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Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery

The FIBRES Randomized Clinical Trial

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IMPORTANCE Excessive bleeding is a common complication of cardiac surgery. An important cause of bleeding is acquired hypofibrinogenemia (fibrinogen level <1.5-2.0 g/L), for which guidelines recommend fibrinogen replacement with cryoprecipitate or fibrinogen concentrate. The 2 products have important differences, but comparative clinical data are lacking.

OBJECTIVE To determine if fibrinogen concentrate is noninferior to cryoprecipitate for treatment of bleeding related to hypofibrinogenemia after cardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial at 11 Canadian hospitals enrolling adult patients experiencing clinically significant bleeding and hypofibrinogenemia after cardiac surgery (from February 10, 2017, to November 1, 2018). Final 28-day follow-up visit was completed on November 28, 2018.

INTERVENTIONS Fibrinogen concentrate (4 g; n = 415) or cryoprecipitate (10 units; n = 412) for each ordered dose within 24 hours after cardiopulmonary bypass.

MAIN OUTCOMES AND MEASURES Primary outcome was blood components (red blood cells, platelets, plasma) administered during 24 hours post bypass. A 2-sample, 1-sided test for the ratio of the mean number of units was conducted to evaluate noninferiority (threshold for noninferiority ratio, <1.2).

RESULTS Of 827 randomized patients, 735 (372 fibrinogen concentrate, 363 cryoprecipitate) were treated and included in the primary analysis (median age, 64 [interquartile range, 53-72] years; 30% women; 72% underwent complex operations; 95% moderate to severe bleeding; and pretreatment fibrinogen level, 1.6 [interquartile range, 1.3-1.9] g/L). The trial met the a priori stopping criterion for noninferiority at the interim analysis after 827 of planned 1200 patients were randomized. Mean 24-hour postbypass allogeneic transfusions were 16.3 (95% CI, 14.9 to 17.8) units in the fibrinogen concentrate group and 17.0 (95% CI, 15.6 to 18.6) units in the cryoprecipitate group (ratio, 0.96 [1-sided 97.5% CI, $-\infty$ to 1.09; $P < .001$ for noninferiority] [2-sided 95% CI, 0.84 to 1.09; $P = .50$ for superiority]). Thromboembolic events occurred in 26 patients (7.0%) in the fibrinogen concentrate group and 35 patients (9.6%) in the cryoprecipitate group.

CONCLUSIONS AND RELEVANCE In patients undergoing cardiac surgery who develop clinically significant bleeding and hypofibrinogenemia after cardiopulmonary bypass, fibrinogen concentrate is noninferior to cryoprecipitate with regard to number of blood components transfused in a 24-hour period post bypass. Use of fibrinogen concentrate may be considered for management of bleeding in patients with acquired hypofibrinogenemia in cardiac surgery.

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Excessive bleeding necessitating blood component transfusion is common after cardiac surgery and is associated with increased risk of morbidity and mortality and associated costs.¹ The pathophysiology of cardiac surgery-related bleeding is often multifactorial but includes acquired hypofibrinogenemia (fibrinogen level <1.5-2.0 g/L), which is associated with excessive bleeding in children² and adults.³ In cases of excessive bleeding and acquired hypofibrinogenemia, guidelines recommend treatment with either cryoprecipitate or fibrinogen concentrate.^{4,5}

Although both products are plasma-derived, they have distinct features. Cryoprecipitate is a nonpurified product; hence, in addition to fibrinogen it contains fibronectin and platelet microparticles, as well as coagulation factors VIII, XIII, and von Willebrand factor.⁶ Its fibrinogen content varies widely (from 3-30 g/L per unit); in most cases it must be maintained and shipped in a frozen state and then thawed and pooled (typically 5-10 unit pools) before administration; and it has a limited shelf life after thawing (<4-6 hours), increasing wastage.^{7,8} Fibrinogen concentrates are pathogen-reduced and purified; have standardized fibrinogen content (20 g/L); are lyophilized, allowing for easy storage, reconstitution, and administration; and have longer shelf life after reconstitution (up to 24 hours), which reduces wastage. There is divergent practice regarding the preferred product for fibrinogen replacement.⁹ Cryoprecipitate remains the therapy of choice in many areas (including North America). In many European countries, however, fibrinogen concentrates have replaced cryoprecipitate, even though very few studies have directly compared these products.^{10,11}

In this multicenter randomized clinical trial in patients undergoing cardiac surgery and requiring fibrinogen replacement because of clinically significant bleeding related to acquired hypofibrinogenemia, the objective was to determine if fibrinogen concentrate was noninferior to cryoprecipitate as measured by the amount of allogeneic blood components (red cells, platelets, and plasma) administered.

Methods

Trial Oversight

This was an investigator-initiated, multicenter, randomized clinical trial conducted at 11 centers in Canada. The trial design and methodology have been previously published¹²; the study protocol and statistical analysis plan are available in [Supplement 1](#), and aspects of the trial design and methodology are included in the eMethods in [Supplement 2](#). The trial coordinating center was the Department of Anesthesia and Pain Management Clinical Trials Unit at the University Health Network (Toronto, Ontario, Canada). The trial was overseen by an independent data and safety monitoring committee, which reviewed adverse events after every 100 patients and reviewed a preplanned interim analysis performed after approximately 600 evaluable patients were enrolled. Study monitors independently reviewed all primary outcomes and adverse events. The trial was performed in accordance with the principles of the Declaration of Helsinki and applicable regulatory requirements. Research ethics board approval was obtained at each site before trial initiation, including approval

Key Points

Question Is fibrinogen concentrate noninferior to cryoprecipitate for treatment of bleeding related to acquired hypofibrinogenemia in cardiac surgery?

Findings In this randomized trial of 735 adult patients who underwent cardiac surgery and developed clinically significant bleeding and hypofibrinogenemia post cardiopulmonary bypass, the mean number of blood components transfused within 24 hours post bypass was 16.3 units in the fibrinogen concentrate group and 17.0 units in the cryoprecipitate group; ratio of the mean number of units transfused was 0.96, which met the prespecified noninferiority margin ratio of less than 1.2.

Meaning For management of cardiac surgery-associated bleeding related to acquired hypofibrinogenemia, fibrinogen concentrate may be considered for fibrinogen replacement.

of a delayed written consent process. Consent was delayed until after treatment (in accordance with the Canadian Tri-Council Policy Statements on the ethical conduct of research involving humans),¹³ in part because it is not possible to reliably predict before surgery which patients will require fibrinogen replacement for bleeding control during or after surgery, at which time there is a need for rapid access to therapy.

Patients

Adult patients undergoing cardiac surgery with cardiopulmonary bypass for whom fibrinogen replacement was ordered in response to clinically significant postbypass bleeding deemed related to acquired hypofibrinogenemia (fibrinogen plasma level <2.0 g/L by the Clauss method or FIBTEM [fibrin-based thromboelastometry test extrinsically activated with tissue factor and containing the platelet inhibitor cytochalasin D]-derived clot amplitude at 10 minutes <10 mm by thromboelastometry) were eligible for enrollment.^{14,15} In line with clinical practice, patients with bleeding were also eligible if hypofibrinogenemia was suspected but plasma fibrinogen levels were unavailable at the time of decision-making.

Blood bank technologists screened and randomized eligible patients if they had none of the following exclusion criteria: receipt of fibrinogen concentrate or cryoprecipitate within 24 hours before surgery; history of severe allergic reaction to fibrinogen concentrate or cryoprecipitate; refusal of blood components for religious or other reasons; plasma fibrinogen level greater than 3.0 g/L within 30 minutes of treatment order (to avoid increasing levels above the upper limit of normal [4.0 g/L]); and known pregnancy.

Trial Procedures

Participants were randomly assigned (1:1) to study groups using a pseudorandom number generator (PROC PLAN procedure in SAS) in randomly permuted blocks of 4, stratified by center. Allocation was blinded; randomization schedule was kept at the blood banks in sequentially numbered opaque sealed envelopes (prepared by Ergomed GmbH), which were opened when the order for fibrinogen replacement was received. Patients in the fibrinogen concentrate group received 4 g of fibrinogen concentrate (Fibryga; Octapharma AG), to be infused over

approximately 10 minutes, and those in the cryoprecipitate group received 10 units of cryoprecipitate, to be infused according to local practice. The dosages for fibrinogen concentrate¹⁶⁻¹⁸ and cryoprecipitate^{19,20} were consistent with recently published trials and guidelines. Cryoprecipitate dose in Canada is standardized at 10 units per dose,²¹ and although the amount of fibrinogen in each unit of cryoprecipitate is variable, on average each 10-unit pool contains approximately 4 g of fibrinogen (Canadian Blood Services data; Dana Devine, PhD, Canadian Blood Services, email communication, September 2019).

Patients were to only receive the allocated product for 24 hours after cardiopulmonary bypass, after which only cryoprecipitate was used for fibrinogen replacement. It was not feasible to blind clinicians involved in product administration, but clinicians not involved in product administration, patients, data collectors, and outcome assessors were blinded. To maintain blinding, chart labels for both products stated "Fibrinogen Study Product 4 grams." Data on race were collected for descriptive purposes as reported by patients based on predefined categories.

There were no other alterations to patient care. Each hospital had an established protocol for bleeding management that was not altered for the purposes of this study. Tranexamic acid use was routine at all centers. Administration of blood components and hemostatic agents (other than cryoprecipitate and fibrinogen concentrate), use of cell salvage, and viscoelastic testing were based on local hospital protocols.

Outcomes

The primary efficacy outcome was cumulative allogeneic blood component units (red blood cells, platelets, and plasma) administered for 24 hours after termination of cardiopulmonary bypass. Since 2 types of platelets are issued in Canada (75% standard buffy-coat pools from 4 allogeneic donors and 25% apheresis units from a single allogeneic donor), both types were counted as a 4-unit transfusion. Secondary outcomes included individual blood component units administered for 24 hours after termination of cardiopulmonary bypass, all transfusions from beginning of surgery to postoperative day 7, bleeding severity (according to the universal definition of perioperative bleeding [UDPB])²² during the 24 hours after cardiopulmonary bypass, and pretreatment and post-treatment fibrinogen levels. The UDPB components "delay in chest closure" and "cryoprecipitate or fibrinogen concentrate administration" were not used. Postoperative follow-up was 28 days. Adverse events were classified using the *Medical Dictionary for Regulatory Activities* (version 21.1) system of nomenclature. Adverse events that started or worsened on or after the first dose of the investigational product were classified as treatment-emergent. Data on duration of mechanical ventilation, intensive care unit stay, and hospitalization after surgery were also collected.

Statistical Analysis

Sample size was based on demonstrating noninferiority of fibrinogen concentrate relative to cryoprecipitate with respect to the primary efficacy outcome. Determination of noninferiority was based on a 1-sided type I error probability of .025 and a noninferiority margin of 20% for the ratio of mean number of units transfused per group. A 20% margin was deemed by an expert panel to be a plausible trade-off in efficacy in exchange

for the potential advantages of fibrinogen concentrate relative to those of cryoprecipitate. An empirical distribution function was calculated based on a mean of 16 units and a standard deviation of 14 units (derived from a recent study on bleeding management in cardiac surgery)²³ and was used to estimate power by performing 10 000 simulations for each of the possible sample sizes. Calculations showed that 1200 patients would provide an empirical power greater than 90% (assuming a 10% dropout rate and equal mean units transfused per group).

The primary analysis set comprised all randomized patients who had undergone cardiac surgery with cardiopulmonary bypass, received at least 1 (partial or complete) dose of either treatment, and for whom informed consent was obtained. The per-protocol analysis excluded patients who did not undergo cardiac surgery with cardiopulmonary bypass, received the incorrect treatment, received less than 80% of the planned dose, or received the first treatment more than 24 hours after cardiopulmonary bypass. The prespecified subgroups for analysis were elective vs nonelective surgery, simple vs complex surgery, and a subgroup excluding patients who were in critical state before surgery (blinded adjudication based on predefined conditions such as acute aortic dissection or cardiac arrest immediately before surgery). Post hoc subgroups analyzed were patients undergoing nonelective surgery and not in critical state before surgery, patients who had a fibrinogen measurement before product administration, patients with confirmed hypofibrinogenemia (with Clauss method) before product administration, and patients with at least moderate blood loss according to the UDPB.²²

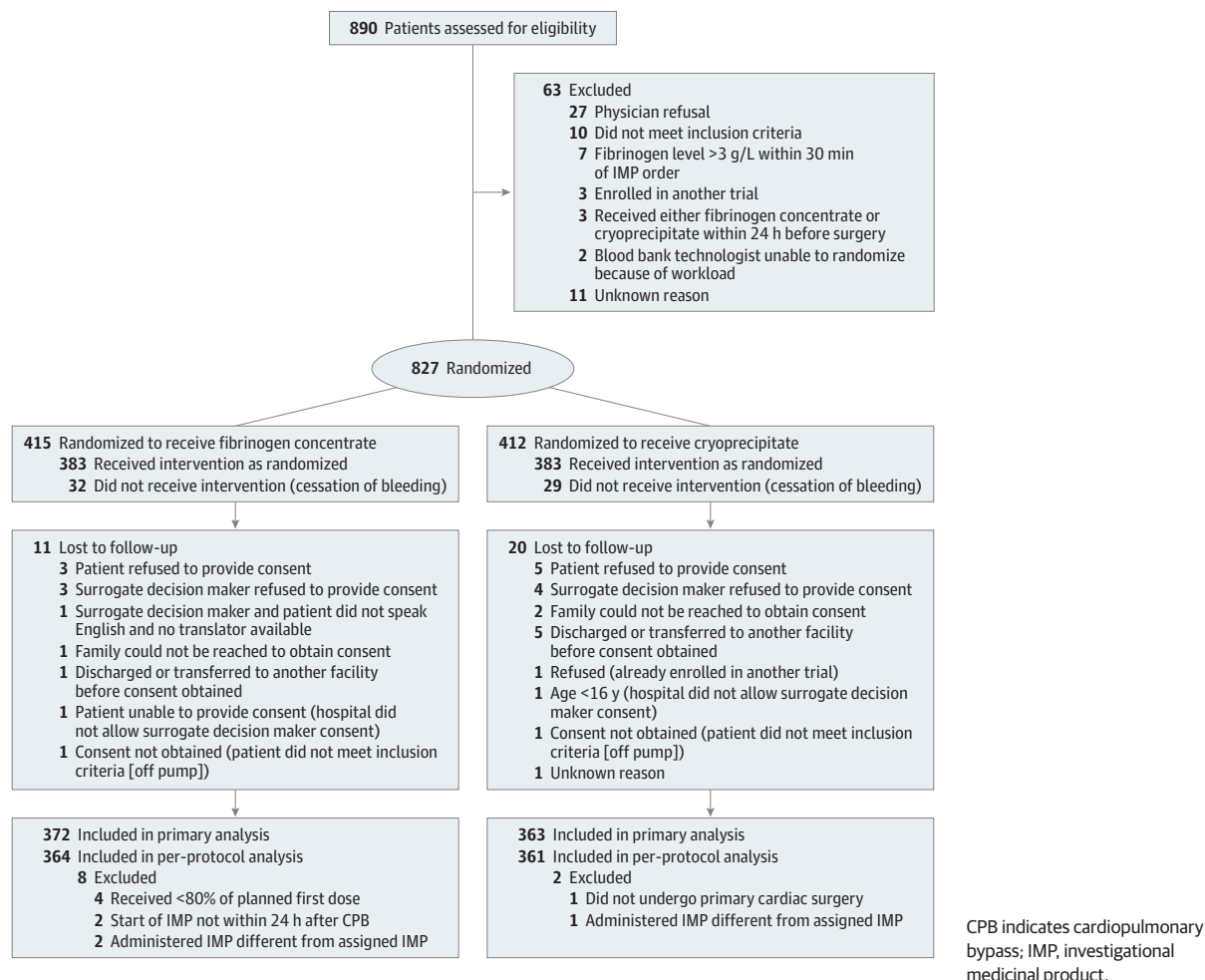
A 2-sample, 1-sided test of the null hypothesis that the treatment group fibrinogen concentrate to cryoprecipitate ratio of the mean number of allogeneic blood components was 1.2 or greater (ie, 20% noninferiority margin) was used to evaluate noninferiority using Poisson regression modeling for count data. Noninferiority would be demonstrated if the upper limit of the model-derived 1-sided 97.5% CI was less than 1.2. If noninferiority was demonstrated, an analogous test for superiority was to be performed, testing the hypothesis that the treatment group ratio of the mean number of allogeneic blood components was 1.0 or greater against the alternative that it was less than 1.0, at a 1-sided type I error level of $\alpha = .025$. No adjustment was made because of the hierarchical ordering of the tests. This analysis was repeated for the secondary allogeneic blood component transfusion outcomes.

There was 1 prespecified interim analysis after approximately 50% of the planned 1200 evaluable patients were enrolled, which used an adjusted type I error rate of .00258 according to the O'Brien-Fleming method²⁴ for a noninferiority stop. The trial was also to be stopped for futility if the predictive power for the test of noninferiority was less than 0.25.

Secondary outcomes were examined using descriptive statistics, the Wilcoxon rank-sum test, point estimates and risk ratios with 2-sided 95% CIs, and the Hodges-Lehmann estimator of median differences with 95% CIs, where appropriate. Kaplan-Meier estimates for time-to-death distribution were calculated and graphically presented. Comparisons were prespecified as superiority analyses with $\alpha = .05$.

Several post hoc analyses were performed: (1) noninferiority was assessed for the outcome of cumulative allogeneic

Figure 1. Patient Flow in the FIBRES Study of the Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery



blood component units administered from investigational product administration to 24 hours after cardiopulmonary bypass; (2) treatment \times site interaction was accounted for by including site in the model for the primary outcome as a fixed-effect variable (as 3 categories based on number of patients enrolled: <40; 40-99; >99); and (3) the relationship of critical state before surgery was explored by adjusting for it in the comparisons for the primary outcome and mortality. The results of secondary outcomes and post hoc analyses should be interpreted as exploratory, as no correction for type I error was made.

Variables with missing values are noted where applicable and patients with missing values were excluded from the relevant analyses. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Patient recruitment continued from February 10, 2017, to November 1, 2018, with the final follow-up visit on November 28, 2018. The trial was stopped based on the recommendation of the independent data and safety monitoring commit-

tee for meeting the criterion for noninferiority at the interim analysis. Of the 15 412 patients who underwent cardiac surgery at the 11 participating sites, 827 (5.3%) were screened and randomized (Figure 1). Sixty-one randomized patients were not treated because of cessation of bleeding. Informed consent could not be obtained for 31 treated patients, leaving 735 patients in the primary analysis set ($n = 372$ for fibrinogen concentrate, $n = 363$ for cryoprecipitate). After excluding 10 patients with major protocol deviations, 725 patients were included in the per-protocol analysis (Figure 1). No patients in the primary analysis set had missing transfusion or adverse event information; thus, they were all included in the relevant analyses.

Baseline demographics and surgical characteristics were well balanced except for critical state before surgery (Table 1). Patients received a median of 4 (interquartile range [IQR], 4-4) g of fibrinogen concentrate and 10 (IQR, 10-10) units of cryoprecipitate (Table 2; eTable 1 in Supplement 2).

Transfusions

In the primary analysis set, mean allogeneic blood component units administered were 16.7 (SD, 16.4) units within

Table 1. Characteristics of the Study Population at Baseline

Characteristic	No. (%)	
	Fibrinogen Concentrate (n = 372)	Cryoprecipitate (n = 363)
Age, median (IQR), y	65 (54-72)	64 (53-72)
Sex		
Women	113 (30.4)	105 (28.9)
Men	259 (69.6)	258 (71.1)
Race		
White	287 (77.2)	273 (75.2)
Asian	51 (13.7)	58 (16.0)
Black	3 (0.81)	6 (1.6)
Aboriginal	5 (1.3)	2 (0.55)
Other ^a	26 (7.0)	24 (6.6)
Body mass index, median (IQR) ^b	22.2 (19.6-25.4)	22.8 (19.6-25.6)
NYHA class ^c		
I (least severe)	104 (27.9)	112 (30.8)
II	110 (29.6)	108 (29.8)
III	110 (29.6)	103 (28.4)
IV (most severe)	48 (12.9)	40 (11.0)
Myocardial infarction, d		
No.	367	358
None	294 (80.1)	299 (83.5)
0-90	39 (10.6)	30 (8.4)
>90	34 (9.3)	29 (8.1)
Ejection fraction, %		
No.	357	347
>50	256 (71.7)	263 (75.8)
31-50	51 (14.3)	57 (16.4)
21-30	28 (7.8)	12 (3.5)
<21	22 (6.2)	15 (4.3)
Pulmonary pressure, mm Hg		
No.	308	303
≤30	225 (73.1)	215 (71.0)
31-55	58 (18.8)	68 (22.4)
>55	25 (8.1)	20 (6.6)
Hypertension	234 (62.9)	240 (66.1)
Dyslipidemia	185 (49.7)	185 (51.0)
Congestive heart failure	113 (30.4)	91 (25.1)
Atrial fibrillation	81 (21.8)	80 (22.0)
Diabetes mellitus	80 (21.5)	74 (20.4)
Chronic lung disease	53 (14.3)	37 (10.2)
Stroke/TIA	46 (12.4)	49 (13.5)
Peripheral vascular disease	37 (10.0)	34 (9.4)
Active endocarditis	19 (5.1)	18 (5.0)
CCS class IV angina	15 (4.0)	13 (3.6)
Dialysis (preoperative)	9 (2.4)	14 (3.9)
Intra-aortic balloon pump	10 (2.7)	3 (0.8)
VAD/ECMO	9 (2.4)	9 (2.5)
Critical state before surgery ^d	63 (16.9)	38 (10.5)

(continued)

Table 1. Characteristics of the Study Population at Baseline (continued)

Characteristic	No. (%)	
	Fibrinogen Concentrate (n = 372)	Cryoprecipitate (n = 363)
Preoperative laboratory values, median (IQR)		
Creatinine, μmol/L	88 (72-107) [n = 359]	86 (72-106) [n = 352]
Hemoglobin, g/dL	13.4 (11.6-14.6) [n = 366]	13.5 (11.7-14.8) [n = 356]
Platelet count, ×10 ³ /μL	189 (154-235) [n = 365]	185 (152-230) [n = 356]
International normalized ratio	1.02 (0.98-1.20) [n = 335]	1.03 (0.98-1.15) [n = 334]
Surgical factors		
Nonelective surgery	141 (37.9)	128 (35.3)
Complex surgery ^e	267 (71.8)	260 (71.6)
Procedure (% of procedures) ^f	653 (100.0)	612 (100.0)
Aortic valve procedure	165 (25.3)	146 (23.9)
Surgery on aorta	161 (24.7)	177 (28.9)
CABG surgery	153 (23.4)	146 (23.9)
Mitral valve procedure	68 (10.4)	70 (11.4)
Tricuspid valve procedure	31 (4.7)	35 (5.7)
ASD/VSD repair	20 (3.1)	8 (1.3)
Heart transplant	18 (2.8)	10 (1.6)
Complex congenital	11 (1.7)	11 (1.8)
Other ^g	26 (4.0)	9 (1.5)
Cardiopulmonary bypass duration, median (IQR), min	143 (102-209)	134 (99-200)

Abbreviations: ASD, atrial septal defect; CABG, coronary artery bypass graft; CCS, Canadian Cardiovascular Society; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; NYHA, New York Heart Association; TIA, transient ischemic attack; VAD, ventricular assist device; VSD, ventricular septal defect.

^a Other races marked as unknown or not applicable.

^b Calculated as weight in kilograms divided by height in meters squared.

^c NYHA functional classification: I = no limitation of physical activity and no symptoms; II = slight limitation of physical activity (ordinary physical activity results in fatigue, palpitation, dyspnea); III = marked limitation of physical activity (less than ordinary activity causes fatigue, palpitation, or dyspnea); IV = unable to carry on any physical activity without discomfort (symptoms of heart failure at rest).

^d Determined by blinded adjudication for patients who underwent emergency surgery deemed to be in a critical state, based on criteria outlined in Supplement 2.

^e Procedures other than CABG surgery only, single valve only, or repair of atrial septal defect only.

^f Totals exceed 100% because some patients underwent more than 1 procedure.

^g Examples of other procedures included aortic root enlargement, left ventricular aneurysmectomy, and left atrial appendage resection.

24 hours after termination of cardiopulmonary bypass and 22.4 (SD, 23.1) units from beginning of surgery to postoperative day 7. The mean 24-hour postbypass cumulative allogeneic blood component transfusions were 16.3 (95% CI, 14.9 to 17.8) units in the fibrinogen concentrate group and 17.0 (95% CI, 15.6 to 18.6) units in the cryoprecipitate group, and the mean ratio was 0.96 (1-sided 97.5% CI, $-\infty$ to 1.09; $P < .001$ for noninferiority; 2-sided 95% CI, 0.84 to 1.09; $P = .50$ for superiority) (Table 3 and Figure 2).

Table 2. Details of Intervention, Perioperative Laboratory Values, Fibrinogen Levels, and Bleeding

Variable	Median (IQR)	
	Fibrinogen Concentrate (n = 372)	Cryoprecipitate (n = 363)
Dosage of investigational product		
Mean (SD)	4.8 (2.1) g	12.9 (8.5) units
Median (IQR)	4 (4-4) g	10 (10-10) units
Doses of investigational product, No. (%)		
1	309 (83.1)	296 (81.5)
2	49 (13.2)	49 (13.5)
3	10 (2.7)	10 (2.8)
≥4	4 (1.1)	8 (2.2)
Time from start of surgery to order of first dose, h	5.8 (4.5-7.3)	5.8 (4.6-7.1)
Time from order of first dose to administration, min	45 (32-62)	47 (37-60)
Time from end of CPB to administration of first dose, min	97 (52-159)	104 (59-160)
Plasma fibrinogen level, g/L		
Pretransfusion	1.6 (1.3-1.9) [n = 352]	1.6 (1.3-1.9) [n = 346]
Posttransfusion	2.5 (2.1-2.9) [n = 324]	2.3 (2.0-2.6) [n = 296]
Change from pretransfusion	0.90 (0.6-1.2) [n = 306]	0.70 (0.5-1.0) [n = 280]
Blood components transfused before randomization, mean (SD), units	4.3 (6.1)	4.5 (6.0)
Cell salvage blood, mL	373 (0-918)	400 (0-876)
Nadir hematocrit during cardiopulmonary bypass, %	26 (23-30)	25 (23-30)
Hemoglobin, g/dL		
Intraoperative post-CPB	9.1 (8.3-9.9) [n = 348]	8.9 (8.2-9.7) [n = 342]
Day of surgery (last recorded value)	9.6 (8.6-10.9) [n = 365]	9.5 (8.7-10.7) [n = 356]
Postoperative day 1 (last recorded value)	9.0 (8.3-9.9) [n = 367]	9.0 (8.3-10.0) [n = 361]
Platelet count, ×10 ³ /μL		
Intraoperative post-CPB	107 (84-136) [n = 280]	103 (81-129) [n = 278]
Day of surgery (last recorded value)	132 (107-165) [n = 362]	133 (107-163) [n = 353]
Postoperative day 1 (last recorded value)	117 (91-145) [n = 366]	115 (92-143) [n = 359]
International normalized ratio		
Intraoperative post-CPB	1.6 (1.4-1.8) [n = 295]	1.6 (1.5-1.8) [n = 277]
Day of surgery (last recorded value)	1.3 (1.2-1.4) [n = 355]	1.3 (1.2-1.4) [n = 340]
Postoperative day 1 (last recorded value)	1.2 (1.1-1.4) [n = 342]	1.2 (1.1-1.3) [n = 335]
Bleeding categories according to modified UDPB classification, No. (%) ^a		
≥2 (moderate to massive)	349 (93.8)	347 (95.6)
<2 (insignificant to mild)	23 (6.2)	16 (4.4)
24-h chest tube drainage, mL	800 (500-1350)	830 (540-1350)
Reexploration, No. (%)	53 (14.2)	44 (12.1)
Prothrombin complex concentrate, No. (%)	110 (29.6)	98 (27.0)
Recombinant factor VII, No. (%)	35 (9.4)	28 (7.7)

Abbreviations: CPB, cardiopulmonary bypass; IQR, interquartile range; UDPB, universal definition of perioperative bleeding.

^a UDPB determinants used in this study include postoperative chest tube output; units of red blood cells, plasma, and platelets transfused; use of factor concentrates; and surgical reexploration (classification scheme included in the eAppendix in Supplement 2).²² For this study the following components of the UDPB score were not used: delay in chest closure and use of cryoprecipitate or fibrinogen concentrate. One intraoperative death was included in the severe or massive category in the fibrinogen concentrate group.

Noninferiority was also observed for the secondary outcomes of individual 24-hour and cumulative 7-day blood component transfusions (Table 3), as well as in the post hoc outcome of cumulative transfusions measured from product administration to 24 hours after termination of cardiopulmonary bypass (mean units, 8.6 [95% CI, 7.5 to 9.9] in the fibrinogen concentrate group vs 8.9 [95% CI, 7.8 to 10.2] in the cryoprecipitate group; mean ratio, 0.97 [1-sided 97.5% CI, $-\infty$ to 1.18; $P = .02$ for noninferiority) and after accounting for treatment × site interaction ($P < .001$) (eFigure 1 in Supplement 2) on the primary outcome (mean ratio, 1.00 [1-sided 97.5% CI,

$-\infty$ to 1.13; $P = .003$ for noninferiority). Noninferiority was also observed for all defined subgroups except for the nonelective group, which included all patients in critical state before surgery (Figure 2; eTable 2 in Supplement 2).

Fibrinogen Levels

Timing and number of doses of investigational product were similar between groups. Fibrinogen response was slightly greater in the fibrinogen concentrate group (median increase, 0.9 [IQR, 0.6-1.2] g/L vs 0.7 [IQR, 0.5-1.0] g/L; $P < .001$) (Table 2; eTable 1 in Supplement 2).

Table 3. Primary and Secondary Outcomes: Allogeneic Blood Component Transfusions

Population	Fibrinogen Concentrate			Cryoprecipitate			Mean Difference (95% CI)	Unadjusted Ratio of LS Means (1-Sided 97.5% CI)	Noninferiority P Value
	No.	Median (IQR)	LS Mean (95% CI)	No.	Median (IQR)	LS Mean (95% CI)			
Primary Outcome: Cumulative Allogeneic Blood Components Transfused Within 24 h After Cardiopulmonary Bypass^a									
Primary analysis set	372	12.0 (5.5 to 22.0)	16.3 (14.9 to 17.8)	363	14.0 (7.0 to 23.0)	17.0 (15.6 to 18.6)	-0.73 (-3.10 to 1.64)	Unadjusted 0.96 (-∞ to 1.09)	<.001
								Adjusted 0.91 (-∞ to 1.03) ^c	<.001
Per-protocol set ^b	364	12.0 (6.0 to 22.0)	16.4 (15.0 to 18.0)	361	14.0 (7.0 to 22.0)	16.9 (15.5 to 18.5)	-0.50 (-2.90 to 1.89)	Unadjusted 0.97 (-∞ to 1.10)	<.001
								Adjusted 0.92 (-∞ to 1.05) ^c	<.001
Secondary Outcome: Red Blood Cell Transfusions Within 24 h After Cardiopulmonary Bypass									
Primary analysis set	372	2.0 (0.0 to 5.0)	3.3 (3.0 to 3.7)	363	2.0 (1.0 to 5.0)	3.3 (2.9 to 3.7)	0.23 (-0.55 to 1.00)	1.00 (0 to 1.18)	.02
Per-protocol set	364	2.0 (0.0 to 5.0)	3.3 (3.0 to 3.7)	361	2.0 (1.0 to 5.0)	3.3 (2.9 to 3.7)	0.25 (-0.53 to 1.03)	1.01 (0 to 1.18)	.02
Secondary Outcome: Platelet Transfusions Within 24 h After Cardiopulmonary Bypass									
Primary analysis set	372	8.0 (4.0 to 12.0)	9.1 (8.3 to 9.9)	363	8.0 (4.0 to 12.0)	9.7 (8.9 to 10.5)	-0.46 (-1.70 to 0.78)	0.94 (-∞ to 1.06)	<.001
Per-protocol set	364	8.0 (4.0 to 12.0)	9.1 (8.3 to 10.0)	361	8.0 (4.0 to 12.0)	9.6 (8.8 to 10.5)	-0.31 (-1.56 to 0.93)	0.95 (-∞ to 1.08)	<.001
Secondary Outcome: Plasma Transfusions Within 24 h After Cardiopulmonary Bypass									
Primary analysis set	372	2.0 (0.0 to 6.0)	3.9 (3.5 to 4.4)	363	3.0 (0.0 to 6.0)	4.1 (3.6 to 4.6)	-0.04 (-0.97 to 0.89)	0.96 (-∞ to 1.15)	.008
Per-protocol set	364	2.0 (0.0 to 6.0)	4.0 (3.5 to 4.5)	361	3.0 (0.0 to 6.0)	4.0 (3.6 to 4.6)	0.04 (-0.91 to 0.98)	0.98 (-∞ to 1.17)	.01
Secondary Outcome: Cumulative Allogeneic Blood Components Transfused Within 7 d After Start of Surgery									
Primary analysis set	372	15.5 (6.0 to 29.5)	22.5 (20.5 to 24.7)	363	17.0 (9.0 to 28.0)	22.3 (20.3 to 24.5)	0.21 (-3.14 to 3.55)	Unadjusted 1.01 (0 to 1.15)	.005
								Adjusted 0.96 (-∞ to 1.09) ^c	<.001
Per-protocol set	364	15.5 (6.0 to 29.0)	22.5 (20.5 to 24.8)	361	17.0 (9.0 to 28.0)	22.2 (20.2 to 24.5)	0.31 (-3.07 to 3.70)	Unadjusted 1.01 (0 to 1.16)	.007
								Adjusted 0.96 (-∞ to 1.09) ^c	<.001

Abbreviation: LS, least-squares.

^a Units of allogeneic blood components counted as follows: each red blood cell unit = 1 unit, each 250-mL plasma unit = 1 unit, each 500-mL plasma unit = 2 units, each platelet dose = 4 units.

^b Per-protocol set excluded patients who did not undergo cardiac surgery with

cardiopulmonary bypass, received the incorrect treatment, received less than 80% of the planned dose, or received the first treatment more than 24 hours after cardiopulmonary bypass.

^c Adjusted for critical state before surgery (post hoc analysis).

Adverse Events and Other Outcomes

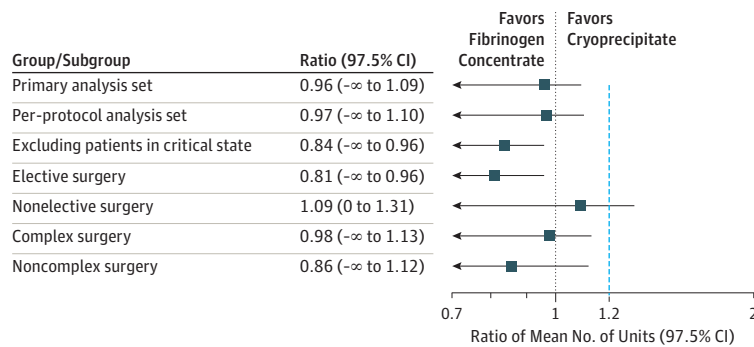
Treatment-emergent adverse event profiles were similar (Table 4; eTable 3 in Supplement 2), as were the duration of intubation, intensive care unit stay, and hospital stay (Table 4). There were 35 deaths (9.4%) in the fibrinogen concentrate group and 27 (7.4%) in the cryoprecipitate group (unadjusted hazard ratio, 1.28 [95% CI, 0.77 to 2.12]; $P = .35$) (Kaplan-Meier curves shown in eFigures 2 and 3 in Supplement 2). Death rates were also not significantly different when stratified by critical state before surgery (fibrinogen concentrate vs cryoprecipitate: 19/63 [30.2%] vs 12/38 [31.6%] in critical state patients; 16/309 [5.2%] vs 15/325 [4.6%] in remaining patients) and after risk adjustment for critical state (post hoc analysis hazard ratio, 1.03 [95% CI, 0.62 to 1.70]; $P = .92$) (results from post hoc analyses reported in eTables 4 and 5 in Supplement 2). Thromboembolic adverse events were observed in 26 patients (7.0%) in the fibrinogen group and 35 patients (9.6%) in the cryoprecipitate group (unadjusted odds ratio, 0.70 [95% CI, 0.42 to 1.20]) (Table 4).

Discussion

In this study of patients who experienced bleeding after cardiac surgery and required fibrinogen replacement as part of routine clinical practice, the primary finding was that fibrinogen concentrate was noninferior to cryoprecipitate as measured by the number of blood components transfused.

The study protocol, which did not modify clinical practice and used a delayed (postintervention) consent process, successfully randomized the small proportion of patients with bleeding who were ordered fibrinogen replacement (comprising approximately 5% of patients who underwent cardiac surgery at participating centers during the study period). The groups were well balanced for baseline variables except for critical state before surgery, an important prognostic variable that was more prevalent in the fibrinogen concentrate group. The occurrence of adverse events was comparable between the groups, although there was

Figure 2. Ratio of Mean Number of Allogeneic Blood Components Transfused in the 24 Hours After Cardiopulmonary Bypass for the Primary Analysis Set, Per-Protocol Analysis Set, and A Priori-Defined Subgroups



All patients in critical state were in the nonelective subgroup. Blue dashed line at x = 1.2 indicates the noninferiority margin.

Table 4. Treatment-Emergent Adverse Events and Other Measured Outcomes at 28-Day Follow-up

Outcome	No. (%)	
	Fibrinogen Concentrate (n = 372)	Cryoprecipitate (n = 363)
Any adverse event	248 (66.7)	264 (72.7)
No. of events	623	673
Any serious adverse event	117 (31.5)	126 (34.7)
No. of events	224	264
Thromboembolic adverse events ^a	26 (7.0)	35 (9.6)
No. of events	27	39
Stroke/TIA	17 (4.6)	18 (5.0)
DVT/PE	5 (1.3)	9 (2.5)
Myocardial infarction	3 (0.8)	4 (1.1)
Other vessel thrombosis	0	7 (1.9)
Amaurosis fugax	0	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)	0
Thrombophlebitis	1 (0.3)	0
Acute kidney injury ^b	48 (12.9)	48 (13.2)
Hepatobiliary disorders ^c	32 (8.6)	37 (10.2)
Duration of mechanical ventilation, median (IQR), d	1.3 (0.7-5.0) [n = 337]	1.3 (0.7-4.2) [n = 342]
Duration of intensive care unit stay, median (IQR), d	2.9 (1.4-5.7) [n = 352]	2.8 (1.2-5.6) [n = 345]
Duration of hospitalization, median (IQR), d	8.2 (6.3-13.0) [n = 314]	9.0 (6.3-13.3) [n = 308]

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

^a Patients who experienced more than 1 event are counted only once in the total.

^b Acute kidney injury was defined as greater than a 2-fold increase in creatinine or kidney failure requiring hemodialysis within 28 days of surgery.

^c Hepatobiliary disorders were defined by the *Medical Dictionary for Regulatory Activities* (version 21.1) system of nomenclature.

a nonsignificant difference of 2.0% in mortality. This seemed to be related to the between-group imbalance in the number of patients in critical state before surgery.

The study objective was to compare the 2 currently recommended therapies for fibrinogen replacement^{4,5} under usual conditions of clinical care. Thus, it did not include a placebo group to determine the efficacy of fibrinogen replacement per se, nor did it attempt to identify the appropriate threshold for fibrinogen replacement.¹⁶ A recent systematic review comparing fibrinogen concentrates with cryoprecipitate in patients with bleeding¹⁰ identified 1 randomized trial (with high risk for bias)¹⁹ and 3 observational studies²⁵⁻²⁷ and concluded that there was insufficient evidence to recommend one product over the other. Another

review of trauma, obstetric, and gastrointestinal bleeding populations reached similar conclusions.⁹ This study provides further data regarding the comparative efficacy and adverse event profile of these 2 products.

The noninferiority finding can inform the choice of cryoprecipitate or fibrinogen concentrate for treatment of bleeding related to acquired hypofibrinogenemia. A core tenet and major regulatory driver in transfusion medicine is the precautionary principle that requires risk-mitigation strategies to be instituted even if there is only a theoretical risk of harm.²⁸ Consistent with this principle, the US Food and Drug Administration blood safety strategy recommends the use of pathogen-reduced blood products when feasible.²⁸ Currently, there are no known impending infectious threats for

recipients of cryoprecipitate; however, the history of blood pathogens suggests that plasma-derived products have transmitted pathogens in the past and may do so in the future.²⁹ In addition, mathematical models of emerging pathogens suggest that the association of plasma-derived products (such as cryoprecipitate) with outcomes and costs may be substantial.³⁰ In this regard, fibrinogen concentrate may be preferred to cryoprecipitate because it is pathogen-reduced. Another advantage of fibrinogen concentrate is that in most situations it can be logistically simpler to deliver to the bedside of a patient with bleeding. One important consideration is the cost differential that currently favors cryoprecipitate, but this varies across regions, and the most recent economic analysis failed to include the costs of future emerging pathogens and did not include comprehensive activity-based costing.³¹

Limitations

This study has several limitations. First, since the aim was to compare the 2 products when used under usual conditions of care, it was not logistically possible to institute a standardized transfusion protocol across the sites or to blind clinicians to treatment assignment. Although a post hoc analysis showed that there were treatment × site interactions, accounting for the interactions did not have a material effect on the primary outcome. Moreover, postoperative hemoglobin, platelet count, and coagulation measures were similar between groups (Table 2), suggesting that transfusion practice was consistent in both groups. In addition, the results were consistent when transfusions were measured from beginning of surgery to postoperative day 7 (a priori analysis) or after administration of investigational product (post hoc analysis), which suggests that lack of blinding did not influence the timing of transfusions relative to product administration. Of note, to ensure that all transfusions and adverse events were collected without bias, patients and outcome assessors were blinded to treatment allocation and independent monitors re-

viewed all transfusion and adverse events. Second, while the study had few exclusion criteria, it included only patients undergoing cardiac surgery with bleeding, and its findings may therefore not be generalizable to other settings where fibrinogen replacement is required. This would primarily be other types of surgery, trauma, and postpartum hemorrhage,³² but most evidence suggests that the role of fibrinogen is similar in these settings.^{33,34} Third, because of the pragmatic design of the study, strict timing of laboratory assessments could not be enforced. However, only less than 5% of patients had no measured fibrinogen levels before product administration. Related to this, a small proportion of patients had fibrinogen values above recommended thresholds when treatment order was received. However, this is consistent with recent experience in major bleeding,³² and ongoing bleeding from sample collection to therapy means that actual fibrinogen levels at the time of therapy were likely lower than measured values. Fourth, fibrinogen content is standardized in fibrinogen concentrate but is highly variable in cryoprecipitate. As a result, some patients in the cryoprecipitate group likely received much less or much more than 4 g of fibrinogen. While this is one of the inherent limitations of cryoprecipitate, observed differences in pretreatment and posttreatment fibrinogen levels suggest that on average both groups received clinically similar amounts of fibrinogen.

Conclusions

In patients undergoing cardiac surgery who develop clinically significant bleeding and hypofibrinogenemia after cardiopulmonary bypass, fibrinogen concentrate is noninferior to cryoprecipitate with regard to number of blood components transfused in a 24-hour period post bypass. Use of fibrinogen concentrate may be considered for management of bleeding in patients with acquired hypofibrinogenemia in cardiac surgery.

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