

ORIGINAL ARTICLE

The Effect of Aprotinin on Outcome after Coronary-Artery Bypass Grafting

Andrew D. Shaw, M.B., Mark Stafford-Smith, M.D., William D. White, M.P.H., Barbara Phillips-Bute, Ph.D., Madhav Swaminathan, M.D., Carmelo Milano, M.D., Ian J. Welsby, M.B., Solomon Aronson, M.D., Joseph P. Mathew, M.D., Eric D. Peterson, M.D., M.P.H., and Mark F. Newman, M.D.

ABSTRACT

BACKGROUND

Aprotinin has recently been associated with adverse outcomes in patients undergoing cardiac surgery. We reviewed our experience with this agent in patients undergoing cardiac surgery at Duke University Medical Center.

METHODS

We retrieved data on 10,275 consecutive patients undergoing surgical coronary revascularization at Duke between January 1, 1996, and December 31, 2005. We fit data to a logistic-regression model predicting each patient's likelihood of receiving aprotinin on the basis of preoperative characteristics and to models predicting long-term survival (up to 10 years) and decline in renal function, as measured by increases in serum creatinine levels.

RESULTS

A total of 1343 patients (13.2%) received aprotinin, 6776 patients (66.8%) received aminocaproic acid, and 2029 patients (20.0%) received no antifibrinolytic therapy. All patients underwent coronary-artery bypass grafting, and 1181 patients (11.5%) underwent combined coronary-artery bypass grafting and valve surgery. In the risk-adjusted model, survival was worse among patients treated with aprotinin, with a main-effects hazard ratio for death of 1.32 (95% confidence interval [CI], 1.12 to 1.55) for the comparison with patients receiving no antifibrinolytic therapy ($P=0.003$) and 1.27 (95% CI, 1.10 to 1.46) for the comparison with patients receiving aminocaproic acid ($P=0.004$). As compared with the use of aminocaproic acid or no antifibrinolytic agent, aprotinin use was also associated with a larger risk-adjusted increase in the serum creatinine level ($P<0.001$) but not with a greater risk-adjusted incidence of dialysis ($P=0.56$).

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.

From the Departments of Anesthesiology (A.D.S., M.S.-S., W.D.W., B.P.-B., M.S., I.J.W., S.A., J.P.M., M.F.N.) and Surgery (C.M.) and the Duke Clinical Research Institute (E.D.P.), Duke University Medical Center, Durham, NC. Address reprint requests to Dr. Shaw at the Department of Anesthesiology, Duke University Medical Center, Durham, NC 27516, or at andrew.shaw@duke.edu.

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APROTININ (TRASYLOL, BAYER HEALTH-Care) is an antifibrinolytic agent in widespread use during cardiac surgery around the world, particularly in high-risk patients. Aprotinin was approved by the Food and Drug Administration on December 29, 1993, for use during cardiac surgery, to reduce the risk of blood transfusion. The literature on aprotinin contains reports of single studies ranging in size from 22 patients¹ to 12,403 patients,² as well as several meta-analyses and systematic reviews. Dozens of clinical trials have been conducted with this agent since the original report of efficacy of the high-dose regimen was published,¹ yet, as pointed out in a recent meta-analysis,³ questions about the use of aprotinin during cardiac surgery still remain.

This issue is an important one because patients undergoing cardiac surgery receive approximately one fifth of all the red-cell transfusions in the United States,⁴ and each unit transfused is known to increase the risk of infection.⁵ Recent observational studies have raised questions over the safety of aprotinin in both the short^{6,7} and longer⁸ terms. In addition, recent articles have suggested that more studies are needed,⁹ that no more studies are needed,¹⁰ that there is no excess risk associated with this drug,^{11,12} and even that the dose should be increased.¹³ Accordingly, we reviewed a large database at a single center in the United States, looking for evidence of an effect of antifibrinolytic therapy on survival and renal function after coronary-artery bypass grafting (CABG).

METHODS

STUDY POPULATION

Patients undergoing medical or surgical coronary revascularization at Duke University Medical Center (Durham, NC) also receive long-term follow-up. We retrieved data from before, during, and after surgery from our institution's surgical database for 10,275 consecutive patients who underwent CABG, with or without an additional cardiac surgical procedure, between January 1, 1996, and December 31, 2005. For patients who underwent more than one surgery during that period, only data from the first surgery were included.

We obtained long-term follow-up data for these patients from a separate institutional database of survival information for patients who have undergone revascularization surgery. Fol-

low-up was conducted by the Duke Clinical Research Institute Follow-up Services Group, which is responsible for collecting annual follow-up data on death and nonfatal end points for the Duke Databank for Cardiovascular Diseases. The annual surveys collect data on general health, hospitalizations, myocardial infarction, stroke, cardiac procedures, and medication use. Patients are surveyed 6 months after the index visit and yearly thereafter, by means of a mailed, self-administered questionnaire; nonresponders are surveyed by telephone. The rate of response is 95% for mortality data, and there is an annual search of the National Death Index for patients who are lost to follow-up (2%) or who have asked to be withdrawn (3%). Information on death is collected through next-of-kin interviews, reviews of hospital-discharge summaries and death certificates, and the National Death Index, which provides the cause of death according to the *International Classification of Diseases, 10th Revision*, after consensus among independent reviews is achieved by a committee.

STUDY DESIGN AND CONDUCT

This was a retrospective, observational, cohort study of prospectively collected data from consecutive patients who underwent CABG at Duke University Medical Center. The study protocol was approved by the Duke University institutional review board, and a waiver of the requirement of written informed consent was obtained. Both the primary and secondary end points (survival and renal function, respectively) were specified in advance of data retrieval and analysis, as was the propensity-score method.

STATISTICAL ANALYSIS

A total of 278 data fields were reviewed for use in analyses. In order to account for differences between patients who received aprotinin and those who did not, we fit the data to a logistic-regression model to estimate the probability that patients would receive aprotinin as part of their intraoperative care.

All reported P values are two-sided, and in all comparisons, P values of less than 0.05 were considered to indicate statistical significance. Post hoc pairwise comparisons between the study groups were adjusted by means of the Tukey or Bonferroni method, as described below.

Propensity-Score Model

We identified 84 preoperative and procedural variables as being potentially related to the use of aprotinin. We tested these variables separately for their association with the use of aprotinin, using chi-square tests for categorical variables and rank-sum tests for continuous variables. Of the 75 that were significantly associated with the use of aprotinin, 24 were redundant, were present in less than 1% of patients, or had missing values for more than 10% of patients. The remaining 51 variables were included in a stepwise, logistic-regression variable-selection analysis, and the 30 for which the association remained significant in this analysis were retained in the final model. A complete list of variables included at each stage is provided in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

This model was used to generate an aprotinin propensity score for each patient: the estimated probability of receiving aprotinin, based on the patient's preoperative characteristics. We then used the propensity score in several ways to account for the differences among the three study groups as we investigated the effect of antifibrinolytic therapy. In our primary analysis, we stratified the data according to the decile of the propensity score, to balance differences and remove any bias within the broad set of characteristics, with the goal of making comparisons within strata of homogeneous patients.¹⁴ In confirmatory follow-up analyses, we stratified the data according to the quintile of the propensity score; used the propensity score as a covariate in the model rather than as a stratifying factor; and performed matched-pairs analysis for a subgroup of patients receiving aprotinin who were matched in a one-to-one ratio, according to the propensity score, to patients who did not receive aprotinin.¹⁵

Survival Analysis

Our planned analysis of the effect of antifibrinolytic therapy on long-term survival included an unadjusted Kaplan–Meier comparison and an adjusted Cox proportional-hazards survival analysis. For descriptive purposes, we report simple 30-day and 1-year survival rates for the three study groups, which was compared using chi-square tests. We calculated unadjusted Kaplan–Meier survival estimates for patients receiving aprotinin, those receiving aminocaproic acid, and those re-

ceiving no antifibrinolytic therapy and compared them using a log-rank test. For our primary test of the effect of antifibrinolytic therapy on survival, we used a parsimonious Cox proportional-hazards model that included values for the risk associated with surgery from the European System for Cardiac Operative Risk Evaluation (the EuroSCORE; www.euroscore.org), age at surgery, year of surgery, and presence or absence of valve surgery, stratified according to the propensity-score decile. The interactions of the covariables with the study group were also tested. This model generated an estimated survival function and hazard ratios for death associated with the individual variables. We confirmed the veracity of the proportional-hazards assumption in the model both by inspecting plots of the Martingale residuals and by testing for an interaction between a constructed time-dependent covariable and the study group. We confirmed the robustness of the treatment effect in a model that included 22 additional preoperative covariables, selected from 48 potential covariables in a manner similar to that used for building the propensity-score model.

Analysis of Renal Function

Information on renal function was derived from analyses of blood samples obtained preoperatively, on the patient's arrival in the intensive care unit, and early in the morning of each postoperative day until hospital discharge, per institutional protocol. The baseline, preoperative serum creatinine level was defined as the last level recorded on the day before surgery. The peak in-hospital postoperative serum creatinine level was defined as the highest of the daily values. The peak fractional change in the creatinine level was used as the primary marker of renal-filtration impairment and was defined as the difference between the preoperative serum creatinine level and the peak in-hospital postoperative level, represented as a percentage of the preoperative level.

The effect of antifibrinolytic therapy on the peak fractional change in the creatinine level was evaluated in a multiple regression model that included adjustment for the aprotinin propensity score and for 17 additional, significant preoperative covariables. The set of covariables was selected by means of stepwise testing in a regression model, as described above for the propensity score. The interaction of age at surgery with

study group was also tested. We adjusted for pairwise comparisons between the study groups using the Tukey method. To check the robustness of the assumption of normality, the model was also tested by ranking the peak fractional change in the creatinine level. The effect of antifibrinolytic therapy on the incidence of renal-replacement therapy was tested with the use of a logistic-regression model adjusted for the aprotinin propensity score, preoperative creatinine level, age at surgery, duration of cardiopulmonary bypass, and presence or absence of diabetes.

RESULTS

CHARACTERISTICS OF PATIENTS

In all, 10,275 patients underwent CABG during the study period, 815 (7.9%) without cardiopulmonary bypass. Combined CABG–valve surgery was performed in 1181 patients (11.5%), and 642 (6.2%) underwent another, nonvalve operation in addition to CABG. For 127 patients who did not receive aprotinin, the study group (i.e., aminocaproic acid or no antifibrinolytic therapy) was not known. Therefore, data for these patients were used in the calculation of aprotinin propensity scores but not in the comparisons of outcomes among the three study groups.

A total of 1343 patients (13.2%) received aprotinin, 6776 patients received aminocaproic acid (66.8%), and 2029 patients (20.0%) received no antifibrinolytic therapy. Aprotinin was used in an increasing number of patients during the study period. Demographic and procedural data are presented in Table 1.

APROTININ PROPENSITY SCORES

We were able to calculate the aprotinin propensity score for 9734 patients. The c statistic for this model was 0.884. Variables entered into the model are listed in Table 1.

SURVIVAL ANALYSIS

Among the patients for whom survival status was known 30 days after surgery, the overall mortality was 2.9% (290 of 10,125 patients died). In the aprotinin group, 85 of the 1337 patients (6.4%) died, as compared with 161 of the 6764 patients (2.4%) receiving aminocaproic acid and 44 of the 2024 (2.2%) receiving no antifibrinolytic therapy. Among the patients for whom survival status was

known 1 year after surgery, the overall mortality was 7.6% (767 of 10,057 patients died). In the aprotinin group, 205 of the 1297 patients (15.8%) died, as compared with 431 of the 6748 patients (6.4%) receiving aminocaproic acid and 131 of the 2012 patients (6.5%) receiving no antifibrinolytic therapy. At each time point, the difference between the percentage for the aprotinin group and that for each of the other two groups was significant (Bonferroni-adjusted $P < 0.001$ for both comparisons), whereas the difference between the percentages for the aminocaproic acid group and the no-therapy group was not (Bonferroni-adjusted $P = 0.59$). The causes of death in each group were similar, except that there were more deaths related to cardiac surgery in the aprotinin group (29.6%) than in the aminocaproic acid group (9.9%) or the no-therapy group (19.1%) ($P < 0.001$) (see the Supplementary Appendix for all causes of death according to treatment group).

Kaplan–Meier survival estimates, both unadjusted and risk-adjusted, are presented in Figure 1. In both analyses, the curves for the three groups are significantly different ($P < 0.001$). Survival data were available for 9719 patients, approximately 972 per decile. The smallest number of deaths within a propensity-score stratum was 157. In this model, pairwise comparisons between the three treatment groups (with Bonferroni adjustment) showed a significantly higher hazard ratio for death associated with aprotinin use than with either no therapy ($P < 0.001$) or aminocaproic acid ($P = 0.001$), but there was no significant difference between the hazard ratios among patients receiving aminocaproic acid and those receiving no therapy ($P = 0.50$). There was an interaction between age and aprotinin use, such that the risk associated with aprotinin therapy was greater at younger ages. Thus, separate hazard ratios for aprotinin and age were not meaningful in this model.

In the main-effects model not including the interaction term, the hazard ratio for death in the aprotinin group as compared with the no-therapy group was 1.32 (95% confidence interval [CI], 1.12 to 1.55; $P = 0.003$), and the hazard ratio for the aprotinin group as compared with the aminocaproic acid group was 1.27 (95% CI, 1.10 to 1.46; $P = 0.004$) (Table 2). All three follow-up survival analyses also showed a significantly higher hazard ratio for death in the aprotinin group.

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)		

* Data for preoperative creatinine level were available for only 10,086 of the 10,148 study patients (1330 in the aprotinin group, 6746 in the aminocaproic acid group, and 2010 in the no-therapy group); for duration of cardiopulmonary bypass, 10,136 patients (1340 in the aprotinin group, 6770 in the aminocaproic acid group, and 2026 in the no-therapy group); for preoperative use of salicylates, 9865 patients (1280 in the aprotinin group, 6600 in the aminocaproic acid group, and 1985 in the no-therapy group); for urgency of procedure, 10,147 patients (1343 in the aprotinin group, 6776 in the aminocaproic acid group, and 2028 in the no-therapy group); for aprotinin propensity score, 9734 patients (1226 in the aprotinin group, 6553 in the aminocaproic acid group, and 1955 in the no-therapy group); for weight, 9564 patients (1188 in the aprotinin group, 6458 in the aminocaproic acid group, and 1918 in the no-therapy group); and for ejection fraction, 9597 patients (1273 in the aprotinin group, 6483 in the aminocaproic acid group, and 1841 in the no-therapy group). P values were calculated for the comparison of all three groups with the use of the chi-square test or the Wilcoxon test. Odds ratios are from the logistic-regression model that was used to generate the aprotinin propensity score. To convert values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, CAD coronary artery disease, and CPR cardiopulmonary resuscitation.

† The Parsonnet score, as defined by Parsonnet et al.,¹⁶ can range from 0% to 100%, with higher scores indicating an increased risk of in-hospital death after cardiac surgery.

‡ Chronic kidney disease was defined as a preoperative serum creatinine level of more than 3 mg per deciliter (265 μ mol per liter) or a condition requiring renal dialysis or renal transplantation.

§ Values for the European System for Cardiac Operative Risk Evaluation (EuroSCORE) can range from 0% to 100%, with higher scores indicating an increased risk of in-hospital death after cardiac surgery.

¶ Race or ethnic group was self-reported.

The results were similar among the follow-up analyses, even after data from patients who had undergone off-pump CABG were removed.

RENAL-FUNCTION ANALYSIS

Unadjusted and adjusted (predicted) percent increases in the serum creatinine level and the incidence of dialysis in each of the three groups are shown in Figure 2. For the creatinine outcome, the final covariable model included values for 19 predictors from 9456 patients. Although the Parsonnet score was significant in this model, neither the EuroSCORE nor the date of surgery was. A significantly greater increase in creatinine was associated with the use of aprotinin than with the

use of aminocaproic acid or no therapy, particularly for older patients; there was a significant interaction between aprotinin use and age ($P < 0.001$). There was no significant difference in the percent increase in serum creatinine level between patients receiving aminocaproic acid and those receiving no antifibrinolytic therapy, regardless of age. Table 3 presents detailed results of the main-effects model without the interaction term to allow direct interpretation of the treatment effects. The effect of the requirement of blood transfusion was tested in a follow-up model but was not significant. Although there were significant differences in the unadjusted incidences of dialysis among the three study groups (Fig. 2), the adjust-

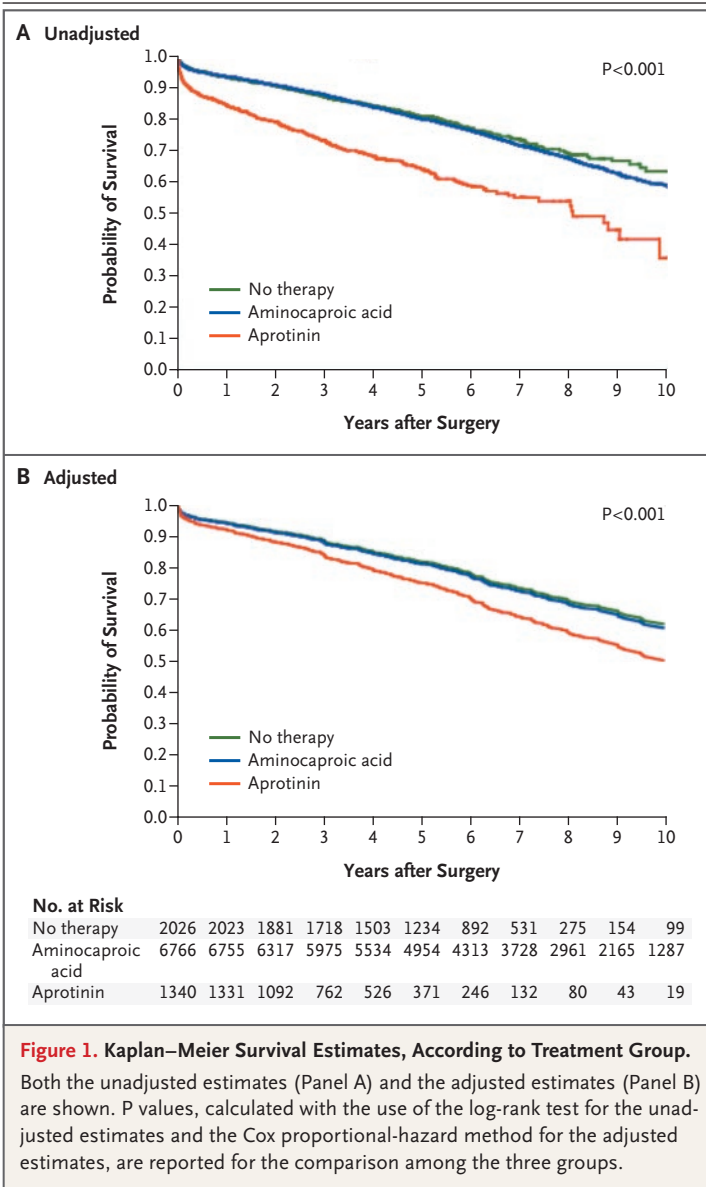


Figure 1. Kaplan–Meier Survival Estimates, According to Treatment Group. Both the unadjusted estimates (Panel A) and the adjusted estimates (Panel B) are shown. P values, calculated with the use of the log-rank test for the unadjusted estimates and the Cox proportional-hazard method for the adjusted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

ed incidences of dialysis were not significantly different (odds ratio for aprotinin vs. aminocaproic acid, 1.32; 95% CI, 0.77 to 2.27).

DISCUSSION

There is debate about the use of antifibrinolytic therapy to reduce bleeding during cardiac surgery, particularly in complex cases such as repeat sternotomy. The discussion over which drug to use continues. In a prospective cohort of 10,275 patients undergoing cardiac surgery at a single

center, we report an association between aprotinin therapy and increased short-term and long-term mortality, as well as an increased degree of acute kidney injury.

The differences in the unadjusted rates of the outcomes between patients receiving aprotinin and those receiving aminocaproic acid or no therapy were striking at 30 days, 1 year, and beyond. These differences in mortality remained significant after risk adjustment (Fig. 1), which raises the question: Does the use of aprotinin increase short-term and long-term mortality after cardiac surgery? This question should be viewed in the context of the potential benefit from aprotinin (which is the indication for the drug): reduced blood transfusion. However, sicker patients undergoing more complex operations are more likely to need blood transfusions, and are thus more likely to be given aprotinin, than are patients undergoing less complex surgeries. Thus, as recently suggested by Furnary et al.,¹⁷ the need for transfusion is an important issue. In our patients, aprotinin therapy did not appear to reduce the need for transfusion, even when year of surgery, type of surgery, and aprotinin propensity score were included in the multivariate analysis. Although this may simply represent residual confounding, it may also mean that the potential risks associated with aprotinin use are not outweighed by the potential benefits.

The use of aprotinin increased substantially through the late 1990s and early 2000s until the reports of Mangano et al.⁶ and Karkouti et al.⁷ were published in 2006. These were followed by much discussion and debate, and subsequently, several other reports on the safety of aprotinin appeared in the literature.^{11,12,17} Our institution collects follow-up data on all patients undergoing coronary revascularization, and our database thus contains information from an unselected cohort of patients with prospectively collected data from a period (1996 through 2005) before the studies by Mangano et al. and Karkouti et al., which raised the issue of the safety of aprotinin, were reported.

In our patients, aprotinin was associated with a larger increase in the serum creatinine level than was either aminocaproic acid or no antifibrinolytic therapy. This result was found in both the analysis of data from the whole cohort and the matched-pair analysis (see the Supplementary

Appendix), and it is consistent with the findings of Mangano et al. and Karkouti et al. but not with that of Furnary et al., despite the inclusion of blood-transfusion data in our model (see the Supplementary Appendix).

We did find a higher incidence of dialysis among patients treated with aprotinin than among those in the other two groups, but this difference disappeared when the multivariable regression model was applied. This finding is consistent with the results reported by Furnary et al. and Karkouti et al. but not those reported by Mangano et al. We believe these differences are due to the fact that we modeled a continuous variable (the relative increase in serum creatinine) rather than a dichotomous outcome (the presence or absence of renal failure). The differences may be explained by aprotinin causing a mild decline in renal function that was not severe enough to affect the dialysis rate. An alternative explanation is that our study was insufficiently powered to find a difference in an event with such a low incidence. The odds ratio for dialysis in the aprotinin group as compared with the aminocaproic acid group (1.32; 95% CI, 0.77 to 2.27) is consistent with that reported in other studies.¹⁷

Strengths of our study include the real-world, unselected nature of the patient population, the prospective and unbiased method of data collection, and the fact that the patients were treated at a single center. Furthermore, our data are supported by the recent suspension of enrollment¹⁸ in a prospective randomized clinical trial assessing the use of aprotinin, aminocaproic acid, or tranexamic acid during high-risk cardiac surgery,¹⁹ although the results of that study have not yet been formally reported. Our finding of a consistently significant treatment effect across deciles of the aprotinin propensity score is further supported by evidence from the multivariate model including the propensity score as a covariable and from the matched-pair analysis.

Limitations of our study include the retrospective nature of the analysis, the uncertainty about whether propensity methods can fully account for differences between groups of patients, and the increasing use of aprotinin over time. We did address the change in the pattern of aprotinin use by including the year of surgery in every model, although this is unlikely to fully account for the pattern. We did not attempt to control for

Table 2. Hazard Ratios for Death from the Main-Effects Multivariable Cox Proportional-Hazards Model with No Interaction Term.*

Variable	P Value	Hazard Ratio (95% CI)
Study group†	0.002	—
Aprotinin vs. no therapy	0.003	1.32 (1.12–1.55)
Aprotinin vs. aminocaproic acid	0.004	1.27 (1.10–1.46)
Aminocaproic acid vs. no therapy	0.51	1.04 (0.92–1.17)
Age at surgery (per year)	<0.001	1.027 (1.02–1.03)
Year of surgery (per year)	<0.001	0.95 (0.93–0.97)
Additive EuroSCORE (per unit)	<0.001	1.11 (1.09–1.13)
Valve surgery vs. no valve surgery	<0.001	1.50 (1.35–1.67)

* Results from the model without the interaction term for age with aprotinin are shown to allow for direct interpretation of the hazard ratios (see the Supplementary Appendix for a full description of the model with the interaction term). EuroSCORE denotes the value for the European System for Cardiac Operative Risk Evaluation.

† The comparison among the three groups and the comparison between the aprotinin group and the aminocaproic acid group were not terms in the model but were tested as combinations of model parameters. The group that did not receive therapy was the reference group, except for the comparison between the aprotinin group and the aminocaproic acid group, for which the hazard ratio was obtained by making the aminocaproic acid group the reference group. The P values for the three pairwise comparisons of study groups were calculated with the use of the Bonferroni adjustment for multiple comparisons.

the practices of individual surgeons, which may be an important confounder for transfusion. There were significant differences between the patients who received aprotinin and those who did not. Although we included the EuroSCORE in our risk-adjustment model, the EuroSCORE system is designed to predict short-term mortality and is unvalidated in the longer term. Lastly, the fact that we were able to successfully fit the data into a propensity-score model indicates that the study groups were not exactly the same. The most important, and unanswered, question therefore is: What are the unobserved differences among the groups (residual confounding), and are these differences sufficient to explain the differences in survival and renal function?

In addition to the primary and secondary end points (which were specified in advance of data gathering and analysis), we also tested many aspects of the association between aprotinin use and outcome, with adjustment for multiple comparisons among groups but not for different tests of the outcome data. We recognize that our data do not permit a rigorous hypothesis test; rather, we wished to examine and present separately

Table 3. Results from the Multivariable Regression Model for Percent Increase in Serum Creatinine Level.*

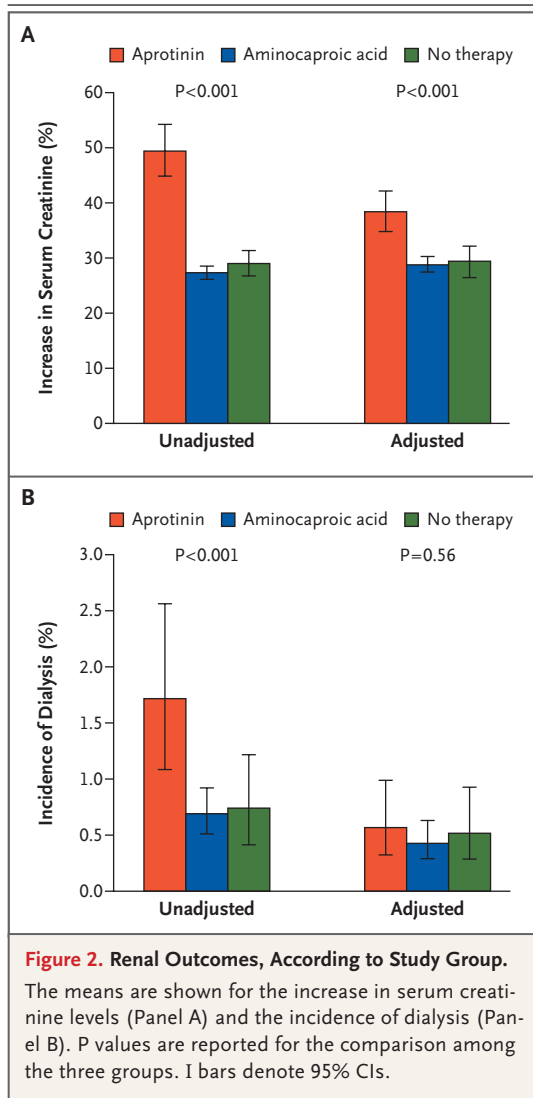
Variable	P Value	Beta Regression Coefficient (95% CI)
Study group†	<0.001	—
Aprotinin vs. no therapy	<0.001	10.03 (5.50 to 14.56)
Aprotinin vs. aminocaproic acid	<0.001	—
Aminocaproic acid vs. no therapy	0.99	0.06 (−3.13 to 3.25)
Duration of cardiopulmonary bypass (per min)	<0.001	0.15 (0.12 to 0.17)
Parsonnet score (per unit)	<0.001	0.45 (0.22 to 0.68)
Cardiopulmonary bypass (yes vs. no)	<0.001	−17.55 (−23.01 to −12.09)
Preoperative creatinine level (per mg/dl)	<0.001	−6.21 (−7.54 to −4.89)
Weight (per kg)	<0.001	0.24 (0.17 to 0.30)
White race vs. other	<0.001	−5.63 (−8.72 to −2.54)
Urgency of procedure (per level)	0.03	2.40 (0.29 to 4.52)
Chronic kidney disease (yes vs. no)	<0.001	11.97 (5.55 to 18.39)
Diabetes (any type) (yes vs. no)	0.007	3.29 (0.91 to 5.67)
Aortic regurgitation (yes vs. no)	0.02	−3.15 (−5.87 to −0.44)
Preoperative nitroglycerin (yes vs. no)	0.007	4.40 (1.21 to 7.60)
Preoperative inotrope (yes vs. no)	0.02	13.23 (1.80 to 24.66)
Hypertension (yes vs. no)	0.01	3.18 (0.69 to 5.67)
Age at surgery (per year)	0.006	0.19 (0.05 to 0.33)
Female sex vs. male sex	0.05	2.52 (0.05 to 4.99)
Aprotinin propensity score (per unit)	0.42	3.66 (−5.26 to 12.59)

* Results from the model without the interaction term for age with aprotinin are shown to allow for direct interpretation of the hazard ratios (see the Supplementary Appendix for a full description of the model with the interaction term). The beta coefficients show the amount of change expected in the percent increase in creatinine per unit increase in each variable.

† The comparison among the three groups and the comparison between the aprotinin group and the aminocaproic acid group were not terms in the model but were tested as combinations of model parameters. The group that did not receive therapy was the reference group. The P values for the three pairwise comparisons of study groups were calculated with the use of the Bonferroni adjustment for multiple comparisons.

many aspects of the data to accumulate the evidence in a straightforward manner.

In summary, we present evidence of an association between aprotinin use and reduced survival at 30 days, 1 year, and beyond and an association between aprotinin use and a decline in renal function. These findings persisted even after we had attempted to account for the factors that increased the likelihood of receiving aprotinin, first by including the propensity score in each model and then by matching patients according to the probability that they would receive



aprotinin (see the Supplementary Appendix). It is unclear whether these associations with adverse outcome are due to aprotinin use, to a degree of residual confounding between the patients who received it and those who did not, or to a combination of these two possibilities.

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