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Effects of Aprotinin Dosage on Renal Function

An Analysis of 8,548 Cardiac Surgical Patients Treated with Different Dosages of Aprotinin

Wulf Dietrich, M.D., Ph.D., Raimund Busley, M.D.,† Anne-Laure Boulesteix, Ph.D.‡*

Background: **The nonspecific serine protease inhibitor aprotinin is widely used in cardiac surgery to limit bleeding. Recently, concerns about the safety of this drug were raised, especially regarding impaired renal outcome. This event rate was supposed to be dose dependent.**

Methods: **In this observational study, the authors analyzed prospectively collected data of a single-center cardiac-anesthetic database. Adult patients treated with various dosages of aprotinin were evaluated. Logistic regression analysis identified independent predictors of renal outcome. The primary endpoint was a composite of novel postoperative renal failure requiring hemodialysis, an increased postoperative creatinine plasma concentration of 2 mg/dl or greater, or a difference between maximal postoperative and preoperative plasma creatinine of 0.7 mg/dl or greater.**

Results: **The study analyzed 8,548 patients. Multiple logistic regression (c index = 0.861) did not show a significant association between aprotinin dosage and renal outcome, as did the bootstrap procedure (odds ratio, 0.98; confidence interval, 0.90–1.07). The most relevant predictor was a preoperatively elevated creatinine concentration (odds ratio, 11.4; confidence interval, 9.05–14.3). Patients with postoperative renal impairment or failure were at higher preoperative risk and/or underwent more complex procedures. In subgroups of patients with preoperatively impaired renal function (creatinine ≥1.5 mg/dl) (n = 1,075), complex procedures (n = 1,920), or insulin-dependent diabetes (n = 650) or patients undergoing isolated myocardial revascularization (n = 4,901), no association between aprotinin dosage and adverse renal outcome was observed.**

Conclusion: **In the current analysis, aprotinin dosage was not associated with increased adverse renal outcome. In regard to renal outcome, this analysis did not demonstrate an essential detrimental influence of aprotinin dosage on renal function.**

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* Professor of Anesthesia, Institute for Research in Cardiac Anesthesia, Munich, Germany. † Consultant, Department of Anesthesiology, Critical Care and Pain Therapy, Behandlungszentrum, Vogtareuth, Germany. ‡ Statistician, Department of Medical Statistics and Epidemiology, Klinikum Rechts der Isar, Munich, Germany. Drs. Dietrich and Busley formerly held positions at the German Heart Center Munich.

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Address correspondence to Dr. Dietrich: Institute for Research in Cardiac Anesthesia, Winthirstr. 4, 80639 Munich, Germany. wulf.dietrich@t-online.de.

THE broad-spectrum serine protease inhibitor aprotinin is used in cardiac surgery to limit perioperative bleeding and to reduce allogeneic blood transfusion. This efficacy has been demonstrated in numerous studies and meta-analyses.[1–3] However, since the advent of aprotinin use in cardiac surgery, concerns have been raised about the safety due to possible procoagulatory properties of the drug.[4,5]

Recently, new doubts were raised with the publication of two observational studies of large cardiac surgical databases. Karkouti *et al.*[6] found an increased rate of renal dysfunction in patients treated with aprotinin in comparison with patients treated with tranexamic acid (24% *vs.* 17%; $P = 0.001$). Mangano *et al.*[7] retrospectively analyzed 4,374 cardiac surgical patients and found an association of the use of aprotinin with renal failure, myocardial infarction or heart failure, and stroke. In addition, a dose-dependent detrimental effect of aprotinin on renal function was proposed.[7] Both studies applied sophisticated statistical methods including propensity scoring in an attempt to eliminate possible confounding factors and biases.[8] These studies provoked extensive discussion in the medical literature.[9–11]

Aprotinin is excreted by the kidneys. After glomerular filtration, it is actively reabsorbed by the proximal tubule. The drug is metabolized by lysosomal enzymes in the kidney.[12] Due to this active process, a transient increase of serum creatinine may be likely and has been reported.[13–15] Other studies did not confirm these potentially detrimental renal effects.[16,17] Analysis of several studies reporting on renal outcome after aprotinin use revealed a potential influence of aprotinin on renal function but no influence on the incidence of renal failure requiring hemodialysis.[18] A recent meta-analysis confirmed these results.[19]

In a previous analysis of our institutional database, we investigated the influence of aprotinin dosage on bleeding and transfusion requirement in cardiac surgery.[20] A secondary endpoint of this analysis was the renal outcome. There was no association of aprotinin dosage and postoperative hemodialysis or renal dysfunction.

In the current investigation, the influence of the dosage of aprotinin on postoperative renal function is analyzed in a larger data set more thoroughly. The hypoth-

esis was that the dosage of aprotinin did not influence renal outcome after cardiac surgery. The primary endpoint of this analysis is the association of aprotinin dosage on postoperative renal outcome.

Materials and Methods

The human studies committee of the medical faculty of the Technical University Munich (Munich, Germany) approved the protocol and agreed that, because of the retrospective setting without a specific study intervention, specific informed consent was not necessary to obtain. All patients had previously granted permission for use of their medical records for research purposes.

The data of all adult patients undergoing cardiac surgery with the help of cardiopulmonary bypass (CPB) treated with aprotinin (Trasylol®; Bayer, Leverkusen, Germany) between January 1, 1995, and June 30, 2005, were analyzed. Data used in this analysis were retrieved from the institutional cardiovascular anesthesia database that includes data collected as part of the national quality assurance project of cardiac anesthesia.[21]

The database prospectively collects a comprehensive list of 238 prespecified items, including demographic, clinical, transfusion, and outcome data. Regarding renal function, preoperative creatinine, creatinine on the first postoperative day and at discharge from the intensive care unit, peak creatinine concentration during the stay in the intensive care unit, and incidence of postoperative renal dialysis or hemofiltration were recorded. The author W.D. had full access to all study data and takes responsibility for the integrity of the data, and A.-L.B. was responsible for the accuracy of the data analysis.

Patients with preoperative renal dialysis (n = 80) and patients who died in the operating room (n = 56) were excluded from the study. A study nurse, who was blinded to details of the current study, completed missing variables of interest from the medical records or recontrolled implausible data.

Only patients undergoing coronary artery bypass grafting (CABG), aortic or mitral valve replacement or repair, combined aortic and mitral valve replacement, or combined valve replacement and CABG were included. Patients were classified as having complex surgery if the index surgery was combined CABG and valve surgery, if the patient had previous cardiac surgery, or if the procedure was nonelective. Urgent procedures were defined as operations within 24 h after an unscheduled admission to the hospital. The preoperative risk was assessed by the Cleveland Clinic Risk Score,[22] because the widespread applied European System for Cardiac Operative Risk Evaluation (EuroSCORE)[23] was recorded since 2002 and was thus not available for all patients. The estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease equation.[24]

Only insulin-dependent diabetes was assumed as diabetes. Antiplatelet medication was taken into account for statistical evaluation, if aspirin, clopidogrel, or the combination of both was administered until the day before surgery. The circulatory state of patients 5 min after skin incision was coded as stable without or low inotropic support (up to 5 μg/kg dopamine), or unstable despite inotropics or intraaortic balloon pump. Intraoperative inotropic support was defined as the continuous infusion of more than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine or dobutamine, or the additional treatment with epinephrine, norepinephrine, or milrinone, respectively. The cardiac rhythm was dichotomized into atrial fibrillation and no atrial fibrillation (which was sinus rhythm in the majority of the cases). Patients were coded as having a history of cerebrovascular disease if they had had a previous cerebrovascular accident with or without residual ischemic neurologic deficits. Preoperative medications as β-blockers, angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers, statins, heparin, or phenprocoumon were recorded within the database.

Aprotinin Treatment and Intraoperative Care

The actual aprotinin dosing was at the discretion of the attending anesthesiologist. Patients received a bolus of 2×10^6 kallikrein inhibitor units (KIU) aprotinin after sternotomy followed by a continuous infusion of 5×10^5 KIU/h. In addition, the oxygenator was primed with 2×10^6 KIU aprotinin. Because the continuous infusion of 5×10^5 KIU/h is not able to maintain constant plasma concentrations,[25] some anesthesiologists applied a continuous infusion of 1×10^6 KIU/h instead of 5×10^5 KIU/h and repeated a bolus of 1×10^6 KIU aprotinin after 60 min of CPB. The infusion was not stopped at a total dose of 6×10^6 KIU, whereas other anesthesiologists preferred a half-dose regimen. These different practice patterns resulted in a wide variation of total aprotinin dosages.

Anesthesia was performed with sufentanil, midazolam, and propofol, supplemented with sevoflurane inhalation; neuromuscular blockade was achieved by either pancuronium bromide or rocuronium. CPB was performed in standard technique with the use of a membrane oxygenator. Patients were anticoagulated for CPB with a porcine heparin bolus of 375 units/kg. Heparinization was controlled with the celite activated clotting time[26] with a target of 480 s.

Measurement of Outcomes

All outcome measures used in this analysis were prespecified. The primary endpoint was the occurrence of a renal event, defined as a composite of first-time dependency on renal dialysis postoperatively, an increase of postoperative creatinine of 2 mg/dl or greater, or a difference of 0.7 mg/dl or greater between the preoper-

ative and maximal postoperative plasma creatinine concentration. These characteristics for renal insufficiency were defined in accordance with published thresholds.[7,27] In addition, the three factors were analyzed separately and considered as secondary endpoints.

Statistical Analyses

Statistical analyses were performed using the computer software SPSS (version 13.0; SPSS Inc., Chicago, IL) and R (R-project, collaborative worldwide effort initiated by the Statistics Department of the University of Auckland, New Zealand).§ Missing values were completed from the medical records if possible. From the 12,026 screened adult patients undergoing cardiac surgery with the help of CPB, patients who were already on hemodialysis preoperatively or died in the operating room and patients who where not treated with aprotinin or did not undergo an index operation were excluded, leaving us with 10,151 patients. Of these 10,151 patients, 1,603 had missing values for at least one of the 29 variables included in the final multivariate model. Analyses were performed to determine whether the variables were missing at random with respect to the primary outcome. For each of the 29 variables included in the multivariate analysis, the chi-square test was applied to test whether the probability of the primary outcome for patients with missing value was the same as for patients with observed value. After Bonferroni adjustment for multiple testing, only three variables were significantly not missing at random (at the level 0.05): weight, aortic cross clamping, and platelet count, which are all continuous. Patients with missing values for categorical variables were excluded. Single imputation of the missing continuous values was performed using the regression methodology but yielded almost identical results as without imputation, in the sense that the set of selected variables was the same with few exceptions and that odds ratios (ORs) were similar. Hence, considering the large size of the data set, only results obtained with observed values are shown.

Univariate Analyses

Initially, potential risk factors were evaluated for the univariate association with renal outcome. The univariate relations between the four renal outcomes (postoperative hemodialysis; maximal postoperative creatinine $\geq$2 mg/dl; difference postoperative to preoperative creatinine $\geq$0.7 mg/dl; composite outcome) and the risk factors were evaluated based on the *t* test or Wilcoxon rank sum test (for continuous variables), Fisher exact test or the chi-square test (for nominal variables), and Somer d test (for ordinal variables).

Multivariate Analyses

Four logistic regression models were constructed using a backward stepwise selection procedure with the primary renal composite endpoint, and the secondary endpoints of peak creatinine 2 mg/dl or greater, delta creatinine 0.7 mg/dl or greater, or the postoperative occurrence of hemodialysis as binary response variables. At each step, the Wald statistic was used as a criterion to evaluate each potential risk factor. The cutoff for variable removal was set at a significance level of 0.1. The following potential risk factors were used as predictors in the logistic regression model: year of operation, sex, previous cardiac surgery, surgical priority (urgent or planned admission), weight, height, age, previous myocardial infarction, insulin-dependent diabetes, preoperative hemoglobin concentration, platelet count, peripheral arterial vascular disease, preoperative creatinine, the preoperative medication with β-blocker, thienopyridines (ticlopidine or clopidogrel), aspirin, phenprocoumon, duration of operation, CPB, and aortic cross clamping, circulatory state 5 min after skin incision, maximum intraoperative dosage of dopamine, epinephrine or norepinephrine, hemoglobin concentration 5 min after the onset of CPB, and intraoperative use of more than 5 units allogeneic blood or fresh frozen plasma (this extreme amount of blood transfusion was considered to be independent of aprotinin dosage). The calender year of surgery was included in the analysis because rates of postoperative renal dysfunction may have varied over time. Because of the large number of involved anesthesiologists and surgeons, the attending anesthesiologist or surgeon was not included as covariate in the calculation. Aprotinin dosage was taken as continuous variable. In order not to lose detailed information, derived variables, such as risk score or glomerular filtration rate, were not included into the model, but the itemized components were taken into the analysis.

Covariates that may be dependent on aprotinin dosage, such as patterns of coagulation, heparin amount, application of additional hemostatic agents, urine output, duration of chest closure, or circulatory state at the end of operation, are not included in the model. As such, we avoid that variables which may be influenced by the aprotinin dosage are selected in the model in place of the aprotinin dosage itself, thus masking its effects.

Odds ratios and their associated 95% confidence intervals (CIs) were estimated. $P < 0.05$ was considered as statistically significant. The goodness of fit of the model was assessed based on the Hosmer-Lemeshow test and the c index (area under the receiver operating characteristic curve), which demonstrates the predictive ability.

To test whether particular patients may be more susceptible to aprotinin treatment, analyses of the primary

§ Available at: http://www.R-project.org. Accessed September 18, 2007.

endpoint were also performed in four *a priori* identified subgroups:

I: patients with preoperatively impaired renal function (defined as creatinine ≥1.5 mg/dl)
II: patients undergoing complex cardiac operations
III: patients undergoing CABG (to obtain a homogenous patient group)
IV: patients with insulin-dependent diabetes[9]

In addition to logistic regression with backward elimination (which turned out to eliminate the variable of aprotinin from the model; see Results section), the variable aprotinin was forced into the model for direct assessment, based on a bootstrap procedure. To simulate random variations of the data, 1,000 bootstrap samples were drawn with replacement from the data set including 8,548 patients, and for each bootstrap sample, a logistic regression model including all of the selected variables and the aprotinin dosis was fitted, yielding bootstrap CIs for the OR of the aprotinin dosis.

The effect of aprotinin dosage was also evaluated using partial least squares (PLS), a dimension reduction technique that is particularly appropriate in the case of highly correlated variables.[28] The PLS component was constructed as a linear combination of the 29 variables selected for multivariate analysis in a supervised manner using the aprotinin dosage as response. It can be interpreted as the predicted aprotinin dosage given all of the other variables. A logistic model was then fitted using the PLS component and the aprotinin dosage as covariates.

Results

Of the 12,026 patients screened, 8,548 were entered into the final analysis. Eighty and 56 patients were excluded because they were already on hemodialysis preoperatively or died in the operating room, respectively. The other patients were excluded because they were not treated with aprotinin or did not undergo an index operation (fig. 1). Of the analyzed patients, 57% underwent coronary bypass surgery, 17% underwent aortic, 10% underwent mitral valve surgery, 12% underwent a combined procedure, 3% underwent double valve replacement, and 23% underwent complex surgery. The baseline characteristics are given in tables 1 and 2.

The composite endpoint was registered in 8.2% of the patients. Hemodialysis was found in 3.4%, a postoperative creatinine plasma concentration greater than 2 mg/dl was found in 5.8%, and a postoperative to preoperative creatinine difference greater than 0.7 mg/dl was found in 3.8% of the patients. The univariate association of the most important variables is presented in tables 1 and 2. This univariate comparison demonstrates that

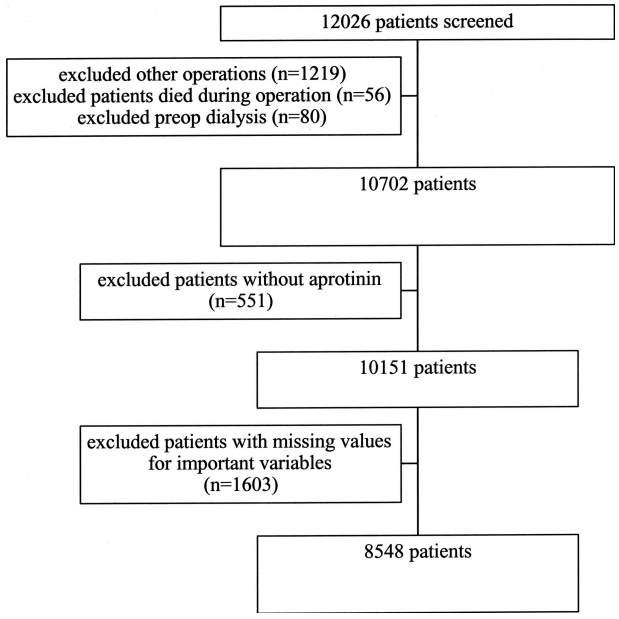

Fig. 1. Consolidated Standards of Reporting Trials diagram of patient enrollment. The diagram shows the number of patients screened and finally included in the analysis.

patients with adverse renal outcome were at significantly higher preoperative risk compared with patients with normal postoperative renal function. The total aprotinin dosage ranged from 0.5 to 12 × 10^6 KIU, with a mean of 5.4 × 10^6 ± 0.9 × 10^6 KIU. Patients with the composite endpoint had a significantly higher total aprotinin dosage compared with patients with normal postoperative renal function (5.62 ± 1.26 *vs.* 5.4 ± 0.86 KIU; $P < 0.001$). Because the dosage of aprotinin is time dependent, patients with complex procedures or double valve replacement had a longer duration of operation and, thus, higher aprotinin dosages compared with the other patients. A dosage of 6 × 10^6 KIU aprotinin or greater was applied in 2,317 patients (27%). But adjusted for duration of operation and body weight, the aprotinin dosage in patients with composite endpoint was even lower compared with patients without the endpoint (not significant; table 2). Over the time period of the data collection, the percentage of patients undergoing complex surgery increased from 16% to 30% ($P < 0.0001$), while the dosage of aprotinin also increased. However, the composite renal event rate was stable over the observation period (table 3). In the univariate analysis, the attending anesthesiologist had no statistically significant influence on renal outcome, but a trend could be observed ($P = 0.057$). Among the anesthesiologists who attended more than 100 operations, the frequency of renal outcomes varied between 6% and 13%. These differences may be because risk patients are usually attended by more experienced anesthesiologists.

An association between aprotinin dosage and renal outcome could not be observed in either of the mul-

Table 1. Patient's Preoperative Characteristics

	Total (n = 8,548)	Composite (n = 655 [8.2%])	*P* Value*
Age, yr	66 ± 11	70 ± 8	<0.0001
Male	68.6%	70.1%	0.37
Height, cm	170 ± 9	169 ± 8	0.10
Weight, kg	76 ± 14	75 ± 14	0.02
Body mass index, kg/m^2	26 ± 4	26 ± 4	0.17
NYHA classification			
I	206 (2.6%)	7 (1.1%)	<0.0001
II	2,158 (27.5%)	81 (12.4%)	
III	4,739 (60.5%)	377 (57.6%)	
IV	733 (9.4%)	143 (21.8%)	
Preoperative risk†	3.2 ± 3.1	6.6 ± 4.3	<0.0001
Preoperative risk category†			
0–2	3,755 (50.7%)	101 (15.1%)	<0.0001
3–5	2,155 (29.1%)	148 (22.6%)	
6–8	950 (12.8%)	154 (23.5%)	
9–11	383 (5.2%)	92 (14.0%)	
>11	157 (2.1%)	81 (12.4%)	
EuroSCORE‡	4.7 ± 2.7	7.3 ± 3.2	<0.0001
Ejection fraction§			
>50%	3,071 (72.5%)	151 (43.3%)	<0.0001
30–50%	843 (19.9%)	92 (26.4%)	
<30%	319 (7.5%)	48 (13.8%)	
Previous myocardial infarction§	2,087 (42.6%)	168 (48.1%)	0.0002
Previous PTCA or stent§	908 (18.5%)	69 (19.8%)	0.49
Insulin-dependent diabetes	650 (7.6%)	91 (13.9%)	<0.0001
Diabetes, orally treated	897 (10.5%)	89 (13.6%)	0.65
Arterial vascular disease	570 (6.7%)	85 (13.0%)	<0.0001
Previous stroke	520 (15.2%)	64 (9.8%)	<0.0001
Hypertension	4,045 (48.4%)	315 (48.1%)	0.69
Preoperative atrial fibrillation	1,110 (13.0%)	120 (18.3%)	<0.0001
Preoperative creatinine, mg/dl	1.2 ± 0.4	1.7 ± 0.8	<0.0001
Glomerular filtration rate, ml·min^{-1}·1.73 m^{-2}‖	76 ± 25	55 ± 27	<0.0001
Glomerular filtration rate <60 ml	26%	64%	<0.0001
Preoperative hemoglobin, g/dl	13.5 ± 1.7	12.6 ± 1.9	<0.0001
Preoperative antithrombin activity, %	95 ± 14	91 ± 17	<0.0001
Preoperative platelets, × 10§/mm^3	239 ± 72	237 ± 85	0.41
Preoperative medication#			
β-Blocker	4,451 (52.1%)	315 (48.1%)	0.04
ACE inhibitors	3,022 (40.6%)	229 (35.0%)	0.49
Ticlopidine/clopidogrel	775 (9.1%)	59 (9.0%)	0.80
Aspirin	1,858 (21.7%)	107 (16.3%)	0.0003
Phenprocoumon	621 (7.3%)	66 (10.1%)	0.004
Heparin, intravenous or subcutaneous	2,082 (24.4%)	251 (38.3%)	<0.0001
Previous sternotomy	765 (8.9%)	93 (14.2%)	<0.0001

* *P* values were calculated for the comparison of patients with and without the renal endpoint. The results for patients without the renal endpoint are not presented because they were virtually identical to the results of all patients. † Preoperative risk was assessed with the Cleveland Clinic Risk Score.[20] ‡ European System for Cardiac Operative Risk Evaluation (EuroSCORE) was calculated for patients undergoing surgery in 2002 or later. § These variables were calculated for coronary artery bypass graft patients only. ‖ Clearance calculated according the Modification of Diet in Renal Disease formula.[22] # Medication is presented for all patients.

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

tivariate models: Aprotinin dosage taken as continuous variable was excluded during the backward selection procedure and thus not included in the final models. The main predictor for adverse renal outcome was the preoperative creatinine plasma concentration (OR, 11.4; CI, 9.05–14.3; $P < 0.0001$). Other significant predictors are presented in table 4. Table 5 depicts the results of the multivariate analysis for secondary outcomes. Interestingly, insulin-dependent diabetes was not predictive for the primary endpoint. Although aprotinin dosage was not selected in any of the models, it was forced into the model with an additional bootstrap procedure to evaluate its effect. The bootstrap procedure showed no significant effect of aprotinin dosage (median OR, 0.98; CI, 0.90–1.07). In the logistic regression model based on the PLS component and the aprotinin dosage, aprotinin dosage was not a significant predictor of the composite outcome ($P = 0.87$) in contrast to the PLS component ($P < 0.0001$), thus indicating that the patient characteristics leading to a high aprotinin dosage, not the dosage itself, increase the risk of renal outcome.

Table 2. Operative Characteristics Univariate Analysis

	Total (n = 8,548)	Composite (n = 655 [8.2%])	*P* Value
Aprotinin dosage, 10^6 KIU	5.4 ± 0.86	5.62 ± 1.26	<0.0001
Aprotinin dosage adjusted for BW and time of operation, KIU·kg^{-1}·min^{-1}	333 ± 230	329 ± 649	0.60
Type of operation			
CABG	4,901 (57.3%)	349 (53.1%)	<0.0001
AVR	1,471 (17.2%)	91 (13.9%)	
Double valve	261 (3.1%)	34 (5.2%)	
Combined procedure	1,043 (12.2%)	122 (18.6%)	
MVR/R	872 (10.2%)	59 (9.0%)	
Surgical priority urgent/emergent	2,299 (26.9%)	289 (44.1%)	<0.0001
Complex procedure	1,920 (22.5%)	220 (33.6%)	<0.0001
CPB, min	102 ± 40	128 ± 63	<0.0001
AoX, min	68 ± 27	79 ± 37	<0.0001
Duration of operation, min	238 ± 73	279 ± 105	<0.0001
Unstable circulatory state at induction*	639 (7.5%)	138 (21.1%)	<0.0001
Unstable circulatory state 5 min after sternotomy*	667 (7.8%)	145 (22.1%)	<0.0001
Heart rate induction, min^{-1}	64 ± 15	70 ± 20	<0.0001
Hemoglobin 5 min CPB, g/dl	7.9 ± 1.7	7.4 ± 1.3	<0.0001
Inotropic support†	2,698 (31.6%)	387 (59.1%)	<0.0001
Dopamine >5 μg·kg^{-1}·min^{-1}	1,406 (16.4%)	225 (34.4%)	<0.0001
Epinephrine >0 μg/h	403 (4.7%)	109 (16.6%)	<0.0001
Norepinephrine >0 μg/h	1,574 (18.4%)	246 (37.6%)	<0.0001
Allogeneic blood intraoperatively >5 units	43 (0.5%)	19 (2.9%)	<0.0002
FFP intraoperative >5 units	27 (0.3%)	12 (1.8%)	<0.0003
Platelet transfusion	266 (3.1%)	72 (11.0%)	<0.0001
Attending anesthesiologist			0.057
Atrial fibrillation end operation	708 (9.4%)	92 (14.0%)	<0.0001
Rethoracotomy for bleeding	169 (2.0%)	53 (8.1%)	<0.0001
In-hospital mortality	326 (3.8%)	189 (28.9%)	<0.0001

* Unstable circulatory state defined as mean arterial pressure less than 60 mm Hg despite inotropic support and/or intraaortic balloon pump or heart rate greater than 100/min. † Inotropic support defined as dopamine or dobutamine infusion greater than 5 μg·kg^{-1}·min^{-1} or epinephrine or norepinephrine greater than 100 μg/h.

AoX = aortic cross clamp time; AVR = aortic valve replacement; BW = body weight; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; KIU = kallikrein inhibitor units; MVR/R = mitral valve repair/replacement.

Subgroup Analysis

In the subgroup of patients with a preoperative creatinine concentration of 1.5 mg/dl or greater (n = 1,075), the aprotinin dosage was not a significant predictor for meeting the primary endpoint of the renal event. Again, the preoperative creatinine concentration was the strongest predictor for adverse outcome (OR, 7.05; CI, 4.70–10.6; $P < 0.0001$). Age (OR, 1.03; CI, 1.01–1.05; $P = 0.002$), preoperative hemoglobin concentration (OR, 0.98; CI, 0.97–0.99; $P < 0.0001$), urgency (OR, 1.48; CI, 1.08–2.01; $P = 0.013$), and duration of CPB in minutes (OR, 1.01; CI, 1.00–1.02; $P = 0.006$) were also significant predictors.

In the subgroup of patients undergoing complex procedures (n = 1,920) the preoperative creatinine concen-

Table 3. Changes in Patients' Profiles over the Observation Period

	Total	1995–1997	1998–1999	2000–2001	2002–2003	2004–2005*	*P* Value
Total n		1,788	1,617	1,833	1,757	962	
Hemodialysis	3.4%	3.5%	3.1%	3.6%	3.8%	2.5%	0.64
Peak creatinine ≥2 mg/dl	5.8%	7.3%	6.6%	5.0%	4.8%	5.3%	0.001
Deltacrea ≥0.7 mg/dl	3.8%	5.4%	4.0%	2.5%	3.1%	4.7%	0.02
Composite	8.2%	9.3%	8.5%	7.5%	7.9%	7.7%	0.07
Aprotinin ≥6 KIU†	27.1%	16.1%	22.2%	29.8%	38.0%	30.8%	<0.0001
Previous cardiac surgery	8.9%	11.3%	9.4%	8.5%	7.5%	7.4%	0.0003
Complex surgery	22.5%	16.0%	21.3%	24.2%	23.8%	30.1%	<0.0001
Age, yr	66 ± 11	65 ± 11	66 ± 11	66 ± 11	66 ± 12	66 ± 11	0.65
Mortality	3.8%	3.6%	4.0%	3.7%	4.6%	2.7%	0.11

* Not all patients in 2005 were included. Patient enrollment stopped June 30, 2005. † This is an arbitrary cutpoint that was chosen to demonstrate the increase of patients with high dosages of aprotinin over the years.

Composite = the primary endpoint was defined as a composite of first-time dependency on renal dialysis postoperatively, an increase of postoperative creatinine of 2 mg/dl or greater, or a difference of 0.7 mg/dl or greater between the preoperative and maximal postoperative plasma creatinine concentration; deltacrea = difference between preoperative and maximal postoperative creatinine; KIU = kallikrein inhibitor units.

Table 4. Multivariate Analysis for the Composite Endpoint

	OR (95% CI)	*P* Value
Aprotinin dosage*	0.98 (0.90–1.07)	0.87
Year of operation	0.94 (0.90–0.98)	0.003
Age, yr	1.03 (1.02–1.05)	<0.0001
Previous infarction	1.24 (1.02–1.52)	0.034
Peripheral vascular disease	1.60 (1.18–2.17)	0.002
Preoperative creatinine, mg/dl	11.4 (9.05–14.3)	<0.0001
Preoperative hemoglobin, g/dl	0.98 (0.98–0.99)	<0.0001
Aspirin	0.64 (0.50–0.83)	0.001
Surgical priority	1.52 (1.24–1.85)	<0.0001
CPB, min	1.01 (1.01–1.01)	<0.0001
AoX, min	0.99 (0.99–1.00)	<0.0001
Duration of operation, min	1.00 (1.00–1.00)	0.001
Circulatory status before induction	1.64 (1.25–2.16)	<0.0001
Dopamine >5 $\mu g \cdot kg^{-1} \cdot min^{-1}$	1.31 (1.05–1.64)	0.017
Epinephrine >100 μg/h	2.47 (1.78–3.43)	<0.0001
Norepinephrine >100 μg/h	1.52 (1.20–1.92)	0.001
C index	0.861	<0.0001
Hosmer-Lemeshow	12.00	0.151

Odds ratios (ORs) are only given for statistically significant variables. The aprotinin dosage* was not significant, but was forced into the model within an additional bootstrap procedure. The following potential risk factors were considered but not selected in the final model: sex, previous cardiac surgery, weight, height, age, insulin-dependent diabetes, platelet count, the preoperative medication with β-blocker, thienopyridines (ticlopidine or clopidogrel), phenprocoumon, circulatory state 5 min after skin incision, hemoglobin concentration 5 min after the onset of cardiopulmonary bypass (CPB), intraoperative use of more than 5 units allogeneic blood or fresh frozen plasma.

AoX = aortic cross clamp time; CI = confidence interval.

tration showed a significant association (OR, 10.05; CI, 6.72–15.03; $P < 0.0001$) with adverse renal outcome. Among others, urgency (OR, 1.74; CI, 1.22–2.49; $P = 0.002$), necessity of intraoperative epinephrine support (OR, 2.09; CI, 1.33–3.29; $P = 0.001$), preexisting peripheral arterial occlusive disease (OR, 2.11; CI, 1.24–3.58; $P = 0.006$), and duration of CPB in minutes (OR, 1.01; CI, 1.00–1.01; $P = 0.001$) were also significant predictors. The dosage of aprotinin, again, was not a significant predictor in this subgroup of patients. This did also apply for patients with insulin-dependent diabetes and the homogenous subgroup of CABG patients.

Discussion

The analysis of the current data set did not demonstrate any association of aprotinin dosage and postoperative renal dysfunction. Consistently, in all tested models, preoperative renal function as assessed by serum creatinine concentration was the strongest predictor for adverse renal outcome. This was observed to apply also in the subgroup analysis of patients having impaired renal function preoperatively, in patients with insulin-dependent diabetes, or in the homogenous group of patients undergoing isolated CABG surgery. Impaired preoperative renal function as estimated by preoperative creatinine concentration or the estimated filtration rate was consistently found to be one of the strongest predictors for adverse renal outcome in other studies evaluating risk assessment in cardiac surgery.[29,30] Chukwuemeka *et al.*[31] demonstrated in a subset of patients with preoperatively impaired renal function (clearance <60/ml/min) that preoperative renal function was the strongest predictor for renal outcome and that renal outcome was not affected by the use of CPB.

Aprotinin is a naturally occurring protein derived from bovine lung tissue. It is excreted by the kidney and metabolized in the proximal tubule. Because this is an active process, concerns about possible nephrotoxicity of aprotinin came up early after introduction in cardiac surgery.[32] These concerns could not be substantiated in *in vitro* studies[33] or clinical studies.[20,34] However, other studies reported impaired renal function with the use of aprotinin.[4,35] Therefore, an influence of aprotinin on renal function is conceivable.

Some studies investigating specifically the influence of aprotinin on renal function reported small but significant differences in renal function compared with control patients.[13] This renal impairment may be aggravated in the presence of other nephrotoxic drugs such as aminoglycosides[36] or angiotensin-converting enzyme inhibitors.[37] The influence of aprotinin on tubular function without tubular damage was confirmed by others.[38] However, these findings may even be interpreted as a nephroprotective property of aprotinin.[39]

Previously, a detrimental effect of aprotinin on renal function in patients with operations in deep hypothermic circulatory arrest was not substantiated.[40] Clinical studies in large patient populations also did not support the hypothesis of renal toxicity of aprotinin.[14,16,17,20,41] Systematic reviews of studies investigating the effect of aprotinin on blood loss and transfusion requirement did not corroborate the safety concerns. A recently updated Cochrane report described a similar incidence of renal dysfunction in aprotinin treated patients and control subjects.[1] These findings were confirmed in patients undergoing CABG surgery.[2] The ORs and 95% CIs for aprotinin and renal failure in these systematic reviews were 1.01 (0.63–1.14)[2] and 1.19 (0.69–1.36).[1] Admittedly, the endpoint of almost all studies included in these systematic reviews was blood loss and not renal safety, and the number of patients might have been insufficient to detect small differences in renal outcome or uncommon complications. A recent meta-analysis postulated an influence of aprotinin on renal impairment but no impact on renal insufficiency.[19] Brown *et al.*[19] analyzed 138 randomized trials using antifibrinolytic agents and did not find an association of these drugs with increased risk of dialysis-dependent renal failure, but demonstrated an increased risk of renal dysfunction with high-dose aprotinin but not with low-dose aprotinin. Because our analysis used higher dosages of aprotinin and a different

Table 5. Multivariate Analysis for Secondary Outcomes

	Hemodialysis, OR (95% CI)	*P* Value	Creamax ≥2 mg/dl, OR (95% CI)	*P* Value	Deltacrea ≥0.7 mg/dl, OR (95% CI)	*P* Value
Year of operation					0.87 (0.82–0.91)	<0.0001
Age, yr	1.04 (1.02–1.05)	<0.0001	1.03 (1.02–1.04)	<0.0001	1.05 (1.04–1.07)	<0.0001
Sex			0.64 (0.48–0.85)	0.002	0.63 (0.47–0.85)	0.003
Weight, kg					1.01 (1.00–1.02)	0.02
Previous infarction			1.28 (1.00–1.63)	0.05		
Diabetes insulin	1.52 (1.05–2.19)	0.03			1.59 (1.10–2.29)	0.01
Peripheral vascular disease	1.56 (1.05–2.30)	0.03	1.74 (1.22–2.48)	0.002	1.67 (1.15–2.41)	0.007
Preoperative creatinine, mg/dl	2.71 (2.23–3.29)	<0.0001	23.3 (17.6–30.8)	<0.0001	1.30 (1.03–1.64)	0.03
Preoperative hemoglobin, g/dl	0.99 (0.98–1.00)	0.03	0.98 (0.98–0.99)	<0.0001	0.99 (0.98–1.00)	0.002
Phenprocoumon			1.49 (0.99–2.23)	0.05		
Aspirin			0.69 (0.50–0.93)	0.02	0.55 (0.40–0.77)	0.001
Surgical priority	1.85 (1.42–2.42)	<0.0001	1.41 (1.10–1.81)	0.007	1.78 (1.38–2.28)	<0.0001
Previous heart surgery			0.69 (0.47–1.03)	0.07		
CPB, min	1.01 (1.01–1.01)	<0.0001	1.01 (1.01–1.01)	<0.0001	1.01 (1.00–1.01)	<0.0001
AoX, min			0.99 (0.98–1.00)	0.0004		
Duration of operation, min	1.00 (1.00–1.01)	0.005	1.00 (1.00–1.01)	0.008	1.00 (1.00–1.00)	0.05
Circulatory status before induction			1.49 (1.07–2.08)	0.02		
Circulatory status 5 min after thoracotomy	2.22 (1.61–3.06)	<0.0001				
Hemoglobin 5 min CPB, g/dl	0.98 (0.97–1.00)	0.005				
Dopamine >5 μg/kg			1.54 (1.18–2.01)	0.001	1.30 (0.99–1.72)	0.06
Epinephrine >100 μg/h	1.94 (1.35–2.80)	0.0004	1.97 (1.31–2.97)	0.001	2.34 (1.59–3.44)	<0.0001
Norepinephrine >100 μg/h	1.43 (1.07–1.90)	0.02	1.32 (0.98–1.77)	0.07	1.48 (1.09–2.00)	0.01
C index	0.840	<0.0001	0.907	<0.0001	0.791	<0.0001
Hosmer-Lemeshow	5.839	0.665	7.311	0.503	10.06	0.261

Odds ratios (ORs) are only given for statistically significant variables. The aprotinin dosage was not significant for any of the endpoints.

AoX = aortic cross clamp time; CI = confidence interval; CPB = cardiopulmonary bypass; creamax = maximal postoperative plasma creatinine concentration; deltacrea = difference between preoperative and maximal postoperative creatinine.

definition of renal impairment, our results do not refute the results of this meta-analysis.

In the assessment of the association of aprotinin dosage and renal function, it should be taken into account that the dosage of aprotinin applied is depending on the time of operation. Therefore, more complicated and complex procedures, which require longer CPB times, receive higher dosages of aprotinin. In the current analysis, the dosage of aprotinin adjusted for body weight and time of operation[20] was not significantly different in the univariate analysis in patients with impaired renal outcome. Therefore, the higher aprotinin dosage is just a surrogate marker for more complex operations and sicker patients.

Recent studies have questioned the risk–benefit ratio of aprotinin treatment. In an observational, nonrandomized, multinational database analysis,[7] the authors reported the outcome data of 4,374 patients undergoing coronary revascularization and found a doubling in the risk of renal events among patients treated with aprotinin (OR, 1.89; 95% CI, 1.01–3.55; $P = 0.04$). Among patients undergoing complex surgery (n = 1,361), aprotinin treatment was associated with increased renal dysfunction and renal failure requiring dialysis. Postoperative renal dialysis was found in 5% in the aprotinin group compared with 1% in the control group, and adverse renal outcome was reported in 8% in the aprotinin group compared with 3% in the control group. Previously, the same group reported in a comparable database an incidence of 7.8% adverse renal outcome for all patients independent of aprotinin treatment.[30] In an unadjusted analysis, the authors postulated a dose-dependent effect of aprotinin on renal events (18% in the high-dose aprotinin group *vs.* 7% in the low-dose group; $P < 0.001$). Apparently, patients treated with aprotinin were at higher preoperative risk compared with the patients treated with lysine analogs or control patients. There was also a significant between-country difference as well as a difference in process of care within this data set.[42] Because the indication for aprotinin use was not standardized within the database and the drug was not on the market in all of the countries participating in the study or not approved for all of the investigated indications, a selection bias cannot be ruled out. The results of this study were the subject of intensive and controversial discussion.[9–11,18,43]

Recently, the same data set, which was used by Mangano *et al.*,[7] was analyzed to investigate the influence of preoperative anemia on outcome.[44] Applying the number of blood transfusions as a continuous variable in their model, the authors demonstrated a direct relation between the number of units transfused intraoperatively and the incidence of adverse renal and cardiac outcome. These results were corroborated in another study[41]: The analysis of a multicenter cardiac surgery database showed an association with the use of aprotinin and acute renal failure. However, this association was totally offset if the model was adjusted for the number of

transfused packed erythrocytes, which was higher in the high-risk patient group receiving aprotinin. Aprotinin was no longer an independent risk factor for acute renal failure, but the number of transfusions was highly associated with adverse outcome. In the study of Mangano *et al.*,[7] intraoperative transfusion was used as a categorical variable (yes/no) and postoperative transfusion was not incorporated in the analysis. This could have confounded their analysis.

Another study analyzed a single-center institutional database and compared from a pool of 10,870 patients the outcome data of 449 patients treated with aprotinin with 449 matched patients treated with tranexamic acid.[6] The analysis did not demonstrate differences in the incidence of postoperative renal failure requiring dialysis ($P = 0.3$). However, in patients with abnormal preoperative renal function, it revealed a significant difference in the incidence of postoperative dysfunction (tranexamic acid: 23/126 [18%]; aprotinin: 34/110 [31%]; $P = 0.03$).

There is no consistent definition of renal dysfunction in the literature. The definition in the current study is comparable to that of Mangano *et al.*,[7] with the exception that our endpoint required either a creatinine increase more than 0.7 mg/dl over baseline *or* a postoperative concentration more than 2 mg/dl, whereas the definition in the other study required both events. Karkouti *et al.*[6] defined renal dysfunction as a greater than 50% increase in creatinine during the first postoperative week to more than 100 μM in women and greater than 110 μM in men or new requirement of dialysis. Brown *et al.*[19] used a lower threshold to define renal impairment: 0.5 mg/dl or greater increase in creatinine from baseline. More confusing, the definition of renal failure in all studies is based on the use of hemodialysis. However, the indication for dialysis and the threshold for its use may vary among institutions and countries, and the duration of the use is not reported in the studies. The incidence of 8.2% in composite renal outcome in our study is comparable to data published by other investigators.[30,45–48] But in contrast to these studies, all of our patients were treated with different aprotinin dosages, and therefore, we can only draw conclusions about the association of the drug dosage with renal outcome.

Because aprotinin is metabolized in the kidneys and the aprotinin clearance is reduced in patients with preexisting renal impairment,[49] a higher risk of renal injury caused by aprotinin could be conceivable.[6] The current data do not substantiate these concerns; however, a dose reduction in the presence of renal dysfunction seems to be advisable. More work on this subject is mandatory.

Our analysis is subject to several limitations: (1) We studied the association of aprotinin dosage on adverse postoperative renal events, not the impact of the drug itself on renal function. From the current data, it cannot be excluded that aprotinin *per se* has an influence on renal function. Because almost all patients in our institution were treated with aprotinin and only patients with special contraindications to aprotinin, such as reexposure within a short time period,[50] or patients with anticipated short operating times, such as closure of an atrium septal defect, were not treated, we did not compare our results with the outcome of patients without aprotinin. However, our incidence data are in good agreement with results reported in studies without aprotinin treatment.[30,45–48] (2) This is a single-center experience with all the strength and weakness of such an analysis. It may be questioned whether these results are generally applicable. (3) This is a retrospective analysis of a large data set with prospectively prespecified variables. Despite the fact that such an analysis may be the only way to identify small differences in outcome or rare adverse events,[51] it may be afflicted with the inherent limitations of retrospective analyses.[8] (4) The continuous variables, such as aprotinin dosage, were not categorized, and it may be possible that categorization slightly alters the results, depending on the chosen cutoff point. (5) Because blood transfusion data may be associated with the dosage of aprotinin,[20] these data were not included in our analysis. Therefore, although transfusion was not a risk factor in our final model, an influence of transfusion on renal outcome[44] cannot be excluded from the current data.

In conclusion, the current analysis of a large, single-center database did not reveal a clinically detrimental influence of aprotinin dosage on postoperative renal function. Renal dysfunction was mainly associated with the preoperative risk of the patient, preoperative renal impairment, and the complexity of the surgical procedure. Neither the incidence of renal failure requiring dialysis nor the occurrence of renal impairment was associated with the dosage of aprotinin.

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