JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Efficacy and Safety of Early Administration of 4-Factor Prothrombin Complex Concentrate in Patients With Trauma at Risk of Massive Transfusion

The PROCOAG Randomized Clinical Trial

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European guidelines: FFP or PCC…

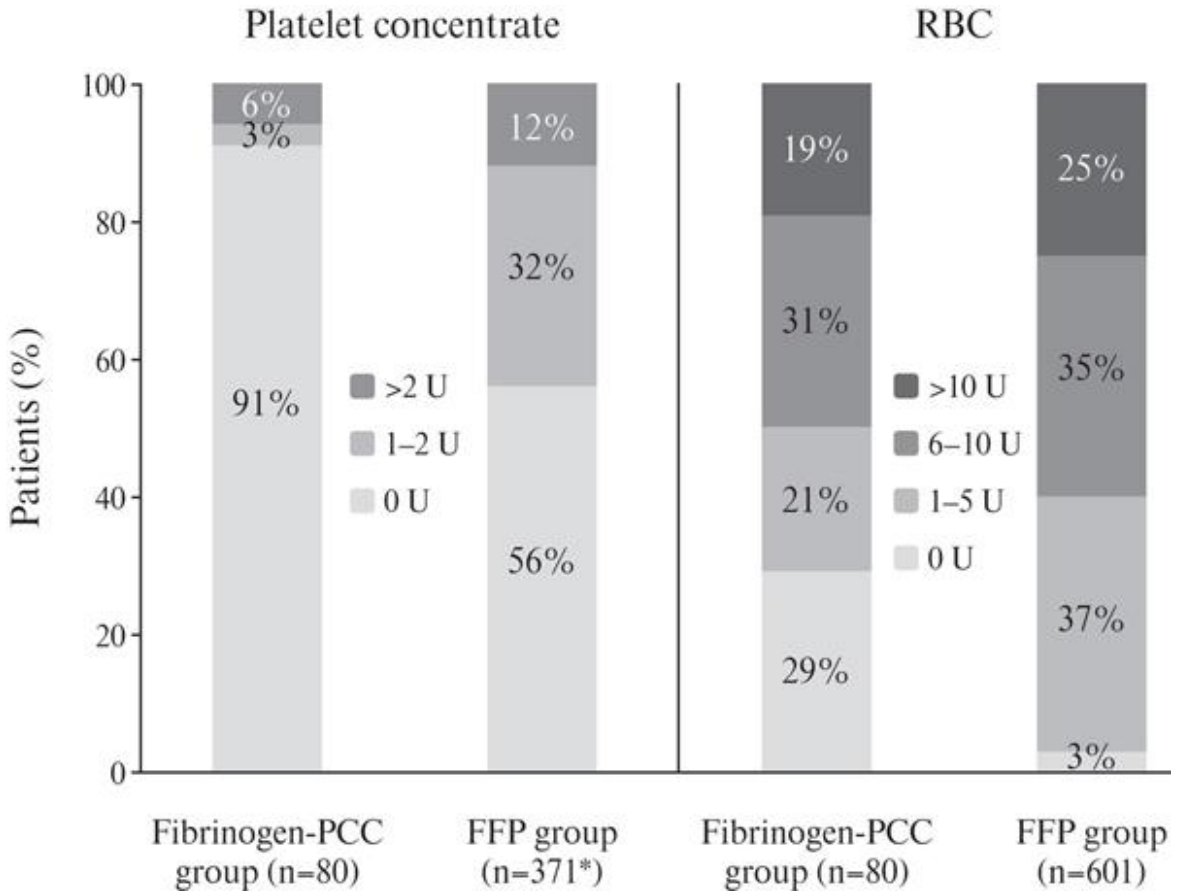
GUIDELINES Open Access

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

Rolf Rossaint[1*], Arash Afshari[2], Bertil Bouillon[3], Vladimir Cerny[4,5], Diana Cimpoesu[6], Nicola Curry[7,8], Jacques Duranteau[9], Daniela Filipescu[10], Oliver Grottke[1], Lars Grønlykke[11], Anatole Harrois[9], Beverley J. Hunt[12], Alexander Kaserer[13], Radko Komadina[14], Mikkel Herold Madsen[2], Marc Maegele[15], Lidia Mora[16], Louis Riddez[17], Carolina S. Romero[18], Charles-Marc Samama[19], Jean-Louis Vincent[20], Sebastian Wiberg[11] and Donat R. Spahn[13]

Provided that fibrinogen levels are normal, we suggest that prothrombin complex concentrate (PCC) is administered to the bleeding patient based on evidence of delayed coagulation initiation using VEM (Grade 2C).

Coagulation factor concentrates



Schöchl *et al. Critical Care* 2011, **15**:R83
http://ccforum.com/content/15/2/R83

CFC vs FFP

Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial

	CFC (n=50)	FFP (n=44)	Estimated difference or odds ratio* (95% CI)	p value
FFP				
Patients†	2 (4%)	44 (100%)	∞ (126·35 to ∞)	<0·0001
Dose (U)	5 (5 to 5)	14 (10 to 14)	−9 (−16 to −2)	0·023
Fibrinogen concentrate				
Patients†	50 (100%)	23 (52%)	0 (0 to 0·10)	<0·0001
Dose (g)	8 (5 to 10)	5 (4·5 to 8)	1 (0 to 3)	0·11
Four-factor PCC				
Patients†	8 (16%)	2 (5%)	0·25 (0·02 to 1·37)	0·098
Dose (IU)	2000 (1875 to 3000)	850 (675 to 1025)	1500 (300 to 4500)	0·046
FXIII				
Patients†	27 (54%)	11 (25%)	0·29 (0·11 to 0·74)	0·0060
Dose (IU)	2000 (2000 to 2500)	1500 (1375 to 2000)	500 (0 to 750)	0·031
Red blood cell concentrate‡				
Patients†	45 (90%)	39 (89%)	0·87 (0·18 to 4·08)	1
Dose (U)	4 (2 to 7)	6 (4 to 11)	−2 (−4 to 0)	0·028
Massive transfusion (U)§†	6 (12%)	13 (30%)	3·04 (0·95 to 10·87)	0·042
Platelet concentrate¶				
Patients†	10 (20%)	21 (48%)	3·60 (1·35 to 10·18)	0·0078
Dose (U)	2 (1 to 4)	2 (1 to 3)	0 (−1 to 2)	0·63

Data are n (%) or median (IQR). CFC=coagulation factor concentrates. FFP=fresh frozen plasma. PCC=prothrombin complex concentrate. FXIII=coagulation factor XIII concentrate. *CFC group minus FFP group. †Binary variables presented with odds ratios. ‡Leucocyte depleted. §≥10 U in 24 h. ¶1 U, 1 apheresis platelet concentrate, or 6 pooled platelet concentrate.

Table 3: **Study drugs and transfusion requirements during the first 24 h after injury**

Innerhofer, Lancet Haematol 2017

Viscoelastic-based therapy



ITACTIC

Subgroup	No. patients	No. alive and free of MT (%) - CCT	No. alive and free of MT (%) - VHA	Odds Ratio (95% CI)	p-value interaction
PTr > 1.2 at baseline					0.872
Yes	102	30/58 (52)	25/44 (57)	1.23 (0.56, 2.69)	
No	254	88/123 (72)	97/131 (74)	1.13 (0.65, 1.97)	
Severe TBI					0.148
Yes	74	16/35 (46)	25/39 (64)	2.12 (0.84, 5.34)	
No	313	106/156 (68)	106/157 (68)	0.98 (0.61, 1.57)	
Prior oral anticoagulants					0.268
Yes	27	10/15 (67)	6/12 (50)	0.50 (0.11, 2.28)	
No	363	112/177 (63)	127/186 (68)	1.25 (0.81, 1.93)	
Per Protocol	313	105/163 (64)	96/150 (64)	0.98 (0.62, 1.56)	
Overall (all patients)	396	125/195 (64)	135/201 (67)	1.15 (0.76, 1.73)	



The effect of VET-guided strategies is uncertain

Thresholds to trigger hemostatic therapies are not consensual

Intensive Care Med (2021) 47:49–59
https://doi.org/10.1007/s00134-020-06266-1

Empiric administration?



Four-factor prothrombin complex concentrate is associated with improved survival in trauma-related hemorrhage: A nationwide propensity-matched analysis

Muhammad Zeeshan, MD, Mohammad Hamidi, MD, Ara J. Feinstein, MD, Lynn Gries, MD, Faisal Jehan, MD, Joseph Sakran, MD, MPH, Ashley Northcutt, MD, Terence O'Keeffe, MD, Narong Kulvatunyou, MD, *and* **Bellal Joseph, MD**, *Tucson, Arizona*

TABLE 3. Primary Outcomes

Variables	FFP Alone (n = 234)	4-PCC + FFP (n = 234)	*p*
4-hour transfusion			
pRBC, mean ± SD, units	5 ± 2	3 ± 2	0.01
Plasma, mean ± SD, units	4 ± 2	2 ± 1	0.01
Platelets, mean ± SD, units	2 ± 1	2 ± 2	0.23
24-hours transfusion			
pRBC, mean ± SD, units	10 ± 4	6 ± 4	0.02
Plasma, mean ± SD, units	6 ± 3	3 ± 2	0.01
Platelets, mean ± SD, units	3 ± 3	3 ± 2	0.72
Mortality, % (n)			
ED mortality	2.5% (6)	2.1% (5)	0.28
Overall in-hospital mortality	27.7% (65)	17.5% (41)	0.01

Empiric administration ?



The role of four-factor prothrombin complex concentrate in coagulopathy of trauma: A propensity matched analysis

Faisal Jehan, MD, Hassan Aziz, MD, Terence O'Keeffe, MD, Muhammad Khan, MD, El Rasheid Zakaria, MD, Mohammad Hamidi, MD, Muhammad Zeeshan, MD, Narong Kulvatunyou, MD, *and* **Bellal Joseph, MD**, *Tucson, Arizona*

TABLE 3. Primary Outcomes

Variables	PCC + FFP (n = 40)	FFP (n = 80)	*p*
INR			
Time to correction, min	373 ± 211	955 ± 524	0.001
Correction of INR, % (n)	95% (38)	92% (74)	0.62
Rate of INR correction	0.31 ± 0.1	0.08 ± 0.1	0.01
Blood products			
Platelets, units	3 ± 3	3 ± 3	0.72
Thromboembolic complications			
DVT	2.5% (1)	1.2% (1)	0.51
PE	0%	0%	0.95
Mesenteric infarction	0%	1.2% (1)	0.84

DVT, deep venous thrombosis, PE, pulmonary embolism.

A RCT was justified to test the efficacy and safety of 4F-PCC



STUDY PROTOCOL Open Access

Four-factor prothrombin complex concentrate to reduce allogenic blood product transfusion in patients with major trauma, the PROCOAG trial: study protocol for a randomized multicenter double-blind superiority study

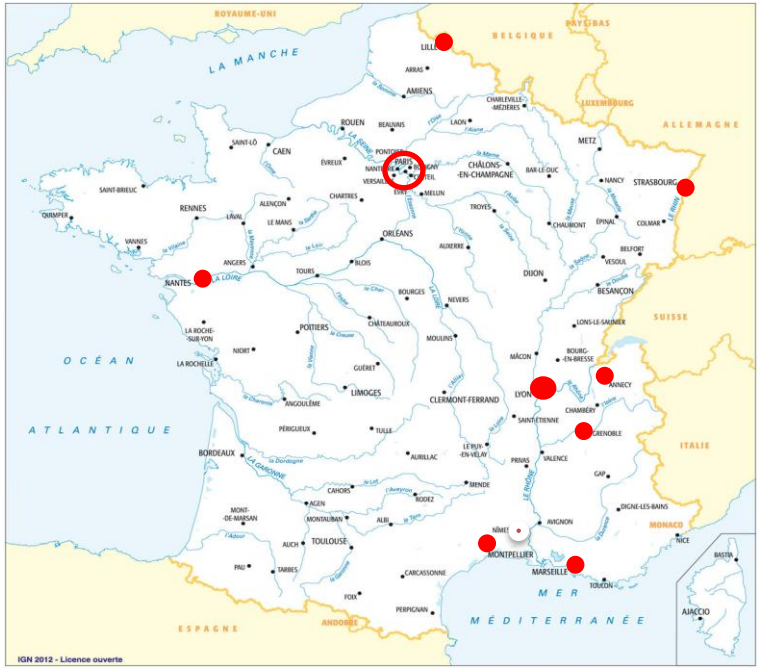
Pierre Bouzat[1*], Jean-Luc Bosson[2], Jean-Stéphane David[3], Bruno Riou[4], Jacques Duranteau[5], Jean-François Payen[1] and on behalf of the PROCOAG study group

SAP written before freezing the database

Design

Multisite, double-blind superiority RCT

12 Level-I trauma centres in France



Inclusion criteria



Adult patients

At risk of massive transfusion:

ABC score > 2 or clinical judgement
AND At least one RBC within the first hour

ABC score
HR > 120 bpm (+1)
SAP < 90 mmHg (+1)
Positive FAST (+1)
Penetrating trauma (+1)

Intervention group / control group



4-factor PCC vs. Placebo (Saline)

1 ml/kg (25 IU / Kg)

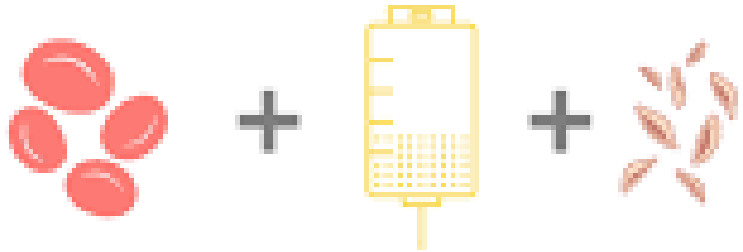
Within the first hour after admission

In opaque syringe / IV line

Both arms were treated according to European guidelines
(TXA, Ratio-based transfusion, Fibrinogen)

Primary outcome

Total blood product consumption at 24 hours



Sample size:
324 patients to observe a reduction of 25% (i.e. 3 units)
from 12 units in the control group

TRENAU Trauma system Trauma Registry
REseau Nord Alpin des Urgences
Northern French Alps Emergency Network

Secondary outcomes

- Individual blood component units consumed within the first 24 hours;
- Time to PTr < 1.5 (severe acute traumatic coagulopathy)
- Time to hemorrhage control
- 24-hour and 28-day mortality
- Number of ICU-free days
- Number of ventilator-free days
- Number of hospital-free days in the first 28 days
- hospitalization status at 28 days
- Glasgow outcome scale extended (GOSE) in patients with brain injury

Safety

Arterial or venous thromboembolic events through day 28

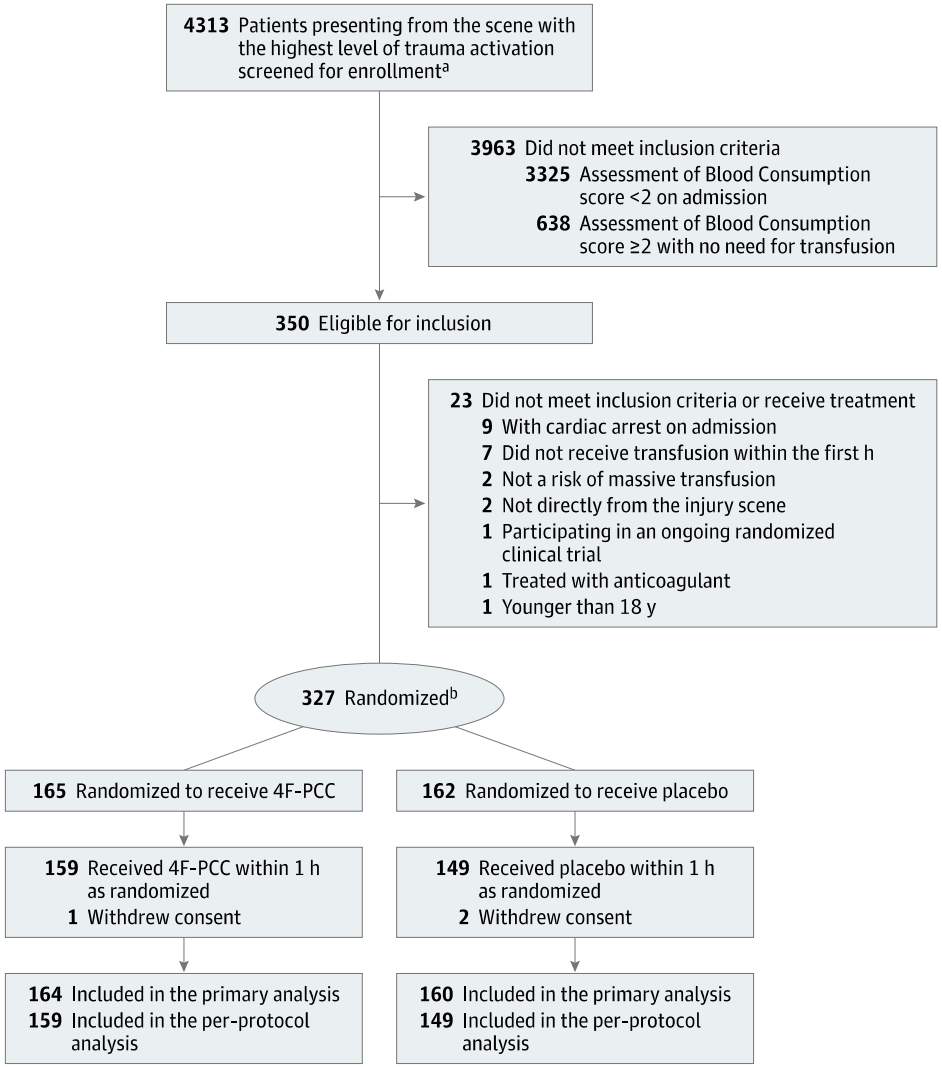
No systematic screening

All events were confirmed by US or CT scan



Results

Flow chart



Patient characteristics

	4F-PCC Group (n=164)	Placebo Group (n=160)
Blunt trauma, No. (%)	135/164 (82%)	125/160 (78%)
Prehospital variables		
Systolic arterial blood pressure, median (IQR), mmHg	101 (80-121) (n=151)	90 (74-111) (n=152)
Glasgow coma score, median (IQR)	14 (9-15) (n=160)	14 (8-15) (n=153)
Tranexamic acid infused, No. (%)	125 (76%)	138 (86%)
Variables on arrival in the trauma bay		
Systolic arterial blood pressure, median (IQR), mmHg	89 (70-115) (n=160)	90 (70-110) (n=156)
Time from arrival to beginning of treatment, median (IQR), min	35 (25-45) (n=154)	30 (15-50) (n=150)

Similar baseline characteristics

Patient characteristics

	4F-PCC Group (n=164)	Placebo Group (n=160)
Lactate (mmol/L), median (IQR)	4.5 (2.7-7.1) (n=132)	4.7 (2.9-7.5) (n=129)
Fibrinogen ≤ 1.5g/L	49 (37%) (n=134)	47 (37%) (n=128)
PTr > 1.2	93 (65%) (n=142)	89 (68%) (n=130)
AIS Head > 2, No. (%)	55 (35%) (n=156)	50 (34%) (n=149)
ISS, median (IQR)	34 (25-50) (n=156)	38 (29-50) (n=149)

Patients with a high traumatic load

Resuscitation indicators

	4F-PCC Group (n=164)	Placebo Group (n=160)
Need for hemostasis control procedure (surgical or radiological), No. (%)	115 (70%)	111 (69%)
Transfusion of at least 3 units of RBCs within the first hour, No. (%)	67 (42%)	60 (38%)
Transfusion of 10 units of RBCs or more within the first 24 hours, No. (%)	42 (26%)	43 (28%)
Fibrinogen concentrate treatment, No. (%)	141 (86%)	129 (81%)
Total dose of fibrinogen concentrate, median (IQR), g	3 (3-7.5)	3 (3-6)

Patients with a high traumatic load

Primary outcome and transfusion-related outcomes

FINDINGS

Median 24-hour blood consumption

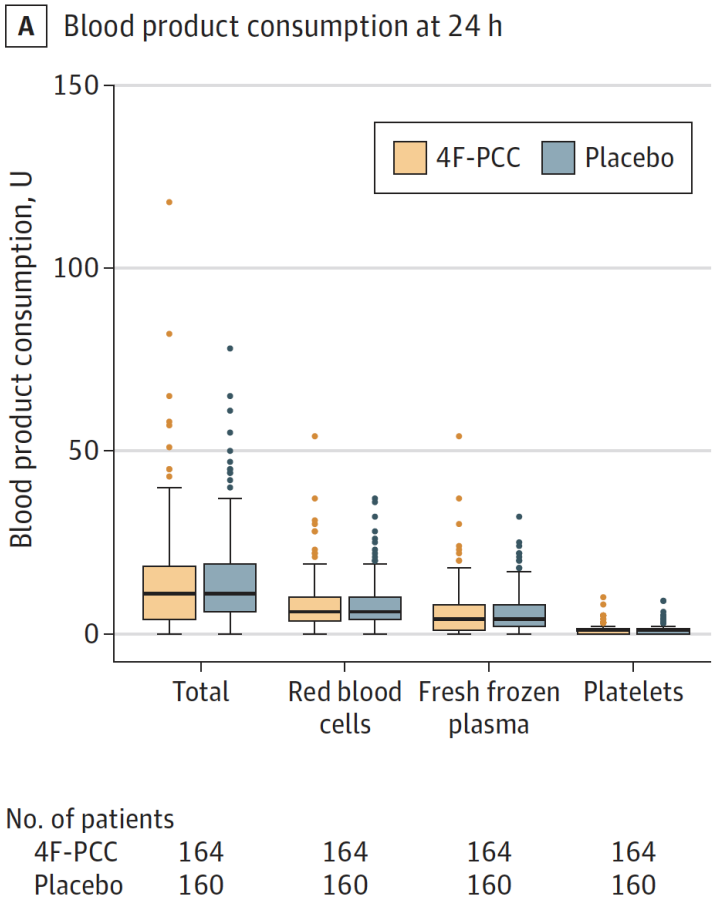
4F-PCC
12 U (IQR, 5-19)

Placebo
11 U (IQR, 6-19)

The between-group difference was not clinically or statistically significant

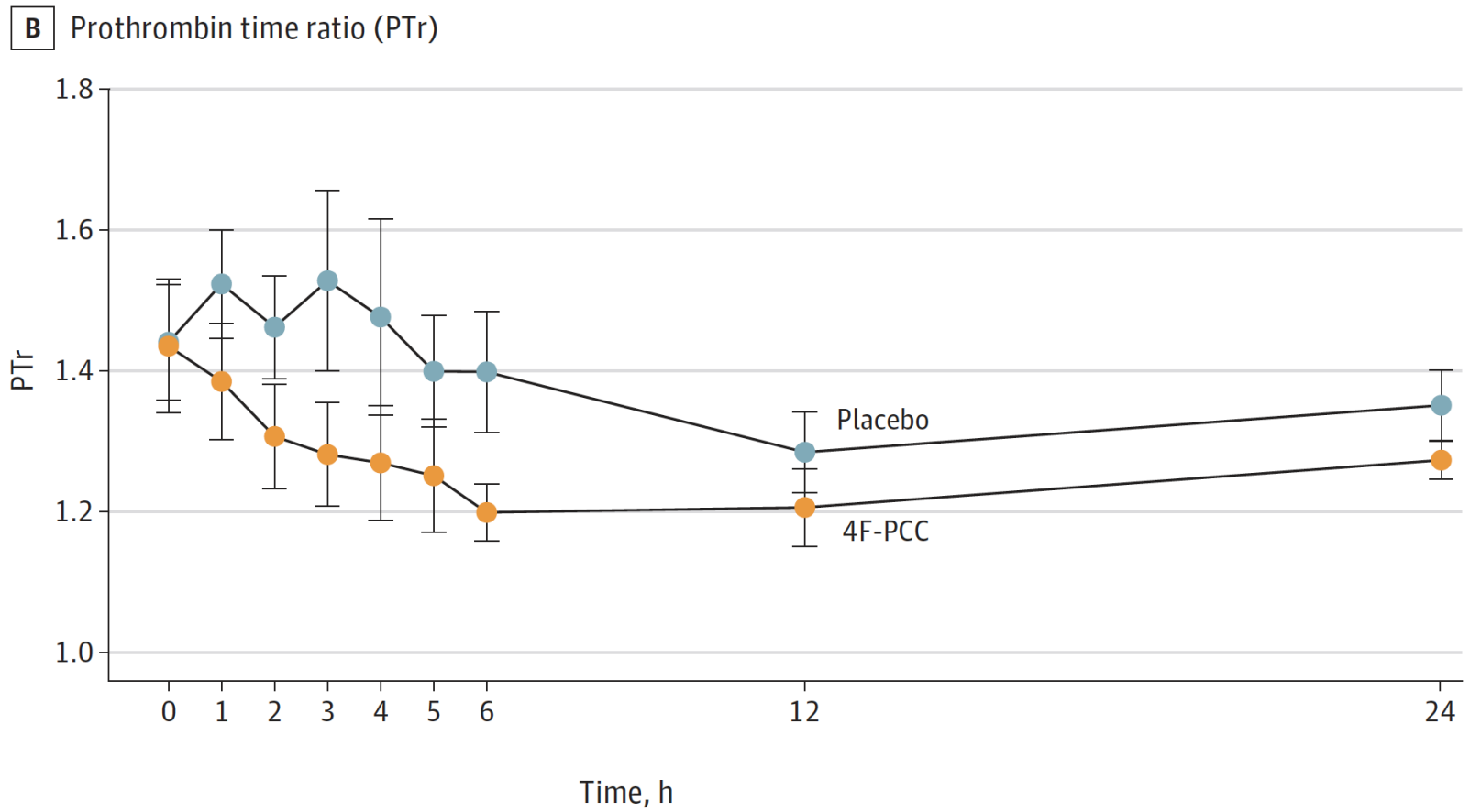
Absolute difference, **0.2 U**

(95% CI, −2.99 to 3.3); *P* = .72



Same results in the per-protocol analysis and in the subgroup of patients with massive transfusion

PT ratio time course



No. of patients									
4F-PCC	142	109	126	129	128	123	127	128	123
Placebo	130	111	119	131	118	115	123	113	110
No. of patients with PTr >1.5									
4F-PCC	36	32	21	18	13	15	13	9	9
Placebo	34	42	41	40	31	29	29	11	19

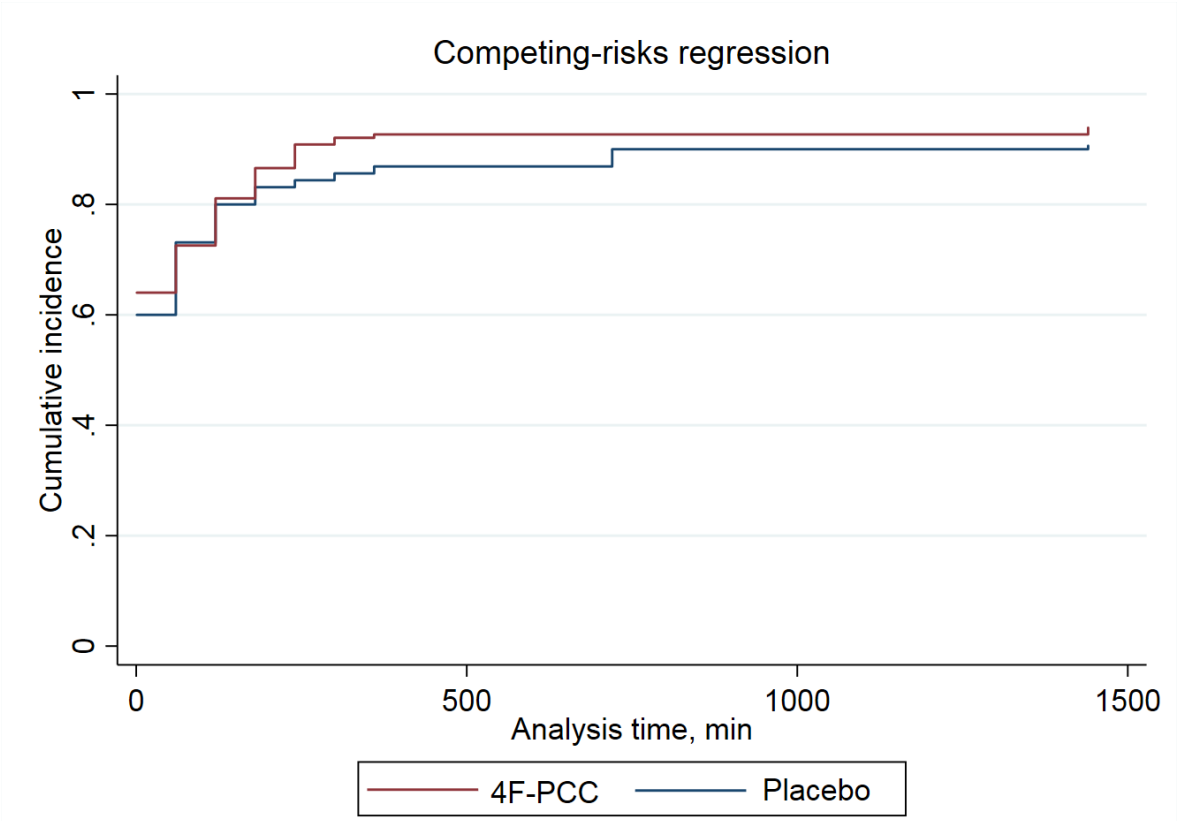
Secondary outcomes

Table 2. Trial Outcomes by Treatment Group

Outcome	No. (%) 4F-PCC (n = 164)	Placebo (n = 160)	Absolute difference (95% CI), %[a]	*P* value[b]
Mortality				
24-h	18 (11)	20 (13)	−2 (−9 to 5)	.67
28-d	26 (17)	30 (21)	−3 (−12 to 5)	.48
Time to achieve anatomic hemostasis, median (IQR) [No.], min[g]	300 (203 to 423) [131]	288 (210 to 404) [128]	22 (−73.3 to 73.8)	.96
Hospital-free days through day 28, median (IQR)	6.5 (0 to 22.5)	7 (0 to 22)	−0.15 (−1.65 to 1.35)	.78
Ventilator-free days through day 28, median (IQR)	4 (0.5 to 7)	4 (0 to 8)	0.33 (−1.0 to 1.6)	.51
ICU-free days through day 28, median (IQR)	6.5 (0 to 22.5)	7 (0 to 22)	1.22 (−5.93 to 8.37)	.78
Disposition at day 28				
Remained hospitalized	44 (33)	44 (35)	0 (−10 to 10)	.81
Intensive care unit	37 (28)	28 (23)	5 (−5 to 16)	
Home	31 (23)	29 (23)	−3 (−12 to 6)	
Died	26 (17)	30 (21)	−3 (−12 to 5)	
Rehabilitation	19 (14)	22 (18)	−2 (−14 to 9)	
Other	2 (2)	1 (1)	1 (−2 to 3)	
Unknown	5 (3)	6 (4)		
Glasgow Outcome Scale-Extended score, median (IQR) [No.][h]	3 (3 to 4) [36]	3 (3 to 5) [27]	−0.5 (−1.91 to 0.91)	.45

Secondary outcomes

Analysis of time to PTr < 1.5 using competing risk regression model by treatment group in the ITT population



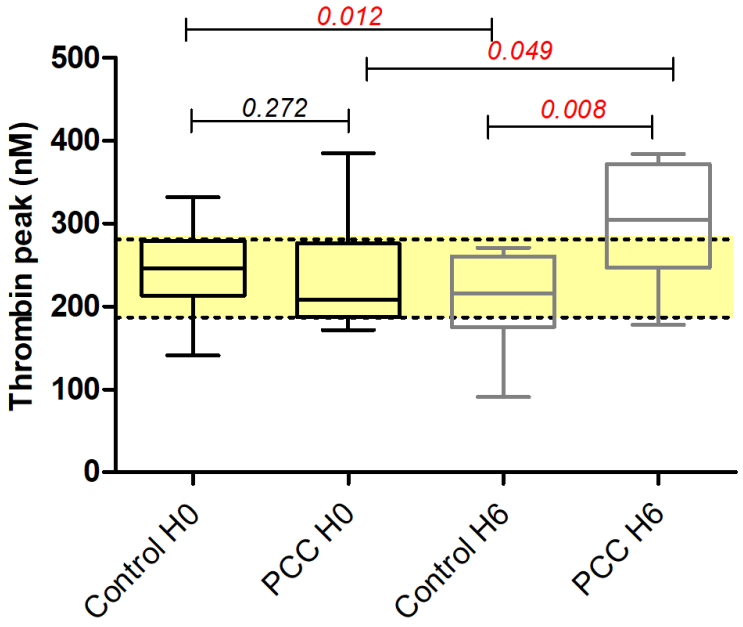
Safety

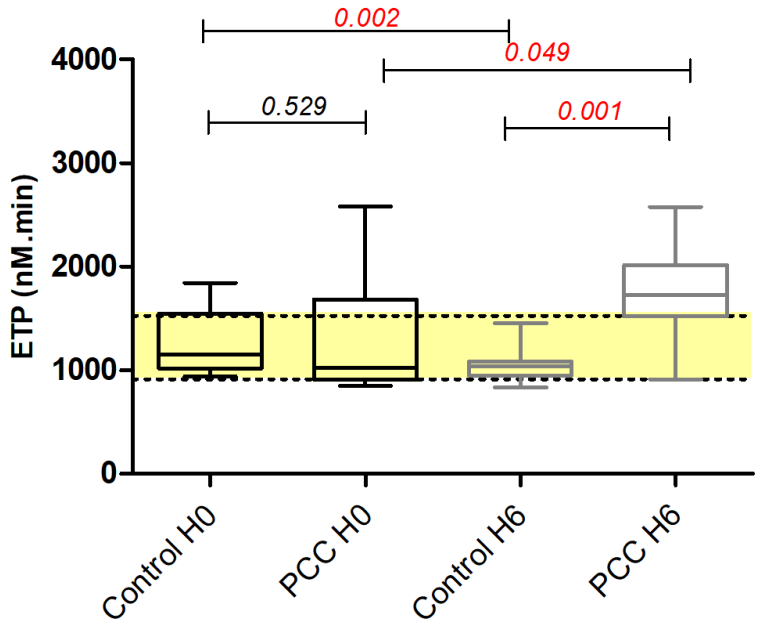
Table 3. Thromboembolic Events by Treatment Group

Thromboembolic event	No. (%) 4F-PCC (n = 164)	No. (%) Placebo (n = 160)	Absolute difference (95% CI), %[a]	Relative risk (95% CI)	*P* value[b]
Patients with at least 1 thromboembolic event, No. (%) [No.]	56 (35) [161]	37 (24) [157]	11 (1 to 21)	1.48 (1.04 to 2.10)	.03
Superficial venous thrombosis	5 (3.1)	1 (0.6)	2 (−1 to 5)		
Deep venous thrombosis	27 (16.8)	23 (14.6)	2 (−6 to 10)		
Pulmonary embolism	20 (12.4)	17 (10.8)	2 (−5 to 9)		
Stroke[c]	2 (1.2)	0	1 (−1 to 3)		
Other[d]	9 (5.6)	5 (3.2)	2 (−2 to 7)		

A post-hoc analysis revealed a higher proportion of thromboembolic events in patients with a PTr > 1.2 given 4F-PCC (31/90, 34%) vs placebo (19/87, 22%) (p=0.06)

Blood samples





N= 11 patients / group

Results in brief

- PCC + FFP is not superior to FFP to decrease total blood product consumption
- PCC increases the thromboembolic risk
- PCC should not be used systematically in bleeding patients at risk of massive transfusion