Diagnosis & treatment of coagulopathies in the bleeding patient: We want it *quick* and we want it *now* - *The Copenhagen Concept*

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COI: None

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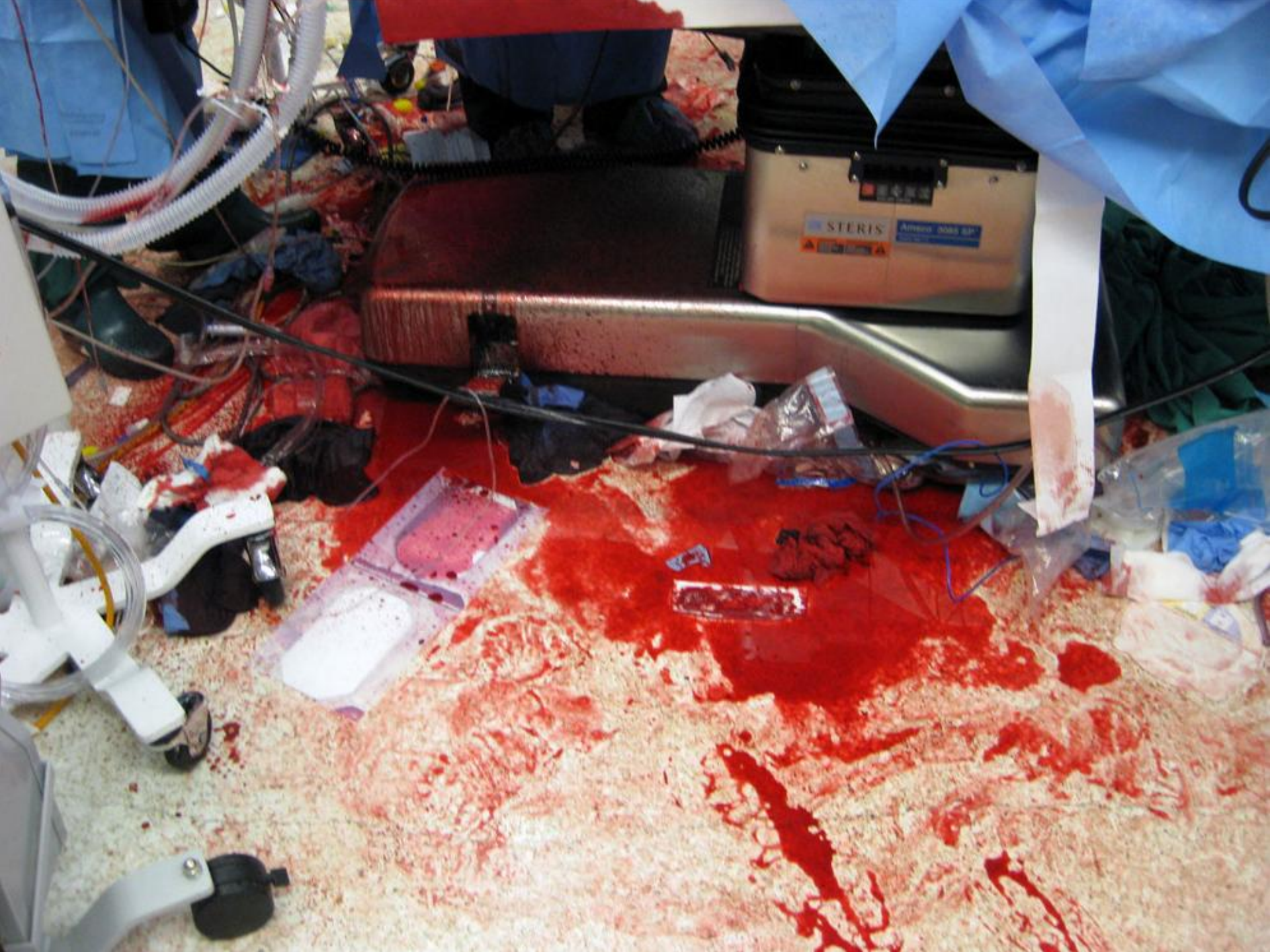
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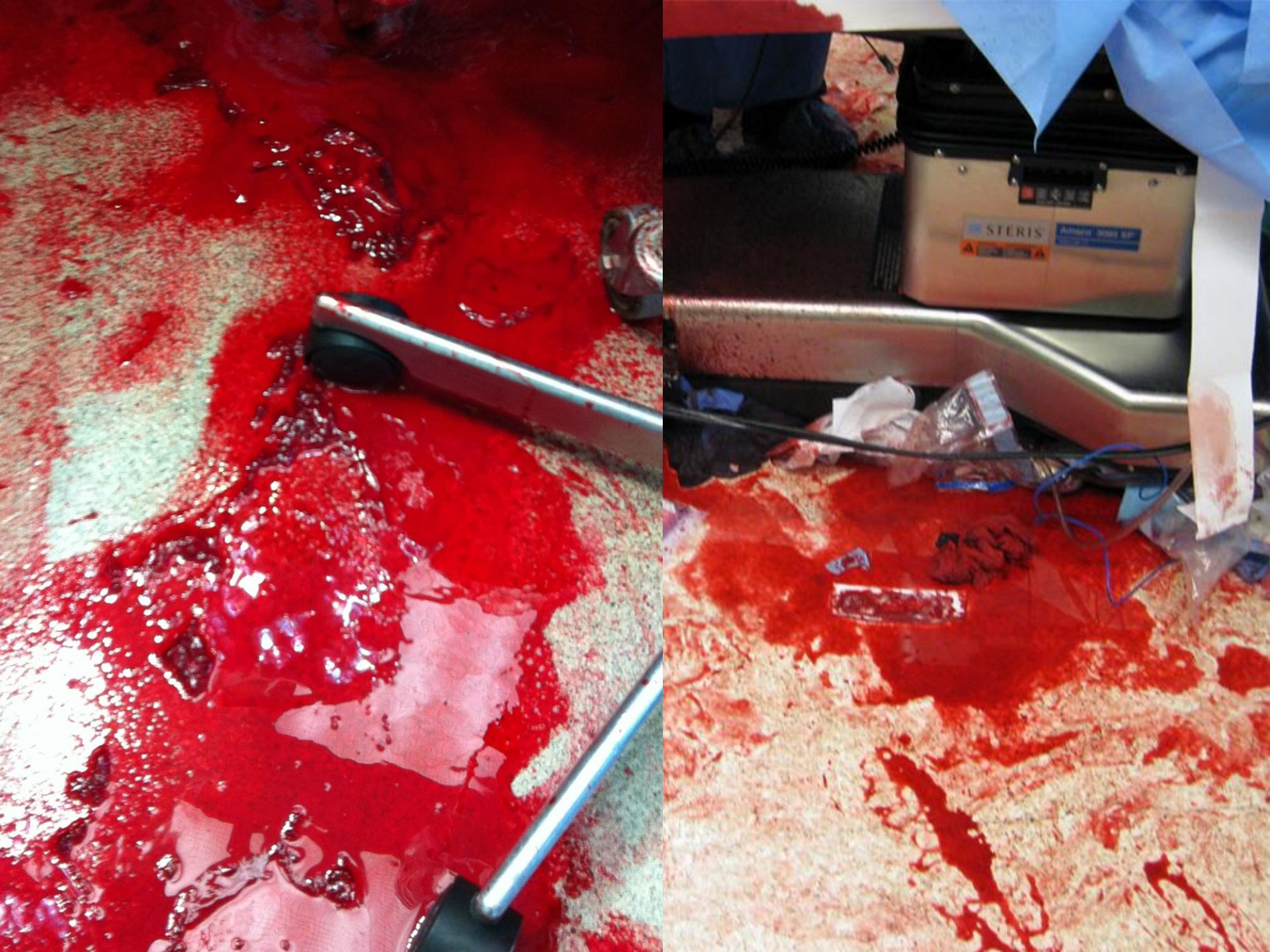
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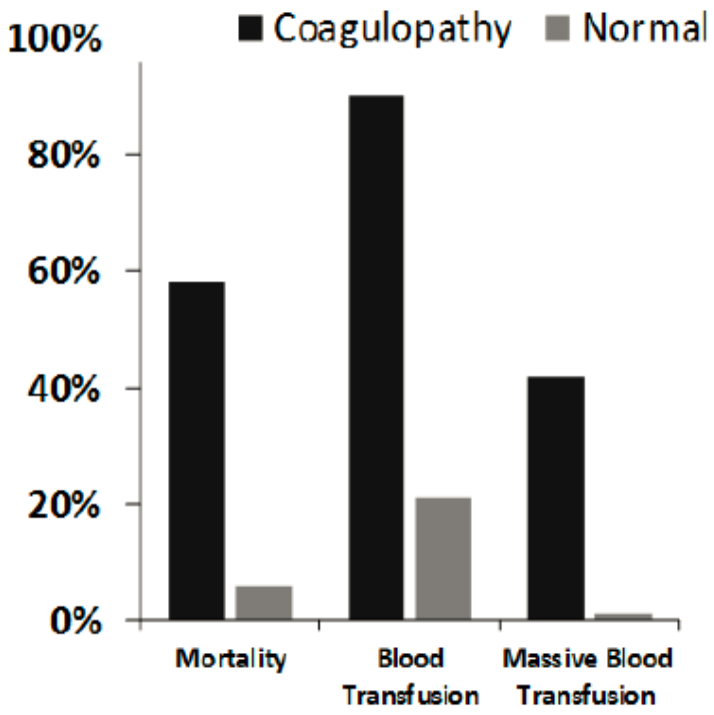
Coagulopathy and bleeding



Pathophysiology

Coagulopathy related to Trauma/Shock - Acute Traumatic Coagulopathy

Coagulopathy secondary to dilution with crystalloids and colloids

Coagulopathy secondary to haemotherapy

Coagulopathy secondary to comsumption (injury, DIC etc.)

Coagulopathy due to hypothermia and metabolic acidosis

Coagulopathy due to ischemia-reperfusion injury

Coagulopathy due to antithrombotics

Hardy J-F et al. Can J Anesth 2004

Brohi K et al. Curr Opinion of Crit Care. 2007

Surgical?

Platelet(dys)function?

Dilution?

olysis?

Sever

otics?

Consumpt

losis?

Coagulopathy?

Dysfibrinogenaemi?

Hypothermia?

Cascade model of coagulation

- PT was introduced in 1940s to evaluate the effect of dicumarins

  Shapiro et al. Ann Surg. 1

- APTT was introduced in 1 with the purpose of reflecting the effe anticoagulants

  Proctor et al. Am J Clin Path 1961

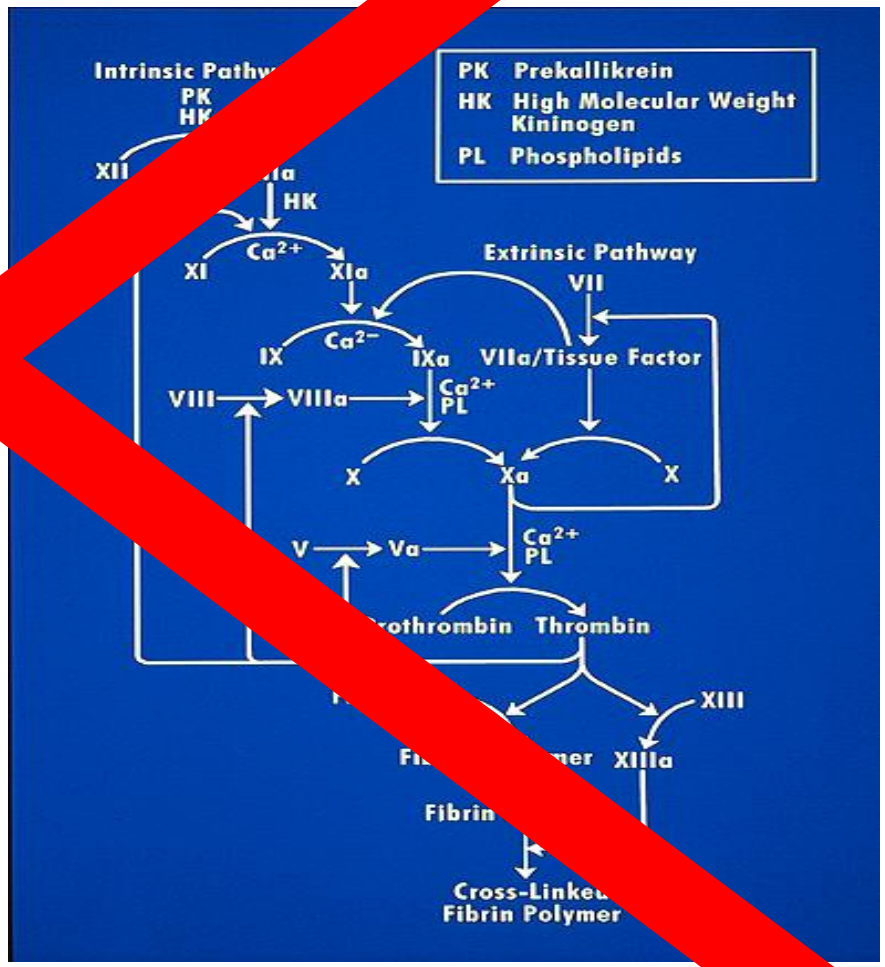
- These assays determine h asma coagulate in a sample

- Platelet coun s not reflect functiona

  Agarw Anesthesiology 2006

  S et al. Platelets 2006

- brinolysis?

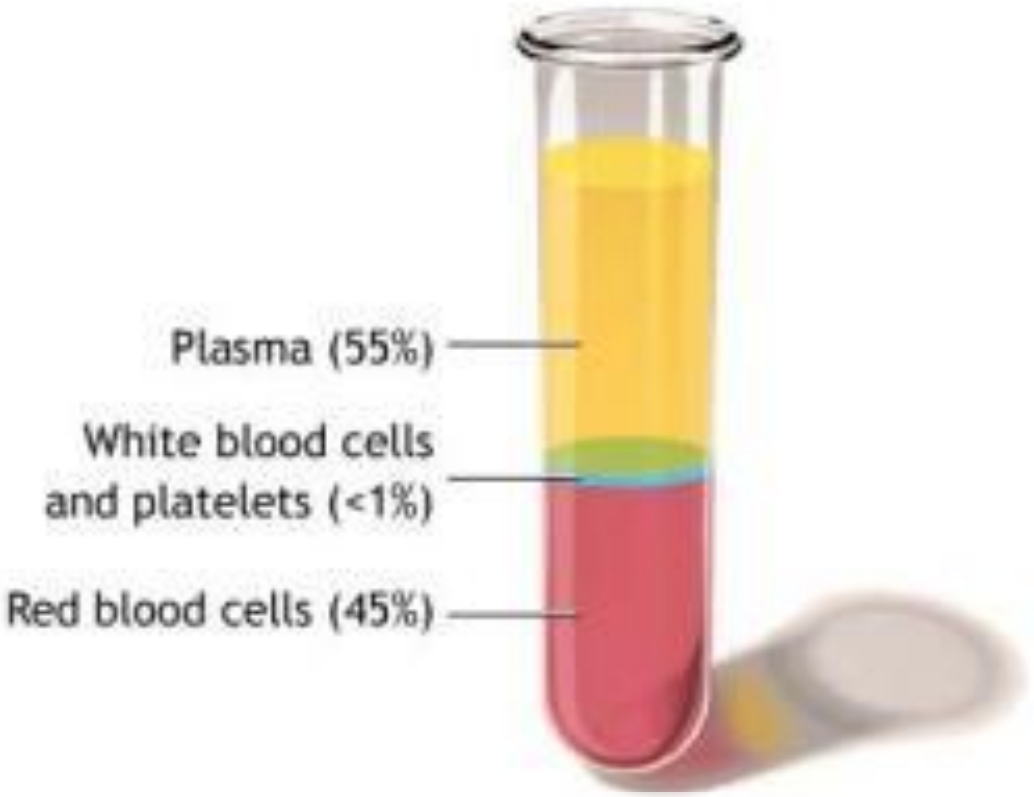


MacFarlane RG. Nature 19

Plasma-based tests?

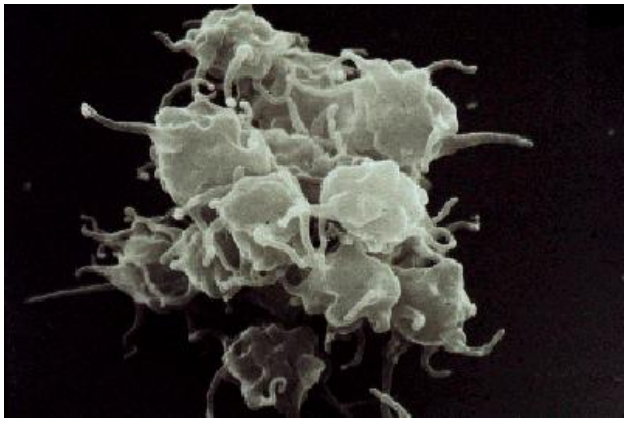
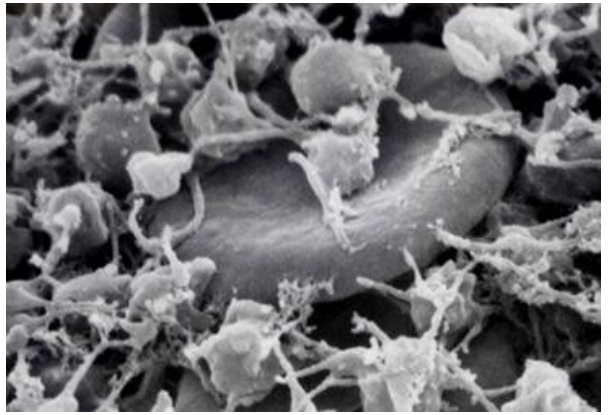
INR/PT EXTRINSIC PATHWAY

INTRINSIC PATHWAY **APTT**

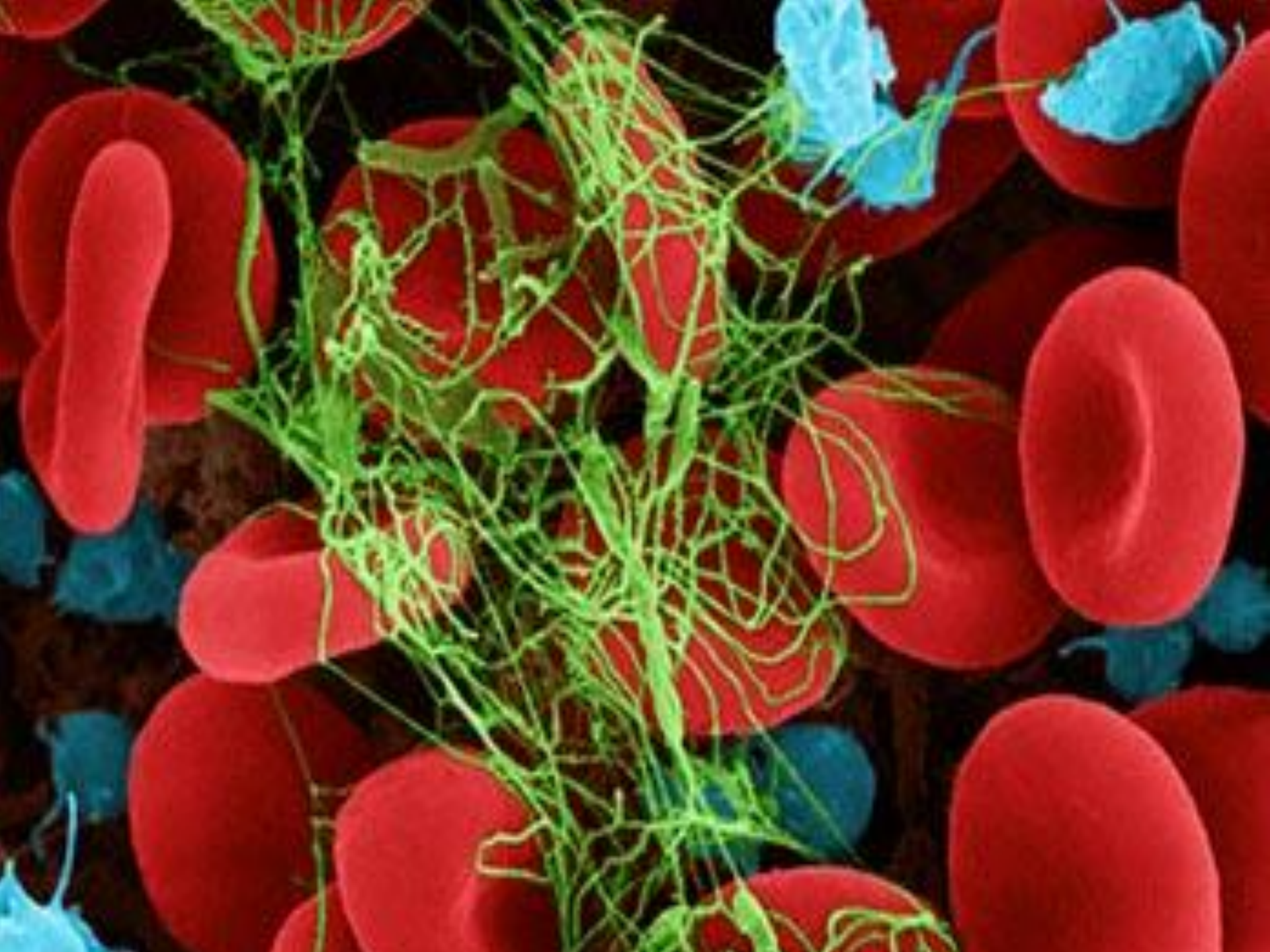


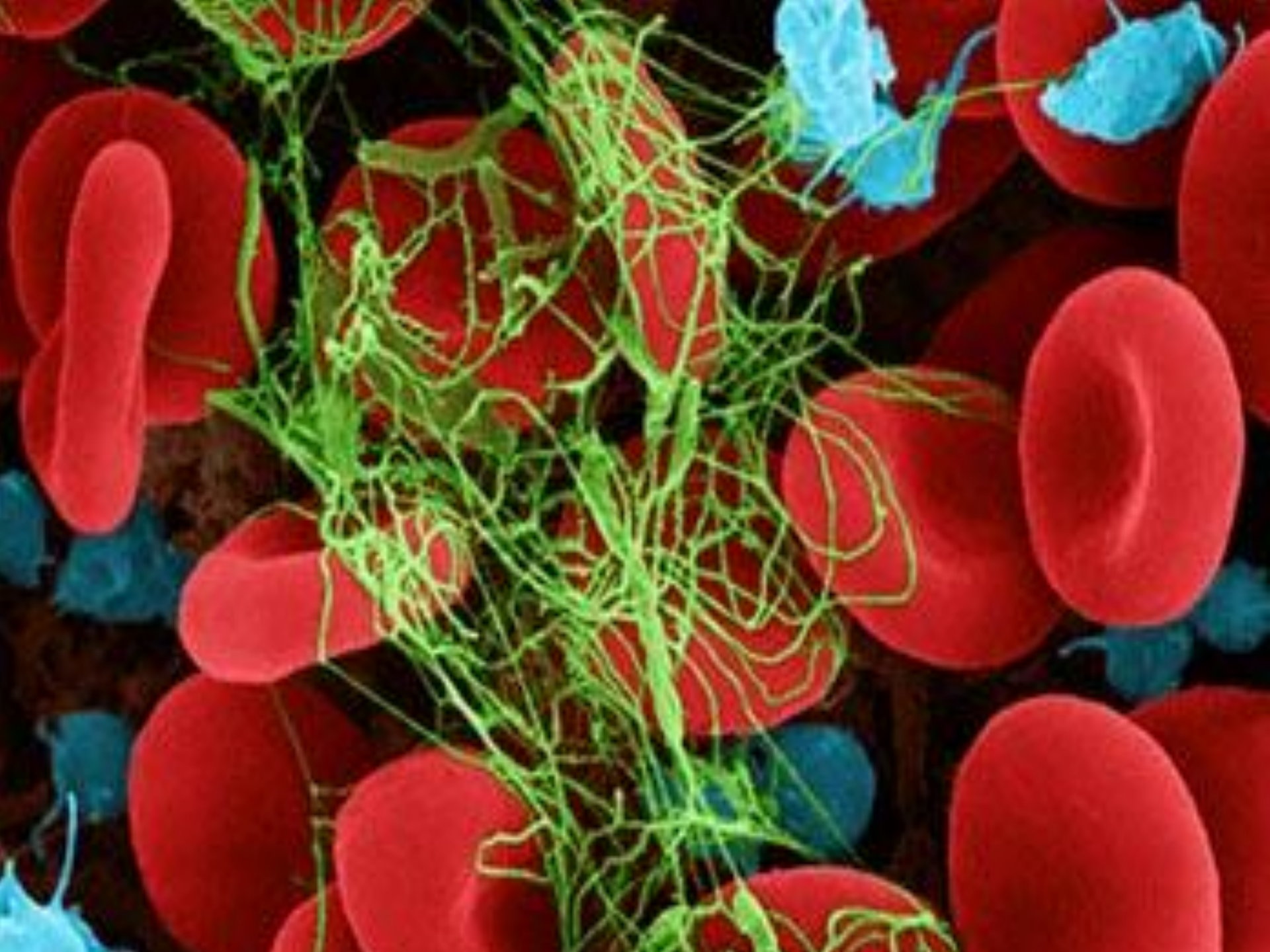
…developed to monitor heparin and vitamin K antagonists…

Platelet count?

…doesn´t reflect platelet function!

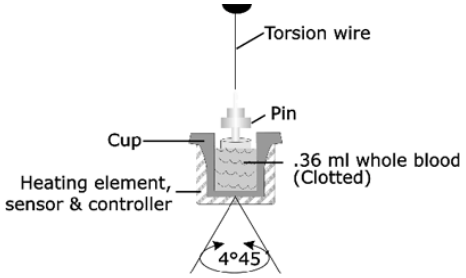


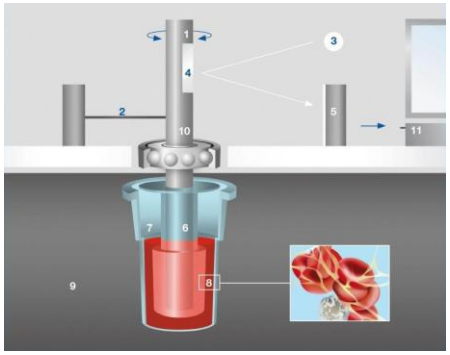


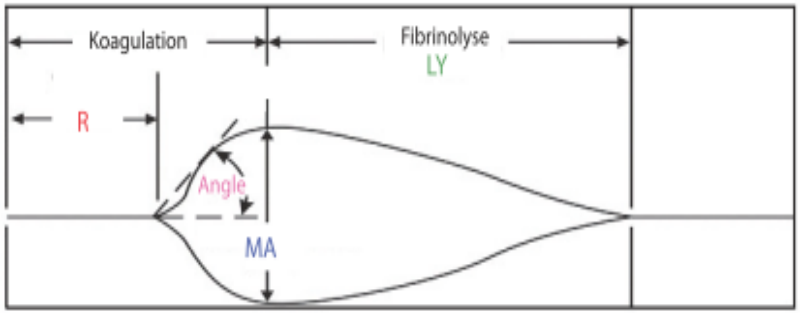
Viscoelastic Hemostatic Assays (VHA)

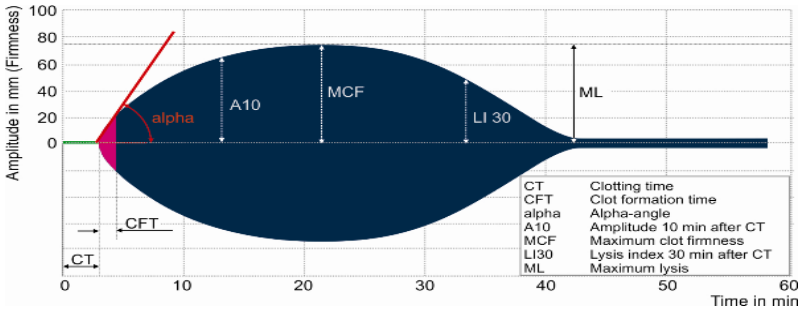
TEG®/ROTEM®

- Whole blood analysis
- Measures the viscoelsatical properties of the clot
- Multiple endpoints reflecting clot formation, strength & degradation
- Real-time (15 min.)

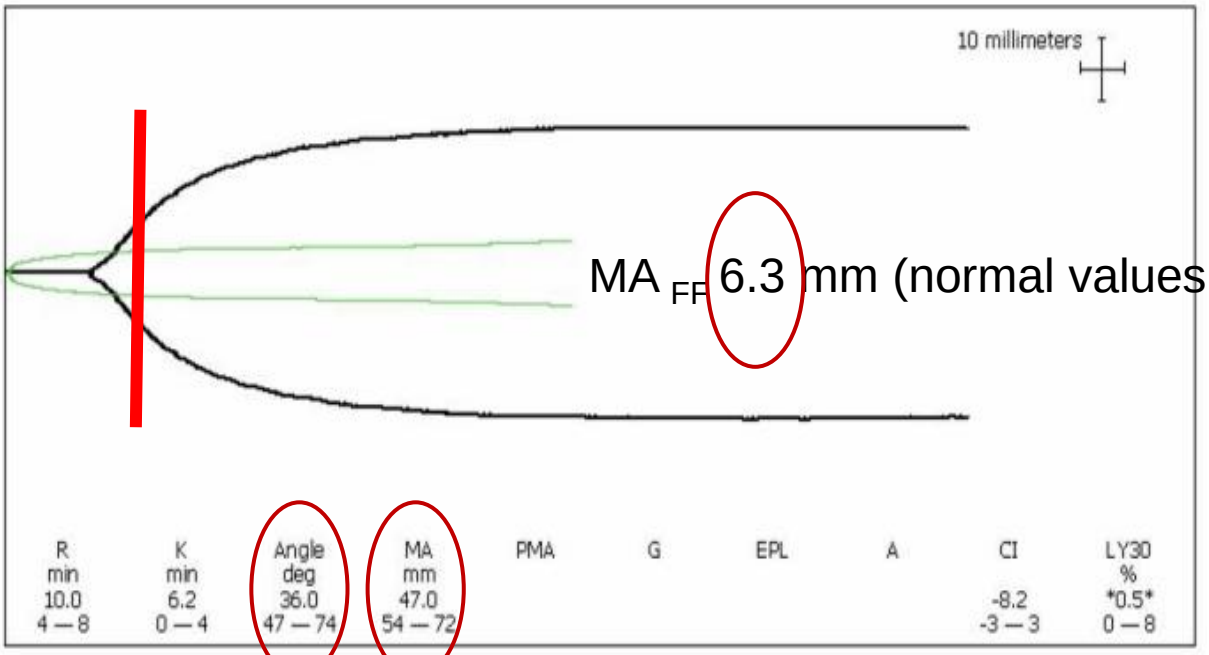




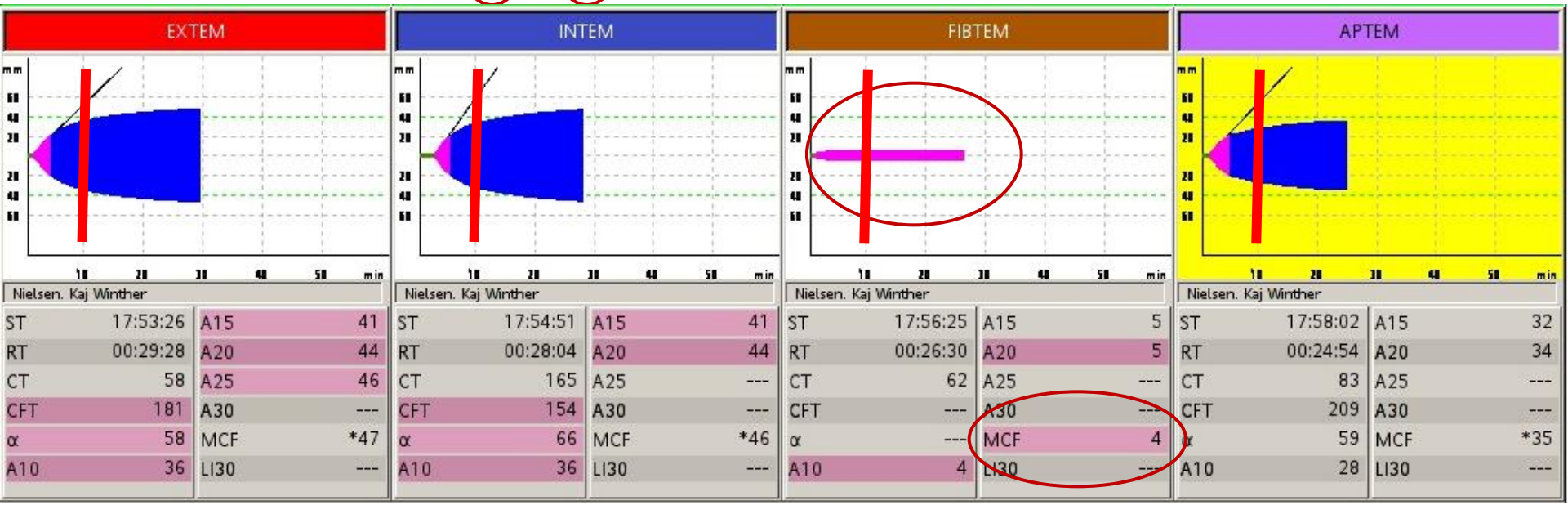




Functional Fibrinogen TEG® / FIBTEM ROTEM®



MA_{FF} 6.3 mm (normal values 14-24)



RapidTEG®

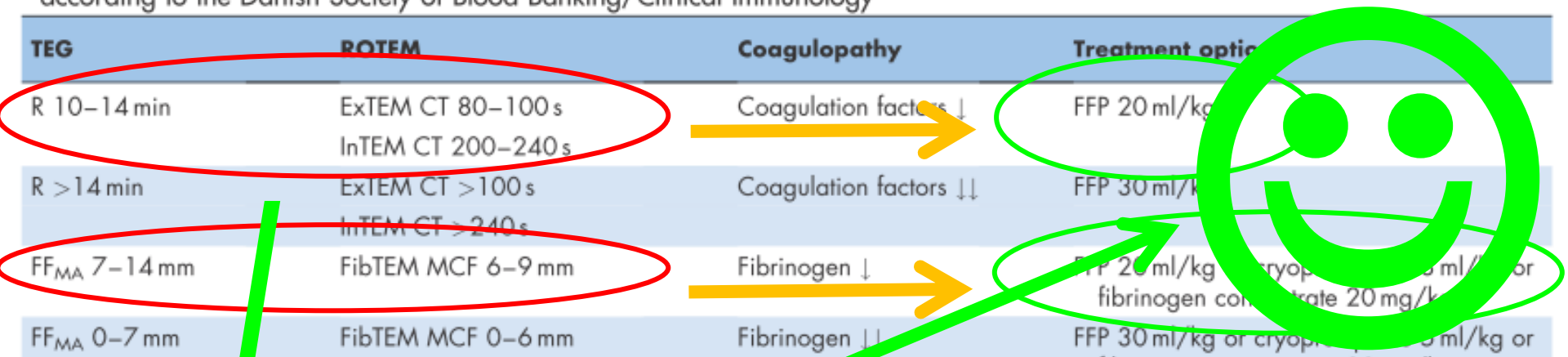
Patient arrives at 6.02

TEG result finished 6.09

Treatment algorithm

Table 1. TEG and ROTEM treatment algorithm for bleeding patients as used in Copenhagen, and adopted across Denmark according to the Danish Society of Blood Banking/Clinical Immunology

TEG	ROTEM	Coagulopathy	Treatment optio
R 10–14 min	ExTEM CT 80–100 s InTEM CT 200–240 s	Coagulation factors ↓	FFP 20 ml/kg
R >14 min	ExTEM CT >100 s InTEM CT >240 s	Coagulation factors ↓↓	FFP 30 ml/k
FF_{MA} 7–14 mm	FibTEM MCF 6–9 mm	Fibrinogen ↓	FFP 20 ml/kg cryop ml/ or fibrinogen con tate 20 mg/k
FF_{MA} 0–7 mm	FibTEM MCF 0–6 mm	Fibrinogen ↓↓	FFP 30 ml/kg or cryop ml/kg or fibrinogen concentrate 30 mg/kg
MA 45- 9 mm an FF_{MA} > 4 mm	ExTEM A_{10} 35–42 mm and FibTEM ≥10 mm ExTEM MCF <50 m and FibTEM ≥1 mm	Platelets ↓	Platelets 5 ml/kg
MA <45 mm FF_{MA} >14 m	ExTEM A_{10} <35 mm and FibTEM ≥10 mm	Platelets ↓↓	Platelets 10 ml/kg
Ly30 >8%	ExTEM Li30 <94%	Hyperfibrinolysis	TXA 1–2 g IV or 10–20 mg/kg
Difference in R Hep TEG vs. standard TEG R >2 min	InTEM CT/HepTEM CT >1.25	Heparinazation	Protamine 50–100 mg or FFP 10–20 ml/kg

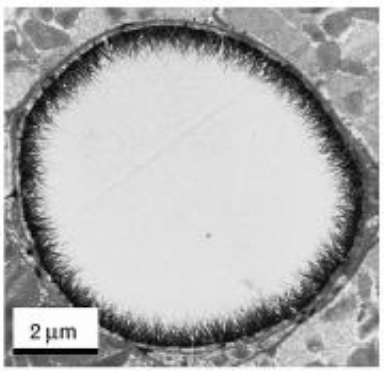


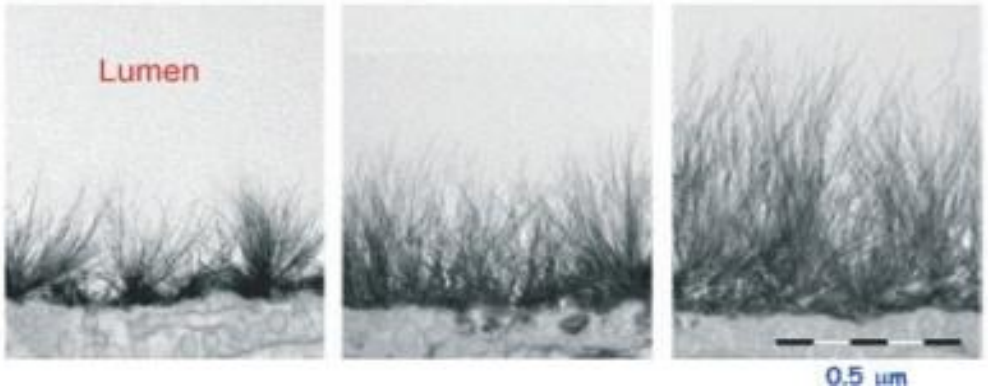
Stensballe et al. Curr Opin Anesthesiol 2014

If treament failure – call Bloodbank

Vascular endothelium

- **Endothelial cells**: A single layer of cells lining the blood vessels, covering a surface area of 4-7,000 m^2 with a total weight of 1 kilogram
- **Glycocalyx**: 0.2-1 µm endothelial surface layer comprising glycoproteins, heparin-like substances and plasma constituents
- Contains a fixed non-circulating plasma volume of 0.7-1.0 L (25-30% of plasma volume) in dynamic equilibrium with the circulating plasma

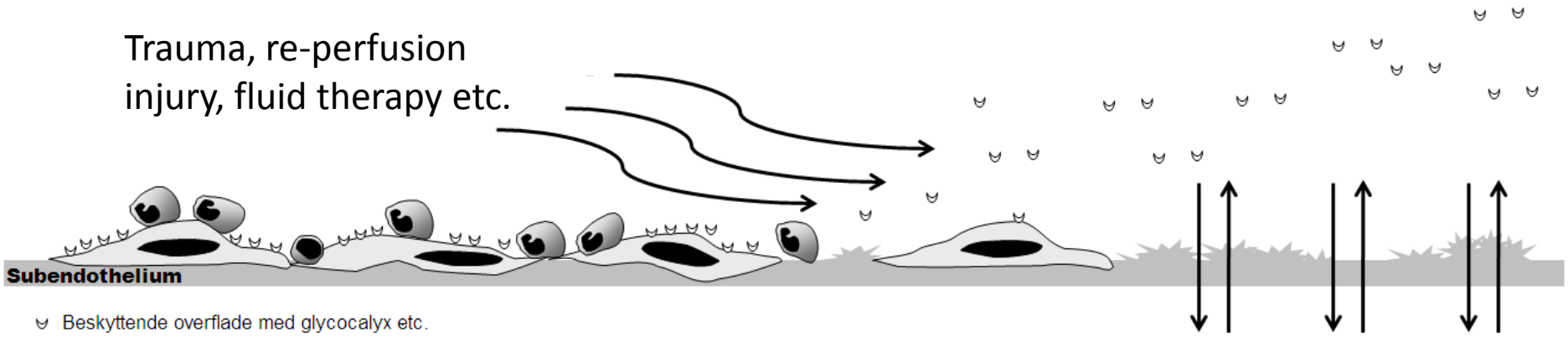




Rehm et al. Anesthesiol 2001; van den Berg et al. Pharmacol Rep. 2006; Nieuwdorp et al. Curr Opin Lipidol 2005; Gouverneur et al. J Int Med 2006, Jacob et al. Best Pract Res Clin Anaesthesiol 2009; Rehm et al. Circulation 2007

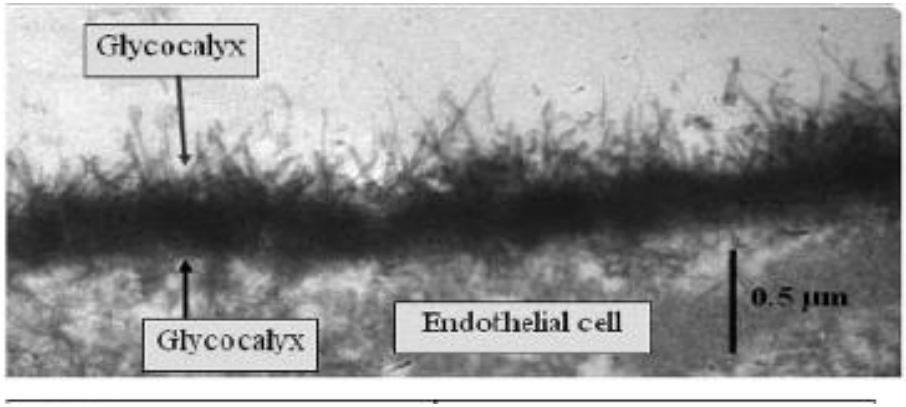
Vascular endothelium

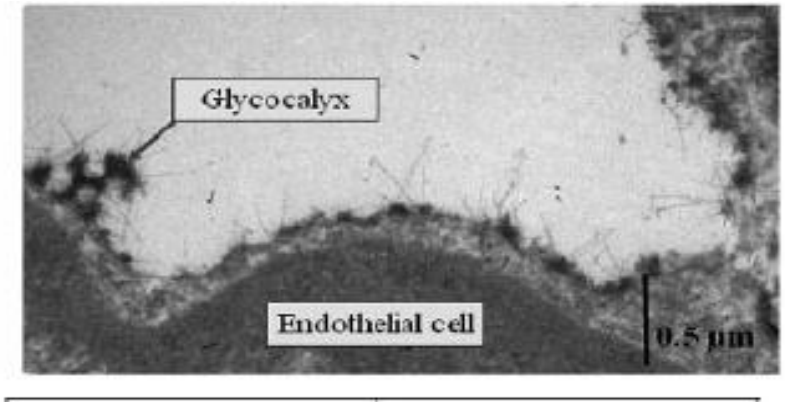
Trauma, re-perfusion injury, fluid therapy etc.



- Beskyttende overflade med glycocalyx etc.

Stensballe et al.





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The Copenhagen Concept

Blood Bank Services

Services since 2004

- Live monitoring
- Thrombelastograph (TEG®)
- TEG Specialist Guidance – 24/7

New ”products” since 2004

- Cryoprecipitate
- Thawed FFP, Liquid plasma
- Acute Transfusion Package
  (5 RBC; 5 FFP, 2 PC)
- PCC (Octaplex®)
- NovoSeven-package
- Fibrinogen
- DDAVP

Johansson, Stensballe et al. Transfusion 2007

Life-threatening
bleeding

1:1:1

3:3:1 → 4:4:1

FFP:RBC ratio…?

- **Cinat et al. (1999) reporterede FFP:SAG M ratio**

  Non-survivors 1:2.5

  Survivors 1:1.8

- **Maegele et al. (2007) fandt**

  Lav FFP:SAG M ratio ~ mortalitet 45 %

  Medium FFP:SAG M (1:1,4) ~ mortalitet 35 %

  Høj FFP:SAG M (1:1) ~ mortalitet 24%

- **Johansson og Stensballe (2009)**

  Non-survivors FFP:SAG M ratio 1:1.6

  Survivors FFP:SAG M ratio of 1:1.2

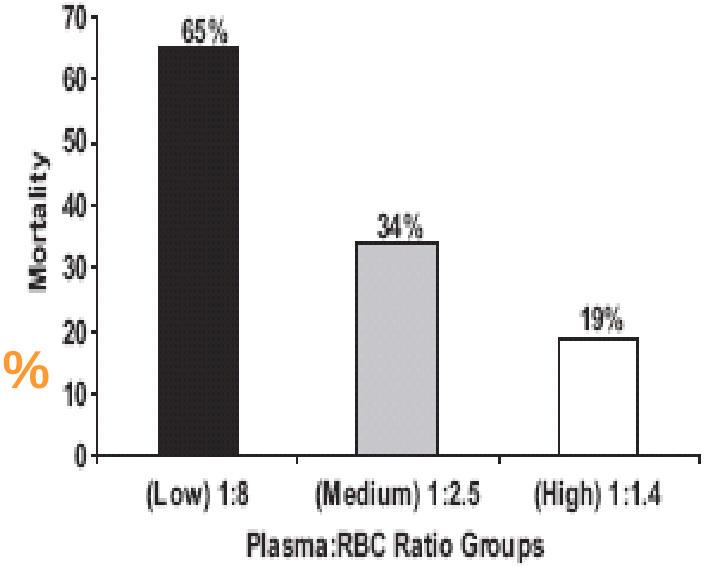


Fig. 1. *Percentage mortality associated with low, medium, and high plasma to RBC ratios transfused at admission. Ratios are median ratios per group and include units of fresh whole blood counted both as plasma and RBCs.*

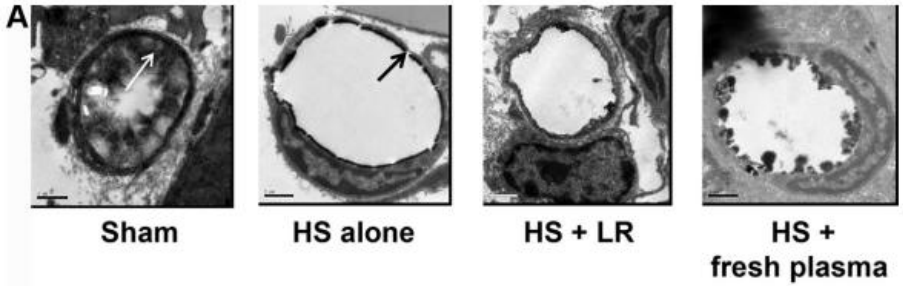
Borgman et al. J Trauma 2007

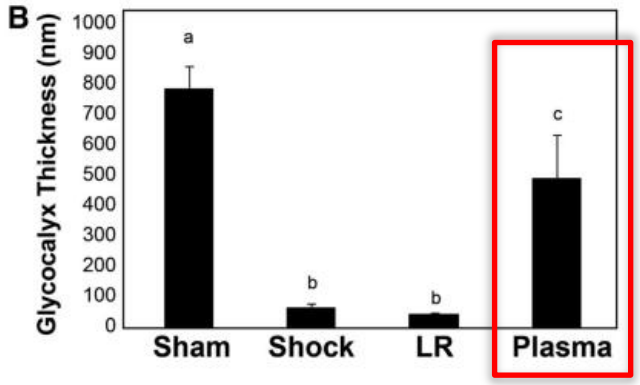
Proof-of-concept → Therapy?

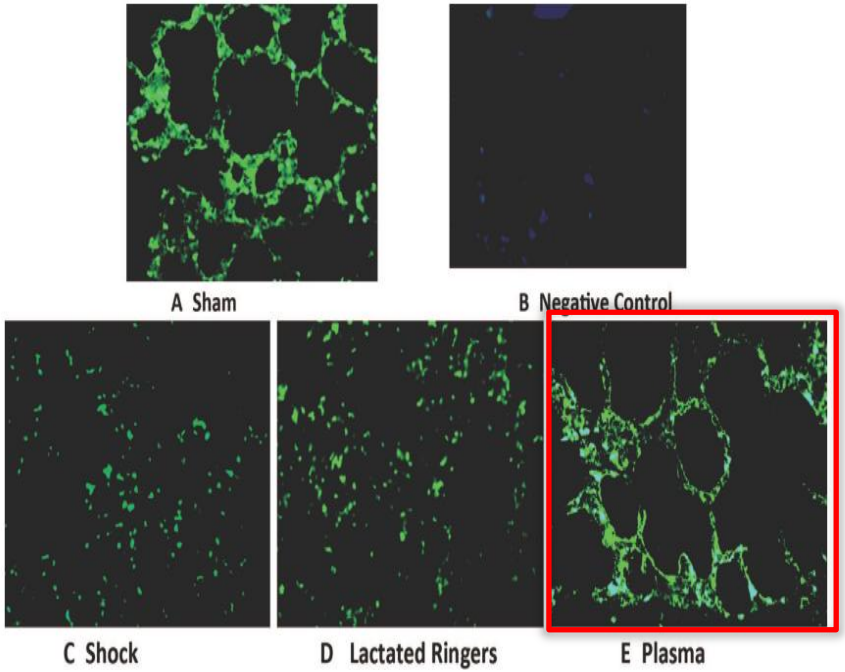
Plasma Restoration of Endothelial Glycocalyx in a Rodent Model of Hemorrhagic Shock

Rosemary A. Kozar, MD, PhD,* Zhanglong Peng, MD, PhD,* Rongzhen Zhang, MD, PhD,* John B. Holcomb, MD,* Shibani Pati, MD, PhD,* Pyong Park, PhD,† Tien C. Ko, MD,* and Angel Paredes, PhD*

June 2011 • Volume 112 • Number 6 www.anesthesia-analgesia.org







Platelets…?

Platelets are crucial for intact haemostasis

1. **Participate in clot building**
2. **Thrombin burst occurs on the activated platelet**

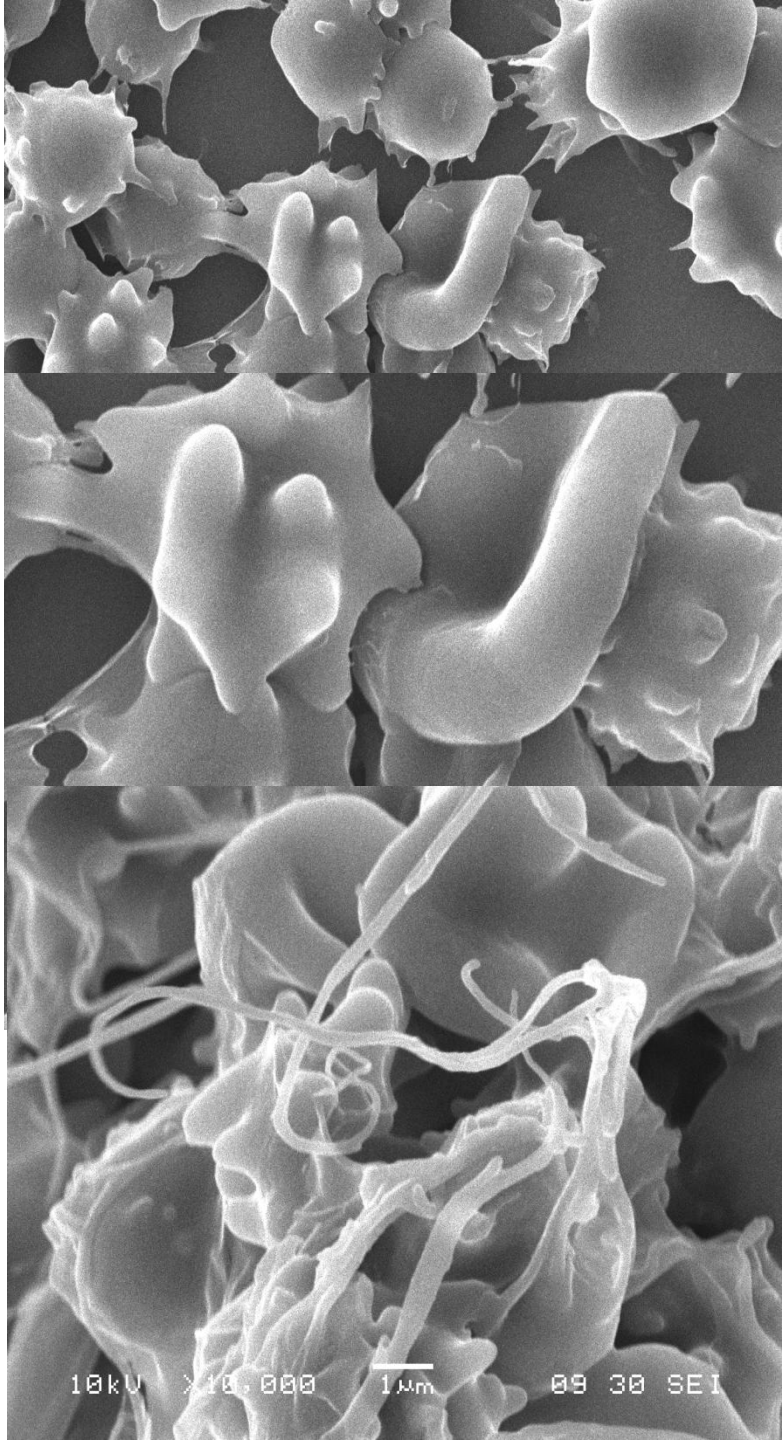


Table 4 Multivariate logistic regression analysis of risk factors for 30-day mortality in 832 patients receiving more than 10 RBCs within 24 h

	Death within 30-days (n = 213)	
Variable	**Odds ratio (95% CI)**	*P*
Platelet count 24 h after first transfusion (increase 1×10^9/l)	0·99 (0·989 to 0·998)	0·008
Period 2002–2003 vs. 2005–2006	1·6 (1·05 to 2·4)	0·0288
RBC transfusion in 24 h (increase 1 unit)	1·05 (1·03 to 1·08)	< 0·0001
Age (increase 1 year)	1·05 (1·0 to 1·1)	< 0·0001
Cause of surgery		0·0151
Trauma vs. abdominal-vascular surgery	1·4 (0·72 to 2·9)	
Orthopaedic vs. abdominal-vascular surgery	0·15 (0·04 to 0·67)	
Miscellaneous vs. abdominal-vascular surgery	1·9 (0·78 to 4·6)	
Cardiothoracic vs. abdominal-vascular surgery	1·2 (0·72 to 2·0)	
Burn vs. abdominal-vascular surgery	5·0 (1·3 to 20·0)	
Not admitted to the intensive care unit	0·36 (0·16 to 0·82)	0·0151
Time from first transfusion to blood sample (increase 1 h)	0·97 (0·93 to 1·01)	0·0787
Time from blood sample to first transfusion (increase 1 h)	1·02 (0·99 to 1·05)	0·16
Male gender	1·1 (0·7 to 1·7)	0·69
Platelet count prior to first transfusion (increase 1×10^9/l)	0·99 (0·99 to 1·01)	0·59

CI, confidence interval.

Transfusion of fresh frozen plasma and platelets concentrates within 24 h was removed from the model because of suspected collinearity with red blood cell transfusion within 24 h (variance proportion > 0·5 and condition index > 10). (Further data are available on request).

All odds ratios were mutually adjusted for the other variables. Hosmer and Lemeshow goodness-of-fit test, $P = 0{\cdot}7381$.

Johansson and Stensballe. Vox sang. 2009

The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study

Arch Surg. Published online October 15, 2012.

Comparative Effectiveness of a Time-Varying Treatment With Competing Risks

John B. Holcomb, MD; Deborah J. del Junco, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Mitchell J. Cohen, MD; Martin A. Schreiber, MD; Louis H. Alarcon, MD; Yu Bai, MD, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Bryan A. Cotton, MD, MPH; Nena Matijevic, PhD; Peter Muskat, MD; John G. Myers, MD; Herb A. Phelan, MD, MSCS; Christopher E. White, MD; Jiajie Zhang, PhD; Mohammad H. Rahbar, PhD; for the PROMMTT Study Group

	Continuous Transfusion Ratio Variables		Categorical Transfusion Ratio Variables				
			Low, <1:2	Moderate, ≥1:2 to <1:1		High, ≥1:1	
Characteristic	HR (95% CI)	*P* Value	HR	HR	*P* Value	HR	*P* Value
Minute 31 to Hour 6 After ED Admission (n = 876)[a]							
Early initial and time-varying plasma:RBC ratios	0.31 (0.16-0.58)	<.001	1 [Reference]	0.42	<.001	0.23	<.001
Early initial and time-varying platelet:RBC ratios	0.55 (0.31-0.98)	.04	1 [Reference]	0.66	.16	0.37	.04
Sum of blood product transfusions	1.05 (1.04-1.06)	<.001	[b]				
Age	1.01 (1.00-1.02)	.03					
Injury Severity Score	1.02 (1.01-1.04)	.001					
Time interval at cohort entry	0.73 (0.63-0.86)	<.001					
Bleeding from head	3.73 (2.15-6.45)	<.001					
Bleeding from chest	1.52 (0.96-2.39)	.07					
Bleeding from limb	0.54 (0.32-0.89)	.02					
Hour >6 to Hour 24 After ED Admission (n = 809)[c]							
6-h cumulative plasma:RBC ratio	0.34 (0.14-0.81)	.02	1 [Reference]	0.79	.63	0.55	.23
6-h cumulative platelet:RBC ratio	0.81 (0.46-1.43)	.46	1 [Reference]	0.79	.56	0.49	.19
Sum of blood product transfusions at hour 6	1.04 (1.03-1.05)	<.001	[b]				
Age	1.01 (0.99-1.03)	.36					
Injury Severity Score	1.02 (0.99-1.04)	.11					
Time interval at cohort entry	0.84 (0.72-0.98)	.03					
Bleeding from head	8.46 (3.82-18.7)	<.001					
Bleeding from chest	0.87 (0.39-1.97)	.74					
Bleeding from limb	0.96 (0.48-1.92)	.90					
Hour >24 to Day 30 After ED Admission (n = 773)[d]							
24-h cumulative plasma:RBC ratio	1.21 (0.90-1.61)	.20	1 [Reference]	1.41	.33	1.47	.26
24-h cumulative platelet:RBC ratio	0.78 (0.57-1.06)	.11	1 [Reference]	1.23	.46	0.69	.19
Sum of blood product transfusions at hour 24	1.02 (1.01-1.03)	<.001	[b]				
Age	1.03 (1.02-1.04)	<.001					
Injury Severity Score	1.04 (1.02-1.05)	<.001					
Time interval at cohort entry	0.98 (0.91-1.06)	.63					
Bleeding from head	5.96 (3.59-9.90)	<.001					
Bleeding from chest	0.45 (0.23-0.90)	.02					
Bleeding from limb	1.22 (0.76-1.96)	.41					

PROPPR

Pragmatic Randomized Optimal Platelet and Plasma Ratios

Lead by prof J.B. Holcomb, Houston, USA

PROPPR finalized dec. 2013

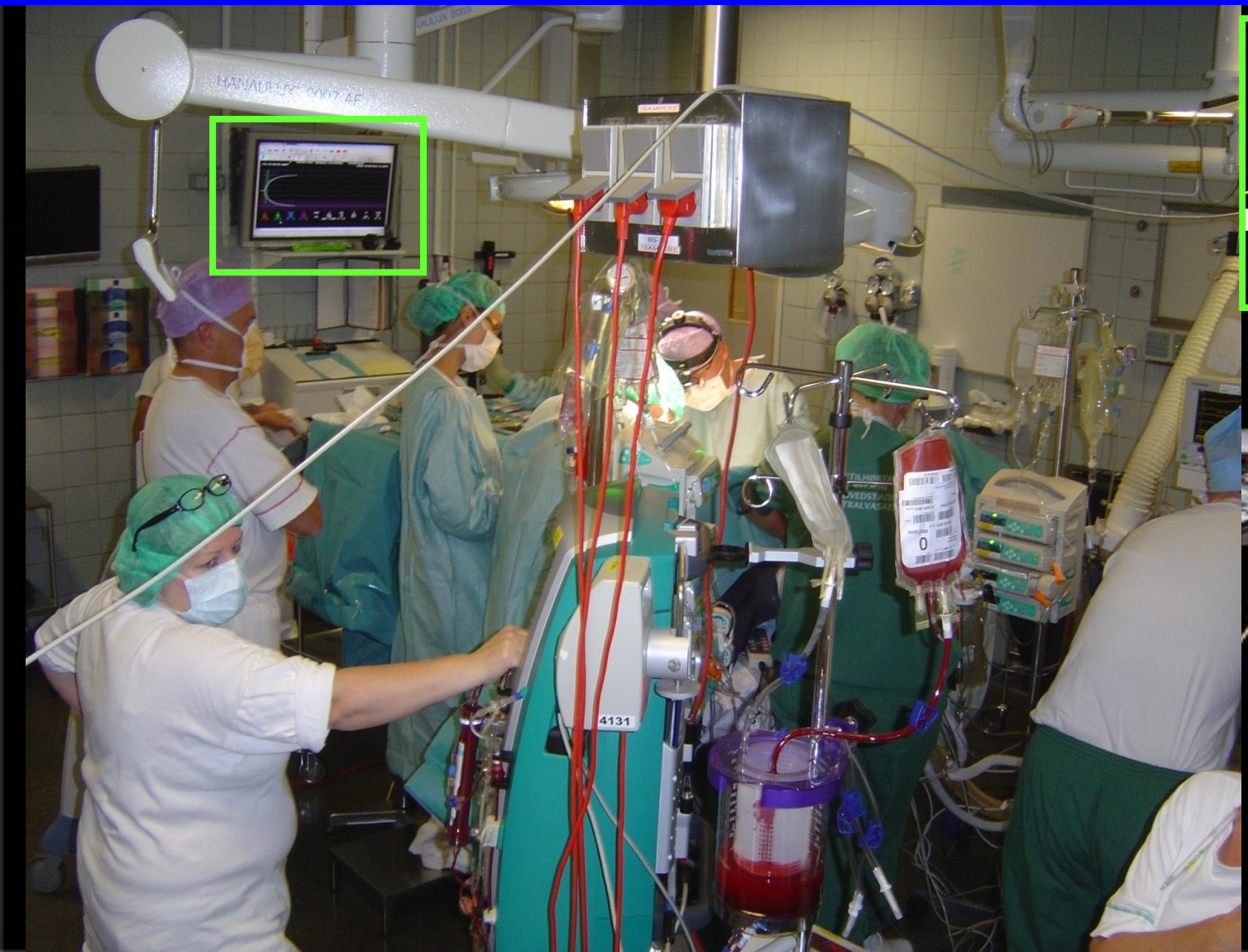
clinicaltrials.gov NCT01545232

Beyond Clotting: The Powers of Platelets

Platelets are known for thwarting blood loss, but new research shows these simplified cells defend against microbes and perform other duties—and they're also drug targets in sepsis and other conditions

The Copenhagen Concept

The Copenhagen Concept



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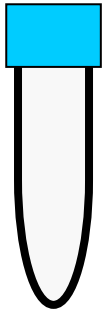
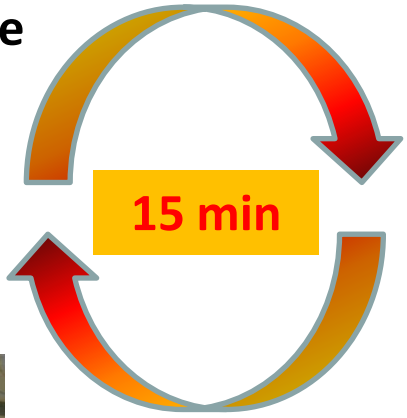
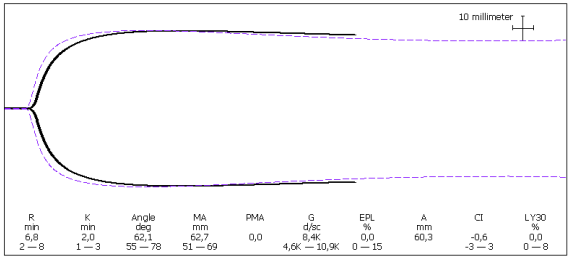
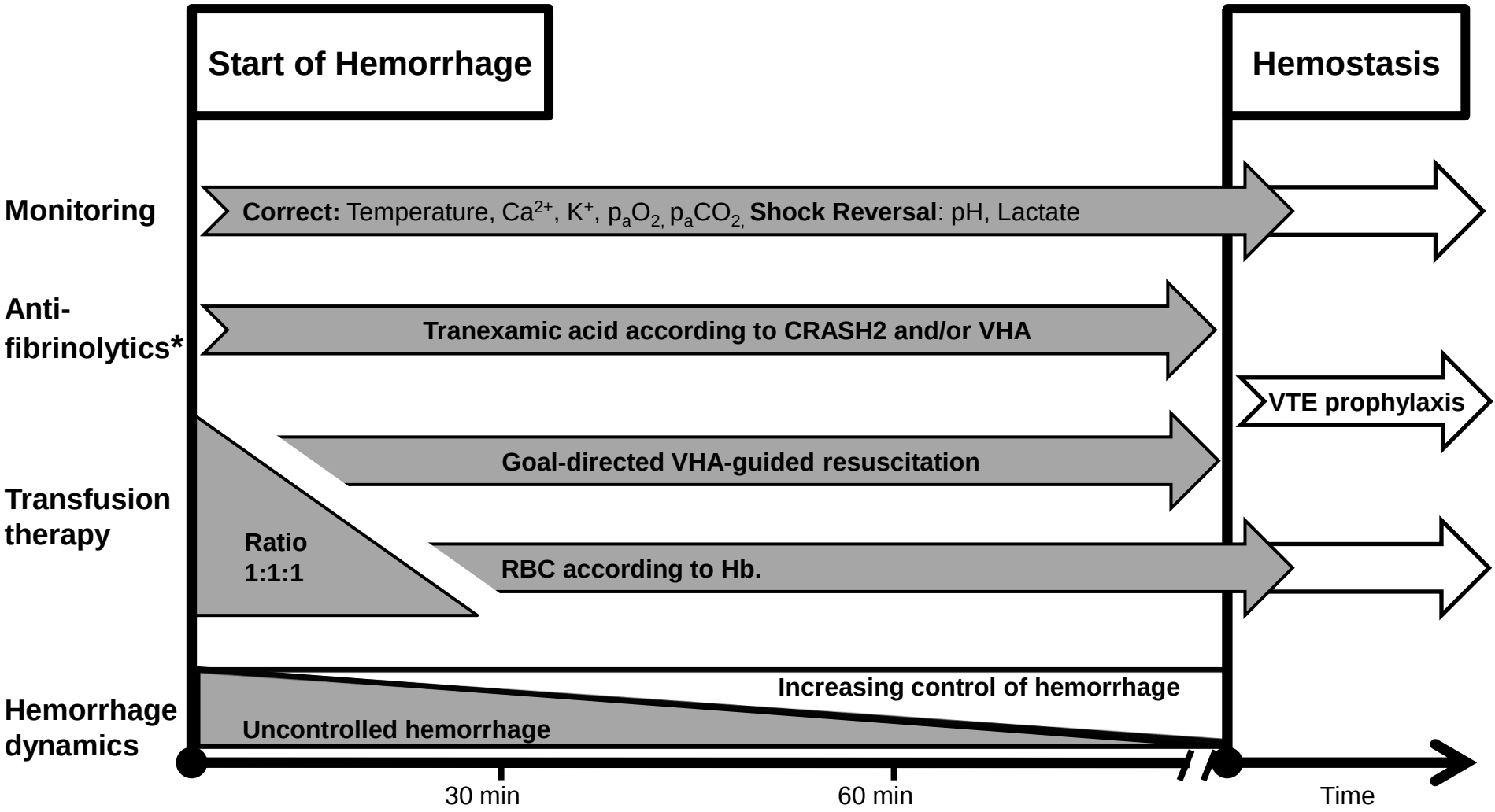


Citrate





The Copenhagen Concept



Johansson, Stensballe et al. Blood. In press 2014

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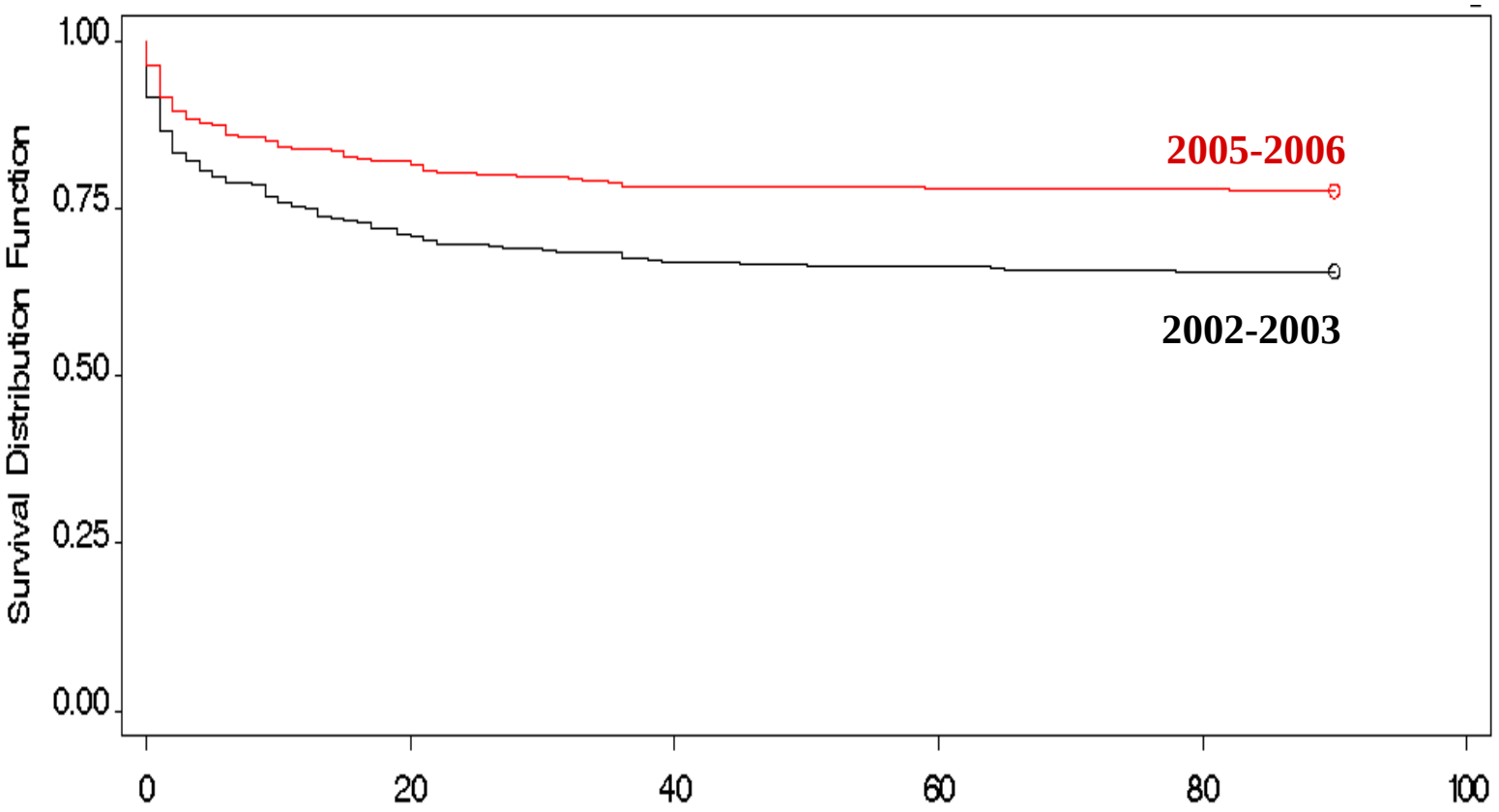
Effect of Haemostatic Control Resuscitation on mortality in massively bleeding patients: a before and after study

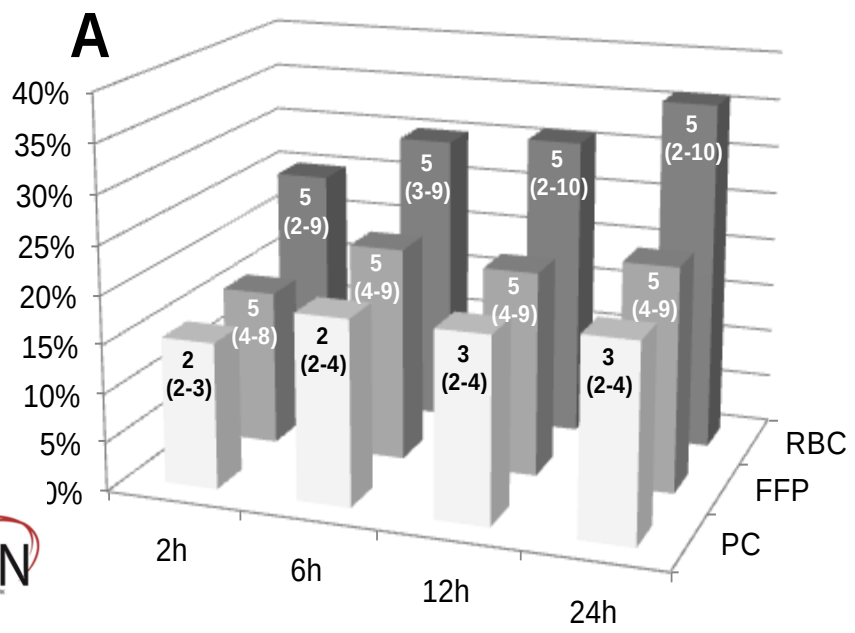
P. I. Johansson & J. Stensballe[1,2]

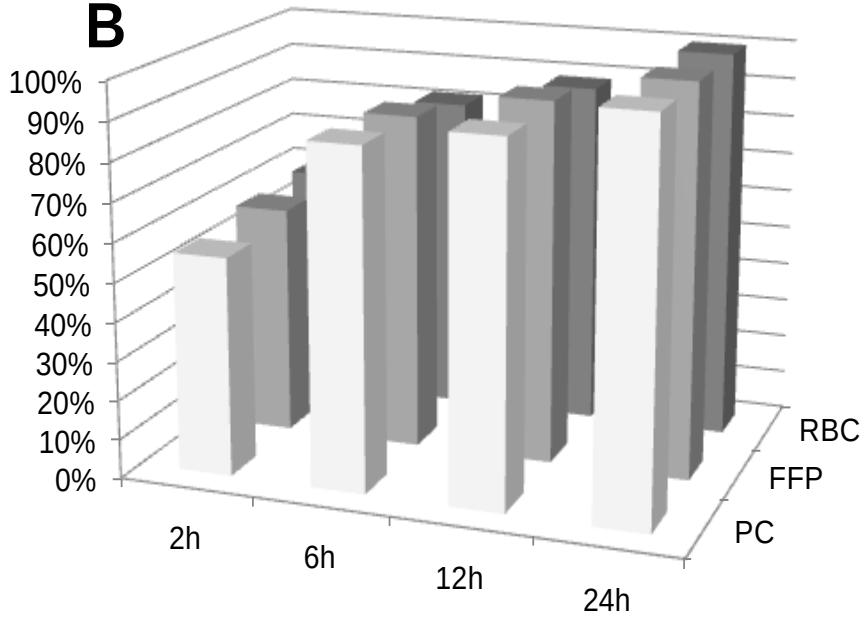


Johansson et Stensballe. Vox Sang 2009

The Copenhagen Concept

ACIT3: 2010-11: 182 trauma patients in Copenhagen





Haemorrhagic mortality < 15% in severely injured trauma patients

Johansson, Stensballe et al. Transfusion 2013

None

Moderate

Life-threatening

Bleeding…

Monitor & plan

Final remarks

- Blood component therapy
  - Be restrictive in the most'
  - Be liberal in the few with life-threatening bleeding

- Monitor the clot – use TEG®/ROTEM®
  - Goal directed resuscitation – give only what is needed

- Haemostatic Control Resuscitation – The Copenhagen Concept
  - Transfusion packages and TEG reduced mortality by >20% in massive bleeding in Copenhagen

- Go talk to your blood banker!