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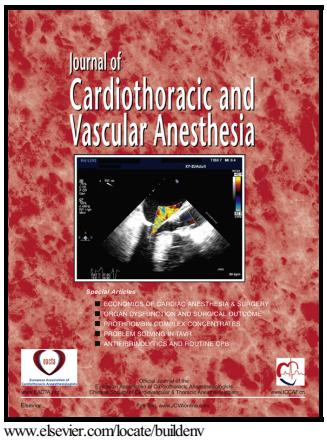

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Effectiveness and safety of aprotinin use in thoracic aortic surgery

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Objective

To compare the effectiveness and safety of aprotinin use in adult patients undergoing thoracic aortic surgery.

Design

Single center retrospective study.

Setting

All cases performed at a single university hospital.

Participants

Between January 2004 and December 2014, 846 adult patients underwent thoracic aortic surgery. Due to missing or duplicated data on primary outcomes, 314 patients were excluded. The final sample of 532 patients had operations on the thoracic aorta.

Intervention

The patients were divided in two groups: a total of 107 patients (20.1%) received aprotinin during the operation representing the study group, while the remaining 425 patients (79.9%) underwent surgery without the use of aprotinin.

Measurements and Main Results

To adjust for patient selection and preoperative characteristics, a propensity score-matched analysis was conducted. Mean total blood loss at 12 hours after surgery was similar between the two groups. The blood product transfusion rates did not differ in the two groups apart for the rate of fresh frozen plasma transfusion, being significantly higher in the aprotinin group. Re-exploration for bleeding and the incidence of a major post-operative bleeding event were similar between the groups. In-hospital mortality, renal failure and cerebrovascular accidents did not show any statistically significant

difference. Aprotinin did not represent a risk factor for mortality over the long term outcome (HR 1.14, 95%CI 0.62-2.08, p=0.66).

Conclusions

The use of aprotinin demonstrated a limited effect in reducing post-operative bleeding and prevention of major bleeding events. Aprotinin did not adversely affect early outcomes and long term survival.

Introduction

Patients undergoing cardiac surgery are at increased risk for excessive perioperative blood loss requiring transfusion of blood products, mainly due to the effects of preoperative medications, cardiopulmonary bypass (CPB) and hypothermia which can cause thrombocytopenia and platelet dysfunction, dilution and consumption of coagulation factors, hyper fibrinolysis and residual heparin effect. Intraoperative and postoperative bleeding remains a major complication of aortic surgery, having a significant impact on the clinical outcomes [1]. A strong relationship between bleeding after cardiac surgery and subsequent mortality has been already described, although it is not completely clear whether this is attributable to blood loss or transfusion-related side effects. Recently, a large single-center retrospective analysis in all types of cardiac surgery, has found major bleeding event was an independent predictor of operative mortality [2].

Three anti-fibrinolytic agents (aprotinin, tranexamic acid and aminocaproic acid) are commonly used to minimize bleeding and reduce the need for blood products after cardiac surgery [3]. Aprotinin is a nonspecific serine protease inhibitor associated with reduced inflammatory response and organ-protective effects [4]. The mechanism for these beneficial effects includes inhibition of kallikrein, preservation of platelet membranes, inhibition of neutrophil activation and decrease in fibrinolysis [5-7]. Several randomized controlled trials have shown that aprotinin decreases perioperative bleeding and the need for allogenic blood

transfusions [8,9]. However, concerns about the safety of aprotinin have been raised based on findings from observational studies suggesting that aprotinin was associated with increased renal dysfunction, cerebrovascular accidents and mortality [10-12].

Limited data are available about the effect of aprotinin in thoracic aortic surgery. Here we report a single centre retrospective analysis comparing the early and mid-term clinical outcomes in patients undergoing adult thoracic aortic surgery with or without the use of aprotinin.

Materials and methods

Study population

This is a single centre retrospective observational study on prospectively collected data obtained from our institutional cardiac surgery dataset with some customized variables (i.e. postoperative bleeding, use of blood products). Between January 2004 and December 2014, 846 adult patients underwent thoracic aortic surgery at Bristol Heart Institute. Data on our primary outcomes were not available for the entire population: for this reason and/or duplicated record we have excluded 314 patients (figure 1). The final sample of 532 patients had operations on the thoracic aorta and included patients requiring circulatory arrest and surgery for acute aortic syndrome. The patients were divided in two groups: a total of 107 patients (20.1%) received aprotinin during the operation representing the study group, while the remaining 425 patients (79.9%) underwent surgery without the use of aprotinin.

End-point and definitions

Our primary end points were post-operative bleeding, reoperation for bleeding and/or tamponade and transfusion of blood products (packed red blood cells, platelets, fresh frozen plasma and cryoprecipitate). A composite outcome of major bleeding was defined as 12 hours post-operative bleeding exceeding the 90th percentile of the entire distribution and/or the

need for reoperation for post-operative bleeding. This parameter was found to be an independent risk factor for postoperative mortality in cardiac surgery [2].

In-hospital mortality was defined as death due to all causes within 30 days from the day of surgery.

Secondary outcomes included acute kidney injury (AKI) defined as per RIFLE criteria (Risk, Injury, Failure, Loss of function, and End-stage renal disease) using maximal change in serum creatinine (sCr) [13], evidence of post-operative stroke (defined clinical and radiological evidence of a new post-operative cerebrovascular event (CVA)) and long term survival.

Surgical and intensive care management

Aprotinin was administered as a 280 mg (2x106 kIU) loading dose, followed by a maintenance infusion of 70 mg/h and priming of the cardiopulmonary bypass pump with 280 mg.

Anticoagulation during CPB was achieved with unfractionated heparin according to standard protocols: the initial dose was 300 IU/kg adjusted with further administration to achieve and maintain an activated clotting time (ACT) higher than 480 seconds. Heparin reversal was achieved with protamine sulphate (100 mg per 300 units of heparin) to normalize ACT after CPB. The indication for re-sternotomy for excessive bleeding was made on the basis of individual patient clinical status mainly depending on the amount of blood drainage from the thoracic drains, hemodynamic instability and/or signs of cardiac tamponade. The indication for blood product transfusion was not guided by a specific protocol, although the usual cut-off for red blood cells transfusion was a haemoglobin value less than 8 g/dL.

Following the withdraw of the aprotinin, all the patients not treated with aprotinin received tranexamic acid as per our institutional protocol: after induction of anesthesia and prior to

skin incision a pre-surgical loading dose of 15 mg/kg followed by infusion of 4.5 mg/kg/hour for the duration of surgery; 0.6 mg/kg of this infusion dose may be added in the priming volume of the heart-lung machine.

Statistical analysis

Data are presented as mean ± one standard deviation for continuous variables or as percentages of the total for dichotomous variables. Continuous variables were tested for normality using the Kolmogorov-Smirnov test and then compared between groups with unpaired Student's t test if normally distributed or Mann-Whitney U test if not normally distributed. In the case of dichotomous or categorical variables Pearson chi-squared or Fisher's exact test were used as appropriate. Overall long-term survival was estimated by Kaplan–Meier analysis. Comparison between unadjusted overall group survivals was assessed by the log–rank test. To further adjust for patient selection and preoperative characteristics, a propensity score-matched analysis and multivariable logistic regression analysis was conducted. The group of patients who did not receive aprotinin was 1:1 matched to the group of patients who did receive it using those preoperative variables which had a p value<0.1 in the unmatched analysis. This resulted in 2 matched groups with 107 patients each group. After matching, the 2 groups were compared using the paired t test or Wilcoxon test for continuous variables and the McNemar or Fisher exact test for categorical variables.

Multivariable logistic regression analysis for independent predictor of major bleeding events was carried out. A stepwise approach was used and confirmed by backward/forward methods with Akaike information selection criteria. The significance within the models was evaluated with the Wald test, whereas the strength of the association of variables with postoperative major bleeding was estimated by calculating the odds ratio (OR) and 95% confidence intervals (CI). Long term survival has been described with the Kaplan-Meier method and the

comparison between groups has been made using the log-rank test. Independent predictors of long term survival were evaluated with a Cox proportional hazard model.

All tests were two-sided with the alpha level set at 0.05 for statistical significance. The statistical analysis was computed using R version 3.0.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria).

Results

Unmatched analysis

The overall in-hospital mortality was 5.45%. There was a higher not statistically significant mortality rate in the aprotinin compared to the non aprotinin group (7.5% vs 4.9 %, p=0.33). Preoperative and operative characteristics are shown in tables 1 and 2 (unmatched population). The two groups were similar in terms of demographic and main pre-operative characteristics, although aprotinin patients were more frequently operated in an emergency setting (31.7 % vs 18.8%, p <0.01) and had a higher preoperative creatinine level. The number of patients operated for type A aortic dissection was similar (23.3% vs 18.3%, p=0.27). The operative times were similar between the two groups (table 2): cardiopulmonary bypass time was 159.9 ± 64.8 minutes (median 149, IQR 75) in group A and 164.3 ± 72.5 minutes (median 148, IQR 67) in group B (p = 0.88); aortic cross-clamp time was 96.3 ± 42.7 minutes (median 95, IQR 57 min) vs 102.2 ± 47 minutes (median 95, IQR 57) respectively (p=0.35). There was a higher number of cases with deep hypothermic circulatory arrest (DHCA) in group A (43.9% vs 33.6%) although this difference had a borderline statistical significance (p=0.054); the DHCA time was significantly higher in group A (16.2 ± 19.6 vs 10.3 ± 23.4 minutes respectively, p = 0.003). The overall mean post-operative bleeding in the first 12 hours after surgery was 520 ± 293 ml (median 450 ml, interquartile range 325 – 650 ml); in the first 24 hours was 759 ± 499 ml (median 650 ml, interquartile range 450 - 925 ml). Fig. 2 shows a density plot for the post-operative chest drainage in the first 12 hours between

the two groups: the mean postoperative bleeding was marginally lower in the aprotinin group although this difference was not statistically significant (506.5 ± 300.8 ml in group A vs 523.6 ± 292.2 ml in group B, p= 0.4). The occurrence of re-sternotomy for bleeding was also similar (6.5% vs 9.5%, p = 0.35). Major postoperative bleeding events involved 16 patients in the aprotinin group (14.9%) and 68 patients in the non-aprotinin group (16%, p = 0.88). Post-operative major bleeding event was independently associated with a significantly higher postoperative in-hospital mortality (OR 3.05, 95% CI 1.36 - 6.8, p = 0.006). As expected, this subgroup of patients had also a higher rate of blood (70.2 vs 34.6%, p <0.01), platelets (47.6 vs 7.4%, p<0.01) and fresh frozen plasma (36.9 vs 8.9%, p < 0.01) transfusions. Aprotinin did not appear to influence this outcome (OR 1.08, 95% CI 0.6-1.96, p=0.79). After multivariate logistic regression analysis, independent predictors for major bleeding were the need for DHCA (OR 1.8, 95% CI 1.13-3.08, p=0.01) and CPB time (OR 1.006, 95% CI 1.001-1.010, p=0.04).

Table 3 reports the total amount of transfusions. There was no difference in red blood cell (RBC), platelet (PLTs) and cryoprecipitate transfusions between groups. Interestingly a higher use of fresh frozen plasma (FFP) was found in the aprotinin group (24.3 % vs 10.6 %, p < 0.01).

Postoperative AKI and CVA rates was not different between the two groups (33.6% vs 25.9, p=0.11 and 4.7% vs 2.5% , p = 0.44, respectively in aprotinin and non-aprotinin group).

The Kaplan-Meier survival curves are shown in figure 3. The long term survival at 5 years was 79.3% in aprotinin patients and 78.2% in non aprotinin; at 10 years was 58.5% vs 74.7 % respectively (p=0.68). Table 4 shows the Cox's proportional hazard model. Independent predictors for long term mortality were hypertension (HR 2.05, 95%CI 1.13-3.6, p=0.01), chronic obstructive pulmonary disease (HR 3.36, 95% CI 1.85-6.11, p<0.01), reduced left ventricular ejection fraction (HR 2.18, 95%CI 1.23-3.84, p<0.01), post-operative transfusions

(HR 2.79 95% CI 1.8-3.4, p<0.01). Although long term survival at 10 years was lower, the Cox's proportional hazard model indicated that the use of aprotinin did not significantly affect the outcome (HR 1.14, 95%CI 0.62-2.08, p=0.66).

A further comparative analysis was conducted in the subgroup of patients who underwent DHCA (190 patients, 35.7% of the total cohort). We observed a tendency to less bleeding at 12 hours in the aprotinin group (477.66 ± 312.09 ml vs 579.79 ± 337.09 ml) although not statistically significant (p = 0.06) and the incidence of re-sternotomy for bleeding was also similar (6.38% vs 8.39 %, respectively; p = 0.89). The volume of blood product transfusion was also similar.

Matched analysis

Distribution of baseline and operative characteristics for the matched analysis is shown in tables 1 and 2 (matched population). Those variables which were significantly different before matching were adjusted trough propensity score and were now comparable. The final number of patients was 107 for each group.

The operative outcomes for the matched population are also shown in table 3. There was a higher but not statistically significant mortality rate in the aprotinin compared to the non aprotinin group even in the matched population (7.5% vs 6.5%, p=1). Twelve hours bleeding was similar in the two groups (median 450 ml, IQR 325 in the aprotinin group vs. median 500 ml, IQR 362 in the non-aprotinin group, p = 0.15). Major postoperative bleeding events involved 16 patients in the aprotinin group (15%) and 21 patients in the non-aprotinin group (21%, p = 0.44). There was no difference in red blood cell (RBC), platelet (PLTs) and cryoprecipitate transfusions between groups. As already seen in the unmatched group, a higher use of fresh frozen plasma (FFP) was found in the aprotinin group (24.3 % vs 11.2%, p < 0.01).

Re-sternotomy for bleeding was also similar (6.5% vs 8%, p = 0.15). Postoperative AKI and CVA rates was not different between the two matched groups (33.6% vs 29%, p = 0.11 and 4.7% vs 5.6% , p = 0.44, respectively in aprotinin and non-aprotinin group).

Discussion

There were three main findings in our study. First, the use of aprotinin did not significantly reduce post-operative bleeding and blood product transfusion rate; secondly, we did not find aprotinin to confer more risk in terms of in-hospital morbidity and mortality; last, long term survival was not significantly different between groups.

The use of aprotinin in cardiac surgery has been extensively debated; however, just a few of the available analysis have focused on a selected cohort of thoracic aortic surgery patients. Thoracic aortic surgery with or without DHCA is associated with significant post-operative bleeding, even in the hands of experienced surgeons[14,15]: it may lead to severe bleeding due to surgical reasons such as poor quality atherosclerotic tissues, coagulopathy due to longer CPB times and hypothermia. Some authors have speculated that the most important factors to prevent blood loss in this type of surgery are secure suture lines and the experience of the surgical and anesthesiology team as early aggressive management of coagulopathy is critical[16]. Our study is a contemporary series reporting accurate measurements of post-operative bleeding after thoracic aortic surgery. The lack of significant differences in bleeding and re-exploration rates between groups suggests that meticulous surgical technique and particular attention to haemostasis are crucial and may play a larger role than aprotinin for reduction of bleeding. Our analysis confirms the prominence of bleeding-related complications in aortic surgery with 15.1% of the patients bleeding more than 800 ml in the first 12 hours and a blood product transfusion rate of 45.3%. These results are in line with similar studies: in a retrospective analysis of thoracic aortic surgery in DHCA[14], Mora Mangano et al. showed no differences in terms of post-operative chest drainage between

aprotinin and non-aprotinin patients, with a first 12 hours bleeding of 947 vs 761 ml respectively (p 0.33). Sedrakyan and colleagues [15], in contrast, showed that there is some evidence of reduction in 24-hour drainage in patient receiving aprotinin compared with a control group, although they considered bleeding at 24 hours that, in our opinion, is not the ideal timing to assess the postoperative bleeding in thoracic aortic surgery, generally associated with severe bleeding and re-exploration in a shorter period of time. In order to reduce the higher risk of bleeding and subsequent need for blood product transfusion, in the last years our practice is evolving towards moderate hypothermia (26-28°C) to avoid DHCA, with increasing use of axillary artery as site of arterial cannulation and antegrade cerebral perfusion for brain protection.

In our study, the RBC transfusion rate was not significantly different between groups both in the unmatched and matched analyses. This result cannot be correlated to the use of aprotinin only as many other variables could have influenced RBC transfusion such as pre-operative anaemia, haemodilution, type of surgery and the local thresholds for transfusions. Therefore, RBC transfusion rates alone should not be used to judge the effectiveness of aprotinin in high bleeding risk cardiac surgery. The use of platelets and FFP would probably be more appropriately related to post-operative bleeding: interestingly we found a higher use of FFP in the aprotinin group (unmatched analysis 24.3 % vs 10.6 %, $p < 0.01$; matched analysis 24.3% vs 11.2%, $p<0.01$), with no difference in the use of platelets (unmatched analysis 13.1% vs 13.9%, $p=0.95$; matched analysis 13.1% vs 15%, $p=0.83$). In the last two decades the rule of prophylactic use of FFP transfusion as part of blood conservation strategies has changed. The most recent STS and SCA guidelines on blood conservation clinical practice in cardiac surgery [17] have revised the clinical indications for plasma use, limiting them mainly to serious bleeding or surgical procedures in the context of multiple or single coagulation factor deficiencies when safer fractionated products are not available. A systemic

review of six clinical trials including a total of 363 patients undergoing cardiac procedures showed no improvement in blood conservation with prophylactic use of plasma [18]. Another review identified seven additional randomized trials of FFP used in cardiovascular procedures (including pediatric operations), and found no association between use of FFP and reduced surgical blood loss [19]. Despite several limitations, the results of FFP trials are consistent, and the available evidence suggests that the prophylactic use of plasma in routine cardiac surgeries is not associated with reduced blood loss or less transfusion requirement, and this practice is not recommended any more. Our results reflect a change in the FFP use in our institution across the years, with a reduction in their prophylactic transfusion from 2011, since the most recent guidelines were published.

Furthermore, aprotinin interferes with all the current tests of the intrinsic coagulation system; our institutional policy for continued blood product transfusion in patients who continued to bleed after arriving in intensive care involved thromboelastography followed by APTT. The results of these tests would have driven the blood product transfusion policy, thus creating an additional mechanism of bias that led to a higher FFP transfusion rate in the study group.

Similar results on increased use of FFP was shown by Jakobsen [20], while higher incidence of blood product transfusion in aprotinin group was reported by Mora Mangano's study [14], where patient treated with aprotinin received more blood products intra-operatively. In a more recent study on thoracic aortic surgery [21], the authors reported a general trend toward less overall blood product transfusion in the aprotinin group. An older study, published in 2000 investigated the impact of the aprotinin use on 23 patients undergoing thoracic aortic surgery with DHCA showing a significant reduction in the need for blood products in a subgroup of patients who received low-dose aprotinin [22]. De Santis and colleagues have shown an increased blood product need in adult cardiac surgery in the post BART era [23].Previous reports have correlated administration of aprotinin with post-operative

cardiovascular complications and reduced survival rate [10,11,24,25]. In 2008 the result from Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART)[12] were published: this was a multicenter randomized controlled trial comparing efficacy and safety of anti- fibrinolytic agents. The trial was terminated earlier because of a higher rate of death in patients receiving aprotinin. As immediate effect, the use of aprotinin was discontinued. More recent studies [23,26,27] have refuted this claim and re-validated its efficacy and safety resulting in reintroduction into clinical practice [28]. Since then, several series and expert reviews have been published with positive comments on the effects and safety of aprotinin [29-31].

Thoracic aortic surgery patients represent a high risk population for postoperative complications like AKI and stroke [32,33]: therefore this subgroup of patients represents an interesting population for analysis to further evaluate the impact of aprotinin on post-operative complications. We did not find differences between the two groups with respect to short term outcomes. In-hospital mortality, postoperative AKI and stroke rate were comparable between the two groups. Midterm and long term survival after cardiac surgery is influenced by many factors such as the preoperative risk profile, the type of operation and the post-operative complications. In our study, the Kaplan-Meier survival curves for both groups showed a slightly worse survival at 10 years in the aprotinin group; however, the Cox's proportional hazard model indicated that the use of aprotinin did not affect significantly the survival in the long term.

Our study has several limitations: it is a retrospective analysis of a single center experience involving a relatively small cohort of patients, and due to missing values on main outcomes around 1/3 of the entire population has been excluded from the analysis. Although we analyzed a select cohort of patients, there is still a degree of heterogeneity: in fact, it involves

higher risk procedures like type A dissection with DHCA and less risky procedure like elective ascending aorta replacements.

In conclusion, in our thoracic aortic surgical practice, the use of aprotinin demonstrated a limited effect in reducing post-operative bleeding and prevention of major bleeding events. It did not have detrimental effects on short–term clinical outcomes and did not compromise long-term survival. A new prospective randomized trial would be desirable to better understand the efficacy of aprotinin especially in the subgroup of patients who have a higher risk of post-operative bleeding.

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Figure legends:

Fig 1. Patients selection flowchart.

Fig 2. Density plot for total chest drainage by aprotinin use in the first 12 post-operative hours.

Fig 3. Kaplan-Meier Survival curves between the two groups.

Table 1. Preoperative characteristics of the study cohort

	Unmatched population			Matched population		
Characteristic	**Aprotinin (n=107)**	**Non Aprotinin (n=425)**	***p* Value**	**Aprotinin (n=107)**	**Non Aprotinin (n=107)**	***p* Value**
Age (years, median, IQR)	59(15)	60(23)	0.93	59(15)	60(15)	0.55
Female gender	37(34.5)	144(33.8)	0.9	37(34.5)	31 (39)	0.42
BMI (Kg/m^2 - mean ± SD)	27.3±4.8	27.4±4.9	0.85	27.3±4.8	27.7±5.3	0.67
Reduced LVEF	22(20.5)	67(15.7)	0.24	22(20.5)	21 (19.6)	1
COPD/Asthma	11(10.2)	60(14.1)	0.34	11(10.2)	19 (17.8)	0.18
Diabetes	1(0.9)	10(2.3)	0.7	1(0.9)	4 (3.7)	0.37
Hypertension	68(63.5)	238(56)	0.66	68(63.5)	61 (57)	0.4
Previous CVA	7(6.5)	21(4.9)	0.47	7(6.5)	2 (1.9)	0.17
Smoking History			0.5			0.59
Current	16(14.9)	49(11.5)		16(14.9)	17 (15.9)	
Ex Smoker	43(40.1)	159(37.4)		43(40.1)	41 (38.3)	
PVD	9(8.4)	51(12)	0.43	9(8.4)	17 (15.9)	0.21
Creatinine (median, IQR)	95(33)	90(31)	<0.01	95(33)	94.5 (30)	0.1
Euroscore (median, IQR)	9(3)	8(4)	0.21	9(3)	9(4)	0.44
Sinus Rhytm	90(84.1)	383(90.1)	0.08	90(84.1)	90 (84.1)	1
Nonelective surgery	51(47.6)	162(38.1)	0.07	51(47.6)	46 (43.0)	0.42
Emergency surgery	34(31.7)	80(18.8)	<0.01	34(31.7)	34 (31.8)	1
Previous Cardiac Surgery	23(21.4)	71(16.7)	0.26	23(21.4)	17 (15.9)	0.41

Definitions: BMI: body mass index; LVEF: Left Ventricular Ejection Function, COPD: Chronic Obstructive Pulmonary Disease, CVA: cerebro-vascular accident, PVD: peripheral vascular disease, IQR: interquartile range, SD: standard deviation. Kg: Kilograms, m2: square meters, min: minutes. Data are expressed as number of events and percentages or otherwise expressed

Table 2. Operative characteristics

Characteristic	Unmatched population			Matched population		
	Aprotinin (n=107)	Non Aprotinin (n=425)	*p* Value	Aprotinin (n=107)	Non Aprotinin (n=107)	*p* Value
Treated Aortic Segment:			0.18			0.25
Ascending Aorta/Arch	54(50.4)	247(58.1)		54(50.4)	60(56.1)	
Aortic Root	53(49.5)	178(41.8)		53(49.5)	47(43.9)	
Type A aortic dissection	25(23.3)	78(18.3)	0.27	25(23.3)	27 (25.2)	0.85
CPB time (min - median,IQR)	149(75)	148(67)	0.88	149(75)	170(73)	0.51
ACC time (min - median, IQR)	95(57)	101(51)	0.35	95(57)	104(46)	0.44
Use of DHCA	47(43.9)	143(33.6)	0.54	47(43.9)	43 (40.2)	0.63

Definitions: CPB: cardio-pulmonary bypass, ACC: Aortic cross-clamp, DHCA: deep hypothermic circulatory arrest. IQR: interquartile range, min: minutes. Data are expressed as number of events and percentages or otherwise expressed

Table 3. Operative outcomes between the two groups

Characteristic	Unmatched population			Matched population		
	Aprotinin (n=107)	Non Aprotinin (n=425)	*p* Value	Aprotinin (n=107)	Non Aprotinin (n=107)	*p* Value
In Hospital Mortality	8 (7.5)	21(4.9)	0.33	8 (7.5)	7 (6.5)	1
Major Bleeding	16 (15.0)	68(16)	0.88	16 (15.0)	21 (19.6)	0.44
Transfusion						
RBC transfusion	39 (36.4)	175(41.2)	0.44	39 (36.4)	51 (47.7)	0.09
PLT transfusion	14 (13.1)	59(13.9)	0.95	14 (13.1)	16 (15.0)	0.83
FFP transfusion	26 (24.3)	45(10.6)	<0.01	26 (24.3)	12 (11.2)	<0.01
Cryoprecipitate transfusion	4 (3.7)	26(6.1)	0.48	4 (3.7)	5 (4.7)	1
12 Hours bleeding (ml, median, IQR)	450(350)	450(325)	0.49	450(350)	500(362)	0.15
Reoperation for Bleeding	7 (6.5)	30(7.1)	1	7 (6.5)	8 (7.5)	1
Renal Failure	36 (33.6)	110(25.9)	0.11	36 (33.6)	31 (29.0)	0.45
CVA	5 (4.7)	11(2.5)	0.44	5 (4.7)	6 (5.6)	1

Definitions: Major bleeding as defined in the method section. Renal failure as per any RIFLE criteria. RBC: red blood cells, PLT: platelets, FFP: fresh frozen plasma, CVA: cerebrovascular accident. IQR: inter-quantile range. Data are expressed as number of events and percentages or otherwise expressed.

Table 4. Adjusted Cox proportional hazard model for patient mortality

		Multivariate Analysis	
Parameter (reference level)	Level	HR(95% CI)	p value
Aprotinin (no)	yes	1.14(0.62-2.08)	0.66
Hyperthension(no)	yes	2.05(1.13-3.69)	0.01
COPD(no)	yes	3.36(1.85-6.11)	<0.01
Reduced LVEF(no)	yes	2.18(1.23-3.84)	<0.01
Post-operative Bleeding (no)†	yes	1.78(0.96-3.28)	0.06
Post-operative Transfusion(no)‡	yes	2.79(1.8-3.4)	0.01

Definitions: COPD: chronic obstructive pulmonary disease, LVEF: left ventricular ejection fraction

†: Defined as major post-operative event

‡: Defined as any blood product transfusion