1)	0.19
History of heart block	176 (12.8)	477 (15.9)	0.008	0.83	0.45	224 (17.3)	0.001	129 (14.6)	0.22	124 (15.1)	0.13
History of carotid disease	143 (11.0)	421 (14.4)	0.002	0.74	0.34	217 (17.2)	<0.001	107 (12.4)	0.29	97 (12.2)	0.38
History of stroke	89 (6.5)	186 (6.2)	0.75	0.83	0.95	88 (6.8)	0.73	61 (7.0)	0.65	37 (4.5)	0.05
History of liver disease	106 (7.7)	282 (9.4)	0.06	0.83	0.81	150 (11.7)	<0.001	66 (7.5)	0.86	66 (8.0)	0.79
History of renal disease	178 (13.0)	523 (17.5)	<0.001	0.92	0.27	240 (18.6)	<0.001	131 (14.9)	0.22	152 (18.5)	<0.001
History of pulmonary disease	238(17.4)	680 (22.8)	<0.001	0.95	0.64	326 (25.3)	<0.001	215 (24.5)	<0.001	139 (17.0)	0.79
Ejection fraction ≤44%	247 (18.0)	508 (16.9)	0.40	0.96	0.51	199 (15.4)	0.07	169 (19.1)	0.49	140 (17.0)	0.57
Creatinine >1.3 mg/dl on admission‖	189 (13.8)	449 (15.0)	0.29	0.92	0.80	195 (15.1)	0.34	132 (14.9)	0.43	122 (14.8)	0.48
History of CABG	31 (2.3)	236 (7.9)	<0.001	NA	0.42	148 (11.4)	<0.001	51 (5.8)	<0.001	37 (4.5)	0.003
History of valve disease	167 (12.3)	616 (20.7)	<0.001	0.89	0.17	326 (25.4)	<0.001	165 (18.8)	<0.001	125 (15.2)	0.05
History of valve surgery	1 (0.1)	26 (0.9)	0.002	NA	0.50	19 (1.5)	<0.001	3 (0.3)	0.14	4 (0.5)	0.05
History of percutaneous transluminal coronary angioplasty	138 (10.1)	542 (18.1)	<0.001	0.93	0.54	223 (17.3)	<0.001	173 (19.7)	<0.001	146 (17.8)	<0.001
History of aortic vascular surgery	15 (1.1)	32 (1.1)	0.94	NA	0.62	12 (0.9)	0.67	11 (1.3)	0.74	9 (1.1)	0.99
History of intracoronary stent	54 (3.9)	227 (7.6)	<0.001	0.87	0.17	95 (7.3)	<0.001	78 (8.8)	<0.001	54 (6.6)	0.006
History of coronary atherectomy	5 (0.4)	19 (0.6)	0.26	0.94	0.68	11 (0.9)	0.10	7 (0.8)	0.17	1 (0.1)	0.29
History of noncoronary angioplasty or stent	20 (1.5)	68 (2.3)	0.08	NA	0.60	40 (3.3)	0.002	11 (1.3)	0.68	14 (1.7)	0.65
Current CABG and valve surgery	96 (7.0)	378 (12.6)	<0.001	NA	0.18	201 (15.5)	<0.001	108 (12.2)	<0.001	69 (8.4)	0.23
Current CABG and other surgery	68 (5.0)	153 (5.1)	0.83	NA	0.99	72 (5.6)	0.48	41 (4.6)	0.74	40 (4.9)	0.93

* NA denotes not applicable (because there were no patients with the characteristic in the subpopulation), and CABG coronary-artery bypass grafting.
† P values are for the comparison between patients treated with an antifibrinolytic agent and control patients.
‡ P values are those calculated after adjustment according to the propensity score (for the use of an antifibrinolytic agent) in 3013 patients undergoing primary surgery.
§ P values are those calculated after adjustment according to the propensity score (for the use of an antifibrinolytic agent) in 1361 patients undergoing complex surgery. Complex surgery was defined as surgery under any of the following conditions: a history of coronary-artery bypass grafting, valve surgery, noncoronary angioplasty or stenting, or other cardiac or vascular noncardiac surgery; combined current heart surgery; and current surgery in emergency status or urgent status with evidence of congestive heart failure preoperatively.
¶ Race or ethnic group was determined by the clinical investigator.
‖ To convert the value for creatinine to micromoles per liter, multiply by 88.4.

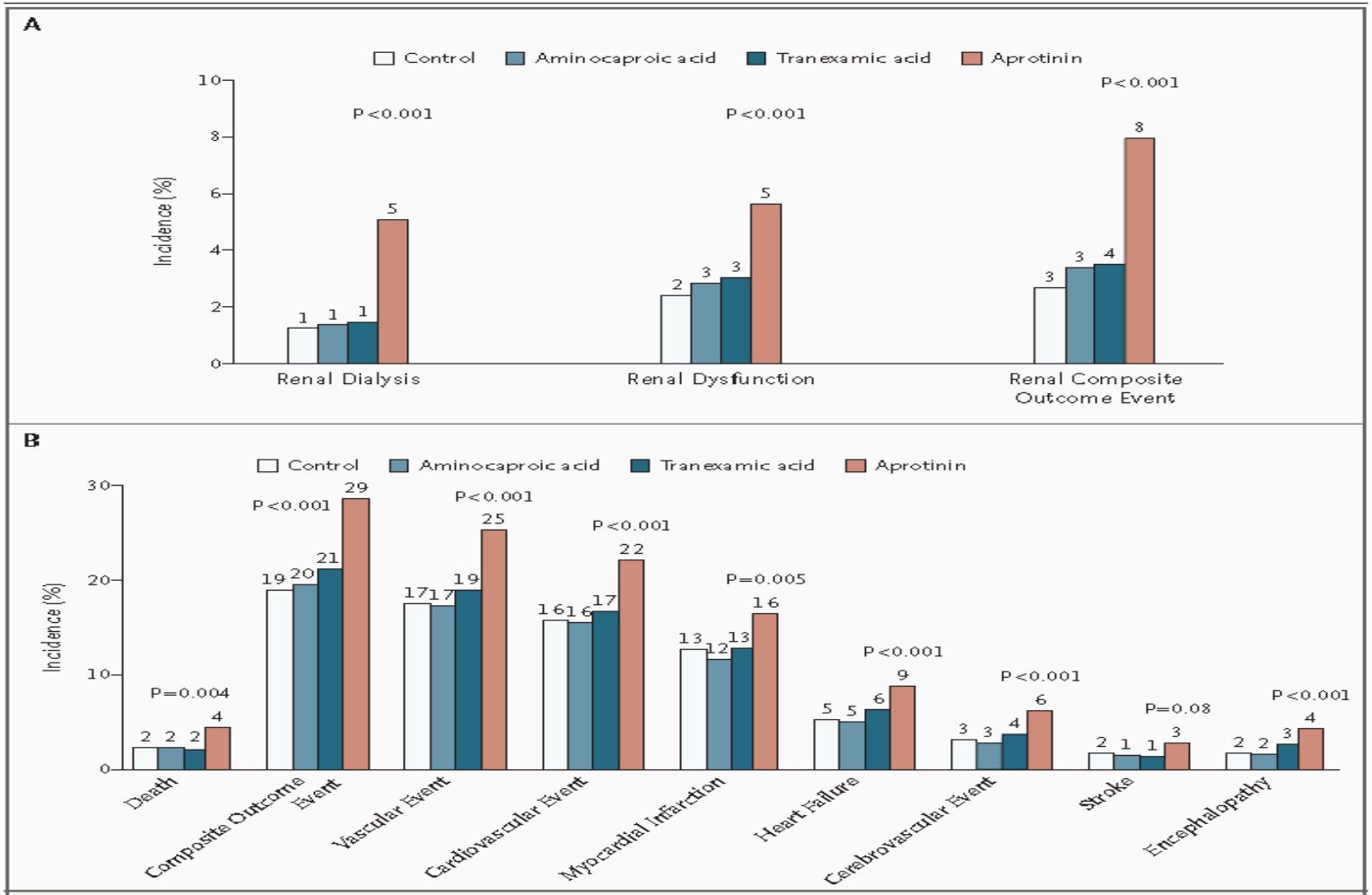


Figure 2. Renal and Nonrenal Outcome Events among the 4374 Study Patients.

Panel A shows the incidence of renal events according to study group. All pairwise comparisons between the aprotinin group and any other group were significant ($P<0.001$ by Bonferroni-adjusted analysis). Comparison of either aminocaproic acid or tranexamic acid with control, or comparison between them, was not significant. Panel B shows the incidence of nonrenal events. In both panels, the numbers above the bars are rounded incidence values, and P values shown are for the comparison between the aprotinin group and any other group (the control group, the aminocaproic acid group, or the tranexamic acid group).

Conclusion of Mangano study

- In conclusion, the observed association between aprotinin and serious end-organ damage indicates that continued use is not prudent, whereas the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

Follow-on study by Karkouti in Canada

- **A propensity score case-control comparison of aprotinin and tranexamic acid in high-transfusion-risk cardiac surgery.**
- Karkouti K, Beattie WS, Dattilo KM, McCluskey SA, Ghannam M, **Hamdy A**, **Wijeysundera DN**, **Fedorko L**, **Yau TM**.
- looked at about 900 patients in two groups, propensity matched, 450 who got aprotinin, 450 who did not, and came to the conclusion that it did not increase mortality, it did not increase stroke, it did increase the creatinine postoperatively, but they had a different definition of renal dysfunction that Dennis Mangano did, and it did increase the risk of dialysis-dependent renal failure.
- Aprotinin and tranexamic acid have similar hemostatic effectiveness in high-transfusion-risk cardiac surgery. Within the confines of propensity score matching, our results suggest that aprotinin may be associated with renal dysfunction.

Advisory Committee in September 2006

- Focused on kidney damage as well as serious allergic reactions to Trasylol.
- FDA narrowed the indicated use in patients at high risk for bleeding from cardiac surgery and they also strengthened the warnings on the label regarding hypersensitivity and kidney damage.

A second paper by D. Mangano

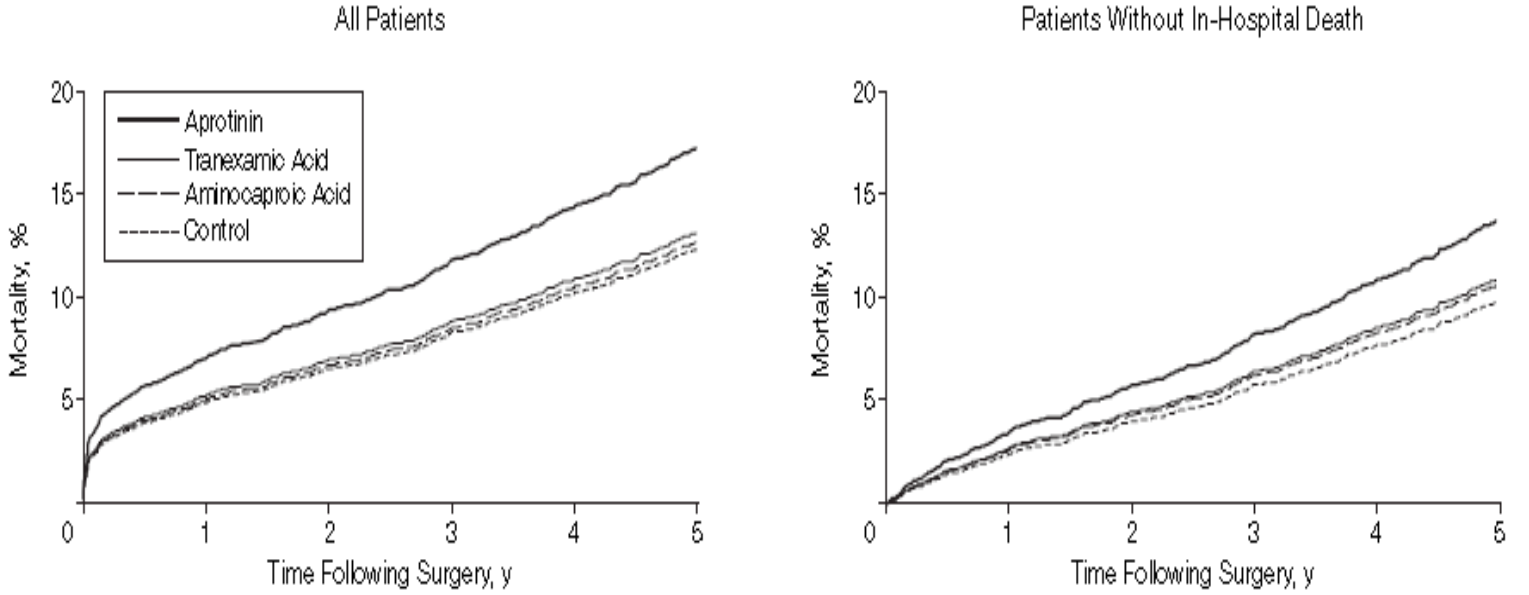
Mortality Associated With Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery

JAMA, February 7, 2007—Vol 297, No. 5
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Mortality Associated With Aprotinin During 5 Years Following Coronary Artery Bypass Graft Surgery

- **Design, Setting, and Participants:**
- Observational study of mortality conducted between November 11, 1996, and December 7, 2006.
- Following index hospitalization (4374 patients; 69 medical centers), survival was prospectively assessed at 6 weeks, 6 months, and annually for 5 years after CABG surgery.
- **Main Outcome Measure** Death (all-cause) over 5 years.

Figure 2. Cumulative Mortality Curves Compared Among Study Groups



No. at Risk												
Aprotinin	1286	1121	1042	971	911	845	1229	1120	1041	970	911	845
Tranexamic Acid	821	465	441	406	393	377	804	465	441	406	393	377
Aminocaproic Acid	873	796	774	753	726	698	847	791	771	751	726	698
Control	1365	1118	1077	1027	985	879	1330	1116	1076	1026	984	878

Left, mortality was calculated from the adjusted survival distributions as 1 minus adjusted survival among 4345 patients by study group: control (1365 patients), aminocaproic acid (873 patients), tranexamic acid (821 patients), aprotinin (1286 patients). Patients with missing covariates were excluded (n=29). Survival was significantly different between aprotinin and control ($P<.001$), but not between aminocaproic acid and control ($P=.81$), or between tranexamic acid and control ($P=.64$). Survival was adjusted using the correct-group-prognosis method (see Methods). Patients participating in the in-hospital, but not long-term phase were censored at 6 weeks. Right, mortality calculated as 1 minus adjusted survival among patients without in-hospital death (n=125): control (1330 patients), aminocaproic acid (847 patients), tranexamic acid (804 patients), aprotinin (1229 patients). Patients with missing covariates were excluded (n=39).

Conclusions

- These findings indicate that in addition to the previously reported acute renal and vascular safety concerns, aprotinin use is associated with an increased risk of long-term mortality following CABG surgery. Use of aprotinin among patients undergoing CABG surgery does not appear prudent because safer and less expensive alternatives (ie, aminocaproic acid and tranexamic acid) are available.

Caused a lot of surgeons to stop using aprotinin

- It showed both early and late adverse outcome, which didn't make a lot of sense to many people how aprotinin is going to be related to late mortality, which is 5 years later.
- Nevertheless, many centres didn't see any of these.

- Waiting for the FDA or the Society of Thoracic Surgeons (STS) to come with some type of a white paper to guide as to what to do in the future.

May 2007

- The STS and the Society of Cardiovascular Anesthesiologists (SCA) came out with guidelines in saying that aprotinin was level A evidence recommended to decrease bleeding didn't have a lot of the data yet and didn't have the FDA Advisory Review on Safety.

FDA hearing in September 2007

- Dennis Mangano presented his data and basically said aprotinin causes renal failure.
- Dr. Karkouti presented his data, and with a second look at his data, found that the more other risk factors they added in, the less important aprotinin was in predicting renal failure.
- Karkouti noted that as more risk factors went in, definitely mortality, stroke, renal insufficiency, all started going away. Mortality and stroke were gone, renal insufficiency and renal failure started going away as an important risk factor.

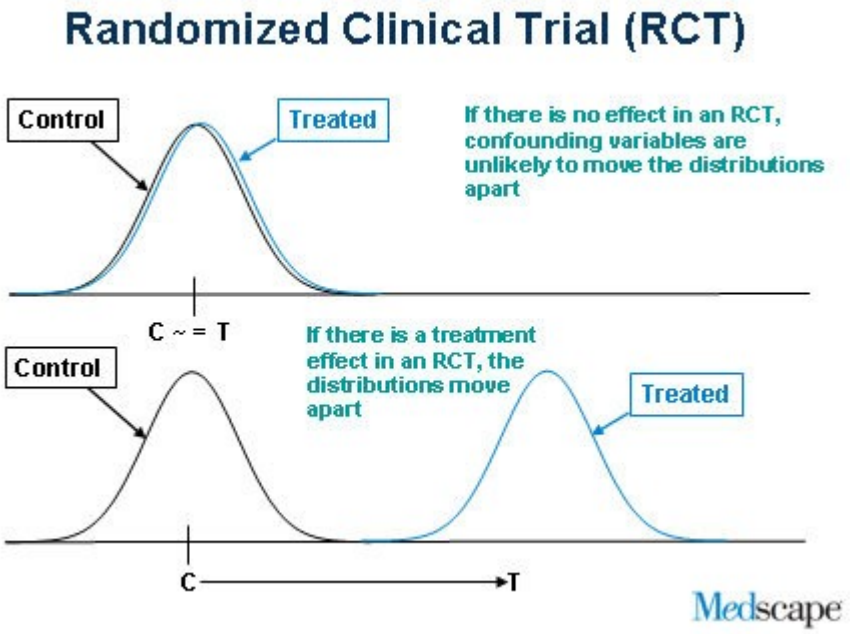
FDA hearing in September 2007

- At the second hearing, the FDA did have the data from the original Mangano paper.
- They were able to reproduce his results, but they really did not come to the same conclusions. Their interpretation of the data was very different.
- The risk profiles in the aprotinin group and the control group were vastly different from each other. So it demanded that there be an adjusted analysis, and an unadjusted analysis would really be unfair.
- The FDA panel once more recommended that aprotinin stay on the market with stronger warnings,

- In the Mangano paper, the transfusions were a categorical variable.
- When you look at the relationship between increasing units transfused and the incidence of renal failure, there is a direct and significant relationship between increasing transfusions and increasing incidence of renal failure.
- And so, the number of units transfused is not a categorical variable; it is a continuous variable.

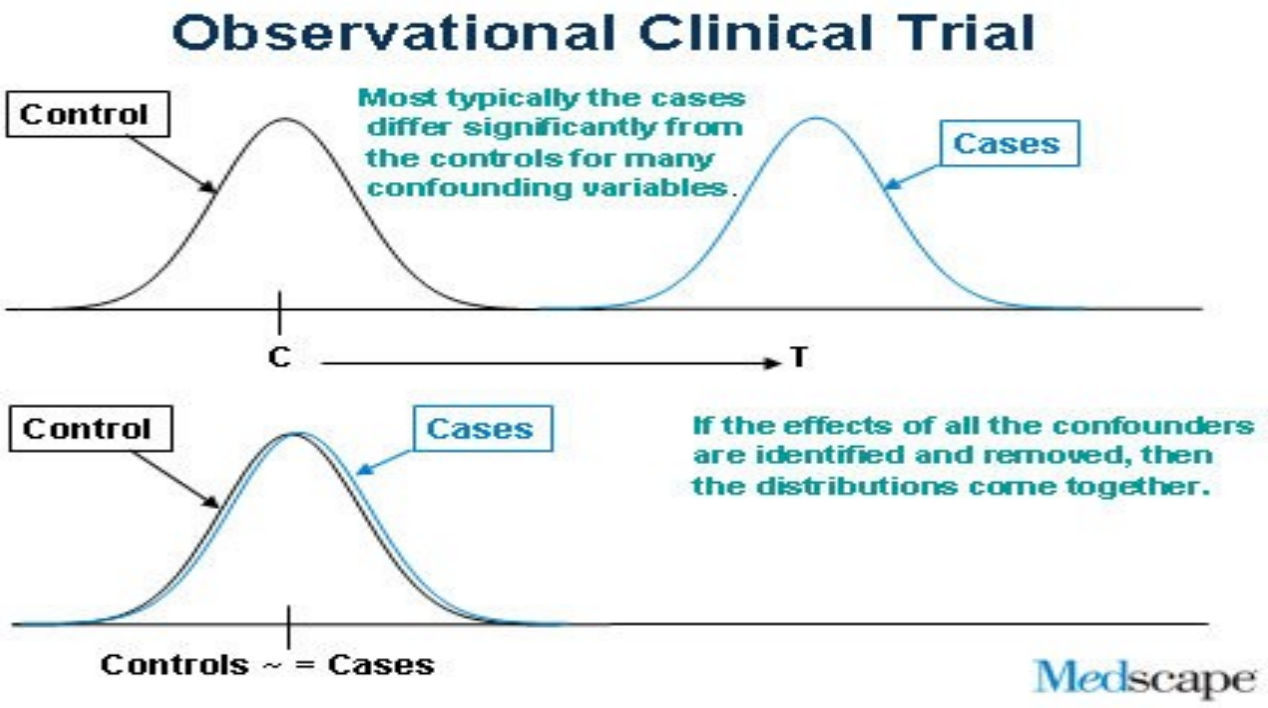
Randomized vs Non randomized

- nonrandomized studies, observational studies are much more complex to look at than randomized clinical trials.
- In randomized clinical trials, people are assigned at random to the treatment, so complicating factors get balanced out between the two treatment groups.
- In nonrandomized studies, the physician or someone is assigning the person to the particular treatment. Given the skill of surgeons and the way they look at their patients, they are very likely to channel the high-risk people to the aprotinin group. That creates enormous difficulties in the statistical analysis.



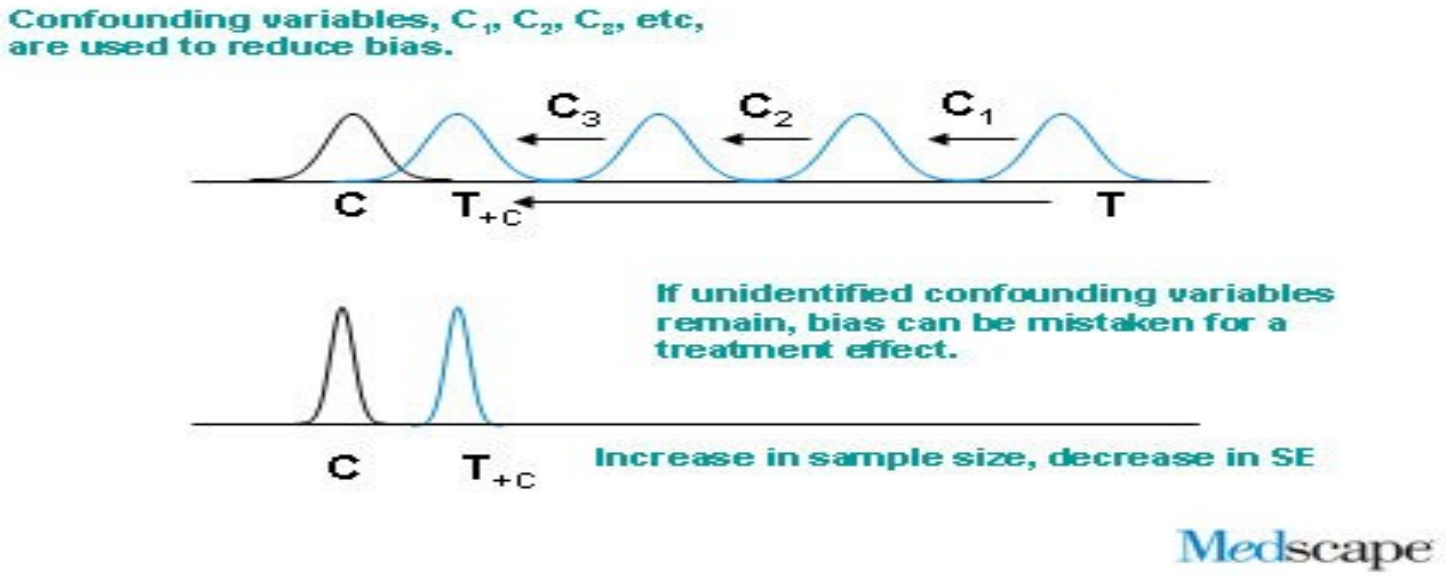
The distribution of the outcomes on a randomized clinical trial through the randomization process are essentially together if there is no treatment effect; if there is a treatment effect, then the groups are pushed apart. But it is very important to keep in mind that the people are assigned at random to the treatment groups, so confounding variables tend to be balanced between the 2 treatment groups.

- So what happens if we have databases and we are trying to look at data back in our own practices?



much more complicated. You will have a control group and a treatment group, aprotinin, for example, but if people have been assigned to aprotinin based on severe risk factors, then you would expect to see a difference between the treatment group and the control group just because of all the other risk factors.

Observational Study



Statistically, we can start removing the risk factors, and as you remove the risk factors, the 2 groups come together. Now, unfortunately, if you do not remove all the risk factors, there can still be a difference between the treatment group and the aprotinin group, and then what has happened over the past 10 or 15 years, databases have gotten larger. So as the databases get larger, the standard error shrinks, and if there is still a biasing factor left in that has not been taken out, then you will say the 2 groups are different but they could be different due to a biasing factor that has not been removed.

- It is very difficult to identify all the confounding factors.
- Epidemiologists believe that if the risk ratio is not above 2, then there could be potentially biasing factors, and so, risk ratios under 2, even though they might be statistically significant, are taken to be nondemanding that there is actually a result there.
- And in this case, once risk factors are removed, even though all the risk factors may not be removed, the risk factors for aprotinin are under 2 and, hence, would not be considered causative.

- If we have a compelling, very large database, and it looks like a very interesting outcome, from database work, can we say cause and effect occurs?

- No, we are looking at associations, and so, the cause and effect is not occurring in observation; it can't be determined really.
- In randomized clinical trials, it's all different because the confounding factors have been balanced across the two treatment groups, so if we see that there is still an effect, then we argue that that is causative. But in nonrandomized studies, that is not the case.

Systematic review

- **Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion**
- Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, McClelland B, Laupacis A, Fergusson D. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database of Systematic Reviews* 2007, Issue 4

Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion

- **Objectives**
- To assess the comparative effects of the anti-fibrinolytic drugs aprotinin, tranexamic acid (TXA), and epsilon aminocaproic acid (EACA) on blood loss during surgery, the need for red blood (RBC) transfusion, and adverse events, particularly vascular occlusion, renal dysfunction, and death.
- **Selection criteria**
- Randomised controlled trials (RCTs) of anti-fibrinolytic drugs in adults scheduled for non-urgent surgery. Eligible trials compared anti-fibrinolytic drugs with placebo (or no treatment), or with each other

Conclusions

- This review summarises data from 211 RCTs that recruited 20,781 participants
- Anti-fibrinolytic drugs provide worthwhile reductions in blood loss and the need for allogeneic red cell transfusion.
- Their efficacy does not appear to be offset by serious adverse effects.
- In most circumstances the lysine analogues are probably as effective as aprotinin and are cheaper; the evidence is stronger for tranexamic acid than for aminocaproic acid.
- In high risk cardiac surgery, where there is a substantial probability of serious blood loss, aprotinin may be preferred over tranexamic acid.
- Aprotinin does not appear to be associated with an increased risk of vascular occlusion and death, but the data do not exclude an increased risk of renal failure.
- There is no need for further placebo-controlled trials of aprotinin or lysine analogues in cardiac surgery. The principal need is for large comparative trials to assess the relative efficacy, safety and cost-effectiveness of anti-fibrinolytic drugs in different surgical procedures.

November 5, 2007 **(Leverkusen, Germany and West Haven, CT)**

- Following consultation with the German Federal Institute for Drugs and Medical Devices (BfArM), the U.S. Food and Drug Administration (FDA), Health Canada, and other health authorities, Bayer announced today that it has elected to temporarily suspend worldwide marketing of Trasylol® (aprotinin injection) until final results from the Canadian BART trial can be compiled, received and evaluated.

- The BART study is an independent randomized, controlled trial being conducted in high-risk cardiac surgery patients.
- The BART Executive Committee had halted the trial after a planned periodic data analysis indicated reduced bleeding but also an increase in all-cause mortality (that almost reached conventional statistical significance for 30-day mortality) for patients in the aprotinin treatment arm compared to patients who received either aminocaproic acid or tranexamic acid.
- Bayer has been informed that data are now being collected from centers throughout Canada and a final data analysis will be undertaken by BART investigators -- a process that is expected to **take up to eight weeks, or perhaps longer**.
- Once the complete BART dataset is available, Bayer will work with health authorities to evaluate whether these data have any impact on the positive benefit-risk assessment for Trasylol. At that time the temporary marketing suspension will be reevaluated.
- Additionally, the U.S. FDA, Health Canada and other health authorities have indicated their interest in working with Bayer to create a program for use during the temporary suspension under which physicians in these markets might request and receive Trasylol for treatment of certain surgical patients with an established medical need. Bayer will work with the FDA, Health Canada, and any other authorities who wish to institute similar programs, to outline appropriate patient profiles and the specific details.

2008

- Mouton R, Finch D, Davies I, et al. Effect of aprotinin on renal dysfunction in patients undergoing on-pump and off-pump cardiac surgery: a retrospective observational study. *Lancet*. 2008;371:475-482.
- Hausenloy DJ, Pagano D, Keogh B. Aprotinin — still courting controversy. *Lancet*. 2008;371:449-450.

- **Methods** Our analysis included 9875 patients undergoing on-pump or off-pump cardiac surgery from Jan 1, 2000, to Sept 30, 2007. Of these patients, 9106 were included in the retrospective observational study analysis.
- **Results**.In 5434 patients undergoing on-pump cardiac surgery, the odds ratio (OR) between aprotinin and an increased risk of renal dysfunction without ACE inhibitor was 1·81 (95% CI 0·79–4·13, p=0·162) and with ACE inhibitor 1·73 (0·56–5·32, p=0·342). In the 848 patients taking ACE inhibitors and undergoing off-pump cardiac surgery, aprotinin was associated with a greater than two-fold increase in the risk of renal dysfunction after off-pump cardiac surgery (OR 2·87 [1·25–6·58], p=0·013).

- **Conclusion**: Our results have shown that aprotinin seems to be safe during on-pump cardiac surgery. However, the combination of aprotinin and ACE inhibitors during off-pump cardiac surgery is associated with a significant risk of postoperative renal dysfunction.

Feb 2008

- Schneeweiss S, Seeger JD, Landon J, Walker AM. Aprotinin during coronary-artery bypass grafting and risk of death. *N Engl J Med*. 2008;358:771-783.
- Shaw AD, Stafford-Smith M, White WD, et al. The effect of aprotinin on outcome after coronary-artery bypass grafting. *N Engl J Med*. 2008;358:784-793.

- **Methods**

Using electronic administrative records of the Premier Perspective Comparative Database, we studied hospitalized patients with operating-room charges for the use of aprotinin (33,517 patients) or aminocaproic acid (44,682 patients) on the day CABG was performed.

Table 2. Relative Risk of In-Hospital Death among the 78,199 Patients Undergoing Coronary-Artery Bypass Grafting (CABG) in the Primary Study Cohort.

Outcome	Any Amount of Aprotinin (N=33,517)	Any Amount of Aminocaproic Acid (N=44,682)	Any Amount of Study Drug		Low or High Amount of Study Drug
			Unadjusted	Adjusted	Adjusted
	no. of patients (%)		*relative risk (95% CI)*		
In-hospital death from any cause	1512 (4.5)	1101 (2.5)	1.83 (1.70–1.98)	1.64 (1.50–1.78)	1.50 (1.36–1.66)
In-hospital death from any cause within 7 days after CABG	631 (1.9)	435 (1.0)	1.93 (1.71–2.18)	1.78 (1.56–2.02)	1.64 (1.41–1.91)

Conclusions

Patients who received aprotinin alone on the day of CABG surgery had a higher mortality than patients who received aminocaproic acid alone. Characteristics of neither the patients nor the surgeons explain the difference, which persisted through several approaches to control confounding.

The effect of aprotinin on outcome after coronary-artery bypass grafting

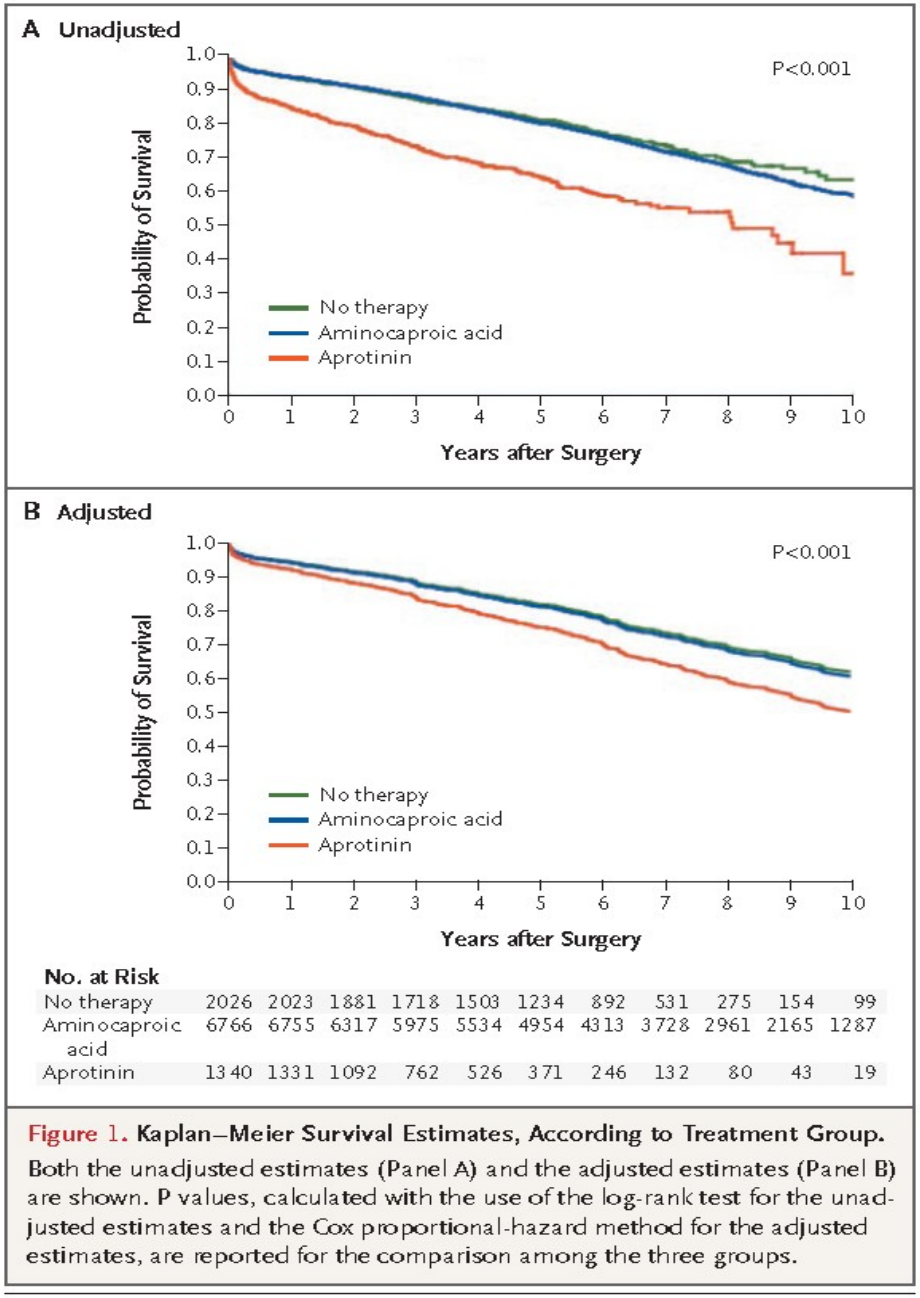
- **Methods**
- We retrieved data on 10,275 consecutive patients undergoing surgical coronary revascularization at Duke between January 1, 1996, and December 31, 2005

Table 1. Baseline Characteristics of the Patients.*

Variable	Aprotinin (N = 1343)	Aminocaproic Acid (N = 6776)	No Therapy (N = 2029)	P Value	Odds Ratio for Aprotinin (95% CI)
Mean age at surgery — yr	66.6	64.4	63.9	<0.001	0.99 (0.98–1.00)
Angina — no. (%)	1024 (76.2)	5527 (81.6)	1745 (86.0)	<0.001	0.78 (0.63–0.95)
Aortic regurgitation — no. (%)				<0.001	1.21 (1.04–1.40)
None	1274 (94.9)	6670 (98.4)	2001 (98.6)		
Mild	29 (2.2)	45 (0.7)	15 (0.7)		
Moderate	29 (2.2)	44 (0.6)	7 (0.3)		
Severe	11 (0.8)	17 (0.3)	6 (0.3)		
Cardiopulmonary bypass — no. (%)	1317 (98.1)	6730 (99.3)	1302 (64.2)	<0.001	3.31 (1.98–5.53)
Mean preoperative creatinine level — mg/dl	1.53	1.18	1.23	<0.001	1.14 (1.07–1.22)
Preoperative stroke — no. (%)	152 (11.3)	666 (9.8)	147 (7.2)	<0.001	1.65 (1.31–2.08)
Family history of CAD — no. (%)	695 (51.7)	1037 (15.3)	712 (35.1)	<0.001	2.31 (1.90–2.82)
Hypertension — no. (%)	967 (72.0)	4623 (68.2)	1413 (69.6)	0.02	0.61 (0.51–0.74)
Hypercholesterolemia — no. (%)	847 (63.1)	3251 (48.0)	1179 (58.1)	<0.001	1.34 (1.14–1.59)
Internal thoracic artery used — no. (%)				<0.001	1.24 (1.09–1.42)
Left artery	890 (66.3)	6083 (89.8)	1747 (86.1)		
Right artery	37 (2.8)	37 (0.5)	21 (1.0)		
Both	10 (0.7)	128 (1.9)	51 (2.5)		
Neither	406 (30.2)	528 (7.8)	210 (10.3)		
Preoperative nitroglycerin — no. (%)	99 (7.4)	937 (13.8)	188 (9.3)	<0.001	0.69 (0.53–0.90)
Preoperative ACE inhibitor — no. (%)	536 (39.9)	913 (13.5)	590 (29.1)	<0.001	1.14 (0.94–1.38)
Preoperative antiplatelet therapy — no. (%)	130 (9.7)	196 (2.9)	146 (7.2)	<0.001	1.04 (0.79–1.36)
Preoperative diuretic therapy — no. (%)	367 (27.3)	415 (6.1)	268 (13.2)	<0.001	1.25 (1.02–1.52)
Mitral-valve procedure — no. (%)				<0.001	0.62 (0.47–0.82)
None	1144 (85.2)	6431 (94.9)	1954 (96.3)		
Annuloplasty	135 (10.1)	252 (3.7)	52 (2.6)		
Replacement	64 (4.8)	93 (1.4)	23 (1.1)		
CABG and another procedure — no. (%)	266 (19.8)	269 (4.0)	105 (5.2)	<0.001	2.86 (2.29–3.56)
Mean Parsonnet score†	13.99	8.79	8.68	<0.001	1.09 (1.08–1.11)
Previous cardiovascular intervention — no. (%)	557 (41.5)	1079 (15.9)	467 (23.0)	<0.001	3.50 (2.97–4.12)
CPR before surgery — no. (%)	20 (1.5)	9 (0.1)	14 (0.7)	<0.001	2.24 (1.02–4.95)
Mean duration of cardiopulmonary bypass — min	165.1	117.7	80.8	<0.001	1.009 (1.007–1.011)
Chronic kidney disease — no. (%) ‡	110 (8.2)	237 (3.5)	100 (4.9)	<0.001	1.59 (1.11–2.28)
Preoperative use of salicylates — no. (%)	242 (18.9)	3921 (59.4)	729 (36.7)	<0.001	0.49 (0.40–0.61)
Former or current smoker — no. (%)	668 (49.7)	2901 (42.8)	1012 (49.9)	<0.001	0.93 (0.79–1.09)
Tricuspid-valve procedure — no. (%)	23 (1.7)	5 (0.1)	3 (0.1)	<0.001	2.48 (0.91–6.74)
Urgency of procedure — no. (%)				<0.001	1.91 (1.66–2.19)
Elective	367 (27.3)	4459 (65.8)	752 (37.1)		
Urgent	813 (60.5)	2162 (31.9)	1179 (58.1)		
Emergency	158 (11.8)	154 (2.3)	91 (4.5)		
Emergency salvage	5 (0.4)	1 (0.01)	6 (0.3)		
Valve surgery — no. (%)	367 (27.3)	656 (9.7)	144 (7.1)	<0.001	0.65 (0.45–0.951)

Table 1. (Continued.)

Variable	Aprotinin (N = 1343)	Aminocaproic Acid (N = 6776)	No Therapy (N = 2029)	P Value	Odds Ratio for Aprotinin (95% CI)
Aortic stenosis — no. (%)	143 (10.6)	255 (3.8)	54 (2.7)	<0.001	0.78 (0.52–1.15)
Mean aprotinin propensity score	0.400	0.081	0.099	<0.001	
Median year of surgery	2003	1999	2002	<0.001	
Mean EuroSCORE§	10.10	6.66	7.43	<0.001	
Any red cells transfused — no. (%)	967 (72.0)	1430 (21.1)	679 (33.5)	<0.001	
Diabetes (any type) — no. (%)	449 (33.4)	2258 (33.3)	660 (32.5)	0.78	
Female sex — no. (%)	411 (30.6)	2120 (31.3)	667 (32.9)	0.30	
Mean weight — kg	84.2	83.8	84.6	0.19	
Mean ejection fraction — %	46.8	51.9	53.4	<0.001	
Race or ethnic group — no. (%) ¶				0.005	
White	1123 (83.6)	5845 (86.3)	1687 (83.1)		
Black	207 (15.4)	884 (13.0)	325 (16.0)		
Hispanic	4 (0.3)	20 (0.3)	10 (0.5)		
Asian	9 (0.7)	27 (0.4)	7 (0.3)		



No. at Risk

No therapy	2026	2023	1881	1718	1503	1234	892	531	275	154	99
Aminocaproic acid	6766	6755	6317	5975	5534	4954	4313	3728	2961	2165	1287
Aprotinin	1340	1331	1092	762	526	371	246	132	80	43	19

Figure 1. Kaplan–Meier Survival Estimates, According to Treatment Group.
Both the unadjusted estimates (Panel A) and the adjusted estimates (Panel B) are shown. P values, calculated with the use of the log-rank test for the unadjusted estimates and the Cox proportional-hazard method for the adjusted estimates, are reported for the comparison among the three groups.

Conclusions

Patients who received aprotinin had a higher mortality rate and larger increases in
serum creatinine levels than those who received aminocaproic acid or no antifibrinolytic
agent.

March 2008

- **Bleeding in cardiac surgery: The use of aprotinin does not affect survival**
- Domenico Pagano, MD, FRCS,a Neil J. Howell, FRCS,b Nick Freemantle, PhD,b David Cunningham, PhD,cRobert S. Bonser, MD, FRCS,a Timothy R. Graham, FRCS,a Jorge Mascaro, FRCS,a Stephen J. Rooney, FRCS,a Ian C. Wilson, MD, FRCS,a Rob Cramb, FRCPath,d and Bruce E. Keogh, MD, FRCSe
- *J Thorac Cardiovasc Surg* 2008;135:495-502

Bleeding in cardiac surgery: The use of aprotinin does not affect survival

- Methods: In this single-institution observational study involving 7836 consecutive patients (1998–2006), we assessed the safety of using aprotinin in risk reduction strategy for postoperative bleeding.

Bleeding in cardiac surgery: The use of aprotinin does not affect survival

- Results: Aprotinin was used in 44% of patients.
- Multivariate analysis identified aprotinin use in risk reduction for reoperation for bleeding and need for blood transfusion postoperatively.
- The use of aprotinin did not affect in-hospital mortality, intermediate-term survival (median follow-up, 3.4 years), incidence of postoperative hemodialysis, and incidence of postoperative renal dysfunction.
- Conclusion: This study demonstrates that aprotinin is effective in reducing bleeding after cardiac surgery, is safe, and does not affect short- or medium-term survival.

TABLE 1. Demographics in patients treated with and without aprotinin

	No aprotinin (n = 4355)	Aprotinin (n = 3481)	*P* value
Age (y)	63.8 + 9.8	64.8 + 11	<.0001
Female sex	1058 (24.3)	78 (28.1)	.0005
CCS class			
I	633 (14.5)	59 (27.6)	.0001
II	1422 (32.7)	123 (32.3)	
III	1037 (23.8)	821 (23.6)	
IV	1263 (29.0)	573 (16.5)	
NYHA class			
I	1387 (31.9)	825 (23.8)	<.0001
II	1864 (42.8)	1533 (44.1)	
III	832 (19.1)	799 (23.0)	
IV	271 (6.2)	316 (9.1)	
Diabetes			
Type I	284 (6.5)	219 (6.3)	<.0001
Type II (oral therapy)	351 (8.1)	407 (11.7)	
Type II (diet)	153 (3.5)	124 (3.6)	
Hypertension	2401 (55.1)	2204 (63.3)	<.0001
Peripheral vascular disease	446 (10.2)	432 (12.4)	.003
LV function			
Good (EF >50%)	2754 (63.2)	2161 (62.1)	.071
Moderate (EF 30%–49%)	1281 (29.4)	1098 (31.5)	
Poor (EF <30%)	315 (7.2)	216 (6.2)	
Previous MI	1957 (44.9)	1127 (32.3)	<.0001
EUROScore	3.8 + 2.8	5 + 3.4	<.0001
Urgent/emergency procedure	1507 (34.6)	1120 (32.1)	<.0001
Procedure			
CABG only	3421 (78.6)	1982 (56.9)	<.0001
Valve only	532 (12.2)	817 (23.5)	
CABG + valve	314 (7.2)	456 (13.1)	
Valve + other	16 (0.4)	103 (3)	
CABG + other	66 (1.5)	74 (2.1)	
Other cardiac surgery	6 (0.1)	49 (1.4)	

TABLE 2. Surgical characteristics

	No aprotinin (n = 4355)	Aprotinin (n = 3481)	*P* value
CABG only			
EUROScore (mean + SD)	3.2 + 2.5	3.6 + 2.7	<.0001
Priority (no. of patients)			
Elective	2196 (64.8)	1296 (67.5)	.19
Urgent	1159 (34.2)	602 (31.3)	
Emergency	36 (1)	23 (1.2)	
Triple-vessel disease (no. of patients)	2676 (78.9)	1559 (81.2)	.05
LMS (no patients)	653 (19.3)	560 (29.2)	<.0001
No. of CABG (mean + SD)	2.8 + 0.8	3.0 + 0.9	.001
Clamp time (mean min + SD)	45 + 20	52 + 21	<.0001
Bypass time (mean min + SD)	80 + 31	91 + 33	<.0001
LCOS (no. of patients)	1183 (34.9)	571 (29.7)	<.0001
Reoperation (no. of patients)	176 (5.3)	56 (2.9)	<.0001
In-hospital mortality (no. of patients)	94 (2.8)	35 (1.8)	.18
Other cardiac surgery			
EUROScore (mean + SD)	6.0 + 2.7	6.8 + 3.3	<.0001
Priority (no. of patients)			
Elective	649 (67.3)	1061 (68)	.001
Urgent	298 (30.9)	430 (27.6)	
Emergency	17 (1.8)	69 (4.4)	
Triple-vessel disease (no. of patients)	218 (22.7)	335 (21.5)	.052
LMS (no. of patients)	52 (5.4)	126 (8.1)	.001
No. of distals (no. of patients)	0.9 + 1.2	0.9 + 1.3	.91
Clamp time (mean min + SD)	75 + 33	91 + 42	<.0001
Bypass time (mean min + SD)	103 + 46	128 + 56	<.0001
LCOS (no. of patients)	449 (46.5)	770 (49.4)	.4
Reoperation (no. of patients)	73 (7.7)	80 (5.2)	<.0001
In-hospital mortality (no. of patients)	58 (6)	102 (6.5)	.779

Values in parentheses are percentages. *CABG*, Coronary artery bypass grafting; *SD*, standard deviation; *LMS*, left main stem; *LCOS*, low cardiac output syndrome (combined end point of use of inotropic agents, intra-operative balloon pump, or both).

TABLE 4. Multivariate analysis of risk factors for in-hospital mortality

	Odds ratio	95% CI	*P* value
Log EuroSCORE	7.36	5.46–9.94	<.0001
Diabetes	1.49	1.08–2.04	.0184
Year of operation			
1998	2.29	1.30–4.06	.0084
1999	1.91	1.06–3.45	.0348
2000	2.28	1.29–4.04	.009
2001	2.41	1.35–4.31	.0065
2002	1.67	0.95–2.93	.0714
2003	1.43	0.82–2.49	.1884
2004	1.01	0.58–1.75	.9729
2005/2006	0	0–0	
Aprotinin	1.03	0.71–1.49	.851

95% CI, 95% Confidence interval.

TABLE 3. Multivariate analysis of risk factors for reoperation for bleeding

	Odds ratio	95% CI	*P* value
Log EuroSCORE	1.71	1.40–2.10	.0001
Diabetes	0.76	0.55–1.04	.0832
Year of operation			
1998	0.35	0.19–0.67	.0041
1999	0.85	0.49–1.47	.5344
2000	1.00	0.58–1.71	.9986
2001	1.51	0.93–2.57	.096
2002	1.11	0.68–1.81	.6503
2003	1.08	0.66–1.77	.739
2004	1.10	0.69–1.75	.6671
2005/2006	0	0–0	
Aprotinin	0.51	0.36–0.72	.0012

95% *CI*, 95% Confidence interval.

TABLE 5. Multivariate analysis of risk factors for medium-term survival

	Hazard ratio	95% CI	*P* value
Log EuroSCORE	3.51	3.12–3.93	<.0001
Diabetes	1.22	1.05–1.42	.008
Year of operation			
1998	1.58	1.17–2.13	.0031
1999	1.50	1.11–2.03	.008
2000	1.37	1.00–1.86	.048
2001	1.46	1.06–2.00	.02
2002	1.29	0.95–1.74	.10
2003	1.17	0.86–1.58	.33
2004	0.93	0.68–1.27	.65
2005/2006	0.00	0–0	
Aprotinin	1.09	0.93–1.28	.30

95% CI, 95% Confidence interval.

TABLE 6. Renal dysfunction by aprotinin group

	No aprotinin (n = 4154)	Aprotinin (n = 3349)	*P* value
Preoperative creatinine (μmol/L)	114 + 52	115 + 67	.0080
Peak Postoperative creatinine (μmol/L)	138 + 84	140 + 93	.1166
Mean increase in creatinine (μmol/L)	27 + 60	25 + 64	.1166
Preoperative renal impairment (no. of patients)	78 (2.1%)	103 (3.3%)	.0046
Increase in creatinine from preoperative value (no. of patients)			
<25%	3072	2449	.32
25%–<50%	536	446	
50%–<100%	296	258	
≥100%	251	196	
Decrease in GFR from preoperative value (no. of patients)			
<25%	3320	2640	.18
25%–<50%	577	511	
50%–<75%	230	182	
≥75%	18	11	
Renal dysfunction†	440	359	.45

Approximately adjusted for log Euroscore, diabetes, year of operation, and surgeon as random effects and preoperative creatinine score for postoperative measures. *GFR*, Glomerular filtration rate. *Preoperative creatinine ≥ 200 μmol/L. †According to definition used by Mangano and associates.[13]

Last but not least

- Bayer believes that the totality of the available data continue to support a favorable risk-benefit profile for Trasylol when used according to labeling.
- First through third quarter estimated global 2007 revenue for Trasylol: € 93 million, including approximately € 63 million from the U.S. and € 5 million in Germany.