SISET

Siset Training Center:

CORSO MALATTIE EMORRAGICHE

Firenze, 26-30 settembre 2016

Mercoledì 28 settembre - sessione pratica

09.00 **Le coagulopatie acquisite**
Marco Marietta (Modena)

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritto **Dott. Marco Marietta** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compens individuali con soggetti portatori di interessi commerciali in campo sanitario:

- **Partecipazione ad Advisory Board per Novo-Nordisk**
- **Consulenze / Relazioni a congressi per Kedrion, Orphan, Novo-Nordisk**

N Engl J Med 2014;370:847-59.

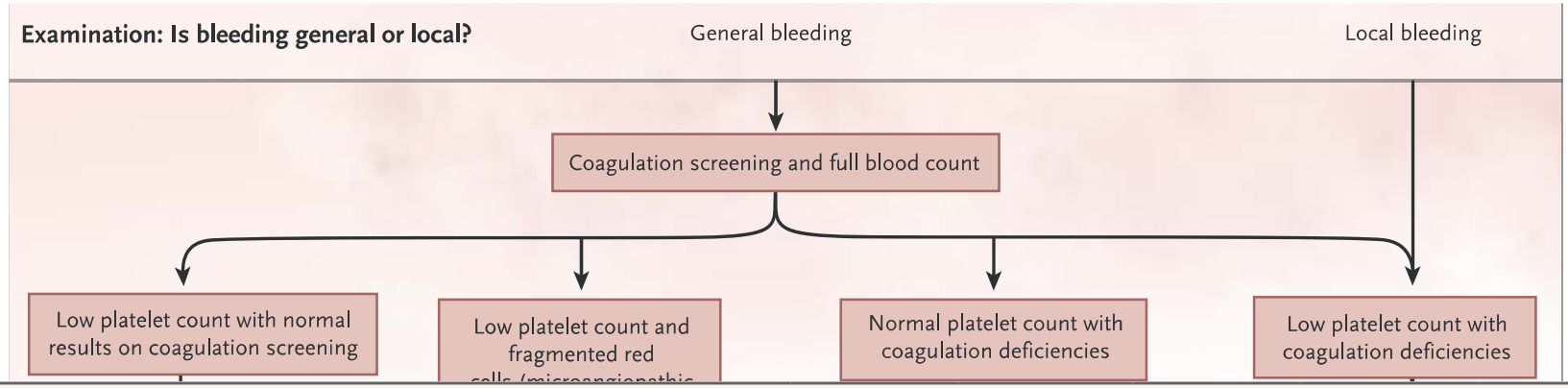


Table 1. Laboratory Findings in Various Platelet and Coagulation Disorders in the ICU.

Condition	Prothrombin Time	Activated Partial-Thromboplastin Time	Fibrinogen Level	D-Dimer Level	Bleeding Time	Platelet Count	Findings on Blood Smear
Vitamin K deficiency or use of vitamin K antagonist	Prolonged	Normal or mildly prolonged	Normal	Unaffected	Unaffected	Unaffected	
Aspirin or thienopyridines	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Liver failure							
Early stage	Prolonged	Unaffected	Unaffected	Unaffected	Unaffected	Unaffected	
End stage	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	
Uremia	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Unaffected	
Disseminated intravascular coagulation	Prolonged	Prolonged	Low	Increased	Prolonged	Decreased	Fragmented red cells
Thrombotic thrombocytopenic purpura	Unaffected	Unaffected	Unaffected	Unaffected	Prolonged	Very low	Fragmented red cells
Hyperfibrinolysis	Prolonged	Prolonged	Low	Very high	Possibly prolonged	Unaffected	

LE COAGULOPATIE ACQUISITE

- ✓ Coagulopatia da trauma
- ✓ Coagulopatia da emorragia massiva
- ✓ Coagulopatia da emorragia post-partum
- ✓ CID
- ✓ Inibitori acquisiti della coagulazione
- ✓ Emorragie da NAO
- ✓ Emorragie da antiaggreganti

Rossaint et al. Critical Care (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

RESEARCH Open Access

The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition

Rolf Rossaint[1], Bertil Bouillon[2], Vladimir Cerny[3,4,5,6], Timothy J. Coats[7], Jacques Duranteau[8],

bjh guideline

A practical guideline for the haematological management of major haemorrhage

Beverley J. Hunt,[1] Shubha Allard,[2] David Keeling,[3] Derek Norfolk,[4] Simon J. Stanworth,[5] Kate Pendry[6] and on behalf of the British Committee for Standards in Haematology

EJA

Eur J Anaesthesiol 2013; **30:**270–382

GUIDELINES

Management of severe perioperative bleeding

Guidelines from the European Society of Anaesthesiology

Sibylle A. Kozek-Langenecker, Arash Afshari, Pierre Albaladejo, Cesar Aldecoa Alvarez Santullano,

Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Green-top Guideline
No. 52

May 2009

Minor revisions November 2009 and April 2011

PREVENTION AND MANAGEMENT OF POSTPARTUM HAEMORRHAGE

SNLG ISS

LINEA GUIDA SU PREVENZIONE E TRATTAMENTO DELL'EMORRAGIA DEL POST-PARTUM

*Blood Transfus 2015; **13**; 498-513*

RECOMMENDATION

Acquired inhibitors of clotting factors: AICE recommendations for diagnosis and management

Massimo Franchini[1], Giancarlo Castaman[2], Antonio Coppola[3], Cristina Santoro[4], Ezio Zanon[5], Giovanni Di Minno[3,6], Massimo Morfini[7], Elena Santagostino[8], Angiola Rocino[9], on behalf of the AICE Working Group*

Supportive management strategies for disseminated intravascular coagulation

An international consensus

Thromb Haemost 2016; 115: ■■■

Alessandro Squizzato[1]; Beverley J. Hunt[2]; Gary T. Kinasewitz[3]; Hideo Wada[4]; Hugo ten Cate[5]; Jecko Thachil[6]; Marcel Levi[7]; Vicente Vicente[8]; Armando D'Angelo[9]; Marcello Di Nisio[7,10]

RECOMMENDATIONS AND GUIDELINES

J Thromb Haemost 2015; DOI:10.1111/jth.12838.

Management of cancer-associated disseminated intravascular coagulation: guidance from the SSC of the ISTH

J. THACHIL,* A. FALANGA,† M. LEVI,‡ H. LIEBMAN§ and M. DI NISIO¶**

OFFICIAL COMMUNICATION OF THE SSC

J Thromb Haemost 2013; **11**: 761–7.

Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines

H. WADA,* J. THACHIL,† M. DI NISIO,‡§ P. MATHEW,¶ S. KUROSAWA,** S. GANDO,††

Regione Emilia-Romagna

Documento regionale di indirizzo

Indicazioni sulla gestione delle emergenze emorragiche in corso di trattamento con farmaci anticoagulanti orali

Aggiornamento luglio 2016

A cura del Gruppo di Lavoro multidisciplinare
della Regione Emilia-Romagna

Direzione Generale alla Sanità e alle Politiche Sociali

E' sui fianchi delle montagne, e non sulla cima, che si sviluppa la vita.
Ma evidentemente senza la cima non si possono avere i fianchi.
E' la cima che determina i fianchi.
E così saliamo.

Robert Pirsig
Lo zen e l'arte della manutenzione della motocicletta

E' sui fianchi delle montagne,
e non sulla cima, che si sviluppa la vita.

British Journal of Anaesthesia **114** (2): 217–24 (2015)
Advance Access publication 8 September 2014 · doi:10.1093/bja/aeu303

BJA

Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence?

T. Haas[1*], D. Fries[2], K. A. Tanaka[3], L. Asmis[4], N. S. Curry[5] and H. Schöchl[6,7]

✓**≥1.5-fold prolongation of aPTT/PT as a transfusion trigger** was identified in 6/11 guidelines for bleeding management

✓PT/ INR and aPTT were basically designed to assess coagulation factor deficiencies and to monitor vitamin K antagonists and heparin

✓All these tests are performed in plasma without platelets or red cells at a standardized temperature, and are unable to correctly diagnose complex settings of fibrinogen deficiency, heparin effects, or fibrinolysis

✓PT and aPTT end when only 5% of thrombin is generated

British Journal of Anaesthesia **114** (2): 217–24 (2015)
Advance Access publication 8 September 2014 · doi:10.1093/bja/aeu303

BJA

Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence?

T. Haas[1*], D. Fries[2], K. A. Tanaka[3], L. Asmis[4], N. S. Curry[5] and H. Schöchl[6,7]

No sound evidence from well-designed studies that confirm the usefulness of SLTs for diagnosis of coagulopathy or to guide haemostatic therapy.

It should be clearly stated that SLT are not per se inappropriate, but have been frequently used to try to answer a question that they were never designed to be able to answer.

E' sui fianchi delle montagne,
e non sulla cima, che si sviluppa la vita.

bjh review

The place of viscoelastic testing in clinical practice

Gregory A. Hans[1] and Martin W. Besser[2]

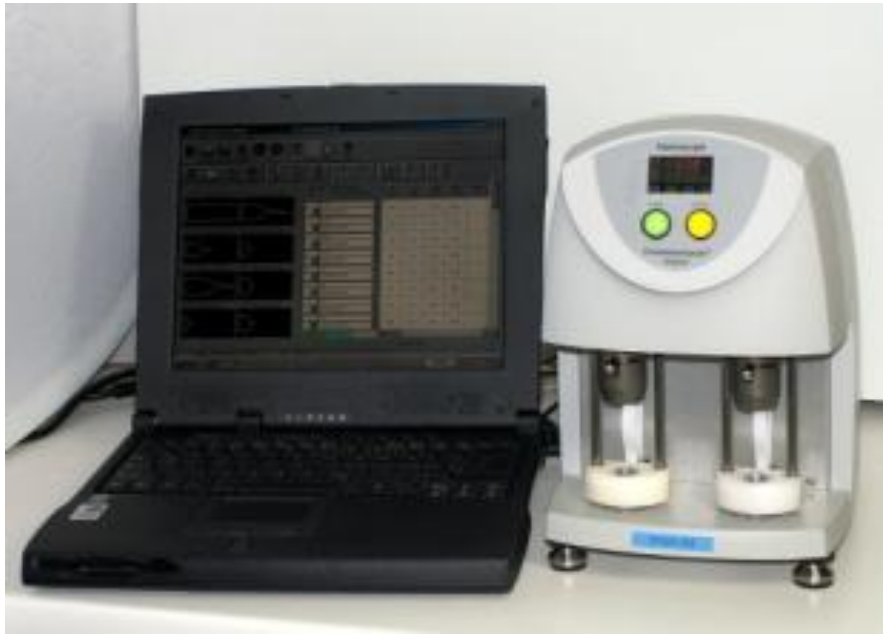
bjh review

British Journal of Haematology, 2016, **174,** 503–514

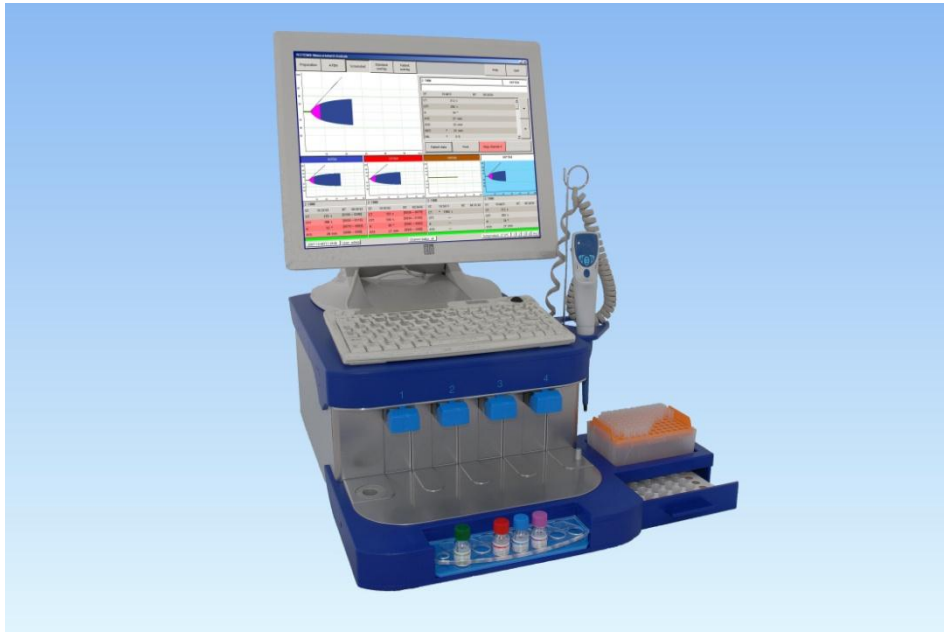
The utility of thromboelastography in inherited and acquired bleeding disorders

Keiji Nogami

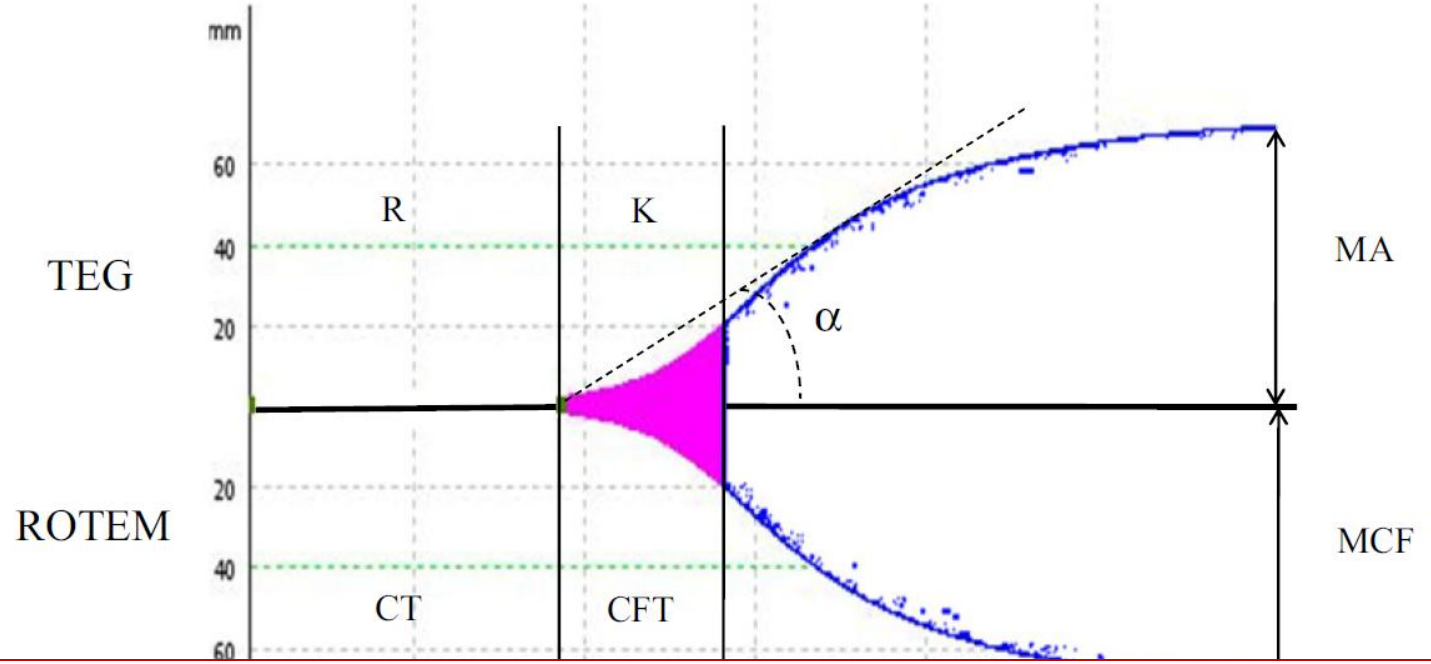
TEG®



ROTEM®



- ✓Lavorano su sangue intero
- ✓Rapidi
- ✓Visione dinamica di coagulazione
- ✓Valutano la fibrinolisi
- ✓Valutano funzione piastrinica
- ✓Lavorano anche in ipotermia



Measurement	TEG® nomenclature	ROTEM® nomenclature	Signification
Time to an amplitude of 2 mm	Reaction time or R time	Clotting time (CT)	Informs about thrombin generation. Prolongation is associated with clotting factor deficiency, inhibitors or anticoagulant.
Time from 2 mm to 20 mm	K time	Clot Formation Time (CFT)	Depicts how fast a visible clot is formed. Depends on thrombin, thrombin generation, fibrinogen and platelets.
Angle formed by a tangential line to the curve starting from the split point.	α-Angle	α-Angle	Closely related to the K time but more precise because it can be determined even when the split does not reach 20 mm of amplitude
Greater width of the tracing	Maximal Amplitude (MA)	Maximal Clot Firmness (MCF)	Mainly affected by platelets and the fibrinogen level.
Per cent reduction of area under the curve (TEG®) or per cent of MCF (ROTEM®) 30 and 60 min after CT.	CLI30 and CL60	LY30 and LY60	Useful in the diagnosis of hyperfibrinolytic states.

Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography

L. RUGERI,* A. LEVRAT,† J. S. DAVID,† E. DELECROIX,* B. FLOCCARD,† A. GROS,† B. ALLAOUCHICHE† and C. NEGRIER*

*Laboratory of Haemostasis; and †Department of Anaesthesia, Intensive Care and EMS, Edouard Herriot Hospital, Hospices Civils de Lyon and Claude Bernard University, Lyon, France

J Thromb Haemost 2007; 5: 289–95.

Table 3 Correlation (*r*) between ROTEM® and standard coagulation

	Prothrombin time	Activated partial thromboplastin time	Fibrinogen	Platelets
EXTEM				
CT	0.53*	(–)	0.40*	(–)
CFT	0.62*	(–)	(–)	0.33*
CA_{15}	**0.66***	(–)	0.69*	0.56*
INTEM				
CT	(–)	0.47*	(–)	(–)

Table 4 Cutoff values for ROTEM® parameters

Transfusion values	ROTEM® Cutoff values	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC
Prothrombin time > 1.5 of control value	CA_{15}-EXTEM = 32 mm	87 (72–87)	100 (99–100)	100 (83–100)	99 (98–99)	0.98
APTT > 1.5 of control value	CFT-INTEM = 112 s	100 (84–100)	74 (73–74)	23 (19–23)	100 (98–100)	0.94
Fibrinogen < 1 g L^{-1}	CA_{10}-FIBTEM = 5 mm	91 (72–93)	85 (84–86)	55 (45–60)	99 (97–100)	0.96
Platelets < 50×10^9 L^{-1}	CA_{15}-INTEM = 46 mm	100 (71–100)	83 (82–83)	17 (12–17)	100 (98–100)	0.92

Rossaint et al. Critical Care (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

RESEARCH Open Access

The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition

Rolf Rossaint[1], Bertil Bouillon[2], Vladimir Cerny[3,4,5,6], Timothy J. Coats[7], Jacques Duranteau[8],

VI. Further resuscitation

Goal-directed therapy

Recommendation 26 **We recommend that resuscitation measures be continued using a goal-directed strategy guided by standard laboratory coagulation values and/or viscoelastic tests. (Grade 1C)**

Consistency of thromboelastometry analysis under scrutiny: Results of a systematic evaluation within and between analysers

Michael Nagler[1]; Hugo ten Cate[2]; Silvio Kathriner[1]; Mattias Casutt[3]; Lucas M. Bachmann[4]; Walter A. Wuillemin[1,5]

- ✓This systematic investigation reveals large differences in the results of some thromboelastometry parameters analyses and lack of homogeneity.
- ✓Differences appear not only between analysers, but also between the different channels of the same analyser, between morning and afternoon measurements and when four weeks apart measured.
- ✓ Furthermore, there is an inconsistency within individual tests (INTEM, EXTEM, FIBTEM, APTEM, HEPTEM). Homogeneity of measurements for MCF, ML, and LI30 were higher than average.

Thromb Haemost 2014; 111: ■■■

Hagemo *et al. Critical C*
DOI 10.1186/s13054-01

AL CARE

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Table 3 ROC analyses of parameters predicting acute traumatic coagulopathy (ATC) and massive transfusion (MT)

	ATC		MT	
	AUC	*(95% CI)*	*AUC*	*(95% CI)*
EXTEM CT (s)	0.73	(0.70-0.76)	0.68	(0.65-0.71)
EXTEM CA5 (mm)	0.79	(0.76-0.81)	0.75	(0.72-0.78)
EXTEM CA10 (mm)	0.78	(0.75-0.81)	0.75	(0.72-0.78)
EXTEM CFT (s)	0.77	(0.74-0.80)	0.73	(0.70-0.76)
EXTEM Alpha (°)	0.78	(0.75-0.81)	0.73	(0.69-0-76)
EXTEM MCF (mm)	0.73	(0.70-0.76)	0.70	(0.67-0.73)
FIBTEM CT (s)	0.72	(0.68-0.75)	0.65	(0.62-0.69)
FIBTEM CA5 (mm)	0.80	(0.77-0.83)	0.78	(0.74-0.81)
FIBTEM CA10 (mm)	0.79	(0.76-0.82)	0.76	(0.73-0.79)
FIBTEM MCF (mm)	0.77	(0.74-0.80)	0.76	(0.73-0.79)
Fibrinogen concentration	0.87*	(0.84-0.89)	0.81	(0.78-0.83)
INR	N/A	N/A	0.82	(0.79-0.84)
Platelet count	0.74	(0.70-0.77)	0.70	(0.66-0.73)

ATC, acute traumatic coagulopathy defined as INR >1.2. MT, massive transfusion defined as 10 or more packed red blood cells. All AUCs values are statistically different from 0.5 with a $P \leq 0.001$. *AUC is significantly larger than

Conclusions: This study confirms previous findings of ROTEM CA5 as a valid marker for ATC and predictor for MT. With optimum threshold for EXTEM CA5 ≤ 40 mm and FIBTEM CA5 ≤ 9 mm, sensitivity is 72.7% and 77.5% respectively. Future investigations should evaluate the role of repeated viscoelastic testing in guiding haemostatic resuscitation in trauma.

Da Luz *et al. Critical Care* 2014, **18**:518
http://ccforum.com/content/18/5/518

CRITICAL CARE

RESEARCH Open Access

- ✓ *Methodologic quality was moderate*
  6.07; standard deviation, 0.49).
- ✓ *With QUADAS-2, only three of 47 studies (6.4%) had a low risk of bias in all domains (patient selection, index test, reference standard and flow and timing); 37 of 47 studies (78.8%) had low concerns regarding applicability.*
- ✓ *Limited evidence from observational data suggest that TEG®/ROTEM® tests diagnose early trauma coagulopathy and may predict blood-product transfusion and mortality in trauma. Effects on blood-product transfusion, mortality, and other patient-important outcomes remain unproven in randomized trials.*

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 19 ISSUE 58 JULY 2015

Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis

Penny Whiting, Maiwenn Al, Marie Westwood, Isaac Corro Ramos, Steve Ryder, Nigel Armstrong, Kate Misso, Janine Ross, Johan Severens and Jos Kleijnen

There was no evidence on the clinical effectiveness of VE testing, using any device, in trauma patients or women with PPH. Available data generally indicated that a positive result on each of the TEG or ROTEM parameters or on SLTs was predictive of transfusion (RBC, any blood component and massive transfusion) and death. This implies a potential for improved intervention based on VE testing; however, there were no data showing that the use of VE devices could change outcomes. There were no clear differences between ROTEM, TEG or SLTs. No studies of the Sonoclot device were identified that fulfilled inclusion criteria for the either the trauma or PPH populations.

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding

Authors' conclusions

We found no evidence on the accuracy of TEG and very little evidence on the accuracy of ROTEM. The value of accuracy estimates are considerably undermined by the small number of included studies, and concerns about risk of bias relating to the index test and the reference standard. We recognise that the reference standards of PT and INR are imperfect, but in the absence of embedded clinical consensus these are judged to be the best reflection of current clinical practice. We are unable to offer advice on the use of global measures of haemostatic function for trauma based on the evidence on test accuracy identified in this systematic review. **This evidence strongly suggests that at present these tests should only be used for research.**

Cochrane Database of Systematic Reviews **2015, Issue 2. Art. No.: CD010438.**

Cochrane Library

Cochrane Database of Systematic Reviews

We found six ongoing trials but were unable to retrieve any data from them. Compared with transfusion guided by any method, TEG- or ROTEM- seemed to reduce overall mortality (7.4% versus 3.9%; risk ratio (RR) 0.52, 95% CI 0.28 to 0.95; I^2 = 0%, 8 studies, 717 participants, low quality of evidence) but only eight trials provided data on mortality, and two were zero event trials. Our analyses demonstrated a statistically significant effect of TEG or ROTEM compared to any comparison on the proportion of participants transfused with pooled red blood cells (PRBCs) (RR 0.86, 95% CI 0.79 to 0.94; I^2 = 0%, 10 studies, 832 participants, low quality of evidence), fresh frozen plasma (FFP) (RR 0.57, 95% CI 0.33 to 0.96; I^2 = 86%, 8 studies, 761 participants, low quality of evidence), platelets (RR 0.73, 95% CI 0.60 to 0.88; I^2 = 0%, 10 studies, 832 participants, low quality of evidence), and overall haemostatic transfusion with FFP or platelets (low quality of evidence). Meta-analyses also showed fewer participants with dialysis-dependent renal failure.

We found no difference in the proportion needing surgical reinterventions (RR 0.75, 95% CI 0.50 to 1.10; I^2 = 0%, 9 studies, 887 participants, low quality of evidence) and excessive bleeding events or massive transfusion (RR 0.38, 95% CI 0.38 to 1.77; I^2 = 34%, 2 studies, 280 participants, low quality of evidence). The planned subgroup analyses failed to show any significant differences.

We graded the quality of evidence as low based on the high risk of bias in the studies, large heterogeneity, low number of events, imprecision, and indirectness. TSA indicates that only 54% of required information size has been reached so far in regards to mortality, while there may be evidence of benefit for transfusion outcomes. Overall, evaluated outcomes were consistent with a benefit in favour of a TEG- or ROTEM-guided transfusion in bleeding patients.

E' sui fianchi delle montagne,
e non sulla cima, che si sviluppa la vita.

La diagnosi di EA: l'APTT

International Journal of Laboratory Hematology
The Official journal of the International Society for Laboratory Hematology

ORIGINAL ARTICLE INTERNATIONAL JOURNAL OF LABORATORY HEMATOLOGY

Int. Jnl. Lab. Hem. 2011, **33**, 154–158

The responsiveness of different APTT reagents to mild factor VIII, IX and XI deficiencies

A. BOWYER*,†, S. KITCHEN*, M. MAKRIS*,†

Table 1. Mean APTT responsiveness in U/dl of normal plasma to FVIII, FIX and FXI in four APTT reagents

APTT reagent	FVIII responsiveness (U/dl)	FIX responsiveness (U/dl)	FXI responsiveness (U/dl)
Synthasil	54	38.5	57.5
Actin FS	67.5	52.5	70
Dapttin	33.5	9.5	14
STA-PTTA	44	30.5	26

Comparison of four commercially available activated partial thromboplastin time reagents using a semi-automated coagulometer

Blood Coagulation and Fibrinolysis 2003, 14:493–497

Shrimati Shetty, Kanjaksha Ghosh and Dipika Mohanty

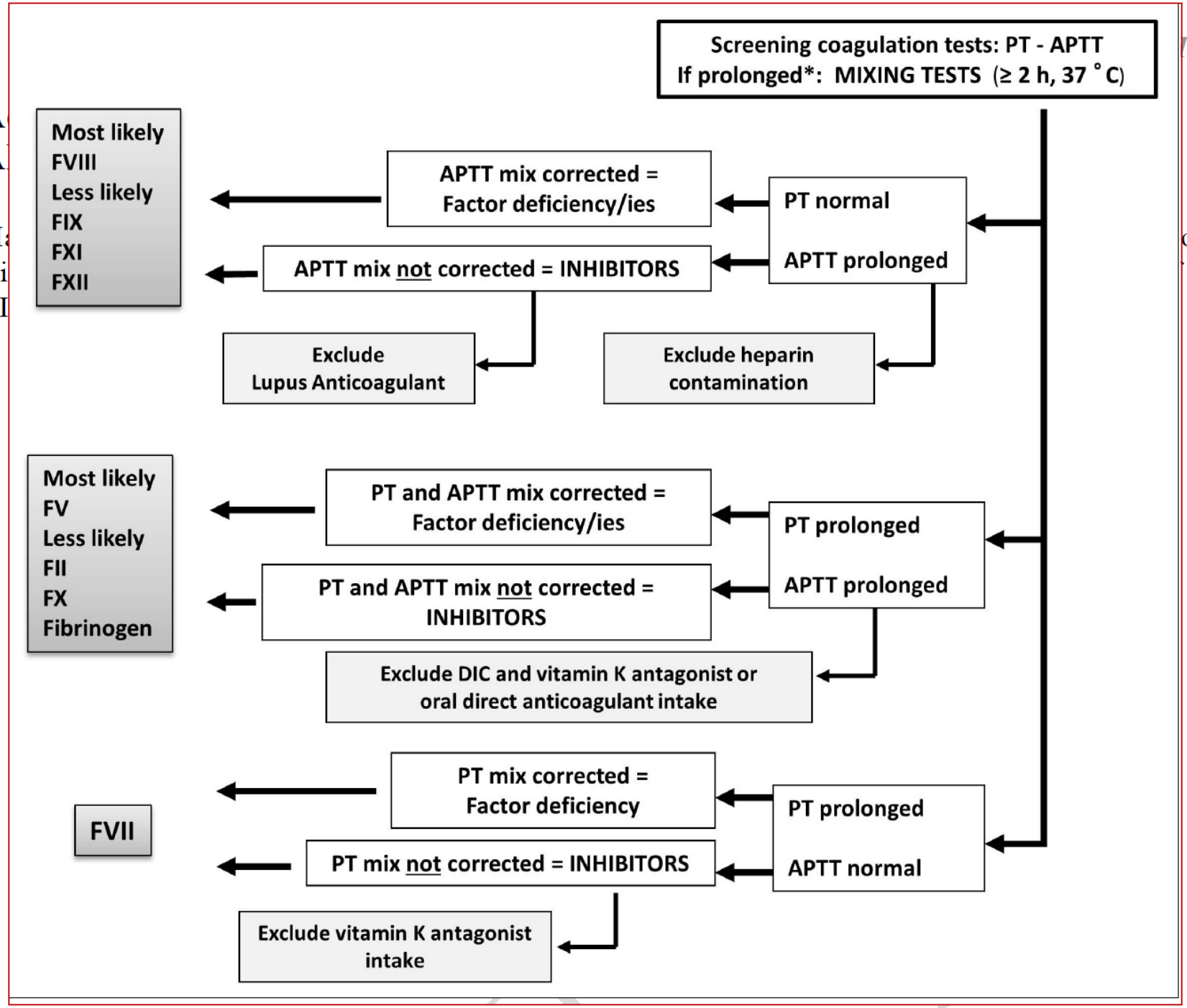
Table 2 Sensitivity of activated partial thromboplastin time reagents in normal and abnormal samples

	Percentage abnormal ratio		
Reagent	Factor VIII/factor IX levels (10–40%)	Lupus anticoagulant-positive	Normal controls
A	36.4	4.6	29.2
B	18.2	4.6	25
C	4.6	0	8.3
D	13.6	9.1	12.5

All four reagents faithfully picked up all the patients with moderate to severe (<10%) factor VIII deficiency

FVIII level category at diagnosis (154)	
Severe, 1 IU/dL or less	46 (29.87)
Moderate, more than 1, less than 5 IU/dL	56 (36.36)
Mild, 5 or more, less than 50 IU/dL	52 (33.77)

La diagnosi di EA: il mixing test


Screening coagulation tests: PT - APTT
If prolonged*: MIXING TESTS (≥ 2 h, 37 °C)
PT normal
APTT prolonged
APTT mix corrected = Factor deficiency/ies
APTT mix not corrected = INHIBITORS
Most likely
FVIII
Less likely
FIX
FXI
FXII
Exclude Lupus Anticoagulant
Exclude heparin contamination
PT prolonged
APTT prolonged
PT and APTT mix corrected = Factor deficiency/ies
PT and APTT mix not corrected = INHIBITORS
Most likely
FV
Less likely
FII
FX
Fibrinogen
Exclude DIC and vitamin K antagonist or oral direct anticoagulant intake
PT prolonged
APTT normal
PT mix corrected = Factor deficiency
PT mix not corrected = INHIBITORS
FVII
Exclude vitamin K antagonist intake

Mixing test

- ✓ Miscela 1:1 di plasma del paziente e plasma “normale”
- ✓ **Incubazione a 37 °C per 2 ore**
- ✓ **Mancata correzione a 2 ore**

- ✓ Necessità di standardizzazione:
  - anche t=0 e 1 ora?
  - Che cos’è “correzione” = più del 50%? Completo rientro negli intervalli di riferimento?

Laboratory Diagnosis of Acquired Hemophilia A: Limitations, Consequences, and Challenges

Andreas Tiede, MD, [illegible] MD, PhD[2]

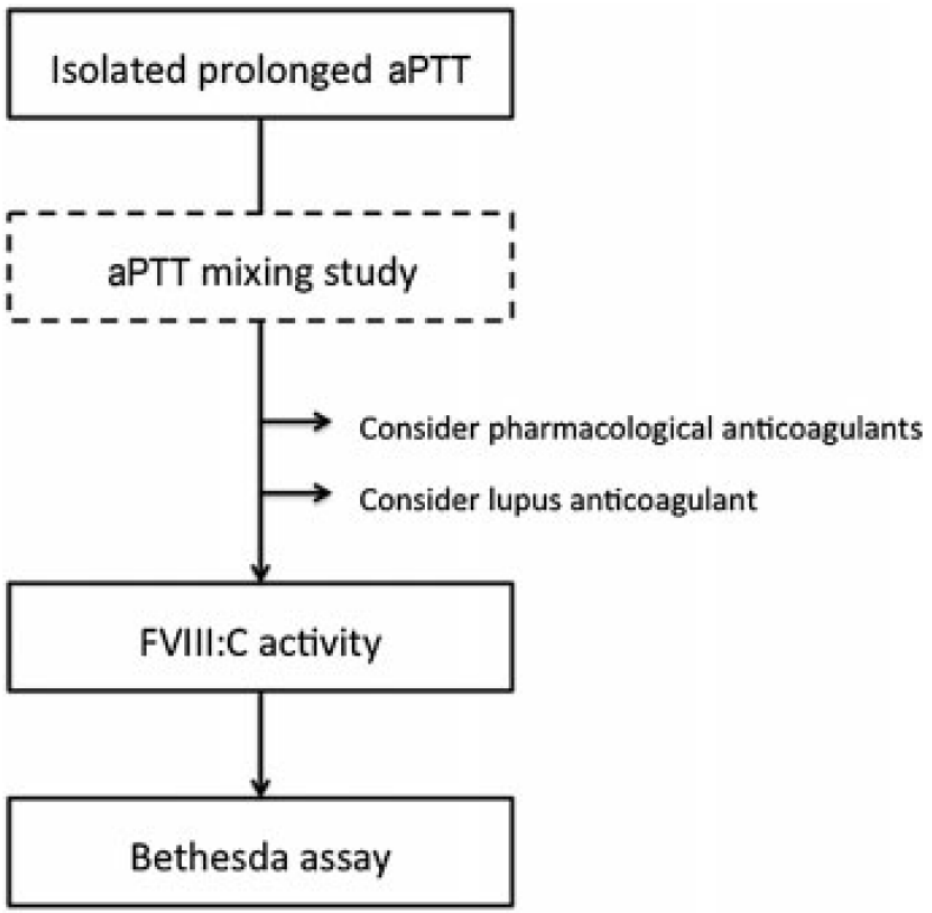


Fig. 1 Proposed diagnostic algorithm for acquired hemophilia A. aPTT, activated partial thromboplastin time; FVIII:C, factor VIII coagulant.

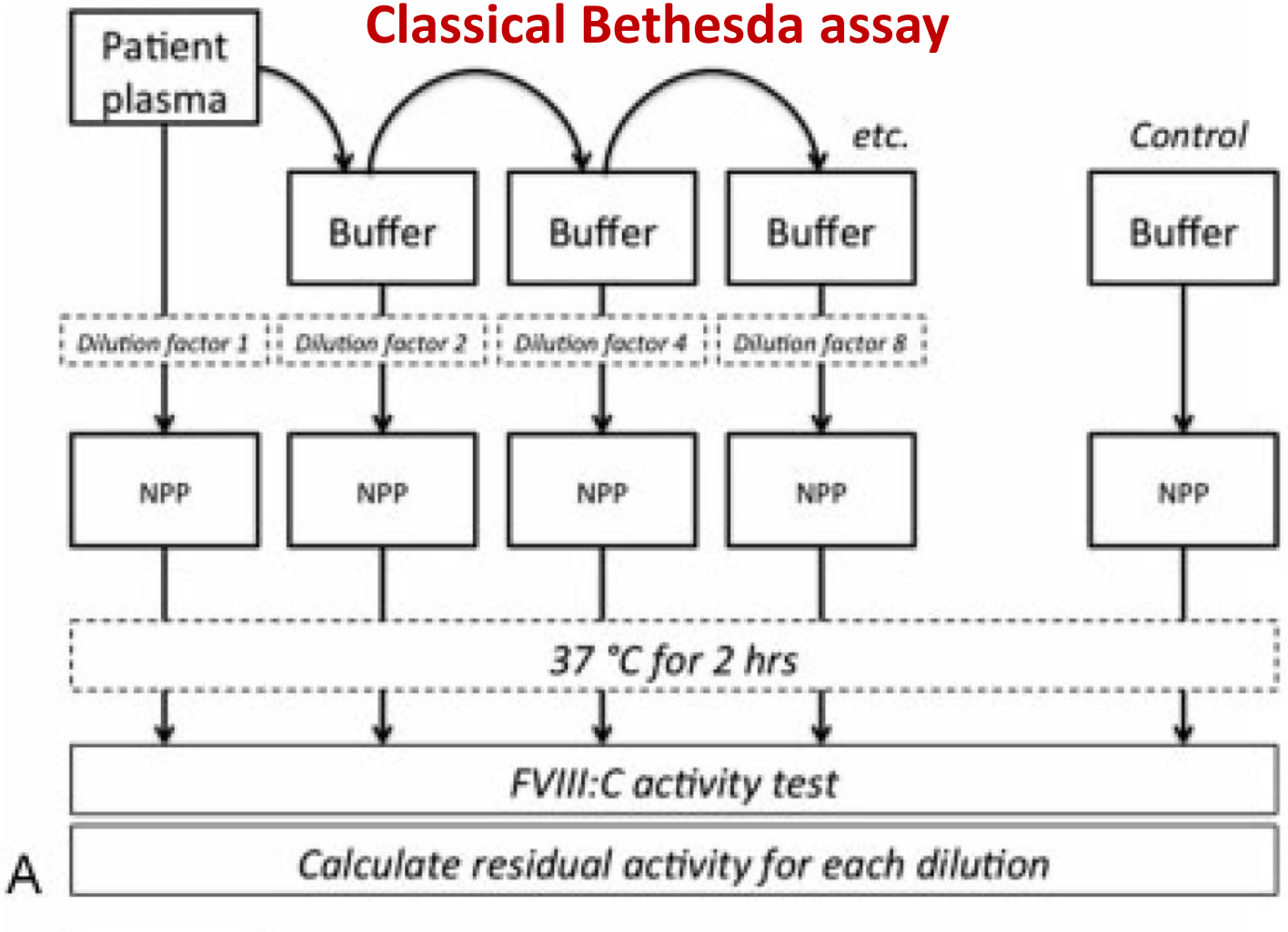
Semin Thromb Hemost 2014;40:803–811.

La diagnosi di EA:
il dosaggio dell'inibitore

Laboratory Diagnosis of Acquired Hemophilia A: Limitations, Consequences, and Challenges

Andreas Tiede, MD, PhD[1] Sonja Werwitzke, MD, PhD[1] Rüdiger E. Scharf, MD, PhD[2]

Classical Bethesda assay

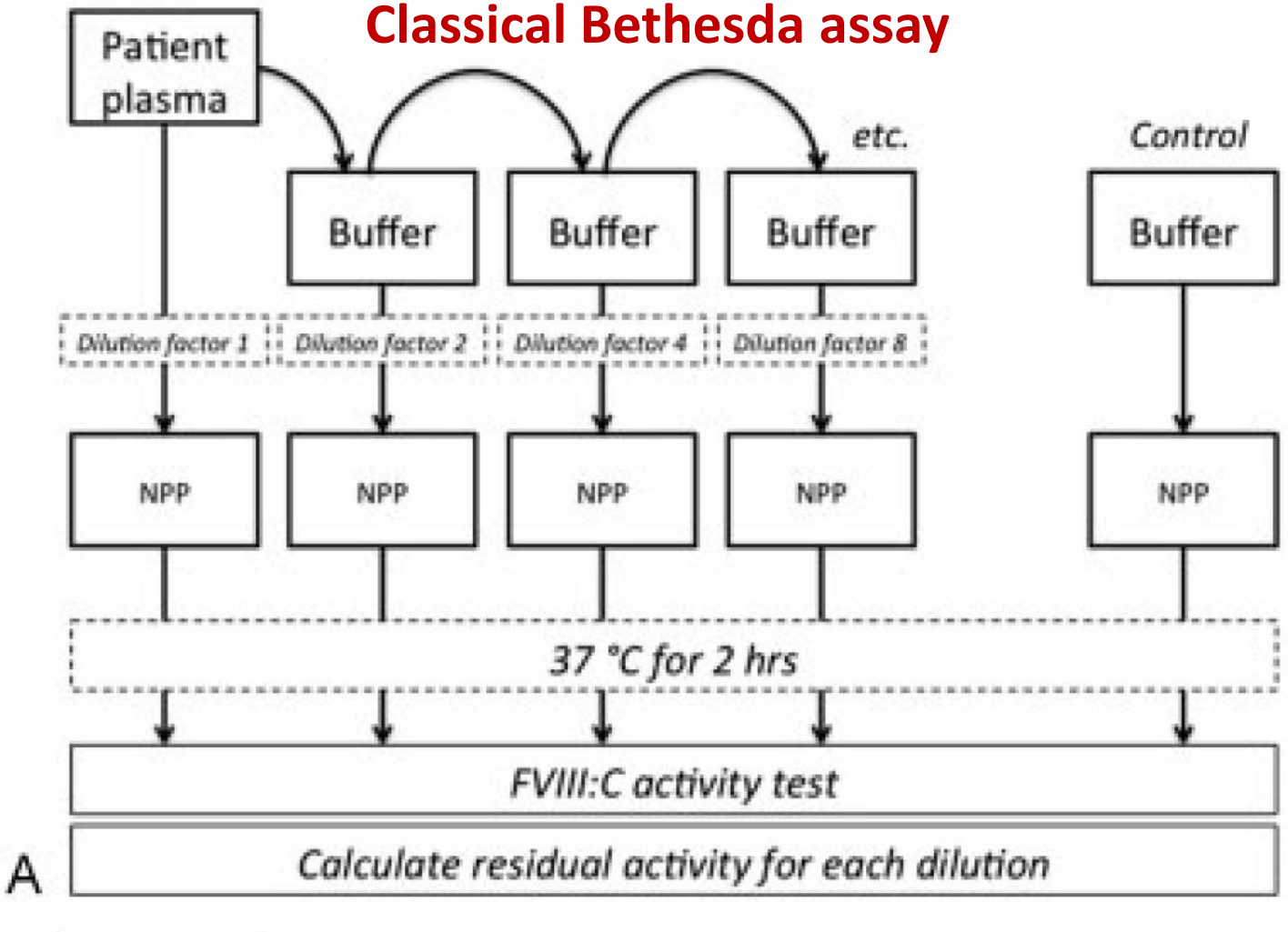


Semin Thromb Hemost 2014;40:803–811.

Laboratory Diagnosis of Acquired Hemophilia A: Limitations, Consequences, and Challenges

Andreas Tiede, MD, PhD[1] Sonja Werwitzke, MD, PhD[1] Rüdiger E. Scharf, MD, PhD[2]

Classical Bethesda assay

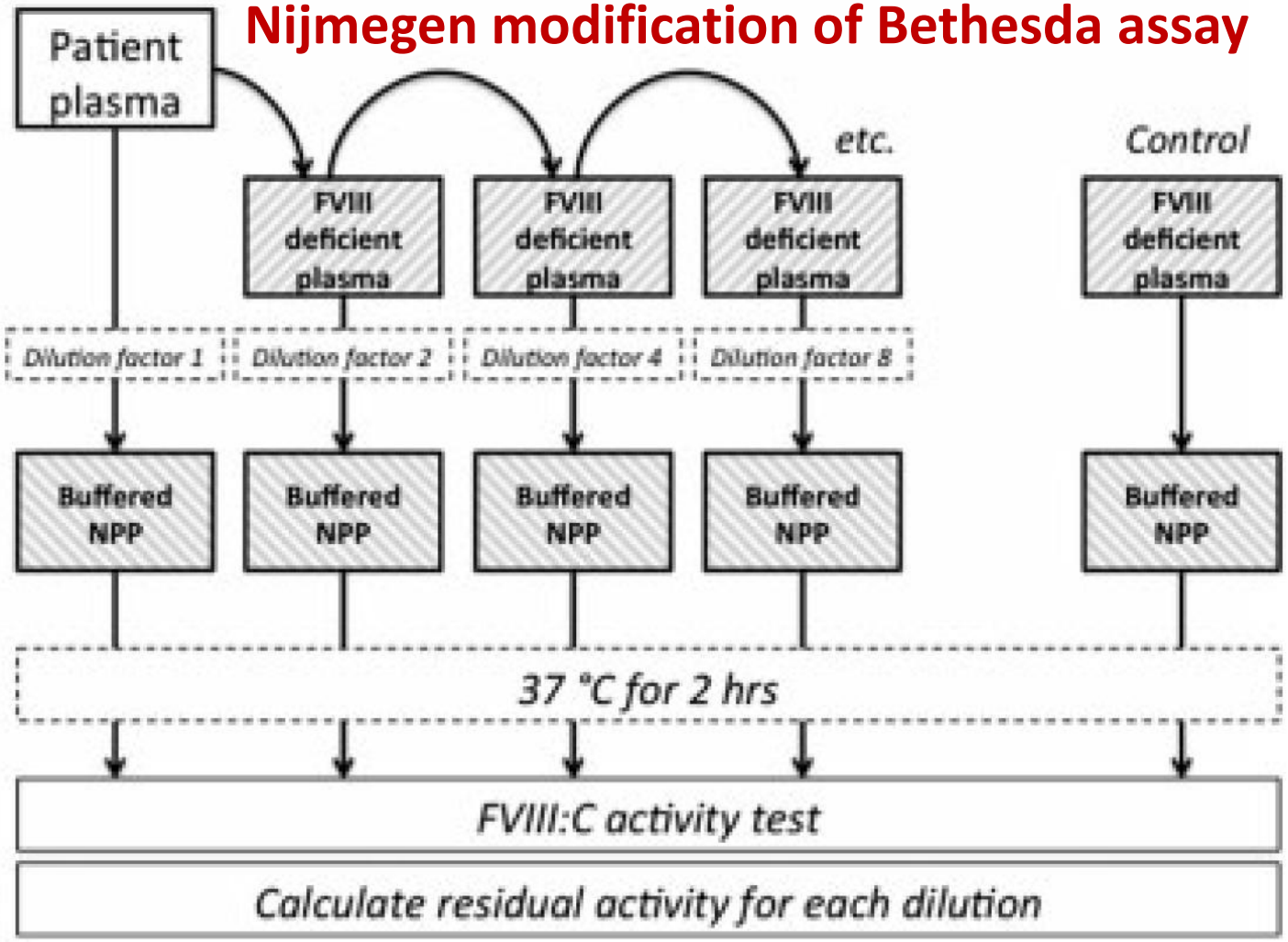


Semin Thromb Hemost 2014;40:803–811.

Laboratory Diagnosis of Acquired Hemophilia A: Limitations, Consequences, and Challenges

Andreas Tiede, MD, PhD[1] Sonja Werwitzke, MD, PhD[1] Rüdiger E. Scharf, MD, PhD[2]

Nijmegen modification of Bethesda assay



Semin Thromb Hemost 2014;40:803–811.

Type 1 inhibitor

C_{inh}[BU/mL] = (2 - $\log_{10}$ RA)/$\log_{10}$ X 2 dilution

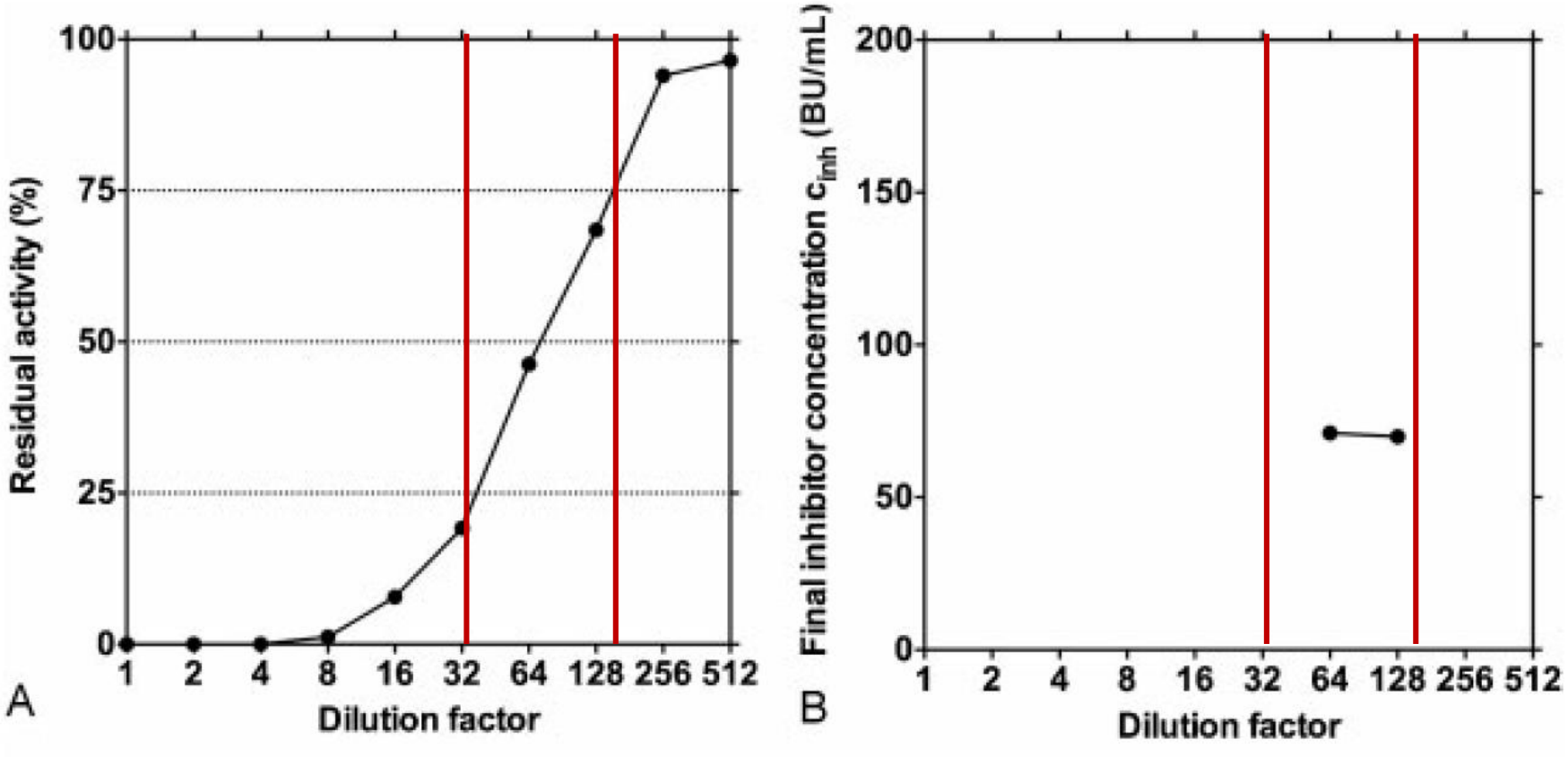
The calculation is best performed in standard working sheets

If more than one RA is between 25 and 75%, the dilution closest to 50% should be preferred to determine C_{inh}

	Patient sample dilutions									
Dilution factor	1	2	4	8	16	32	64	128	256	512
Type 1										
FVIII:C (IU/dL)	< 1	< 1	< 1	0.5	3.3	8.2	19.7	29.1	40.8	41.0
RA (%)	0									
C_{inh} (BU/mL)	–	–	–							
Final result										

Tiede A et al. Sem Thromb Hemost 2014;40:803-811

Type 1 inhibitor



Tiede A et al. Sem Thromb Hemost 2014;40:803-811

Type 2 inhibitor

	Patient sample dilutions

$$C_{inh}[BU/mL] = (2 - \log_{10} RA)/\log_{10} X\ 2\ \text{dilution}$$

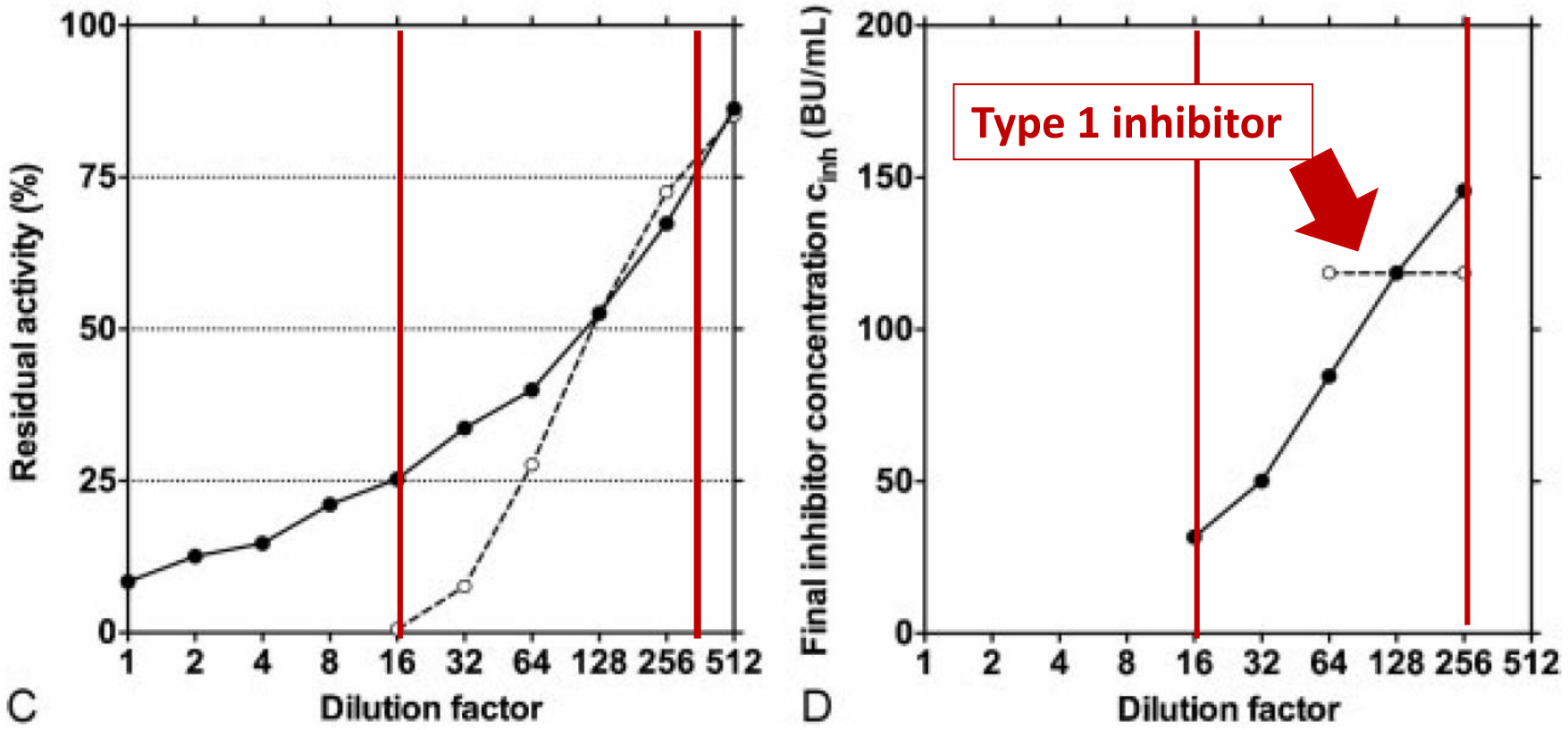
The calculation is best performed in standard working sheets

If more than one RA is between 25 and 75%, the dilution closest to 50% should be preferred to determine C_{inh}

Type 2										
FVIII:C (IU/dL)	4.1	6.2	7.2	10.4	12.4	16.6	19.7	25.9	33.1	42.4
RA (%)										
C_{inh} (BU/mL)										
Final result										

Tiede A et al. Sem Thromb Hemost 2014;40:803-811

Type 2 inhibitor



Tiede A et al. Sem Thromb Hemost 2014;40:803-811

Type 2 inhibitor

	Patient sample dilutions									
Dilution factor	1	2	4	8	16	32	64	128	256	512
Type 1										
FVIII:C (IU/dL)	< 1	< 1	< 1	0.5	3.3	8.2	19.7	29.1	40.8	41.0
RA (%)	0	0	0	1.2	7.8	19.2	46.3	68.5	96.0	96.5
C_{inh} (BU/mL)	–	–	–	51.3	59.0	76.2	71.1	69.9	15.1	26.5
Final result							71.1			
Type 2										
FVIII:C (IU/dL)	4.1	6.2	7.2	10.4	12.4	16.6	19.7	25.9	33.1	42.4
RA (%)										
C_{inh} (BU/mL)										
Final result										

Tiede A et al. Sem Thromb Hemost 2014;40:803-811

E' sui fianchi delle montagne,
e non sulla cima, che si sviluppa la vita.

Quesito 3

Quali sono gli esami di laboratorio che devono essere disponibili in urgenza per la gestione dei NAO?

RACCOMANDAZIONE

In situazioni cliniche di urgenza/emergenza nei pazienti in trattamento certo o presunto con un NAO (dabigratan, rivaroxaban, apixaban) il GdL raccomanda l'esecuzione di specifici test per conoscere la presenza dell'effetto anticoagulante e misurarne l'entità.

- per i pazienti in trattamento con **dabigatran**:
  - ⇒ Tempo di Trombina diluito o dosaggio cromogenico dell'attività anti-IIa
- per i pazienti in trattamento con **rivaroxaban** e **apixaban**
  - ⇒ Dosaggio cromogenico dell'attività anti Xa

Thrombosis Research 137 (2016) 178–183

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Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

Sophie Testa [a,*], Armando Tripodi [b], Cristina Legnani [c], Vittorio Pengo [d], Rosanna Abbate [e], Claudia Dellanoce [a], Paolo Carraro [f], Luisa Salomone [c], Rita Paniccia [e], Oriana Paoletti [a], Daniela Poli [f], Gualtiero Palareti [g], for the START-Laboratory Register

Table 1
Methods, analytical performances, in house intra- and inter-assay coefficient of variation (CV%).

	Bologna (A)	Cremona (B)	Padua (C)	Florence (D)
Coagulometer	STA compact (Stago)	STA-R (Stago)	CA7000 (Sysmex)	ACL TOP 700 (Werfen)
Reagents				
Dabigatran	Thrombin Siemens	Thrombin Stago	Hyphen Hemoclot	Hyphen Hemoclot
Rivaroxaban	Liquid antiXa Stago	Liquid antiXa Stago	Hyphen DiXal	-
Apixaban	Liquid aXa Stago	Liquid aXa Stago	–	Hyphen DiXal
Calibrators				
Dabigatran	Hyphen Biomed	Hyphen Biomed	Hyphen Biomed	Hyphen Biomed
Rivaroxaban	Calibrator Stago	Calibrator Stago	Biophen Stago	–
Apixaban	Calibrator Stago	Calibrator Stago	–	Biophen apixaban
d-TT intra-assay CV%	2.4–5.1	2.7–5.8	2.8–3.6	1.4–7.6
dTT inter-assay CV%	1.9–7.3	3.1–7.9	4.2–8.1	3.1–6.0
Anti-FXa rivaroxaban intra-assay CV%	0.5–2.2	0.8–3.3	2.2–2.6	–
Anti-FXa rivaroxaban inter-assay CV%	0.6–4.4	1.0–4.3	2.2–6.2	–
Anti-FXa apixaban intra-assay CV%	1.3–2.4	1.1–3.6	–	1.5–6.6
Anti-FXa apixaban inter-assay CV%	1.7–3.6	2.0–4.5	–	2.2–6.9

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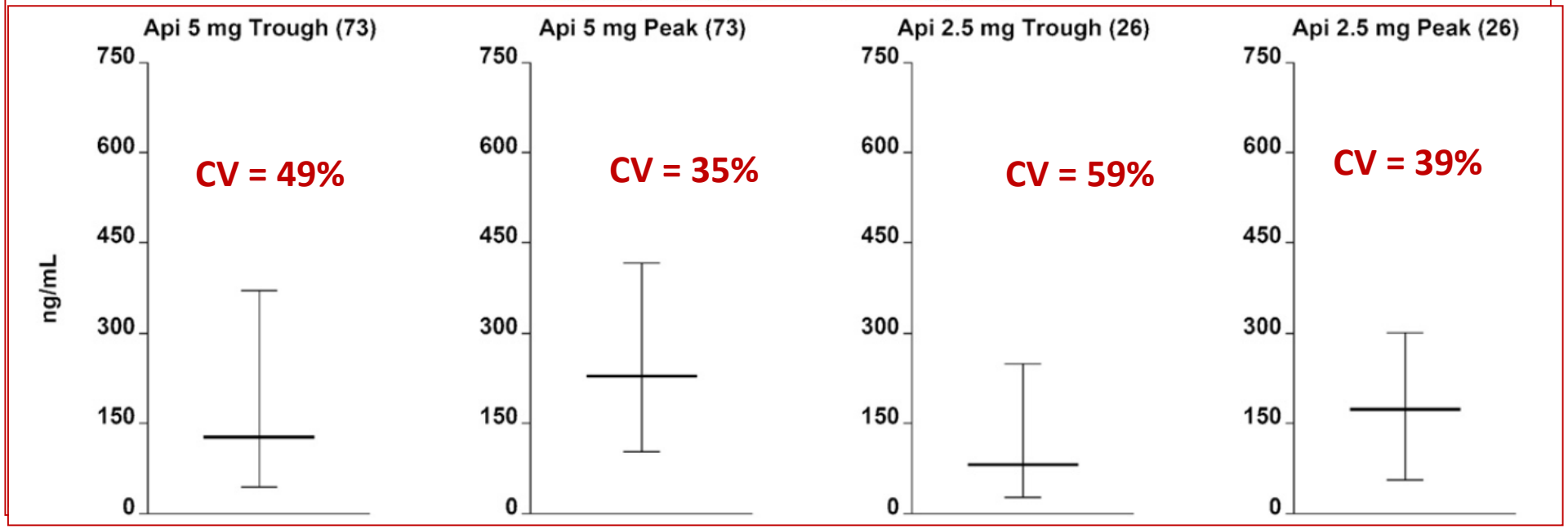

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Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

Table 6
Correlation (r value), coefficient of determination (r^2) and statistical significance (p) of DOAC plasma concentrations (at peak or trough) vs. creatinine clearance.

Drug and dose (mg)	C trough (r/r^2)	p	C peak (r/r^2)	p
Dabigatran 110	−0.25/0.0625	0.04	−0.12/0.014	ns
Dabigatran 150	−0.32/0.1024	0.03	−0.18/0.0324	ns
Rivaroxaban 20	−0.18/0.0324	ns	−0.15/0.0225	ns
Rivaroxaban 15	−0.09/0.0081	ns	0.07/0.0049	ns
Apixaban 5	−0.03/0.0009	ns	−0.17/0.0289	ns
Apixaban 2.5	−0.02/0.0004	ns	−0.01/0.0001	ns

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Variabilità intra-individuale (CV%)		
	Through	Peak
Dabigatran 150mg	49	51
Dabigatran 110 mg	59	60
Rivaroxaban 20 mg	39	27
Rivaroxaban 15 mg	35	31
Apixaban 5 mg	23	22
Apixaban 2.5 mg	15	14

(J Am Coll Cardiol 2014;63:321–8)

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,†

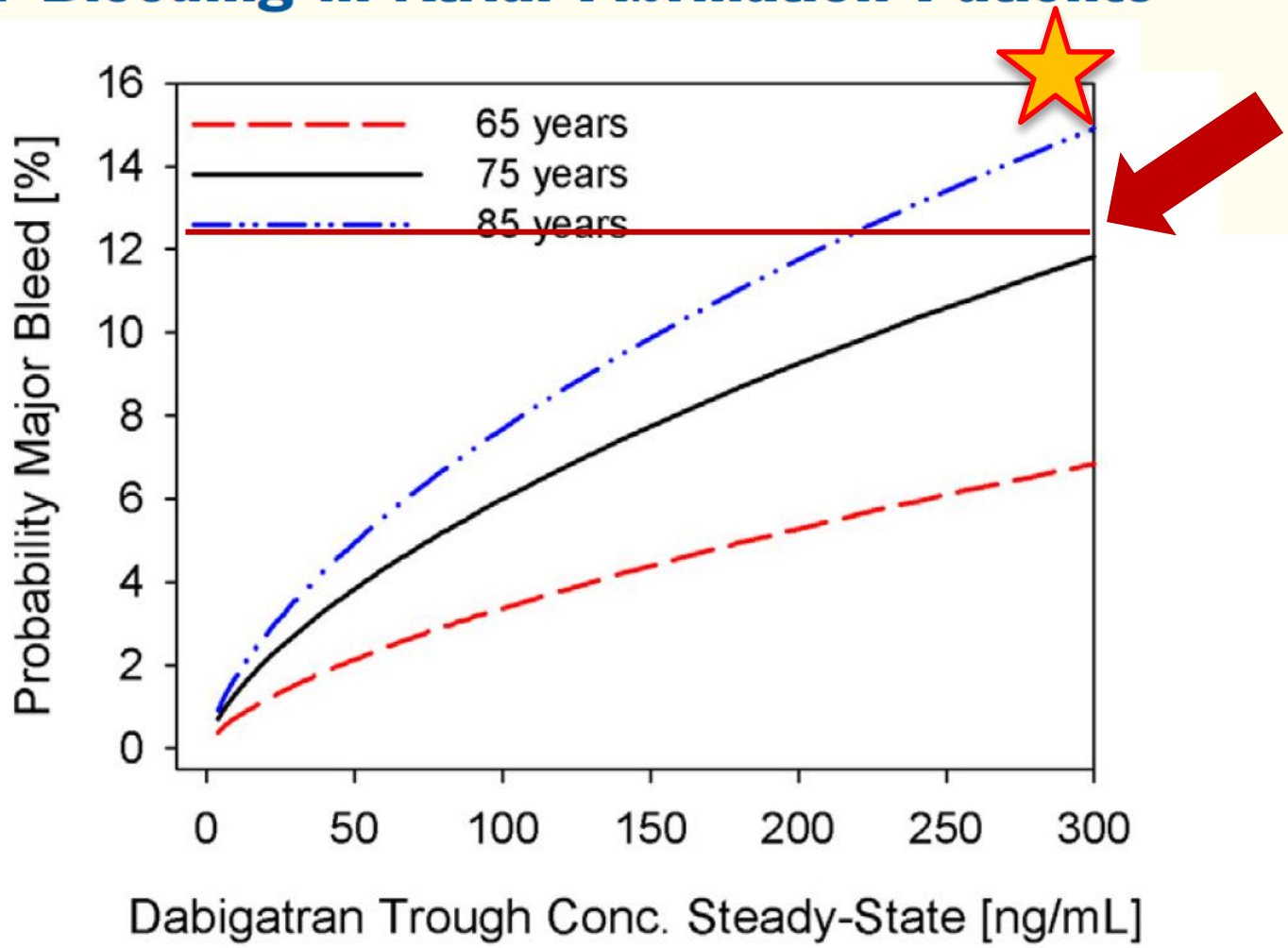
Table 3 Trough Concentrations of Dabigatran (ng/ml/mg) Grouped by Outcome Event Occurrence

	Major Bleed (n = 323)	Any Bleed (n = 2,319)	No Bleed (n = 5,899)	Stroke/SEE (+) (n = 129)	No Stroke/SEE (−) (n = 8,250)	Stroke/SEE/Death (+) (n = 387)	No Stroke/SEE/Death (−) (n = 7,789)	CV Events* (+) (n = 391)	No CV Events (−) (n = 7,865)
gMean	113	86.9	72.8	76.6	76.5	88.5	75.4	87.8	75.6
gCV, %	79.8	81.4	84	84.1	83.9	84.7	83.3	89.5	83.1
Median	116	88.2	75.3	80.6	78.3	91.4	77.6	90.7	77.6
P10	46.7	35.7	30.7	26.4	32.1	33.1	31.8	31.2	32
P90	269	211	175	185	186	226	181	229	182

*Cardiovascular (CV) events include stroke, systemic embolism, pulmonary embolism, myocardial infarction, and vascular deaths.
(+) = with event on-treatment; (−) = without event; other abbreviations as in Table 1.

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

(J Am Coll Cardiol 2014;63:321–8)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 June 2011
EMA/CHMP/203468/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Pradaxa

of the increased risk of bleeding. Dabigatran concentration under 48 ng/mL is equivalent to elimination of at least 75% of dabigatran and should be recommended before special intervention such as surgery.

Procedure No. EMEA/H/C/000829/X/13/G

It is possible to extrapolate a clinical haemostatic safety threshold corresponding to a new oral anticoagulant plasma concentration allowing urgent surgery

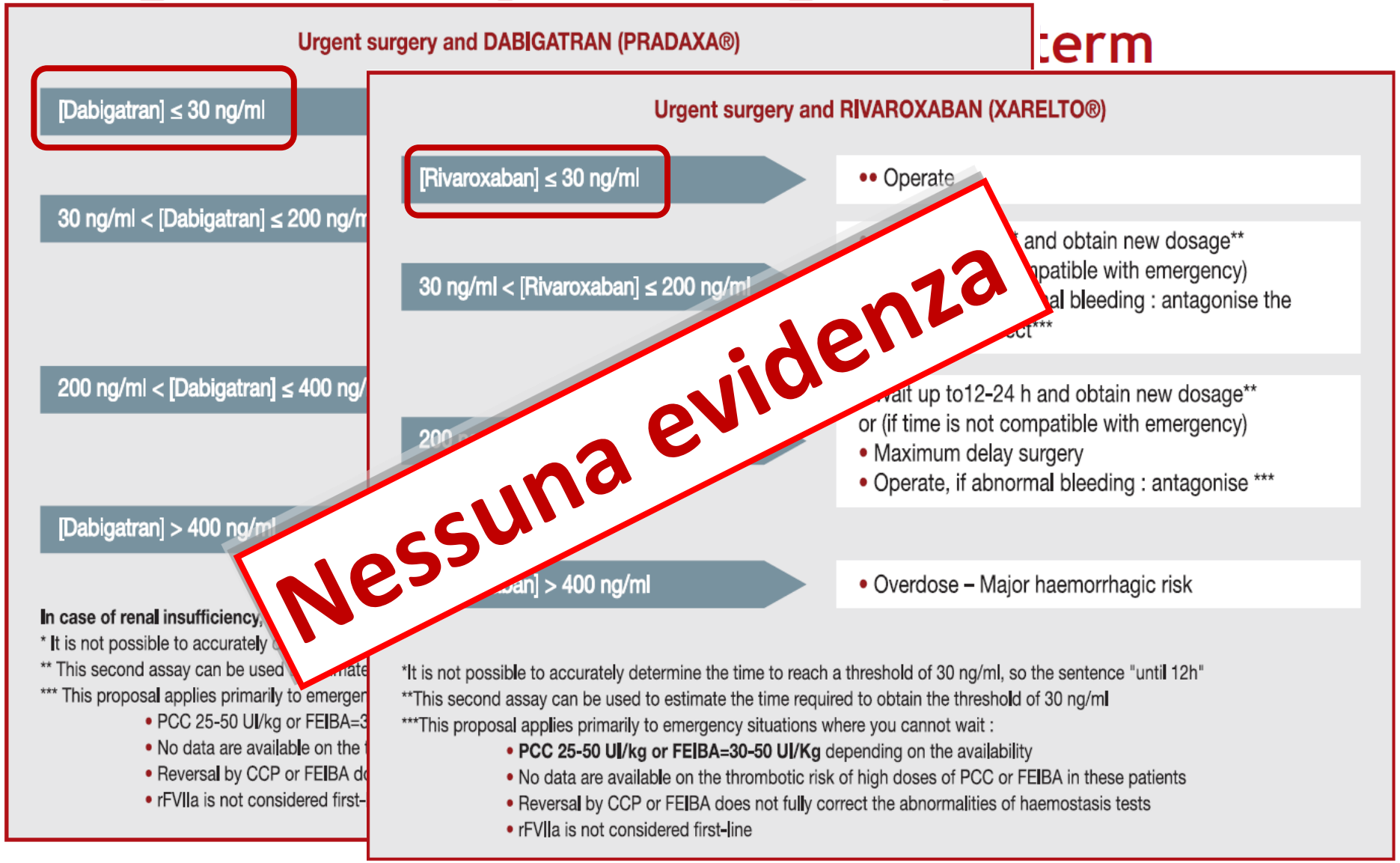
Regarding rivaroxaban, the only data available are derived from the ROCKET-AF design study [3]. In this study, rivaroxaban was stopped 2 days before any surgical elective procedure again, four half-lives (7—13 h). Given the mean C_{max} of rivaroxaban in this population, these patients were operated upon while the plasma concentration of the drug was probably less or equal to 30 ng/mL.

It appears that we can regard the same concentration of 30 ng/mL as compatible with surgical management, without increasing the risk of bleeding, especially in an emergency.

Archives of Cardiovascular Disease (2013) **106**, 382–393

CLINICAL RESEARCH

Management of major bleeding complications and



Nessuna evidenza

ORIGINAL ARTICLE

This article was published on June 22, 2015, at NEJM.org.

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,

Patients in group A were those with overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent.

Patients in group B were those who required surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required.

The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran

Clinical outcomes, as assessed by the treating clinicians, were secondary end points.

ORIGINAL ARTICLE

This article was published on June 22, 2015, at NEJM.org.

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S.,

The time to the cessation of bleeding could not be ascertained in 13 (26%) patients, of whom 5 had intracranial hemorrhage, 4 had gastrointestinal bleeding, 2 had intramuscular bleeding, 1 had pericardial bleeding, and 1 had retroperitoneal bleeding.

In the remaining patients, the median investigator-reported time to the cessation of bleeding was 11.4 hours.

Table 2. Characteristics of Acute Major Bleeding Episodes and Clinical Outcomes.*

Characteristic	Safety Population (N=67)	Efficacy Population (N=47)
Gastrointestinal bleeding — no./total no. (%)	33/67 (49)	25/47 (53)
Patients receiving rivaroxaban	20/33 (61)	16/25 (64)
Patients receiving apixaban	11/33 (33)	8/25 (32)
Site of bleeding		
Upper gastrointestinal tract	9/33 (27)	7/25 (28)
Lower gastrointestinal tract	10/33 (30)	8/25 (32)
Unknown	14/33 (42)	10/25 (40)
Baseline hemoglobin ≤10 g/dl	20/33 (61)	16/25 (64)
Pretreatment red-cell transfusion	21/33 (64)	19/25 (76)
Intracranial bleeding — no./total no. (%)	28/67 (42)	20/47 (43)
Patients receiving rivaroxaban — no./total no. (%)	10/28 (36)	8/20 (40)
Patients receiving apixaban — no./total no. (%)	17/28 (61)	12/20 (60)
Baseline score on Glasgow Coma Scale†	14.1±1.7	14.1±1.7
Intracerebral site — no./total no. (%)	14/28 (50)	12/20 (60)
Baseline score on modified Rankin scale‡	3.0±1.8	2.8±1.9
Hematoma volume — no./total no. (%)		
≤10 ml	8/14 (57)	8/12 (67)
11 to 60 ml	6/14 (43)	4/12 (33)
Subdural site — no./total no. (%)	11/28 (39)	7/20 (35)

N Engl J Med 2016;375:1131-41.

Andexanet Alfa for Acute Major Bleeding

Stu D.,

Subgroup	No. of Patients	Percent Adjudicated as Excellent or Good Hemostasis (95% CI)
All patients with efficacy analyses	47	79 (64–89)
Drug		
Rivaroxaban	26	81 (61–93)
Apixaban	20	75 (51–91)
Enoxaparin	1	100
Sex		
Male	24	71 (49–87)
Female	23	87 (66–97)
Site of bleeding		
Gastrointestinal	25	84 (64–96)
Intracranial	20	80 (56–94)
Other	2	0
Age		
<65 yr	7	71 (29–96)
65–75 yr	9	89 (52–100)
≥75 yr	31	77 (59–90)
Andexanet dose		
Low	42	76 (61–88)
High	5	100 (48–100)
Anti–factor Xa <75 ng/ml or <0.5 IU/ml	17	82 (57–96)

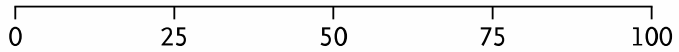
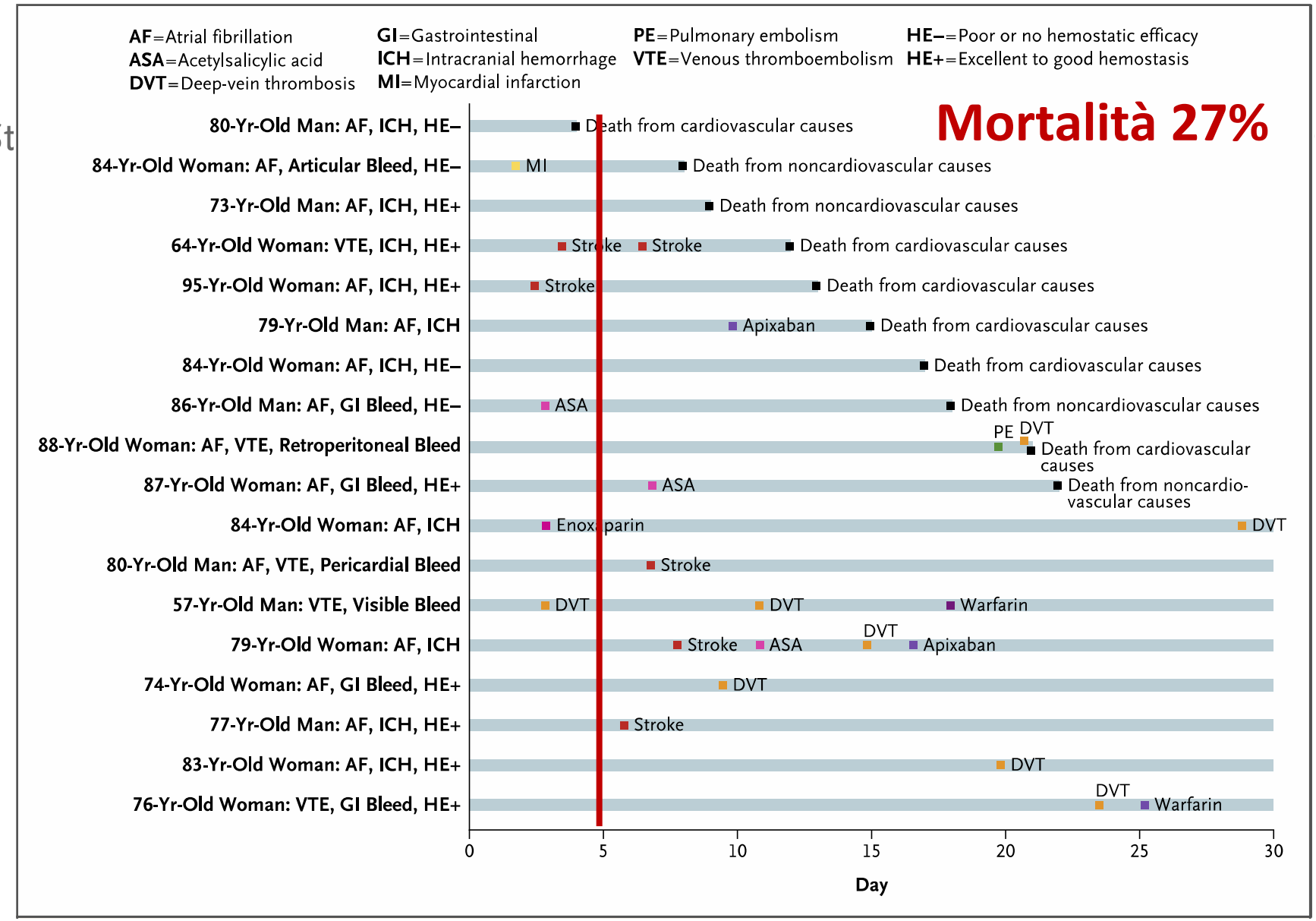


Figure 2. Subgroup Analysis of Hemostatic Efficacy.

Shown are the percentages of patients in the efficacy population who were adjudicated as having excellent or good hemostatic efficacy 12 hours after treatment with andexanet on the basis of prespecified criteria (Table S3 in the Supplementary Appendix). The size of the data points is proportional to the number of patients included in the subgroup analysis.

N Engl J Med 2016;375:1131-41.

Andexanet Alfa for Acute Major Bleeding



N Engl J Med 2016;375:1131-41.

Quesito 5

Quali sono i trattamenti specifici da adottare in caso di emorragia maggiore a rischio di vita o di perdita di organo/funzione in corso di trattamento con i NAO?

RACCOMANDAZIONE

In caso di emorragia maggiore a rischio di vita o di perdita di organo/funzione in corso di trattamento con NAO il GdL suggerisce, pur in assenza di evidenze solide, di adottare i seguenti provvedimenti specifici (in aggiunta alle misure generali di trattamento indicate nella Raccomandazione 2):

- somministrare concentrati del complesso protrombinico alle dosi di 25 UI/kg eventualmente ripetibili 1-2 volte dopo attenta valutazione del rischio trombotico;
- somministrare acido tranexamico alle dosi di 15 mg/kg 3 volte al dì per via endovenosa oppure 25 mg/kg 3 volte al dì per os fino al controllo dell'emorragia;
- in caso di emorragia non responsiva ai precedenti trattamenti considerare la possibilità di una somministrazione di concentrati del complesso protrombinico attivati (FEIBA®) alle dosi indicative di 50 UI/kg fino a un massimo di 200 UI/kg al giorno;
- solo per dabigatran: valutare l'opportunità di dialisi classica in emergenza o emoperfusione con filtri a carbone.

Queste misure sono da attuare per concentrazioni di farmaco al di sopra del limite inferiore di riferimento del test di laboratorio, o nel caso in cui il valore del test di laboratorio non sia ottenibile in tempi compatibili con la situazione clinica del paziente.

Estima … erioperative setting …

An *ex vi* …

Jonathan D… anka[3]; Maximilien …

	LC-MS/MS (in ng/ml)	HTI (in ng/ml)	HTI LOW (in ng/ml)	STA®-ECA-II (in ng/ml)
	Time elapsed since the last dose: 0 hours† (n=2)			
Median	0	0	0	0
Range (min – max)	0 to 0	0 to 0	0 to 0	0 to 0
	Time elapsed since the last dose: 2 hours (n=4)			
Median	133	122	138	153
Range (min –max)	65 to 185	64 to 191	87 to 168	77 to 204
	Time elapsed since the last dose: 3 hours (n=4)			
Median	125	119	132	146
Range (min – max)	49 to 200	68 to 194	79 to 179	77 to 161
	Time elapsed since the last dose: 12 hours (n=5)			
Median	76	46	76	83
Range (min – max)	52 to 88	22 to 83	61 to 103	65 to 118
	Time elapsed since the last dose: 20 hours (n=8)			
Median	41	17	42	34
Range (min – max)	0 to 76	0 to 56	0 to 95	0 to 83

Consigliato per chirurgia 30-48 ng/ml

Thromb Haemost 2015;113:862-9

	HTI	HTI LOW	STA®-ECA-II	STA®-Thrombin
	0 to 200 ng/ml (n=33)			
R-square	0.94	0.94	0.85	0.79
slope	0.9748	0.9663	1.002	
95 % CI	(0.8803 to 1.069)	(0.8773 to 1.055)	(0.8490 to 1.154)	
intercept	-8.633	3.204	3.635	
95 % CI	(-15.93 to –1.336)	(-3.672 to 10.08)	(-8.159 to 15.43)	
Bland-Altman (in ng/ml)	-10	1	4	
95 % CI	(-38 to 18)	(-25 to 28)	(-41 to 48)	
	0 to 50 ng/ml (n=17)			
R-square	0.69	0.84	0.61	0.67
slope				
95 %				
intercept	-4.03	-2.629	-0.2403	
95 % CI	(-11.60 to 3.00)	(-8.994 to 3.736)	(-9.182 to 8.701)	
Bland-Altman (in ng/ml)	-6	1	-1	
95 % CI	(-25 to 14)	(-18 to 19)	(-25 to 23)	

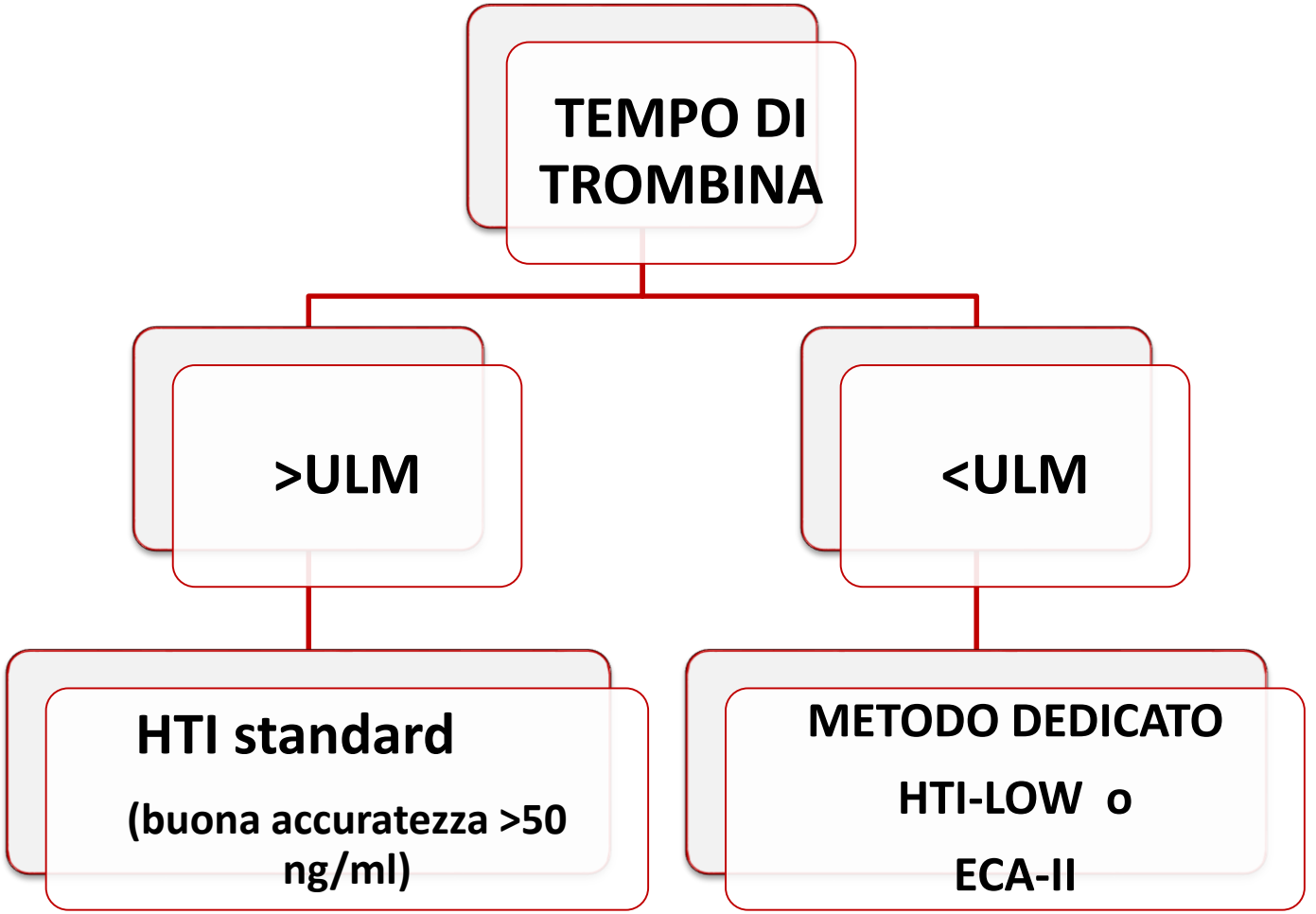
LOD = 2 ng/ml; LOQ = 7 ng/ml

Douxfils J et al. Thromb Haemost 2015;113:862-9

Estimation of dabigatran plasma concentrations in the perioperative setting

An *ex vivo* study using dedicated coagulation assays

Jonathan Douxfils[1*]; Sarah Lessire[1,2*]; Anne-Sophie Dincq[2]; Paul Hjemdahl[3]; Yuko Rönquist-Nii[3]; Anton Pohanka[3]; Maximilien Gourdin[2]; Bernard Chatelain[4]; Jean-Michel Dogné[1]; François Mullier[1,4]



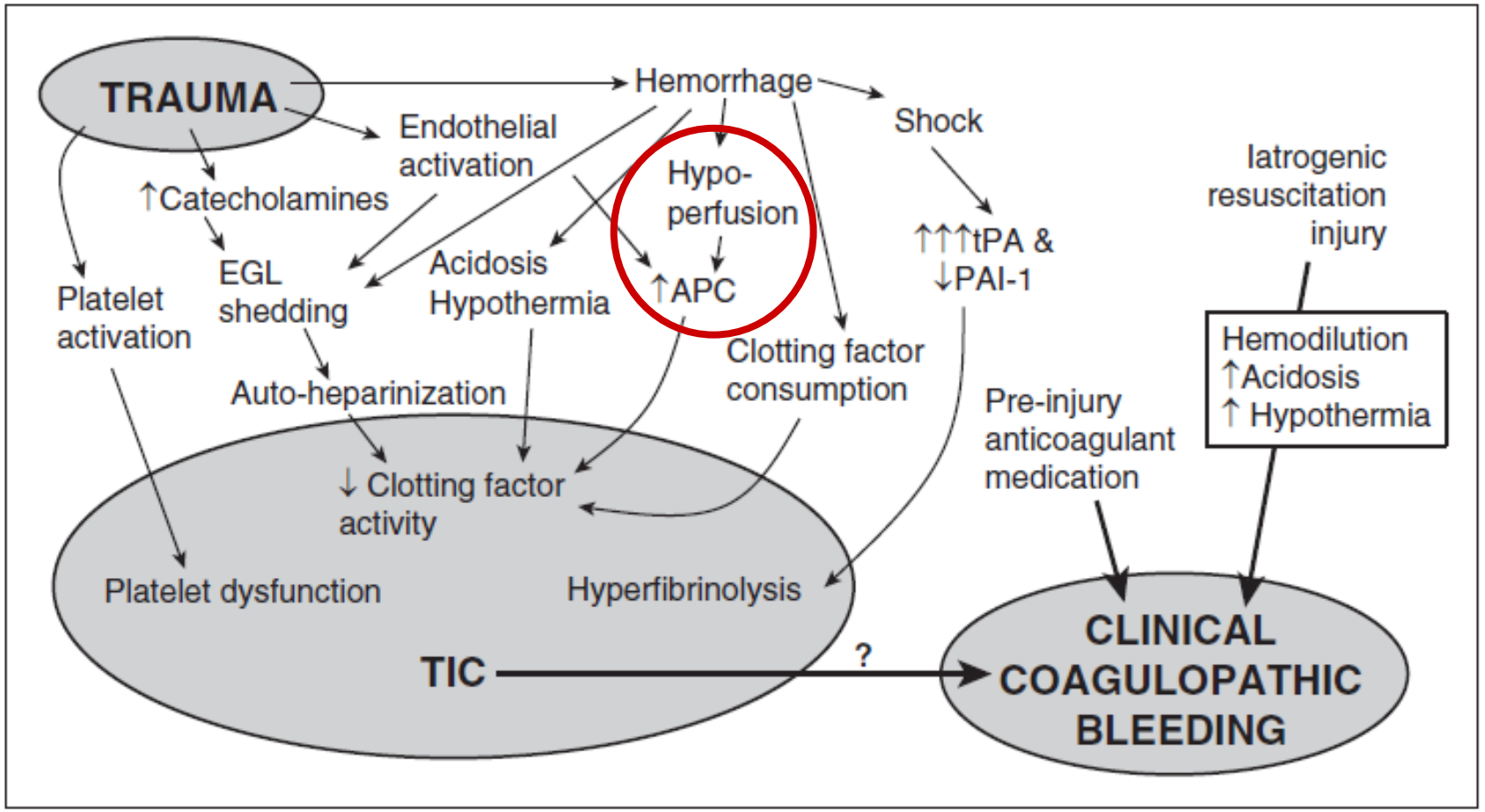
Thromb Haemost 2015;113:862-9

E' sui fianchi delle montagne,
e non sulla cima, che si sviluppa la vita.

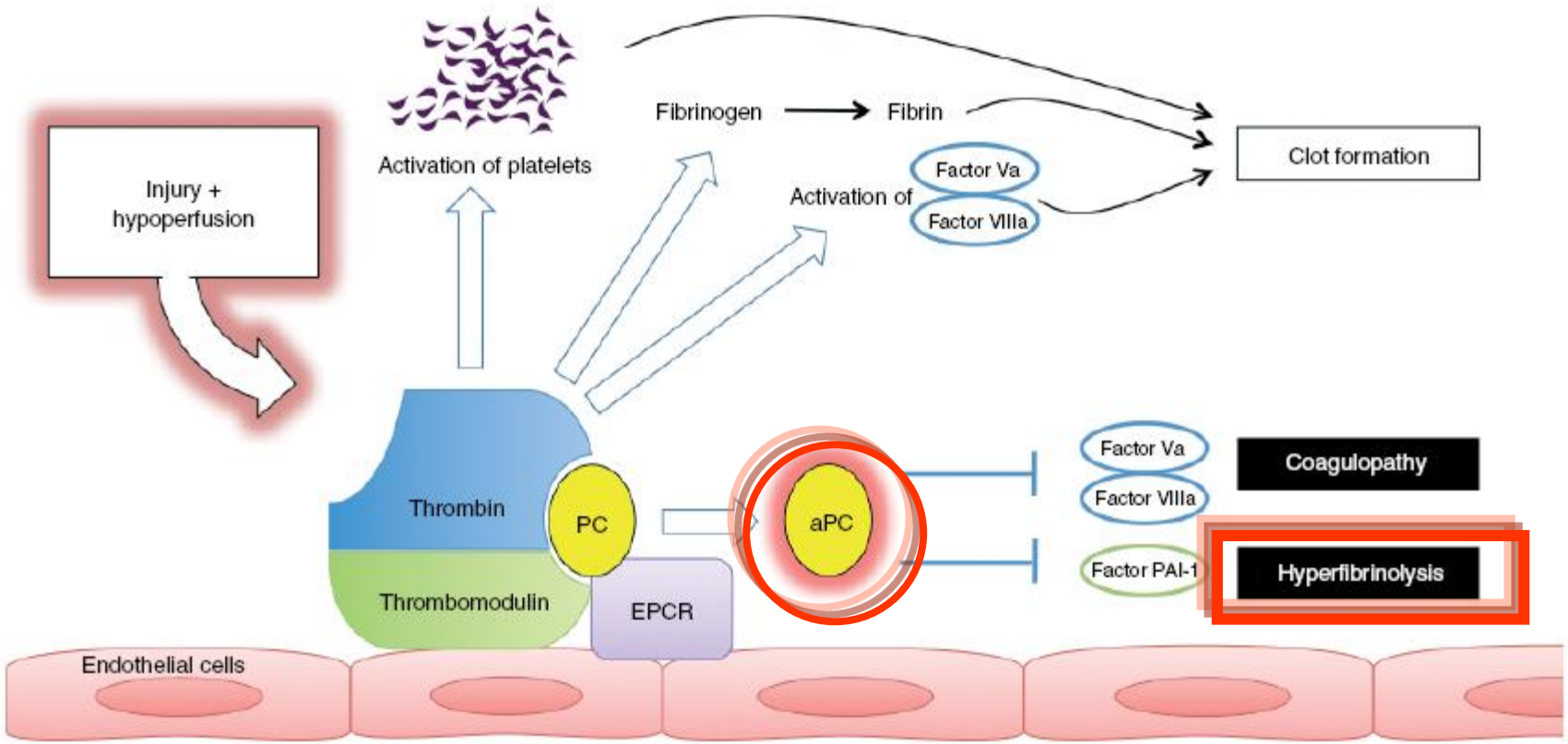
blood

Advances in the understanding of trauma-induced coagulopathy

Ronald Chang,[1,2] Jessica C. Cardenas,[1,2] Charles E. Wade,[1,2] and John B. Holcomb[1,2]



Blood 2016;128(8):1043-1049



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

blood

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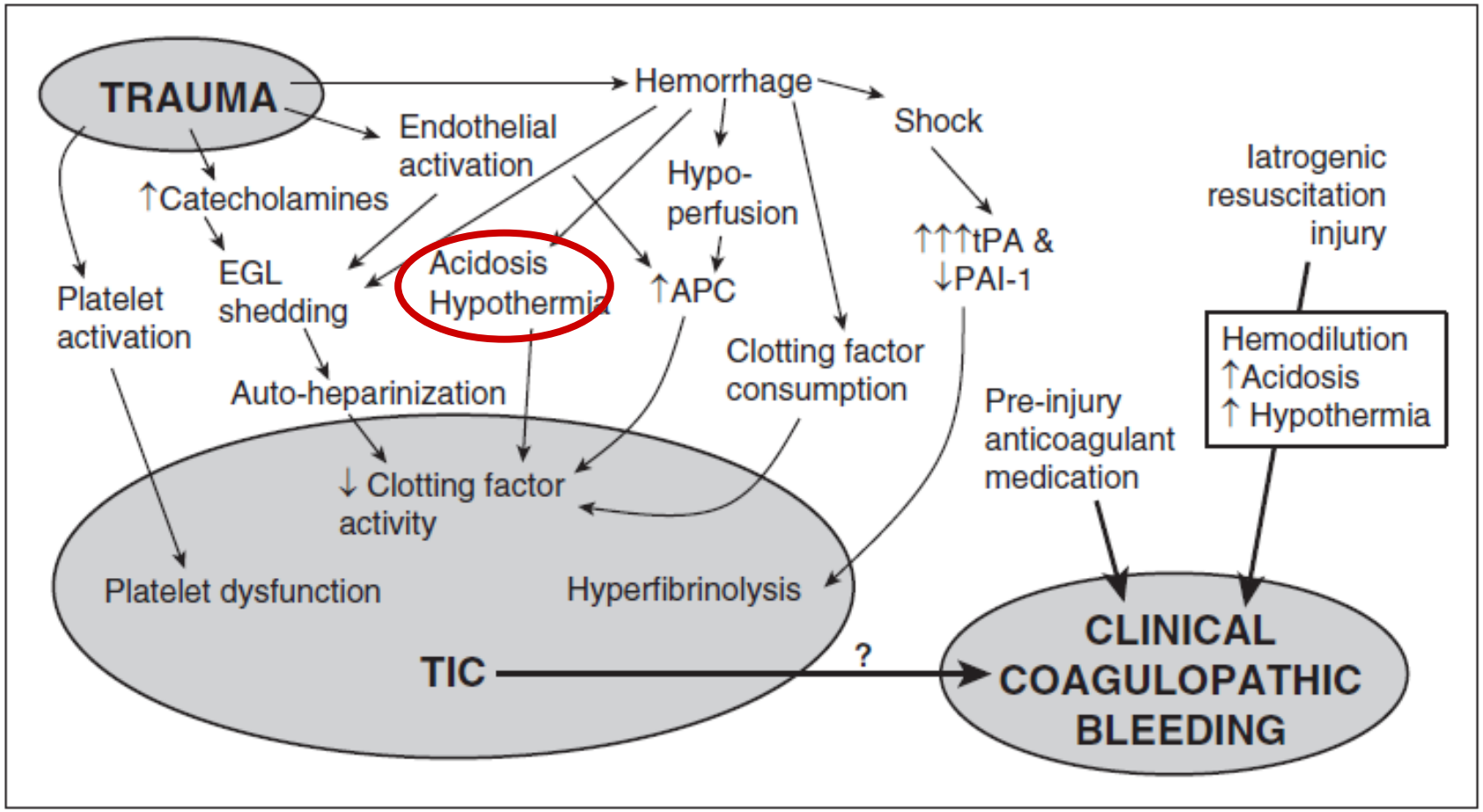


Blood 2016;128(8):1043-1049

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

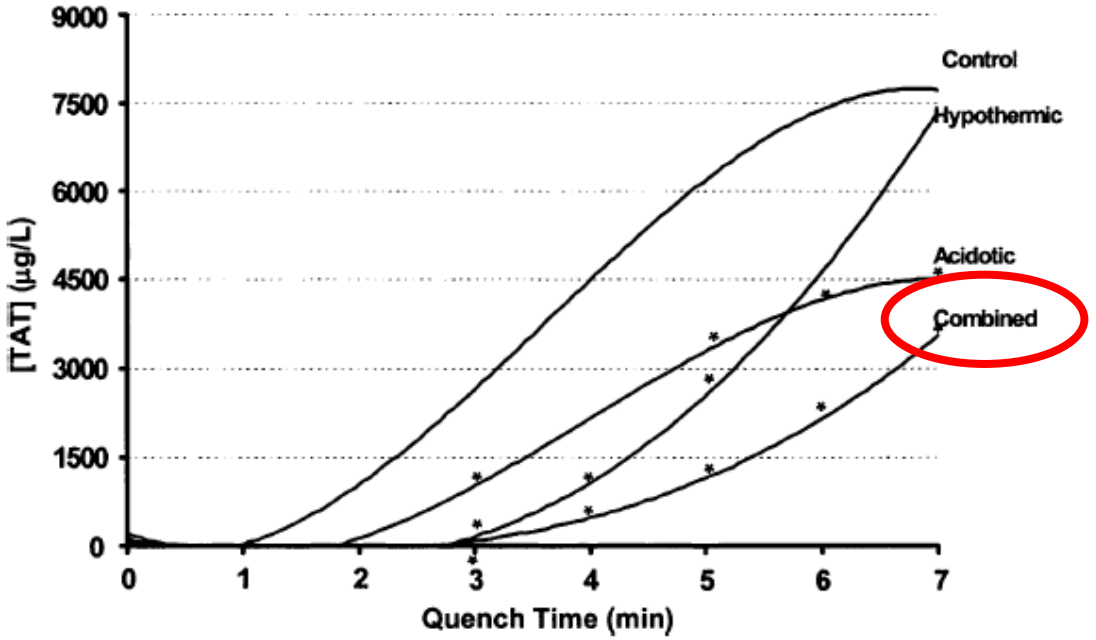


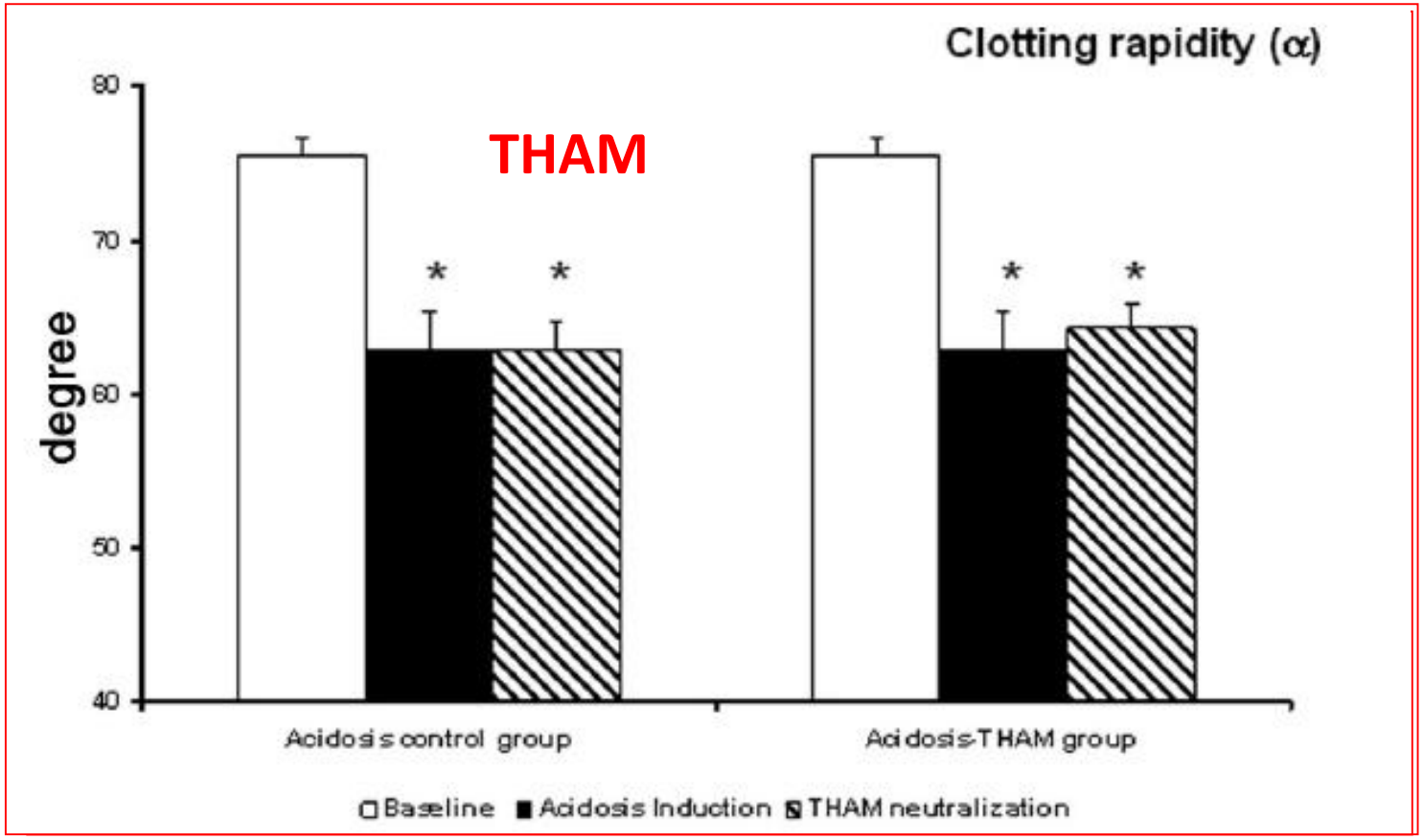
Figure 3. Thrombin generation rate in blood samples measured as thrombin-antithrombin III (TAT) complex concentration.

J Trauma. 2005;58:1002–1010.

Coagulopathy by Hypothermia and Acidosis: Mechanisms of Thrombin Generation and Fibrinogen Availability

(*J Trauma*. 2009;67: 202–209)

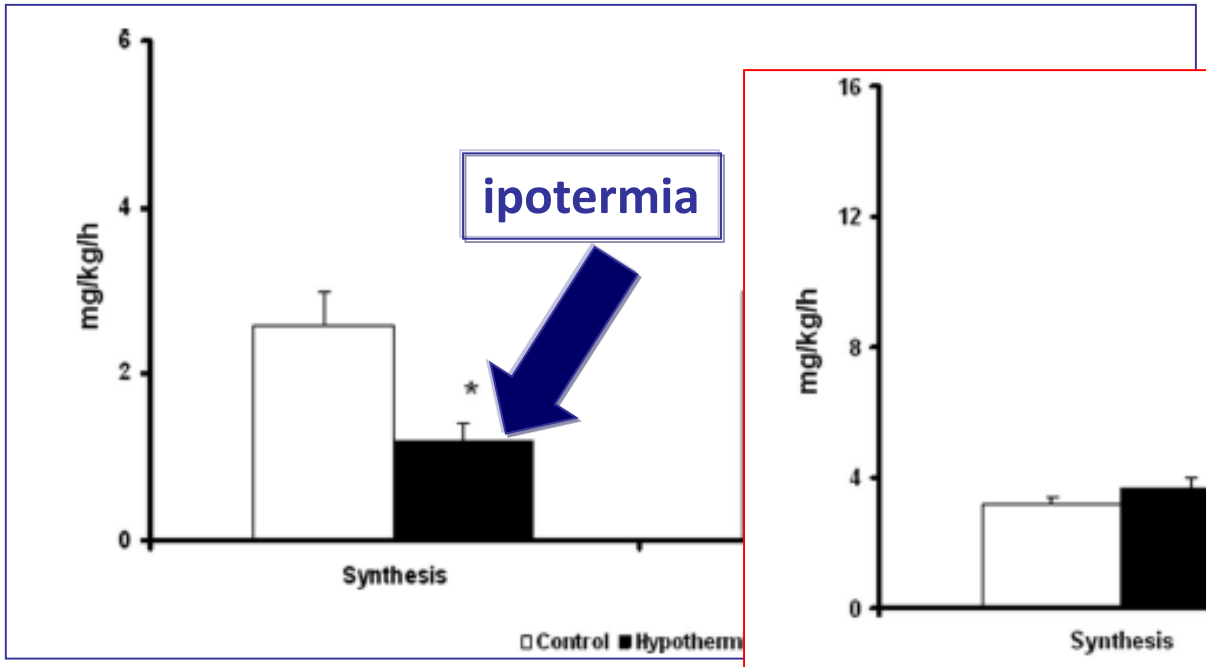
Wenjun Zhou Martini, PhD

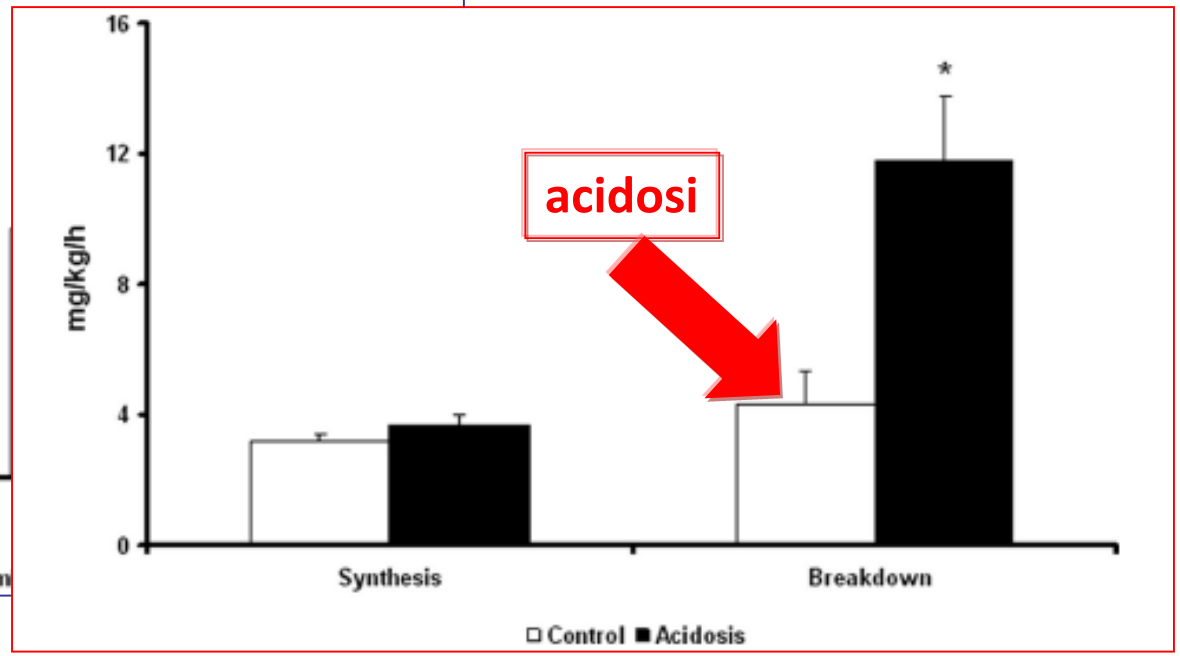


Coagulopathy by Hypothermia and Acidosis: Mechanisms of Thrombin Generation and Fibrinogen Availability

Wenjun Zhou Martini, PhD

(*J Trauma*. 2009;67: 202–209)

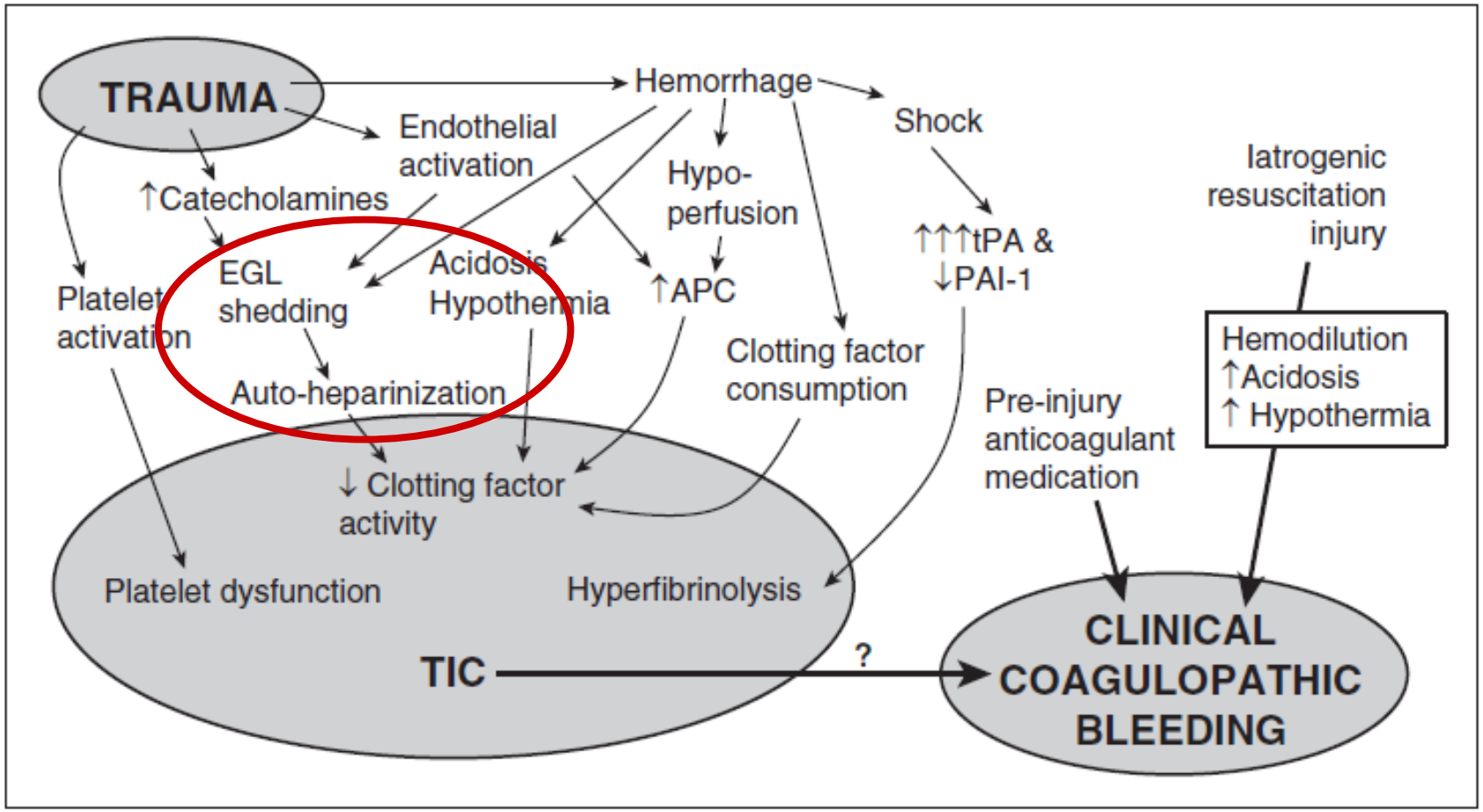




blood

Advances in the understanding of trauma-induced coagulopathy

Ronald Chang,[1,2] Jessica C. Cardenas,[1,2] Charles E. Wade,[1,2] and John B. Holcomb[1,2]



Blood 2016;128(8):1043-1049

A High Admission Syndecan-1 Level, A Marker of Endothelial Glycocalyx Degradation, Is Associated With Inflammation, Protein C Depletion, Fibrinolysis, and Increased Mortality in Trauma Patients

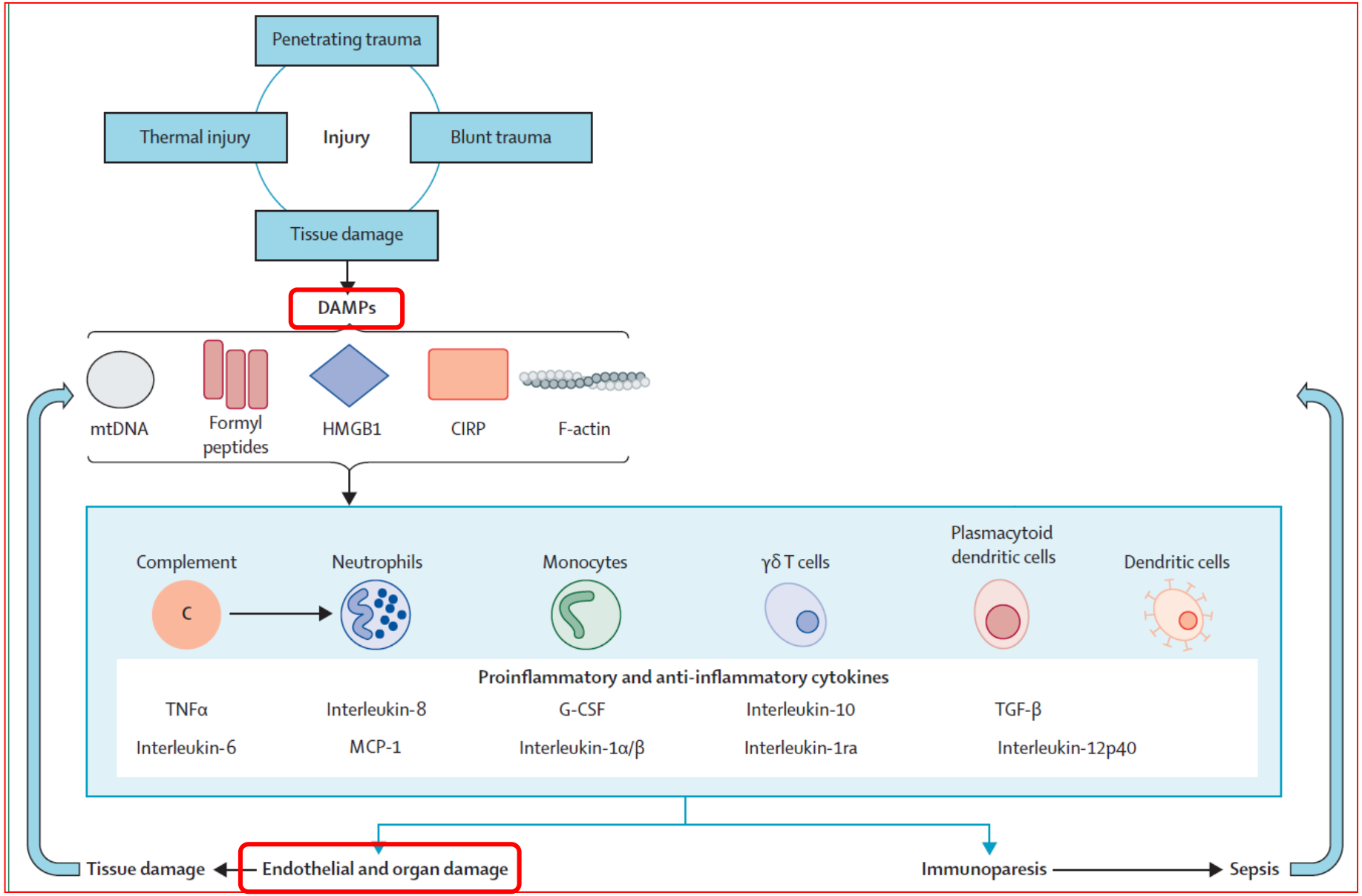
(*Ann Surg* 2011;254:194–200)

Pär I. Johansson, MD, DMSc, MPA, Jakob Stensballe, MD, PhD,† Lars S. Rasmussen, MD, PhD, DMSc,† and Sisse R. Ostrowski, MD, PhD, DMSc**

	Alta degradazione glicocalice	Bassa degradazione glicocalice	p
Sat O_2 (%)	93	96	0.021
Mortalità (%)	**42**	**14**	**0.006**
Lattato (mmol/L)	3	2	0.006
IL-6 (pg/mL)	44.9	7.8	<0.001
IL-10 (pg/mL)	13.3	3.7	0.001
HMGB1 (ng/mL)	10.8	6.8	0.006
t-PA (ng/mL)	15.3	9.2	0.005

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

Lancet 2014; 384: 1455–65



olved cell-specific prothrombotic pathways that
s to protect hosts from non-self and altered-self.

I NETs attivano direttamente il F XII, che lega il fattore von Willebrand factor (VWF) che aggrega altre piastrine.

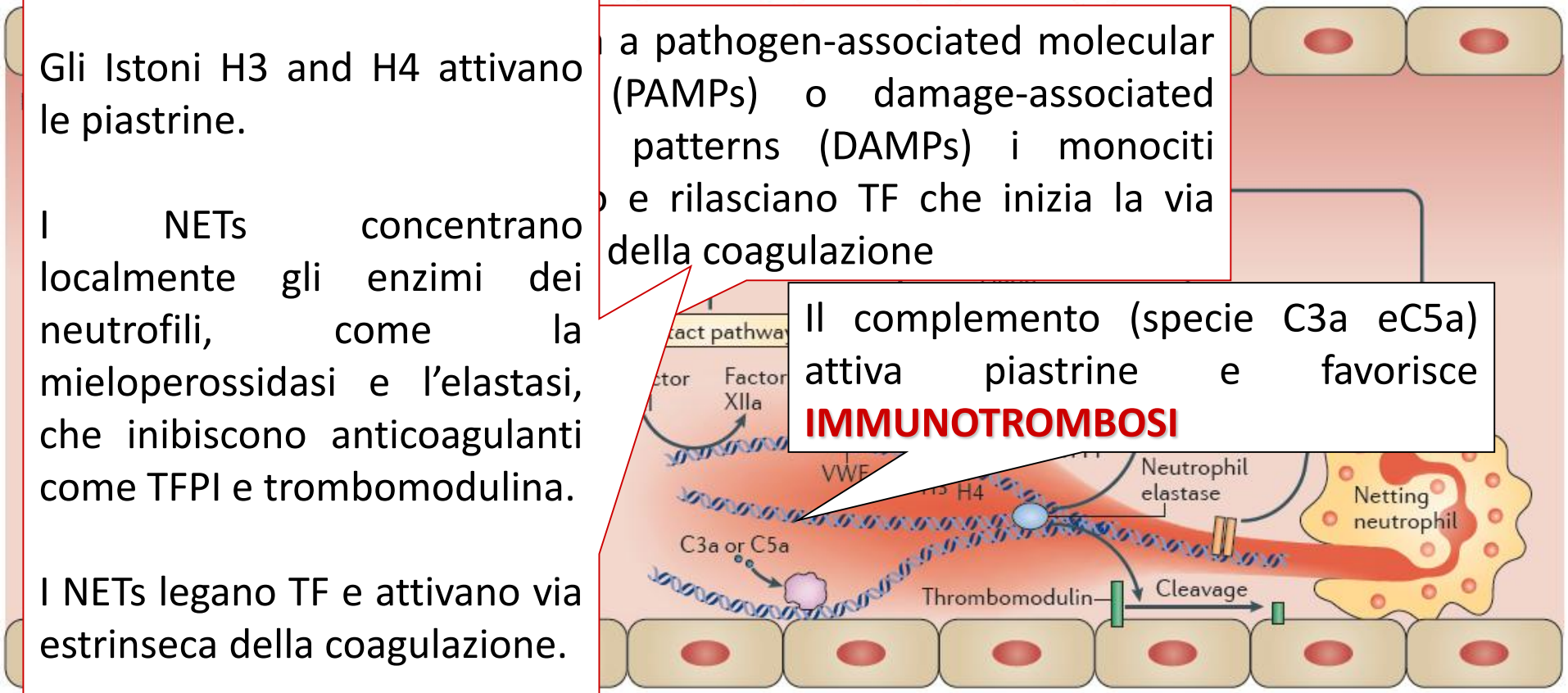
Gli Istoni H3 and H4 attivano le piastrine.

I NETs concentrano localmente gli enzimi dei neutrofili, come la mieloperossidasi e l'elastasi, che inibiscono anticoagulanti come TFPI e trombomodulina.

I NETs legano TF e attivano via estrinseca della coagulazione.

a pathogen-associated molecular (PAMPs) o damage-associated patterns (DAMPs) i monociti e rilasciano TF che inizia la via della coagulazione

Il complemento (specie C3a eC5a) attiva piastrine e favorisce **IMMUNOTROMBOSI**



Nat Rev Immunol 2013;13:34

OPEN

Results: Patients had a median ISS of 17 with 72% suffering from blunt injury. Adrenaline and noradrenaline correlated with syndecan-1 ($r = 0.38$, $P<0.001$ and $r = 0.23$, $P<0.001$, respectively) but adrenaline was the only independent predictor of syndecan-1 by multiple linear regression adjusted for age, injury severity score, Glascow Coma Scale, systolic blood pressure, base excess, platelet count, hemoglobin, prehospital plasma, and prehospital fluids (100 pg/mL higher adrenaline predicted 2.75 ng/mL higher syndecan-1, $P < 0.001$). By Cox analyses adjusted for age, sex, injury severity score, Glascow Coma Scale, base excess, platelet count and hemoglobin, adrenaline and syndecan-1 were the only independent predictors of both < 24-hours, 7-day and 28-day mortality (all $P < 0.05$). Furthermore, noradrenaline was an independent predictor of < 24-hours mortality and thrombomodulin was an independent predictor of 7-day and 28-day mortality (all $P < 0.05$).

Conclusions: We confirmed that sympathoadrenal activation was strongly and independently associated with endothelial glycocalyx and cell damage (ie, endotheliopathy) and furthermore that sympathoadrenal activation and endotheliopathy were independent predictors of mortality in trauma patients.

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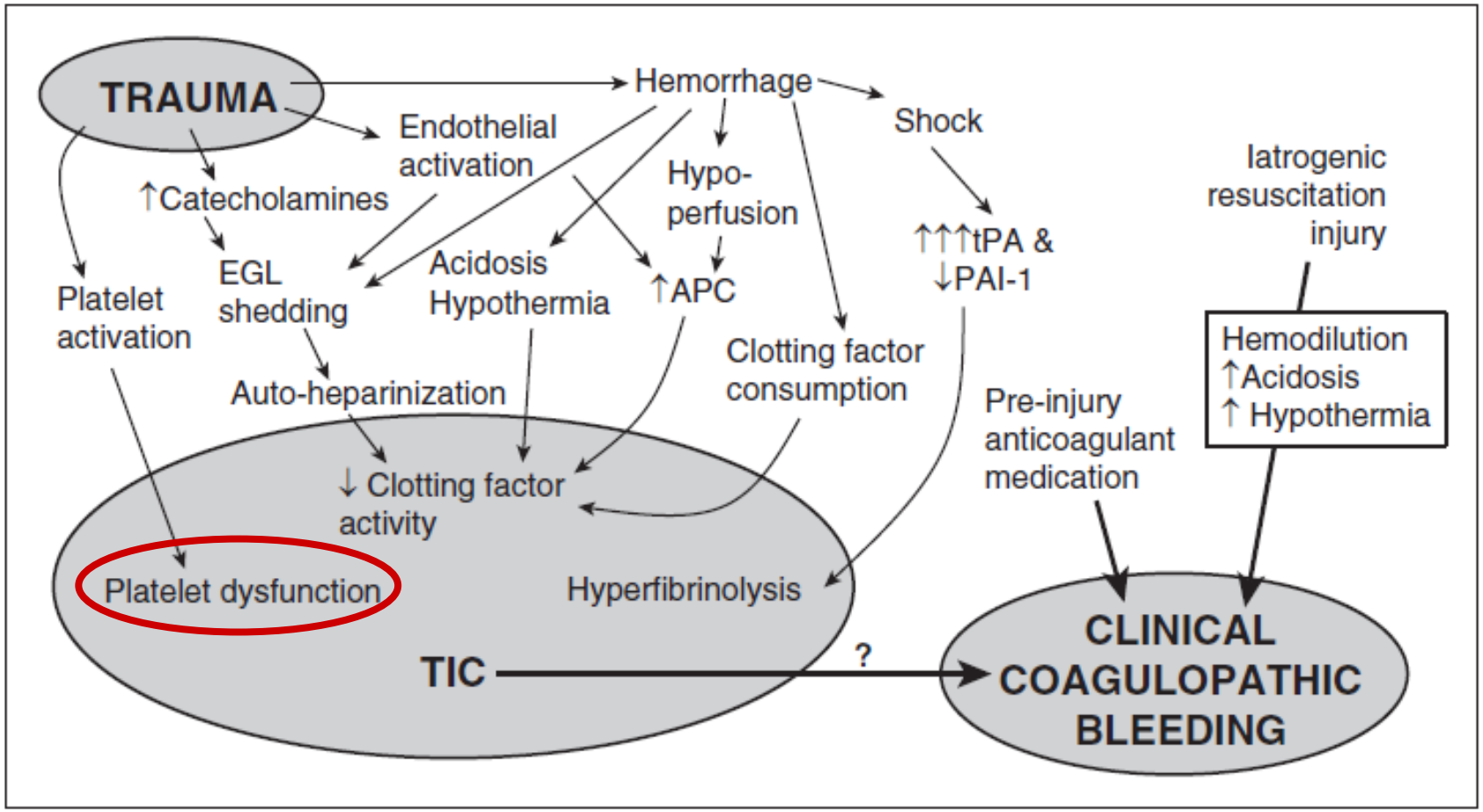

Blood 2016;128(8):1043-1049

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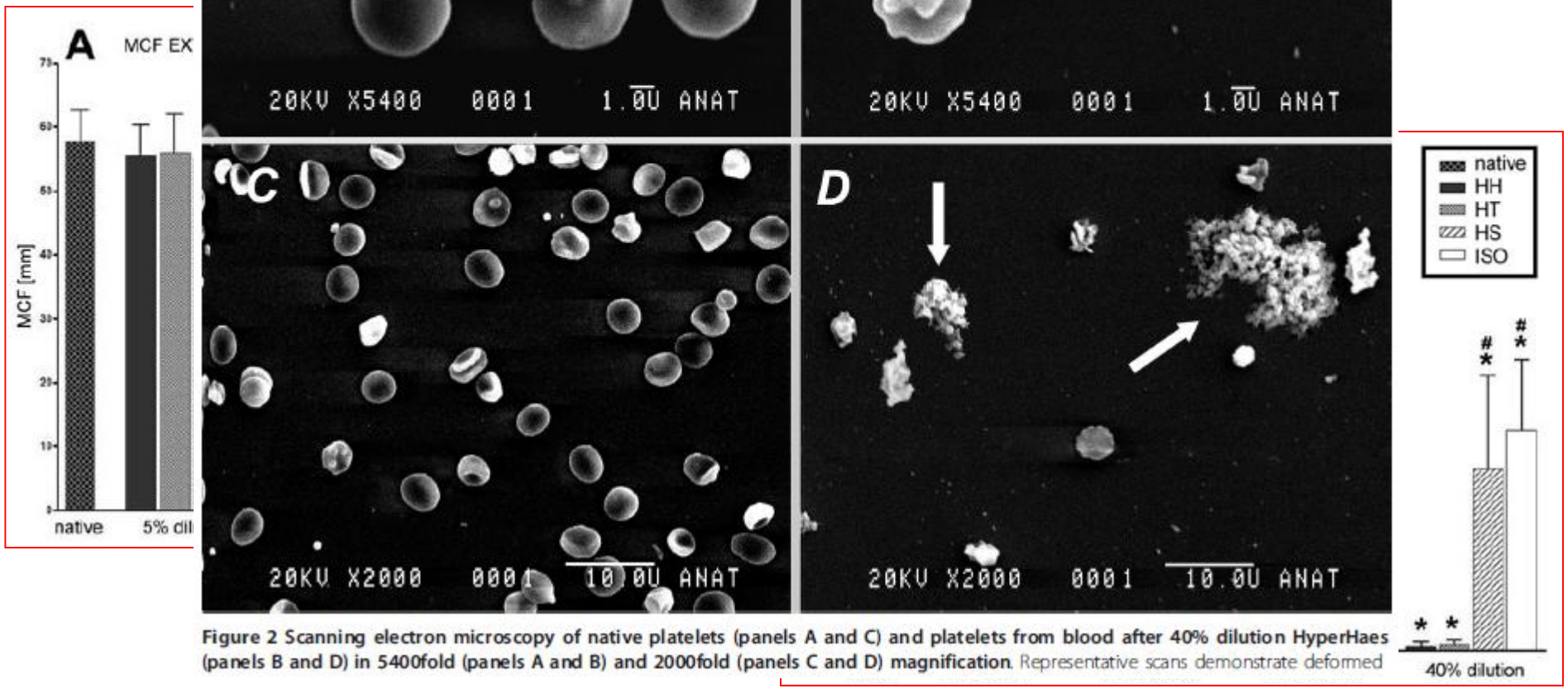

Figure 2 Scanning electron microscopy of native platelets (panels A and C) and platelets from blood after 40% dilution HyperHaes (panels B and D) in 5400fold (panels A and B) and 2000fold (panels C and D) magnification. Representative scans demonstrate deformed

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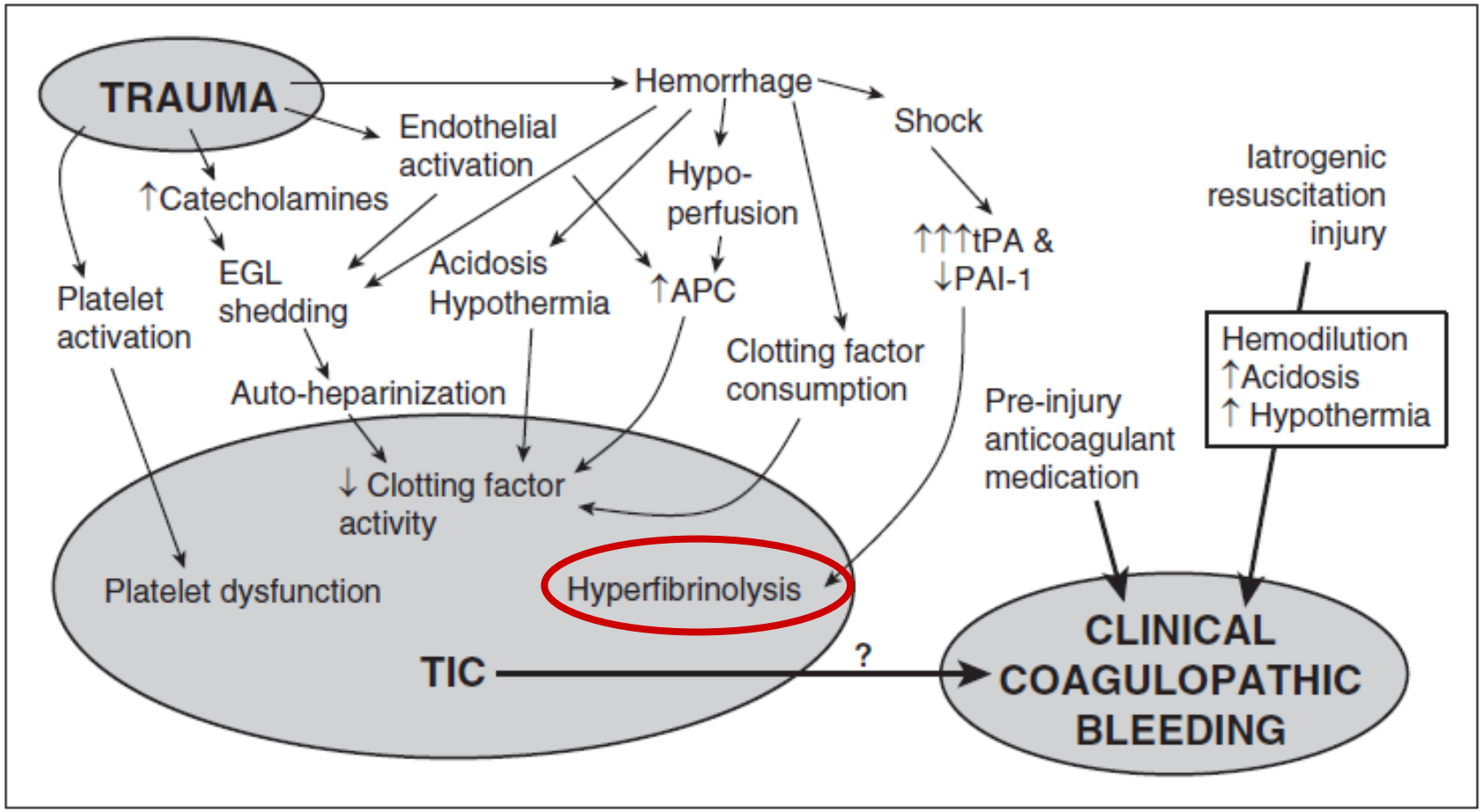
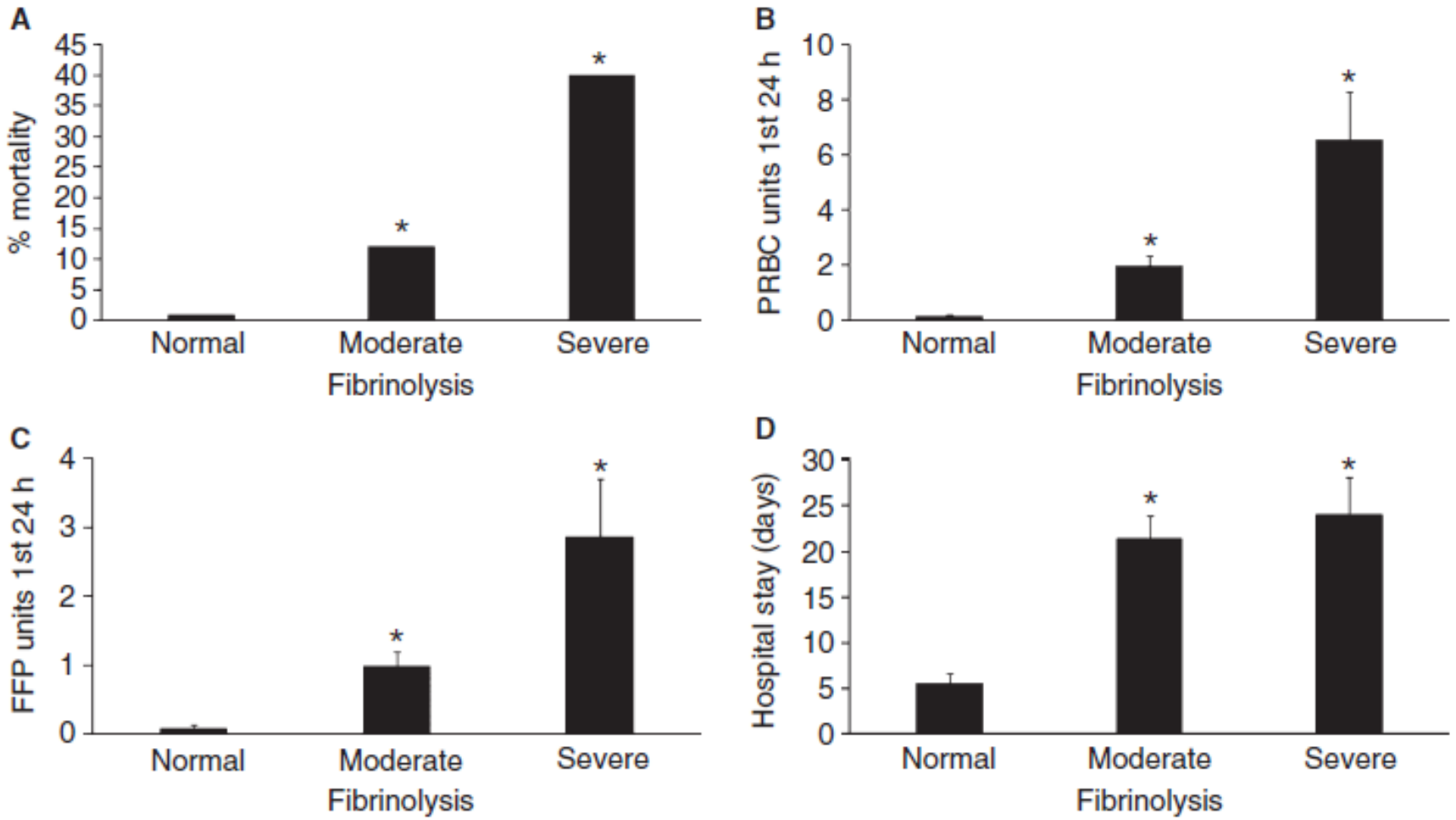


Blood 2016;128(8):1043-1049

The incidence and magnitude of fibrinolytic activation in trauma patients

. J Thromb Haemost 2013; 11 307–14.

I. RAZA,* R. DAVENPORT,* C. ROURKE,* S. PLATTON,† J. MANSON,* C. SPOORS,* S. KHAN,* H. D. DE'ATH,* S. ALLARD,‡ D. P. HART,§ K. J. PASI,§ B. J. HUNT,¶ S. STANWORTH,‡ P. K. MACCALLUM§ and K. BROHI*



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

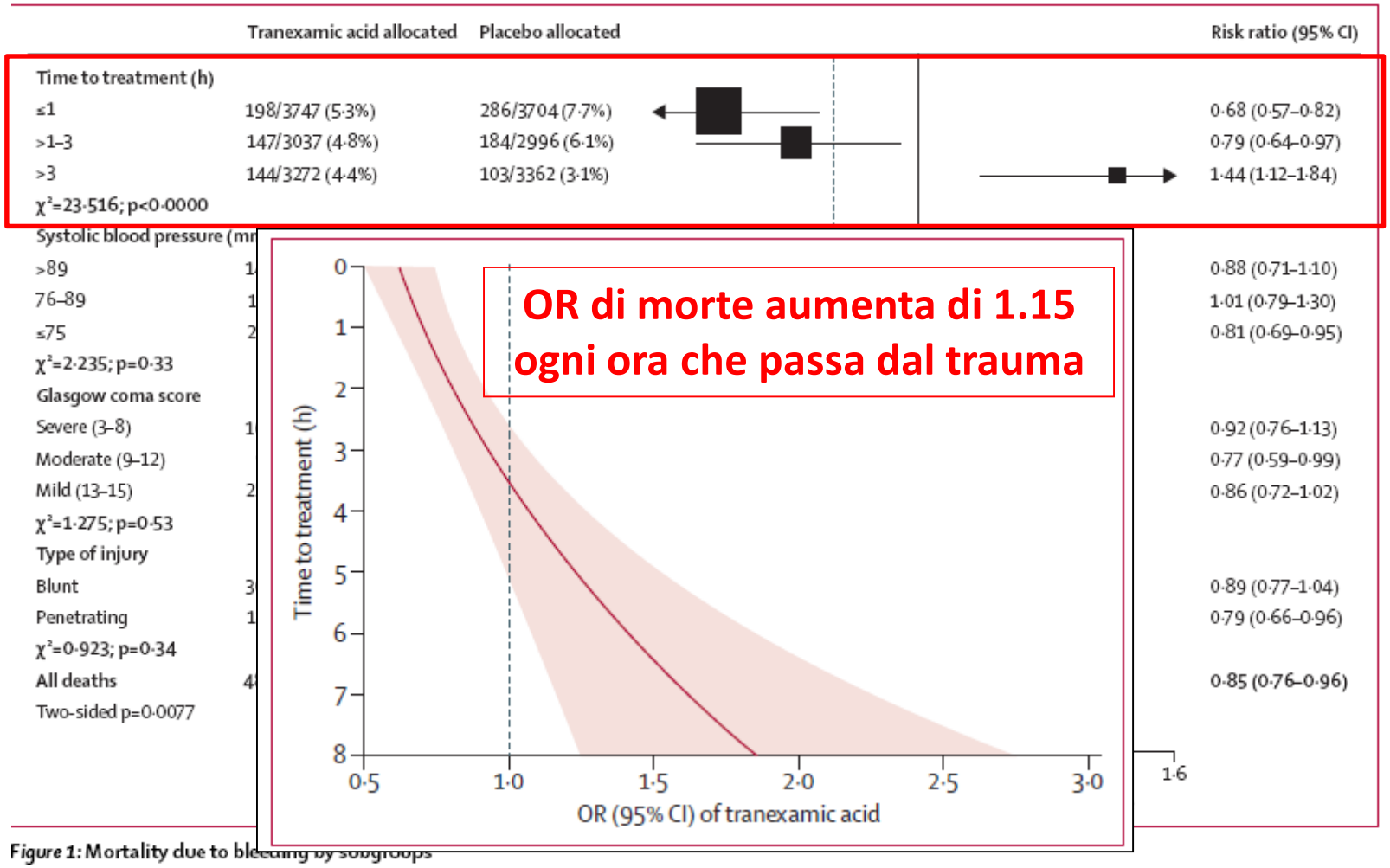


Figure 1: Mortality due to bleeding by subgroups

blood

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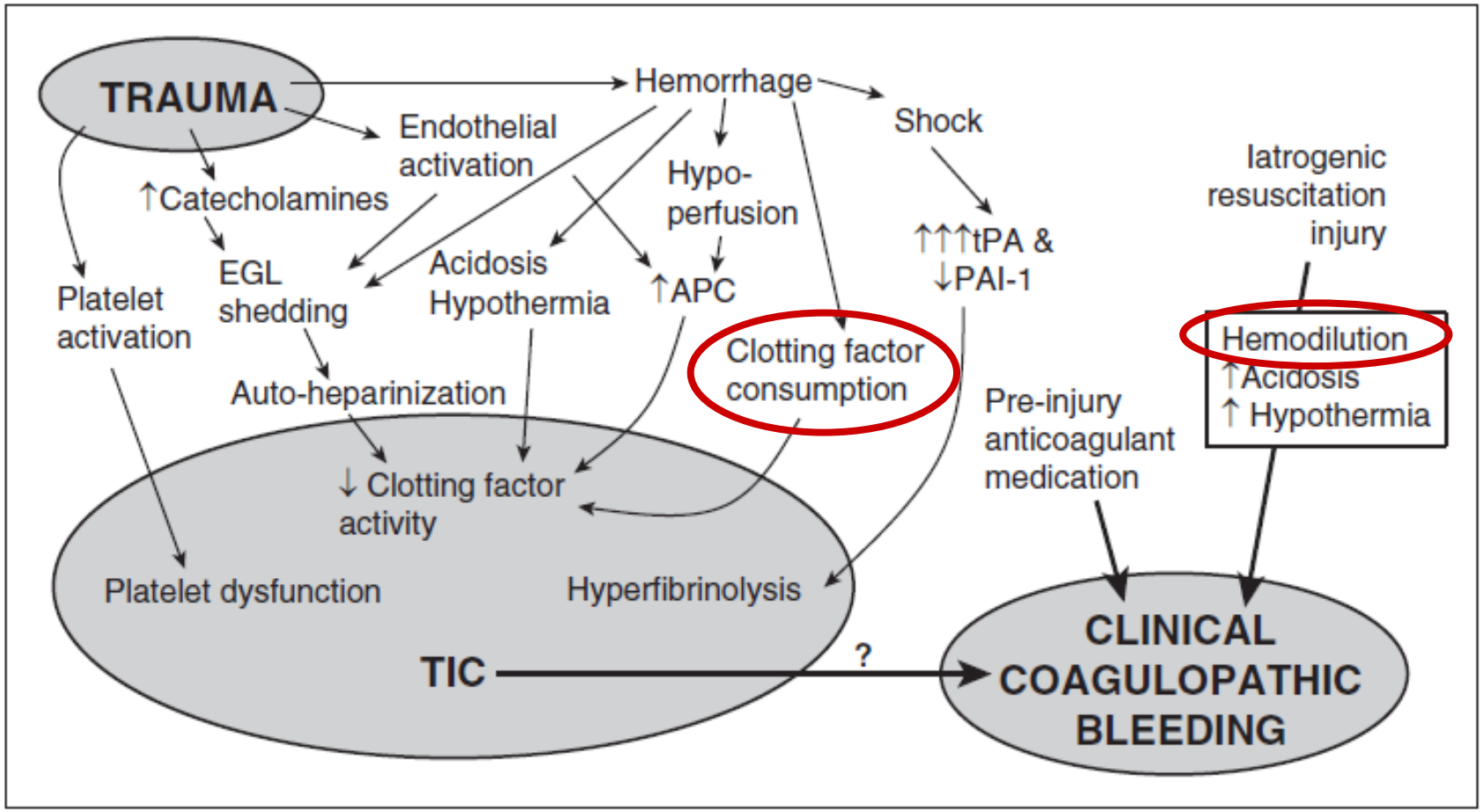

Blood 2016;128(8):1043-1049

SHOCK, Vol. 38, No. 5, pp. 450–458, 2012

Review Article

THE ACUTE COAGULOPATHY OF TRAUMA: MECHANISMS AND TOOLS FOR RISK STRATIFICATION

Marc Maegele,*† Philip C. Spinella,‡§ and Herbert Schöchl‖¶

Incidenza di coagulopatia	FATTORI LEGATI AL TRAUMA
1%	TRAUMA MODERATO
39%	ISS>25 + PAS < 70 mmHg
58%	ISS>25 + pH < 7.1
98%	ISS>25 + PAS < 70 mmHg + pH 7.1 + TC < 34 °C
	FATTORI LEGATI A RISUSCITAZIONE
40%	>2000 mL fluidi in pre-hospital
50%	>3000 mL fluidi in pre-hospital
70%	>4000 mL fluidi in pre-hospital

Rossaint *et al. Critical Care* (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

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III. Tissue oxygenation, type of fluid and temperature management

Tissue oxygenation

Recommendation 13 **We recommend a target systolic blood pressure of 80–90 mmHg until major bleeding has been stopped in the initial phase following trauma without brain injury. (Grade 1C)**

In patients with severe TBI (GCS ≤8), we recommend that a mean arterial pressure ≥80 mmHg be maintained. (Grade 1C)

Restricted volume replacement

Recommendation 14 **We recommend use of a restricted volume replacement strategy to achieve target blood pressure until bleeding can be controlled. (Grade 1B)**

Rossaint et al. Critical Care (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Type of fluid

Recommendation 16 **We recommend that fluid therapy using isotonic crystalloid solutions be initiated in the hypotensive bleeding trauma patient. (Grade 1A)**

We suggest that excessive use of 0.9 % NaCl solution be avoided. (Grade 2C)

We recommend that hypotonic solutions such as Ringer's lactate be avoided in patients with severe head trauma. (Grade 1C)

We suggest that the use of colloids be restricted due to the adverse effects on haemostasis. (Grade 2C)

Il modello della coagulopatia da trauma

René Magritte – L'uso della parola I, 1928-1929

Rossaint et al. Critical Care (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

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Initial coagulation resuscitation

Fresh frozen plasma

Recommendation 27 **If a plasma-based coagulation resuscitation strategy is used, we recommend that plasma (FFP or pathogen-inactivated plasma) be administered to maintain PT and APTT <1.5 times the normal control. (Grade 1C)**

We recommend that plasma transfusion be avoided in patients without substantial bleeding. (Grade 1B)

Rossaint et al. Critical Care (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

Fibrinogen and cryoprecipitate

Recommendation 28 **If a concentrate-based strategy is used, we recommend treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5–2.0 g/l. (Grade 1C)**

We suggest an initial fibrinogen supplementation of 3–4 g. This is equivalent to 15–20 single donor units of cryoprecipitate or 3–4 g fibrinogen concentrate. Repeat doses must be guided by viscoelastic monitoring and laboratory assessment of fibrinogen levels. (Grade 2C)

Rossaint *et al. Critical Care* (2016) 20:100
DOI 10.1186/s13054-016-1265-x

Critical Care

Platelets

Recommendation 29 **We recommend that platelets be administered to maintain a platelet count above 50×10^9/l. (Grade 1C)**

We suggest maintenance of a platelet count above 100×10^9/l in patients with ongoing bleeding and/or TBI. (Grade 2C)

If administered, we suggest an initial dose of four to eight single platelet units or one aphaeresis pack. (Grade 2C)

- ✓ The great majority of studies dealing with coagulopathy and transfusions are observational.
- ✓ "Immortal time bias": patients who die within the first few hours are less likely to receive the treatment (e.g. FFP or fibrinogen). Thus, at least in part, patients receive the treatment because they survive and not the opposite.
- ✓ Selection bias risk in studies addressing the efficacy of FFP:PRBC high ratios, fibrinogen administration, and blood transfusions
- ✓ Design of studies: patients are frequently included a posteriori in studies on the basis the number of PRBC units that have been administered within a specific time frame.
- ✓ Many studies do not account for main bleeding source control with surgery or interventional radiology, so we cannot discriminate between coagulopathy as a cause and coagulopathy as the consequence of haemorrhage, and thus to identify the target of possible treatments.

bjh guideline

A practical guideline for the haematological management of major haemorrhage

Beverley J. [illegible] of the British Co[illegible]

D: Specific clinical situations

Managing established bleeding in different patient subgroups

Major bleeding occurs in a number of different patient subgroups, treated by different sets of clinicians. The broad principles of management as described above should apply, but it is recognized that the pathophysiological derangements of haemostasis are likely to differ by site and different aetiologies of major bleeding. A priority for research is to understand how guidelines should be adapted for different aetiologies of bleeding. The areas where there is deviation from this or additional guidance are described below.

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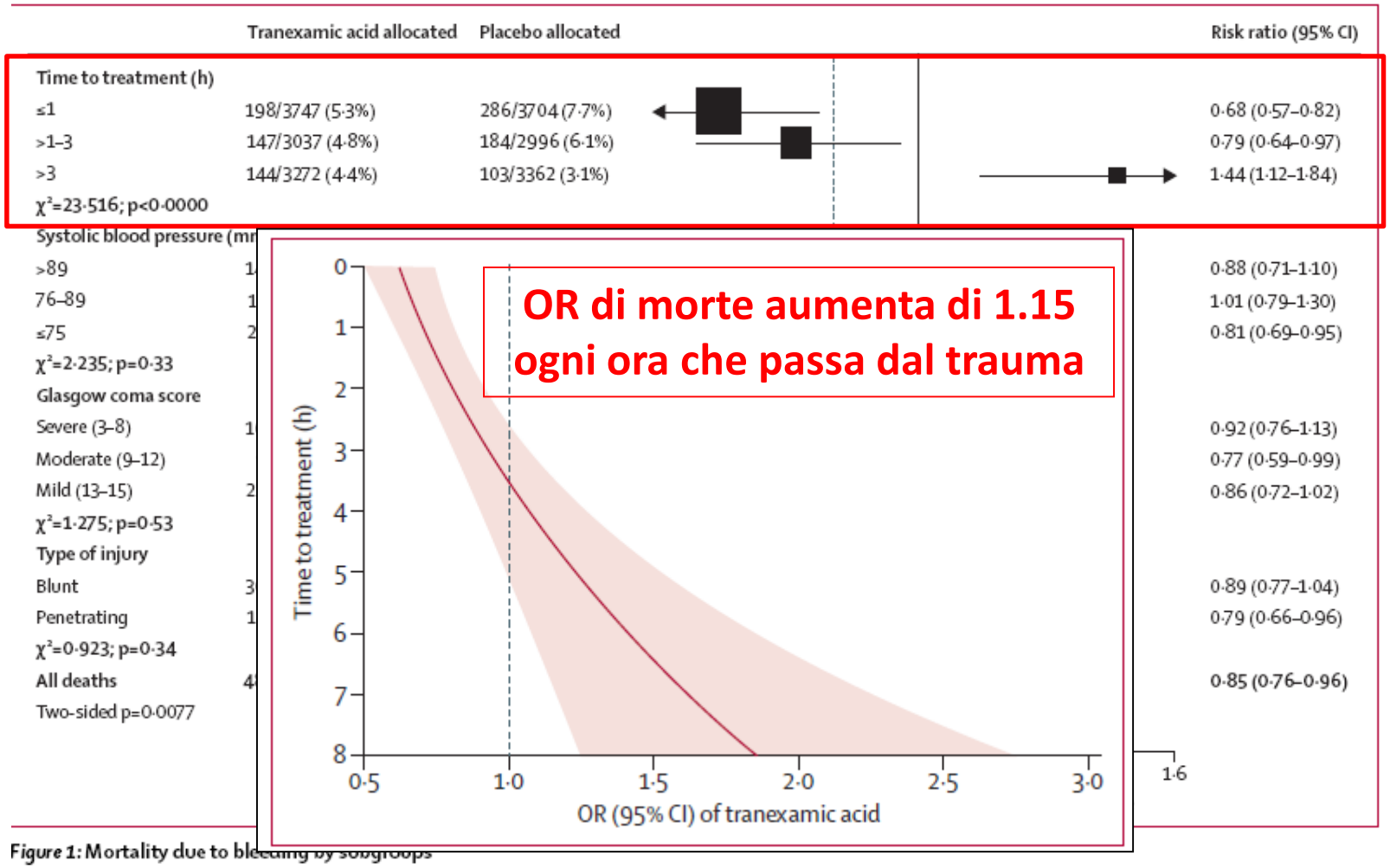

Figure 1: Mortality due to bleeding by subgroups

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Table 1| **Meta-analysis of effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality**

Outcomes	Events (tranexamic acid/control)	Pooled risk ratio (95% CI)	P value*	Heterogeneity I^2 (%)	Heterogeneity P value
Blood transfusion:					
All trials	1067/1520	0.62 (0.58 to 0.65)	<0.001	69	<0.001
Well concealed trials	459/ 609	0.68 (0.62 to 0.74)	<0.001	55	<0.001
Adequate blinding	847/1182	0.63 (0.59 to 0.68)	<0.001	54	<0.001
Myocardial infarction:					
All trials	23/35	0.68 (0.42 to 1.09)	0.11	0	0.90
Well concealed trials	16/25	0.70 (0.39 to 1.25)	0.22	0	0.82
Adequate blinding	18/33	0.59 (0.36 to 0.98)	0.04	0	0.81
Stroke:					
All trials	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Well concealed trials	5/4	1.18 (0.36 to 3.83)	0.78	0	0.92
Adequate blinding	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Deep vein thrombosis:					
All trials	25/29	0.86 (0.53 to 1.39)	0.54	0	0.96
Well concealed trials	13/14	0.92 (0.45 to 1.85)	0.81	0	0.81
Adequate blinding	18/22	0.82 (0.46 to 1.44)	0.49	0	0.98
Pulmonary embolism:					
All trials	4/8	0.61 (0.25 to 1.47)	0.27	0	0.96
Well concealed trials	1/3	0.52 (0.10 to 2.75)	0.44	0	0.80
Adequate blinding	4/6	0.70 (0.26 to 1.87)	0.48	0	0.91
Mortality:					
All trials	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97
Well concealed trials	9/15	0.67 (0.33 to 1.34)	0.25	0	0.85
Adequate blinding	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97

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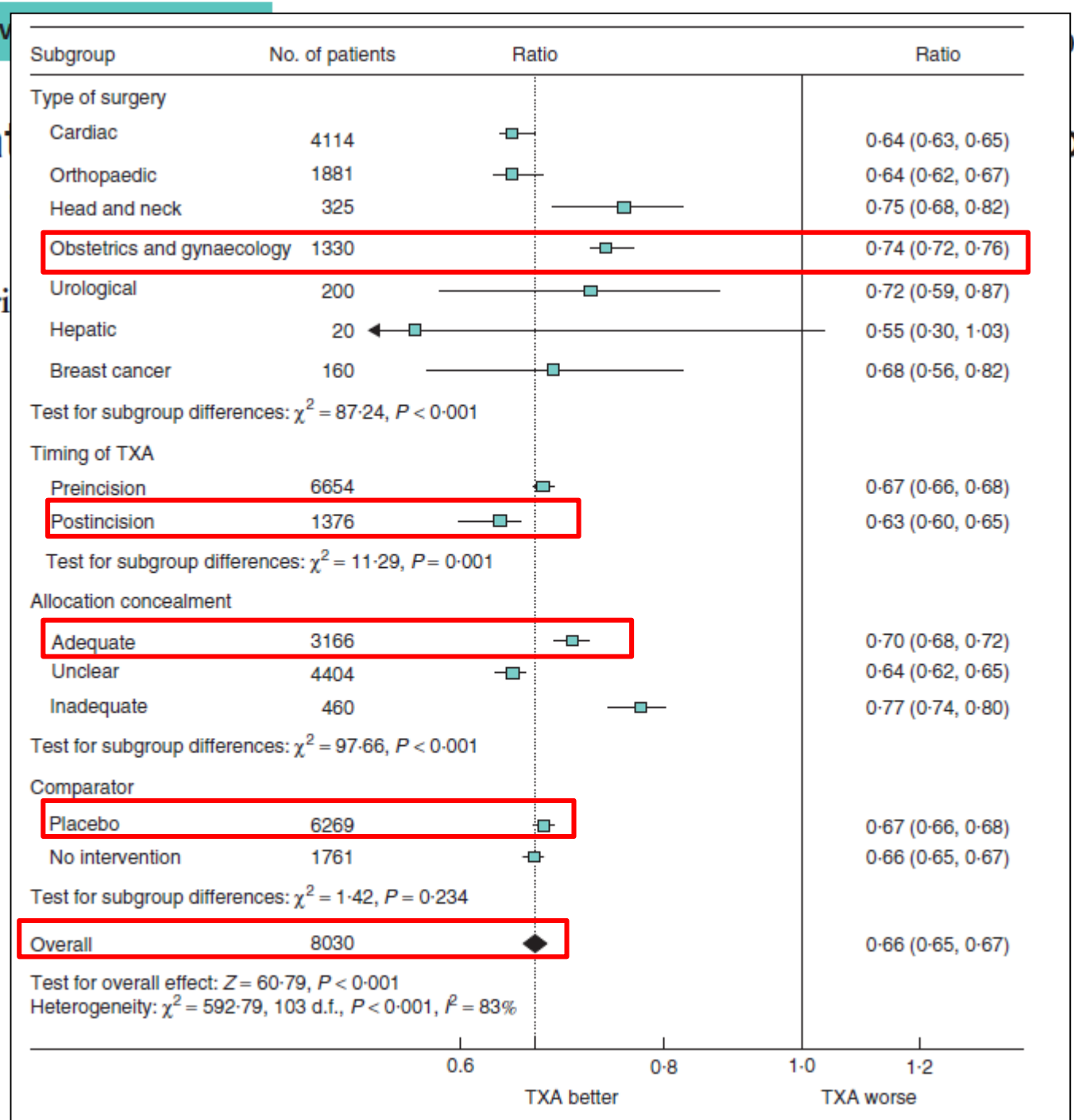

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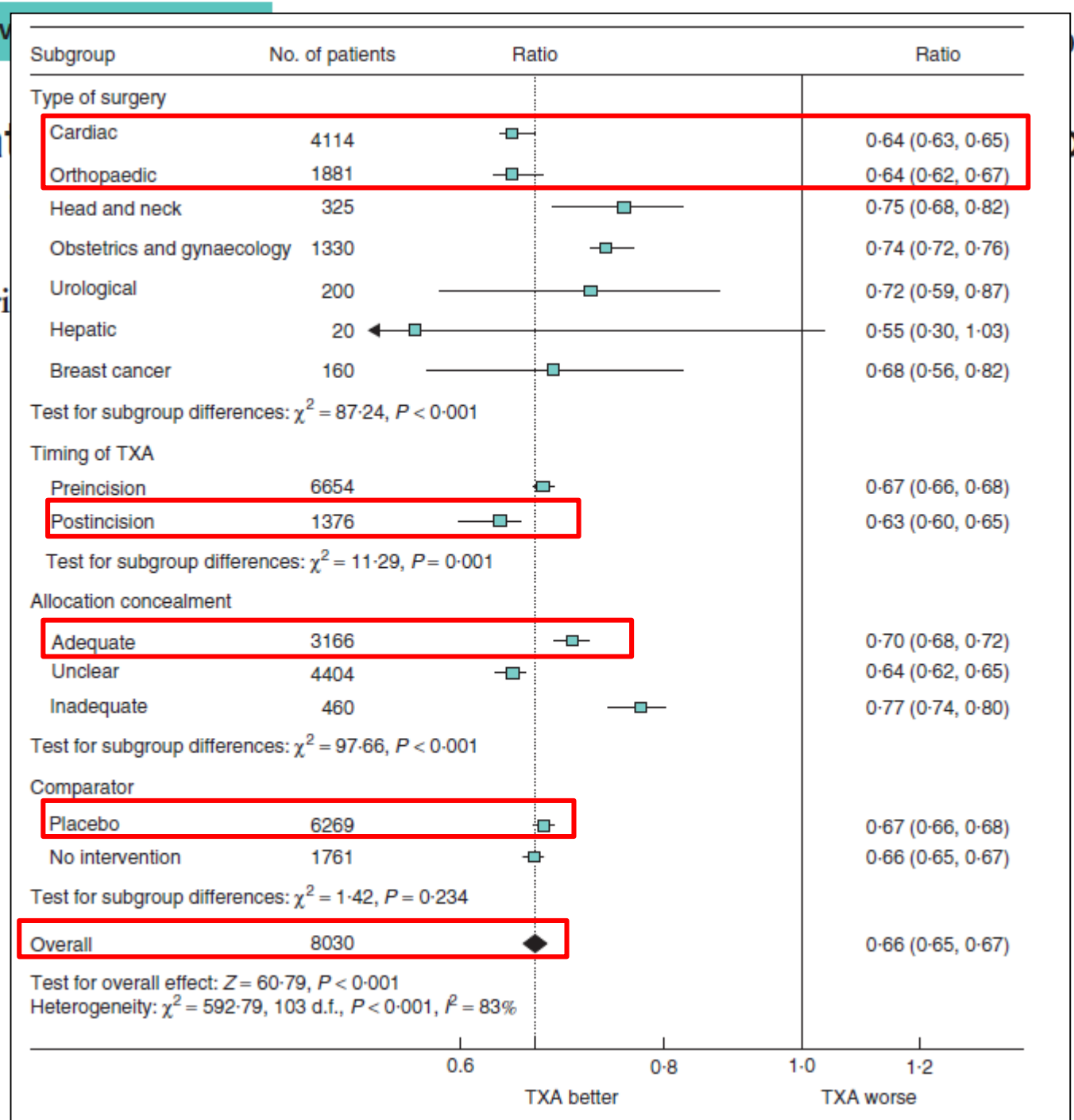

bjh guideline

A practical guideline for the haematological management of major haemorrhage

Beverley J. Hunt,[1] Shubha Allard,[2] David Keeling,[3] Derek Norfolk,[4] Simon J. Stanworth,[5] Kate Pendry[6] and on behalf of the British Committee for Standards in Haematology

Recommendation

In high-risk surgery tranexamic acid at a dose of 10 mg/kg followed by 1 mg/kg/h is recommended to prevent bleeding (1B).

Recommendation

In gastro-intestinal non-massive haemorrhage a restrictive strategy of red cell transfusion is recommended for many patients (1A).