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## Comparative Analysis of Prothrombin Complex Concentrate and Fresh Frozen Plasma in Coronary Surgery

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**Clinical Trials Identifier:** NCT02319083 (<https://clinicaltrials.gov/ct2/show/NCT02319083>)

**Running head:** PCC vs. FFP in CABG

**Funding statement:** Financial support was provided solely from institutional sources.

**Conflicts of interest:** The authors declare no competing interests.

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**Abstract word count:** 243 words

**Text word count:** 4745 words

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**Abstract**

**Background:** Recent studies suggested that prothrombin complex concentrate (PCC) might be more effective than fresh frozen plasma (FFP) to reduce red blood cell (RBC) transfusion requirement after cardiac surgery.

**Methods:** This is a comparative analysis of 416 patients who received postoperatively FFP and 119 patients who received PCC with or without FFP after isolated coronary artery bypass grafting (CABG).

**Results:** Mixed-effects regression analyses showed that PCC significantly decreased RBC transfusion (67.2% vs. 87.5%, adjusted OR 0.319, 95%CI 0.136-0.752) and platelet transfusion requirements (11.8% vs. 45.2%, adjusted OR 0.238, 95%CI 0.097-0.566) compared with FFP. The use of PCC increased the risk of KDIGO acute kidney injury (41.4% vs. 28.2%, adjusted OR 2.300, 1.203-4.400), but not of KDIGO acute kidney injury stage 3 (6.0% vs. 8.0%, OR 0.850, 95%CI 0.258-2.796) when compared with the FFP cohort. Among 101 propensity score matched pairs, PCC was associated with decreased blood loss at 12 h (mean, 622 vs. 779 mL,  $p=0.018$ ) and lower rates of RBC transfusion (67.3% vs. 83.2%,  $p=0.008$ ), platelet transfusion (10.9% vs. 39.6%,  $p<0.0001$ ) and UDPB bleeding grades 3-4 (25.7% vs. 45.5%,  $p=0.002$ ). On the contrary, PCC cohort received more frequently fibrinogen (39.6% vs. 22.0%,  $p=0.004$ ) and had a significantly higher risk of acute kidney injury (40.4% vs. 16.2%,  $p=0.0003$ ). Acute kidney injury stage 3 was similar between these matched cohorts (6.1% vs. 4.0%,  $p=0.527$ ).

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**Conclusions:** These results suggest that the use of PCC compared with FFP may reduce the need of blood transfusion after CABG.

**Key words:** Prothrombin complex concentrate; Fresh frozen plasma; Bleeding; Transfusion; Cardiac Surgery.

## Introduction

Coronary artery bypass grafting (CABG) is frequently complicated by significant perioperative bleeding, with prognostic implications (1). Coagulopathy occurring after cardiac surgery is a multifactorial and poorly understood condition (2-4), which is often treated by administering fresh frozen plasma (FFP) as this allows replacement of most coagulation factors, including fibrinogen (5). However, the administration of FFP is associated with a risk of transmission of viral, bacterial, parasitic as well as prion diseases, febrile and allergic reactions, transfusion-associated circulatory overload, transfusion-related acute lung injury, acute hemolytic transfusion reactions in addition to ABO blood group incompatibility (5,6). Prothrombin complex concentrate (PCC) has been proposed as a potential valid alternative to FFP in patients with excessive bleeding after cardiac surgery (7-10) and this issue had been investigated in this study.

## Methods

The E-CABG registry (Clinical Trials Identifier NCT02319083) is a prospective, multicenter study that enrolled patients undergoing isolated CABG from Finland, France, Italy, Germany, Sweden and United Kingdom. The

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detailed protocol and definition criteria have been previously published (11). The study was approved by the Institutional Review Board of the participating centers.

The study cohorts consisted of patients who received postoperatively only FFP and those who received PCC with or without FFP. One center used solvent/detergent treated pooled human plasma (Octaplas®) and this was considered equivalent to FFP in the present analysis. The risk of postoperative bleeding was estimated using the WILL-BLEED (12) and CathPCI bleeding risk scores (13).

### *Patient treatment*

Patients were treated according to institutional practice. In general, anticoagulation was achieved with heparin 300-400 IU/kg to maintain an activated clotting time >400-480 s. Shed pericardial blood was salvaged into the cardiotomy reservoir and/or cell salvage device and reinfused intraoperatively or at the end of the procedure. Reversal of heparin anticoagulation was achieved with a dose of protamine sulphate of 1 mg for each 100 units of heparin administered. Tranexamic acid was routinely administered intraoperatively and when needed postoperatively. Aprotinin was not used in these patients. Postoperative point-of-care bleeding tests (thromboelastography, prothrombin and activated partial thromboplastin times, and platelet count) were performed to assess the nature of coagulopathy in patients with excessive bleeding and to guide administration of procoagulants. The participating centers did not adopt a common strategy of patient-blood management and the indication for blood transfusion varied between centers. FFP and PCC were administered only after point-of-care bleeding tests were performed. Six centers administered PCC containing coagulation factors II, VII, IX, X, protein C and protein S, while three centers administered PCC containing coagulation factors II, IX, X. One of these centers used 4-components PCC containing antithrombin and heparin. The initial dose was 1000 IU in eight centers and 500 IU in one center. Maximal dose of PCC ranged from 2000 to 3000 IU.

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## *Outcomes*

The main outcome measure of this study was red blood cell (RBC) transfusion. Secondary outcomes were chest drain output 12 hours after surgery, reoperation for bleeding, surgical site bleeding detected at reoperation, severe-massive bleeding defined as UDPB classes 3-4 (1) and E-CABG bleeding classes 2-3 (11), amount of red blood cell (RBC) transfusions, platelet transfusion, use of recombinant factor VIIa, cryoprecipitate and fibrinogen as well as hospital/30-day death, length of stay in the intensive care unit, stroke, prolonged inotropic support, deep sternal wound infection/mediastinitis, postoperative atrial fibrillation and acute kidney injury.

In brief, E-CABG bleeding grades 2-3 were defined as any reoperation for excessive bleeding and/or transfusion of more than 4 units of red blood cells (11). UDPB bleeding grades 3-4 were defined as chest tube blood loss within 12 hours >1000 mL and/or reoperation for excessive bleeding and/or transfusion of more than 4 units of red blood cells and/or transfusion >4 units of fresh frozen plasma after closure of the chest (1). Acute kidney injury was defined according to the KDIGO classification criteria (14), i.e. an increase in serum creatinine  $\geq 1.5$  times the baseline level or serum creatinine increase  $\geq 26.5$   $\mu\text{mol/l}$  and/or de novo renal replacement therapy within seven days after surgery. Stage 3 acute kidney injury was defined as any increase in serum creatinine  $\geq 3.0$  times the baseline level or serum creatinine increase  $\geq 353.65$   $\mu\text{mol/l}$  within seven days after surgery and/or de novo renal replacement therapy within seven days after surgery. The definition criteria of the other outcomes are published (11).

## *Statistical Analysis*

Statistical analyses were performed using SPSS statistical software v. 24.0 (IBM Corporation, New York, USA), and Stata v. 14.2 (SAS Institute Inc., Cary, NC, USA). Covariates and outcomes were reported as counts and percentages, and as mean  $\pm$  standard deviation or median and interquartile range (IQR). Mann-Whitney, Chi-square and Fisher exact tests were used to compare baseline and operative covariates. Since the participating

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centers did not adopt a common strategy of patient-blood management and the indication for blood transfusion varied between centers, the impact of PCC and FFP on the outcomes was adjusted for participating centers in multilevel mixed-effects logistic, linear and proportional hazards regression models for all covariates listed in Table 1. The use of multilevel mixed-effect regression analysis is indicated when data is nested in more than one category, i.e. multiple participating centers, and allows study effects that possibly vary by nested groups and to estimate group level averages. A one-to-one propensity score matching was performed to adjust the study cohorts for baseline and operative covariates using the nearest neighbour method and a caliper of 0.2 of the standard deviation of the logit of the propensity score. Propensity score was calculated by implementing a generalized boosted regression methodology including the covariates listed in Table 1. Aortic cross-clamping time and cardiopulmonary bypass time were not included in to this regression model because a significant number of patients underwent off-pump surgery. After matching, we used the t-test for paired samples to evaluate the balance between the matched cohorts for continuous variables, the McNemar test for dichotomous variables, and the analysis of the standardized difference. A standardized difference  $\leq 0.10$  was considered as an acceptable balance between the study cohorts. The t-test for paired samples and the McNemar test were employed to evaluate any difference in the early outcomes of propensity score matched pairs. Survival was estimated by the Kaplan-Meier method and study cohorts were compared with the log-rank test by Klein-Moeschberger method and by the mixed effect proportional hazards test adjusted for the covariates mentioned above as well as for the participating centers. A  $p < 0.05$  was set for statistical significance.

## **Results**

### *Overall series*

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Among 7118 consecutive patients operated at 15 centers from January 2015 to December 2016, 416 patients received postoperatively only FFP and 119 patients received PCC with or without FFP (Tab. 1). PCC was used in 9 out of 15 centers and one of these centers used only PCC.

Mixed-effects regression analyses adjusted for multiple covariate and participating centers showed that the use of PCC was associated with significantly lower risk of RBC transfusion and platelet transfusion compared with the FFP (Tab. 2). Furthermore, PCC cohort received more frequently cryoprecipitate and fibrinogen. The PCC cohort received less RBC units than the FFP cohort (Tab. 2).

The use of PCC increased significantly the risk of KDIGO acute kidney injury (41.4% vs. 28.2%), but not of KDIGO acute kidney injury stage 3 (6.0% vs. 8.0%) compared with the FFP cohort (Tab. 2).

One-year survival was higher in the PCC cohort compared with the FFP cohort (94.0% vs. 90.5%, adjusted multilevel mixed-effects, HR 0.850, 95%CI 0.343-2.108), but the difference did not reach statistical significance.

When patients who received solvent/detergent treated pooled human plasma were excluded from the analysis, multilevel mixed-effects analyses showed that the use of PCC was still associated with lower RBC transfusion requirement, platelet transfusion as well as lower rate of UDPB bleeding grades 3-4. Patients in the PCC cohort had a significantly higher risk of KDIGO acute kidney injury, but similar risk of KDIGO acute kidney injury stage 3 compared to the FFP cohort. One-year survival was similar in the study cohorts (PCC, 94.8% vs. FFP, 92.2%, adjusted HR 0.897, 95%CI 0.345-2.334).

### *Propensity score matching analysis*

The study cohorts differed in most of baseline and operative covariates as shown by standardized differences  $\geq 0.10$  (Tab. 1). Propensity score matching resulted in 101 pairs with similar baseline and operative covariates as demonstrated by standardized difference  $< 0.10$ . Even if not included in to the regression model for the estimation of the propensity score, aortic cross-clamping time ( $p=0.688$ ) and cardiopulmonary bypass time

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( $p=0.930$ ) did not differ significantly between the matched cohorts (Tab. 1), but the standardized difference of aortic cross-clamping time was 0.15. These propensity score matched cohorts had similar rates of hospital/30-day mortality, stroke, prolonged use of inotropes and of mechanical circulatory assist devices. One-year survival was 94.9% in the PCC cohort and 91.7% in the FFP cohort ( $p=0.405$ ), but the difference did not reach statistical significance (Fig. 1).

PCC cohort had a significantly higher risk of acute kidney injury (40.4% vs. 16.2%), but acute kidney injury stage 3 was similar between the PCC and FFP cohort (6.1% vs. 4.0%).

PCC was associated with decreased blood loss at 12 h (mean, 622 vs. 779 mL) and lower rate of RBC transfusion (67.3% vs. 83.2%), platelet transfusion (10.9% vs. 39.6%) and UDPB bleeding grades 3-4 (25.7% vs. 45.5%). On the contrary, PCC cohort received more frequently fibrinogen (39.6% vs. 22.0%) (Tab. 2).

## **Discussion**

This study showed that the several European centres of cardiac surgery started to adopt PCC as an alternative to FFP in patients with postoperative coagulopathy after isolated CABG and this policy seems to be associated with a significant reduction in RBC and platelet transfusion requirements. A risk reduction for RBC and platelet transfusion was observed both in mixed-effect logistic regression and propensity score matched analyses (Tab. 2). These statistical approaches showed that chest drain output at 12 hours and the amount of transfused RBC units were also significantly reduced in the PCC cohort. Finally, the administration of PCC did not result in an increased risk of stroke. These findings couples those of a few previous non-randomized studies comparing PCC and FFP in the management of perioperative bleeding after adult cardiac surgery, without increased risk of thromboembolism (7-10). A recent study evaluating PCC versus FFP for warfarin effect reversal in left ventricular assist device recipients before heart transplantation showed a significant reduction of postoperative transfusion requirements with the use of PCC (15).



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The potential advantages of using PCC over FFP include a proved efficacy in reversing coagulopathies related to vitamin K antagonists, higher concentrations of coagulation factors in the product, reduction of risk of circulatory volume overload, lower risk of infectious agent transmission, does not require ABO compatibility testing and its preparation and administration is faster (5,16). However, PCC may be associated with thromboembolic complications. Post-mortem histology of a porcine model of coagulopathy with blunt liver injury demonstrated diffuse thromboemboli in the lung arterioles of all pigs receiving supra-therapeutical dose of PCC (50 IU/kg) (17), and in 33% of animal receiving PCC 35 IU/kg (17). However, a few studies showed that PCC compares favorably with FFP when vitamin K antagonist reversal is required (18). Hickey et al. (19) demonstrated that when PCC 1000-1500 IU were administered for prompt vitamin K antagonist reversal for intracranial and gastrointestinal bleeding or trauma, these patients required a significantly lower amount of blood transfusion without increased risk of thromboembolism. However, evidence on the safety and efficacy of PCC is gathered mostly from vitamin-K antagonist reversal studies, whereas data from patients with trauma and perioperative bleeding is scant (20). In particular, there is a need of studies evaluating venous and arterial thromboembolism in order to better assess and eventually improve the safety of PCC.

The present study showed that PCC was associated with a significant risk of acute kidney injury, still without increased risk of KDIGO acute kidney injury stage 3. Three studies (8-10) showed a trend toward increased of acute kidney injury as well. This could be related to a relative hypovolemia in patients treated with PCC compared to those receiving FFP. This finding requires further investigation in randomized trials.

Patients in the PCC cohort more frequently received fibrinogen and cryoprecipitate (Tab. 2). This approach is in line with the current knowledge suggesting that adequate levels of fibrinogen should be ensured before administration of PCC (20,21). A recent ex-vivo study showed that blood bank products are inferior to coagulation factor concentrates and that concomitant administration of fibrinogen and PCC as well as rVIIa and PCC proved to be most effective combinations of coagulation factor concentrates in the treatment of

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coagulopathy after cardiac surgery (22). However, the safety and efficacy of combining these coagulation factor concentrates should be assessed in larger studies.

This analysis has several limitations, especially the observational nature of this study. Propensity score matching and multilevel mixed effects analyses were employed to avoid any bias related to differences between the study cohorts and patient-blood management strategies among centers. However, significant differences in terms of severity of bleeding before administration of FFP and PCC as well as the type of coagulopathy might have persisted even after non-parsimonious adjustment by multiple baseline and operative variables. Second, we do not have data on platelet reactivity, fibrinogen level, thrombin generation and other coagulation parameters for an analysis of baseline and postoperative coagulopathy in these patients, a limitation shared with other studies published in the same context. Third, the lack of information on whether PCC was administered as a salvage treatment after administration of FFP or vice versa does not allow a more in depth analysis of the efficacy of PCC in the setting of severe bleeding. Fourth, previous studies excluded patients who receive both FFP and PCC, whereas in the present analysis we decided to include them in the PCC cohort. In fact, the exclusion of patients receiving both FFP and PCC might introduce a bias related to patients with excessive perioperative bleeding, who otherwise would have been treated only with larger amount of FFP. Fifth, participating centers used different types of and dosages of PCC and limited number of patients prevents an analysis of the risk and benefits of PCC with different compounds. Finally, the limited size of this series prevents conclusive results on the impact of PCC on end-points of clinical relevance such as early death, stroke and renal replacement therapy. However, this remains the largest study analyzing the effects of PCC in CABG patients and the prospective nature and the availability of data on preoperative antithrombotics are important strength of this analysis. Furthermore, data gathered from several institutions with different clinical practices makes the present findings generalizable.

## *Conclusions*

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These results suggest that the use of PCC compared with FFP may reduce the need of blood transfusion after CABG. In view of the observational nature of this study, these results should be considered hypothesis generating and need to be confirmed in randomized trials.

### **Conflict of interest**

None.

### **Financial support**

This study was not financially supported.

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**Table 1.** Baseline characteristics and operative data of patients undergoing coronary surgery in the participating centers.

Covariates	Overall series				Propensity score matched			
	FFP no. 416	PCC no. 119	Standardized difference	p-value	FFP no. 101	PCC no. 101	Standardized difference	p-value
<i>Baseline risk factors</i>								
Age (years)	69.1±9.3	65.1±9.6	0.42	<0.0001	65.9±9.7	65.3±9.3	0.07	0.536
Female	76 (18.3)	11 (9.2)	0.24	0.032	14 (13.9)	11 (10.9)	0.09	0.862
Body mass index (kg/m <sup>2</sup> )	27.4±4.2	27.3	0.01	0.912	27.4±4.3	27.1±3.9	0.08	0.503
eGFR (mL/min/1.73 m <sup>2</sup> )	70.4±22.7	75.5±21.6	0.23	0.024	77.6±17.9	77.3±19.2	0.02	0.896
Hemoglobin (g/L)	131±20	140±18	0.48	<0.0001	140±18	139±18	0.02	0.863
Platelets count <150 10 <sup>9</sup> /L	51 (12.3)	11 (9.2)	0.10	0.361	11 (10.9)	10 (9.9)	0.03	0.827
Dialysis	8 (1.9)	2 (1.7)	0.02	0.863	0	0	0	-
Diabetes	132 (31.0)	37 (31.1)	0.01	0.895	26 (25.7)	29 (28.7)	0.07	0.623
Poor mobility	15 (3.6)	4 (3.4)	0.01	0.899	0	0	0	-
Recent myocardial infarction	185 (44.5)	39 (32.8)	0.24	0.023	36 (35.6)	34 (33.7)	0.04	0.739
Prior stroke/transient ischemic attack	23 (5.5)	10 (8.4)	0.11	0.250	7 (6.9)	6 (5.9)	0.04	0.763
Atrial fibrillation	58 (13.9)	11 (9.2)	0.15	0.178	7 (6.9)	9 (8.9)	0.07	0.617
Pulmonary disease	42 (10.1)	24 (20.2)	0.28	0.003	20 (19.8)	18 (17.8)	0.05	0.706
Extracardiac arteriopathy	96 (23.1)	29 (24.4)	0.03	0.769	22 (21.8)	23 (22.8)	0.02	0.862
Left ventricular ejection fraction ≤50%	137 (32.9)	39 (32.8)	0	0.981	31 (30.7)	29 (28.7)	0.04	0.742
Prior PCI	91 (21.9)	31 (26.1)	0.10	0.338	27 (26.7)	28 (27.8)	0.02	0.866
Prior cardiac surgery	6 (1.4)	1 (0.8)	0.06	0.610	0	0	0	-
Critical preoperative state	63 (15.1)	9 (7.6)	0.24	0.033	7 (6.9)	6 (5.9)	0.04	0.782
Emergency procedure	55 (13.2)	7 (5.9)	0.25	0.027	6 (5.9)	6 (5.9)	0	1.000
EuroSCORE II (%)	5.2±8.2	3.1±5.6	0.30	0.002	3.0±5.0	2.9±5.6	0.01	0.957
<i>Preoperative antithrombotics</i>								
Aspirin pause<7 days	69 (16.6)	16 (13.4)	0.09	0.409	13 (12.9)	15 (14.9)	0.07	0.695
P2Y12 rec. antagonists pause <5 days	90 (21.6)	18 (15.1)	0.16	0.132	16 (15.8)	16 (15.8)	0	1.000
LMWH/ Fondaparinux/Unfractionated heparin	201 (48.3)	70 (58.8)	0.21	0.043	62 (61.4)	60 (59.4)	0.04	0.773
Oral anticoagulation pause <2 days	19 (4.6)	0	0.31	0.018	0	0	0	-
WILL-BLEED bleeding score	5.9±4.5	4.2±3.6	0.43	<0.0001	4.1±3.5	4.1±3.4	-0.01	0.796
CathPCI bleeding score	53±24	41.0±23	0.50	<0.0001	42±21	41±24	0.05	0.365
<i>Operative data</i>								
Off-pump surgery	72 (17.3)	35 (29.4)	0.29	0.004	27 (26.7)	24 (23.8)	0.07	0.612
Aortic cross-clamping time (min)	62±34	48±31	0.44	<0.0001	52±34	47±31	0.15	0.483
Cardiopulmonary bypass time (min)	104±56	90±52	0.26	<0.0001	95±71	91±54	0.06	0.930
No. of distal anastomoses	2.9±1.0	2.4±0.9	0.56	<0.0001	2.5±0.9	2.5±0.9	0.03	0.796
BIMA grafting	101 (24.3)	38 (9.2)	0.17	0.093	30 (29.7)	34 (33.7)	0.09	0.555

Continuous variables are reported as mean and standard deviation. Categorical variables are reported as counts and percentages (in parentheses). FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; eGFR: estimated glomerular filtration rate according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; PCI: percutaneous coronary intervention; P2Y12 rec. antagonists: clopidogrel, ticagrelor, prasugrel; LMWH: low molecular weight heparin; BIMA: bilateral internal mammary artery.

**Table 2.** Outcomes in the overall series and in propensity score matched pairs.

Outcomes	Overall series				Propensity score matched pairs		
	FFP no. 416	PCC no. 119	Univariate analysis	Multivariate analysis Risk estimate (95%CI)	FFP no. 101	PCC no. 101	p-value
Hospital/30-day mortality	30 (7.2)	7 (5.9)	0.614	0.752, 0.280-2.022	5 (5.0)	5 (5.0)	1.000
Intensive care unit stay (days)	3.0 (4.0)	2.0 (3.0)	0.012	-1.429, -3.231-0.372	3.0 (3)	2.0 (3.0)	0.154
IABP/ECMO <sup>a</sup>	44 (11.5)	8 (7.0)	0.173	0.419, 0.141-1.245	9 (9.8)	7 (7.6)	0.617
Prolonged inotropes	232 (67.2)	39 (32.8)	<0.0001	<b>0.435, 0.216-0.878</b>	40 (39.6)	35 (34.7)	0.475
Stroke	13 (3.1)	6 (5.0)	0.319	2.416, 0.660-8.832	3 (3.0)	5 (4.0)	0.480
Atrial fibrillation	182 (43.8)	31 (26.1)	0.001	0.556, 0.299-1.037	41 (40.6)	27 (26.7)	<b>0.023</b>
DSWI/mediastinitis	19 (4.6)	5 (4.2)	1.000	0.988, 0.297-3.283	2 (2.0)	3 (3.0)	0.655
KDIGO acute kidney injury <sup>b</sup>	113 (28.2)	48 (41.4)	0.007	<b>2.300, 1.203-4.400</b>	16 (16.2)	40 (40.4)	<b>0.0003</b>
KDIGO acute kidney injury, stage 3 <sup>b</sup>	32 (8.0)	7 (6.0)	0.485	0.850, 0.258-2.796	4 (4.0)	6 (6.1)	0.527
<i>Bleeding-related outcomes</i>							
Chest drain output, 12 h (mL)	600 (550)	550 (450)	0.045	-58.447, -185.584-68.69	700 (595)	540 (425)	<b>0.018</b>
RBC transfusion	364 (87.5)	80 (67.2)	<0.0001	<b>0.319, 0.136-0.752</b>	84 (83.2)	68 (67.3)	<b>0.008</b>
RBC units transfused	3.0 (4.0)	2.0 (4.0)	<0.0001	<b>-1.926, -3.357-0.494</b>	2.0 (4.0)	2.0 (4.0)	0.07
Fresh frozen plasma	416 (100)	27 (22.7)	<0.0001	-	101 (100)	22 (21.8)	-
Platelet transfusion	188 (45.2)	14 (11.8)	<0.0001	<b>0.238, 0.097-0.566</b>	40 (39.6)	11 (10.9)	<b>&lt;0.0001</b>
rFVIIa	4 (1.0)	0	0.580	1.000	1 (1.0)	0	1.000
Cryoprecipitate	2 (0.5)	4 (3.4)	0.024	<b>29.983, 1.225-733.944</b>	1 (1.0)	3 (3.0)	0.317
Fibrinogen	63 (15.2)	51 (42.9)	<0.0001	1.820, 0.743-4.456	22 (22.0)	40 (39.6)	<b>0.004</b>
Resternotomy for bleeding	77 (18.5)	17 (14.3)	0.286	0.605, 0.286-1.278	20 (19.8)	12 (11.9)	0.103
Surgical site bleeding <sup>c</sup>	46 (11.1)	10 (8.4)	0.396	0.738, 0.263-2.070	9 (9.0)	7 (7.0)	0.593
UDPB bleeding grades 3-4	191 (46.9)	34 (28.6)	<0.0001	0.517, 0.265-1.007	46 (45.5)	26 (25.7)	<b>0.002</b>
E-CABG bleeding grades 2-3	165 (39.7)	30 (25.2)	0.004	0.604, 0.306-1.193	34 (33.7)	24 (23.8)	0.114

Continuous variables are reported as median and interquartile range (in parentheses). Categorical variables are reported as counts and percentages (in parentheses). FFP: fresh frozen plasma; PCC: prothrombin complex concentrate; <sup>a</sup>: excluding patients with preoperative IABP; <sup>b</sup>: excluding patients with preoperative chronic kidney disease class V; <sup>c</sup>: proportion of among patients who underwent resternotomy for bleeding excluding three patients without data on the source of bleeding; IABP: intra-aortic balloon pump; ECMO: extra-corporeal membrane oxygenation; DSWI: deep sternal wound infection; KDIGO: Kidney Disease: Improving Global Outcomes; RBC: red blood cell; rFVIIa: recombinant factor VIIa; UDPB: Universal Definition of Perioperative Bleeding; E-CABG: European Coronary Artery Bypass Grafting.

### Legend to figure

**Figure 1.** Kaplan-Meier estimates of survival in the propensity score matched fresh frozen plasma (FFP) and prothrombin complex concentrate (PCC) cohorts (p=0.405).