Prothrombin complex concentrate in cardiac surgery: A systematic review and meta-analysis

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Abstract

Background: Bleeding after cardiac surgery has significant deleterious effects on patient recovery. Prothrombin complex concentrate (PCC) has recently emerged as effective alternative to fresh frozen plasma (FFP) in treating perioperative excessive bleeding. We performed a systematic review to evaluate the safety and efficacy of PCC administration as first-line treatment in coagulopathy following adult cardiac surgery.

Methods: We searched PubMed/MEDLINE, EMBASE, and the Cochrane Library from inception to the end of March 2018 to identify the eligible articles. Adult patients undergoing cardiac surgery and receiving perioperative PCC were compared to those receiving fresh frozen plasma (FFP). Odds ratios (OR) with corresponding 95% confidence intervals (CI) were adopted for synthesizing the outcomes of interest.

Results: A total of 861 adult patients from a total of 4 studies were obtained. No randomized studies were identified. Pooled ORs showed that PCC cohort was associated with a significant reduction in the risk of RBC transfusion (OR 2.22; 95%CI 1.45-3.40; I^2 = 0%) and units of RBC received (OR 1.34; 95%CI 0.78-1.90; I^2 =27%). No differences between groups were observed for re-exploration for bleeding (OR 1.09; 95%CI 0.66-1.82; I^2 =35%), chest drain output at 24 hours (OR 66.36; 95%CI -82.40-216.11; I^2 =0%), hospital mortality (OR 0.94; 95%CI 0.59-1.49; I^2 =0%), stroke (OR 0.80; 95%CI 0.41-1.56; I^2 =0%), and AKI occurrence (OR 0.80; 95%CI 0.58-1.12; I^2 =0%) (Figure 2). A trend toward increased risk of RRT was observed in the PCC group (OR 0.41; 95%CI 0.16-1.02; I^2 =0%). No side effects related to direct PCC administration were reported.

Conclusions: In patients with coagulopathy following cardiac surgery, PCC administration seems to be more effective than FFP in reducing perioperative blood transfusion requirements. No additional risks of thromboembolic events or other adverse reactions were observed. However, randomized controlled trials are needed to definitively establish the safety and efficacy of PCC in cardiac surgical patients.

Keywords: cardiac surgery; surgical blood loss, prothrombin complex concentrate, coagulopathy.

Summary

Bleeding after cardiac surgery has significant adverse effects on patient recovery, affecting early and late patient prognosis.[1-5] Its impact on hospital resources is also substantial, since the excessive blood loss frequently necessitates transfusion of allogeneic blood, blood products, and surgical re-exploration.[1] Prothrombin complex concentrate (PCC) has recently emerged as effective alternative to fresh frozen plasma (FFP) in treating excessive bleeding following cardiac surgery.[6-10]

Overview of Prothrombin complex concentrates

PCCs typically contain 3 (II, IX, and X) or 4 (II, VII, IX, and X) vitamin K-dependent clotting factors derived from human plasma. Additionally, most PCCs are inactivated and contain a small amount of unfractionated heparin proteins C, S, and Z and/or antithrombin to prevent clotting factor activation and thrombogenesis.

Indications and mechanism of action

Inactive PCCs have gained popularity after FDA approval, currently being indicated in the emergency reversal of Warfarin or refractory bleeding. The mechanism of action consists of the supplementation of these coagulation factors (especially Factor II and Factor VII) in the context of reduced thrombin generation, pro-coagulant and anticoagulant factors.

A previously published consensus recommends the administration of PCC (20 to 30 IU/kg bodyweight) in the case of persistent bleeding and/or prolonged clotting time, but in clinical practice there is a dose variation between different publications and centres.

Study justification

Despite the benefits of PCCs in the rapid correction of coagulation disorder, a raised thrombogenic risk is often advocated as a limiting factor for the universal use of PCCs in cardiac surgery. The purpose of the present systematic review with meta-analysis is to summarise the existing literature that evaluates the safety and efficacy of PCC administration as first-line treatment in coagulopathy following adult cardiac surgery.

Methods

Protocol Registration, Search Strategy and Outcome Measures

The review protocol with its complete details was published online and registered in PROSPERO International Prospective Register of Systematic Reviews (CRD42017074677).[16] The review adhered to MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Supplementary Appendix I and II).[17,18] PubMed/MEDLINE, EMBASE, and the Cochrane Library were searched from inception to the end of March 2018 without date or language restriction. Search criteria, adopted keywords and MeSH terms used in relevant combinations are reported in the Supplement Material, and included: prothrombin complex concentrate, cardiac surgery, bleeding disorders, coagulopathy, coronary artery bypass grafting, valve surgery, aortic surgery, cardiac transplant, ventricular assist device, mortality, morbidity, and patient outcome. To supplement electronic search, the "first generation" reference lists of pertinent articles were also reviewed.

The exposure of interest was the administration of PCC as first-line treatment in coagulopathy following cardiac surgery. The primary outcome was the rate and number of units of perioperative/postoperative red blood cell blood (RBC) transfusions. Secondary outcomes included all-cause mortality in hospital or within 30 days from the index admission or procedure, re-exploration for bleeding, 24 h chest drain output, adverse events, the rate of thromboembolic events, renal replacement therapy (RRT), and acute kidney injury (AKI).

Study Selection and Participants

Randomized controlled trials and observational studies irrespective of blinding that consider the administration of PCC the first-line treatment in coagulopathy following cardiac surgery were included. All adult cardiac surgical procedures were considered for the purpose of this systematic review. Inclusion and exclusion criteria for qualitative/quantitative analyses were summarized according to the PICOS (population, intervention, comparator, outcomes, and study design) approach (Supplementary Table 1). Titles, abstracts, and full-text articles against the specified inclusion criteria

were independently reviewed by two investigators M.R. and G.M. Discrepancies were resolved through consensus and consultation with a third investigator (F.B.).

Data collection, Extraction and Quality Assessment

Two reviewers (M.R. and G.M.) extracted key data from the selected studies using standard dedicated pro-forma, while a third reviewer checked the collected data for completeness and accuracy (F.B.). Year of publication, study design, country, sample size, recruitment period, number of patients in each treatment group, inclusion/exclusion criteria, type of cardiac operations, measured outcomes, baseline patient demographics, cardiac status, comorbidities, and outcomes among relevant subgroups of patients were all extracted. The Newcastle-Ottawa Scale and the Cochrane Risk of Bias tool also was used to evaluate the methodological quality of all included studies.[19,20]

Statistical analysis

Statistical analysis was performed using Review Manager v. 5.3 and Open Meta-analyst statistical software packages.[21-23] Continuous variables reported as median and interquartile range were included in the analysis considering the median as mean and calculating the standard deviation as the interquartile range divided by 1.35. Baseline risk factors and outcomes are reported as pooled proportions or mean differences with 95% confidence intervals (CI). Outcomes were pooled with random-effects method, leading to computations of mean differences and odds ratios with 95% CI.[24] I^2 statistic was used to estimate the percentage of total variation across studies attributed to heterogeneity rather than chance. Suggested thresholds for heterogeneity were used, with I^2 values of 25% to 49%, 50% to 74%, and ≥75%, indicative of low, moderate, and high heterogeneity.[25] Publication bias was evaluated using visual inspection of funnel plot asymmetry and by Egger's test.[26] Statistical significance for hypothesis testing was set at the 0.05 level.

Results

Study design, selection and quality assessment

Of the 1402 records identified, only 4 studies were included in the systematic review, and they were published between 2012 and 2018 (Supplementary Figure 1).[7-10] The list of excluded studies and the reason for exclusion is reported in Supplementary Table 2. No randomized trials were identified comparing PCC with FFP in the treatment of excessive bleeding following cardiac surgery. Demographic and surgical characteristics between the studies and the patient groups were comparable (Tables 1 and 2). Full study characteristics and collected outcomes are summarized in Table 3. The final analysis included 861 patients; 423 subjects received PCC while 438 FFP. In two studies PCC administration was supplemented with other blood components, including FFP.[8,9] The dose of PCC varies among the studies with a reported range between 15 and 25 IU · Kg^{-1}. The management of perioperative coagulopathy was based on defined algorithms in two studies only, based on a combination of whole-blood point-of-care assays and standard laboratory assays (generally INR > 1.5, ROTEM>90 s or TEG® R-time > 10 min).[9,10] In the remaining two studies, the administration of PCC and other blood products was left to discretion of the individual surgeon and attending intensivist, and no clear algorithms were followed.[7,8]

Quality assessment indicated that all the included studies were at significant risk of bias (mean NOS score: 2.8; Supplementary Table 3), especially selection bias, attrition bias and reporting bias.

Outcome measures

Pooled ORs showed that PCC cohort was associated with a significant reduction in the risk of RBC transfusion as well as units of RBC received (OR 2.22, 95% CI 1.45-3.40, and OR 1.34, 95% CI 0.78-1.90, respectively) with no heterogeneity among studies (I^2 = 0% and I^2 = 27%, respectively) (Figure 1). No differences between groups were observed for re-exploration for bleeding and chest drain output at 24 h (Figure 1). Similarly, no differences were detected for other secondary outcomes, including hospital mortality (OR 0.94, 95%CI 0.59-1.49), stroke (OR 0.80, 95% CI 0.41-1.56) and AKI occurrence (OR 0.80, 95%CI 0.58-1.12) (Figure 2). Conversely, a trend toward increased risk of RRT was observed in the PCC group (OR 0.41, 95% CI 0.16-1.02) (Figure 2).

Restraining the analysis to propensity score matched studies,[8,9] the PCC cohort revealed a significant reduced risk of blood transfusion (OR 2.55, 95% CI 1.58-4.10), and a similar risk of postoperative stroke and hospital mortality (OR 0.80, 95% CI 0.41-1.56, and OR 0.94, 95% CI 0.57-1.54, respectively) compared to the FFP cohort. A trend toward lower risk of AKI (OR 0.81, 95%CI 0.58-1.12) was observed in the FFP cohort. No direct side effects related to PCC administration were reported in any of the included studies.

Discussion

A limited number of studies have evaluated the safety and efficacy of PCC as first-line treatment in coagulopathy following adult cardiac surgery, despite its proven efficacy as warfarin and vitamin K antagonist (VKA) reversal in both randomised and non-randomised clinical trials.[27-30] Administration of PCC is now recommended for severe bleeding from warfarin and VKA in different guidelines, while its use in the perioperative management of haemostasis in cardiac surgery has not been established yet.[13,31] Our systematic review is the first review to highlight the efficacy of PCC over FFP in reducing RBC transfusions in the context of excessive bleeding following cardiac surgery, without increasing the perioperative risk of thromboembolic events.

Benefits of PCC treatment

PCC has certainly several advantages in the cardiac surgery population, especially in patients with severe comorbidities. It can be reconstituted readily, and completely replenishes coagulation factors without any reductions in haematocrit, fibrinogen, or platelet count.[32] Avoiding administration of large of volumes of blood products prevents transfusion-associated circulatory overload (TACO), and the risks of transfusion-related acute lung injury (TRALI). These are both serious conditions in patients with an imbalanced cardiac and renal function.[32] Refaai et al.[33] in a post-hoc analysis of two randomized studies observed that fluid overload and cardiac events occurred three times more often in FFP patients compared to those receiving PCC. In an observational study including more than 5 million inpatient records, Magee et al.[34] demonstrated that the fluid overload associated with the number of units of FFP transfused led to an increased hospital mortality, non-home discharge, and intensive care unit admittance. PCC has been also proved to be more cost-effective than FFP, with a documented significant decrease in hospital cost for patients receiving PCC when compared to those receiving FFP.[7,35]

Patients receiving PCC had a significant lower amount of units of RBC transfused with a 10% overall decrease in the rate of RBC transfusion, and this has been clearly demonstrated to have an indirect impact on hospital resources and patient outcome even after transfusion of as little as 1 or 2 RBC units.[1,36] Different point of care tests (e.g. Thromboelastography) are becoming more widely available to further aid and guide the indications for blood transfusion in cardiac surgery patients. A point of

care transfusion algorithm using PCCs has been reported previously by Gorlinger et al and Weber et al.

Risks of PCC treatment

Nevertheless, the advantages exerted by PCC use are often overcome by the concerns related to the potential thromboembolic risk, especially when incremental doses of PCCs are administered.[37-40] Lusher et al.[38] firstly reported thrombotic events, including stroke and disseminated intravascular coagulopathy in patients with haemophilia B after repeated PCC doses. Other cases of intra-cardiac thrombosis including myocardial infarction have also been described.[39,40] However, the thrombogenic risk associated with PCC administration has not been substantiated in more recent evidence.[7-10] Possible explanations included the lack of anticoagulants Protein C and Protein S in the earlier PCC formulations,[41] or the imbalance with anticoagulants subsequent to the administration of procoagulants with the risk of unopposed thrombotic events.[42] An increased risk of thromboembolism was observed in hemodiluted and antithrombin-deficient patients in an in-vitro dilutional model,[43] while antithrombin deficiency and hemodilution are very common perioperative conditions encountered in cardiac surgery, especially during and after cardiopulmonary bypass.[45] In our systematic review and meta-analysis we did not observe any increased risk of stroke. However, it should be highlighted that the low-incidence of thromboembolic events requires large patient populations to be studied, and all the studies investigating safety end-points following PCC administration are limited by their small sample size.[7-10] In their randomized multicentre, open-label, non-inferiority trial comparing 4-factor PCC with FFP for VKA reversal in major bleeding, Sarode et al.[29] observed a similar rate of thromboembolic events between the two cohorts of patients (3.9% *vs* 2.8%). Consonant data were reported by Cappabianca et al.[8] in the cardiac surgical field. Perioperative administration of PCC was not associated with a higher stroke rate than FFP.[8] Similarly, our systematic review did not demonstrate an increased hospital mortality following the perioperative administration of PCC. Again, the reduced number of patients enrolled in the analysed studies is a relevant limitation for solid conclusive evidence regarding the safety of PCC in cardiac surgery.

Finally, the use of PCC has been associated with an increased incidence of postoperative AKI, including RRT.[8,44] A possible explanation is related to the relative hypovolemia often encountered in the PCC patients compared to those receiving FFP or to the fact that PCC was administered to sicker patients with multiple comorbidities.[8] In our systematic review, we observed a trend toward lower risk of AKI and RRT in the FFP cohort, although this did not reach the statistical significance. This is consistent with the existing reports, but this should be interpreted cautiously due to only 2 of studies reporting these outcomes in our meta-analysis.

Study limitations

Certainly, our systematic review is limited by the reduced number of included studies, and this paucity of data restricts the possible recommendations for the universal adoption of PCC in cardiac surgery. Even the optimal dose of PCC administration has not been established yet, with some evidence recommending a body weight based dosage regimen while some others a targeted INR correction.[8,13] This variability is also reflected in the studies included in our analysis. The management of perioperative coagulopathy was based on defined algorithms in two studies only.[9,10] Our analysis is also biased by the lack of randomized trials investigating the safety and efficacy of PCC in the first-line treatment of coagulopathy following adult cardiac surgery, therefore limiting our qualitative and quantitative analysis to retrospective observational studies only, often with a limited sample size.[7-10] Retrospective studies are subject to confounders and bias, possibly affecting the conclusive power of our meta-analysis. Severe methodological flaws, unclear inclusion/exclusion criteria, and different patient group comparisons prevent us from a large study analysis. Finally, observed unadjusted estimates close to the statistical significance should be considered carefully in light of possible bias related to the small number of the studies included in the systematic review.

Conclusion

In conclusion, the results of the present analysis seem to indicate that in patients with coagulopathy following cardiac surgery, the administration of PCC is more effective than FFP in reducing perioperative blood transfusion requirements. Our results also suggest that administration of PCC is not associated with additional risks of thromboembolic events or other adverse reactions. However, clinical validation studies and randomised control trials are needed to definitively establish the safety

and efficacy of PCC in cardiac surgical patients. Furthermore these should address the incorporation of PCCs in transfusion algorithms in bleeding patients following surgery.

Author's contributions

MR, FB, and GM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: MR, FB, AA and GM.

Acquisition of data: MR, FB, and GM.

Analysis and interpretation of data: MR, FB, AA, LH, AA, AO, MF, GJM and GM.

Writing paper: MR, FB, AA and GM.

Critical revision of the manuscript for important intellectual content: MR, FB, AA, LH, AA, AO, MF, GJM and GM.

Paper supervision: MR, FB, AA, LH, AA, AO, MF, GJM and GM.

Language revision: AA, AO and MF.

Declaration of interest

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Table 1. Patient characteristics

Variables	Arnékian et al, 2012[4]		Cappabianca et al, 2016[2]		Ortmann et al, 2015[3]		Fitzgerald et al, 2018[4]	
	PCC	FFP	PCC	PCC	FFP	FFP	PCC	FFP
N. Patients	51	26	225	117	45	55	117	117
Demographics								
Age, yrs	64 ± 13	72 ± 14	69 ± 12	70 ± 11	61 ± 13	62 ± 13	60 ± 14	61 ± 18
Gender, F/M (%)	25/75	31/69	40/60	40/60	19/81	18/82	34/66	38/62
Body mass index, kg/m^2	27.0 ± 3.6	26.0 ± 4.1	25.0 ± 4.7	25.4 ± 4.9	28.8 ± 6.1	27.3 ± 5.0	-	-
Cardiac Status								
Myocardial Infarction	-	-	41 (18.2)	43 (19.1)	-	-	-	-
Previous Cardiac Surgery	0	2 (8)	34 (15.1)	37 (16.4)	-	-	-	-
NYHA class III/IV, n (%)	-	-	44 (19.6)	42 (18.7)	-	-	-	-
Comorbidities								
Preoperative Haemoglobin, g/d)	14.2 ± 4.2	13.3 ± 1.4	12.1 ± 1.9	11.8 ± 2.0	13.6 ± 0.5	13.6 ± 0.6	14.6 ± 1.8	14.3 ± 2.0
Preoperative Platelets, 10^9/L	238 ± 79	211 ± 54	209 ± 74	216 ± 88	-	-	213.4 ± 67.0	234.5 ± 130.8
Preoperative eGFR, ml/min/1.73 m^2	-	-	64 ± 26	64 ± 23	-	-	-	-
Hypertension, n (%)	19 (79)	18 (69)	142 (3.1)	143 (3.6)	65 (55.6)	67 (57.3)	-	-
Diabetes, n (%)	6 (25)	6 (23)	36 (16.0)	37 (16.4)	15 (12.8)	20 (17.1)	-	-
Arrhythmia, n (%)	3 (12)	3 (11)	50 (22.2)	49 (21.8)	21 (18)	20 (18.8)	-	-
Previous thromboembolic events, n (%)	2 (8)	1 (4)	-	-	-	-	-	-
Anticoagulation use								
Warfarin, n (%)	3 (12)	1 (4)	21 (9.3)	24 (10.7)	-	-	-	-

Aspirin, n (%)	12 (50)	19 (73)	60 (26.7)	60 (26.7)	-	-	-	-
Clopidogrel, n (%)	5 (21)	6 (23)	22 (9.8)	22 (9.8)	-	-	-	-
Type of Surgery								
Isolated CABG, n (%)	9 (38)	9 (35)	36 (16.0)	39 (17.3)	n/a	n/a	n/a	n/a
Isolated Valve Surgery, n (%)	13 (54)	9 (42)	88 (39.1)	92 (40.9)	n/a	n/a	n/a	n/a
Valve Surgery + CABG, n (%)	2 (8)	6 (23)	53 (23.6)	47 (20.9)	n/a	n/a	n/a	n/a
Aortic Surgery, n (%)	n/a	n/a	48 (21.3)	47 (20.9)	n/a	n/a	n/a	n/a
Heart Transplantation, n (%)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pulmonary Endarterectomy, n (%)	n/a	n/a	n/a	n/a	45 (100)	55 (100)	n/a	n/a
Postoperative complications								
RBC rate, n (%)	0	5 (19.2)	189 (84)	210 (93)	34 (75.5)	44 (80)	90 (76.9)	104 (88.9)
Units of RBC, n	1 (2.2)	2 (1.5)	3.4 (3.1)	5.2 (4.3)	2 (2.2)	3 (3)	-	-
Chest drains output 24 hours, mL	1261 ± 780	1250 ± 441	836 ± 1226	935 ± 583	-	-	-	-
Reoperation for bleeding, n (%)	11 (41)	2 (8)	33 (14.7)	42 (18.7)	-	-	27 (23.1)	30 (25.6)
Stroke, n (%)	0	1 (2)	14 (6.2)	9 (4)	1 (2.2)	1 (1.8)	7 (6)	8 (6.8)
AKI, n (%)	-	-	68 (30.2)	60 (26.7)	-	-	46 (40.7)	39 (34.2)
RRT, n (%)	-	-	8 (3.6)	4 (1.8)	7 (15.6)	3 (5.5)	-	-
Hospital Mortality, n (%)	3 (5.8)	1 (3.8)	21 (9.3)	19 (8.4)	3 (6.7)	4 (7.3)	15 (12.8)	15 (12.8)

AKI, acute kidney injury; CABG, coronary artery bypass grafting; FFP, fresh frozen plasma; n/a, not applicable; NYHA, New York Heart Association; RBC, red blood cell; PCC, prothrombin complex concentrate; RRT, renal replacement therapy.

Table 2. Comparison of patient characteristics between PCC and FFP cohorts

Baseline characteristics	No. of studies	FFP	PCC	Random-effects estimates	p-value	I^2
Age, years	4	66.1 (60.7-71.37)	64.8 (59.7-69.9)	0.83 (-0.84-2.50)	0.33	0%
Female	4	38.2 (33.6-42.8)	38.3 (33.7-42.8)	0.99 (0.75-1.30)	0.93	0%
Hemoglobin (g/dL)	4	13.2 (12.1-14.4)	13.4 (12.4-14.5)	-0.2 (-0.4-0.1)	0.13	0%
Isolated CABG	3	15.3 (0.1-30.6)	15.0 (0.7-29.3)	1.11 (0.71-1.73)	0.64	0%
Emergency surgery	3	0.9 (0.0-3.4)	11.4 (0.0-23.6)	1.04 (0.70-1.55)	0.84	0%

CABG, coronary artery bypass grafting; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate. Values are proportions, mean differences and odds ratios with 95% confidence intervals (in parentheses).

Table 3. Pooled outcomes

Outcomes	No. of studies	FFP	PCC	Random-effects estimates	p-value	I^2
RBC transfusion	3	89.0 (82.8-95.2)	80.3 (74.7-85.9)	2.22 (1.45-3.40)	<0.0001	0%
RBC units transfused, n	3	3.4 (1.3-5.4)	2.1 (0.7-3.6)	1.3 (0.8-1.9)	<0.0001	27%
Chest drain output 24 h, mL	2	1083 (775-1391)	1042 (626-1459)	66 (-82-215)	0.38	0%
Re-exploration for bleeding	3	17.9 (9.5-26.3)	18.8 (12.7-24.8)	1.09 (0.66-1.82)	0.73	35%
Stroke	4	3.9 (2.0-5.7)	3.7 (0.9-6.6)	0.87 (0.46-1.63)	0.66	0%
Acute kidney injury	2	29.7 (22.5-37.0)	34.9 (24.7-45.1)	0.81 (0.58-1.12)	0.20	0%
Renal replacement therapy	2	2.4 (0.0-5.2)	8.4 (0.0-19.9)	0.41 (0.16-1.02)	0.06	0%
ICU stay, days	3	4.5 (3.5-5.6)	4.3 (2.8-5.7)	0.3 (-0.5-1.1)	0.47	0%
Hospital stay, days	3	14.5 (13.2-15.8)	13.3 (9.9-16.7)	1.1 (-2.4-4.6)	0.54	59%
Hospital mortality	4	8.5 (5.5-11.5)	9.1 (6.4-11.7)	0.94 (0.59-1.49)	0.78	0%

Values are proportions, mean differences and odds ratios with 95% confidence intervals (in parentheses).
FFP, fresh frozen plasma; ICU, intensive care unit; PCC, prothrombin complex concentrate.

Figure legends

Figure 1. Forest plot with unadjusted risk estimates for RBC transfusion rate, unit of RBC received, chest drain output at 24 hours, and re-exploration for bleeding. FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; RBC, red blood cell; CI: confidence intervals.

Figure 2. Forest plot with unadjusted risk estimates for secondary outcomes, including rate of stroke, acute kidney injury, renal replacement therapy, and hospital mortality. FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; CI: confidence intervals.