Karkouti K, Callum JL, Bartoszko J, et al; FARES-II Study Group

Prothrombin Complex Concentrate vs Frozen Plasma for Coagulopathic Bleeding in Cardiac Surgery

The FARES-II Multicenter Randomized Clinical Trial

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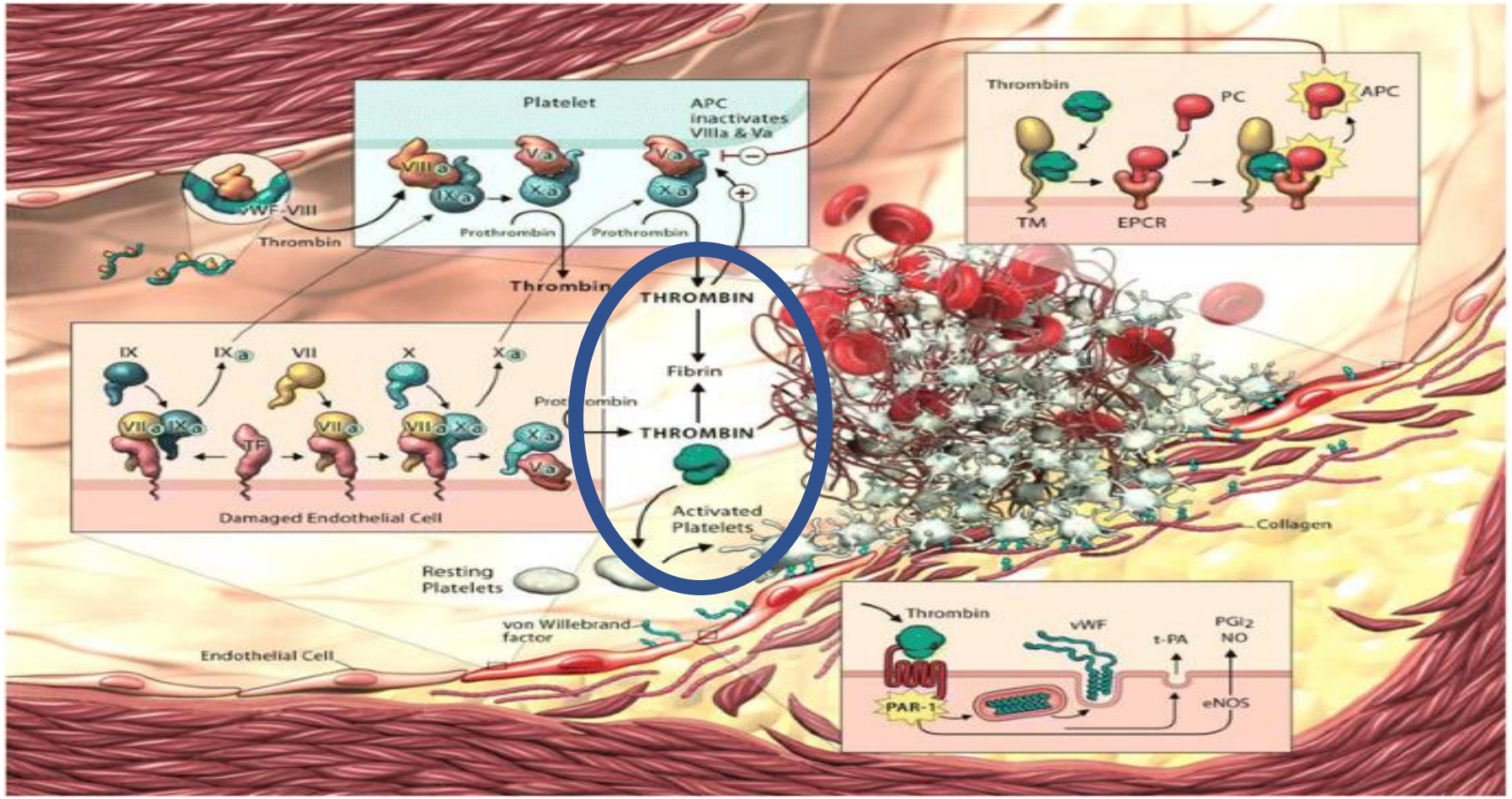
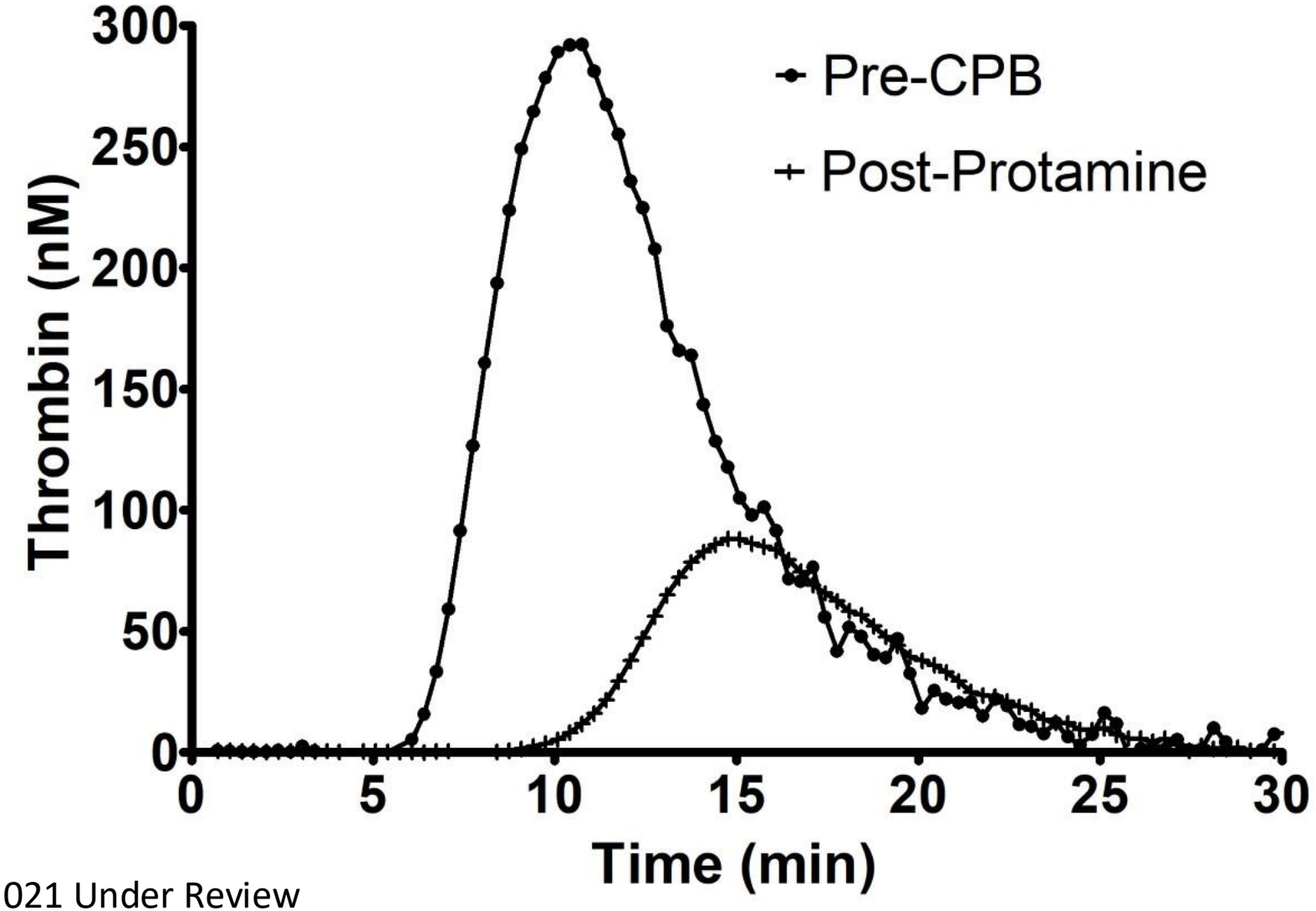
American College of Cardiology Annual Scientific Session (ACC.25)

Coagulopathic Bleeding



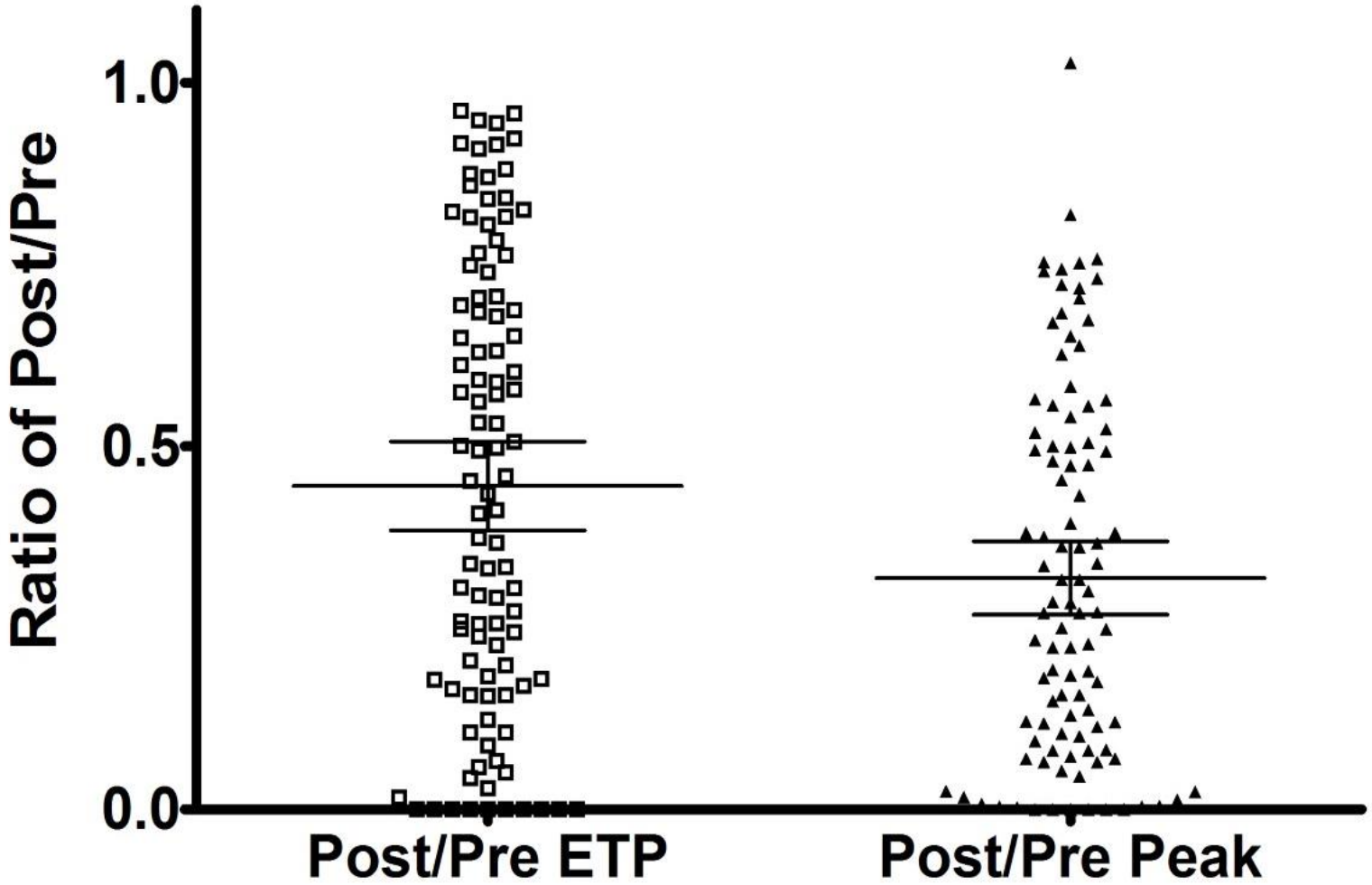
Yau BMC Cardiovascular Disorders. 2015;15:130

Impaired Thrombin Generation



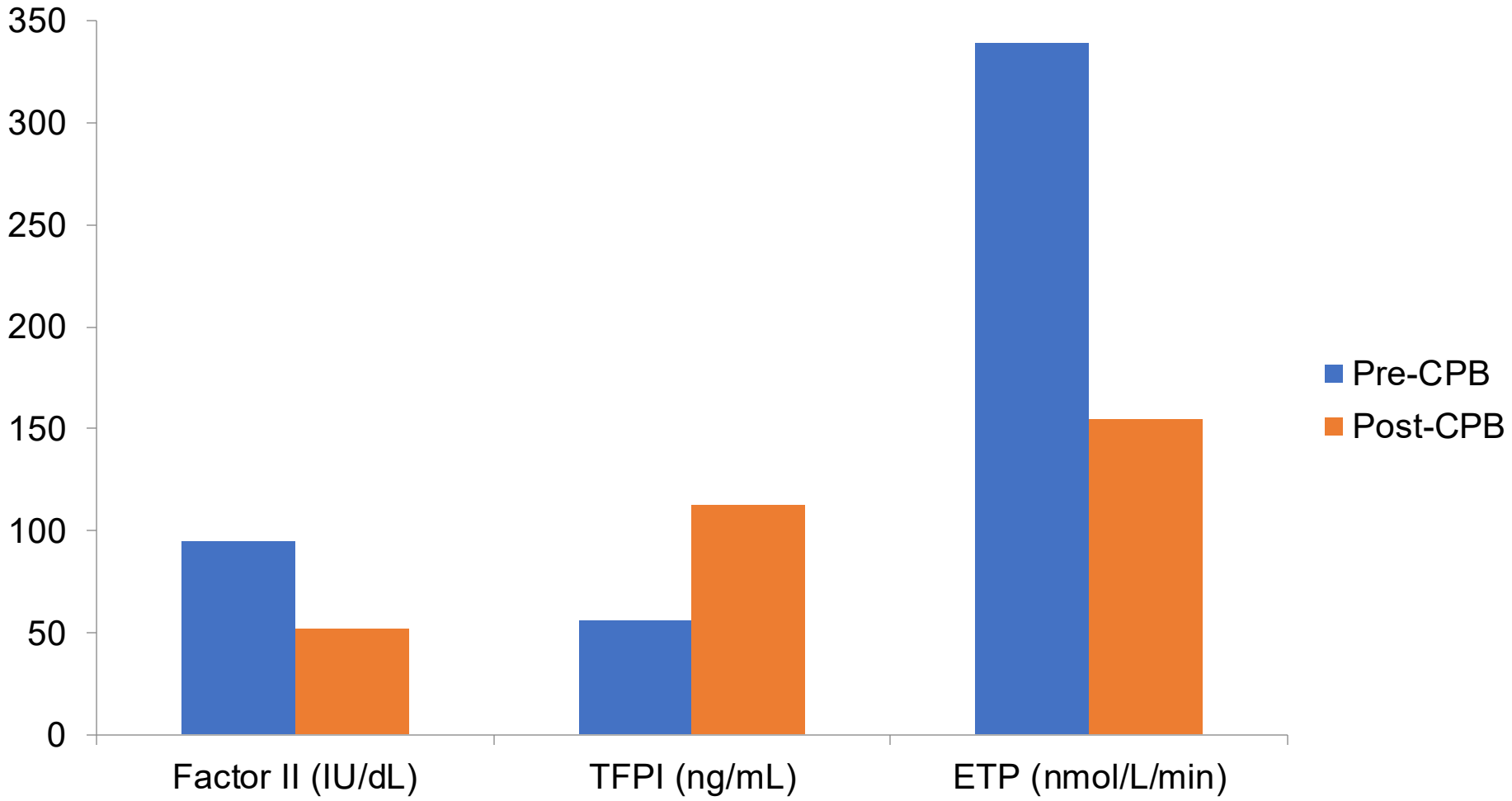
Bartoszko et al. BJA 2021 Under Review

Impaired Thrombin Generation



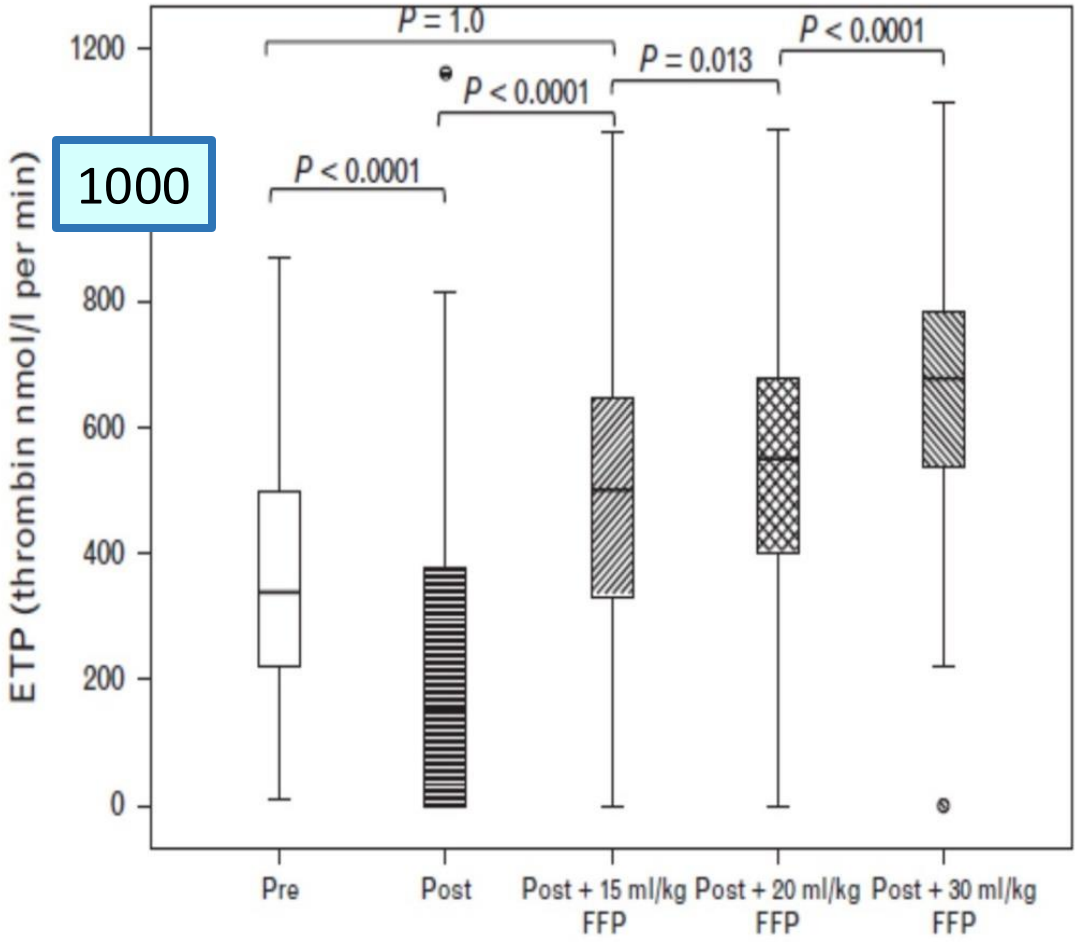
Bartoszko et al. BJA 2021 Under Review

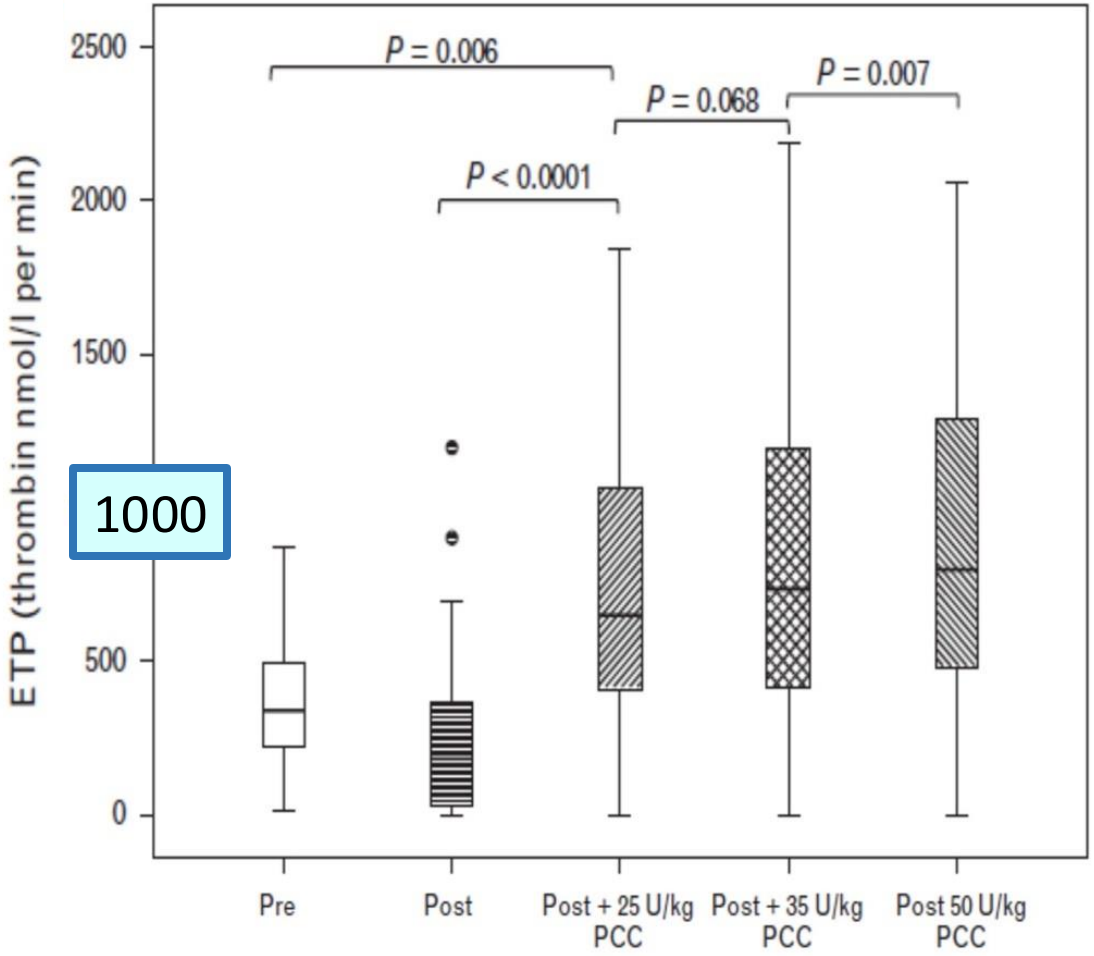
Impaired Thrombin Generation after CVS



Percy et al. Blood Coag Fibrinol 2015;26:357-367

4F-PCC Versus FP for Thrombin Generation

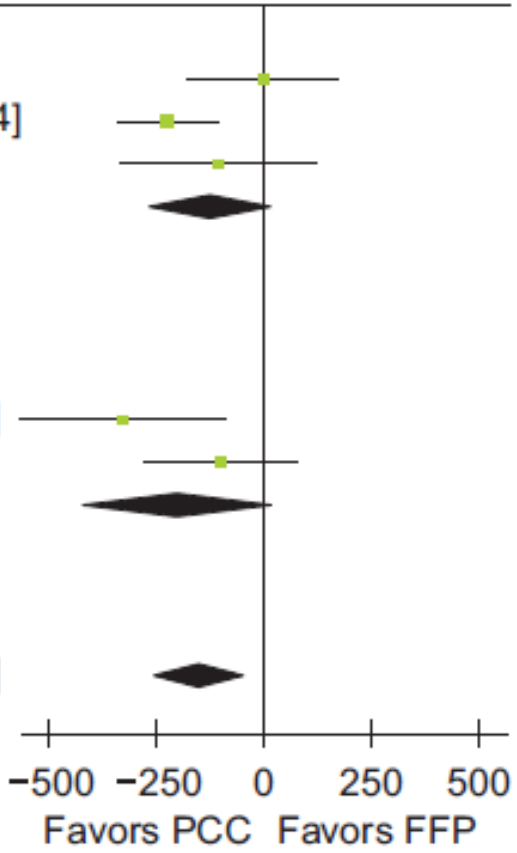




Percy et al. Blood Coag Fibrinol 2015;26:357-367

Meta-analysis: Chest Tube Drainage

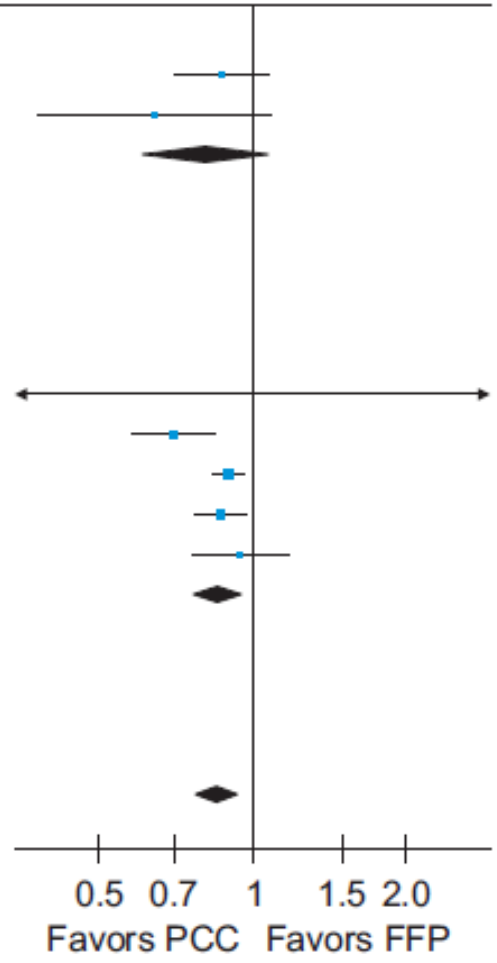
Study or subgroup	PCC Mean±SD	PCC Total	FFP Mean±SD	FFP Total	Weight (%)	Mean difference IV, random, 95% CI
1.3.1 RCTs						
Green et al. [4] (2021)	583±364	25	584±255	25	20.7	−1.00 [−175.21 to 173.21]
Karkouti et al. [3] (2021)	485±198	54	707±367	47	30.2	−222.00 [−339.46 to −104.54]
Smith et al. [13] (2022)	1,035±561	51	1,139±593	48	14.7	−104.00 [−331.70 to 123.70]
Subtotal (95% CI)		**130**		**120**	**65.7**	**−122.08 [−266.07 to 21.90]**
Heterogeneity: tau^2=8,810.43; chi^2=4.40, df=2 (p=0.11); I^2=55%						
Test for overall effect: z=1.66 (p=0.10)						
1.3.2 Non-randomized studies						
Arnékian et al. [11] (2012)	923±441	24	1,250±441	26	14.0	−327.00 [−563.16 to −90.84]
Cappabianca et al. [12] (2016)	836±1,226	225	935±583	225	20.3	−99.00 [−276.38 to 78.38]
Subtotal (95% CI)		**249**		**251**	**34.3**	**−199.12 [−420.90 to 22.65]**
Heterogeneity: tau^2=14,637.32; chi^2=2.29, df=1 (p=0.13); I^2=56%						
Test for overall effect: z=1.76 (p=0.08)						
Total (95% CI)		**379**		**371**	**100.0**	**−148.50 [−253.02 to −43.99]**
Heterogeneity: tau^2=5,811.33; chi^2=6.86, df=4 (p=0.14); I^2=42%						
Test for overall effect: z=2.78 (p=0.005)						
Test for subgroup differences: chi^2=0.33, df=1 (p=0.57); I^2=0%						



Viana et al. J Chest Surg 2024;57:25-35

Meta-analysis: RBC Transfusion

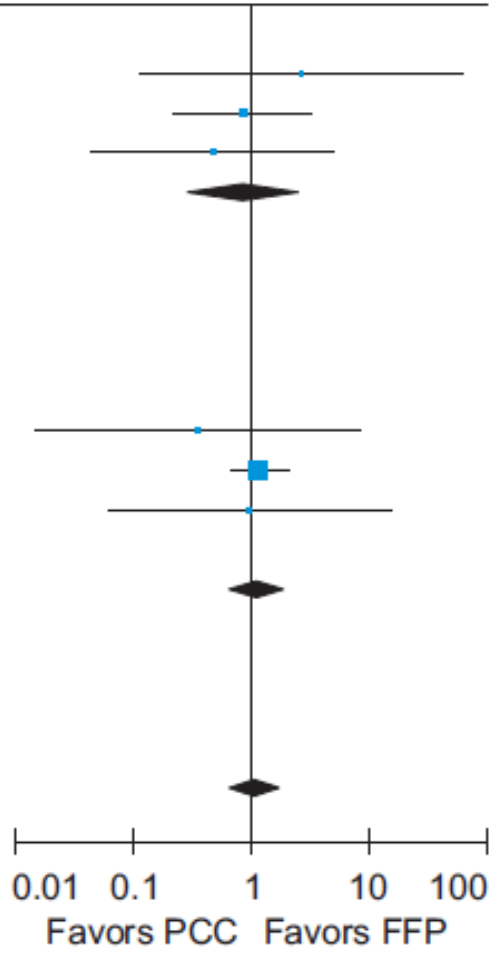
Study or subgroup	PCC Events	PCC Total	FFP Events	FFP Total	Weight (%)	Risk ratio M-H, random, 95% CI
1.7.1 RCTs						
Karkouti et al. [3] (2021)	39	54	39	47	13.0	0.87 [0.71 to 1.07]
Smith et al. [13] (2022)	15	51	22	48	2.9	0.64 [0.38 to 1.08]
Subtotal (95% CI)		**105**		**95**	**15.9**	**0.81 [0.60 to 1.08]**
Total events	54		61			
Heterogeneity: tau^2=0.02; chi^2=1.42, df=1 (p=0.23); I^2=30%						
Test for overall effect: z=1.44 (p=0.15)						
1.7.2 Non-randomized studies						
Arnékian et al. [11] (2012)	0	24	2	26	0.1	0.22 [0.01 to 4.28]
Bartoszko et al. [14] (2021)	44	72	299	343	14.9	0.70 [0.58 to 0.85]
Cappabianca et al. [12] (2016)	189	225	210	225	32.3	0.90 [0.84 to 0.96]
Fitzgerald et al. [15] (2018)	90	117	104	117	23.9	0.87 [0.77 to 0.97]
Ortmann et al. [20] (2015)	34	45	44	55	12.8	0.94 [0.76 to 1.17]
Subtotal (95% CI)		**483**		**766**	**84.1**	**0.85 [0.77 to 0.95]**
Total events	357		659			
Heterogeneity: tau^2=0.01; chi^2=8.91, df=4 (p=0.06); I^2=55%						
Test for overall effect: z=2.86 (p=0.004)						
Total (95% CI)		**588**		**861**	**100.0**	**0.85 [0.78 to 0.93]**
Total events	411		720			
Heterogeneity: tau^2=0.01; chi^2=10.89, df=1 (p=0.09); I^2=45%						
Test for overall effect: z=3.40 (p=0.0007)						
Test for subgroup differences: chi^2=0.13, df=1 (p=0.72); I^2=0%						



Viana et al. J Chest Surg 2024;57:25-35

Meta-analysis: Thromboembolic Events

Study or subgroup	PCC Events	PCC Total	FFP Events	FFP Total	Weight (%)	Risk ratio M-H, random, 95% CI
1.8.1 RCTs						
Green et al. [4] (2021)	1	29	0	26	2.3	2.70 [0.11 to 63.52]
Karkouti et al. [3] (2021)	4	54	4	47	13.0	0.87 [0.23 to 3.29]
Smith et al. [13] (2022)	1	51	2	49	4.1	0.48 [0.04 to 5.13]
Subtotal (95% CI)		**134**		**122**	**19.4**	**0.88 [0.30 to 2.61]**
Total events	6		6			
Heterogeneity: tau^2=0.00; chi^2=0.74, df=2 (p=0.69); I^2=0%						
Test for overall effect: z=0.23 (p=0.82)						
1.8.2 Non-randomized studies						
Arnékian et al. [11] (2012)	0	24	1	26	2.3	0.36 [0.02 to 8.43]
Bartoszko et al. [14] (2021)	13	72	52	343	75.3	1.19 [0.69 to 2.07]
Fitzgerald et al. [15] (2018)	1	117	1	117	3.0	1.00 [0.06 to 15.80]
Ortmann et al. [20] (2015)	0	45	0	55		Not estimable
Subtotal (95% CI)		**258**		**541**	**80.6**	**1.14 [0.67 to 1.95]**
Total events	14		54			
Heterogeneity: tau^2=0.00; chi^2=0.55, df=2 (p=0.76); I^2=0%						
Test for overall effect: z=0.49 (p=0.62)						
Total (95% CI)		**392**		**663**	**100.0**	**1.09 [0.67 to 1.75]**
Total events	20		60			
Heterogeneity: tau^2=0.00; chi2=1.47, df=5 (p=0.92); I^2=0%						
Test for overall effect: z=0.34 (p=0.73)						
Test for subgroup differences: chi^2=0.18, df=1 (p=0.67); I^2=0%						



Viana et al. J Chest Surg 2024;57:25-35

What does it all mean?

- For management of bleeding due to coagulation factor deficiency during or after cardiac surgery
  - Pilot RCT (and observational studies) suggest that PCC may be more effective without compromising safety
- Existing data (on efficacy and safety) not conclusive
- Adequately powered multicentre randomized trial warranted
  - Feasibility of study procedures confirmed by pilot RCT
  - Dose of 25 IU/kg recommended in cardiac surgery guidelines appears to be appropriate

Erdoes G, et al. A European consensus statement on the use of four-factor prothrombin complex concentrate for cardiac and non-cardiac surgical patients. Anaesthesia. 2021 Mar;76(3):381-392.

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FARES-II study sites

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The FARES-II (LEX-211) trial was supported with funding from Octapharma AG (Lachen, Switzerland) and the Canadian Institutes of Health Research

Background

- In cardiac surgery, up to 15% of patients experience excessive bleeding, which is directly linked to increased morbidity and mortality.
- Standard therapy for coagulopathic bleeding is frozen plasma (FP), occurring in up to 30% of patients.
- Preliminary data suggest that a suitable alternative may be 4-factor prothrombin complex concentrate (PCC).
  - PCCs have logistical advantages (ease, speed, volume of administration)
  - PCCs are concentrated → Do they increase TEE risk?
  - PCCs contain a subset of FP pro-coagulant factors → Are they as effective?

Objective

The objective of the FARES-II phase 3, non-inferiority, randomized controlled trial was to compare the efficacy and safety of PCC with FP in bleeding cardiac surgery patients.

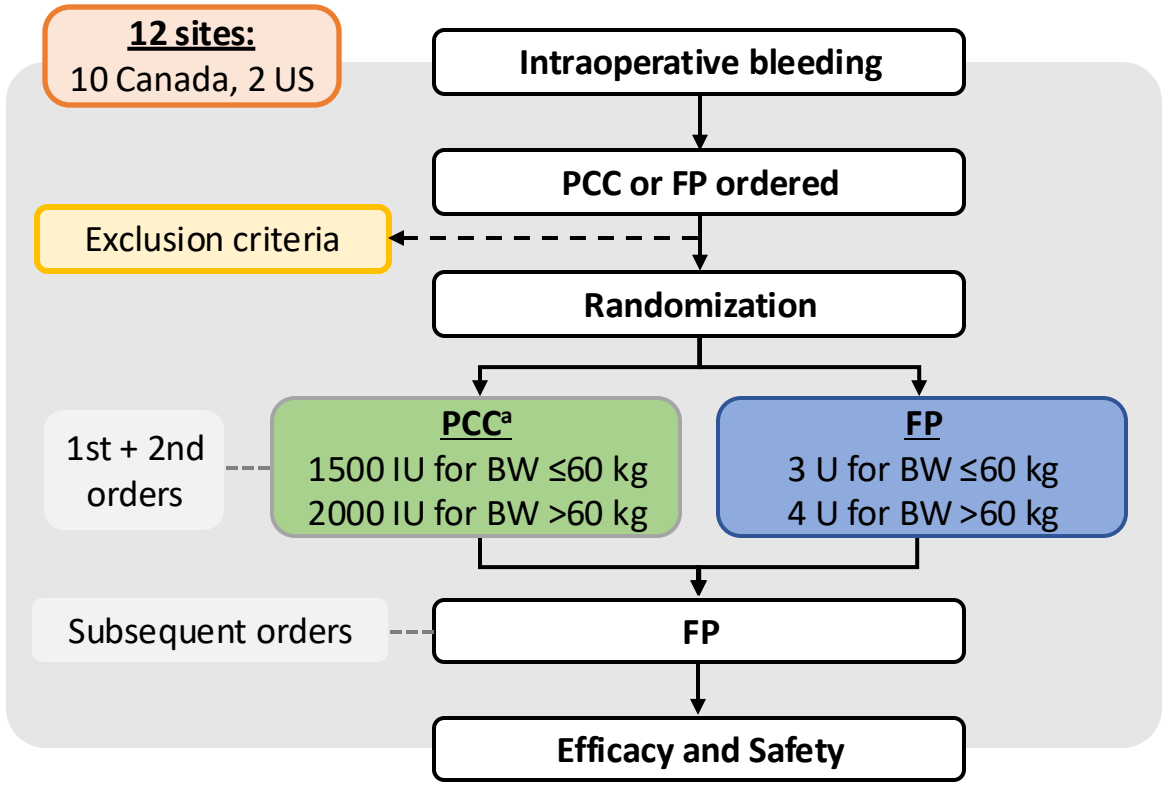
Study design – FARES-II

Inclusion criteria:

- Age ≥18 years undergoing cardiac surgery with CPB
- Coagulation factor replacement with PCC or FP ordered in the OR for:
  a) management of bleeding, or
  b) anticipated bleeding
- Known or suspected acquired coagulation factor deficiency
- Final eligibility for initiating treatment post-CPB:
  At least moderate bleeding and INR ≥ 1.5

Exclusion criteria:

Including heart transplantation, insertion or removal of ventricular assist devices, repair of thoracoabdominal aneurysm, or TEE within 3 months prior to surgery

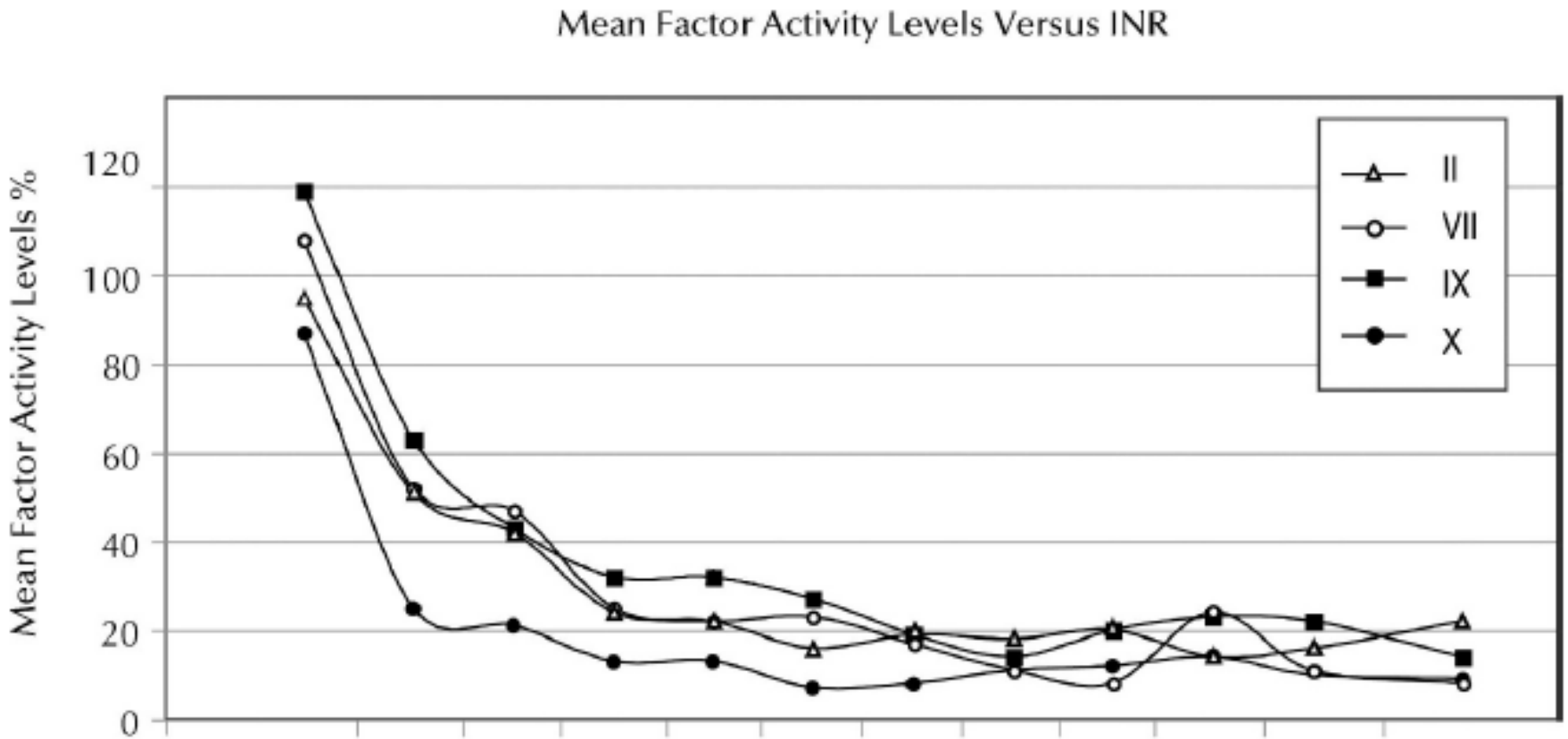


Significant Study Procedures

- Informed consent before surgery in USA sites and after surgery in Canadian sites
- Randomized once PCC or FP ordered by clinicians
- Treatment indication based on visual bleeding score and INR
  - Moderate to severe bleeding
  - INR ≥ 1.5 (POC)
- Anticipated 20% of randomized patients to not receive treatment
- Blinding maintained until treatment indications were met

Why INR to guide therapy?

- The goal is to enhance thrombin generation
- There are no good assays for measuring thrombin generation
  - PT/INR: measures thrombin initiation
  - CT: measures thrombin initiation
  - CFT: measures dynamics of clot formation, a component of which is thrombin generation
- They are surrogate measures of thrombin generation as they correlate to coagulation factor levels

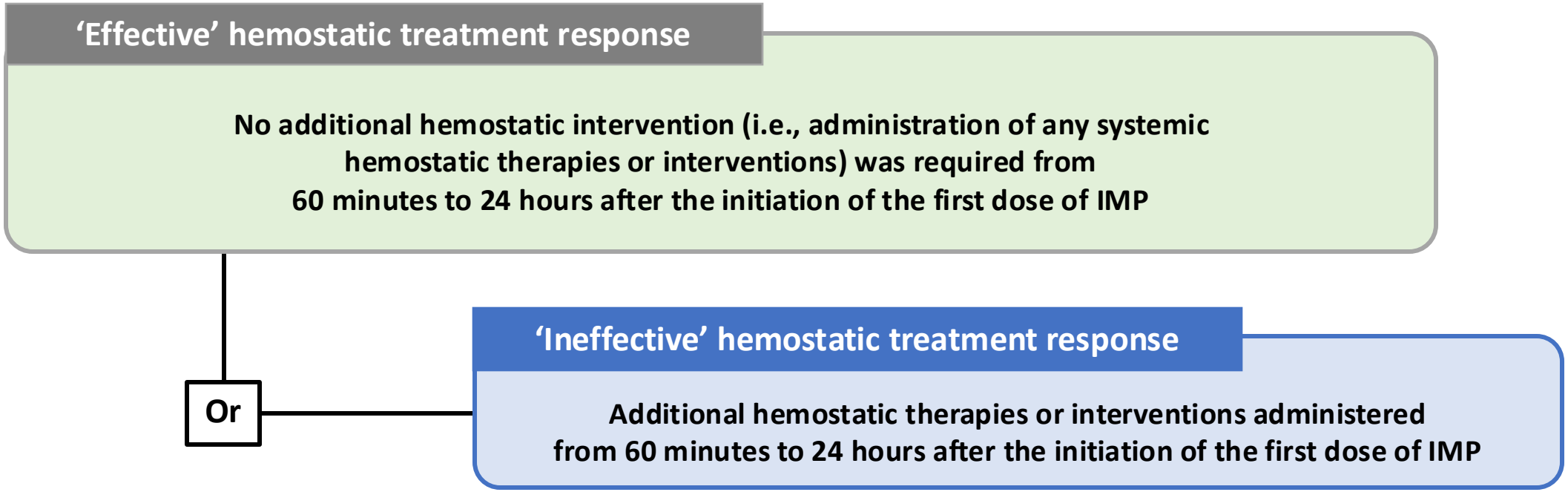


Mean INR	1.25	1.8	2.3	2.8	3.3	3.8	4.3	4.8	5.3	5.8	6.3	7.05
INR Range	1.0–1.5	1.6–2.0	2.1–2.5	2.6–3.0	3.1–3.5	3.6–4.0	4.1–4.5	4.6–5.0	5.1–5.5	5.6–6.0	6.1–6.5	6.6–7.0
N	6–7	4	4–8	6–9	5	5–6	4–5	5–6	5	3–4	7	4–5

Gulati et al. Arch Pathol Lab Med 2011;135:490-494

Primary endpoint

- **Hemostatic treatment response**



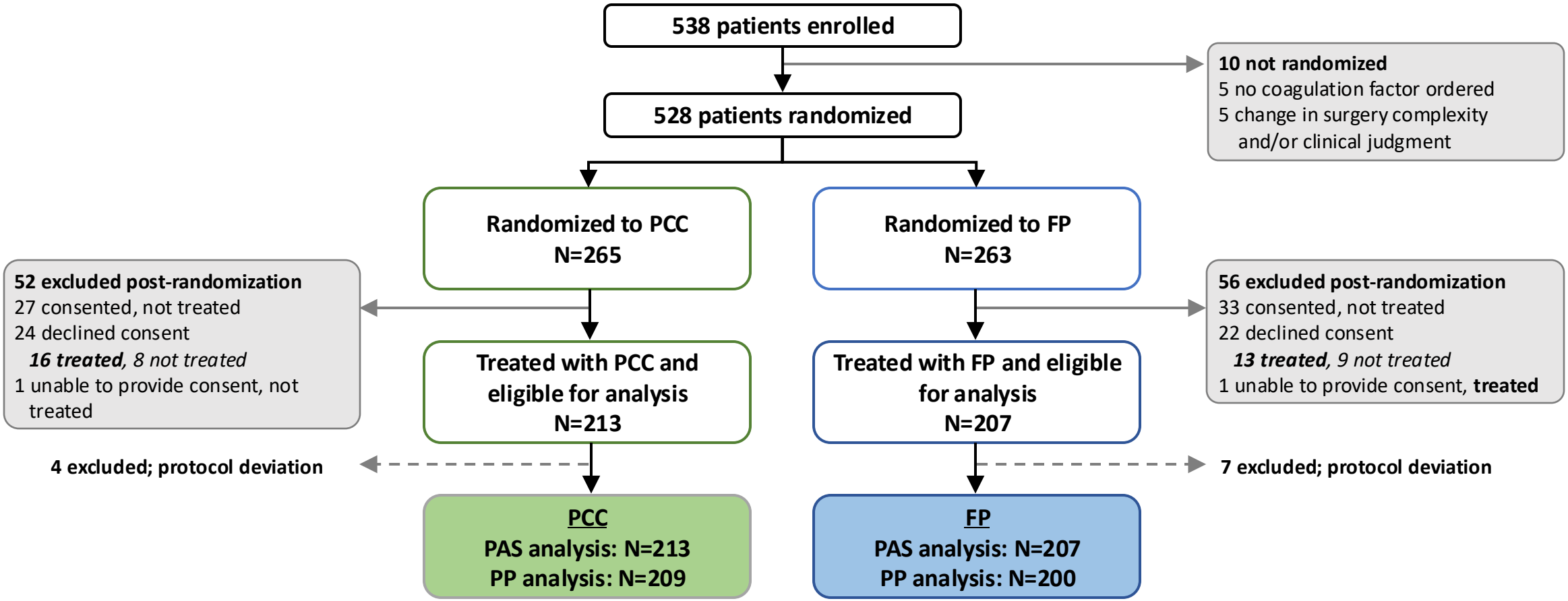
Sample size: 410 patients provided ≥90% power to demonstrate non-inferiority (margin 0.10; one-sided α 0.025; PCC 70% effective vs. FP 65% effective)

Selected other endpoints

Efficacy endpoints	
Incidence of severe to massive bleeding	If received ≥5 RBC units or ≥5 non-IMP FP units, underwent surgical re-exploration due to bleeding, or received rFVIIa during the measured 24-hour time; or chest tube drainage >1 L at 12 hours after chest closure
Total number of ABPs (IMP and non-IMP)	Within 24 hours after CPB end
Total number of ABPs (non-IMP)	Within 24 hours after CPB end
Change in INR	Within 30 minutes before to 60 minutes after IMP initiation

Safety endpoints
Included the incidence of treatment-emergent AEs, treatment-emergent serious AEs, thromboembolic events, acute kidney injury, death, duration of mechanical ventilation, duration of intensive care unit stay, and duration of hospitalization; all measured up to postoperative day 30.

Results – patient disposition



Patient baseline characteristics

- Demographics and surgical characteristics were similar between the groups.

Demographics	PCC Group (N=213)	FP Group (N=207)
Age, median (IQR), years	67 (58–73)	64 (55–72)
Male/Female, No. (%)	157/56 (74/26)	152/55 (73/27)
Weight, mean (SD), kg	85 (19)	84 (20)
Myocardial infarction, No. (%)	49 (23)	48 (23)
Congestive heart failure, No. (%)	36 (17)	37 (18)
Stroke / TIA, No. (%)	14 (7)	15 (7)
Creatinine, median (IQR), mg/dL	0.96 (0.8–1.1)	0.95 (0.8–1.2)
Hemoglobin, median (IQR), g/dL	13.7 (12.1–14.7)	13.6 (11.9–14.6)
Platelets, median (IQR), x10^3/µL	201 (171–242)	199 (163–244)

Surgical characteristics	PCC Group (N=213)	FP Group (N=207)
Previous cardiac surgery, No. (%)	53 (25)	56 (27)
Non-elective surgery, No. (%)	36 (17)	44 (21)
Complex surgery, No. (%)	144 (68)	152 (73)
Procedures, No. (%)		
Aortic valve	110 (52)	98 (47)
Coronary artery bypass graft	91 (43)	86 (42)
Ascending aorta	65 (31)	61 (29)
Mitral valve	48 (23)	47 23)
Aortic arch	26 (12)	24 (12)
CPB duration, mean (SD), min	171 (76.4)	176 (80.5)
Circulatory arrest, No. (%)	33 (15)	34 (16)

Patient intervention details

- High adherence to study protocol.

IMP characteristics	PCC Group (N=213)	FP Group (N=207)
Doses of IMP, No. (%)		
1	213 (100)	207 (100)
2	37 (17)	47 (23)
Amount of IMP, Mean (SD)		
1	23.9 (4.3) IU/kg	11.8 (2.8) mL/kg
2	22.9 (6.3) IU/kg	10.3 (3.8) mL/kg
Time from end of CPB to start of first dose of IMP, median (IQR), min	41 (26–67)	45 (28–69)
Time to complete IMP administration, median (IQR), min	7 (4–10)	26 (17–45)

Hemostatic response – primary endpoint

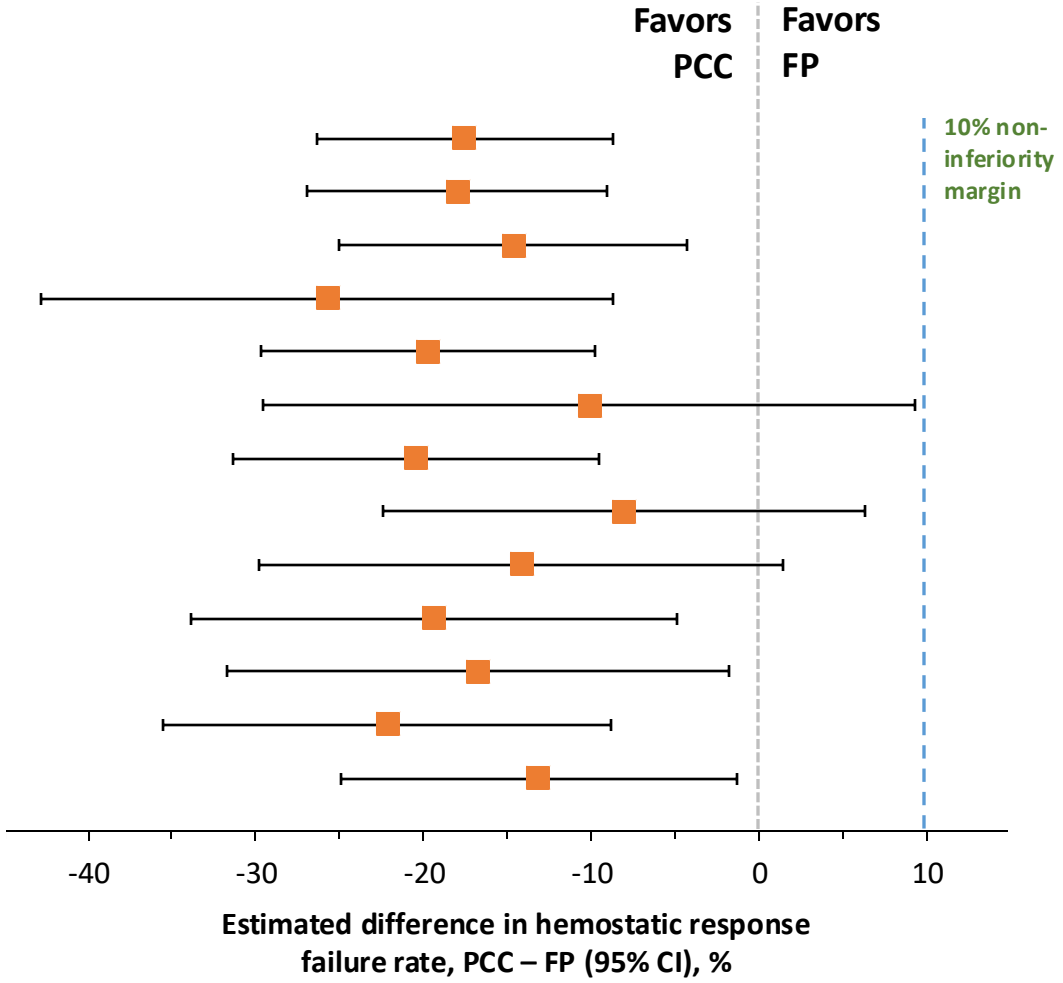
Hemostatic treatment response	PCC Group (N=213)	FP Group (N=207)
Effective, No. (%)	166 (77.9)	125 (60.4)
Ineffective, No. (%)	47 (22.1)	82 (39.6)
PCC to FP		
Treatment difference (95% CI)	**17.55 (8.70, 26.40), P<0.001[a,b]**	
Relative risk (95% CI) of hemostatic failure	**0.56 (0.41, 0.75), P<0.001[a,b]**	

- **PCC was non-inferior and superior to FP** for hemostatic effectiveness.[a,b]

[a]Non-inferiority tested using a one-sided Farrington-Manning score test with a non-inferiority margin of 10% at a significance level of 2.5%; [b]Superiority tested using a two-sided Farrington-Manning score test with a significance level of 5%.

Hemostatic response failure – *a priori* subgroups

Group/Subgroup (PAS)	PCC Group, n/N (%)	FP Group, n/N (%)	Estimated difference, PCC – FP (95% CI), %
Primary analysis set	**47/213 (22.1)**	**82/207 (39.6)**	**−17.55 (−26.40, −8.70)**
Per-protocol analysis set	45/209 (21.5)	79/200 (39.5)	−17.97 (−26.91, −9.03)
Male	38/157 (24.2)	59/152 (38.8)	−14.61 (−24.98, −4.25)
Female	9/56 (16.1)	23/55 (41.8)	−25.75 (−42.76, −8.73)
Elective surgery	40/177 (22.6)	69/163 (42.3)	−19.73 (−29.67, −9.80)
Non-elective surgery	7/36 (19.4)	13/44 (29.5)	−10.10 (−29.58, 9.37)
Complex surgery	35/144 (24.3)	68/152 (44.7)	−20.43 (−31.31, −9.55)
Simple surgery	12/69 (17.4)	14/55 (25.5)	−8.06 (−22.47, 6.35)
CPB duration ≤120 minutes	9/60 (15.0)	14/48 (29.2)	−14.17 (−29.80, 1.47)
CPB duration 121–180 minutes	12/72 (16.7)	27/75 (36.0)	−19.33 (−33.81, −4.85)
CPB duration >180 minutes	26/81 (32.1)	41/84 (48.8)	−16.71 (−31.66, −1.76)
Age <65 years	19/90 (21.1)	45/104 (43.3)	−22.16 (−35.53, −8.79)
Age ≥65 years	28/123 (22.8)	37/103 (35.9)	−13.16 (−24.97, −1.35)



Selected other hemostatic efficacy endpoints

Efficacy endpoint (PAS)	PCC Group (N=213)	FP Group (N=207)	Difference (95% CI)	RR / LS mean ratio (95% CI)	P-value
Severe/massive bleeding, during 24 hours after CPB, No. (%)	30 (14.1)	57 (27.5)	**13.5 (5.8, 21.1)**	**RR: 0.51 (0.34, 0.76)**	**0.001**
Total ABPs (IMP and non-IMP) within 24 hours after CPB, LS mean (95% CI), units	6.6 (5.9, 7.5)	13.8 (12.3, 15.5)	**7.2 (5.4, 9.0)**	**Ratio: 0.48 (0.41, 0.57)**	**<0.001**
Total ABPs (non-IMP) within 24 hours after CPB, LS mean (95% CI), units	6.6 (5.7, 7.7)	9.3 (8.0, 10.8)	**2.7 (1.0, 4.4)**	**Ratio: 0.71 (0.57, 0.88)**	**0.002**
Change in INR, LS mean (95% CI)	−0.84 (−0.77, −0.92)	−0.70 (−0.62, −0.77)	**0.15 (0.04, 0.26)**	NA	**0.008**

Safety (within 30 days after surgery start)

	PCC Group (N=213)	FP Group (N=207)
Any AE, No. (%) [No. events]	206 (96.7) [936]	201 (97.1%) [976]
Any serious AE, No. (%) [No. events]	77 (36.2) [138]	98 (47.3) [201]
Thromboembolic AEs, No. (%) [No. events]	18 (8.5) [26]	15 (7.2) [18]
Stroke	5 (2.3) [5]	5 (2.4) [5]
Vascular thrombosis	15 (7.0) [16]	11 (5.3) [11]
Other	5 (2.3) [5]	2 (1.0) [2]
Death, No. (%)	7 (3.3)	8 (3.9)
Acute kidney injury, No. (%)	22 (10.3)	39 (18.8)
Duration of mechanical ventilation, median (IQR), days	1.0 (1.0–2.0)	1.0 (1.0–2.0)
Duration of initial ICU stay, median (IQR), days	4.0 (2.0–6.0)	4.0 (2.0–7.0)
Duration of initial hospitalization, median (IQR), days	8.0 (7.0–12.0)	9.0 (7.0–13.0)

Safety (within 30 days after surgery start)

	PCC Group (N=213)	FP Group (N=207)
Any serious AE, No. (%)	77 (36.2)	98 (47.3)
Relative risk (95% CI), PCC to FP	**0.76 (0.61, 0.96), P=0.02**	
Acute kidney injury, No. (%)	22 (10.3)	39 (18.8)
Relative risk (95% CI), PCC to FP	**0.55 (0.34, 0.89), P=0.02**	

Conclusions

- PCC is non-inferior and superior to FP for hemostatic response in the management of excessive bleeding related to coagulation factor deficiency in patients undergoing cardiac surgery.
- The greater hemostatic efficacy of PCC over FP was shown across multiple endpoints and was not accompanied by an increase in thromboembolic events.
- PCC may have safety advantages over FP, as shown by the significantly reduced risk of serious adverse events and acute kidney injury.
- **These potentially practice-changing results support the use of PCC over FP for bleeding management in cardiac surgery.**

Thank you