

STUDY PROTOCOL

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Fibrinogen concentrates versus cryoprecipitate for intraoperative hypofibrinogenemia in liver transplantation: study protocol for a randomized trial (FIBCRYO-LT trial)

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Abstract

Background Lyophilized factor concentrates, such as fibrinogen concentrate (FC), are considered superior to frozen products, such as cryoprecipitate, due to their rapid availability. Unlike frozen products, lyophilized factor concentrates do not require thawing or ABO blood type cross-matching, which can be time-consuming. We compared the time required for goal-directed management of hypofibrinogenemia using two strategies during liver transplantation (LT): a conventional cryoprecipitate-based strategy versus a lyophilized fibrinogen concentrate (FC)-based strategy.

Methods This randomized trial will be performed in a tertiary university hospital from December 2025 to June 2026. Patients undergoing liver transplantation (LT) who provide written informed consents and develop intraoperative coagulopathy requiring fibrinogen supplementation—defined as serum fibrinogen < 100 mg/dL in standard central lab (SCL) tests or citrated functional fibrinogen maximum amplitude < 15 mm on thromboelastography (TEG6S™)—will be enrolled and randomized (1:1) to receive either cryoprecipitate (Group- C) or fibrinogen concentrate (Group- L). The primary outcome is an inter-group comparison of the treatment time (T-time, the duration from ordering cryoprecipitate or fibrinogen concentrate (FC) to completing its intravenous administration). Secondary outcomes include perioperative bleeding, blood transfusion requirements, coagulation profiles, reoperation, thromboembolic complications, mortality, oxygenation profiles, fibrinolysis phenotypes, bleeding-related costs, and length of hospital stay.

Discussion A significantly shorter T-time in Group-L would support the superiority of the factor concentrate-based strategy for prompt intraoperative coagulation management during liver transplantation (LT). Its rapidity could reduce bleeding, transfusion requirements, and transfusion-related complications, thereby improving perioperative outcomes.

Trial registration This trial was registered on ClinicalTrials.gov with the registration number of NCT06144112 on November 16, 2023 (<https://classic.clinicaltrials.gov/ct2/show/NCT06144112>).

Keywords Liver transplantation, Clinical trial, Intraoperative hypofibrinogenemia, Fibrinogen, Lyophilized factor concentrates, Cryoprecipitate, Fresh frozen plasma, Thromboelastography, Viscoelastic test

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Administrative information

Title {1}	Fibrinogen concentrates versus cryoprecipitate for intraoperative hypofibrinogenemia in liver transplantation: study protocol for a randomized trial (FIBCRYO-LT trial)
Trial registration {2a and 2b}.	This trial was registered on ClinicalTrials.gov with the registration number of NCT06144112 on November 16, 2023 (https://classic.clinicaltrials.gov/ct2/show/NCT06144112).
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Role of sponsor {5c}	Konkuk University Medical Center sponsored this study and performed study design and management.

Introduction

Background and rationale {6a}

In managing coagulopathy and bleeding during liver transplantation (LT), any delay in restoring procoagulants aggravates dilutional coagulopathy and leads to increased bleeding and allogeneic plasma transfusion needs. Delayed coagulation management, in extreme cases, can create a vicious cycle that exacerbates bleeding and significantly increases the need for allogeneic transfusions. Therefore, promptly restoring plasma coagulation factors and avoiding delays in preparing therapeutic agents are essential to rapidly achieve their targeted therapeutic levels and effectively manage intraoperative coagulopathy and bleeding during LT.

Conventionally, transfusion of allogeneic frozen plasma products, such as fresh frozen plasma (FFP) and cryoprecipitate, has been employed to manage and correct coagulopathy. However, several limitations, such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO), compromise the efficacy of plasma-based coagulation management, and their risks sometimes exceed benefits [1–3].

Furthermore, extended preparation time required for ABO blood type cross-matching and thawing delays the administration of frozen plasma products. Clinically, these delays in preparing and administering frozen plasma products compromise the prompt correction of coagulopathy, may exacerbate overall bleeding, and can increase the total transfusion requirements in patients with severe coagulopathic bleeding. Even in the activation and application of the massive transfusion protocol (MTP) for bleeding caused by trauma, achieving the targeted MTP ratio of red blood cells (RBCs) to frozen plasma was difficult and unfeasible within half an hour in a previous study [4].

Fibrinogen concentrate (FC) is human plasma-derived, lyophilized factor concentrate that can be reconstituted rapidly at the bedside. It has beneficial features including ambient storage, rapid availability, and precise dosing. Most importantly, FC eliminates the need for time-consuming procedures associated with the use of cryoprecipitates, such as blood type cross-matching and thawing, and enables rapid administration on demand. Due to its fast availability, precise dosing, and a favorable safety profile, FC-based strategies have recently emerged as effective alternatives to plasma-based approaches for managing perioperative coagulopathy and bleeding [2, 5–9] A recent unblinded prospective trial demonstrated that prothrombin complex concentrate (PCC), another factor concentrate, had superior hemostatic efficacy and safety advantages to FFP for managing coagulopathic

bleeding during cardiac surgery [10]. However, few previous studies demonstrated the possible time-saving benefit of replacing frozen plasma products with lyophilized factor concentrates and analyzed their beneficial impacts on other clinical outcomes.

Objectives {7}

We hypothesize that the time required for ordering, delivering, and administering FC will be shorter than that required for cryoprecipitate during LT. Accordingly, the primary outcome of this trial is the comparison of effective treatment time (T-time), defined as the interval from ordering FC or cryoprecipitate for fibrinogen supplementation—based on coagulopathy diagnosed by standard central laboratory (SCL) or thromboelastography (TEG) tests—to the completion of administering the assigned product as part of goal-directed coagulation management in patients undergoing LT. Secondary outcomes include the amount of postoperative bleeding collected in the drainage during the first 24 h after surgery, the preparation time for FC and cryoprecipitate (from unpacking of FC in its storage area or the start of cross-matching and thawing of cryoprecipitate to the time of its delivery to patients in the operating room), dosages of FC and cryoprecipitate as the 1st coagulation management for supplementing fibrinogen, the success rate of the 1st coagulation management, the dosages of additional FC, cryoprecipitate, FFP, and platelets as the 2nd coagulation management, the incidences and total amounts of intraoperative and postoperative allogeneic transfusions (packed RBCs, FFP, cryoprecipitate, and platelets), the amount of intraoperative salvaged blood, the volume of intraoperative intravenous fluid used for resuscitation, urine output, the postoperative nadir hemoglobin level, reoperations due to bleeding, perioperative coagulation profiles (SCL tests and TEG tests, as well as the distribution of fibrinolysis phenotypes), and oxygenation parameters ($\text{PaO}_2/\text{FiO}_2$ ratio).

Tertiary prognostic outcomes include in-hospital mortality, 30-day mortality, myocardial infarction, stroke, pulmonary embolism, bowel infarction, delirium, acute kidney injury, need for renal replacement therapy, use of mechanical circulatory support, duration of mechanical ventilation, oxygenation profiles—including the lowest $\text{PaO}_2/\text{FiO}_2$ ratio recorded during the first 7 postoperative days or for the duration of mechanical ventilation, whichever is longer—length of intensive care unit and hospital stay, total cost of hospitalization, and costs related to bleeding management.

The translation of logistical advantages of FC is also analyzed as a measure of enhancing goal-directed coagulation management in patients undergoing LT.

Trial design {8}

This trial is an investigator-initiated, randomized, single-center, superiority study with two parallel groups with a 1:1 allocation ratio, conducted at a tertiary university hospital in Seoul, South Korea, for 12 months, from September 2025 to August 2026.

Protocol modification could be considered when requested by investigators only during the first week of recruitment. Since the main goal of this trial is to compare the treatment times of factor concentrate–based and frozen plasma–based strategies, perioperative management practices—including surgical techniques, anesthesia, transfusion practices, and coagulation management—are not strictly standardized apart from the administration of the study interventions. However, institutional protocols for perioperative transfusion and coagulation management are based on current guidelines [11].

Methods: participants, interventions, and outcomes

Study setting {9}

This randomized trial will be performed in a tertiary university hospital. The data from this study and perioperative information are conveyed to the contract research organization (CRO, Helptrial Co., Seoul, Korea) using an electronic case report form (e-CRF, product name™, Helptrial Co., Seoul, Korea). An overview of the trial enrollment, treatment, and follow-up processes is presented in Fig. 1. The data collected will be retained until the end of the data collection period.

Eligibility criteria {10}

Patients aged 19 years or older who are scheduled for LT will be eligible for enrolment. Detailed eligibility, inclusion, and exclusion criteria are as follows. Eligibility includes adult patients undergoing elective LT and patients who signed informed consent for the study. Written informed consent to participate will be obtained from all participants during the preoperative visit. Inclusion criteria include intraoperative bleeding with coagulation dysfunction, as diagnosed by SCL or TEG tests, defined as a serum fibrinogen level < 100 mg/dL on SCL testing or a CFF-MA < 15 mm on TEG (TEG6S™, Haemonetics Corp., USA).

Exclusion criteria include pregnancy, refusal of allogeneic blood transfusion, administration of thrombin, history of myocardial ischemia or infarction, history of ischemic stroke within 30 days, history of thromboembolism, familial history of hypercoagulation, and heparin-induced thrombocytopenia.

The primary investigator, a senior investigator, along with certified research associates, is responsible for screening patients eligible for inclusion.

Who will take informed consent? {26a}

All investigators (anesthesiologists) will explain trial details and will obtain written informed consent from potential eligible participants.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This trial does not consider collecting or using participant data and biological specimens in ancillary studies.

Interventions**Explanation for the choice of comparators {6b}**

Lyophilized factor concentrates, such as fibrinogen concentrate (FC), are considered superior to frozen products, such as cryoprecipitate, due to its rapid availability. Unlike frozen products, lyophilized factor concentrates do not require ABO blood type cross-matching or thawing, which can be time-consuming.

We hypothesize that the time required for ordering, delivering, and administering FC will be shorter than that required for cryoprecipitate during LT. Accordingly, the primary outcome of this trial is the comparison of effective treatment time, defined as the interval from ordering FC or cryoprecipitate for fibrinogen supplementation—based on coagulopathy diagnosed by standard central laboratory (SCL) or thromboelastography (TEG) tests—to the completion of administering the assigned product as part of goal-directed coagulation management in patients undergoing LT.

Intervention description {11a}

Patients undergoing LT with signed informed consents and showing intraoperative coagulopathy (serum-fibrinogen < 100 mg/dl in SCL tests or CFF-MA < 15 mm in TEG test) will be included. After being included in the study, the participants are randomly allocated into one of two groups. The participants are randomly assigned to either Group-C or Group-L (with a 1:1 allocation ratio) through the web-based randomization system managed by the CRO (<https://icreat2.nih.go.kr/>): patients in Group-C will receive conventional cryoprecipitate and those in Group-L will receive FC.

TEG tests, with or without SCL tests, are performed at the following stages: before the skin incision, every 2 h after the skin incision, start of the an-hepatic phase, 1 h after the an-hepatic phase, 3 h after the an-hepatic phase, 5 min after the reperfusion phase, 1 h after the reperfusion phase, 3 h after the reperfusion phase, and at the end of surgery. Additional TEG tests can be performed at the need of the attending anesthesiologist.

TEG tests include reaction-time (R-time), lysis at 30 min after the maximal amplitude (LY30) in the citrated kaolin (CK) assay, the maximal amplitude (MA) in the citrated functional fibrinogen (CFF) assay, and MA in the citrated rapid TEG (CRT) assay. SCL test includes prothrombin time-international normalized ratio (PT-INR), platelet concentration, and serum-fibrinogen level.

When SCL or TEG testing in the setting of ongoing or massive intraoperative bleeding indicates hypofibrinogenemia—defined

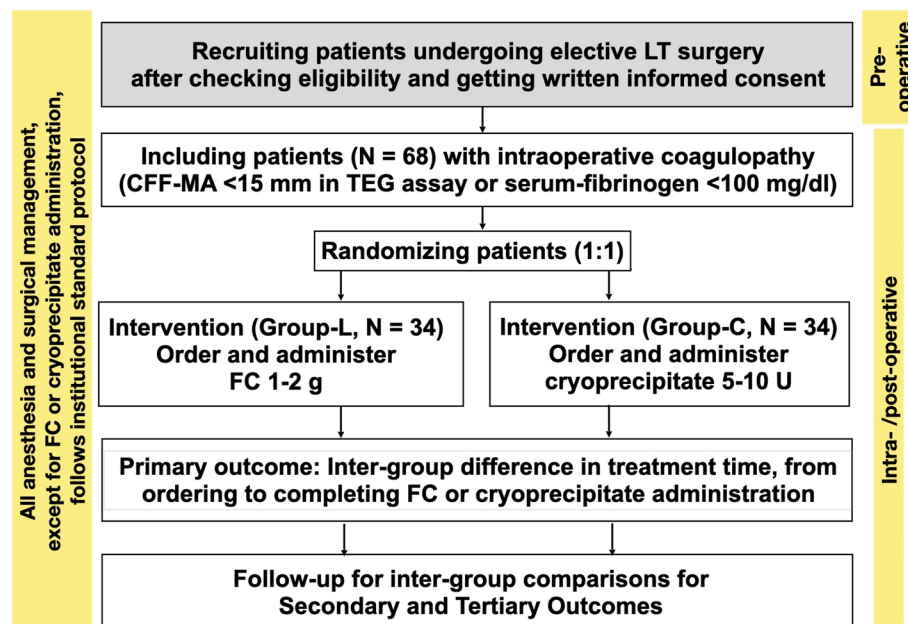


Fig. 1 A study flow chart for eligibility, randomization, interventions, and follow up. FC: fibrinogen concentrate, CFF: citrated functional fibrinogen assay, LT: liver transplantation, MA: maximal amplitude, TEG: thromboelastography

as serum fibrinogen < 100 mg/dL on SCL testing or CFF-MA < 15 mm on TEG testing—the patient meeting these criteria is enrolled in the study.

The senior investigator confirms the group assignment and conveys the group assignment information to the attending anesthesiologists. Attending anesthesiologists administer FC in Group-L or cryoprecipitate in Group-C, respectively, according to the patient's group assignment.

The dosages of each procoagulant are as follows: 1–2 g of FC for 60–80 kg; and 5–10 U of cryoprecipitates 5–10 U for 60–80 kg.

Figure 1 summarizes the study interventions.

Criteria for discontinuing or modifying allocated interventions {11b}

If there is diffuse oozing or massive bleeding after administering 2 g of FC 2, at the discretion of the attending anesthesiologists, additional coagulation management will be provided by administering FFP or cryoprecipitate in both groups. If a patient wants to withdraw from the study, participation can be terminated. The reason for withdrawal will be reported. All withdrawn participants will be managed in accordance with the institutional standard procedures. In other cases where modification or discontinuation of interventions is considered beneficial in patients' clinical outcomes or is necessary for patient management in certain cases, the senior investigator and attending anesthesiologists will intervene accordingly.

Strategies to improve adherence to interventions {11c}

As the study intervention is administered intraoperatively according to a predefined transfusion protocol, participant-related non-adherence is not anticipated. The attending anesthesiologist will determine whether fibrinogen replacement is needed based on the coagulation test results provided by the research personnel. Once eligibility for fibrinogen replacement is confirmed, randomization will be performed using the web-based randomization system. At least two study personnel will independently verify the randomized group allocation before prescribing fibrinogen concentrate or cryoprecipitate. For the administration of fibrinogen concentrate, participant registration in the institutional clinical research management system at Samsung Medical Center is required prior to prescribing. Because fibrinogen concentrate can only be prescribed after registration in the institutional participant management system, protocol violations related to study intervention allocation can be effectively prevented. Any protocol deviations or unblinding events will be documented, reported to the principal investigator, and considered in the per-protocol analysis.

Relevant concomitant care permitted or prohibited during the trial {11d}

Since the main goal of the trial is to compare the treatment times of factor concentrate-based and frozen plasma-based strategy, apart from their administration, strategies and disciplines for perioperative patient management, such as surgical procedures, anesthesia, transfusions, and coagulation management, are not strictly controlled. However, institutional protocols for perioperative transfusion and coagulation management are based on current guidelines [11].

Provisions for post-trial care {30}

All participants who suffered any harm will be compensated by the coverage of the contracted insurance company (Hyundai Marine and Fire Insurance Group, contract number F-22CT-00000171).

Outcomes {12}

The trial compares clinically meaningful and objective outcome measures.

The primary outcome of this trial is the comparison of effective treatment time (T-time), defined as the interval from ordering FC or cryoprecipitate for fibrinogen supplementation—based on coagulopathy diagnosed by standard central laboratory (SCL) or thromboelastography (TEG) tests—to the completion of administering the assigned product as part of goal-directed coagulation management in patients undergoing LT.

Secondary outcomes include the amount of postoperative bleeding collected in the drainage during the first 24 h after surgery, the preparation time for FC and cryoprecipitate (from unpacking of FC in its storage area or the start of cross-matching and thawing of cryoprecipitate to the time of its delivery to patients in the operating room), dosages of FC and cryoprecipitate as the 1st coagulation management for supplementing fibrinogen, success rate of 1st coagulation management for fibrinogen supplementation (achieving serum-fibrinogen > 100 mg/dl in SCL tests or CFF-MA > 15 mm in TEG tests), dosages of additional FFP, cryoprecipitate, and platelets for relieving coagulopathy as the 2nd coagulation management, the incidences and total amounts of allogeneic transfusions (packed RBCs, FFP, cryoprecipitate, and platelets) during intraoperative period and within 24 h postoperatively (packed RBCs, FFP, cryoprecipitate, and platelets), changes of hemoglobin level and coagulation profiles after administering FC or cryoprecipitate (SCL tests and TEG tests, as well as the distribution of fibrinolysis phenotypes), the amount of intraoperative salvaged blood, the volume of intraoperative intravenous fluid used for resuscitation, urine output, the postoperative nadir hemoglobin level,

reoperations due to bleeding, perioperative coagulation profiles (SCL tests and TEG tests, as well as the distribution of fibrinolysis phenotypes), and oxygenation parameters (PaO₂/FiO₂ ratio). The preparation time, from the start of cross-matching and thawing of cryoprecipitate or unpacking of FC in its storage area, to the time of its delivery to patients in the operating room, is also included.

Tertiary prognostic outcomes include in-hospital mortality, 30-day mortality, myocardial infarction, stroke, pulmonary embolism, bowel infarction, delirium, acute kidney injury, renal replacement therapy, applications of mechanical circulatory support, duration of mechanical ventilation, oxygenation profiles including the lowest PaO₂/FiO₂ ratio recorded during the first 7 postoperative days or up to the duration of mechanical ventilation, whichever is longer, length of intensive care unit and hospital stay, total cost of hospitalization and that for getting bleeding management.

Detailed definitions of the outcomes are provided in Tables 1 and 2.

Participant timeline {13}

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT**	Pre-operative	Intra-operative	Intra-operative	Post-operative 7 days or discharge	Post-operative 30 days	
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Inclusion at bleeding and coagulopathy		X				
Allocation		X				
INTERVENTIONS:						
Group-C			X			
Group-L			X			
ASSESSMENTS:						
Baseline variables	X	X				
Primary outcome			X			
Secondary outcomes			X	X	X	
Tertiary outcomes				X	X	
Transferring institutional data to CRO						
Data analyses						
Statistical consultation						

Sample size {14}

In a preliminary review of electronic medical records from 5 patients who underwent liver transplantation, the time from the ordering cryoprecipitate to the completion of administration for managing associated coagulopathy was 60.2 ± 12.7 min. This study

investigates whether a strategy using FC can reduce the time to manage coagulation by 10 min. Assuming the standard deviation of the treatment time of the plasma-based strategy (employing cryoprecipitate) is equal to that of the lyophilized factor concentrate-based strategy (employing FC), the estimated effect size (Cohen's *D*) was 0.79. The required sample size was calculated to be 27 patients per group, applying a two-sided significance level of 5% and a statistical power of 80%. Accounting for a dropout rate of 20%, the total sample size was determined to be 68 patients.

Recruitment {15}

All patients aged 19 years or older scheduled for elective LT at Samsung Medical Center during the study period will be screened consecutively for eligibility and recruited. The principal investigator, a senior investigator, along with certified research associates, will identify potentially eligible participants through regular review of the liver transplantation surgical schedule. Written informed consent to participate will be obtained from all participants during the preoperative visit.

To facilitate adequate enrollment, scheduled liver transplantation cases will be routinely screened in advance through close coordination with the liver transplantation surgical and anesthesiology teams. Because Samsung Medical Center is a high-volume liver transplantation center, adequate participant recruitment is anticipated during the study period. If recruitment is slower than anticipated, the recruitment period may be extended to achieve the target sample size.

Detailed eligibility, inclusion, and exclusion criteria are as follows. Exclusion criteria include pregnancy, refusal of allogenic blood transfusion, administration of thrombin, history of myocardial ischemia or infarction, history of ischemic stroke within 30 days, familial history of hypercoagulation, and heparin-induced thrombocytopenia.

The primary investigator, a senior investigator, along with certified research associates, is responsible for screening patients eligible for inclusion and recruitment.

Assignment of interventions: allocation

Sequence generation {16a}

The randomization sequence for allocation is generated using a computerized random number generator by an independent statistician in the CRO. The participants are randomly assigned to either Group-C or Group-L (with a 1:1 allocation ratio) through the web-based randomization system managed by the CRO (<https://icreat2.nih.go.kr/>).

Concealment mechanism {16b}

Other investigators other than the senior investigator cannot access the randomization sequences and the

Table 1 Primary and secondary outcomes

Outcomes	Definition
Primary outcome	
Treatment time (min)	The duration from the time of diagnosing coagulopathy, as determined by SCL tests or TEG, to the time of the complete administration of cryoprecipitate or FC
Secondary outcomes	
Success rate as the 1st coagulation management	Incidence of achieving serum-fibrinogen > 100 mg/dl or CFF-MA > 15 mm, respectively
Preparation time	Duration from the start of cross-matching and thawing of cryoprecipitate or unpacking of FC in its storage area to its delivery to patients in the operating room
Postoperative bleeding	Volume of postoperative bleeding collected in the drainage during the first 6 and 24 h after surgery (mL)
Incidence of transfusion	Patients who had intraoperative and postoperative transfusion until discharge: packed RBC, FFP, platelet, and cryoprecipitate (number of patients, %)
Amount of transfusion	Amount of intraoperative and postoperative transfused packed RBC, FFP, platelet, and cryoprecipitate per patient until discharge (units)
Amount of intraoperative salvaged blood	Volume of intraoperatively salvaged and reinfused blood (ml)
Postoperative nadir hemoglobin value	Lowest hemoglobin level measured during the first 24 h after surgery (g/dl)
Reoperation due to bleeding	Patients who underwent reoperation due to postoperative bleeding (number of patients, %)
Perioperative coagulation profiles	The following coagulation profiles will be compared immediately after anesthesia induction, before and after weaning from cardiopulmonary bypass, and at the end of surgery
Standard laboratory test	Hemoglobin (g/dl), prothrombin time (INR), activated partial thromboplastin time (sec), serum fibrinogen level (mg/dl), and platelet counts (/μl)
TEG test	Values of TEG tests including CK R-time (min), CK MA (mm) CRT MA (mm), CFF MA (mm); CK LY30 (%)
Fibrinolysis phenotypes	Hyperfibrinolysis: CK LY30 < 85% Physiologic fibrinolysis: CK LY30 of 85–97.9% Fibrinolysis shutdown: CK LY30 ≥ 98%

CFF assay citrated functional fibrinogen assay, *CK* citrated kaolin, *CRT assay* citrated rapid TEG assay, *FFP* fresh frozen plasma, *LY30* lysis at 30 min after the maximal amplitude, *MA* maximal amplitude, *R-time* reaction-time, *RBC* red blood cell

group assignment, which are secured on the web-based randomization system, till the end of data acquisition. The group assignment also remains confidential and blinded to the following individuals: participants, nursing and medical staff in the intensive care unit, and outcome assessors.

Implementation {16c}

Patients undergoing LT with signed informed consents and showing intraoperative coagulopathy (serum-fibrinogen < 100 mg/dl in SCL tests or CFF-MA < 15 mm in TEG test) will be included. After being included in the study, the participants are randomly allocated into one of two groups. The randomization sequence is generated using a computerized random number generator by an independent statistician in the CRO. The participants are randomly assigned to either Group-C or Group-L (with a 1:1 allocation ratio) through the web-based randomization system managed by the CRO (<https://icreat2.nih.gov/kr/>): patients in Group-C will receive conventional cryoprecipitate and those in Group-L will receive FC.

A senior investigator, responsible for ensuring compliance with the institutional protocol, refrains from making

any perioperative adjustments and oversees the randomization process. According to the group assignments, the senior investigator oversees perioperative anesthesia and coagulation management. Other investigators cannot access the randomization sequences and the group assignment, which are secured on the web-based randomization system, till the end of data acquisition. The group assignment also remains confidential and blinded to the following individuals: participants, nursing and medical staff in the intensive care unit, and outcome assessors. However, if unblinding is beneficial to patients' clinical outcomes or is necessary for patient management in certain cases, the information on the group assignment can be disclosed. All unblinded cases are reported to the principal investigator and excluded from the per-protocol analysis.

Assignment of interventions: blinding

Who will be blinded {17a}

The senior investigator oversees perioperative anesthesia and coagulation management. Other investigators cannot access the randomization sequences and the group

Table 2 Tertiary prognostic outcomes

Outcomes	Definition
In-hospital mortality	Death due to any cause during hospitalization (number of patients, %)
Postoperative death	30-day mortality: patients who expired within 30 days after surgery (number of patients, %)
Myocardial infarction	Patients with following episodes: Type 5 periprocedural myocardial infarction within postoperative 48 h defined by Valve Academic Research Consortium (VARC) 3; In patients with normal baseline CK-MB, the peak CK-MB measured within 48 h of the procedure $\geq 10 \times$ the local laboratory ULN or CK-MB $\geq 5 \times$ ULN with one or more of the following: New pathologic Q-waves in ≥ 2 contiguous lead, new persistent LBBB, flow-limiting angiographic complications in a major epicardial vessel or > 1.5 mm diameter branch, substantial new loss of viable myocardium on imaging related to the procedure. In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to $\geq 70 \times$ the local laboratory ULN or $\geq 35 \times$ ULN with one or more of the above criteria. In patients with elevated baseline CK-MB (or cTn), the CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described. (number of patients, %)
Stroke	Patients with following episodes until discharge: sudden onset of neurological signs or symptoms with neuroimaging confirmation of CNS infarction in the corresponding vascular territory; symptomatic ICH and SAH; symptomatic hypoxic-ischemic injury (non-focal neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death confirmed by neuroimaging); or persistent (> 24 h) neurologic deficit presumed to be ischemia or hemorrhage (e.g., no neuroimaging) (number of patients, %)
Pulmonary embolism	Definite pulmonary embolism in the enhanced CT or angiogram or high probability ventilation-perfusion scan until discharge (number of patients, %)
Bowel infarction	Bowel resection surgery or bowel infarction confirmed by imaging until discharge (number of patients, %)
Delirium	Positive screening result on the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) or a diagnosis confirmed by psychiatrist or neurologist until discharge (number of patients, %)
Acute kidney injury	Defined by KIDGO serum creatinine criteria; 0.3 mg/dL increase within 48 h or ≥ 1.5 times baseline within 7 days (number of patients, %)
Renal replacement therapy	Need for renal replacement therapy until discharge (number of patients, %)
Mechanical circulatory support	Need for mechanical circulatory support such as extracorporeal membrane oxygenation, intra-aortic balloon pump, ventricular assist device until discharge (number of patients, %)
Duration of mechanical ventilation	Total time (hour) a patient supported by a mechanical ventilator
Oxygenation profile	PaO ₂ /FiO ₂ ratio at the admission to the ICU
Length of the ICU stay	Total time (hour) a patient spends in the ICU from admission to discharge
Length of the hospital stay	Total time (day) a patient spends from surgery to discharge
Total cost (Korean Won, USD)	Total cost associated with a patient's entire hospital stay
Cost for bleeding management (Korean Won, USD)	Cost related to bleeding management (cost associated with the coagulation test, allogeneic blood products, antifibrinolytic agents, and lyophilized blood products)

CAM confusion assessment method, CK-MB creatine kinase-MB, CNS central nervous system, CT computed tomography, cTn cardiac troponin, ECG electrocardiogram, FiO₂ fraction of inspired oxygen, ICH intracranial hemorrhage, ICU intensive care unit, KIDGO Kidney Disease: Improving Global Outcomes, LBBB left bundle branch block, PaO₂ partial pressure of oxygen in arterial blood, SAH subarachnoid hemorrhage, UNL upper limit of normal

assignment, which are secured on the web-based randomization system, till the end of data acquisition. The group assignment also remains confidential and blinded to the following individuals: participants, nursing and medical staff in the intensive care unit, and outcome assessors. The CRO independently monitors the conveyed data from the institution and keeps the data confidential in the registry.

Procedure for unblinding if needed {17b}

If unblinding is beneficial to patients' clinical outcomes or is necessary for patient management in certain cases, the information on the group assignment can be disclosed. All unblinded cases are reported to the principal investigator and excluded from the per-protocol analysis.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All collected data are conveyed to the CRO data registry through e-CRF. The participant's follow-up is scheduled 24 and 48 h after surgery, discharge, or 30 days after surgery or death. The following data are included in the e-CRF: admission date, surgery data, dates of in-hospital and out-of-hospital death, discharge date, last follow-up date, discharge destination (home, other facility), and discharge status (completely recovered, incompletely recovered: risk of out-of-hospital death related to the surgery).

The Trial Steering Committee (TSC), consisting of primary and other investigators, reviews the trial's course each month to oversee its conduct and progress. There

is no Stakeholder and Public Involvement Group (SPIG). Adverse events and serious adverse events (SAEs) are monitored and collected. The CRO independently monitors data provided by the institution and maintains the confidentiality of the data in the registry. The CRO is independent from the sponsor and competing interests.

Patient data are entered into a blank e-CRF in a web-based data entry program. The data are collected and delivered to the CRO through the web-based system (MyTrial™, San Diego, USA). The data are stored after repeated query management processes between the CRO and the senior investigator. Data completeness and accuracy will be ensured through regular data verification procedures, repeated query management processes between the CRO and investigators, and independent monitoring by the CRO, principal investigator, and DSMB.

The CRO independently manages the data received from the institution and keeps it confidential. The CRO performs medical coding once data entry is complete and the rate of erroneous data is acceptable (less than 0.1%).

The trial will not perform an interim analysis. The principal investigator, senior investigators, CRO, and the data safety and monitoring board (DSMB) monitor the adherence to the trial protocol. The primary investigator will access the stored data regularly.

Plans to promote participant retention and complete follow-up {18b}

Every reasonable effort will be made to maintain protocol compliance and retain patient participation in the trial. If a patient wants to withdraw from the study, participation can be terminated. The reason for withdrawal will be reported. All withdrawn participants will be managed in accordance with the institutional standard procedures.

Unblinded cases will be reported to the primary investigator and classified as a protocol violation. These cases will remain in the intention-to-treat (ITT) analysis as the primary analysis. In addition, a separate as-treated analysis will be performed to evaluate the impact of the treatment actually received, and the results from both analyses will be compared.

The participant's follow-up is scheduled 24 and 48 h after surgery, discharge, or 30 days after surgery or death. The following data are included in the e-CRF: admission date, surgery data, in-hospital and out-of-hospital dates of death, discharge date, last follow-up date, discharge destination (home, other facility), discharge status (completely recovered, incompletely recovered: risk of out-of-hospital death related to the surgery).

Data management {19}

Patient data are entered into a blank e-CRF in a web-based data entry program. The data are collected and delivered to the CRO through the web-based system (MyTrial™, San Diego, USA). The data are stored following repeated query-management processes between the CRO and the senior investigator. The participant's postoperative follow-up is scheduled regularly for up to 30 days after the surgery.

The CRO independently manages the data received from the institution and keeps it confidential. The CRO performs medical coding once data entry is complete and the rate of erroneous data is acceptable (less than 0.1%).

Confidentiality {27}

No identifying images or other personal or clinical details of participants are presented in this trial or will be presented in reports of the trial results. The participant information materials and informed consent forms are available from the corresponding author on request. All data and materials will be available in clinicaltrials.gov after the completion of the trial.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable (These issues were not described because the current trial does not store biological specimen for other purposes.)

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary analyses will adhere to an intention-to-treat (ITT) approach, including all randomized participants regardless of the treatment they ultimately received. Additional secondary analyses will focus on the as-treated population, which comprises individuals who received the treatment irrespective of their initial randomization, and the per-protocol population, which excludes participants due to factors like non-compliance, lack of adherence, or incomplete data.

We will present continuous variables using descriptive statistics, including the mean and standard deviation, with group differences evaluated using the *t*-test or the Wilcoxon rank sum test, depending on the data distribution. Normality will be assessed using the Shapiro–Wilk test, and appropriate transformations (e.g., log transformation) will be applied if necessary. Outliers will be identified based on predefined criteria and either excluded or

addressed separately in sensitivity analyses. Categorical variables will be expressed as frequencies and percentages, and group differences will be assessed using the chi-squared test or Fisher's exact test, as applicable. To adjust for confounding factors, linear regression will be utilized to compare mean times between the groups as needed. For variables measured repeatedly over time or across different phases, mixed-effects models will be employed to account for within-subject correlations.

All statistical analyses will include the relevant statistics, estimated differences, *p*-values, and effect sizes. Estimates will be reported along with their corresponding 95% confidence intervals. Multiple testing corrections will be applied using the Benjamini–Hochberg procedure to control the false discovery rate (FDR). Statistical significance will be defined as a two-sided *p*-value less than 0.05. Analyses will be conducted using R version 4.4.2 or later (R Foundation for Statistical Computing).

Interim analyses {21b}

The trial will not perform an interim analysis. The principal investigator, senior investigators, CRO, and the DSMB monitor the adherence to the trial protocol. The primary investigator will access the stored data regularly.

Methods for additional analyses (e.g., subgroup analyses) {20b}

SPIRIT guidance: Methods for any additional analyses (e.g., subgroup and adjusted analyses). The trial does not plan to perform any additional analyses.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Cases that fail to adhere to the protocol will be reported to the primary investigator and classified as a protocol violation. These cases will remain in the ITT analysis as the primary analysis. In addition, a separate as-treated analysis will be performed to evaluate the impact of actual treatment received, and the analyzed results from both will be compared.

In this study, missing data are anticipated due to incomplete measurements, early transfer of patients from the operating room, or technical errors. To address this, adjustments for missing data will involve both complete case analysis and multiple imputations, with sensitivity analyses conducted to ensure robustness. The patterns of missingness will be evaluated to determine whether the data is missing completely at Random, missing at random, or missing not at random. Descriptive statistics and visualization techniques, such as missingness heatmaps, will be used to assess the extent and nature of the missing data. Additionally, Little's MCAR (missing completely at

random) test will be applied to evaluate the randomness of missingness.

Multiple Imputation using Chained Equations (MICE) will serve as the primary method for missing data replacement. Predictive models will incorporate relevant covariates, and mixed-effects imputation methods will be applied for hierarchical or repeated-measures data to account for group-level clustering and within-subject correlations. The quality of imputations will be assessed by comparing the distributions of observed and imputed data, and Rubin's Rules will be used to combine results from the imputed datasets.

We will conduct sensitivity analyses to evaluate the robustness of our findings under various assumptions and imputation scenarios. Complete case analysis will provide a baseline for comparison by excluding cases with missing data. Extreme-case imputations will test the influence of assumptions by replacing missing values with the variable's maximum and minimum plausible values. These analyses will assess the potential impact of missing data on the study's conclusions, ensuring the robustness of our findings.

To further ensure the consistency of results, sensitivity analyses will compare outcomes across different imputation models, such as fixed-effects and mixed-effects approaches. Key differences in results across these models will be documented and analyzed, reinforcing the validity of the findings under varying assumptions. This thorough approach to handling missing data will enhance the reliability and credibility of the study's results.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

All data and materials will be available in clinicaltrials.gov after the completion of the trial.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The trial is performed in a single tertiary institution. The principal investigator, senior investigators, CRO, and the DSMB monitor the adherence to the trial protocol. The primary investigator will access the final data registry after the completion of data acquisition and storage. The Trial Steering Committee (TSC), consisting of primary and other investigators, reviews the trial's course to oversee its conduct and progress every month (online or offline). There is no Stakeholder and Public Involvement Group (SPIG). The CRO independently monitors the conveyed data from the institution and keeps the data confidential in the registry.

Composition of the data monitoring committee, its role, and reporting structure {21a}

Along with the principal investigator, senior investigators, and CRO, the DSMB monitors adherence to the trial protocol. All adverse events will be reported to the CRO and the DSMB. DSMB audits the reported data related to adverse events. SAEs are directly reported to the PI and the DSMB, and the follow-up data should be reported after 24 h. The trial will be paused till the judges of the DSMB allow it to continue.

Adverse event reporting and harms {22}

Any unexpected adverse event not included in the trial outcomes will be reported through the e-CRF form by the participants or attending anesthesiologists, surgeons, and nursing staff. The CRO regularly communicates the event to the primary investigator and the Korea Health Industry Development Institute, which includes experts in anesthesia practice and anesthetic pharmacology, free of conflict of interest, monthly, to obtain feedback from the DSMB. All adverse events will be reported to the CRO and the DSMB. DSMB audits the reported data related to adverse events.

SAE is defined as any untoward medical occurrence or effect that results in death, is life-threatening (at the time of the event), prolongs the length of hospital stay, or results in persistent or significant disability or incapacity, or any other important medical event that does not result in any of the outcomes listed above. SAEs are directly reported to the PI and the DSMB, and the follow-up data should be reported after 24 h. The trial will be paused till the judges of the DSMB allow it to continue. SAEs are also reported to the IRB within 24 h.

Frequency and plans for auditing trial conduct {23}

Any unexpected adverse event not included in the trial outcomes will be reported via the e-CRF form by participants or by attending anesthesiologists, surgeons, and nursing staff. Formal adverse event coding systems, such as the Medical Dictionary for Regulatory Activities (MedDRA) or the Common Terminology Criteria for Adverse Events (CTCAE), will not be used in this study. Instead, harms and adverse events will be assessed and recorded according to predefined clinical outcome definitions and the institutional adverse event reporting procedures of Samsung Medical Center. The CRO regularly communicates the event to the primary investigator and the Korea Health Industry Development Institute, which includes experts in anesthesia practice and anesthetic pharmacology, free of conflict of interest, monthly, to obtain feedback from the DSMB. All adverse events will be reported to the CRO and the DSMB. DSMB audits the reported data related to adverse events.

In addition, the TSC reviews trial conduct, protocol adherence, recruitment progress, and data quality monthly throughout the study period. The CRO and DSMB independently monitor study conduct and protocol deviations during the trial.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Protocol modification may be considered by investigators only during the first week of recruitment.

Dissemination plans {31a}

All data and materials will be available in clinicaltrials.gov after the completion of the trial.

Discussion

During a progressive hemodilution, as occurs with massive bleeding and IV fluid resuscitation, fibrinogen is the first coagulation factor to fall to critically low levels, resulting in hypofibrinogenemia. Therefore, fibrinogen should be supplemented early during coagulopathy caused by severe bleeding to prevent further deterioration of coagulation status and ongoing hemorrhage.

Either cryoprecipitate or FC can be used to manage perioperative hypofibrinogenemia, depending on regional or local availability. However, there has been a trend shifting from a plasma-based strategy to an FC-based strategy. The latest update in major guidelines for major bleeding and coagulopathy following trauma newly recommended the use of FC rather than cryoprecipitate or FFP for managing hypofibrinogenemia [7–9]. This paradigm shift was effective in managing coagulopathy, reducing the total amount of blood products required, decreasing the number of patients who need transfusions, and decreasing the incidence of circulatory overload in postpartum bleeding [12].

Compared to the conventional plasma-based strategies requiring the time-consuming preparation process, including cross-matching and thawing, FC's feature would provide a more rapid and appropriate correction of perioperative factor deficiency and coagulopathic bleeding. A key advantage of FC is that it can be stored at ambient temperature, eliminating the need for freezers or thawing devices. This greatly improves its readiness and availability, allowing for faster administration across a wide range of clinical settings. FC's precise dosing feature is also beneficial for rapidly correcting coagulopathy in a predictive manner, even during ongoing massive bleeding.

Meanwhile, in a recent trial comparing PCC and FFP for coagulopathic bleeding in cardiac surgery, the median times from the end of CPB to administration were similar

(41 vs. 45 min, respectively). However, the median time required to complete administration was shorter for PCC than for FFP (7 vs. 26 min) [10]. This interpretation, however, must consider potential bias: many institutions implement clinical pathways in which ABO-matched FFP is thawed pre-emptively—before overt bleeding or the need for coagulation management becomes apparent—specifically for surgeries with a high risk of intraoperative bleeding. This early thawing practice can artificially shorten the apparent administration time for FFP. Most institutions use more proactive pathways to prevent delays in administering frozen plasma and to reduce the risk of adverse outcomes.

Institutional variations in how frozen plasma is prepared, thawed, and supplied can affect the timeliness of factor concentrate administration. Factors such as the type of thawing device used (warm-water bath or microwave) and the location of thawing (remote or within the operating theater) contribute to these differences [13].

To achieve an effective improvement in coagulopathy, administering a relatively large volume of cryoprecipitate or FFP is required. This larger volume, sometimes inducing TACO, dilutes other blood components (e.g., RBCs and platelets), resulting in a paradoxical increase of allogeneic transfusion [1, 2]. In addition to the absence of time-consuming preparation processes, FC's small-volume, high-concentration features would be beneficial in avoiding iatrogenic dilution of RBCs and platelets, caused by transfusion of cryoprecipitates and FFP for managing coagulopathy. Factor concentrates reduce iatrogenic dilution of RBC and other plasma components compared to frozen plasma products in coronary artery bypass surgery [2]. A recent trial demonstrated superiority of PCC to FFP in hemostatic efficacy and safety in patients requiring coagulation factor replacement during cardiac surgery [10].

There is a growing concern about the seriousness of various transfusion-related adverse effects upon using allogeneic plasma products, such as cryoprecipitate and FFP. The simultaneous administration of cellular components contained in donor plasma products can increase the risk of TRALI, which remains the leading cause of transfusion-related mortality associated with plasma-containing blood products. Given its lack of cellular blood components and cytokines, along with its pathogen-free formulation, FC offers a substantially safer profile than conventional cryoprecipitate. These characteristics reduce the risk of transfusion-related reactions—including TRALI—and minimize the potential for bacterial or viral transmission [14, 15]. In addition, its high-concentration, low-volume formulation, greater purity, improved efficacy, and enhanced safety profile

provide clear advantages from a patient blood management (PBM) perspective.

As in the review of 21 major randomized trials, FC did not increase the occurrence of perioperative thrombosis [13]. Even in LT, FC did not increase the incidence of thromboembolic events compared to cryoprecipitate [16]. PCC and FC provided more effective management of excessive post-CPB bleeding and reduced the requirement of allogeneic blood transfusion, without increasing thromboembolic events, in cardiac surgery [1, 17].

As secondary outcomes, this trial evaluates the relative rapidity of administering FC versus cryoprecipitate in relation to postoperative bleeding and total allogeneic transfusion requirements. It also examines the impact of each treatment on adverse outcomes, including mortality, thromboembolic events, lung injury, oxygenation profiles, and fibrinolysis. Differences between the groups in these outcomes may highlight the advantages of an FC-based strategy over a cryoprecipitate-based strategy in managing coagulopathy and reducing transfusion-related risks and adverse effects. These measures would support the superiority of FC over conventional plasma products in promoting PBM and patient safety in LT.

Intraoperative algorithms employing POC viscoelastic testing (VETs), such as TEG and ROTEM, enable prompt goal-directed bleeding and coagulation management in LT [18–23]. VETs tend to underestimate coagulation capacity compared to conventional laboratory tests in patients undergoing LT [24]. However, VETs rapidly capture the balance between procoagulants and anticoagulants of the whole blood and provide valuable information regarding the dynamic changes in fibrinolysis status during LT [25, 26]. This trial also evaluates whether using FC enhances the efficacy of POC VET in prompt coagulopathic management in LT. Positive findings of this trial would provide a foundation for subsequent trials assessing direct hemostatic efficacy and long-term outcomes, as well as for economic analyses and broader clinical adoption.

Trial status

This trial was registered in the clinical registration on November 16, 2023 (clinicaltrials.gov, NCT06144112) and it was revised to the second version of its protocol (version No. 1.2) on November 20, 2024. The trial was revised to the third version (version No. 2) with a modified title in June 2025. It was revised to the fourth version on Jul 16, 2025. The trial was approved by the institutional review board (IRB) of Samsung Medical Center (SMC 2025-03–126-002, June 2, 2025). Its recruitment will start on December 1, 2025, and be completed on June 31, 2026.

Abbreviations

CFF assay	Citrated functional fibrinogen assay
CK assay	Citrated kaolin assay
CPB	Cardiopulmonary bypass
CRT assay	Citrated rapid TEG assay
CRO	Clinical research organization
DSMB	Data safety and monitoring board
e-CRF	Electronic case report form
FC	Fibrinogen concentrate
FDR	False discovery rate
FFP	Fresh frozen plasma
FiO ₂	Fraction of inspired oxygen
Group-C	Group of patients taking cryoprecipitate
Group-L	Group of patients taking fibrinogen concentrate
IRB	Institutional review board
ITT	Intention-to-treat
IV	Intravenous
KHIDI	Korea Health Industry Development Institute
LT	Liver transplantation
LY30	Lysis at 30 min after the maximal amplitude
MA	Maximal amplitude
MCAR	Missing completely at random
MICE	Multiple Imputation using Chained Equations
MTP	Massive transfusion protocol
PaO ₂	Partial pressure of oxygen in arterial blood
PaO ₂ /FiO ₂ ratio	Ratio of the partial pressure of oxygen in arterial blood per the inspired oxygen fraction
PBM	Patient blood management
PCC	Prothrombin complex concentrate
PI	Principal investigator
PT-INR	Prothrombin time-international normalized ratio
POC	Point-of-care
R-time	Reaction-time
RBC	Red blood cell
ROTEM	Rotational thromboelastometry
SAE	Serious adverse event
SCL	Standard central laboratory test
SMC	Samsung Medical Center
SPIC	Stakeholder and Public Involvement Group
T-time	Treatment time
TACO	Transfusion-associated circulatory overload
TEG	Thromboelastography
TRALI	Transfusion-related acute lung injury
TSC	Trial Steering Committee
VET	Viscoelastic test

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Authors' contributions {31b}

Y. B., C. O., T. K., and G. K. contributed to the trial conception and design, data collection, analysis and interpretation of results, and manuscript preparation. D. L. and H. K. contributed to the trial conception, design, and manuscript preparation, as well as the analysis and interpretation of results. K. K. contributed to the trial design and manuscript preparation. H.K. and H. L. contributed to the trial conception and design and data collection. All authors read and approved of the final manuscript. All authors and investigators do not have any conflict of interest related to this trial.

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Data availability {29}

All data and materials will be available in clinicaltrials.gov after the completion of the trial.

Declarations

Ethics approval and consent to participate {24}

The trial was approved by the institutional review board (IRB) of Samsung Medical Center (SMC 2025-03-126-002, June 2, 2025). Written, informed consent to participate will be obtained from all participants.

Consent for publication {32}

Not applicable (No identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. The participant information materials and informed consent forms are available from the corresponding author on request.)

Competing interests {28}

The authors declare no competing interests.

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