V Jornadas Hematológicas del Sur

Terapia Transfusional en Medicina de Urgencia

Uso de Hemoderivados en Coagulación Intravascular Diseminada

V Jornadas Hematológicas del Sur:
Terapia Transfusional en Medicina de Urgencia
Valdivia, 12 de Junio de 2015

Mauricio Chandía C.

Scientific and Standardization Committee Communications

Towards Definition, Clinical and Laboratory Criteria, and a Scoring System for Disseminated Intravascular Coagulation*

On behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH)

Fletcher B. Taylor Jr.[1], Cheng-Hock Toh[2], W. Keith Hoots[3], Hideo Wada[4], Marcel Levi[5]

- "CID es un síndrome adquirido caracterizado por la ***activación intravascular de la coagulación*** con ***pérdida de la localización de ésta*** por diferentes causas. Puede originarse a consecuencia de ***daño a la microvasculatura*** o dar origen a éste en forma lo suficientemente severa como para producir ***disfunción orgánica***".

Taylor, F. Thromb Haemost 2001; 86: 1327–30

Criterios dg. ISTH CID sintomática

Parámetro	Puntaje		
	0	1	2
Condición predisponente			
Rcto plaquetario	>100	<100	<50
PT prolongado	<3 segs	>3 o < 6 segs	> 6 segs
FDP	N	↑ leve	↑↑
Fibrinógeno	> 100	< 100	

Diagnóstico de CID con ≥ 5 puntos. Si es menor, repetir en 1-2 ds

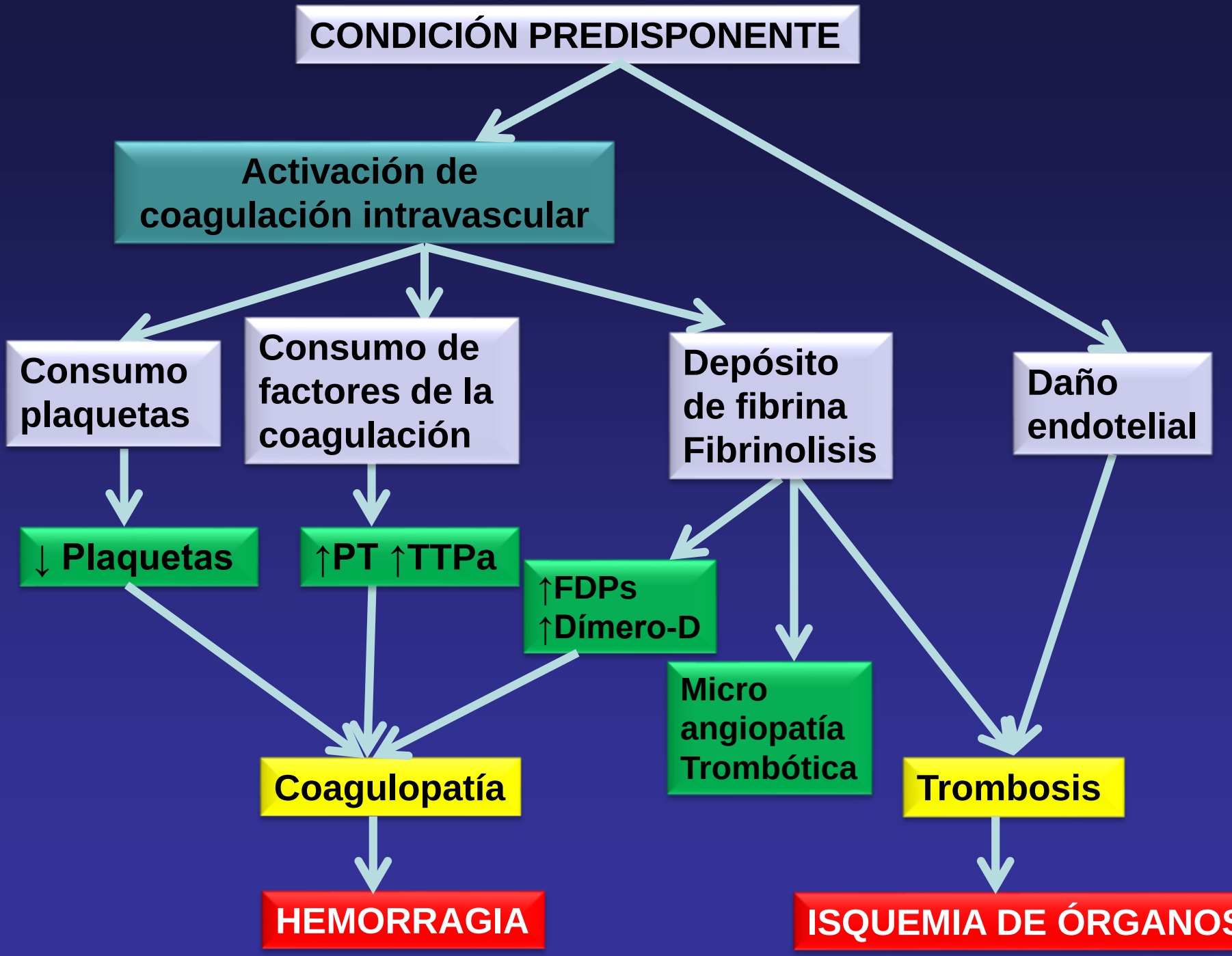
Taylor, F. Thromb Haemost 2001; 86: 1327–30

Criterios dg. ISTH CID asintomática

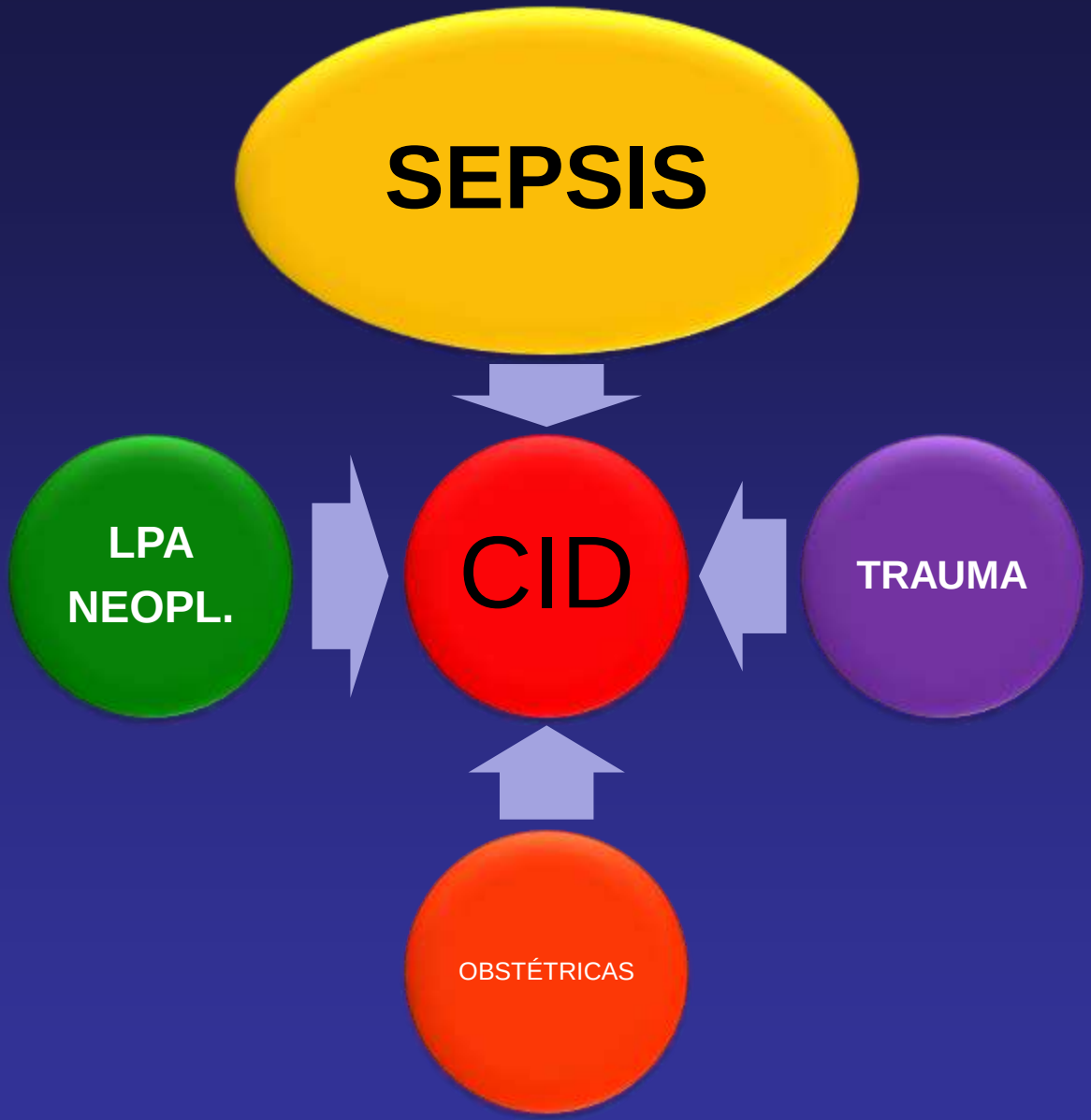
Parámetro	Puntaje				
	0	1	-1	0	+1
Condición predisponente					
Criterios mayores					
Rcto plaquetario	>100	<100	en ↑	estable	en ↓
PT prolongado	<3 segs	>3 segs	en ↑	estable	en ↓
FDP	N	↑	en ↑	estable	en ↓
Criterios específicos					
AT	N	↑			
PC	N	↑			
TAT	N	↑			

Diagnóstico de CID con > 5 puntos

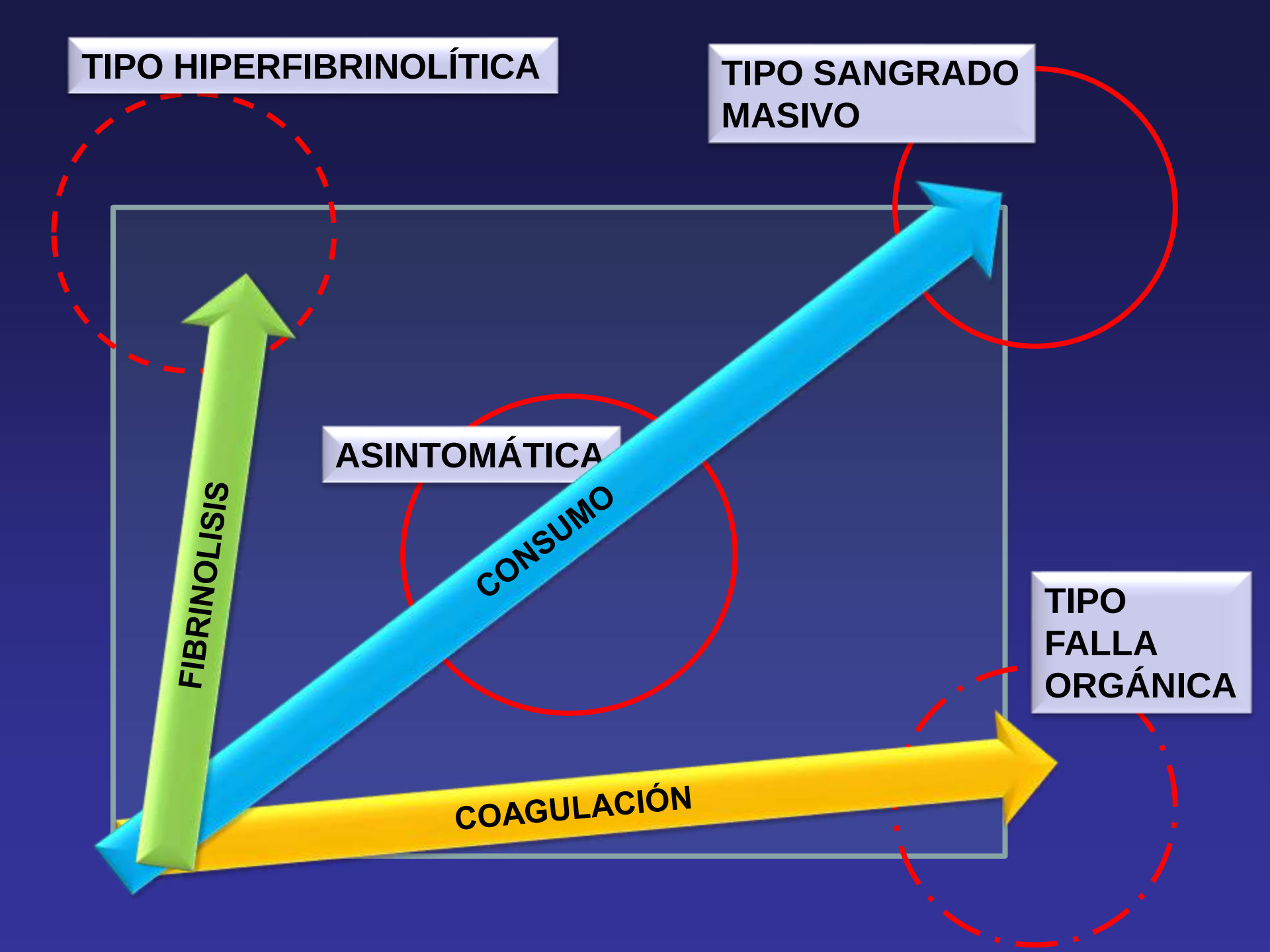
Taylor, F. Thromb Haemost 2001; 86: 1327–30


CONDICIÓN PREDISPONENTE
Activación de coagulación intravascular
Consumo plaquetas
Consumo de factores de la coagulación
Depósito de fibrina Fibrinolisis
Daño endotelial
↓ Plaquetas
↑PT ↑TTPa
↑FDPs ↑Dímero-D
Micro angiopatía Trombótica
Coagulopatía
Trombosis
HEMORRAGIA
ISQUEMIA DE ÓRGANOS

Factores a considerar en el tratamiento de la CID


SEPSIS
LPA
NEOPL.
CID
TRAUMA
OBSTÉTRICAS

Factores a considerar en el tratamiento de la CID


TIPO HIPERFIBRINOLÍTICA
TIPO SANGRADO MASIVO
ASINTOMÁTICA
FIBRINOLISIS
CONSUMO
COAGULACIÓN
TIPO FALLA ORGÁNICA

CID CON FALLA MULTIORGÁNICA: INMUNOTROMBOSIS

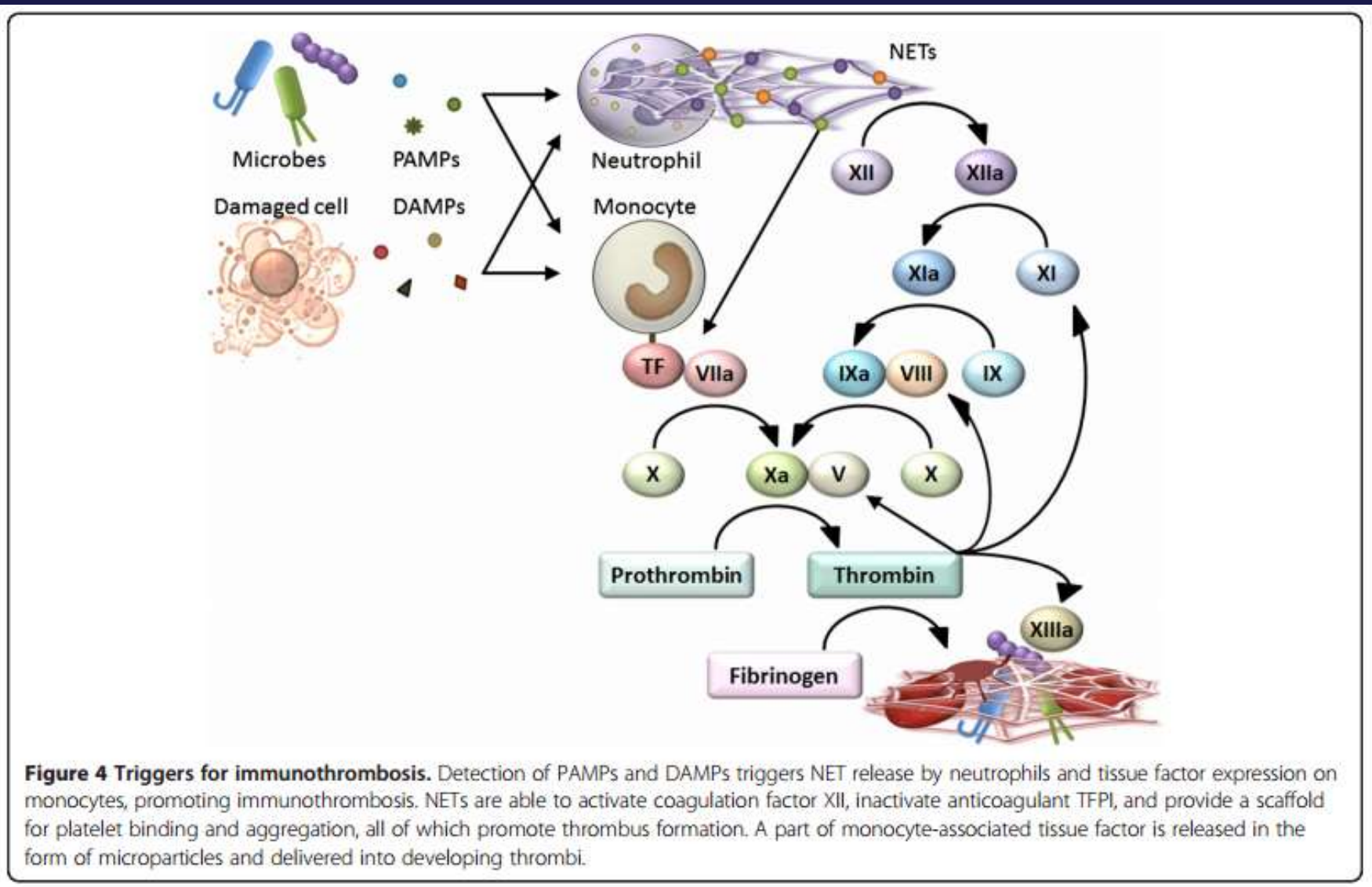
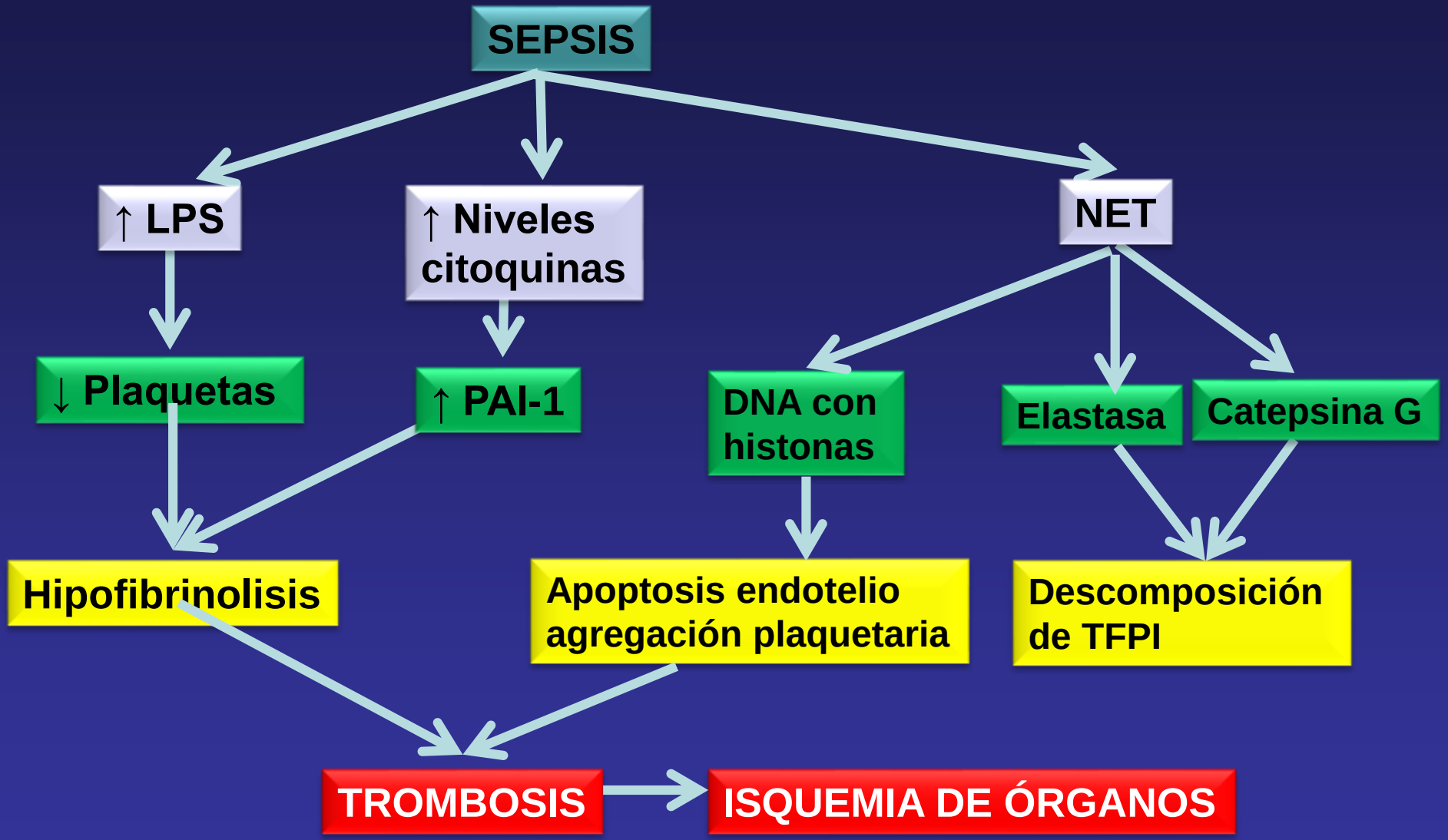


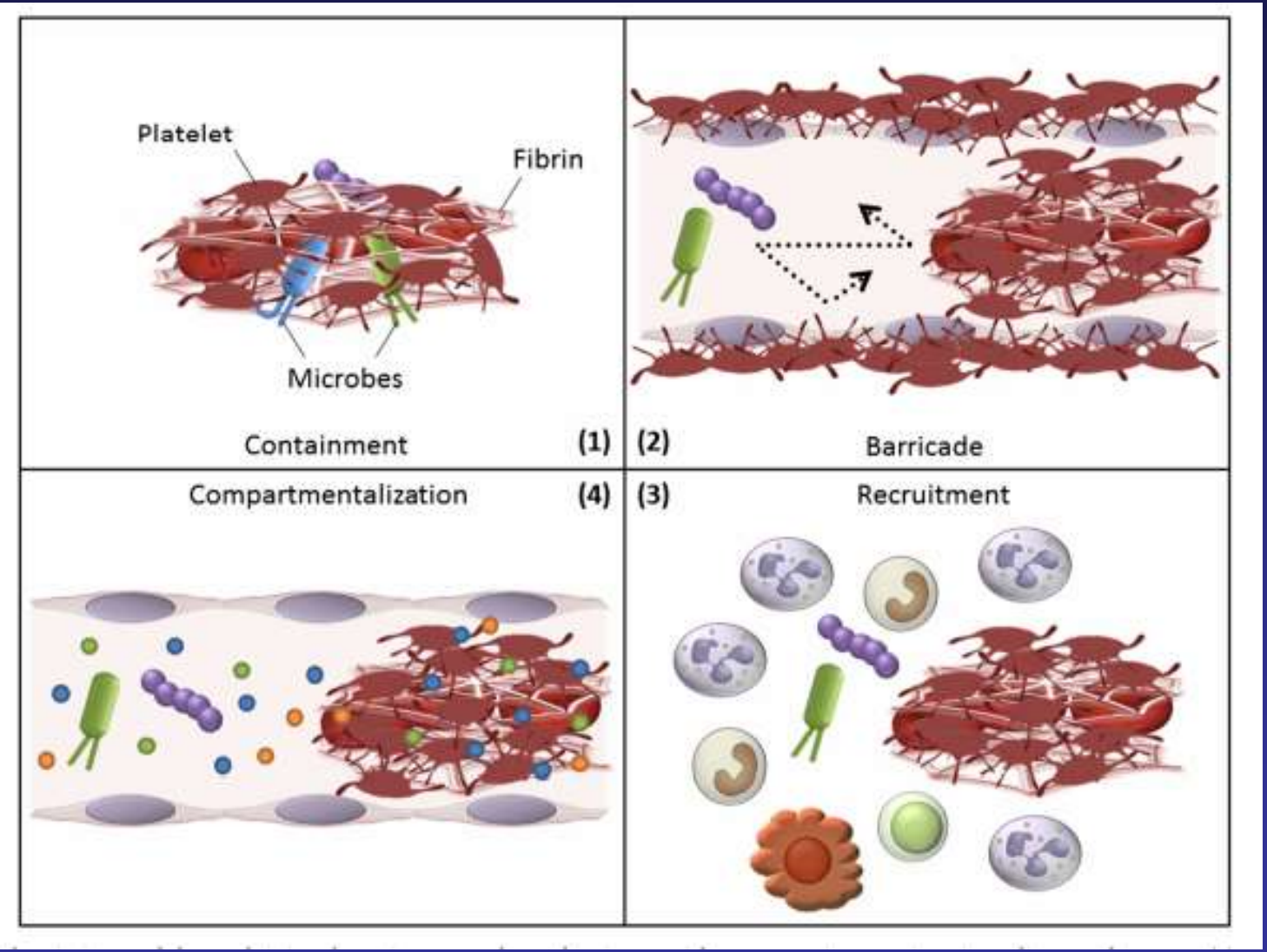
Figure 4 Triggers for immunothrombosis. Detection of PAMPs and DAMPs triggers NET release by neutrophils and tissue factor expression on monocytes, promoting immunothrombosis. NETs are able to activate coagulation factor XII, inactivate anticoagulant TFPI, and provide a scaffold for platelet binding and aggregation, all of which promote thrombus formation. A part of monocyte-associated tissue factor is released in the form of microparticles and delivered into developing thrombi.

Ito Journal of Intensive Care (2014)2:65

CID CON FALLA MULTIORGÁNICA

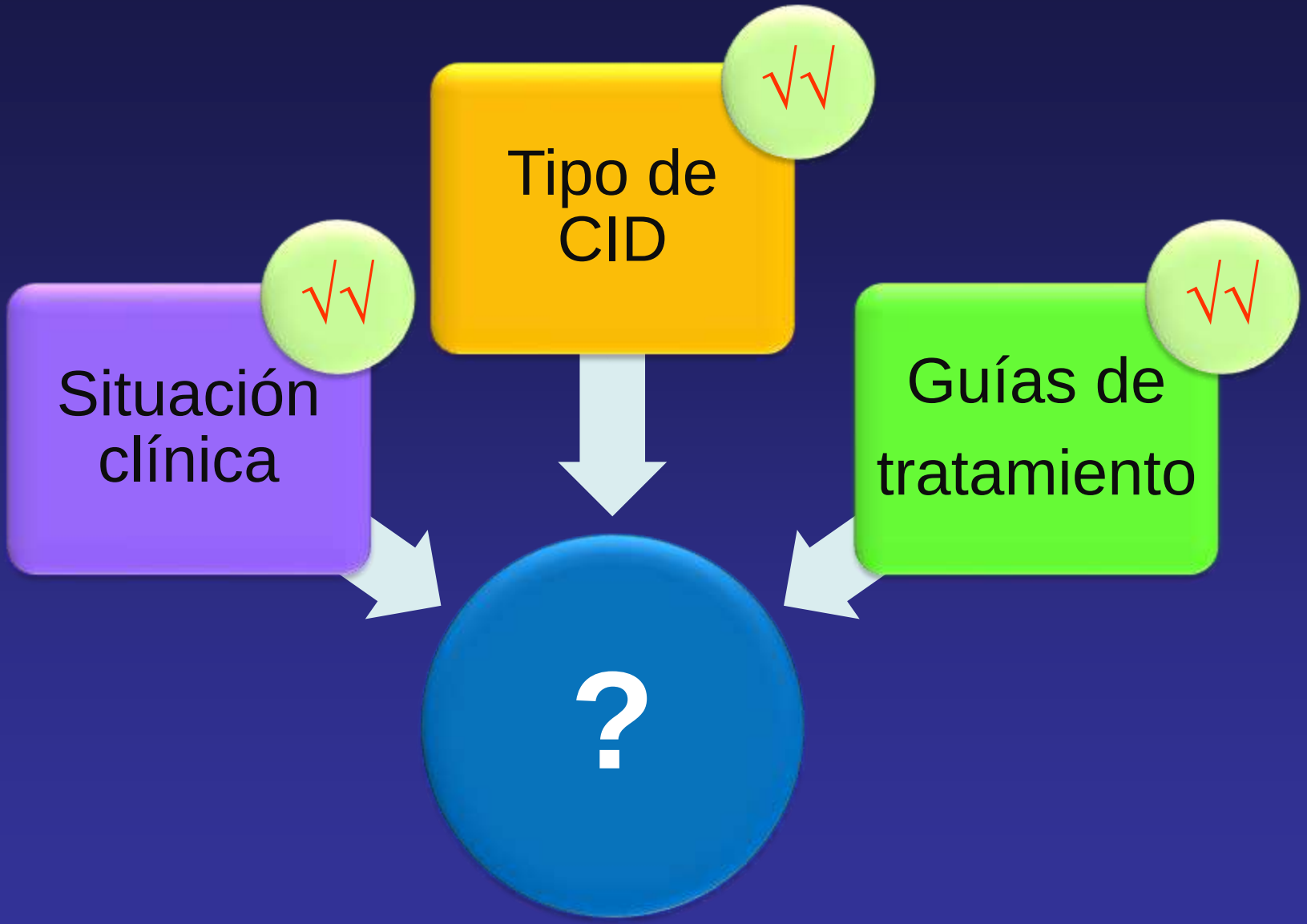


MODELOS DE EFECTIVIDAD DE LA INMUNOTROMBOSIS EN CID



Ito Journal of Intensive Care (2014)2:65

Factores a considerar en el tratamiento de la CID



Guías de tratamiento de la CID

- BCSH

  Br J Haematol 2009; 145: 24–33.

- JCSH

  Thromb Res 2010; 125: 6–11.

- SISET

  Thromb Res 2012; 129: e177–84.

Journal of Thrombosis and Haemostasis, **11**: 761–767 DOI: 10.1111/jth.12155

OFFICIAL COMMUNICATION OF THE SSC

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,††
H.K. KIM,‡‡ J.D. NIELSEN,§§ C-E. DEMPFLE,¶¶ M. LEVI,§ C-H. TOH***††† and THE SCIENTIFIC AND STANDARDIZATION COMMITTEE ON DIC OF THE ISTH

Calidad de recomendaciones (GRADE modificado)

HQ: **Futuras investigaciones probablemente no cambiarán la confianza en el efecto esperado.**

MQ: **Futuras investigaciones es probable que tengan un importante impacto en la confianza en el efecto esperado efecto y puedan cambiarla.**

LQ: **Futuras investigaciones es muy probable que tengan un importante impacto en la confianza en el efecto esperado y puedan cambiarla.**

Transfusión de plaquetas en CID

- Sangramiento activo con recuentos
  < 50.000/mm3.
- Alto riesgo de sangramiento y plaquetas
  < 20.000.
- ***LQ (Low Quality).***

Transfusión de Plasma fresco congelado

- ***Sangramiento activo con*:**
  - PT/TTPa prolongados > 1,5 veces lo normal.
  - Fibrinógeno disminuido < 150 mg/dl.
- ***Pacientes sin sangrado:***
  - Que van a procedimientos con similares alteraciones de laboratorio.
- Dosis: 15-30 ml/kg.
- ***LQ.***

Transfusión de Crioprecipitados o concentrado de fibrinógeno

- Pacientes con sangrado activo e hipofibrinogenemia persistente (< 150 mg/dl) *a pesar de reemplazo de PFC*.
- **LQ**

Concentrados de complejo protrombínico en CID

- ***Recomendados*** por guías ISTH para pacientes con sangrado activo que no pueden recibir plasma.
- ***Contraindicado*** por otros autores por riesgo alto de trombosis.
- ***LQ.***

Increasing concentrations of prothrombin complex concentrate induce disseminated intravascular coagulation in a pig model of coagulopathy with blunt liver injury

Oliver Grottke,[1,2] Till Braunschweig,[3] Henri M. H. Spronk,[4] Stephanie Esch,[1] Annette D. Rieg,[1] Rene van Oerle,[4] Hugo ten Cate,[4] Christina Fitzner,[5] Rene Tolba,[2] and Rolf Rossaint[1]

27 cerdos se reemplazo volemia por 70% de coloide+ Ringer /lactato →Trauma hepático cerrado →Reinfusión de PCC (35 o 50 UI/kg) o S Fisiológico+ GR.

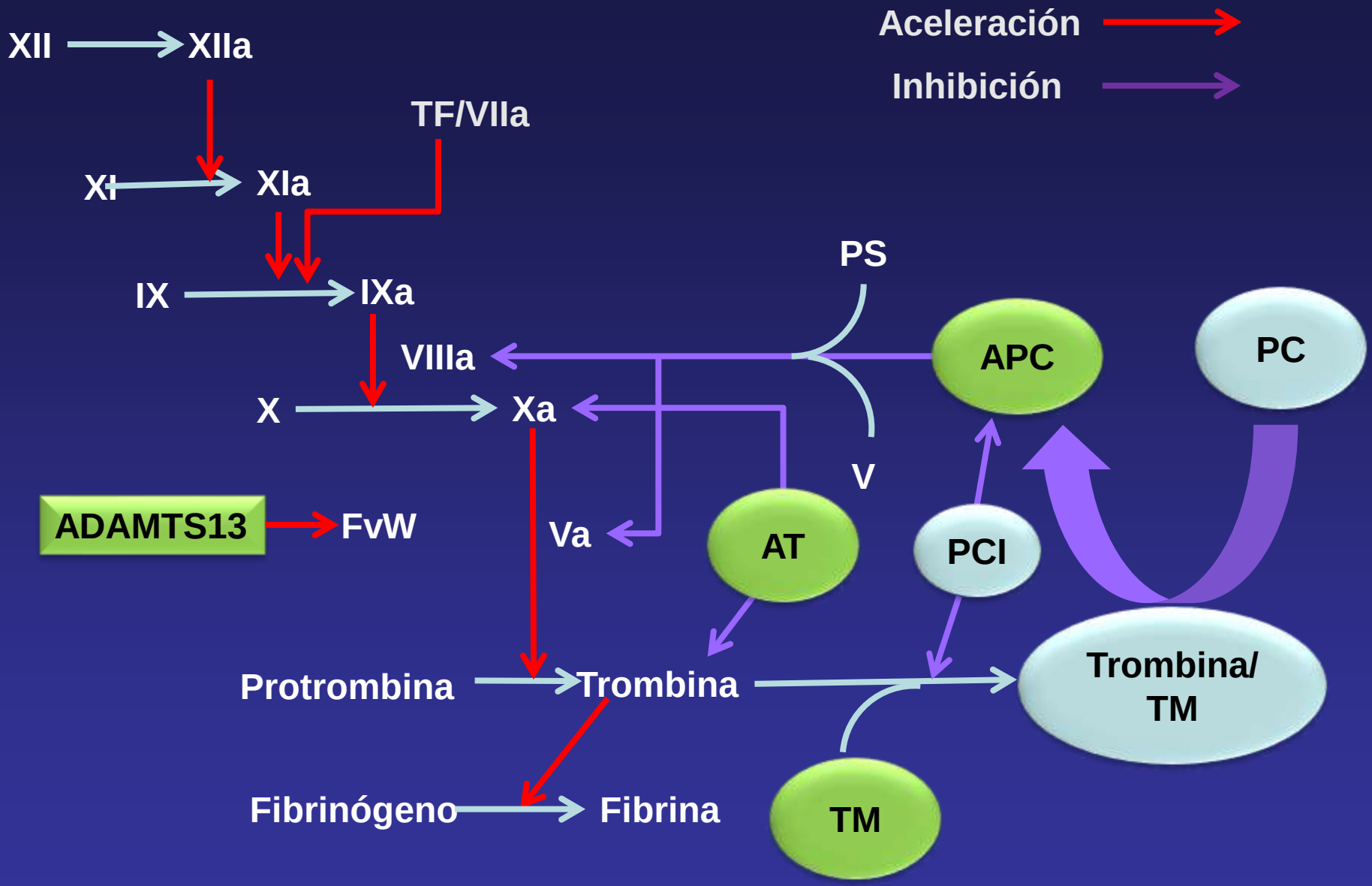
Por 2 horas, se monitorizó experimento con TEG, Generación de trombina y pérdida de sangre.

A las 2 hrs, la pérdida de sangre fue menor y la sobrevida fue mayor en los 2 grupos tratados con PCC.

Signos de TE fue encontrado en todos los casos tratados con dosis alta de PCC y 44% de ellos tenían CID.

Blood. 2011;118(7):1943-1951

REGULACIÓN DEL SISTEMA DE LA COAGULACIÓN



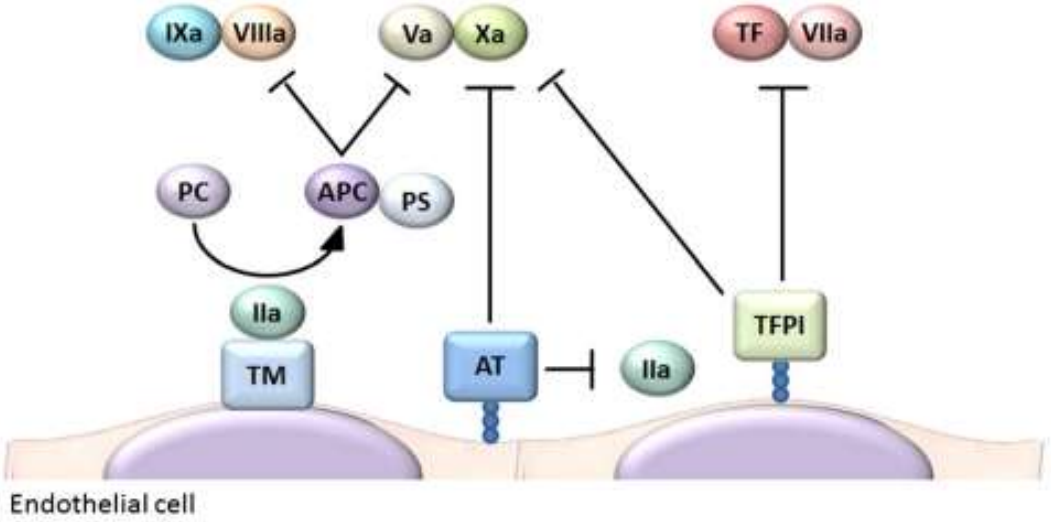


Figure 2 Anticoagulant properties of endothelial cells. Endothelial cells express several anticoagulants, including thrombomodulin (TM), tissue factor pathway inhibitor (TFPI), and heparan sulfate. Upon binding to TM, thrombin loses its ability to activate platelets, fibrinogen, and coagulation factors V, VIII, XI, and XIII. Furthermore, the thrombin-TM complex activates protein C, which in turn stops thrombin generation by inactivating coagulation factors Va and VIIIa. Endothelial cells also synthesize and display heparan sulfate proteoglycans on their surface, which bind to TFPI and antithrombin (AT), inhibiting the factor VIIa-tissue factor complex, factor Xa, and thrombin activity. *IIa* thrombin, *PS* protein S.

Concentrados de factor en CID

- Proteína C activada (aPC).
- Trombomodulina (TM).
- Antitrombina (AT).

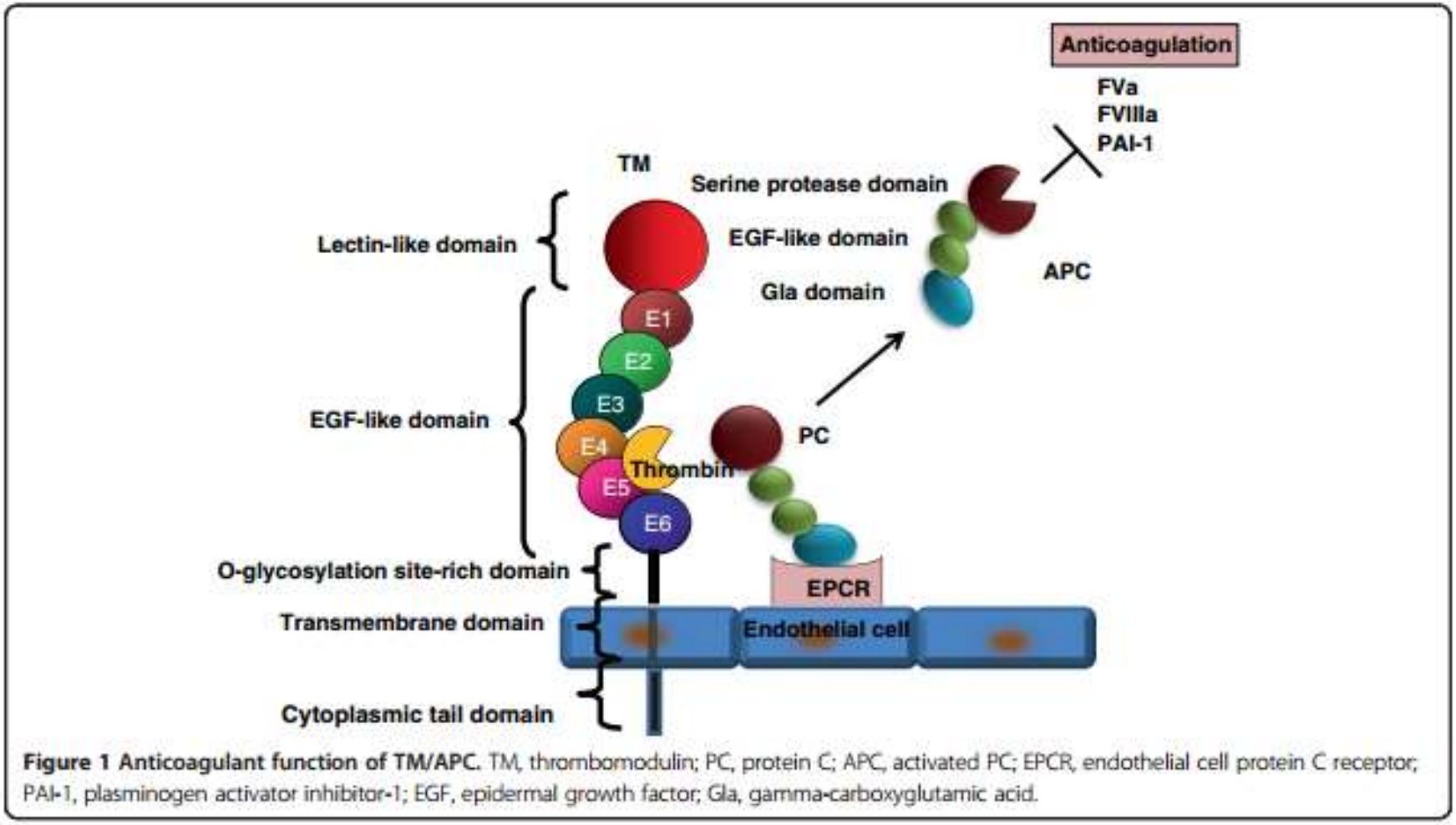


Figure 1 Anticoagulant function of TM/APC. TM, thrombomodulin; PC, protein C; APC, activated PC; EPCR, endothelial cell protein C receptor; PAI-1, plasminogen activator inhibitor-1; EGF, epidermal growth factor; Gla, gamma-carboxyglutamic acid.

Ikezoe Journal of Intensive Care (2015) 3:1

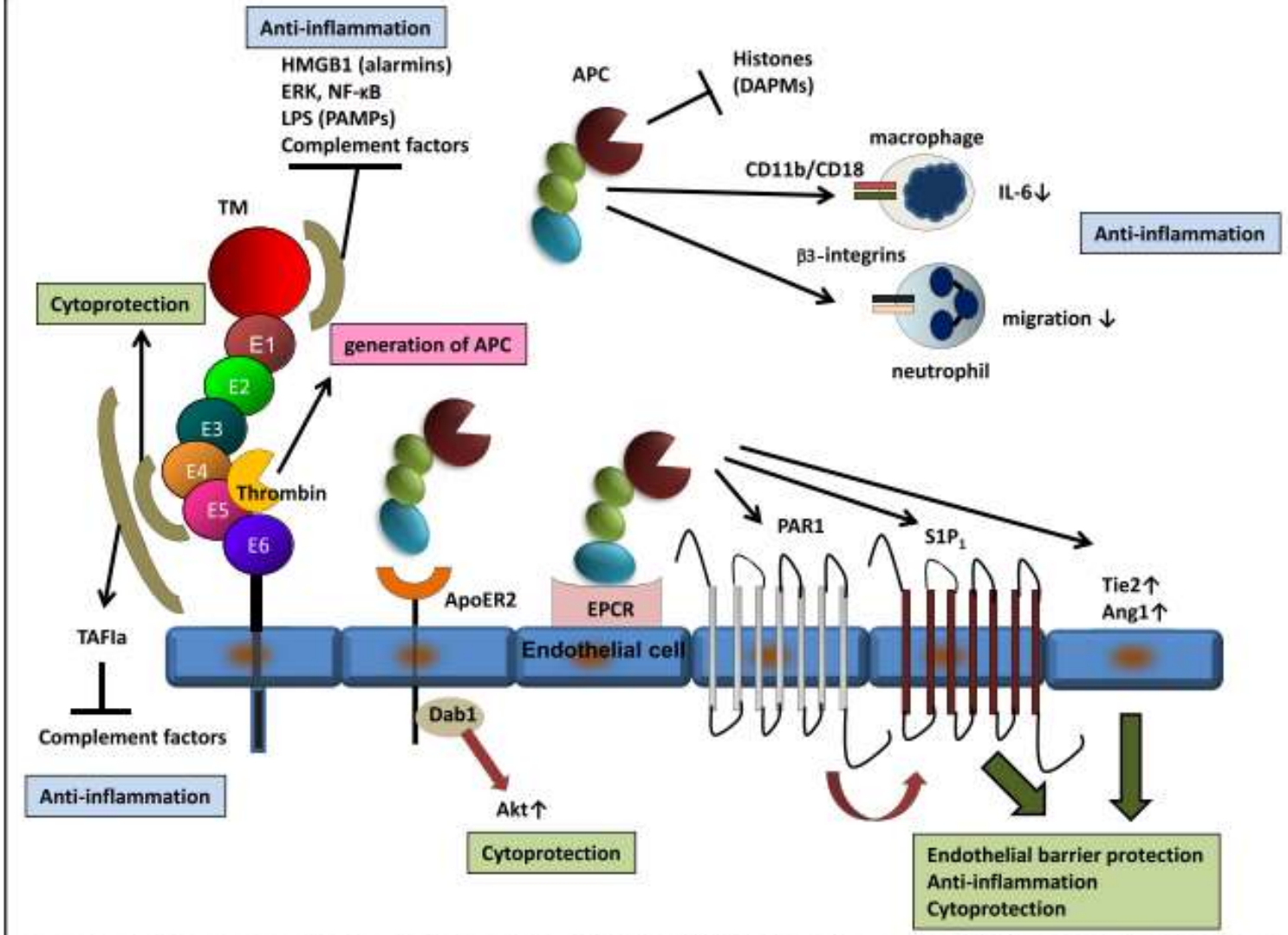


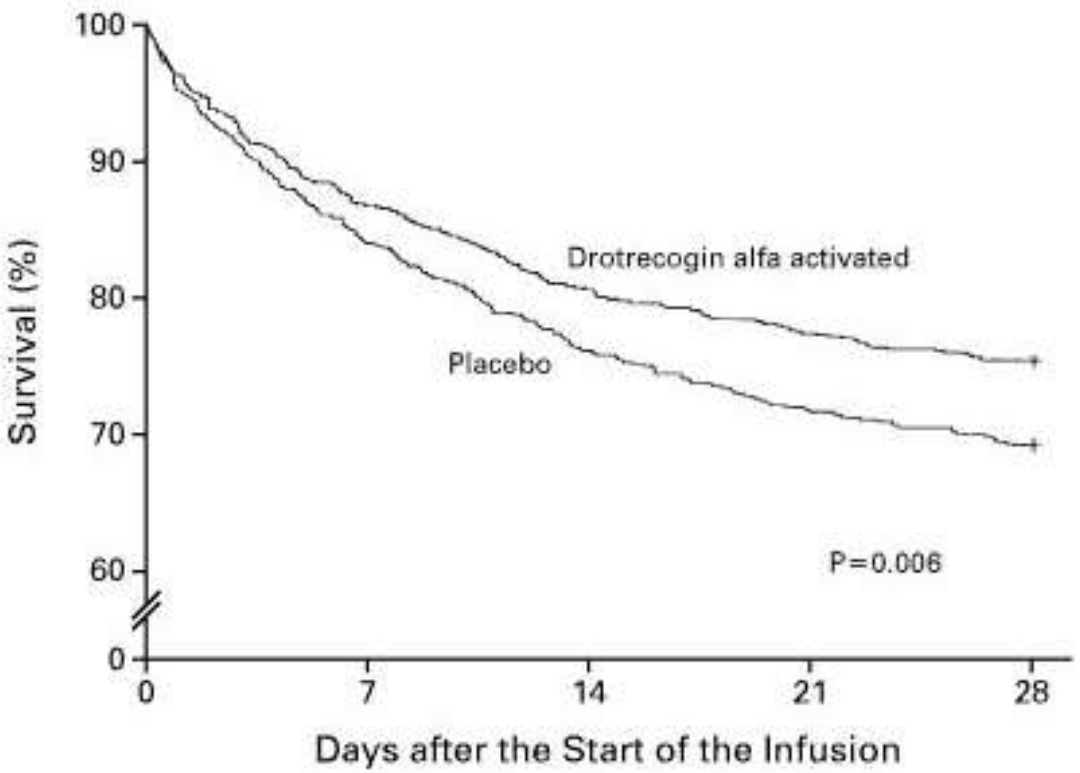
Figure 2 Anti-inflammatory and cytoprotective functions of TM/APC. HMGB1, high-mobility group box 1; PAR1, protease-activated receptor-1; $S1P_1$, sphingosine 1-phosphate receptor; TAFIa, active thrombin-activatable fibrinolysis inhibitor; EPCR, endothelial cell protein C receptor; ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor-κ B; Ang1, angiopoietin 1; Tie2, tyrosine kinase with Ig-like loops and epidermal growth factor homology domains-2, ApoER2, apolipoprotein E receptor 2; Dab1, disabled-1; PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns.

Ikezoe Journal of Intensive Care (2015) 3:1

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*

- RCT de rh-aPC por 96 hrs vs placebo.
- Endpoint: mortalidad por cualquier causa a 28 ds.
- 1690 pcts: 840 placebo y 850 rh-aPC, con sepsis y falla multiorgánica (APACHE≈ 25)
- *rh-aPC:*
  - *Mortalidad 24.7% vs placebo 30.8%.*
  - *Reducción riesgo relativo de mortalidad de 19,4% y reducción absoluta de riesgo de muerte de 6,1% (P=0.005).*



No. at Risk					
Drotrecogin alfa activated	850	737	684	657	640
Placebo	840	705	639	602	581

N Engl J Med. 2001;344(10):699.

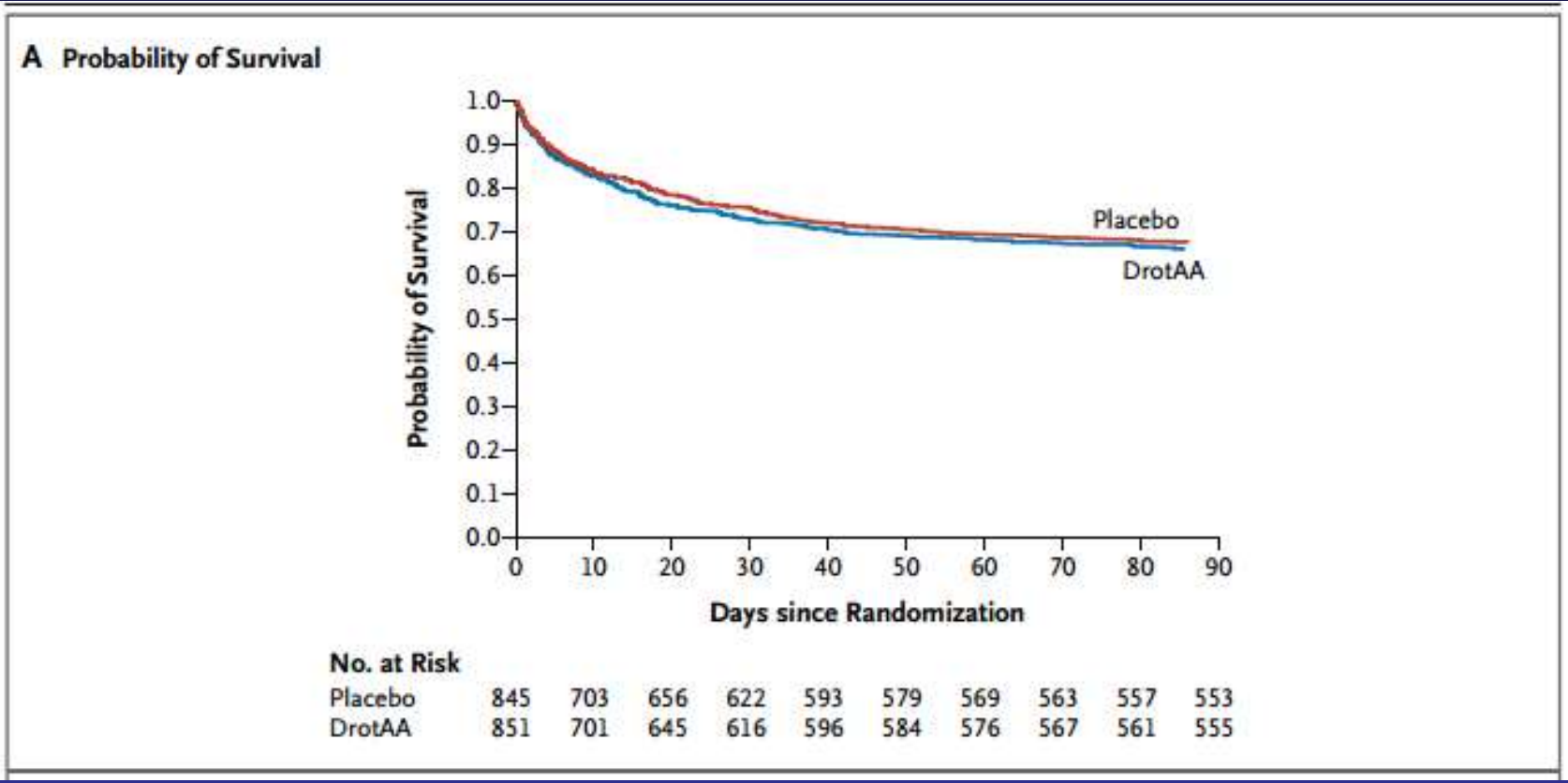
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 31, 2012 VOL. 366 NO. 22

Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*

- RCT 1697 pacientes con sepsis y necesidad de DVA.
- Mortalidad:
  - 28 días: 26.4% en rh-APC vs 24,2% en placebo. P=0.31.
  - 90 días: 34.1% en rh-APC vs 32,7% en placebo. P=0.56.



N Engl J Med 2012;366:2055-64

International Journal of
HEMATOLOGY

A Comparative Double-Blind Randomized Trial of Activated Protein C and Unfractionated Heparin in the Treatment of Disseminated Intravascular Coagulation

Nobuo Aoki,[a] Tamotsu Matsuda,[b] Hidehiko Saito,[c] Kiyoshi Takatsuki,[d] Kenji Okajima,[d] Hoyu Takahashi,[e] Junki Takamatsu,[c] Hidesaku Asakura,[b] Nobuya Ogawa,[f] for the CTC-111-IM Clinical Research Group*

- RCT 142 pacientes con CID dg por Score del JMHW.
- 63 pacientes con PD-APC y 69 pctes con Heparina no fraccionada en infusión de 6 ds.
- Se midió eficacia, seguridad y mortalidad a los 28 días.

Aoki N, Int J Hematol. 2002;75:540-7

Table 2.
Characteristics of Patients Subjected to Efficacy Assessment*

Background	APC Group	Heparin Group
Sex		
Male	31	34
Female	18	21
Age, mean ±SD	60.0 ± 18.8 y	56.9 ± 18.8 y
Body weight, mean ±SD	55.7 ± 9.8 kg	54.7 ± 11.1 kg
Underlying diseases		
APL	6	6
Non-APL	17	26
Other hemopoietic malignancy†	10	4
Cancer	5	10
Infection	6	6
Others‡	5	3

*APC indicates activated protein C; APL, acute promyelocytic leukemia.
†Including malignant lymphoma and adult T-cell lymphoma-leukemia.
‡Liver diseases (hepatitis, liver cirrhosis) and aortic aneurysm.

Aoki N, Int J Hematol. 2002;75:540-7

Table 7.
The Effect of Treatment on Intravascular Coagulation Assessed by the Changes of Scores of 4 Parameters (FM Test, D-Dimer, TAT, and PIC)*

	Grade						
Drugs	Remarkable Alleviation	Alleviation	Poor Alleviation	Aggravation	Impossible to Judge	Total	Wilcoxon Rank Sum Test
APC group	28 (58.3)	7 (72.9)	6	7	1	49	$Z = 1.99$, $P = .046$
Heparin group	23 (42.6)	6 (53.7)	8	17	1	55	

*Cumulative percentage in parentheses. Abbreviations are defined in the Table 3 footnote.

Table 8.
Comparison of the Mortality between the APC Group and the Heparin Group*

Patient group	Survivors	Nonsurvivors	Mortality, %	χ^2 Test
APC group (n = 49)	39	10	20.4	$P < .05$
Heparin group (n = 55)	33	22	40.0	

*The mortality was calculated using numbers of patients who had died during the treatment or within 28 days after the treatment. APC indicates activated protein C.

Aoki N, Int J Hematol. 2002;75:540-7

Journal of Thrombosis and Haemostasis, 5: 31–41

ORIGINAL ARTICLE

Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial

H. SAITO,* I. MARUYAMA,† S. SHIMAZAKI,‡ Y. YAMAMOTO,§ N. AIKAWA,¶ R. OHNO,** A. HIRAYAMA,†† T. MATSUDA,‡‡ H. ASAKURA,§§ M. NAKASHIMA¶¶ and N. AOKI***

- RCT de rh-TM (ART-123) con heparina.
- Endpoint: Resolución de CID y seguridad.
- Resultados: CID se resolvió en 66,1% de grupo con rh-TM y en 49,9% de heparina.
- Hemorragias a los 7 días fueron menores en grupo con rh-TM (43.1% vs. 56.5%, P = 0.0487).
- No hubo diferencias en la mortalidad a 28 ds.

J Thromb Haemost. 2007;5:31-41

	Underlying disease	
	Hematologic malignancy	Infection
DIC resolution rate*		
ART-123 group	42/64 patients (65.6)	32/48 patients (66.7)
Heparin group	28/61 patients (45.9)	28/51 patients (54.9)
Difference (95% CI)	19.7% (2.6 to 36.8)	11.8% (−7.3 to 30.9)
The disappearance rate of bleeding symptoms at day 7		
ART-123 group	14/43 patients (32.6)	17/45 patients (37.8)
Heparin group	6/45 patients (13.3)	13/46 patients (28.3)
Difference (95% CI)	19.2% (2.1 to 36.4)	9.5% (−9.7 to 28.8)
The mortality rate at day 28		
ART-123 group	11/64 patients (17.2)	14/50 patients (28.0)
Heparin group	11/61 patients (18.0)	18/52 patients (34.6)
Difference (95% CI)	−0.8% (−14.2 to 12.5)	−6.6% (−24.6 to 11.3)

J Thromb Haemost. 2007;5:31-41

Yamakawa et al. Critical Care 2011, 15:R123
http://ccforum.com/content/15/3/R123

CRITICAL CARE

RESEARCH Open Access

Treatment effects of recombinant human soluble thrombomodulin in patients with severe sepsis: a historical control study

Kazuma Yamakawa[1,2*], Satoshi Fujimi[1], Tomoyoshi Mohri[1], Hiroki Matsuda[1], Yasushi Nakamori[1], Tomoya Hirose[2], Osamu Tasaki[2], Hiroshi Ogura[2], Yasuyuki Kuwagata[2], Toshimitsu Hamasaki[3] and Takeshi Shimazu[2]

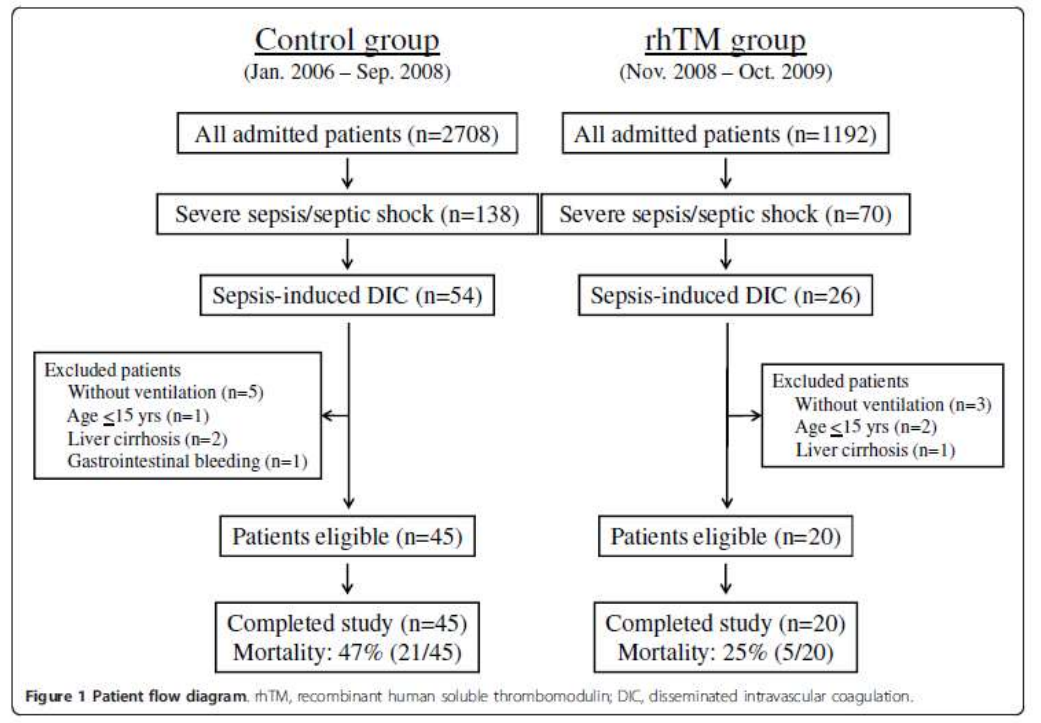


Figure 1 Patient flow diagram. rhTM, recombinant human soluble thrombomodulin; DIC, disseminated intravascular coagulation.

Yamakawa et al. Critical Care 2011, 15:R123

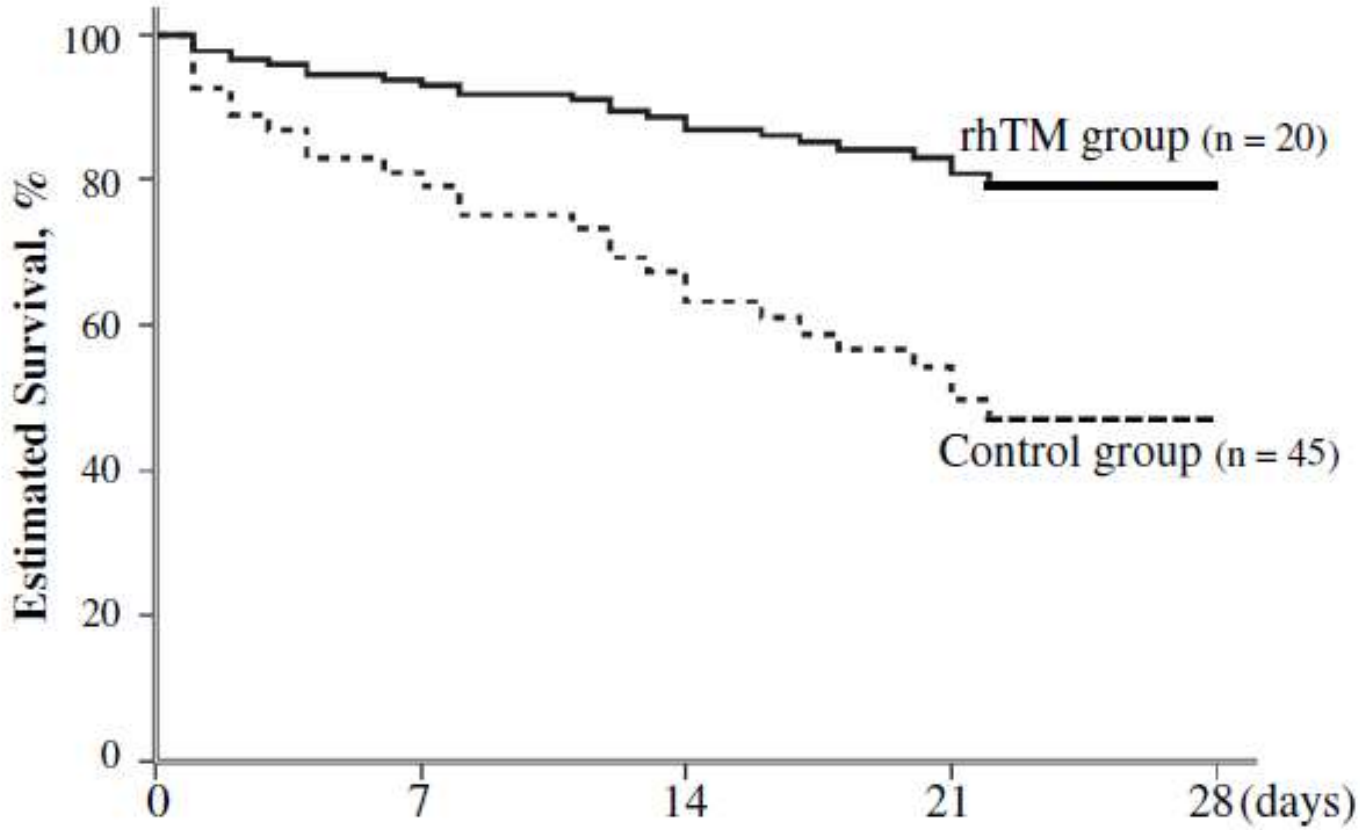


Figure 2 Adjusted estimated survival curves by covariates of APACHE II score and sex in final multivariate Cox regression models. The solid line represents patients in the rhTM group, and the dotted line represents patients in the control group. Treatment with rhTM was associated with a significantly higher rate of survival ($P = 0.027$ by stratified Cox regression analysis). APACHE II, Acute Physiology and Chronic Health Evaluation II; rhTM, recombinant human soluble thrombomodulin.

Yamakawa et al. Critical Care 2011, 15:R123

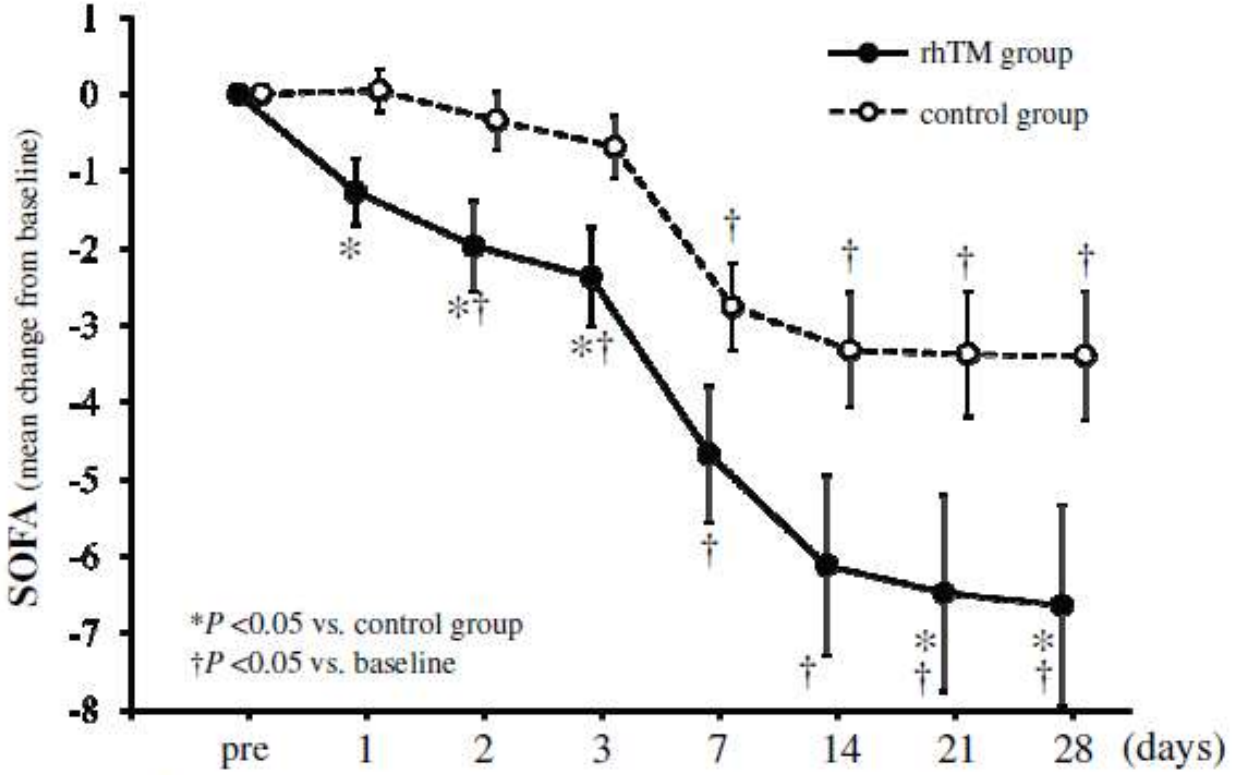


Figure 3 Serial changes from baseline in SOFA score in the two groups. Data are expressed as group means ± standard error of the mean. SOFA score decreased over time in both groups ($P = 0.016$). The degree of decrease in SOFA score was significantly greater in the rhTM group than in the control group ($P = 0.028$). There was no interaction between treatment and time ($P = 0.192$). The last-observation-carried-forward method of imputation was used for missing data. The imputation was accomplished in a total of 13 values in four patients for the rhTM group and in a total of 83 values in 27 patients for the control group. *$P < 0.05$ compared to the control group. †$P < 0.05$ compared to baseline. SOFA, Sequential Organ Failure Assessment; rhTM, recombinant human soluble thrombomodulin.

Yamakawa et al. Critical Care 2011, 15:R123

EFECTOS DE LA ANTITROMBINA EN CIRCULACIÓN Y SOBRE SUPERFICIE ENDOTELIAL

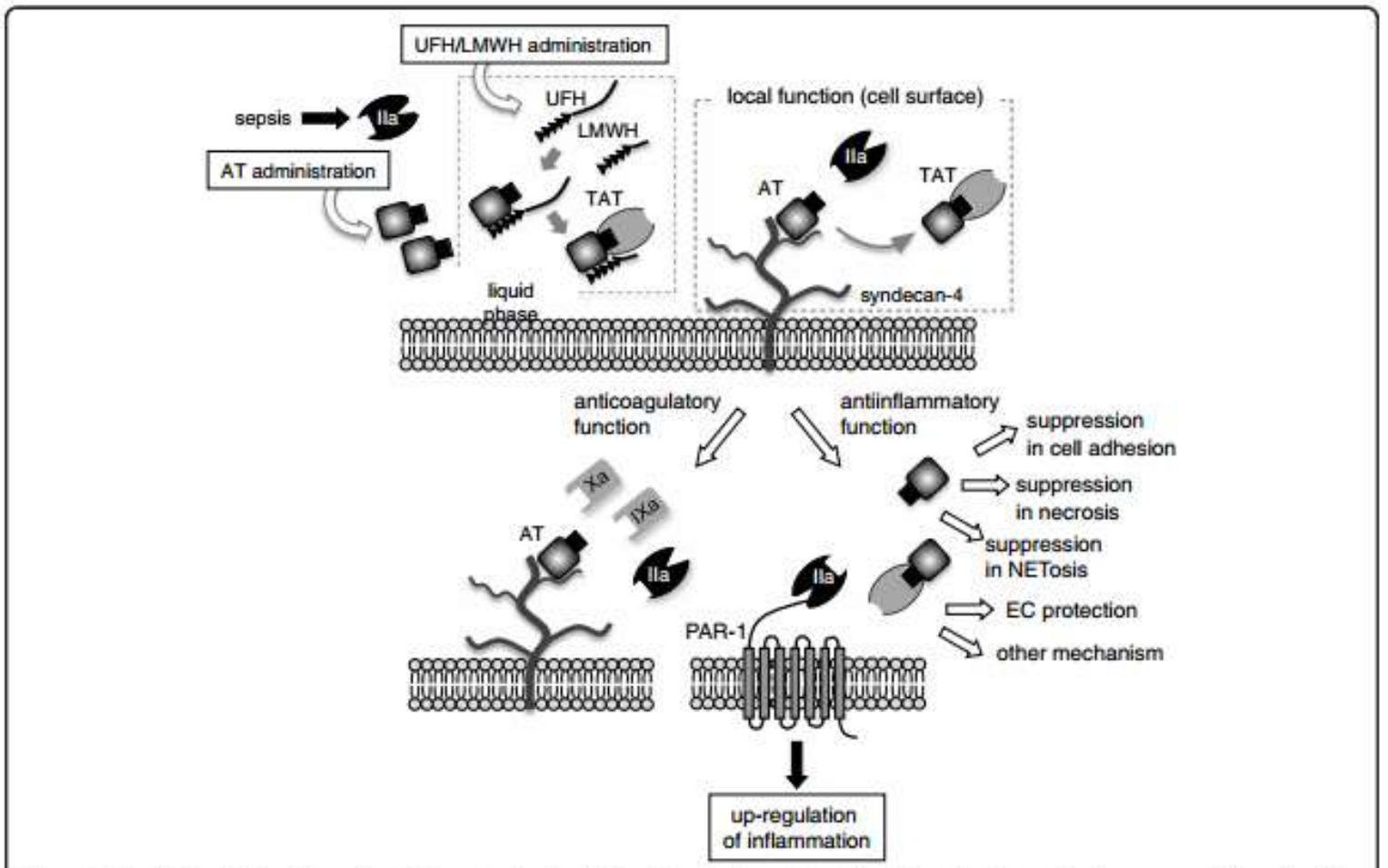


Figure 1 Multifactorial functions of antithrombin in circulating blood and on the cell surface. The interactions between antithrombin (*AT*) and the endothelium are shown in the figure. The affinity of antithrombin to thrombin and its enzymatic inhibition are increased by the binding of the heparin-binding site of AT to syndecan-4 on the cell surface or externally administered heparins. Thrombin loses its coagulant activity after the formation of a thrombin-antithrombin complex. Other than thrombin, AT inactivates factors Xa and IXa. As for its anti-inflammatory function, AT inactivates thrombin, thereby attenuating the cellular reactions through the activation of protease-activated receptor (*PAR*)-1.

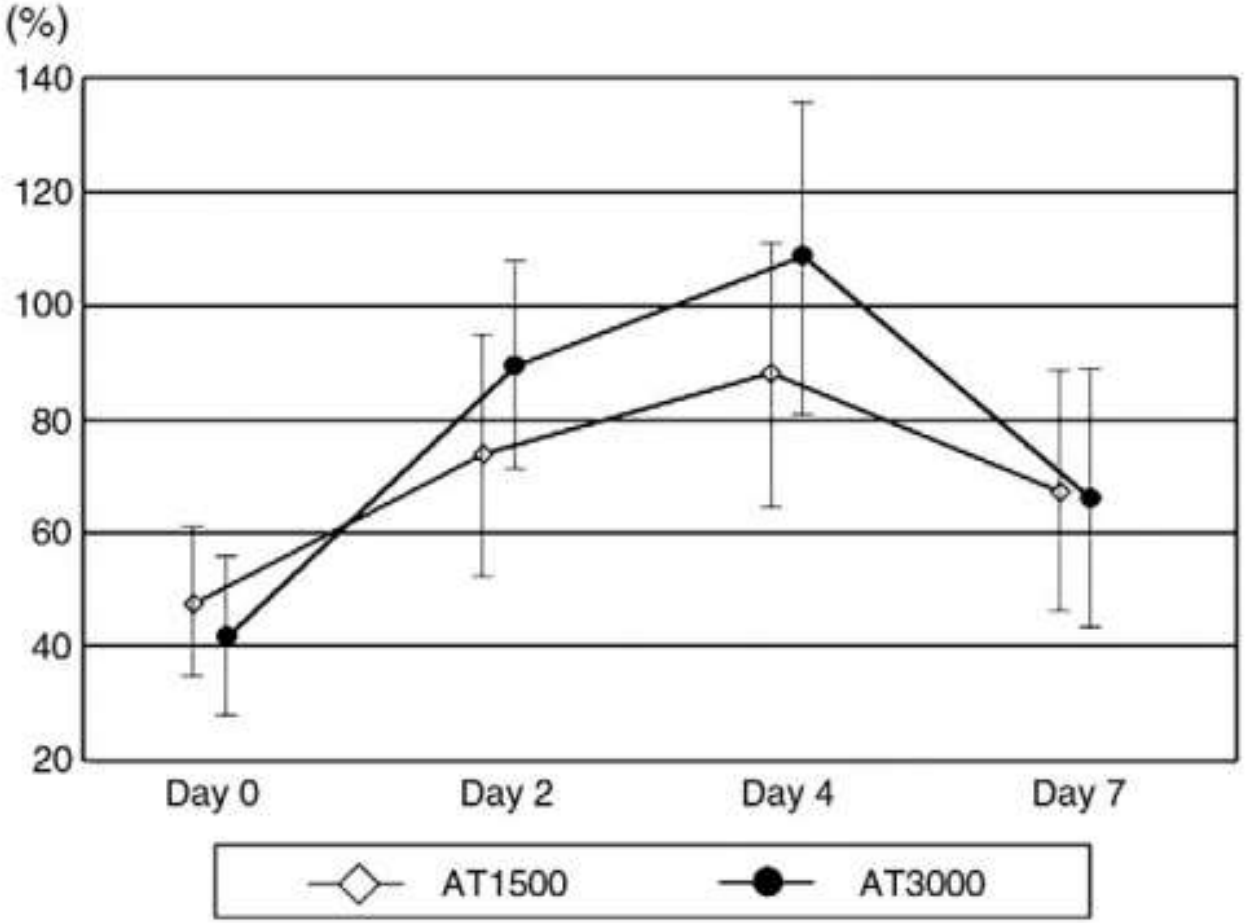


Fig. 1. Changes in antithrombin activity.The mean antithrombin activities in the treatment groups were plotted. Baseline antithrombin activity was less than 50% in both groups. AT1500: 1500 IU/day of antithrombin substitution for 3 days; AT3000: 3000 IU/day of antithrombin substitution for 3 days.

Thrombosis Research 130 (2012) e129–e133

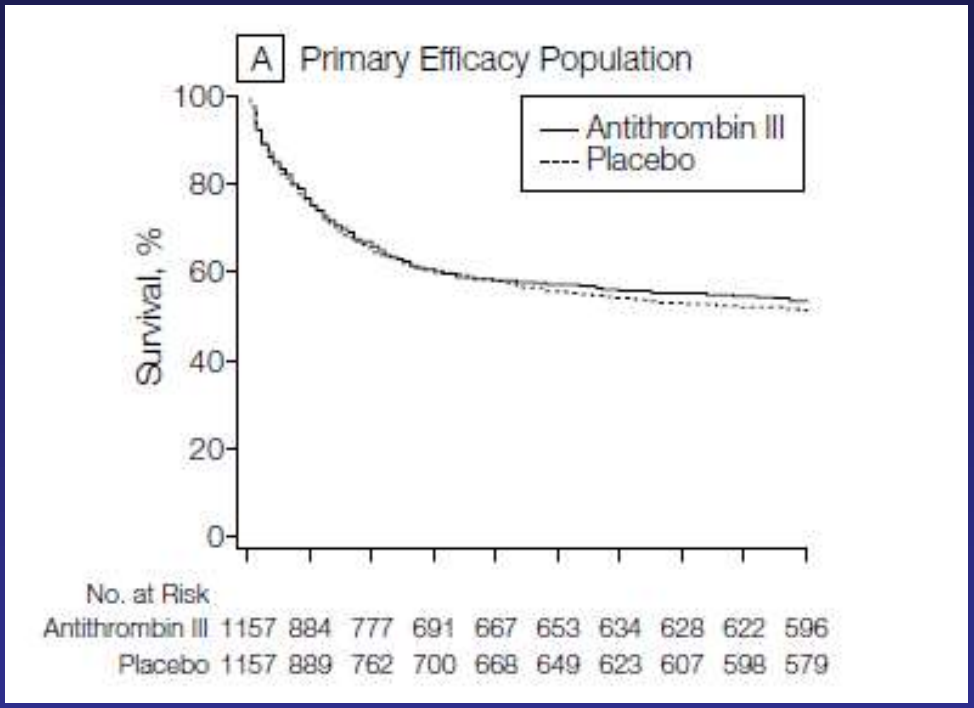
CARING FOR THE
CRITICALLY ILL PATIENT

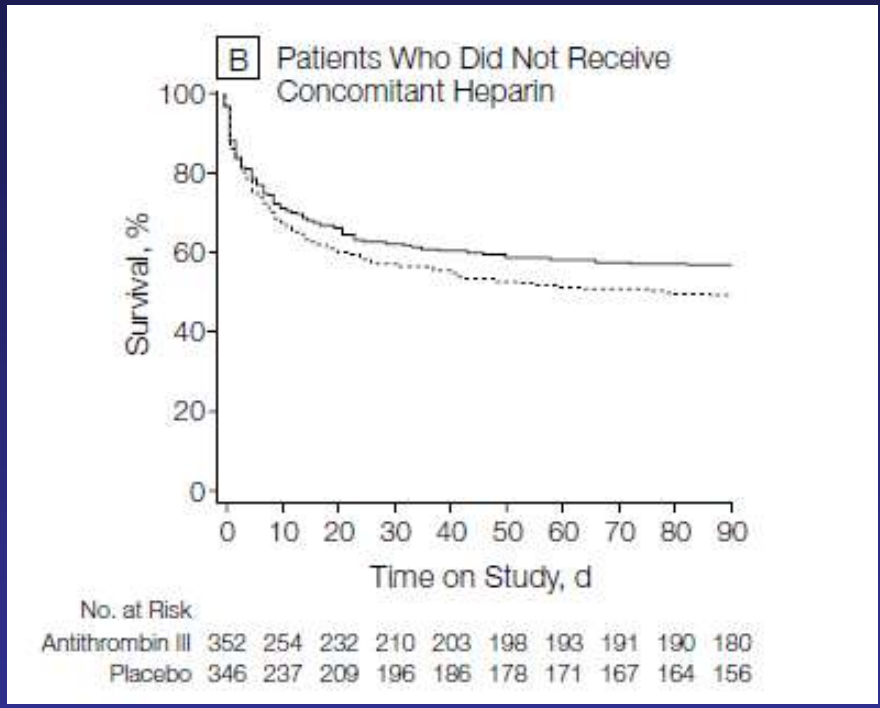
High-Dose Antithrombin III in Severe Sepsis

A Randomized Controlled Trial

- RCT 2314 adultos con sepsis severa o shock séptico con o sin CID (*KyberSept*)
- 1157 pctes en rama AT y 1157 en placebo.
- Endpoint: mortalidad a los 28 días.
- ***Hubo beneficio marginal*** de mortalidad a los 28 días en pacientes que no usaron heparina (37,8% vs. 43,6% p=0,08).

JAMA. 2001; 286: 1869-1878





JAMA. 2001; 286: 1869-1878

Journal of Thrombosis and Haemostasis, 4: 90–97

ORIGINAL ARTICLE

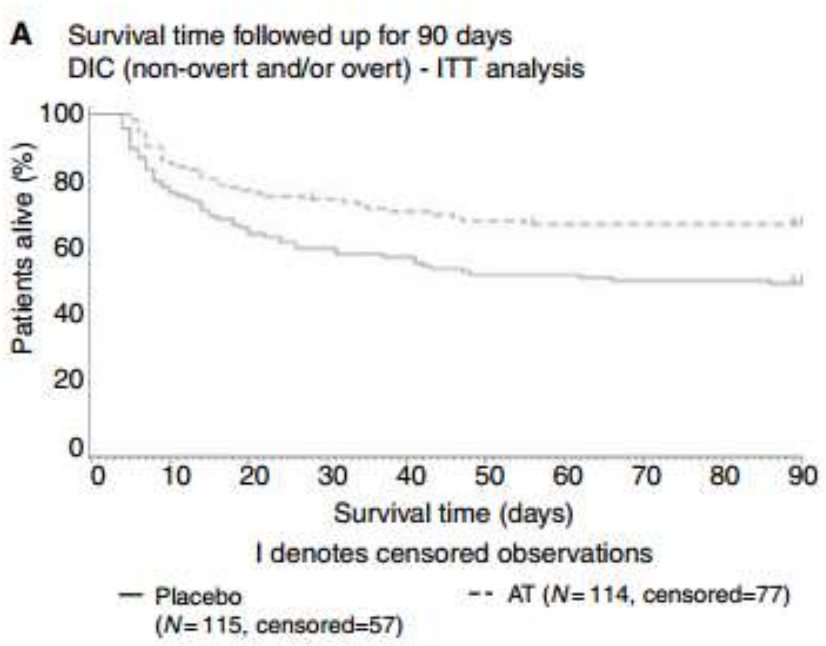
Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation

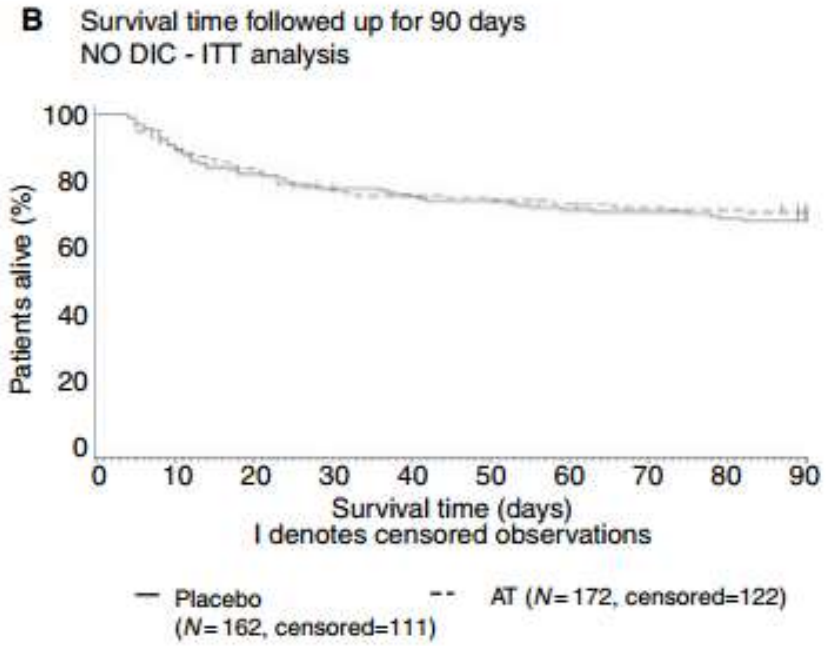
J. KIENAST,* M. JUERS,† C. J. WIEDERMANN,‡ J. N. HOFFMANN,§ H. OSTERMANN,¶ R. STRAUSS,** H-O. KEINECKE,†† B. L. WARREN‡‡ and S. M. OPAL§§ FOR THE KYBERSEPT INVESTIGATORS

*Department of Internal Medicine, Hematology/Oncology, Westfaelische Wilhelms University, Muenster, Germany; †Department of Medical Affairs, ZLB Behring GmbH, Hattersheim, Germany; ‡Department of Medicine, Central Hospital of the Province of Bolzano, Bolzano, Italy; §Departments of Surgery and ¶Hematology/Oncology, Ludwig-Maximilian University of Munich, Munich, Germany; **Department of Medicine I, University of Erlangen-Nuremberg, Erlangen, Germany; ††Accovion GmbH, Marburg, Germany; ‡‡Department of Surgery, University of Stellenbosch, Tygerberg, South Africa; and §§Infectious Disease Division, Brown Medical School, Memorial Hospital of Rhode Island, Pawtucket, RI, USA

- Evaluación de subgrupo de pacientes de KyberSept sin y con CID y sepsis sin administración de heparina, 277 en placebo y 286 con AT.
- *Pacientes con CID tratados con AT tuvieron una reducción de la mortalidad de 14,6% comparados con placebo (p< 0,02)*

J Thromb Haemost 2006; 4: 90–7.





J Thromb Haemost 2006; 4: 90–7.

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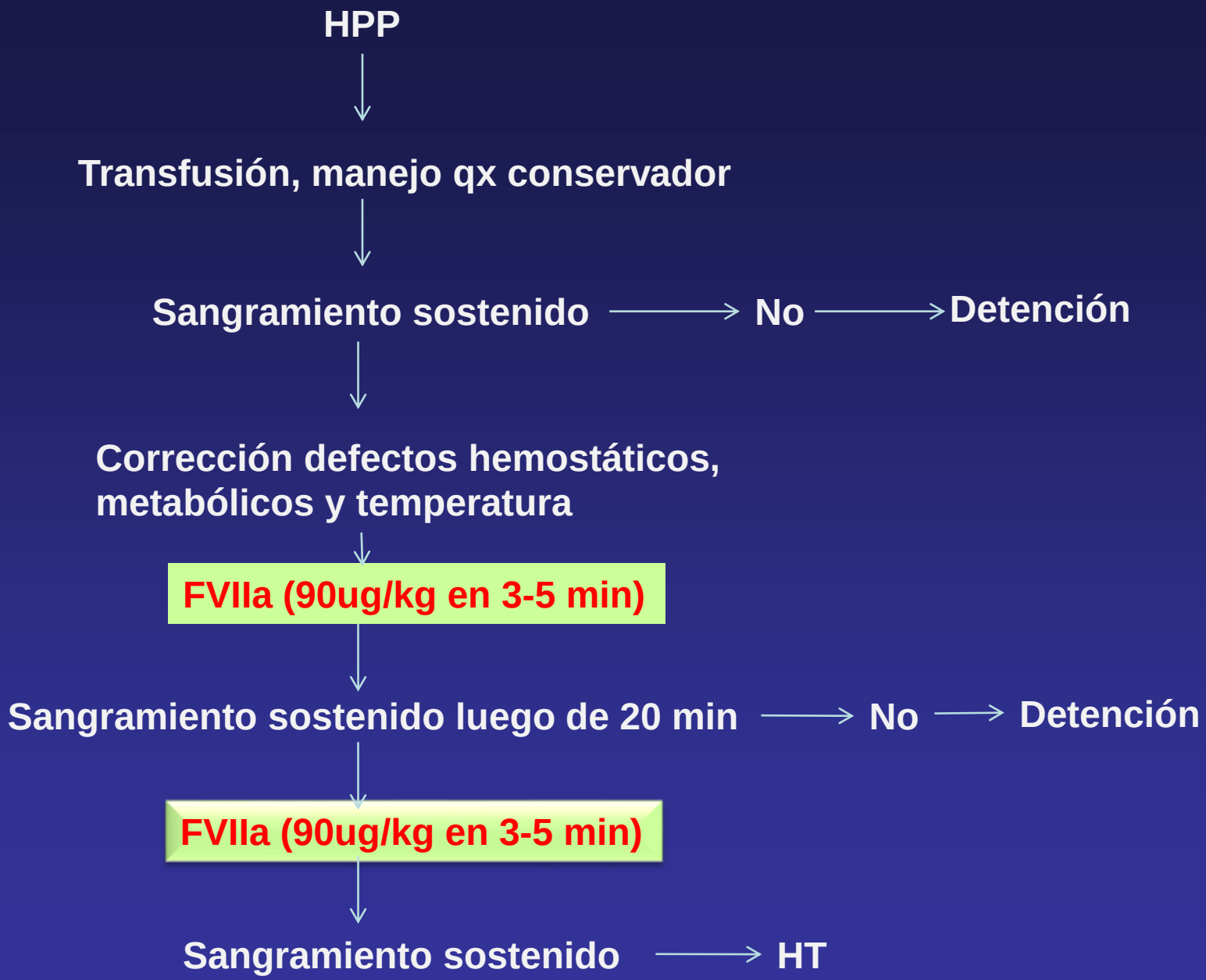
The Use of Recombinant Activated FVII in Postpartum Hemorrhage

MASSIMO FRANCHINI, MD,*
MASSIMO FRANCHI, MD, PhD,†
VALENTINO BERGAMINI, MD,†
MARTINA MONTAGNANA, MD,‡
GIAN LUCA SALVAGNO, MD,‡
GIOVANNI TARGHER, MD,§
and GIUSEPPE LIPPI, MD‡

- Se analizan 272 casos de hemorragia postparto (HPP) publicadas en la literatura.
- HPP: Hgia > 500 ml después de parto vaginal o > 1000 ml post cesárea.
- Se encontró que dosis de 81,5 mg/kg de FVIIa es efectivo en ***detener o reducir el 85% de los casos de HHP.***
- Efectos adversos trombóticos: 2,5%.

Franchini, M. Clin Obstet Gynecol. 2010;53:219-27



Franchini, M. Clin Obstet Gynecol. 2010;53:219-27

Uso de hemoderivados y concentrados de factor en CID

	Asintomática	Falla orgánica	Hiper fibrinolítica	Hemorragia masiva
Condición predisponente	R	R	R	R
Plaquetas			R	R
PFC			R	R
Criopp			R	R
PCC			R?	R?
rh-aPC		NR		
PD-APC		R?		
rh-TM		R?		
AT		R?		
FVIIa				R??

V Jornadas Hematológicas del Sur

Terapia Transfusional en Medicina de Urgencia