Progetto
Ematologia-Romagna

CESENA, 21 SETTEMBRE 2019

EDIFICIO B, Centro Servizi Pievesestina – AUSL ROMAGNA

12:00 – 13:30 **SI PUÒ ANCORA MORIRE PER UN SANGUINAMENTO DIFFICILMENTE CONTROLLABILE?**

Inquadramento dell'argomento: il concetto di emorragia critica

Marco Marietta – Modena

marco.marietta@unimore.it

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- ✓**Advisory board**: Novo-Nordisk, BioVIIIx, Bristol-Myers Squibb, Daiichi-Sankyo
- ✓**Consulenza**: Gilead, Kedrion, Octapharma Italy
- ✓**Relazioni a convegni**: Novo-Nordisk, Orphan, Sanofi, BioFVIIIx

N Engl J Med 2018;378:370-9.

Table 1. Estimated Hemorrhage-Related Deaths per Year and Years of Life Lost in the United States and Worldwide, According to the Cause of Hemorrhage.

Cause of Hemorrhage	Deaths from Hemorrhage*	U.S. Cases of Hemorrhage		Global Cases of Hemorrhage	
		No. of Deaths per Yr	Yr of Life Lost	No. of Deaths per Yr	Yr of Life Lost
	percent				
Abdominal aortic aneurysm	100	9,988†	65,273‡	191,700§	2,881,760¶
Maternal disorder	23§	138‖	7,572**	69,690‖	4,298,240**
Peptic ulcer disease	60††	1,860‖	38,597**	141,000‖	3,903,600**
Trauma	30‡‡	49,440‖	1,931,786**	1,481,700‖	74,568,000**
Total		61,426	2,043,228	1,884,090	85,651,600

* This column lists the best estimates of deaths from hemorrhage as a percentage of all deaths from the given diagnosis (e.g., all deaths from abdominal aortic aneurysm are ultimately related to hemorrhage).

† Information is from Leading Causes of Death Reports, 1981–2015, Centers for Disease Control and Prevention, 2017 (https://webappa.cdc.gov/sasweb/ncipc/leadcause.html).

‡ Data are from Years of Potential Life Lost (YPLL) Reports, 1999–2015, Centers for Disease Control and Prevention, 2017 (https://webappa.cdc.gov/sasweb/ncipc/ypll10.html).

§ Data are from Lozano et al.[5]

¶ Data are from Global Health Data Exchange, 2016 (http://ghdx.healthdata.org/gbd-results-tool).

‖ Data are from Global Health Estimates 2015: Global Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015. World Health Organization, 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html).

** Data are from Global Health Estimates 2015: Disease Burden by Cause, Age, Sex, by Country and Region, 2000–2015. World Health Organization, 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).

†† Information is from Christensen et al.[6]

‡‡ Information is from Kauvar et al.[7]

Il concetto di emorragia CRITICA

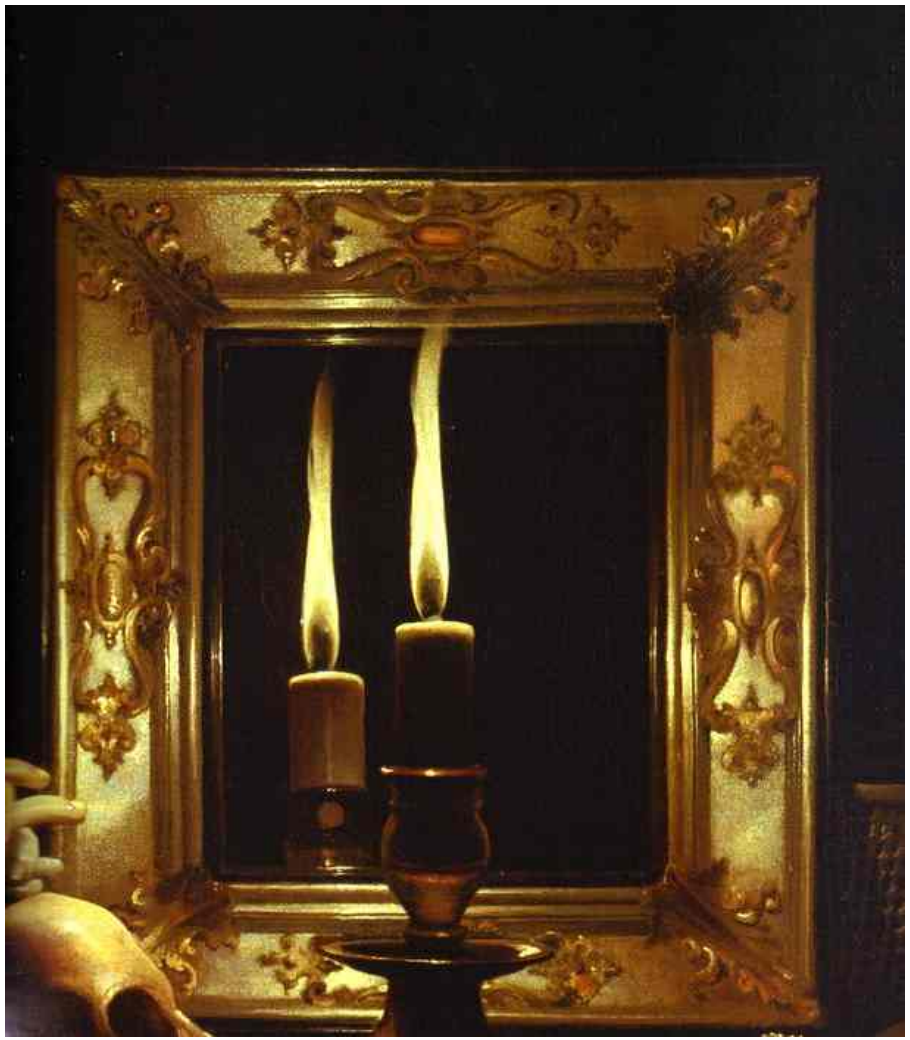
- *Per ENTITA'*
- *Per SEDE*
- *Per FISIOPATOLOGIA*

→ - **paziente** (comorbità/farmaci)
→ - **setting** (pre-H, Emer, ICU)

Per ENTITA'

▪ INTRAOPERATORIA	> 500-1000 ml/ora per 1 ora
▪ POSTOPERATORIA	> 200-500 ml/ora per 2 ore
▪ TRAUMA PENETRANTE	> 2 gr Hb/ora per 1 ora
▪ MASSIVA	> 150 ml/min

Fisiopatologia dell’ emorragia critica: luci…



Georges de La Tour, Maddalena penitente (particolare), 1639- 1634
(New York, Metropolitan Museum of Art)

Received: 12 November 2018 | Accepted: 3 April 2019
DOI: 10.1111/jth.14450

REVIEW ARTICLE

jth

Trauma-induced coagulopathy: The past, present, and future

MECHANISMS AND MEDIATORS

- ✓Tissue injury and shock
- ✓Factor depletion, impaired thrombin generation, and fibrinogen deficiency
- ✓Activation and depletion of protein C
- ✓ Dysregulated fibrinolysis
- ✓Inflammation and immune dysfunction: endotheliopathy, DAMPs, and others
- ✓Altered postinjury platelet biology

ACIDOSI e IPOTERMIA

Independent Contributions of Hypothermia and Acidosis to Coagulopathy in Swine

Wenjun Z. Martini, PhD, Anthony E. Pusateri, PhD, John M. Uscilowicz, BS, Angel V. Delgado, PhD, and John B. Holcomb, MD

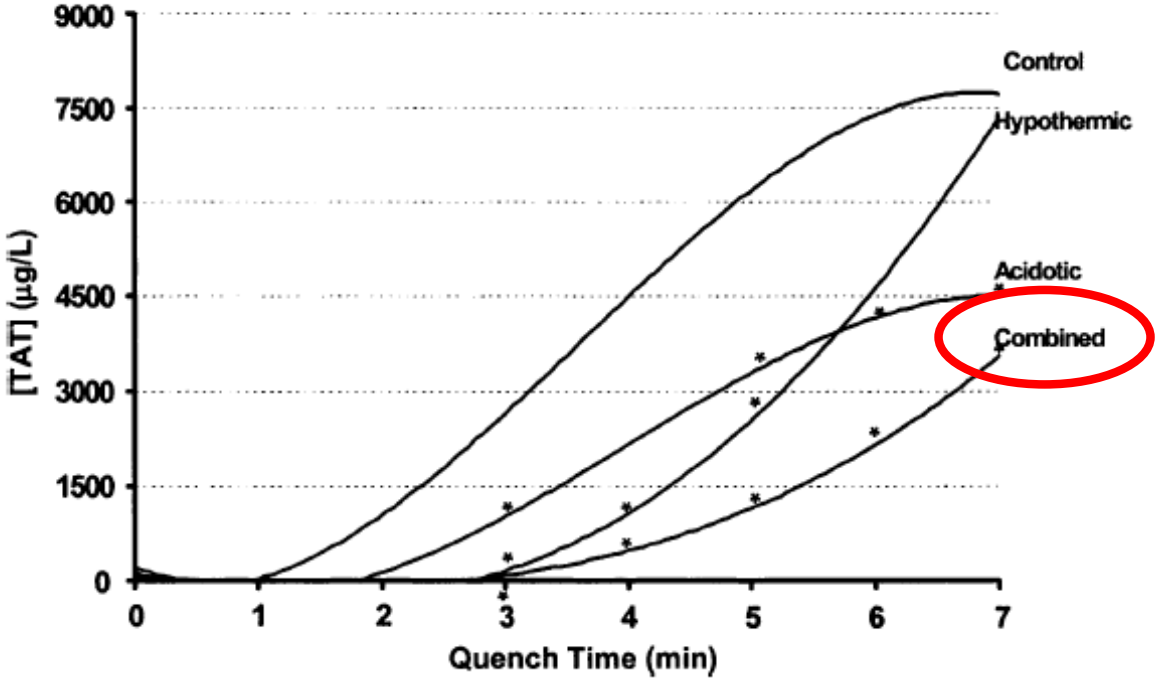


Figure 3. Thrombin generation rate in blood samples measured as thrombin-antithrombin III (TAT) complex concentration.

J Trauma. 2005;58:1002–1010.

(Anesth Analg 1995;81:360–5)

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

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)

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*

J Thromb Haemost 2012; **10:** 1342–51.

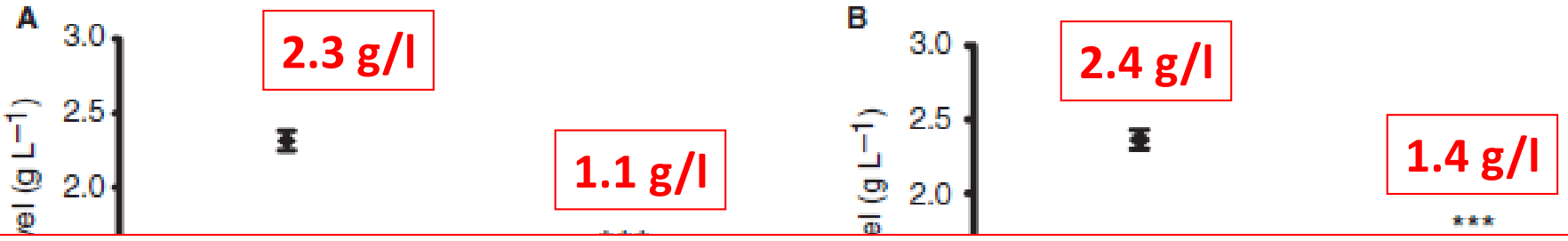


Table 3 Independent variables associated with mortality

Parameter	Odds ratio	95% CI	*P*-value
Fibrinogen level	0.22	0.10–0.47	< 0.001
Injury severity	1.03	1.00–1.06	0.07
APTT	1.05	1.01–1.09	0.02
Gender (female)	2.46	1.04–5.81	0.04
Age	1.05	1.02–1.07	< 0.001

APTT, activated partial thromboplastin time; CI, confidence interval.

J Thromb Haemost 2007; 5: 266–73.

ORIGINAL ARTICLE

The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage

UI,‡‡‡ H. KEITA,‡¶
UISSE,¶‡‡
)P

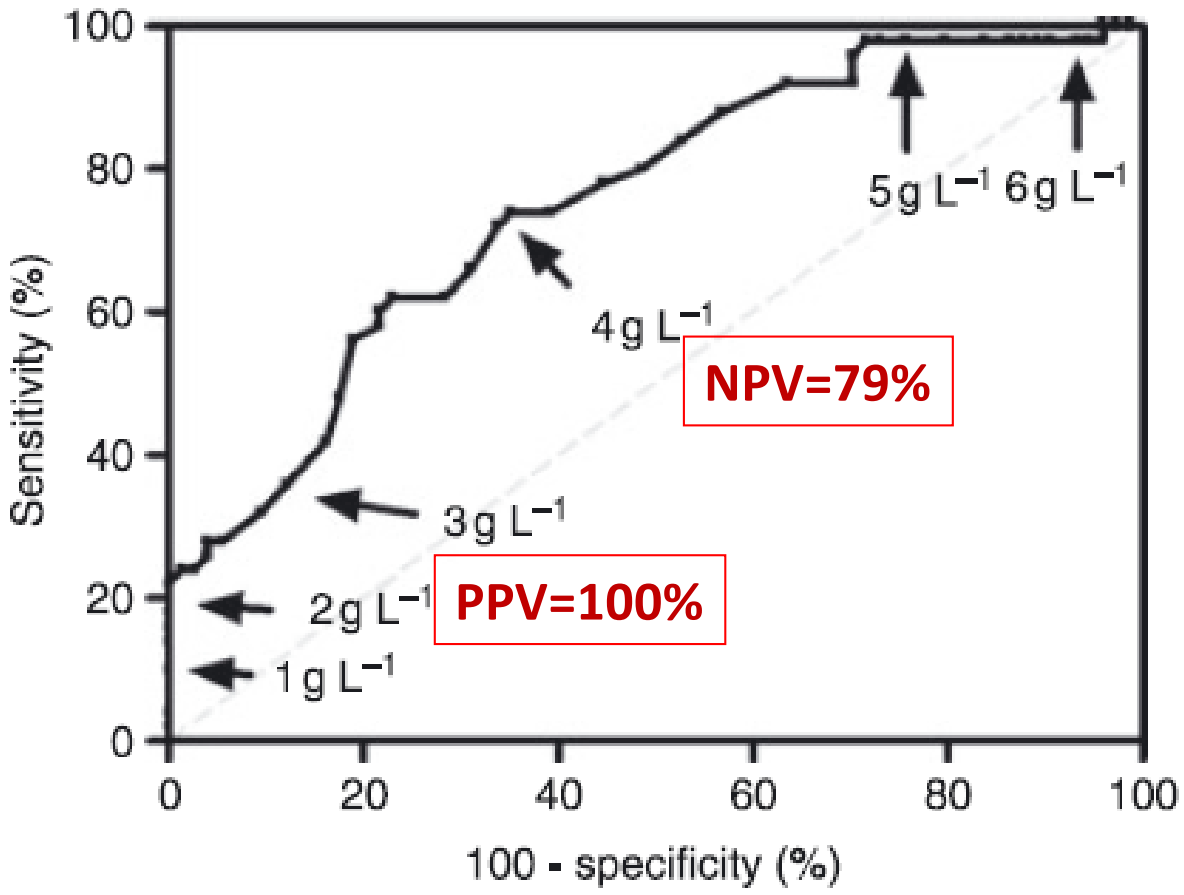


Fig. 3. ROC curve of fibrinogen plasma concentration at H0 for the diagnosis of severe postpartum hemorrhage.

Metodo Clauss

J Trauma. 2008;64:1211–1217.

Acute Coagulopathy of Trauma: Hypoperfusion Induces Systemic Anticoagulation and Hyperfibrinolysis

Karim Brohi, FRCS, FRCA, Mitchell J. Cohen, MD, Michael T. Ganter, MD, Marcus J. Schultz, MD, PhD, FCCS, Marcel Levi, MD, PhD, Robert C. Mackersie, MD, and Jean-François Pittet, MD

All current efforts to correct traumatic coagulopathy are currently directed at augmenting the clotting factor pathway, through the administration of fresh frozen plasma or recombinant factor VIIa.

In theory, while patients are shocked and thrombomodulin is present in excess, thrombin that is generated will be anticoagulant, and stable clot will not be formed.

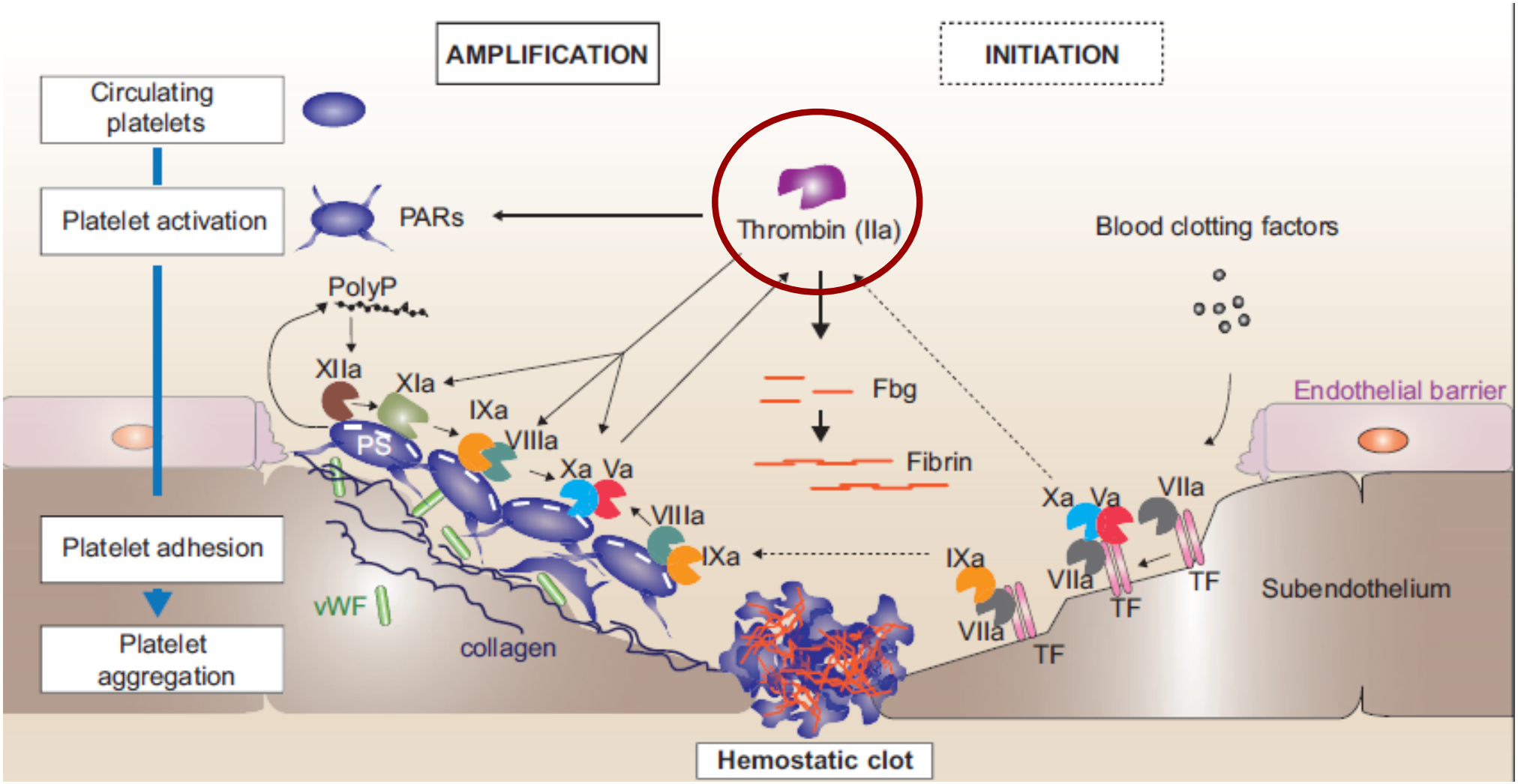
Although it may be possible to overwhelm thrombomodulin with massive thrombin generation, this would also be associated with widespread activation of protein C.

This would lead to consumption of PAI-1 and increased fibrinolysis, breaking down the clot that had formed.

Seminars in Immunology 28 (2016) 561–569

Blood coagulation in immunothrombosis—At the frontline of intravascular immunity

Florian Gaertner*, Steffen Massberg



Thromb Haemost 2011; 106: 1020–1033

Thrombin as a multi-functional enzyme

Focus on *in vitro* and *in vivo* effects

Jolanta M. Siller-Matula[1]; Michael Schwameis[2]; Andrew Blann[3]; Christine Mannhalter[4]; Bernd Jilma[2]

	Thrombin functions in coagulation
Procoagulant properties	• cleavage of fibrinogen and liberation of fibrinopeptide A and B (10) • activation of factors: V (128), VIII (129), XI (130) and XIII (131) • induction of platelet aggregation, platelet secretion and platelet procoagulant activity (132) • release of adenosine diphosphate from platelets (132) • expression of P-selectin on endothelial cells (133, 134) • stimulation of expression of the platelet activating factor (PAF)
Anticoagulant properties	• binding to thrombomodulin (TM) and activation of protein C • decrease in the binding of von Willebrand factor (vWF) to glycoprotein (GP) Ib (135) • decrease in ristocetin-induced agglutination (135)

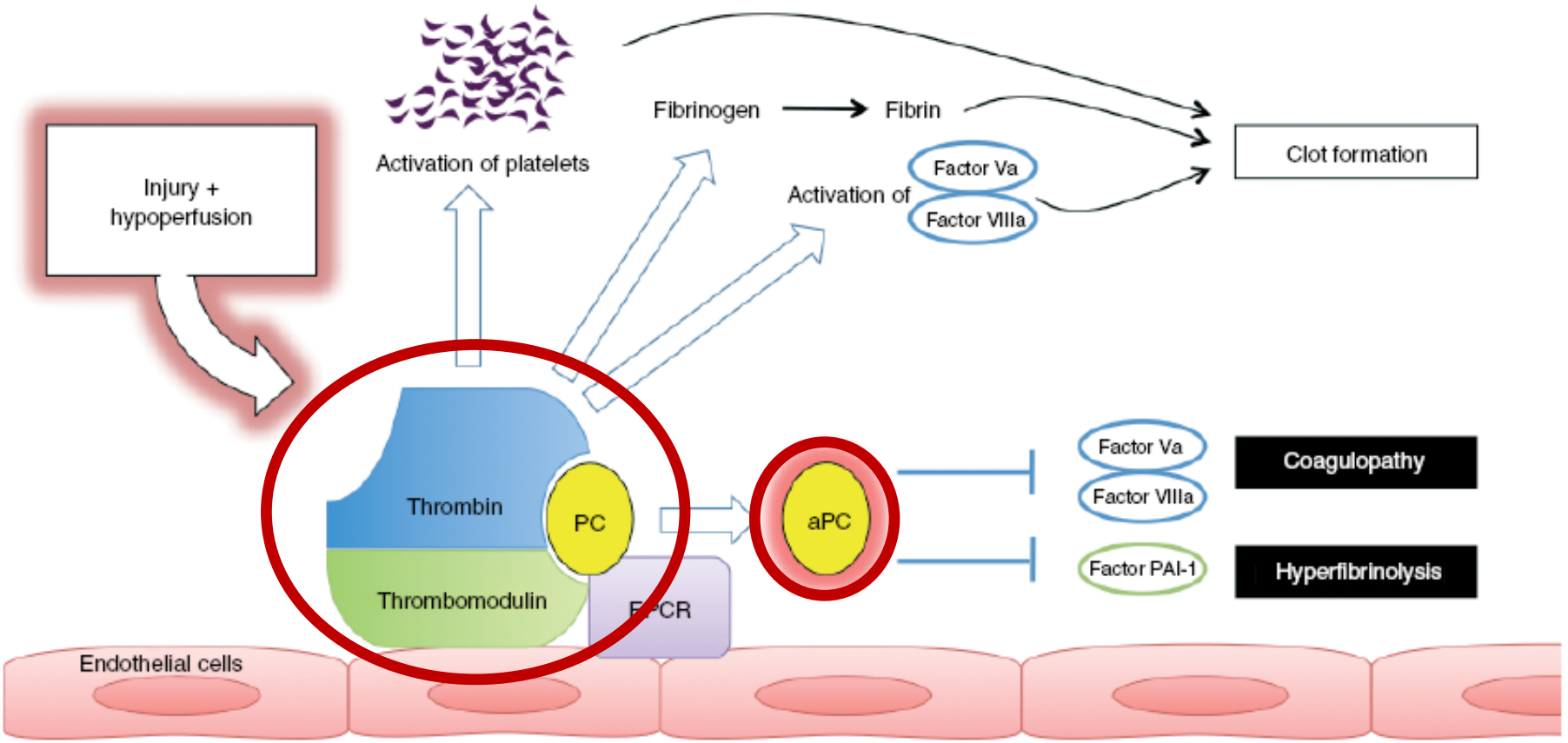
Thromb Haemost 2011; 106: 1020–1033

Thrombin as a multi-functional enzyme

Focus on *in vitro* and *in vivo* effects

Anticoagulant properties	• binding to thrombomodulin (TM) and activation of protein C • decrease in the binding of von Willebrand factor (vWF) to glycoprotein (GP) Ib (135) • decrease in ristocetin-induced agglutination (135)
Fibrinolytic properties	• release of the tissue plasminogen activator (138)
Antifibrinolytic properties	• activation of thrombin-activable fibrinolysis inhibitor (TAFI) (136) • release of the plasminogen activator inhibitor-1 (137)

PROTEIN C IN TRAUMA :
"TOO MUCH OF A GOOD THING"



aPC has **cytoprotective functions** [levels between 1 and 6 ng/mL] :

- ✓ stabilization of endothelial and epithelial junctions,
- ✓ anti-apoptosis,
- ✓ cleavage of extracellular histones

Thorsen K et al. Br J Surg 2011;98:894-907

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

Published Online
March 24, 2011

*The CRASH-2 collaborators**

1 gr in 10 min, poi 1 gr in 8 ore

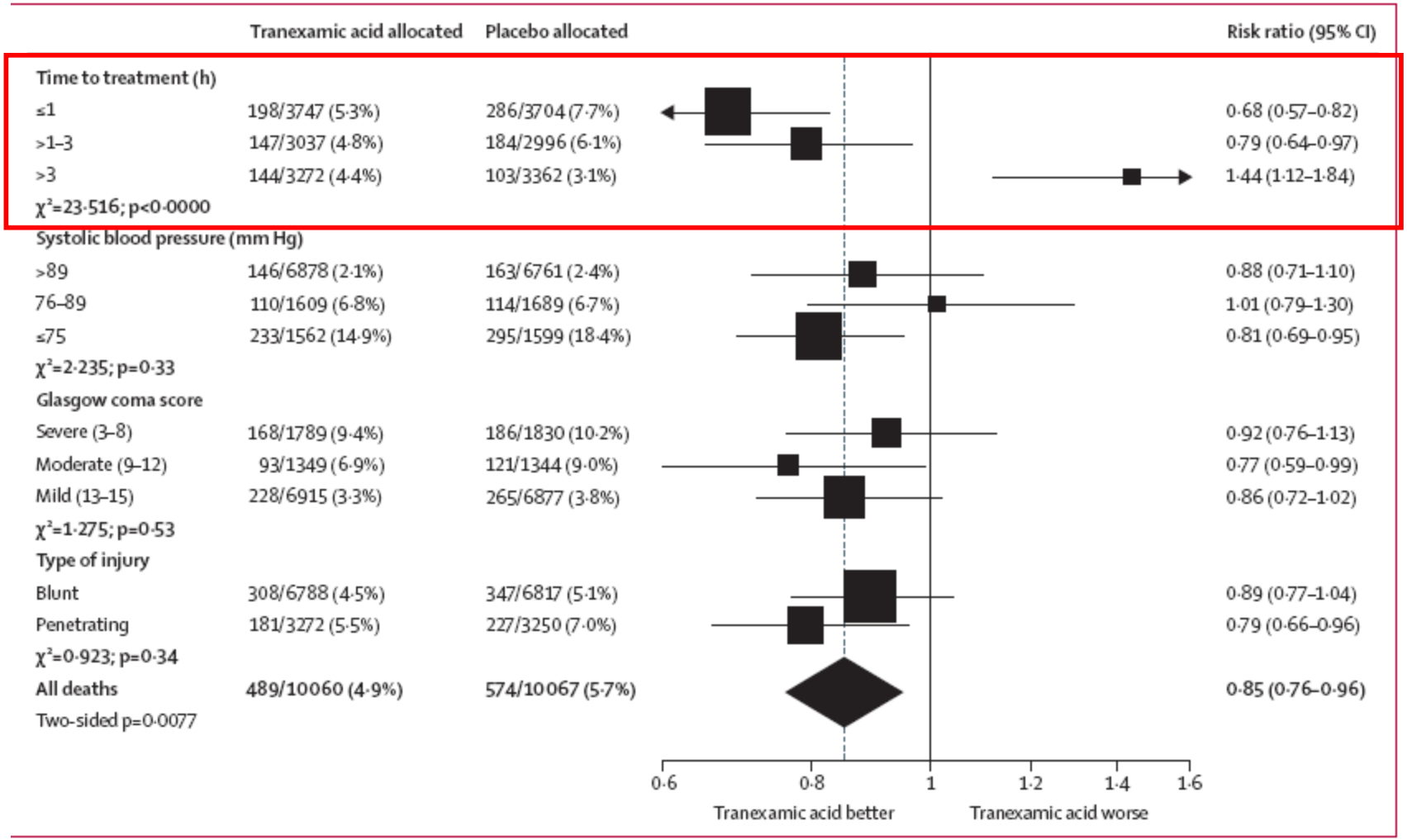


Figure 1: Mortality due to bleeding by subgroups

Lancet 2017; 389: 2105–16

Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

1 g TXA i.v in 10 min,
repeated if bleeding continued after 30 min or stopped and restarted within 24 h

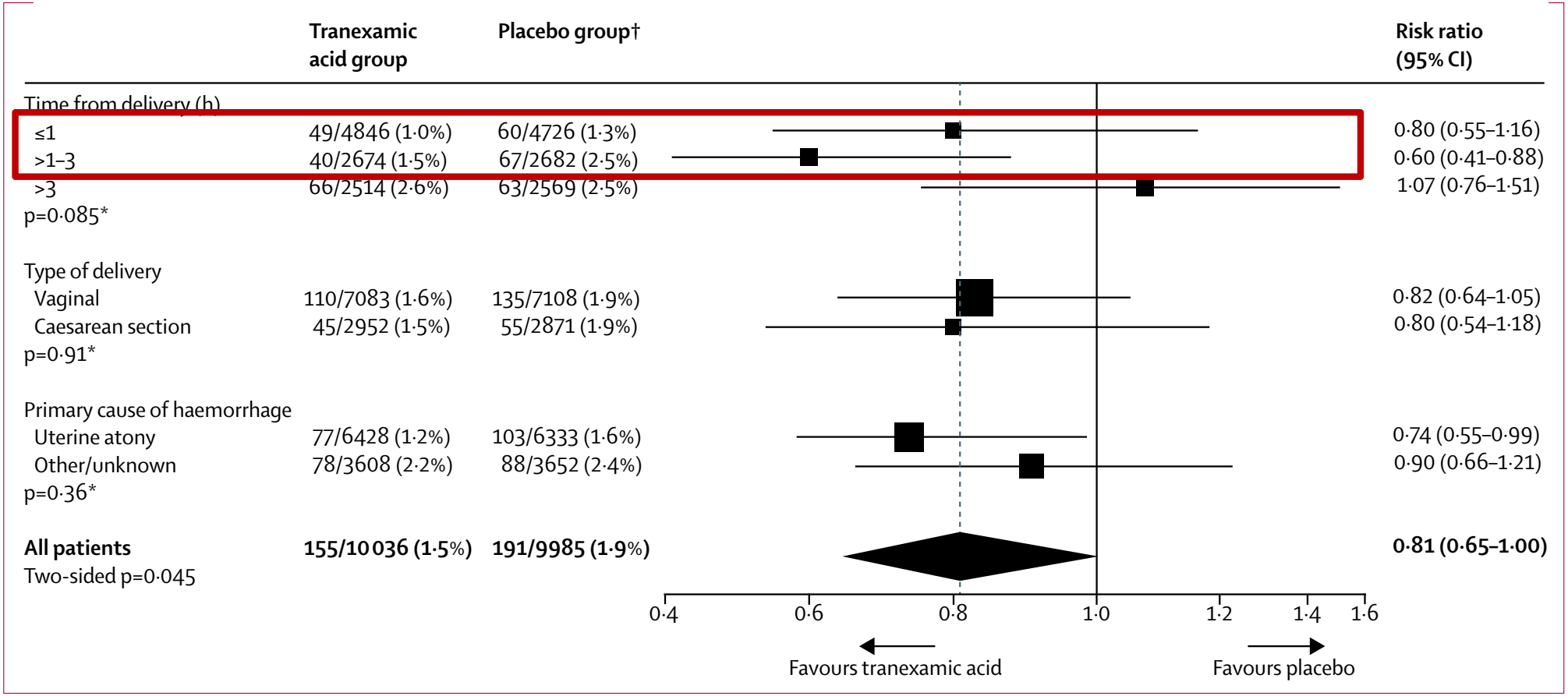


Figure 2: Death from bleeding by subgroup

Lancet 2018; 391: 125–32

Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients

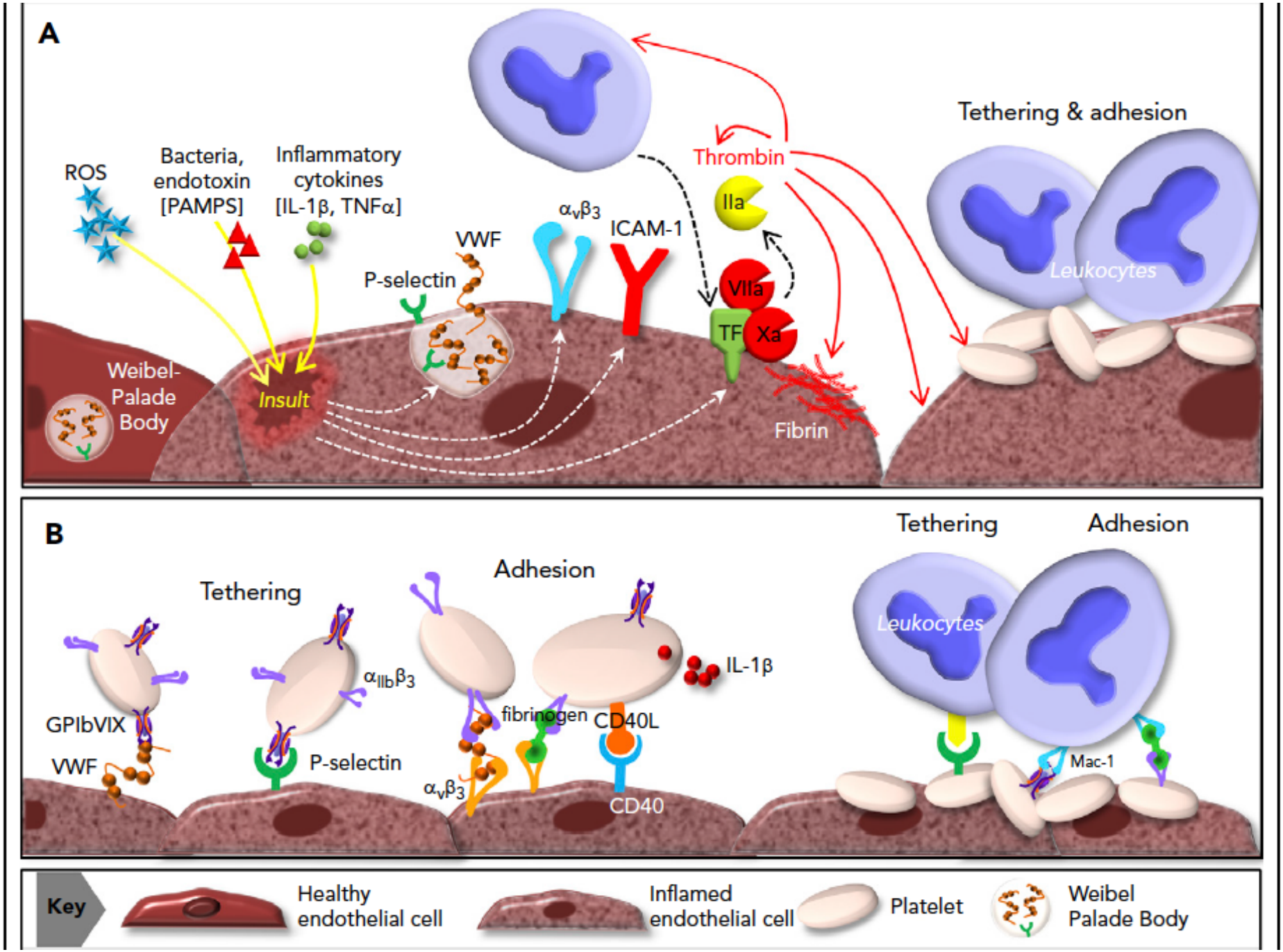
*Angèle Gayet-Ageron, David Prieto-Merino, Katharine Ker, Haleema Shakur, François-Xavier Ageron, Ian Roberts, for the Antifibrinolytic Trials Collaboration**

	CRASH-2 trial		WOMAN trial		Total	
	Tranexamic acid (n=10 060)	Placebo (n=10 067)	Tranexamic acid (n=10 034)	Placebo (n=9977)	Tranexamic acid (n=20 094)	Placebo (n=20 044)
Any cause of death	1463 (14·5%)	1613 (16·0%)	227 (2·3%)	255 (2·6%)	1690 (8·4%)	1868 (9·3%)
Death due to bleeding	489 (4·9%)	574 (5·7%)	155 (1·5%)	190 (1·9%)	644 (3·2%)	764 (3·8%)
Non-bleeding death	974 (9·7%)	1039 (10·3%)	72 (0·7%)	65 (0·7%)	1046 (5·2%)	1104 (5·5%)
Vascular occlusive events	168 (1·7%)	201 (2·0%)	31 (0·3%)	34 (0·3%)	199 (1·0%)	235 (1·2%)
Vascular death	33 (0·3%)	48 (0·5%)	10 (0·1%)	11 (0·1%)	43 (0·2%)	59 (0·3%)
Myocardial infarction*	35 (0·4%)	55 (0·5%)	2 (0·0%)	3 (0·0%)	37 (0·2%)	58 (0·3%)
Stroke*	57 (0·6%)	66 (0·7%)	8 (0·1%)	6 (0·1%)	65 (0·3%)	72 (0·4%)
Pulmonary embolism*	72 (0·7%)	71 (0·7%)	17 (0·2%)	20 (0·2%)	89 (0·4%)	91 (0·5%)
Deep vein thrombosis*	40 (0·4%)	41 (0·4%)	3 (0·0%)	7 (0·1%)	43 (0·2%)	48 (0·2%)

*Includes both fatal and non-fatal events.

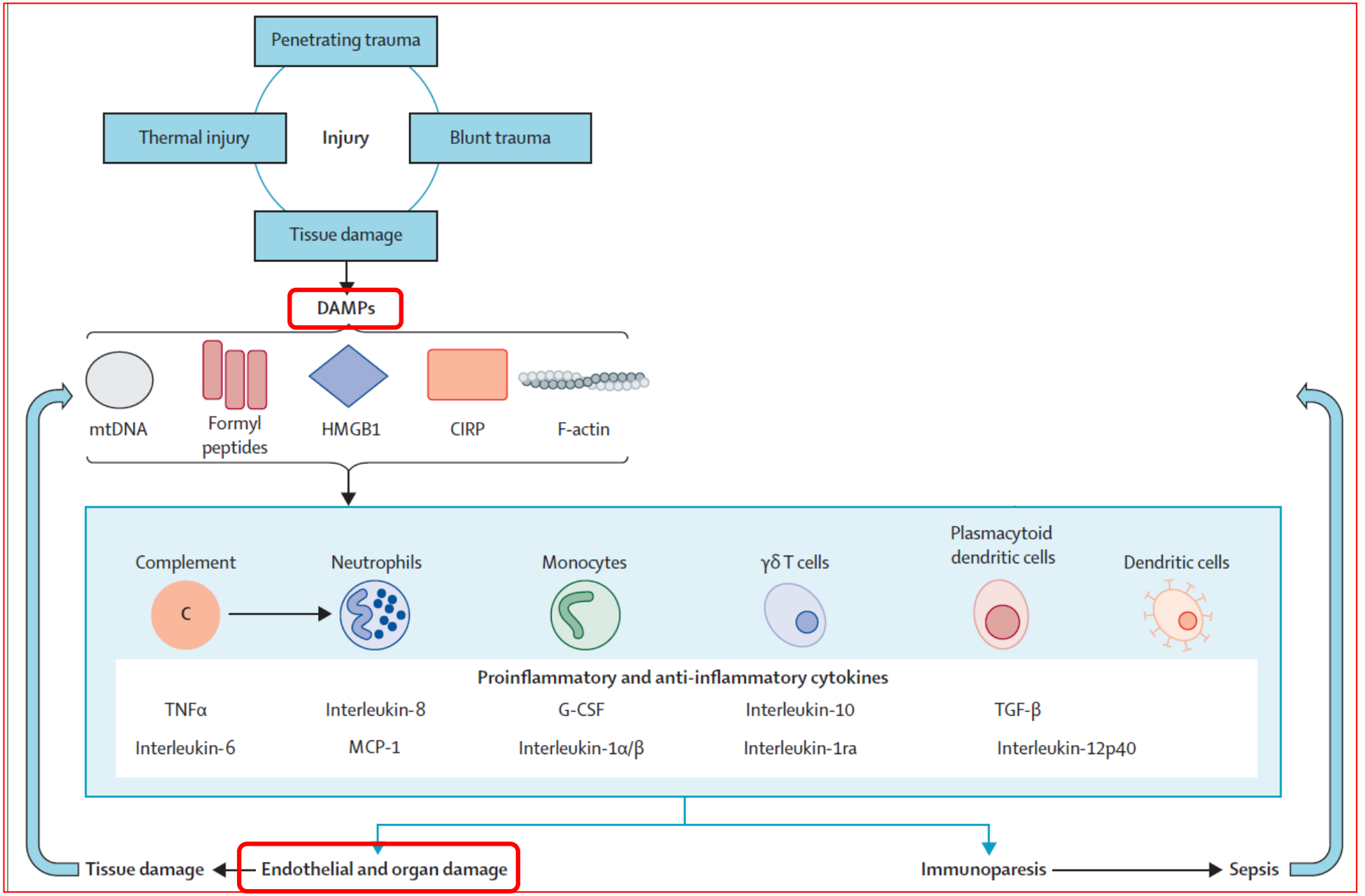
Table 2: **Deaths and vascular occlusive events by treatment allocation**

(*Blood.* 2019;133(9):906-918)

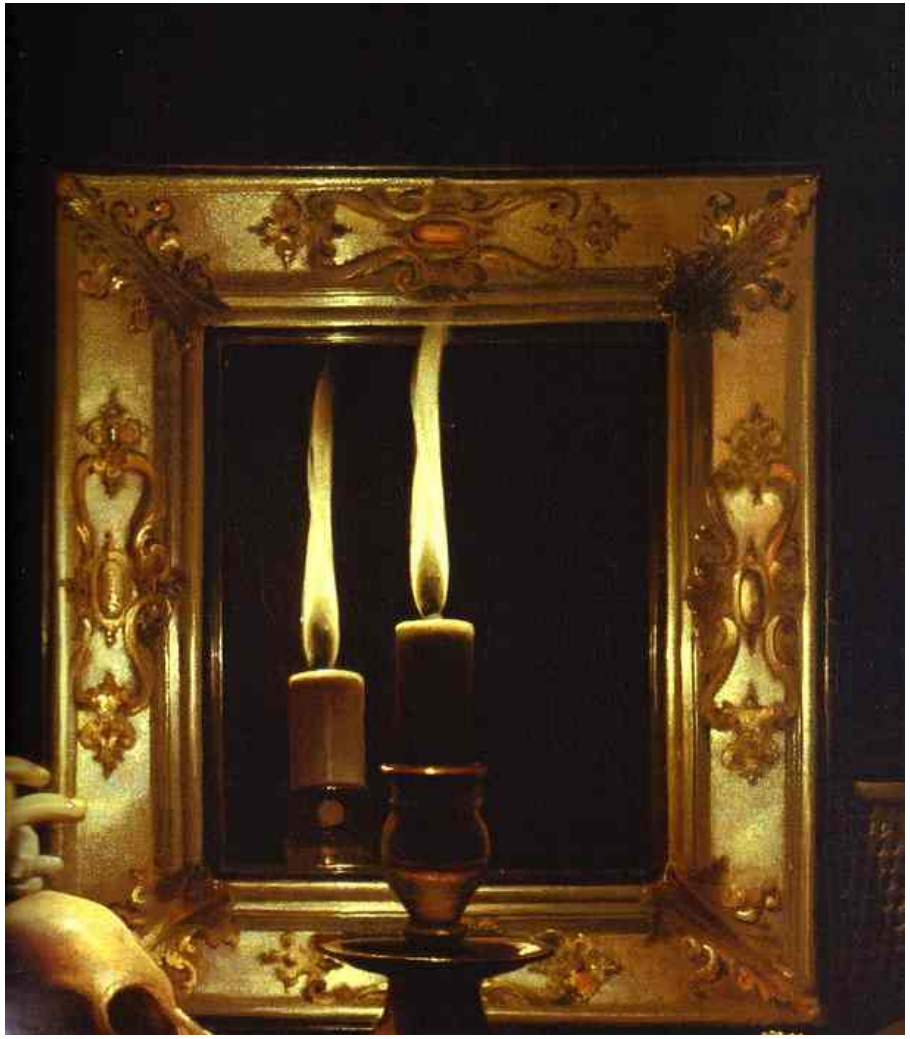


The systemic immune response to trauma: an overview of pathophysiology and treatment

Lancet 2014; 384: 1455–65



Fisiopatologia dell'emorragia critica: …e ombre



Georges de La Tour, Maddalena penitente (particolare), 1639- 1634
(New York, Metropolitan Museum of Art)

Il concetto di emorragia CRITICA

- *Per ENTITA'*
- *Per SEDE*
- *Per FISIOPATOLOGIA*

→ - **paziente** (comorbità/farmaci)
→ - **setting** (pre-H, Emer, ICU)

Per ENTITA'

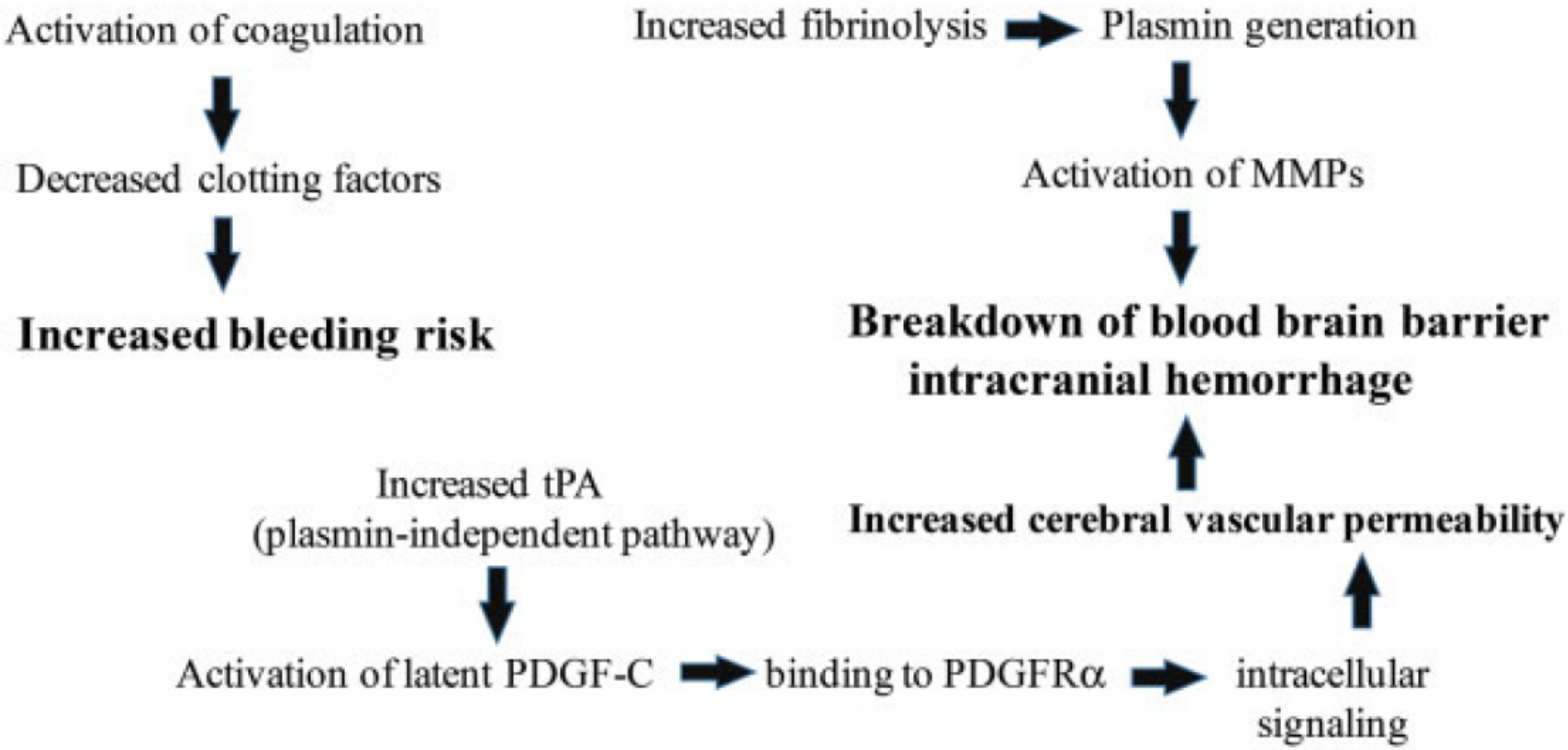
INTRAOPERATORIA	> 500-1000 ml/ora per 1 ora
POSTOPERATORIA	> 200-500 ml/ora per 2 ore
TRAUMA PENETRANTE	> 2 gr Hb/ora per 1 ora
MASSIVA	> 150 ml/min

Early death in APL-post ATRA era

Reference	Year	No. of patients	% ED	% Hemorrhage	Cooperative group study
Fenaux et al[139]	1991–1992	54	9 8	69	European APL 91
	ATRA	47		79	
	ChemoRx				
Mandelli et al[140]	1993–1996	240	5	73	Gruppo Italiano per ole Malattie Ematologicich dell'Adulto (GIMEMA)-AIEOP "AIDA"
Reference	**Year**	**No. of patients**	**% ED**	**% Hemorrhage**	**Population-based study**
Lengfelder et al[141]	1994–1999	51	13	75	German AML cooperative group
Yanada et al[28]	1997–2002	283		89	Japan adult leukemia study group (JALSG) APL97
Lehmann et al[56]	1997–2006	105	29	41	Swedish adult acute leukemia registry
Paulson et al[142]	1999–2010	131	15		Canada
Jácomo et al[143]	2003–2006	134	32	67	Brazil
Serefhanoglu et al[144]	2003–2008	49	41	65	Turkey (PETHEMA protocol)
Iland et al[145]	2004–2009	124	3	25	Australasian leukaemia and lymphoma group
Rahmé et al[57]	2006–2011	399	10	28	French
Karim et al[31]	2007–2012	26	61	44	Pakistan
Silva et al[146]	2007–2017	61	20	86	Brazil

Kwaan HC et al. Semin Thromb Hemost. 2019 Sep;45(6):612-621

Factors contributing to increased risk of intracranial hemorrhage in APL



Kwaan HC et al. Semin Thromb Hemost. 2019 Sep;45(6):612-621

Non solo quantità: il concetto di emorragia CRITICA

- *Per ENTITA'*
- *Per SEDE*
- *Per FISIOPATOLOGIA*

→ - **paziente** (comorbità/farmaci)
→ - **setting** (pre-H, Emer, ICU)

Per ENTITA'

▪ INTRAOPERATORIA	> 500-1000 ml/ora per 1 ora
▪ POSTOPERATORIA	> 200-500 ml/ora per 2 ore
▪ TRAUMA PENETRANTE	> 2 gr Hb/ora per 1 ora
▪ MASSIVA	> 150 ml/min

Per SEDE

- INTRACEREBRALE
- INTRAEPATICA

Per FISIOPATOLOGIA

- DIFETTO DELL'EMOSTASI CONGENITO O ACQUISITO

REVIEW Journal of Intensive Care (2017) 5:14

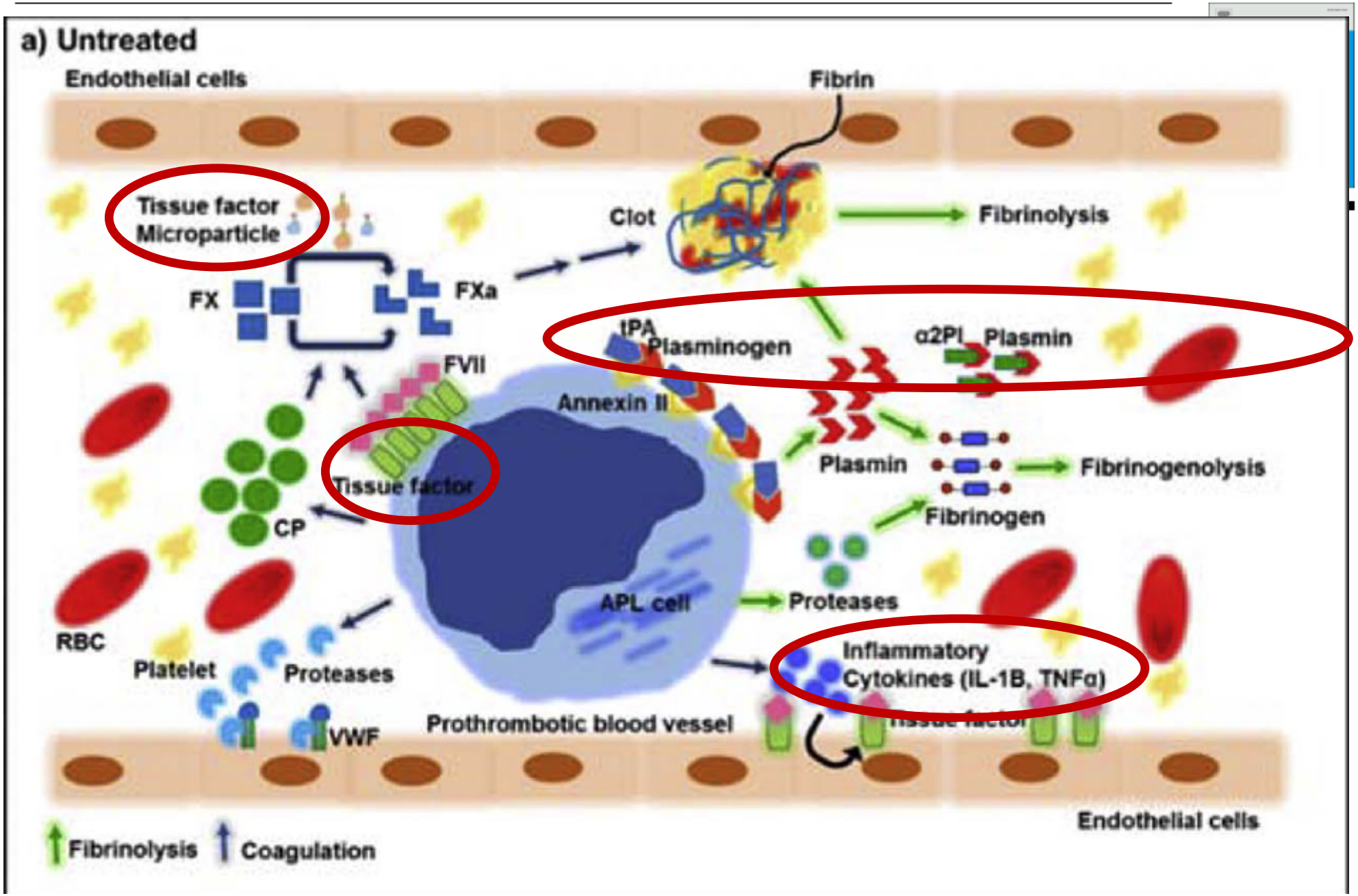
Pathophysiology of trauma-induced coagulopathy: disseminated intravascular coagulation with the fibrinolytic phenotype

Mineji Hayakawa

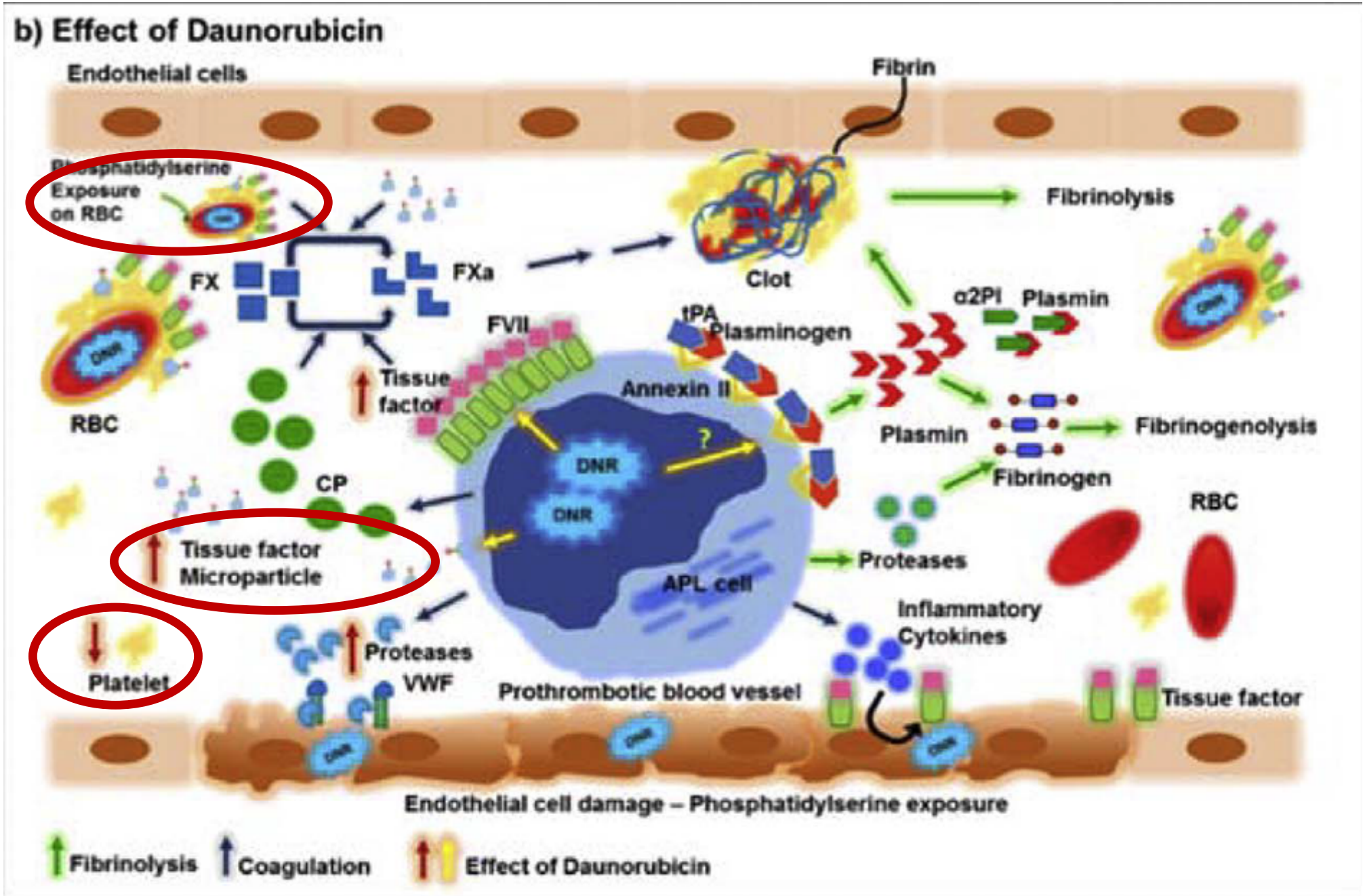
Table 1 Characteristics of DIC phenotypes

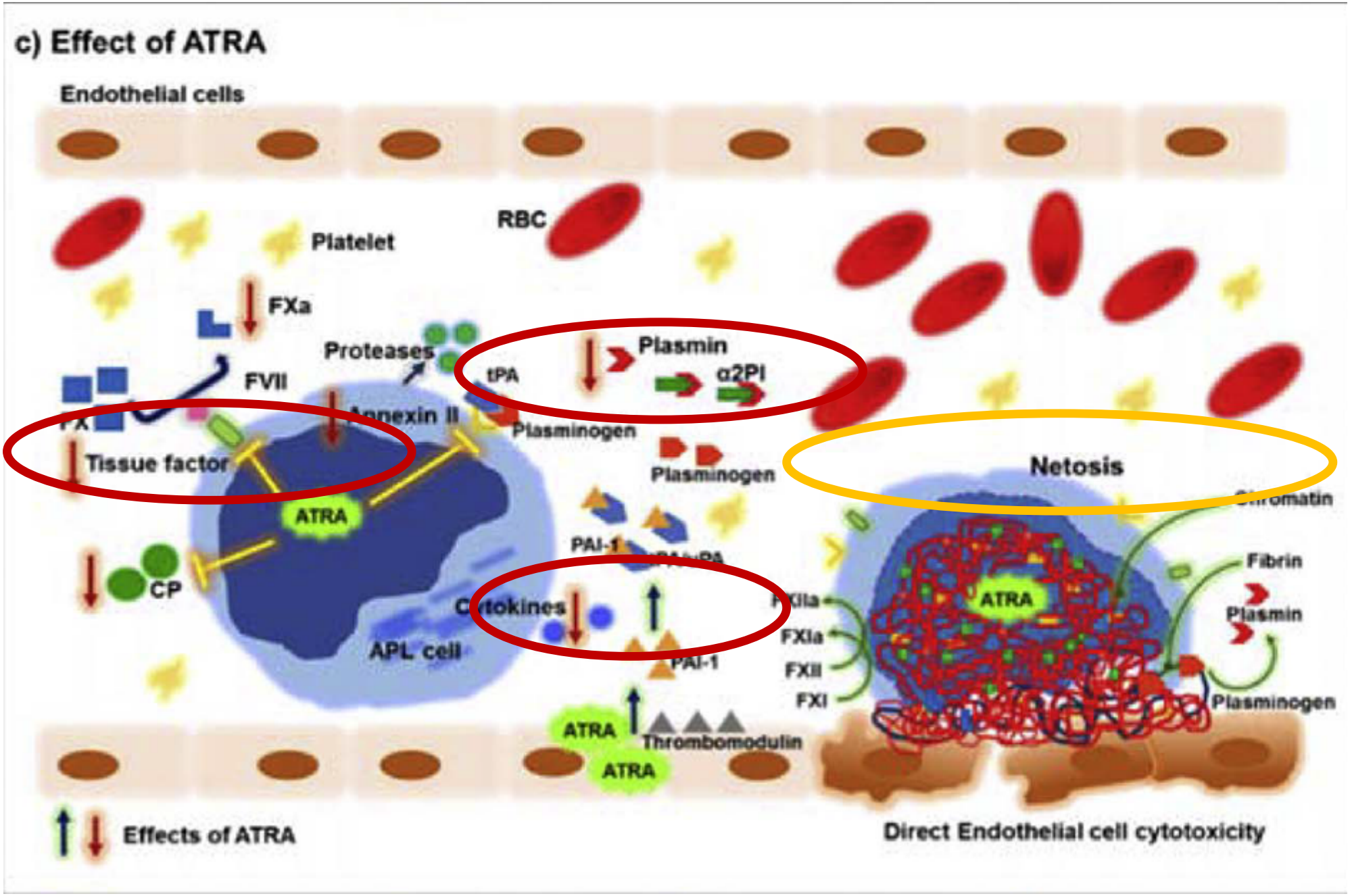
	Fibrinolytic phenotype	Thrombotic phenotype
Representative cause	**Acute promyelocitic leukemia**	Sepsis
Coagulation	Activated	Activated
Fibrinolysis	Activated	Suppressed
PAI-1	Low	High
Clinical symptom	Bleeding	Organ dysfunction

DIC disseminated intravascular coagulation, *PAI* plasminogen activator inhibitor


a) Untreated
Endothelial cells
Fibrin
Tissue factor Microparticle
Clot
Fibrinolysis
FX
FXa
tPA
Plasminogen
α2PI
Plasmin
FVII
Annexin II
Tissue factor
Plasmin
Fibrinogenolysis
CP
Fibrinogen
APL cell
Proteases
RBC
Platelet
Proteases
Inflammatory Cytokines (IL-1B, TNFα)
VWF
Prothrombotic blood vessel
Endothelial cells
Fibrinolysis
Coagulation

- ✓ Acute promyelocytic leukaemia(APL) is characterized by a high rate of life-threatening haemorrhagic events related to hyperfibrinolysis.
- ✓ **Low TAFI activity** has been reported in APL patients
- ✓ PML-RAR-a enhances the expression of S100A10 (p11) which forms a eterotetrameric (S100A10)2-(annexin A2)2 complex on the surface of various cells
- ✓ **The (S100A10)2-(annexin A2)2 complex provides a template for plasminogen activation on the cell surface** and protects plasmin against plasma inhibitors in a similar way to fibrin.
- ✓ These S100A10-related pro-fibrinolytic effects are consistent with the bleeding profile in APA
- ✓ An additional factor for the profibrinolytic state in APL could be the release of neutrophil elastase from the leukaemic promyelocytes
- ✓ The evidence justifies the classification of the haemostatic imbalance in APL as **primary hyperfibrinolysis**, and this conclusion is supported by the typical laboratory findings in the blood of APL patients


b) Effect of Daunorubicin
Endothelial cells
Fibrin
Phosphatidylserine Exposure on RBC
FX
FXa
Clot
Fibrinolysis
α2PI
Plasmin
tPA
Plasminogen
FVII
Tissue factor
Annexin II
RBC
DNR
DNR
?
Plasmin
Fibrinogenolysis
Fibrinogen
CP
RBC
Tissue factor Microparticle
Proteases
APL cell
Inflammatory Cytokines
Platelet
Proteases
VWF
Prothrombotic blood vessel
Tissue factor
Endothelial cell damage – Phosphatidylserine exposure
Fibrinolysis
Coagulation
Effect of Daunorubicin


c) Effect of ATRA
Endothelial cells
RBC
Platelet
FXa
Proteases
FVII
Annexin II
Tissue factor
tPA
Plasmin
α2PI
Plasminogen
Plasminogen
ATRA
PAI-1
CP
Cytokines
APL cell
PAI-1
ATRA
Thrombomodulin
ATRA
Netosis
Chromatin
Fibrin
ATRA
Plasmin
FXIIa
FXIa
FXII
FXI
Plasminogen
Effects of ATRA
Direct Endothelial cell cytotoxicity

(*Blood*. 2019;133(15):1630-1643)

Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet

Miguel A. Sanz,[1-3] Pierre Fenaux,[4,5] Martin S. Tallman,[6] Elihu H. Estey,[7] Bob Löwenberg,[8] Tomoki Naoe,[9] Eva Lengfelder,[10] Hartmut Döhner,[11]

Recommendation	Level of evidence–grade of recommendation	Changes compared with the 2009 recommendations
Management of coagulopathy		
1.5. Treatment with ATRA should be started immediately when a diagnosis of APL is suspected	Ib–A	Unchanged
1.6. Transfusions of fibrinogen and/or cryoprecipitate, platelets, and fresh-frozen plasma should be given immediately upon suspicion of the diagnosis, and then daily or more than once a day if needed, to maintain the fibrinogen concentration above 100-150 mg/dL, the platelet count above 30×10^9/L to 50×10^9/L, and the INR below 1.5	IIb–B	Slightly modified
1.7. Platelet counts and routine coagulation parameters, prothrombin time, activated partial thromboplastin time, and thrombin time, as well as levels of fibrinogen and fibrinogen-fibrin degradation products, should be monitored at least daily and more frequently if required, until disappearance of all clinical and laboratory signs of the coagulopathy	IIb–B	New recommendation
1.8. The benefit of heparin, tranexamic acid, or other anticoagulant or antifibrinolytic therapy remains questionable and should not be used routinely outside of the context of clinical trials	IV–C	Unchanged
1.9. Central venous catheterization, lumbar puncture, and other invasive procedures (eg, bronchoscopy) should be avoided before and during remission induction therapy due to high risk of hemorrhagic complications	IV–C	Unchanged

Thrombosis Research 164 (2018) S98–S102

Predictive factors of fatal bleeding in acute promyelocytic leukemia

Simon Mantha[a,*], Martin S. Tallman[b], Sean M. Devlin[c], Gerald A. Soff[a]

Authors, year	Pts.	End-point	Predictor
Abla et al.	683	Thrombo-hemorrhagic early death	WBC count, PB blast count, morphological subtype, ethnicity, BMI
Mantha et al.	995	Hemorrhagic early death	WBC count, PB blast count, ECOG PS
Mitrovic et al.	56	Hemorrhagic early death	WBC count, ECOG PS, fibrinogen, PT, ISTH DIC score
Kim et al	90	Hemorrhagic death	Platelet count, LDH, fibrinogen
de la Serna et al.	732	Hemorrhagic induction death	Age, creatinine, WBC count, PB blast count, coagulopathy
Higuchi et al.	19	Hemorrhagic early death	Fibrinogen

Univariate; multivariate

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2019.1581187

Predictors of early hemorrhage in acute promyelocytic leukemia

Leonard Naymagon[a], Erin Moshier[b], Douglas Tremblay[a] and John Mascarenhas[a]

- ✓ Retrospective study applying group based trajectory modeling over continously recorded variables
- ✓ Significantly higher risk for major bleeding in pts. with:
  - WBC > 20.000/mmc uptrending during the initial days of induction
  - LDH > 700 U/L uptrending during the initial days of induction

Our findings urge that the transfusion strategy in APL should not be dictated by PLT, FGN, and coagulation parameters alone, but should incorporate consideration of WBC and LDH values and trends

Endoscopy 2015; 47: 1–46

Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE does not recommend the use of tranexamic acid in patients with NVU-GIH (strong recommendation, low quality evidence).

A Cochrane meta-analysis evaluating the use of tranexamic acid in 1654 UGIH patients showed a beneficial effect of TXA on mortality when compared with placebo (relative risk [RR] 0.61, 95%CI 0.42–0.89), but not on other patient outcomes including bleeding, surgery, or transfusion requirements.

However, the beneficial effect on mortality did not persist in subgroup analysis.

The studies included in this meta-analysis have important limitations that affect their generalizability including their methodological quality and the fact that the majority were conducted before the widespread use of therapeutic endoscopy and PPIs.

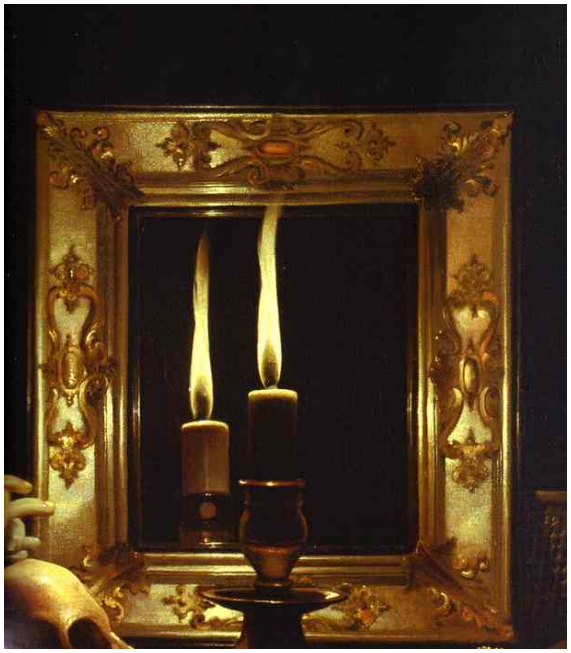
Lancet 2018; 391: 2107–15

Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial

Nikola Sprigg, Katie Flaherty, Jason P Appleton, Rustam Al-Shahi Salman, Daniel Bereczki, Maia Beridze, Hanne Christensen, Alfonso Ciccone,

	Tranexamic acid (n=1161)	Placebo (n=1164)	Adjusted	
			Effect estimate (95% CI)	p value
Primary outcome, day 90				
Participants with mRS outcome	1152	1155	Ordinal OR 0·88 (0·76 to 1·03)	0·11
mRS 0	26 (2%)	24 (2%)	..	..
mRS 1	115 (10%)	124 (11%)	..	..
mRS 2	197 (17%)	181 (16%)	..	..
mRS 3	187 (16%)	194 (17%)	..	..
mRS 4	213 (18%)	221 (19%)	..	..
mRS 5	164 (14%)	162 (14%)	..	..
mRS 6, death	250 (22%)	249 (22%)	..	..
Sensitivity analysis, day 90				
mRS, unadjusted	..	..	Ordinal OR 1·00 (0·86 to 1·15)	0·97
mRS >3	814 (71%)	826 (72%)	Binary OR 0·82 (0·65 to 1·03)	0·08
Haematoma				
Change in volume from baseline to 24 h*, mL	3·72 (15·9)	4·90 (16·0)	MD −1·37 (−2·71 to −0·04)	0·0432
Participants with haematoma expansion†	265 (25%)	304 (29%)	Binary OR 0·80 (0·66 to 0·98)	0·0300
Day 7				
Death by day 7	101 (9%)	123 (11%)	Binary OR 0·73 (0·53 to 0·99)	0·0406
NIHSS day 7	10·13 (8·3)	10·29 (8·3)	MD −0·43 (−0·94 to 0·09)	0·10

Il concetto di emorragia critica: ombre…



Georges de La Tour, Maddalena penitente (particolare), 1639- 1634

- ✓ Test di base dell'emostasi: utili, inutili, dannosi?
- ✓ Metodiche viscoelastiche: quali evidenze cliniche?
- ✓ Tips & tricks per la gestione del circolo e dell'emostasi nel paziente con emorragia critica