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**An exploratory cohort study comparing prothrombin complex concentrate and fresh frozen plasma for the treatment of coagulopathy after complex cardiac surgery**

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## Abstract

### **Background:**

Administration of coagulation factor concentrates to treat bleeding after cardiopulmonary bypass (CPB) might be a strategy for reducing allogeneic blood transfusions particularly for those treated with warfarin preoperatively. Our aim was to perform an exploratory analysis on whether the use of prothrombin complex concentrate is safe and effective compared with fresh frozen plasma to treat coagulopathy after pulmonary endarterectomy surgery with deep hypothermic circulatory arrest.

### **Methods:**

Consecutive adult patients who underwent pulmonary endarterectomy surgery between January 2010 and September 2012 and received prothrombin complex concentrate or fresh frozen plasma to treat coagulopathy were studied. Blood loss during the first twelve hours of intensive care unit admission and patient outcomes were compared using propensity score adjustment.

### **Results:**

A total of 351 patients underwent pulmonary endarterectomy surgery all of whom had warfarin discontinued for up to 5 days prior to surgery; Bleeding complications requiring transfusion of blood products were observed in 108 (31%) patients. Of those, 55 received only fresh frozen plasma and 45 received only prothrombin complex concentrate, whilst 8 received both. Blood loss was significantly higher in the fresh frozen plasma group compared with the prothrombin complex concentrate group after 12 hours (median, interquartile range [IQR], 650 ml [325-1075] vs. 277 ml [175-608],  $p=0.008$ ). However, there was no difference in the frequency of patients receiving a red blood cell transfusion (number, [percent] 44 [80%] vs. 34 [76%],  $p=0.594$ ) or in

the number of units of red blood cells transfused (median, [IQR] 2 [1-4] vs. 3 [1-5] units,  $p=0.181$ ). The final propensity score included preoperative INR, postoperative activated partial thromboplastin time, and platelet count. After inclusion of the propensity score in the regression analyses, there were no differences in the need for renal replacement therapy (odds ratio [OR] 2.39, 95% confidence interval [CI] 0.51 to 11.20,  $p=0.27$ ), 30-day-mortality (OR 0.32, 95%CI 0.03 to 3.36,  $p=0.35$ ), intracranial hemorrhage (0.73, 95%CI 0.14 to 3.89,  $p=0.71$ ), hospital (HR=0.77, 95%CI 0.50 to 1.19,  $p=0.24$ ), or duration of intensive care stay (HR 0.91, 95%CI 0.59 to 1.40,  $p=0.66$ ).

**Conclusion:**

These retrospective analysis suggest that prothrombin complex concentrate may be an alternative to fresh frozen plasma in patients previously treated with warfarin who are coagulopathic after major cardiac surgery. Randomized controlled studies powered to evaluate efficacy and important postoperative outcomes for patients receiving prothrombin complex concentrate versus fresh frozen plasma for coagulopathic bleeding after CPB are warranted.

## Introduction

Bleeding is a major complication after cardiac surgery using cardiopulmonary bypass (CPB) that exposes patients to the risk of allogeneic blood transfusion and reoperation. Although there are conflicting data, the use of warfarin anti-coagulant treatment before surgery may increase the risk of bleeding complications after CPB surgery<sup>2-4</sup>. In recent years, coagulation factor concentrates have been increasingly used to reduce patient exposure to allogeneic blood components<sup>6</sup>. Four factor prothrombin complex concentrates (PCC) contains a high concentration of lyophilized clotting factors II, VII, IX, X and protein C and S. This compound is currently licensed in Europe and the United States for the treatment of congenital or acquired deficiency of those clotting factors and for the emergency reversal of vitamin-K antagonists, such as warfarin for patients who are bleeding or when urgent surgery is planned<sup>7</sup>. In some European countries, PCCs have replaced FFP as the treatment for perioperative bleeding even though there are little data on the efficacy and safety of its use in this setting particularly the risk for prothrombotic complications<sup>8,9</sup>. The clinical demand for PCC may further increase given the questionable efficacy of fresh frozen plasma in critically ill patients<sup>10</sup>, its cost and the potential of transmission of prions\* and other well described complications.

\*Joint United Kingdom Blood Transfusion Services and Health Protection Agency Professional Advisory Committee. Position statement: Creutzfeldt-Jacob disease; available at [http://www.transfusionguidelines.org.uk/docs/pdfs/dl\\_ps\\_vcjd\\_2012-11.pdf](http://www.transfusionguidelines.org.uk/docs/pdfs/dl_ps_vcjd_2012-11.pdf) (last accessed 29 Feb 2014).

Pulmonary endarterectomy (PEA) is complex surgery to treat chronic thromboembolic pulmonary hypertension that is performed under deep hypothermic circulatory arrest and requires prolonged CPB (greater than five hours)<sup>11</sup>. The majority of patients undergoing PEA are receiving long-term warfarin therapy, which is usually stopped five days before surgery. Despite

thi,s many patients do not have normalized prothrombin time at the time of surgery (i.e. International Normalized Ratio [INR] > 1.5). Under these circumstances, clinicians may transfuse FFP and/or PCCs for treating coagulopathic bleeding after CPB<sup>12,13</sup>. Transfusion of large volumes of FFP is balanced by the competing demands of the treatment of right heart failure, a common complication after long standing pulmonary hypertension, and the risk of reperfusion injury to the lung after PEA surgery<sup>14</sup>. Prothrombin complex concentrates have a smaller volume of administration than FFP for a similar concentration of coagulation factors, making the former therapy attractive in this situation. However, patients undergoing PEA surgery have underlying pro-thrombotic conditions and a high risk of ischemic neurological complications<sup>11</sup>. There are few data on the safety and efficacy of PCC use for treatment of coagulopathic bleeding after CPB particularly for patients undergoing PEA.

Our aim was to provide an exploratory analysis of the safety and efficacy of PCC compared to FFP in consecutive patients with coagulopathic bleeding after PEA surgery.



## Methods

The Research and Development Department of Papworth Hospital NHS Trust (Cambridge, UK) gave approval for this study and waived the requirement for individual consent. All adult patients undergoing elective PEA surgery between January 2010 and September 2012 at our institution, who received hemostatic therapy, were included. Data were collected from a dedicated pulmonary hypertension database, and an institutional transfusion database. Patients were classified based on whether they received only PCC or only FFP after PEA surgery. Patients who received both or who received treatment more than 48 hrs after surgery were excluded from the analysis.

The anesthetic and surgical management for PEA has been described<sup>9</sup>. In brief, all patients received heparin 400 IU.kg<sup>-1</sup> before CPB with additional doses given to maintain an activated clotting time (ACT) above 400 sec throughout surgery. Tranexamic acid 1g was administered before CPB and then as an infusion at 500 mg.hr<sup>-1</sup> continued intra-operatively<sup>15</sup>. Upon adequate heparinization CPB was initiated and the patient's body temperature lowered to 18°C to 20°C. Deep hypothermic circulatory arrest was then performed for periods of up to 20 minutes during which the PEA was performed. The patients temperature was then rewarmed to 37°C and then they were carefully weaned from CPB. All patients received intra-operative cell salvage and hemofiltration during CPB. Hemoglobin was maintained >6 g.dL<sup>-1</sup> during the hypothermic CPB phase and > 10 g.dL<sup>-1</sup> during rewarming for separation from CPB and in the postoperative period..

Thrombelastography (TEG®, Haemonetics, Nile, IL, USA) was performed when the patient temperature reached 32 °C during rewarming, using a heparinase containing cup. After rewarming and separation from CPB, protamine 4 mg.kg<sup>-1</sup> was administered, and further boluses

given aiming for an ACT within 10% of baseline. After administration of protamine, blood was sent to the laboratory to measure platelet count, prothrombin time, INR, activated partial thromboplastin time, thrombin time, and fibrinogen concentration. . Transfusion of PCC or FFP was considered if the INR was  $> 1.7$  or the TEG R-time was  $> 10$  mins, and excessive bleeding was observed while the chest was open or if there were  $> 2 \text{ ml.kg}^{-1}.\text{hr}^{-1}$  chest drainage after chest closure.<sup>1</sup> In the presence of these conditions PCC (15 IU.kg<sup>-1</sup> to the nearest 250 IU vial) or FFP (15 ml.kg<sup>-1</sup>) was given. The decision to administer FFP or PCC was at the discretion of the clinical team in the operating room in collaboration with the hematologist.

### **Statistical Analysis**

As this was an exploratory analysis, no formal sample size calculation was conducted before the start of the study. The sample size of approximately 50 cases per group was large enough to detect an effect size of one half of one standard deviation, with 2-sided type I error of 5% and power of 80%. The study is not powered to detect smaller effect sizes.

Initially patient and operative characteristics were summarized and unadjusted exploratory comparisons between the two groups were performed. In this analysis we used the student t-test for Normally distributed variables (age, weight, BMI, 6-minute walk distance, CPB time, cross-clamp time, circulatory arrest time, INR, aPTT, platelet count, haemoglobin, creatinine and fibrinogen levels), the Mann-Whitney test for skewed or other non-Normally distributed variables (PVR, blood loss, ICU stay and hospital stay) or Chi-squared/ Fisher's exact test for categorical variables (sex, disease type, numbers undergoing transfusions, 30-day mortality, incidence of other post-operative events and use of renal replacement therapy or ECMO).

There is a high chance of bias in estimation of group differences in observational studies due to systematic allocation of patients to the groups. In order to minimise this bias a propensity score was developed using all variables that were considered related either to the outcome or to the allocation to either PCC or FFP<sup>16</sup>. Many of these variables were correlated with each other and were grouped according to the size of this correlation. The propensity score was developed using both statistical criteria (change in deviance associated with p-value < 0.1) and to ensure that selected variables that had large amounts of missing data were replaced by correlated variables that did not have missing data. The following variables were included in the final propensity score: pre-operative INR, post-CPB aPTT and post-CPB platelet count. No specific methods for dealing with missing covariates were attempted due to the exploratory nature of the studies and the number of variables recorded. Rather we excluded any covariates with a large proportion of missing values.

Once the propensity score was developed the effect of PCC on binary outcomes (survival at 30 days, reperfusion injury of the lungs, intra-cranial hemorrhage, renal impairment, renal replacement therapy) was assessed using logistic regression models including PCC and propensity score, where the logit of the estimated probability of having PCC was included in the regression. For ICU and hospital stay a range of time-to-event models were assessed and final models were based on Cox proportional hazards models after checking the proportional hazards assumption using Schoenfeld residuals. PCC and logit(propensity score) were included in these models. The linearity of the relationship between the outcome (after applying the appropriate link function) and the logit(propensity score) was assessed by splitting the logit score into quartiles and refitting. Informal visual assessment of plots between the four levels and the

estimated regression parameters was made and no major departures from linearity were seen.

Analysis was implemented using Stata/IC version 12.0 for windows (StataCorp LP,USA).

## Results

During the 33 months study period, 351 patients underwent PEA surgery, and 108 (31%) suffered bleeding complications and received hemostatic treatment. Of the latter, 55 received only FFP (51%) and 45 received only PCC (42%). Eight patients (7%) received both FFP and PCC and were excluded from the analysis. A schematic diagram of the patients is shown in Figure 1. At baseline, there were significantly more patients with distal thromboembolic disease (type III and IV) in the PCC group (Table 1)<sup>17</sup>. This was reflected by the higher pulmonary vascular resistance (PVR) both pre-operatively and postoperatively in patients who received PCC. Cardiopulmonary bypass and circulatory arrest times were similar between the two groups. Baseline INR and aPTT were higher in the PCC group, as was the aPTT after CPB (Table 2). In the FFP group, patients received a mean (SD) 3.8 (1.8) units of FFP. In the PCC group 33 patients (73%) were treated with Beriplex (CSL Behring UK Ltd, Haywards Heath, UK) and 12 patients (27%) with Octaplex (Octapharma Ltd, Manchester, UK). The choice of product was due to a change in the National Health Service procurement contract. The mean (SD) dose was 14.8 (5.4) IU.kg<sup>-1</sup>.

Cumulative blood loss in the immediate postoperative period was higher in the FFP group compared with the PCC group one (p=0.027), six (p=0.002) and twelve (p=0.008) hours after surgery (Figure 2 and Table 3). Similar numbers of patients in the FFP and PCC groups received a transfusion of , platelets, cryoprecipitate, or fibrinogen in the postoperative period (Table 4). In addition, patients who received PCC received a similar number (median, IQR) units of red blood cells as those receiving FFP (2, 1-4 vs. 3, 1-5 units, respectively, p=0.181).

The 30-day mortality 4.6%, median (IQR) ICU stay 4 (2-7) days, and hospital stay 14 (9-19) days for the 351 patients who underwent PEA surgery. There were no differences in

outcomes ( Table 5) between the FFP and PCC groups. No patient suffered deep vein thrombosis, pulmonary embolism, or myocardial infarction in either group, and the incidence of cerebral infarction and hemorrhage was low and similar between the two groups (Table 5).

The final propensity adjusted risk model is listed in Table 6. Regression models that included the propensity score did not identify any significant effects of PCC use on outcomes compared with patients receiving only FFP for treating coagulopathic bleeding after CPB (Table 7). Despite the adjustment for propensity to use PCC, these effects on outcomes are measured imprecisely with very wide confidence intervals, particularly for postoperative complications.

## Discussion

In our cohort of patients who underwent PEA surgery with deep hypothermic circulatory arrest, those who received PCC had less chest tube drainage in the 12 hours after surgery compared with patients given FFP. We did not find a difference between the PCC and FFP groups in the number of patients transfused after surgery or in the number of transfused units of packed red blood cells or other haemostatic products. Although, this preliminary analysis did not find a difference in major patient outcomes between patients given PCC versus FFP for coagulopathic bleeding after CPB the small sample size precludes drawing firm conclusions regarding the safety of PCC versus FFP.

Fresh frozen plasma is administered to patients with coagulopathic bleeding after cardiac surgery despite a paucity of data on the efficacy of this treatment<sup>18</sup>. There are many recognized risks associated with the transfusion of FFP including transfusion related acute lung injury, transfusion associated circulatory overload, transmission of bacterial and non-bacterial infection, and multiple organ failure, which are independent of the effect of hemorrhage and transfusion<sup>19</sup>. The time delay necessary to thaw the frozen blood product (up to 40 min) is another limitation of the use of FFP. The dose of FFP most commonly prescribed in the UK is 15 ml.kg<sup>-1</sup>, therefore a 70kg patient would require more than a liter of plasma containing approximately 1 IU/ml of hemostatic factors (around three to four units of FFP). Such a volume of fluid may lead to circulatory overload, a particular issue in patients after PEA surgery as the right ventricle is prone to failure and excessive fluid administration can predispose to or worsen pulmonary reperfusion injury.

In contrast, PCC is stored as a powder for reconstitution and can be administered within minutes<sup>20</sup>. Administration of PCC, thus, requires approximately 40 ml of fluid co-administration

at the dose of  $15 \text{ IU.kg}^{-1}$  used in this study (1000 IU in a 70kg patient). PCC is approved for the prophylactic administration before urgent or emergency surgery in patients with reduced levels of Vitamin K-dependent clotting factors due to warfarin treatment. The manufacturer recommended dose depends on the exact INR, and it is generally given for  $\text{INR} > 2$ . The patients in this study were receiving long-term warfarin treatment, but we did not correct an elevated INR pre-operatively, preferring instead only to treat elevated INR in the presence of excessive bleeding after CPB. PCC is also more expensive than FFP (820 USD for 1000 IU compared to 190 USD for 3 units of FFP in the UK). Additionally, there is some concern that PCC use may be associated with increased risk for thrombo-embolic events, which would be a particular issue in our patients with chronic thromboembolic disease. A porcine laboratory study found that  $35 \text{ IU.kg}$  PCC safely improved coagulation and attenuated blood loss<sup>21</sup>. However, at a dose of  $50 \text{ IU.kg}^{-1}$  (very much higher than the  $15 \text{ IU.kg}^{-1}$  administered in our study) PCC was associated with an increased risk of thromboembolism in all animals when organs were examined microscopically after death, and 44% of animals also developed disseminated intravascular coagulation. A recent meta-analysis of 27 clinical studies involving 1032 patients receiving PCC for emergency reversal of warfarin for bleeding or need of surgery revealed an overall incidence of thromboembolism of 1.4% (95% CI, 0.8–2.1)<sup>22</sup>. Mortality in that study was high at 11%, however death was only rarely attributed to the PCC itself. Analysis of a pharmacovigilance report after 15 years clinical use of a four factor PCC also showed a low risk of thromboembolic events (1:31 000)<sup>23</sup>.

An explanation for the lack of difference in blood transfusion with PCC administration compared with FFP despite lower chest tube drainage in our study is not clear. This finding may be related to the fact that the cohort of patients who received PCC had a more complicated distal



pulmonary artery obstruction requiring more complicated surgery. Gorlinger et al. did report retrospectively reduced blood transfusion when PCC was used as part of a point of care-guided transfusion algorithm in more than 3800 patients, but most patients received multiple treatments including fibrinogen, FFP and platelets, so it is very difficult to attribute any effect to PCC alone<sup>24</sup>. Weber et al found a similar effect with PCC in a point of care-guided algorithm in a randomized controlled study, compared to conventional treatment guided by laboratory analysis<sup>25</sup>.

We did observe an increased requirement for renal replacement therapy in patients who received PCC (Table 5); although this was not statistically significant, it remains a concern. This may be related to the increased hemodynamic instability in this cohort of patients who had higher residual pulmonary hypertension.

There are very few published studies comparing FFP and PCC in the peri-operative period; most report observational data from cohorts of patients or case series. Arnekian et al also showed decreased blood loss only in the first hour in patients treated with PCC compared to FFP<sup>26</sup>. In comparison, we gave a slightly larger dose of PCC compared with Arnkian et al<sup>26</sup>, and found the lower chest tube drainage persisted for 12 hours. Demeyere et al randomized 40 patients to receive FFP or PCC before CPB for urgent surgery, but reported no significant effect on blood loss<sup>27</sup>. Bruce et al reported data from 24 patients who received PCC following severe hemorrhage during cardiac as well as other surgical procedures and reported a reduction in the administration of other blood products<sup>28</sup>. A number of studies in non-cardiac surgical patients have demonstrated the effectiveness of PCC in lowering the INR<sup>29-31</sup>. Other authors have raised concerns about thromboembolic complications attributed to PCC administration, however none compared PCC with other treatment options<sup>32-35</sup>. Further study in a large prospective cohort is

clearly required to determine whether rapid reversal of the INR as a result of warfarin is indeed offset by a potential increase of morbidity and mortality by thromboembolic events.

There are several limitations to our study. We included several outcomes and did not make adjustments for the large number of statistical tests conducted. We think this is appropriate since the study was designed to be exploratory and sensitive to any potential effects that might be present. However interpretation of significant results should recognize this potential for false positives. A further limitation of our study was the retrospective study design and the fact that patients were not randomly assigned to a treatment group. Although we used propensity score adjustment in an attempt to limit bias related to whether FFP or PCC therapy was chosen, this method is only completely effective if all mediating factors are included in the score. This assumption is unlikely as other important covariates that are not routinely recorded may have influenced our findings. Thus there may be residual biases in these comparisons. Finally, the number of patients in each group was relatively small so that power to detect important differences in outcomes was low. This is shown in Table 6 in which there are important estimated effects of PCC on, for example reperfusion injury, but very wide confidence intervals ranging from a 53% reduction in odds over a ten-fold increase. Thus negative results are to be interpreted with caution.

Our study is associated with some advantages as well. First, patient management was standardized according to our institutional protocol. Management of bleeding was based on results of TEG and/or laboratory data. However, there is some evidence that kaolin activated TEG has a reduced sensitivity and specificity for identifying deficiency of vitamin K dependent coagulation factors compared to the INR<sup>36</sup>. Finally, patients treated with PCC received either Beriplex or Octaplex. The choice of PCC during the period of study was determined by the

National Health Service procurement contract, which changed its preferred supplier at one point for a period of one year. However, Octaplex has also been shown to be effective and safe and the composition and quantity of clotting factors compared in both products is very similar<sup>37</sup>.

In conclusion, we have shown that PCC may be an alternative to FFP in patients who are coagulopathic and bleeding after cardiac surgery, particularly when intravascular fluid administration must be limited due to concerns of right ventricular dysfunction. We found that PCC administration was associated with reduced blood loss 12-hours after surgery compared with patients receiving FFP, but there were no differences in the frequency of blood transfusion or number of other haemostatic products administered. These exploratory analysis support the need for a prospectively randomized controlled study of the safety and efficacy of PCC for reducing bleeding after surgery using CPB.

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Tables

**Table 1.** Descriptive summary for baseline and surgical characteristics of entire cohort of patients undergoing PEA and for those patients who received only fresh frozen plasma (FFP only) or prothrombin complex concentrate (PCC only) for treating coagulopathy after cardiopulmonary bypass. Values are mean (SD), number (proportion) or median (IQR)\*.

	Entire cohort (n=351)	FFP only (n=55)	PCC only (n=45)	P-Values for (PCC only vs. FFP only)
Age (years)	58 (14.5)	62 (13)	61 (13)	0.805
Women	170 (48%)	18 (33%)	19 (42%)	0.328
Weight (kg)	84.6 (19.2)	81.4 (18.9)	82.5 (17.8)	0.779
BMI (kg.m <sup>-2</sup> )	29.5 (6.3)	27.3 (5.0)	28.8 (6.1)	0.172
6-min walk test (m)	296.6 (121.9)	299.0 (142.3)	274.8 (96.0)	0.452
Disease type 3 or 4	67/314 (21%)	6/46 (13%)	13/40 (33%)	0.03
Pre-operative PVR; (dyn.s.cm <sup>-5</sup> )*	573 (381- 818)	598 (420-940)	711 (474-862)	0.45
Postoperative PVR; (dyn.s.cm <sup>-5</sup> )*	231 (167- 309)	209 (140-260)	303 (241-415)	<0.0001
Duration of CPB (min)	341.0 (66.0)	344.4 (51.2)	350.8 (60.7)	0.564
Duration of aortic	70.1 (36.7)	82.8 (69.3)	70.5 (25.5)	0.262

cross clamp (min)				
Duration of circulatory arrest; (min)	34.8 (11.2)	38.2 (11.3)	36.3 (12.1)	0.431

BMI= body mass index, PVR= pulmonary vascular resistance, CPB= cardiopulmonary bypass

**Table 2.** Descriptive summaries for hematological data before and after cardiopulmonary bypass (CPB) for patients who received either fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) for treating coagulopathic bleeding. Values are mean (SD).

	<b>FFP group</b>	<b>PCC group</b>	<b>p-value</b>
<b>Pre-operative</b>			
INR	1.7 (0.5)	1.9 (0.5)	0.044
aPTT (sec)	34.4 (5.4)	36.6 (5.3)	0.07
Platelet count ( $10^9/L$ )	234.5 (130.8)	213.4 (67.0)	0.329
Hemoglobin ( $g \cdot dL^{-1}$ )	14.3 (2.0)	14.6 (1.8)	0.546
Creatinine ( $\mu mol \cdot l^{-1}$ )	102.1 (26.0)	110.9 (33.5)	0.142
<b>Post-CPB</b>			
INR	2.4 (0.4)	2.6 (0.9)	0.144
aPTT (sec)	77.7 (52.3)	108.9 (73.86)	0.0169
Platelet count ( $10^9/L$ )	93.0 (42.7)	75.3 (35.5)	0.033
Hemoglobin ( $g \cdot dL^{-1}$ )	9.4 (1.1)	9.6 (1.2)	0.916
Fibrinogen ( $g/l^{-1}$ )	1.5 (0.4)	1.5 (0.5)	0.916

**Table 3.** Observed cumulative blood loss at one, six and twelve hours after ICU admission. The values are median (IQR).

	Entire cohort (n=351)	FFP only (n=55)	PCC only (n=45)	P-values for (PCC only vs. FFP only)
1 <sup>st</sup> hour (ml)	50 (25-150)	175 (50-250)	75 (25-175)	0.027
6 hours (ml)	175 (100- 375)	475 (175-750)	175 (100-400)	0.0023
12 hours (ml)	275 (150 - 550)	650 (325-1075)	277 (175-608)	0.0078

**Table 4.** Comparisons of the number (percent) of patients given various blood transfusion products for the patients treated with either only fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC) for coagulopathy after cardiopulmonary bypass.

	FFP group (n=55)	PCC group (n=45)	P-Value
Red blood cells	44 (80%)	34 (76%)	0.594
Platelets	34 (62%)	28 (62%)	0.967
Cryoprecipitate	11 (20%)	6 (13%)	0.377
Fibrinogen concentrate	4 (7%)	6 (13%)	0.315



**Table 5.** Comparisons of outcomes for patients treated with either only fresh frozen plasma (FFP only), only prothrombin complex concentrate (PCC only) or neither (No FFP or PCC) for coagulopathy after cardiopulmonary bypass. Values are number (proportion) or median (IQR)\*.

	No FFP or PCC (n=237)	FFP only (n=55)	PCC only (n=45)	P-Value (PCC only vs. FFP only)
30-day mortality	6 (2.5%)	4 (7.3%)	3 (6.7%)	0.906
ICU stay (days)*	3 (2-6)	5 (3-8)	6 (4-15)	0.059
Hospital stay (days)*	13 (9-17)	15 (11-22)	17 (14-28)	0.114
Cerebral infarct	4 (1.7%)	1 (1.8%)	1 (2.2%)	0.886
Cerebral haemorrhage	8 (3.4%)	3 (5.5%)	4 (8.9%)	0.503
Seizure	0 (0%)	2 (3.6%)	3 (6.7%)	0.489
Reperfusion injury of the lungs	0 (0%)	3 (5.5%)	6 (13.3%)	0.171
Renal replacement therapy	5 (6.8%)	3 (5.5%)	7 (15.6%)	0.094
ECMO	4 (1.7%)	7 (12.7%)	6 (13.3%)	0.929

ECMO= extracorporeal membrane oxygenation.

**Table 6.** Variables included in the final propensity score for the use of prothrombin complex concentrate (PCC).

Predictor	Log odds ratio	95% CI	Wald P-value
Pre-op INR	0.945	(-0.305, 1.924)	0.058
Post-CPB aPTT	0.008	(0.0003,0.015)	0.040
Post-CPB PLT	-0.012	(-0.024, 0.0008)	0.066
Constant term	-1.641	(-3.72, 0.434)	0.121

INR= international normalised ratio, CPB= cardiopulmonary bypass, aPTT= activated partial thromboplastin time; PLT= platelet count.

\* These results are based on a Cox proportional hazards model

**Table 7.** Outcomes for patients receiving only prothrombin complex concentrate (PCC) for treating coagulopathic bleeding after cardiopulmonary bypass adjusted for propensity.

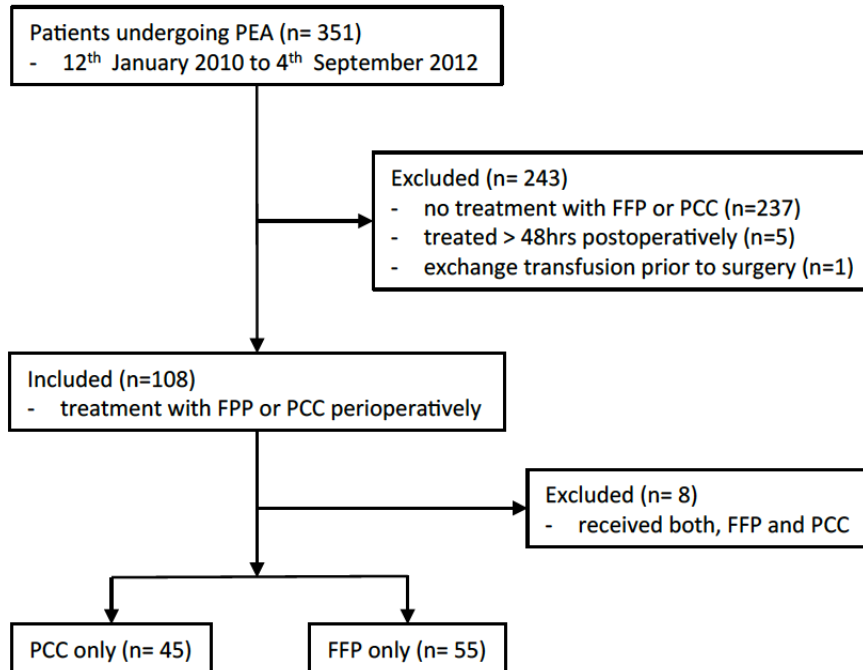
Outcome	Odds Ratio	95% CI	Wald P-value
CVVH	2.39	(0.51, 11.20)	0.268
Renal impairment	1.67	(0.54, 5.17)	0.377
Death in 30 days	0.32	(0.03, 3.36)	0.345
Reperfusion injury	2.22	(0.47, 10.45)	0.310
Intracranial hemorrhage	0.73	(0.14, 3.89)	0.709
Outcome	Hazard ratio	95% CI	Wald P-value
Hospital stay*	0.77	(0.50, 1.19)	0.243
ICU stay*	0.91	(0.59, 1.40)	0.655

CVVH= continuous veno-venous hemofiltration; ICU=intensive care unit

\* These results are from Cox proportional hazards models

Figures and Illustrations

**Figure 1** Flow diagram of the study population.



PEA = pulmonary endarterectomy; PCC = prothrombin complex concentrate; FFP = fresh frozen plasma.

**Figure 2.** Cumulative chest tube drainage for patients treated with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) for coagulopathic bleeding after pulmonary artery endarterectomy. The data are reported as median (horizontal line) and interquartile range (box).

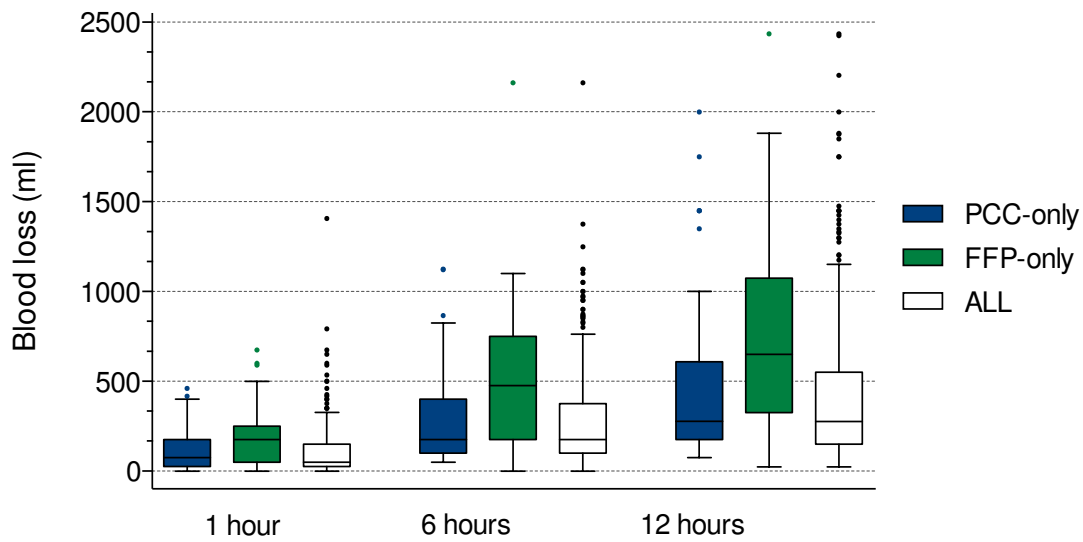


Figure Legends

**Figure 1.** Flow diagram of the study population.

**Figure 2.** Cumulative chest tube drainage for patients treated with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) for coagulopathic bleeding after pulmonary artery endarterectomy. The data are reported as median and interquartile range

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