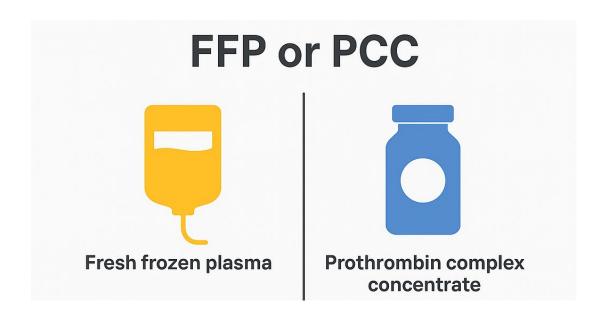
Prothrombin Complex Concentrate vs Fresh Frozen Plasma in Perioperative Bleeding Management



2025.10.23

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Clinical Importance of Perioperative Bleeding

- Major cause of morbidity & mortality in cardiac and liver surgery
- Bleeding → ↑ transfusion → ↑ complications (infection, AKI, mortality)
- Traditional reliance on FFP for coagulopathy correction



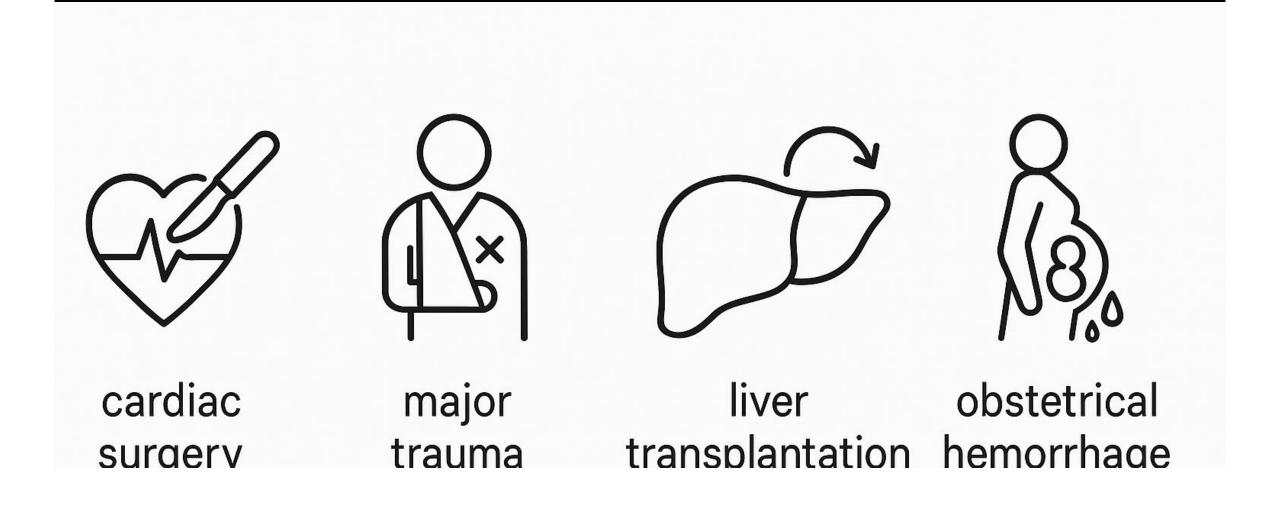
Eur J Anaesthesiol 2023; 40:226-304

GUIDELINES

Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care

Second update 2022

- **Bleeding management** during surgery requires a multimodal and multidisciplinary approach.
- **Preoperative interventions** are key, including:
 - Identifying coagulation disorders (inherited/acquired)
 - Withholding antithrombotic drugs
 - Treating anemia before major surgery
- Emphasis is growing on **evidence-based use** of blood products in the perioperative setting.
- The WHO supports PBM programs that use multimodal strategies to **preserve a patient's own red cell volume and reduce transfusions** (RBCs, platelets, FFP).
- Allogeneic blood transfusions can increase the risk of infectious, immunological, and pulmonary complications.



Coagulation factor deficiency d/t major bleeding

Fibrinogen Concentrate	Human Plasma	Fibrinogen, may contain FXIII
Cryoprecipitate	Human Plasma	Fibrinogen, Factors VII, XIII, vWF, Fibronectin
Prothrombin Complex Concentrates	Human Plasma	Four-factor: II, VII, IX, X, Protein C and S, heparin Three-factor: II, IX, X, Protein C and S, heparin
Plasma	Human Plasma	All clotting factors, albumin, fibrinogen (not sufficient for replacement), Proteins C, S, TFPI
	Concentrate Cryoprecipitate Prothrombin Complex Concentrates	Concentrate Cryoprecipitate Human Plasma Prothrombin Human Plasma Complex Concentrates

Potential treatment thresholds for fibrinogen replacement by studied patient population.

Patient Population	Potential Treatment Thresholds for Fibrinogen Replacement from the Literature			
	Conventional Coagulation Testing	Viscoelastic Testing	Notes	
Trauma	Fibrinogen Concentration >1.5–2 g/L [22–24]	 FIBTEM A5 < 10 mm [22,24,25] FIBTEM A10 < 7 mm [26] FIBTEM MCF < 10 mm [27] EXTEM A5 < 35 mm and FIBTEM A5 < 9 mm [28] TEG Functional Fibrinogen MA < 20 mm [22] TEG Functional Fibrinogen MA < 20 mm [24] 	Evidence base generally supporting both the use of conventional tests of coagulation and viscoelastic testing [22,29]	
Cardiac Surgery	Fibrinogen Concentration >1.5–2 g/L [30–32]	 FIBTEM A10 < 10 mm and EXTEM A10 < 40 mm [30] FIBTEM A10 ≤ 8 mm [31,33] TEG MA < 40 mm and Functional Fibrinogen <8 mm [30] 	Evidence base generally supporting both the use of conventional tests of coagulation and viscoelastic testing [30]. Recent guidelines support the use of point-of-care hemostatic testing over conventional tests of coagulation [32].	
Liver Transplant	Fibrinogen Concentration >1.2–2 g/L [34,35]	 EXTEM A5 < 25 mm and FIBTEM A5 < 8 mm [36] EXTEM MCF<35 mm and FIBTEM MCF < 8 mm [26,37] 	No clear consensus on validated algorithm to guide transfusion management [34,38]. The weight of the evidence suggests that in conjunction with conventional coagulation tests, viscoelastic testing should be used for liver transplantation where available and feasible [38].	
Obstetrical	Fibrinogen Concentration >1.5–2 g/L (some authors advocate for >3 g/L) [17,18]	 FIBTEM A5 < 10 mm [39] FIBTEM A5 < 5 mm or FIBTEM A10 < 6 mm, targeting A10 of 8 mm for controlled hemorrhage and 10 mm for ongoing hemorrhage [40] 	Limited randomized trials and evidence base to guide	
		 FIBTEM A5 < 12 mm [18,41] FIBTEM A5 < 7 mm or < 12 mm in active bleeding and EXTEM A5 < 47 mm [21] 	Best Practice & Research Clinical Anaesthesiology 37 (2023) 527–536	

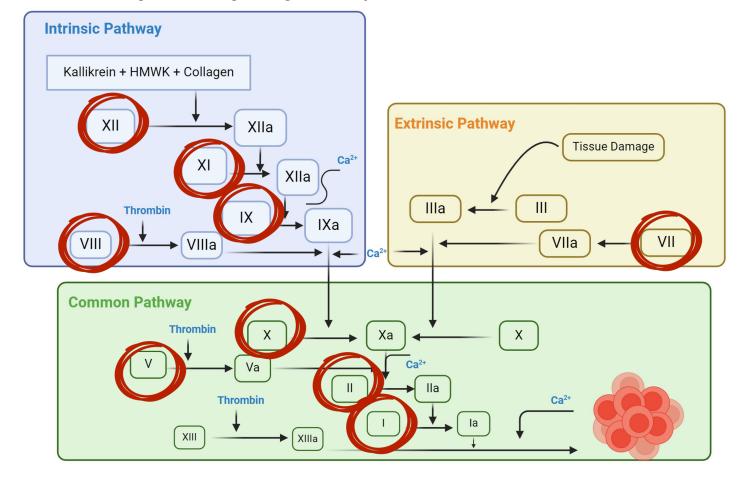
otential treatment thresholds for generalized coagulation factor replacement by studied patient population. Best Practice & Research Clinical			
Patient	Potential Treatment Thresholds for Coagulation F	Anaesthesiology 37 (2023) 527–53	
Population	Conventional Coagulation Testing	Viscoelastic Testing	Notes
Trauma	INR >1.2 [22,24] INR >1.2–1.5 [23]	 EXTEM CA5 ≥ 40 mm and EXTEM CT > 80 s [22] EXTEM CA5 ≤37 mm [63] EXTEM CT > 1.5 x normal [27] FIBTEM A5 > 10 mm and EXTEM CT ≥ 90 mm [25] rTEG MA ≥ 65 mm and rTEG ACT > 120 s [22] 	Evidence base generally supporting both the use of conventional tests of coagulation and viscoelastic testing [22,29]
Cardiac Surgery	INR >1.5 [30]	 EXTEM CT > 100 s [30] EXTEM CT > 90 s [33] hTEG R > 12 min [30] 	Evidence base generally supporting both the use of conventional tests of coagulation and viscoelastic testing [30]. Recent guidelines support the use of point-of-care hemostatic testing over conventional tests of coagulation, particularly when combined with transfusion algorithms rather than clinical judgement alone [32].
Liver Transplant	Little evidence for administering FFP based on INR in this population [34,36] In acute liver failure, a moderately elevated INR may not require correction with the exception of intracranial pressure monitor insertion [32]	 EXTEM A10 > 35 mm and EXTEM CT > 120 s or FIBTEM MCF > 6 mm and EXTEM MCF < 35 mm [37] EXTEM CT > 75 s and FIBTEM A5 > 8 mm [36,64] Prolongation of TEG R time or ROTEM EXTEM CT [34] 	No clear consensus on validated algorithm to guide transfusion management [34,38]. The weight of the evidence suggests that in conjunction with conventional coagulation tests, viscoelastic testing should be used for liver transplantation and in patients with liver failure undergoing invasive procedures where available and feasible [32,38]. In patients with high thrombotic risk where PCC is used, addition of antithrombin concentrate can be considered [36]
Obstetrical	INR >2 and microvascular bleeding; Empiric therapy in presence of excessive microvascular bleeding with suspected coagulation deficiency may be warranted when INR, PT, or aPTT not available [65]	• EXTEM CT > 80 s [41]	Limited randomized trials and evidence base to guide management [41–43] Recent reviews have suggested that where available, point of care testing should be used to guide targeted treatment [18].

INR >1.5 [41]

- FFP is the plasma separated from whole blood, frozen within 6-8 hours of collection and stored at -30°C and below.
- FFP from a standard donation of whole blood (450ml) usually measures 175-250 ml, containing 70-80 units/dl of factor VIII, IX, vWF, and other plasma clotting factors.
- Separate the plasma into satellite bag using plasma expresser.



Blood Coagulation Signaling Pathway





- All clotting factors
- ❖ (XII, XI, VIII, IX, VII, X, V,
- II: thrombin, I: fibrinogen)
- **❖** Albumin
- Protein C
- Protein S
- ❖ Antithrombin III

Fresh frozen plasma



- FFP refers to plasma frozen within 8 hours after phlebotomy.
- Full complement of procoagulant and anticoagulant factors
- 30% of patients who have undergone cardiac surgery

- Serious allergic reactions
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated circulatory overload (TACO)

- Higher RBC transfusion rates in cardiovascular surgery are linked to negative outcomes like infection, lung injury, mortality, and longer hospital stays, partly due to fluid overload.
- Intraoperative FFP use is associated with fluid overload, higher mortality, and complications such as pulmonary edema and heart failure, more so than PCC.

Crit Care Med 2008;36:2667-74. Circulation 2007;116:2544-52. J Cardiothorac Vasc Anesth 2018;32:1062-7. Transfusion 2015;55:2722-9.

Prothrombin complex concentrate (PCC)



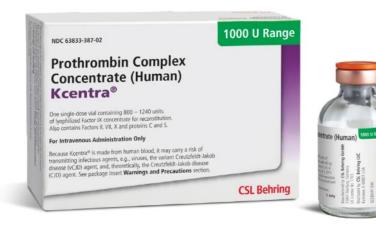
Key Features of Plasma-Derived Products

- 1. Purified, concentrated products derived from plasma
- 2. Contain concentrated factors II, VII, IX, and X
- 3. Include small amounts of anticoagulants like protein C, S, and heparin
- 4. Undergo purification, concentration, and pathogen reduction
- 5. Contain a standard amount of coagulation factors
- 6. Do not require thawing or ABO matching
- 7. More effective than plasma for emergency anticoagulant reversal

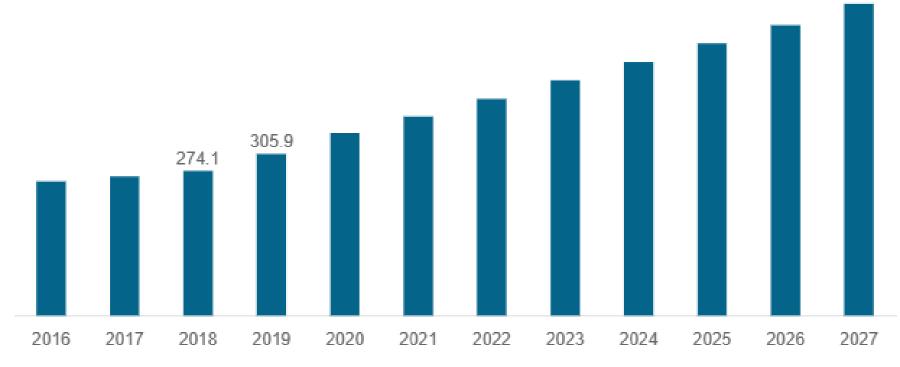
Four-Factor PCC Production

- 1. Use chromatographic procedures with ion exchange resins
- 2. Contain clotting factors II, VII, IX, and X
- 3. Reduce viruses via solvent/detergent viral inactivation
- 4. Remove viruses through nanofiltration step





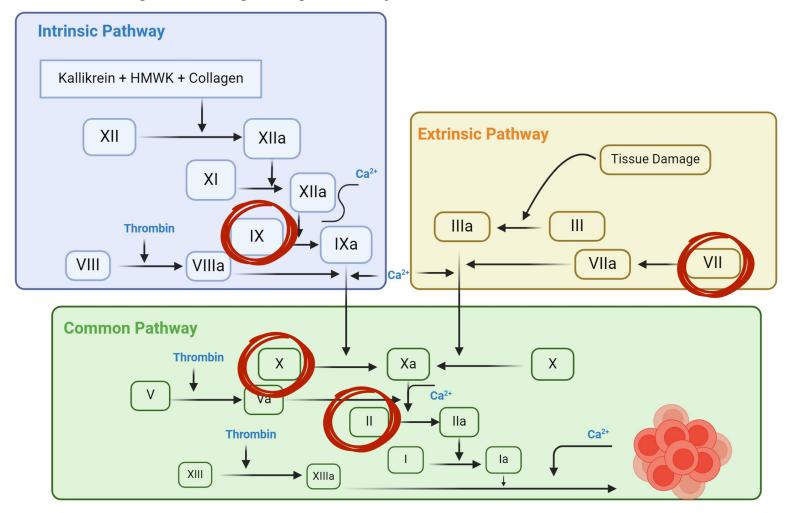
North America Prothrombin Complex Concentrate (PCC) Market Size, 2016-2027 (USD Million)



www.fortunebusinessinsights.com

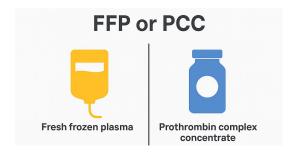
- Grifols, S.A. (Spain)
- CSL Behring (United States)
- Octopharma AG (Switzerland)
- Sanquin (Netherlands)
- Kedrion S.P.A. (Italy)
- China Biologic Products Holdings, Inc. (China)
- Takeda Pharmaceutical Company Limited (Japan)

Blood Coagulation Signaling Pathway





- ❖ II, VII, IX, and X
- protein C, protein S
- ❖ heparin



Comparative differences in product characteristics of frozen plasma and prothrombin complex concentrate.

Attributes	Plasma	PCC
Origin	Human Plasma	Human Plasma
Storage	Frozen (≤30 °C)	Room Temperature, Lyophilized
Shelf life	1 year	2 years
Typical adult dose	15 mL/kg (approx. 1000 mL)	12.5-50 IU/kg depending on indication (approx.
		80 mL)
Near-Patient Storage Possible	No	Yes
Rapid preparation/ injection	No, requires approximately 30 min for thawing	Yes, rapidly reconstituted
Pathogen reduction	No	Yes
Side-effects	Similar to all allogeneic blood products, in particular transfusion associated circulatory overload (TACO), and transfusion associated acute lung injury (TRALI)	Pro- vs anti-coagulant imbalance theoretically possible due to concentrated dose of factors
Factor Content	High variability dependent on the donor pool	Low variability, standardized for FIX content [84]



JAMA Surg 2013;148:127–36. JAMA 2015;313:471–82. Lancet 2018;392:283–91. N Engl J Med 2018; 379:315–26.

- Commonly guided by <u>empiric, ratio-based</u> component transfusion
- PROMMTT & PROPPR Trials:
 - Support 1:1:1 transfusion of RBCs, **FFP**, and platelets in trauma patients.
- Impact of <u>pre-hospital</u> resuscitation
- COMBAT (n=144): Control of Major Bleeding After Trauma
 - **FFP** vs. saline in hemorrhagic shock.
 - No difference in 28-day mortality.
- PAMPer (n=501): Prehospital Air Medical Plasma
 - **FFP** (230) vs. standard care prehospital (271).
 - 9.8% absolute reduction in 30-day mortality with plasma group.
 - Longer transport times may have influenced benefit.
 - No comparison with PCC.



Retrospective Meta-Analysis:

- Suggested added benefit when **PCC used with FFP** vs. plasma alone.
- Improved mortality and transfusion-related outcomes.
- PCC did not improve in-hospital mortality, nor it is reported to increase VTE.



FFP or PCC

PROCOAG Trial (n=327): Early Administration of Prothrombin Concentrate Complex in Patients With

Acute Hemorrhage Following Severe Trauma

- 4F-PCC (164) vs. placebo (160) in massive transfusion risk.
- No difference in 24-hour blood product use.
- Increased <u>thromboembolic events</u> in PCC group:
 - 11% absolute increase, RR 1.48 (p = 0.03)

Ongoing Trial – FiiRST-2: Factor In the Initial Resuscitation of Severe Trauma 2 Patients

- PCC + fibrinogen vs. standard transfusion.
- Primary outcome: 24-hour allogeneic blood product use.
- Trial stopped early, results pending (expected 2024).

J Acute Med 2021;11: 81-9. Critical Care 2023; 27:422. JAMA 2023;329:1367-75. BMJ Open 2021;11:e051003.

REVIEW



Restoring hemostasis with prothrombin complex concentrate: benefits and risks in trauma-induced coagulopathy

Oliver Grottke^a and Lars Heubner^b



Mechanism of Action:

- •PCC (3F or 4F) contains clotting factors II, IX, X (\pm VII) \rightarrow boosts **thrombin generation** \rightarrow promotes clotting.
- •4F-PCC preferred for urgent reversal of <u>Vitamin K antagonists (VKAs)</u> and increasingly used for <u>DOAC</u>-associated bleeding.

Challenges:

- •PCC not suitable for all coagulopathic bleeding cases due to thromboembolic risk.
- •Use should be **guided by thrombin generation markers**, not empirically.

Vitamin K

- Vitamin K is involved in the synthesis of many factors of the coagulation cascade.
- Vitamin K is antagonized (inhibited) by the anticoagulant drug warfarin.
- <u>Calcium and phospholipids</u> are needed to activate tenase, which converts prothrombin to thrombin.
- Both calcium and vitamin K are needed to synthesize Protein C, an anticoagulant that prevents excessive coagulation after the coagulation cascade occurs.
- Deficiency of any of these clotting cofactors will cause an impaired ability for blood to coagulate, which can contribute to excessive bleeding and hemorrhage.





Clinical Evidence & Monitoring

VKAs:

- 4F-PCC proven effective in rapid INR correction, reduces transfusion, recommended over FFP.
- Meta-analysis: Higher success and fewer adverse effects vs. FFP.

DOACs:

- Off-label but supported: hemostatic success ~65–89%.
- Used when specific antidotes (e.g., andexanet alfa) are unavailable.

Fresh frozen plasma Prothrombin complex concentrate

Monitoring PCC Effectiveness:

- Traditional: PT/ROTEM EXTEM CT.
- Advanced: Thrombin Generation Assays, TEG, ClotPro (better predictors but not widely available).

Risks, Recommendations & Conclusions

Thromboembolic Risks:

- Risk: 4–9% in DOAC reversal, up to 35% in trauma (PROCOAG trial).
- **<u>DIC</u>** observed in animal models with high-dose PCC or fibrinogen combo.

Guidelines & Best Practices:

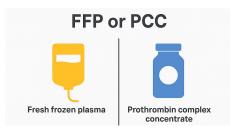
- **DOAC reversal**: PCC or and examet alfa (equal strength in 2024 ESAIC guidelines).
- **VKA reversal**: 4F-PCC over FFP endorsed globally.
- Use goal-directed, lab-based protocols (e.g., EXTEM CT, R-time) in trauma.

Conclusion:

- PCC is valuable in anticoagulant reversal, especially VKAs.
- Caution in trauma settings without clear thrombin deficiency.
- Need for **RCTs**, refined **diagnostic markers**, and **patient stratification** to improve outcomes and safety.



Clinical Guidelines:



• 2019 SCA Guidelines:

- Insufficient evidence to recommend routine PCC over FFP.
- PCC may be preferable in right ventricular failure.
- Dosing not standardized, but experience includes (post-CPB):
 - **Low dose**: 10–15 IU/kg.
 - High dose: 20–25 IU/kg.

2022 ESAIC Guidelines:

 Recommend PCC preferentially over FFP for coagulation factor deficiency.



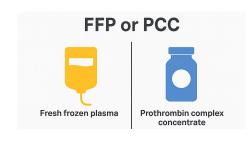
GUIDELINES

Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care

Second update 2022

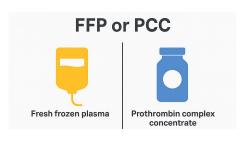
•A systematic review of 4 nonrandomized studies (861 patients) found that **PCC reduced RBC transfusion** compared to FFP but <u>did not significantly reduce chest drain output</u>.

- •Two RCTs have been conducted:
 - RCT 1 (n=101): PCC significantly <u>reduced 24-hour chest drainage and allogeneic</u> <u>transfusion</u> (P<0.001), with <u>no increase in adverse events</u>.
 - RCT 2 (n=50): Transfusion needs were similar between PCC and FFP groups; no increase in thromboembolic events with PCC.





[Ann Thorac Surg 2019; 107:1275–1283] [JAMA Netw Open 2021; 4:e213936] [Anaesthesia 2021; 76:892–901]





Clinical Evidence:

Supportive Data: Mostly from observational studies and small RCTs.

•FARES-I Trial:

- Pilot RCT (n=101, Canada).
- PCC group had less bleeding and lower allogeneic transfusion than plasma group.
- Aimed to test feasibility for a larger study.

•FARES-II Trial:

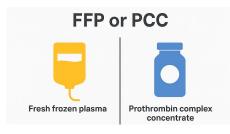
- Multicenter RCT, 13 centers of North America (n=500)
- High-risk cardiac surgery patients.
- Primary outcome: need for additional hemostatic intervention within 60 min–24 hrs.
- Trial registered: NCT05523297.

JAMA Netw Open 2021;4:e213936-e. JAMA. doi:10.1001/jama.2025.3501 Published online March 29, 2025. Research

JAMA | Original Investigation

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

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





Study Design (FARES-II Trial):

•Type: Multicenter, randomized, noninferiority trial.

•Participants: 538 adults with post-CPB coagulopathic bleeding at 12 centers (Canada/US).

•Intervention:

• **PCC group**: 1500–2000 IU.

• **FFP group**: 3–4 units.

•**Primary Outcome**: Effective hemostasis (no need for further hemostatic intervention from 60 min–24 hrs post-treatment).

Primary Outcome – Hemostatic Effectiveness:

•PCC: **77.9**%

•FFP: **60.4%**

•P < .001 (both noninferiority & superiority confirmed)



•Serious Adverse Events:

• PCC: 36.2%

• FFP: 47.3% (**P = .02**)

•Acute Kidney Injury:

• PCC: 10.3%

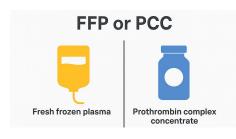
• FFP: 18.8% (**P = .02**)

•Fewer transfusions in PCC group:

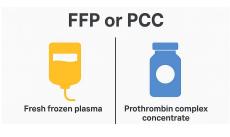
• 6.6 vs 9.3 units (first 24 hrs)

• Less chest drainage: 691 mL vs 923 mL (first 24 hrs)

The proportion of patients who died or had thromboembolic events was similar









Conclusions:

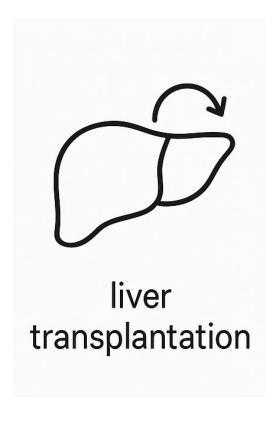
- PCC was superior to FP for controlling surgical bleeding after cardiac surgery.
- Improved safety profile: fewer adverse events and less kidney injury.
- Reduced transfusion needs and potential to conserve plasma supplies.

Clinical Implications:

- Supports **preferential use of PCC** over FP for coagulopathic bleeding in cardiac surgery.
- Could benefit both patients (fewer complications) and the healthcare system (lower blood product use).

Next Steps:

- Assess long-term outcomes and cost-effectiveness.
- Validate findings in broader surgical populations.



ESAIC Recommendation:

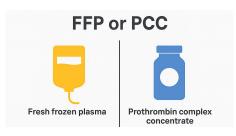
Grade **2C** (Weak recommendation, Low quality evidence for <u>low-dose PCC</u> (10–15 IU/kg) use, ideally guided by viscoelastic testing.

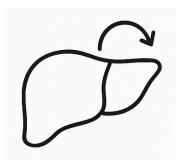
Potential Benefits of PCC:

- Avoids increased portal pressure.
- Reduces risks of **TACO**, **TRALI**, **alloimmunization**, and **hemodilution**.

Limitations & Cautions:

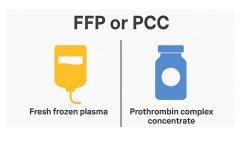
- Not universally accepted; practice varies by institution.
- **Product monographs caution** PCC use due to risk of **antithrombin deficiency**.
- Suggest **antithrombin monitoring and supplementation** if PCC is used.
- FFP is generally preferred in this setting.

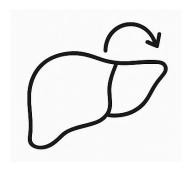




PCC in Liver Disease and Liver Transplantation (OLT)

- •PCC is effective in improving coagulation markers (PT, INR) in patients with <u>acute or chronic liver</u> <u>disease (CLD)</u> without increasing thrombotic risk.
- •Viscoelastic hemostatic assay (VHA)-guided PCC use during orthotopic liver transplantation (OLT) has been shown to:
 - Reduce transfusion requirements
 - Be safe without using FFP





- •In a study of **372 consecutive OLT cases**, safe management was achieved **without FFP**, using **coagulation factor concentrates guided by VHA**.
- •Prolonged coagulation time on VHA suggests impaired thrombin generation only if fibrinogen is normal—in such cases, factor correction is warranted only in bleeding patients.
- •Thrombin generation studies show:
 - PCC at 10 IU/kg restores normal thrombin levels
 - PCC at **20 IU/kg may lead to supranormal thrombin generation**, increasing thrombosis risk
- •Recommended PCC use in OLT:
 - Low doses (10–15 IU/kg)
 - Avoid severe antithrombin deficiency (under 10–30%) before PCC administration





Evidence Base:

- Limited RCT data for PCC use in postpartum hemorrhage (PPH).
- Current resuscitation practices rely on trauma data (e.g., **PROMMTT**, **PROPPR** trials) supporting **1:1:1 transfusion** (RBC:Plasma:Platelets).
- Findings from PROMMTT (Post-hoc):
 - Early FFP administration (within 3h, part of first 3–6 units) associated with lower mortality at:
 - **24h** (OR 0.47, *p* < 0.01)
 - **30 days** (OR 0.44, *p* < 0.01)
- Guideline Perspective:
 - **2022 International Federation of Gynecology and Obstetrics (FIGO)**: Emphasizes <u>early FFP</u> use based on trauma data.
 - Expert Opinion: PCC use in PPH not recommended; thrombin generation generally intact in PPH.
 - RCT attempt (PCC vs. plasma in PPH, NCT01910675) withdrawn due to consent challenges.

Comparison of FFP and PCC – Pros & Cons



	FFP (Fresh Frozen Plasma)	PCC (Prothrombin Complex Concentrate)
Pros	 Contains all clotting factors Widely available and familiar Cost-effective in some settings Useful in DIC, TTP, massive transfusion protocols Liver transplantation (AT III deficiency) 	 Rapid INR correction Small volume required (↓ TACO risk) No need for thawing or cross-matching Lower transfusion-related reaction risk (e.g., TRALI) Effective in VKA reversal, cardiac surgery, some liver cases Long shelf life (lyophilized)
Cons	 Requires thawing and blood type matching Large volume needed (个 TACO risk) Risk of TRALI, allergic reactions Slower action vs. PCC Ineffective in DOAC reversal 	 - Higher cost than FFP - Risk of thromboembolism (especially at high doses) - Requires antithrombin monitoring - Limited data in obstetrics and some off-label uses - Risk of DIC if combined with fibrinogen or overused

Conclusion

- •FFP and PCC play complementary roles in hemostatic management.
- •PCC offers rapid effect, smaller volume, and plasma conservation.
- •FFP remains essential for broader indications and antithrombin support.
- •Clinical context should guide the tailored use of both agents.

Future Directions

- 1 Develop standardized protocols for FFP/PCC use
- 2 Conduct RCTs in various clinical settings (e.g., liver, obstetrics)
- 3 Analyze cost-effectiveness and resource impact
- 4 Expand VHA-guided personalized transfusion strategies

THANK YOU

