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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BACKGROUND: Administration of coagulation factor concentrates to treat bleeding after cardiac surgery with cardiopulmonary bypass might be a strategy for reducing allogeneic blood transfusions, particularly for patients treated with warfarin preoperatively. We performed an exploratory analysis on whether the use of prothrombin complex concentrate (PCC) is safe and effective compared with fresh frozen plasma (FFP) 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 PCC or FFP to treat coagulopathy were studied. Blood loss during the first 12 hours of admission to the intensive care unit and patient outcomes were compared with propensity score adjustment.

RESULTS: Three hundred fifty-one patients underwent pulmonary endarterectomy surgery, all of whom had warfarin discontinued for up to 5 days before surgery; bleeding complications requiring transfusion of blood products were observed in 108 (31%) patients. Of those, 55 received only FFP and 45 received only PCC, whereas 8 received both. Blood loss was significantly greater in the FFP group compared with the PCC group after 12 hours (median [interquartile range], 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 (percentage, 44 [80%] vs 34 [76%], P = 0.594) or in the number of units of red blood cells transfused (median [interquartile range], 2 [1–4] vs 3 [1–5] units, P = 0.181). The final propensity score included preoperative international normalized ratio, postoperative activated partial thromboplastin time, and postoperative platelet count. After inclusion of the propensity score in the regression analyses, there were no differences between patients receiving only PCC and patients receiving only FFP in the need for renal replacement therapy (odds ratio [OR] 2.39, 95% confidence interval [CI] 0.51–11.20, P = 0.27), 30-day-mortality (OR 0.32, 95% CI 0.03–3.36, P = 0.35), intracranial hemorrhage (OR 0.73, 95% CI 0.14–3.89, P = 0.71), hospital length of stay (hazard ratio 0.77, 95% CI 0.50–1.19, P = 0.24), or duration of intensive care stay (hazard ratio 0.91, 95% CI 0.59–1.40, P = 0.66).

CONCLUSIONS: This retrospective analysis suggests that PCC may be an alternative to FFP 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 PCC versus FFP for coagulopathic bleeding after cardiopulmonary bypass are warranted. (Anesth Analg 2015;121:26–33)

A fter cardiac surgery in which cardiopulmonary bypass (CPB) is used, bleeding is a major complication that exposes patients to the risk of allogeneic blood transfusion and reoperation, which increases morbidity.1,2 The etiology of CPB-associated coagulopathy is multifactorial and includes platelet dysfunction, coagulation factor dilution, endothelial dysfunction, and fibrinolysis.3 Although data are conflicting, the use of warfarin anticoagulant treatments before surgery may increase the risk of bleeding complications after CPB surgery.4,5 In recent years, coagulation factor concentrates have been used increasingly to reduce patient exposure to allogeneic blood components.6,7 Four-factor prothrombin complex concentrates (PCCs) contain a high concentration of lyophilized clotting factors II, VII, IX, X, and protein C and S. These compounds currently are 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.9 In some European countries, PCCs have replaced fresh frozen plasma (FFP) as the treatment for perioperative bleeding, even though there are few data on the efficacy and safety of its use in

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Reprints will not be available from the authors.

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was performed when the patient’s temperature reached
32°C during rewarming, using a heparinase-containing
cup. After rewarming and separation from CPB, protamine
4 mg·kg⁻¹ was administered, and further boluses were
given with the aim of an activated clotting time 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 (aPTT),
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 minutes, and excessive bleeding
was observed while the chest was open or if there was
>2 mL·kg⁻¹·h⁻¹ chest drainage after chest closure. In
the presence of these conditions, PCC (15 IU·kg⁻¹ to the nearest
250 IU vial) or FFP (15 mL·kg⁻¹) 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
Because this was an exploratory study, 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 1 SD dif-
fERENCE in blood loss between patients receiving PCC versus
FFP, with 2-sided type I error of 5% and power of 80%. The
study was not powered to detect smaller effect sizes.

Initially, patient and operative characteristics were sum-
marized, and unadjusted exploratory comparisons between
the 2 groups were performed. In this analysis, we used the
Student t test for normally distributed variables (age,
weight, body mass index, 6-minute walk distance, CPB
time, cross-clamp time, circulatory arrest time, INR, aPTT,
platelet count, hemoglobin, creatinine, and fibrinogen lev-
eels), the Mann-Whitney U test for skewed or other non-nor-
mally distributed variables (pulmonary vascular resistance,
blood loss, intensive care unit [ICU] stay, and hospital stay),
or χ²/Fisher exact test for categorical variables (sex, dis-
 ease type, numbers undergoing transfusions, 30-day mor-
 tality, incidence of other postoperative events, and use of
renal replacement therapy or extracorporeal membrane
oxygenation).

There is a high chance of bias in estimation of group dif-
f erences in observational studies attributable to the system-
atic allocation of patients to the groups. To minimize 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.18 Many of these variables
were correlated with each other and were grouped accord-
ing to the size of this correlation. The propensity score was
developed by the use of 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: preoperative INR, post-CBP aPTT,
and post-CBP platelet count. No specific methods for deal-
ing with missing covariates were attempted because of the
exploratory nature of the studies and the number of vari-
ables recorded. Rather, we excluded any covariates with
a large proportion of missing values. The clinical team,
including surgeon, anesthesiologist, and hematologist, was

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 col-
lected from a dedicated pulmonary hypertension database, and
an institutional transfusion database. Patients were classified on
the basis of whether they received only PCC or only FFP after
PEA surgery. Patients who received both or who received treat-
ment >48 hours after surgery were excluded from the analysis.

The anesthetic and surgical management for PEA has
been described.17 In brief, all patients received heparin 400
IU·kg⁻¹ before CPB with additional doses given to maintain
an activated clotting time greater than 400 seconds through-
surgery. Tranexamic acid 1 g was administered before
CPB and then as an infusion at 500 mg·h⁻¹ continued intra-
operatively. Upon adequate heparinization, CPB was initi-
ated and the patient’s body temperature was decreased to
18°C to 20°C. Deep hypothermic circulatory arrest was then
performed for periods of up to 20 minutes during which
PEA was performed. After the patients were rewarmed to
37°C, they were carefully weaned from CPB. All patients
received intraoperative cell salvage and hemofiltration dur-
ing CPB. Hemoglobin was maintained >6 g·dL⁻¹ during the
hypothermic CPB phase and >10 g·dL⁻¹ during rewarming
for separation from CPB and in the postoperative period.

Thrombelastography (TEG®; Haemonetics, Nile, IL) was performed when the patient’s temperature reached

this setting, particularly regarding the risk of prothrombotic complications.10,11 The clinical demand for PCC may further
increase, given the questionable efficacy of FFP in critically ill patients,12 its costs, and the potential of transmission of
prions and other well-described complications.

Pulmonary endarterectomy (PEA) is a complex surgery
used to treat chronic thromboembolic pulmonary hyperten-
sion, is performed with the patient under deep hypothermic
circulatory arrest, and requires prolonged CPB (>5 hours).13
The majority of patients undergoing PEA are receiving long-
term warfarin therapy, which usually is stopped 5 days before
surgery. Despite this, many patients do not have a normalized
prothrombin time at the time of surgery (i.e., international
normalized ratio [INR] > 1.5). Under these circumstances, cli-
nicians may transfuse FFP and/or PCCs for treating coagu-
lopathic bleeding after CPB.14,15 Transfusion of large volumes
of FFP is balanced by the competing demands of the treat-
ment of right heart failure, a common complication after long-
standing pulmonary hypertension, and the risk of reperfusion
injury to the lung after PEA surgery.16 PCCs 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 prothrombotic conditions and a high risk of
ischemic neurologic complications.13 There are few data on
the safety and efficacy of PCC use for treatment of coagulo-
pathic bleeding after CPB particularly for patients undergo-
ing PEA. Our aim was to provide an exploratory analysis of
the safety and efficacy of PCC compared with FFP in consecu-
tive patients with coagulopathic bleeding after PEA surgery.


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not included in the analysis as a covariate. The combination of different individuals from 3 departments would have produced a single multilevel covariate or 3 different covariates with a small number of levels for each, which was expected to produce less reliable estimates for the statistical model fitting than leaving them out. Furthermore, we have previously studied the impact of individual clinicians in >18,000 cardiac surgical patients and found that <3% of variation in outcome was attributable to nonpatient characteristics.19

Once the propensity score was developed, the effect of PCC on binary outcomes (survival at 30 days, reperfusion injury of the lungs, intracranial hemorrhage, renal impairment, renal replacement therapy) was assessed via logistic regression models including PCC and propensity score, where the logic of the estimated probability of having PCC was included in the regression. For ICU and hospital stay, a range of time-to-event models was 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 among the 4 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, College Station, TX).

RESULTS

During the 33-month study period, 351 patients underwent PEA surgery, and 108 (31%) suffered bleeding complications and received PCC or FFP as 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 patient bleeding and treatment allocation 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).20 This was reflected by a greater pulmonary vascular resistance both preoperatively and postoperatively in patients who received PCC. The duration of CPB and circulatory arrest were similar between the 2 groups. Baseline INR and aPTT were greater 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 PCC product was attributed to a change in the National Health Service procurement contract. The mean (SD) dose was 14.8 (5.4) IU·kg⁻¹.

Cumulative blood loss in the immediate postoperative period was greater in the FFP group compared with the PCC group 1 (P = 0.027), 6 (P = 0.002), and 12 (P = 0.008) hours after surgery (Fig. 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, interquartile range) of 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 was 4.6%, median (interquartile range) ICU stay was 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 2 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 patient adverse outcomes compared with patients receiving only FFP for treating coagulopathic bleeding after CPB (Table 7). Despite the adjustment for propensity to use PCC,

Figure 1. Flow diagram of the study population. PEA = pulmonary endarterectomy; FFP = fresh frozen plasma; PCC = prothrombin complex concentrate.
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 first 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 hemostatic 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.

FFP is administered to patients with coagulopathic bleeding after cardiac surgery despite a paucity of data on the safety and efficacy of this treatment. 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 nonbacterial infection, and multiple organ failure, which are independent of the effect of hemorrhage and transfusion. The time delay necessary to thaw the frozen blood product (up to 40 minutes) is another limitation of the use of FFP. The dose of FFP most commonly prescribed in the United Kingdom is 15 mL·kg⁻¹; therefore, a 70-kg patient would require more than a liter of plasma containing approximately 1 IU/mL of hemostatic factors.

**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**

<table>
<thead>
<tr>
<th></th>
<th>Entire cohort (n = 351)</th>
<th>FFP only (n = 55)</th>
<th>PCC only (n = 45)</th>
<th>P values for (PCC only versus FFP only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58 (14.5)</td>
<td>62 (13)</td>
<td>61 (13)</td>
<td>0.805</td>
</tr>
<tr>
<td>Women</td>
<td>170 (48%)</td>
<td>18 (33%)</td>
<td>19 (42%)</td>
<td>0.328</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.6 (19.2)</td>
<td>81.4 (18.9)</td>
<td>82.5 (17.8)</td>
<td>0.779</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>29.5 (6.3)</td>
<td>27.3 (5.0)</td>
<td>28.8 (6.1)</td>
<td>0.172</td>
</tr>
<tr>
<td>6-min walk test (m)</td>
<td>296.6 (121.9)</td>
<td>299.0 (142.3)</td>
<td>274.8 (96.0)</td>
<td>0.452</td>
</tr>
<tr>
<td>Disease type 3 or 4</td>
<td>67/314 (21%)</td>
<td>6/46 (13%)</td>
<td>13/40 (33%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Preoperative PVR (dyn·s·cm⁻⁵)</td>
<td>573 (381–818)</td>
<td>598 (420–940)</td>
<td>711 (474–862)</td>
<td>0.45</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>341.0 (66.0)</td>
<td>344.4 (51.2)</td>
<td>350.8 (60.7)</td>
<td>0.564</td>
</tr>
<tr>
<td>Duration of aortic cross clamping (min)</td>
<td>70.1 (36.7)</td>
<td>82.8 (69.3)</td>
<td>70.5 (25.5)</td>
<td>0.262</td>
</tr>
<tr>
<td>Duration of circulatory arrest (min)</td>
<td>34.8 (11.2)</td>
<td>38.2 (11.3)</td>
<td>36.3 (12.1)</td>
<td>0.431</td>
</tr>
</tbody>
</table>

Values are mean (SD), number (proportion), or median (IQR).

PEA = pulmonary endarterectomy; BMI = body mass index; PVR = pulmonary vascular resistance; CPB = cardiopulmonary bypass; IQR = interquartile range.

**Table 2. Descriptive Summaries for Hematologic 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**

<table>
<thead>
<tr>
<th></th>
<th>FFP group</th>
<th>PCC group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.7 (0.5)</td>
<td>1.9 (0.5)</td>
<td>0.044</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>34.4 (5.4)</td>
<td>36.6 (5.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Platelet count (10⁹/L)</td>
<td>234.5 (130.8)</td>
<td>213.4 (67.0)</td>
<td>0.529</td>
</tr>
<tr>
<td>Hemoglobin (g·dL⁻¹)</td>
<td>14.3 (2.0)</td>
<td>14.6 (1.8)</td>
<td>0.546</td>
</tr>
<tr>
<td>Creatinine (µmol·L⁻¹)</td>
<td>102.1 (26.0)</td>
<td>110.9 (33.5)</td>
<td>0.142</td>
</tr>
<tr>
<td><strong>After CPB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.4 (0.4)</td>
<td>2.6 (0.9)</td>
<td>0.144</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>77.7 (52.3)</td>
<td>108.9 (73.9)</td>
<td>0.0169</td>
</tr>
<tr>
<td>Platelet count (10⁹/L)</td>
<td>93.0 (42.7)</td>
<td>75.3 (35.5)</td>
<td>0.033</td>
</tr>
<tr>
<td>Hemoglobin (g·dL⁻¹)</td>
<td>9.4 (1.1)</td>
<td>9.6 (1.2)</td>
<td>0.916</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>0.916</td>
</tr>
</tbody>
</table>

Values are mean (SD).

INR = international normalized ratio; aPTT = activated partial thromboplastin time.
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This volume of fluid may lead to circulatory overload, a particular issue in patients after PEA surgery because 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. Administration of PCC, thus, requires approximately 40 mL of fluid co-administration at the dose of 15 IU·kg\(^{-1}\) used in this study (1000 IU in a 70-kg patient). PCC is approved for the prophylactic administration before urgent or emergency surgery in patients with reduced levels of vitamin K–dependent clotting factors, for example, due to warfarin treatment. The manufacturer recommended dose depends on the exact INR, and it is generally given for INR > 2. The patients in this study were receiving long-term warfarin treatment, but we did not correct an elevated INR preoperatively, 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 with 190 USD for 3 units of FFP in the United Kingdom). Additionally, there is some concern that PCC use may be associated with increased risk for thromboembolic events, which would be a particular issue in our patients with chronic thromboembolic disease. A porcine laboratory study found that 35 IU·kg\(^{-1}\) PCC safely improved coagulation and attenuated blood loss. However, at a dose of 50 IU·kg\(^{-1}\) (very much greater than the 15 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

<table>
<thead>
<tr>
<th>Table 3. Observed Cumulative Blood Loss at 1, 6, and 12 Hours After ICU Admission</th>
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</thead>
<tbody>
<tr>
<td>Patient group</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Entire cohort (n = 351)</td>
</tr>
<tr>
<td>FFP only (n = 55)</td>
</tr>
<tr>
<td>PCC only (n = 45)</td>
</tr>
<tr>
<td>P values for (PCC only versus FFP only)</td>
</tr>
</tbody>
</table>

The values are median (IQR).

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood product</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Red blood cells</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Fibrinogen concentrate</td>
</tr>
</tbody>
</table>

Values are number (proportion).

ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range.

<table>
<thead>
<tr>
<th>Table 5. Comparisons of Outcomes for Patients Treated with Either Fresh Frozen Plasma Only (FFP Only), Prothrombin Complex Concentrate Only (PCC Only), or Neither (No FFP or PCC) for Coagulopathy After Cardiopulmonary Bypass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>30-day mortality</td>
</tr>
<tr>
<td>ICU stay (days)*</td>
</tr>
<tr>
<td>Hospital stay (days)*</td>
</tr>
<tr>
<td>Cerebral infarct</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
<tr>
<td>Reperfusion injury of the lungs</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>ECMO</td>
</tr>
</tbody>
</table>

Values are number (proportion) or median (IQR).

ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range.

<table>
<thead>
<tr>
<th>Table 6. Variables Included in the Final Propensity Score for the Use of Prothrombin Complex Concentrate (PCC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictor</td>
</tr>
<tr>
<td>Preoperative INR</td>
</tr>
<tr>
<td>After CPB aPTT</td>
</tr>
<tr>
<td>After CPB PLT</td>
</tr>
<tr>
<td>Constant term</td>
</tr>
</tbody>
</table>

CI = confidence interval; INR = international normalized ratio; CPB = cardiopulmonary bypass; aPTT = activated partial thromboplastin time; PLT = platelet count.
of surgery revealed an overall incidence of thromboembolism of 1.4% (95% confidence interval, 0.8–2.1).25 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 of clinical use of a 4-factor PCC also showed a low risk of thromboembolic events (1:31,000).26

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. Görlinger et al.27 retrospectively reported reduced blood transfusion when PCC was used as part of a point-of-care-guided transfusion algorithm in >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. Weber et al.28 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.

We observed 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 have been 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 perioperative period; most report observational data from cohorts of patients or case series. Arnékian et al.29 also showed decreased blood loss only in the first hour in patients treated with PCC compared with FFP after cardiac surgery. In comparison, we administered a slightly larger dose compared with Arnékian et al.29 and found the lower chest tube drainage persisted for 12 hours. Demeyere et al.30 randomized 40 patients receiving oral anticoagulant therapy to receive FFP or PCC before CPB for urgent cardiac surgery but reported no significant effect on blood loss. Bruce and Nokes31 reported data from 24 patients who received PCC after severe hemorrhage during cardiac as well as other surgical procedures and reported a reduction in the administration of other blood products. A number of studies in noncardiac surgical patients have demonstrated the effectiveness of PCC for decreasing the INR.32–34 Other authors have raised concerns about thromboembolic complications attributed to PCC administration; however, none compared PCC with other treatment options.35–38 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 because 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 because 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 10-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 with the INR.39 Patients treated with PCC received either Beriplex (CSL Behring UK Ltd., Haywards Heath, UK) or Octaplex (Octapharma Ltd., Manchester, UK). 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 1 year. Octaplex also has been shown to be effective and safe, and the composition and quantity of clotting factors compared in both products is very similar.40

In conclusion, we have shown that PCC may be an alternative to FFP in patients who are coagulopathic and bleeding.

### Table 7. Outcomes for Patients Receiving Only Prothrombin Complex Concentrate (PCC) for Treating Coagulopathic Bleeding After Cardiopulmonary Bypass Adjusted for Propensity

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

*These results are from Cox proportional hazards models. CI = confidence interval; CVVH = continuous veno-venous hemofiltration; ICU = intensive care unit.

<https://www.anesthesia-analgesia.org>
after cardiac surgery, particularly when intravascular administration of fluid must be limited due to concern of right ventricular dysfunction and the risk of lung injury. We found that administration of PCC was associated with reduced blood loss 12 hours after surgery compared with FFP, but there were no differences in the frequency of blood transfusion or number of other hemostatic products administered. These exploratory analyses support the need for a prospectively randomized controlled study of the safety and efficacy of PCC for reducing bleeding after cardiac surgery using CPB.

DISCLOSURES

Name: Erik Ortmann, MD, DESA.
Contribution: This author helped design the study, conduct the study, collect the data, analyze the data, and prepare the manuscript.
Attestation: Erik Ortmann has reviewed the original study data and the data analysis and has approved the final manuscript.
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Attestation: Andrew A. Klein has approved the final manuscript and is responsible for archiving the study files.
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