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Original Article

Perioperative Factor Concentrate Use is Associated With More Beneficial Outcomes and Reduced Complication Rates Compared With a Pure Blood Product–Based Strategy in Patients Undergoing Elective Cardiac Surgery: A Propensity Score–Matched Cohort Study

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ABSTRACT

Objective: The goal of this study was to compare factor concentrate (FC)–based and blood product–based hemostasis management of coagulopathy in cardiac surgical patients in terms of postoperative bleeding, required blood products, and outcome.
Design: Retrospective, propensity score–matched analysis.
Setting: Single, tertiary, academic medical center.
Participants: One hundred eighteen matched pairs of 433 consecutive patients scheduled for cardiac surgery in two isolated periods with distinct strategies of hemostasis management.
Interventions: Patients received either blood product–based (period I) or FC-based (period II) hemostasis management to treat perioperative coagulopathy.
Measurements and Main Results: Patients treated with FC management experienced less postoperative blood loss (907 *v* 1,153 mL, $p = 0.014$) and required less red blood cell and fresh frozen plasma transfusion (2.3 *v* 3.7 units $p < 0.0001$, and 2.0 *v* 3.4 units $p < 0.0001$, respectively) compared with subjects in the blood product–based management group. The frequency of Stage 3 acute kidney injury and 30-day mortality rate were significantly higher in the blood product–based group than in the FC management group (6.8% *v* 0.8%, $p = 0.016$, and 7.2% *v* 0.8%, $p = 0.022$, respectively). FC management-related thromboembolic events were not registered. The FC strategy was associated with a 2.19-fold decrease in the odds of massive postoperative bleeding ($p < 0.0001$), a 2.56-fold decrease in the odds of polytransfusion ($p < 0.0001$), and a 13.16-fold decrease in the odds of early postoperative death ($p = 0.003$).

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Conclusions: FC-based versus blood product–based management is associated with reduced blood product needs and fewer complications, and was not linked to a higher frequency of thromboembolic events or a decrease in long-term survival in cardiac surgical patients developing perioperative coagulopathy and bleeding.

Key Words: cardiac surgery; factor concentrates; blood products

CLINICALLY SIGNIFICANT coagulopathy is a frequent complication of cardiac surgery, leading to increased risk of postoperative massive blood loss, reexploration, anemia, and polytransfusion.[1,2] An extensive amount of data support that these complications of coagulopathy contribute to higher rates of early and long-term mortality and elevate the incidence of acute kidney injury (AKI), respiratory failure, infection, and atrial fibrillation, as well as an increase in related healthcare costs.[3-5] The perioperative blood loss, hemodilution, platelet activation, hypothermia, and large surgical surface result in a rapid development of hypofibrinogenemia and fibrinogen dysfunction, one of the key mechanisms of the complex coagulopathy associated with cardiac surgery.[6] Additionally, cardiopulmonary bypass (CPB) surgery also might impair thrombin generation, another key process associated with increased bleeding risk.[7,8]

Fresh frozen plasma (FFP) contains all the clotting factors, and is an essential agent used for the hemostatic resuscitation of bleeding patients.[9,10] Whereas the limitations of FFP are well-described, data for its effectiveness in the treatment of massive bleeding also are controversial.[10] Fibrinogen concentrate (Factor I) and prothrombin complex concentrate (PCC; factors II, VII, IX, and X; proteins C, S, antithrombin, and heparin) are ABO-independent, purified products. Their major advantages of FFP are the predictable pharmacologic effect, lack of immunologic and circulatory interactions, and suitability for goal-directed component therapy.[11] Furthermore, in a recent ex vivo study, PCC appeared to be a more potent agent than FFP for restoring thrombin generation, although the former carries a higher risk for adverse thromboembolic events.[11-13] Fibrinogen concentrate and PCC have shown an expanding clinical use in the management of coagulopathy, including cardiac surgery.[11,14,15] Although several randomized control trials (RCT) have been performed regarding fibrinogen concentrate use in this field over the past decade, to date there are no published RCTs evaluating PCC in cardiac surgical patients.[11,14-16] Despite the reinforcing results regarding their blood- product-sparing effects, current evidence remains insufficient to provide absolute support of the routine perioperative administration of coagulation factor concentrates over allogeneic blood products.[4,14-18] Hence, data proving the benefits of factor concentrate (FC)–based hemostasis management on short-term or long-term mortality also are scarce; an important field ,therefore, remains to be established.[14-18] As a dominant module of the patient blood management concept in cardiac surgery, in 2012 the authors' institution changed its blood product–based hemostasis management to a coagulation FC-based strategy in the treatment of perioperative coagulopathy.

The aim of this retrospective study was to evaluate the clinical impact of FC-based versus blood product–based hemostasis management in terms of perioperative blood loss, ability to replace blood product transfusions, and clinical outcomes of elective cardiac surgical patients, using propensity-score matching of cohorts from two different time frames.

Methods

Patients

This study retrospectively analyzed the clinical data of 1,000 consecutive adult, elective cardiac surgical cases performed in 2011 (n = 500) and 2013 (n = 500) at a tertiary, academic medical center. Patients who underwent cardiac surgery in 2012 were not included in the analysis, as this year there was a transition in perioperative hemostasis management from a blood product–based strategy to a coagulation FC-based one. Over the screened periods (2011 and 2013), there were no relevant changes in surgical or anesthetic techniques in perioperative treatment apart from hemostasis management. Due to their chronologically close time frames, significant differences in the patient characteristics were not expected between the twwo observed periods. Demographic, perioperative clinical, and outcome data were collected from cardiac surgical, intensive care unit, and hospital healthcare digital databases and individual treatment charts (including anesthetic, transfusion, and observational charts, and perioperative FC use audit forms) provided by the institutional medical archives and the Department of Pharmacology and Pharmacotherapy. The study was approved by the Regional and Institutional Committee of Science and Research Ethics, and the written informed consent requirement was waived because of the retrospective observational design of this study (No: 192/2019). Exclusion criterion was long-term left ventricular assist device implantation.

Perioperative Management

All elective patients received standardized anesthetic and surgical perioperative care according to the institutional protocol. Oral anticoagulants or directly-acting oral anticoagulants were converted to a subcutaneous low-molecular-weight heparin agent seven days before the scheduled surgery, and antiplatelet drugs were stopped five days before surgery. CPB was provided by a roller pump and membrane oxygenator, with the CPB prime solution consisting of 1,200 mL of Ringer's lactate, 100 mL of mannitol, and 60 mL of sodium bicarbonate 8.4%.

The clinical management of CPB was based on institutional standards, including unfractionated heparin anticoagulation, hemodynamic, temperature, and metabolic targets (α-stat acid-base management). The shed pericardial blood was suctioned into the CPB reservoir until the beginning of heparin reversal. The intraoperative application of cell salvage was based on the clinical judgment of the medical team. The antifibrinolytic treatment was protocolized for on-pump surgeries administering tranexamic acid at 50 mg/kg of total intraoperative dose, while during off-pump procedures its indication depended on the discretion of the clinician. Institutional red blood cell transfusion trigger criteria were defined as hemoglobin <7.0 g/dL during CPB, and <8.5 g/dL for the post-CPB and postoperative period.

The diagnoses of coagulopathy were based on conventional static hemostasis parameters such as fibrinogen concentration, prothrombin time, international normalized ratio (INR), activated partial thromboplastin time (APTT), and platelet count, as well as dynamic hemostasis parameters of thromboelastography (TEG − period I) or rotational thromboelastometry (period II) like R time, K time, α-angle (α), maximal amplitude, maximal lysis or clotting time (CT), clot formation time, amplitude of firmness 20 minutes, maximum clot firmness (MCF), and maximum lysis, respectively. The post-CPB and postoperative management of hemostasis therapy consisted of FFP and/or platelet transfusion in period I, and fibrinogen concentrate (Haemocomplettan, CSL Behring, Marburg, Germany) and/or PCC (Beriplex, CSL Behring, Marburg, Germany) as first-line agents, and FFP and/or platelet transfusion as additional agents were administered in period II. The primary targets of hemostasis parameters were INR <1.5, APTT <40 seconds, fibrinogen concentration >2.0 g/L, platelet count ≥100 G/L, TEG-kaolin R <eight minutes, TEG-kaolin K <four minutes, TEG-kaolin α >40 degrees, TEG-kaolin maximal amplitude >50 mm, and maximal lysis <5% (period I); or rotational thromboelastometry−INTEM CT <200 seconds, INTEM clot formation time <130 seconds, INTEM MCF >50 mm, EXTEM CT <80 seconds, FIBTEM amplitude of firmness 20 minutes >nine mm, and maximum lysis <5% (period II). The prescribed doses of each hemostatic agent were not strictly protocolized but were established on the clinical judgment of the medical team. Usual starting doses were the following: FFP 5/10 mL/kg; platelet transfusion 8/12 units; fibrinogen concentrate 1.0/2.0 g; and PCC 500/1,000 units. Depending on the clinical response and follow-up diagnostic results, these doses were repeated to achieve the hemostatic targets.

Outcome Parameters

The primary outcomes of this study were the cumulative blood loss (chest drain output) of the first postoperative 48 hours, and the required blood product transfusions in the post-CPB time frame of 48 hours. Postoperative massive blood loss and polytransfusion were determined as >1,000 mL blood loss/48 hours and >four units of RBC/48 hours, respectively. The secondary outcome parameters were defined as major postoperative complications, intensive care unit stay, hospital stay, and 30-day mortality. AKI was classified according to the Kidney Disease: Improving Global Outcomes creatinine-based definition criteria.[19]

Statistical Analysis

Descriptive statistics of data were displayed as mean ± standard deviation and median (interquartile range). Categorical variables were summarized as number of patients and frequency. The univariate analyses were carried out by unpaired t test, Mann-Whitney U test, and χ^2 test or Fisher exact test where appropriate. The authors performed a 1:1 match, nearest-neighbor method of propensity score matching (PSM), with a caliper width of 0.2,[20] using the unbalanced covariates of the baseline and intraoperative characteristics (platelet count, INR, APTT, C-reactive protein, unfractionated heparin dose, protamine dose, left ventricle ejection fraction ≤35%, single procedure, three procedures, and four procedures). The improvement of the overall imbalance was checked, computing standardized mean differences of all adjusted covariates. The comparative analyses of outcome parameters in the matched cohort of patients receiving blood product−based or FC-based hemostasis management were performed by a paired *t* test for continuous variables and a McNemar test for categorical variables. To determine independent predictors of major secondary outcome parameters, the authors used a multivariate, logistic regression, backward elimination, likelihood-ratio method. The authors completed a five-year follow-up for all patients and analyzed one-year and five-year survival applying the Kaplan-Meier method, and the two study groups were compared with a log-rank test using the Mantel-Cox method. Statistical significance was defined at the $p < 0.05$ level in all tests. Analyses were performed with IBM SPSS Statistics for Windows, version 23.0. (IBM Corp., Armonk, NY) and R-statistics for Windows, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

During the screened time periods, due to perioperative bleeding, 271 of 500 patients (54.2%) received blood product−based management, and 162 of 500 patients (32.4%) were treated with an FC strategy (with or without blood product transfusion). The remaining 229 and 338 patients from the two groups did not require any hemostasis therapy in the perioperative period. The PSM procedure involving 433 subjects receiving hemostasis therapy resulted in 118 matched pairs. After the matching, the absolute values of standardized mean differences were found to be less than 0.22 in all adjusted covariates. Variables of preoperative coagulation profile, operative complexity, and CPB procedures achieved balance by PSM, which indicated similar risks for postoperative coagulopathy and bleeding in both groups. The baseline clinical data of the unmatched and matched populations are summarized in Table 1.

Table 1
Patient Characteristics and Perioperative Clinical Data in the Unmatched and Matched Cohorts

	Study Population N = 1,000	Blood Product Group n = 271	FC Group n = 162	*p*	Blood Product Group n = 118	FC Group n = 118	*p*
		Unmatched Cohort n = 433			PS Matched Cohort n = 236		
Preoperative variables							
Age, y	66 (59, 72)	67 (61, 73)	68 (61, 74)	0.374	67 (61, 73)	68 (59, 74)	0.766
Male sex, n	638 (63.8%)	163 (60.1%)	95 (58.6%)	0.757	69 (58.5%)	68 (57.6%)	0.895
Body mass index, kg/m^2	29.9 (24.8-30.9)	27.4 (24.5-30.4)	27.2 (23.9-29.9)	0.374	27.3 (24.4-30.6)	27.1 (23.9-30.1)	0.669
Hypertension, n	820 (82.0%)	212 (78.2%)	121 (74.7%	0.398	94 (79.7%)	88 (74.6%)	0.352
DM, n	334 (33.4%)	72 (26.6%)	49 (30.2%)	0.409	29 (24.6%)	35 (29.7%)	0.380
COPD, n	162 (16.2%)	50 (18.5%)	24 (14.8%)	0.331	20 (16.9%)	19 (16.1%)	0.861
Chronic kidney disease							
GFR_{45-59}, n	132 (13.2%)	42 (15.5%)	24 (14.8%)	0.848	16 (13.6%)	18 (15.3%)	0.856
GFR_{30-44}, n	53 (5.3%)	15 (5.5%)	15 (9.3%)	0.140	10 (8.5%)	10 (8.5%)	1.00
$GFR_{<30}$, n	25 (2.5%)	10 (3.7%)	6 (3.7%)	0.994	4 (3.4%)	2 (1.7%)	0.687
Preoperative anemia, n*	187 (18.7%)	54 (19.9%)	41 (25.3%)	0.190	27 (22.9%)	31 (26.3%)	0.644
Chronic liver disease, n	30 (3.0%)	13 (4.8%)	8 (4.9%)	0.947	6 (5.1%)	6 (5.1%)	1.00
Chronic GI disease, n	188 (18.8%)	50 (18.5%)	27 (16.7%)	0.639	24 (20.3%)	22 (18.6%)	0.742
Previous stroke, n	72 (7.2%)	23 (8.5%)	8 (4.9%)	0.166	9 (7.6%)	5 (4.2%)	0.409
Peripheral vascular disease, n	207 (20.7%)	56 (20.7%)	22 (13.6%)	0.063	20 (16.9%)	18 (15.3%)	0.723
Chronic endocrine disease, n	70 (7.0%)	21 (7.7%)	14 (8.6%)	0.742	11 (9.3%)	12 (12.2%)	0.826
Malignancy, n	94 (9.4%)	23 (8.5%)	18 (11.1%)	0.367	8 (6.8%)	13 (11.0%)	0.253
Previous cardiac surgery, n	47 (4.7%)	21 (7.7%)	11 (6.8%)	0.712	9 (7.6%)	9 (7.6%)	1.00
ACEI, n	552 (55.2%)	144 (53.1%)	86 (53.1%)	0.992	56 (47.5%)	56 (47.5%)	1.00
BARB, n	756 (75.6%)	204 (75.3%)	122 (75.3%)	0.994	91 (77.1%)	89 (75.4%)	0.760
CCB, n	313 (31.3%)	73 (26.9%)	50 (30.9%)	0.381	36 (30.5%)	38 (32.2%)	0.779
GTN, n	199 (19.9%)	52 (19.2%)	18 (11.1%)	0.027	23 (19.5%)	15 (12.7%)	0.157
Diuretic, n	488 (48.8%)	148 (54.6%)	91 (56.2%)	0.752	71 (60.2%)	65 (55.1%)	0.429
Statin, n	616 (61.6%)	159 (58.7%)	83 (51.2%)	0.132	58 (49.2%)	63 (53.4%)	0.515
Single antiplatelet, n	409 (40.9%)	87 (32.1%)	57 (35.2%)	0.510	40 (33.9%)	41 (34.7%)	0.891
Dual antiplatelet, n	178 (17.8%)	60 (22.1%)	21 (13.0%)	0.018	18 (15.3%)	19 (16.1%)	0.858
OAC	127 (12.7%)	51 (18.8%)	29 (17.9%)	0.812	23 (19.5%)	26 (22.0%)	0.630
Hemoglobin, g/dL	13.8 ± 1.6	13.8 ± 1.7	13.5 ± 1.6	0.093	13.6 ± 1.7	13.4 ± 1.6	0.399
Platelet count, G/L	207 (174-246)	216 (178-261)	191 (161-228)	<0.0001	194 (158-245)	199 (168-238)	0.892
INR	1.04 (1.00-1.10)	1.07 (1.01-1.16)	1.04 (1.00-1.10)	0.003	1.08 (1.01-1.15)	1.04 (1.0-1.12)	0.080
Fibrinogen, g/L	3.67 (3.10-4.21)	3.62 (3.08-4.18)	3.50 (3.00-4.12)	0.334	3.58 (2.92-4.08)	3.55 (3.00-4.21)	0.698
APTT, s	36.6 (33.5-40.0)	36.5 (33.3-40.1)	38.3 (34.6-41.8)	0.010	37.0 (34.6-41.1)	38.0 (34.5-42.1)	0.537
Creatinine, μmol/L	81.0 (69.0-97.0)	81.0 (69.0-101.0)	83.0 (70.0-99.3)	0.641	81 (71.0-100.3)	82.5 (69.0-97.3)	0.739
GFR, mL/min/1.73 m^2	79.8 (63.2-93.0)	75.7 (60.3-92.2)	74.6 (58.0-92.2)	0.748	74.3 (57.6-90.9)	76.0 (59.7-92.5)	0.460
Bilirubin, μmol/L	10.6 (7.7-15.0)	11.6 (8.1-16.3)	11.8 (8.2-16.8)	0.722	11.8 (8.4-16.9)	12.3 (7.9-16.6)	0.988
CRP, mg/L	2.22 (1.10-4.48)	2.6 (1.2-5.0)	1.95 (0.95-4.01)	0.027	2.75 (1.1-5.0)	2.14 (0.9-4.5)	0.185
Left ventricle EF, %	59 (54-64)	60 (52-65)	60 (55-65)	0.142	60 (50-65)	60 (55-65)	0.579
Left ventricle EF ≤35%, n	38 (3.8%)	15 (5.5%)	2 (1.2%)	0.038	5 (4.2%)	1 (0.8%)	0.125
EuroSCORE II	1.84 (1.14-3.14)	2.27 (1.33-3.91)	2.17 (1.30-4.49)	0.896	2.21 (1.58-4.6)	2.16 (1.33-4.03)	0.273
Type of surgery							
Single procedure, n	357 (35.7%)	68 (25.1%)	20 (12.3%)	0.001	14 (11.9%)	16 (13.6%)	0.696
2 procedures, n	455 (45.5%)	145 (53.5%)	78 (48.1)	0.280	58 (49.2%)	63 (53.4%)	0.515
3 procedures, n	171 (17.1%)	53 (19.6%)	55 (34.0%)	0.001	42 (35.6%)	34 (28.8%)	0.265
4 procedures, n	17 (1.7%)	5 (1.8%)	9 (5.6%)	0.035	4 (3.4%)	5 (4.2%)	1.00
DHCA, n	11 (1.1%)	4 (1.5%)	7 (4.3%)	0.110	1 (0.9%)	7 (5.9%)	0.033
Intraoperative variables							
On-CPB, n	714 (71.4%)	216 (79.7%)	153 (94.4%)	<0.0001	110 (93.2%)	109 (92.4%)	0.801
CPB time, min	95 (77-120)	101 (85-137)	104 (85-147)	0.379	100 (85-141)	101 (82-146)	0.974
AoXC time, min	68 (54-85)	75 (59-99)	74 (58-102)	0.871	75 (58-105)	72 (58-95)	0.440
Lowest temperature, °C†	34.7 ± 1.6	34.0 ± 1.7	34.2 ± 1.6	0.322	33.8 ± 1.3	34.0 ± 1.8	0.353
Tranexamic acid, mg/kg	29 (0-48)	31 (0-55)	36 (22-49)	0.131	36 (0-59)	35 (23-47)	0.910
UFH, mg/kg	4.0 (2.3-4.7)	4.2 (3.1-4.8)	4.4 (3.5-5.4)	<0.0001	4.4 (3.6-5.0)	4.5 (3.6-5.4)	0.372
Protamine, mg/kg	3.5 (2.7-4.2)	3.6 (3.0-4.3)	3.8 (3.3-4.5)	0.002	3.8 (3.4-4.6)	3.8 (3.3-4.5)	0.923

NOTE. Data are presented as median (interquartile range), mean ± standard deviation and number of patients (frequency).

* Preoperative anemia was defined according to sex-based criteria of World Health Organization: women hemoglobin <12.0 g/dL and men hemoglobin <13.0 g/dL.

† Lowest temperature measured during cardiopulmonary bypass.Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AoXC, aorta cross-clamp; APTT, activated partial thromboplastin time; BARB, beta-adrenergic receptor blocker; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CRP, C-reactive protein; DHCA, deep hypothermic circulatory arrest; DM, diabetes mellitus; EF, ejection fraction; GFR, estimated glomerular filtration rate; GI, gastrointestinal; GTN, glyceryl trinitrate; INR, international normalized ratio; OAC, oral anticoagulant; PS, propensity score; UFH, unfractionated heparin.

Table 2
Comparative Analysis of the Primary Outcome Parameters in the Propensity Score Matched Cohort

Primary Outcome Parameters	Blood Product Group n = 118 PS matched cohort n = 236	FC Group n = 118	*p*
PO blood loss/48 h, mL	1,153 ± 949	907 ± 715	0.014
PO blood loss >1,000 mL/48 h, n (%)	52 (44.1%)	38 (32.2%)	0.082
PRC/post-CPB intraoperative, unit	1.5 ± 1.5	1.1 ± 1.2	0.011
PRC/post-CPB 48 h, unit	3.7 ± 2.8	2.3 ± 2.5	<0.0001
PRC >4 units/post-CPB 48 h, n (%)	51 (43.2%)	30 (25.9%)	0.0002
FFP/post-CPB intraoperative, unit	2.0 ± 1.3	1.4 ± 1.2	0.002
FFP/post-CPB 48 h, unit	3.4 ± 2.6	2.0 ± 1.6	<0.0001
FFP >15 mL/kg/post-CPB 48 h, n (%)	14 (12.2%)	4 (3.1%)	0.007
PLT/post-CPB intraoperative, unit	2.6 ± 4.5	2.6 ± 4.7	0.933
PLT/post-CPB 48 h, unit	5.7 ± 6.8	5.2 ± 6.0	0.534
Fibrinogen concentrate/post-CPB 48 h, g	-	2 (1-2)*	-
PCC/post-CPB 48 h, unit	-	500 (0-500)†	-

NOTE. Data are presented as mean ± standard deviation, number of patients (frequency) and median (interquartile range).
Abbreviations: FC, factor concentrate; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PLT, platelet transfusion; PO, postoperative; PRC: packed red cell; PS, propensity score.
* Frequency of the applied fibrinogen concentrate therapy: 1 g – 25.4% (30 patients); 2 g – 48.3% (57 patients); >2 g – 15.2% (18 patients).
† Frequency of the applied PCC therapy: 500 units – 49.2% (58 patients); 1,000 units – 15.3% (18 patients); >1,000 units – 8.5% (10 patients).

Among patients of the PSM cohort (n = 118 pairs), the hemostasis therapy in the blood product–based group consisted of FFP in 47.5%, and FFP + platelet transfusion in 44.1%. Patients in the FC management group received FC in 8.5% of cases, FC + FFP in 66.1%, and FC + FFP + platelet transfusion treatment in 31.4%. Subjects of the FC management group experienced significantly less bleeding in the postoperative period than the blood product–based management group (907 mL *v* 1,153 mL, $p = 0.014$). Patients in the FC management group required a mean of 2.3 units of PRC and 2.0 units of FFP during the hemostasis management, and in the blood product–based management group these requirements were 3.7 units of RBC and 3.4 units of FFP ($p < 0.0001$ in both cases). Characteristically, there was a significantly higher frequency of polytransfusion (PRC >four units/48 hours) and large-volume FFP therapy (FFP >15 mL/kg/48 hours) in the blood product–based management group than in the FC management group. The platelet transfusion demands were similar in the two groups. The details of primary outcome parameters of the blood product–based and FC management groups are presented in Table 2.

The authors did not find differences in the frequency of early reoperation for bleeding or tamponade between the groups, and the postoperative ventilation time was similar in both groups. Although the overall frequency of AKI did not differ in the two groups, the authors registered more cases of Stage 3 AKI in the blood product–based management group than in the FC management group (6.8% *v* 0.8%, $p = 0.016$). Major adverse postoperative events showed comparable frequencies in the blood product–based and FC management groups. The mean length of intensive care unit and hospital stays were similar in the two groups, nevertheless prolonged hospital stays (>14 days) were more frequent in the blood product–based management group than in the FC management group (33.1% *v* 18.6%, $p = 0.021$). The authors registered nine cases of 30-day death in the blood product–based management group compared with one case in the FC management group, $p = 0.022$. The secondary outcome parameters are summarized in Table 3.

Multivariate logistic regression performed on the unmatched cohort of patients who had hemostasis therapy in the perioperative period revealed that subjects receiving FC management are 2.19 times less likely to experience major blood loss ($p < 0.0001$), 2.56 times less likely to require polytransfusion ($p < 0.0001$), and 13.16 times less likely to suffer from fatal outcome within 30 days postoperatively ($p = 0.003$). The post hoc calculated statistical power of the FC versus blood product–based management odds ratio for 30-day mortality was 0.846. The independent predictors of major outcome factors are demonstrated in Table 4. Cumulative one-year and five-year survival analysis did not confirm a difference between the blood product–based and FC management groups (Fig. 1 and 2).

Discussion

This propensity score–matched cohort study demonstrated that patients who underwent elective cardiac surgery experienced less postoperative blood loss and required fewer PRC and FFP blood products when receiving FC compared with blood product–based management in the treatment of perioperative coagulopathy and bleeding. Although there were no registered perioperative thromboembolic events in the two study groups, the stage 3 AKI and 30-day mortality were less frequent in the FC management group than in the blood product–based management group. FC management was associated with a 2.19-fold decrease in the odds of massive postoperative bleeding, a 2.56-fold decrease in the odds of polytransfusion, and a 13.16-fold decrease in the odds of early postoperative mortality.

Table 3
Comparative Analysis of the Secondary Outcome Parameters in the Propensity Score Matched Cohort

Secondary Outcome Parameters	Blood Product Group n = 118	FC Group n = 118	*p*
	PS Matched Cohort n = 236		
RO for bleeding/tamponade, n	14 (11.9%)	15 (12.7%)	1.00
MV time, h	21.4 ± 33.7	18.6 ± 34.2	0.537
MV >24 h, n	16 (13.7%)	12 (10.3%)	0.524
AKI overall, n	16 (13.6%)	11 (9.3%)	0.383
AKI stage 1, n	6 (5.1%)	3 (2.5%)	0.508
AKI stage 2, n	2 (1.7%)	7 (5.9%)	0.125
AKI stage 3, n	8 (6.8%)	1 (0.8%)	0.016
RRT, n	6 (5.1%)	1 (0.8%)	0.063
New onset AF, n	19 (16.1%)	19 (16.1%)	1.00
Postoperative MI, n	2 (1.7%)	2 (1.7%)	1.00
Postoperative LCOS, n	32 (27.1%)	37 (31.4%)	0.576
Postcardiotomy ECMO support, n	0	0	
Postoperative stroke, n	2 (1.7%)	0	0.500
Thromboembolic events, n	0	0	
Pneumonia, n	7 (5.9%)	9 (7.6%)	0.774
Sepsis, n	5 (4.2%)	3 (2.5%)	0.727
Length of ICU stay, d	2.8 ± 2.6	2.9 ± 3.0	0.672
Length of ICU stay >48 h, n	38 (32.2%)	49 (41.5%)	0.479
Length of hospital stay, d	12.0 ± 4.5	11.3 ± 5.3	0.515
Length of hospital stay >14 d, n	39 (33.1%)	22 (18.6%)	0.021
30-d death, n	9 (7.2%)	1 (0.8%)	0.022

NOTE. Data are presented as mean ± standard deviation and number of patients (frequency).
Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; FC, factor concentrate; ICU, intensive care unit LCOS, low cardiac output state; MI, myocardial infarction; MV, mechanical ventilation; PS, propensity score; RO, reoperation; RRT, renal replacement therapy.

Table 4
Independent Predictors of Major Outcome Parameters

Outcome parameters	OR	95% CI	*p*
Postoperative blood loss >1,000 mL/48 h			
FC management	0.456	0.300-0.692	<0.0001
Female sex	2.275	1.510-3.428	<0.0001
Polytransfusion (PRC >4 units/48 h)			
FC management	0.309	0.187-0.509	<0.0001
Female sex	1.542	0.984-2.416	0.059
Preoperative GFR <50 mL/min/1.73 m^2	1.716	0.947-3.112	0.075
Combined cardiac surgery	2.182	1.328-3.584	0.002
Preoperative anemia	2.923	1.721-4.963	<0.0001
RO for bleeding/tamponade	7.698	4.082-14.516	<0.0001
30-day mortality			
FC management	0.076	0.014-0.415	0.003
Female sex	3.73	1.134-12.326	0.030
Low cardiac output state	6.544	1.841-23.265	0.004
Acute kidney injury	13.400	3.890-46.166	<0.0001
Sepsis	18.649	3.565-97.553	0.001

NOTE. Multivariable logistic regression, backward elimination likelihood-ratio, unmatched cohort, n = 433. Adjusted covariates: female sex; age >70 years; body mass index <20; diabetes mellitus; chronic obstructive pulmonary disease; preoperative left ventricle ejection fraction <35%; preoperative anemia; preoperative eGFR <50 mL/min/1.73 m^2; preoperative dual antiplatelet therapy; aorta cross-clamp >120 minutes; combined cardiac surgery; previous cardiac surgery; deep hypothermic circulatory arrest; low-cardiac-output state; reoperation for bleeding/tamponade; mechanical ventilation >24 hours; postoperative acute kidney injury; postoperative sepsis; postoperative stroke; intensive care unit treatment >48 hours; factor concentrate hemostasis management.
Abbreviations: CI, confidence interval; FC, factor concentrate; GFR, estimated glomerular filtration rate; OR, odds ratio; RO, reoperation.

Cardiac surgery–associated acquired coagulopathy is induced by multifactorial processes involving blood loss, consumption of coagulation factors, hemodilution and interaction of CPB with the hemostatic system, resulting in low fibrinogen level and fibrinogen dysfunction, impaired thrombin generation, and platelet dysfunction as key mechanisms.[1] Among these, fibrin formation is the most affected physiologic alteration compared with thrombin generation and platelet-linked processes immediately after cardiac surgery.[21]

In patients with established post-CPB coagulopathy, FFP might be used to treat persistent bleeding but the evidence is insufficient to confirm reduced blood loss after cardiac surgery.[4] Accordingly, administration of FFP or FFP combined with platelet concentrates was not effective in achieving improved fibrin formation, thrombin generation, or platelet-linked clot formation.[21] As a single-agent therapy, the use of fibrinogen concentrates significantly reduced the number of required allogeneic blood products in randomized, placebo-controlled trials of complex cardiac surgery.[22,23] Solomon et al. presented similar results in terms of decreased postoperative allogeneic blood component transfusion requirements independently of intraoperative platelet count when they administered fibrinogen concentrate according to a thromboelastometric fibrin-based hemostasis test-guided strategy during aortic surgery.[24] Conversely, Bilecen et al.[25] did not confirm a difference in intraoperative blood loss in high-risk cardiac surgical patients treated with fibrinogen concentrate compared with controls, and they registered more postoperative adverse events numerically in the fibrinogen group such as stroke, myocardial infarction, and death in their randomized, placebo-controlled, double-blind trial. Additionally, a recent meta-analysis of eight RCTs concluded that besides the positive effects of fibrinogen concentrate for reducing the need for allogeneic blood product transfusion in high-risk cardiovascular surgery patients, its definitive benefit in risk reduction of mortality, or other clinical outcomes was not proven.[14]

In treating perioperative coagulopathy, PCC versus FFP therapy also has been investigated comparatively in the last decade. Two large-volume, propensity score-matched observational studies found that the use of PCC was more effective than FFP therapy in reducing bleeding and the need for blood transfusions.[13,26] Nevertheless, these studies could not confirm any benefit for postoperative mortality; indeed, a higher risk of postoperative AKI was observed regarding PCC use.[13,26] In a recent meta-analysis of four nonrandomized cardiac surgery studies, Roman et al.[15] confirmed the advantages of PCC versus FFP administration in the context of required perioperative blood transfusion, and they did not prove additional risks of

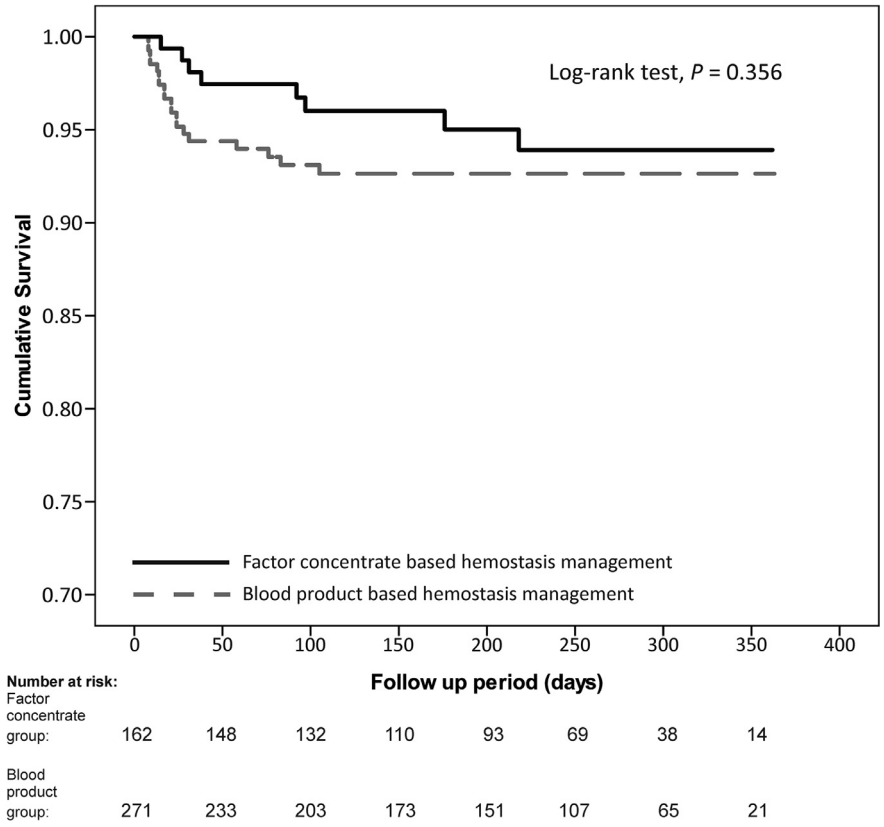

Fig 1. Kaplan-Meier estimates of cumulative one-year survival according to the applied hemostasis therapy in the perioperative period. The solid line represents the factor concentrate–based hemostasis management group, and the dashed gray line represents the blood product–based hemostasis management group; *p* value (log-rank test) indicates the difference in survival.

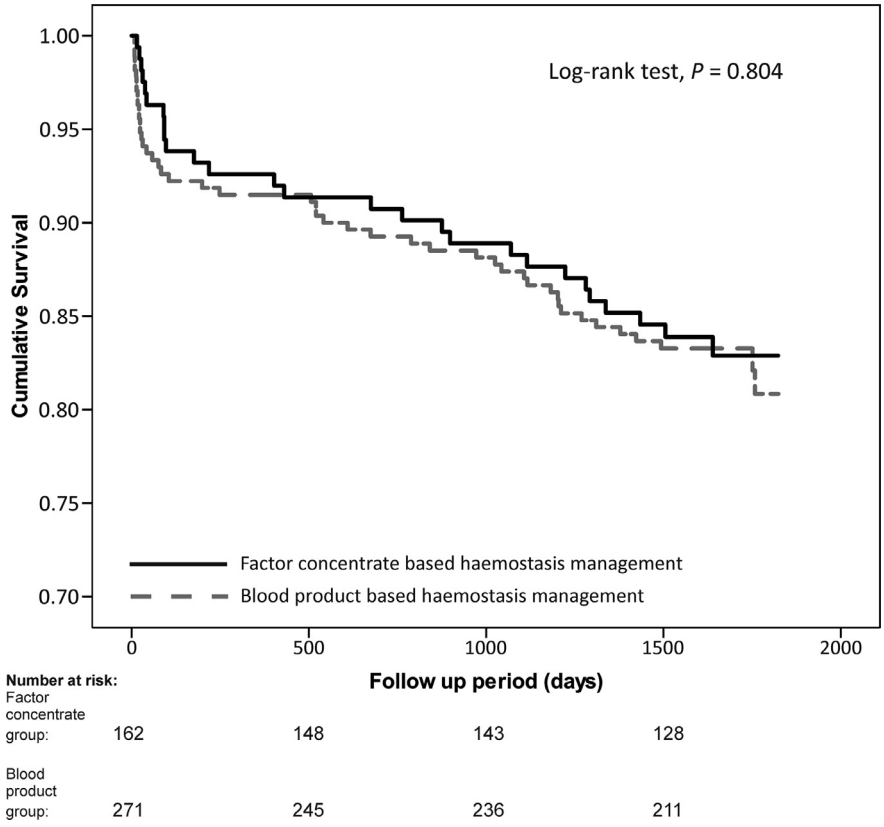

Fig 2. Kaplan-Meier estimates of cumulative five-year survival, according to the applied hemostasis therapy in the perioperative period. The solid line represents the factor concentrate–based hemostasis management group, and the dashed gray line represents the blood product–based hemostasis management group; *p* value (log-rank test) indicates the difference in survival.

thromboembolic or other adverse events associated with PCC use.

The primary outcome of this study was in line with previous findings, as the FC management of perioperative coagulopathy contributed substantially to reduced postoperative blood loss and a reduced need for blood products or massive transfusion compared with blood product–based management. However, the required platelet transfusions were found to be similar in the two groups. The FC management strategy did not represent single-agent therapy in this study. In the FC group, 89% of patients received fibrinogen concentrate in the perioperative period, and more than 70% of them were treated with at least 2 g of fibrinogen concentrate. In addition, 73% of subjects required treatment with 500 units or more of PCC in the same group. Despite the average doses of applied FCs in the authors' investigation being lower than the doses of fibrinogen concentrates (2-8 g) and PCC (1,500 units) used in eight recent RCTs, and a propensity-score matched analysis, the substantial role of their combined effects in successfully stabilizing hemostasis can be assumed according to the findings of an ex vivo investigation.[14,26,27] Because the dominant pathomechanism of perioperative coagulopathy could differ between individuals, the FC management strategy provides rapid, specific restoration of adequate hemostasis with pharmacologically predictable substitution of depleted factors, resulting in reduced blood loss.[1,11] These advantages of fibrinogen concentrate and PCC have been demonstrated by earlier investigations.[14,15] Conversely, unlike coagulation FCs, none of the blood product combinations could restore hemostatic abnormalities manifested two hours after cardiac surgery in a systematic investigation of hemostatic effect of coagulation FCs and blood products.[27] The authors' data were consistent with these findings. Despite a significantly higher volume of transfused blood products registered in the blood product–based management group, these patients experienced more blood loss than the subjects in the FC group.

Whereas previous investigations—both retrospective and randomized—could not present better postoperative mortality related to fibrinogen concentrate or PCC compared with FFP treatment, the authors revealed a greater than 13-fold decrease in the odds of early postoperative death when perioperative bleeding was treated with FC instead of blood product–based management.[13,23,25,26,28,29] In the meta-analysis of Li et al.[14] a definitive advantage of fibrinogen concentrate treatment for reduction in risk of mortality or other outcome parameters including postoperative blood loss has not been confirmed compared with controls. Similarly, Roman et al.[15] did not observe differences for reexploration for bleeding and chest drain output at 24 hours between the PCC and control groups. The authors' results were different from these findings, as they registered significantly higher blood loss in the blood product–based group than in the FC management group. Based on the data presented by Tang et al.,[27] the authors presume that the combined FCF therapy (ie, fibrinogen concentrate and PCC) might have a strong impact on achieving adequate hemostasis resulting in significantly less postoperative blood loss in the FC management group. Christensen et al.[3] presented important data about the relationship between the volume of postoperative chest tube drainage and mortality. Their retrospective analysis demonstrated that postoperative hemorrhage (>495 mL) within six hours increased the risk of 30-day mortality 1.719-fold.[3] The authors' data were comparable to these results, as multivariate logistic regression confirmed significant risk reductions in terms of major blood loss (ie, >1,000 mL/48 hours), polytransfusion (ie, >four units PRC/48 hours), and 30-day mortality if the patient received FC management.

In this study, the authors also found supporting data regarding the safety of FC therapy. Unlike the significantly higher risk of AKI and renal replacement therapy found in the PSM analysis of Cappabianca et al.,[26] the authors have not recorded a higher rate of AKI related to FC management. In fact, a significantly higher rate of stage 3 AKI was registered in the blood product–based management group. However, the median PCC dose administered in FC management was 500 units versus a median dose of 1,500 units received by the PCC subjects in Cappabianca et al.[26]

Despite the marked difference in 30-day mortality, the one-year and five-year cumulative survivals were similar in the two groups. The possible explanation for these results was the significantly higher frequency of combined cardiac surgery registered in the FC management group (unmatched cohort, see Table 1) that could influence the long-term survival of those patients. On the other hand, these results supported the hypothesis that the two study groups were similar in terms of patient profile, risk for postoperative bleeding, and estimated survival. Therefore, it can be assumed that the present study cohorts (unmatched and matched) were valid for comparing the clinical effectiveness of the different hemostasis therapies.

The present analysis did have limitations. This observational study was carried out with a retrospective design, analyzing data of patients sourced from two distinct periods (2011 and 2013), limiting the applicability of the presented results to current practice. To mitigate bias related to characteristic discrepancy between the study cohorts, PSM was performed. However, even with this modelling approach latent confounders can be present. The diagnosis and therapeutic management of coagulopathy were not strictly protocolized and guided by standardized transfusion algorithms at the authors' institution in the two periods, leaving clinical decisions to the discretion of the involved medical teams and contributing to the variability of the diagnostic and therapeutic steps applied. These limitations and the sample sizes of the analyzed cohorts somewhat restricted the interpretation of the authors' results.

In conclusion, this propensity score–matched cohort study showed that FC management of perioperative coagulopathy was accompanied by less postoperative blood loss, reduced requirements for PRC and FFP blood products, and a reduced frequency of both stage 3 AKI and 30-day mortality in contrast to blood product–based management in patients undergoing elective cardiac surgery. These results also demonstrated that the FC management of perioperative coagulopathy resulted in a more than two-fold decrease in the odds of massive postoperative bleeding and polytransfusion, and a 13.16-fold decrease

in the odds of early postoperative death. In this study, FC-based perioperative hemostasis treatment was not linked to a higher frequency of thromboembolic events or decreased long-term survival in cardiac surgical patients developing perioperative coagulopathy and bleeding compared with pure blood product–based management. However, further randomized controlled studies are warranted in this field.

Conflict of Interest

Within the past five years, Endre Nemeth has received honoraria for lecturing from CSL Behring. All other authors declare that they have no competing financial or other interest in relation to their work.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2021.03.043.

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