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Prothrombin Complex Concentrate vs Frozen Plasma for Coagulopathic Bleeding in Cardiac Surgery
The FARES-II Multicenter Randomized Clinical Trial

Keyvan Karkouti, MD; Jeannie L. Callum, MD; Justyna Bartoszko, MD; Kenichi A. Tanaka, MD; Sigurd Knaub, PhD; Sukhpal Brar, MD; Kamrouz Ghadimi, MD; Antoine Rochon, MD; Darren Mullane, MB; Etienne J. Couture, MD; Yulia Lin, MD; Christopher Harle, MD; Michelle Zeller, MD; Diem T. T. Tran, MD; Cristina Solomon, MD; Vivek Rao, MD; Michael Law, MD; Amir L. Butt, MD; Edward P. Chen, MD; Maria Rosal Martins, MD; Tarit Saha, MD; Andrew W. Shih, MD; Marie-Claude Vézina, MD; Fuad Moussa, MD; Raffael Pereira Cezar Zamper, MD; Summer Syed, MD; Hakan Buyukdere, MD; Sylvia Werner, MS; Deep Grewal, MD; Daniel Wong, MD; Kofi B. Vandyck, MD; Robert Tanzola, MD; Bevan Hughes, MD; Olivier Royer, MD; Sophia Wong, MD; Jerrold H. Levy, MD; for the FARES-II Study Group

IMPORTANCE Excessive bleeding is a common and prognostically important complication of cardiac surgery. For bleeding related to coagulation factor deficiency, frozen plasma is the most used therapy. Preliminary trials indicate that 4-factor prothrombin complex concentrate (PCC) may be a suitable alternative.

OBJECTIVE To compare the efficacy and safety of PCC with frozen plasma in patients undergoing cardiac surgery with coagulopathic bleeding.

DESIGN, SETTING, AND PARTICIPANTS Unblinded randomized noninferiority controlled clinical trial at 12 hospitals in Canada and the US involving adults (≥18 years) who had developed bleeding related to coagulation factor deficiency after termination of cardiopulmonary bypass during surgery (November 30, 2022, to May 28, 2024). Final 30-day follow-up visit was completed on June 28, 2024.

INTERVENTION A total of 265 patients were randomized to receive PCC (1500 IU ≤60 kg; 2000 IU >60 kg) and 263, frozen plasma (3 U ≤60 kg; 4 U >60 kg) in the operating room. A second dose was allowed over the next 24 hours if indicated; thereafter, only frozen plasma could be used.

MAIN OUTCOMES AND MEASURES The primary outcome was hemostatic response (effective if no hemostatic interventions occurred from 60 minutes to 24 hours after treatment initiation). The noninferiority of PCC vs frozen plasma was assessed using a 10% margin and a 1-sided α of .025, with subsequent testing for superiority if noninferiority was demonstrated. Secondary outcomes included allogeneic blood transfusions and adverse events. Patients were followed up until postoperative day 30.

RESULTS Of 538 enrolled patients, 420 patients (median age, 66 years [IQR, 57-73 years]; 74%, male; 10%, Asian; 1%, Black; and 65%, White) were included in the primary analysis; of those, 296 (70%) underwent complex surgeries. Compared with the 207 patients in the frozen plasma group, the 213 patients in the PCC group had higher hemostatic effectiveness (166 [77.9%] vs 125 [60.4%]; difference, 17.6%; 95% CI, 8.7%-26.4%; $P < .001$ for noninferiority and superiority) and had received fewer transfusions including red blood cells, platelets, and noninvestigational frozen plasma units (mean, 6.6 units; 95% CI, 5.7-7.7 vs 9.3 units; 95% CI, 8.0-10.8; difference, 2.7; 95% CI, 1.0-4.4; $P = .002$). Seventy-seven patients (36.2%) in the PCC group vs 98 (47.3%) in the frozen plasma group experienced serious adverse events (relative risk [RR], 0.76; 95% CI, 0.61-0.96; $P = .02$). Twenty-two patients (10.3%) in the PCC group and 39 (18.8%) in the frozen plasma group had acute kidney injury (RR, 0.55; 95% CI, 0.34-0.89; $P = .02$).

CONCLUSIONS AND RELEVANCE In this unblinded randomized clinical trial, PCC had superior hemostatic efficacy and safety advantages to frozen plasma among patients requiring coagulation factor replacement for bleeding during cardiac surgery.

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Visual Abstract
Editorial
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The FARES-II Study Group appears in Supplement 4.

Corresponding Author: Keyvan Karkouti, MD, Department of Anesthesia and Pain Management, Toronto General Hospital, 200 Elizabeth St, 3EB-463, Toronto, ON M5G 2C4, Canada (keyvan.karkouti@uhn.ca).

In cardiac surgery, up to 15% of patients experience excessive bleeding,[1,2] which necessitates the transfusion of blood products and is associated with increased morbidity and mortality.[3-5] Although the causes of excessive bleeding in cardiac surgery are multifactorial, an important contributing cause is the depletion of enzymatic coagulation factors to a degree that impairs thrombin generation, which in turn impairs fibrin clot formation.[6] The mainstay of therapy for coagulopathic bleeding is the transfusion of frozen plasma,[7,8] which contains the full complement of procoagulant and anticoagulant factors. Currently, frozen plasma is administered to as many as 30% of patients who have undergone cardiac surgery.[2,9,10] This widespread use persists despite a lack of robust data on the hemostatic effectiveness of frozen plasma for the management of coagulopathic bleeding and the recognition that it can infrequently cause life-threatening complications such as serious allergic reactions, transfusion-related acute lung injury, and transfusion-associated circulatory overload.[7,8,11,12]

Recent preliminary data suggest that 4-factor prothrombin complex concentrate (PCC), which is derived from pooled plasma and contains the vitamin K-dependent coagulation factors II, VII, IX, and X, the anticoagulant proteins C and S (some products also contain antithrombin), and small amounts of heparin, may be a suitable alternative to frozen plasma in cardiac surgery.[13] The recognized advantages of PCC relative to frozen plasma are that it has undergone the process of purification, concentration, and pathogen reduction; contains a standard amount of coagulation factors; and does not require thawing or ABO matching. Because PCC does not contain the full complement of coagulation factors that are present in frozen plasma, it is uncertain whether it can effectively restore hemostasis in surgical patients with excessive bleeding that may be due to a broad depletion of coagulation factors, without increasing the risk of thromboembolic complications.

A recently completed randomized pilot trial involving 101 patients with bleeding who had undergone cardiac surgery found that PCC may restore hemostasis more effectively than frozen plasma without increasing risk.[14] This confirmatory, multicenter, randomized clinical trial aimed to delineate the relative efficacy and safety of PCC and frozen plasma in managing bleeding in patients undergoing cardiac surgery.

Key Points

Question Is prothrombin complex concentrate (PCC) efficacious and safe compared with frozen plasma for treatment of coagulopathic bleeding in cardiac surgery?

Findings In this unblinded randomized trial that included 420 adults who had undergone cardiac surgery requiring coagulation factor replacement due to excessive bleeding after cardiopulmonary bypass surgery, PCC had noninferior and superior hemostatic effectiveness compared with frozen plasma (77.9% vs 60.4%). Serious adverse events (36.2% vs 47.3%) and acute kidney injury (10.3% vs 18.8%) were less frequent in the PCC group.

Meaning PCC has superior hemostatic efficacy and may have safety advantages over frozen plasma in patients who require coagulation factor replacement for bleeding during cardiac surgery.

Methods

Trial Oversight

The Factor Replacement in Surgery (FARES) research program was initiated to delineate the relative efficacy and safety of PCC and frozen plasma for management of surgical bleeding. The design of this trial (FARES-II; also known as LEX-211) was based on the FARES pilot trial,[14] with funding provided by Octapharma AG and the Canadian Institutes of Health Research. FARES-II was a phase 3, multicenter, unblinded (treating clinicians were unblinded once treatment was initiated, but patients and outcome assessors were blinded to treatment assignment), randomized, clinical trial conducted at 12 sites in Canada and the US. The trial protocol, which has been published,[15] is provided in Supplement 1 and the statistical analysis plan in Supplement 2. The site principal investigators for the trial are listed in eTable 1 in Supplement 3. The members of the FARES-II (LEX-211) Study Group are listed in Supplement 4.

Trial oversight was provided by the sponsor, the coordinating investigators (K.K. and J.L.C.), and an independent data and safety monitoring committee (IDSMC). The trial was conducted jointly by the sponsor, the Department of Anesthesia and Pain Management Clinical Trials Unit at the University Health Network, Toronto, Ontario, Canada, and Ozmosis Research Inc, Toronto. Database management and data analysis were outsourced to Ergomed PLC (Guildford).

The trial was performed in accordance with the principles of the Declaration of Helsinki and applicable regulatory requirements. Approval from relevant institutional review boards and research ethics boards was obtained at each site before trial initiation. This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline

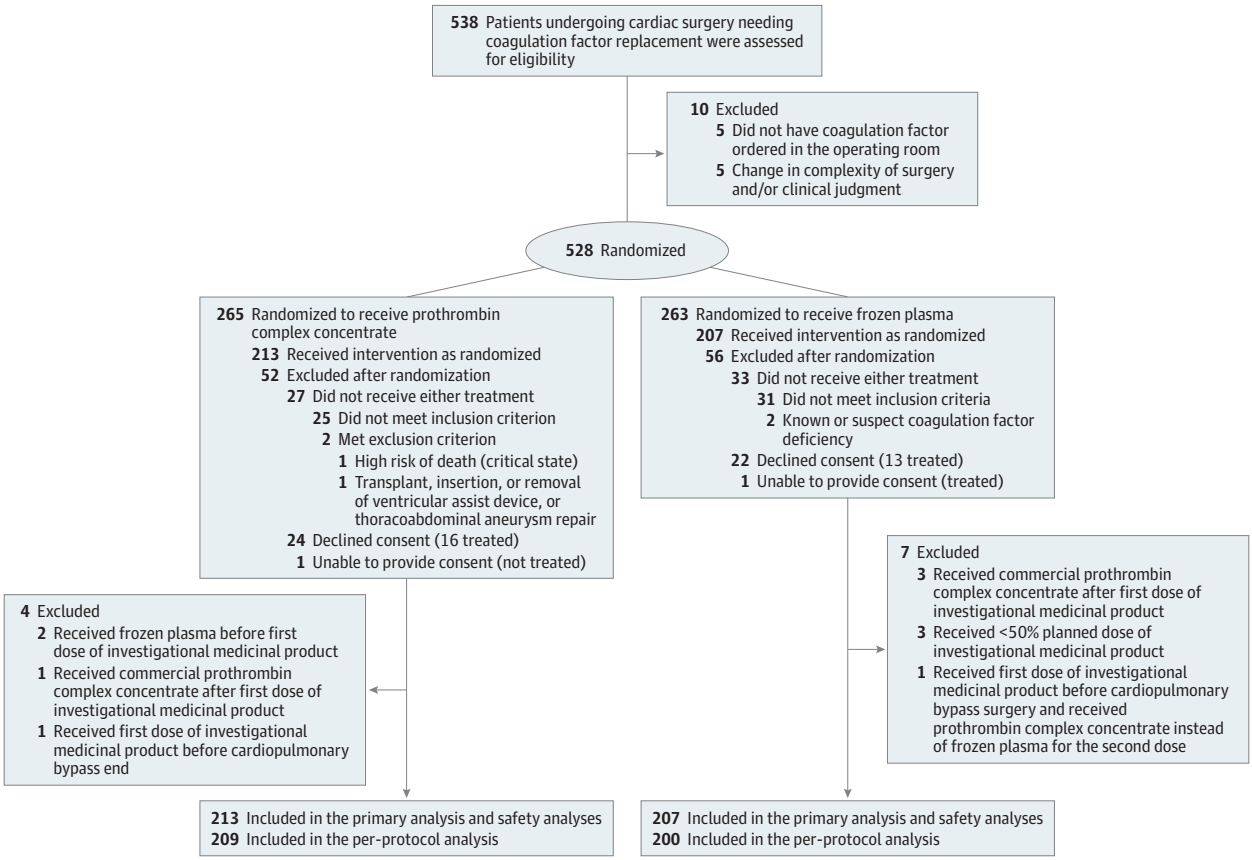
Patients

Adult (≥18 years) patients undergoing cardiac surgery with cardiopulmonary bypass were eligible for inclusion in the study if the treating clinicians ordered coagulation factor replacement with PCC or frozen plasma for active or anticipated bleeding after termination of the cardiopulmonary bypass. Exclusion criteria included heart transplant, insertion or removal of ventricular assist devices, repair of a thoracoabdominal aneurysm, or any concomitant noncardiac surgery (see eTable 2 in Supplement 3 for detailed eligibility criteria).

Trial Procedures

Eligible patients were randomized (1:1) to receive PCC (Balfaxar or Octaplex, Octapharma) or frozen plasma (standard ABO-compatible product) using a permuted-block randomization schedule that was stratified by site and maintained in the blood bank or pharmacy in sequentially numbered opaque sealed envelopes (**Figure 1**). Randomization occurred only when the order for PCC or frozen plasma was received by the blood bank

Figure 1. Enrollment, Randomization, and Treatment of Patients in the Factor Replacement in Surgery II Trial



or pharmacy, at which point the investigational medicinal product (IMP) was prepared and transported to the operating room in weighted tamper-proof boxes that were opened only when the clinical team made the final decision to administer it. This decision was based on the study criteria of at least moderate bleeding, pursuant to a validated bleeding severity scale[16] and international normalized ratio (INR) of 1.5 or more, measured at the bedside using the Hemochron Signature Elite (Werfen), after heparin neutralization following cardiopulmonary bypass. The need for INR confirmation was waived if bleeding was severe enough to merit immediate treatment. Sites were permitted to also use other point-of-care assays such as viscoelastic testing consistent with their standard practice, but they were required to confirm the patient's INR prior to initiating the intervention.

Written informed consent was obtained from patients before surgery at US sites, whereas in Canada written consent was obtained from patients or their surrogate decision-maker as soon as possible after surgery. Relevant institutional review boards deemed the delayed consent process (which was also used in the pilot study)[14] to be appropriate because both treatments were being used according to regulatory approved indications in Canada (unlike the US), because trial interventions were consistent with clinical practice standards and therefore did not expose patients to excess risks, and because identifying potentially eligible patients before surgery was impracticable (accurately predicting which patients would develop excessive bleeding due to coagulation factor deficiency during surgery is not possible, as was obtaining consent at the time of randomization during surgery). Study participants did not receive a stipend. Data on race were collected for descriptive purposes as reported by patients based on predefined categories.

The intervention group received intravenous PCC at a dose of 1500 IU for patients weighing 60 kg or less or 2000 IU for those weighing more than 60 kg. The control group received frozen plasma at a dose of 3 units for those weighing 60 kg or less and 4 units for those weighing more than 60 kg. A second dose of IMP was allowed if an order was received during the treatment period of 24 hours after initiation of the first dose. For any additional doses, both groups received frozen plasma (non-IMP) at the dose specified by their care team. The protocol allowed for the use of non-IMP PCC (ie, commercially available PCC) in the frozen plasma group if their care team deemed it necessary for management of ongoing bleeding after 2 doses of IMP frozen plasma were administered. The maximum permitted cumulative dose of PCC was about 50 IU/kg, which is in line with international dosing recommendations for vitamin K antagonist reversal because there is scant dosing data in cardiac surgery.[17] There were no other alterations to patient care. Participating hospitals had established bleeding management practices that were not otherwise modified.

Antifibrinolytic agents were routinely used prophylactically at all participating hospitals.

Outcome Measures

The primary outcome was hemostatic response, defined as effective if no additional hemostatic intervention was required from 60 minutes to 24 hours after initiation of the first IMP dose. Hemostatic interventions consisted of surgical reopening for bleeding, administration of a second dose of IMP, transfusion of any allogeneic blood products (excluding red blood cells), and administration of any coagulation factor concentrates. The 60-minute window was provided to allow for the full administration of the IMP. The 24-hour period was selected due to its clinical relevance because this is the critical period during which excessive bleeding occurs and needs to be controlled.

Secondary outcomes are listed in eTable 3 of Supplement 3. Secondary efficacy outcomes included global hemostatic response (composite of the primary outcome and 24-hour hemoglobin drop after accounting for any red blood cell transfusions),[15] incidence of severe to massive bleeding (meeting criteria for the universal definition of perioperative bleeding classes 3 or 4),[18] amount of allogeneic blood products and non-IMP coagulation factors administered, chest tube drainage to 24 hours after surgery, and change in INR and hemoglobin from within 30 minutes before to 60 minutes after IMP administration. Safety outcomes included the incidence of serious adverse events due to the treatment and death up to postoperative day 30.

Statistical Analysis

A sample size of 410 evaluable (randomized, treated, and consented) patients was estimated to have at least a 90% power to demonstrate noninferiority for the primary outcome of hemostatic effectiveness, assuming an effectiveness of 70% and 65% (conservative estimates based on the results of the pilot trial)[14] in the PCC and frozen plasma groups, respectively, noninferiority margin of 0.10, and a 1-sided α of .025. It was estimated that approximately 500 patients would need to be randomized because previous experience had shown that approximately 20% would drop out, due to either not receiving the IMP (primarily by not meeting the bleeding or INR administration criteria after randomization) or not being able to obtain informed consent after surgery (Canadian sites only). A preplanned administrative unblinded interim analysis was conducted after 200 patients were enrolled for sample size reestimation or futility assessment. The IDSMC did not recommend any changes to the trial after reviewing the results of the interim analysis.

All analyses followed the a priori defined statistical analysis plan (Supplement 2), unless otherwise specified as described below. The primary analysis set comprised all randomized patients who received at least 1 (partial or complete) dose of IMP and provided informed consent. The per-protocol analysis set excluded patients with major protocol deviations that may have impacted the primary outcome. The prespecified subgroups for analysis included male and female, elective and nonelective surgery, complex and simple surgery, cardiopulmonary bypass duration of 120 minutes or less, 121 minutes to 180 minutes, or more than 180 minutes, and age younger than 65 years or 65 years or older.

The noninferiority of the primary outcome was assessed with the Farrington-Manning score test (unweighted inverse normal statistic combining *P* values from the first and second stages). Because noninferiority of PCC was demonstrated within the 10% margin at a significance level of 2.5%, superiority of PCC was subsequently assessed in accordance with the statistical analysis plan. Analyses of exploratory secondary outcomes, including specific components of the primary outcome (which was not specified in the statistical analysis plan), were conducted as superiority analyses, with $P < .05$ considered significant without adjustment for multiplicity. Patients with missing values were excluded from the relevant analyses. SAS version 9.4 (SAS Institute Inc) was used for the analyses.

Results

A total of 538 patients who underwent cardiac surgery from November 30, 2022, to May 28, 2024, at the 12 participating sites were enrolled. Of these, 528 were randomized and 450 (85.2%) were treated with PCC or frozen plasma. Twenty-nine treated patients refused to provide consent and consent could not be obtained from another treated patient (all at sites in Canada where consent was obtained after surgery), leaving 420 patients in the primary analysis set (213 in the PCC group and 207 in the frozen plasma group). The median number of patients per site was 21.5 (IQR, 13.5-42.5; range, 5-158). The per-protocol analysis set excluded 11 patients who had major protocol deviations (Figure 1).

Baseline demographics and surgical characteristics were similar in the 2 groups (median age, 66 [IQR, 57-73] years; 309 male [74%]; and 296 [70%] had undergone complex operations; **Table 1**). Hemoglobin levels and platelet counts were similar between the groups throughout the study period, except for the hemoglobin level at 60 minutes after IMP administration, which was significantly higher in the PCC group than in the frozen plasma group (eTable 4 in Supplement 3).

All patients were randomized in the operating room. But for 37 patients (8.8%), the IMP infusion was not initiated until they had transferred to the intensive care unit (which was allowed by the study protocol). Time from cardiopulmonary bypass termination to initiation of IMP was similar between the groups, and approximately 20% of patients required a second dose of IMP (Table 1).

Efficacy outcomes are detailed in **Table 2** and **Figure 2**. In the primary analysis set, hemostatic effectiveness was achieved in 166 patients (77.9%) in the PCC group vs 125 (60.4%) in the frozen plasma group; thus, hemostatic response failure was 17.6% (95% CI, 8.7%-26.4%) lower in the PCC group than in the frozen plasma group (relative risk [RR], 0.56; 95% CI, 0.41-0.75; $P < .001$) for noninferiority and superiority. This was consistent in the per-protocol set and a priori defined subgroups (Figure 2). The individual components leading to an ineffective hemostatic response are also

Table 1. Characteristics of the Study Population and Dosing Details

Characteristic	No. (%) of patients	
	Prothrombin complex concentrate (n = 213)	Frozen plasma (n = 207)
Age, median (IQR), y	67 (58-73)	64 (55-72)
Sex		
Female	56 (26.3)	55 (26.6)
Male	157 (73.7)	152 (73.4)
Race		
American Indian or Alaska Native	3 (1.4)	0
Asian	20 (9.4)	21 (10.1)
Black or African American	2 (0.9)	3 (1.4)
White	138 (64.8)	137 (66.2)
Other[a]	50 (23.5)	46 (22.2)
Weight, kg		
Mean (SD)	85 (19.3)	84 (19.5)
≤60	19 (8.9)	20 (9.7)
>60	194 (91.1)	187 (90.3)
BMI, mean (SD)	29 (6.0)	28 (5.4)
Past history and comorbidities[b]		
NYHA class[c]	n = 207	n = 197
I (Least severe)	64 (30.9)	56 (28.4)
II	82 (39.6)	76 (38.6)
III	43 (20.8)	55 (27.9)
IV (Most severe)	18 (8.7)	10 (5.1)
Myocardial infarction	n = 195	n = 194
None	146 (74.9)	146 (75.3)
0-90 d	33 (16.9)	28 (14.4)
>90 d	16 (8.2)	20 (10.3)
Ejection fraction [left ventricle function], %	n = 210	n = 206
>50	157 (74.8)	165 (80.1)
31-≤50	48 (22.9)	34 (16.5)
21-30	5 (2.4)	7 (3.4)
Pulmonary artery systolic pressure [pulmonary hypertension]	n = 187	n = 177
<30 mm Hg (none)	158 (84.5)	145 (81.9)
31-55 mm Hg (moderate)	20 (10.7)	23 (13.0)
>55 mm Hg (severe)	9 (4.8)	9 (5.1)
Hypertension	144 (67.6)	141 (68.1)
Dyslipidemia	135 (63.4)	133 (64.3)
Congestive heart failure	36 (16.9)	37 (17.9)
Atrial fibrillation	42 (19.7)	52 (25.1)
Diabetes	48 (22.5)	45 (21.7)
Chronic lung disease	25 (11.7)	36 (17.4)
CVA or TIA	14 (6.6)	15 (7.3)
Peripheral vascular disease	8 (3.8)	11 (5.3)
Active endocarditis	8 (3.8)	15 (7.3)
Dialysis preoperative	0	5 (2.4)
Preoperative laboratory values, median (IQR)		
Creatinine, mg/dL	0.96 (0.81-1.14) [n = 206]	0.95 (0.81-1.19) [n = 198]
Hemoglobin, g/dL	13.7 (12.1-14.7)	13.6 (11.9-14.6)
Platelet count, $\times 10^3/\mu L$	201 (171-242)	199 (163-244)
International normalized ratio, median	1.1 (1.0-1.2)	1.1 (1.0-1.1)

(continued)

Table 1. Characteristics of the Study Population and Dosing Details (continued)

Characteristic	No. (%) of patients	
	Prothrombin complex concentrate (n = 213)	Frozen plasma (n = 207)
Surgical factors		
Previous cardiac surgery	53 (24.9)	56 (27.1)
Nonelective surgery	36 (16.9)	44 (21.3)
Complex surgery[d]	144 (67.6)	152 (73.4)
Procedure[e]		
Aortic valve	110 (51.6)	98 (47.3)
Coronary artery bypass graft surgery	91 (42.7)	86 (41.5)
Ascending aortic	65 (30.5)	61 (29.5)
Mitral valve	48 (22.5)	47 (22.7)
Aortic arch	26 (12.2)	24 (11.6)
Tricuspid valve	18 (8.5)	15 (7.3)
Pulmonary valve	6 (2.8)	7 (3.4)
Descending aortic	4 (1.9)	0
Other[f]	69 (32.4)	89 (11.1)
Cardiopulmonary bypass duration, mean (SD), min	171 (76.4)	176 (80.5)
Tranexamic acid (prophylactic)		
Patients	178 (83.6)	176 (85.0)
Dose, mean (SD), g	3.4 (1.6)	3.6 (4.0)
Aminocaproic acid (prophylactic)		
Patients	30 (14.1)	31 (15.0)
Dose, mean (SD), g	12.1 (5.0)	13.1 (5.5)
Heparin dose, mean (SD), IU	50 343 (20 288)	51 114 (21 474)
Protamine dose, mean (SD), mg	381 (116) [n = 209]	390 (152) [n = 205]
Cell salvage blood collected, mean (SD), mL	1908 (1859) [n = 115]	2111 (2283) [= 106]
IMP administration details		
Doses		
1	213 (100)	207 (100)
2[g]	37 (17.4)	47 (22.7)
Amount of first dose		
Mean (SD)	23.9 (4.3) IU/kg	11.8 (2.8) mL/kg[g]
Median (IQR)	23.7 (21.1-27.0) IU/kg	11.8 (10.0-13.8) mL/kg[g]
Amount of second dose		
Mean (SD)	22.9 (6.3) IU/kg	10.3 (3.8) mL/kg[h]
Median (IQR)	23.1 (20.1-28.2) IU/kg	10.5 (7.3-13.3) mL/kg[g]
Time from end of CPB to start of first dose of IMP, median (IQR), min	41 (26-67)	45 (28-69)
Time to complete administration of IMP, median (IQR), min	7 (4-10)	26 (17-45)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CPB, cardiopulmonary bypass; CVA, cerebrovascular accident; IMP, investigational medicinal product; NYHA, New York Heart Association; PCC, prothrombin complex concentrate; TIA, transient ischemic attack.

SI conversion factor: To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

[a] Other races marked as multiple, unknown, or refused.

[b] Medical history and investigations (for ejection fraction and pulmonary pressure determination) were obtained before surgery from patients' medical records.

[c] Class I indicates no limitation of physical activity and no symptoms; II, slight limitation of physical activity; III, marked limitation of physical activity; and IV, unable to carry on any physical activity without discomfort, symptoms of heart failure at rest.

[d] Procedures other than coronary artery bypass graft surgeries only, single valve only, or repair of atrial septal defect only.

[e] Some patients underwent more than 1 procedure.

[f] Examples of other procedures include Maze, myectomy, atrial septal defect repair, left ventricular aneurysm resection, intra-aortic balloon pump insertion, and other minor cardiac procedures.

[g] One patient in the frozen plasma group received PCC as the second dose of IMP, ie, different treatment than randomized.

[h] Frozen plasma volume conversion factor for 1U is 250 mL.

Table 2. Efficacy Outcomes in the Primary Analysis Set

Outcomes	No. (%) of patients		% Difference (95% CI)	Relative risk or LS mean ratio (95% CI)	*P* value
	PCC (n = 213)	Frozen plasma (n = 207)			
Primary outcome					
Hemostatic response					
Effective	166 (77.9)	125 (60.4)	17.6 (8.7 to 26.4)	RR: 0.56 (0.41 to 0.75)	<.001
Ineffective[a]	47 (22.1)	82 (39.6)			
Components for response					
Surgical reopening for bleeding	11 (5.2)	15 (7.3)	2.1 (−2.5 to 6.7)	RR: 0.71 (0.34 to 1.5)	.38
Second dose of IMP	19 (8.9)	40 (19.3)	10.4 (3.8 to 17.0)	0.46 (0.28 to 0.77)	.003
Platelets	32 (15.0)	63 (30.4)	15.4 (7.5 to 23.3)	0.49 (0.34 to 0.72)	<.001
Fibrinogen concentrate	14 (6.6)	23 (11.1)	4.5 (−0.9 to 10.0)	0.59 (0.31 to 1.12)	.11
Cryoprecipitate	6 (2.8)	7 (3.3)	0.6 (−2.8 to 3.9)	0.83 (0.28 to 2.44)	.74
Non-IMP PCC	0	14 (6.8)	6.8 (3.3 to 10.2)	0.03 (0.002 to 0.56)	.02
Non-IMP frozen plasma	7 (3.3)	7 (3.4)	0.1 (−3.3 to 3.5)	0.97 (0.35 to 2.72)	.96
Activated recombinant factor VII	0	9 (4.4)	4.4 (1.6 to 7.1)	0.05 (0.003 to 0.87)	.04
Secondary outcomes					
Ineffective global hemostatic response[b]	56 (26.3)	83/205 (40.5)	14.2 (5.3 to 23.2)	RR: 0.65 (0.49 to 0.86)	.003
Severe or massive bleeding[c]	30 (14.1)	57 (27.5)	13.5 (5.8 to 21.1)	RR: 0.51 (0.34 to 0.76)	.001
Total allogeneic blood product transfusions, LS mean (95% CI), units[d]					
≤24 h After cardiopulmonary bypass end					
RBC + platelets + frozen plasma [IMP and non-IMP]	6.6 (5.9 to 7.5)	13.8 (12.3 to 15.5)	7.2 (5.4 to 9.0)	Ratio: 0.48 (0.41 to 0.57)	<.001
RBC + platelets + frozen plasma [non-IMP]	6.6 (5.7 to 7.7)	9.3 (8.0 to 10.8)	2.7 (1.0 to 4.4)	Ratio: 0.71 (0.57 to 0.88)	.002
≤7 d From surgery start					
RBC + platelets + frozen plasma [IMP and non-IMP]	8.6 (7.6 to 9.7)	16.7 (14.8 to 18.8)	8.1 (5.9 to 10.3)	Ratio: 0.51 (0.44 to 0.61)	<.001
RBC + platelets + frozen plasma [non-IMP]	8.6 (7.4 to 9.9)	12.2 (10.6 to 14.1)	3.6 (1.5 to 5.8)	Ratio: 0.70 (0.57 to 0.86)	<.001
RBC transfusion					
≤24 h After IMP initiation	97 (45.5)	132 (63.8)	18.2 (8.9 to 27.6)	RR: 0.71 (0.60 to 0.85)	<.001
LS mean (95% CI), units	1.1 (0.9 to 1.3)	2.0 (1.7 to 2.4)	1.0 (0.5 to 1.4)	Ratio: 0.52 (0.40 to 0.68)	<.001
≤24 h After cardiopulmonary bypass end	109 (51.2)	135 (65.2)	14.0 (4.7 to 23.4)	RR: 0.78 (0.67 to 0.93)	.004
LS mean (95% CI), units	1.2 (1.0 to 1.5)	2.2 (1.8 to 2.6)	1.0 (0.5 to 1.4)	Ratio: 0.55 (0.43 to 0.72)	<.001
≤7 d After surgery start	154 (72.3)	159 (76.8)	4.5 (−3.8 to 12.8)	RR: 0.94 (0.84 to 1.05)	.29
LS mean (95% CI), units	2.5 (2.1 to 2.9)	3.7 (3.2 to 4.3)	1.2 (0.5 to 1.9)	Ratio: 0.67 (0.54 to 0.84)	<.001
Platelet transfusions[d]					
≤24 h After IMP initiation	97 (45.5)	108 (52.2)	6.6 (−2.9 to 16.2)	RR: 0.87 (0.72 to 1.06)	.17
LS mean (95% CI), units	2.9 (2.2 to 3.7)	4.5 (3.5 to 5.8)	1.6 (0.2 to 2.9)	Ratio: 0.65 (0.45 to 0.92)	.02
≤24 h After cardiopulmonary bypass end	150 (70.4)	152 (73.4)	3.0 (−5.6 to 11.6)	RR: 0.96 (0.85 to 1.08)	.49
LS mean (95% CI), units	5.2 (4.4 to 6.1)	6.9 (5.9 to 8.1)	1.7 (0.3 to 3.1)	Ratio: 0.75 (0.60 to 0.95)	.01
≤7 d After surgery start	151 (70.9)	152 (73.4)	2.5 (−6.0 to 11.1)	RR: 0.97 (0.86 to 1.09)	.56
LS mean (95% CI), units	5.9 (4.9 to 7.0)	8.2 (6.9 to 9.7)	2.3 (0.5 to 4.0)	Ratio: 0.72 (0.56 to 0.92)	.009
Other hemostatic products ≤7 d after surgery start					
Frozen plasma transfusion (non-IMP)	10 (4.7)	12 (5.8)	1.1 (−3.2 to 5.4)	RR: 0.81 (0.36 to 1.83)	.61
PCC administration (non-IMP)	1 (0.5)	17 (8.2)	7.7 (3.9 to 11.6)	RR: 0.06 (0.01 to 0.43)	.005
Fibrinogen concentrate administration	91 (42.7)	97 (46.9)	4.1 (−5.4 to 13.6)	RR: 0.91 (0.74 to 1.13)	.39
Cryoprecipitate transfusion	13 (6.1)	17 (8.2)	2.1 (−2.8 to 7.0)	RR: 0.74 (0.37 to 1.49)	.40
Recombinant-activated factor VII administration; first 7 d after surgery start	2 (0.9)	10 (4.8)	3.9 (0.7 to 7.1)	RR: 0.19 (0.04 to 0.88)	.03
Chest tube drainage, LS mean (95% CI), mL					
12 h	471 (415 to 527)	642 (585 to 699)	171 (91 to 250)	NA	<.001
24 h	691 (616 to 766)	923 (847 to 999)	232 (126 to 338)	NA	<.001

(continued)

Table 2. Efficacy Outcomes in the Primary Analysis Set (continued)

Outcomes	No. (%) of patients		% Difference (95% CI)	Relative risk or LS mean ratio (95% CI)	*P* value
	PCC (n = 213)	Frozen plasma (n = 207)			
Change in INR, LS mean (95% CI)[e]	−0.84 (−0.77 to −0.92) [n = 200]	−0.70 (−0.62 to −0.77) [n = 193]	0.15 (0.04 to 0.26)	NA	.008
Time from start of first dose of IMP to ICU arrival, median (IQR), h[f]	1.0 (0.6 to 1.7) [n = 199]	1.2 (0.7 to 2.0) [n = 178]	0.19 (−0.02 to 0.40)	NA	.07

Abbreviations: ICU, intensive care unit; IMP, investigational medicinal product; INR, international normalized ratio; LS, least squares; NA, not applicable; PCC, prothrombin complex concentrate; RBC, red blood cells; RR, relative risk.

[a] Patient received any hemostatic therapies or interventions from 60 minutes to 24 hours after initiation of the first dose of IMP.

[b] Patient received any hemostatic therapies or interventions or hemoglobin level dropped by 30% or more (after accounting for RBC transfusions by making an adjustment of −1.0 g/dL for each unit) from 60 minutes to 24 hours after initiation of the first dose of IMP. Two patients missing hemoglobin values in frozen plasma group were not included.

[c] Meeting criteria for universal definition of perioperative bleeding classes 3 or 4 (not including IMP frozen plasma) during the first 24 hours after termination of cardiopulmonary bypass. Positive if during the measured 24-hour time interval: received 5 or more RBC units or 5 or more non-IMP frozen plasma units; underwent surgical reexploration due to bleeding; or received recombinant-activated factor VII or if chest tube drainage was more than 1 L at 12 hours after chest closure.[18]

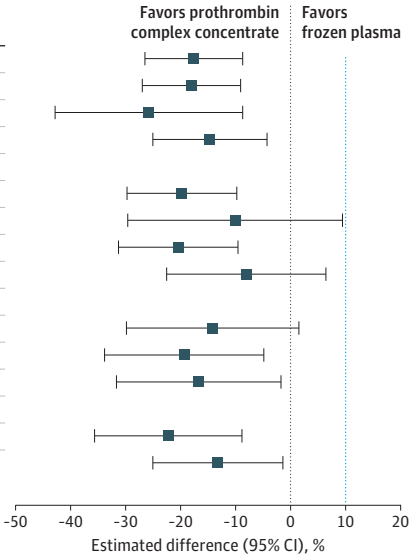
[d] Administered as a single dose of apheresis platelets or a 4-unit dose of pooled buffy-coat prepared platelets; each dose counted as 4 units.

[e] Measured at the bedside within 30 minutes before IMP initiation and at 60 (±15) minutes after IMP completion.

[f] Excludes patients with incomplete data or who were randomized in the operating room but received interventional product after leaving the operating room.

Figure 2. Difference in Hemostatic Response Failure Rates

Group or subgroup	No. hemostatic response failure/total (%) of patients		Estimated difference (95% CI), %
	Prothrombin complex concentrate group	Frozen plasma group	
Primary analysis set	47/213 (22.1)	82/207 (39.6)	-17.55 (-26.40 to -8.70)
Per-protocol analysis set	45/209 (21.5)	79/200 (39.5)	-17.97 (-26.91 to -9.03)
Female	9/56 (16.1)	23/55 (41.8)	-25.75 (-42.76 to -8.73)
Male	38/157 (24.2)	59/152 (38.8)	-14.61 (-24.98 to -4.25)
Surgery			
Elective	40/177 (22.6)	69/163 (42.3)	-19.73 (-29.67 to -9.80)
Nonelective	7/36 (19.4)	13/44 (29.5)	-10.10 (-29.58 to 9.37)
Complex	35/144 (24.3)	68/152 (44.7)	-20.43 (-31.31 to -9.55)
Simple	12/69 (17.4)	14/55 (25.5)	-8.06 (-22.47 to 6.35)
Cardiopulmonary bypass duration, min			
≤120	9/60 (15.0)	14/48 (29.2)	-14.17 (-29.80 to 1.47)
121-180	12/72 (16.7)	27/75 (36.0)	-19.33 (-33.81 to -4.85)
>180	26/81 (32.1)	41/84 (48.8)	-16.71 (-31.66 to -1.76)
Age, y			
<65	19/90 (21.1)	45/104 (43.3)	-22.16 (-35.53 to -8.79)
≥65	28/123 (22.8)	37/103 (35.9)	-13.16 (-24.97 to -1.35)



Ineffective hemostatic response rates in the primary analysis set, the per-protocol analysis set, and a priori defined subgroups. Difference in the proportion of patients who had ineffective hemostatic response (ie, received any hemostatic therapies or interventions from 60 minutes to 24 hours after the initiation of the first dose of investigational medicinal product [IMP]) in the prothrombin complex concentrate (PCC) group minus the frozen plasma group. The blue dotted line indicates the noninferiority margin. Tests for noninferiority were 1-sided Farrington-Manning score tests with a noninferiority margin of 10% and a significance level of 2.5%. If the 95% CI for the treatment effect (PCC minus frozen plasma) lay not only below 10% (the noninferiority margin) but also below 0, then there was evidence of superiority. Complex surgery was defined as procedures other than coronary artery bypass graft only, single valve only, or repair of atrial septal defect only.

shown in Table 2. All instances of surgical reopening for bleeding were confined to this period (11 patients [5.2%] in the PCC group and 15 [7.3%] in the frozen plasma group).

Ninety-seven patients (45.5%) in the PCC group vs 132 (63.8%) in the frozen plasma group received red blood cell transfusions in the 24 hours after IMP administration (RR, 0.71; 95% CI, 0.60-0.85). Similarly, the rate of severe or massive bleeding and the cumulative number of allogeneic blood product transfusions were statistically significantly lower in the PCC group (Table 2).

Almost all patients experienced at least 1 adverse event (96.7% in the PCC group and 97.1% in the frozen plasma group), which was anticipated in patients who had developed excessive bleeding after cardiac surgery (**Table 3**). Seventy-seven patients (36.2%) in the PCC group vs 98 (47.3%) in the frozen plasm group experienced serious adverse events (RR, 0.76;

Table 3. Adverse Events and Other Outcomes Measured Through 30 Days of Follow-Up

Outcomes	Group, No. (%) [No. of events][a]	
	Prothrombin complex concentrate (n = 213)	Frozen plasma (n = 207)
Death	7 (3.3)	8 (3.9)
Thromboembolic adverse events	18 (8.5) [26]	15 (7.2) [18]
Vascular thrombosis[b]	15 (7.0) [16]	11 (5.3) [11]
Stroke[c]	5 (2.3) [5]	5 (2.4) [5]
Other[d]	5 (2.3) [5]	2 (1.0) [2]
Acute kidney injury[e]	22 (10.3)	39 (18.8)
Any serious adverse event[f]	77 (36.2) [138]	98 (47.3) [201]
Any adverse event[g]	206 (96.7) [936]	201 (97.1%) [976]
Duration of mechanical ventilation, median (IQR), d	1.0 (1.0-2.0)	1.0 (1.0-2.0)
Duration of initial intensive care unit stay, median (IQR), d	4.0 (2.0-6.0)	4.0 (2.0-7.0)[h]
Duration of initial hospitalization, median (IQR), d[i]	8.0 (7.0-12.0)	9.0 (7.0-13.0)[j]

[a] Data are for treatment-emergent adverse events, for which first onset or worsening was after the first treatment with study drug. No. is the number of patients with an event (patients who experienced >1 event are counted only once); the percent is the number of patients with an event as a percentage of all patients in that treatment group; and No. of events is the number of all relevant events (including multiple events in a single patient).

[b] Includes aortic thrombosis, catheter site thrombosis, deep vein thrombosis, disseminated intravascular coagulation, extremity necrosis, intestinal ischemia, jugular vein thrombosis, myocardial infarction, peripheral artery thrombosis, peripheral ischemia, prosthetic cardiac valve thrombosis, splenic infarction, subclavian vein thrombosis, superficial vein thrombosis, vascular graft thrombosis, and vessel puncture site thrombosis.

[c] Data are for any treatment-emergent stroke, including cerebrovascular accident, embolic stroke, and ischemic stroke.

[d] Includes cardiac arrest, cardiorespiratory arrest, intrapericardial thrombosis, pulmonary necrosis, scrotum erosion, and death (1 patient with cause of death unknown was classified by the sponsor as having experienced a thromboembolic adverse event).

[e] Data are for any treatment-emergent acute kidney injury (defined by the Kidney Disease: Improving Global Outcomes criteria[19]), including acute kidney injury and renal failure.

[f] Includes data on 2 patients in whom informed consent could not be obtained but the research ethics board approval was obtained to collect serious adverse events.

[g] There were no treatment-emergent adverse events of transfusion-related acute lung injury in the study and a single treatment-emergent adverse event of transfusion-associated circulatory overload, which occurred in the frozen plasma group (≤48 hours after surgery start).

[h] Three patients were excluded from this analysis (n = 204): 2 had missing dates of initial intensive care unit stay and 1, no intensive care unit stay.

[i] Censored at 30 days.

[j] One patient in the frozen plasma group was excluded from this analysis (N = 206) due to missing dates of initial hospitalization.

95% CI, 0.61-0.96; P = .02). Twenty-two patients (10.3%) in the PCC group and 39 (18.8%) in the frozen plasma group had acute kidney injury, as defined by the Kidney Disease: Improving Global Outcomes criteria[19] (RR, 0.55; 95% CI, 0.34-0.89; P = .02). The proportion of patients who died or had thromboembolic events was similar, as were the durations of intubation, intensive care unit stay, and hospital stay (Table 3).

Discussion

In this unblinded randomized clinical trial, PCC was found to have significantly better efficacy than frozen plasma for management of excessive bleeding related to coagulation factor deficiency in patients undergoing cardiopulmonary bypass surgery. Compared with frozen plasma, PCC had significantly better hemostatic effectiveness and significantly reduced the rate of severe to massive bleeding events and the rate of exposure to allogeneic blood product transfusions. The increased hemostatic efficacy was not accompanied by an increase in thromboembolic events, which were comparable between the study groups. Rather, PCC use was found to significantly reduce the risk of serious adverse events and acute kidney injury.

The efficacy findings herein are consistent with those of several observational studies and the study's predecessor pilot trial that found PCC to be associated with reduced blood loss and red cell transfusions compared with frozen plasma in cardiac surgery.[13,14] To our knowledge, only 2 other randomized trials (not counting the pilot trial) have compared PCC with frozen plasma in cardiac surgery.[20,21] Those 2 trials did not find significant differences in efficacy measures; however, their sample sizes were limited to 100 or fewer patients. Thus, they were not adequately powered to detect clinically meaningful differences between treatment groups. Furthermore, both studies limited the dose of PCC to 15 IU/kg, which was likely too low to optimize thrombin generation.[22] The current study elected to use approximately 25 IU/kg as the initial dose of PCC based on experimental data showing that it is more effective than lower doses in correcting impaired thrombin generation after cardiopulmonary bypass surgery,[22] the positive results of the pilot study,[14] and in alignment with clinical guidelines that recommend a starting dose of 25 IU/kg of PCC for bleeding management in various settings.[17,23]

The finding herein that PCC had superior hemostatic efficacy to frozen plasma is biologically plausible because PCC is designed to be more prohemostatic than frozen plasma.

Although PCC does not contain the full array of coagulation factors that are present in frozen plasma, its procoagulant factor levels are 25 times more concentrated than in frozen plasma (the product also contains a low concentration of anticoagulants sufficient to prevent hemostatic activation during processing and storage).[24] As such, PCC is well suited for rapid replenishment of procoagulant factors to boost thrombin generation, which is often impaired after cardiopulmonary bypass surgery and can be an important cause of excessive bleeding.[6]

The key safety consideration with enhanced hemostatic activity is the potential for thromboembolic events; thus, the safety assessment was an important objective of this study. As in existing evidence in cardiac surgery and other settings, such as urgent reversal of vitamin K antagonists,[25] this trial found that PCC (at a starting dose of ≈ 25 IU/kg up to a maximum of ≈50 IU/kg) did not increase the risk of thromboembolic events. Moreover, the incidences of serious adverse events and acute kidney injury were statistically significantly lower in the PCC group. Although these were exploratory analyses, it seems plausible that the intervention could improve these outcomes by reducing major bleeding and transfusions, which are important modifiable risk factors for serious adverse outcomes, including acute kidney injury.[4,5,26-28]

The study's findings are clinically relevant for 2 reasons. The first is that the use of PCC in place of frozen plasma in cardiac surgery will markedly reduce overall frozen plasma usage. In this study, the PCC group received approximately 95% fewer frozen plasma units than the frozen plasma group (49 units vs 1001 units). In the US alone, this would translate to an annual saving of approximately 350 000 units of frozen plasma that can be redirected to help address supply challenges in plasma-derived medicinal products.[29]

Another reason is that the superior hemostatic efficacy of PCC will benefit patients and the health care system by reducing major bleeding, red blood cell and platelet transfusions, and use of other hemostatic therapies such as recombinant activated factor VII, all of which have been linked to increased adverse outcomes and overuse of health care resources.[4,5,26-28,30-32]

Limitations

This study has several important limitations. First, because the study compared the treatments under usual conditions of care, a standardized transfusion protocol was not implemented across participating hospitals. All participating hospitals, however, had established transfusion algorithms that adhered to current guidelines. Furthermore, processes of care measures related to transfusion practice (such as timing of therapy; perioperative hemoglobin and platelet levels; and dosing of heparin, protamine, and antifibrinolytic drugs) were similar between the groups, indicating that bleeding management, other than the trial intervention, was similar in the 2 groups. Second, due to the nature of the therapies, treating clinicians could not be blinded to group assignment. However, blinding was maintained until the decision was made to initiate treatment, outcome assessors were blinded, and the observed treatment effect on blood product transfusions was consistent irrespective of the period analyzed (ie, from beginning of surgery, end of cardiopulmonary bypass surgery, or IMP administration). Third, 108 patients (20.4%) who were randomized were excluded from the analyses because they either did not receive study interventions (n = 60) or did not provide their consent to participate (n = 48). Among the latter, 18 patients did not receive study interventions, leaving only 30 of 450 treated patients (6.7%) who were not included in the primary analysis set (Figure 1). Moreover, the drop-out rate was similar in the 2 study groups, and the sample size estimate assumed a 20% dropout rate. Fourth, to our knowledge, there is no single reliable and objective measure of hemostatic effectiveness in cardiac surgery; thus, we used a primary outcome that was a composite of hemostatic therapies that have been linked, individually and in combination, to important clinical outcomes.[30-32] Fifth, generalizability of findings to excluded groups (eg, those with recent thromboembolic events) and other surgical populations cannot be assumed.

Conclusions

PCC had superior hemostatic efficacy and may have safety advantages to frozen plasma in patients who require coagulation factor replacement for bleeding during cardiac surgery. Given the magnitude of the treatment effect, preferentially using PCC over frozen plasma for bleeding management in cardiac surgery could have benefits for patients (by reducing bleeding and exposure to allogeneic blood products) and for the health care system (by relieving pressures on the blood supply and hospital resources). Because this would entail a major change in current practice, the clinical and financial impacts of this change need to be assessed in future studies. In addition, the generalizability of these findings to other surgical settings needs to be further evaluated.

ARTICLE INFORMATION

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Author Affiliations: Department of Anesthesia and Pain Management, University Health Network, Sinai Health, Women's College Hospital, University of Toronto, Toronto, Ontario, Canada (Karkouti, Bartoszko, Grewal); Peter Munk Cardiac Centre and Toronto General Hospital Research Institute, University Health Network, Toronto, Ontario, Canada (Karkouti, Bartoszko, Rao, Grewal); Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada (Karkouti, Bartoszko, S. Wong); Department of Pathology and Molecular Medicine, Kingston Health Sciences Centre and Queen's University, Kingston, Ontario, Canada (Callum); Sunnybrook Research Institute, Toronto, Ontario, Canada (Callum); Department of Anesthesiology, University of Oklahoma Health Sciences Center, Oklahoma City (Tanaka, Butt, Vandyck); Octapharma AG, Lachen, Switzerland (Knaub, Solomon); Department of Anesthesiology and Perioperative Medicine, Royal Columbian Hospital, Vancouver, British Columbia, Canada (Brar, Law); University of British Columbia, Vancouver, Canada (Brar, Law); Clinical Research Unit, Department of Anesthesiology & Critical Care, Duke University Health System, Durham, North Carolina (Ghadimi); Department of Anesthesia, University of Montreal, Montreal Heart Institute, Montreal, Quebec, Canada (Rochon, Martins); Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Canada (Mullane, Hughes); Vancouver General

Hospital, Vancouver, British Columbia, Canada (Mullane, Shih, Hughes); Department of Anesthesiology, Quebec Heart and Lung Institute, Laval University, Quebec, Quebec, Canada (Couture, Vézina, Royer); Precision Diagnostics and Therapeutics Program, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (Lin); Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada (Lin); London Health Sciences Centre, London, Ontario, Canada (Harle, Pereira Cezar Zamper); Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada (Harle); Micheal G. DeGroote Centre for Transfusion Research, Department of Medicine, McMaster University, Hamilton, Ontario, Canada (Zeller); Canadian Blood Services, Ottawa, Ontario, Canada (Zeller); Division of Cardiac Anesthesiology and Critical Care, University of Ottawa Heart Institute, Ottawa, Ontario, Canada (Tran); Department of Surgery, University of Toronto, Toronto, Ontario, Canada (Rao, Moussa); Cardiothoracic Surgery Division, Department of Surgery, Duke University Health System, Durham, North Carolina (Chen); Department of Anesthesiology and Perioperative Medicine, Kingston Health Sciences Centre and Queen's University, Kingston, Ontario, Canada (Saha, Tanzola); Current affiliation: Department of Pathology and Molecular Medicine, McMaster University, Hamilton General Hospital, Hamilton, Ontario, Canada (Shih); Division of Cardiac Surgery, Sunnybrook Health Sciences Centre, Schulich Heart Centre, Toronto, Ontario, Canada (Moussa); Department of Anesthesia, McMaster University, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada (Syed); Department of Anesthesia, Oakville Trafalgar Memorial Hospital, Oakville, Ontario, Canada (Syed); Division of Hematopathology and Transfusion Medicine, University of Ottawa, Ottawa, Ontario, Canada (Buyukdere); Octapharma USA, Paramus, New Jersey (Werner); Division of Cardiac Surgery, Royal Columbian Hospital, New Westminster, British Columbia, Canada (D. Wong); Department of Surgery, University of British Columbia, Vancouver, Canada (D. Wong); Department of Anesthesia, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (S. Wong); Department of Anesthesiology, Critical Care, and Surgery, Duke University School of Medicine, Durham, North Carolina (Levy).

Author Contributions: Drs Karkouti and Knaub had full access to all of the data in the study. They along with the study sponsor take responsibility for the integrity of the data and the accuracy of the data analysis. Site principal investigators (eTable 1 in Supplement 3) assume responsibility for the fidelity of the trial and its adherence to the protocol.
Drs Karkouti and Callum contributed equally to the study.
Concept and design: Karkouti, Callum, Tanaka, Knaub, Ghadimi, Rochon, Mullane, Solomon, Rao, Buyukdere, Grewal, Vandyck, Levy.
Acquisition, analysis, or interpretation of data: Karkouti, Callum, Bartoszko, Tanaka, Knaub, Brar, Ghadimi, Rochon, Couture, Lin, Harle, Zeller, Tran, Solomon, Rao, Law, Butt, Chen, Martins, Saha, Shih, Vezina, Moussa, Pereira Cezar Zamper, Syed, Buyukdere, Werner, Grewal, D. Wong, Vandyck, Tanzola, Hughes, Royer, S. Wong, Levy.
Drafting of the manuscript: Karkouti, Callum, Tanaka, Tran, Buyukdere.
Critical review of the manuscript for important intellectual content: Karkouti, Callum, Bartoszko, Tanaka, Knaub, Brar, Ghadimi, Rochon, Mullane, Couture, Lin, Harle, Zeller, Tran, Solomon, Rao, Law, Butt, Chen, Martins, Saha, Shih, Vezina, Moussa, Pereira Cezar Zamper, Syed, Werner, Grewal, D. Wong, Vandyck, Tanzola, Hughes, Royer, S. Wong, Levy.
Statistical analysis: Karkouti, Callum, Knaub, Werner.
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Administrative, technical, or material support: Karkouti, Callum, Bartoszko, Tanaka, Brar, Rochon, Mullane, Couture, Lin, Harle, Zeller, Tran, Solomon, Rao, Law, Butt, Chen, Saha, Shih, Moussa, Syed, Buyukdere, Werner, Grewal, D. Wong, Vandyck.
Supervision: Karkouti, Callum, Bartoszko, Knaub, Brar, Ghadimi, Rochon, Mullane, Couture, Lin, Zeller, Tran, Solomon, Rao, Law, Pereira Cezar Zamper, Buyukdere, Grewal, Tanzola, Hughes, Royer.
Other - Accountability, final approval, supervision: Ghadimi.
Other - ongoing review of study, progression, and overview: Levy.

Conflict of Interest Disclosures: Dr Karkouti reported receiving personal fees from Octapharma-Werfen outside the submitted work. Dr Callum reported serving on the advisory board of Octapharma and receiving grants from the Canadian Blood Services outside the submitted work. Dr Bartoszko reported receiving grants from Canadian Blood Services, Grifols, and the Heart and Stroke Foundation outside the submitted work. Dr Tanaka reported receiving grants from Grifols, Hikari Dx, and VarmX outside the submitted work. Dr Knaub reported being an employee of Octapharma AG during the conduct of the study. Dr Ghadimi reported receiving personal fees from UptoDate/Wolter Kluwer outside the submitted work. Dr Couture reported receiving personal fees from Edwards Lifesciences outside the submitted work. Dr Lin reported receiving grants from the Canadian Blood Services, consulting fees from Choosing Wisely Canada, and honoraria from Pfizer outside the submitted work. Dr Harle reported receiving grants from Octapharma outside the submitted work. Dr Zeller reported receiving grants from Pfizer Global Medical; serving on the advisory board and scientific committee of Pfizer; and receiving travel expenses from Pfizer, honoraria from the American Society of Hematology, speaker fees from McMaster University, Queens University, and Oregon Health and Science University, and grants from CIHR and Canadian Blood Services all outside the submitted work. Dr Rao reported serving as a consultant to Medtronic and Abbott outside the submitted work. Dr Butt reported receiving grants from Cellphire Therapeutics and HemoSonics Inc outside the submitted work. Dr Shih reported receiving personal fees from CSL Behring and Octapharma Canada; grants from CSL Behring, Octapharma Canada, and Takeda Canada outside the submitted work. Dr Werner reported being an employee of Octapharma. Dr Grewal reported receiving support from Octapharma AG outside the submitted work. Dr Levy reported serving on research steering committee for Bayer, Octapharma, Takeda, and Werfen and as an advisor to Grifols outside the submitted work. No other disclosures were reported.

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