ACCADEMIA di FORMAZIONE

SIMTI

Attualità nella gestione della raccolta di plasma e del suo utilizzo clinico

Indicazioni nell'utilizzo del complesso protrombinico (PCC): livelli di evidenza

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La sottoscritta, in qualità di Relatrice
dichiara che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

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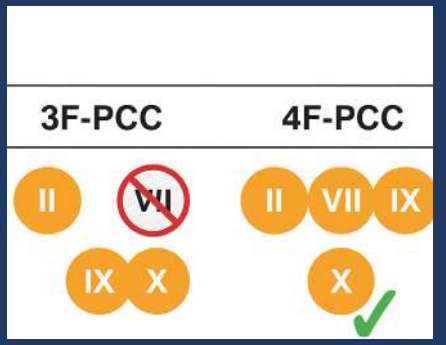
Conflict	Disclosure - if conflict of interest exists
Research Support	**None**
Director, Officer, Employee	**None**
Shareholder	**None**
Honoraria	**Bayer, Sobi, Takeda, Novonordisk, Roche, Viatris, Kedrion, Pfizer**
Advisory Committee	**Bayer, Sobi, Kedrion**
Consultant	**Sobi, CSL Bohering**

Concentrato di complesso protrombinico (PCC)

Il concentrato del complesso protrombinico (PCC) si riferisce a qualsiasi concentrato purificato derivato dal plasma umano di fattori della coagulazione utilizzato nel trattamento o nella profilassi del sanguinamento.

Il PCC può essere prodotto sia come tre fattori (3F-PCC), contenente tre dei quattro fattori della coagulazione vitamina K-dipendenti (VKDF), cioè i fattori II, IX e X, sia come quattro fattori (4F-PCC), contenente tutti i VKDF, cioè i fattori II, VII, IX e X.



Perchè preferire i concentrate al plasma fresco congelato?

4F-PCC vs Plasma Fresco Congelato (FFP)

4F-PCC	Plasma Fresco Congelato (FFP)
Minuti, ricostituzione rapida	Ore, scongelamento e preparazione
Breve, volume ridotto	Obbligatoria
Non necessaria	Circa 25× più alta
✓ Minore	✗ Maggiore

Karkouti K, Gareis M, Li C, et al. *Transfus Apher Sci*. 2025;64(3):104115. doi:10.1016/j.transci.2025.104115

Differenze tra 3F-PCC e 4F-PCC

Caratteristica	3F-PCC	4F-PCC
Fattori contenuti	II, IX, X (❌ manca VII)	II, VII, IX, X (✔ completo)
Reversal INR (warfarin)	❌ Meno efficace	✔ Più rapido ed efficace
Efficacia in sanguinamenti da VKA	❌ Limitata	✔ Superiore, evidenze migliori
Vs Plasma Fresco Congelato (FFP)	❌ Più lento, richiede gruppo ABO	✔ Più rapido, nessuna compatibilità ABO, 25× concentrazione fattori
Costo-efficacia	❌ Peggiore	✔ Migliore complessivamente

Karkouti K, Gareis M, Li C, et al. *Transfus Apher Sci*. 2025;64(3):104115. doi:10.1016/j.transci.2025.104115

Panoramica dei Prothrombin Complex Concentrates (PCC)

Tipo PCC		Indicazioni
4F-PCC (non attivato)		💉 Trattamento sanguinamenti da VKA 🏥 Profilassi perioperatoria (acquisito/congenito) 🧬 Deficit congeniti VKDFs (quando non disponibili concentrati specifici) ⏱️ Reversal urgente VKA
4F-PCC (attivato)		🧩 Emofilia con inibitori 💉 Trattamento sanguinamenti spontanei 🏥 Copertura chirurgica 🔄 Profilassi di routine
3F-PCC (non attivato)		💉 Emofilia B (deficit FIX)

Karkouti K, Gareis M, Li C, et al. *Transfus Apher Sci*. 2025;64(3):104115. doi:10.1016/j.transci.2025.104115

Indicazioni cliniche principali dei PCC

- 💉 **Trattamento di sanguinamenti maggiori** (da VKA, DOAC o altre cause)

- 🏥 **Profilassi perioperatoria** nei pazienti con deficit acquisiti (es. da VKA) o congeniti (se non disponibili concentrati specifici)

- ⏱️ **Reversal urgente** dell'anticoagulazione da VKA in caso di emorragia o chirurgia non procrastinabile

- 🧬 **Deficit congeniti dei fattori vitamina K-dipendenti** (II, VII, IX, X) – quando mancano concentrati specifici

- 🧩 **Emofilia con inibitori** (solo aPCC/FEIBA) – per trattamento, perioperatorio e profilassi

Karkouti K, Gareis M, Li C, et al. *Transfus Apher Sci*. 2025;64(3):104115. doi:10.1016/j.transci.2025.104115

Reversal urgente in paziente in terapia con anticoagulanti

Trial spotlight: reversal VKA e DOAC

Scenario	Studio	Intervento	Risultato principale
💊 **VKA – Urgenza**	Goldstein 2015 (Lancet, RCT)	4F-PCC vs 🩸 FFP	⏱️ Reversal più rapido 💉 Migliore emostasi
🧠 **VKA – ICH**	INCH 2016 (RCT)	PCC vs 🩸 FFP	📉 Espansione ematoma ridotta ⚠️ Nessun chiaro beneficio mortalità
🧠 **FXa-ICH**	ANNEXA-I 2024 (RCT)	Andexanet vs usual care (86% PCC)	📉 Espansione ematoma ↓ ⚠️ ↑ Tromboembolismo ❌ Nessun beneficio su outcome funzionali
💉 **DOAC major bleeding**	Scoping review 2025 (20 studi)	4F-PCC (25–50 U/kg)	✅ Emostasi 70–85% ⚠️ TE 2–14%

1. **Goldstein JN,** et al. *Lancet*. 2015;385(9982):2077–2087.
2. **Kuramatsu JB, Gerner ST, Schellinger PD, et al. (INCH Trial Investigators)** *JAMA*. 2015;313(8):824–836.
3. **Anderson CS, Al-Shahi Salman R, et al. (ANNEXA-I Investigators)** *N Engl J Med*. 2024;391:1431–1442.
4. **Ibrahim NA, et al.** *J Emerg Med*. 2025;75(1):24–46.

PCC in DOAC reversal (20 studi, n=2710 pazienti)

Ibrahim et al., J Emerg Med 2025

Parametro	Risultato
📊 Popolazione	1504 rivaroxaban (56%), 910 apixaban (34%), 285 dabigatran (10%), 11 edoxaban (0.4%)
💉 Indicazioni	62% ICH, 19% GI, 1% interventi urgenti
💊 Dose PCC	25–50 U/kg; prevalente 26–49 U/kg (81%); re-dosing raro (4–5%)
✅ Efficacia	70–85% (ISTH/MSS); Apixaban 54–100%, Rivaroxaban 53–93%, Dabigatran 100%
⚠️ Eventi trombotici	2–14% a 30 giorni
☠️ Mortalità	10–21% (nessuna correlazione diretta con PCC)
🧪 Monitoring	ISTH/MSS nel 60% degli studi; Hb, PT/INR, APTT; TC cerebrale per ICH

Ibrahim, Nazedah Ain et al. “Prothrombin Complex Concentrate in Direct Oral Anticoagulant Reversal: A Systematic Scoping Review.” *The Journal of emergency medicine* vol. 75 (2025): 24-46. doi:10.1016/j.jemermed.2025.05.013

EUROPEAN STROKE JOURNAL

Reversal of anticoagulation in patients with intracerebral haemorrhage related to oral anticoagulants – state of the evidence

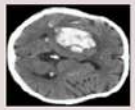
A quarter of ICH occur in context of oral anticoagulation. We review evidence for reversal therapies that aim to normalize coagulation, limit haematoma expansion and improve outcomes.

Methods

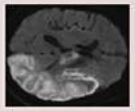
Systematic review for reversal of:

- Vitamin K antagonist
- Direct thrombin inhibitor
- Factor Xa inhibitors

Outcomes:



Haemostatic efficacy



Thromboembolic complications

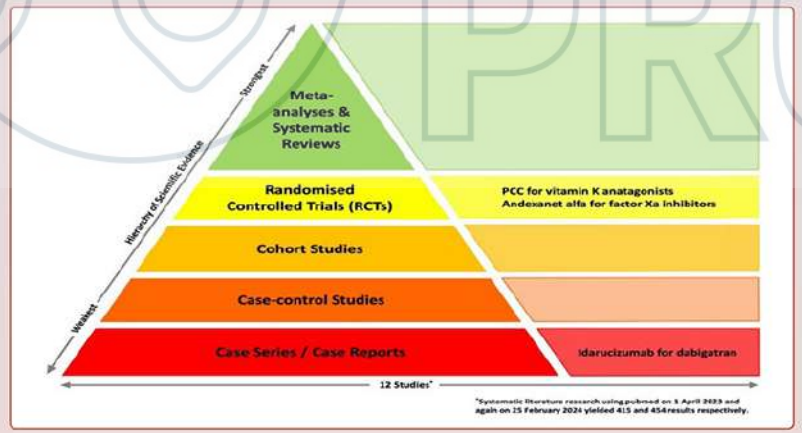
Functional outcome

Results

454 papers screened ⟶ 12 papers included

Evidence is limited and heterogenous:

- Mainly cohort studies and case series
- Only 2 RCT (INCH and ANNEXa-I)



Conclusion

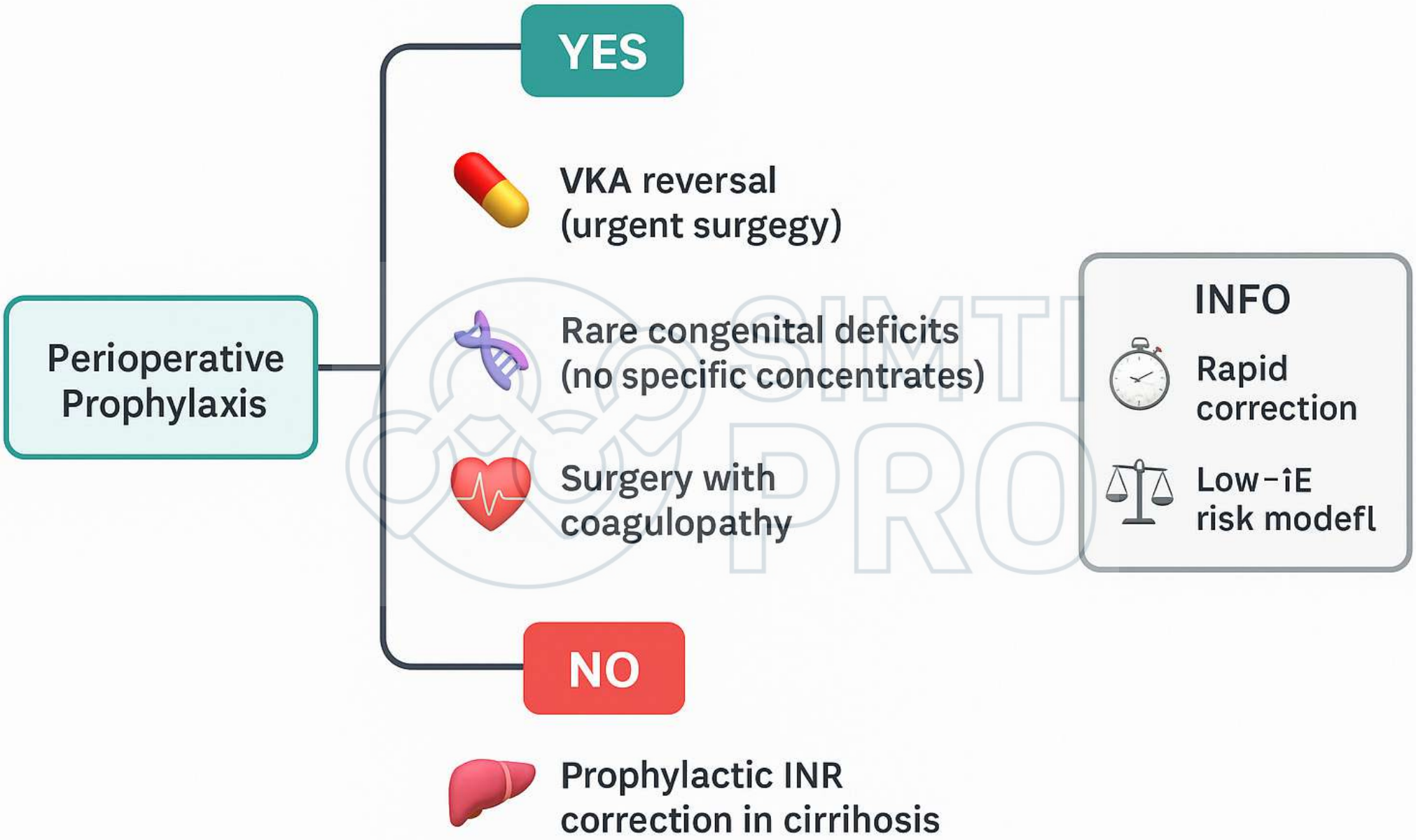
Effective reversal may prevent haematoma expansion

Risk of thromboembolic complications may be significant

No study has successfully translated haemostatic efficacy into better functional outcome

Seiffge, D., et al. European Stroke Journal, 2024 david.seiffge@insel.ch doi.org/10.1177_23969873241281477

Chirurgia in paziente con coagulopatia


Perioperative Prophylaxis
YES
VKA reversal (urgent surgegy)
Rare congenital deficits (no specific concentrates)
Surgery with coagulopathy
NO
Prophylactic INR correction in cirrihosis
INFO
Rapid correction
Low-îE risk modefl

Profilassi perioperatoria con PCC: quando sì, quando no..

Aspetto	Punti chiave
🎯 **Setting**	Pazienti in **VKA** con chirurgia urgente • Deficit congeniti rari (FII/FX) se mancano concentrati specifici
🚫 **Non indicato**	Correzione profilattica INR in cirrosi (emostasi ribilanciata, linee guida EASL 2022)
⚙️ **Operatività**	Uso in strategie *goal-directed* (ROTEM/TEG) • Ottimizzare fibrinogeno ≥1.5–2.0 g/L e piastrine ≥50–100×10^9/L
⏱️ **Obiettivo**	Correzione rapida del deficit fattoriale • Riduzione ritardi procedurali e volumi trasfusi (↓ rischio TACO)
📑 **Evidence**	Goldstein *Lancet* 2015: reversal più rapido vs FFP • JAMA 2025: PCC superiore a FFP in cardiochirurgia • Registri: ↓ volumi trasfusionali
⚠️ **Safety**	Rischio TE basso–moderato • Attenzione a dosi elevate/ripetute • Necessario monitoraggio clinico-lab (PT/INR, ROTEM/TEG)

ARTICLES · Volume 385, Issue 9982, P2077-2087, May 23, 2015 Download Full Issue

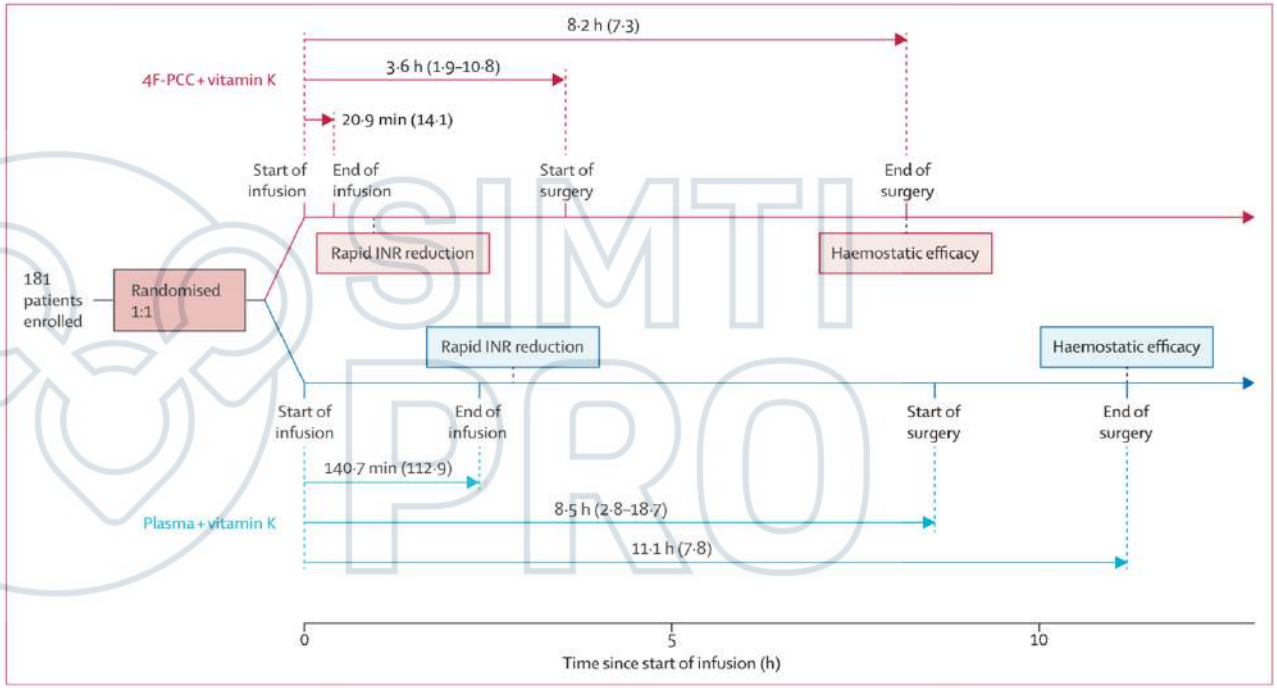
Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial

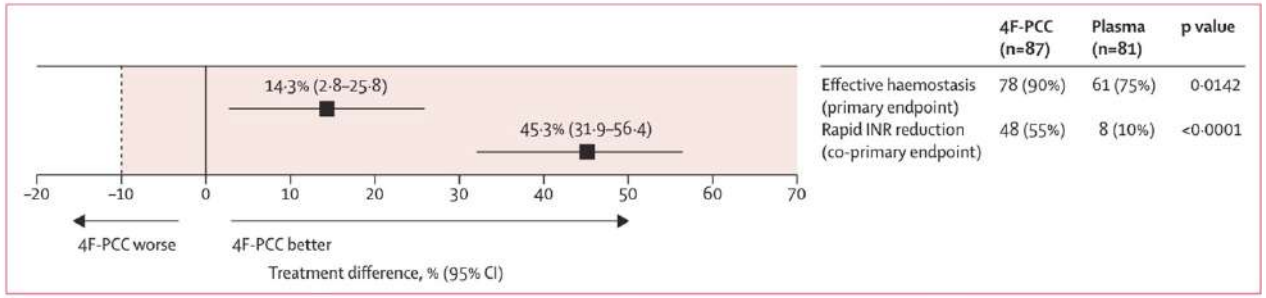
Dr Joshua N Goldstein, MD [a] · Majed A Refaai, MD [b] · Truman J Milling, Jr, MD [c] · Brandon Lewis, DO [d] · Robert Goldberg-Alberts, MA [e] · Bruce A Hug, MD [e] · et al. Show more

	4F-PCC (n=87)	Plasma (n=81)
Sex		
Female	37 (43%)	31 (38%)
Male	50 (57%)	50 (62%)
Age, years	69·4 (13·5)	66·0 (13·2)
Region		
USA	44 (51%)	37 (46%)
Europe/Lebanon	43 (49%)	44 (54%)
Body-mass index, kg/m²	27·9 (6·4)	28·5 (7·9)
Baseline INR	2·90 (2·0–17·0)	2·90 (2·0–26·7)
Type of surgery or procedure		
Cranial neurosurgical	1 (1%)	1 (1%)
Cardiothoracic surgical	3 (3%)	3 (4%)
Major orthopaedic surgical	20 (23%)	15 (19%)
Other surgical	50 (57%)	47 (58%)
Invasive	13 (15%)	15 (19%)
Vitamin K dose		
Oral vitamin K dose ≤2 mg	6 (7%)	2 (2%)
Oral vitamin K dose >2 mg	9 (10%)	10 (12%)
Any IV vitamin K	70 (80%)	69 (85%)
No vitamin K	1 (1%)	0
Not available	1 (1%)	0
Reason for oral VKA therapy		
Arrhythmia	42 (48%)	31 (38%)
Vascular disease	17 (20%)	18 (22%)
Artificial heart valve or joint	13 (15%)	14 (17%)
Thromboembolic event	12 (14%)	16 (20%)
Other	3 (3%)	2 (2%)

Data are n (%), mean (SD), or median (IQR). 4F-PCC=four-factor prothrombin complex concentrate. INR=international normalised ratio. ITT-E=intention-to-treat efficacy. IV=intravenous. VKA=vitamin K antagonist.

***Table 1*: Demographic and baseline characteristics (ITT-E population)**

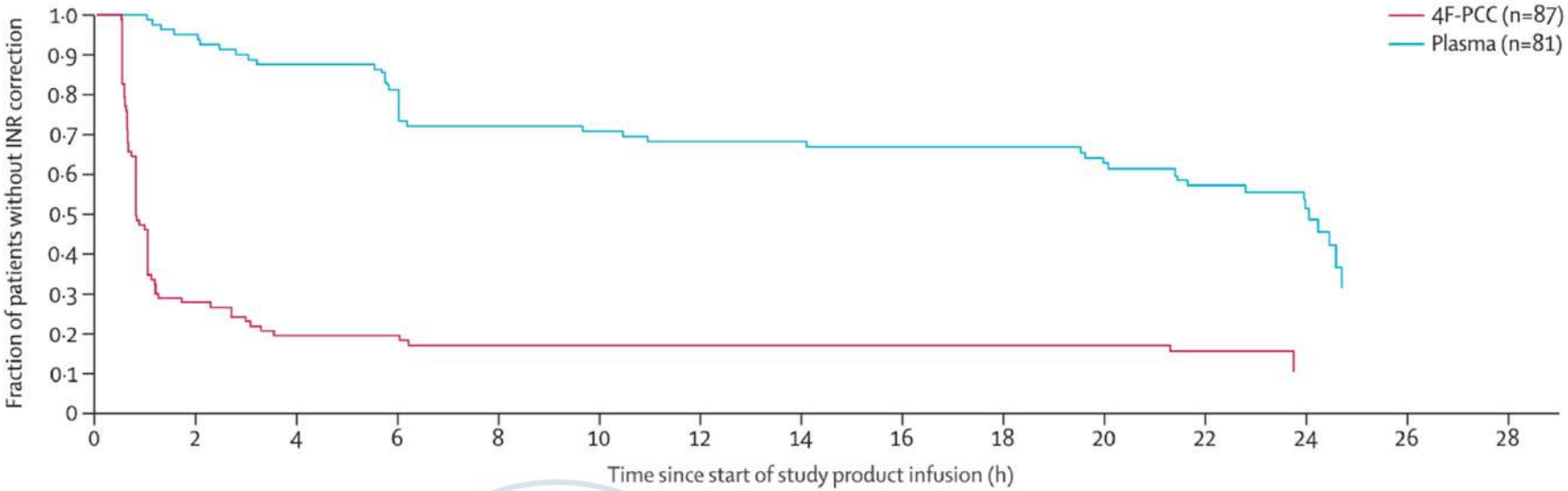




	4F-PCC (n=87)	Plasma (n=81)	p value
Effective haemostasis (primary endpoint)	78 (90%)	61 (75%)	0·0142
Rapid INR reduction (co-primary endpoint)	48 (55%)	8 (10%)	<0·0001

***Figure 3*: Primary and co-primary endpoints**
Figure shows effective haemostasis (haemostatic efficacy rating of excellent or good) and rapid INR reduction (INR ≤1·3 at 0·5 h after end of infusion) by non-inferiority analysis in the ITT-E population. Treatment difference refers to between-group difference of 4F-PCC minus plasma. Tinted area shows zone of non-inferiority, bounded by non-inferiority margin (dotted line) set at −10%. Superiority margin was set at 0% (solid line), meaning that 4F-PCC is superior to plasma if the lower limit of the 95% CI is to the right of the solid line. 4F-PCC=four-factor prothrombin complex concentrate. INR=international normalised ratio. ITT-E=intention-to-treat efficacy.

Lancet. 2015;385(9982):2077–2087.



	4F-PCC (n=87)		Plasma (n=81)		Treatment difference (95% CI)*	p value*
	Endpoint achieved	Endpoint not achieved	Endpoint achieved	Endpoint not achieved		
Haemostatic efficacy endpoint						
Cranial neurosurgical	0	1 (100%)	1 (100%)	0	NA†	..
Cardiothoracic surgical	3 (100%)	0	3 (100%)	0	0%	1·00
Major orthopaedic surgical	16 (80%)	4 (20%)	9 (60%)	6 (40%)	20·0% (−9·6 to 47·0)	0·27
Other surgical	46 (92%)	4 (8%)	35 (74%)	12 (26%)	17·5% (2·6 to 32·3)	0·0279
Invasive procedure	13 (100%)	0	13 (87%)	2 (13%)	13·3% (−11·4 to 37·9)	0·48
Rapid INR reduction endpoint (INR ≤1·3 at 0·5 h after end of infusion)						
Cranial neurosurgical	0	1 (100%)	0	1 (100%)	NA†	..
Cardiothoracic surgical	2 (67%)	1 (33%)	0	3 (100%)	66·7% (−5·9 to 93·9)	0·4
Major orthopaedic surgical	11 (55%)	9 (45%)	2 (13%)	13 (87%)	41·7% (9·5 to 63·1)	0·0158
Other surgical	27 (54%)	23 (46%)	2 (4%)	45 (96%)	49·7% (32·9 to 63·1)	<0·0001
Invasive procedure	8 (62%)	5 (38%)	4 (27%)	11 (73%)	34·9% (−1·4 to 60·9)	0·12

Treatment difference refers to between-group difference of 4F-PCC minus plasma. Endpoint achieved refers to effective haemostasis or rapid reduction in INR; endpoint not achieved refers to non-effective haemostasis or no rapid reduction in INR. 4F-PCC=four-factor prothrombin complex concentrate. ITT-E=intention-to-treat efficacy. NA=not available. *95% CIs and p values generated post hoc using a basic χ^2 test for homogeneity (Fisher's exact test used for small cell sizes). †Analysis not done because fewer than five patients were in this subgroup.

Table 2: **Haemostatic efficacy and rapid INR reduction by type of procedure (ITT-E population)**

Lancet. 2015;385(9982):2077–2087.

Original Investigation

FREE

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

The FARES-II Multicenter Randomized Clinical Trial

JAMA®

QUESTION Is prothrombin complex concentrate (PCC) as efficacious and safe as frozen plasma for treating coagulopathic bleeding in cardiac surgery?

CONCLUSION Among adult patients who required coagulation factor replacement for bleeding during cardiac surgery, PCC was associated with better hemostatic efficacy and safety advantages over frozen plasma.

POPULATION

309 Men
111 Women

Adults ≥18 years who developed bleeding related to coagulation factor deficiency during cardiac surgery

Mean age: 66 years

LOCATIONS

12 Hospitals in Canada and the US

INTERVENTION

528 Patients randomized
420 Patients analyzed

213 PCC

Randomized to receive PCC after cardiopulmonary bypass while in the operating room and within 24 hours if necessary

207 Frozen plasma

Randomized to receive frozen plasma after cardiopulmonary bypass while in the operating room and within 24 hours if necessary

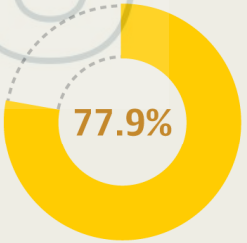
PRIMARY OUTCOME

Effective hemostatic response, defined as requiring no hemostatic intervention between 60 minutes and 24 hours after treatment.

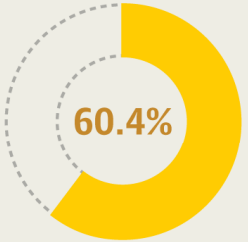
FINDINGS

Effective hemostatis response

PCC
166 of 213 patients



Frozen plasma
125 of 207 patients



The findings were significant:

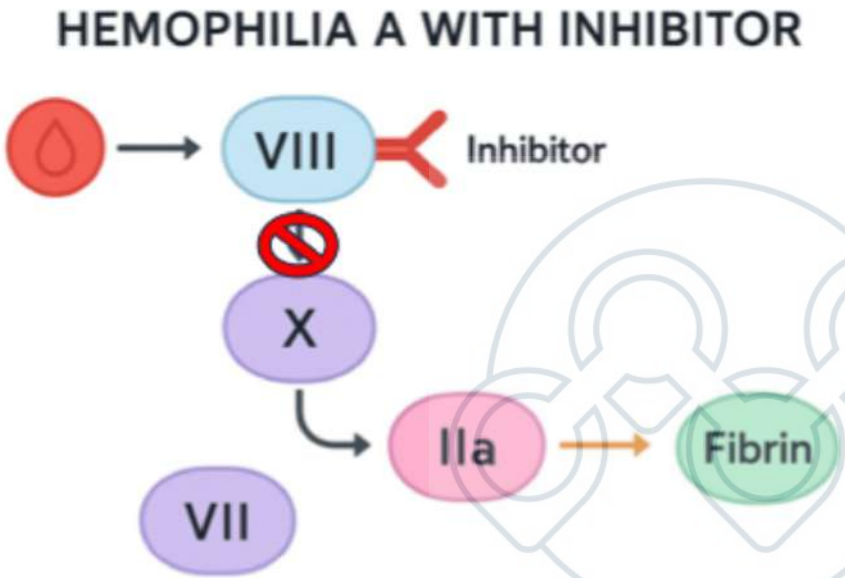
Difference, **17.6%** (95% CI, 8.7% to 26.4%)

Relative risk, **0.56** (95% CI, 0.41 to 0.75; *P*<.001)

Karkouti K, Callum JL, Bartoszko J, et al; the FARES-II Study Group. Prothrombin complex concentrate vs frozen plasma for coagulopathic bleeding in cardiac surgery: the FARES-II multicenter randomized clinical trial. *JAMA*. Published March 29, 2025. doi:10.1001/jama.2025.3501

Trattamento di Breaktrough Bleeding di pazienti con Emofilia ed inibitore

Clinical setting: emofilia A in profilassi con emicizumab

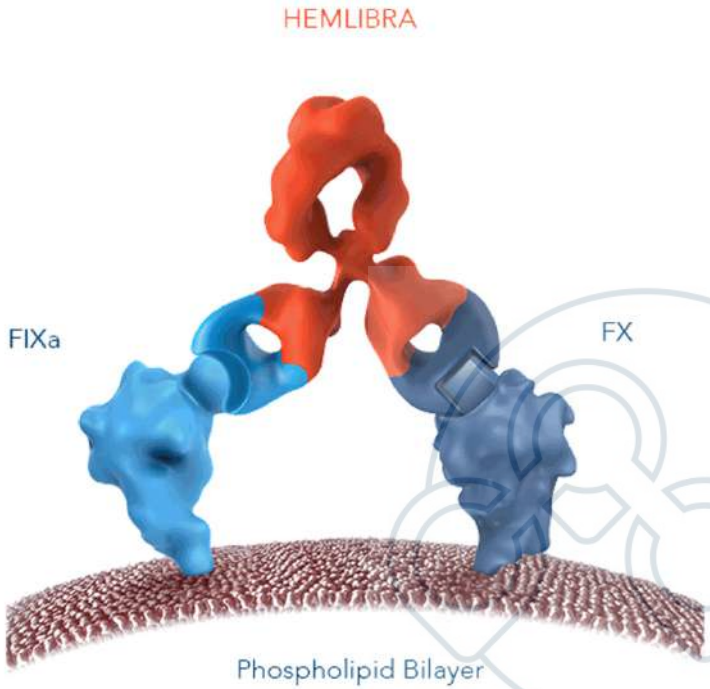


📦 **Definizione di inibitore**
Autoanticorpi neutralizzanti diretti contro il **FVIII**, capaci di bloccarne l'attività coagulativa.
👉 Complicanza immunologica più grave della terapia sostitutiva nell'emofilia A.

📦 **Emofilia A con inibitore:** Paziente emofilico A che sviluppa anticorpi anti-FVIII → il FVIII non può più agire come cofattore tra **FIXa e FX**.

🔴 Risultato: ridotta efficacia della terapia sostitutiva, rischio emorragico aumentato.
💊 Trattamento: necessità di **terapie bypassanti** (aPCC, rFVIIa) o di **nuove strategie** (emicizumab).

Clinical setting: emofilia A in profilassi con emicizumab



📦 **Definizione di emicizumab:**

- Anticorpo monoclonale **bispecifico IgG4**
- Si lega contemporaneamente a **FIXa** e **FX** mimando il ruolo cofattoriale del **FVIIIa**
- Somministrazione **sottocutanea**, emivita lunga (~28 giorni)
- Utilizzato in **profilassi**, non per il trattamento acuto del sanguinamento

📦 **Emicizumab nella pratica clinica:**

- Efficace anche nei pazienti con **inibitori anti-FVIII**
- Riduce drasticamente gli episodi emorragici
- **Breakthrough bleeds**: gestiti preferenzialmente con **rFVIIa**
- ⚠️ **Uso concomitante di aPCC solo a dosi basse e limitate** → rischio **TE/TMA**
- Interferisce con test coagulativi basati su **aPTT** → servono metodi alternativi

Evidenze dal programma HAVEN

Studio	Popolazione	ABR (Annual Bleeding Rate)	TMA / Eventi trombotici
HAVEN 1	Adulti/adolescenti con inibitori	↓ **87%** vs bypassanti	🔴 3 casi TMA/TE con alte dosi aPCC
HAVEN 2	Bambini con inibitori	↓ >80%, ABR mediano 0.3	🟢 Nessun TMA
HAVEN 3	Adulti/adolescenti senza inibitori	↓ **80%** vs FVIII on-demand	🟢 Nessun TMA
HAVEN 4	≥12 anni, con/senza inibitori	ABR 1.5 con profilassi mensile	🟢 Nessun TMA

- Oldenburg J, et al. *NEJM*. 2017;377:809–818 (HAVEN 1)
- Young G, et al. *Lancet Haematol*. 2019;6(6):e295–e305 (HAVEN 2)
- Mahlangu J, et al. *NEJM*. 2018;379:811–822 (HAVEN 3)
- Pipe SW, et al. *Blood*. 2019;134(24):1973–1982 (HAVEN 4)

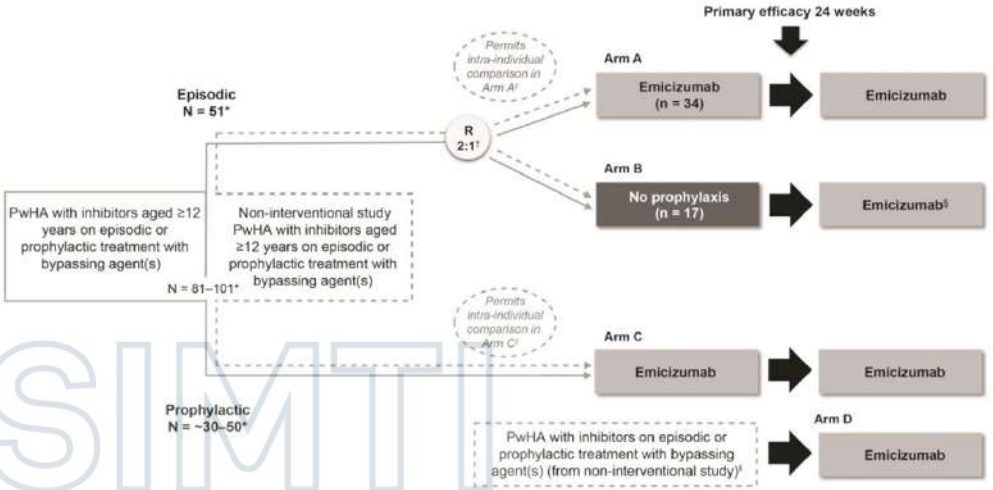
Data from the HAVEN 1 trial

ORIGINAL ARTICLE

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Authors: Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D. Author Info & Affiliations

Published August 31, 2017 | N Engl J Med 2017;377:809-818 | DOI: 10.1056/NEJMoa1703068 | VOL. 377 NO. 9



Of 104 participants who received emicizumab prophylaxis, 28 (27%) used activated prothrombin complex concentrate, 34 (33%) used recombinant factor VIIa, and 13 (12%) used both bypassing agents (Table S4 in the Supplementary Appendix). A range of doses of recombinant factor VIIa was used, although treatment episodes generally lasted for 1 day. Most use of activated prothrombin complex concentrate was less than 100 U per kilogram for 1 day, but a small number of treatment episodes averaged more than 100 U per kilogram daily and lasted more than 1 day (19 treatment events) (Table S5 in the Supplementary Appendix). The 5 participants who had thrombotic microangiopathy or thrombosis did so after treatment with activated prothrombin complex concentrate that averaged more than 100 U per kilogram daily for more than 1 day (see the Results section in the Supplementary Appendix). No events occurred after the use of activated prothrombin complex for 1 day, after treatment with recombinant factor VIIa alone (even at high doses), or with emicizumab prophylaxis alone.

Oldenburg J, et al. *NEJM*. 2017;377:809–818 (HAVEN 1)

Activated prothrombin complex concentrate in patients receiving emicizumab prophylaxis: from evidence to clinical practice

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rpth research & practice in thrombosis & haemostasis

⚠️ **Uso cauto e limitato**: solo se necessario e ≤ 100 U/kg/24h

🔄 **Cambio di paradigma**: ridurre al minimo l'uso di aPCC, preferire alternative (es. rFVIIa)

🧪 **Meccanismo**: combinazione emicizumab + aPCC → resistenza all'activated protein C → rischio trombotico

📊 **SAFE Study (NCT04563520)**: in corso per definire dosaggi sicuri e personalizzati (monitoraggio trombina)

✅ **Raccomandazione pratica**: usare la dose minima efficace e limitare durata trattamento

📝 Take home messages 📝

✅ 4F-PCC è la terapia di scelta per il reversal urgente di VKA: più rapido ed efficace del plasma fresco.

📊 Evidenze crescenti supportano l'uso del PCC nei sanguinamenti maggiori da DOAC in assenza di antidoti specifici (successo emostatico 70–85%, rischio TE 2–14%).

🩸 In chirurgia/trauma con coagulopatia il PCC è utile in strategie *goal-directed* (ROTEM/TEG), ma non va usato per la correzione profilattica in cirrosi.

🧩 Emofilia A con inibitori: i PCC attivati restano un'opzione, ma **emicizumab** ha rivoluzionato la profilassi.

⚠️ Casi di TMA solo in HAVEN 1 con alte dosi di aPCC concomitanti → oggi raccomandato l'uso di **rFVIIa** nei breakthrough bleeds.

🚀 Nuove evidenze (SAFE trial) stanno definendo dosi sicure e personalizzate di aPCC in pazienti trattati con emicizumab.