

High-Dose Aprotinin in Cardiac Surgery: Is High-Dose High Enough? An Analysis of 8281 Cardiac Surgical Patients Treated with Aprotinin

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In this retrospective analysis we tested the hypothesis that aprotinin doses of more than 6×10^6 kallikrein inhibiting units (KIU) per patient may be more effective in reducing bleeding compared with the high-dose regimen of $5\text{--}6 \times 10^6$ KIU aprotinin. The aprotinin doses administered for 8281 adult cardiac surgical patients were correlated to body weight and time of operation and calculated in KIU per kg body weight and minute of operation. Linear and logistic regression models were designed to detect potential associations between dose and postoperative bleeding, transfusion, and other covariates. The 6-h chest tube drainage in the lowest quartile dosing group was 447 ± 319 mL (mean $\pm$ sd) compared with 360 ± 290 mL in the highest quartile dosing group ($P < 0.001$). The proportion of patients requiring allogeneic blood transfusion was reduced from 55% to 47% comparing the lowest with the highest dosing group ($P < 0.01$). Aprotinin dose was also an independent predictor for rethoracotomy for surgical hemostasis (1.9% in the highest quartile to 2.4% in the lowest dosing quartile; $P < 0.01$). The risk of renal failure requiring dialysis (2.3% in the highest dosing group vs 3.3% in the lowest dosing group; $P < 0.01$) or impairment of renal function (creatinine increase of ≥ 2 mg/dL postoperatively, 6.4% in the highest dosing group vs 10.0% in the lowest dosing group; $P < 0.01$) was lower with higher doses of aprotinin. Thus, there was no association between aprotinin dose and renal function. Our results support the hypothesis that a more individualized aprotinin regimen with potentially higher doses may optimize the effectiveness of aprotinin therapy in cardiac surgery.

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The administration of high-dose aprotinin to reduce bleeding in cardiac surgery was introduced by Royston et al. almost 20 years ago (1). Since then, many studies have confirmed the effectiveness of this dosing regimen regarding reduction of blood loss and allogeneic blood transfusion (2,3). No additional studies are required to prove the blood-sparing effect of aprotinin in cardiac surgery (4).

This dosing regimen of aprotinin was introduced in cardiac surgery as the “Hammersmith” or high-dose regimen. Later on, lower aprotinin doses were investigated mostly for economic reasons because of the expense of the drug (5). However, a clear link between dose and bleeding tendency could be established (6): the higher the aprotinin dose, the greater the efficacy (7).

The high-dose regimen was developed to achieve aprotinin plasma concentrations of >200 kallikrein inhibiting units (KIU)/mL plasma to inhibit biologic kallikrein activity by 50% (8). The rationale for this high concentration was to inhibit platelet activation (1) and the activation of the intrinsic pathway of coagulation (9) with the consequence of reduced bleeding tendency and less inflammatory activation (10). However, this dose was based solely on theoretical calculation and was not confirmed in the clinical setting. Almost all studies measuring aprotinin plasma concentrations revealed much lower concentrations than the expected 200 KIU/mL, especially at the end of cardiopulmonary bypass (CPB) (11–14).

The high-dose regimen is a mixture of fixed dose, the 2×10^6 KIU bolus to the patient and to the pump prime, and a time-dependent maintenance dose by continuous infusion of 5×10^5 KIU/h. Depending on the duration of operation, this regimen results in a total aprotinin dose of $5\text{--}6 \times 10^6$ KIU.

The dose is not weight-adjusted. Weight-adjusted doses have been proposed (15) but have not been extensively studied for safety and efficacy. Surprisingly, although the target aprotinin plasma concentration was not achieved in most studies (9,11,12), doses

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exceeding the high-dose regimen have not been tested so far.

The total administered dose of aprotinin varies in daily routine because, due to the continuous infusion, patients with longer operations may receive considerably more aprotinin than the recommended total dose of 6×10^6 KIU. To investigate the association of aprotinin dose with bleeding tendency, we performed a retrospective analysis of our institutional database. The aim of the present investigation was to test the hypothesis that larger doses of aprotinin may be associated with reduced postoperative bleeding compared with lower doses.

METHODS

We analyzed the data of all adult patients undergoing cardiac surgery with the help of CPB treated with aprotinin (Trasylol®, Bayer, Leverkusen, Germany) between January 1, 1995 and December 31, 2003. The data used in this analysis were retrieved from the institutional database that includes data collected as part of the national quality assurance project of cardiac anesthesia (16). The database prospectively collects a comprehensive list of 238 prespecified items in all consecutive patients, including demographic, clinical, transfusion, and other outcome data. A study nurse, who was blinded to details of the present study, completed missing values of variables of interest from the medical records. The ethics committee of the medical faculty of the Technical University Munich approved the protocol. Because of the retrospective setting without a specific study intervention, informed consent was not obtained from the patients.

After identification of all adult patients receiving aprotinin, patients with maximum and minimum 5% duration of operation were excluded from the analysis, assuming, that patients with very long or extremely short operation times were outliers and would skew the results. In the remaining patients, the total aprotinin dose was divided by individual body weight and the skin incision-to-skin closure duration of operation in minutes, since the study is based on the assumption that a given amount of aprotinin administered over a shorter duration of operation to a patient with a lower body weight results in higher plasma concentrations, and thus, may be more effective than the same dose given to heavy patients over a longer duration of operation. This calculation resulted in an aprotinin dose in KIU per kilogram body weight and minute of operation (KIU/kgBW/min). In addition, the same calculation was performed with the duration of CPB instead of time of operation. The preoperative risk was assessed by the Cleveland Clinic Risk Score (15) in all patients.

The definite aprotinin dosing was at the discretion of the attending anesthesiologist. In almost all cases, a slightly modified high-dose protocol was applied. For safety reasons, and in contrast to the original description,

the first bolus of the drug was postponed after sternotomy and not given until the surgeon was ready to cannulate the aorta quickly in case of a hypersensitivity reaction to the drug. Since the continuous infusion of 5×10^5 KIU/h is not able to maintain constant plasma concentrations (12), some anesthesiologists used a continuous infusion of 1×10^6 KIU/hour and repeated a bolus of 1×10^6 KIU aprotinin after 120 min of CPB. The infusion was not stopped at a total dose of 6×10^6 KIU. Therefore, this regimen resulted in much higher doses in operations lasting longer. Because not all anesthesiologists in the department adopted this technique, the different practice patterns resulted in a wide variation of total aprotinin doses.

Anesthesia was performed with sufentanil, midazolam, and propofol, supplemented with inhaled sevoflurane; neuromuscular blockade was achieved by either pancuronium bromide or rocuronium. CPB was performed in standard technique. The membrane oxygenator was primed with 1500–1800 mL crystalloid solution, the flow rate was set to 2.4 L/m^2 , and the patient was moderately cooled to 32°C . Either cold crystalloid or blood cardioplegia was used to rest the heart. Intraoperative blood salvage by cardiotomy suction and retransfusion of the shed blood during CPB was used in all patients. Anticoagulation for CPB was achieved with porcine unfractionated heparin with a dose of 375 U/kg and controlled with the activated clotting time (ACT) with a target ACT of 480 s. If the ACT was <480 s an additional bolus of 125 U/kg heparin was added. After separation from CPB, heparin was antagonized by protamine chloride in a 1:1 ratio to the initial dose of heparin.

Postoperatively, the patients' lungs were ventilated in the intensive care unit until the patients warmed up to 37°C , the oxygenation, hemodynamics, and neurologic function were sufficient, and blood loss was $<100 \text{ mL/h}$. Indication for repeat surgical hemostasis was driven by clinical judgment and a blood loss exceeding 200 mL in 2 consecutive hours.

Allogeneic packed red blood cells were transfused if the hematocrit decreased to $<18\%$ during CPB, below 21% – 24% in the postoperative period, or if the patient's physiologic signs indicated a need to improve oxygen supply.

Renal dysfunction was defined as postoperative creatinine of at least 2 mg/dL or an increase over preoperative baseline levels of at least 0.7 mg/dL . Renal failure required new dialysis support.

Eighty-six items were considered relevant to the current study and entered in the dataset for statistical analysis. Continuous variables are given as mean $\pm$ SD. Categorical data are reported in percentages. The three primary end points were blood loss 6 h postoperatively, the amount of allogeneic blood transfusion during the hospital stay, and the occurrence of a rethoracotomy for bleeding. As mentioned, 10% of the patients were excluded from the analyses, namely those with the longest and shortest operation times.

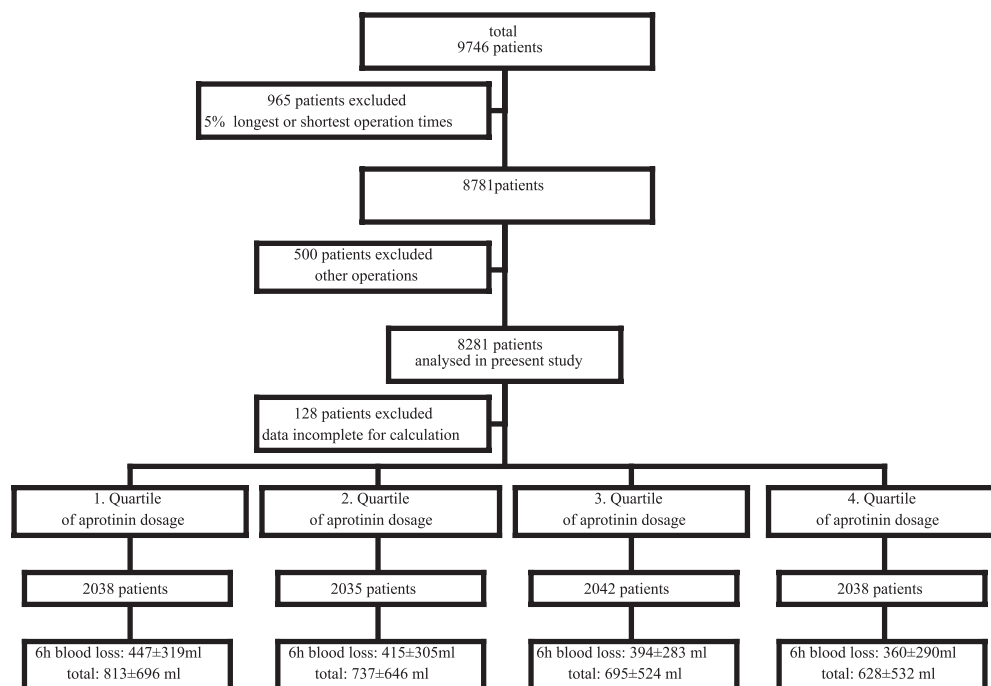


Figure 1. Study design and main results. In this analysis, 128 patients were excluded because data for one of the variables were missing.

Type of operation was coded for coronary artery bypass graft (CABG), aorta ascending replacement, aortic valve replacement (AVR), mitral valve replacement or repair (MVR/R), combined aortic and mitral valve operation (A/MVR), and combined CABG and valve replacement (CABG plus valve). Patients with other operations were excluded. Collinearity diagnostics were performed by calculating the Spearman's rank correlation coefficient and the variance inflation factor (17) for all potential covariates. Multiple linear and logistic regression models were performed to detect potential associations between the outcome of one of the end points and the covariates age, gender, preoperative risk score, body weight, type of operation, aprotinin dose in KIU/kgBW/min, and previous cardiac surgery. Stepwise forward procedures with an inclusion significance level of 5% and an exclusion significance level of 10% were applied. To exemplify the results, the patients were divided into four groups according to the quartiles of the aprotinin dose in KIU/kgBW/min. Baseline characteristics of interest were compared using the Mann-Whitney test for continuous and the χ^2 test for categorical covariates.

The impact of aprotinin dose on renal function was assessed with a multivariate logistic regression model, with renal failure as a dependent variable and all covariables that could be associated with aprotinin dose or hemorrhage as predictor variables. The discriminative power of these models was assessed by determination of the area under the receiver-operating-curve (c-statistics). Linear logistic regression models were constructed with aprotinin dose as an independent variable and the highest postoperative creatinine concentration or the

difference between pre- and postoperative creatinine concentration respectively as the dependent variable.

SPSS statistical software (version 13) (SPSS, Chicago, IL) was used for statistics. A *P* value of <0.05 (two-tailed) was considered to indicate statistical significance.

RESULTS

We evaluated 9,746 patients, of which 8281 were included in the final analysis (Fig. 1). Demographics and intraoperative patient characteristics are presented in Table 1. The Spearman's correlation coefficient yielded no clue that the potential covariates were jointly correlated. Besides, we observed variance inflation factor values <2 for all variables (Tables 4 and 5). Thus there is no hint of multicollinearity of the predictors. Therefore, the authors assumed independence of the variables in the following analyses. The association between aprotinin dose and 6 h postoperative blood loss is given in Figure 2. The mean total aprotinin dose was $5.38 \pm 0.86 \times 10^6$ KIU with a variation from 1 to 12×10^6 KIU. Totally 911 patients received a total aprotinin dose exceeding the 6×10^6 KIU standard high-dose.

The analysis of the four dosing groups demonstrated a reduction of postoperative chest tube drainage with increased dose (Table 2, Fig. 2): the higher the dose per kilogram body weight and minute of operation the lower was the postoperative 6 h blood loss. Transfusion requirements were also significantly reduced in patients with higher aprotinin doses. Since there was no proportionate distribution of types of

Table 1. Patients and Procedural Characteristics ($n = 8281$) (mean $\pm$ SD or %)

	Quartiles				
	First	Second	Third	Fourth	Total
Age (yr)	63 $\pm$ 11	64 $\pm$ 12	64 $\pm$ 13	66 $\pm$ 14	64 $\pm$ 13
Gender (male/female %)	84/16	78/22	64/36	49/51	68/32
Preoperative risk score ^a	3.1 $\pm$ 3.1	3.0 $\pm$ 3.0	3.3 $\pm$ 3.2	3.8 $\pm$ 3.4*	3.3 $\pm$ 3.2
Ejection fraction (%)	55	56	56	56	56
BMI (kg/m ²)	28.8 $\pm$ 4.0	27.0 $\pm$ 3.3	25.8 $\pm$ 3.3	24.0 $\pm$ 3.0*	26.4 $\pm$ 3.8
Weight (kg)	86 $\pm$ 13	79 $\pm$ 11	73 $\pm$ 11	65 $\pm$ 10*	76 $\pm$ 9
Height (cm)	173 $\pm$ 8	172 $\pm$ 9	169 $\pm$ 9	165 $\pm$ 9	170 $\pm$ 9
CPB duration (min)	114 $\pm$ 34	103 $\pm$ 31	97 $\pm$ 30	88 $\pm$ 26*	101 $\pm$ 32
AoX duration (min)	75 $\pm$ 26	70 $\pm$ 24	66 $\pm$ 23	60 $\pm$ 21*	68 $\pm$ 24
Duration of operation (min)	281 $\pm$ 46	244 $\pm$ 40	219 $\pm$ 39	192 $\pm$ 34*	234 $\pm$ 51
Hemoglobin preoperative (g/L)	126 $\pm$ 16	124 $\pm$ 16	122 $\pm$ 16	118 $\pm$ 27*	122 $\pm$ 20
Creatinine preoperative (mg/dL)	1.3 $\pm$ 0.6	1.2 $\pm$ 0.4	1.2 $\pm$ 0.5	1.2 $\pm$ 0.5	1.2 $\pm$ 0.5
Type of operation (%)					
CABG	69.5	66.2	55.9	45.0*	59.0
Aorta asc. replacement	2.6	2.2	2.5	1.7	2.4
AVR	8.9	11.6	17.1	24.0*	15.4
A + MVR	1.8	1.9	2.9	3.0	2.4
CABG + valve	11.5	11.0	10.8	10.1	10.9
MVR/repair	5.6	7.1	10.7	16.1	9.9
Previous cardiac surgery (%)	15	11	9	6*	10

BMI = body mass index; CPB = cardiopulmonary bypass; AoX = aortic cross clamp time; CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVR = mitral valve replacement/repair.

^a The preoperative risk was calculated according to the Cleveland Clinic Risk Score.

* $P < 0.001$ for fourth quartile compared to the first quartile of aprotinin dose.

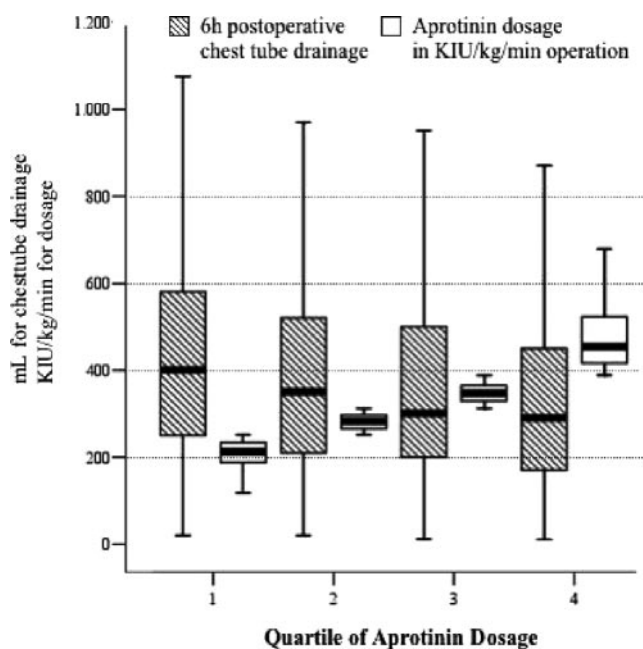


Figure 2. Box plots of aprotinin dose in KIU/kg/min of operation and 6 h blood loss. While the aprotinin dose increased with the dosing quartile, the blood loss decreased over the cohorts.

operation, we compared the results for patients undergoing only CABG surgery ($n = 4762$) separately (Table 3). The results from this homogenous subgroup did not differ from that of the whole study population.

The results of the multiple regression models for the dependent variables 6 h blood loss ($R^2 = 0.225$) and amount of allogeneic blood ($R^2 = 0.401$) are shown in Tables 4 and 5. The c-index for the logistic regression

model (rethoracotomy) was 0.648 (Table 6). All models demonstrate that the higher the aprotinin dose, the lower the blood loss, the amount of allogeneic blood, and the incidence of rethoracotomy, respectively. One-hundred KIU more of aprotinin/kgBW/min results in 11.7 mL less blood loss in 6 h, or 100 additional KIU of aprotinin/kgBW/min decreases the probability of a rethoracotomy about 20% (OR = 0.998; CI 0.997–1.000). Female patients had a reduced bleeding tendency (24-h chest tube drainage: 565 ± 434 vs 711 ± 477 mL; $P < 0.001$) ($\beta = -63.1$; CI -82.47 to -43.72) but a higher total transfusion requirement (2.46 ± 3.3 vs 1.46 ± 3.1 U; $P < 0.001$) ($\beta = 0.46$; CI 0.28 – 0.65) as compared to male patients.

The adjustment of our dosing calculation on CPB duration instead of duration of operation did not alter the results substantially (data not shown).

Linear and logistic regression analysis did not demonstrate an association between aprotinin dose and renal outcome. The c-index for the logistic regression model with renal failure as an outcome was 0.811 (Table 7). Preoperative creatinine, preoperative risk score, preoperative ejection fraction, and age were predictors for the increase of postoperative creatinine and the difference in pre- to postoperative creatinine. There was even a small (CI -0.001 to 0.00 ; $P < 0.001$) inverse association between aprotinin dose and postoperative creatinine increase. Higher aprotinin doses per kgBW and minute of operation postoperative was associated with less renal impairment. This analysis was also performed with the total dose of aprotinin in KIU and the maximum postoperative creatinine as a dependent variable (data not shown). Again, in this

Table 2. Operative Data of All Patients ($n = 8281$)^a

	Quartiles				
	First	Second	Third	Fourth	Total
Aprotinin (KIU/kg/min)	214 ± 32	283 ± 16	343 ± 19	454 ± 71	323 ± 97
Aprotinin (10 ⁶) (KIU)	5.1 ± 1.0	5.4 ± 0.7	5.4 ± 0.8	5.6 ± 0.9	5.4 ± 0.9
6-h chest tube drainage (mL)	447 ± 319	415 ± 305	394 ± 283	360 ± 290	404 ± 301
12-h chest tube drainage (mL)	604 ± 420	550 ± 377	532 ± 374	484 ± 384	543 ± 391
24-h chest tube drainage (mL)	750 ± 495	681 ± 463	652 ± 453	589 ± 454	668 ± 469
Total chest tube drainage (mL)	813 ± 695	737 ± 646	695 ± 524	628 ± 532	718 ± 606
Packed red blood cells OP (units)	0.5 ± 1.2	0.4 ± 1.1	0.5 ± 0.9	0.6 ± 0.9	0.5 ± 1.0
Packed red blood cells ICU (units)	1.2 ± 2.8	0.8 ± 2.2	0.8 ± 2.2	0.9 ± 2.4	0.9 ± 2.4
Total packed red blood cells (units)	1.95 ± 3.6	1.6 ± 3.0	1.7 ± 3.1	1.79 ± 2.9	1.8 ± 3.2
Patients without allogeneic blood (%)	47	44	47	55	48
Hemoglobin arrival ICU (g/L)	114 ± 17	112 ± 17	112 ± 17	110 ± 16	112 ± 17
Hemoglobin ICU end (g/L)	110 ± 26	116 ± 23	111 ± 15	111 ± 26	110 ± 17
Highest postoperative creatinine (mg/dL)	1.4 ± 0.9	1.2 ± 0.7	1.2 ± 0.7	1.2 ± 0.6	1.2 ± 0.7
Patients with postoperative creatinine ≥2 mg/dL (%)	10.0	6.6	6.6	6.4	7.3
Postoperative dialysis (%)	3.3	1.8	1.9	2.3	2.3
Rethoracotomy for bleeding (%)	2.4	1.9	1.6	1.9	2.0

ICU = intensive care unit.

^a The outcome variables were divided in the quartile cohorts of aprotinin dose to illustrate the results. The first to fourth quartile comparison was only performed for demographic characteristics.

Table 3. Operative Data CABG Patients Only^a

	Quartiles				
	First	Second	Third	Fourth	Total
N	1422	1330	1100	910	4762
Gender (male %)	88	82	73	62	78
Preoperative risk score	2.8 ± 2.9	2.93.0	3.3 ± 3.1	3.9 ± 3.4	3.2 ± 3.1
Aprotinin (KIU/kg/min)	213 ± 32	283 ± 16	343 ± 18	447 ± 65	307 ± 90
Total aprotinin dose (10 ⁶) (KIU)	5.1 ± 0.9	5.3 ± 0.6	5.4 ± 0.7	5.7 ± 0.9	5.3 ± 0.8
6-h chest tube drainage (mL)	448 ± 277	420 ± 269	410 ± 257	388 ± 258	420 ± 267
12-h chest tube drainage (mL)	607 ± 374	556 ± 327	550 ± 333	518 ± 333	563 ± 346
24-h chest tube drainage (mL)	753 ± 447	693 ± 415	678 ± 419	622 ± 391	693 ± 424
Total postoperative chest tube drainage (mL)	805 ± 511	747 ± 495	723 ± 472	664 ± 444	743 ± 488
Packed red blood cells OP (units)	0.4 ± 0.9	0.4 ± 1.0	0.4 ± 0.9	0.5 ± 0.9	0.4 ± 0.9
Packed red blood cells ICU (units)	1.0 ± 2.3	0.7 ± 1.9	0.8 ± 2.2	0.8 ± 2.3	0.8 ± 2.2
Total packed red blood cells (units)	1.54 ± 3.0	1.39 ± 2.5	1.59 ± 3.0	1.62 ± 2.7	1.52 ± 2.8
Patients without allogeneic blood transfusion (male/female %)	62/27	65/24	65/26	60/26	63/26
Rethoracotomy for bleeding (%)	1.5	1.4	0.9	1.1	1.2
Highest postoperative creatinine (mg/dL)	1.4 ± 0.9	1.2 ± 0.7	1.2 ± 0.7	1.2 ± 0.6	1.2 ± 0.7
Patients with postoperative creatinine ≥2mg/dL (%)	10.6	7.1	6.6	6.3	7.6
Postoperative dialysis (%)	3.3	2.1	1.9	2.2	2.3

CABG = coronary artery bypass grafting; ICU = intensive care unit.

^a The outcome variables were divided in the quartile cohorts of aprotinin dose to illustrate the results. The first to fourth quartile comparison was only performed for demographic characteristics.

model there was no association between total dose of aprotinin and renal impairment.

DISCUSSION

The present observational study data provide some evidence that higher doses of aprotinin in comparison to the traditional high-dose or Hammersmith regimen proposed by Royston et al. (1) may be associated with less bleeding and reduced transfusion requirement in cardiac surgery. Our models demonstrate that apart from the aprotinin dose other variables influence bleeding and

transfusion requirement. However, in all models aprotinin dose remained a significant predictor. We attained a dose of 447 ± 65 KIU/kg/min in the upper quartile of dose. In comparison, the traditional high-dose given to an 80 kg patient in a 4 h operation would theoretically result in a dose of 310 KIU/kg/min, which is 44% less than our highest dosing quartile. No doubt, the current high-dose regimen is a potent and effective tool for reducing bleeding in cardiac surgery (18). However, the current data call into question whether a total amount of 5–6 × 10⁶ KIU treatment, regardless of duration of operation or body weight, is really the most effective

Table 4. Multiple Linear Regression Model: 6 h Blood Loss as Response

Variable	β	P-value	95% CI for β		VIF
			Lower bound	Upper bound	
Preoperative risk score ^a	5.764	<0.001	3.631	7.897	1.043
Gender (male = 1, female = 2)	-63.095	<0.001	-82.469	-43.721	1.841
Height (cm)	2.368	<0.001	1.361	3.375	1.872
Aprotinin (KIU/kg/min)	-0.117	0.002	-0.192	-0.043	1.208
Type of operation ^b					
Aorta asc. replacement	92.251	<0.001	47.299	137.204	1.028
AVR	-75.543	<0.001	-94.840	-56.246	1.120
A + MVR	49.997	0.023	6.804	93.189	1.036
CABG + valve	49.078	<0.001	27.382	70.774	1.070
MVR/repair	-39.608	0.001	-63.153	-16.064	1.134

CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVR = mitral valve replacement; KIU = kallikrein inhibiting unit; VIF = variance inflation factor.

^a The risk score was calculated with the Cleveland Clinic Risk Score.

^b Reference category: CABG.

Table 5. Multiple Linear Regression Model: Amount of Allogeneic Blood as Response

Variable	β	P-value	95% CI for β		VIF
			Lower bound	Upper bound	
Preoperative risk score ^a	0.294	<0.001	0.271	0.316	1.313
Age (yr)	0.033	<0.001	0.026	0.039	1.288
Gender (male = 1, female = 2)	0.460	<0.001	0.275	0.646	1.842
Type of operation ^b					
Aorta asc. replacement	0.522	0.019	0.086	0.959	1.050
AVR	0.091	0.338	-0.095	0.278	1.152
A + MVR	0.748	<0.001	0.327	1.169	1.047
CABG + valve	1.133	<0.001	0.922	1.343	1.088
MVR/repair	0.706	<0.001	0.476	0.936	1.191
Aprotinin (KIU/kg/min)	-0.003	<0.001	-0.004	-0.003	1.246
Previous cardiac surgery	-0.658	<0.001	-0.909	-0.407	1.261
Height (cm)	-0.020	<0.001	-0.030	-0.010	1.921

CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVR = mitral valve replacement; KIU = kallikrein inhibiting unit; VIF = variance inflation factor.

^a The risk score was calculated with the Cleveland Clinic Risk Score.

^b Reference category: CABG.

Table 6. Multiple Logistic Regression: Rethoracotomy as Response

Variable	P-value	OR	95% CI for OR	
			Lower bound	Upper bound
Type of operation ^a				
Ascending aorta replacement	<0.001	3.288	1.804	5.993
AVR	0.010	1.650	1.129	2.414
A + MVR	0.023	2.277	1.122	4.621
CABG + valve	0.005	1.767	1.188	2.629
MVR/repair	<0.001	3.050	2.083	4.464
Gender (male = 1, female = 2)	0.018	0.687	0.502	0.938
Preoperative risk score ^b	<0.001	1.094	1.059	1.130
Aprotinin (KIU/kg/min)	0.021	0.998	0.997	1.000

CABG = coronary artery bypass grafting; AVR = aortic valve replacement; MVR = mitral valve replacement; KIU = kallikrein inhibiting unit.

^a Reference category: CABG.

^b The risk score was calculated with the Cleveland Clinic Risk Score.

dose for all aprotinin indications. Future, randomized, controlled trials should investigate this question.

We selected blood loss via chest tube drainage as the primary end point of our investigation because it most objectively reflects the drug's influence on bleeding. Gender, preoperative risk score, type of operation,

and aprotinin dose were independently associated with bleeding tendency. Although a higher risk score was significantly more prevalent in the fourth dose quartile, blood loss was significantly reduced in this patient group. There was an uneven distribution of types of operations among the dose groups: patients

Table 7. Multiple Logistic Regression: Renal Dialysis as Response

Variable	P-value	OR	95% CI for OR	
			Lower	Upper
Age (yr)	0.010	1.032	1.008	1.057
Preoperative risk score	<0.001	1.132	1.070	1.198
Preoperative creatinine (mg/dL)	<0.001	2.608	2.074	3.280
Preoperative ejection fraction (%)	0.022	0.985	0.972	0.998
Aprotinin (KIU/kg/min)	0.053	0.998	0.995	1.000

undergoing AVR had a significantly shorter operation times and were therefore over-represented in the higher dose group. Hence, we tested our model in the homogeneous subgroup of patients undergoing CABG surgery separately and found similar results compared with the entire patient population (Table 3).

The optimal dose of aprotinin in cardiac surgery is still a matter of discussion: in response to the first promising results, the high-dose regimen of aprotinin has been subject to extensive research and an almost innumerable amount of studies (19) have confirmed the primary results. Surprisingly, studies with higher doses have not been performed, despite the early consideration of Royston that higher doses may be more effective for some indications (10). Instead, subsequent studies investigated lower doses. These studies were not based merely on pharmacologic considerations, but rather, were driven by economic concerns caused by the expense of the drug (5,6).

Admittedly, the established high-dose regimen, or even a lower dose of aprotinin, is effective in reducing bleeding and transfusion requirements in most cardiac surgical patients (2,3). Aprotinin, at currently recommended dosing, completely inhibits plasmin, an important enzymatic pathway that appears to contribute to impaired platelet function and bleeding and may also, with high plasma concentrations, attenuate thrombin generation. The target aprotinin plasma concentration was set to 200 KIU/mL (10), which should inhibit biologic kallikrein by 50% (8). However, this is a rather arbitrary number. Why should we inhibit kallikrein by just 50% and not by more or less? Do we really clinically accomplish this task with the so-called high-dose regimen? It was demonstrated that the target plasma concentration of 200 KIU/mL could not be achieved with the currently recommended dosing (12). Although we have stunning clinical information about the use of aprotinin in cardiac surgery, there are many open questions about the mode of action of this drug and the most effective dose or plasma concentration.

With respect to our own results (9,12), we proposed modifying the dosing of aprotinin. Because of the possibility of anaphylactic reactions (20), we postponed the first bolus and the continuous infusion of aprotinin until the surgeon was ready to initiate CPB. Instead, we increased the continuous infusion rate to 1×10^6 KIU/h and, in pump runs >120 min, we

repeated a bolus injection of 1×10^6 KIU to avoid a decline of aprotinin plasma concentration.

Recent studies claimed there was a negative effect of aprotinin on renal function (21), which ought to be dose-dependent (22). In the present dataset, we could not identify such a dose-effect: regression analysis identified preoperative creatinine (OR 2.61, CI 2.07–3.28; $P < 0.001$), preoperative risk score (OR 1.13; CI 1.07–1.19; $P < 0.001$), and age (OR 1.03; CI 1.01–1.06, $P = 0.01$) as predictors of the incidence of postoperative renal dialysis. In contrast, there was even a small inverse association between dose and renal function. These different results may be caused by the fact that, in the cited studies (21,22), aprotinin was selectively limited to patients with the highest risk of hemorrhage and, presumably, to those patients with a higher risk of postoperative renal impairment. It is questionable whether propensity scoring could correct this possible bias (23). In contrast to these studies, in our investigation, aprotinin had a broader indication and patients of all risk groups received aprotinin.

There are some potential limitations in the present study. For example, it is based on the retrospective analysis of a large institutional database with all the inherent limitations of retrospective analyses. This analysis permits only associations and cannot imply causation. It can only be hypothesis-generating, since none of the hypotheses tested in this investigation was prespecified. It was just recently emphasized (24,25) that only the analysis of large databases may accomplish the generation of hypotheses if there are only slight differences in outcome. A second limitation of the current study is that it could not consider plasma concentrations of aprotinin. The underlying consideration is that higher doses of aprotinin given over a shorter time period are more effective because they may result in higher plasma concentrations. This sounds reasonable, but has not yet been proven by clinical studies measuring plasma concentrations of aprotinin. Third, there may be unknown influences, not identified as potential predictors for bleeding or transfusion requirement in the regression analysis, that were not identified in this investigation, and therefore, could not be controlled for. Finally, our analysis provided no evidence of a dose-dependent association of aprotinin on renal function. However, since all patients received aprotinin and since we

excluded all patients without that drug, we can only state that the dose had no impact; we cannot preclude any general effect of aprotinin on renal function. The incidence of renal dysfunction and renal insufficiency was much lower in our dataset than that reported in other studies (22). The study was not designed to investigate other possible side effects.

CONCLUSIONS

The implications of our findings are several-fold. They do not prove, but only suggest the hypothesis, that higher doses of aprotinin may be more effective compared to lower doses as achieved with the traditional high-dose regimen. The traditional, and effective, high-dose regimen is a fixed-dosed regarding body weight and partially disregarding the duration of the operation. It is conceivable that the "one-size-fits-all" approach may not generate optimal results, and that a more individualized high-dose regimen could optimize the effectiveness of aprotinin administration. The current study supports this consideration.

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