Prise en charge de la transfusion massive en chirurgie programmée et chez le polytraumatisé

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CAN J ANESTH 2006 / 53: 6 / pp S40–S58

Massive transfusion and coagulopathy: pathophysiology and implications for clinical management

[Transfusion massive et coagulopathie-: physiopathologie et implications cliniques]

Jean-François Hardy MD FRCPC, Philippe de Moerloose MD, Charles Marc Samama MD PhD, Members of the Groupe d'Intérêt en Hémostase Périopératoire

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Vox Sanguinis (2005) **89**, 123–127

REVIEW

DOI: 10.1111/j.1423-0410.2005.00678.x

The coagulopathy of massive transfusion

J.-F. Hardy,[1] P. de Moerloose[2] & C. M. Samama[3]

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[2]*Hôpital Universitaire de Genève, Genève, Suisse*
[3]*Centre Hospitalier Universitaire Avicenne, Bobigny, France*

+ importante mise à jour pour l'évolution des connaissances depuis 2006

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Objectives

- To review the pathophysiology of disturbed hemostasis in massively transfused patients in elective surgery and trauma
- Accordingly, to describe the management of massive transfusion in
  - Elective surgery
  - Trauma

Massive transfusion in elective surgery

- Tissue trauma is controlled
- Initiation of transfusion is rapid
- Normovolemia is maintained
- Normothermia is maintained
- Monitoring of hemostasis is ongoing
- Coagulopathy is a late event

Crystalloids and colloids

- Hemodilution ↓ Hb, coagulation factors and platelets
- But rapid hemodilution with crystalloids ↑ coagulation (TEG)
  - Clinical significance remains unclear
- Colloids may affect hemostasis
  - Colloids affect fibrinogen polymerization

Safety of Modern Starches Used During Surgery

Philippe Van Der Linden, MD, PhD,* Michael James, MB ChB, PhD, FRCA, FCA(SA),‡
Michael Mythen, MD FRCA,‡§‖ and Richard B. Weiskopf, MD¶

Various hydroxyethyl starch (HES) preparations have been used for decades to augment blood volume. There has been concern recently regarding possible adverse outcomes when using HES in the intensive care setting, especially in patients with septic shock. However, the pharmacokinetic and pharmacodynamic properties of HES preparations depend on their chemical composition and source material. Thus, different clinical conditions could result in differing effectiveness and safety for these preparations. Consequently, we assessed the safety of tetrastarches when used during surgery, using a formal search, that yielded 59 primary full publications of studies that met a priori inclusion criteria and randomly allocated 4529 patients with 2139 patients treated with tetrastarch compared with 2390 patients treated with a comparator. There were no indications that the use of tetrastarches during surgery induces adverse renal effects as assessed by change or absolute concentrations of serum creatinine or need for renal replacement therapy (39 trials, 3389 patients), increased blood loss (38 trials, 3280 patients), allogeneic erythrocyte transfusion (20 trials, 2151 patients; odds ratio for HES transfusion 0.73 [95% confidence interval = 0.61–0.87], $P = 0.0005$), or increased mortality (odds ratio for HES mortality = 0.51 [0.24–1.05], $P = 0.079$). (Anesth Analg 2013;116:35–48)

N = 59 études au total
N = 4529 patients (2139 HEA 0,4 vs 2390 comparateur)

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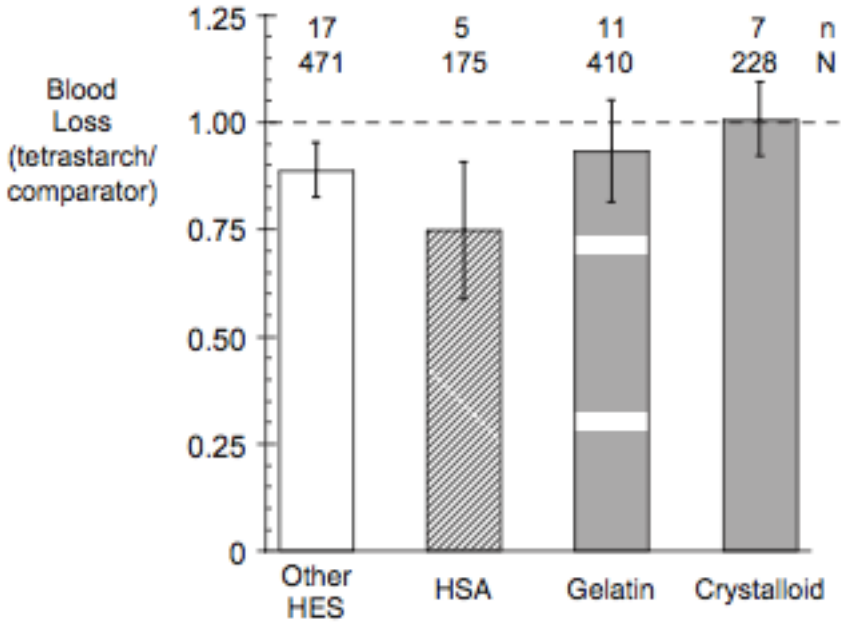
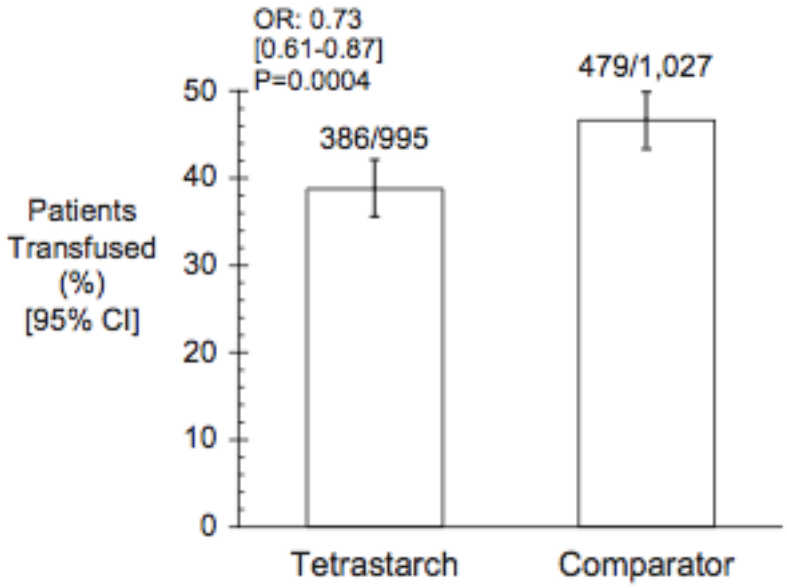
Pas de différence dans les pertes sanguines ni dans les transfusions





n = nombre de publications
N = nombre de patients
HSA = human serum albumin

n = 20 études
N = 2151 patients

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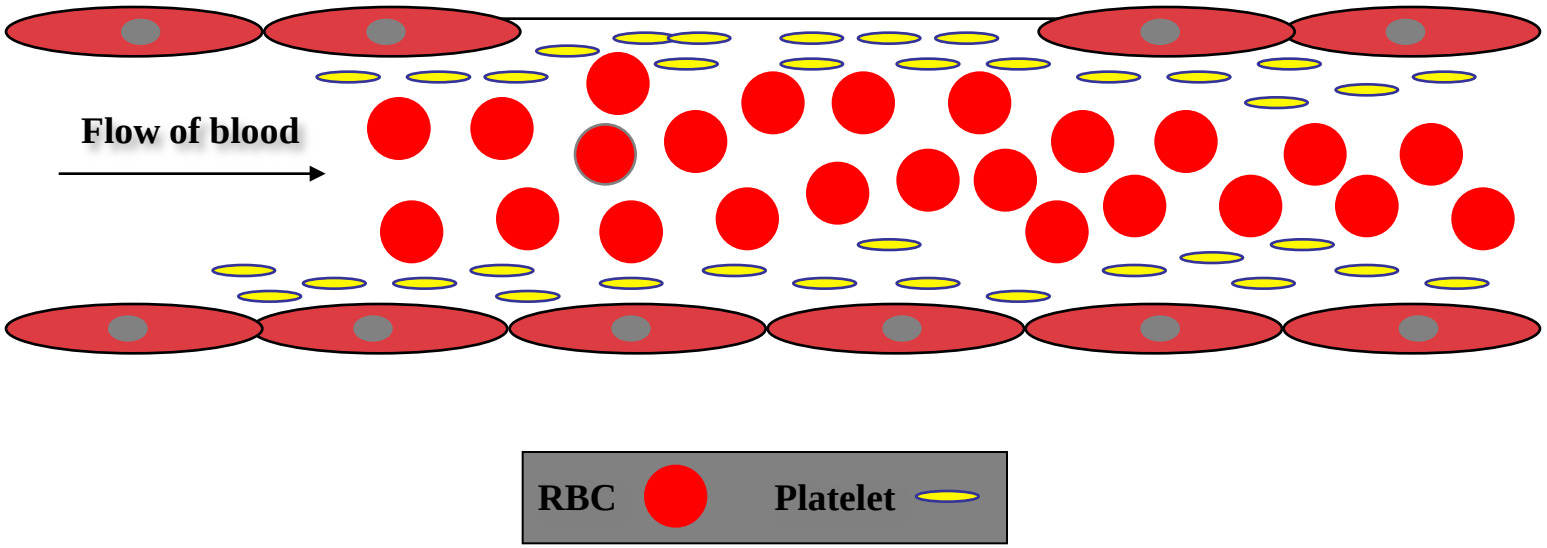
Erythrocytes and hemostasis: Rheological mechanisms

Hematocrit > 30%



Eberst and Berkowitz, Am J Med 1994

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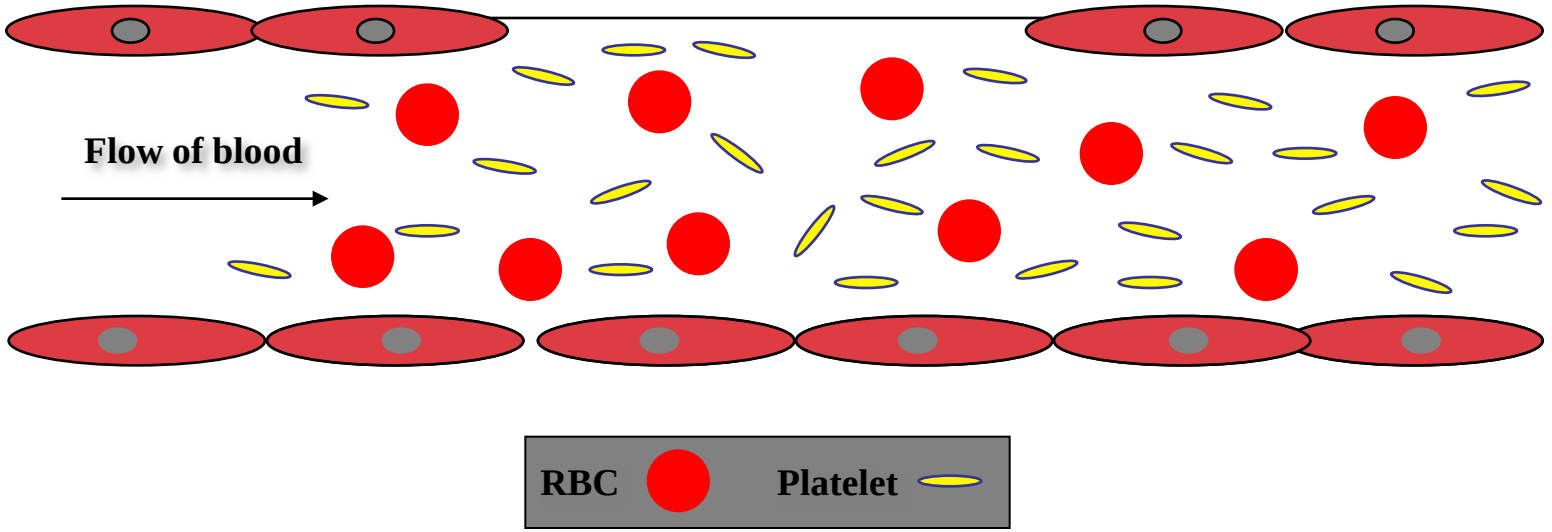
Anemia and hemostasis: ↓ margination of platelets

Hematocrit < 25%



Eberst and Berkowitz, Am J Med 1994

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Optimal hematocrit for hemostasis?

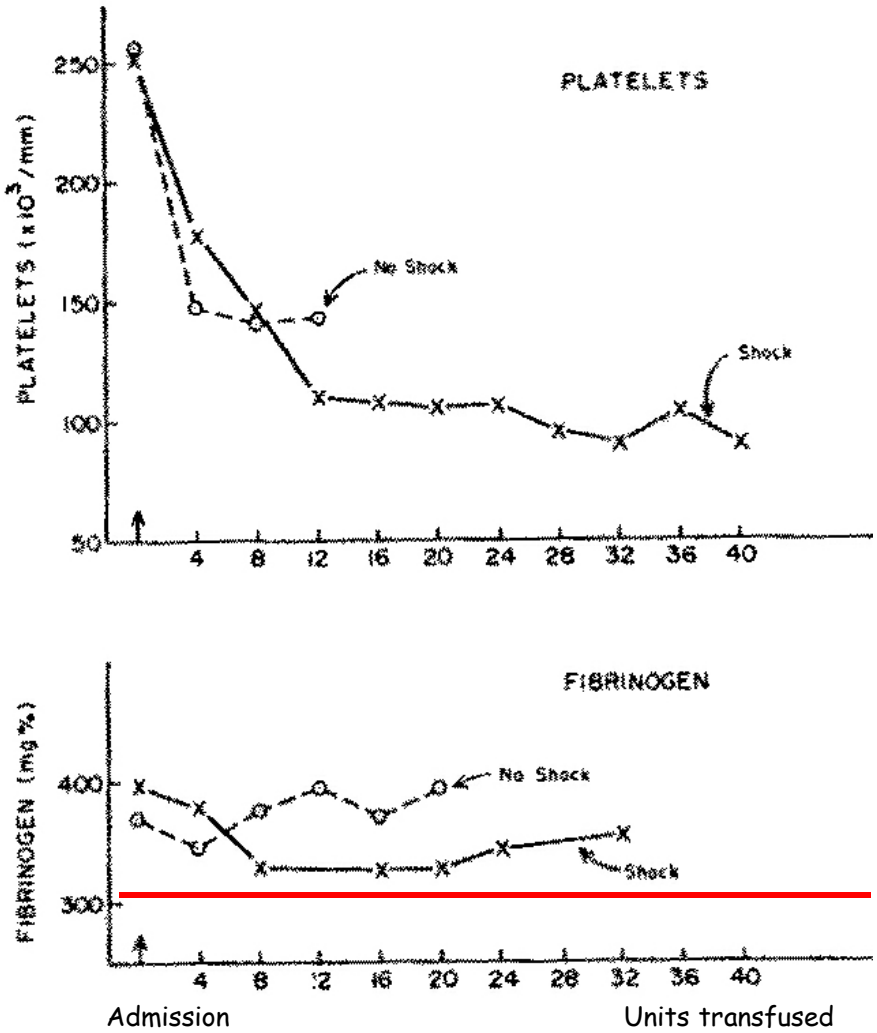
- Hematocrit correlates with the BT
  - In rabbits, BT ↑ when the Hct < 35%
  - In humans, the BT ↑ 60% when HCT ↓ 15%
- UF to ↑ Hct (36-42%) ↓ transfusions in pediatric CPB
- The optimal Hct to sustain hemostasis in the bleeding patient is unknown

Coagulation factors

- Prior to 1990 (approximately)
  - Fresh, stored or modified whole blood
  - Labile coagulation factors not a problem

- Since 1990
  - Use of packed red cells (30-60 mL of plasma)
  - Coagulation factors have become an issue

Coagulation disorders in combat casualties



"During sequential transfusions fibrinogen levels in peripheral blood fell slightly. There was no fall below normal in any patient."

"The mean platelet count remained about 100 G/L after the first 6L of blood."

"No clinical evidence of hemorrhagic diatheses appeared in any of these young men despite large volumes of transfused blood"

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Simmons RL. Ann Surg 1969;169:455-82

Coagulation factors

- Prior to 1990 (approximately)
  - Fresh, stored or modified whole blood
  - Labile coagulation factors not a problem

- Since 1990
  - Use of packed red cells (30-60 mL of plasma)
  - Coagulation factors have become an issue

Hemostatic Factors and Replacement of Major Blood Loss with Plasma-Poor Red Cell Concentrates

Seppo T. Hiippala, MD, Gunnar J. Myllylä, MD, and Elina M. Vahtera, PhD

Department of Anesthesiology, Helsinki University Central Hospital, and Finnish Red Cross Blood Transfusion Service, Helsinki, Finland

Anesth Analg 1995;81:360–5

Université de Montréal

Table 1. Critical Level of Hemostatic Factors and the Inversely Predicted Corresponding Blood Loss (95% Confidence Interval) as Percent of Calculated Blood Volume

Hemostatic factor	Critical level	Blood loss (%)
Platelets	$50 \times 10^3/mm^3$	230 (169–294)
Fibrinogen	1.0 g/L	142 (117–169)
Prothrombin	20	201 (160–244)
Factor V	25	229 (167–300)
Factor VII	20	236 (198–277)

For prothrombin, factor V, and factor VII, the critical level is expressed as percent of normal activity. (Edmunds LH, Salzman EW. Hemostatic problems, transfusion therapy, and cardiopulmonary bypass in surgical patients. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and thrombosis: basic principles and clinical practice. Philadelphia: JB Lippincott, 1994:956–68).

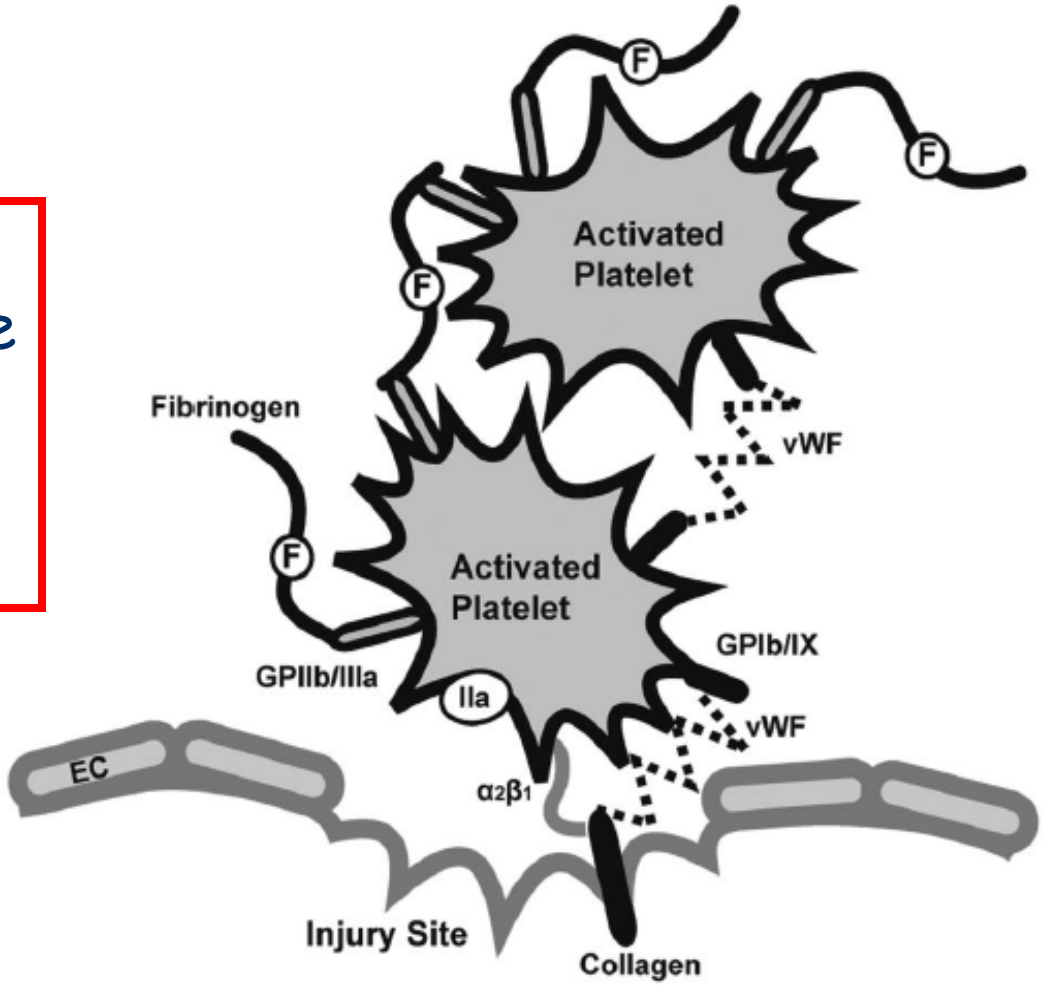
Anesth Analg 1995;81:360–5

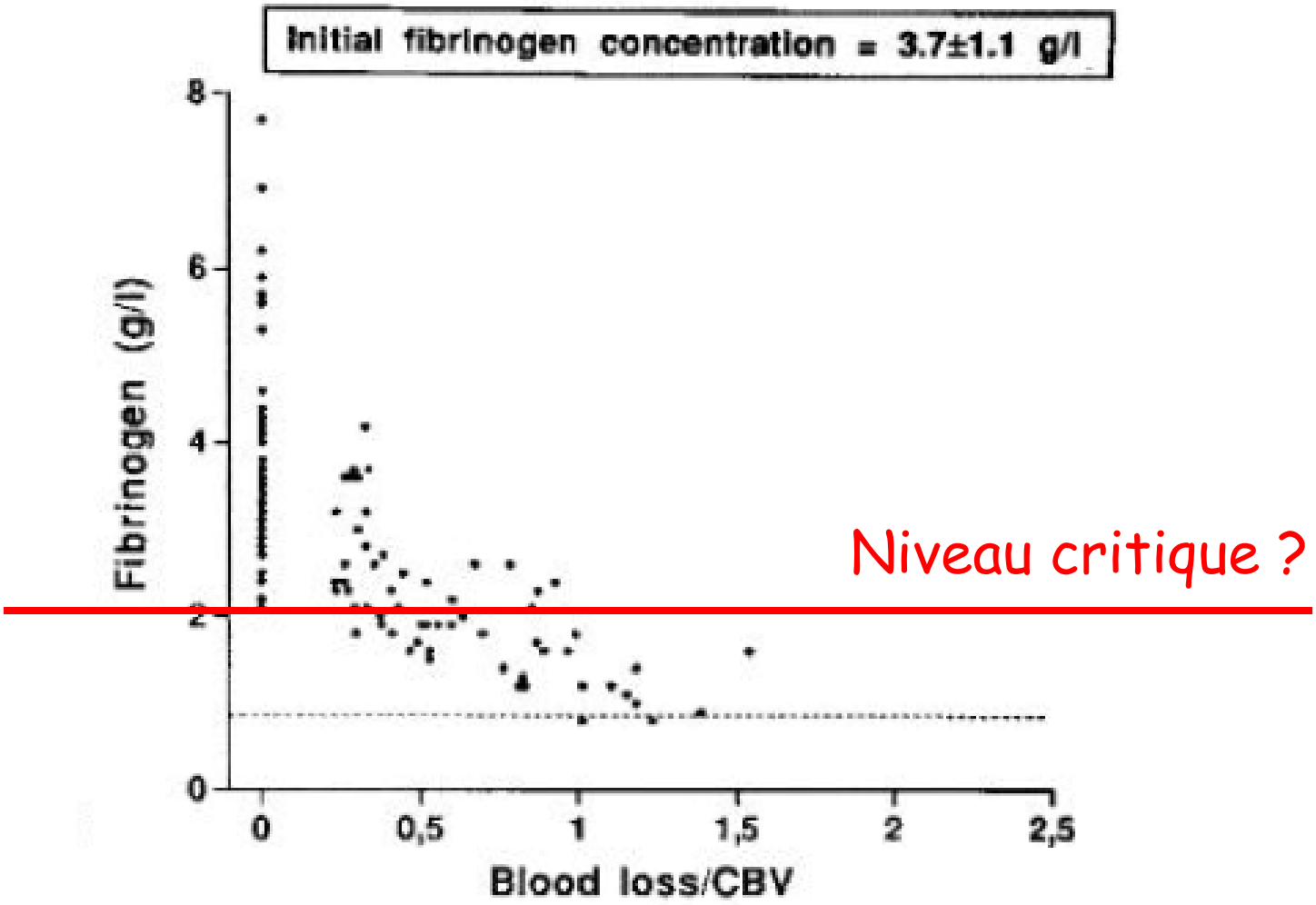
Pathophysiology and Treatment of Coagulopathy in Massive Hemorrhage and Hemodilution

Daniel Bolliger, M.D.,* Klaus Görlinger, M.D.,† Kenichi A. Tanaka, M.D., M.Sc.‡

Anesthesiology, V 113 • No 5 • November 2010

Importance de l'interaction entre l'endothélium, les plaquettes et le fibrinogène





Niveau critique ?

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Anesth Analg 1995;81:360–5

Coagulopathie de la TM: 2 visions s'affrontent

- Vision « classique »
  - Administration de CGR, PFC et CP
  - Cryoprécipités au besoin

- Vision émergente (Allemagne, Autriche)
  - Évaluation par ROTEM
  - Administration de concentrés de facteurs
    - Fibrinogène (2-6g)
    - CCP (e.g. Octaplex®)
    - rFVIIa

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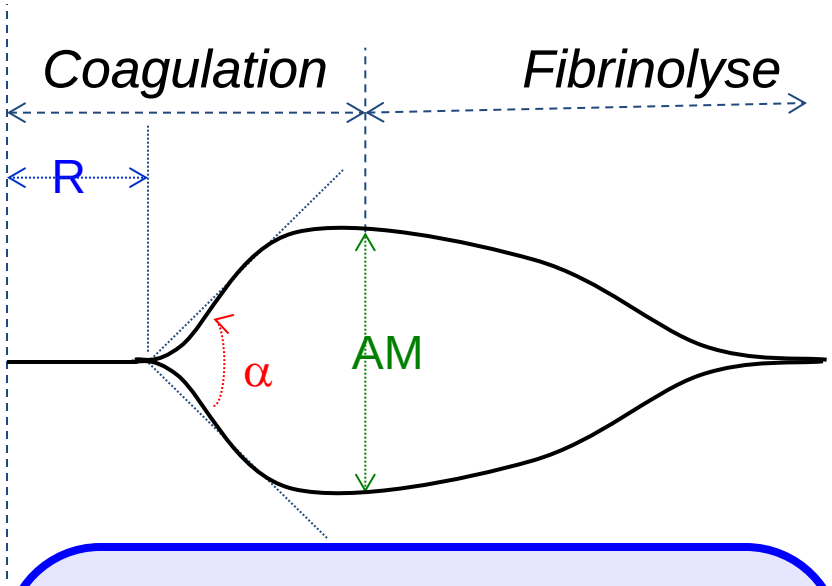
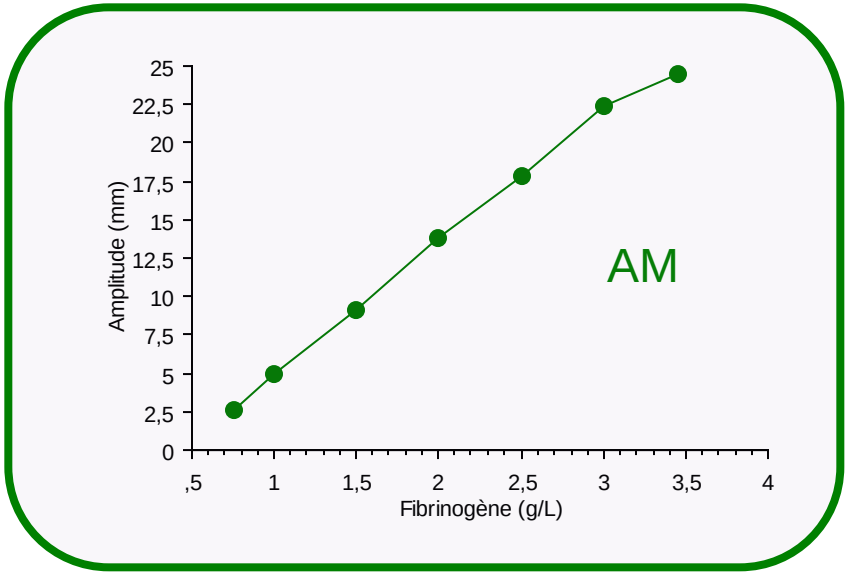
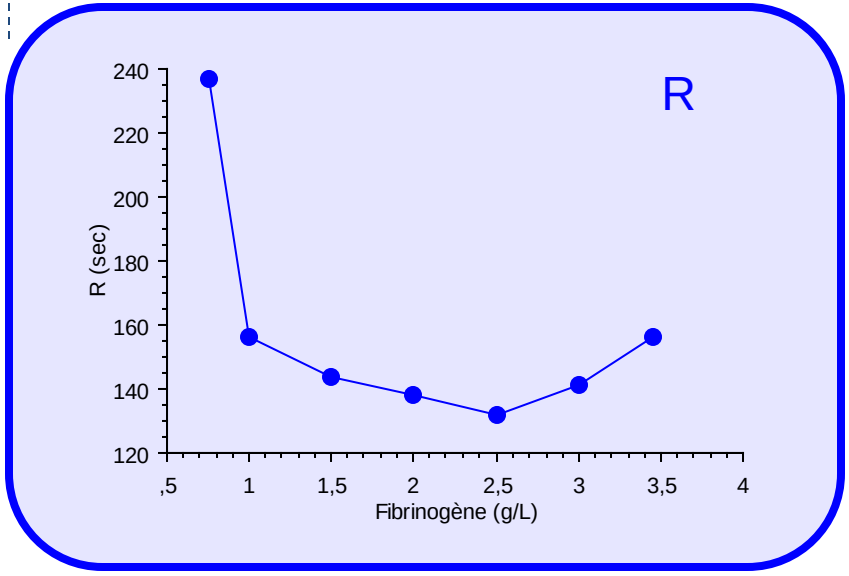
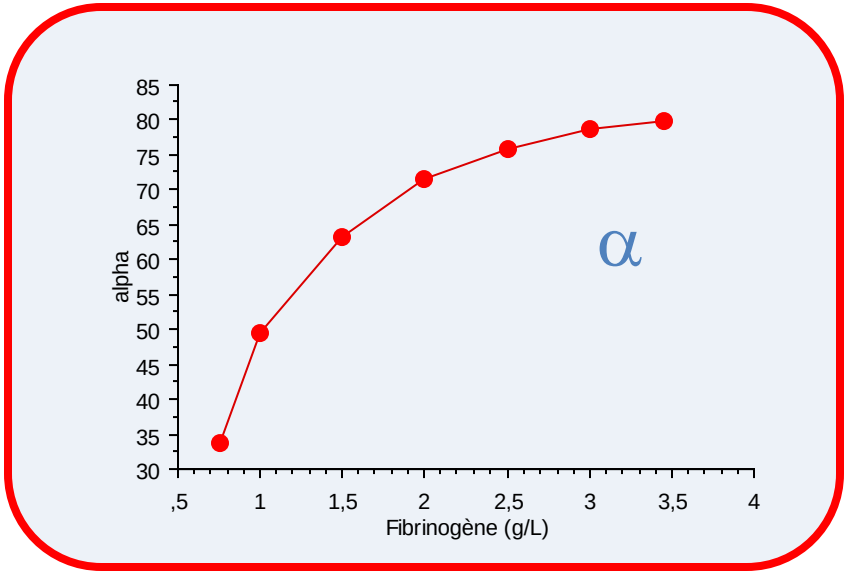
Effects of coagulation factor deficiency on *plasma* coagulation kinetics determined via thromboelastography

VG Nielsen et al. Acta Anaesthesiol Scand 2005; 49:222-231









RESEARCH Open Access

Effects of different fibrinogen concentrations on blood losss and coagulation parameters in a pig model of coagulopathy with blunt liver injury

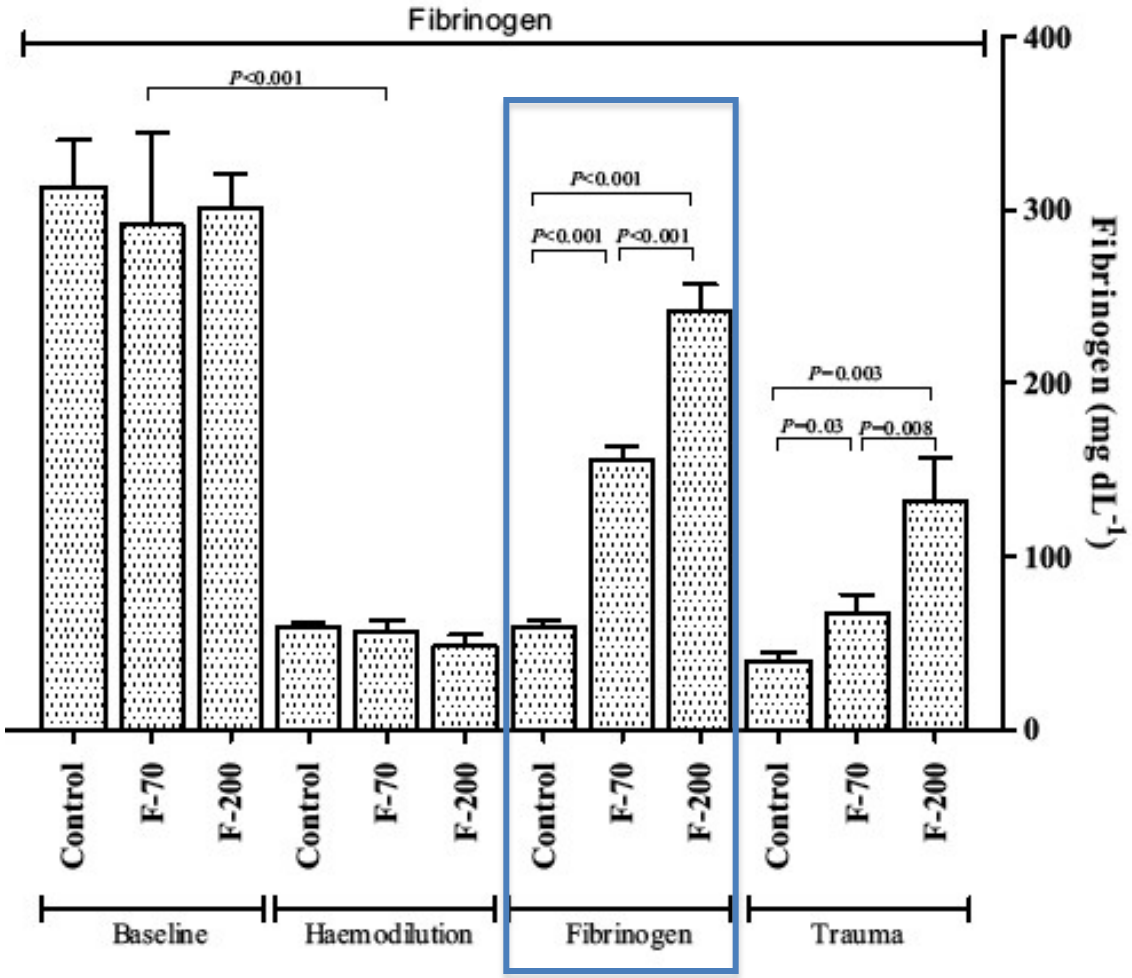
Oliver Grottke*[1,2], Till Braunschweig[3], Dietrich Henzler[4], Mark Coburn[1], Rene Tolba[2] and Rolf Rossaint[1]

Crit Care 2010; 14:R62

N = 18

Placebo
F-70 = 70 mg/kg
F-200 = 200 mg/kg

Coagulopathie mesurée par TEG



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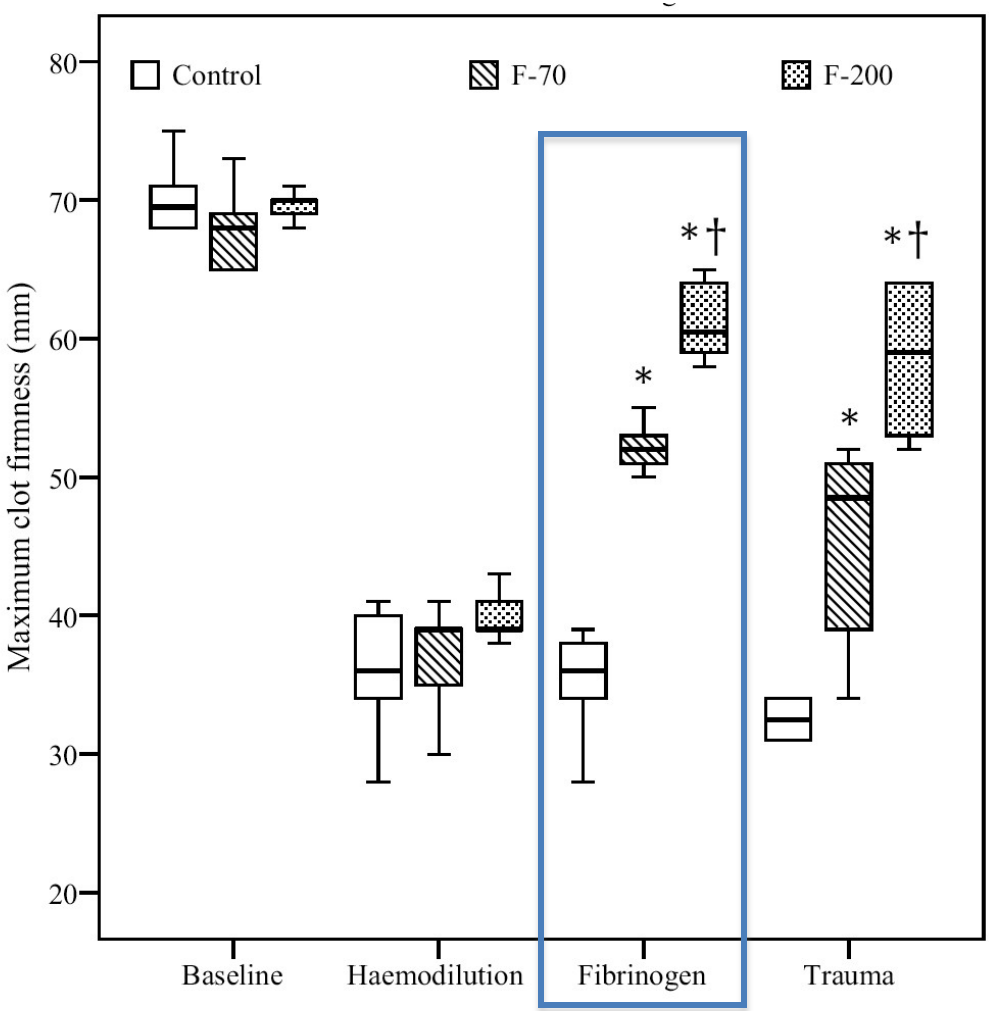
Crit Care 2010; 14:R62



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Crit Care 2010; 14:R62

Groupe	Pertes sanguines (mL)
Contrôle	1803 ± 248
F-70	1317 ± 113
F-200	1155 ± 232

P < 0.05 - Contrôle (<1 g/L) vs. Fibrinogène
P = NS - F-70 (1,5 g/L) vs. F-200 (2,5 g/L)

ORIGINAL ARTICLE

Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes

C. ROURKE,*[1] N. CURRY,†[1] S. KHAN,* R. TAYLOR,† I. RAZA,* R. DAVENPORT,* S. STANWORTH† and K. BROHI*

*Trauma Sciences, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London; and † National Health Service Blood & Transplant/Haematology, John Radcliffe Hospital, Oxford, UK

To cite this article: Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 2012; **10:** 1342–51.

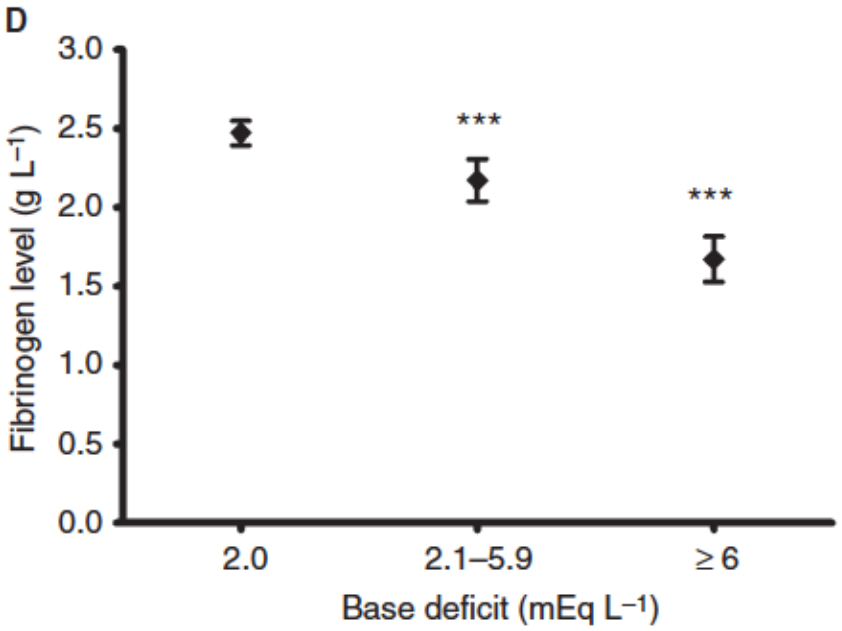
Étude prospective(2008-2010)
Cohorte de 517 patients traumatisés
Relation entre la fibrinogénémie et

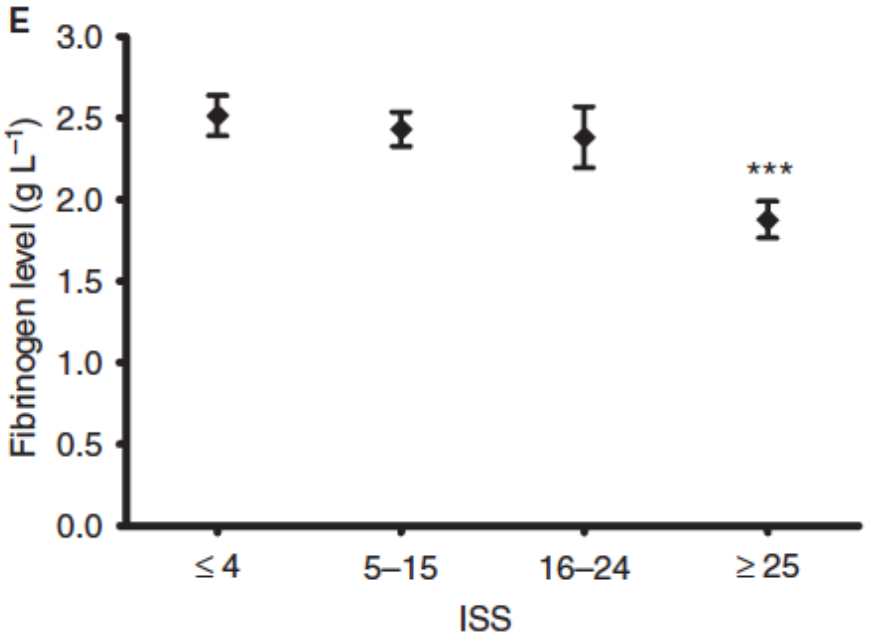
- Facteurs associés au trauma
- ROTEM (étude ex-vivo)
- Outcomes cliniques

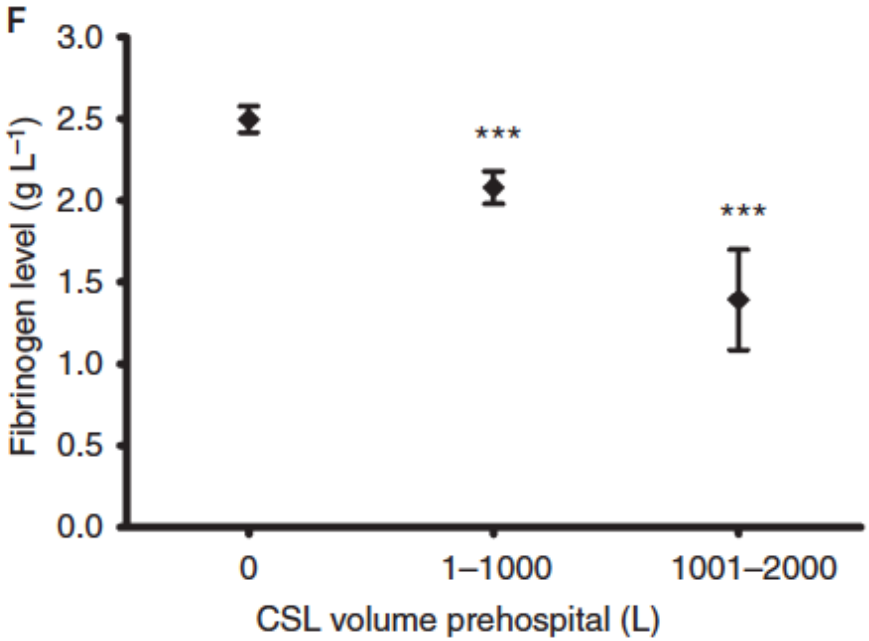
Fibrinogénémie à l'entrée indépendamment associée:

- Au choc
- À la sévérité du trauma (ISS)
- Au volume de cristalloïdes infusés avant l'arrivée à l'hôpital

Journal of Thrombosis and Haemostasis, **10**: 1342–1351







Journal of Thrombosis and Haemostasis, **10**: 1342–1351

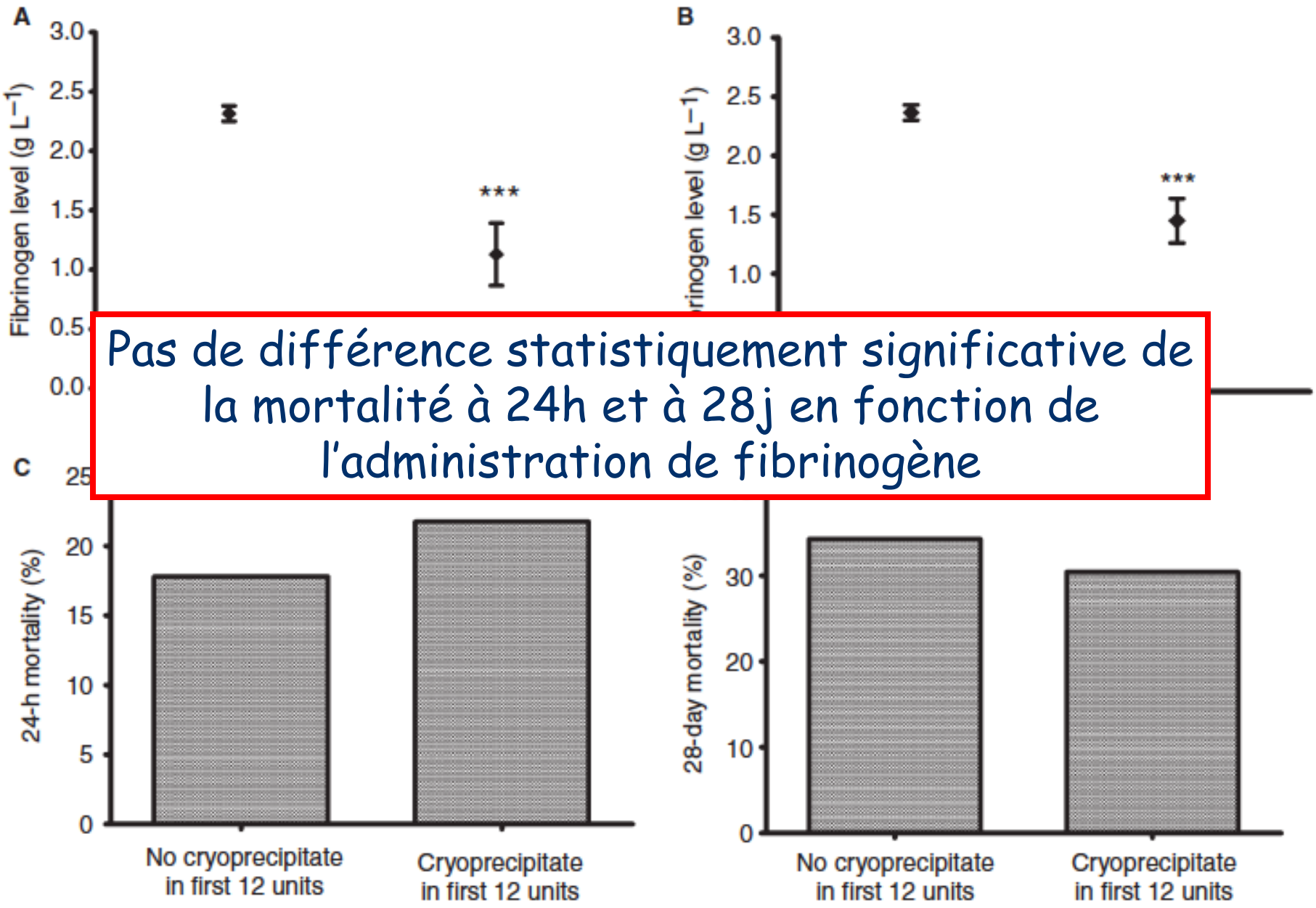
Table 2 Transfusion data for patients receiving ≥ 4 units of packed red blood cells (PRBCs)

	Four-unit window	Eight-unit window	Twelve-unit window
Fibrinogen levels (g L^{-1})			
Whole cohort	1.5 (1.2–1.8)	1.5 (1.1–2.0)	1.3 (1.0–1.7)
Received PRBCs alone	1.2 (1.0–1.8)	0.5 (0.4–0.6)	1.0§
PRBCs plus fibrinogen in any form	1.6 (1.4–1.8)^{NS}	1.5 (1.2–2.0)*	1.3 (1.0–1.7)^{NS}
PRBCs plus fibrinogen from FFP or PLTs alone	1.6 (1.4–1.9)	1.5 (1.1–1.5)	1.0 (0.8–1.0)
PRBCs plus fibrinogen from cryoprecipitate and FFP/PLTs¶	1.4 (1.2–1.7)^{NS1}	1.7 (1.3–2.0)^{NS1}	1.6 (1.1–1.9)^{NS1}

FFP, fresh frozen plasma; PLT, platelet; NS, not significant (vs. PRBC alone group); NS1, not significant (vs. FFP/PLT-only group). Values are given as median (interquartile range). *$P < 0.05$ (vs. PRBC-only group). †A cryoprecipitate ratio of 1 relates to two pools of cryoprecipitate (one adult dose). ‡Two pools of cryoprecipitate equates to one adult dose of cryoprecipitate. §One patient received PRBCs alone by 12 units.

L'administration de PFC et de plaquettes
- Maintient la fibrinogénémie (ad 8 unités de GR)
- Mais ne permet pas de l'augmenter

L'administration de cryoprécipités (source concentrée de fibrinogène) n'augmente pas la fibrinogénémie mais permet de la maintenir ad 12 unités de GR



Pas de différence statistiquement significative de la mortalité à 24h et à 28j en fonction de l'administration de fibrinogène

Journal of Thrombosis and Haemostasis, **10**: 1342–1351

Fibrinogénémie, en résumé

- Fibrinogène bas associé
  - À la coagulopathie du trauma
  - À une augmentation de la mortalité (marqueur ou déterminant?)
- Fibrinogénémie optimale demeure inconnue (mais probablement > 1g/L)
- L'effet thérapeutique de l'augmentation de la fibrinogénémie reste à démontrer

L'incertitude se traduit dans les recommandations…

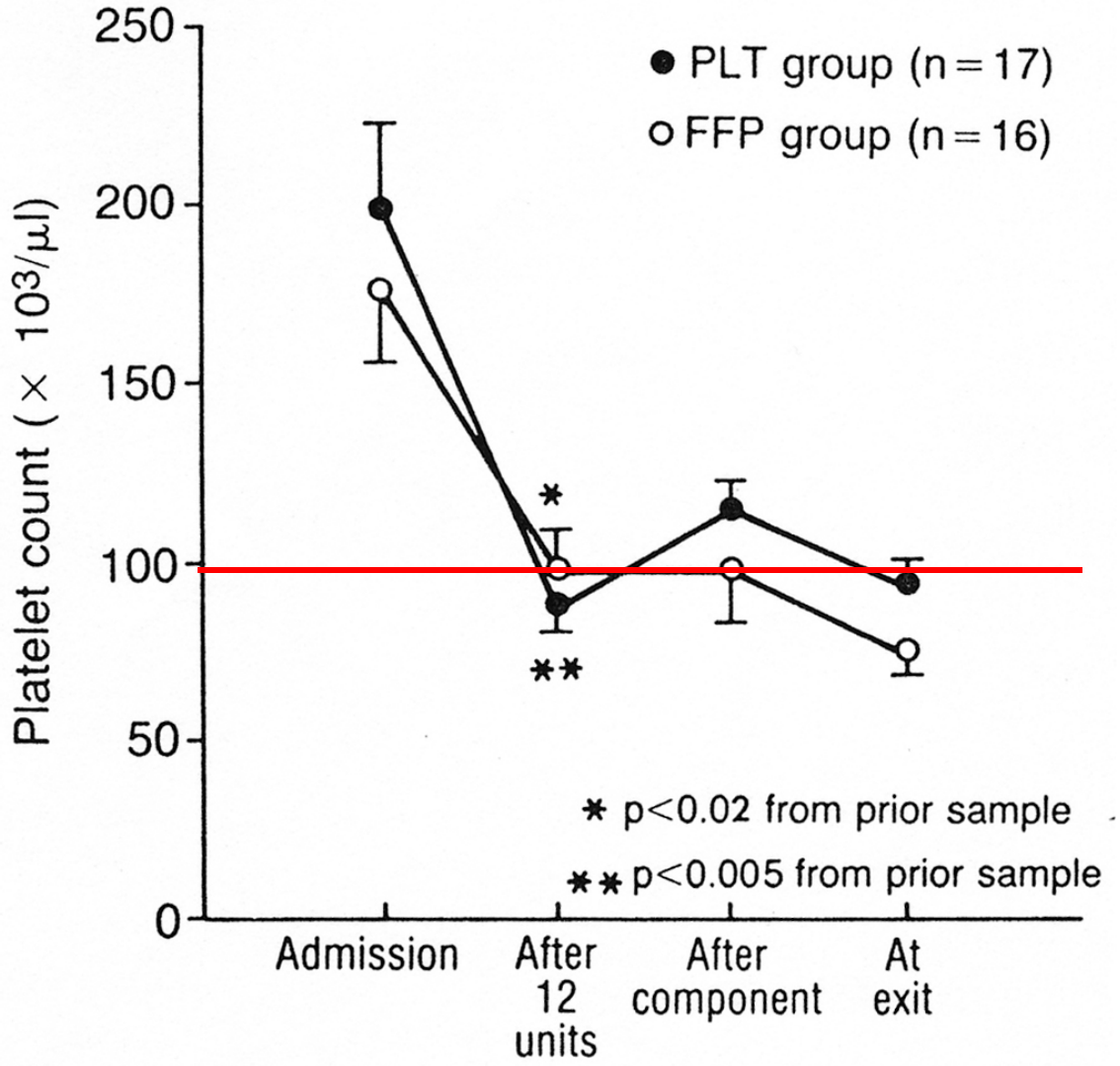
Table 3. Minimal Fibrinogen Levels in Different International Guidelines

Study	Year	Fibrinogen Level (g/l)	Source
ASA[1]	2006	> 0.8–1	American Guideline
O'Shaughnessy *et al.*[63]	2004	1	British Guideline
American Red Cross	2007	1	American Guideline
Spahn *et al.* [64]	2007	1	European Guideline
Bundesärztekammer[66]	2009	1.5	German Guideline
ÖGARI	2010	1.5–2	Austrian recommendations
Rossaint *et al.* [67]	2010	1.5–2	European Guideline

Platelets and hemostasis

- In anesthesia, the focus has been on platelets:
  - Plt counts are decreased in pts who bleed BUT
  - Plt counts are similar whether pts bleed or not
- Importance of:
  - Coagulation factors (specially fibrinogen)
  - Red cells
  - Temperature

Prophylactic platelet administration during massive transfusion



There was no difference in platelet counts in patients receiving platelet concentrates or FFP

Prophylactic therapy with platelet concentrates was ineffective in preventing diffuse microvascular bleeding

Reed RL. Ann Surg 1986;203:40-8

Coagulopathy of MT in elective surgery

In summary

- Dilution
  - Red cells
  - Coagulation factors
  - Platelets
- Coagulopathy
  - Infrequent
  - Late event

Massive transfusion in trauma

- Tissue trauma is massive and uncontrolled
- Initiation of transfusion may be late
- Hypovolemia and shock are present
- Temperature is not controlled => hypothermia
- Monitoring of hemostasis is late
- Coagulopathy occurs early on

Coagulopathy => Microvascular bleeding

- Often complicates the management of MT
- Relates to:
  - The nature and importance of tissue trauma: brain trauma - ISS > 25
  - Shock and tissue anoxia: pH < 7.10 - SBP < 70 mmHg
  - Hypothermia: temperature < 34°C
- Incidence of coagulopathy = 98% if all factors +

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Cosgriff N. J Trauma 1997;42:857-62

Temperature: hypothermia

- Hypothermia
  - Slows the coagulation cascade
  - Reduces the synthesis of coag. factors
  - Increases fibrinolysis
  - Causes a reversible platelet dysfunction
  - Prolongs the BT
- Important contributor to coagulopathy in trauma patients

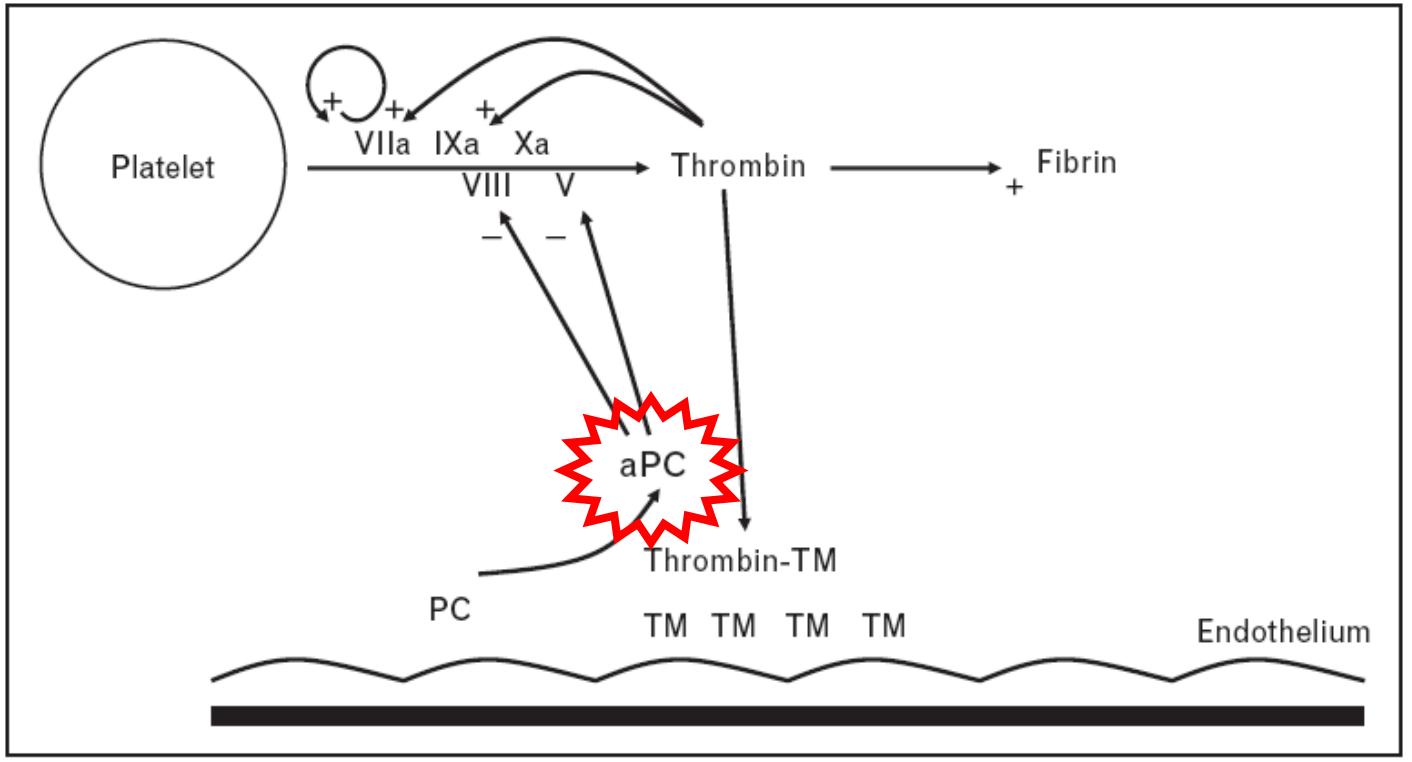
Acute coagulopathy of trauma: mechanism, identification and effect

Karim Brohi[a], Mitchell J. Cohen[b] and Ross A. Davenport[a]

Current Opinion in Critical Care 2007, 13:680–685

Anticoagulation

- Thrombomoduline (TM) complexe la thrombine ➔ ↓ génération de fibrine
- Complexe thrombine –TM active la protéine C ➔ ↓ génération de thrombine



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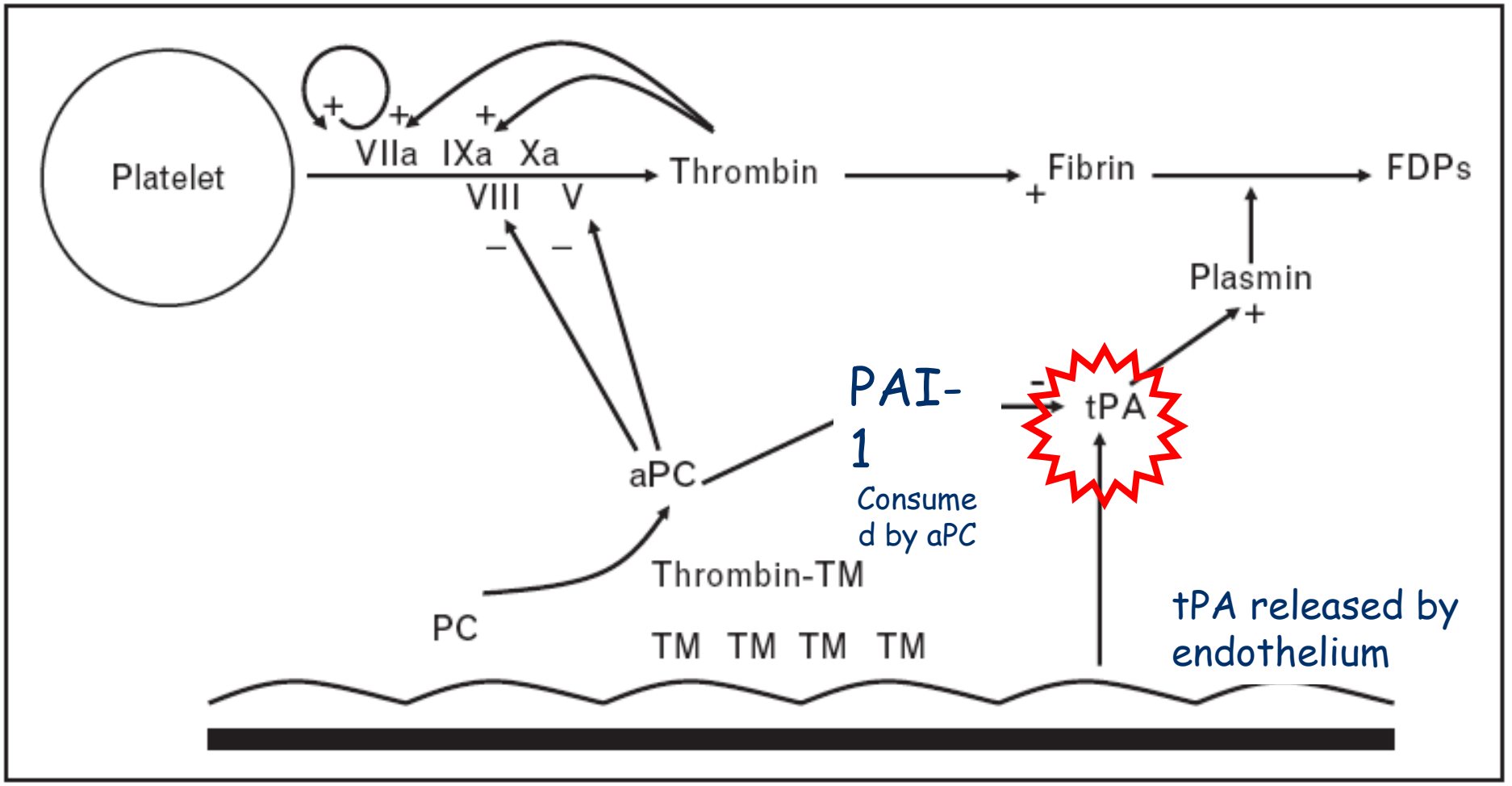
Hyperfibrinolysis



Current Opinion in Critical Care 2007, 13:680–685

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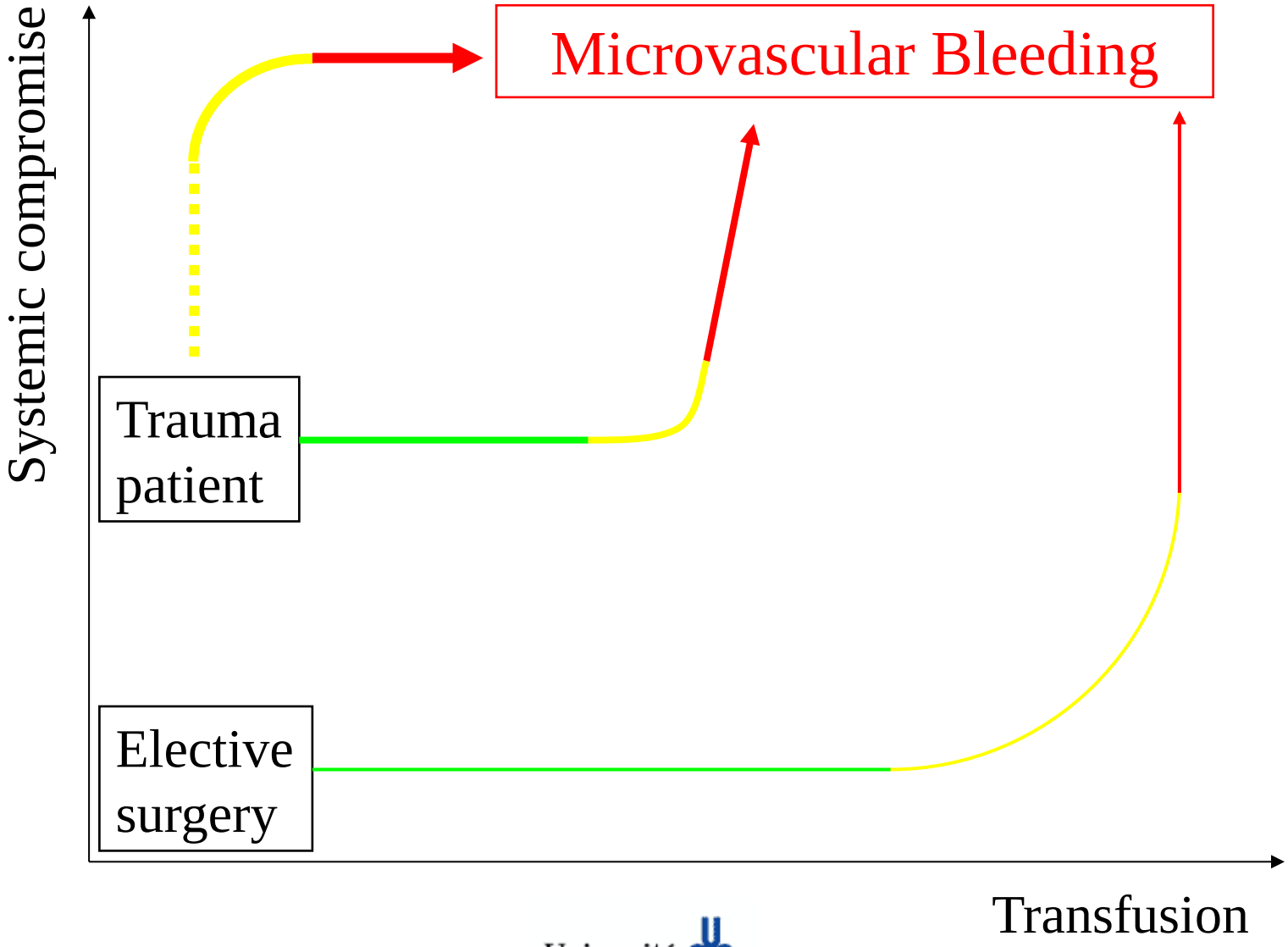
In summary

	Elective surgery	Trauma
Tissue trauma	Controlled	Massive and uncontrolled
Initiation of MT	No delay	Can vary widely
Volume status / shock	Normovolemia	Hypovolemia and shock
Temperature	Normothermia	Hypothermia
Monitoring of hemostasis	Ongoing	Late
Coagulopathy	1st: decreased coagulation factors 2nd: decreased platelets	Microvascular bleeding: early & exact mechanism remains controversial

The "road to coagulopathy"



Vox Sanguinis (2005) 89, 123–127

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Monitoring of coagulopathy

- No simple and reliable test available
- PT & aPTT
  - Require centrifugation = delays
  - Increases are very common
  - Marked prolongations (1.5 to 1.8 x control)
    - Predict factor V and VIII < 30%
    - Correlate with MVB
- Platelet count: to be interpreted in context
- TEG and ROTEM

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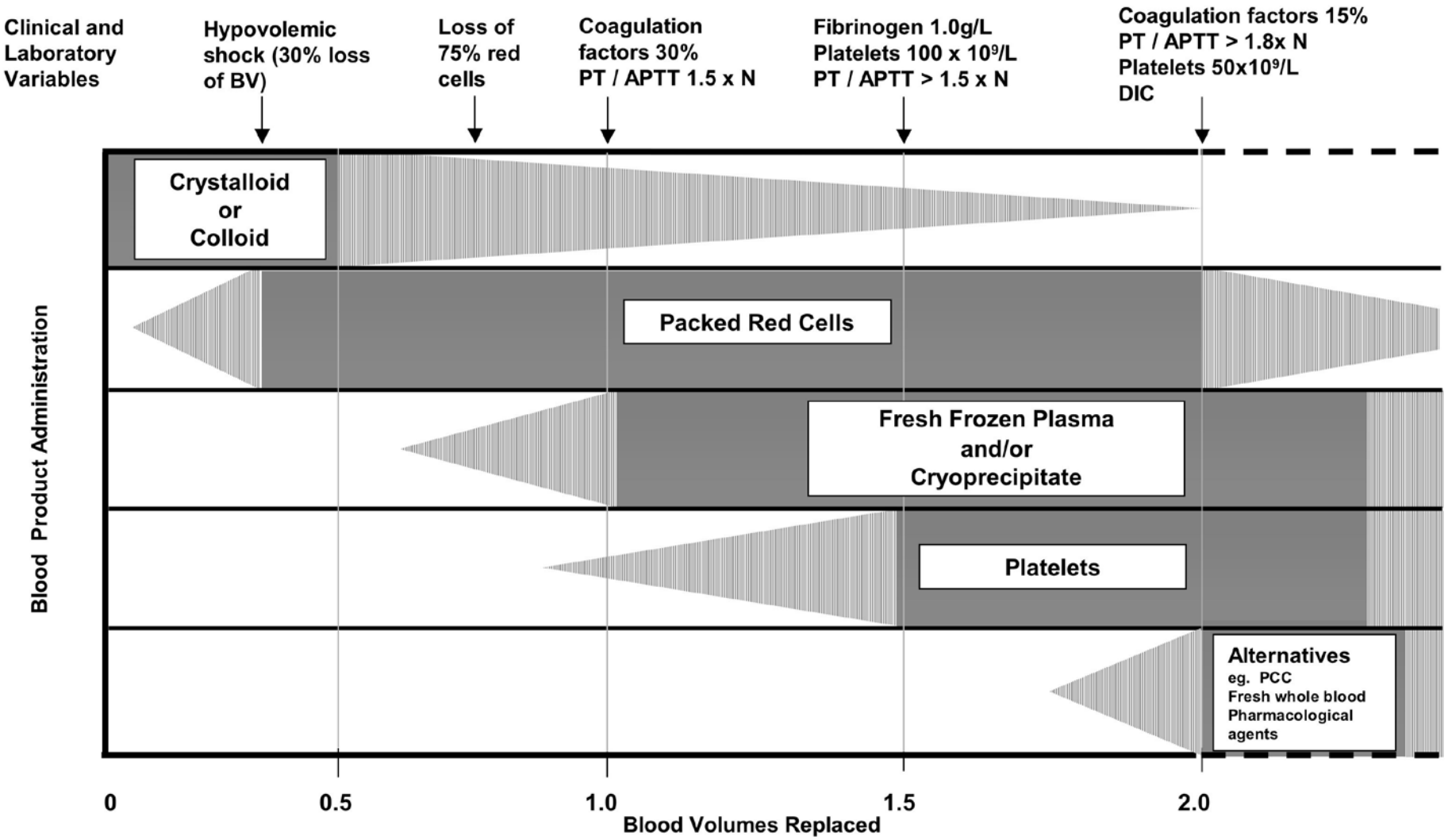
Ciavarella D. Br J Haematol 1987;67:365-8

Basic management of the bleeding patient

- Correct hypothermia
- Transfuse red cells (optimal Hct?)
- Transfuse FFP
  - For a markedly prolonged PT/aPTT
  - To correct a low fibrinogen concentration (consider cryoprecipitate if ineffective)
- Transfuse platelets
  - Decreased number
  - Decreased function

Massive transfusion in the elective surgical setting



Erber WN. Transfus Apheresis Sci 2002;27:83-92

Massive transfusion in trauma

- The recent military experience suggests « damage control resuscitation »
  - « Damage control surgery »
  - Minimal use of crystalloids
  - RBC:FFP:Plts in a 1:1:1 ratio
- Specific demographic characteristics
  - Healthy and young (21-30y) males
  - Combination of blast and penetrating injury

Mais qu'en est-il de la TM chez les civils?

- Les populations sont différentes
  - Plus de femmes
  - Plus de personnes âgées
- Les traumas sont différents
  - Plus d'accidents d'automobile
  - Moins de traumas pénétrants
- Résultats des études (rétrospectives) sont contradictoires

Vox Sanguinis (2008) **95**, 112–119

ORIGINAL PAPER

DOI: 10.1111/j.1423-0410.2008.01074.x

Red blood cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiply injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie

M. Maegele,[1,2] R. Lefering,[2] T. Paffrath,[1] T. Tjardes,[1] C. Simanski,[1] B. Bouillon[1] &
the Working Group on Polytrauma of the German Society of Trauma Surgery (DGU)

[1]*Department of Trauma and Orthopedic Surgery, and* [2]*Institute for Research in Operative Medicine (IFOM), University of Witten/Herdecke, Cologne-Merheim Medical Center (CMMC), Cologne, Germany*

Retrospective analysis of 713 trauma patients admitted between 2002 and 2006 with

- serious injury (ISS > 16)
- massive transfusion (RBC > 10)

Note: - relatively old population (mean age 40y)
- largest proportion of females (30.3%)

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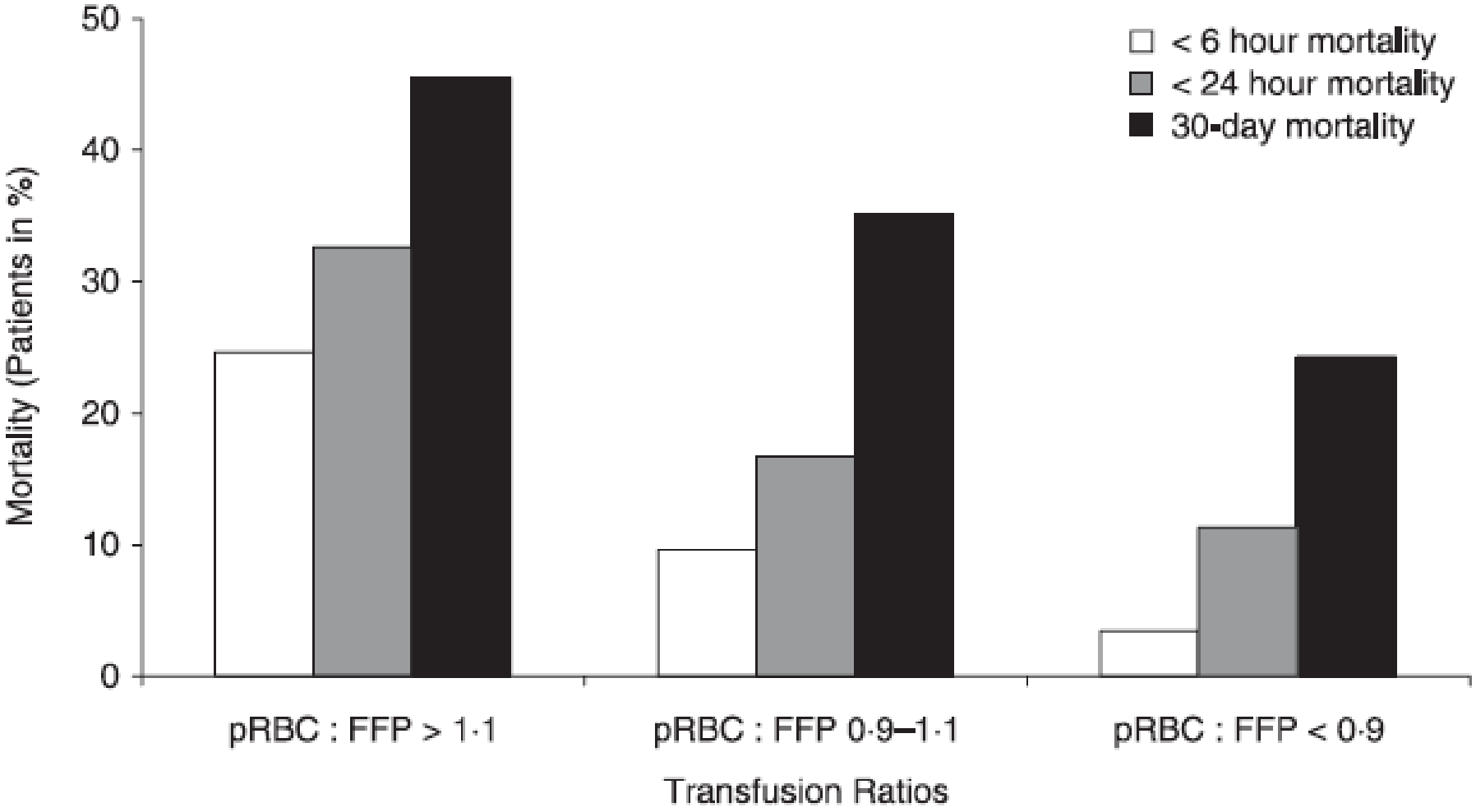

Mortality decreased with a RBC to FFP ratio < 0.9
but ventilator days and LOS increased (TRALI ?)

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Vox Sanguinis (2008) **95**, 112–119

Nascimento et al. Critical Care 2010, 14:202
http://ccforum.com/14/1/202

CRITICAL CARE

REVIEW

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

Bartolomeu Nascimento[1], Jeannie Callum[2], Gordon Rubenfeld[3], Joao Baptista Rezende Neto[4,5], Yulia Lin[2] and Sandro Rizoli[*5]

Controversy in Trauma Resuscitation: Do Ratios of Plasma to Red Blood Cells Matter?

Lynn G. Stansbury, Richard P. Dutton, Deborah M. Stein, Grant V. Bochicchio, Thomas M. Scalea, and John R. Hess

Editorial: "Formula-Driven" Versus "Lab-Driven" Massive Transfusion Protocols: At a State of Clinical Equipoise

Jeannie L. Callum[a], Bartolomeu Nascimento[a], Homer Tien[b,c], and Sandro Rizoli[b]

Transfusion Medicine Reviews, Vol 23, No 4 (October), 2009: pp 247-254

Limites des études

- Études rétrospectives
  - « Survivorship bias »: les pts qui sont morts <2h n'ont pas eu le temps de recevoir du FFP
  - « Ascertainment bias »: difficulté à colliger des données valides dans un environnement extrême
- Différences entre civils et militaires
  - Importantes différences démographiques
  - Traumas pénétrants vs. traumas non pénétrants
  - Diponibilité des produits sanguins

Le protocole 1:1:1 ne s'applique pas d'emblée aux traumas civils

- Environ 17% des traumas civils sont transfusés
- 2-5% des patients sont transfusés massivement > 10 U
- Le protocole 1:1:1 ne s'applique donc qu'à un très petit nombre de traumas civils
- Trauma ≠ 1:1:1

Le protocole 1:1:1 ne s'applique pas en chirurgie programmée

- Conduite suggérée demeure
  - Cristalloïdes + GR
  - Monitorer la coagulopathie
  - PFC si PT/PTT > 1,5 x normale (dose usuelle 3-6 unités)
  - Plaquettes si < 50 G/L
- Transfusion de GR ≠ 1:1:1

En résumé: prise en charge

- Pas de démonstration claire (non-équivoque) des bénéfices ou des inconvénients de différentes stratégies:
  - Ratio 1:1:1
  - Administration de concentrés de facteurs
- Besoin d'études prospectives randomisées
- Mieux comprendre la coagulopathie du trauma/de la transfusion massive
- Outils diagnostiques performants requis

Efficacy and Safety of Recombinant Activated Factor VII to Control Bleeding in Nonhemophiliac Patients: A Review of 17 Randomized Controlled Trials

Jean-François Hardy, MD, FRCPC, Sylvain Bélisle, MD, FRCPC, and Philippe Van der Linden, MD, PhD

Department of Anesthesiology, University of Montreal, Université Libre de Bruxelles, Montreal, Quebec, Canada; Department of Anesthesiology, CHU Brugmann, Université Libre de Bruxelles, Belgium, Germany

We reassess all published randomized controlled trials that have evaluated the hemostatic efficacy or safety of recombinant activated factor VII (rFVIIa), or both, in nonhemophiliac patients. Seventeen trials published in 16 articles dealt either with the prophylactic (nine trials) or the therapeutic (eight trials) use of rFVIIa to prevent or to treat excessive bleeding. At present, the role of rFVIIa to prevent or to control bleeding and reduce transfusions in various patient populations remains unclear. In addition, the safety of rFVIIa remains a concern. Consequently, we conclude that the generalized use of rFVIIa to prevent or to control bleeding in nonhemophiliac patients can not be recommended.

(Ann Thorac Surg 2008;86:1038–48)

Conclusions (1/2)

- Coagulopathy of Massive Transfusion is different in elective surgery vs. trauma
  - Intricate, multicellular and multifactorial
  - Infrequent and late event in elective surgery
  - More frequent in trauma
    - Shock, acidosis, hypothermia
    - "Acute coagulopathy of trauma"
    - Exact mechanism remains unclear
- Consequently, management will differ

Conclusions (2/2)

- Management
  - Red cells to raise the Hct
  - FFP/cryos to correct a low fibrinogen/factor level
  - Platelets to correct low/ineffective platelets
  - Timing/quantity may vary according to context
- Monitoring
  - Reliable POC monitors of coagulation are needed

Questions?