



Factor-based therapy

Rational Use of Allogeneic Blood Products

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Disclosures and conflicts of interest

Apiro, Bayer Healthcare, Boehringer Ingelheim,
CSL Behring, Haemonetics, Octapharma

Patent for endothelial-coated microbeads

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Trauma-induced Coagulopathy



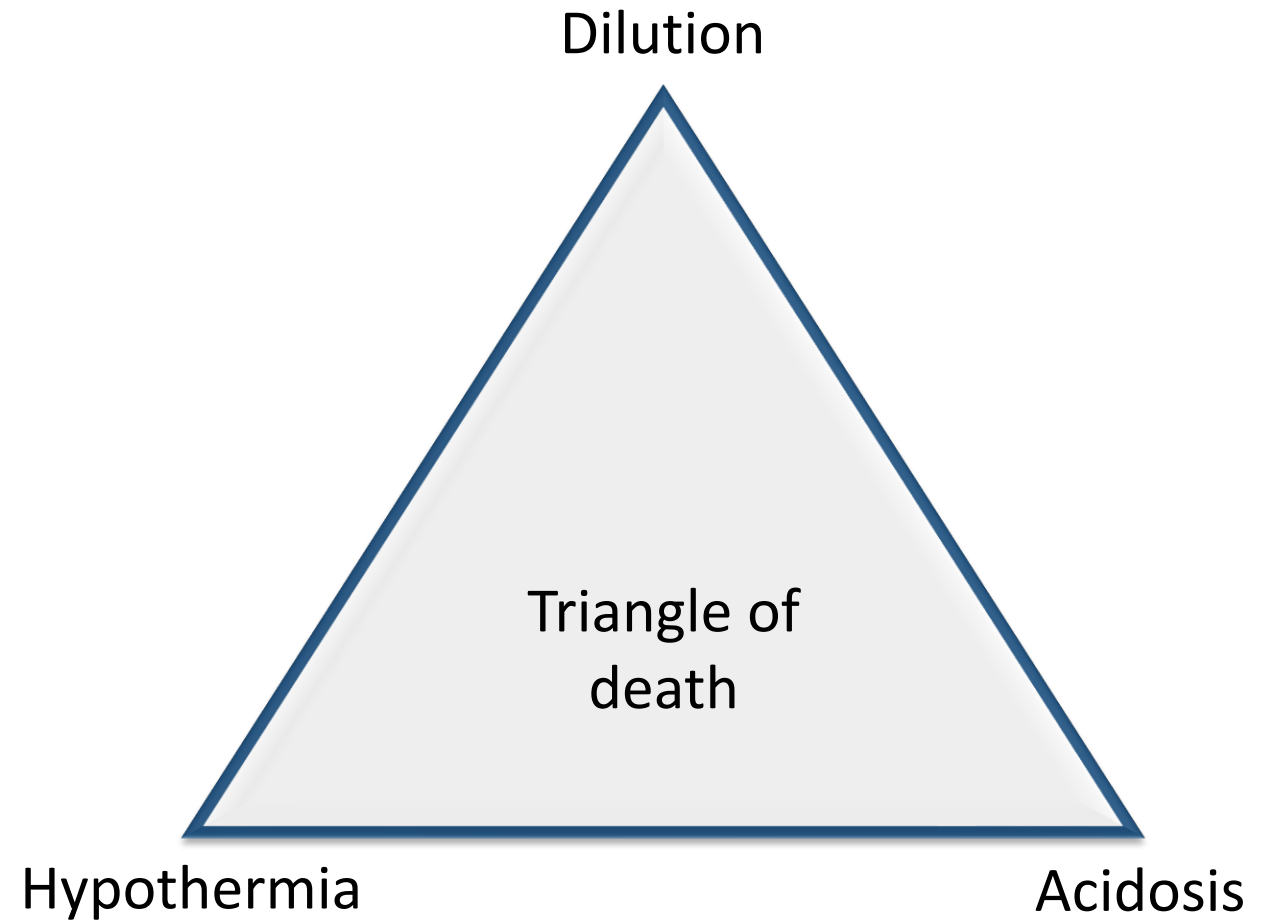
Update 2023

Polytrauma/Schwerverletzten-Behandlung S3-Leitlinie

Trauma-induced coagulopathy (TIC) is a distinct clinical condition that significantly affects survival!

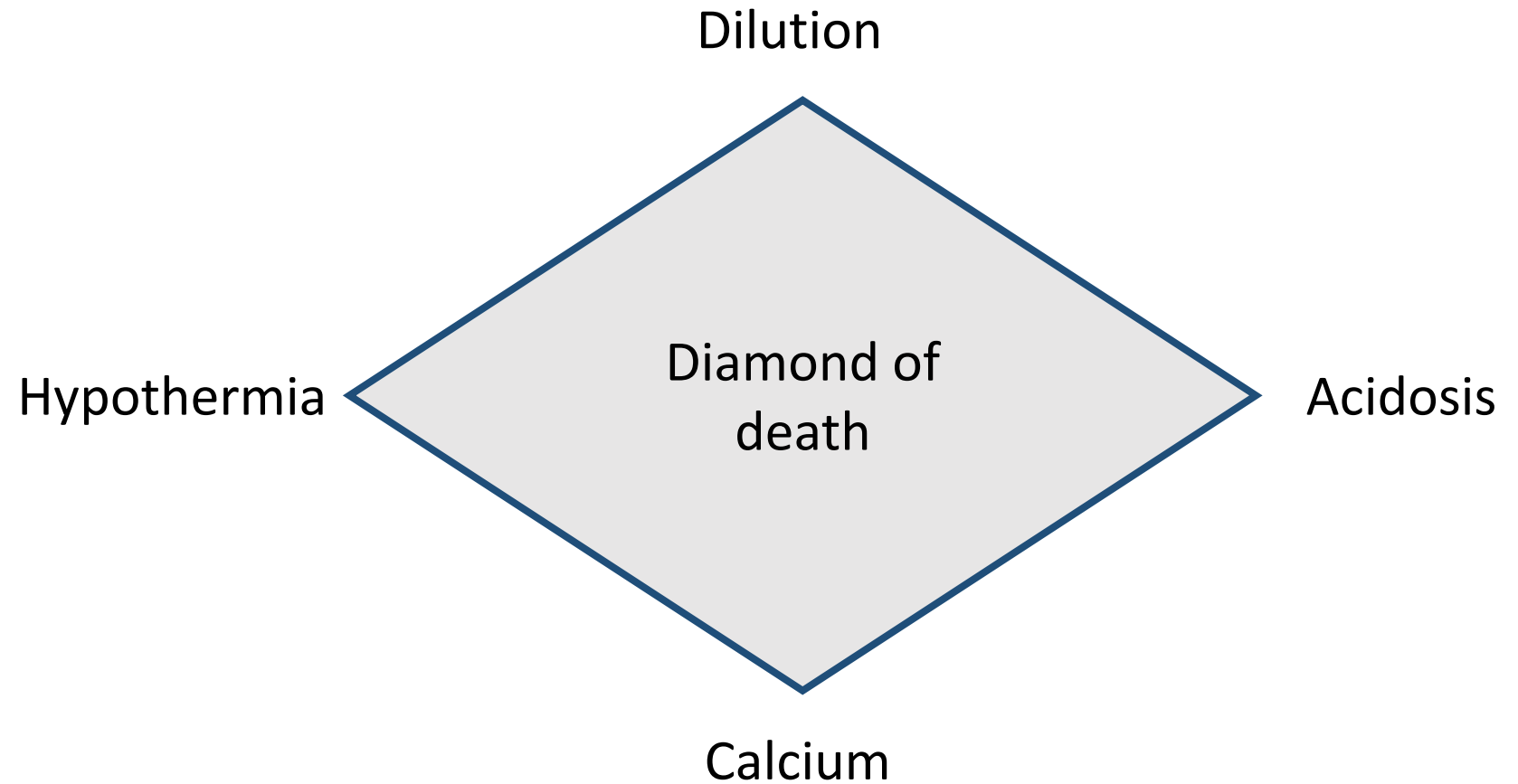
Trauma-induced Coagulopathy

Pathophysiology



Trauma-induced Coagulopathy

Pathophysiology

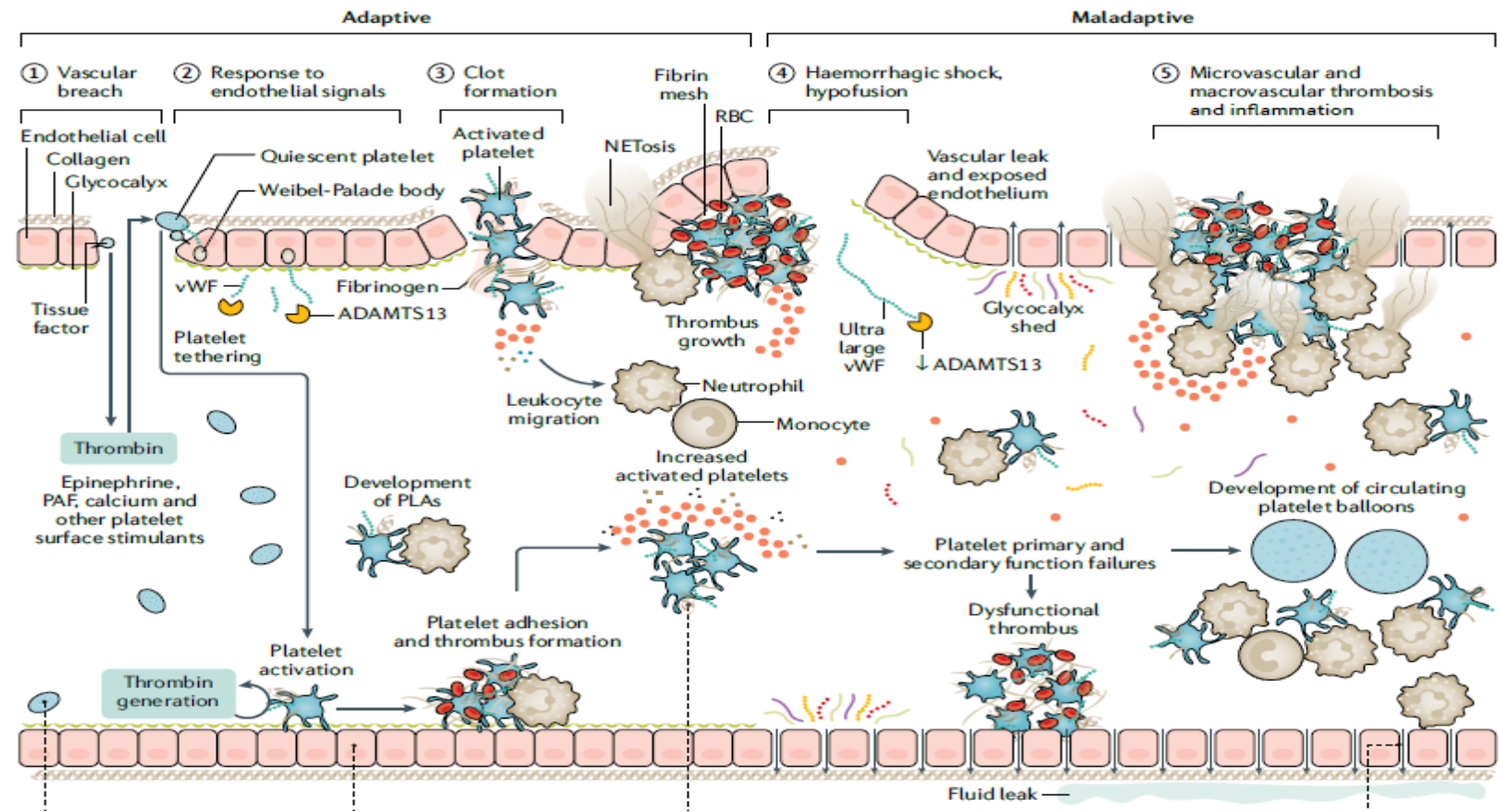


Trauma-induced Coagulopathy

Pathophysiology

Trauma-induced coagulopathy

Moore EE, et al. Nat Rev Dis Primers 2021;7:30



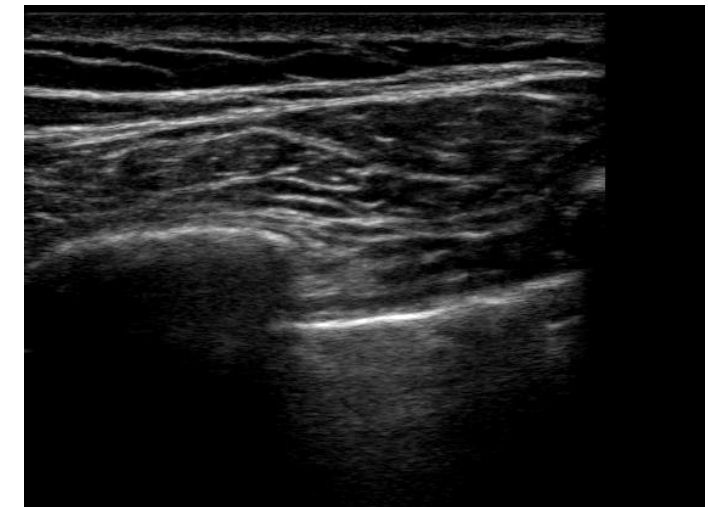
Male, aged 17 years



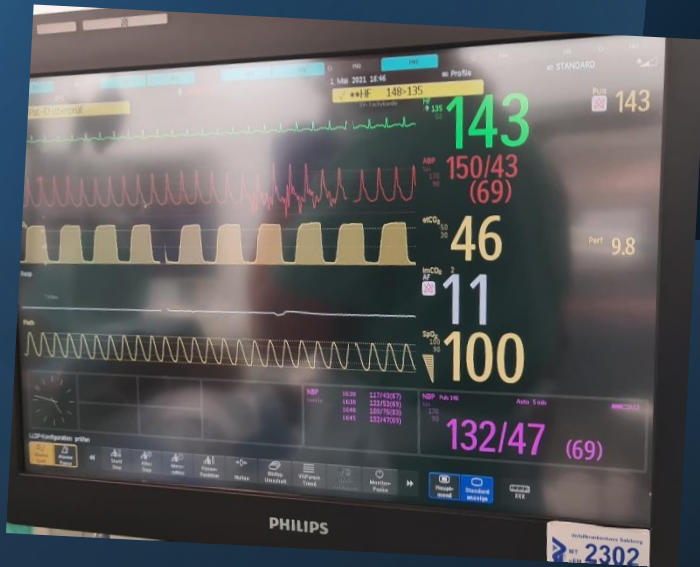
Male, aged 17 years

ER admission

- **Airway**
 - Uncompromised
- **Breathing**
 - Respiratory rate 30/min
 - “Can’t breathe”
- **Circulation:**
 - Systolic BP: 150 mmHg
 - HR: 140/min
 - Positive FAST
- **GCS: 15**



ISS 50



- Liver rupture IV
- Pancreatic tail rupture
- Spleen rupture
- Diaphragmatic rupture
- Stomach rupture
 - Gastric content in left hemithorax
- Bilateral renal rupture
- Left pneumothorax



Lab results upon ER-Admission

Blood cell count

Hb (g/dL)	16
Hct (%)	45.7
Platelet count (g/L)	281

Coagulation tests

PTI (%)	84
aPTT (sec)	26.3
Fibrinogen (mg/dL)	225

BGA

Lactate (mmol/L)	3.0
BE (mmol/L)	-3.5
IL-6 (pg/mL)	25.4

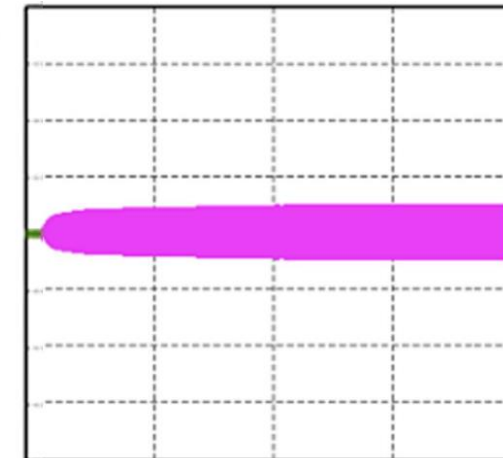
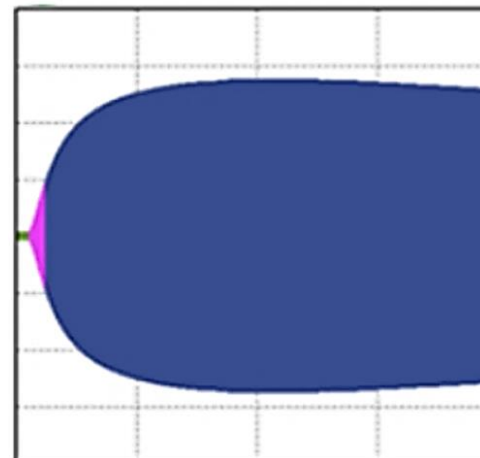
Viscoelastic tests ClotPro®

EX-Test

CT 71 s (38–65)
A5 44 mm (38–65)
A10 52 mm (47–67)
A20 55 mm (52–67)
MCF 56 mm (53–65)
ML 6 % (2–12)

Fib-Test

CT 73 s (55–87)
A5 7 mm (6–21)
A10 9 mm (7–23)
A20 11 mm (8–25)
MCF 13 mm (9–27)
ML 2 % (0–2)



A5, amplitude at 5 minutes; A10, amplitude at 10 minutes ; A20, amplitude at 20 minutes; aPTT, activated partial thromboplastin time; BE, base excess; CT, clotting time; ER, emergency room; Hb, hemoglobin; Hct, hematocrit; IL-6, interleukin-6; MCF, maximum clot firmness; ML, maximum lysis; PTI, prothrombin time index.

Male, aged 17 years



Male, aged 17 years

ISS 38

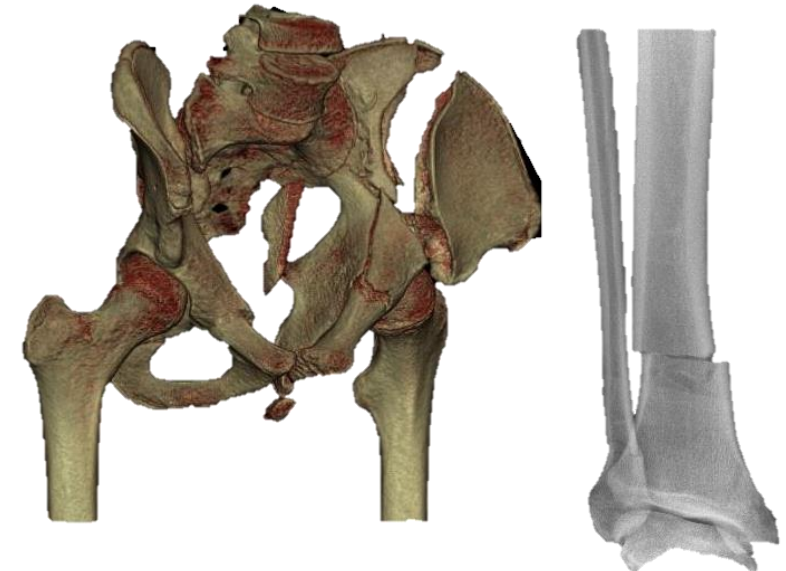
ER-Admission

Syst. BP: 50mm Hg

HR: 145/min

19:56	47/28(33)
19:59	100/54(65)
20:02	77/39(48)
20:05	79/57(63)
20:07	45/20(23)
20:10	87/51(60)
20:16	60/40(45)

- unstable pelvic ring injury
- vertical shear–type pelvic fracture (Tile C)
- Tibia fracture
- Abdominal contusion
- Severe haemorrhagic shock



ER-Admission

Lab - Test

Blood cell count

Hb (g/dL)	8.2
Hct (%)	24.4
Platelet count (g/L)	112

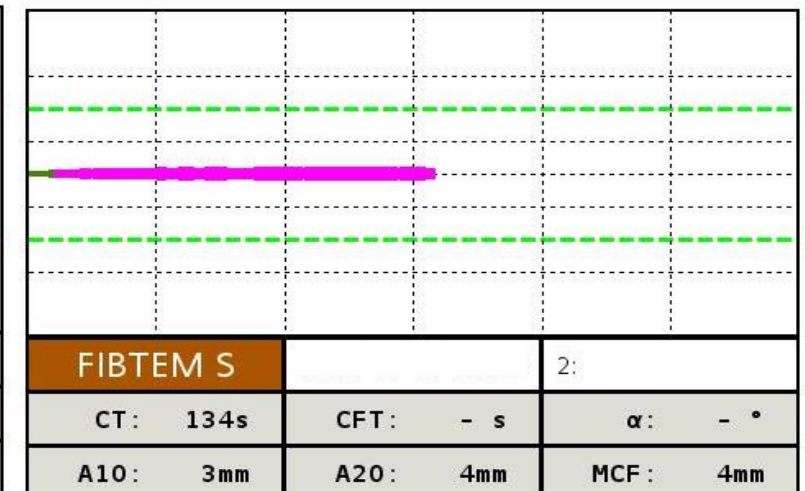
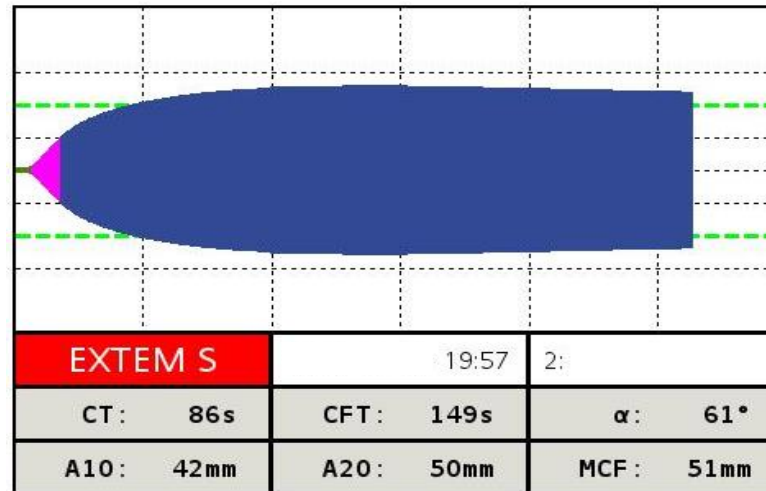
Coagulation tests

PTI (%)	54
aPTT (sec)	45.2
Fibrinogen (mg/dL)	95

BGA

Lactate (mmol/L)	8.2
BE (mmol/L)	-10.4
IL-6 (pg/mL)	355.4

Viscoelastic tests ROTEM



Shock

is the most
important trigger
for TIC!

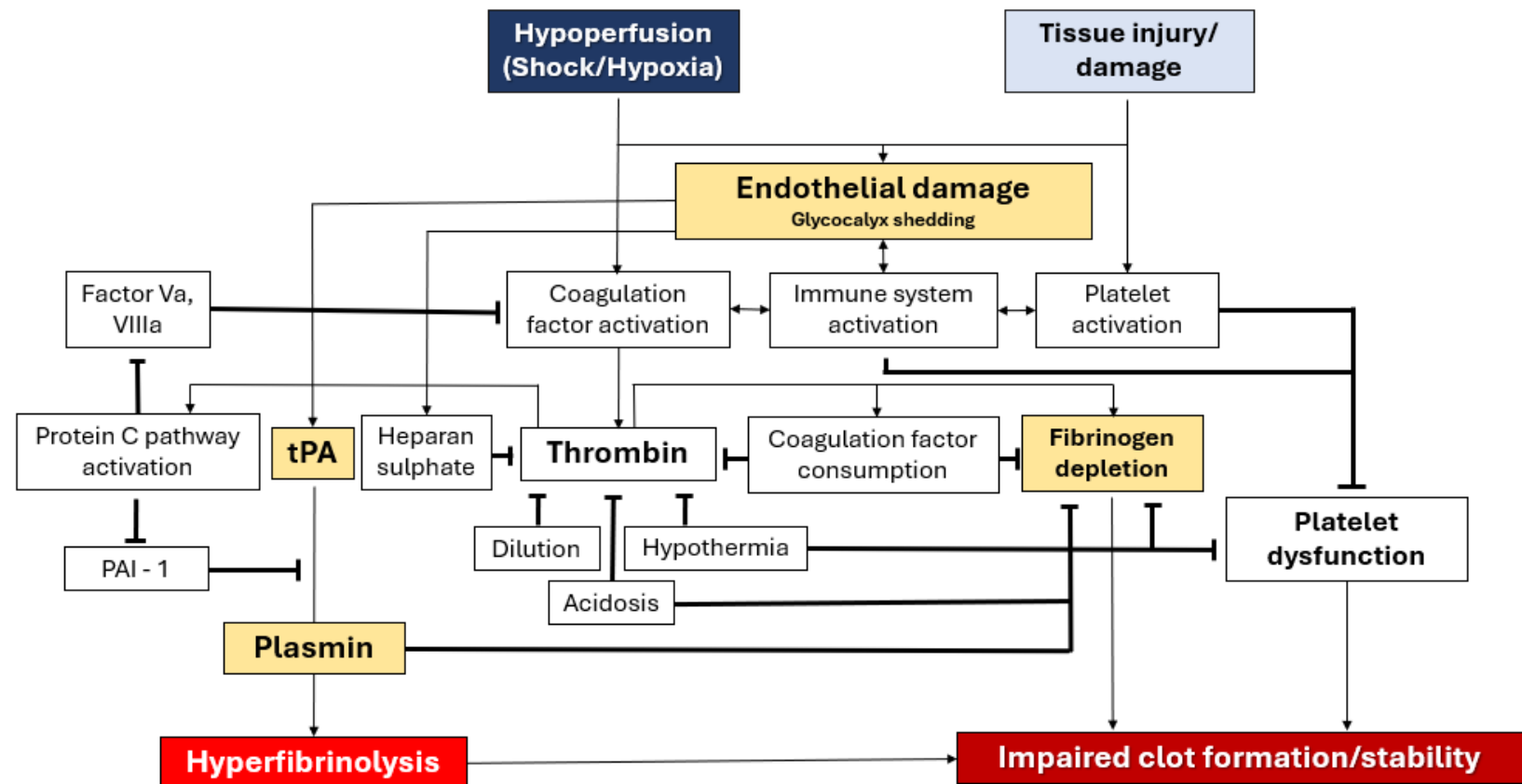


Trauma-induced Coagulopathy

Hyperfibrinolysis

Pathophysiology of Trauma-Induced Coagulopathy

Schöchl H, et al. *Hamostaseologie* 2024;44:31–39

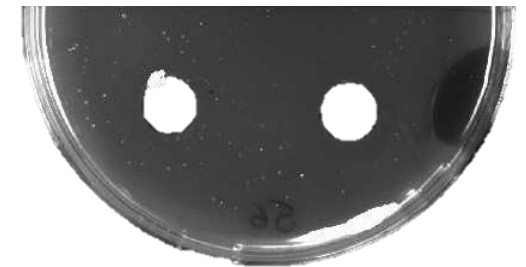
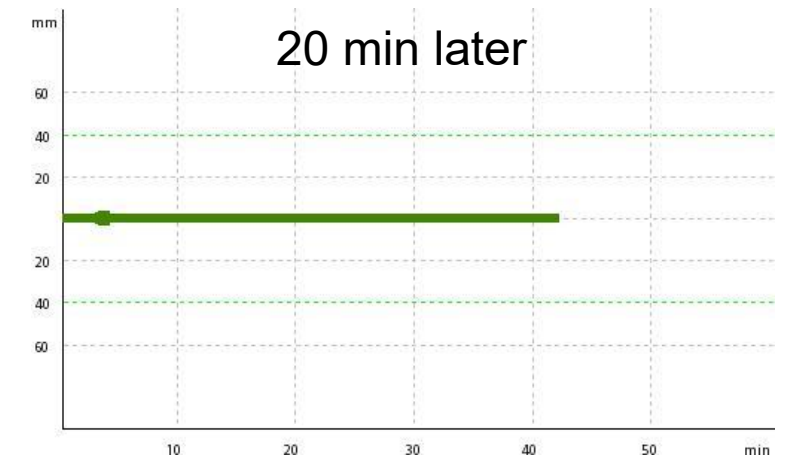
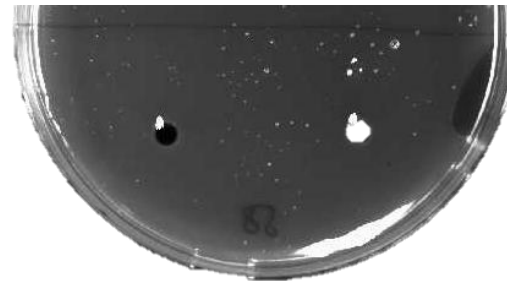
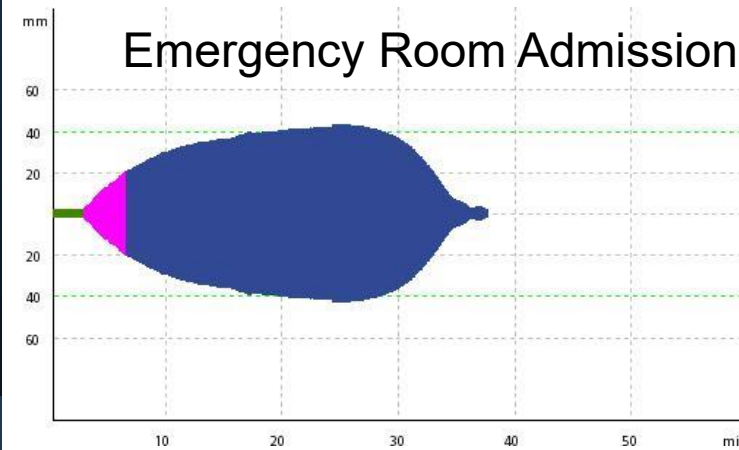


Trauma-induced Coagulopathy

Hyperfibrinolysis

Trauma-associated hyperfibrinolysis

Schöchl H, et al. Haemostaseologie 2012;32:22-27



Trauma-induced Coagulopathy

Tranexamic acid



The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

We recommend that **TXA** be administered
to the trauma patient who
is bleeding or at risk of significant bleeding
as soon as possible, if feasible enroute to the hospital, and
within 3 h after injury at a loading dose of 1 g infused over
10 min, followed by an IV infusion of 1 g over 8 h.

(Grade 1A)

Trauma-induced Coagulopathy

Tranexamic acid

- TXA: n=661
- Placebo: n=646

Median ISS: 29

- in both groups

Intervention

- 1 g prehospital and 1 g over 8 h in hospital

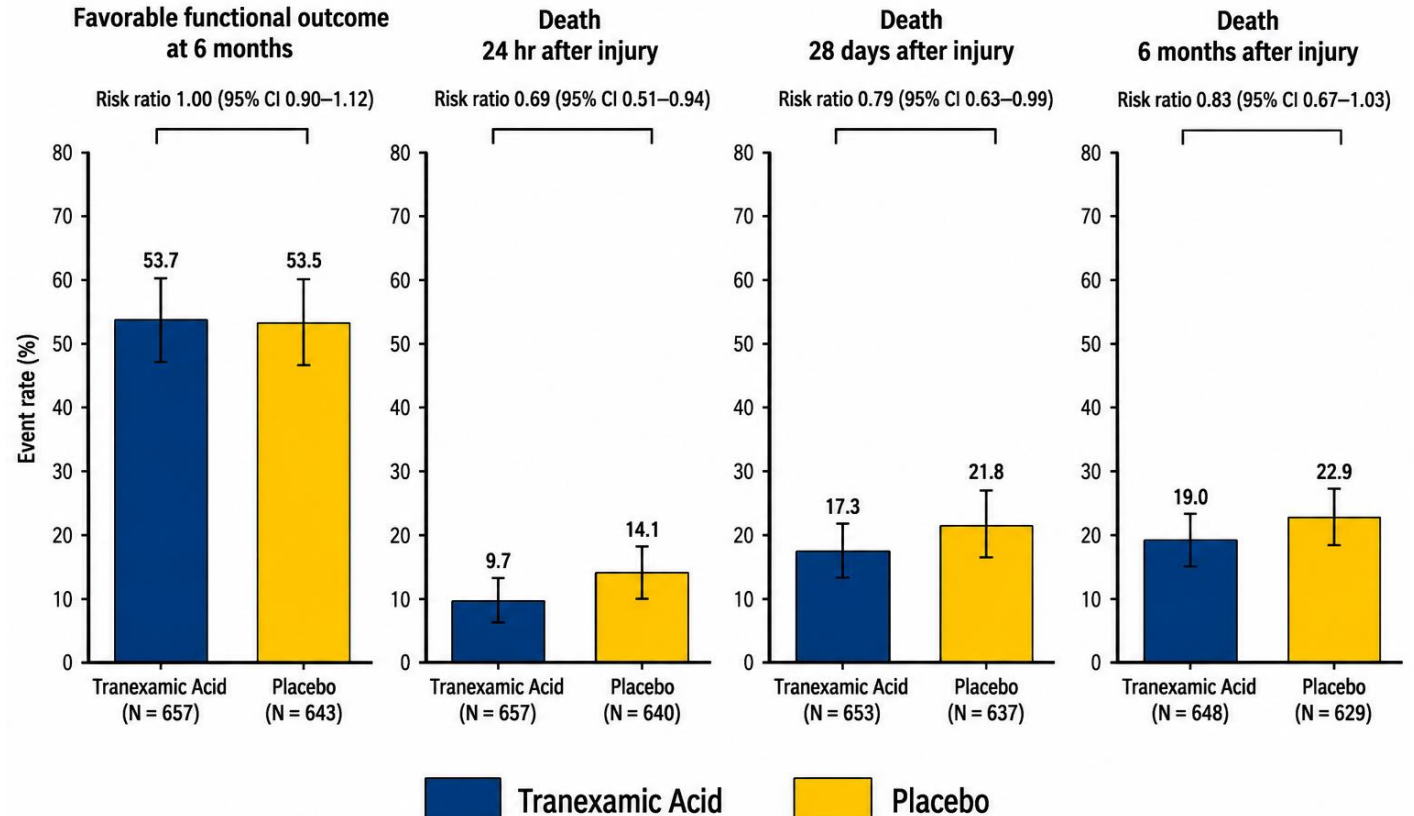


Prehospital Tranexamic Acid for Severe Trauma

The PATCH study International, double-blind, placebo-controlled RCT

Clinical Trials Group. N Engl J Med 2023;389:127–136

Effects of Tranexamic Acid on Mortality After Injury



Trauma-induced Coagulopathy

Tranexamic acid

PATCH study

Bottom line:



Prehospital Tranexamic Acid for Severe Trauma The PATCH study International, double-blind, placebo-controlled RCT

Clinical Trials Group. N Engl J Med 2023;389:127–136

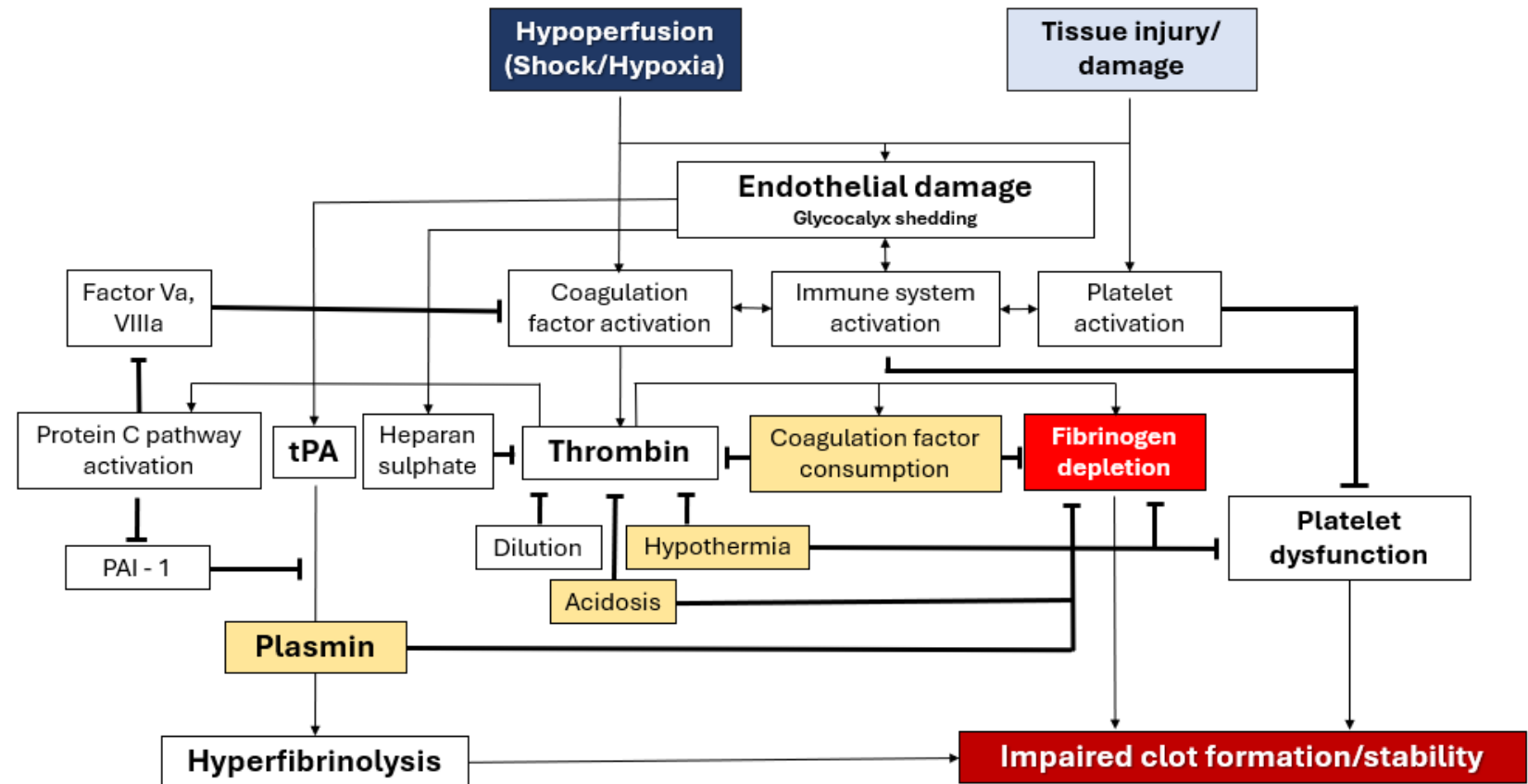
- Prehospital TXA reduced early mortality
 - **TXA: 9.7 % vs Placebo: 14.1 % (RR 0,69 [95%-KI 0,51–0,94])**
- No difference in number of serious adverse events between groups

Trauma-induced Coagulopathy

Fibrinogen

Pathophysiology of Trauma-Induced Coagulopathy

Schöchl H, et al. *Hamostaseologie* 2024;44:31–39



Trauma-induced Coagulopathy

Fibrinogen

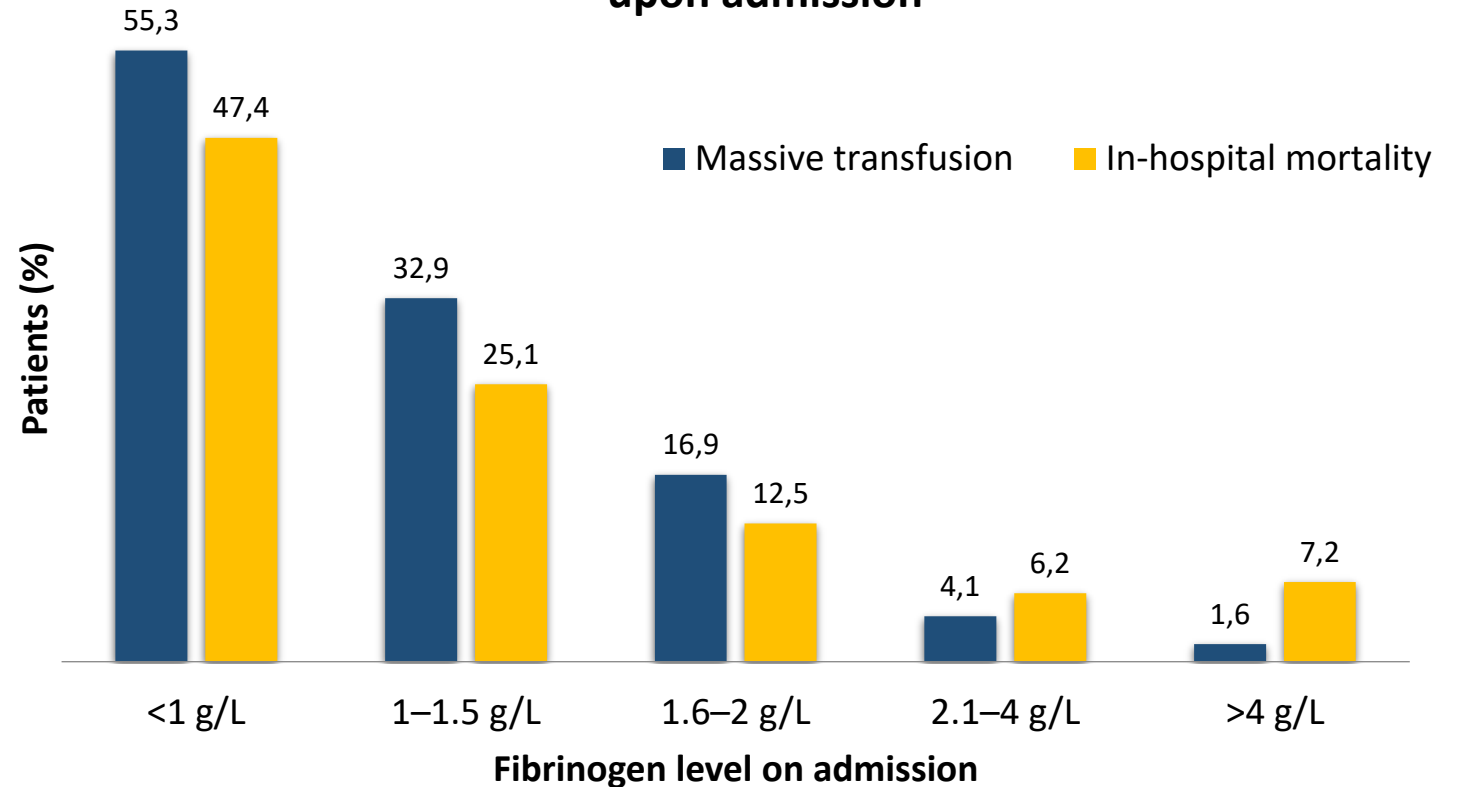
Prospective registry

N=4,773

Fibrinogen is an independent predictor of mortality in major trauma patients

McQuilten Z, et al. Injury 2017;48:1074

Patient outcomes according to fibrinogen levels
upon admission



Trauma-induced Coagulopathy

Fibrinogen

The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

In the initial management of patients with expected
massive haemorrhage, we recommend

one of the two following strategies:

Fibrinogen concentrate/cryoprecipitate and pRBC

(Grade 1C)

Trauma-induced Coagulopathy

Fibrinogen

The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

We suggest an initial

fibrinogen supplementation of 3–4 g.

(15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate)

Repeat doses should be guided by VEM and
laboratory assessment of fibrinogen levels

(Grade 2C)

Trauma-induced Coagulopathy

Fibrinogen

Intervention within 1 h
after ER arrival (matched pairs)

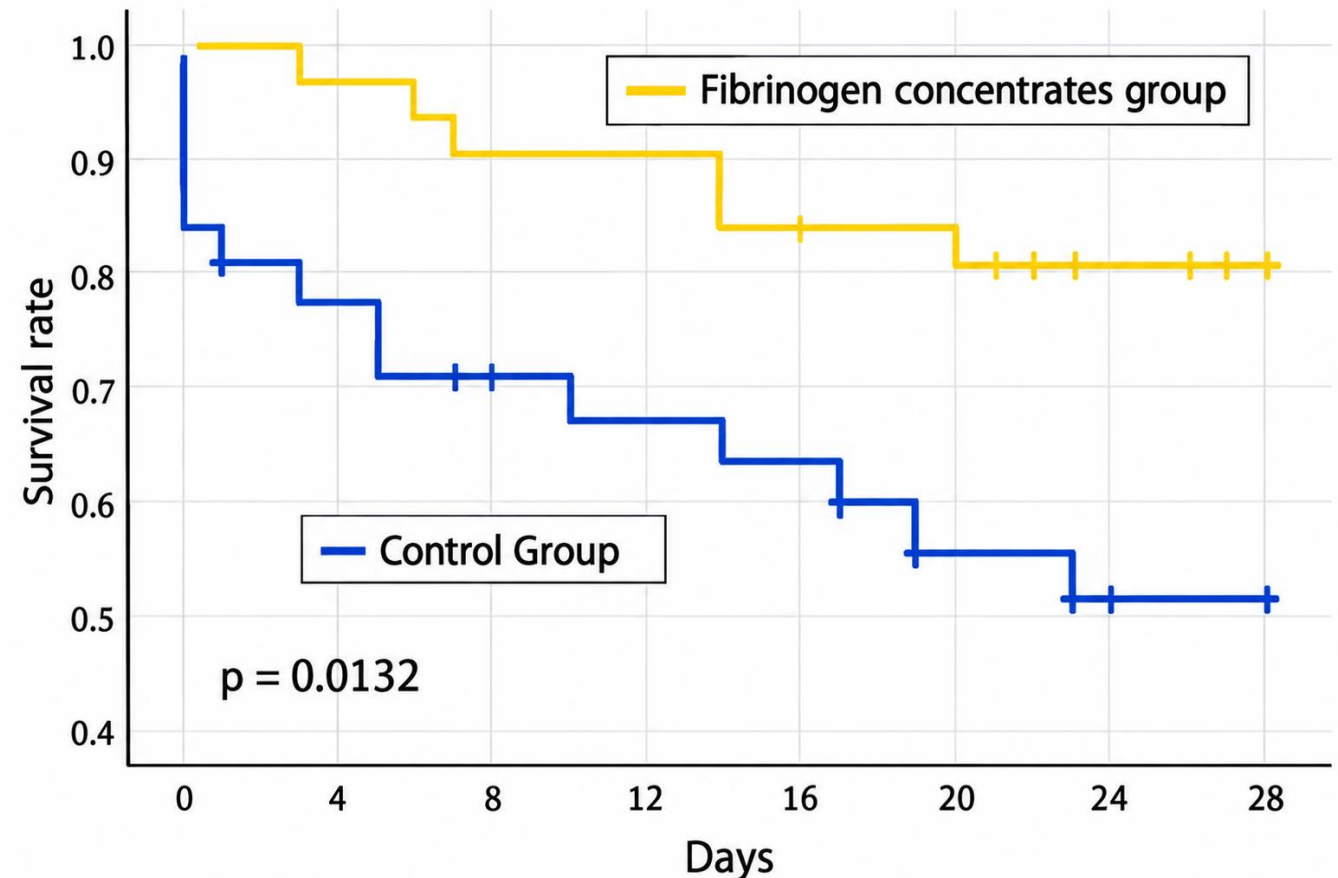
- FC group: 31
- Control group: 31

• ISS

- FC group: 34 (25–41)
- Control group: 30 (21–36)

Early administration of fibrinogen concentrate is associated with improved survival among severe trauma patients: a single-centre propensity score-matched analysis

Itagaki Y, et al. World J Emerg Surg 2020;15:7



Trauma-induced Coagulopathy

Fibrinogen



Cryo administered in addition to 1:1:1 (RBC:FFP:platelets)

N=1,604

- Standard care: 805
- Cryoprecipitate: 799

Inclusion:

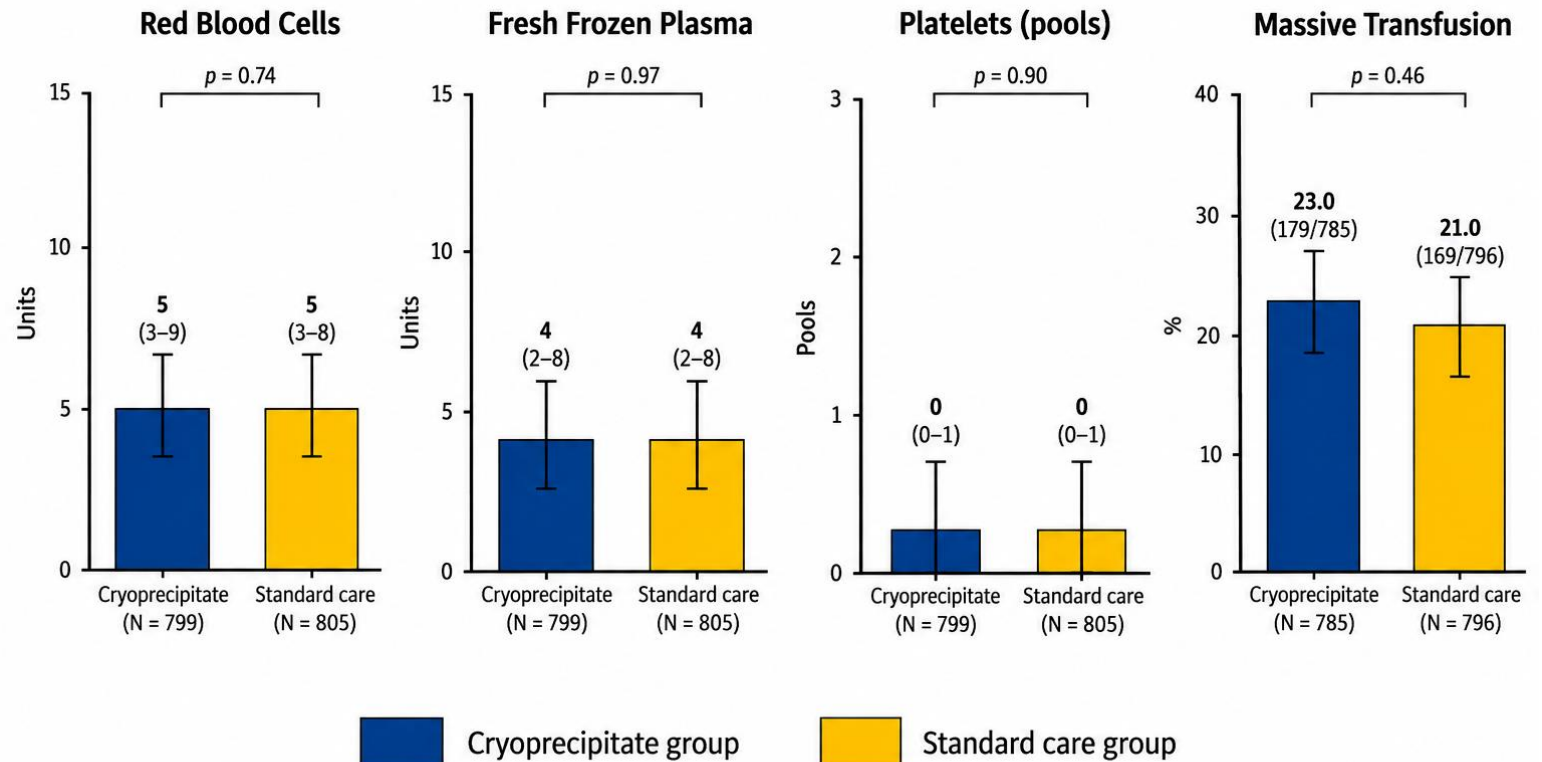
- Syst BP <90 mmHg at any time
- ≥1 U of any blood component
- Activation of an MTP

Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury: The CRYOSTAT-2 Randomized Clinical Trial

Davenport R, et al. JAMA 2023;330:1882–1891

Transfusion of Allogeneic Blood Products and Massive Transfusion

Components Transfused in the First 24 Hours (Median, IQR)



Data are median (IQR) or % (no./total no.).

Trauma-induced Coagulopathy

Fibrinogen

CRYOSTAT-2
EARLY CRYOPRECIPITATE IN TRAUMA

Critique:

Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury: The CRYOSTAT-2 Randomized Clinical Trial

Davenport R, et al. JAMA 2023;330:1882–1891

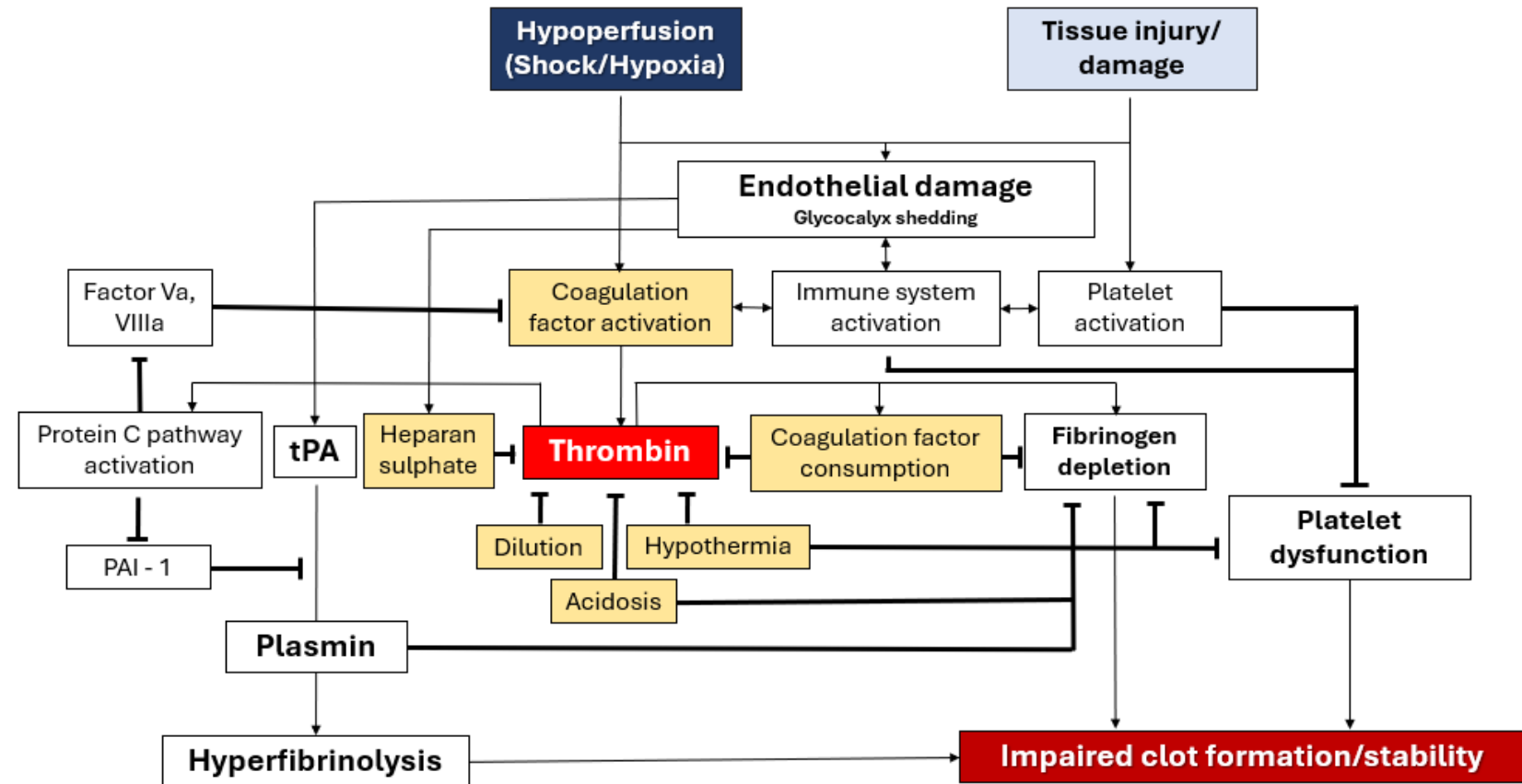
- All patients received RBC:FFP:PC in a 1:1:1 ratio
- Fibrinogen levels were not measured in CRYOSTAT-2
- 1st Cryo: administered at a median of 68 min after arrival
- The study may not have enrolled enough patients with uncontrolled bleeding

Trauma-induced Coagulopathy

Thrombin Generation

Pathophysiology of Trauma-Induced Coagulopathy

Schöchl H, et al. *Hamostaseologie* 2024;44:31–39



Trauma-induced Coagulopathy

RBC-FFP Ratio

The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

In the initial management of patients with expected
massive haemorrhage, we recommend

one of the two following strategies:

- **FFP in a FFP/pRBC ratio** of at least 1:2 as needed

(Grade 1C)

Trauma-induced Coagulopathy

RBC-FFP Ratio

Prospective multicentre RCT

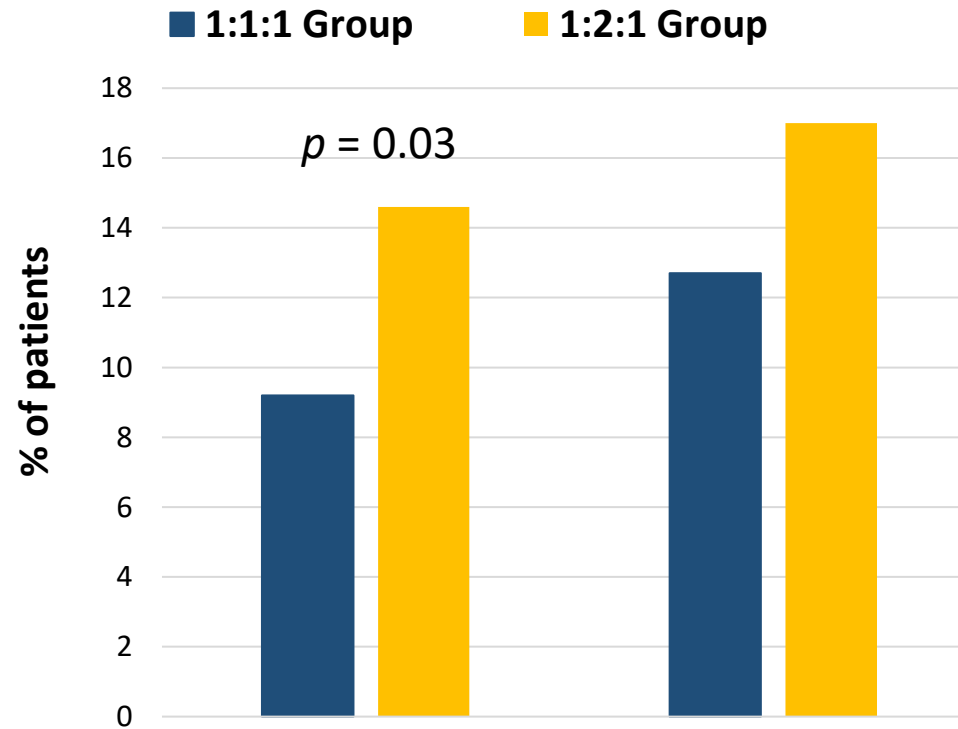
N = 680

predicted to need MT (ABC score or clinician judgment)

- **87% met critical administration threshold (≥ 3 U RBC in 1 h)**
- **46% reached ≥ 10 U/24 h MT**

Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR study

Holcomb J, et al. JAMA 2015;313:471



As part of this study, thawed plasma and platelets were made available in the emergency room and were immediately accessible!

Trauma-induced Coagulopathy

RBC-FFP Ratio

Secondary analysis of non-survivors of the SWAT study

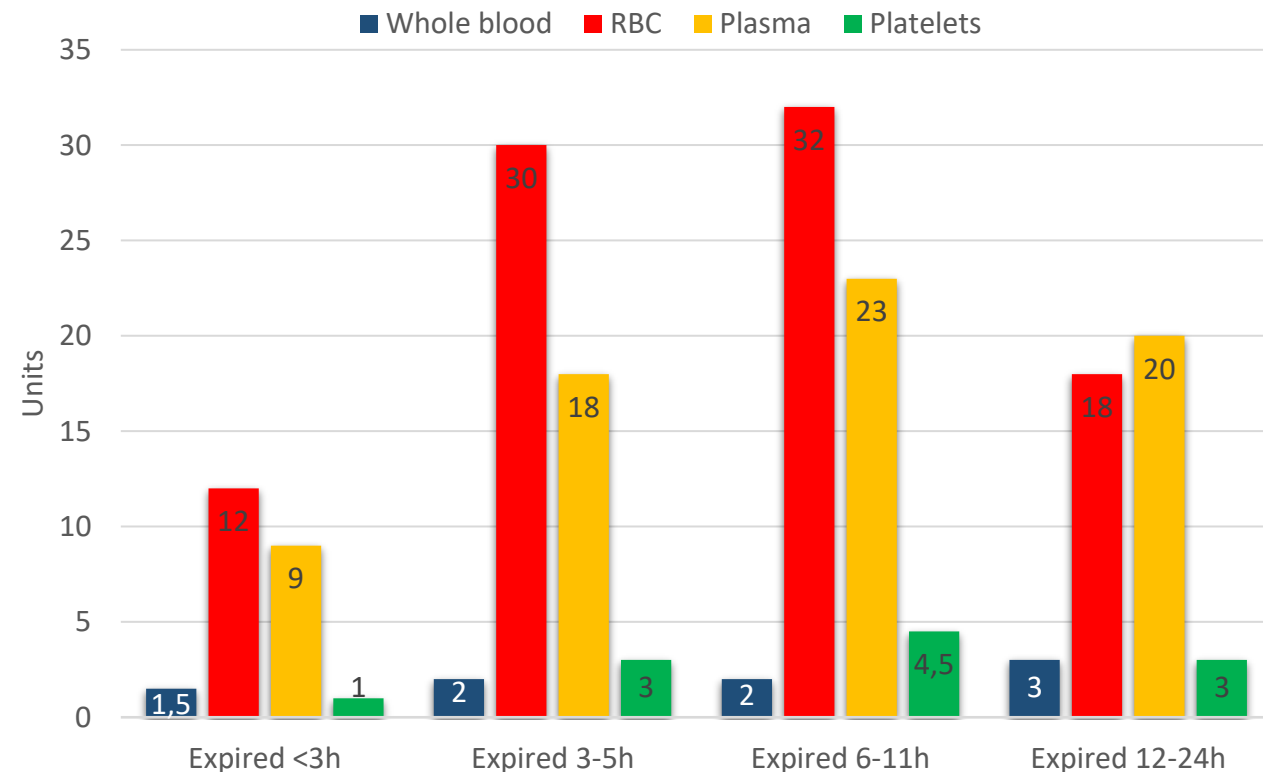
N = 1,051 patients
Mortality: 176 (16.7 %)

Timing of trauma deaths due to uncontrolled bleeding have not changed in three decades:

A multicenter study of patients in hemorrhagic shock

Bernhardt IM, et al. Am J Surg 2025;250:116510

Ratio of blood products within time



Trauma-induced Coagulopathy

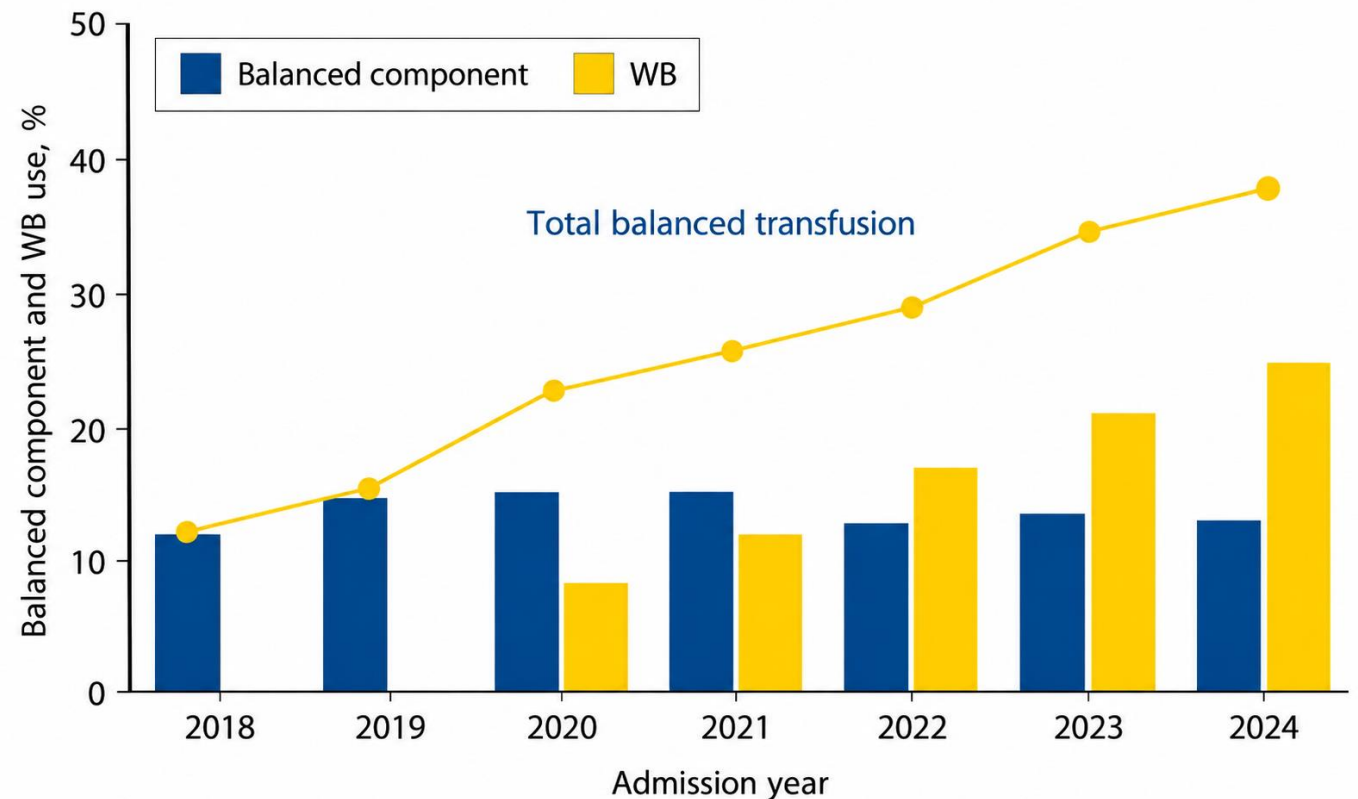
RBC-FFP Ratio

Retrospective study
Trauma patients receiving
blood transfusion ($\geq 1L$) in
the first 4h

N = 71.997 patients

Balanced Component and Whole-Blood Transfusion Practices in US Trauma Centers

Acharya P, et al. JAMA Netw Open. 2026;9:e2632334



Trauma-induced Coagulopathy

RBC-FFP Ratio

Prospective cohort study
N=106

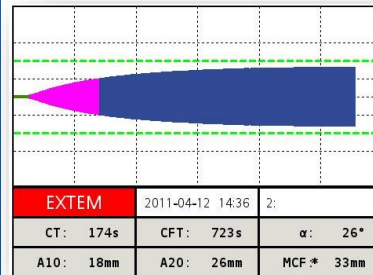
Median ISS (IQR)
34 (25–41)

Intervention*:

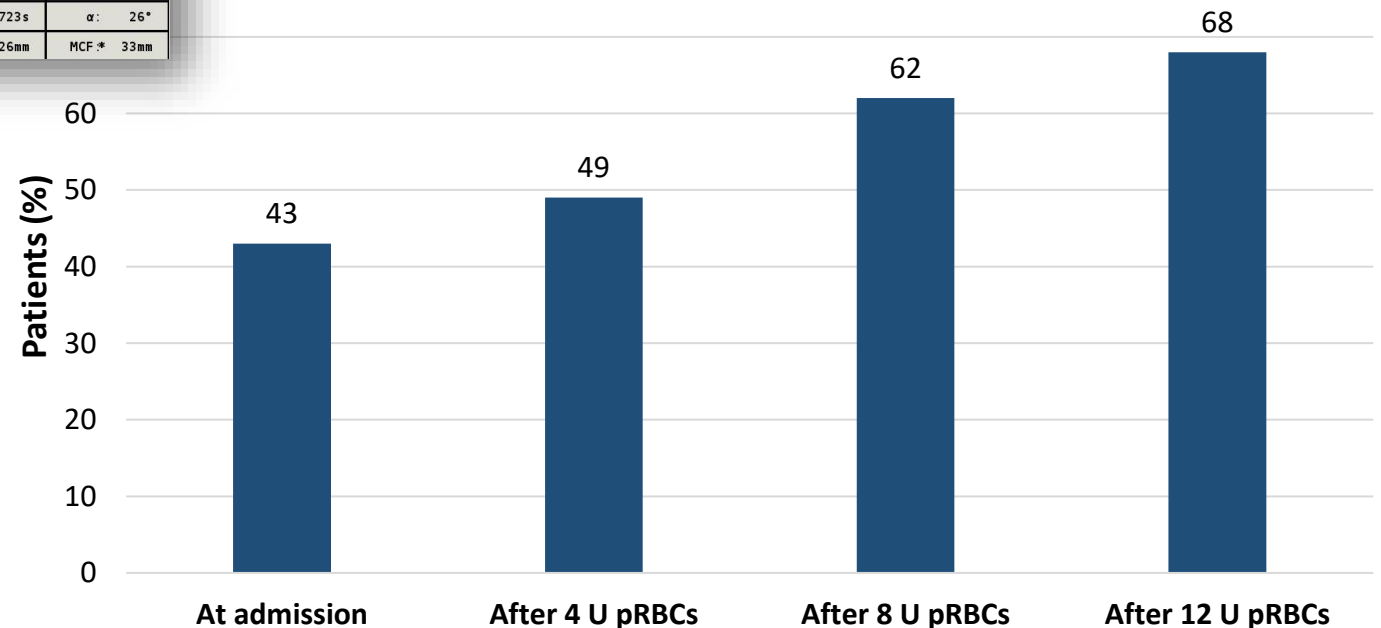
- Target FFP:pRBC ratio: 2:3
- Platelets and cryoprecipitate after every 6 U pRBC

Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage

Khan S, et al. J Trauma Acute Care Surg 2014;76:561–568



Incidence of coagulopathy
(EXTEM clot amplitude at 5 min ≤ 35 mm)



EXTEM, extrinsically activated ROTEM test; FFP, fresh frozen plasma; IQR, interquartile range; ISS, Injury Severity Score; pRBCs, packed red blood cells; U, unit.

Composition of FFP

N = 66



Use of activated partial thrombin time and prothrombin time for quality assessment of fresh frozen plasma

Layibo Y, et al. *Int J Hematol* 2025;122:392–399

Parameter	Unit	Mean	SD	Median	IQR	Range
Volume	mL	177.8	17.3	178	167–190	143.6–218.2
aPTT	s	40.8	5.7	40.5	37.9–43.4	22.4–67.7
PT	%	74.2	10.3	74.9	67.8–78.6	40–100
PT	s	15.9	2.1	15.4	14.7–16.8	11.6–23.9
PT ratio	–	1.18	0.16	1.18	1.09–1.25	0.86–1.77
INR	–	1.37	0.26	1.30	1.24–1.45	0.94–2.4
Fibrinogen	g/L	2.3	0.7	2.3	1.8–2.8	1.1–4.6
Fibrinogen	g/bag	0.415	0.138	0.422	0.308–0.468	0.189–0.981

aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio; IQR, interquartile range; PT, prothrombin time; SD, standard deviation.

Trauma-induced Coagulopathy

RBC-FFP Ratio

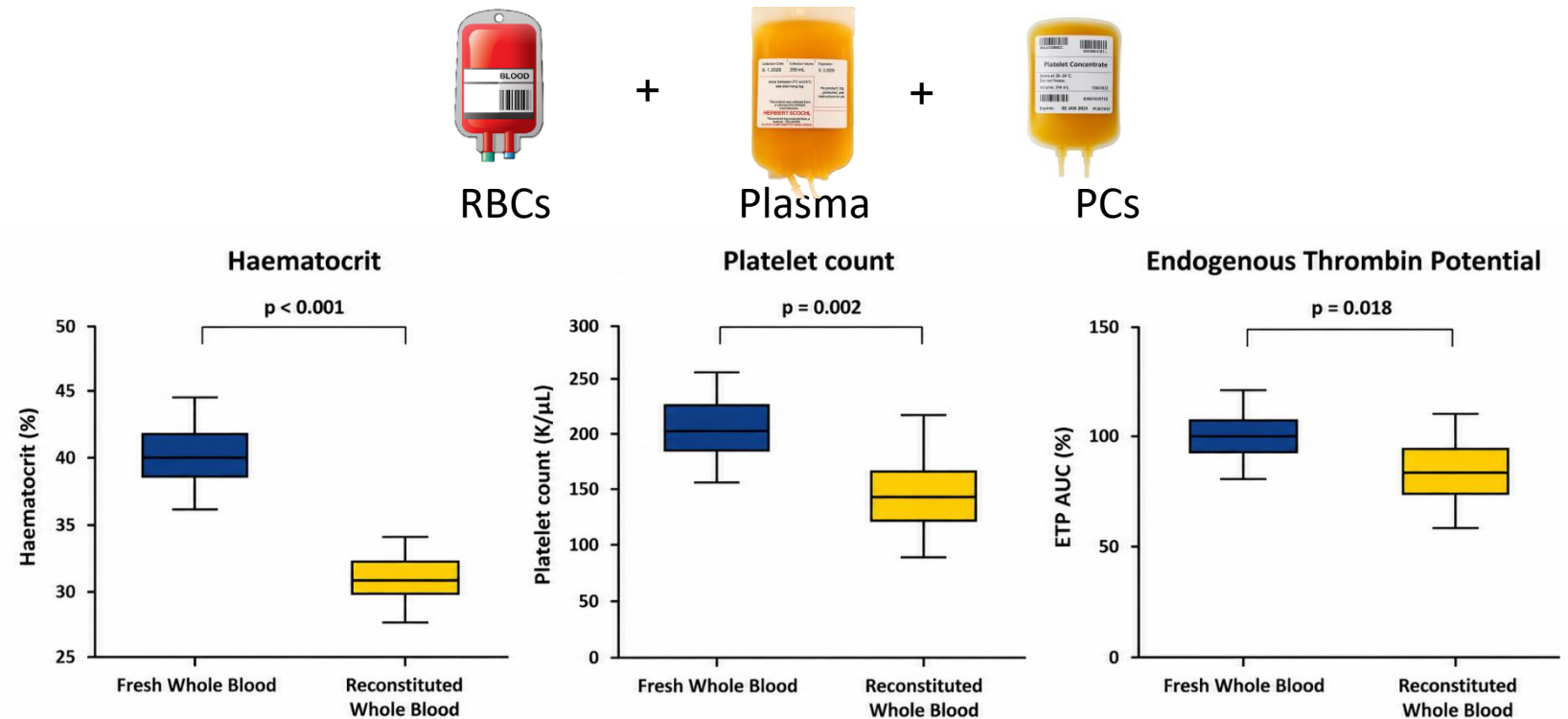
Prospective observational study

“Reconstituted whole blood”

RBC, plasma and PC in a 1:1:1 ratio

Haemostatic profile of reconstituted blood in a proposed 1:1:1 ratio of packed red blood cells, platelet concentrate and four different plasma preparations

Ponschab M, et al. Anaesthesia 2015;70:528–536



This strategy does not reliably prevent or treat TIC!

Trauma-induced Coagulopathy

PCC

TIC: defined PTr >1.2
severe TIC: PTr >1.5

Median (IQR) ISS:

4F-PCC: 34 (25–50)

Placebo: 38 (29–50)

Intervention:

All patients received pRBC:FFP at
a 1:1 or 2:1 ratio

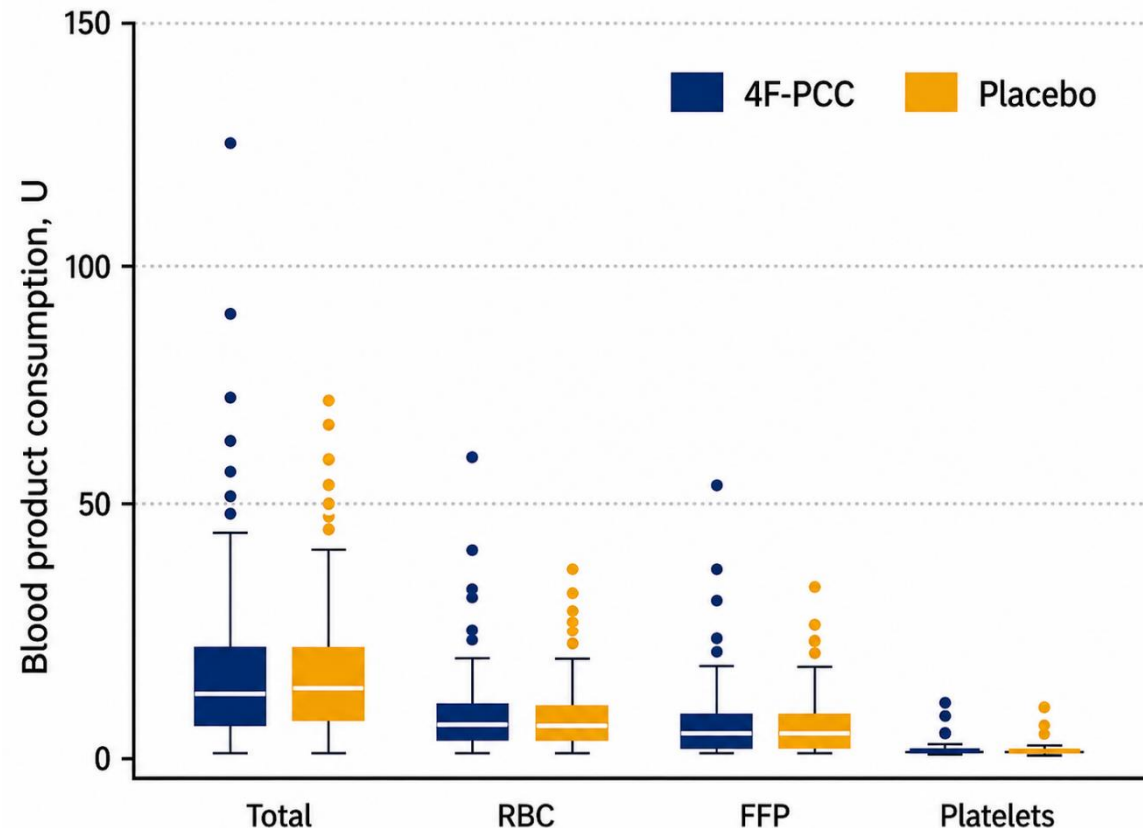
4F-PCC: 25 U/kg, n=164

Placebo: saline 1 mL/kg, n=160

Efficacy and Safety of Early Administration of 4-Factor PCC in Patients With Trauma at Risk of Massive Transfusion:

The PROCOAG Randomized Clinical Trial

Bouzat P, et al. JAMA 2023;329:1367–1375



4F-PCC, four-factor prothrombin complex concentrate; FFP, fresh frozen plasma; IQR, interquartile range; ISS, Injury Severity Score; pRBC, packed red blood cell; PTr, prothrombin time ratio; RBC, red blood cell; RCT, randomized controlled trial; TIC, trauma-induced coagulopathy; U, unit.

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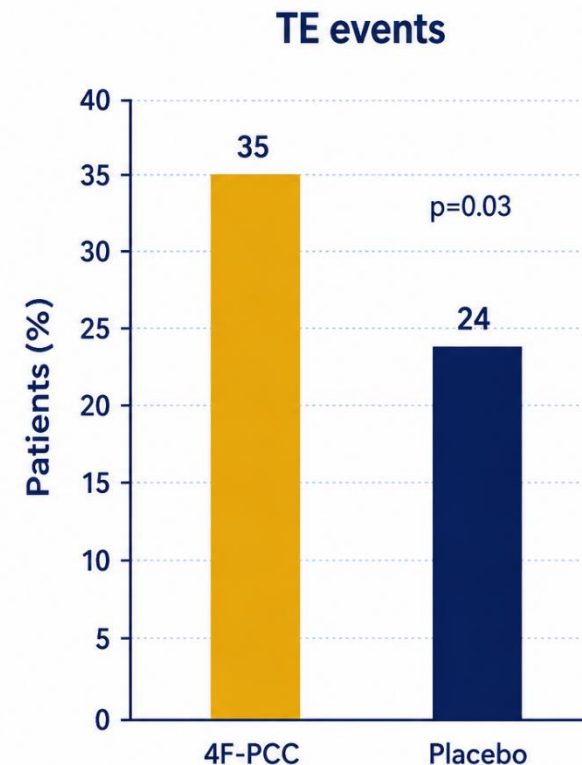
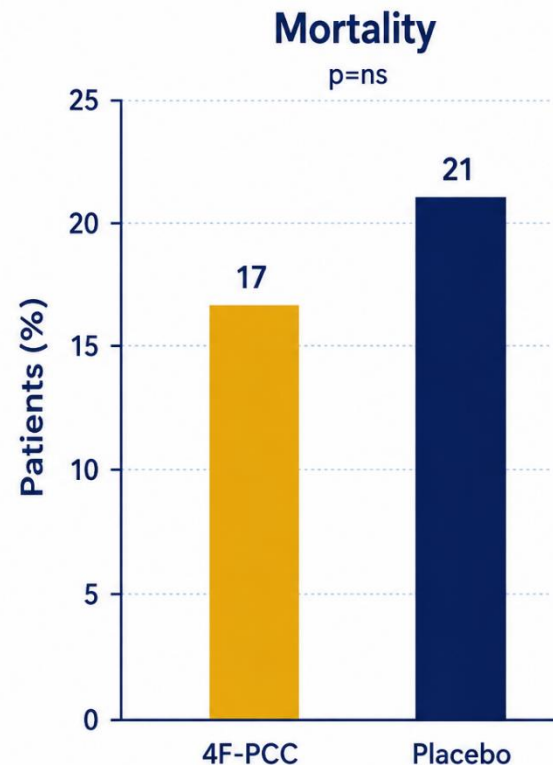
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4F-PCC, four-factor prothrombin complex concentrate; FFP, fresh frozen plasma; IQR, interquartile range; ISS, Injury Severity Score; ns, non-significant; pRBC, packed red blood cell; PTr, prothrombin time ratio; RCT, randomized controlled trial; TE, thromboembolic; TIC, trauma-induced coagulopathy; U, unit.

Trauma-induced Coagulopathy

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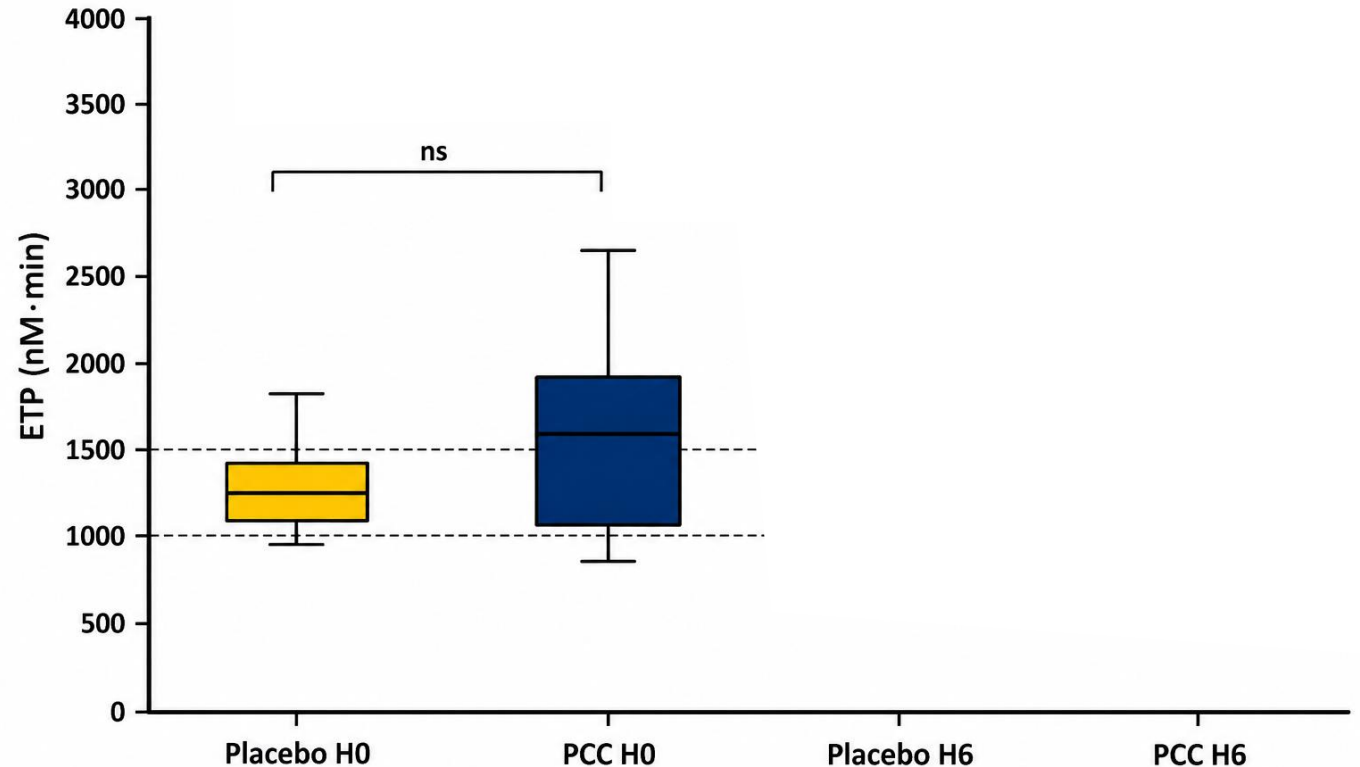
The administration of 4-factor PCC exacerbates thrombin generation in trauma patients at risk of massive transfusion:

An ancillary study of the PROCOAG trial

Greze J, et al. Critical Care 2024;28:51



Endogenous Thrombin Potential (ETP)



Trauma-induced Coagulopathy

PCC

Multicentre RCT

Impact of a single iv bolus of PCC on 6-hour all-cause mortality

Placebo: 436

PCC: 432

Terminated

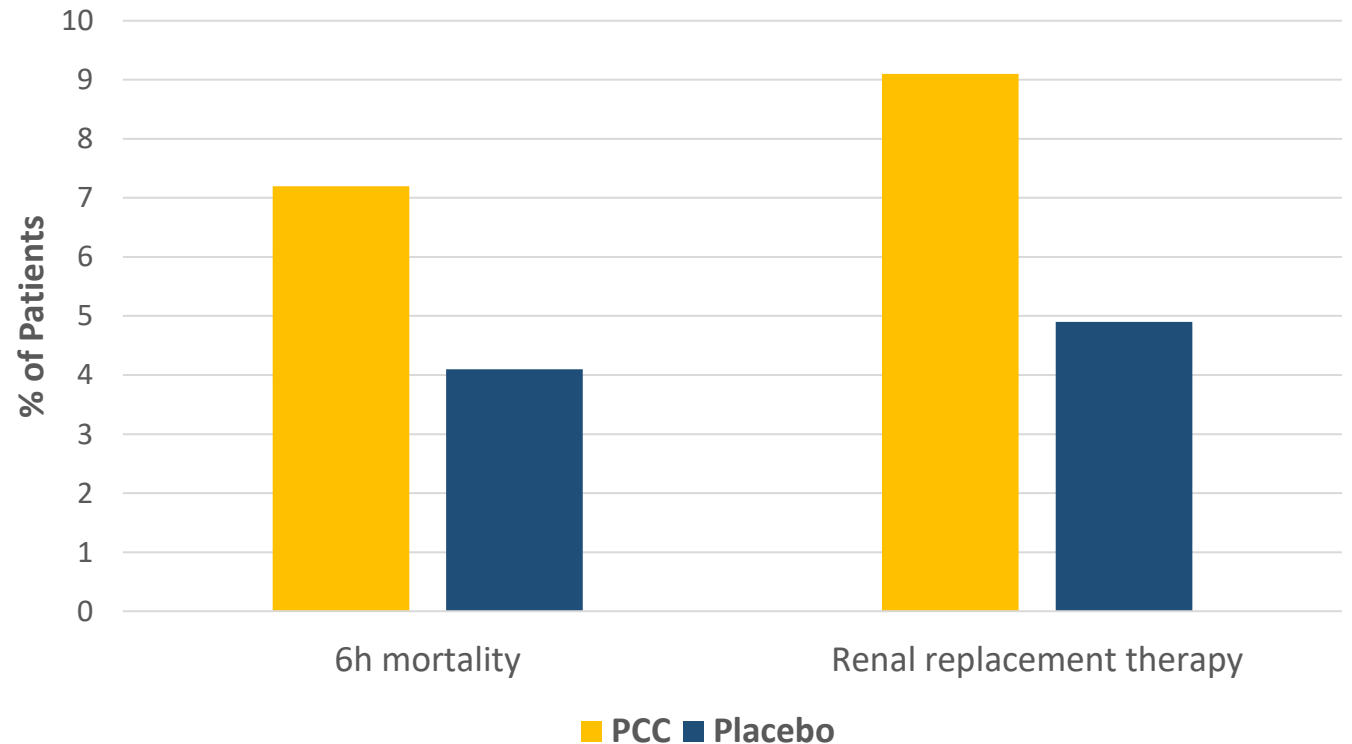
Early, empiric 4-factor PCC in trauma patients predicted to require a larger volume blood transfusion:

Results of the phase III TAP trial

ASST, Session I: Plenary Papers 1



Mortality and acute kidney injury



Trauma-induced Coagulopathy

PCC

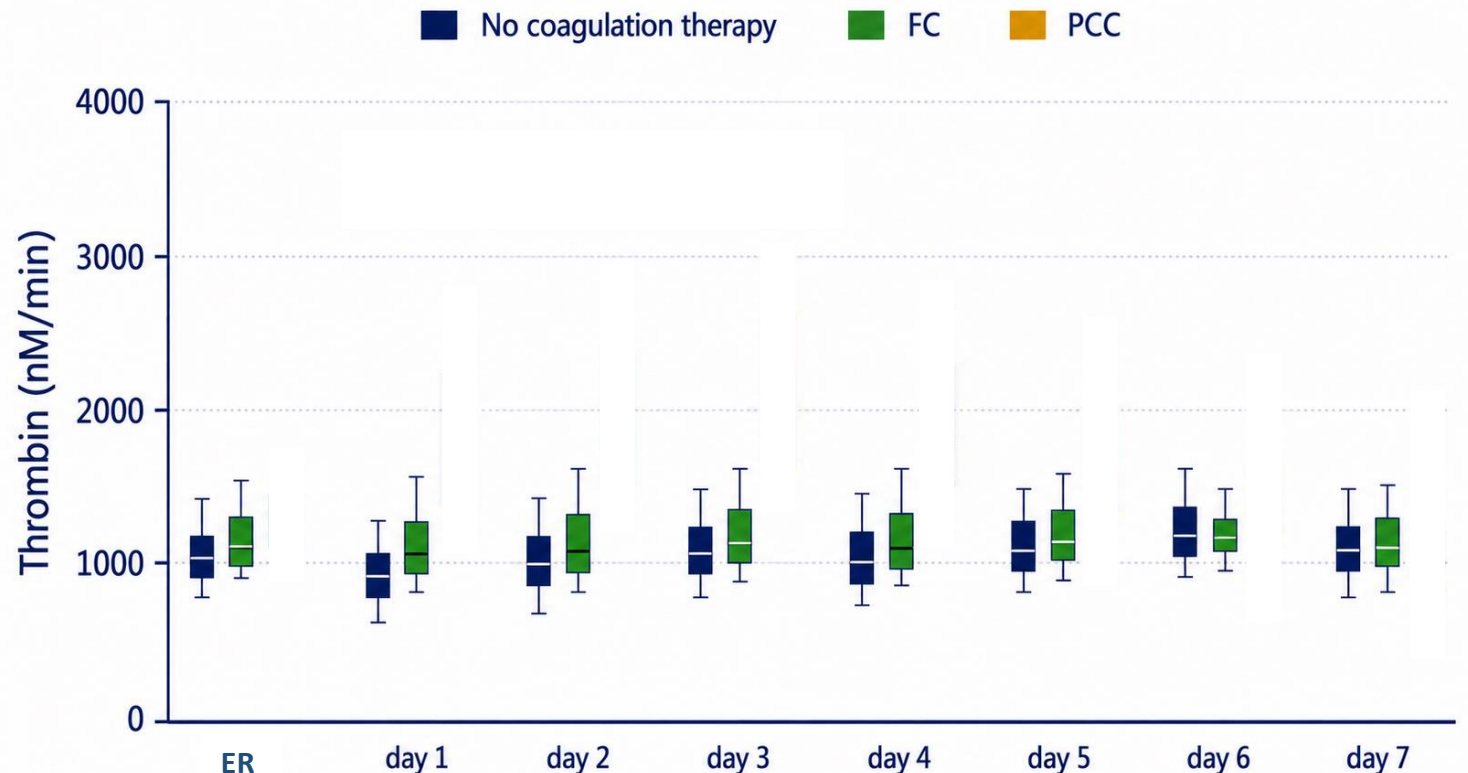
Prospective
observational study

N=77

Endogenous thrombin potential following hemostatic therapy with 4-PCC: a 7-day observational study of trauma patients

Schöchl H, et al. Crit Care 2014,18:R147

Endogenous thrombin generation



****p<0.0001 (no coagulation therapy and FC vs PCC)

ER, emergency room; FC, fibrinogen concentrate; PCC, prothrombin complex concentrate.

Trauma-induced Coagulopathy

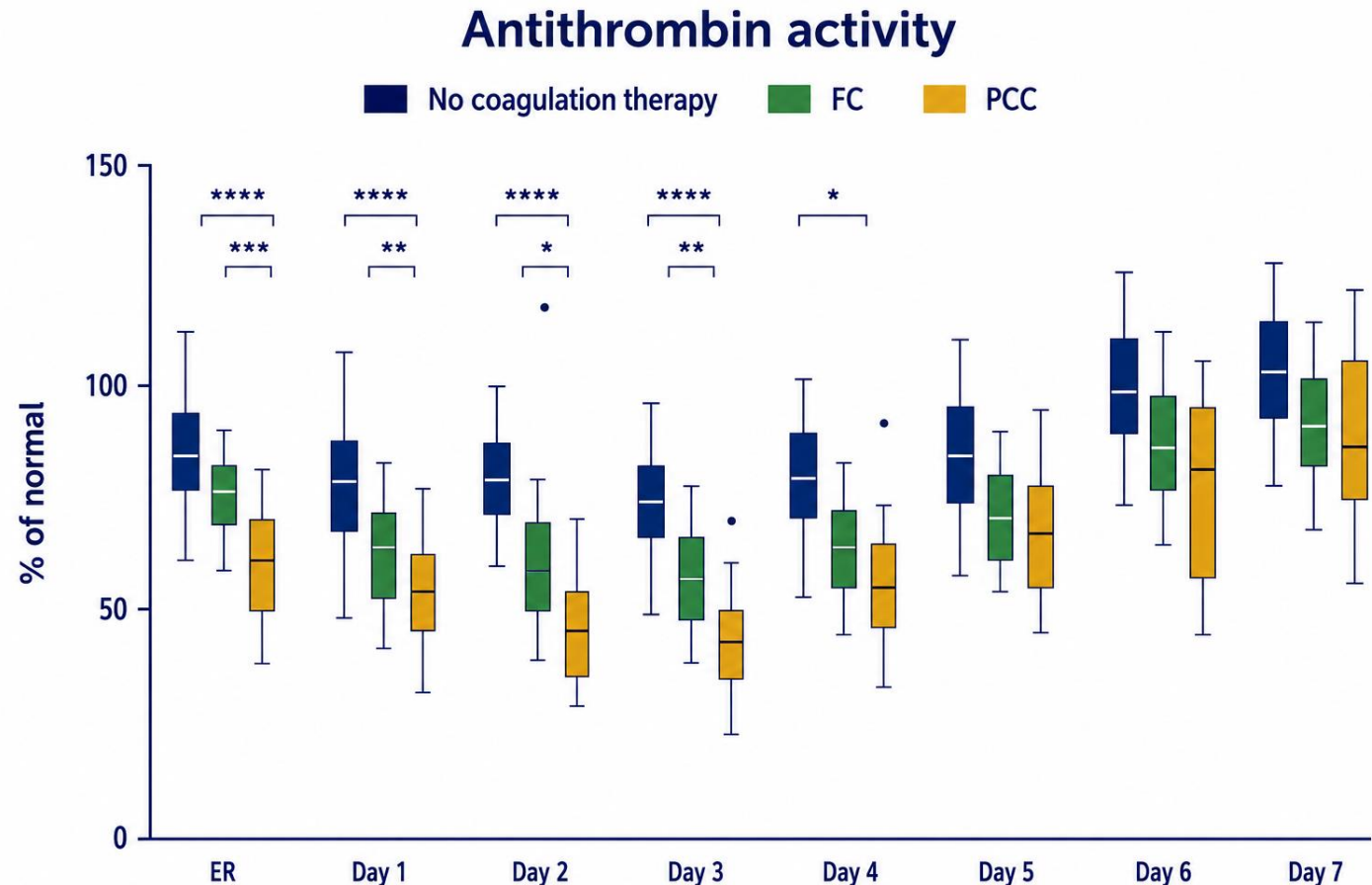
PCC

Prospective observational study

N=77

Endogenous thrombin potential following hemostatic therapy with 4-PCC: a 7-day observational study of trauma patients

Schöchl H, et al. Crit Care 2014,18:R147



****p<0.0001 (no coagulation therapy and FC vs PCC)

ER, emergency room; FC, fibrinogen concentrate; PCC, prothrombin complex concentrate.

Trauma-induced Coagulopathy

PCC + FC

Intervention:

- CFC-group: FC 4 g and PCC 2000 IU
- FP: 4 U FFP

107 were randomly assigned

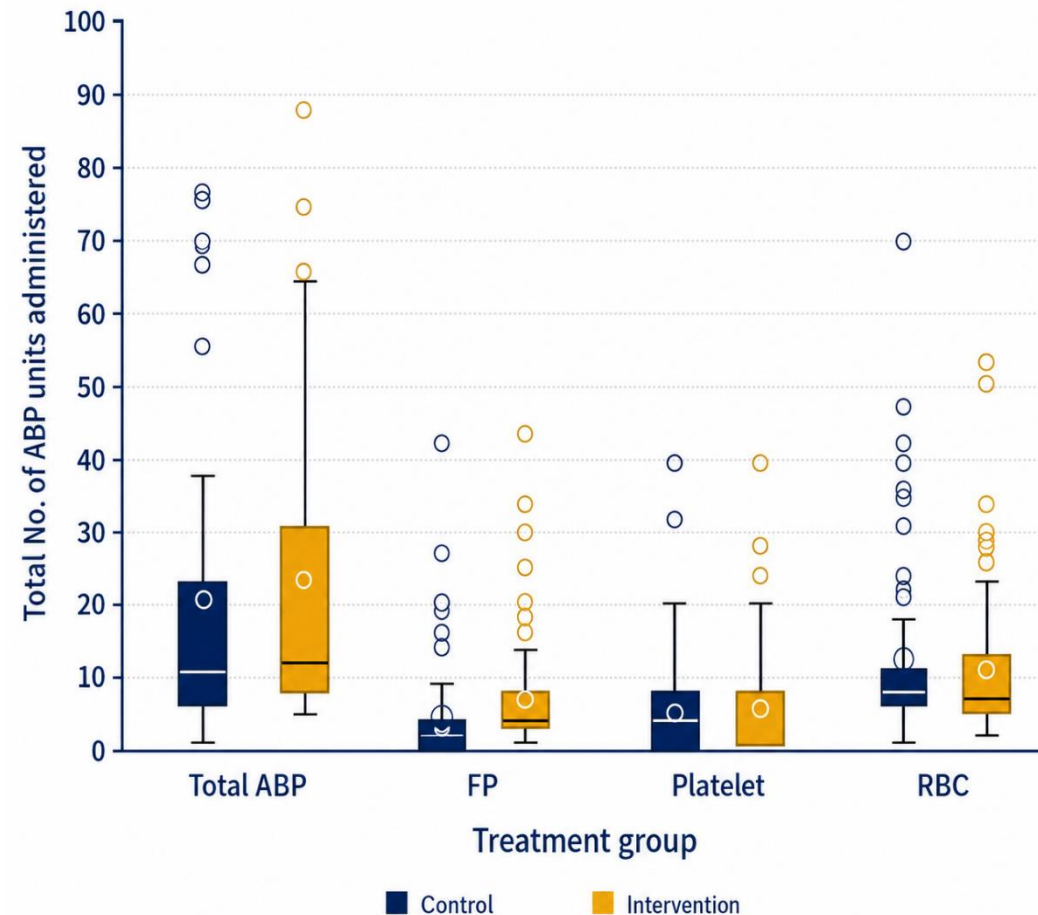
Primary analysis:

- FC-PCC group: 66
- FC-PCC FP group: 71

Factors in the Initial Resuscitation of Patients With Severe Trauma: The FiiRST-2 Randomized Clinical Trial

Da Luz LT, et al. JAMA Network Open 2025;8:e2532702

Total allogeneic blood products including FFP as active control



Trauma-induced Coagulopathy

PCC + FC

FiiRST-2 RCT

Bottom line:

Factors in the Initial Resuscitation of Patients With Severe Trauma: The FiiRST-2 Randomized Clinical Trial

Da Luz LT, et al. JAMA Network Open 2025;8:e2532702

- FiiRST-2 was underpowered to detect differences in transfusion or mortality
- Inclusion was based on MHP-activation, rather than confirmed TIC!
- 4F-PCC as a preemptive first-line therapy offers no proven clinical benefit and may cause harm
- Factor concentrate-based therapy is most beneficial when guided by POC monitoring

Trauma-induced Coagulopathy

PCC



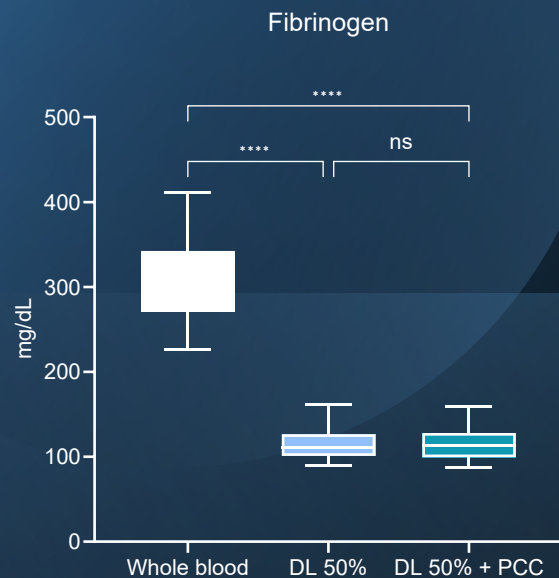
The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

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

Prothrombin Complex Concentrate

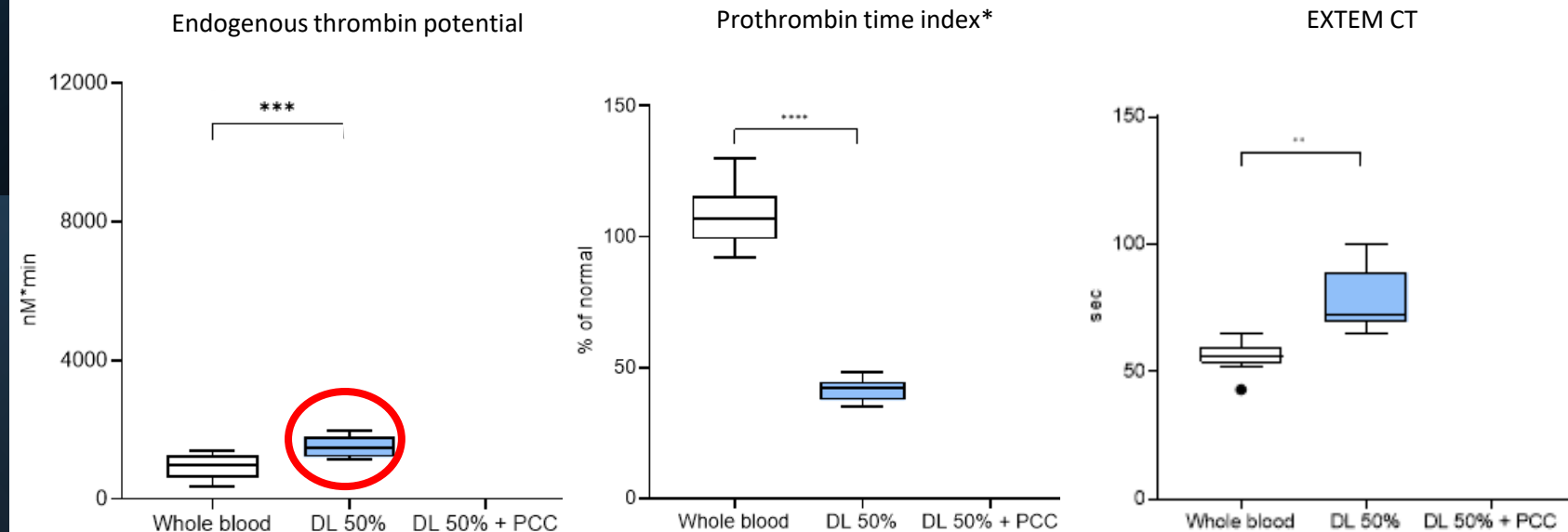
TG vs. CT-EXTEM



Altered thrombin generation with PCC is not detected by viscoelastic testing: an *in vitro* study

Hofmann N, et al. *Brit J Anaesth* 2025;134:1392–1401

Thrombin generation vs PTI and EXTEM CT



. **P<0.01; ***P<0.001; ****P<0.0001.

CT, clotting time; DL 50%, 50% dilution of whole blood; EXTEM, extrinsically activated thromboelastometric test; ns, non-significant; PCC, prothrombin complex concentrate; PTI, prothrombin time index.

Trauma-induced Coagulopathy

Thrombin Generation

Prospective observational study

Trauma with possible acute coagulopathy of trauma (ACT)

- PT >18 sec or INR >1.5
- n=15

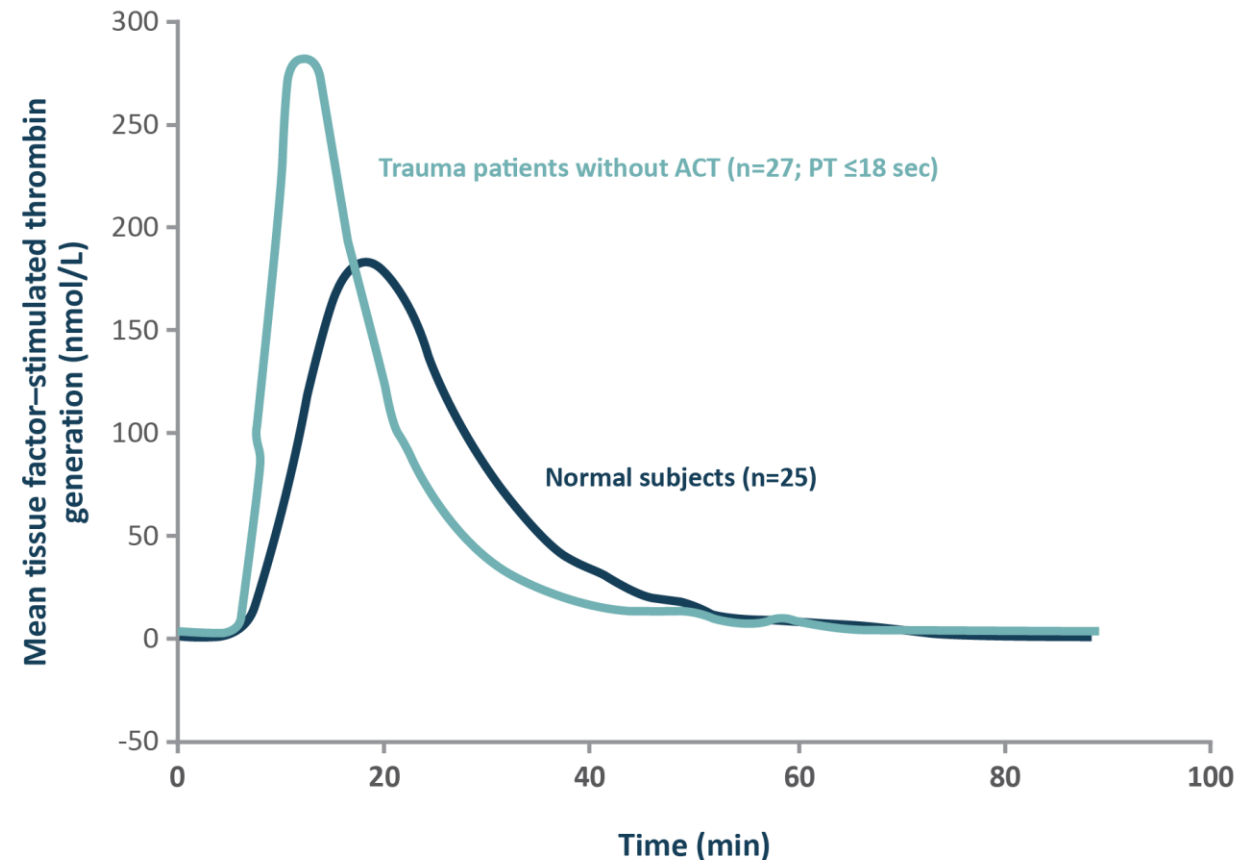
Thrombin generation Trauma with TIC vs normal patients:

- Lag times: 68% shorter
- Peak TG: 3-fold higher

Thrombin generation in trauma patients

Dunbar N and Chandler W. Transfusion 2009,49:2652–2660

Tissue factor-stimulated thrombin generation



ACT, acute coagulopathy of trauma; INR, international normalized ratio; PT, prothrombin time; TG, thrombin generation.

Thrombin generation in major trauma

Prospective observational study

N = 118

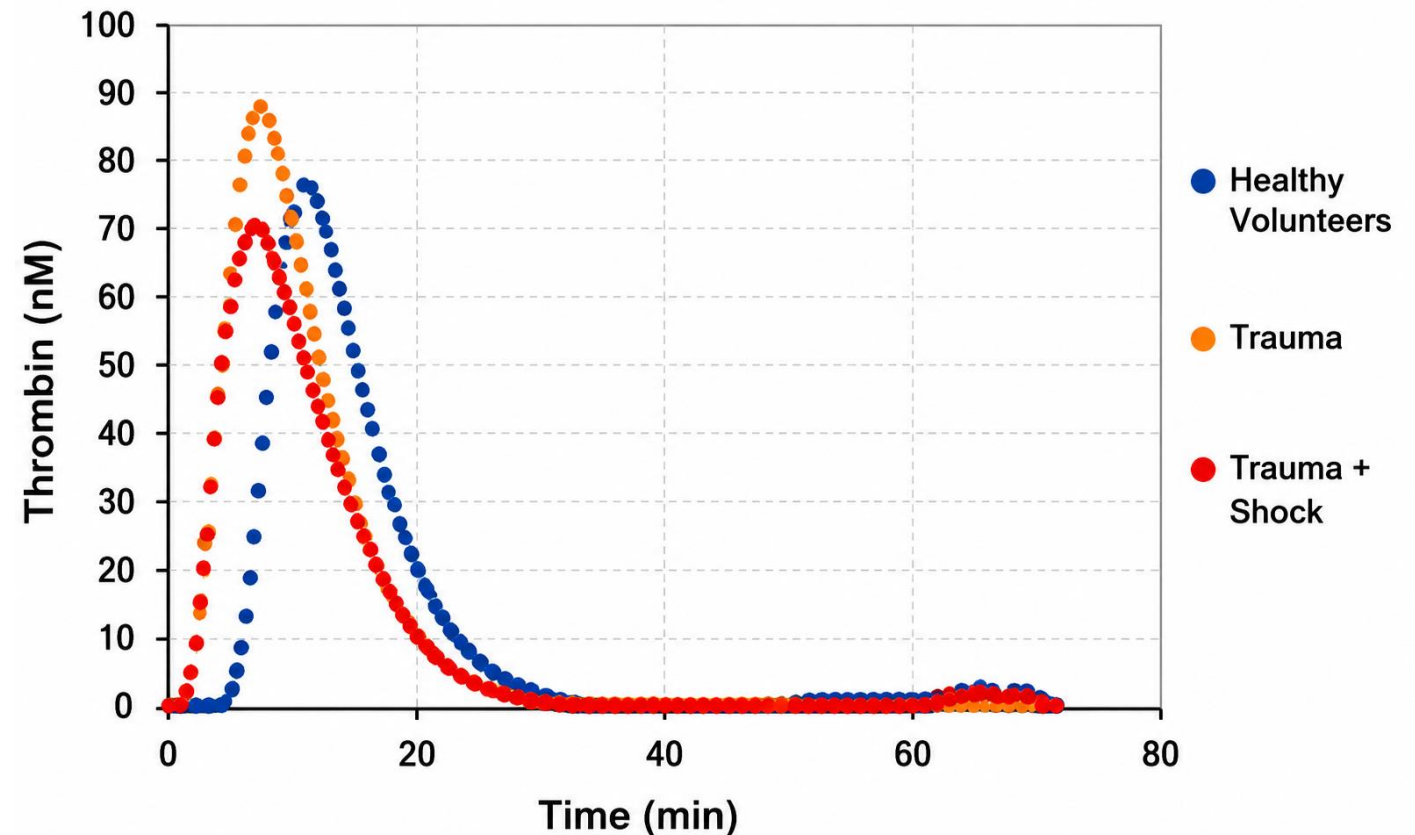
ISS: 22

Shock (syst BP <90mmHg): 23

Massive transfusion (>4U/1h): 26

Whole Blood Thrombin Generation in Severely Injured Patients Requiring Massive Transfusion

Coleman JR, et al. J Am Coll Surg 2021; 232:709–716



Vitamin K Antagonist Reversal

PCC



The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

**In the bleeding trauma patient, we
recommend the emergency reversal of VKA with the early
use of both
PCC and 5–10 mg i.v. vitamin K1
(Grade 1A).**

Vitamin K Antagonist Reversal

PCC



The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

25 IU/kg if INR 2–4.0

35 IU/kg if INR 4–6.0

50 IU/kg if INR >6.0

F-Xa Inhibitor Reversal

Andexanet alfa vs PCC

The European guideline on management of major bleeding and coagulopathy following trauma: 6th edition

Rossaint R, et al. Crit Care 2023;27:80

If bleeding is life-threatening in the presence of an Apixaban or Rivaroxaban effect, especially in patients with TBI, we suggest reversal with Andexanet alfa

Grade 2C

If Andexanet alfa is not available, or in patients receiving edoxaban, we suggest administration of PCC (25–50 U/kg)

Grade 2C

F-Xa Inhibitor Reversal

Andexanet alfa vs PCC



Management of severe peri-operative bleeding: Guidelines from the European Society of Anaesthesiology and Intensive Care: Second update 2022

Kietaibl S, et al. Eur J Anaesthesiol 2023;40:226–304

We suggest the use of
**PCC (25 IU kg BW at first) rather than
Andexanet alfa**
in bleeding patients treated with anti-Xa agents
(Rivaroxaban, Apixaban, and Edoxaban).

Grade of recommendation 2C

Image provided by Prof. Schöchl.

anti-Xa, anti-activated factor X; BW, body weight; FXa, activated factor X; IU, international unit; PCC, prothrombin complex concentrate.

F-Xa Inhibitor Reversal

Andexanet alfa vs PCC

Mata-analysis 22 studies

Controlled studies: 6

- 4F-PCC: N=816
- Andexanet alfa: N=973

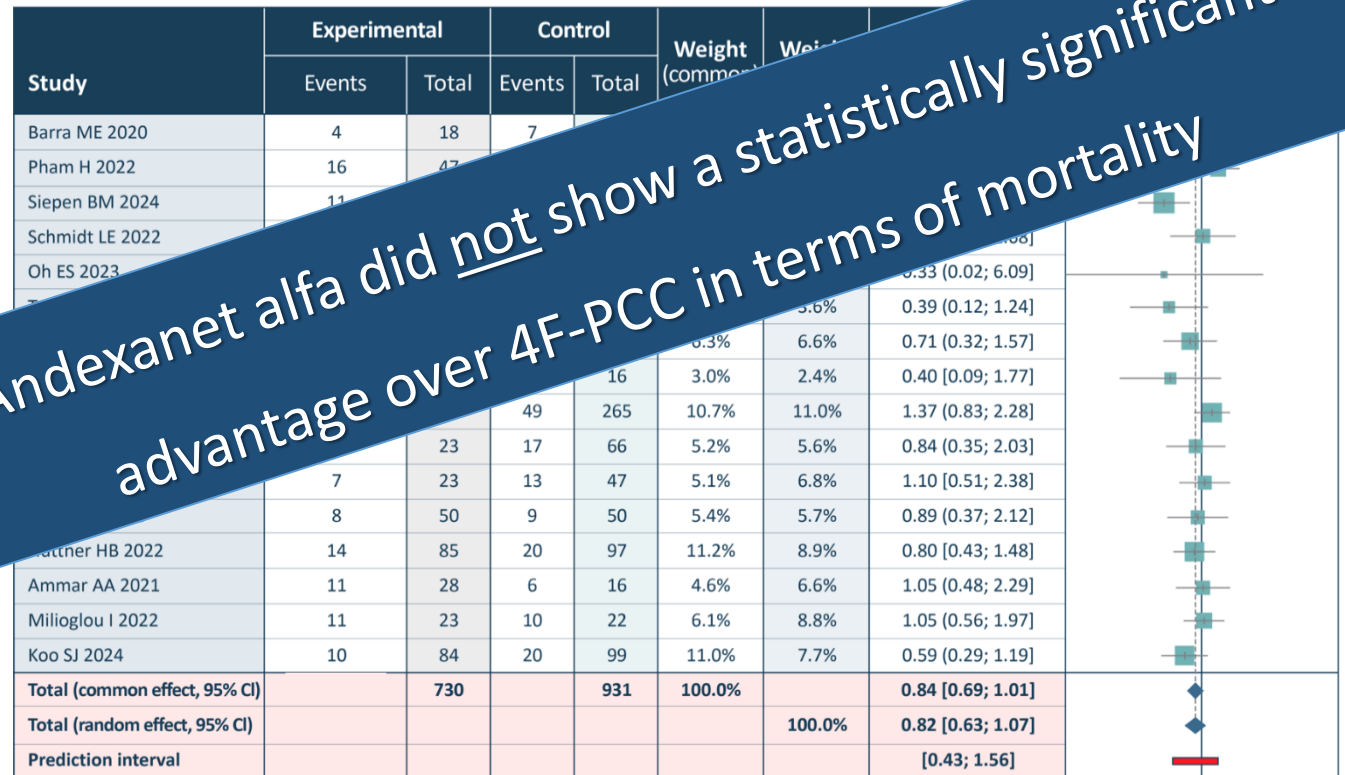
Retrospective studies: 16

- 4F-PCC: N=931
- Andexanet alfa: N=730

Andexanet alpha versus four-factor prothrombin complex concentrate in DOACs anticoagulation reversal: an updated systematic review and meta-analysis

Orso D, et al. Crit Care 2024;28(1):221

All case mortality – retrospective studies



Heterogeneity: Tau² = 0.0746; Chi² = 22.79, df = 15 (P = 0.09); I² = 34%

4F-PCC, four-factor prothrombin complex concentrate; CI, confidence interval; df, degrees of freedom; DOAC, direct oral anticoagulant; MH, Mantel-Haenszel method.

Conclusion

■ TIC¹

- is an independent clinical condition

■ Resuscitation Goals:^{1–4}

- TXA early – within 3 h, in shock
- FFP:RBC:PC = 1:1:1 does **not** prevent dilution
- Fibrinogen drops early → replace early
- PCC is not first-line therapy
- PCC for VKA reversal
- PCC for FXa-reversal
- Factor concentrate-based therapy should be guided by POC monitoring

**No preemptive
coagulation therapy!**



Thank you for your attention