THROMBOMODULINE & CHOC SEPTIQUE

Université de Lille 2 DROIT ET SANTÉ

Centre Hospitalier Régional Universitaire de Lille

G. DEGOUY 1er année DESC – Pr. JOURDAIN

Thrombomoduline : FONCTION(S)

• La Thrombomoduline est une protéine ubiquitaire :
- Présent sur les ¢ endothéliales (Kératinocyte, ¢ mésangiale)
- PROTEINES DE LA FAMILLE DES PROTEOGLYCANES

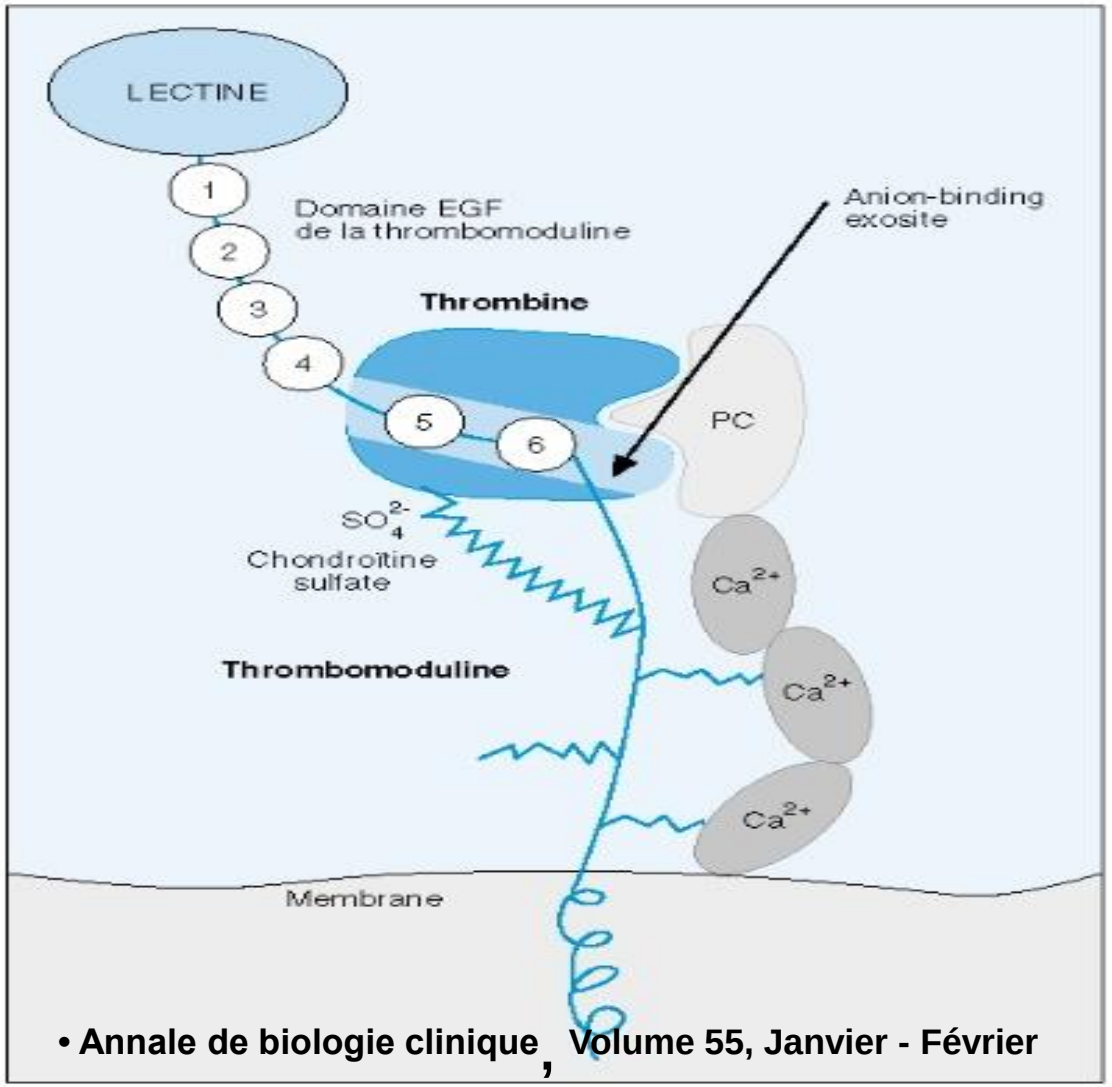
1• Fonction extra-membranaire :
- Protéine à forte **activité anticoagulante +++**
- Site de glycosylation : Domaine Chondroïtine sulfate liant ATIII

2• Fonction intra-membranaire :
- Rôle de signalisation intracellulaire (prolifération/différenciation cellules endothéliales)
- Mécanismes d'endocytoses

• Rev med. interne 1997 ; M. Kalimochkine, M.C Boffa
• Annale de biologie clinique, Volume 55, Janvier - Février 1997

Thrombomoduline : Extra - Membranaire

- Potentialise l'activité de la protéine C et S sur l'inhibition des facteurs Va et VIIIa
- Inhibition directe de la THROMBINE (IIa)
- Faible activité « héparine like » en présence d' ATIII



• **Annale de biologie clinique, Volume 55, Janvier - Février**

UNE ACTIVITE ANTICOAGULANTE MULTISPECTRE

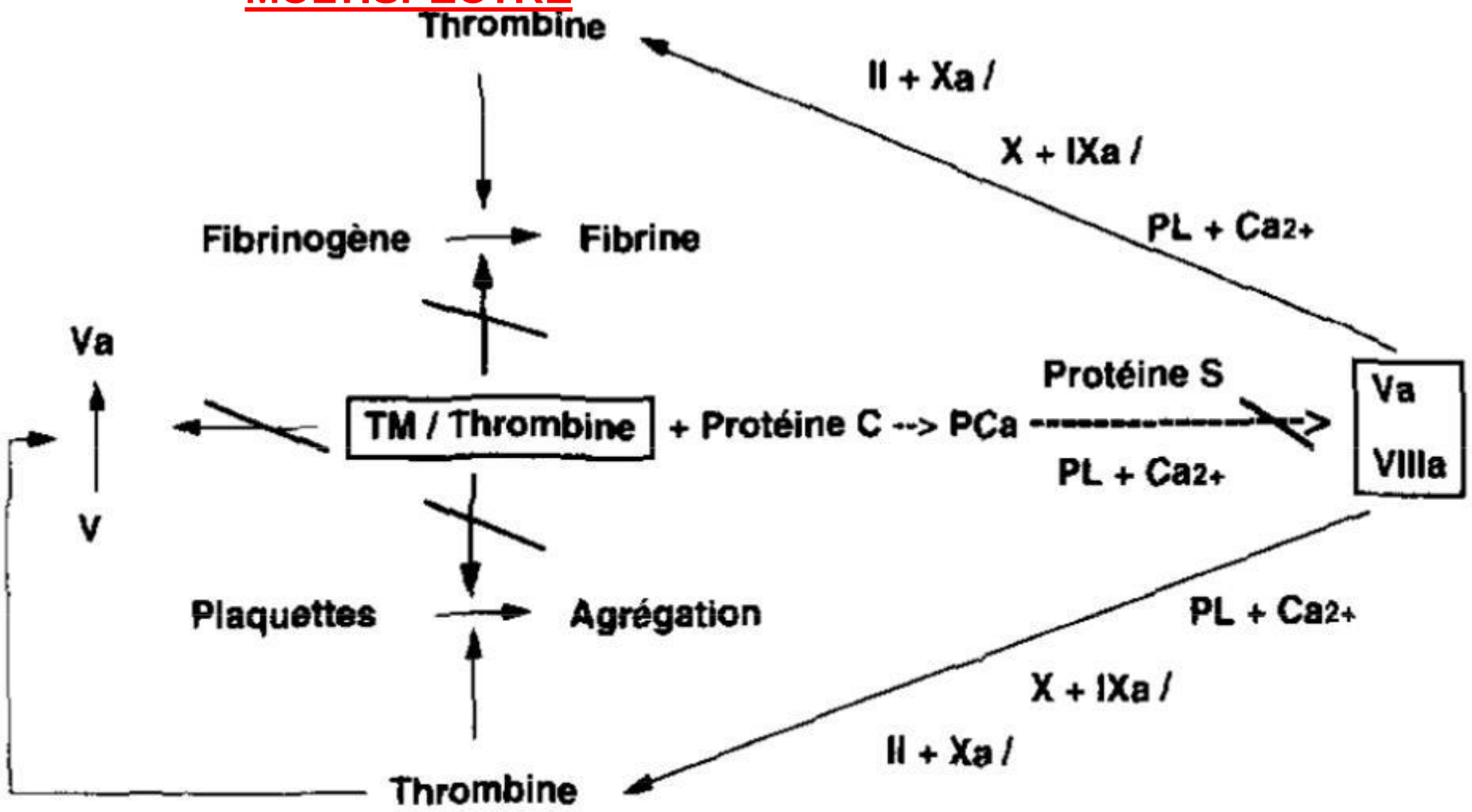
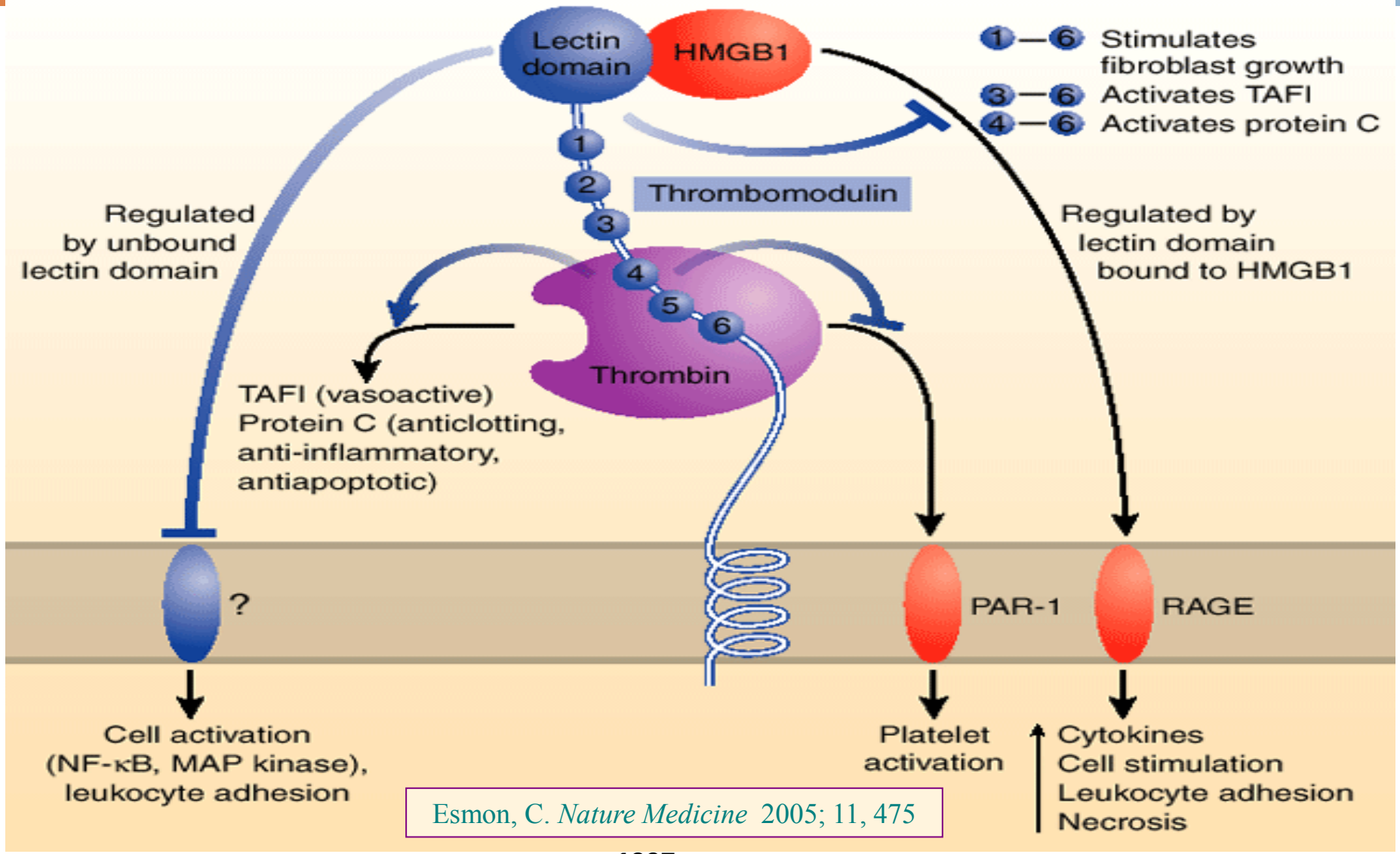


Fig 1. Mécanismes d'action anticoagulante de la thrombomoduline.

- Rev méd. interne 1997 : M. Karmochkine, M.C Reffa

THROMBOMODULINE : PROTEINE ANTI INFLAMMATOIRE



Esmon, C. *Nature Medicine* 2005; 11, 475

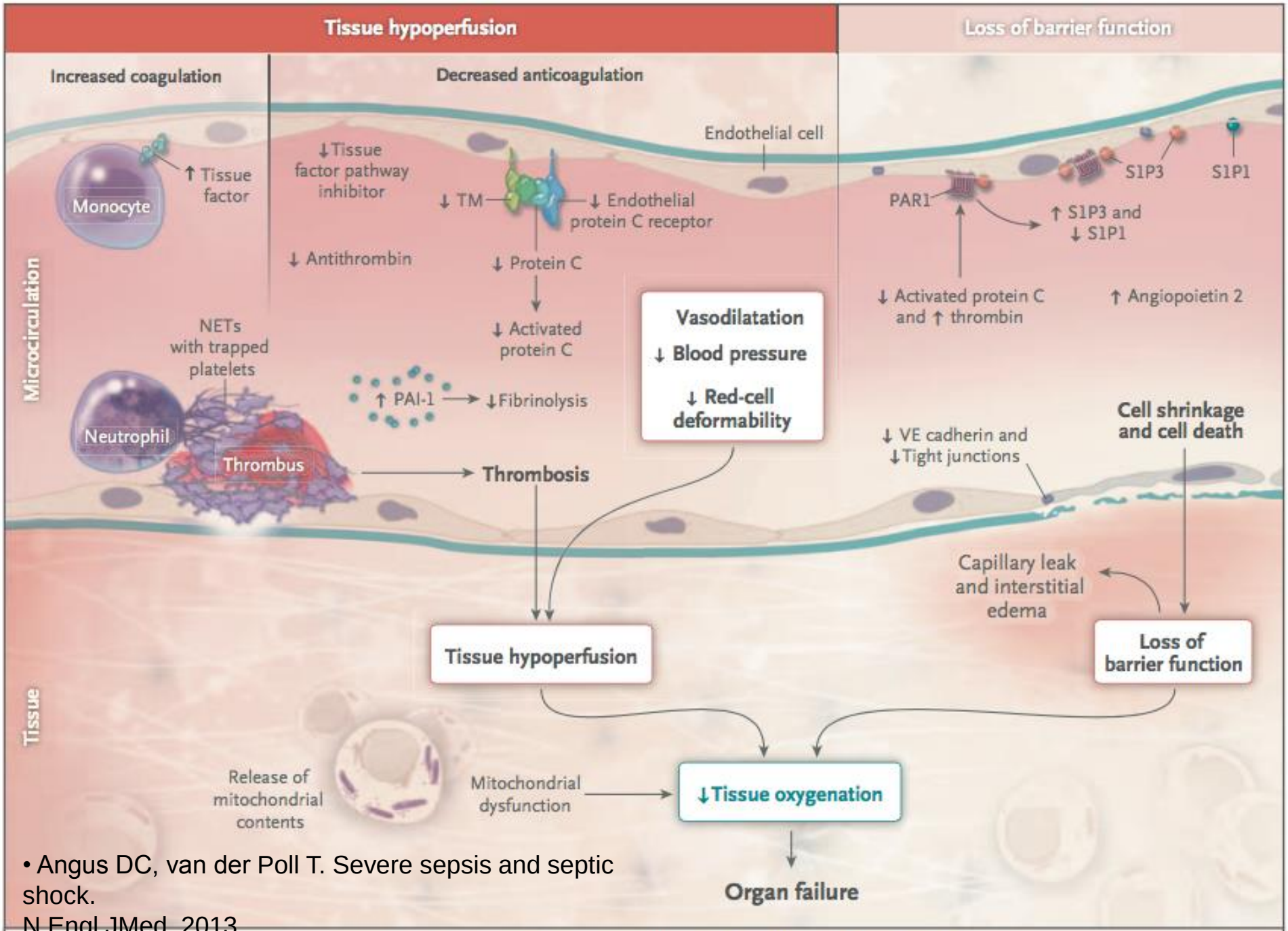
THROMBOMODULINE = ANTI-INFLAMMATOIRE

1• Domaine de glycosylation à chondroïtine sulfate domaine ➔ inhibition direct du signal de la thrombine sur les récépteurs PAR1

2• LECTINE domaine qui se lie à l'HMGB1(high mobility group box 1) ➔ Activateur des **récepteurs RAGE**

3• Inhibition de libération pNETs (protein neutrophil extra-cellular Traps) ➔ favorise la formation de thrombus et l'adhésion leucocytaire

• Fourrier F, Jourdain M, Chopin C, Coagulation inhibitor substitution during sepsis, Intensive Care Med. 1995 Nov;21
• Angus DC, van der Poll T. Severe sepsis and septic shock. N.Engl JMed. 2013
• Helms *et al. Ann. Intensive Care (2017) 7:118*
• Levi M. Recombinant soluble thrombomodulin: coagulation takes another chance to reduce sepsis mortality. J Thromb Haemost. 2015



• Angus DC, van der Poll T. Severe sepsis and septic shock.
N.Engl JMed. 2013

Figure 2. Organ Failure in Severe Sepsis and Dysfunction of the Vascular Endothelium and Mitochondria.

THROMBOMODULINE & SEPSIS

Un sepsis entraine via un signal cytokinique une adhésion leucocytaire endothéliale et une réponse endothéliale

➔ACTIVATION DE LA COAGULATION : Activité augmentée du TF* sous l'effet des cytokines pro-inflammatoires – consommation de l'ATIII et diminution du TFPI

➔ DEFAUT DE FIBRINOLYSE : Augmentation du Plasminogène Activate Inhibitor type 1

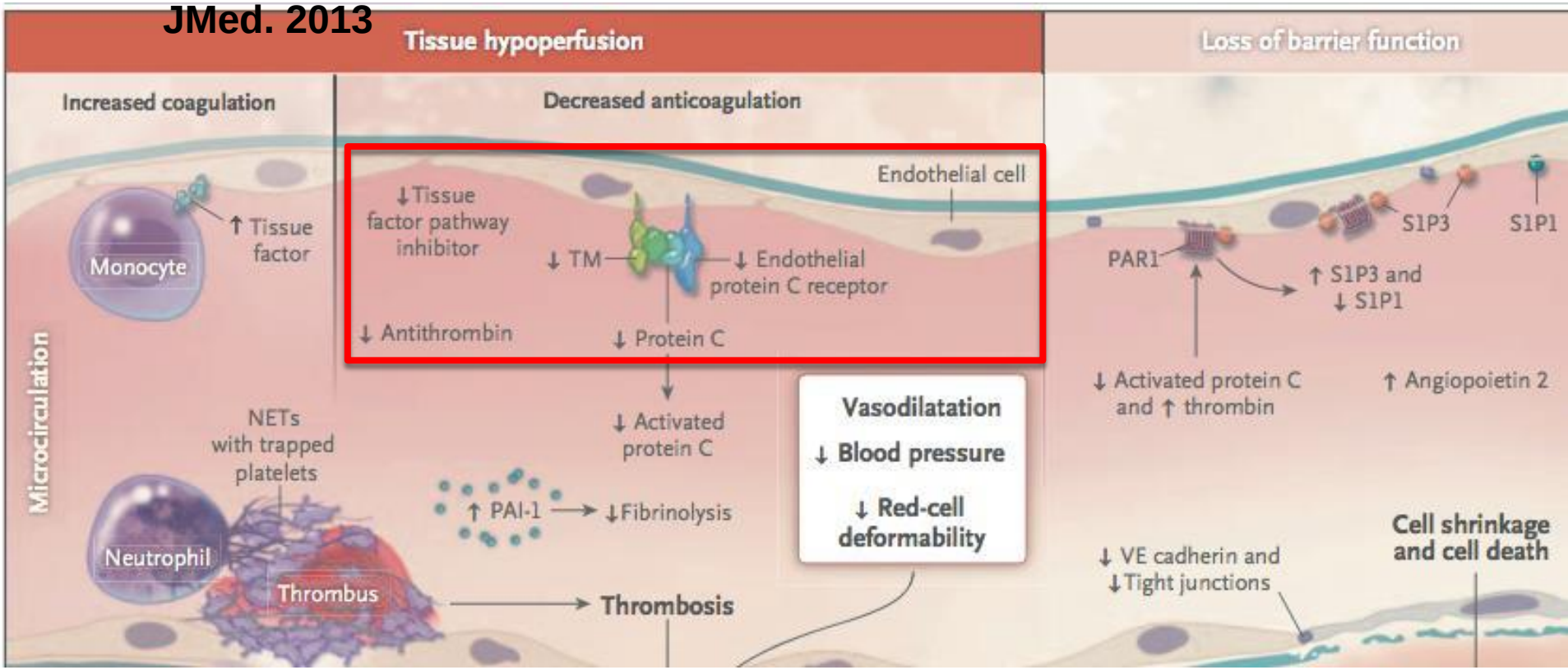
➔ CIVD : consommation des protéines C & S

➔ Diminution de l'activité de la THROMBOMOLINE

• Fourrier F, Jourdain M, Chopin C. Coagulation inhibitor substitution during sepsis, Intensive Care Med. 1995 Nov;21

• Angus DC, van der Poll T. Severe sepsis and septic shock. N.Engl JMed. 2013

• **Angus DC, Van Der Poll T. Severe sepsis and septic shock. N.Engl JMed. 2013**



- Une relation démontrée entre CIVD et dysfonction d'organe
- Corrélation significative d'une défaillance hématologique et de la mortalité des patients +++

• Fourrier F, Chopin C, Goudemand J, et al : Septic shock & multiple organ failure, and disseminated intravascular coagulation. Compared patterns ATIII, protein C, and protein S deficiencies. Chest 1992.
• Bakhtiari K, Meijers JC, de Jonge E, et al : Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for DIC. *Crit Care Med* 2004; 32:2416-2421

THROMBOMODULINE : un marqueur de sévérité ?

Figure 1 A

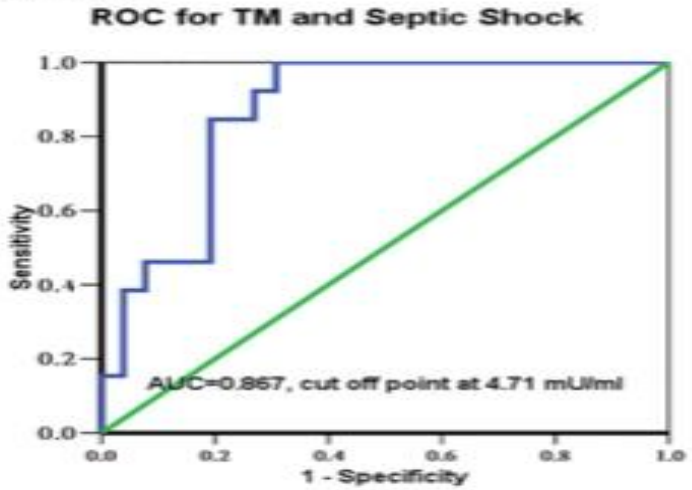


Figure 1 B

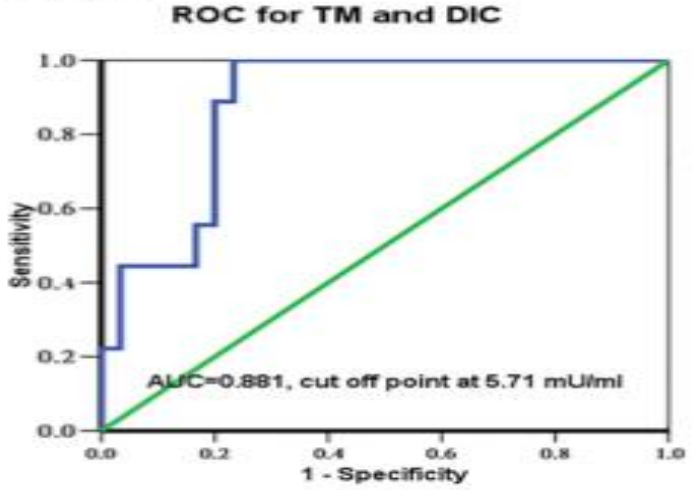


Figure 1 C

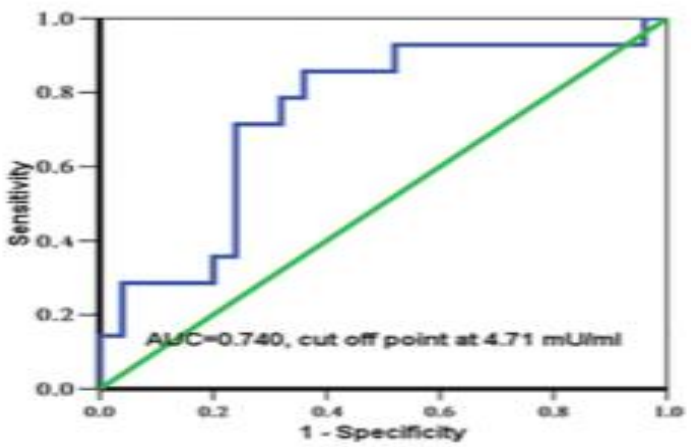
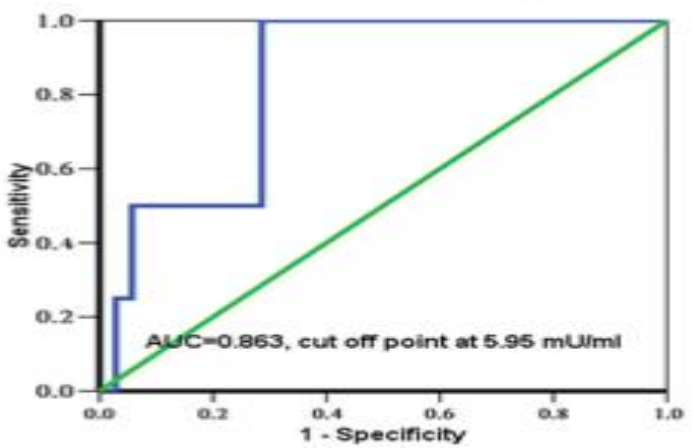


Figure 1 D



• *Increased serum thrombomodulin level is associated with disease severity and mortality in pediatric sepsis. Lin JJ, Hsiao HJ Et Al. PLoS One. 2017*

THROMBOMODULINE & SEPSIS

• Analogie rationnelle de **l'utilisation de la protéine C**

<u>Rationnel de l'utilisation d'une Thrombomoduline recombinant humaine :</u>

1- Limiter les effets pro-coagulants du SEPSIS
2- Limiter la CIVD et les phénomènes µ-thrombotiques
3- Ne pas aggraver la dysfonction d'organe
4- Valoriser l'activité anti-inflammatoire de la rhTM sur l'activation des PAR1** et

Vers une substitution de thrombomoduline ?

• A randomized double-blind placebo-controlled, Phase 2b study to evaluate the safety and efficacy of recombinant human soluble **thrombomodulin**, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation.
Vincent JL, et Al. Crit Care Med. 2013

A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Safety and Efficacy of Recombinant Human Soluble Thrombomodulin, ART-123, in Patients With Sepsis and Suspected Disseminated Intravascular Coagulation*

Jean-Louis Vincent, MD, PhD, FCCM[1]; Mayakonda K. Ramesh, MS[2]; David Ernest, MBBS[3]; Steven P. LaRosa, MD[4]; Jan Pachl, MD, PhD[5]; Naoki Aikawa, MD, DMSc, FACS[6]; Eric Hoste, MD, PhD[7]; Howard Levy, MB, BCh, PhD[8]; Joe Hirman, PhD[9]; Marcel Levi, MD, PhD[10]; Mradul Daga, MD, FCCP[11]; Demetrios J. Kutsogiannis, MD, MHS[12]; Mark Crowther, MD, MSc, FRCPC[13]; Gordon R. Bernard, MD[14]; Jacques Devriendt, MD[15]; Joan Vidal Puigserver, MD[16]; Daniel U. Blanzaco, MD[17]; Charles T. Esmon, PhD[18]; Joseph E. Parrillo, MD[19]; Louis Guzzi, MD, FCCM[20]; Seton J. Henderson, MB, ChB[21]; Chaicharn Pothirat, MD, FCCP[22]; Parthiv Mehta, MD[23]; Jawed Fareed, PhD, FAHA[24]; Deepak Talwar, MD, DM, DNB[25]; Kazuhisa Tsuruta, PhD[26]; Kenneth J. Gorelick, MD, FCCP[27]; Yutaka Osawa, MPharm[26]; Inder Kaul, MD, MPH[26]

Méthodologie :

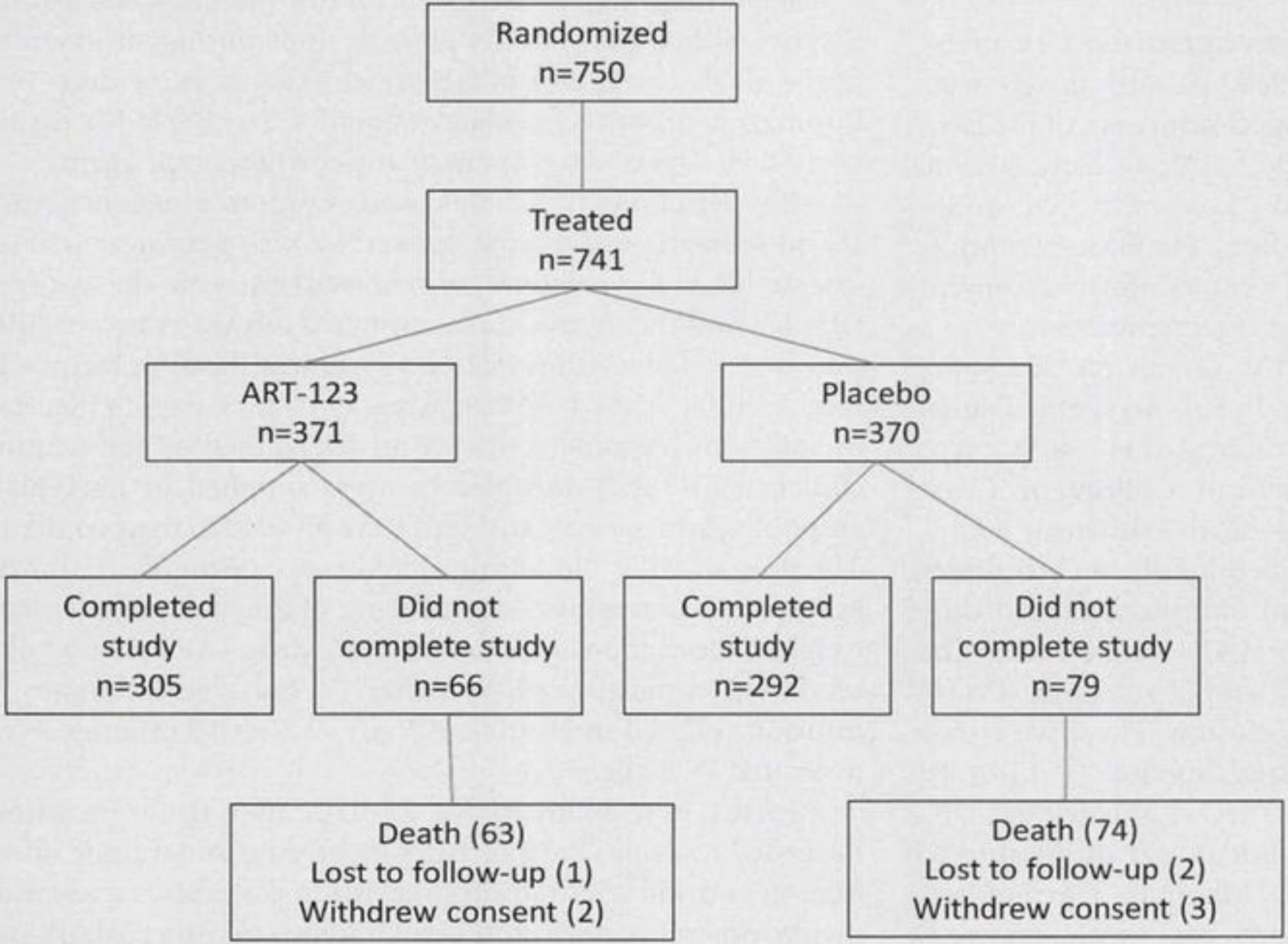
- Inclusion sur la base d'un score modifié et simplifié de CIVD (S > 2)
- ≠ du score ISTH
- Exclusion des patients à haut risque hémorragique (chirurgie lourde < 12h)

CIVD non septique, traitement anticoagulant dans les 48h

- Délai moyen d'inclusion environ 36h
- Analyse en ITT avec une analyse intermédiaire à n = 100 patients

TABLE 3. Patient Baseline Characteristics

Characteristics	ART-123 (*n* = 370)	Placebo (*n* = 371)	Total (*n* = 741)
Age, yr			
Mean (SD)	57.5 (19.1)	56.9 (17.9)	57.2 (18.5)
Range	18–93	18–93	18–93
Male, *n* (%)	231 (62.4)	224 (60.4)	455 (61.4)
Body mass index (kg/m^2)			
Mean (SD)	25.0 (6.1)	25.3 (6.4)	25.2 (6.3)
Range	13.6–51.9	13.8–59.7	13.6–59.7
Site of infection[a], *n* (%)			
Lung	160 (43)	150 (41)	310 (42)
Gastrointestinal	80 (22)	90 (24)	170 (23)
Urinary tract/kidney	54 (15)	65 (18)	119 (16)
Bacteremia/endocarditis	39 (11)	36 (10)	75 (10)
Skin/soft tissue	11 (3)	13 (4)	24 (3)
Other	45 (12)	39 (11)	84 (11)
Overt disseminated intravascular coagulation score[a], *n* (%)			
<5 (not overt)	257 (69.5)	263 (70.9)	520 (70.2)
≥5 (overt)	45 (12.2)	53 (14.3)	98 (13.2)
Modified disseminated intravascular coagulation score, *n* (%)			
=2	84 (22.7)	83 (22.4)	167 (22.5)
>2	286 (77.3)	288 (77.6)	574 (77.5)
Heparin or low–molecular weight heparin use, *n* (%)	55 (14.9)	45 (12.1)	100 (13.5)
Platelet count, ×10^9/L, mean (SD)[a]	141.0 (114.4)	140.8 (114.2)	140.9 (114.2)
Diabetes, *n* (%)	65 (18)	68 (18)	133 (18)
Organ dysfunction (at least one), *n* (%)	253 (68)	262 (71)	515 (70)
Serum creatinine, *n* (%)			
<1.5 mg/dL	232 (62)	237 (64)	469 (63)
1.5–2 mg/dL	132 (36)	131 (35)	263 (35)
>2 mg/dL	71 (19)	76 (20)	147 (20)


Randomized
n=750
Treated
n=741
ART-123
n=371
Placebo
n=370
Completed
study
n=305
Did not
complete study
n=66
Completed
study
n=292
Did not
complete study
n=79
Death (63)
Lost to follow-up (1)
Withdrew consent (2)
Death (74)
Lost to follow-up (2)
Withdrew consent (3)

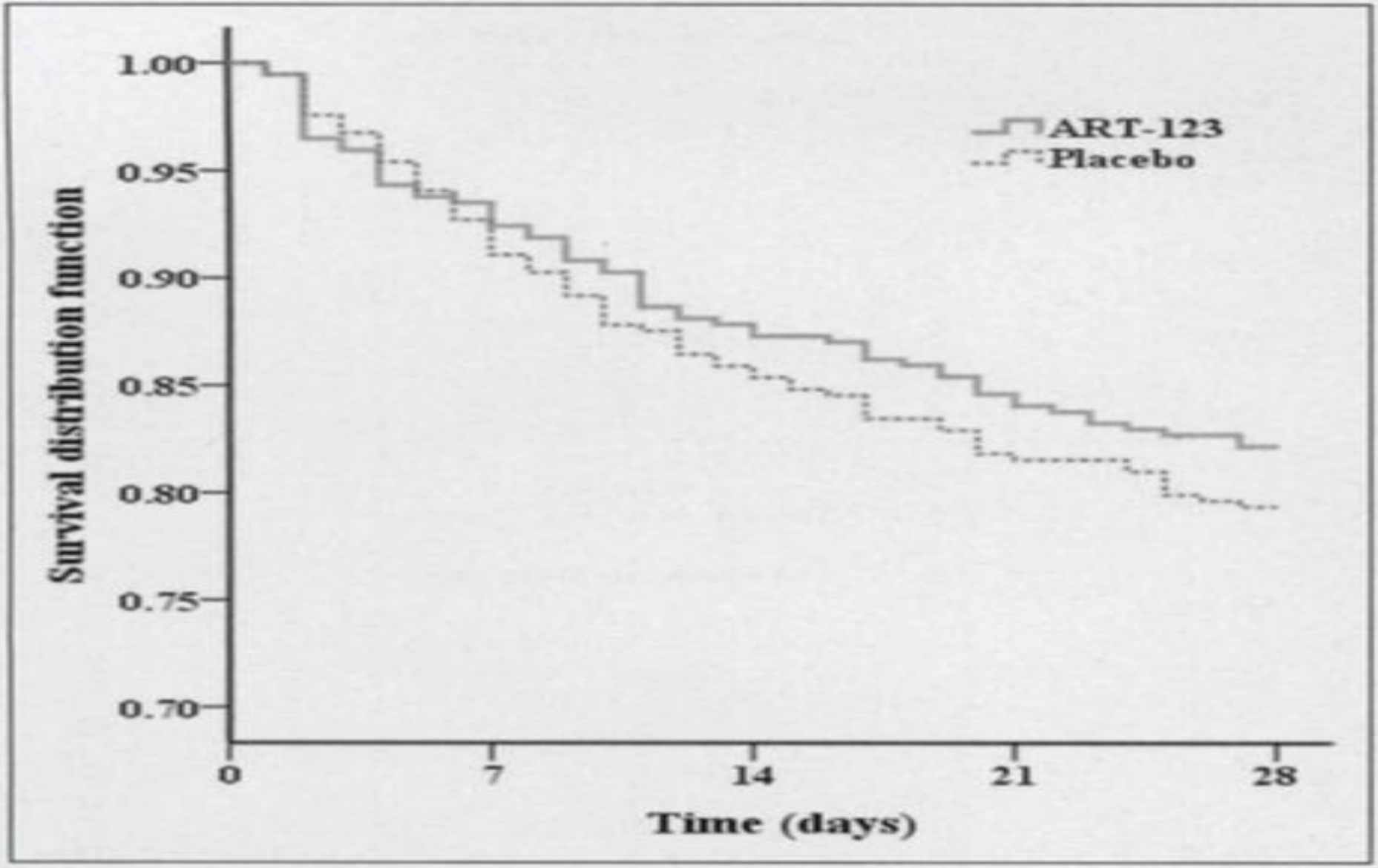


Figure 2. Kaplan–Meier plots of survival time for the two treatment arms: 28-d survival was 82.2% (95% CI, 77.9%, 85.7%) for the ART-123 group and 79.4% (95% CI, 74.9%, 83.2%) for the placebo group (one-sided log-rank p value = 0.17). Observations occurring after day 28 were censored at day 28.

Yoshimura et al. Critical Care (2015) 19:78
DOI 10.1186/s13054-015-0810-3

CRITICAL CARE

RESEARCH Open Access

Benefit profile of recombinant human soluble thrombomodulin in sepsis-induced disseminated intravascular coagulation: a multicenter propensity score analysis

Jumpei Yoshimura[1], Kazuma Yamakawa[1*], Hiroshi Ogura[2], Yutaka Umemura[1], Hiroki Takahashi[2], Miki Morikawa[3], Yoshiaki Inoue[3], Satoshi Fujimi[1], Hiroshi Tanaka[3], Toshimitsu Hamasaki[4] and Takeshi Shimazu[2]

Table 1 Baseline characteristics of all patients with sepsis-induced DIC untreated or treated with rhTM

	Overall ($n = 162$)	rhTM group ($n = 68$)	Control group ($n = 94$)	P value[a]
Patient characteristics				
Age (years)[b]	69 (59 to 76)	69 (61 to 76)	70 (57 to 77)	0.953
Male sex[b]	93 (57%)	36 (53%)	57 (61%)	0.339
Illness severity				
APACHE II score[b]	23 (19 to 29)	25 (21 to 32)	22 (18 to 27)	0.008
SOFA score[b]	11 (9 to 13)	12 (9 to 13)	11 (8 to 12)	0.029
Number of dysfunctional organs[b]	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)	0.383
Positive blood culture[b]	72 (44%)	41 (60%)	31 (33%)	0.001
Coagulation parameters				
Platelet count (/mm^3)	4.9 (2.7 to 6.5)	4.4 (2.6 to 6.4)	5.3 (2.8 to 6.6)	0.081
PT-INR	1.40 (1.23 to 1.70)	1.40 (1.20 to 1.67)	1.50 (1.30 to 1.78)	0.169
FDP (μg/ml)	22.3 (11.0 to 55.5)	24.6 (13.2 to 60.0)	20.3 (10.2 to 48.9)	0.380
Fibrinogen level (mg/dl)	350 (224 to 495)	357 (225 to 553)	328 (213 to 456)	0.231
JAAM DIC score[b]	6 (5 to 8)	6 (5 to 8)	6 (5 to 8)	0.555
ISTH DIC score	4 (3 to 5)	4 (4 to 5)	4 (3 to 5)	0.457

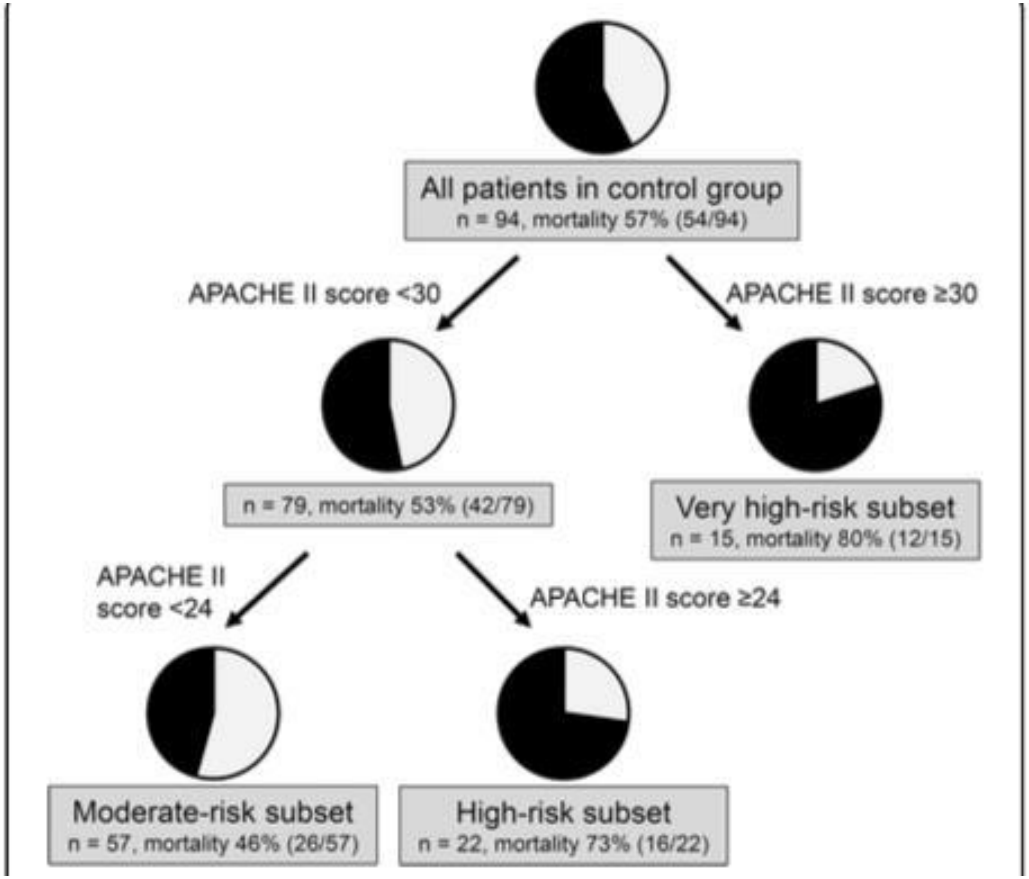
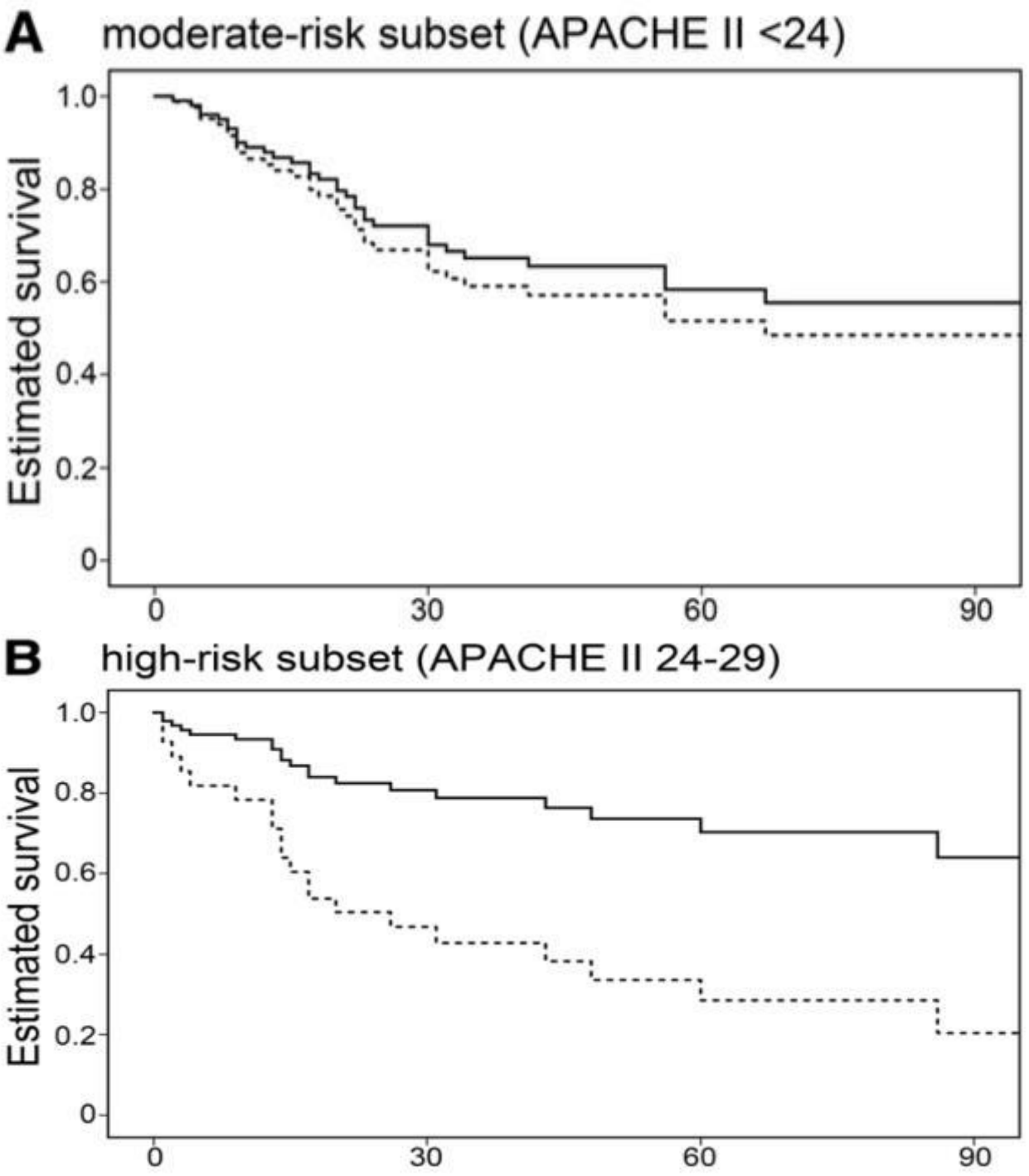


Table 2 Baseline characteristics of different subsets stratified by baseline APACHE II score

	Moderate risk ($n = 86$)	High risk ($n = 41$)	Very high risk ($n = 35$)	P value[a]
Patient characteristics				
Age (years)	67 (57 to 76)	69 (58 to 76)	72 (66 to 78)	0.171
Male sex	50 (58%)	26 (63%)	17 (49%)	0.419
Illness severity				
APACHE II score	19 (16 to 21)	27 (25 to 28)	33 (32 to 36)	<0.001
SOFA score	9 (7 to 11)	12 (11 to 13)	13 (11 to 15)	<0.001
Number of dysfunctional organs	3 (2 to 4)	4 (3 to 5)	5 (4 to 5)	<0.001
Positive blood culture	31 (36%)	23 (56%)	18 (51%)	0.067
JAAM DIC score	6 (5 to 8)	6 (5 to 8)	8 (6 to 8)	0.092
ISTH DIC score	4 (3 to 5)	4 (4 to 5)	5 (4 to 5)	0.018


A
moderate-risk subset (APACHE II <24)
Estimated survival
1.0
0.8
0.6
0.4
0.2
0
0
30
60
90
B
high-risk subset (APACHE II 24-29)
Estimated survival
1.0
0.8
0.6
0.4
0.2
0
0
30
60
90

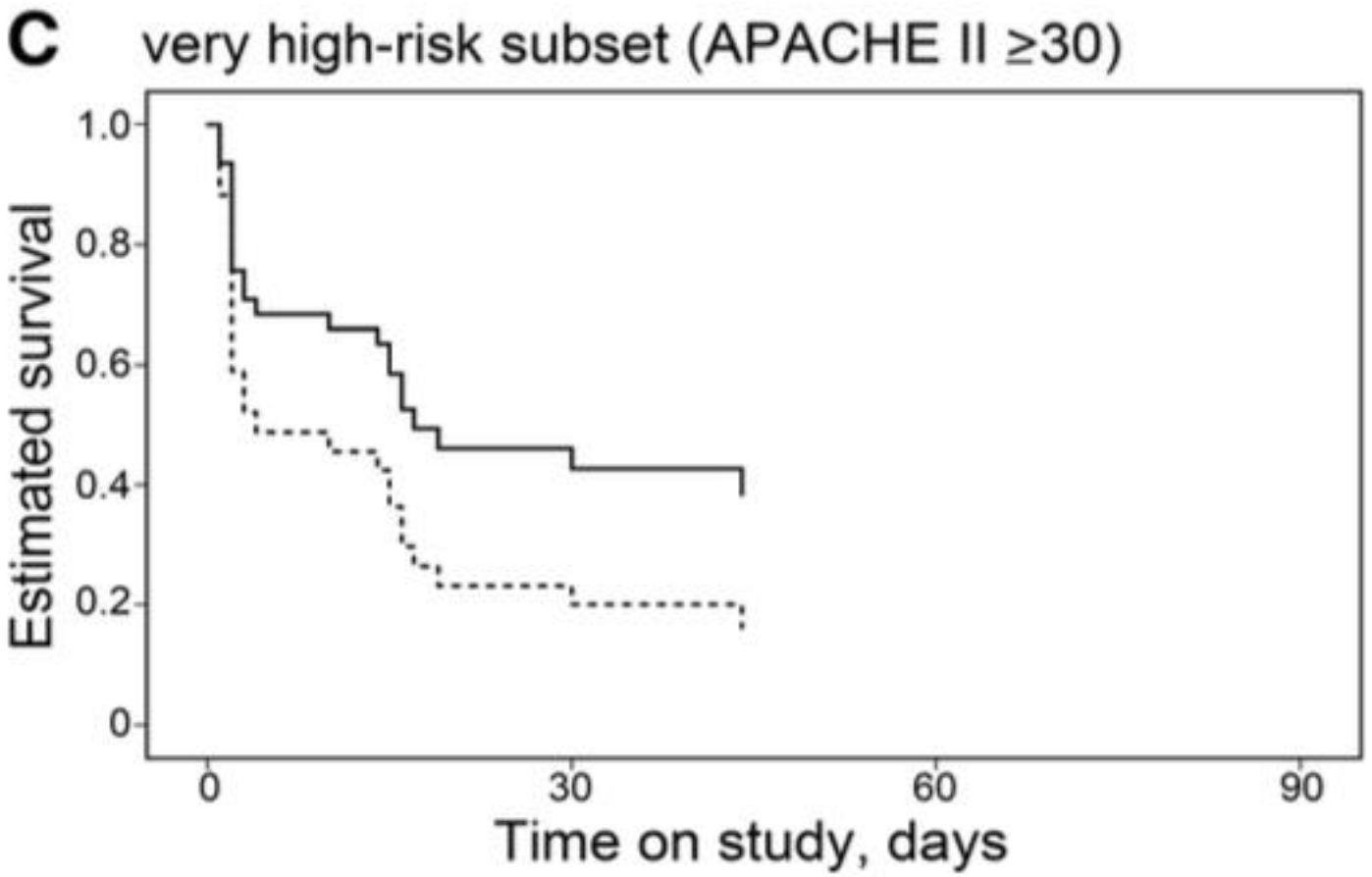


Figure 2 Adjusted estimated survival curves in subsets stratified according to baseline APACHE II scores. (A) Moderate-risk subset of patients (APACHE II score <24). **(B)** High-risk subset (APACHE II score = 24 to 29). **(C)** Very high-risk subset (APACHE II score ≥30). Solid line, patients in the rhTM group; dotted line, patients in the control group. Administration of rhTM was only associated with significantly reduced mortality in patients in the high-risk subset (APACHE II score = 24 to 29; $P = 0.025$, Cox regression

Subsets	n	In-hospital mortality		Hazard ratio (95% CI)	*p* value
		rhTM	Control		
All cases	162	40%	57%	0.54 (0.32-0.92)	0.023
APACHE II score					
<24	86	35%	46%	0.81 (0.35-1.88)	0.630
24-29	41	26%	73%	0.28 (0.09-0.85)	0.025
≥30	35	60%	80%	0.53 (0.20-1.39)	0.195
SOFA score					
<11	73	31%	49%	0.65 (0.26-1.66)	0.368
≥11	89	45%	66%	0.51 (0.27-0.98)	0.042
JAAM DIC score					
<8	102	40%	53%	0.69 (0.36-1.34)	0.273
=8	60	40%	66%	0.33 (0.13-0.83)	0.019
ISTH overt DIC					
Negative	95	37%	49%	0.58 (0.28-1.19)	0.138
Positive	67	43%	70%	0.51 (0.23-1.14)	0.101
Septic shock					
Negative	28	36%	41%	1.02 (0.27-3.80)	0.982
Positive	134	40%	61%	0.43 (0.24-0.78)	0.005
Infection site					
Lung	32	50%	55%	0.73 (0.23-2.33)	0.590
Abdomen	62	44%	56%	0.67 (0.26-1.70)	0.397
Soft tissue	31	31%	72%	0.24 (0.07-0.83)	0.024
Urinary tract	21	14%	43%	0.22 (0.03-1.69)	0.147

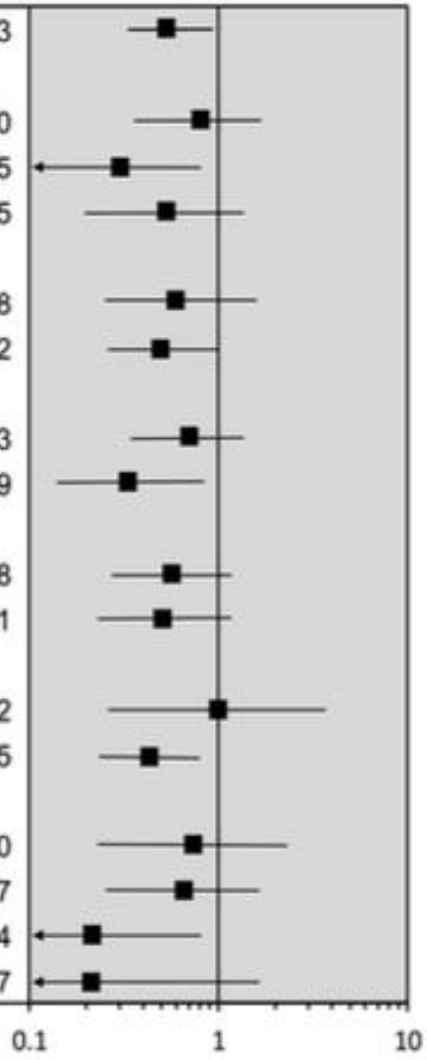


Figure 3 In-hospital mortality across subsets defined according to measures of baseline disease severity and infection characteristics. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; DIC, disseminated intravascular coagulation; ISTH, International Society of Thrombosis and Hemostasis; JAAM, Japanese Association for Acute Medicine; rhTM, recombinant human soluble thrombomodulin; SOFA, Sequential Organ Failure Assessment.

Recombinant human soluble thrombomodulin and mortality in sepsis-induced disseminated intravascular coagulation

A multicentre retrospective study

Mineji Hayakawa[1]; Kazuma Yamakawa[2]; Shinjiro Saito[3]; Shigehiko Uchino[3]; Daisuke Kudo[4]; Yusuke Iizuka[5,9]; Masamitsu Sanui[5]; Kohei Takimoto[6]; Toshihiko Mayumi[7]; Kota Ono[8]; Japan Septic Disseminated Intravascular Coagulation (JSEPTIC DIC) study group

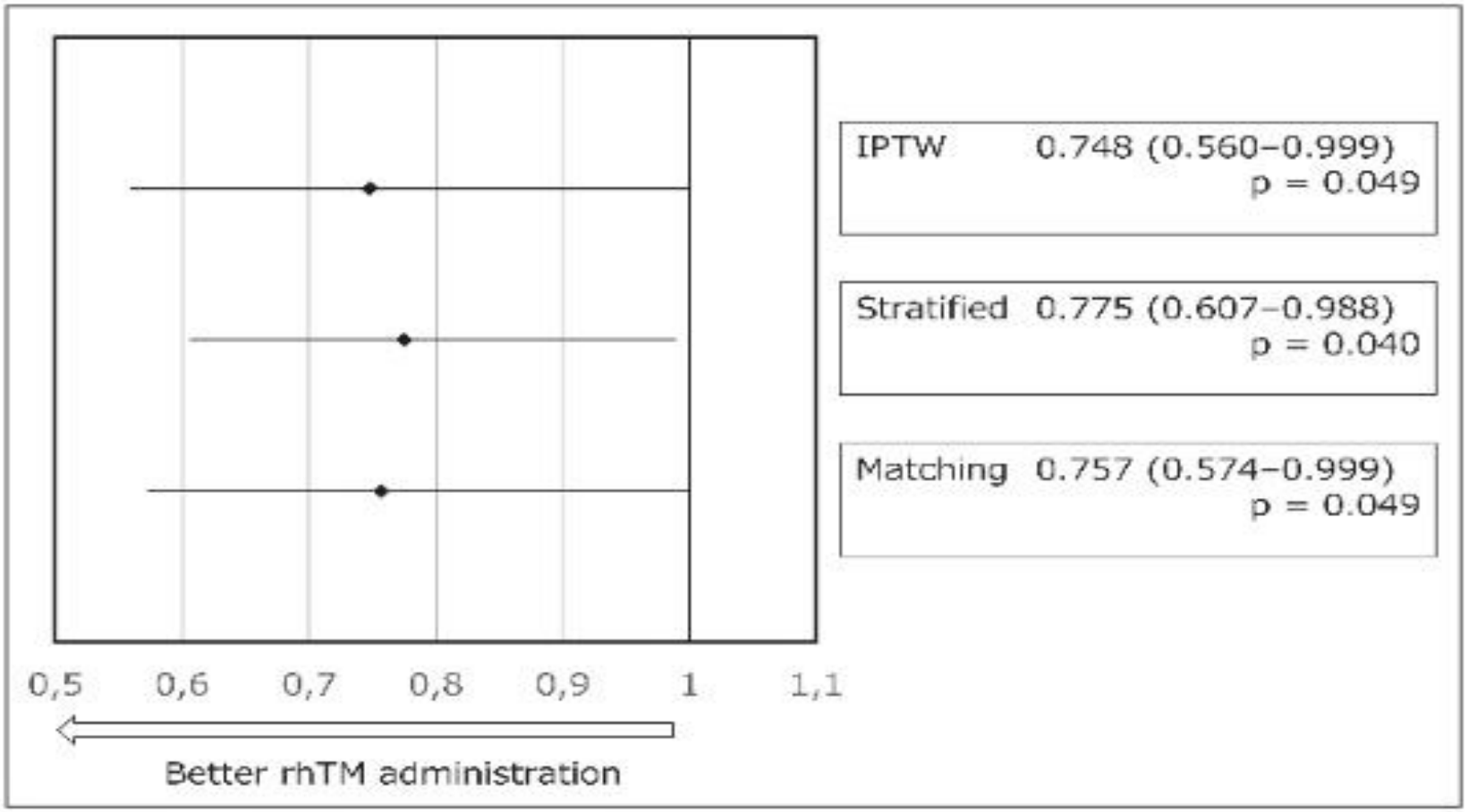
[1]Emergency and Critical Care Center, Hokkaido University Hospital, Japan; [2]Department of Emergency and Critical Care, Osaka General Medical Center, Japan; [3]Intensive Care Unit, Department of Anesthesiology, Jikei University School of Medicine, Japan; [4]Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine,

Table 2: Characteristics of the patients with disseminated intravascular coagulation in the unmatched and propensity-matched groups.

	Unmatched group		Unmatched stand. diff. (%)	Matched group		Matched stand. diff. (%)
	Control (n = 1,139)	rhTM (n = 645)		Control (n = 452)	rhTM (n = 452)	
Age, years	70 ± 15	70 ± 14	–2.24	70 ± 14	70 ± 14	–4.13
Male sex	657 (57.7)	356 (55.2)	5.02	253 (56.0)	252 (55.8)	0.45
Body weight, kg	55.7 ± 14.0	55.8 ± 13.6	2.53	56.1 ± 13.6	55.8 ± 13.7	–2.66
Admission route to the ICU						
Emergency department	558 (49.0)	252 (39.1)	–20.08	195 (43.1)	191 (42.3)	–1.79
Other hospital	281 (24.7)	235 (36.4)	25.75	149 (33.0)	152 (33.6)	1.41
Hospital ward	300 (26.3)	158 (24.5)	–4.23	108 (23.9)	109 (24.1)	0.52
Pre-existing organ dysfunction						
Liver insufficiency	9 (0.8)	8 (1.2)	4.49	5 (1.1)	6 (1.3)	2.02
Chronic respiratory disorder	50 (4.4)	14 (2.2)	–12.48	11 (2.4)	10 (2.2)	–1.47
Chronic heart failure	61 (5.4)	28 (4.3)	–4.72	20 (4.4)	23 (5.1)	3.12
Chronic haemodialysis	118 (10.4)	38 (5.9)	–16.41	28 (6.2)	31 (6.9)	2.69
Immunocompromised	109 (9.6)	81 (12.6)	9.54	51 (11.3)	51 (11.3)	0
Severity						
APACHE II score	23 (17–29)	24 (18–29)	2.72	24 (17–30)	24 (18–29)	–1.50
SOFA score total	10 (7–13)	11 (8–13)	24.95	11 (8–13)	11 (8–13)	–1.03
Respiratory	2 (1–3)	2 (1–3)	–0.09	2 (1–3)	2 (1–3)	–5.74
Renal	2 (0–3)	2 (1–3)	10.31	2 (1–3)	2 (1–3)	–0.93
Liver	0 (0–1)	0 (0–1)	10.07	0 (0–1)	0 (0–1)	4.18
Cardiovascular	3 (1–4)	3 (2–4)	25.20	3 (1–4)	3 (2–4)	–1.62
Coagulation	1 (0–2)	2 (1–3)	31.18	2 (1–2)	2 (1–2)	7.61

	Control	rhTM	Odds ratio (95 % CI)	P-value
IPTW analysis	460/1,746 (26.3)	385/1,691 (22.7)	0.786 (0.557–1.111)	0.172
Stratified analysis	276/1,072 (25.7)	141/628 (22.5)	0.769 (0.579–1.021)	0.070
Matching analysis	116/452 (25.7)	102/452 (22.6)	0.794 (0.574–1.098)	0.163

rhTM, recombinant human soluble thrombomodulin; CI, confidence interval; IPTW, inverse probability of treatment weighted. Data are presented as n (%) or odds ratio (95 % confidence interval).



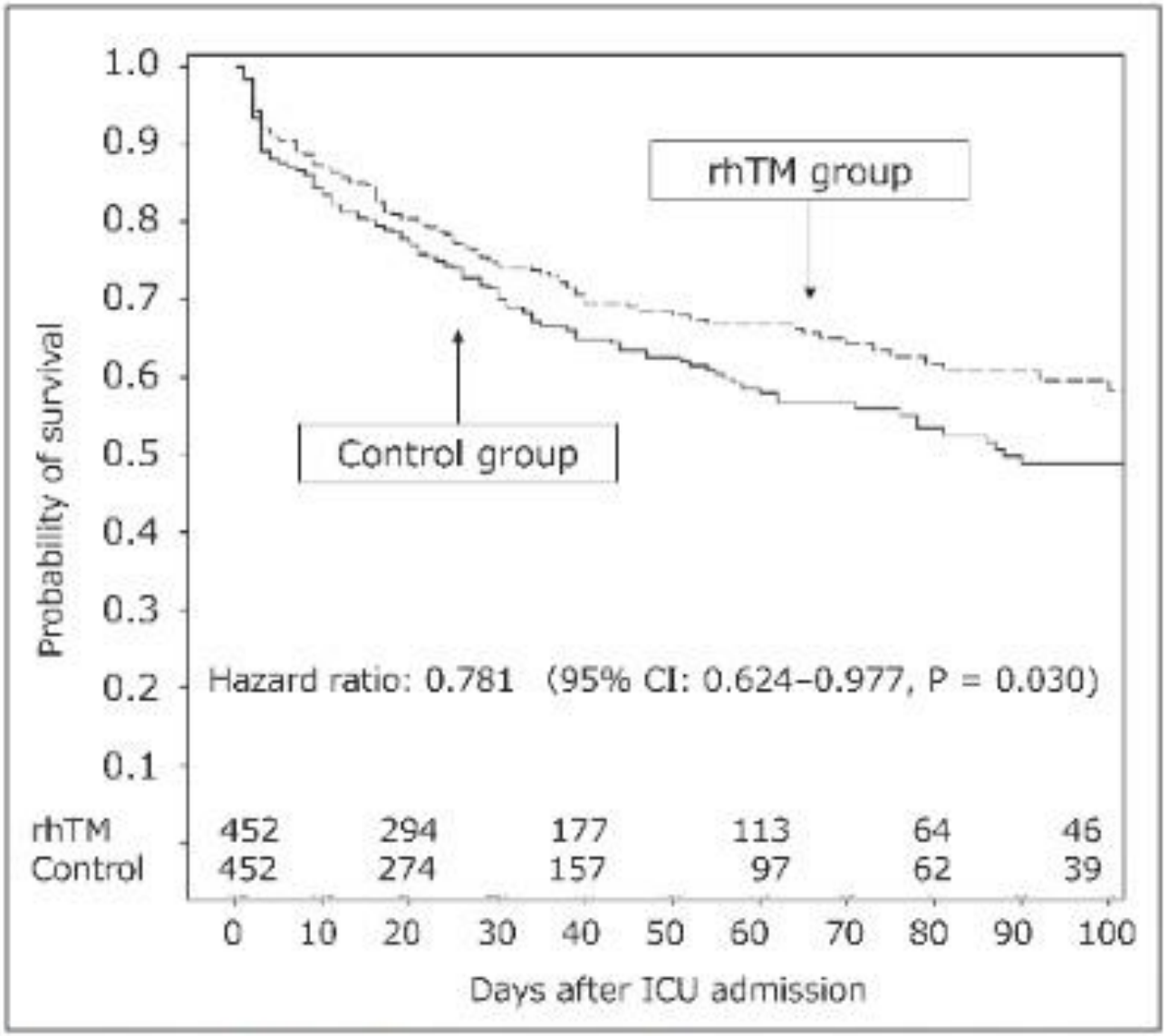


Figure 3: Survival plots for patients in the propensity score-matched control and rhTM groups. The survival rate was higher in the rhTM group, compared to that in the control group. rhTM, recombinant human soluble thrombomodulin.

Journal of Thrombosis and Haemostasis, **13**: 508–519 DOI: 10.1111/jth.12841

IN FOCUS

Recombinant human soluble thrombomodulin in severe sepsis: a systematic review and meta-analysis

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Revue systématique des registres d'études où apparaissent l'utilisation
de la Thrombomoduline : 71 études retrouvées

12 études contenant des données analysables qualitatives et quantitatives :

- 3 Etudes RCT (OUTCOME princeps ➔ Mortalité)
- Critères de jugement secondaires : Résolution CIVD & Hémorragie(s)
- 9 Etudes observationnelles prospective et rétrospective

BIAIS PRINCIPAUX RELEVES PAR LES AUTEURS SUR LES ETUDES SELECTIONNEES

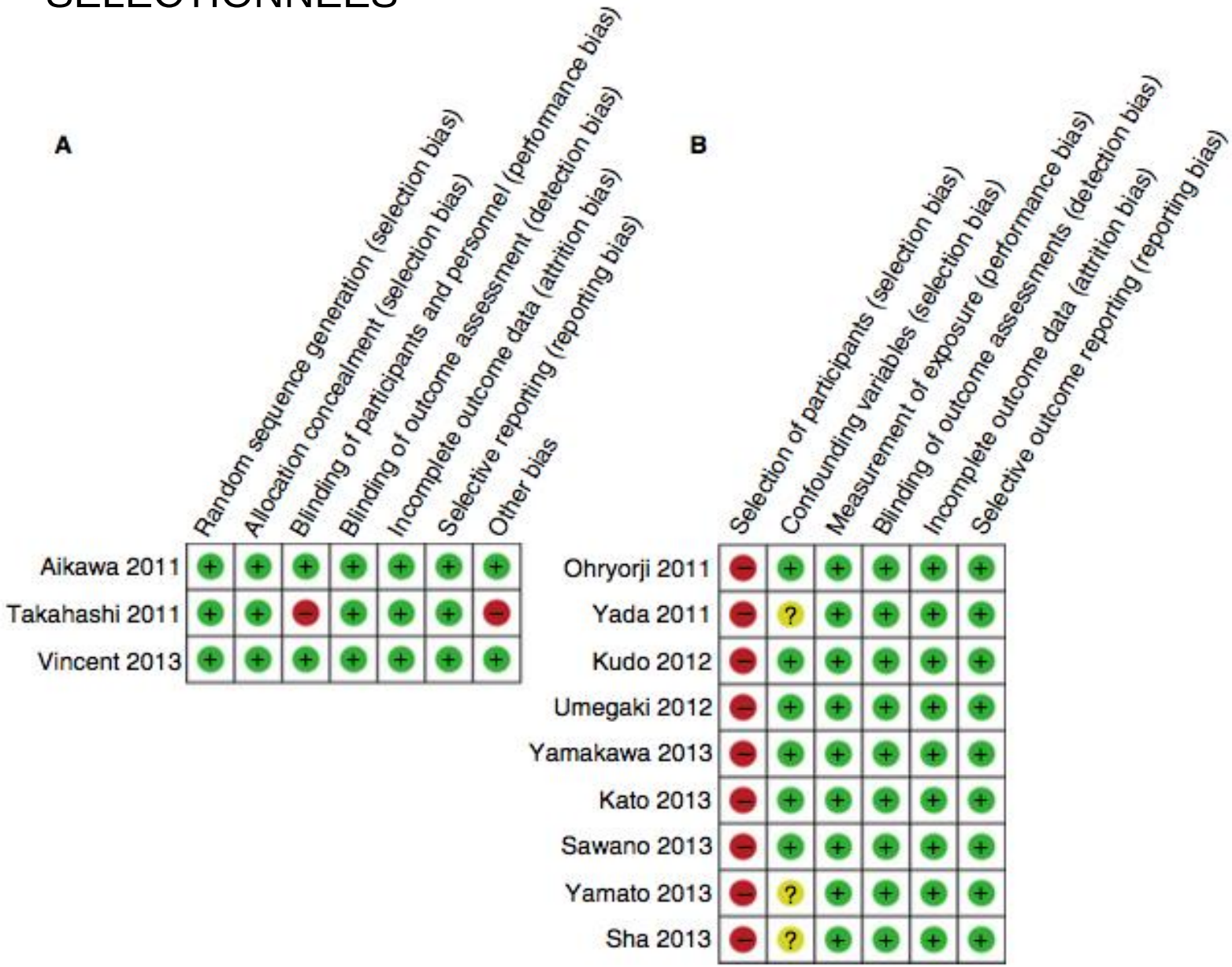

Table 1 Characteristics of included studies

Source	Study venue	Design	Population	No. of patients			Mean age (yrs)	Intervention		Follow-up
				Total	rhTM	Control		rhTM	Control	
Randomized controlled trials										
Aikawa *et al.* [14]	Japan	RCT	JMHW DIC	80	42	38	NA	0.06 mg kg^{-1} day^{-1} for 6 days	Unfractionated heparin (8 U kg^{-1} h^{-1})	28 days
Takahashi *et al.* [25]	Japan	RCT	JAAM DIC	17	9	8	75	0.06 mg kg^{-1} day^{-1} for 6 days*	w/o rhTM	In-hospital
Vincent *et al.* [23]	Multi-national	RCT	Modified ISTH DIC	741	370	371	57	0.06 mg kg^{-1} day^{-1} for 6 days	Placebo	28 days
Observational studies										
Ohryorji *et al.* [26]	Japan	HC	JAAM DIC	33	17	16	NA	0.06 mg kg^{-1} day^{-1} for 6 days*	w/o rhTM	90 days
Yada *et al.* [27]	Japan	RC	JAAM DIC	28	12	16	68	0.06 mg kg^{-1} day^{-1} for 6 days*	w/o rhTM	30 days
Kudo *et al.* [28]	Japan	HC	JAAM DIC	53	30	23	NA	0.06 mg kg^{-1} day^{-1} for 6 days	w/o rhTM	30 days
Umegaki *et al.* [29]	Japan	HC	JAAM DIC	73	33	40	70	0.06 mg kg^{-1} day^{-1} for 7 days*	Danaparoid	90 days
Yamakawa *et al.* [30]	Japan	RC	JAAM DIC	162	68	94	66	0.06 mg kg^{-1} day^{-1} for 6 days	w/o rhTM	In-hospital
Kato *et al.* [31]	Japan	RC	JAAM DIC	35	12	23	67	0.06 mg kg^{-1} day^{-1} for 7 days*	w/o rhTM	28 days
Sawano *et al.* [32]	Japan	RC	JAAM DIC	111	51	60	69	0.06 mg kg^{-1} day^{-1} for 6 days	w/o rhTM	28 days
Yamato *et al.* [33]	Japan	HC	JAAM DIC	22	14	8	NA	0.06 mg kg^{-1} day^{-1}, duration unknown	w/o rhTM	60 days
Sha *et al.* [34]	Japan	HC	JAAM DIC	54	31	23	75	0.06 mg kg^{-1} day^{-1} for 5–7 days*	w/o rhTM	1 month

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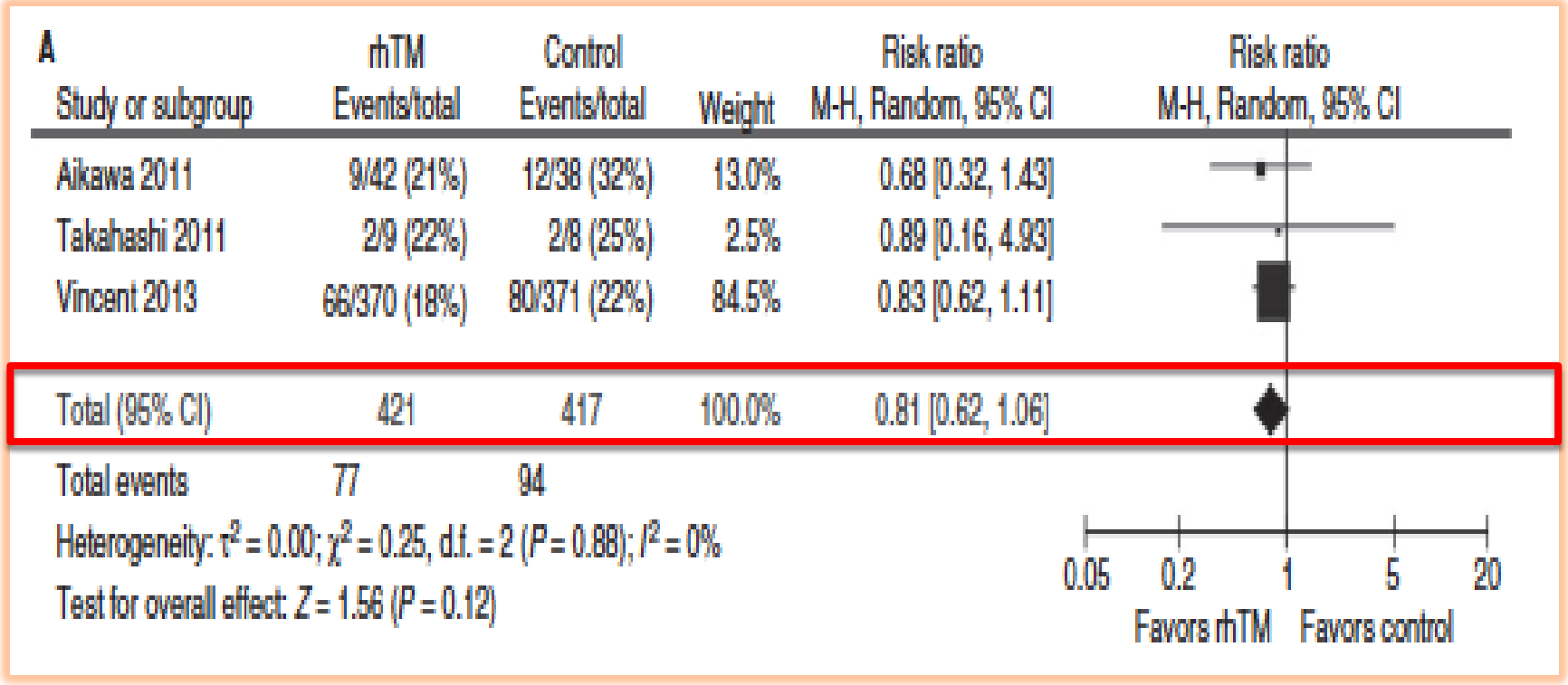
Méta-analyses des données des 3 principales études RCT sur l'utilisation de la THROMBOMODULINE recombinante :

- Pas de différence significative sur le critère de MORTALITE à 28J



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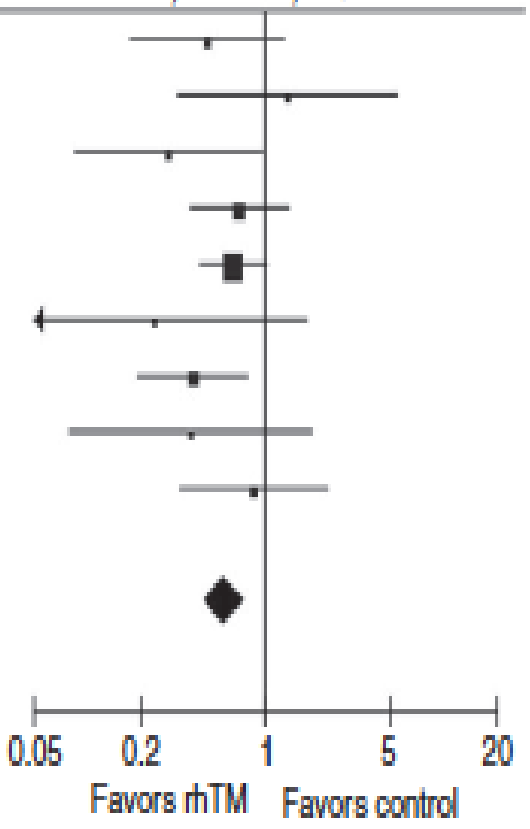
B

Study or subgroup	rhTM Events/total	Control Events/total	Weight	Risk ratio M-H, Random, 95% CI
Ohryorji 2011	4/17 (24%)	8/16 (50%)	7.4%	0.47 [0.18, 1.26]
Yada 2011	3/12 (25%)	3/16 (19%)	3.6%	1.33 [0.32, 5.49]
Kudo 2012	3/30 (10%)	8/23 (35%)	4.9%	0.29 [0.09, 0.96]
Umegaki 2012	10/33 (30%)	17/40 (43%)	18.1%	0.71 [0.38, 1.34]
Yamakawa 2013	20/68 (29%)	42/94 (45%)	38.7%	0.66 [0.43, 1.01]
Kato 2013	1/12 (8%)	8/23 (35%)	1.9%	0.24 [0.03, 1.70]
Sawano 2013	8/51 (16%)	24/60 (40%)	14.4%	0.39 [0.19, 0.80]
Yamato 2013	2/14 (14%)	3/8 (38%)	2.9%	0.38 [0.08, 1.82]
Sha 2013	7/31 (23%)	6/23 (26%)	8.0%	0.87 [0.34,2.23]
Total (95% CI)	268	303	100.0%	0.59 [0.45, 0.77]
Total events	58	119		

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 6.53$, d.f. = 8 ($P = 0.59$); $I^2 = 0\%$

Test for overall effect: $Z = 3.88$ ($P = 0.0001$)



Analyse statistique en propension rétrospective sur le critère : Mortalité J28

Résolution de la CIVD à J7 : RCT* et Etude observationnelle

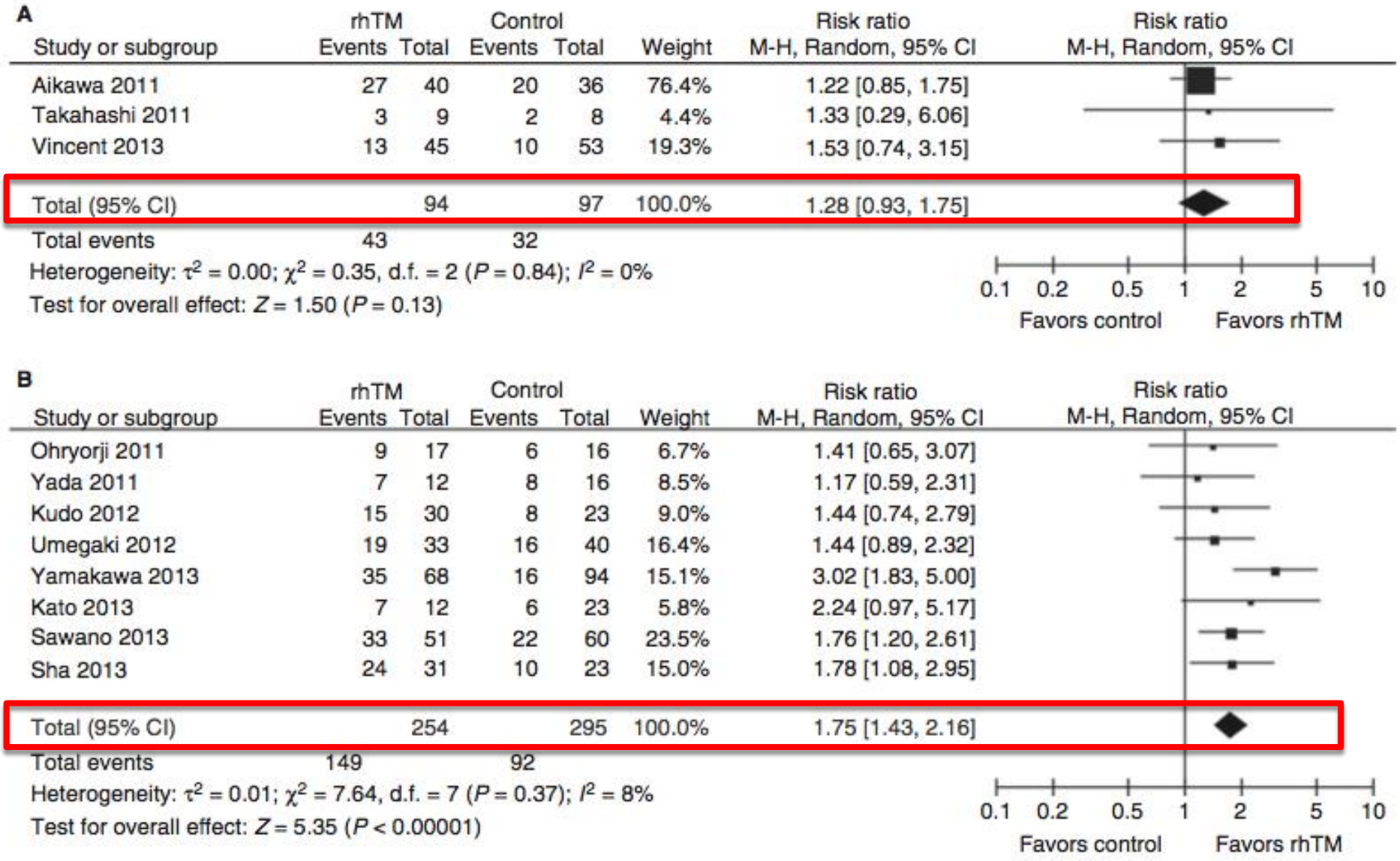


Fig. 5. Forest plot of the comparison: rhTM vs. no rhTM: DIC resolution rate on day 7. (A) Randomized controlled trials; (B) observational studies. rhTM, recombinant human thrombomodulin; M-H, Mantel-Haenszel; CI, confidence interval.

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Pas plus d'évenements hémorragiques et/ou de saignement dans le groupe traitement Vs contrôle

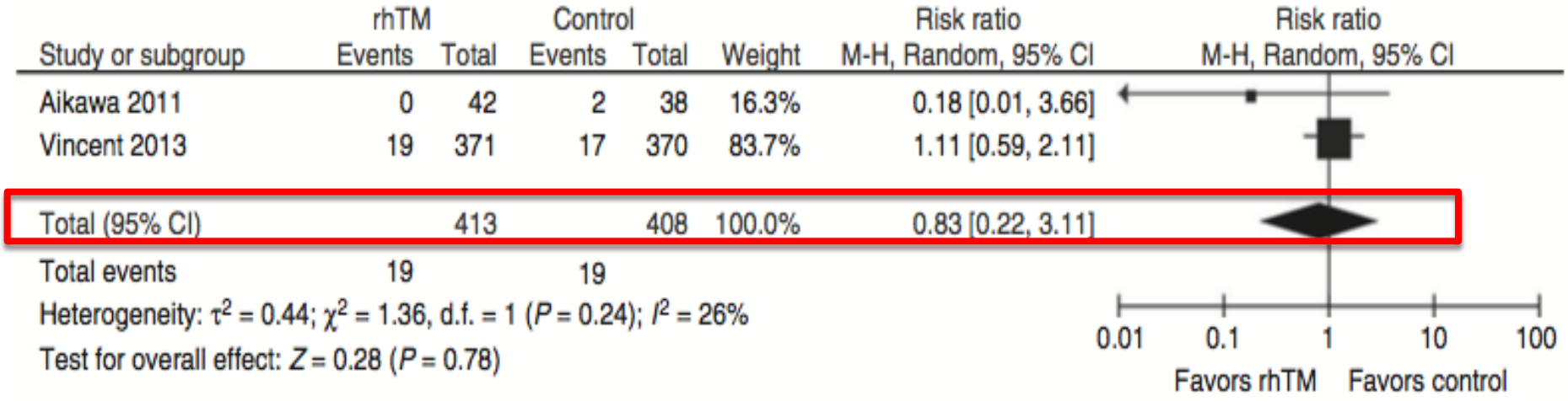
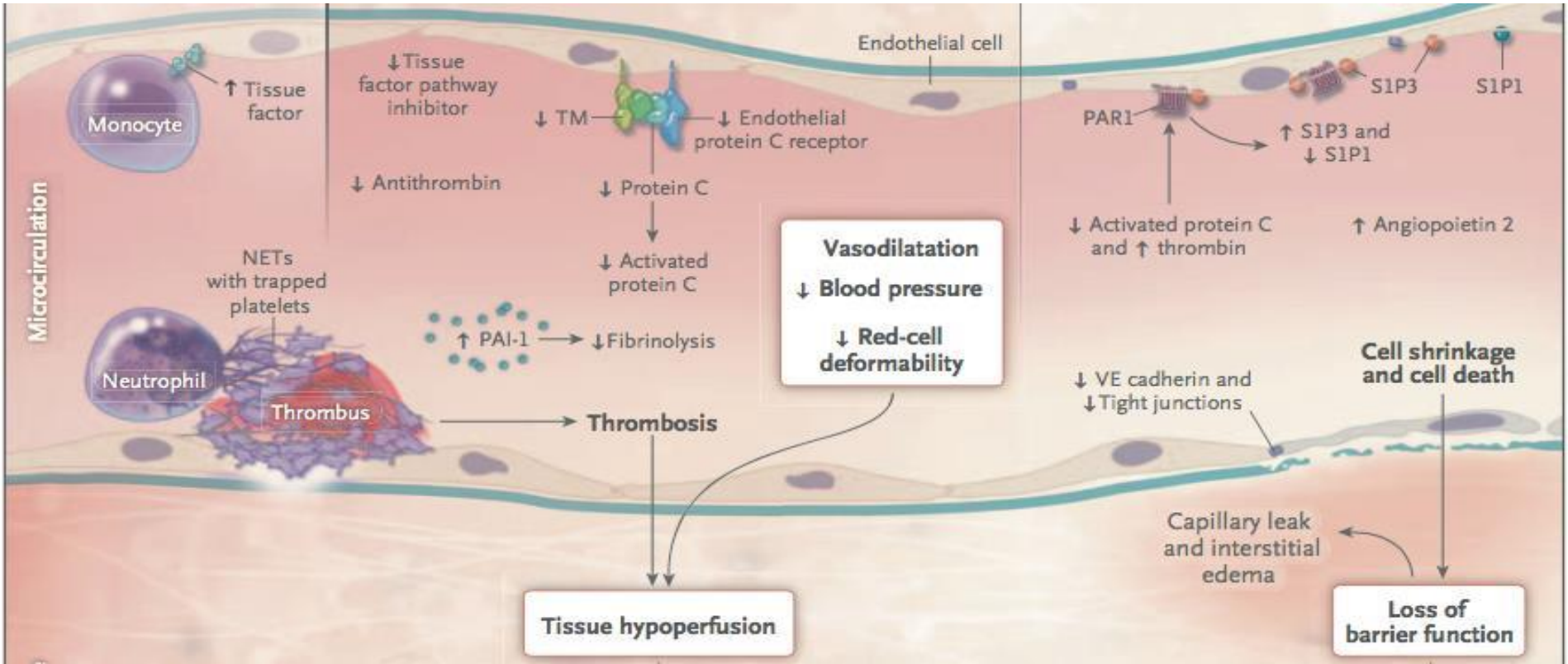


Fig. 6. Forest plot of the comparison: rhTM vs. no rhTM: serious bleeding complications in randomized controlled trials. rhTM, recombinant human thrombomodulin; M-H, Mantel-Haenszel; CI, confidence interval.

CONCLUSION :

- Rôle de la thrombomoduline dans la protection endothéliale
- ANTICOAGULATION : via PC/S & Activité ATIII-like – inhibition IIa
- ANTI-INFLAMMATOIRE : inhibition de la HMBG1

Inhibition de la cascade du complément et de l'adhésion leucocytaire



CONCLUSION :

• Actuellement pas d'essai RCT en faveur clairement de l'utilisation de la rhTM* dans le choc septique avec CIVD

• Une tendance en FAVEUR de l'utilisation de la ***Thrombomoduline sur les analyses en propension***

• Dans les études RCT phase 2b ou en phase III :
Absence de sur-risque d'hémorragique
• IDEM dans les méta-analyses rétrospectives et les analyses en propension

➔ ETUDE SCARLET

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