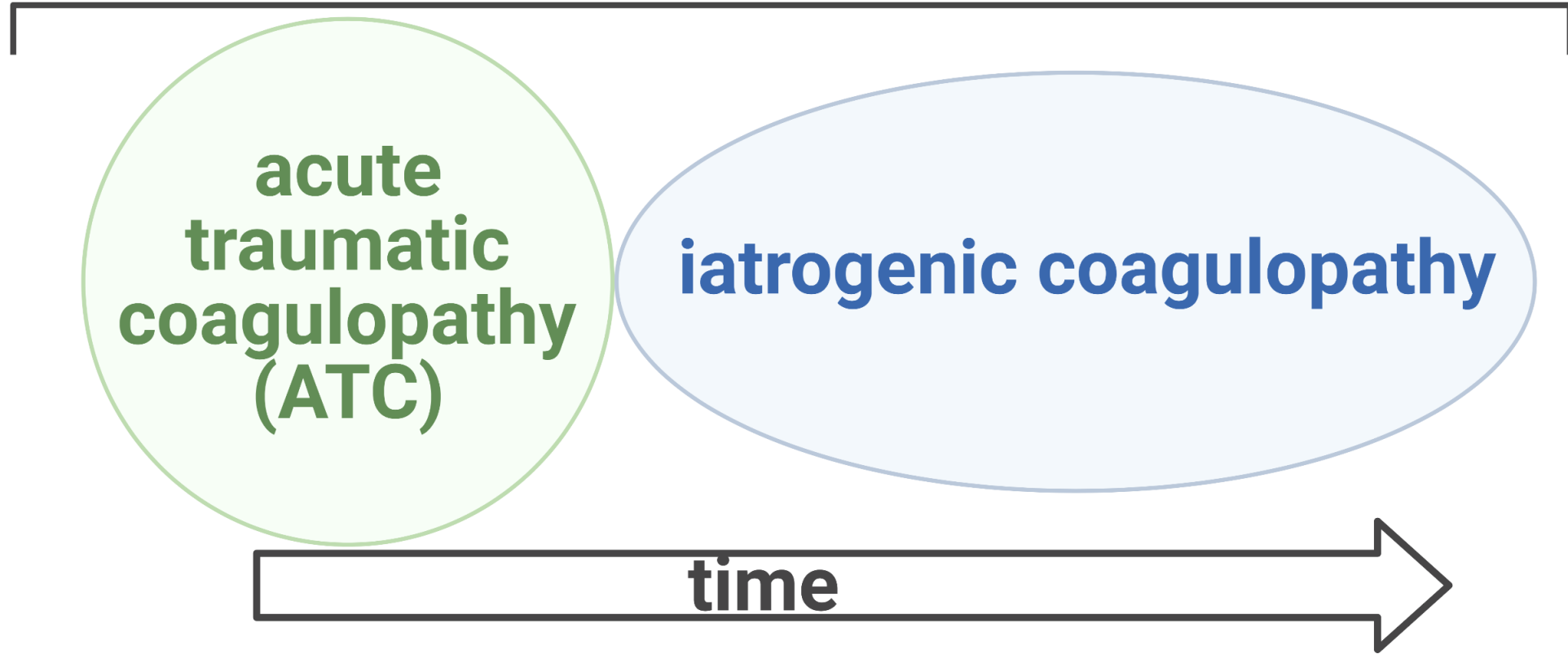


Blood Product & Fibrinogen Concentrate Manufacturing: Methods Matter

Dr Gael Morrow

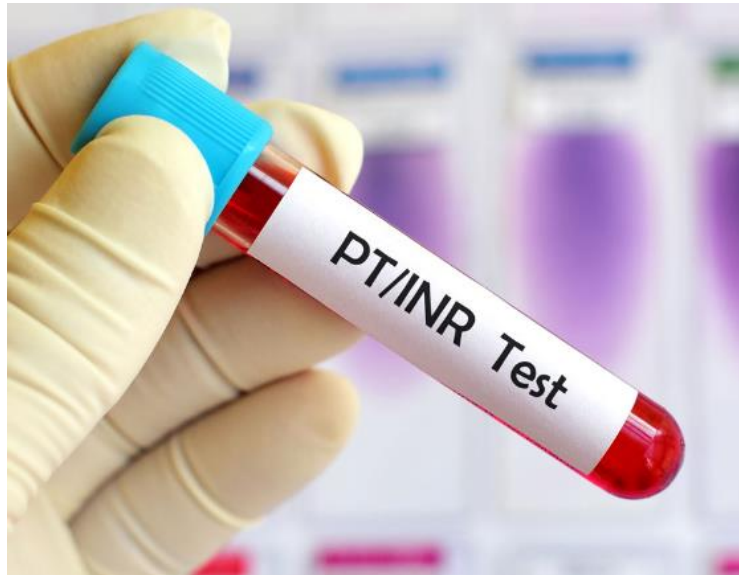


trauma induced coagulopathy (TIC)



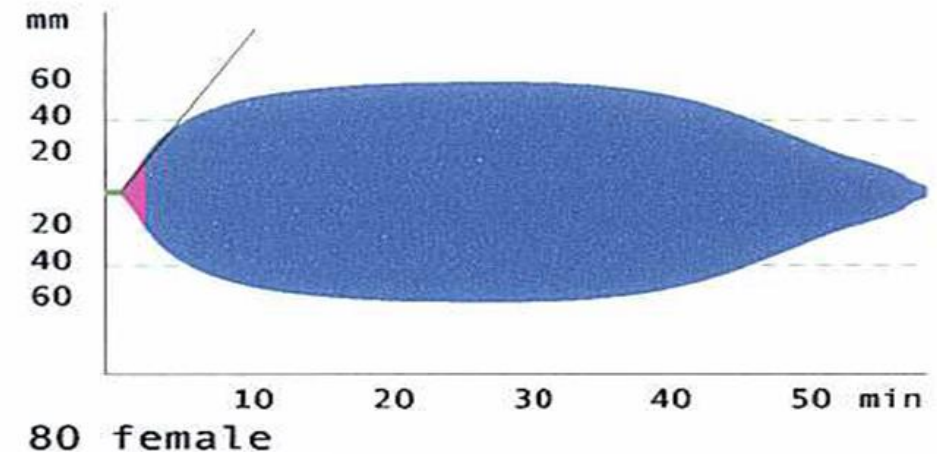
- fibrinogen depletion
- increased fibrinolysis

TIC: Clinical Definition



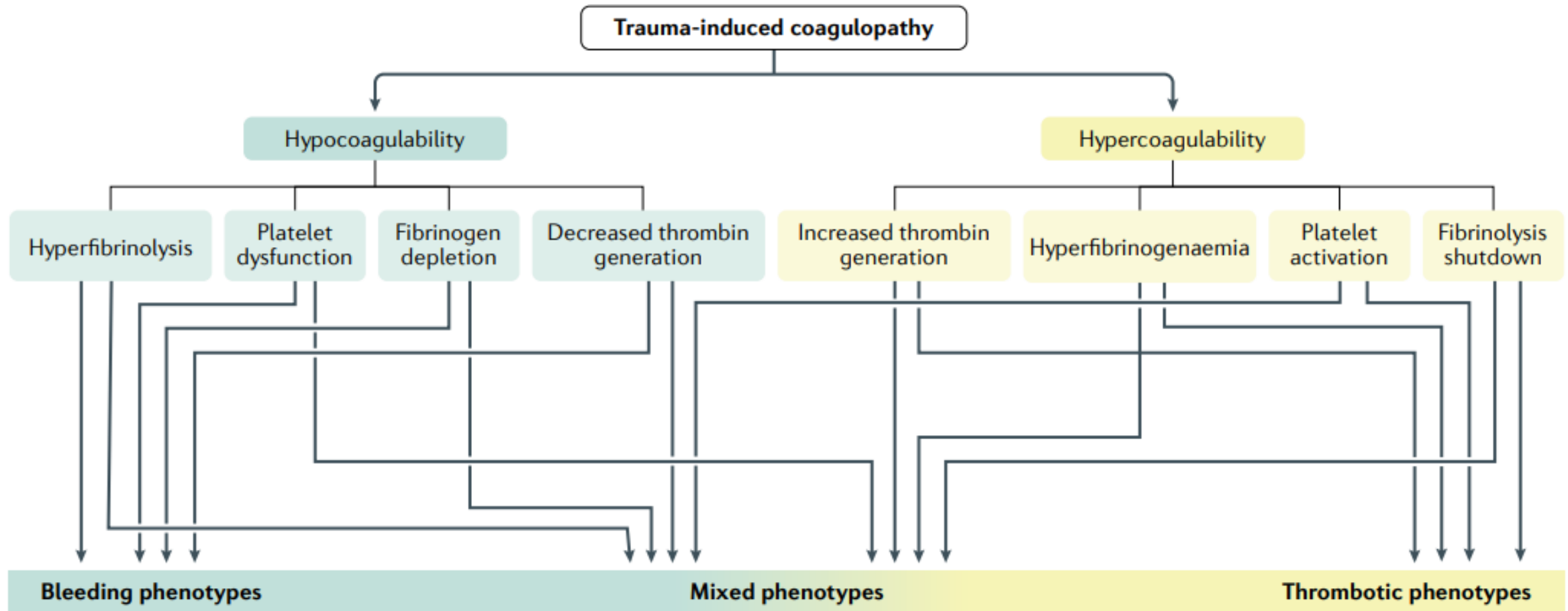
INR > 1.5

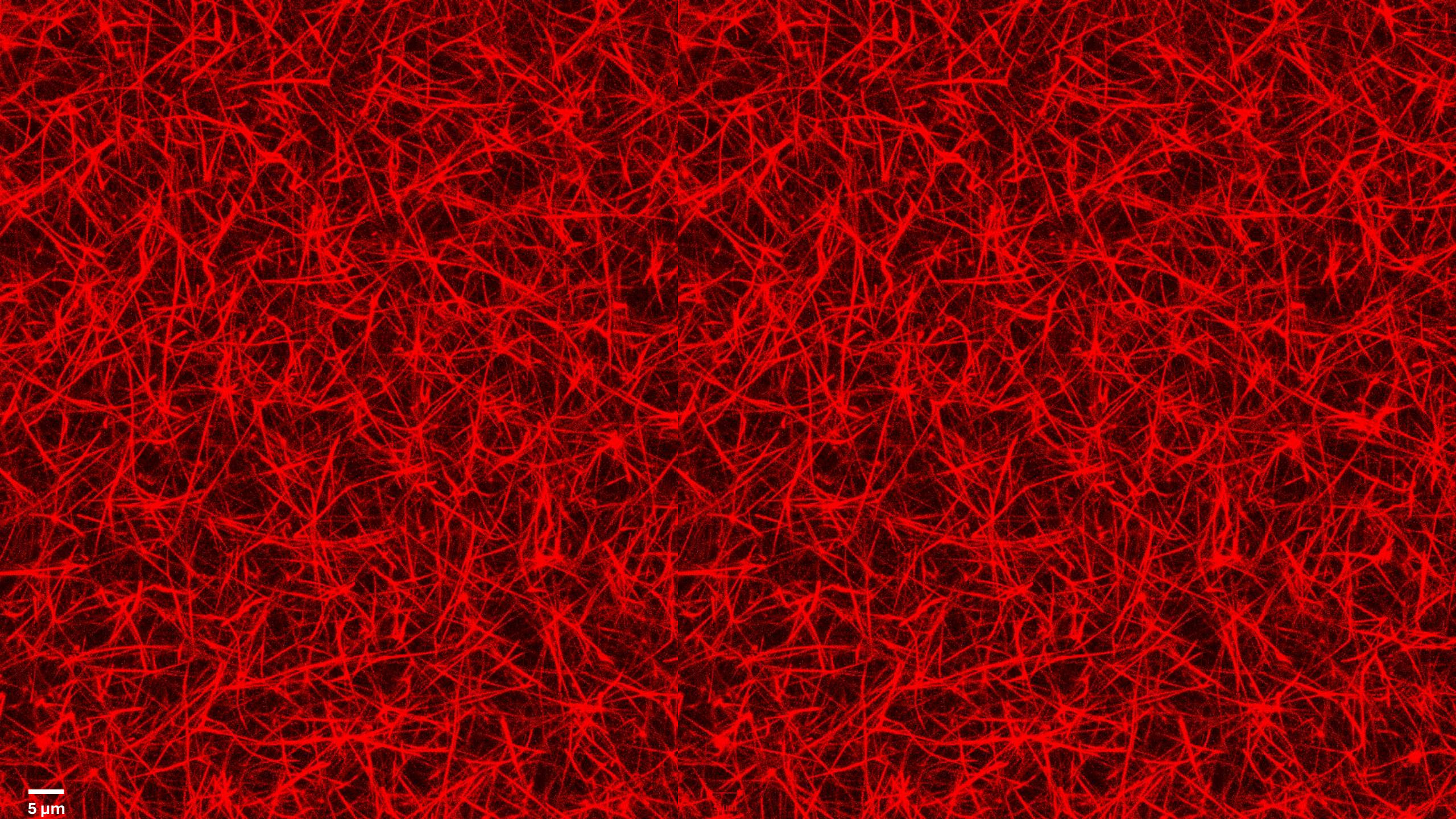
INR > 1.2



Reduced clot
firmness
+
increased lysis

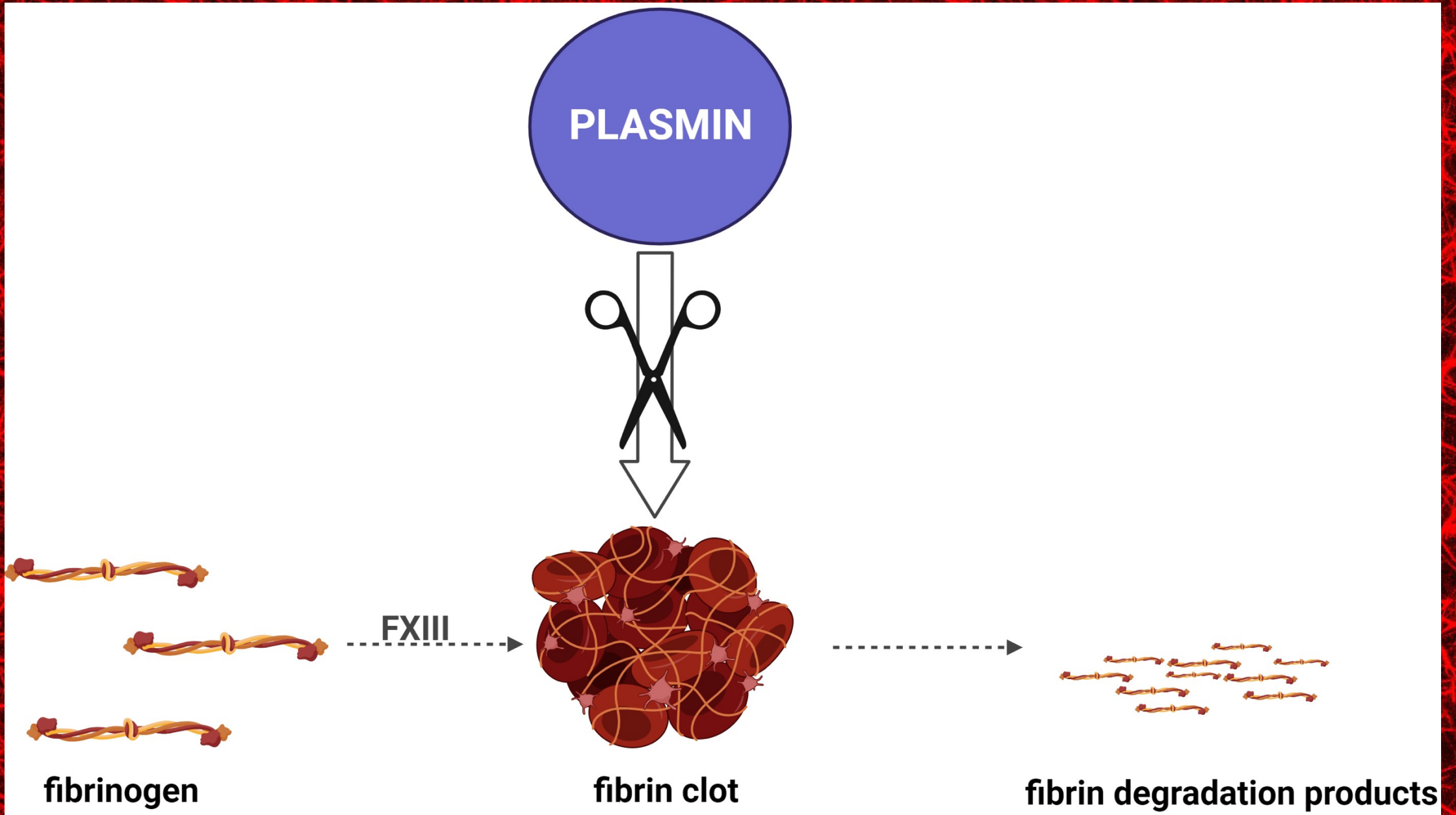
TIC: Complexities



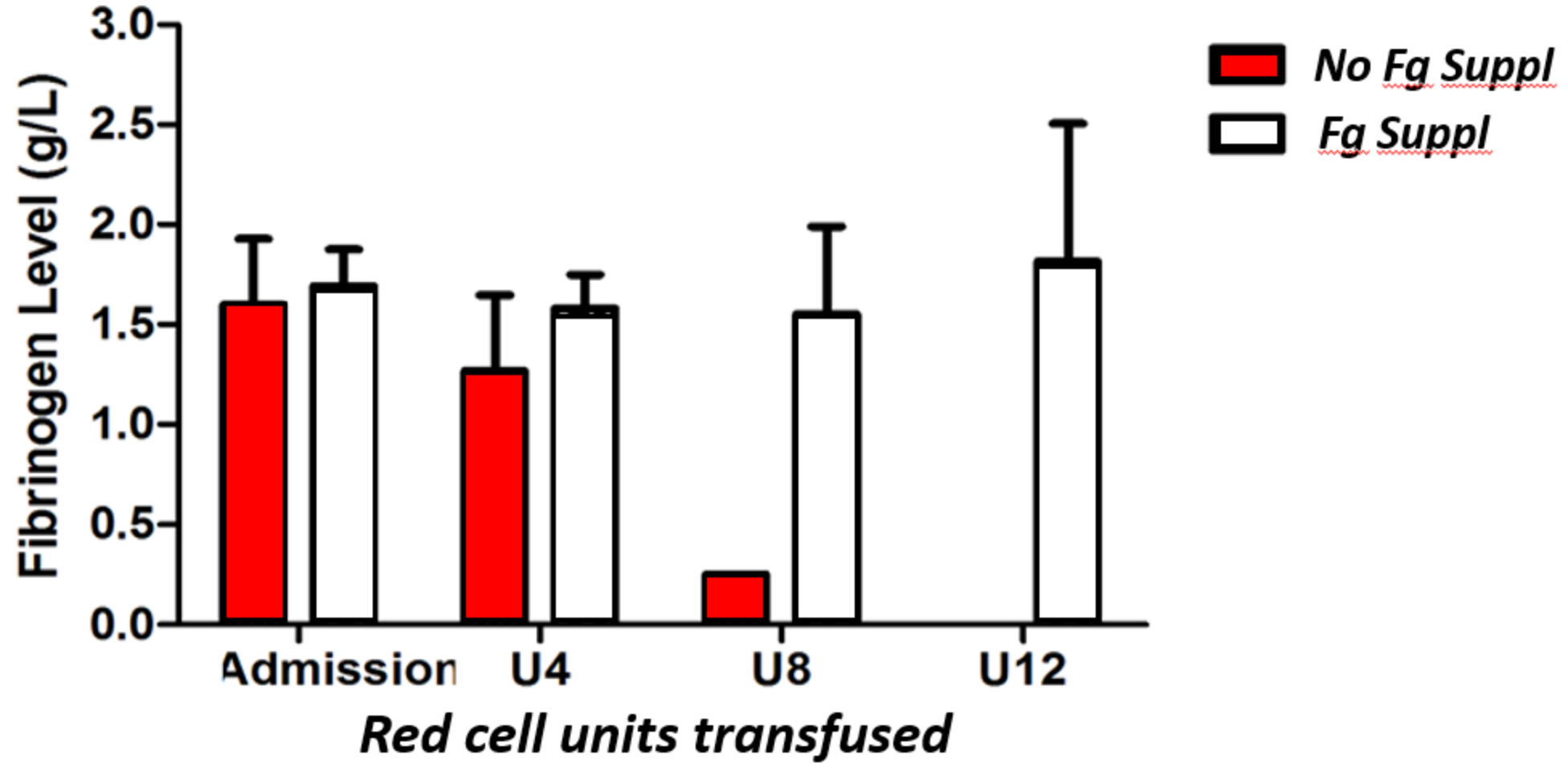


5 μm

Fibrinogen & Fibrinolysis

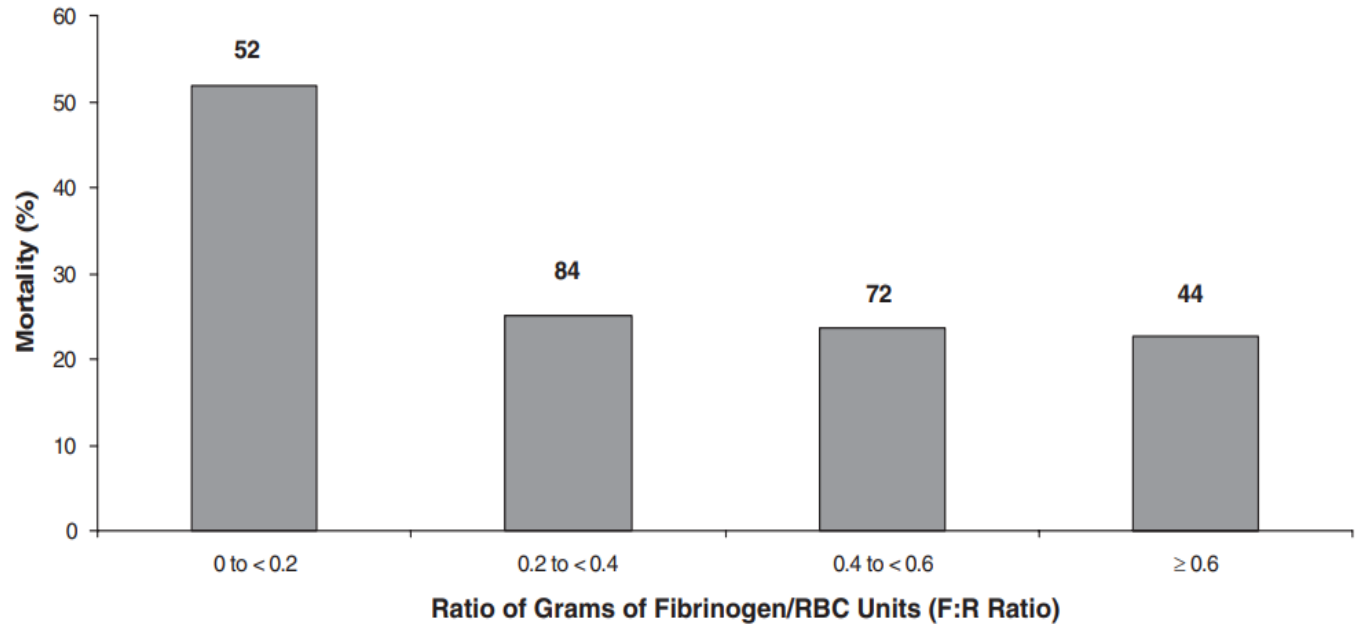


Fibrinogen in Trauma

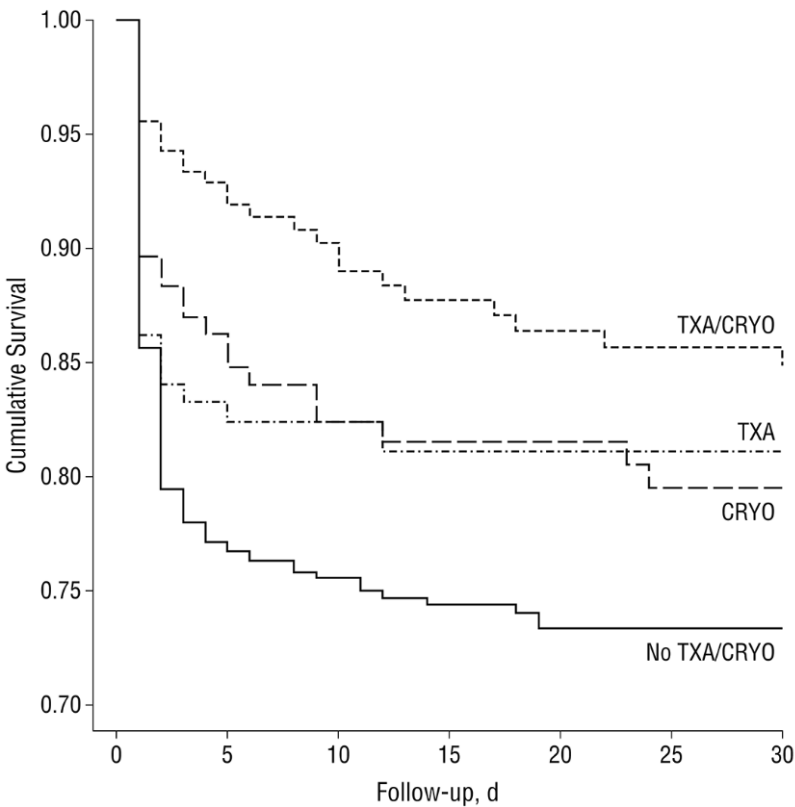


Fibrinogen in Trauma: Military Cohort Studies

US Iraq



UK Afghanistan



Stinger, Harry K. MD et al. The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusions at an Army Combat Support Hospital. *The Journal of Trauma: Injury, Infection, and Critical Care* 64(2):p S79-S85, February 2008. | DOI: 10.1097/TA.0b013e318160a57b

Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of Cryoprecipitate and Tranexamic Acid With Improved Survival Following Wartime Injury: Findings From the MATTERS II Study. *JAMA Surg.* 2013;148(3):218–225. doi:10.1001/jamasurg.2013.764

Fibrinogen replacement therapy

Cryoprecipitate

- Pooled blood component derived from whole blood donation
- Variable but high fibrinogen content (8-16 g/l)
- Rich in additional coagulation factors

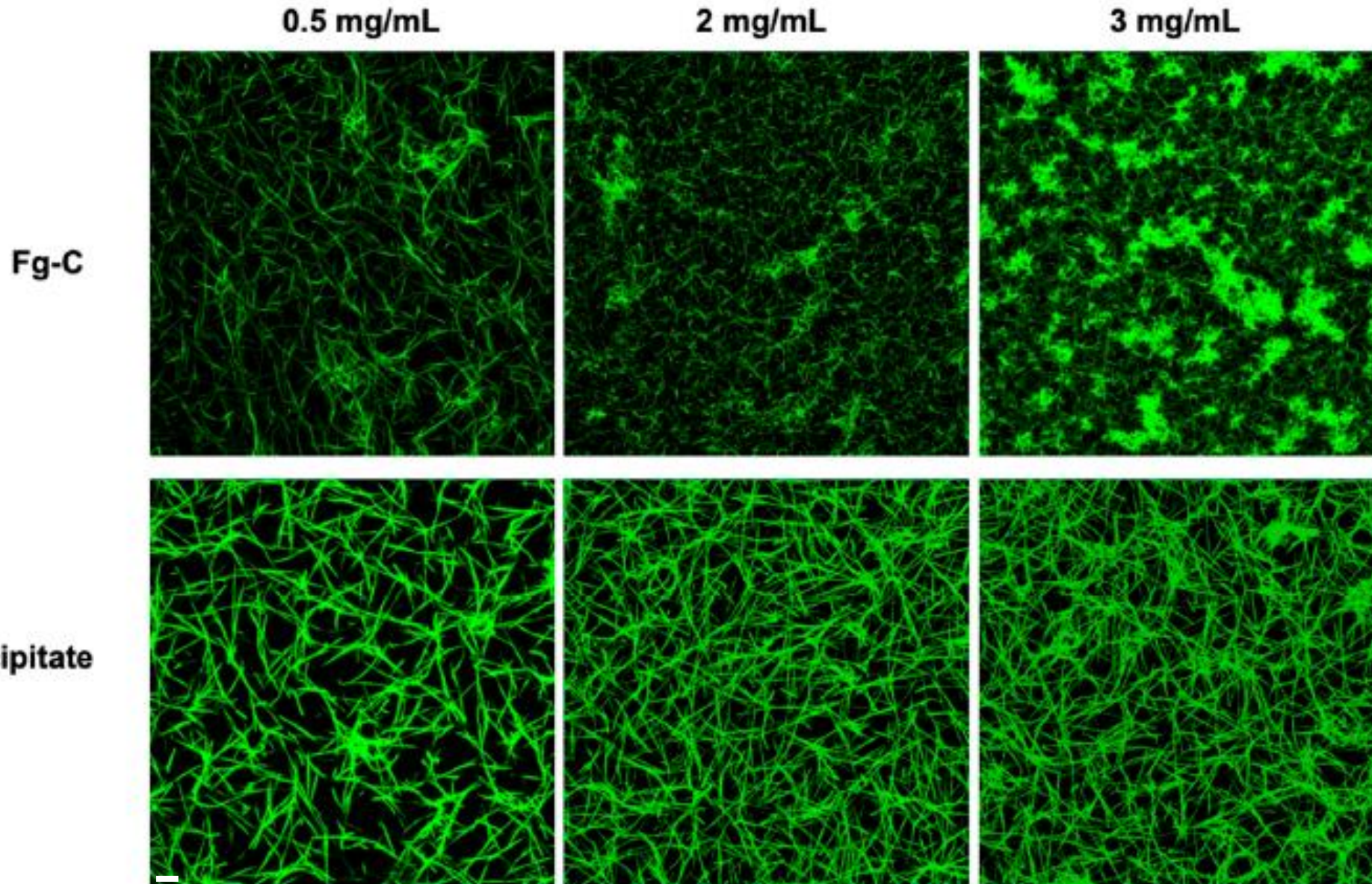


Fibrinogen concentrate

- Standard dose of 20 g/l
- Good safety profile
- Variable concentrations of other clotting factors



Does the fibrinogen source matter?



AF488 fibrinogen
Scale bar – 5 μ m

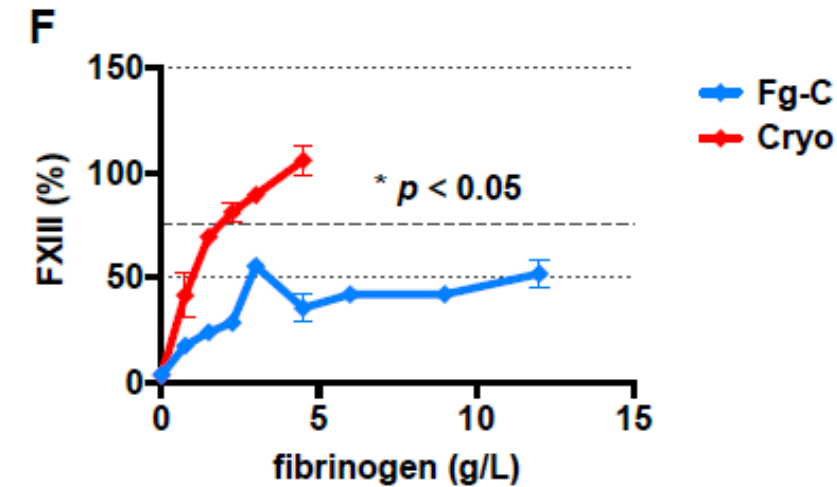
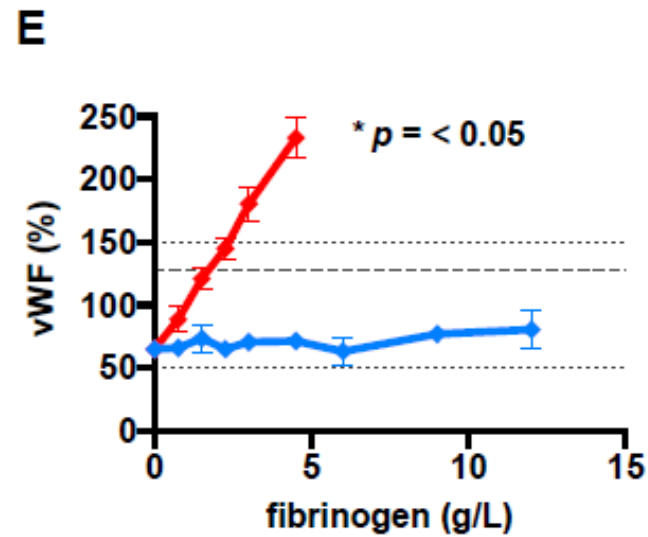
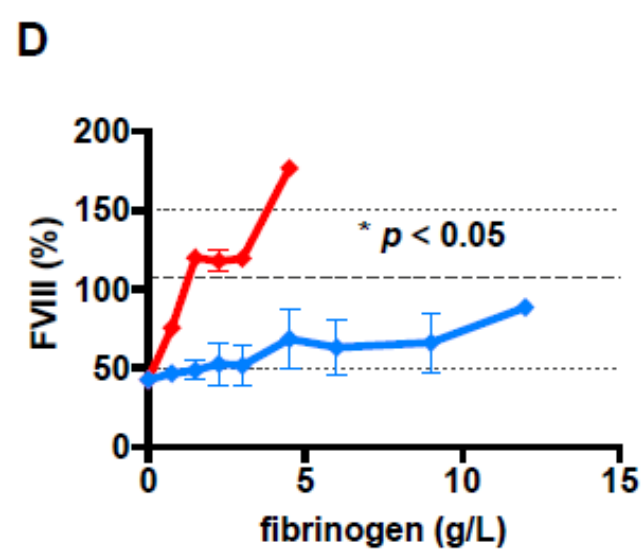
Morrow, G.B.; Carlier, M.S.A.; Dasgupta, S.; Craigen, F.B.; Mutch, N.J.; Curry, N. Fibrinogen Replacement Therapy for Traumatic Coagulopathy: Does the Fibrinogen Source Matter? *Int. J. Mol. Sci.* **2021**, *22*, 2185. <https://doi.org/10.3390/ijms22042185>

Does the fibrinogen source matter?

Table 1. Constituents of fibrinogen sources.

	PNP	FDP	Cryoprecipitate	Fg-C
1-5 Clauss Fg (g/L)	3.3 ± 0.3	<0.15	6.8 ± 0.1	21.6 ± 0.1
1-5 FII (%)	98 ± 4	98 ± 7	101 ± 12	<1
1-5 FV (%)	82	36 ± 0.7	68 ± 9	<1
1-5 FVII (%)	84 ± 1	75 ± 4	81 ± 7	<1
1-5 FVIII (%)	107 ± 14	43 ± 5	190 ± 0.6	<1
1-5 FIX (%)	127 ± 25	106 ± 3	105 ± 8	2
1-5 FX (%)	92 ± 7	95 ± 3	98 ± 14	<1
1-5 FXI (%)	100 ± 16	107 ± 4	92 ± 3	<1
1-5 FXIII (%)	80 ± 7	<5	105 ± 3	<1
1-5 vWF:Ag (%)	127 ± 33	65 ± 1	288 ± 66	66
1-5 α ₂ AP (μg/mL)	72 ± 20	38 ± 3	98 ± 8	1 ± 3

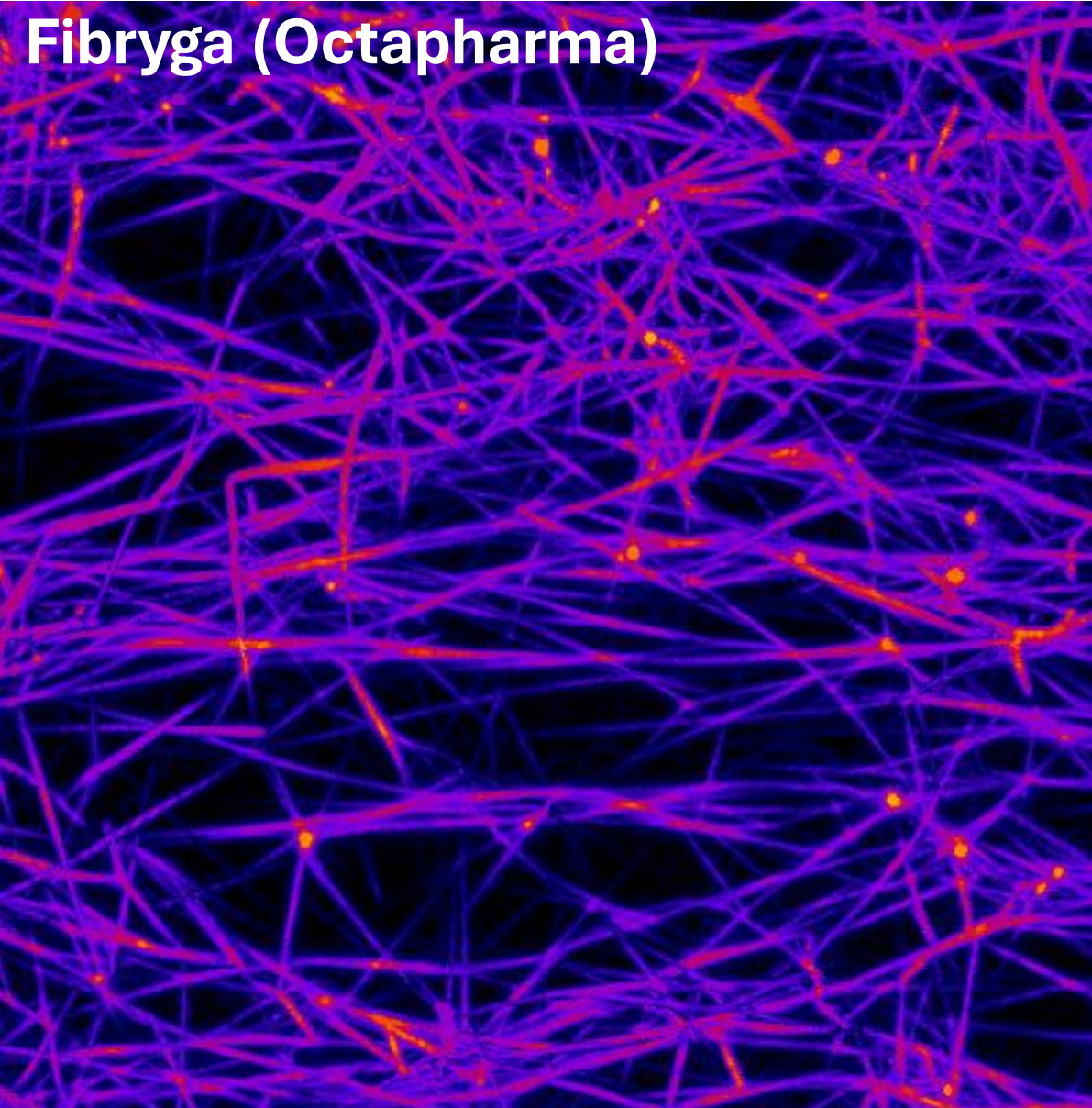
Does the fibrinogen source matter?



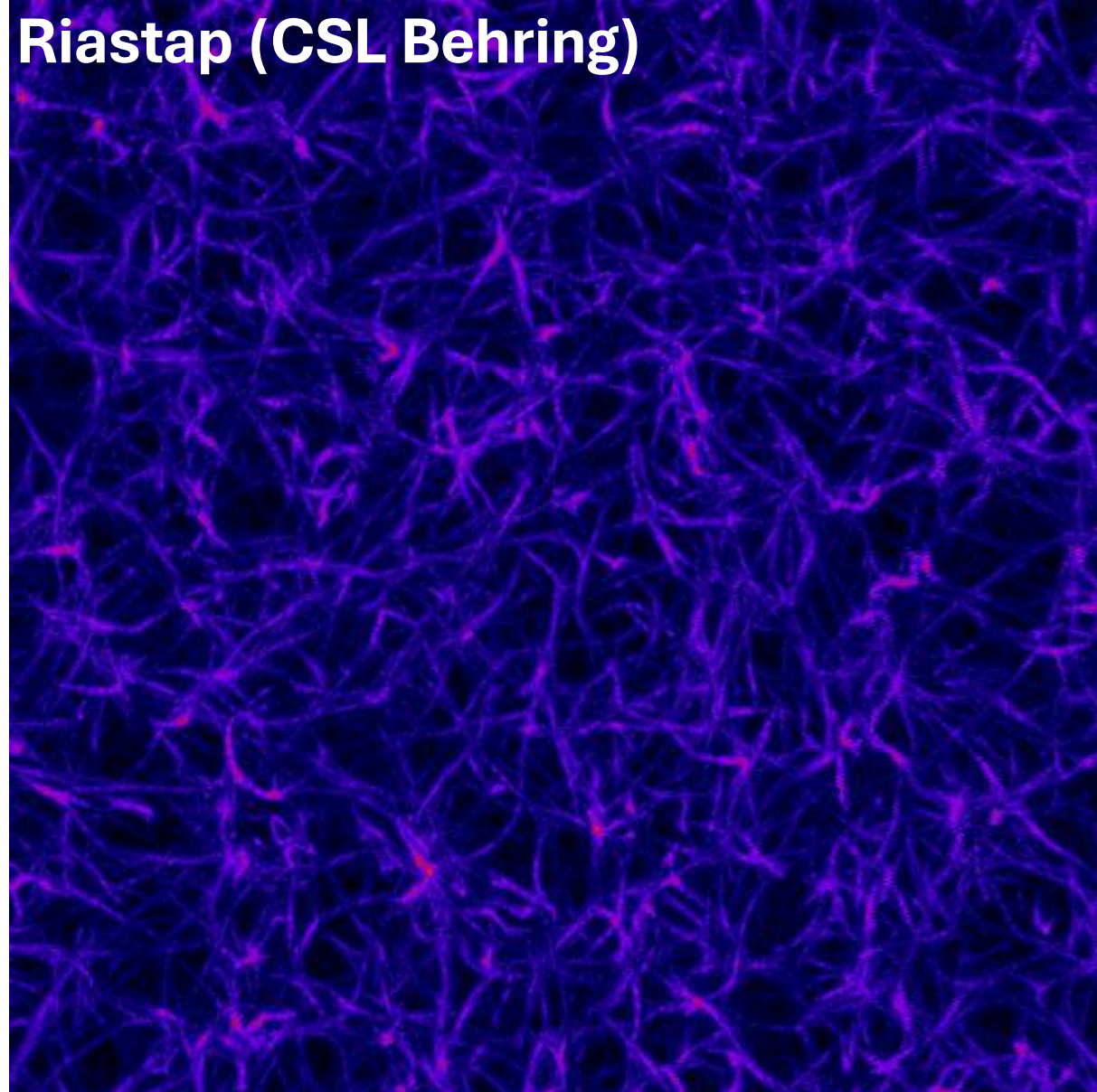
Morrow, G.B.; Carlier, M.S.A.; Dasgupta, S.; Craigen, F.B.; Mutch, N.J.; Curry, N. Fibrinogen Replacement Therapy for Traumatic Coagulopathy: Does the Fibrinogen Source Matter? Int. J. Mol. Sci. **2021**, *22*, 2185. <https://doi.org/10.3390/ijms22042185>

Not all fibrinogen concentrates are the same...

Fibryga (Octapharma)



Riastap (CSL Behring)





Differences in the biochemical composition of three plasma derived human fibrinogen concentrates

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Soutiam Goodarzi^{1,2}, Jeries Abu-Hanna^{2,3}, Sarah Harper³,
Dalia Khan³, Gael Morrow^{2,4} and Nicola Curry^{2,3*}

Are all fibrinogen concentrates the same? The effects of two fibrinogen therapies in an afibrinogenemic patient and in a fibrinogen deficient plasma model. A clinical and laboratory case report

Soutiam Goodarzi^{1,2}, Jeries Abu-Hanna^{2,3}, Sarah Harper³,
Dalia Khan³, Gael Morrow^{2,4} and Nicola Curry^{2,3*}

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Comparison of Two Different Fibrinogen Concentrates in an in vitro Model of Dilutional Coagulopathy

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RESEARCH ARTICLE



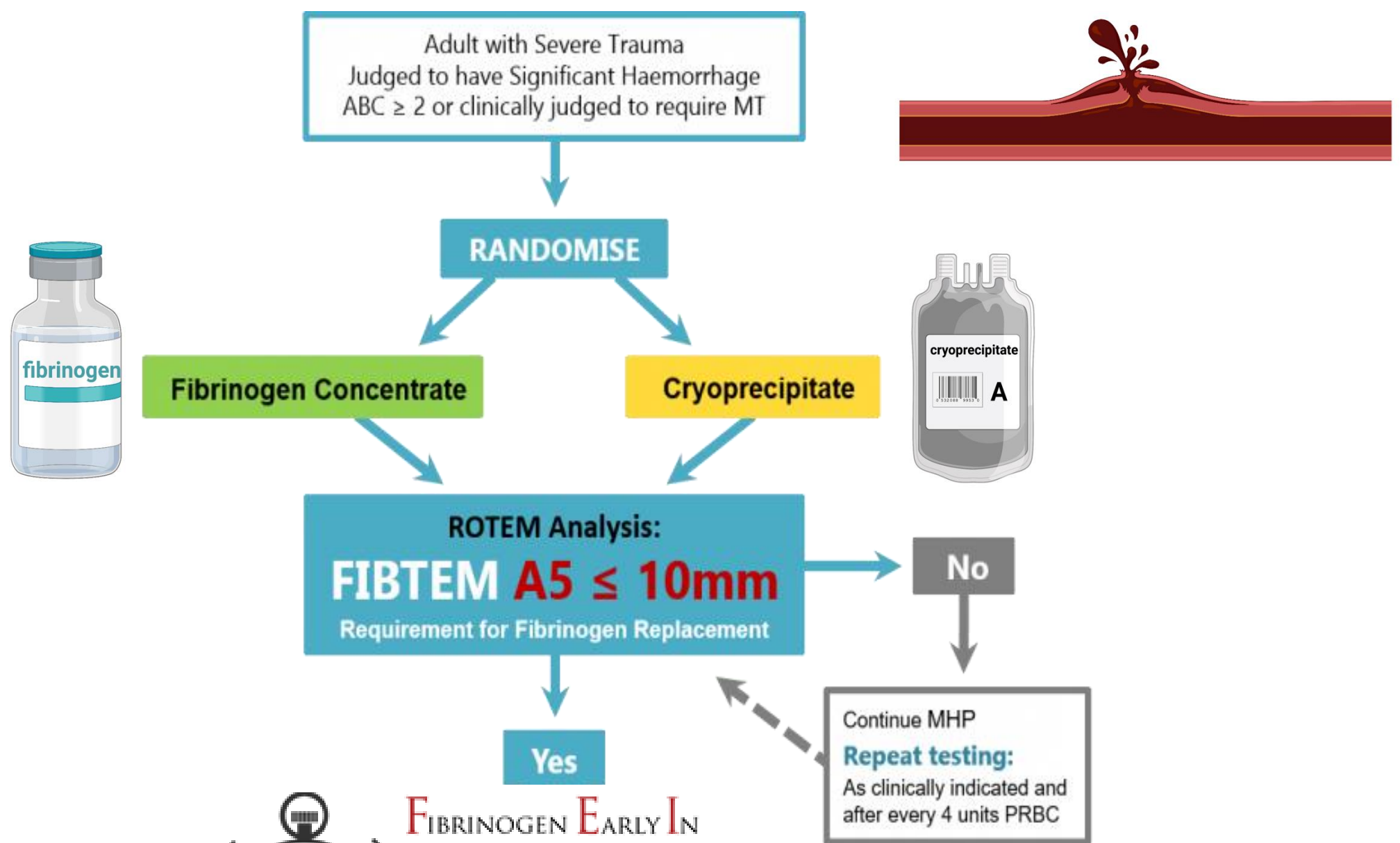
A comparison of the in vitro effects of three fibrinogen concentrates on clot strength in blood samples from cardiac surgery patients

Henrik Stolt¹ | Caroline Shams Hakimi¹ | Sukhi Singh¹ | Anders Jeppsson^{1,2} |
Martin Karlsson^{1,3}



The Efficacy of Fibrinogen Concentrates in Relation to Cryoprecipitate in Restoring Clot Integrity and Stability against Lysis

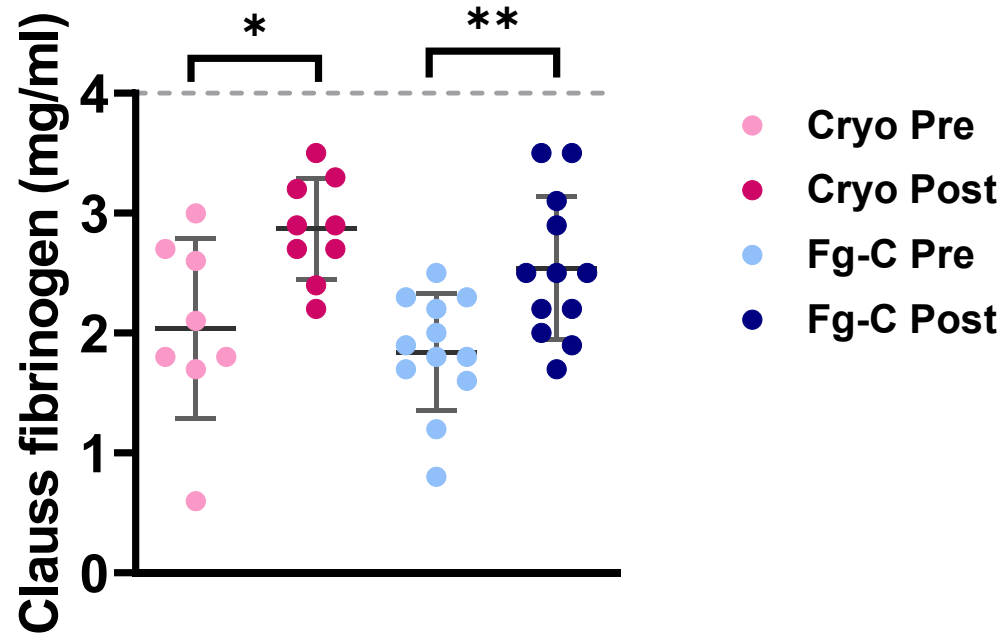
Claire S. Whyte¹, Akriti Rastogi, Ellis Ferguson, Michela Donnarumma and Nicola J. Mutch^{1*}



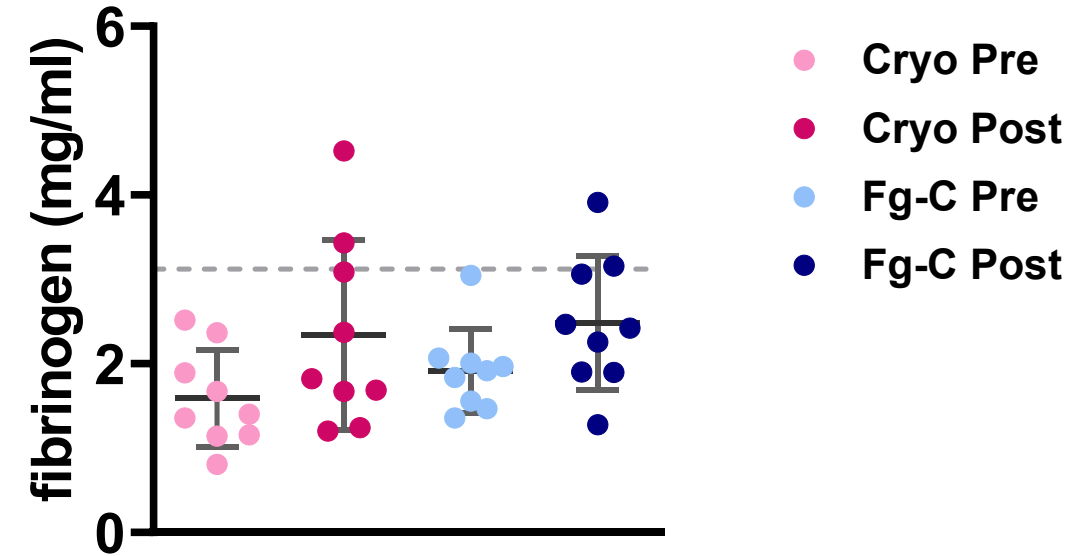
FIBRINOGEN EARLY IN
FEISTY
SEVERE TRAUMA STUDY

Fibrinogen levels are decreased in trauma patients

A

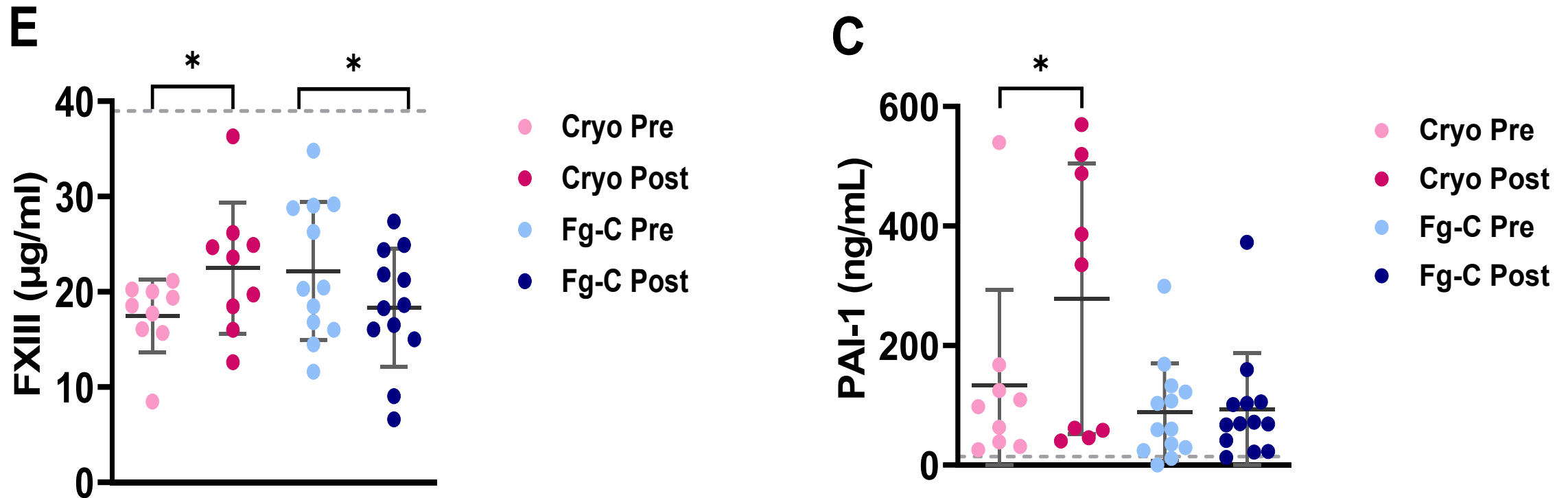


B



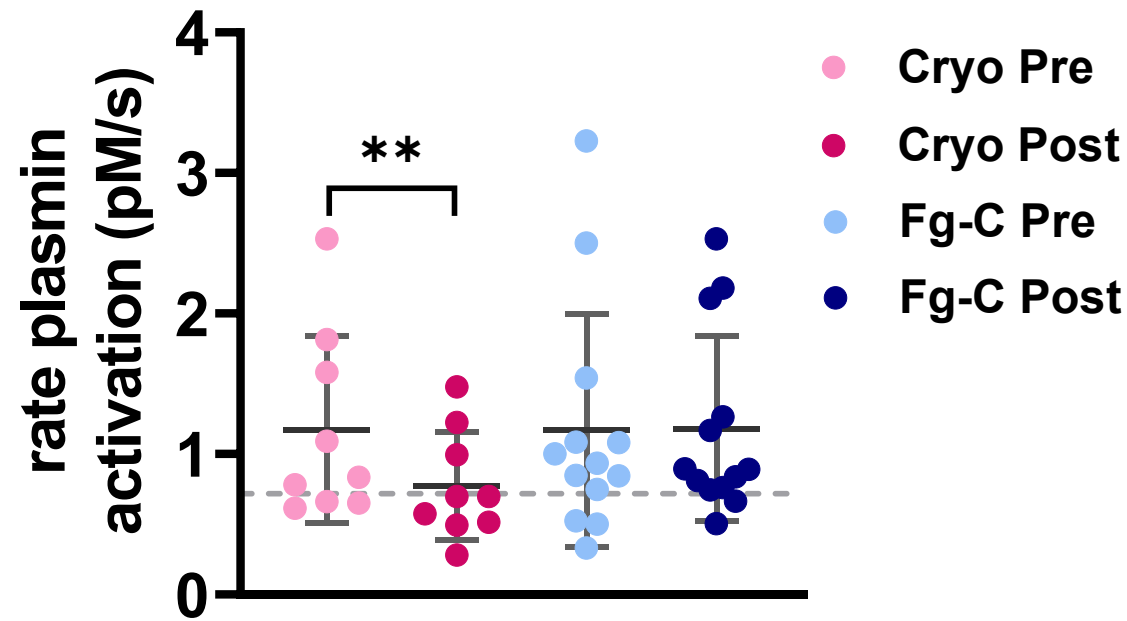
* $p < 0.05$, ** $p < 0.01$

Cryoprecipitate supplements FXIII and PAI-1 levels



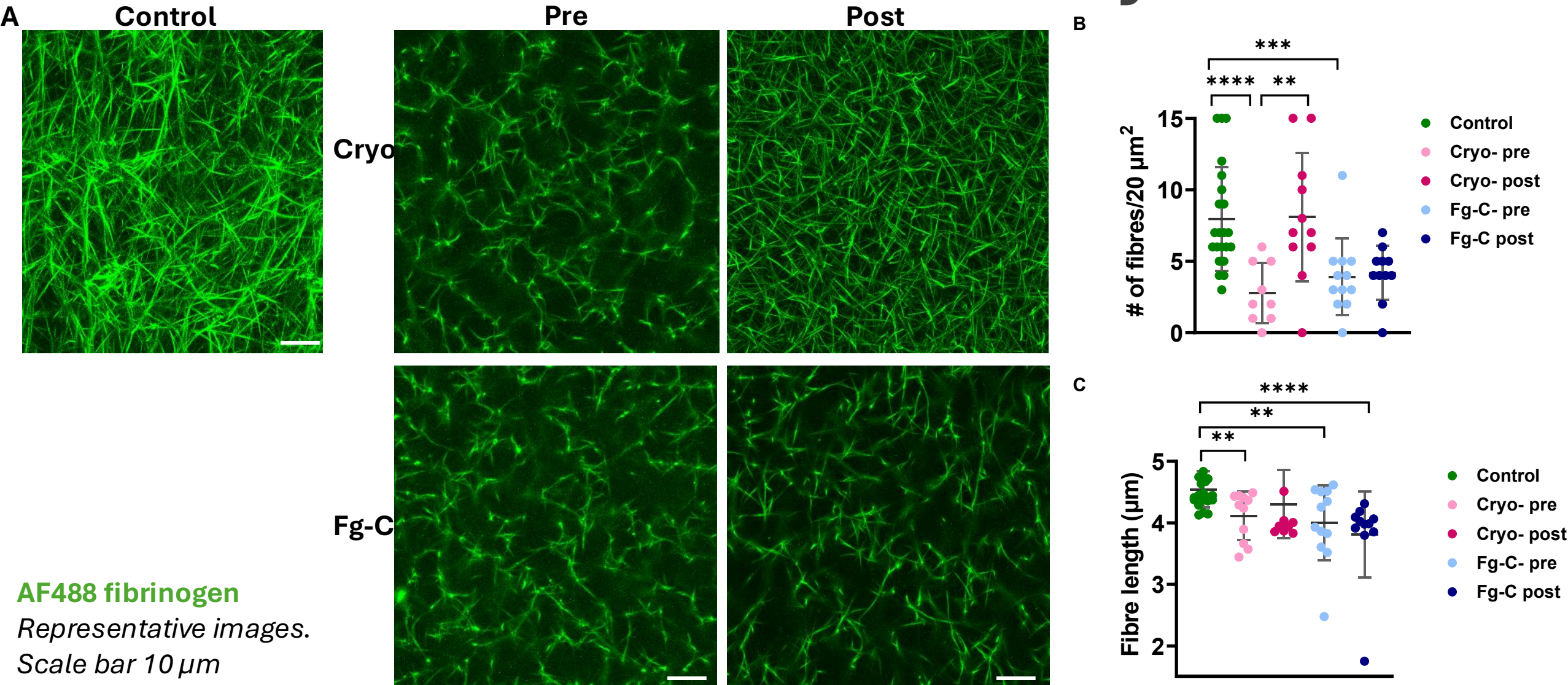
Cryoprecipitate attenuates plasmin activation and fibrinolysis

A

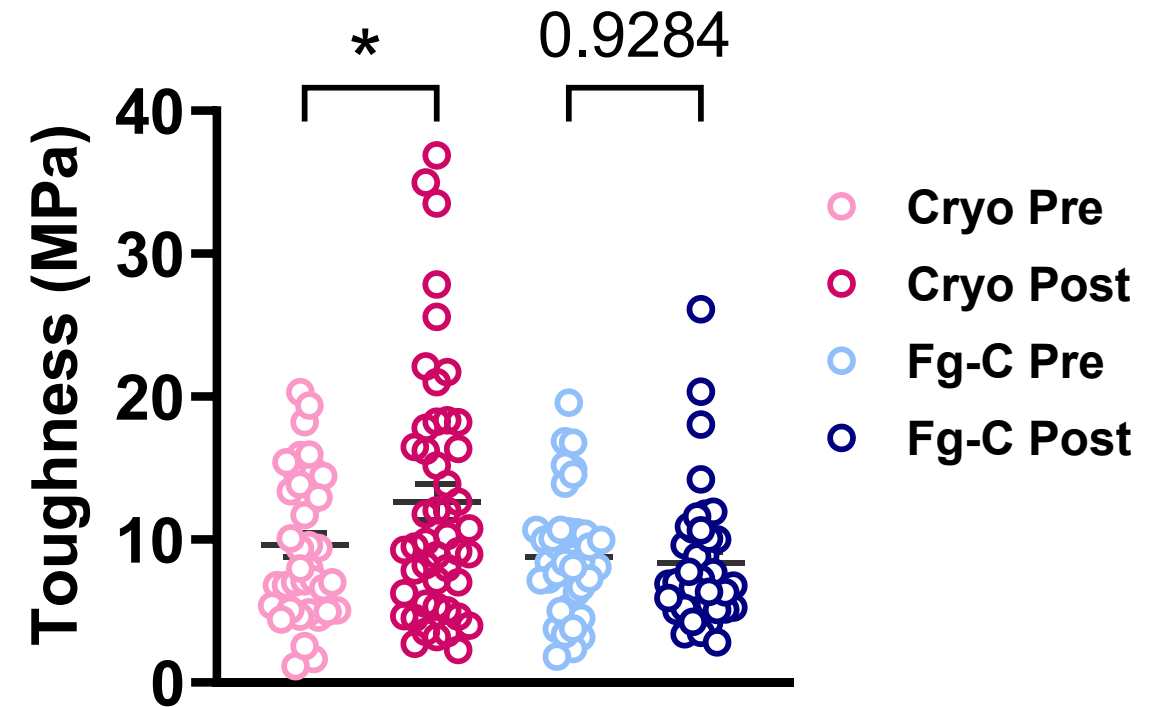
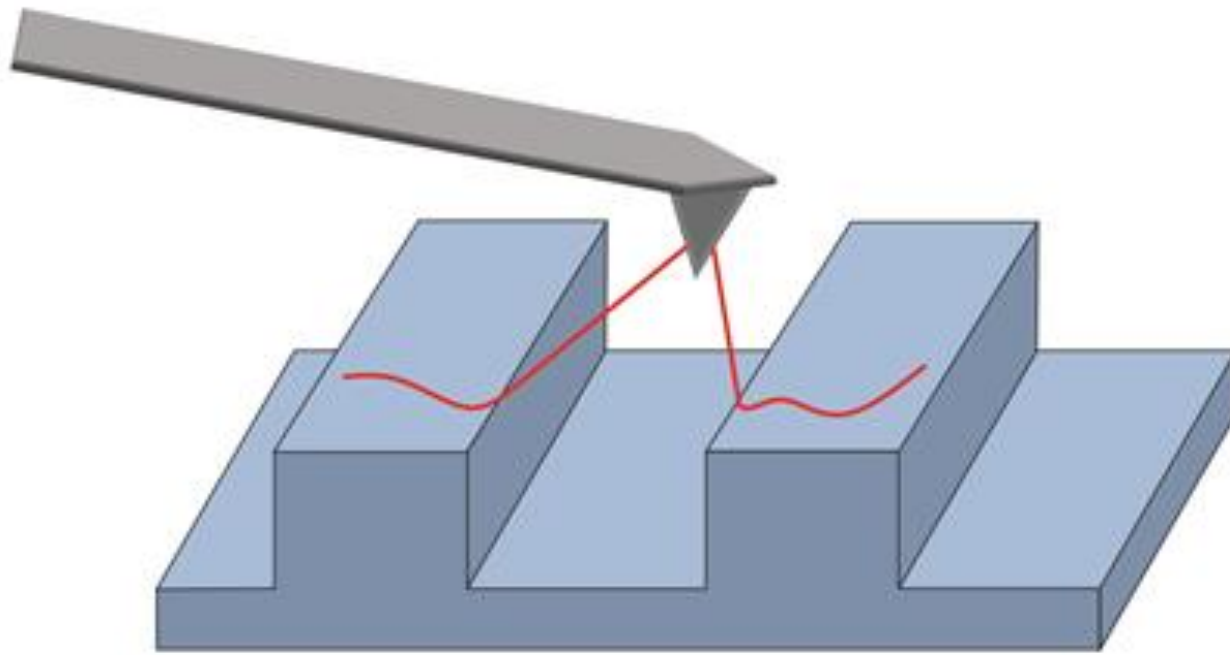


** $p < 0.01$

Clots formed post cryoprecipitate have increased fibre density



Cryoprecipitate transfusion augments fibrin fibres strength



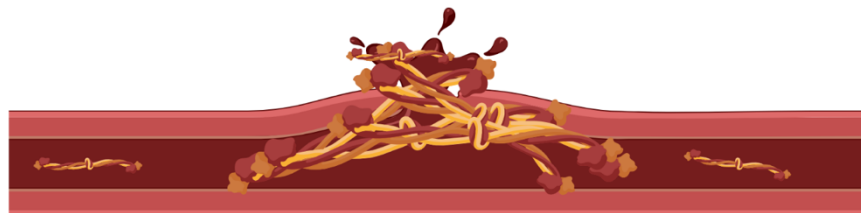
which
fibrinogen source?



- attenuates plasmin generation
- forms more dense fibrin clot with increased cross-links
- individual fibrin fibres are tougher

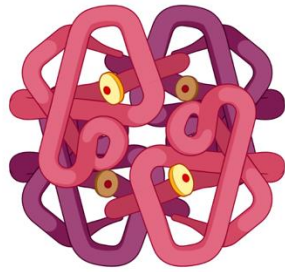


- faster time to administration
- rationale for co-administration with FXIII concentrate?

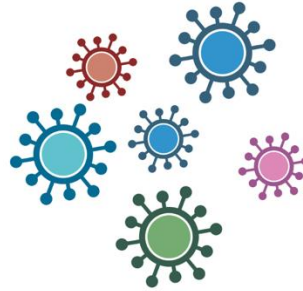


Manufacturing Methods Matter:

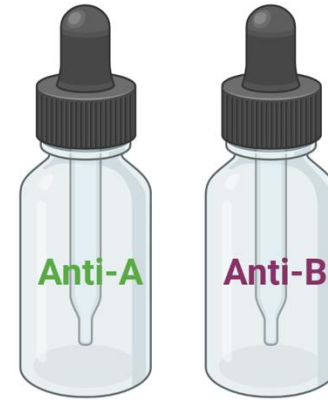
Current component therapy testing



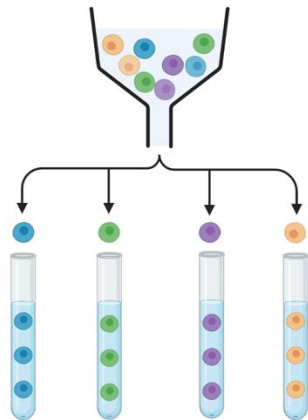
Hb levels



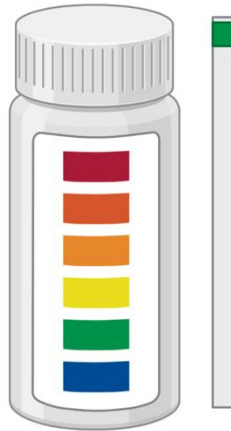
bacterial/
viral
infection



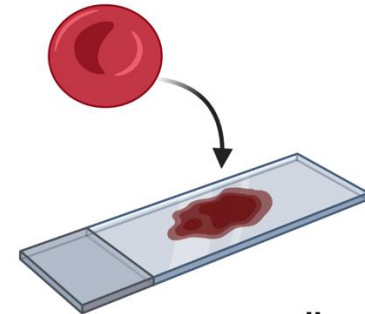
Antibody
titre



cell counts



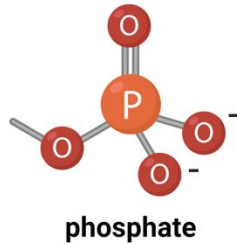
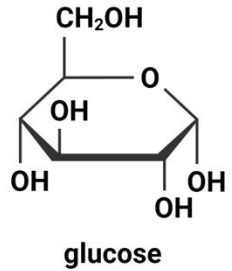
pH



cell
morphology

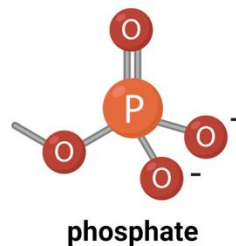
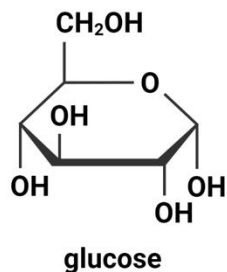
Manufacturing Methods Matter:

Additive solutions in component therapies



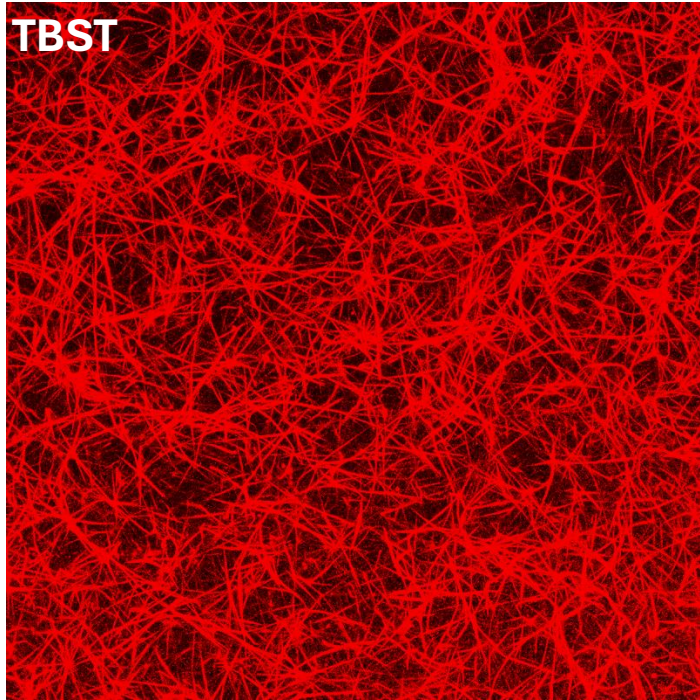
Manufacturing Methods Matter:

Platelet Additive Solutions

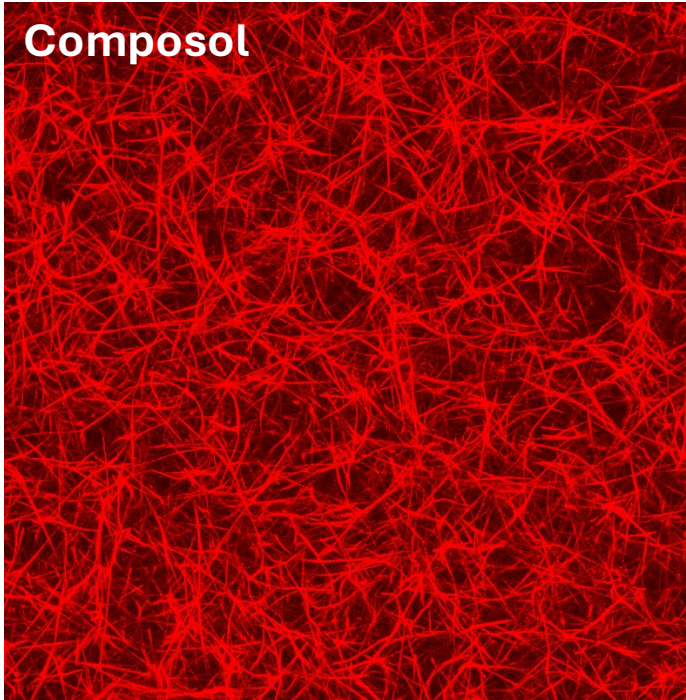


Chemical (mmol/L)	Intersol (PAS-3)	SSP +	Composol
NaCl	452	69.3	90
Monosodium phosphate NaH ₂ PO ₄	93	28.2	-
KCL	-	5	5
MgCl ₂	-	1.5	-
Sodium Citrate Na ₃ C ₆ H ₅ O ₇	318	10.8	11
Sodium Acetate C ₂ H ₃ NaO ₂	442	32.5	27
Sodium Gluconate NaC ₆ H ₁₁ O ₇	-	-	23
Disodium Phosphate Na ₂ HPO ₄	305	-	-

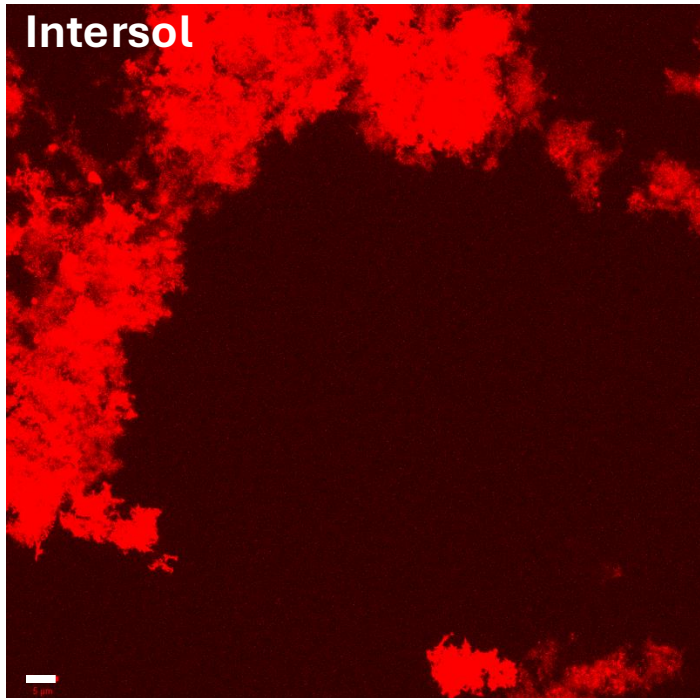
TBST



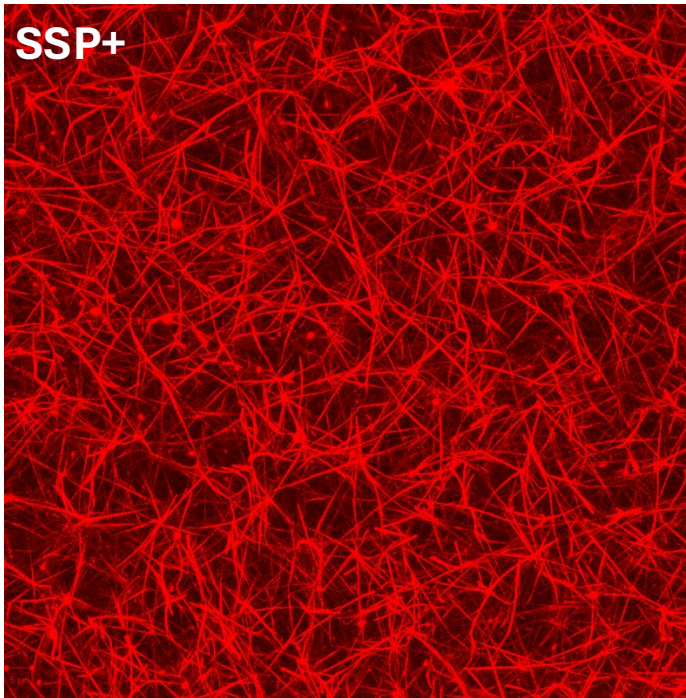
Composol



Intersol



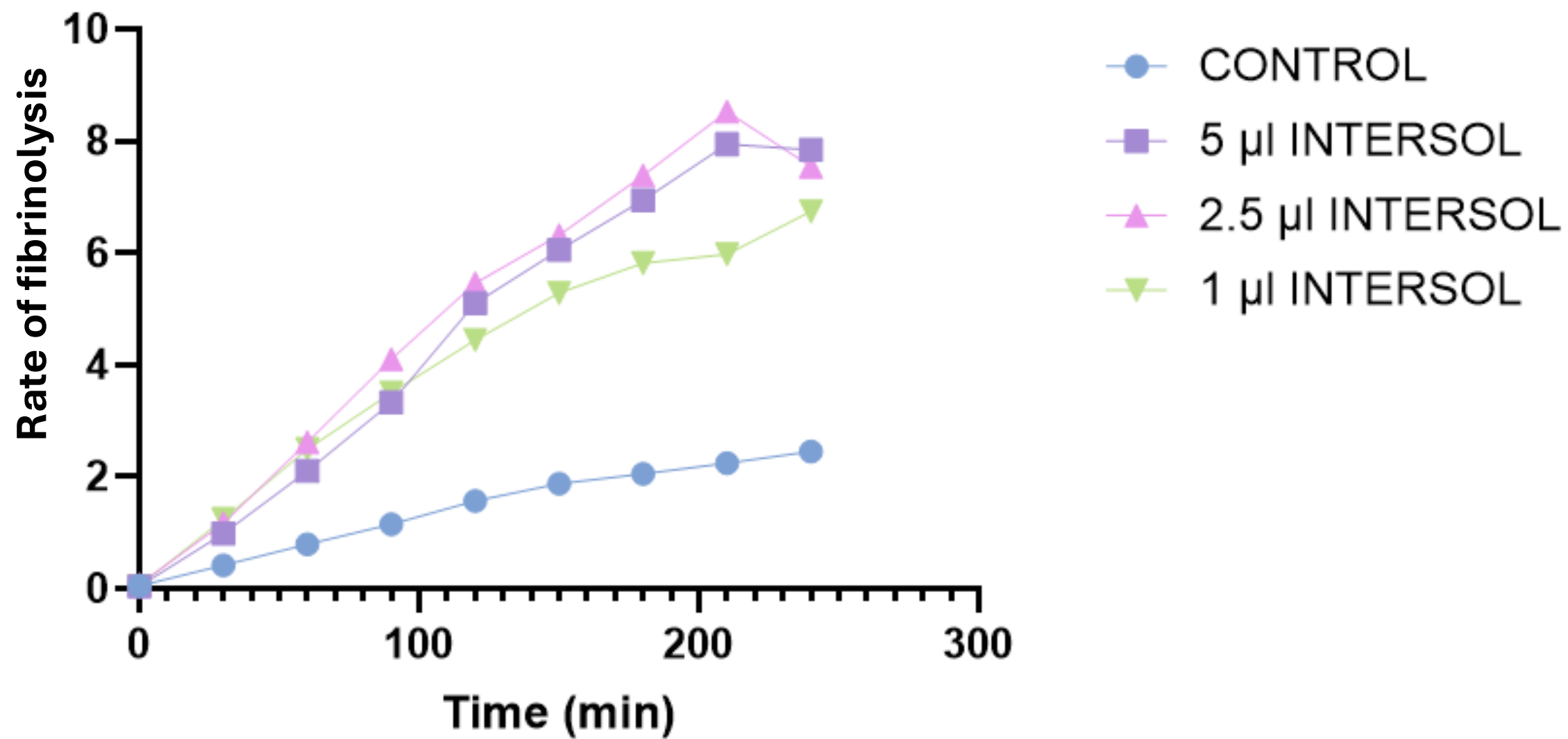
SSP+



The effect of platelet additive solutions on fibrin clot structure

AF488 fibrinogen

Scale bar – 5 μ m



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Dr Liz Wake



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