

Aprotinin in cardiac surgery patients: is the risk worth the benefit?

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Abstract

Background: Aprotinin is the only Food and Drug Administration-approved agent to reduce haemorrhage related to cardiac surgery and its safety and efficacy has been extensively studied. Our study sought to compare the efficacy, early and late mortality and major morbidity associated with aprotinin compared with e-aminocaproic acid (EACA) in cardiac surgery operations. **Methods:** Between January 2002 and December 2006, 2101 patients underwent coronary artery bypass grafting (CABG), valve surgery or CABG and valve surgery in our institution with the use of aprotinin (1898 patients) or EACA (203 patients). Logistic regression and propensity score analysis were used to adjust for imbalances in the patients' preoperative characteristics. The propensity score-adjusted sample included 570 patients who received aprotinin and 114 who received EACA (1–5 matching). **Results:** Operative mortality was higher in the aprotinin group in univariate (aprotinin 4.3% vs EACA 1%, $p = 0.023$) but not propensity score-adjusted multivariate analysis (4% vs 0.9%, $p = 0.16$). In propensity score-adjusted analysis, aprotinin was also associated with a lower rate of blood transfusion (38.8% vs 50%, $p = 0.04$), a lower rate of haemorrhage-related re-exploration (3.7% vs 7.9%, $p = 0.04$) and a higher risk of in-hospital cardiac arrest (3.7% vs 0%, $p = 0.03$) and a marginally but not statistically significantly higher risk of acute renal failure (6.8% vs 2.6%, $p = 0.09$). In Cox proportional hazards regression analysis, the risk of late death was higher in the aprotinin compared to EACA group (hazard ratio = 4.33, 95% confidence interval (CI) = 1.60–11.67, $p = 0.004$). **Conclusion:** Aprotinin decreases the rate of postoperative blood transfusion and haemorrhage-related re-exploration, but increases the risk of in-hospital cardiac arrest and late mortality after cardiac surgery when compared to EACA. Cumulative evidence suggests that the risk associated with aprotinin may not be worth the haemostatic benefit.

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1. Introduction

Aprotinin administration has been used during cardiac surgery to decrease blood loss and haemorrhage-related re-exploration rates [1,2]. Recent studies have demonstrated an increase in the risk of death with aprotinin administration during cardiac surgery [3,4]. Specifically, in a study by Schneeweiss et al., aprotinin was associated with a 64% higher risk of death compared to the e-aminocaproic acid (EACA) group (relative risk = 1.64; 95% confidence interval (CI): 1.50–1.78) [3]. Recently, the data and safety board of a large randomised trial suspended the recruitment of patients in the aprotinin group because of an increased risk of death.

As a result of this and other studies [5,6], the Food and Drug Administration (FDA) revised labelling for aprotinin to strengthen its safety warnings and to limit its approved usage to specific indications. The new labelling specifies that Trasylol 'should only be given to patients who are at an increased risk for blood loss and blood transfusion in the

setting of coronary bypass graft surgery, when patients undergo cardiopulmonary bypass.' The changes also include a warning that aprotinin increases the possible risk for kidney damage, and suggest ways to manage and reduce the patient's risk for hypersensitivity (exaggerated immune) reactions. The manufacturer has temporarily suspended the marketing of aprotinin, but it 'believes that the totality of the available data continue to support a favorable risk–benefit profile for Trasylol when used according to labeling.'

Our study sought to investigate the association of aprotinin use and the risk of adverse events (including the risk of early and late death, stroke, haemorrhage-related re-exploration, blood transfusions, acute renal failure and acute myocardial infarction) and compare it with the use of EACA in patients undergoing cardiac surgery.

2. Patients and methods

2.1. Patients

The database of the Division of Cardiothoracic Surgery at the Carolinas Medical Center was queried to identify all the

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patients who underwent coronary artery bypass grafting (CABG), isolated valve surgery or valve and CABG in our institution between January 2002 and December 2006 and received aprotinin or EACA for haemostasis. Patients who underwent an off-pump CABG or received both EACA and aprotinin were excluded from the analysis. Between January 2002 and December 2006 in our institution, 2101 patients underwent CABG, valve surgery or CABG and valve surgery with the use of aprotinin ($n = 1898$) or EACA ($n = 203$). The operations were performed by the same group of cardiac surgeons for the period of study. The full Hammersmith hospital dose of aprotinin was used in all patients who received aprotinin. For EACA, 5 g bolus dose was administered prior to initiation of cardiopulmonary bypass, followed by a maintenance infusion of 1 g h^{-1} for 5 h. No additional medication was added to the bypass circuit. Baseline demographics, procedural data and perioperative outcomes were recorded and entered prospectively in a pre-specified database by a dedicated data-coordinating centre.

Long-term follow-up and survival data were obtained from the Social Security National death index.

2.2. Study design and conduct

This is a retrospective cohort study of prospectively collected data from consecutive patients who underwent CABG, valve or combined CABG/valve surgery at the Carolinas Medical Center. Before data identification and analysis, study approval was sought and obtained from the Institutional Review Board at our institution. Confidentiality of patient personal information was maintained at all times, consistent with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations. None of the pharmaceutical companies making the drugs of study contributed financially or had any role in the study design, analysis or reporting.

2.3. Definitions

The Society of Thoracic Surgeons' national cardiac surgery database definitions were used for the purposes of the study. 'Previous cerebrovascular accident' is defined as history of central neurological deficit persisting for more than 24 h. 'Chronic renal insufficiency' is defined as a serum creatinine value $\geq 2.0 \text{ mg dl}^{-1}$. 'Diabetes' is defined as a history of diabetes mellitus, regardless of the duration of disease or the need for oral agents or insulin. 'Recent myocardial infarction' is defined as a myocardial infarction occurring within 7 days. 'Depressed ejection fraction' is defined as an ejection fraction $< 40\%$. 'Prolonged ventilatory support' is defined as a pulmonary insufficiency requiring ventilatory support $> 24 \text{ h}$. 'Postoperative stroke' is defined as any new major (type II) neurological deficit presenting in-hospital and persisting $> 72 \text{ h}$ [7]. Transient ischaemic attacks were not included in this analysis. Strokes were confirmed by an independent neurologist and/or appropriate brain imaging. 'Acute renal failure' is defined as both the increase of serum creatinine level to $> 2.0 \text{ mg dl}^{-1}$ and greater than twice the value of most recent preoperative creatinine level. 'Prolonged hospital length of stay' is defined as a hospital stay greater than the 75th percentile (9 days) of hospital length of stay.

'Prolonged pump time and prolonged operation' are defined as the pump time and operation times greater than the 75th percentile of pump time ($> 125 \text{ min}$) and operation time ($> 293 \text{ min}$), respectively. 'In-hospital cardiac arrest' was defined as any one of the following: (1) ventricular fibrillation, (2) rapid ventricular tachycardia with haemodynamic instability and (3) asystole. 'Operative mortality' includes both (1) all deaths occurring during the hospitalisation in which the operation was performed, even if after 30 days; and (2) those deaths occurring after discharge from the hospital, but within 30 days of the procedure unless the cause of death is clearly unrelated to the operation.

2.4. Data analysis

2.4.1. Univariate analysis

Univariate comparisons of preoperative, operative and postoperative variables were performed between the groups (aprotinin and EACA). The variables were summarised using medians and ranges for continuous variables, and frequencies and percentages for categorical variables. Continuous variables were tested using the Wilcoxon and Kruskal–Wallis test for association, while categorical variables were assessed by the chi-square or Fisher's exact test, depending upon the distribution of the data. A p -value of < 0.05 was considered statistically significant.

2.4.2. Multivariate analysis

A multivariable, stepwise forward logistic regression analysis was conducted to determine the independent predictors of (1) acute renal failure, (2) stroke, (3) blood transfusion, (4) haemorrhage-related re-exploration, (5) acute myocardial infarction and (6) in-hospital cardiac arrest. The criterion for variable entry into the logistic models was a univariate probability level of $p < 0.1$ for association with the particular outcome in the model. The predictors that remained significant below the 0.05 alpha level were chosen for the final model. The quality of the fit of the logistic models was tested with the C-statistic.

2.4.3. Propensity score model

Propensity score adjustment was used to compare the postoperative outcomes between the aprotinin and EACA groups to correct for imbalances between the groups at baseline [8,9]. A logistic regression model was fit where the haemostatic agent (EACA/aprotinin) was the outcome, and baseline characteristics ($p < 0.1$) from the bivariate analysis were the covariates. Propensity scores were generated and used to match EACA and aprotinin patients in a nearest-neighbour fashion. Five aprotinin patients were matched to each EACA patient to gain the most statistical power. The propensity score-adjusted sample included 570 patients who received aprotinin and 114 who received EACA.

The ability of the propensity score to effectively balance the groups at baseline was confirmed by showing that the variables put into the propensity score were no longer significant in the matched sample (Table 1). Hence, the groups were more balanced for the subsequent testing of outcomes in the matched sample. No variables which were non-significant at the univariate analysis became significant after propensity score matching.

Table 1
Propensity score adjustment effectively balance the groups at baseline.

	Before adjustment			After adjustment		
	OR	95% CI	p-value	OR	95% CI	p-value
Gender	1.31	0.96–1.79	0.087	0.75	0.49–1.15	0.188
NYHA class						
I–IV	1.02	0.39–2.69	0.089	0.94	0.29–3.01	0.754
II–IV	1.60	1.05–2.44		1.34	0.74–2.44	
III–IV	1.58	1.06–2.34		1.26	0.70–2.26	
Previous CAB	4.02	1.47–10.99	0.003	0.39	0.12–1.32	0.123
Congestive heart failure	2.35	1.46–3.78	<0.001	1.05	0.61–1.83	0.853
Status	4.38	1.78–10.77	0.002	0.92	0.34–2.46	0.798
Age >75	1.73	1.05–2.86	0.029	0.99	0.56–1.74	0.962
Surgeon	5.99	4.00–8.96	<0.001	1.13	0.72–1.80	0.592
Type of surgery	0.64	0.44–0.93	0.014	1.27	0.86–1.06	0.350

Variables adjusted by propensity score were no longer significant in the matched sample.

2.4.4. Survival analysis

Unadjusted survival estimates were calculated using Kaplan–Meier scores for the aprotinin and EACA groups, and compared them using the log-rank test. A proportional hazard Cox model was used to evaluate the effect of aprotinin and EACA on survival, adjusting for the patients' baseline characteristics.

All analyses were conducted using SAS[®] version 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Preoperative characteristics

Univariate comparisons between the aprotinin and EACA patients are presented in Table 2. The patients who received aprotinin were more likely to be elderly (>75 years), have previous sternotomy and congestive heart failure compared to the patients who received EACA. Use of EACA and aprotinin was not equally distributed during the study period as shown in Table 2.

3.2. Operative characteristics

Operative patient characteristics are presented in Table 3. The patients who received aprotinin were more frequently likely to have valve or combined valve and CABG surgery and more likely to be operated on urgently or have surgery more recently compared to the patients who received EACA. Some surgeons (B, D and E) preferentially used aprotinin, while others preferentially used EACA (surgeons A and C).

3.3. Postoperative characteristics

3.3.1. Univariate analysis

Postoperative characteristics are shown in Table 3. Aprotinin administration increased a patient's risk of post-operative acute renal failure ($p = 0.014$), in-hospital cardiac arrest ($p = 0.01$) and operative mortality ($p = 0.023$) compared to EACA. Of the 2101 patients, 54 deaths in the

aprotinin group (2.8%) were attributed to a cardiac cause of death compared to one in the EACA group (0.4%). There was no difference in the rates of haemodialysis between the groups. Aprotinin was also associated with a decreased rate of blood transfusion ($p = 0.026$).

3.3.2. Multivariate analysis

The results of the multivariable logistic regression analysis are presented in Table 4, while propensity score adjustment is shown in Table 5. In multivariate analysis, aprotinin was associated with a decrease in blood transfusion rates ($p = 0.01$) and a twofold increased risk of acute renal failure ($p = 0.04$). The propensity score-adjusted odds ratio demonstrated only marginal increase in the rate of acute renal failure for the aprotinin group ($p = 0.09$), increase in the risk of in-hospital cardiac arrest ($p = 0.03$) and decrease in the risk for haemorrhage-related re-exploration ($p = 0.04$) and blood transfusion requirements ($p = 0.03$).

3.3.3. Survival analysis

Nineteen patients were lost to follow-up (0.9%). Unadjusted Kaplan–Meier survival estimates are presented in Fig. 1, while adjusted estimates are presented in Fig. 2. In both the unadjusted ($p = 0.002$) and adjusted analyses ($p = 0.047$), the curves are significantly different up to 16 months after surgery. Covariates included in the Cox proportional hazard analysis are presented in Table 6. In the Cox proportional hazard analysis for comparison between aprotinin and EACA, the relative risk of death of patients receiving aprotinin was 3.35 (95% confidence intervals: 1.24–9.04; $p = 0.017$).

4. Discussion

In 1993, aprotinin was first approved in the United States as a drug that limits blood loss in patients undergoing surgery. However, during 2006, the safety of aprotinin came under scrutiny when a sponsor-independent, propensity-adjusted, retrospective study reported that aprotinin use was associated with an increased risk of acute renal failure, myocardial infarction, cerebrovascular events and mortality

Table 2
Patient demographic characteristics (univariate analysis).

	Aprotinin, N = 1898	EACA, N = 203	p-value
Gender (male)	1388 (73.1%)	137 (67.5%)	0.087
Hypertension	1459 (76.9%)	160 (78.8%)	0.53
Diabetes	709 (37.4%)	74 (36.5%)	0.80
Chronic renal insufficiency	100 (5.3%)	7 (3.5%)	0.26
Cerebrovascular accident	206 (10.9%)	19 (9.4%)	0.51
Acute myocardial infarction	403 (21.2%)	40 (19.7%)	0.61
COPD			
Mild	138 (7.3%)	15 (7.4%)	0.087
Moderate	88 (4.6%)	8 (3.9%)	
Severe	75 (4.0%)	1 (0.5%)	
None	1598 (84.2%)	179 (88.2%)	
NYHA class			
I	65 (3.4%)	5 (2.5%)	0.086
II	537 (28.3%)	65 (32.0%)	
III	806 (42.5%)	96 (47.3%)	
IV	490 (25.8%)	37 (18.2%)	
Repeat sternotomy	193 (10.2%)	7 (3.5%)	0.002
Percutaneous coronary intervention	393 (20.7%)	33 (16.3%)	0.13
Congestive heart failure	388 (20.4%)	20 (9.9%)	<0.001
Unstable angina	254 (13.4%)	22 (10.8%)	0.30
Number diseased vessels			
One	96 (5.1%)	8 (3.9%)	0.33
Two	368 (19.5%)	50 (24.6%)	
Three	1137 (60.4%)	118 (58.1%)	
None	283 (15.0%)	27 (13.3%)	
Ejection fraction <40	486 (25.6%)	52 (25.6%)	0.99
Case priority			
Elective	539 (28.4%)	67 (33.0%)	0.002
Urgent	1170 (61.6%)	131 (64.5%)	
Emergent	189 (10.0%)	5 (2.5%)	
Age >75	274 (14.4%)	18 (8.9%)	0.029
Age (median and range)	63 (19–91)	62 (28–82)	0.14
Preoperative atrial fibrillation	116 (6.1%)	10 (4.9%)	0.49
Year of surgery			
2002	461 (24.3%)	75 (37.0%)	<0.001
2003	366 (19.3%)	36 (17.7%)	
2004	429 (22.6%)	14 (6.9%)	
2005	387 (20.4%)	0	
2006	255 (13.4%)	78 (38.4%)	
Surgeon			
A	371 (19.6%)	95 (46.8%)	<0.001
B	478 (25.2%)	30 (14.8%)	
C	431 (22.7%)	71 (35.0%)	
D	464 (24.5%)	7 (3.5%)	
E	154 (8.1%)	0	

COPD: chronic obstructive pulmonary disease; and NYHA: New York Heart Association.

after cardiac surgery [8]. Recently, the data and safety board of a large randomised trial suspended the recruitment of patients in the aprotinin group because of an increased risk of death. This prospective randomised trial (Blood Conservation Using Antifibrinolytics in a Randomised Trial or BART trial) evaluating the haemostatic effects and adverse events of aprotinin and other lysine analogues was terminated early because of the higher rate of death in patients receiving aprotinin (6% for aprotinin vs 3.9% for tranexamic acid and 4% for EACA) [10]. An editorial on the same journal concluded



Fig. 1. Kaplan–Meier survival estimates, according to treatment group. *p*-value, calculated with the log-rank test is reported.

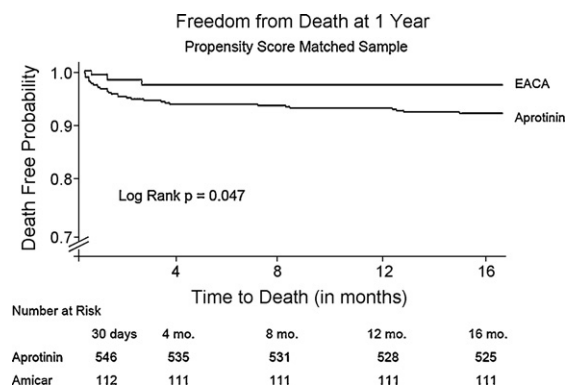


Fig. 2. Survival estimates for the comparisons between aprotinin and EACA in propensity-matched groups. *p*-value calculated with the log-rank test is reported for the group comparison.

that this article is in all likelihood the end of the aprotinin story [11]. Based on the results of this study, on 5 November 2007, the US FDA announced that Bayer Pharmaceuticals Corp. agreed to an FDA-requested marketing suspension of Trasylol, removing its remaining stocks, while limiting its use for investigational purposes only. Our study compared the early and late mortality and major morbidity between aprotinin and EACA in patients undergoing cardiac surgery and resulted in similar findings with the above-mentioned studies.

4.1. Principal findings

4.1.1. Operative mortality and in-hospital cardiac arrest

We conducted a non-sponsor-supported observational study to address the safety of antifibrinolytic and serine–protease inhibition therapy for thrombosis-related cardiac and renal events using propensity score matching to allow comparative safety assessment between aprotinin and EACA. Although in univariate analysis aprotinin was associated with an increased risk of operative mortality, this finding was not confirmed at the multivariate analysis level. Aprotinin rather than EACA was used in sicker patients, so this reduction in risk-adjusted mortality after controlling for confounding variables is consistent with the hypothesis of confounding on the basis of indication [12]. Multivariate analyses resulted in

Table 3
Operative and postoperative patient characteristics (univariate analysis).

	Aprotinin, N = 1898	EACA, N = 203	p-value
<i>Operative variables</i>			
Type of surgery			
CABG	1429 (75.3%)	168 (82.8%)	0.014
Valve	313 (16.5%)	29 (14.3%)	
CABG + valve	156 (8.2%)	6 (3.0%)	
Prolonged pump time (>125 min)	497 (26.2%)	56 (27.6%)	0.66
Pump time (median and range)	104 (21–398)	105 (29–230)	0.64
Prolonged cross clamp time (>78 min)	493 (26.0%)	63 (31.0%)	0.120
Cross clamp time (median and range)	61 (0–288)	60.5 (0–177)	0.77
Prolonged operation (>293 min)	500 (26.3%)	50 (24.6%)	0.59
Operation time (median and range)	252 (53–1036)	256 (143–432)	0.59
<i>Postoperative variables</i>			
Stroke	40 (2.1%)	5 (2.5%)	0.61
Sepsis	66 (3.5%)	2 (1.0%)	0.057
Acute renal failure	145 (7.6%)	6 (3.0%)	0.014
Haemodialysis	40 (2.1%)	2 (1.0%)	0.42
Atrial fibrillation	471 (24.8%)	43 (21.2%)	0.25
In-hospital cardiac arrest	60 (3.2%)	0	0.010
Intraaortic balloon pump	3 (0.2%)	0	1.00
Haemorrhage-related re-exploration	100 (5.3%)	13 (6.4%)	0.49
Postoperative blood transfusion	718 (37.8%)	93 (45.8%)	0.026
Cardiac tamponade	22 (1.2%)	2 (1.0%)	1.00
Mediastinitis	20 (1.1%)	1 (0.5%)	0.71
Operative mortality	81 (4.3%)	2 (1.0%)	0.023
Cause of mortality (operative)			
Cardiac	54	1	0.56
Infection	3	0	
Stroke	8	0	
Respiratory failure	9	1	
Acute renal failure	4	0	
Other	2	0	
Unknown	1	0	
Return to the ICU	169 (8.9%)	13 (6.4%)	0.229
Prolonged ICU LOS (>24 h)	1171 (61.7%)	112 (55.2%)	0.070
ICU LOS (median and range)	26.4 (0–1733.5)	24.5 (11–504.7)	0.020
Prolonged hospital LOS (>9 days)	446 (23.5%)	32 (15.8%)	0.013
Hospital LOS (median and range)	7 (0–162)	7 (3–46)	0.14
Reintubation	117 (6.2%)	12 (5.9%)	0.88
Pneumonia	132 (7.0%)	8 (3.9%)	0.10
Pulmonary embolism	8 (0.4%)	0	1.00
Multi system organ failure	39 (2.1%)	2 (1.0%)	0.42
Early extubation (ventilated <6 h)	789 (41.6%)	93 (45.8%)	0.24

CABG: coronary artery bypass graft; LOS: length of stay; and ICU: intensive care unit.

a weaker association between aprotinin and death than those reported in unadjusted analyses. Another explanation is that our study is not sufficiently powered to identify differences in mortality secondary to the low number of index events (type II error). Importantly, among the adjudicated deaths, the use of aprotinin was associated with a higher risk of death from cardiac causes compared to EACA. In propensity score matching, aprotinin also increased the risk of in-hospital cardiac arrest (odds ratio = 1.04, 95% confidence interval: 1.02–1.06; $p = 0.035$) a unique finding of the present study.

4.1.2. Late mortality

In our study, aprotinin was associated with decreased survival after cardiac surgery compared to EACA. We found a decrease in late survival that is persistent up to 16 months after cardiac surgery in Cox proportional hazard analysis. Importantly, aprotinin's association with late death sustained comprehensive covariate challenges, remaining significant

with or without propensity correction, echoing the previous reports [5,6,11].

4.1.3. Renal events and blood transfusion requirements

In our study, aprotinin was associated with a decrease in blood transfusion requirements and haemorrhage-related re-exploration rates, as previously shown [13–15]. However, aprotinin increased the risk of acute renal failure after cardiac surgery compared to EACA, as previously documented by other authors [3,5,6]. This result was found in univariate analysis and multivariate logistic regression model; however, it was not confirmed at the propensity-matched risk model, possibly secondary to a small sample size (type II error). There was no difference in the rate of acute renal failure requiring haemodialysis between the aprotinin and EACA groups. This finding may be explained by aprotinin causing only a small decrease in renal function, not severe enough to result in an increase in haemodialysis rates.

Table 4
Multivariate logistic regression analysis models.

Variable	OR	CI	p
Operative mortality			
Diabetes	1.72	1.08–2.74	0.023
Chronic renal insufficiency	2.44	1.22–4.86	0.011
Congestive heart failure	2.84	1.77–4.53	<0.001
Unstable angina	2.49	1.45–4.28	0.001
Age >75	2.57	1.53–4.34	<0.001
Prolonged pump time (>125 min)	3.21	2.03–5.07	<0.001
C-statistic	0.79		
Stroke			
Hypertension	4.96	1.52–16.14	0.008
Type of surgery	0.43	0.22–0.85	0.014
Prolonged cross clamp time (>78 min)	1.98	1.01–3.87	0.046
C-statistic	0.70		
Acute renal failure			
Aprotinin	2.39	1.03–5.53	0.042
Diabetes	1.52	1.08–2.15	0.017
Congestive heart failure	2.77	1.94–3.94	<0.001
Prolonged pump time (>125 min)	2.32	1.65–3.28	<0.001
C-statistic	0.71		
Transfusion			
Aprotinin	0.68	0.50–0.91	0.010
Gender	0.59	0.48–0.72	<0.001
Chronic renal insufficiency	3.97	2.57–6.13	<0.001
COPD	1.32	1.03–1.70	0.028
Ejection fraction <40	1.53	1.24–1.89	<0.001
Age >75	1.97	1.52–2.56	<0.001
Prolonged pump time (>125 min)	1.68	1.32–2.14	<0.001
Prolonged operation (>293 min)	1.41	1.11–1.80	0.005
C-statistic	0.62		
Haemorrhage-related re-exploration			
Chronic renal insufficiency	1.98	1.05–3.73	0.035
Type of surgery	0.40	0.26–0.60	<0.001
Ejection fraction <40	1.87	1.25–2.80	0.002
Prolonged pump time (>125 min)	1.59	1.05–2.40	0.027
C-statistic	0.67		
Acute myocardial infarction			
Prolonged pump time (>125 min)	2.57	1.09–6.09	0.032
C-statistic	0.67		
In-hospital cardiac arrest			
Gender	0.49	0.29–0.83	0.007
Chronic renal insufficiency	3.07	1.47–6.39	0.003
Congestive heart failure	2.96	1.73–5.05	<0.001
C-statistic	0.71		

SE: standard error; OR: odds ratio; 95% CI: 95% confidence intervals; and COPD: chronic obstructive pulmonary disease.

Table 5
Propensity score adjustment between aprotinin and EACA.

	Aprotinin, N = 570	EACA, N = 114	p-value
Acute myocardial infarction	5 (0.9%)	1 (0.9%)	1.000
Stroke	11 (1.9%)	3 (2.6%)	0.71
Acute renal failure	39 (6.8%)	3 (2.6%)	0.087
Haemodialysis	8 (1.4%)	2 (1.8%)	0.67
In-hospital cardiac arrest	21 (3.7%)	0	0.035
Haemorrhage-related re-exploration	21 (3.7%)	9 (7.9%)	0.045
Postoperative blood transfusion	221 (38.8%)	57 (50.0%)	0.026
Cardiac tamponade	4 (0.7%)	1 (0.9%)	1.00
Operative mortality	23 (4.0%)	1 (0.9%)	0.15

Table 6
Hazard ratios for death from the main-effects multivariable Cox proportional hazards model.

Variable	Hazard ratio	95% CI	p-value
Aprotinin	3.35	1.24–9.04	0.017
Diabetes	1.40	1.02–1.93	0.036
Chronic renal failure	2.43	1.58–3.75	<0.001
NYHA	0.53	0.34–0.85	0.008
Reoperation	1.50	1.10–2.06	0.011
Congestive heart failure	2.20	1.57–3.07	<0.001
Age >75	2.72	1.94–3.82	<0.001
Prolonged operation (>293 min)	1.73	1.26–2.38	<0.001

NYHA: New York Heart Association; and CI: confidence intervals.

4.2. Clinical implications

This study included a real-world unselected cohort, a single-institution methodology and prospective data entry by a dedicated data management collection centre. We were able to document an increased risk of in-hospital cardiac arrest and late mortality with aprotinin administration. Aprotinin was also associated with a decreased rate of postoperative blood transfusions and haemorrhage-related re-exploration. Although the risk of acute renal failure was higher in the aprotinin group, this finding was not confirmed by the propensity-matched control analysis.

4.3. Study limitations

Limitations of the study include the retrospective, single-institution methodology. Use of propensity score analysis may adjust but not completely eliminate differences between the compared groups. In our study, aprotinin was not associated with an increased risk of 30-day mortality and acute renal failure, possibly secondary to a small sample size (type II error).

In conclusion, our analysis documented an association between aprotinin use and a decline in blood transfusion requirements and haemorrhage-related re-exploration rates. Aprotinin, however, increased the risk of in-hospital cardiac arrest and late mortality compared to EACA. Cumulative evidence from this and the previous studies indicate that the mortality risk associated with aprotinin may not be worth the benefit of decreased transfusions after cardiac surgery.

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Editorial comment

Keywords: Aprotinin; Cardiac surgery; Mortality; Late survival

Stamou and colleagues present another critical article about adverse outcome following administration of aprotinin in adult cardiac surgery [1]. In this retrospective study, haemostatic effects of aprotinin were confirmed but the authors found an increased risk for in-hospital cardiac arrest. Another intriguing finding was found, namely that the risk of late cardiac death was higher in patients who received aprotinin than after aminocaproic acid (EACA). Unfortunately, neither the cause of early mortality nor the problem of cardiac-related attrition (graft occlusion, perioperative myocardial infarction, malignant arrhythmias or others) were analysed or specified.

Because of the retrospective character of the study, several limitations and bias have to be considered: the use of aprotinin or EACA was left at the discretion of the surgeons. The patients who received aprotinin were older, had more prior surgery, suffered more frequently from congestive heart failure (NYHA class IV) and underwent more often complex and emergency surgery than those who received EACA. It is questionable if propensity score matching may be sufficient to eliminate 'confounding by treatment' differences of the two study groups. The authors conclude that the risk of aprotinin may not be worth the benefit of reduced transfusion requirements.

There are a tremendous number of publications dealing with aprotinin, but a single finding seems to be consistent: aprotinin is associated with decreased transfusion requirement and re-exploration rate because of bleeding. This was already the main finding of the initial report of Royston and colleagues [2]. In more recent years, the question appeared if aprotinin increases the risk of renal dysfunction and is an independent predictor of increased mortality. Concerning the last two end-points, conflicting results are present in literature.

The two most important 'negative' trials for aprotinin (Mangano et al. [3] as well as the Bart trial [4]) have been

largely discussed in literature. Not only the power but also the limitations of these trials are very well pointed out. Some authors believe that the recent 'attacks' against aprotinin may have been statistically unsound [5]. Even extensive meta-analysis of the Cochrane collaboration in 2007 have not found an increased risk of death caused by the use of aprotinin compared to lysine analogues. The use of aprotinin was recommended especially in high-risk patients in whom a substantial blood loss has to be expected [6]. In a more recent update, this option has been contradicted by the same authors [7].

What are the remaining questions? There has been an increasing concern that questions the safety of aprotinin. If we accept this, we are forced to ask why this was not detected during the two decades of extensive use of the drug with published good results. As a result of the aprotinin story [8], studies should – if ever possible – focus on clinical end-points that are not confounded with surrogate markers. Independent clinical safety studies are mandatory even after regulatory approval.

Unfortunately, the large majority of studies that demonstrated adverse outcome following aprotinin were performed using the original Hammersmith protocol, which means a high dosage. More than 15 years ago, we published similar beneficial haemostatic results with low-dose aprotinin and no adverse cardiac outcome was observed, neither early nor late [9]. We do not understand why the low-dose regime was not adopted by more institutions.

Finally, it is today still not clear which patient subgroups may benefit from aprotinin. However, this is more of theoretical interest since the drug is no longer available on a regular basis. Considering that low-risk cardiac surgical patients are at increased risk for bleeding events (e.g., having operation under ongoing combined anti-platelet therapy), other potent measures in addition to the available lysine analogues in order to reduce postoperative bleeding,