Management of Massive Transfusion

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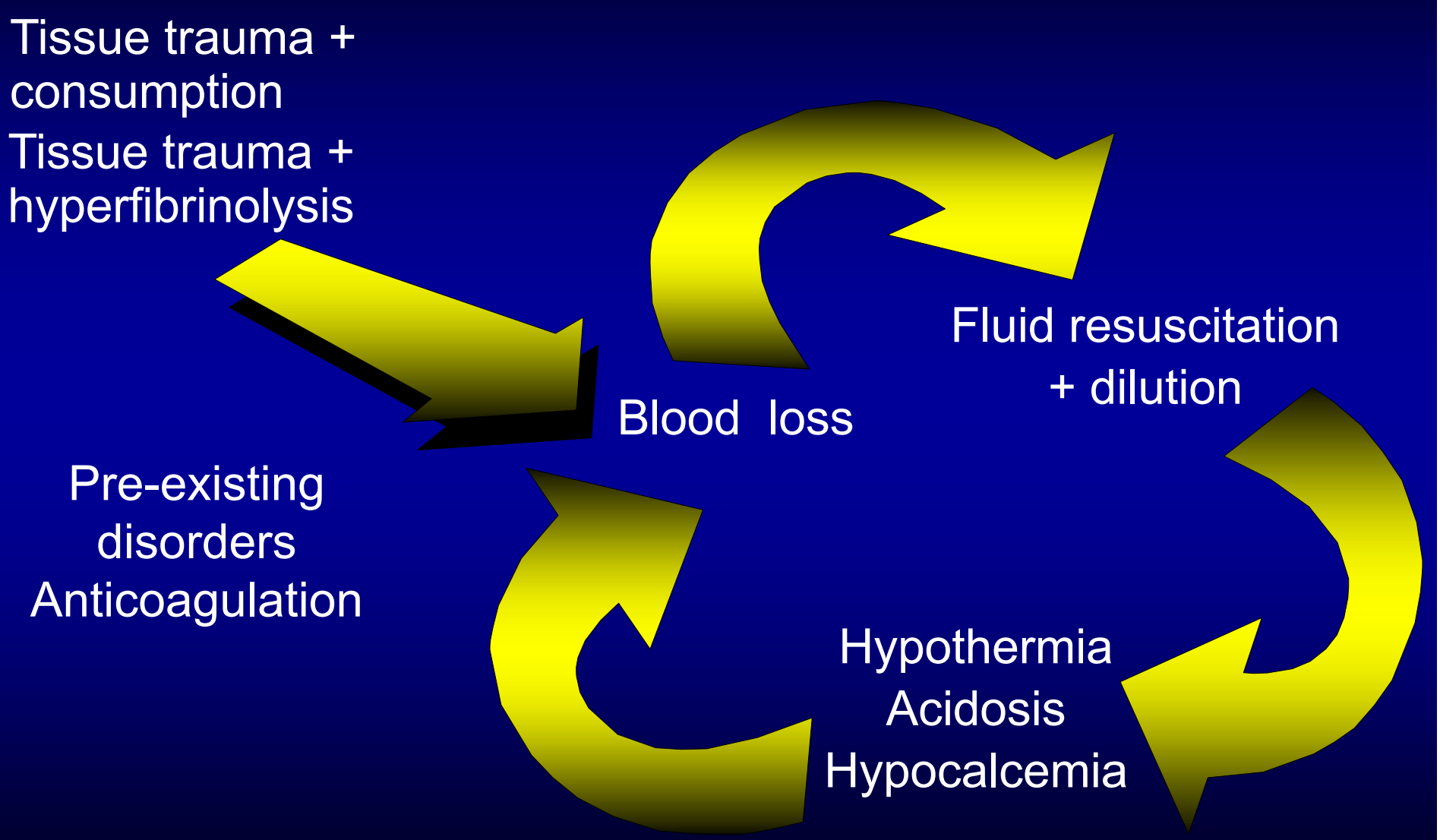
Massive Hemorrhage: definition ?

- ✓ Replacement of one blood mass in less than 24 hours
- ✓ Dynamic definition more relevant in the acute clinical setting:
  - Transfusion of four or more red cell concentrates within one hour when ongoing need is foreseeable
  - Replacement of 50 % of the total blood volume within 3 hours

Coagulopathy in Massive Transfusion



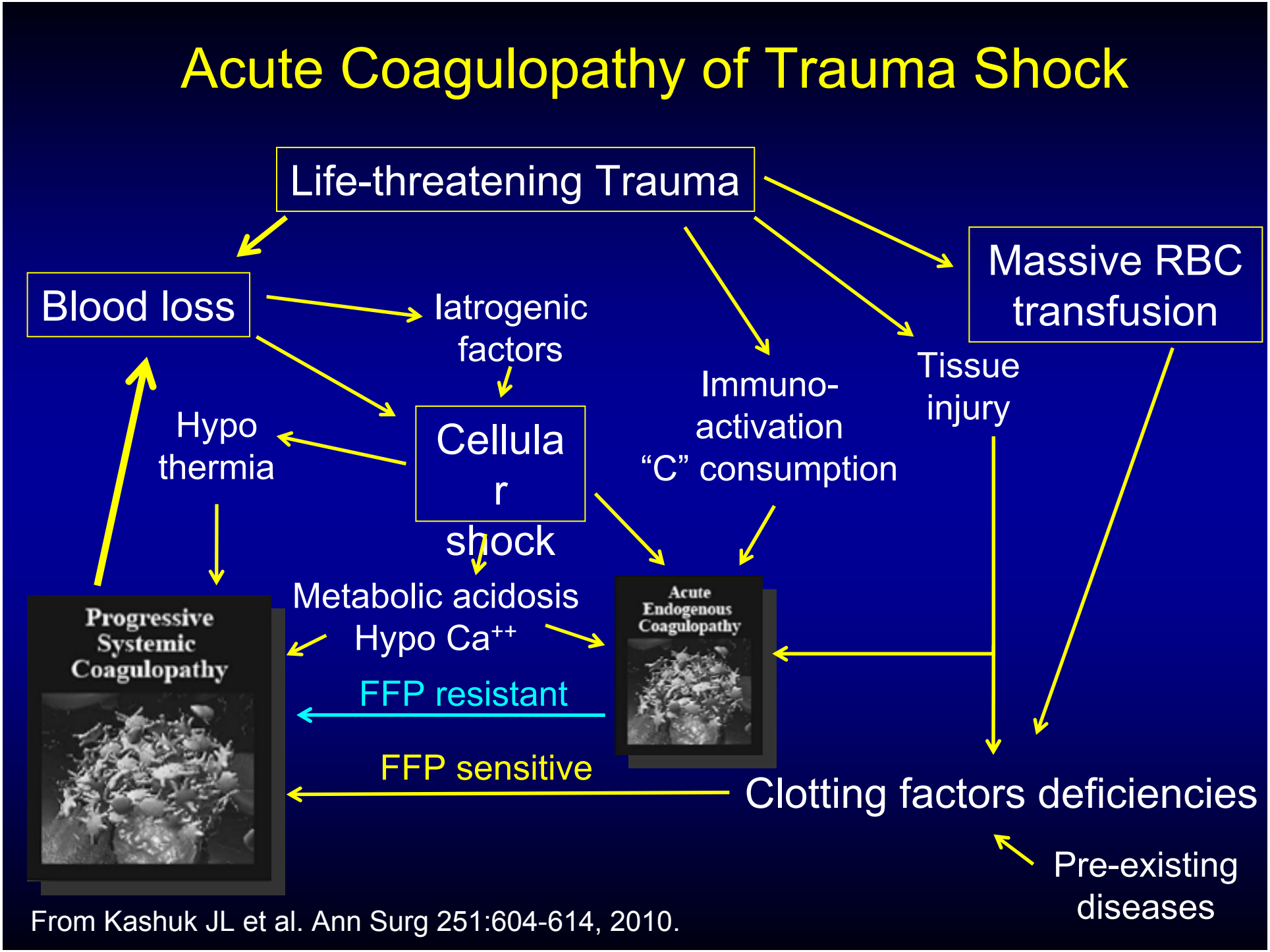
From Kozek-Langenecker S. Minerva Anesthesiol 73:401-15, 2007.

Acute Coagulopathy of Trauma (Endogenous Coagulopathy)

- ✓ Coagulopathy may exist very early after injury, without significant fluid administration, clotting factor depletion or hypothermia:
  - ✓ Present in 1/4 to1/3 of severe traumatized patients
  - ✓ Increased risk of morbidity and mortality
- ✓ Risk factors
  - ✓ Injury severity
  - ✓ Shock with hypoperfusion

From Frith D and Brohi K. The Surgeon 8:159-163, 2010.

Acute Coagulopathy of Trauma Shock



From Kashuk JL et al. Ann Surg 251:604-614, 2010.

Acute Coagulopathy of Trauma (Endogenous Coagulopathy)

- ✓ Rather than being a consumptive coagulopathy, it is due to systemic anticoagulation and hyperfibrinolysis
- ✓ Mechanisms?
  - ✓ Hypoperfusion-related ↑ in plasma soluble thrombomodulin
  - ✓ Activation of protein C which consumes plasminogen activator inhibitor (PAI-1)

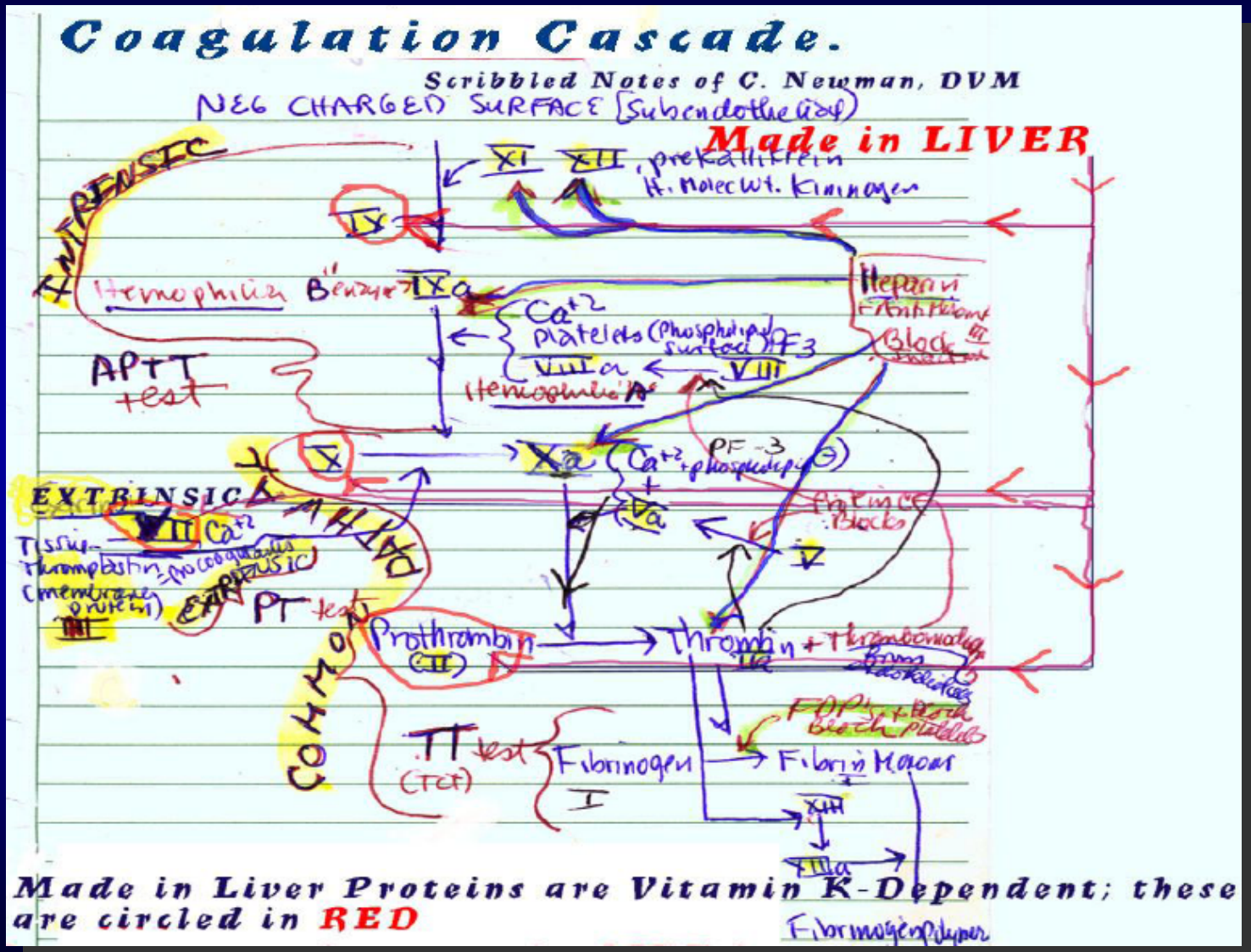
From Frith D and Brohi K. The Surgeon 8:159-163, 2010.

Massive Transfusion During Elective Surgery or Major Trauma

	Elective Surgery	Major Trauma
Tissue trauma	Controlled	Uncontrolled
Initiation of MT	No delay	Variable
Volume status	Normovolemia	Hypovolemia
Temperature	Normothermia	Hypothermia
Hemostasis monitoring	Ongoing	Late
Coagulopathy	↓ factors	Complex

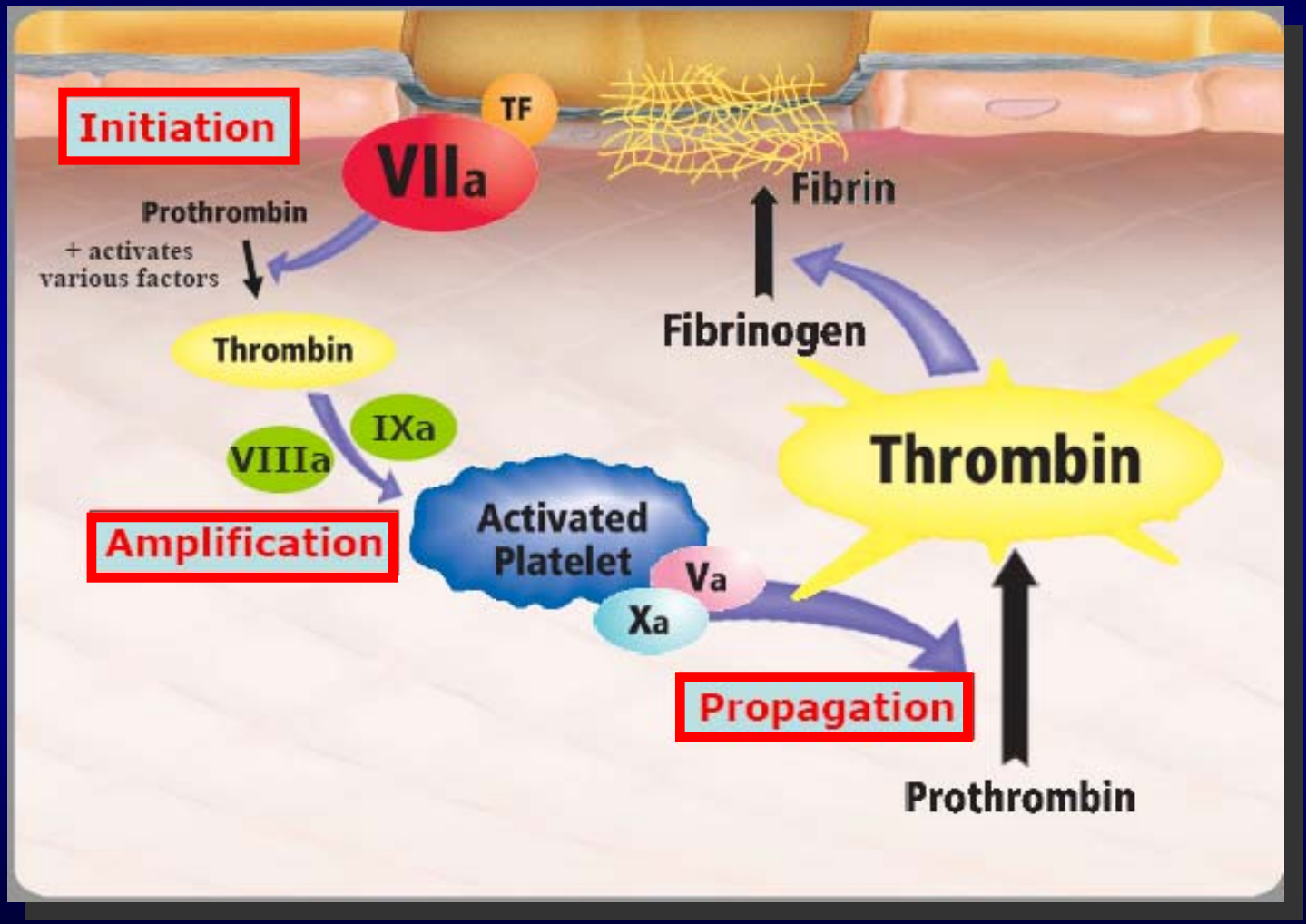
From Hardy JF et al. Can J Anesth 53:S40-S58, 2006.

The « Old Classic » View of Coagulation



From Moresco M. University di Roma via Internet.

The « Cell-based» Model of Coagulation



From Hoffman M& Munroe DM. Thromb Haemost 85:958-965, 2001.

Rossaint et al. Critical Care 2010, 14:R52
http://ccforum.com/content/14/2/R52

CRITICAL CARE

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Management of bleeding following major trauma: an updated European guideline

Rolf Rossaint[1], Bertil Bouillon[2], Vladimir Cerny[3], Timothy J Coats[4], Jacques Duranteau[5], Enrique Fernández-Mondéjar[6], Beverley J Hunt[7], Radko Komadina[8], Giuseppe Nardi[9], Edmund Neugebauer[10], Yves Ozier[11], Louis Riddez[12], Arthur Schultz[13], Philip F Stahel[14], Jean-Louis Vincent[15], Donat R Spahn[16*]

Optimal Hematocrit For Hemostasis

- ✓ Hematocrit correlates with bleeding time…
  …Bleeding time does not correlate with perioperative blood losses

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Management of bleeding following major trauma: an updated European guideline

Rossaint *et al. Critical Care* 2010, **14**:R52
http://ccforum.com/content/14/2/R52

V. Management of bleeding and coagulation

Erythrocytes

Recommendation 21 We recommend a target haemoglobin (Hb) of 7 to 9 g/dl (Grade 1C).

Red Blood Cell and Hemostasis

- Mechanical effect
  - Margination of the platelets to the periphery of the vessels
- Biological effects
  - Platelet activation through the release of intracellular ADP

    Santos MT et al. J Clin Invest 87:571-580, 1991.
  - Thrombin generation through exposure of procoagulant phospholipids on their outer surface

    Peyrou V et al. Thromb Haemost 81:400-406, 1999.

Strategies for Blood Component Replacement: FFP

- ✓ Contains factors allowing the conversion of prothrombin in thrombin
- ✓ Rapid decrease in FV and FVIII upon FFP thawing
- ✓ Exact dosing and timing ?
  - ✓ Within 6 hours postinjury
  - ✓ High dose: traditionally 10-15 ml/kg: much higher?

Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients

	10-15 mL/kg N=10	30 mL/kg N=12
Fibrinogene g/L	+0.4	+1.0
II %	+16	+41
V %	+10	+28
VII %	+11	+38
IX %	+8	+28
X %	+15	+37
XI %	+9	+23
XII %	+30	+44

From Chowdhury P et al. Br J Haematol 2004;125:69-73, 2004.

Clinical review: Fresh frozen plasma in massive bleedings - more questions than answers

Adoption of early formula-driven hemostatic resuscitation in trauma (FFP:RBC ratio 1:1): pros & cons

	Pros	Cons
Mortality	Retrospective studies suggesting a reduction in mortality from exsanguination	Data limited by survivorship bias
		Increase in FFP and platelet use might increase the risk of acute lung injury, multiple organ failure, thrombosis, sepsis and death
Coagulopathy	Prevention and treatment of coagulopathy due to transfusion of clotting factors	Difficult to identify patients early on who will develop coagulopathy and in fact need transfusion of FFP and platelets
	Minimize crystalloid use (decrease the risk of dilution)	Uncertainty about the ideal dose of FFP in the trauma situation
Laboratory tests	No need for coagulation tests	Unnecessary exposure to AB plasma (in some countries, a higher risk of transfusion-related acute lung injury due to higher proportion of female donors)
	Avoid the delay of waiting for blood test results	
Blood bank systems	More timely issuing of blood components	The waste of FFP will increase (shortage of AB plasma)
	No time needed to thaw FFP (AB plasma available at all times)	May increase the complications associated with FFP and platelet transfusion
	Decrease the need for communication between blood bank and the medical team	

From Nascimeto B et al. Crit Care 14:202, 2010.

Strategies for Blood Component Replacement: Platelets

- ✓ Apheresis platelets may contain some plasma, although clotting factors decrease rapidly due to storage temperature
- ✓Platelet number ≠ platelet function
- ✓ No direct evidence to support an absolute trigger for platelet transfusion in trauma (50 – 100 $10^3/mm^3$?)
- ✓ One “Cup” (≈8 units containing each 0.5 10^{11} platelets) may increase platelet count by 30-50 10^3 $/mm^3$

Strategies for Blood Component Replacement: Fibrinogen

- ✓ Actual guidelines: replacement threshold for plasma fibrinogen levels < 150 - 200 mg/dl using either fibrinogen concentrate (3-4 g) or cryoprecipitate (contains FVIII, FXIII, vWF and fibrinogen) (50 mg/kg)
- ✓ More aggressive administration when using ROTEM (cf. german approach)

Cost of 1 g fibrinogen ? 307,94 € (not reimbursed)

Efficacy & Safety of Fibrinogen Concentrate Substitution in Adults

- ✓ Systematic literature search 1985-2010
- ✓4 studies: 2 randomized & 2 non-randomized (total: N=74)
- ✓Fibrinogen:
  - ↑ clot firmness
  - ↓ use of blood products
  - ↓ postop bleeding and drainage
  - Safe with regard to thrombo-embolic complications and mortality

"However, because all studies identified were of inadequate quality, these results need to be confirmed by randomized controlled trials of sufficient size and long term follow-up"

From Warmuth M et al. Acta Anaesthesiol Scand 56:539-48, 2012.

Strategies for Blood Component Replacement: Prothrombin Complex Concentrates

- ✓ Contains vit K-dependent factors (II, VII, IX and X), + anticoagulants (protein C and protein S)
- ✓Usefulness in posttraumatic coagulopathy?

Use of rVIIa for Treatment of Hemorrhage

- ✓ RCTs concerning different bleeding conditions: N=17
- ✓ Significant reduction in transfusion requirements and/or blood loss observed in 3 pilot studies not confirmed in large randomized trials
- ✓ No difference in thromboembolic complications

Little evidence to support routine use of rVIIa for patients with massive bleeding

From Johansson PI. Vox Sang Apr 23, 2008.

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Activated recombinant coagulation factor VII

Recommendation 28 We suggest that the use of recombinant activated coagulation factor VII (rFVIIa) be considered if major bleeding in blunt trauma persists despite standard attempts to control bleeding and best-practice use of blood components (Grade 2C).

- ✓Hct > 24% -Plts > 50.000/mm^3 - Fibrinogen > 0.5 – 1.0 g/L
- ✓pH > 7.20 – Temp > 32°C- Ca++ > 0.8 mmol/L

Monitoring of Hemostasis During Massive Transfusion

- Preoperative evaluation and preparation
- Clinical evaluation: visual assessment of the surgical field, blood loss measurements, communication with the surgeons…
  - Caution with epistaxis, blood issued from tracheal or gastric tubes, hematomas after venous puncture, hematuria?

Clinical judgment alone is insufficient as an indication for transfusion

Monitoring of Hemostasis During Massive Transfusion: PT (INR) & aPTT

Developed to monitor hemophilia & anticoagulation therapy (50 years ago)

Predictors of mortality in trauma

MacLeod JB et al. J trauma 55:39-44, 2003.

Not validated to predict hemorrhage in a clinical setting : plasma-based assays reflect only the small amount of thrombin formed during initiation of coagulation

al JB et al. Transfusion 45:1413-25, 2005.

Monitoring of Hemostasis During Massive Transfusion: PT (INR) & aPTT

igh sensitivity, low specificy

arked prolongations (1.5 to 1.8 x control)

- Predict factor V and VIII < 30%
- Correlates with microvascular bleeding

From blood sampling to results: 30 min to…?

Monitoring of Hemostasis During Massive Transfusion

Platelet count

- Readily available via automated counters
- Must be interpreted in the clinical situation:
  - Hypothermia?
  - Expected platelet function?
  - Hemoglobin concentration?
  - Fibrinogen concentration?
  - DIC?

Low platelet count ≠ platelet transfusion

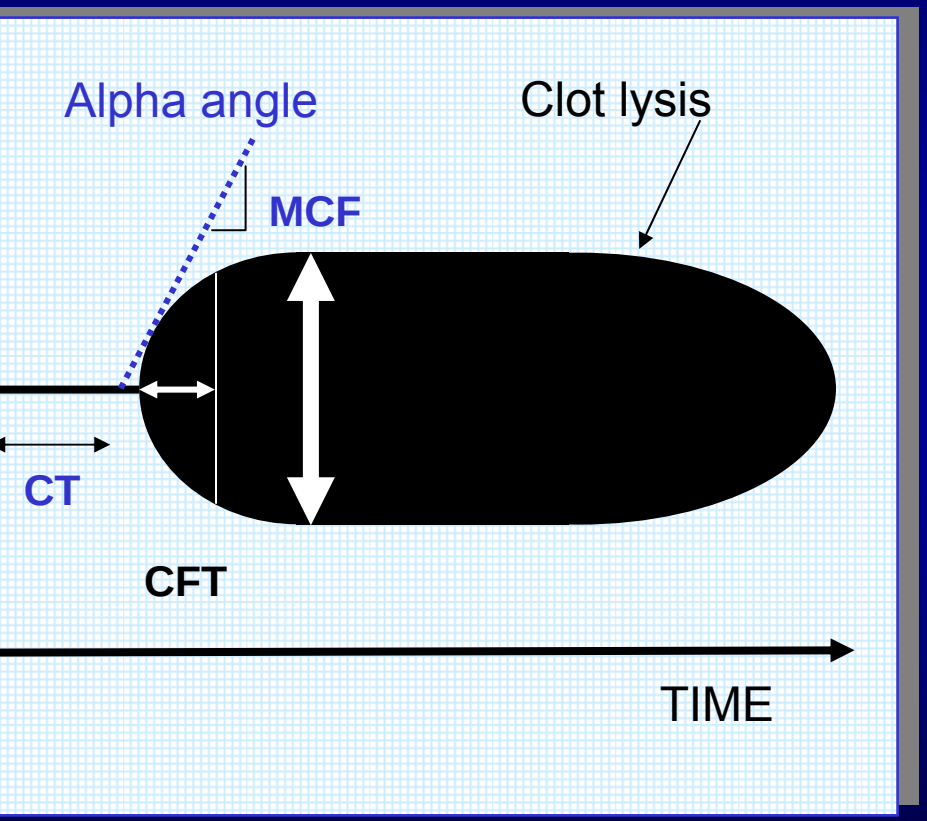
Monitoring of Hemostasis During Massive Transfusion

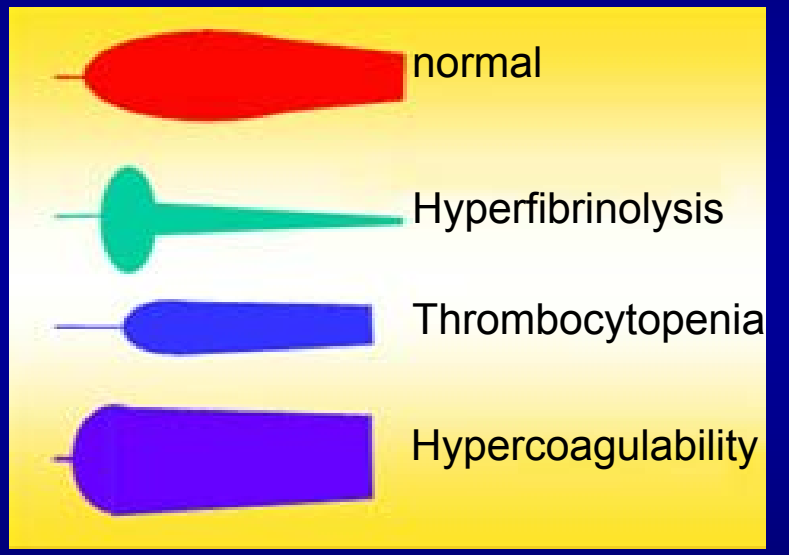
TEG (thromboelastography) & ROTEM (rotational thromboelastometry):

- Measure the viscoelastic properties of non-anticoagulated or anticoagulated blood after induction of clotting under low shear conditions
  - Reaction and coagulation time
  - Clotting time
  - Stability and firmness of the clot (MA & MCF)
  - Fibrinolysis

Monitoring of Hemostasis During Massive Transfusion

TEG & ROTEM





Monitoring of Hemostasis During Massive Transfusion

TEG & ROTEM: advantages

- Informative test results (Chowdhury P et al. Br J Haematol 2004.)
  → differentiation of the pathomechanisms of bleeding
- Predictor of bleeding (Kaufmann et al. J Trauma 1997)
- Detection of hyperfibrinolysis, hypercoagulability
- Fast sample reading time
- Reductions in transfusions

Avidan MS et al. Br J Anaesth 2004; Royston D et al. Br J Anaesth 2001;Shore-Lesserson L et al. Anesth Analg 1999; Nuttall GA et al. Anesthesiology 2001; Spiess BD et al. J Cardiothorac Vasc Anesth 1995; Kang Y. Liver Trans surg

Monitoring of Hemostasis During Massive Transfusion

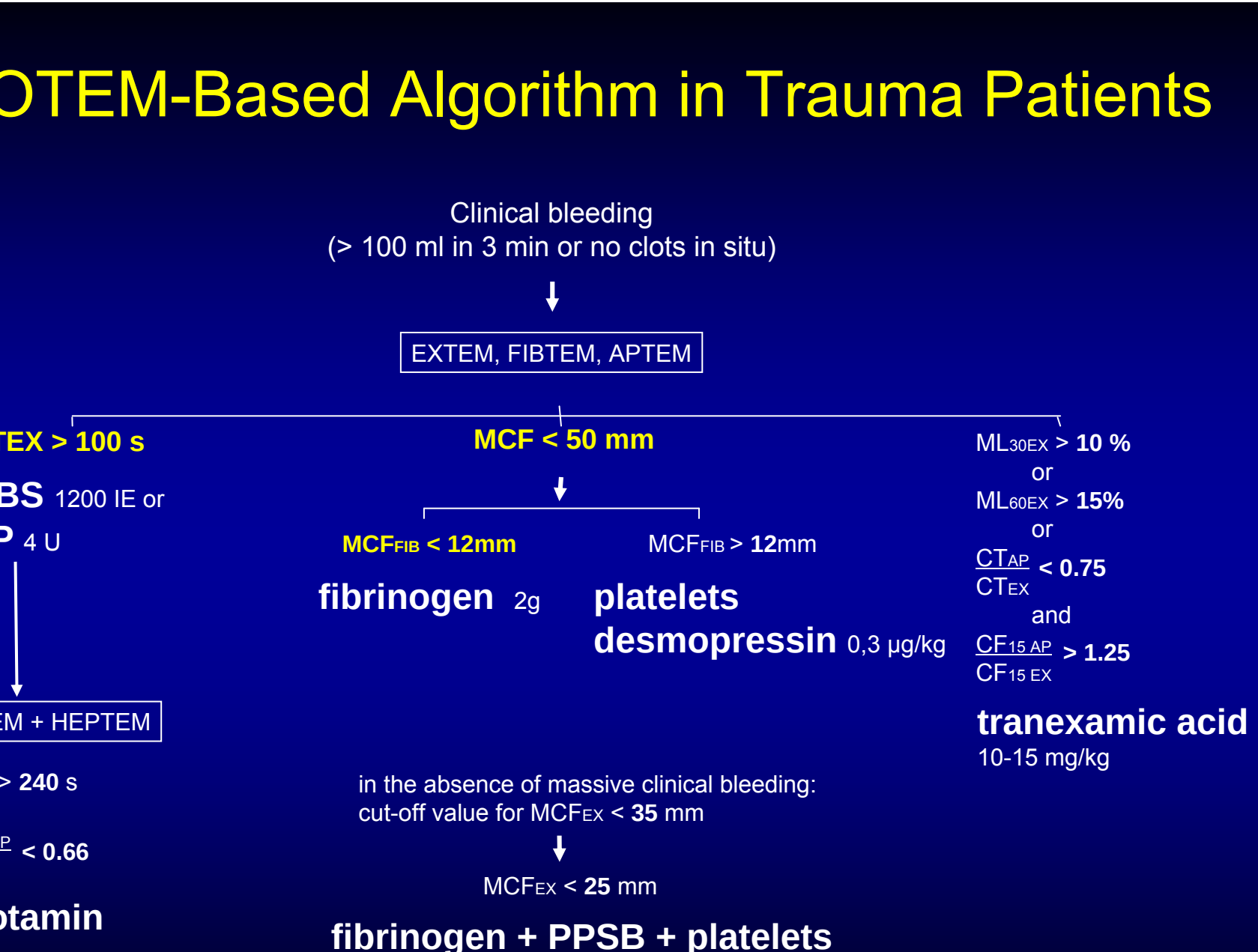
TEG & ROTEM: limitations

- Easy of use ?
- Costs ?
- Platelet disorders (cf. Von Willebrand Σ) ?
- Antiplatelet therapies
- Moderate correlation with routine coagulation tests

  Preanalytic preparations, test medium, validation (CV < 5% MCF, CT)

Lang et al. Blood Coagul Fibrinolysis 2005

OTEM-Based Algorithm in Trauma Patients



Monitoring of Hemostasis During Massive Transfusion

Platelet function tests

- Static tests (b-thromboglobulin measurement)
- Dynamic test (bleeding time)
- Tests of platelet response to agonists
  - Hemostatus (Medtronic; PAF, ACT)
  - Rapid Platelet Function analyser (Ultegra, Accumetrics; TRAP)
  - Clot Signature Analyzer (Xylum; collagen, flow)
  - PlateletWorks (ICHOR, Helena Bio Science; collagen, ADP, counts)
  - Hemodyne Platelet Analysis System (retraction)
  - Cone and Plate Analyser (Impact, Diamed; shear, imaging)
- Flow cytometry

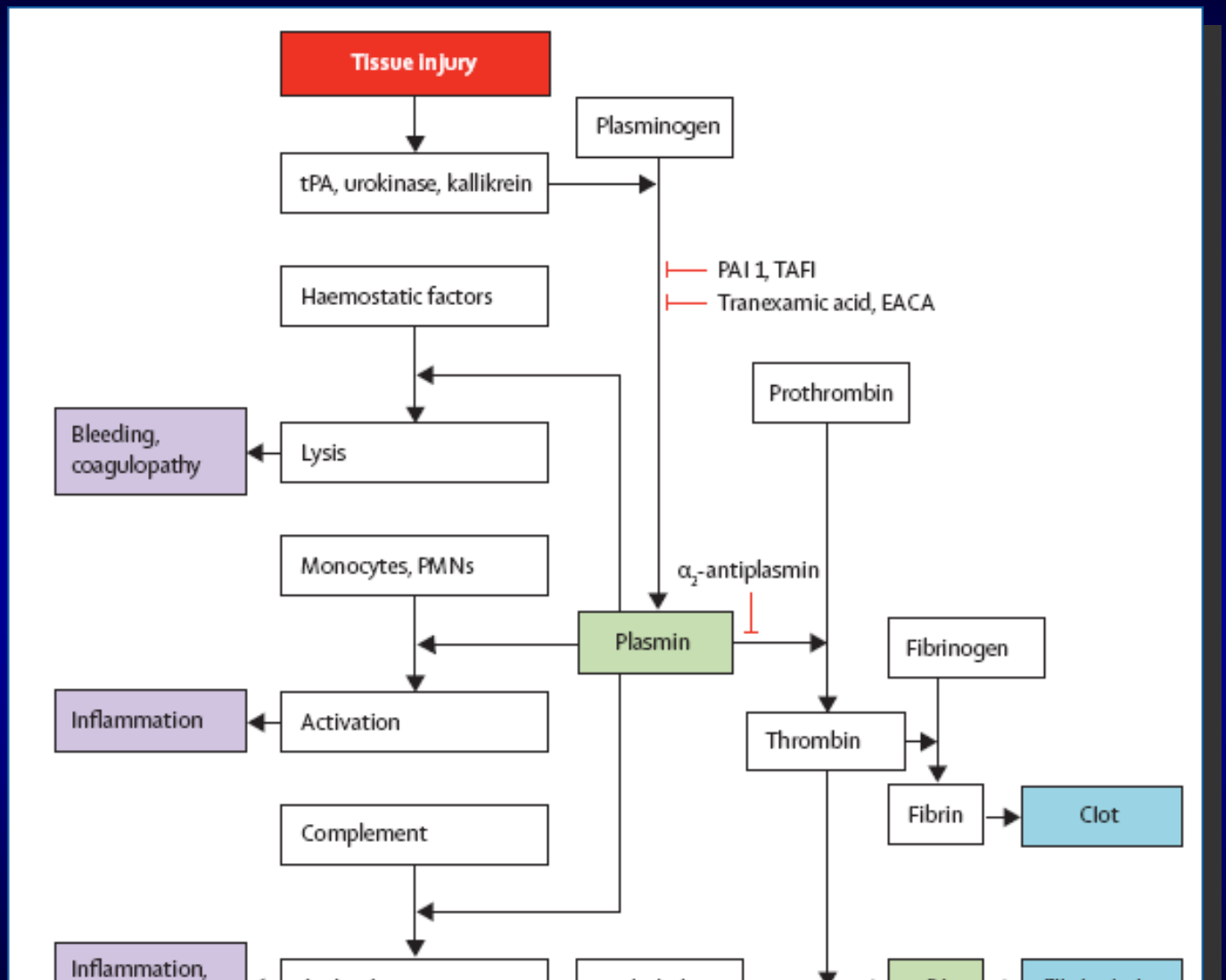
Clinical usefulness ?

Monitoring of Hemostasis During Massive Transfusion

When ?

- After admission to the Trauma Unit or at baseline of surgery with high risk of bleeding
- When relevant bleeding occurs (overt or not surgically correctable)
- After each blood volume exchange
- After pro-coagulant therapeutic intervention
- Postoperatively to detect hypercoagulability

Tissue Injury & Fibrinolysis



ects of Tranexamic Acid in Trauma Patients With Significant Haemorrhage

ndomized placebo-controlled trial

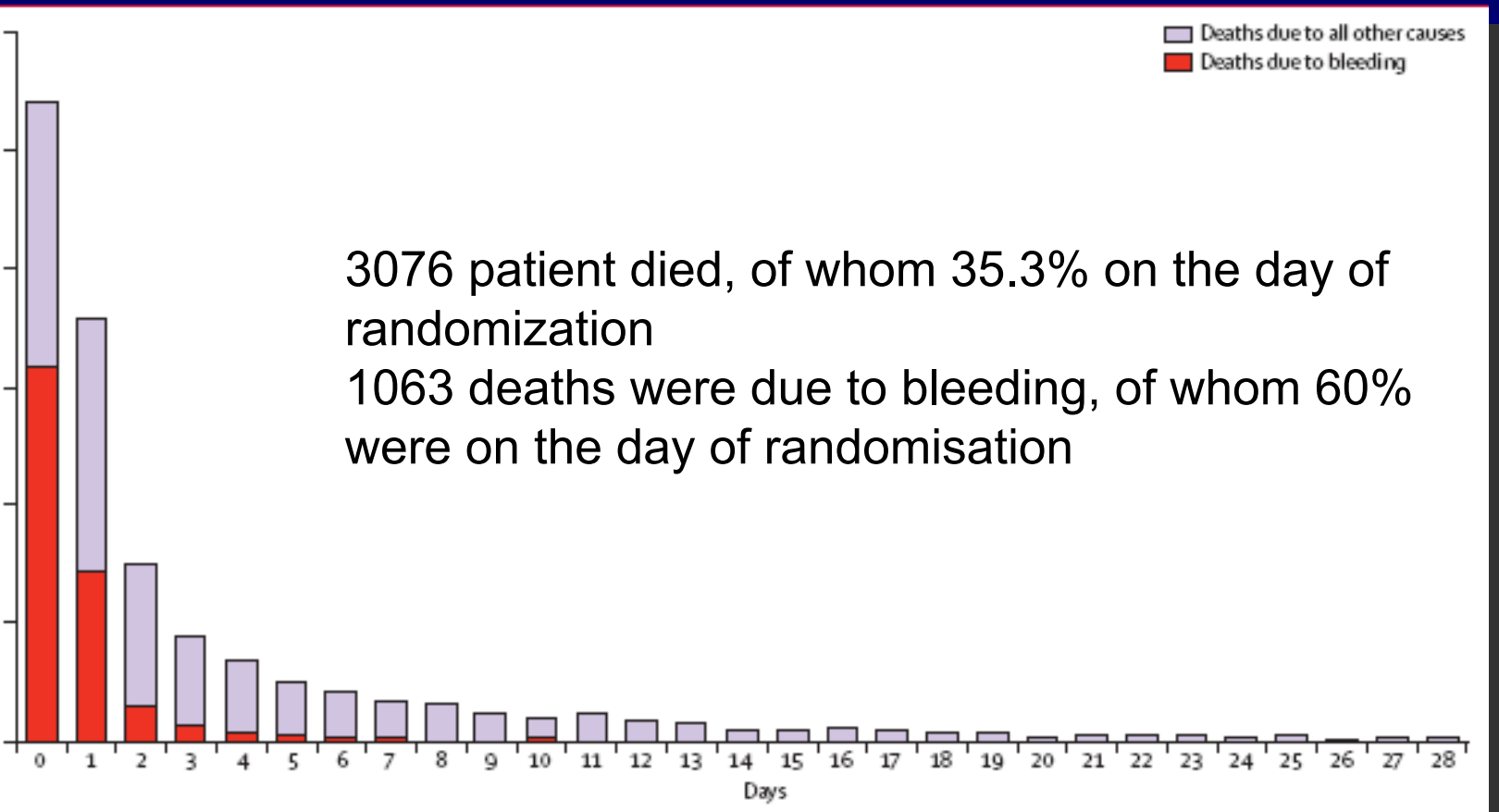
ult trauma patients with or at risk of significant bleeding
n 8h of injury (274 hospitals/40 countries)
Tranexamic acid: 1g over 10 min + infusion of 1g over 8h (N=10060)
Placebo (N=10067)

imary outcome: death in hospital within 4 weeks of injury
Bleeding, vascular occlusion MOF, head injury and other

ects of Tranexamic Acid in Trauma Patients With Significant Haemorrhage

	Tranexamic acid	Placebo
	83.6%	84.0%
years)	34.6 ±14.1	34.5 ± 14.4
since injury (h)	2.8 ± 2.2	2.9 ± 2.6
/penetrating (%)	68/32	68/32
cal intervention (%)	47.9	48.0
lic pressure ≥ 90 mmHg (%)	68.4	67.1
rate > 107/min (%)	48.3	48.0
13-15 (%)	68.7	68.3

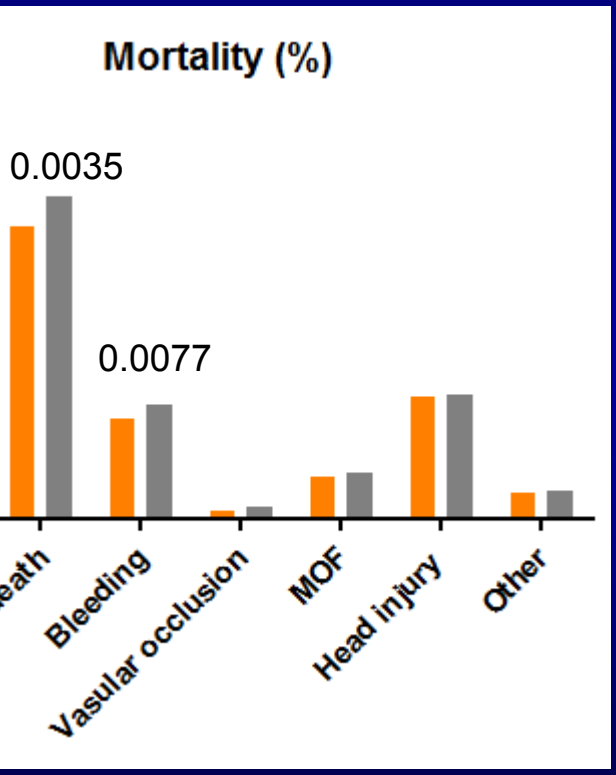
ects of Tranexamic Acid in Trauma Patients With Significant Haemorrhage

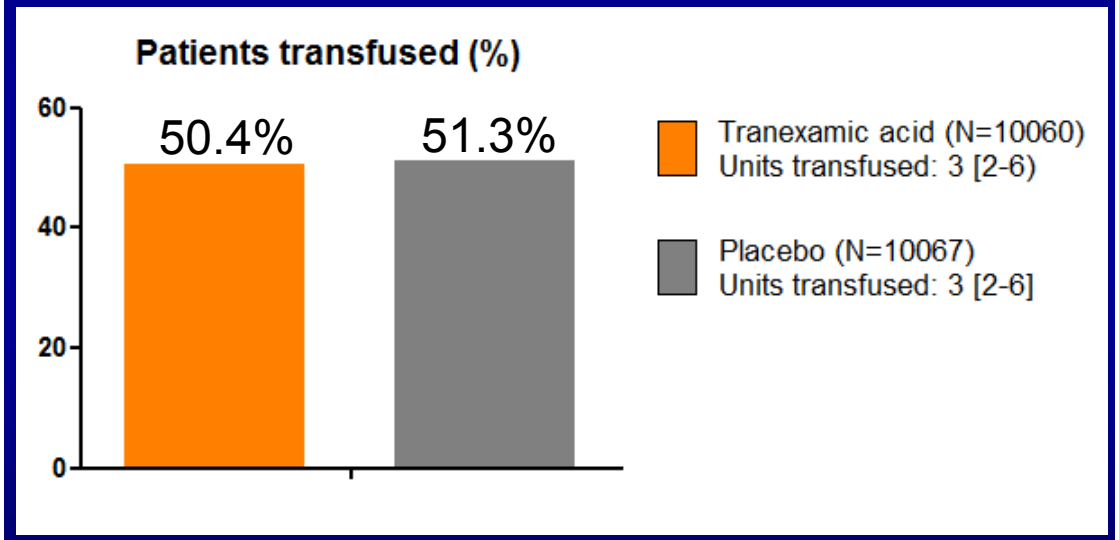


3076 patient died, of whom 35.3% on the day of randomization

1063 deaths were due to bleeding, of whom 60% were on the day of randomisation

ects of Tranexamic Acid in Trauma Patients With Significant Haemorrhage





The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

The CRASH-2 collaborators*

cts of TXA
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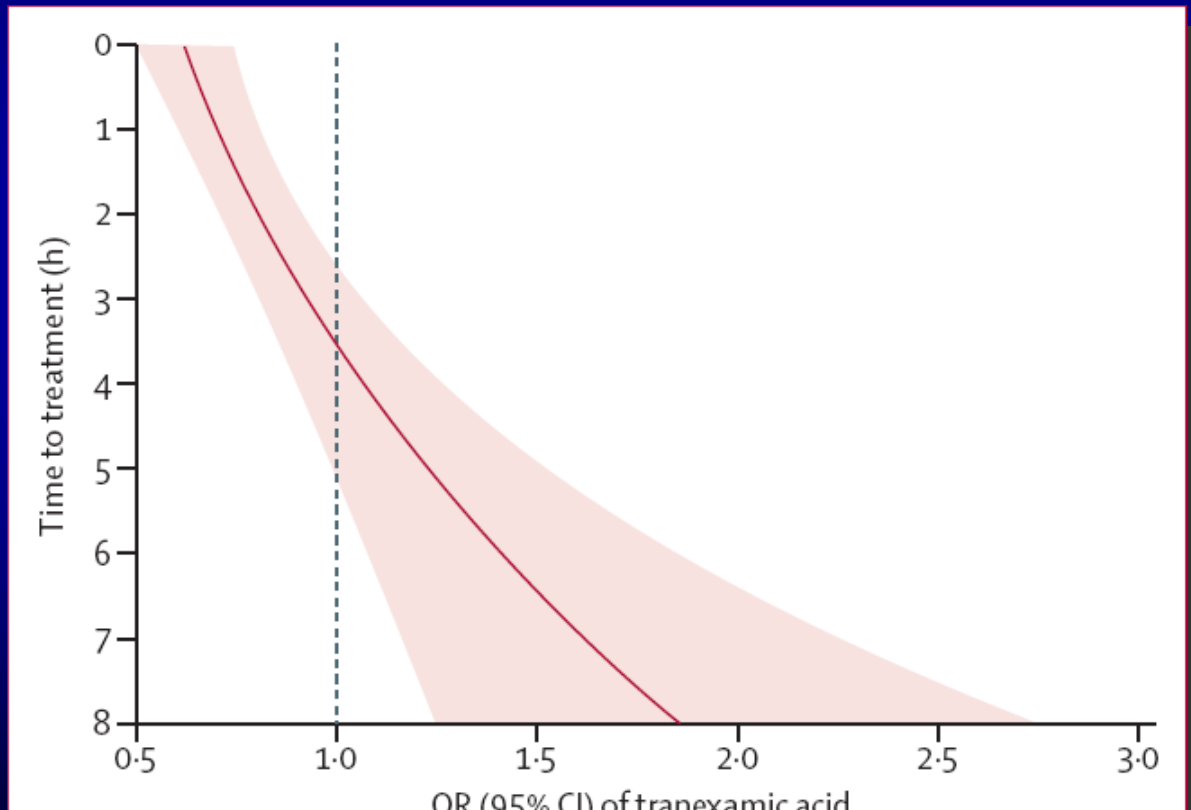
me to treatment



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Antifibrinolytic agents

Recommendation 27 We suggest that antifibrinolytic agents be considered in the bleeding trauma patient (Grade 2C). We recommend monitoring of fibrinolysis in all patients and administration of antifibrinolytic agents in patients with established hyperfibrinolysis (Grade 1B).

TXA: 10-15 mg/kg + 1-5 mg/kg.h

Antifibrinolytic therapy should be guided by thrombelastometric monitoring if possible and stopped once bleeding has been adequately con-

Management of Massive Transfusion: Conclusions (1)

ntification of early post-injury coagulopathy has challenged entional understanding of traumatic coagulopathy

rrent difficulties with obtaining rapid and comprehensive ssments of the hemostatic system means clinicians should ect & empirically treat acute coagulopathy in patients at risk

rly and aggressive use of plasma and other clotting ucts might be associated with improved outcome

Management of Massive Transfusion: Conclusions (2)

ncurrent development and validation of robust point of care
of coagulation should permit a “goal-directed” approach,
ed to individual needs

nfirmation of an intrinsic mechanism in the early post-injury
ulopathy may offer the prospect of a novel pharmaceutical
oach

Thank you very much for your attention