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SFTH SOCIÉTÉ FRANÇAISE DE THROMBOSE ET D'HÉMOSTASE

Is Tranexamic Acid a Universal Hemostatic Agent?

What is Left to Learn about Mechanism, Dosing, Timing, Risks?

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Conflict of Interest Disclosure

- **U.S. Patent**: *Compositions and methods for detecting hyperfibrinolysis and monitoring and guiding treatment*

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Objectives

- Basics of fibrinolysis and inhibition by tranexamic acid (TXA)
- Fibrinolytic activation in major bleeding
- TXA clinical trials; focus on trauma and post partum hemorrhage
- Controversy regarding the use of TXA in trauma
- Can the efficacy of TXA clarify the contribution of fibrinolysis in bleeding disorders?

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What is a 'Universal Hemostatic Agent'?

Review Blood Coagul Fibrinolysis. 2000 Apr:11 Suppl 1:S107-11.
doi: 10.1097/00001721-200004001-00020.

NovoSeven as a universal haemostatic agent

U Hedner [1]

Double Blind Placebo-Controlled 'Off Label' Trials of rFVIIa (1998-2006):

- Trauma
- Intracranial hemorrhage
- Bleeding in stem cell transplant
- Percutaneous liver biopsy
- Partial hepatectomy

Open Label Placebo-Controlled 'Off Label' Trial of rFVIIa (2015):

- Post Partum Hemorrhage

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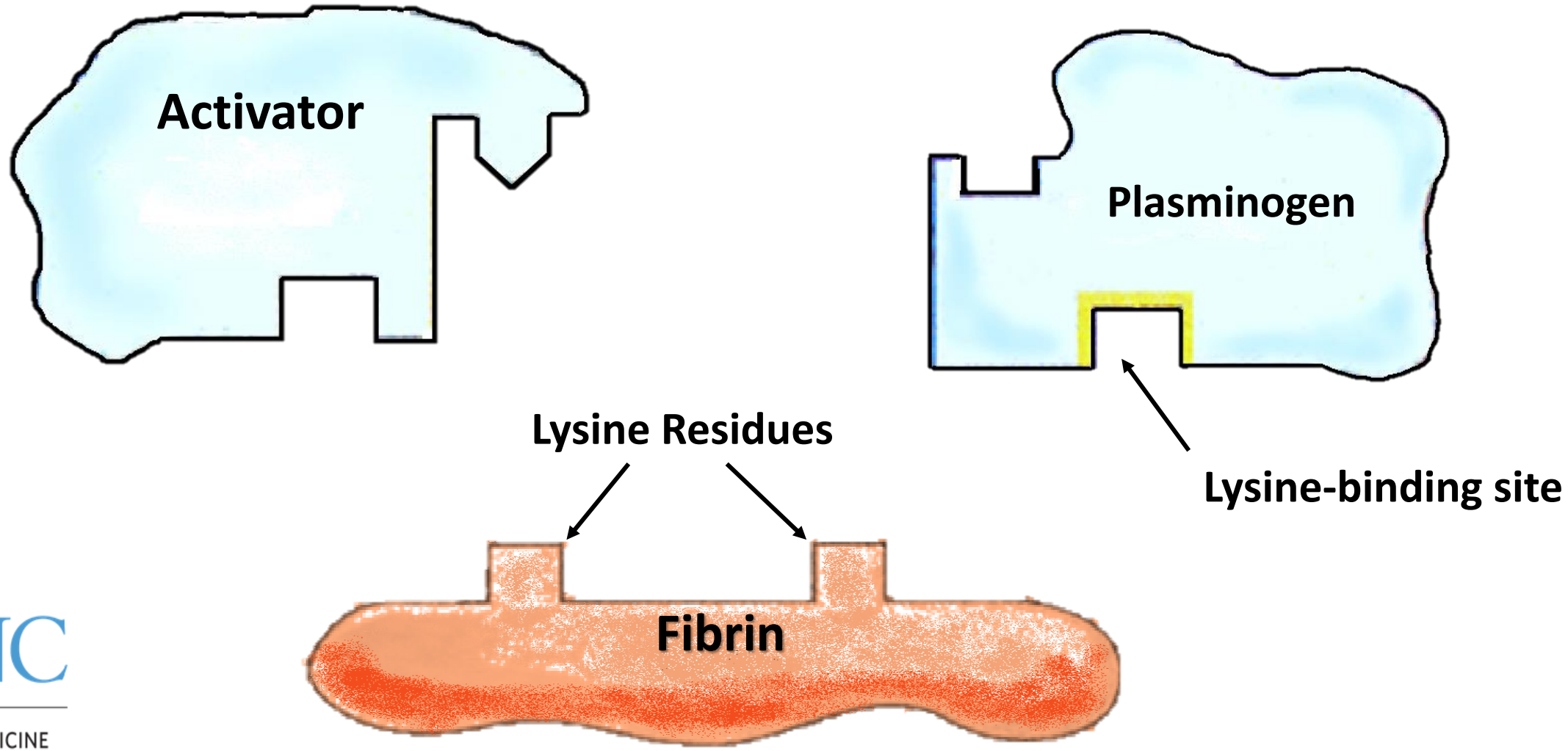
Mechanism of Fibrinolysis



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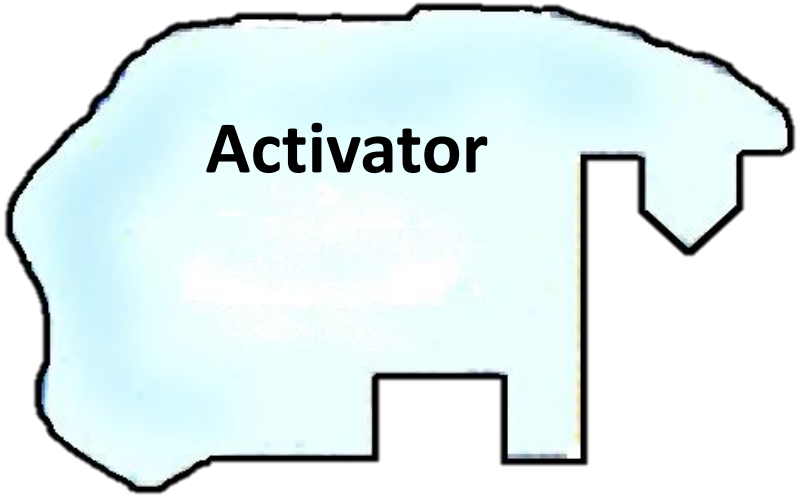
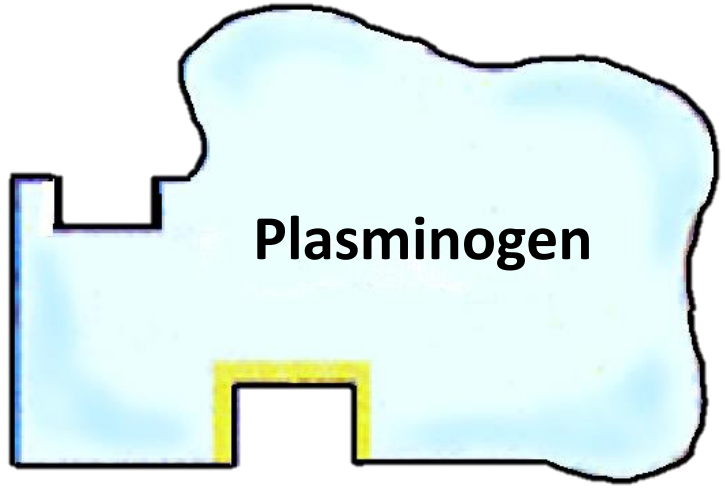
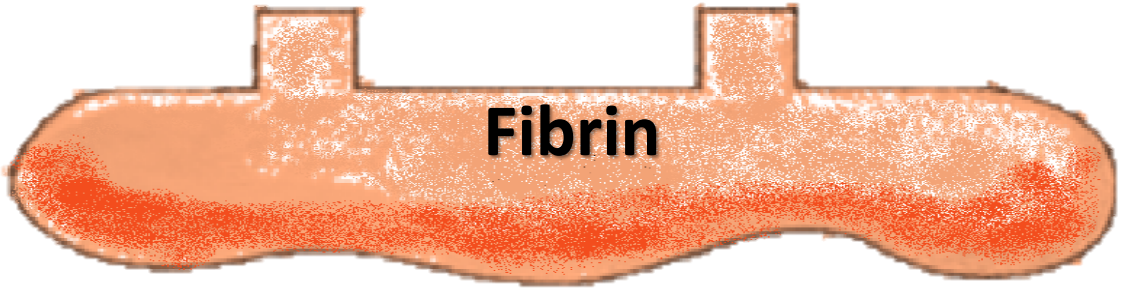
Mechanism of Fibrinolysis







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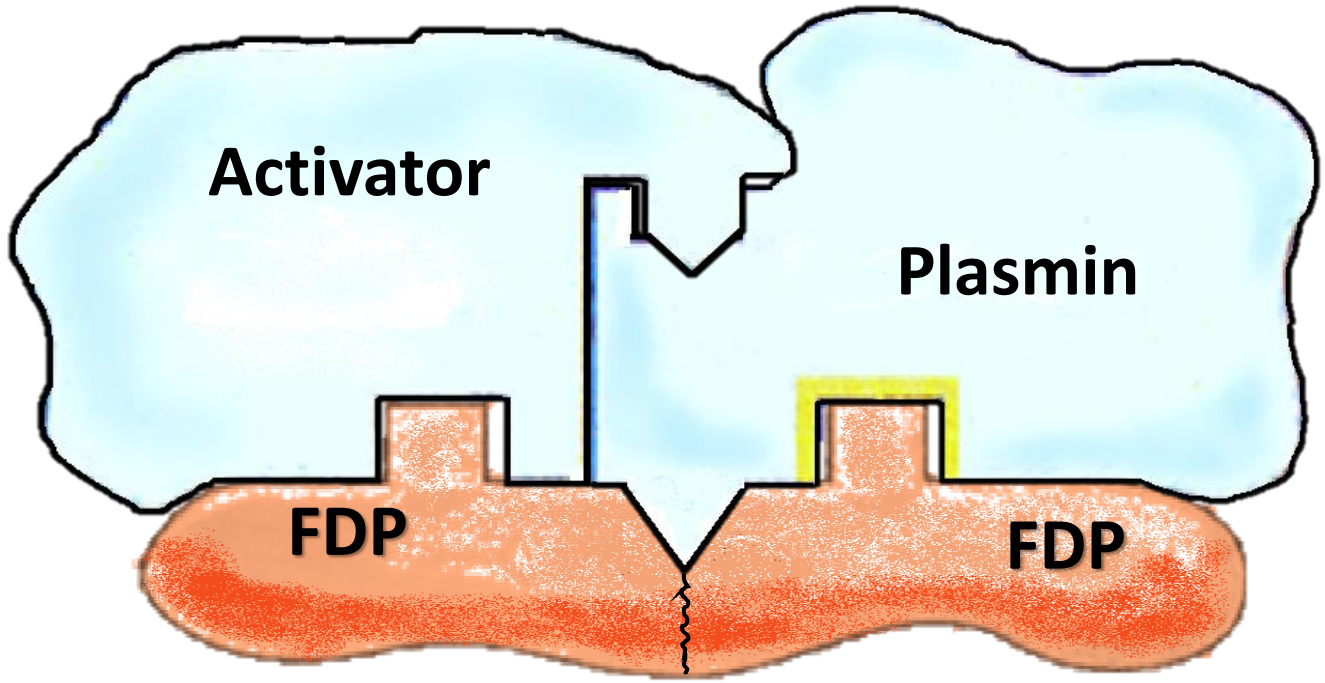
Mechanism of Fibrinolysis



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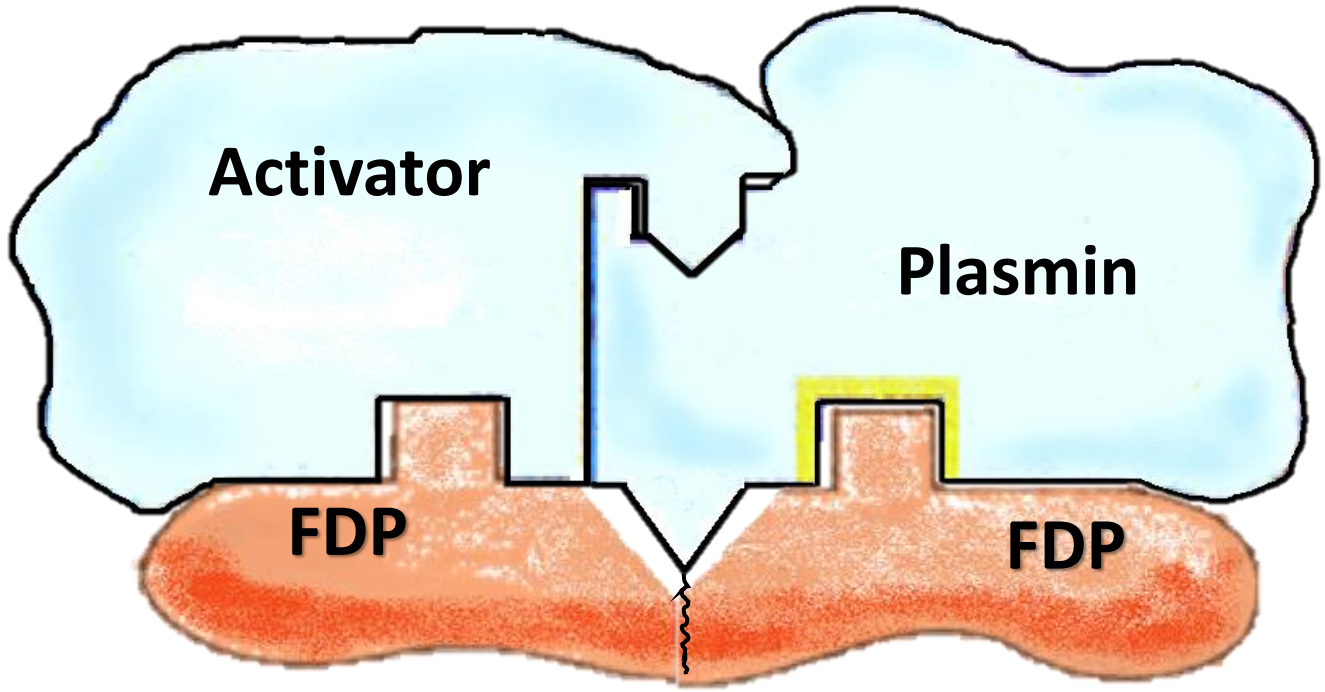
Mechanism of Fibrinolysis



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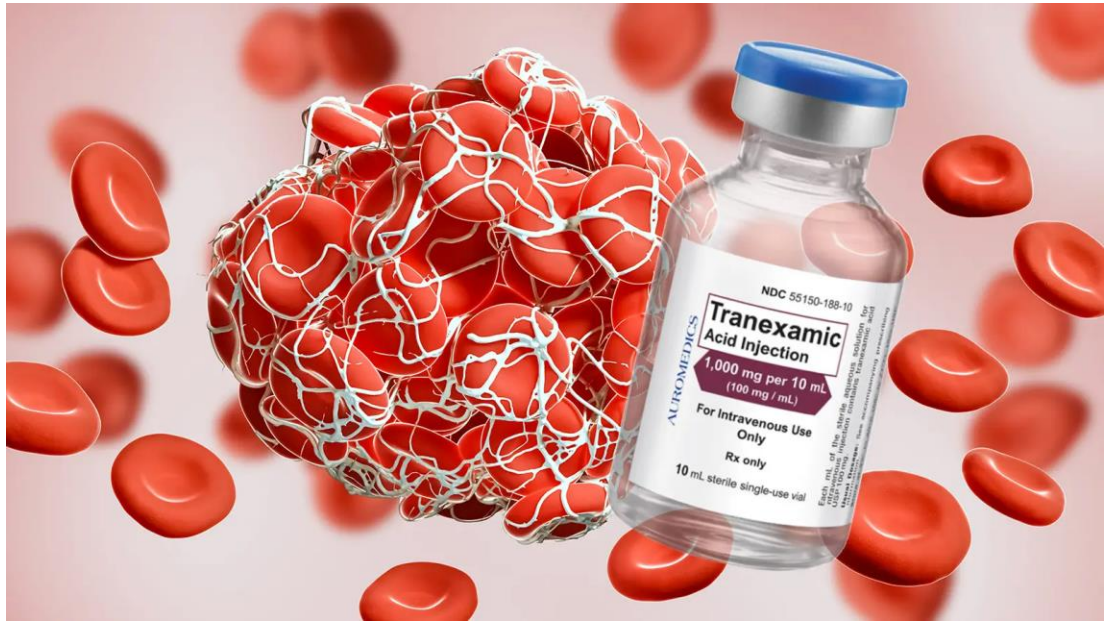
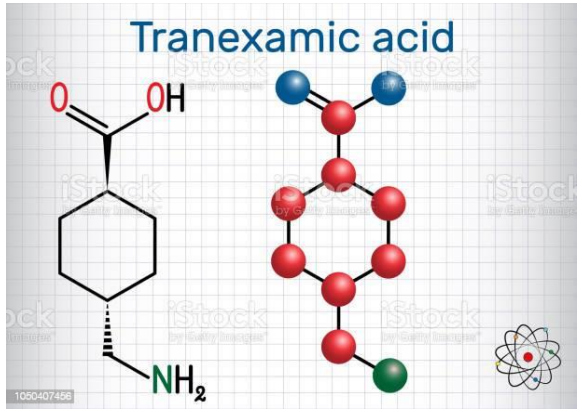
Development of Tranexamic Acid (TXA)



Utako Okamoto MD 1918-2016



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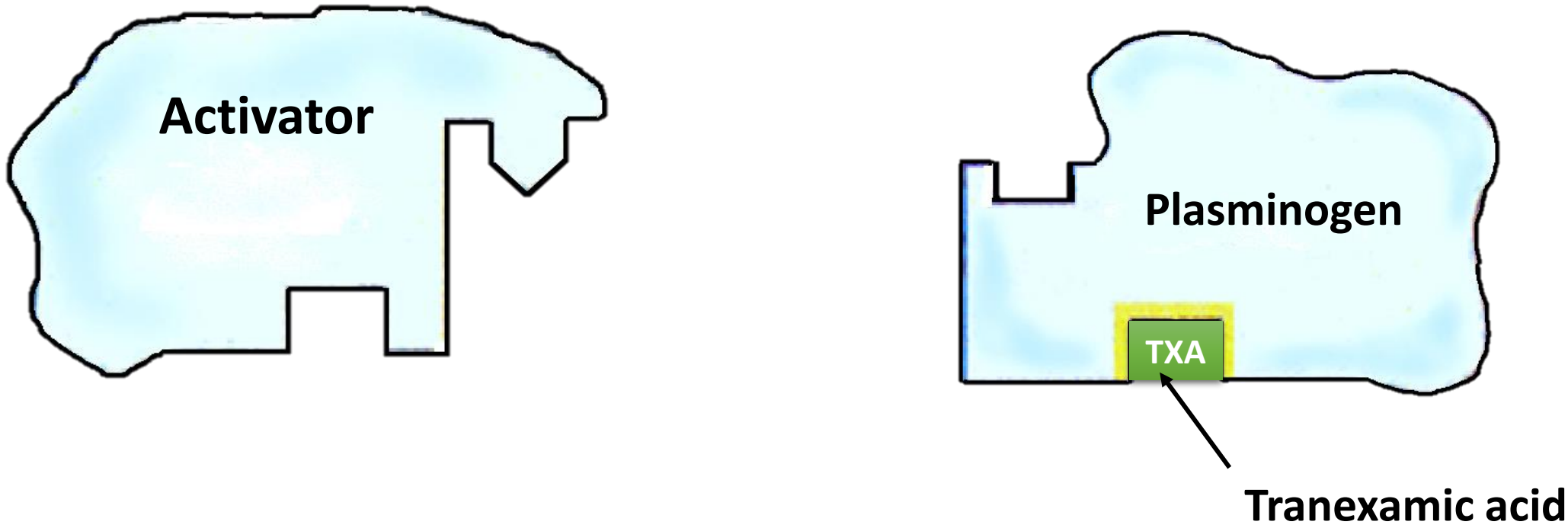
Tranexamic Acid Inhibits Fibrinolysis



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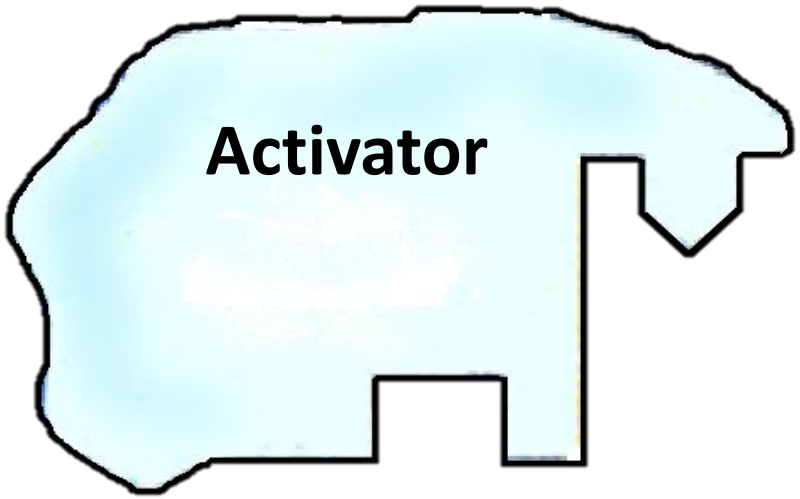
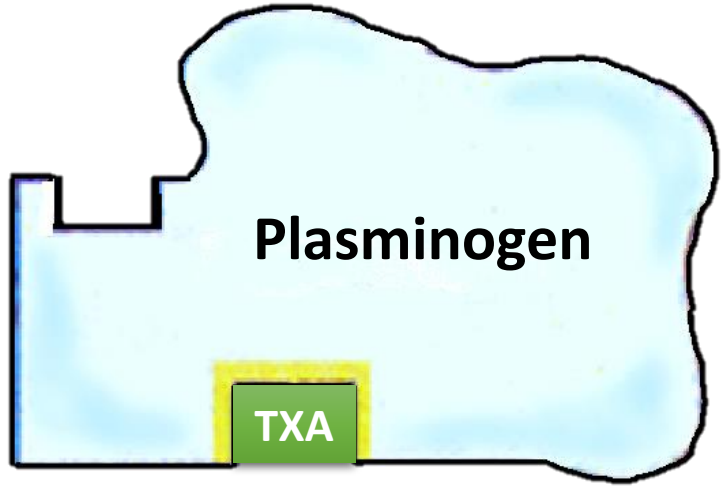
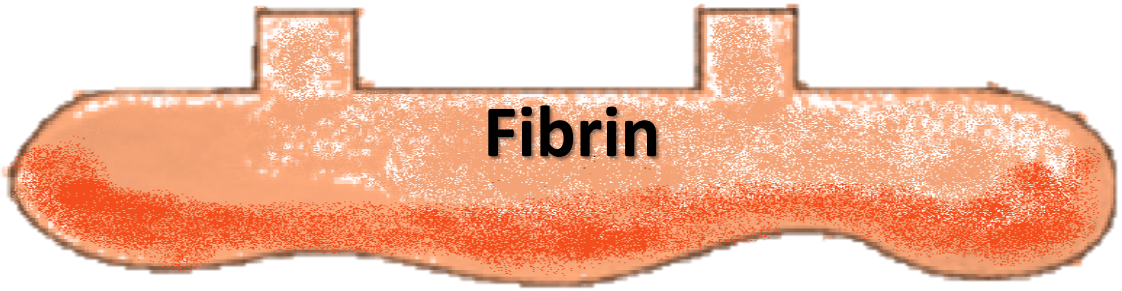
Tranexamic Acid Inhibits Fibrinolysis







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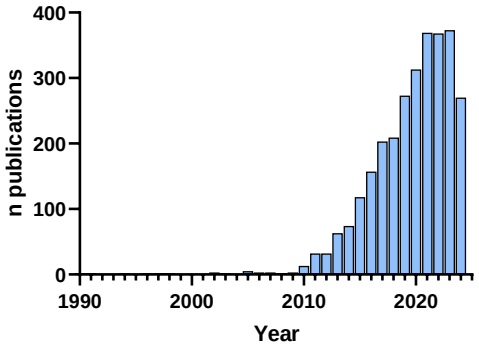
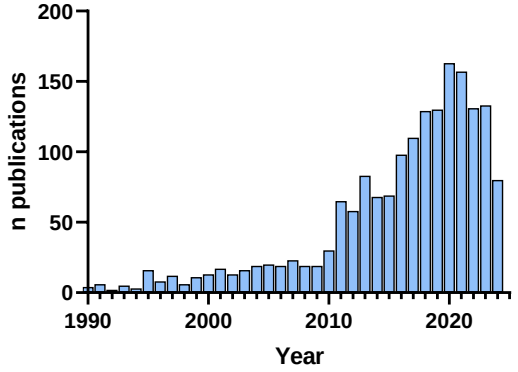
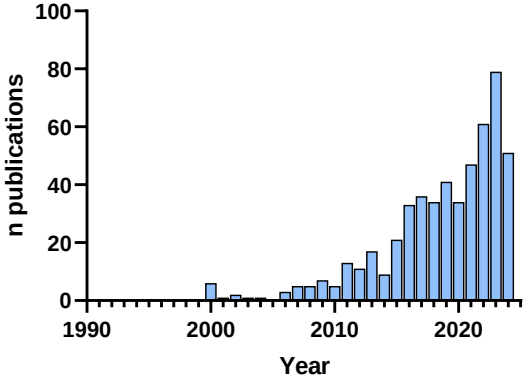
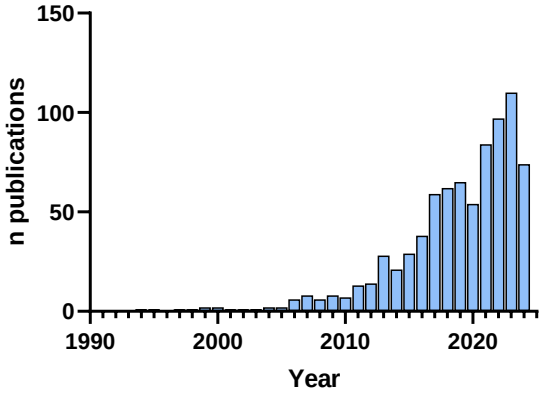
TXA ‘Hits’ in PubMed: January 2000-September 2024

- **Tranexamic acid (TXA)**: 6,960
- **TXA + Randomized Clinical Trial**: 2,097
- **TXA + Cochrane Review**: 459
- **TXA + Meta-analysis**: 679

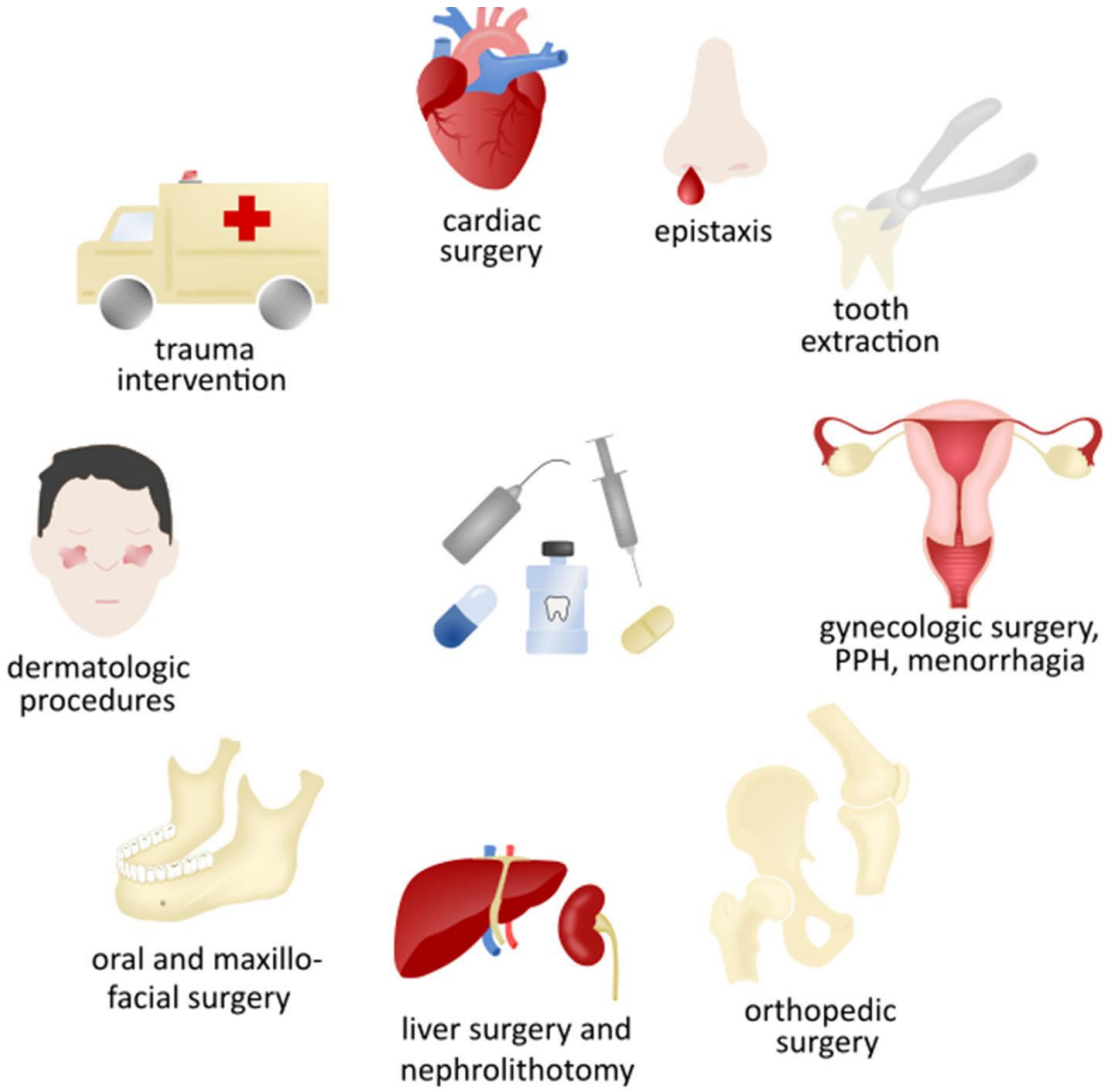








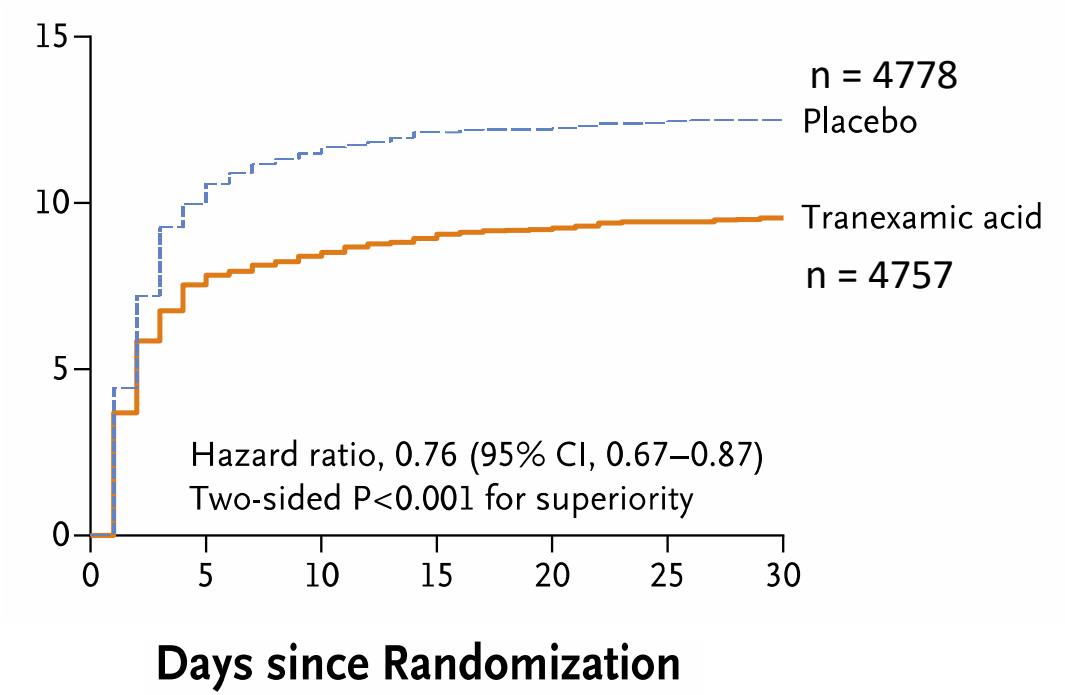
TXA for Prevention and Treatment of Bleeding



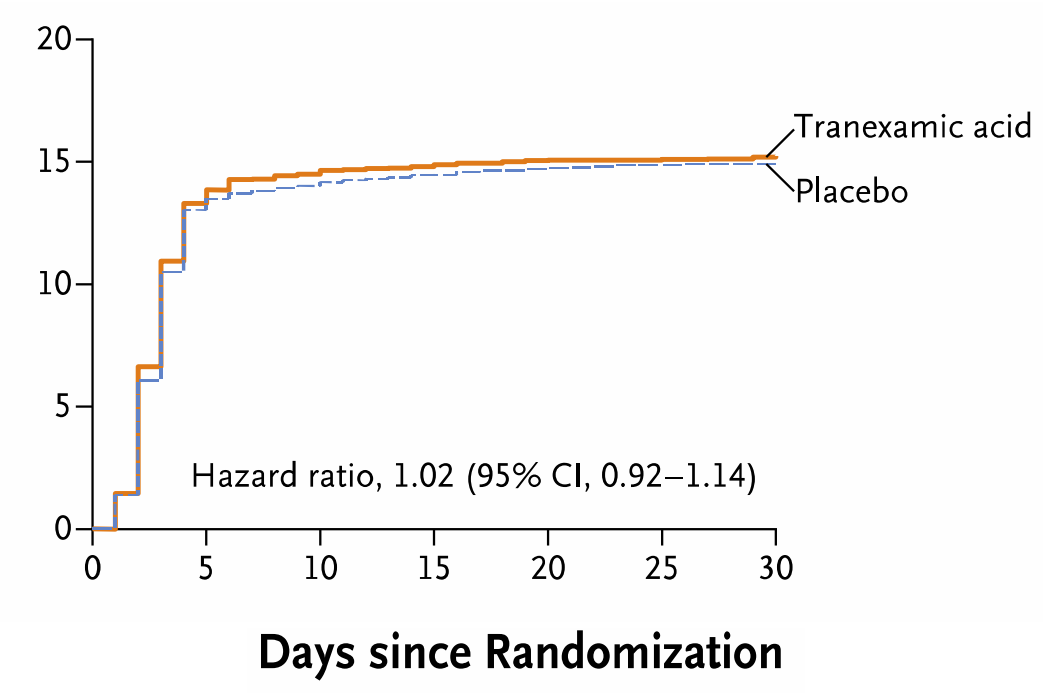
Ockerman A. *Thromb. J.* 2021:19;54

POISE-3 Trial: TXA in Non-Cardiac Surgery

A Composite Bleeding Outcome



B Composite Cardiovascular Outcome



Devereaux PJ. *New Engl J Med* 2022:386;1986

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Wider use of tranexamic acid to reduce surgical bleeding could benefit patients and health systems

Ian Roberts and colleagues call for greater use of this inexpensive generic drug that can improve surgical outcomes, avoid unnecessary blood transfusion, and conserve blood stocks

Ian Roberts, [1] Michael F Murphy, [2] Ramani Moonesinghe, [3,4] Michael P W Grocott, [5,6] Chimwemwe Kalumbi, [7] Rob Sayers, [8] Cheng-Hock Toh[9], on behalf of UK Royal Colleges Tranexamic Acid in Surgery Implementation Group

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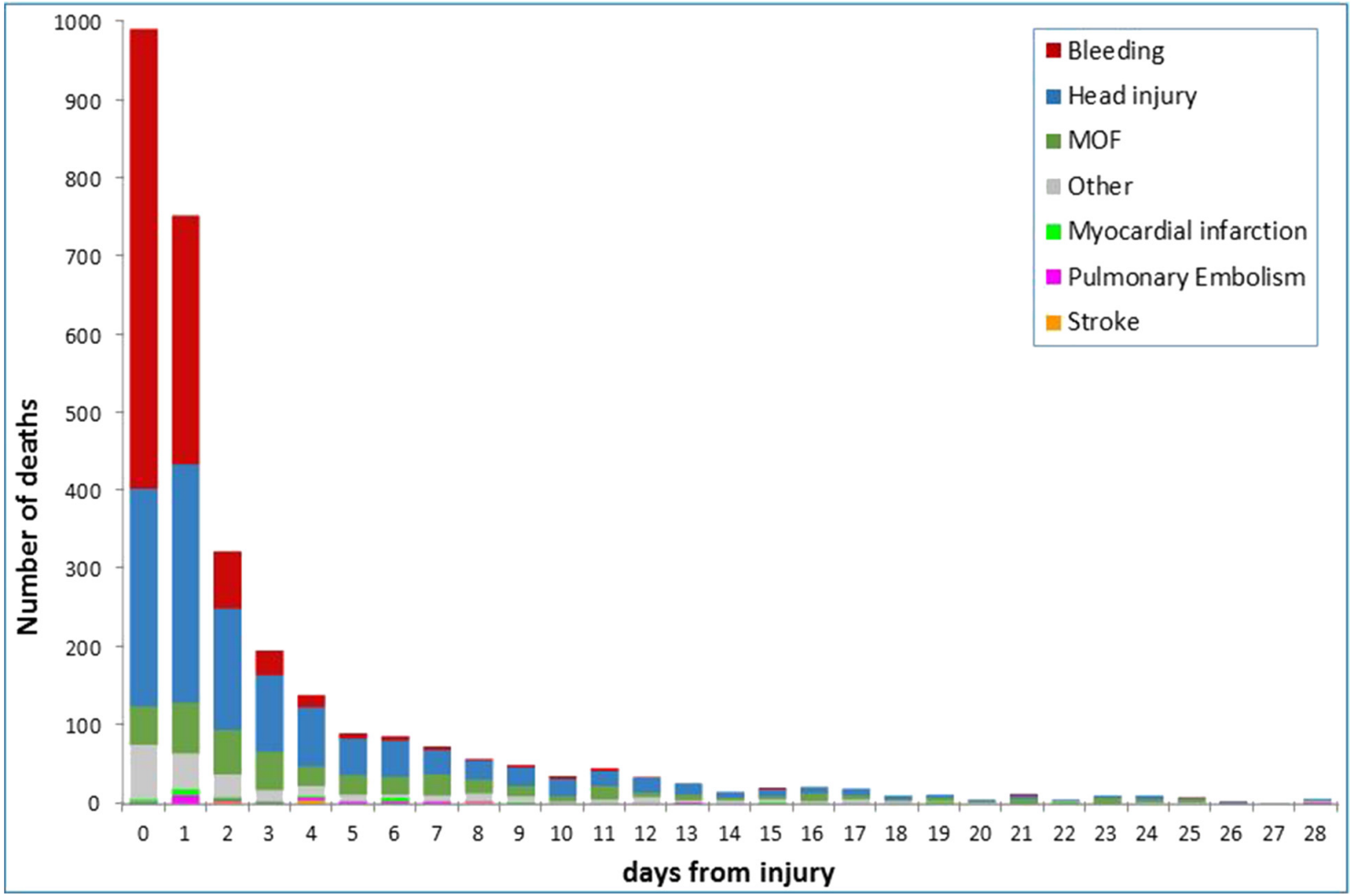
BMJ 2024;385:e079444 | doi: 10.1136/bmj-2024-079444

US FDA-Approved Indications for TXA

- Prevention of bleeding in hemophilia following dental surgery (1986)
- Management of abnormal uterine bleeding (2012)

* 'Black box warning' about potential thrombotic risk

Trauma: Causes of Death by Day Since Injury



Roberts I. *Critical Care* 2014

The CRASH-2 Trial:

Clinical Randomization of an Anti-Fibrinolytic in Significant Hemorrhage

- Pragmatic 20,211 subject RCT comparing TXA to placebo in trauma patients
- Conducted in 40 (including many low resource) countries
- Dosing occurred within 8 hours of injury
- Treatment within 3 hours significantly reduced deaths from bleeding and all-cause mortality
- Later administration was ineffective with more deaths from bleeding, although no increase in all-cause mortality

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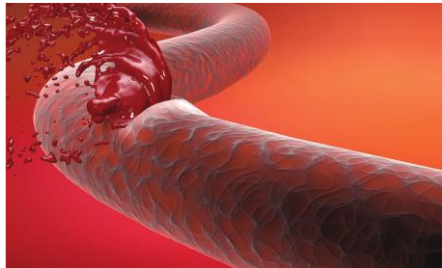
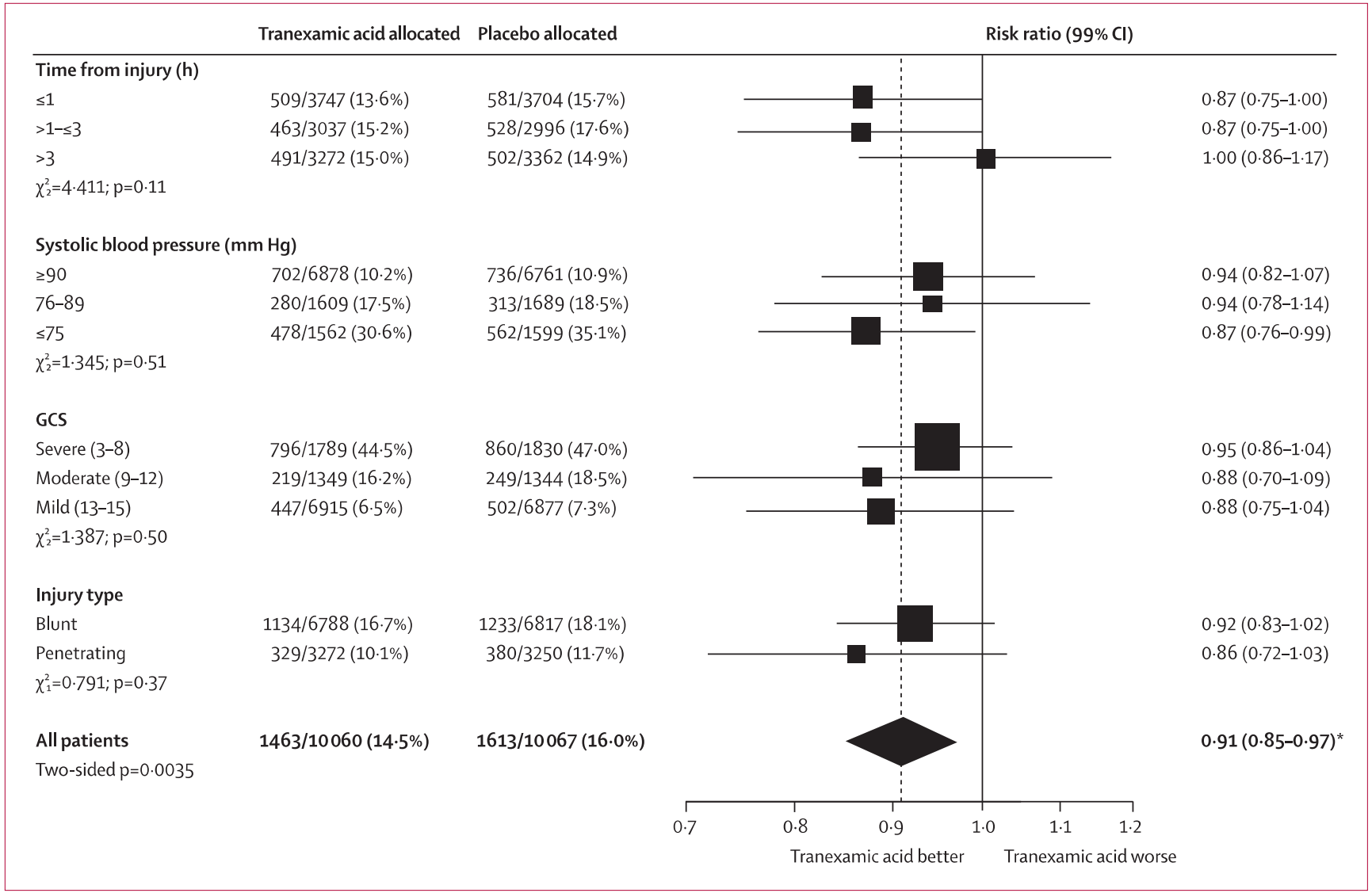
Roberts I. *Lancet* 2011:101;1101.e1-2



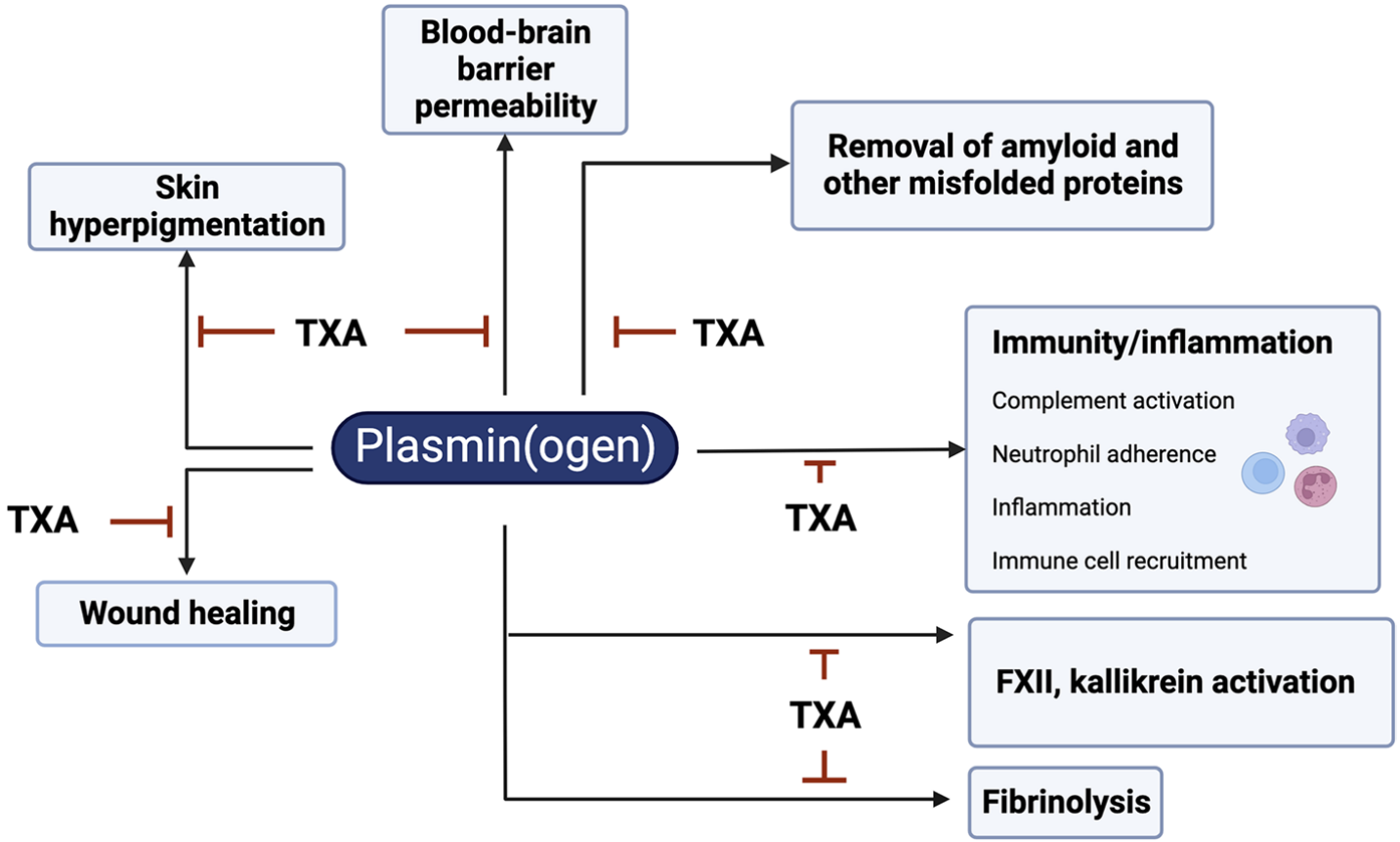
All-Cause Mortality in the CRASH-2 Trial



	Tranexamic acid allocated	Placebo allocated	Risk ratio (99% CI)
Time from injury (h)			
≤1	509/3747 (13·6%)	581/3704 (15·7%)	0·87 (0·75–1·00)
>1–≤3	463/3037 (15·2%)	528/2996 (17·6%)	0·87 (0·75–1·00)
>3	491/3272 (15·0%)	502/3362 (14·9%)	1·00 (0·86–1·17)
χ^2_2=4·411; p=0·11			
Systolic blood pressure (mm Hg)			
≥90	702/6878 (10·2%)	736/6761 (10·9%)	0·94 (0·82–1·07)
76–89	280/1609 (17·5%)	313/1689 (18·5%)	0·94 (0·78–1·14)
≤75	478/1562 (30·6%)	562/1599 (35·1%)	0·87 (0·76–0·99)
χ^2_2=1·345; p=0·51			
GCS			
Severe (3–8)	796/1789 (44·5%)	860/1830 (47·0%)	0·95 (0·86–1·04)
Moderate (9–12)	219/1349 (16·2%)	249/1344 (18·5%)	0·88 (0·70–1·09)
Mild (13–15)	447/6915 (6·5%)	502/6877 (7·3%)	0·88 (0·75–1·04)
χ^2_2=1·387; p=0·50			
Injury type			
Blunt	1134/6788 (16·7%)	1233/6817 (18·1%)	0·92 (0·83–1·02)
Penetrating	329/3272 (10·1%)	380/3250 (11·7%)	0·86 (0·72–1·03)
χ^2_1=0·791; p=0·37			
All patients	**1463/10 060 (14·5%)**	**1613/10 067 (16·0%)**	**0·91 (0·85–0·97)***
Two-sided p=0·0035			

Roberts I. *Lancet* 2011:101;1101.e1-2

Described Inhibitory Effects of TXA on Non-Hemostatic Properties of Plasmin



Lam T. *Thromb. J.* 2023:21;94

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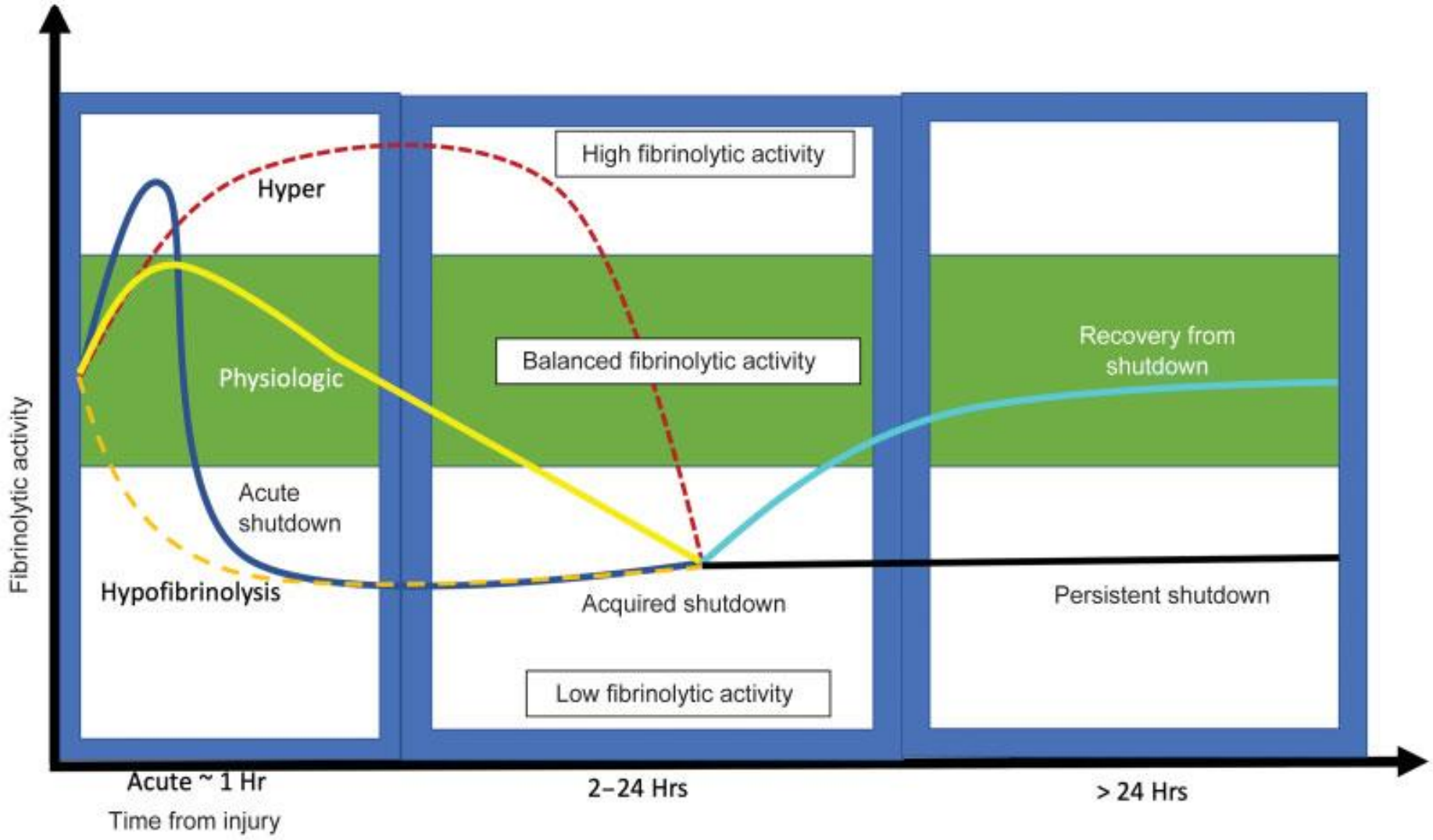
Mechanisms of Systemic Fibrinolytic Activation

- During severe hypoperfusion, tPA is released from the endothelium, probably as an evolutionary response to maintain blood fluidity and perfusion of critical organs.
- tPA release may be further exacerbated by thrombin, vasopressin and adrenaline
- tPA release is also a manifestation of the 'endotheliopathy of trauma' (endothelial activation and shedding of the glycocalyx)
- Massive tPA release overwhelms free PAI-1 → free circulating tPA →plasmin generation ('systemic fibrinolytic activation/hyperfibrinolysis')

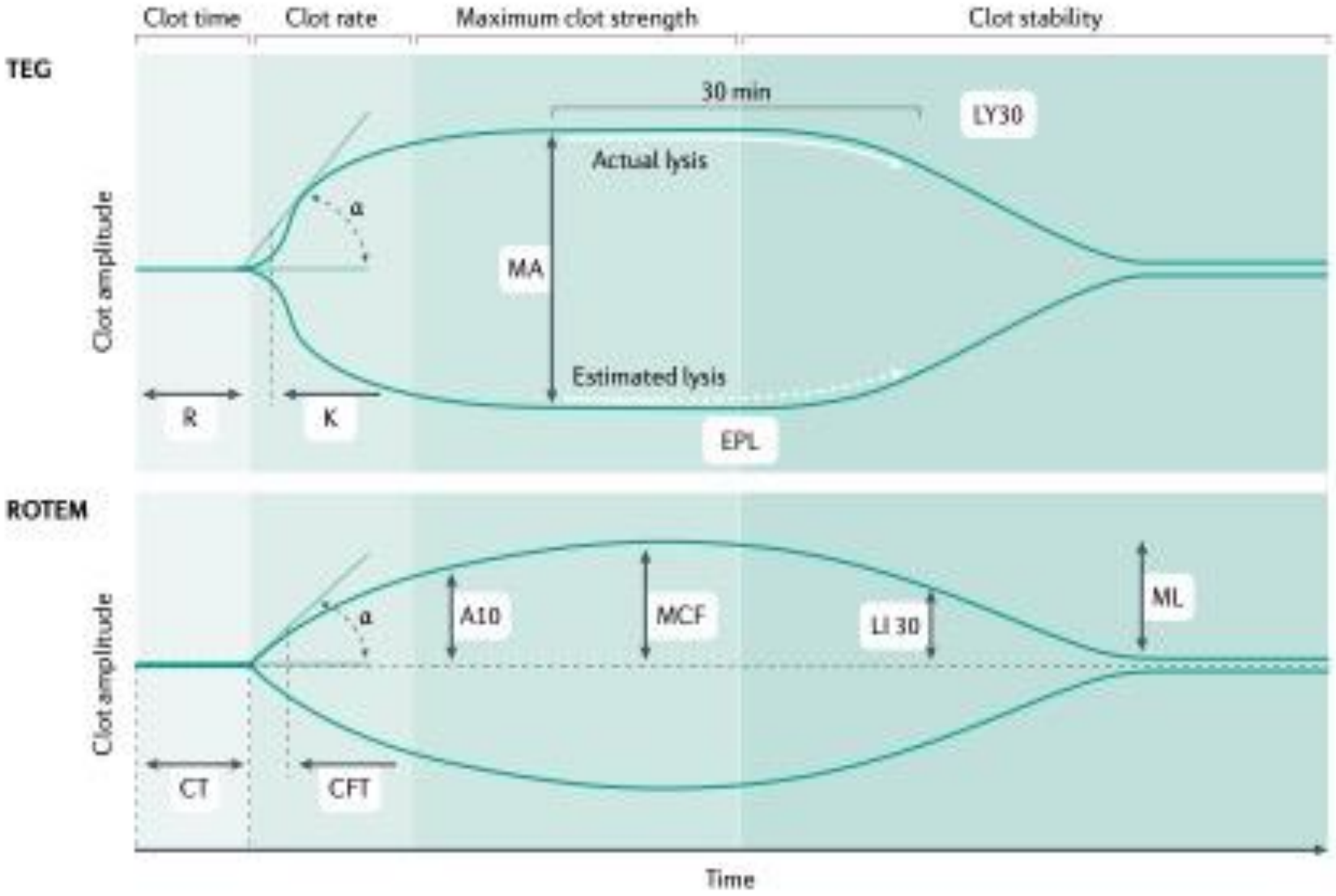
[1]Chapman MC. *J Trauma Acute Care Surg* 2016;80(1);60

Proposed Fibrinolytic Phenotypes in Trauma With Time-Dependent Changes

Moore HB & Moore EE. *Semin Thromb Hemost* 2020:46;189



Viscoelastic Hemostatic Assays (ROTEM and TEG)

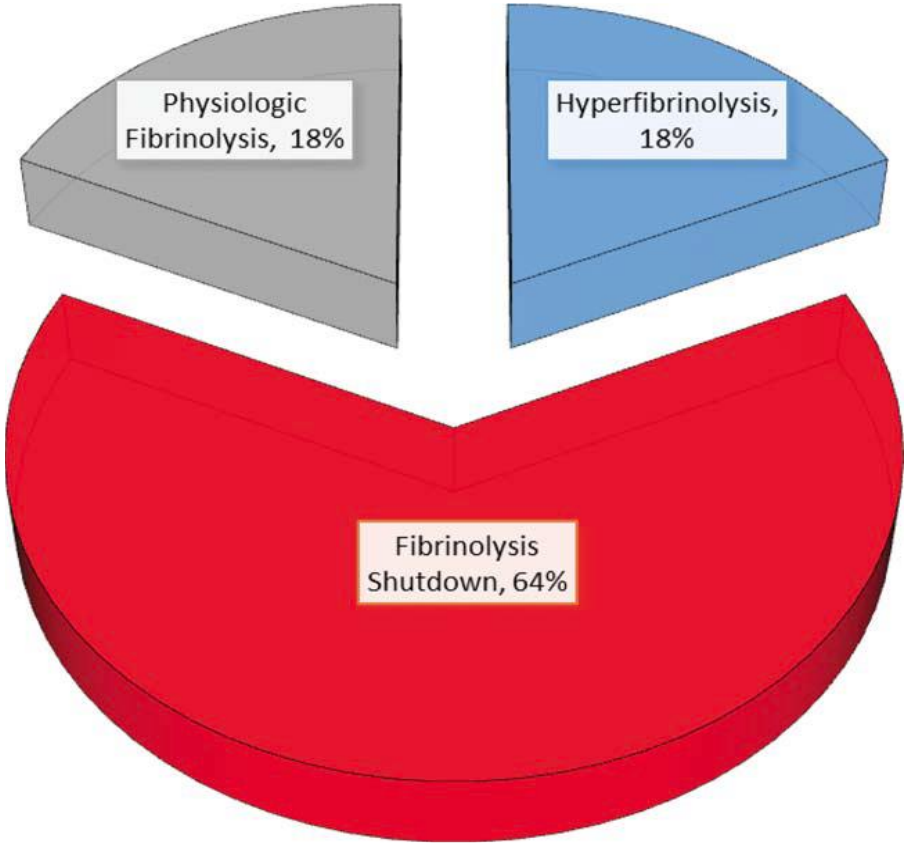


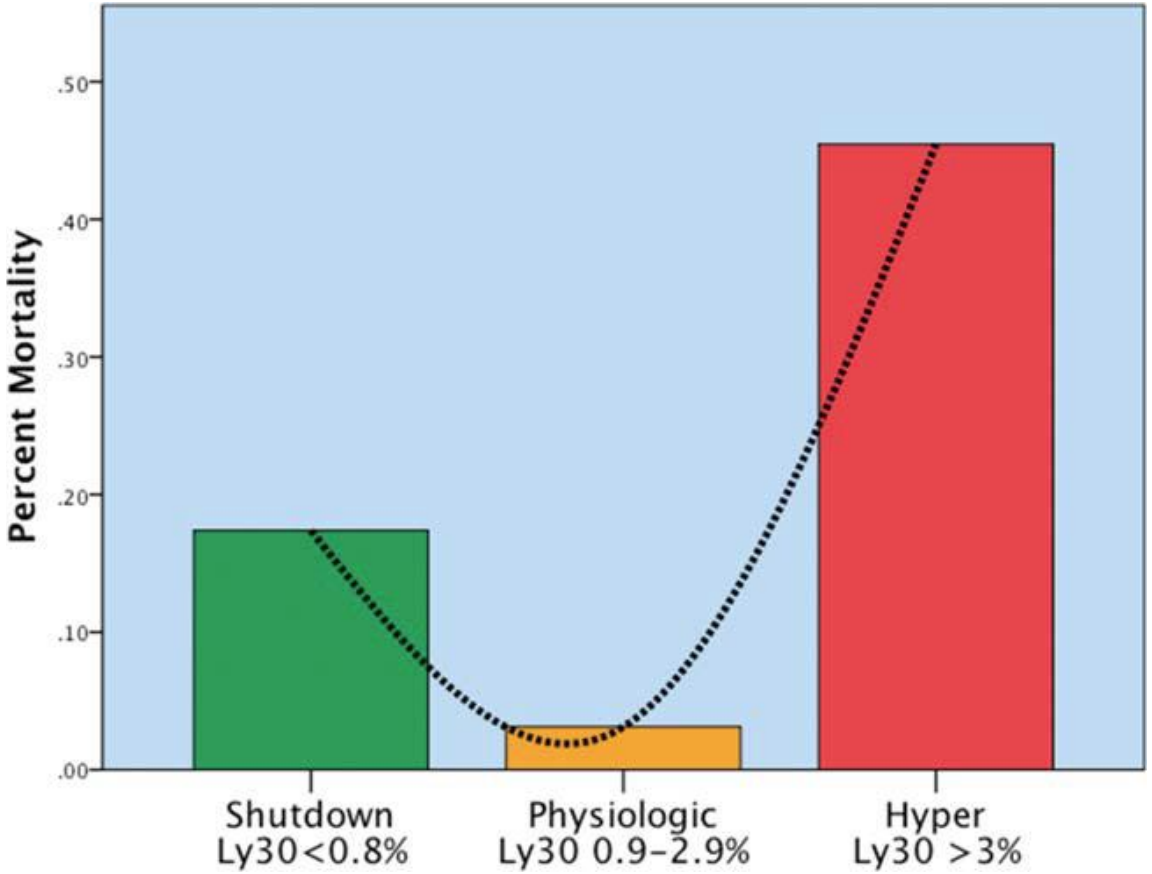
What Clotting Processes Can VHAs Address?

1. **Prolongation of Clot Formation**
2. **Reduction in Clot Strength**
3. **Increase in Fibrinolysis**

Moore EE. *Nat Rev Dis Prim* 2021

Baseline TEG-Defined Fibrinolytic Phenotypes in Trauma





Moore EE. *Transfusion* 2016:56 (Suppl 2);S110

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Two Schools of Thought Emerged….

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POINT: Viscoelastic Hemostatic Assays Should be Be Used to Guide TXA Dosing in Trauma

"It is important to confirm the diagnosis of systemic hyperfibrinolysis before subjecting a patient to a potentially thrombogenic agent"

Ramos CR **JTH** 2013:11(7);1435

>3% lysis at 30 minutes by TEG (Ly30*) -- a threshold that was defined by a dramatic increase in mortality -- is the *"critical value for initiation of anti-fibrinolytic therapy"*

Chapman MC **J Trauma** 2013

*Equivalent to Maximum Lysis (ML) >15% by ROTEM

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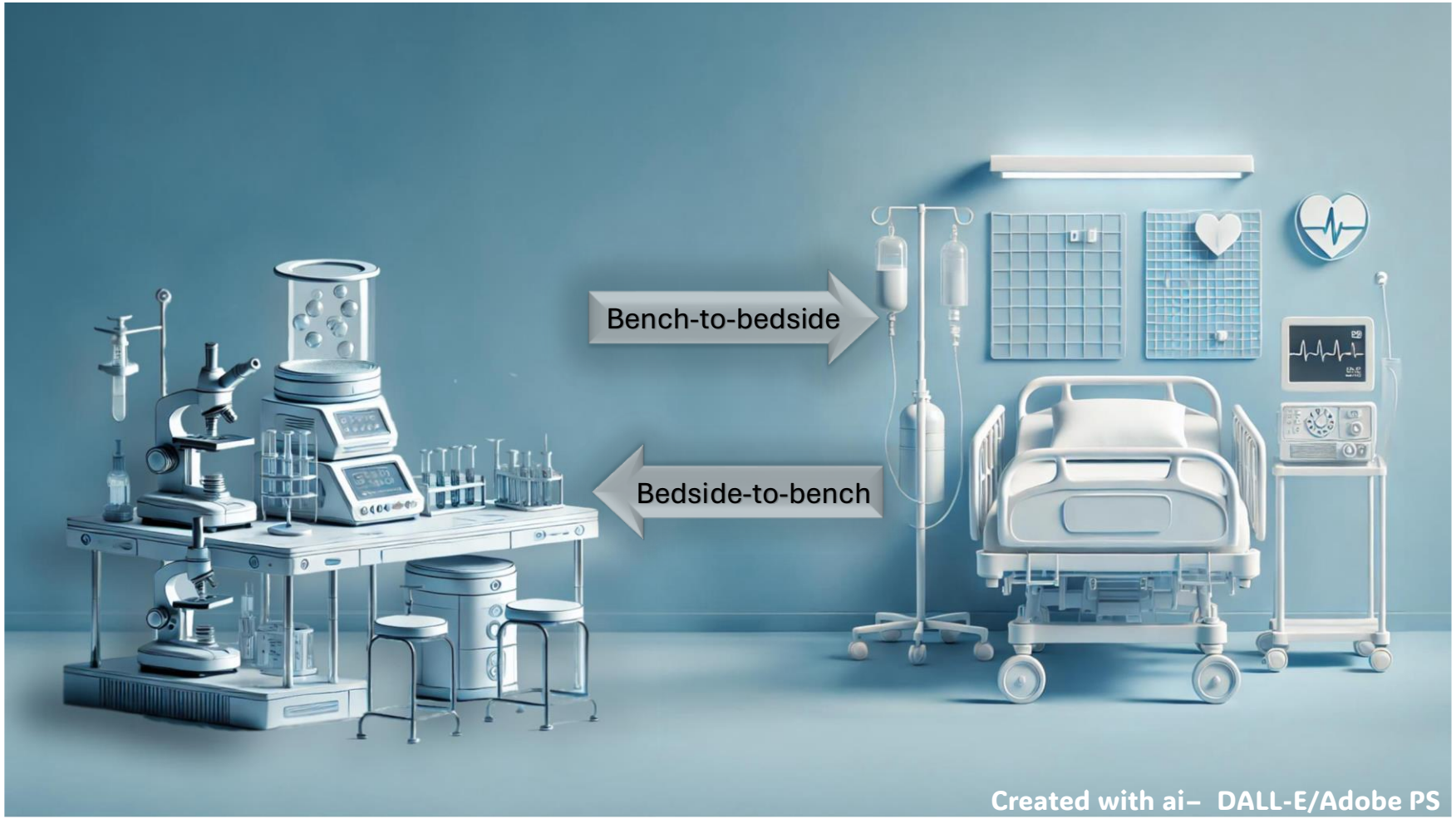
'Translational Research' is Bi-Directional….



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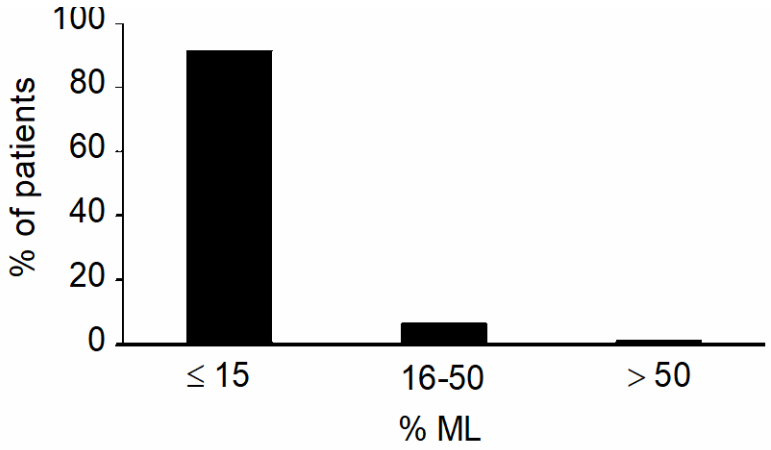
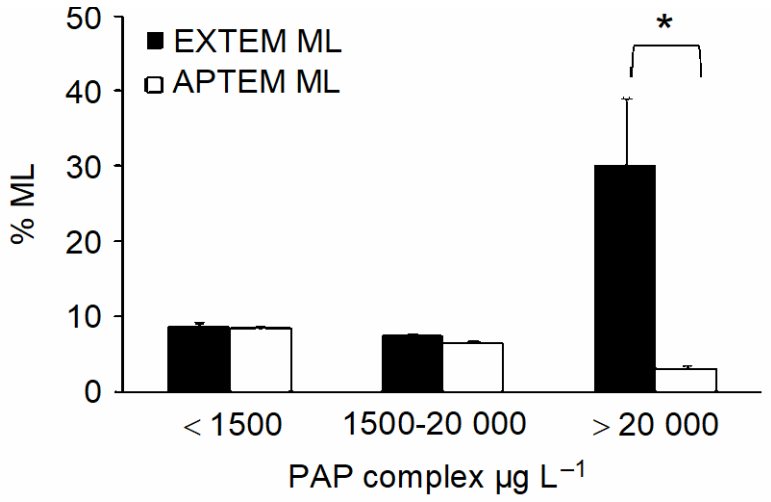
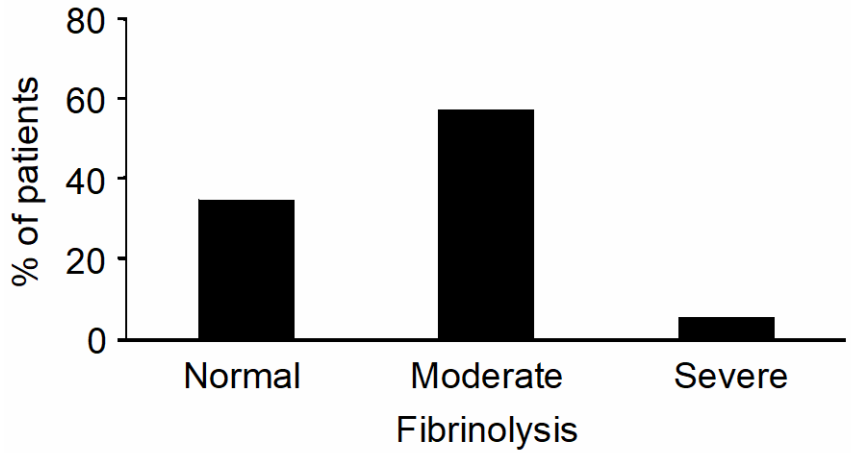
Thromboelastometry (TEM) Underestimates the Incidence and Severity of Fibrinolytic Activation in Trauma



'Hyperfibrinolysis' incidence by TEM (ML >15%)



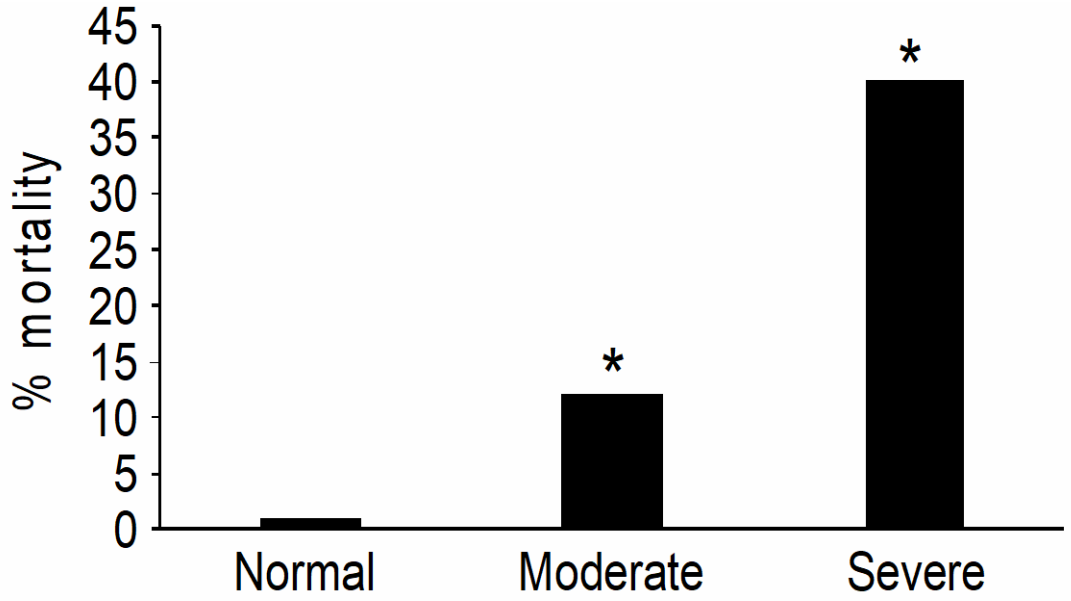
Plasmin-antiplasmin complexes may be markedly elevated with no 'Hyperfibrinolysis' by TEM



Moderate Fibrinolytic Activation = ML <15% with PAP >1500 µg/L

Raza I. *JTH* 2013:11;307

Mortality is Related to Degree of PAP Complex-Defined Fibrinolytic Activation in Trauma



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Raza I. *JTH* 2013:11;307

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COUNTERPOINT: Viscoelastic Hemostatic Assays Should Not be Used to Guide TXA Dosing in Trauma

KEY POINTS

- Massive fibrinolytic activation occurs in over 80% of severely injured trauma patients.
- Fibrinolytic protein biomarkers (e.g. PAP) are the gold standard for assessing hyperfibrinolysis but are currently confined to the research setting.
- Point-of-care viscoelastic haemostatic assays (ROTEM and TEG) are faster but relatively insensitive for accurate diagnosis of increased fibrinolytic activation.
- Best practice mandates empirical administration of TXA within 3 h of injury to all patients with suspected or confirmed traumatic haemorrhage, an immediate need for transfusion or evidence of haemorrhagic shock.

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Gall LS and Davenport RA. *Curr Opin Anaesthesiol* 2018:31;227

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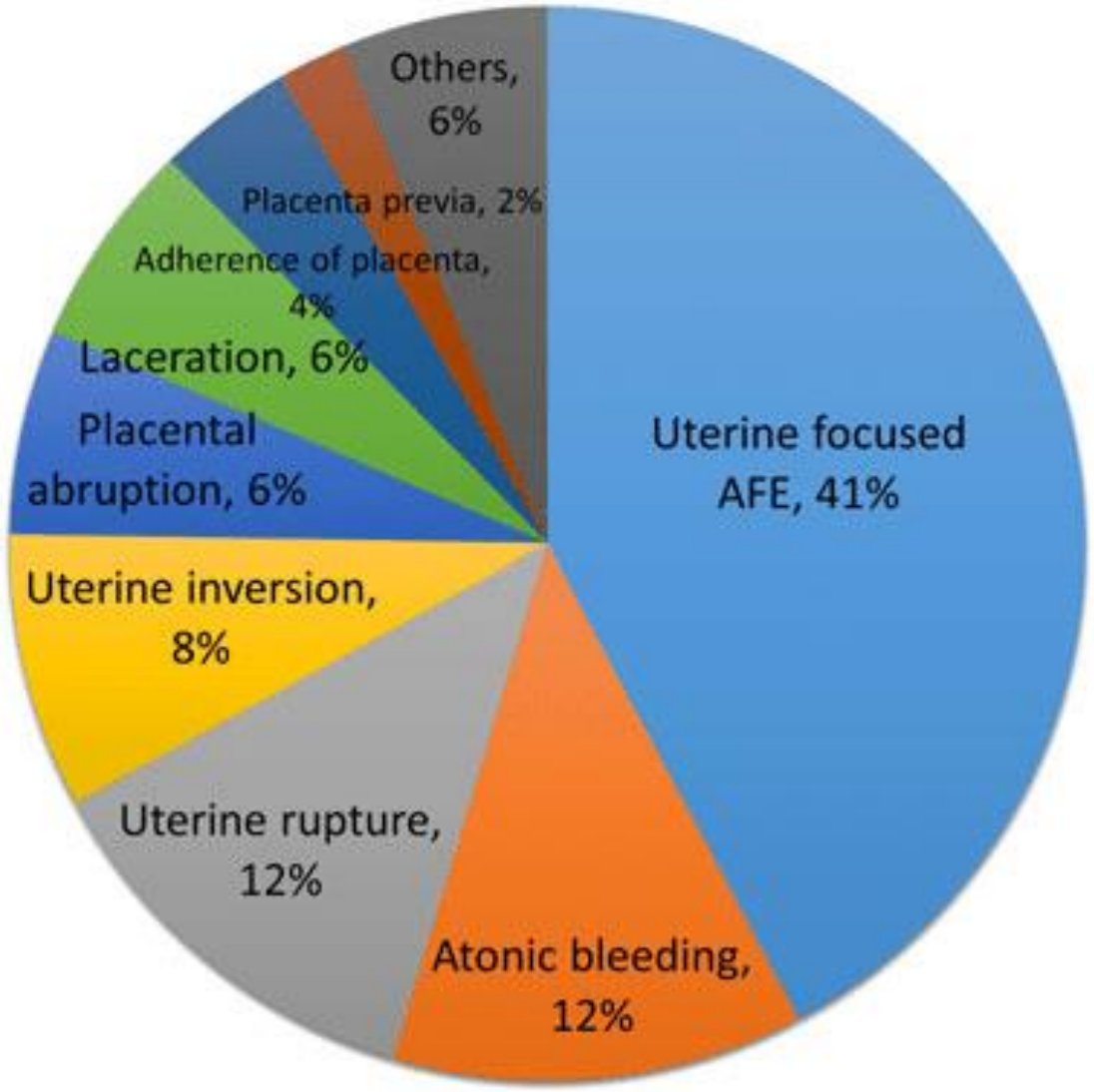
Most PPH is Not Primarily Due to Coagulopathy



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Post-Partum Hemorrhage (PPH)

- PPH defined as estimated blood loss > 1000 mL during Cesarean section, or > 500 mL after vaginal delivery. Severe PPH generally defined as EBL > 1500 mL

- Coagulopathy occurs in only a minority of women with PPH, but it is difficult to predict, and requires urgent intervention once identified

- No data exist to suggest that VHAs should be used to decide on TXA administration

Henriquez DD. *JTH* 2018:16;1523

Progessive Coagulopathy in PPH

PPH (>1000 mL blood loss) identified in 518/11,279 (4.6%)* of pregnancies. Changes in PT, aPTT, platelet count were minimal during PPH (*even up to 3000 mL blood loss)

However, a drop in fibrinogen to <2 g/dL may be associated with progression to a larger bleed.

Rarely, 'Acute Obstetric Coagulopathy' characterized by massive fibrinolytic activation with PAP complexes > 40,000 ng/mL) and hypodysfibrinogenemia follows. 50% fetal demise. Incidence = 12/518 (2.3%)* of PPH patients

*De Lloyd L. *JTH* 2023:21;862

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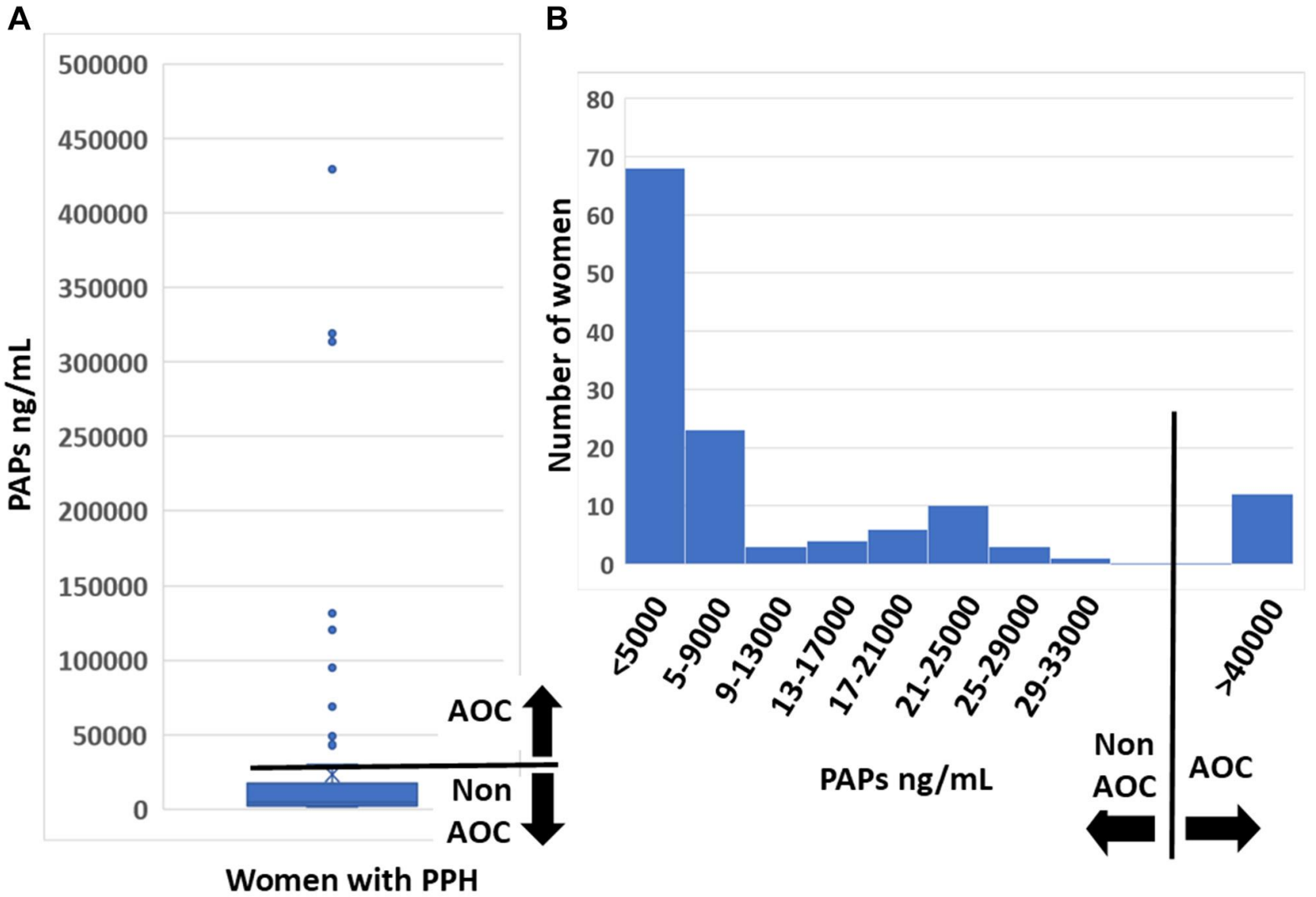
Plasmin-Antiplasmin (PAP) Complexes in PPH:

Acute Obstetric Coagulopathy (AOC) is Associated with Massive Fibrinolytic Activation



De Lloyd L.
JTH 2023:21;862

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LILLE GRAND PALAIS

Evolution of PPH to Acute Obstetric Coagulopathy:

Walking on the Precipice……

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The World Maternal Antifibrinolytic (WOMAN) Trial

- Pragmatic worldwide RCT (TXA vs. placebo) involving 20,600 women presenting with clinical evidence of PPH
- PPH defined as 500 or 1000 mL blood loss (depending on mode of delivery) or hemodynamic instability
- All cause mortality did not differ in the study arms
- However, there was a significant reduction in death from bleeding in the TXA arm (RR 0.81 [0.65-1.00]) and particularly when administered within 3 hours following birth (RR 0.69 [0.52-0.91])
- No increased risk of VTE

WOMAN Trial Collaborators. *Lancet* 2017:389;2105

Effect of Timing of TXA Administration on Bleeding-Related Mortality in the WOMAN Trial

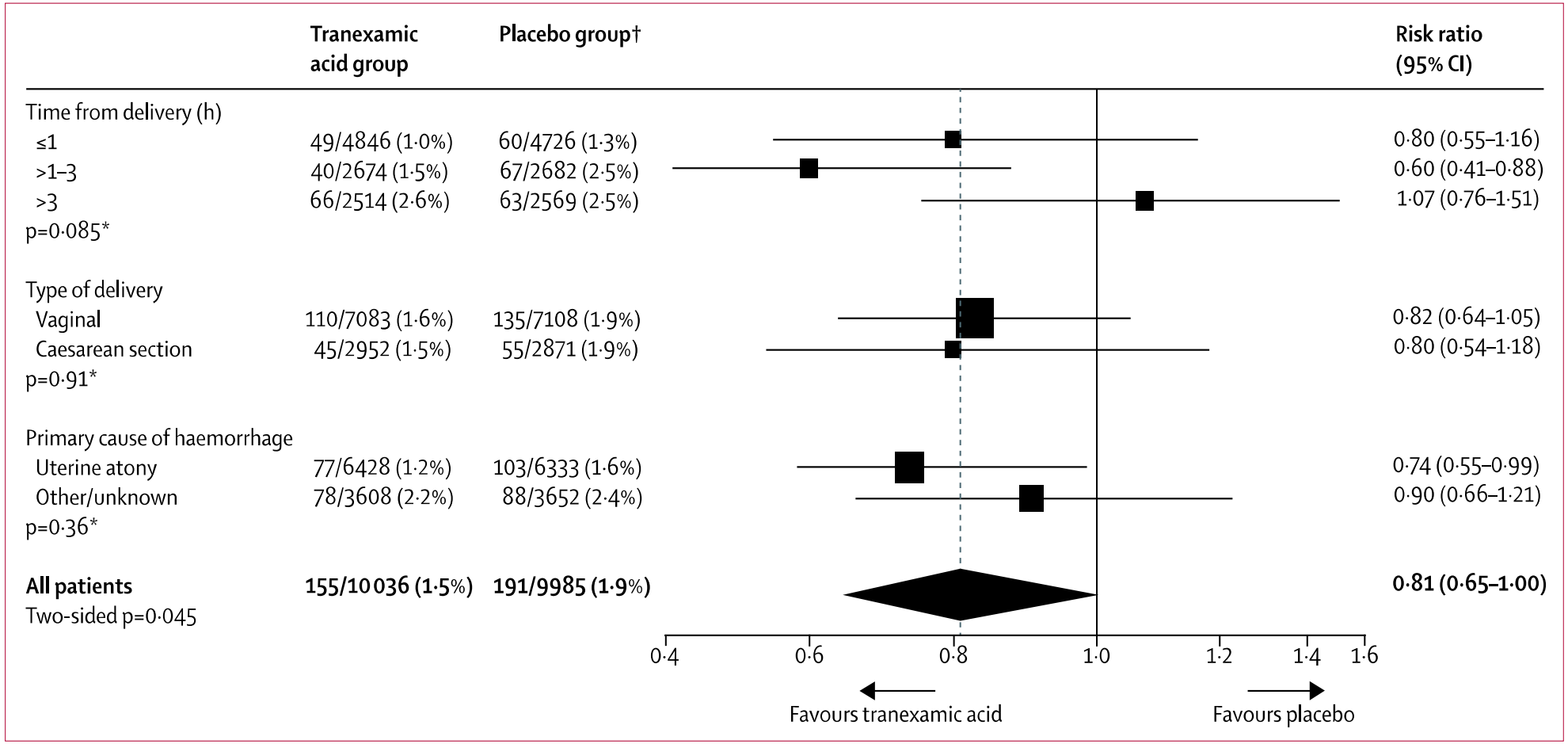


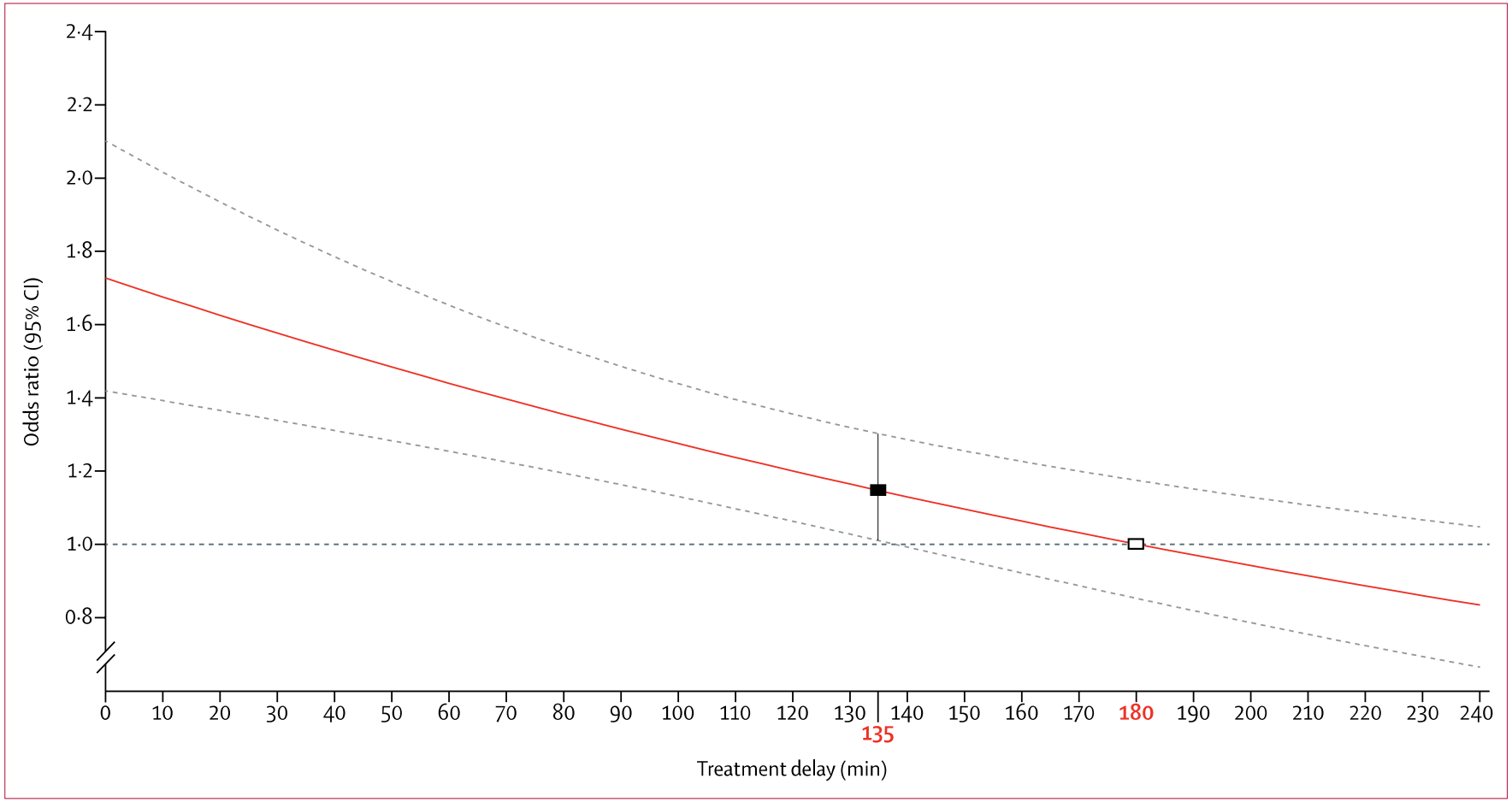
Figure 3: **Death from bleeding by subgroup**

*Heterogeneity p value. †One patient excluded from subgroup analysis because of missing baseline data.

Lancet 2017; 389: 2105–16

Effect of Treatment Delay on Efficacy and Safety of TXA in Acute Severe Hemorrhage

Odds Ratio for *not* dying of bleeding with TXA vs. placebo (40,138 CRASH-2 + WOMAN trial participants)



Lancet 2018; 391: 125–32

Why is it so Difficult to Measure Fibrinolysis?

- Methods used to assess fibrinolysis have lagged behind methods used to assess coagulation.
- Normally in blood, (endogenous) fibrinolysis takes hours or days to develop, in large part due to the large molar excess of inhibitors (PAI-1, a_2-anti-plasmin) over plasminogen activators and plasmin itself.
- Fibrinolysis assays are often technically difficult and not easily automated.

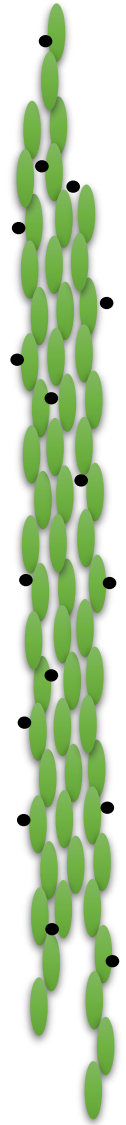
Longstaff C. *JTH* 2016

Why is it so Difficult to Measure Fibrinolysis?

PAI-1

sct-PA

Fibrin+plasminogen

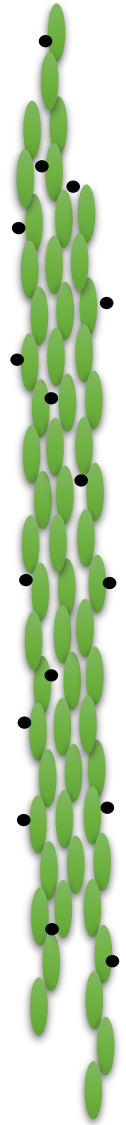


Why is it so Difficult to Measure Fibrinolysis?

PAI-1

dct-PA

Fibrin+plasminogen



Implication of Large Molar Excess of Inhibitors

- Spontaneous clot lysis is not observed within a reasonable time window

therefore…..

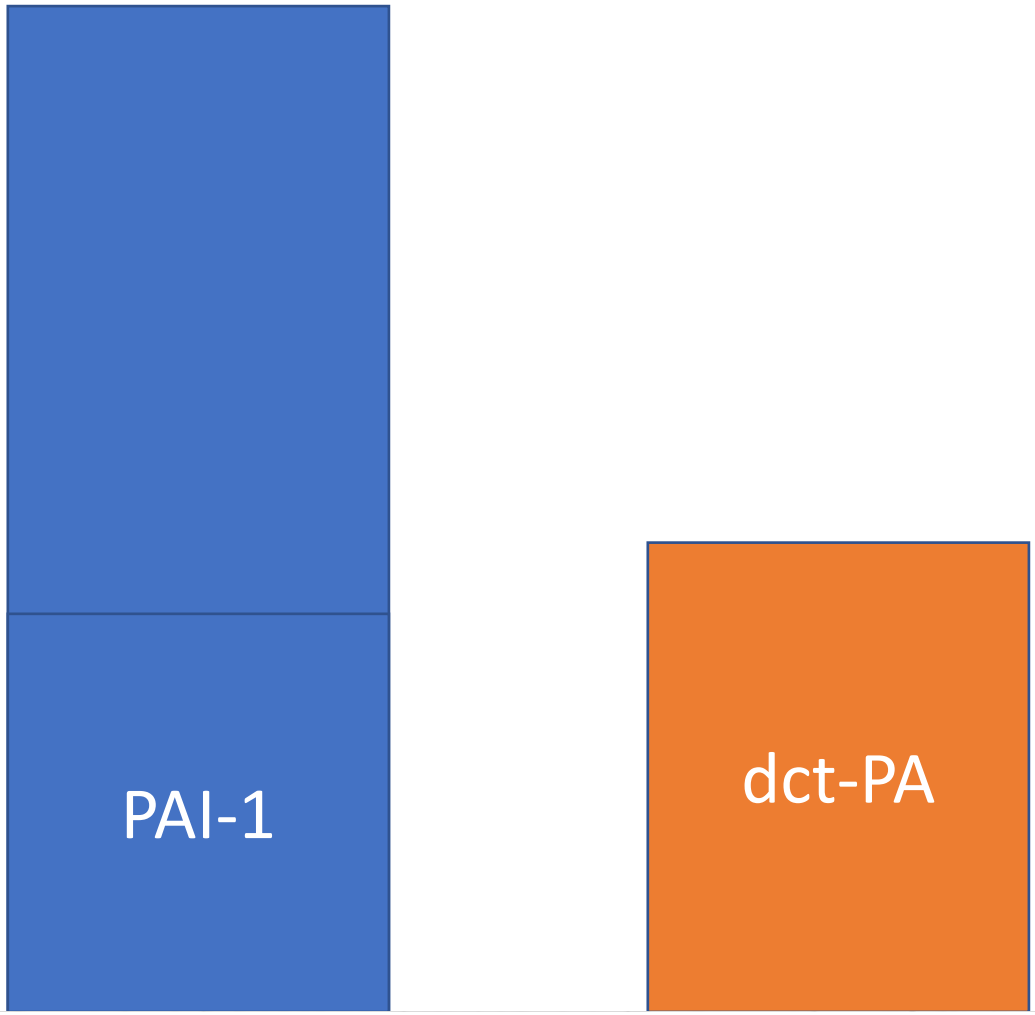
- In order to evaluate fibrinolysis *ex vivo*, it is necessary to 're-balance' the fibrinolytic pathway; this can be achieved by…..

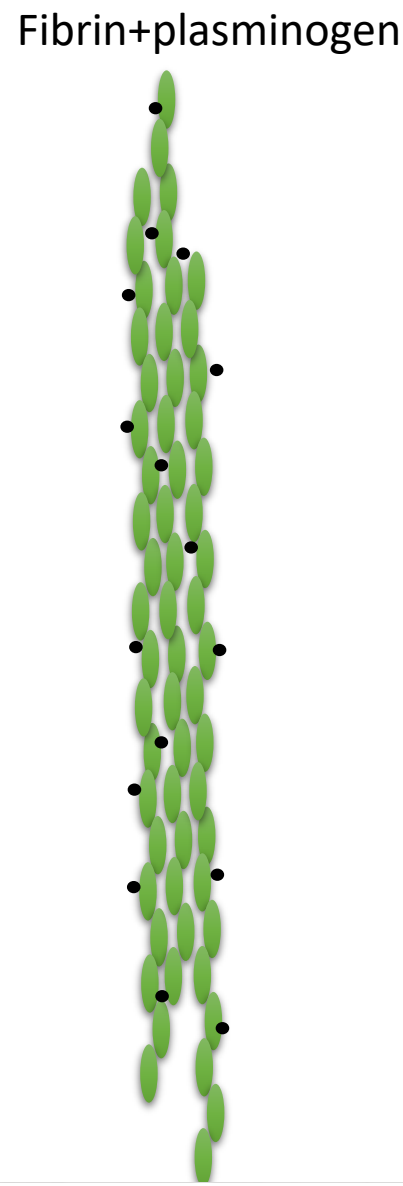
  A] reducing or inactivating endogenous inhibitors of fibrinolysis (e.g. euglobulin clot lysis assay)

  or….

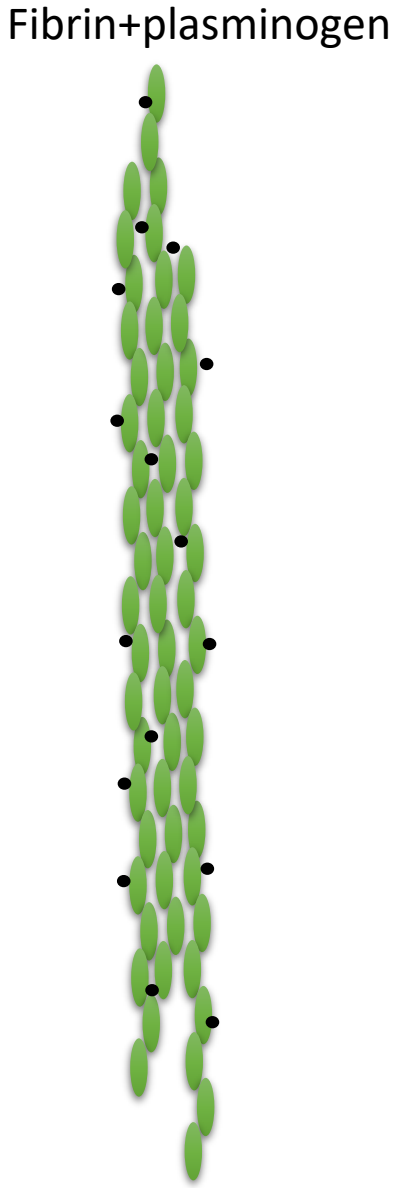
  B] adding exogenous tPA to clotted whole blood or plasma

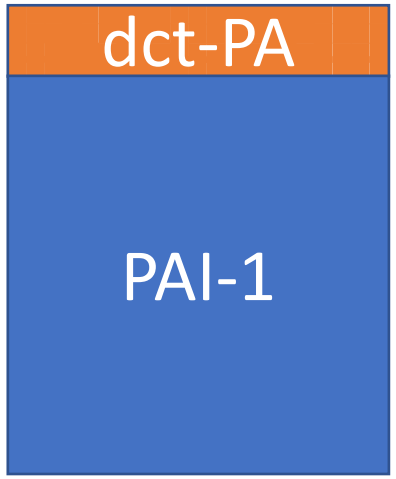
Euglobulin Fractionation of Plasma





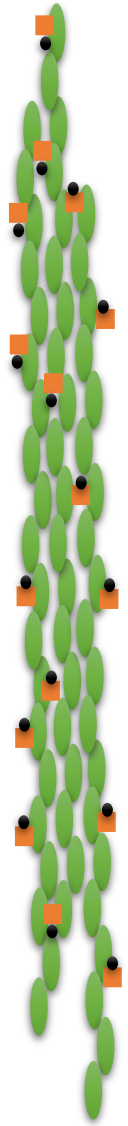
Euglobulin Fractionation of Plasma





Euglobulin Fractionation of Plasma

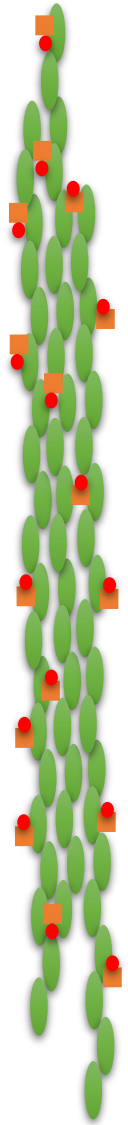
Fibrin+plasminogen



PAI-1

Euglobulin Fractionation of Plasma

Fibrin+plasminogen



PAI-1

(Modified) Euglobulin Clot Lysis Assay

	n	Plasma concentration	EuFr concentration	Reduction in EuFr (%)
		(mean±SD)	(mean±SD)	(mean±SEM)
aPAI-1	31	214.4±381.4 nM	7.7±16.4 nM	96.9±1.3
tPA	36	4.1±5.2 pM	1.1±1.7 pM	52.4±9.3
α2AP	16	0.7±1.4 µM	0.02±0.005 µM	95.4±0.8
α2MG	36	2.2±1.7 µM	0.007±0.008 µM	99.1±0.5
Plasminogen	35	1.7±0.5 µM	1.5±0.6 µM	20.4±2.9

Ilich A. *RPTH* 2020

Contents lists available at ScienceDirect

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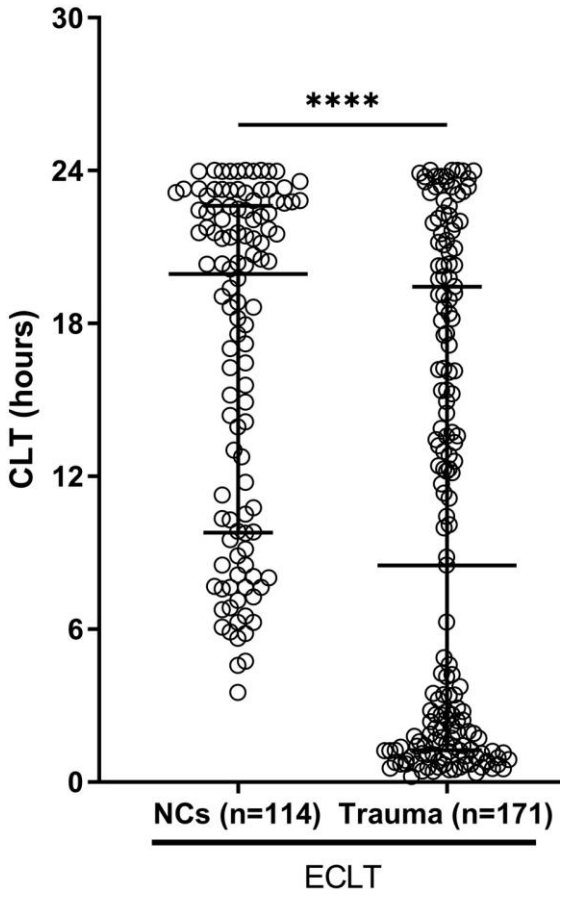
journal homepage: www.elsevier.com/locate/thromres

Euglobulin clot lysis time reveals a high frequency of fibrinolytic activation in trauma

Anton Ilich [a], Vaibhav Kumar [a], Michael J. Ferrara [b], Michael W. Henderson [a], Denis F. Noubouossie [a], Donald H. Jenkins [c], Rosemary A. Kozar [d], Myung S. Park [b], Nigel S. Key [a,*]



Variables	ECLT <4.6 hours (N=83)	ECLT ≥4.6 hours (N=88)	p value
Sex Male *(n, %)*	64 (77%)	61 (70%)	0.39
ISS *Median (IQR)*	14.0 (9.0-22.0)	14 (6-22)	0.38
Age (years) *Median (IQR)*	53 (30-63)	50 (28-62)	0.31
SBP (mmHg) Mean±SD	117.6±29.27	118.1±23.18	0.91
DBP (mmHg) *Mean±SD*	70.1±16.6	70.0±16.20	0.87
Heart rate (bpm) *Mean±SD*	93.2±23.1	98.6±21.6	0.07
PAP (µg/ml) *Median (IQR)*	5.6 (2.6-10.3)	3.7 (2.2-5.4)	<0.01
D-Dimer (µg/ml) *Median (IQR)*	10.0 (2.4-20.5)	4.3 (1.1-13.2)	0.046
S100A10 (ng/ml) *Median (IQR)*	1.9 (0.5-4.4)	1.6 (0.3-4.5)	0.59
free tPA (IU/ml) *Median (IQR)*	0.36 (0.25-0.72)	0.31 (0.24-0.41)	0.01
tPA res (hours) *Median (IQR)*	1.6 (1.3-1.9)	2.5 (1.6-4.2)	<0.01
TEG LY30 (%) *Median (IQR)*	1.3 (0.2-5.4)	0.9 (0.0-3.4)	0.155
CAT *n (%)*	13 (15.7%)	3 (3.4%)	0.01

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Tranexamic Acid Is Not a Universal Hemostatic Agent

Roger E. G. Schutgens[1], Ton Lisman[2]

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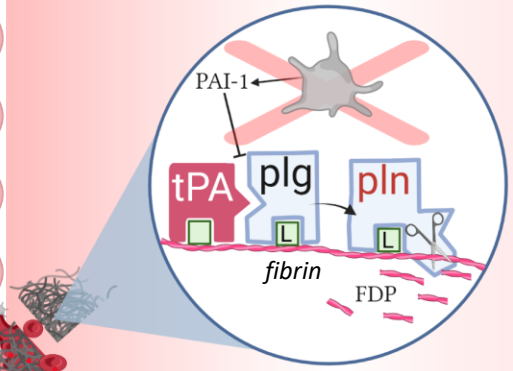
Hemasphere 2021:5(8);e625

Hypothesis

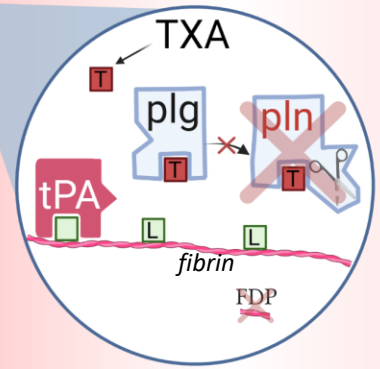
Bleeding



low plt ----→ ↑fibrinolysis?

No bleeding

TXA ------ ↓fibrinolysis?



Randomized double blind placebo-controlled clinical trial

3120 Assessed for eligibility

– 2764

356 Enrolled

– 19

337 Randomized

– 4 → **165** Placebo

– 3 → **165** TXA

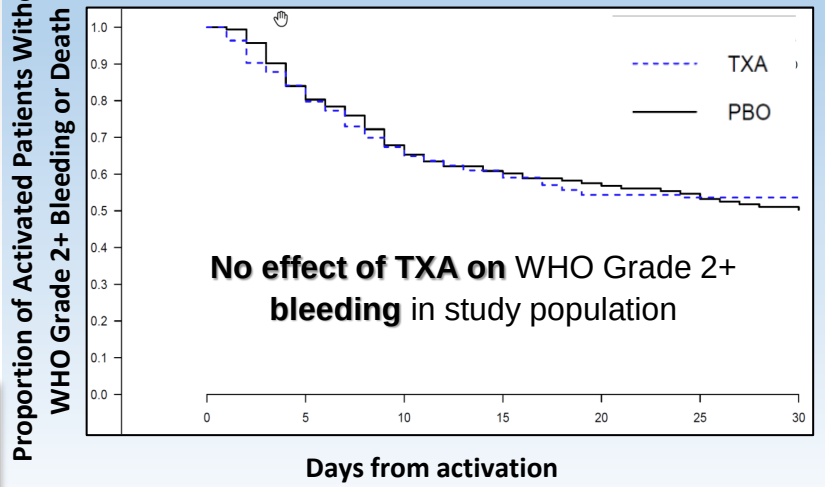
Primary outcome

WHO grade 2+ bleeding

Population

Patients with hematologic malignancy

Results

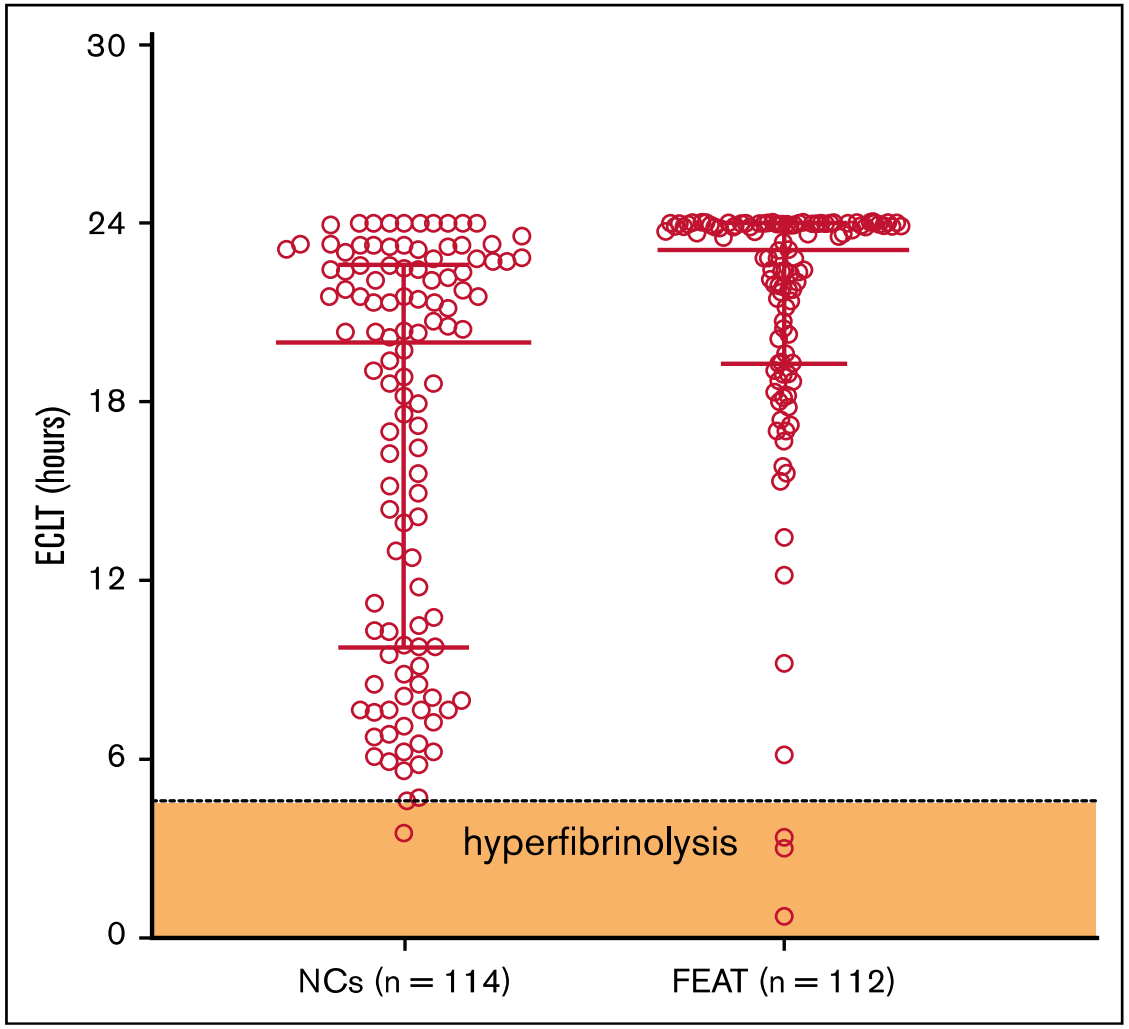


No effect of TXA on WHO Grade 2+ **bleeding** in study population

Bleeding in thrombocytopenic patients is common despite platelet transfusion. Platelets are a rich source of PAI-1 – a major fibrinolysis inhibitor. The A-TREAT study tested whether TXA reduces bleeding in thrombocytopenic patients by inhibiting fibrinolysis. TXA did not significantly reduce WHO grade 2+ bleeding in this study.

Gernsheimer TB. *Blood* 2022

Absence of Hyperfibrinolysis in A-TREAT Cohort



Ilich A. *Blood Advances* 2023:7(6);900

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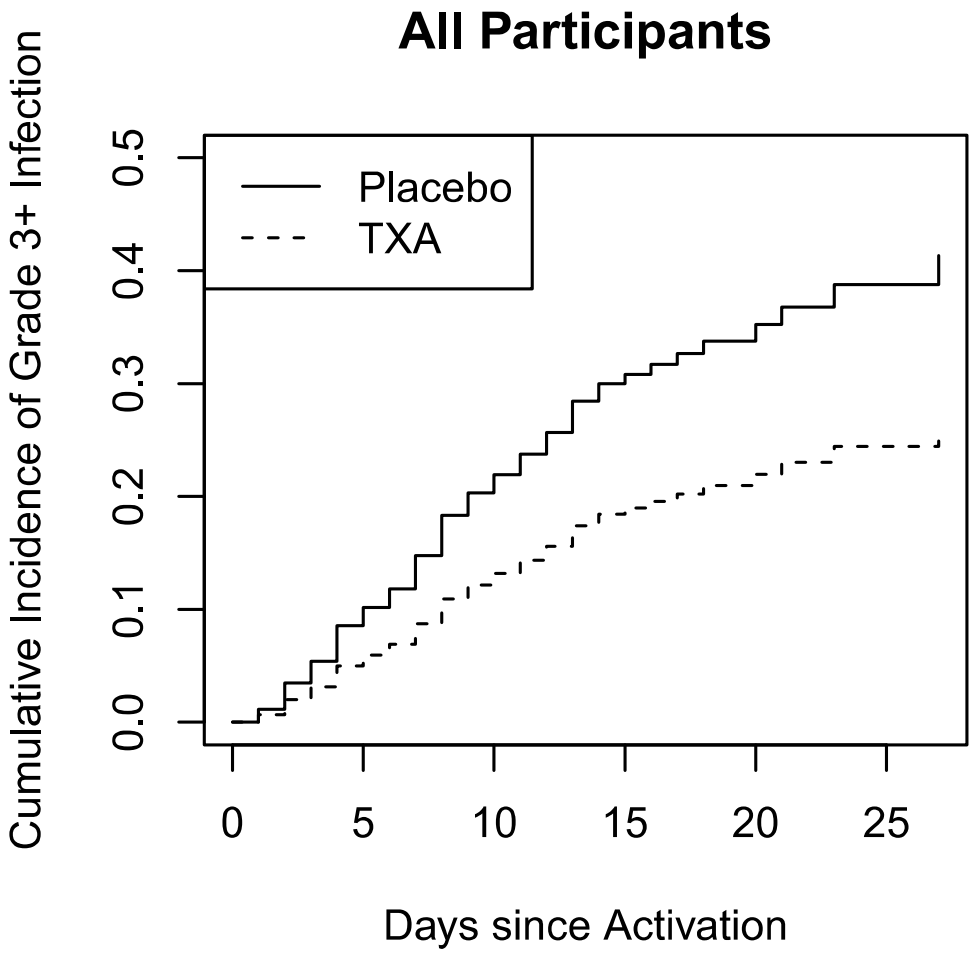
Less Grade 3+ Infection In A-TREAT Patients on TXA



Poston JN. *RPTH.* 2024:8;e102358

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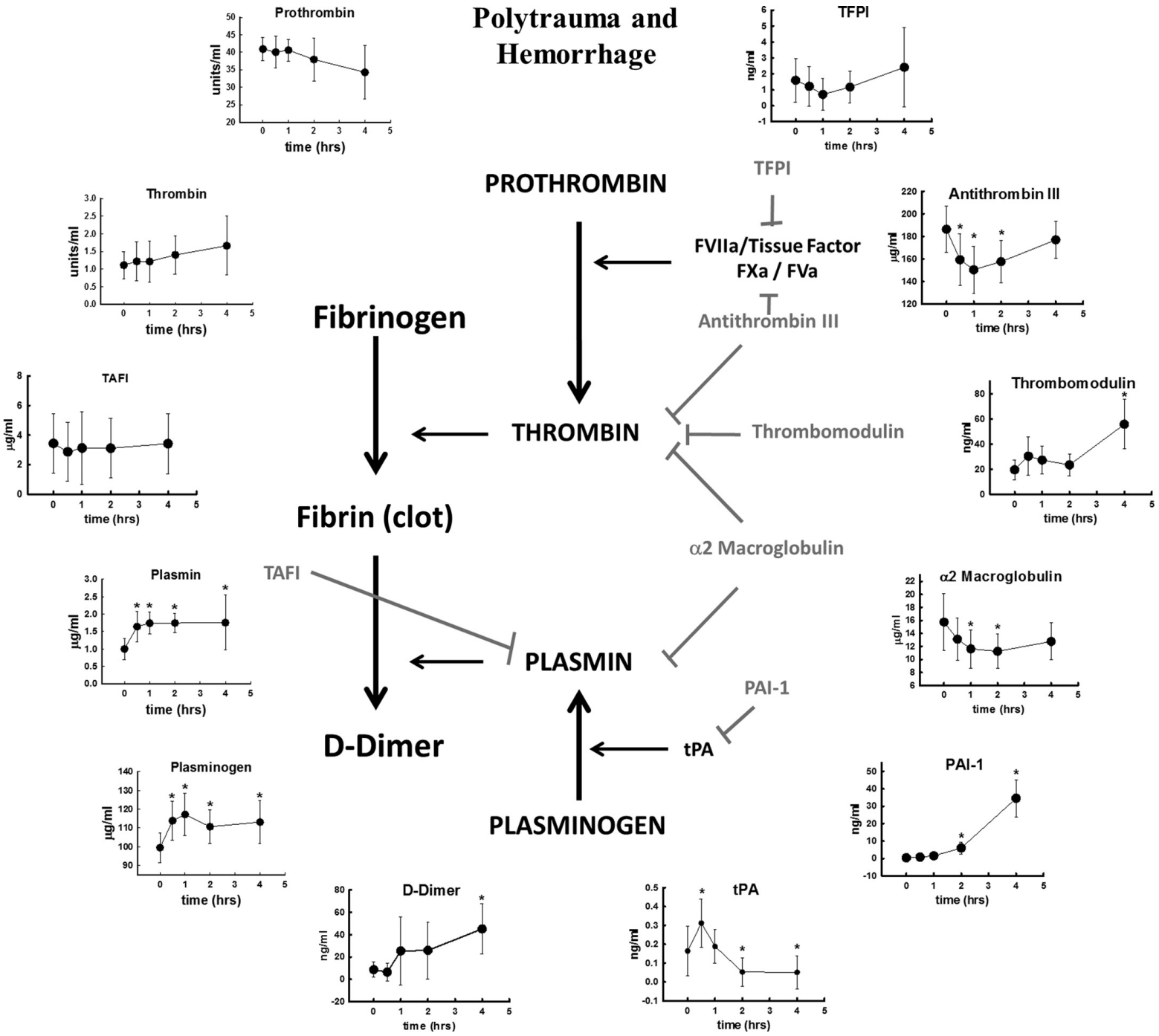
Coagulation Changes Over 4 Hours in a Rat Model of Polytrauma and Hemorrhage



Wu X. *Am J Physiol* 2016:310;R323

TXA Reduces Fibrinolytic Activity in Menstrual Fluid

Abdominopelvic pain	9 (20)	11 (26)	n.s.
Nausea	0	7 (16)	**$p < 0.01$
Headache	12 (27)	7 (16)	n.s.
Backache	13 (29)	11 (26)	n.s.
Chest pain	2 (4)	0	**n.s.
Urinary frequency	1 (2)	2 (5)	**n.s.
Leg cramps	1 (2)	6 (14)	**p < 0.05
Paresthesia	3 (7)	0	**n.s.
Allergic skin reaction	–	1 (2)	

* 2×2 Contingency table – the Chi-square test with Yates' correction
** Fisher's exact test.

Gleeson NC. *Acta Obstet Gynecol Scand* 1994:73;274

Table II. Menstrual blood loss (MBL) and endometrial fibrinolytic enzymes in control and tranexamic acid treated menstrual cycles

•	Untreated cycles	Treatment cycles	Significance level