폐혈관 School 2025

Coagulation and anticoagulants in ARDS and sepsis

Won-Young Kim, MD, PhD
Chung-Ang University Hospital
Republic of Korea

중앙대학교병원
CHUNG-ANG UNIVERSITY HOSPITAL

Disclosures

- The following presentation will NOT include discussion on any commercial products or service.
- I have no conflicts of interest with regard to the presentation.

Acute respiratory distress syndrome (ARDS)

- Acute onset, bilateral opacities on chest imaging, noncardiogenic respiratory failure → mild, moderate, or severe oxygenation impairment[1]

- Direct lung insult (pneumonia, aspiration) or systemic event (sepsis, massive transfusion, trauma)

- Treatment remains supportive: lung protective mechanical ventilation, neuromuscular blockade, prone position, conservative fluid administration

- Mortality rate: 30-50%

[1]JAMA 2012;307:2526-33

Sepsis

- Life-threatening organ dysfunction caused by dysregulated host response to infection[1]
- Results in more than 5 million deaths globally each year → major public health concern
- In-hospital mortality is around 20%, septic shock: 40-50%
- Treatment is focused on adequate antibiotic therapy, source control, supportive care and organ replacement
- Novel therapeutic interventions have been explored over last several decades → inconsistent benefits

[1]JAMA 2016;315:801-10

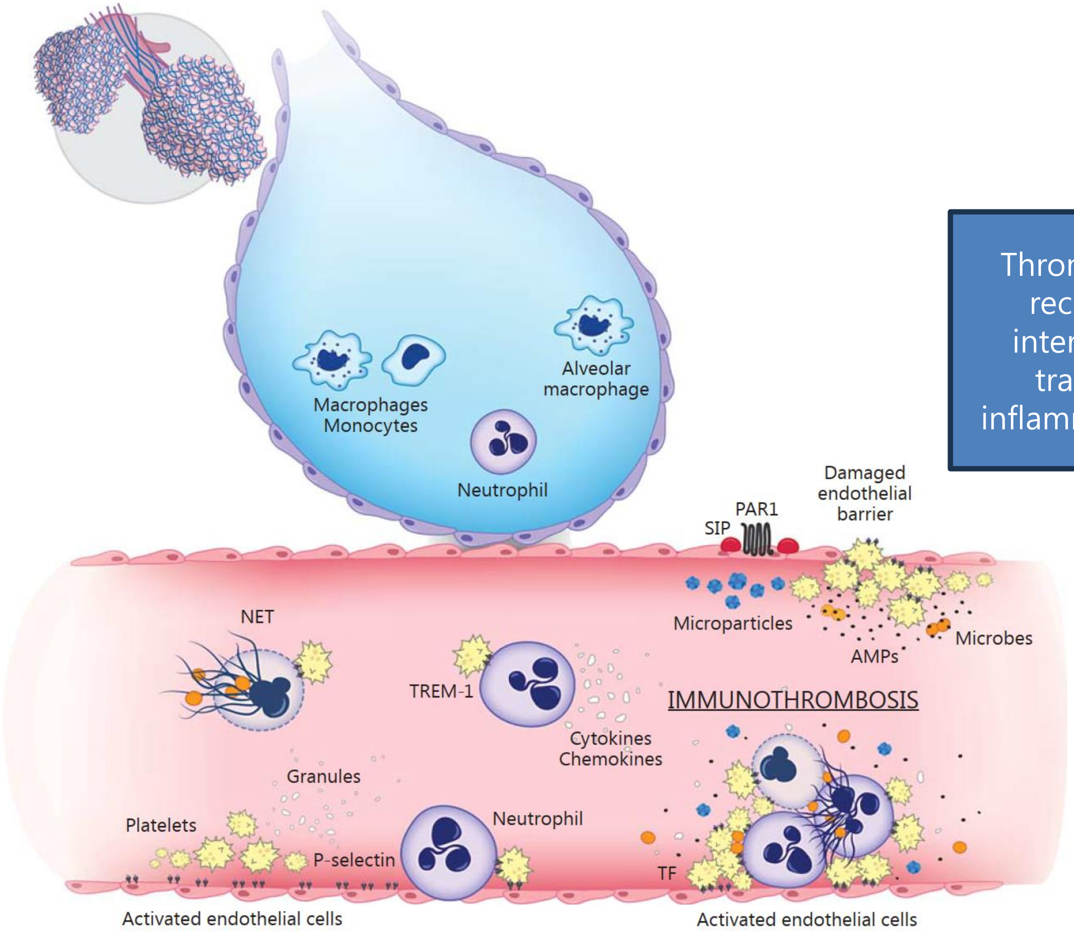
ARDS and sepsis

- Share many pathological mechanisms
  - endothelial dysfunction
  - increased vascular permeability
  - leukocyte activation
  - initiation of coagulation
  - inhibition of fibrinolysis

- Sepsis: diffuse microvascular thrombosis → organ ischemia and multiorgan dysfunction

- ARDS: intra-alveolar fibrin that lines denuded alveolar surface → gas exchange abnormalities

Coagulation and inflammation are linked

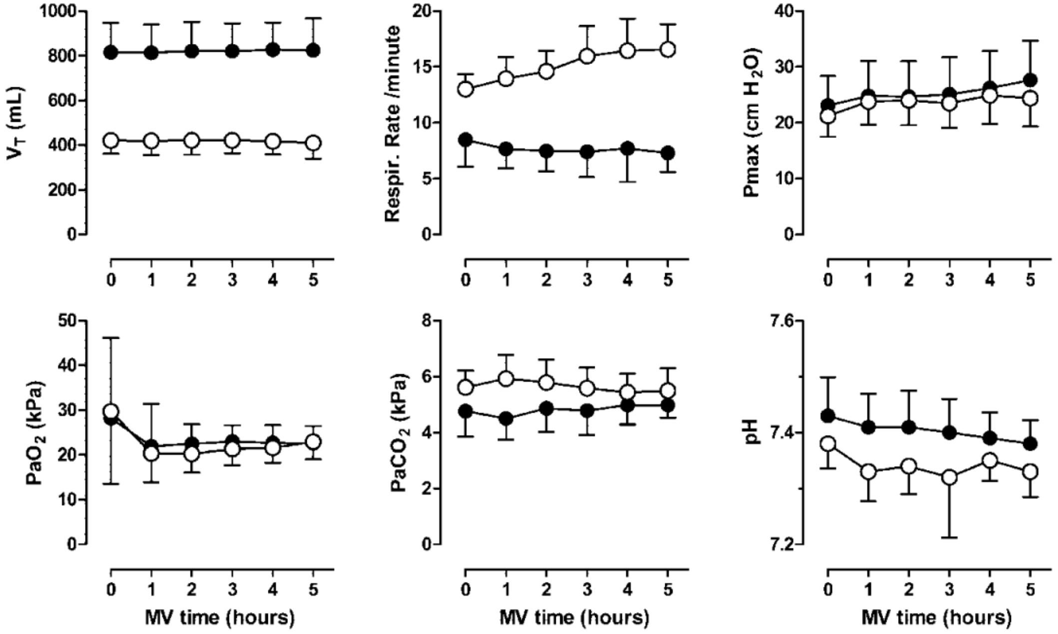


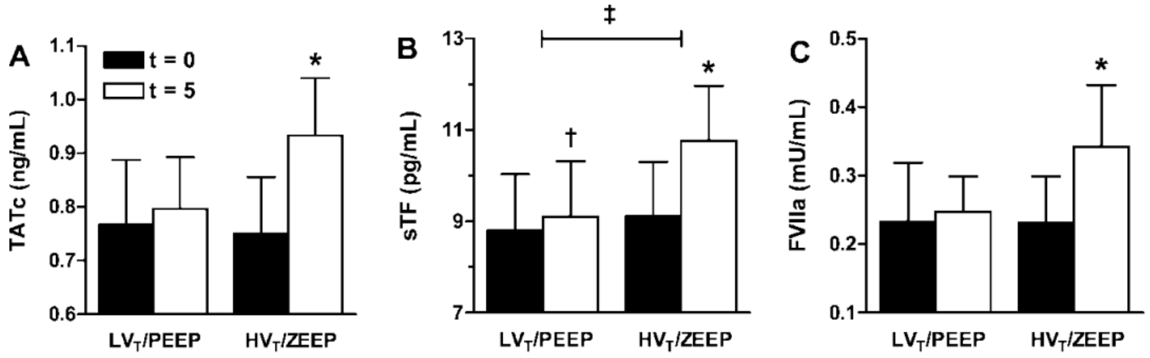
Thrombin binds to protease-activated receptors (PARs) → thrombin-PAR interaction leads to G protein signal transduction and transcription of inflammatory mediators in immune cells

Inflammatory mediators induce tissue factor expression and downregulate protein C and protein S → favoring thrombin formation and fibrin deposition

Respiration 2017;93:212-25

MV can activate coagulation cascade





Thrombin-antithrombin complexes

Soluble tissue factor

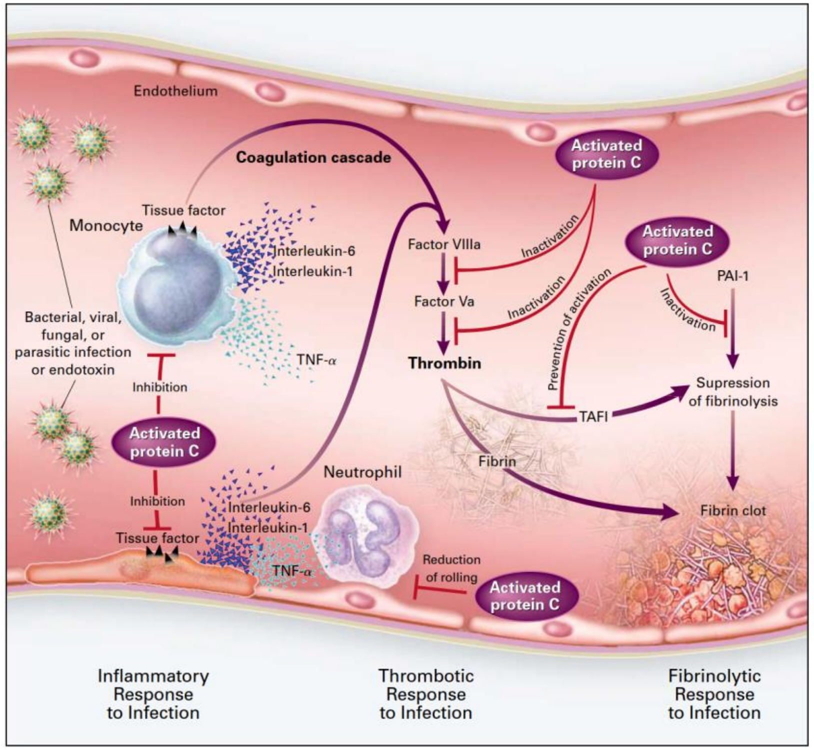
Factor VIIa

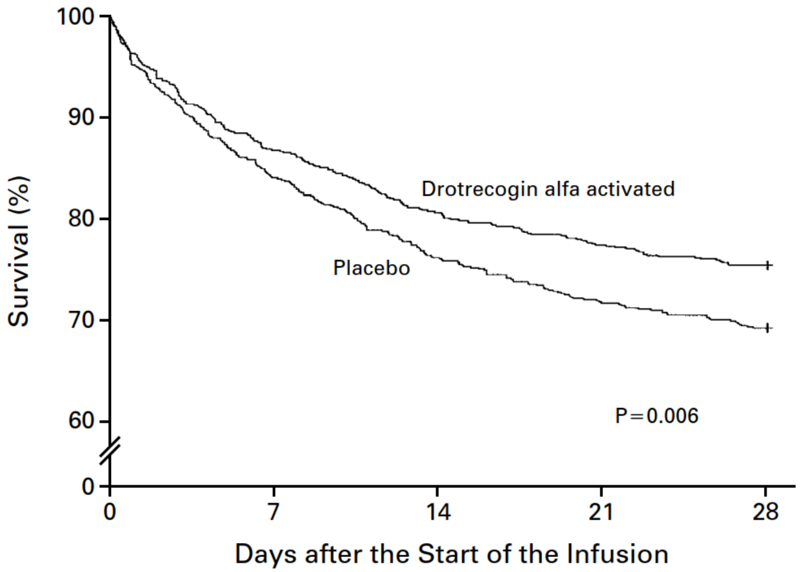
Anesthesiology 2006;105:689-95

PROWESS study

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*



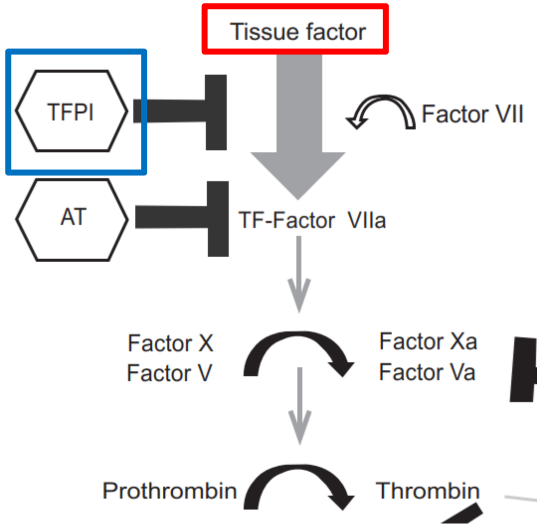


NO. AT RISK					
Drotrecogin alfa activated	850	737	684	657	640
Placebo	840	705	639	602	581

N Engl J Med 2001;344:699-709

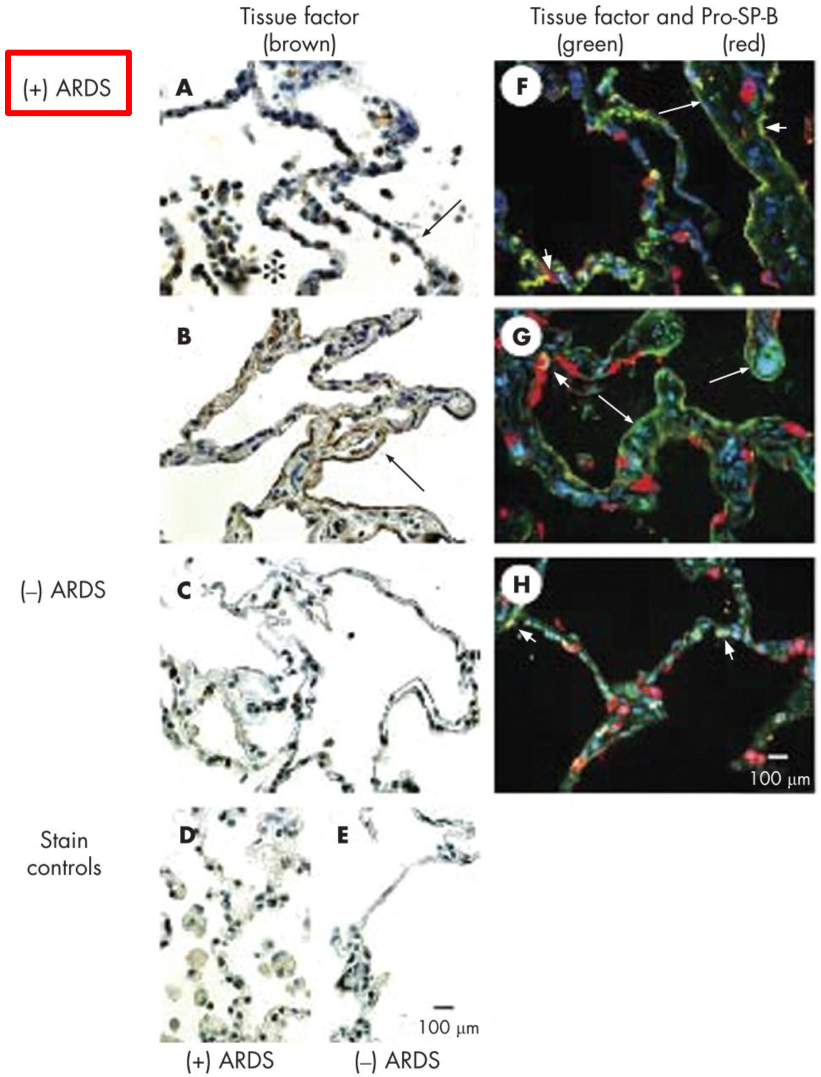
Tissue factor (TF)

- Most potent known initiator of coagulation
- 47 kD membrane-bound protein
- Bound to factor VIIa → catalyzes conversion of factor X to Xa → leading to thrombin generation
- TF pathway inhibitor (TFPI) can bind to TF:VIIa:X complex → prevent formation of Xa → inhibiting thrombin formation and fibrin deposition

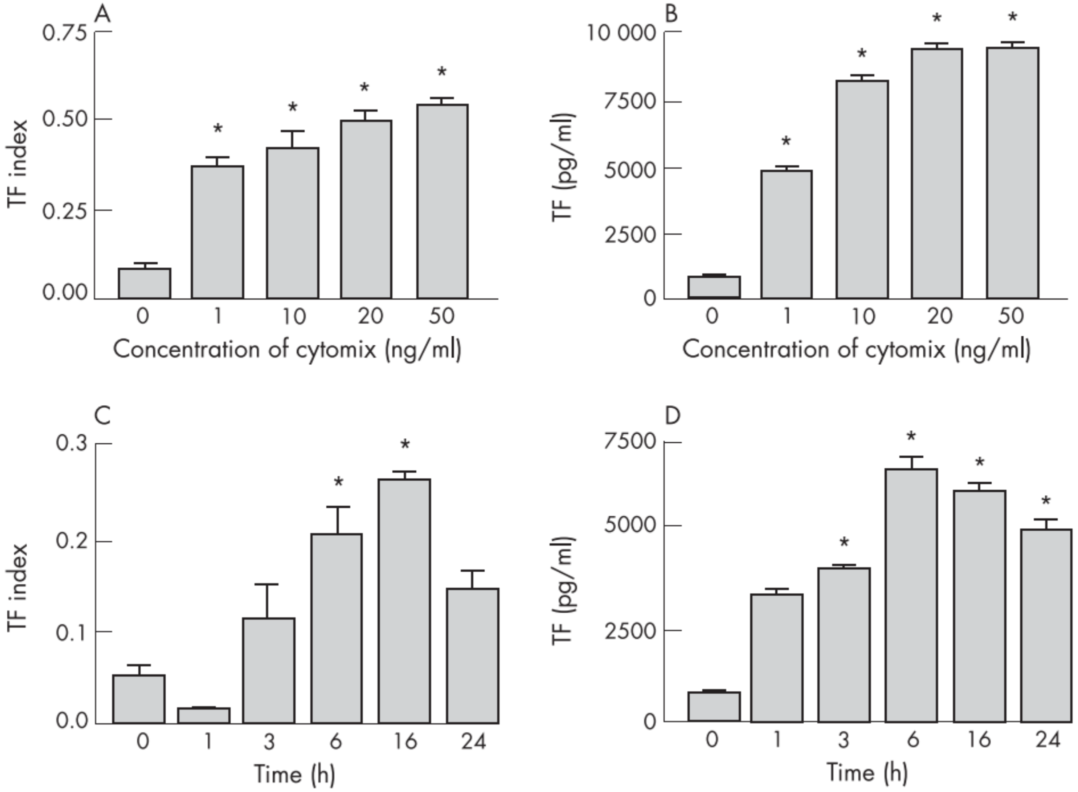


Curr Pharm Biotechnol 2011;12:1481-96

Alveolar epithelium modulates TF in ARDS



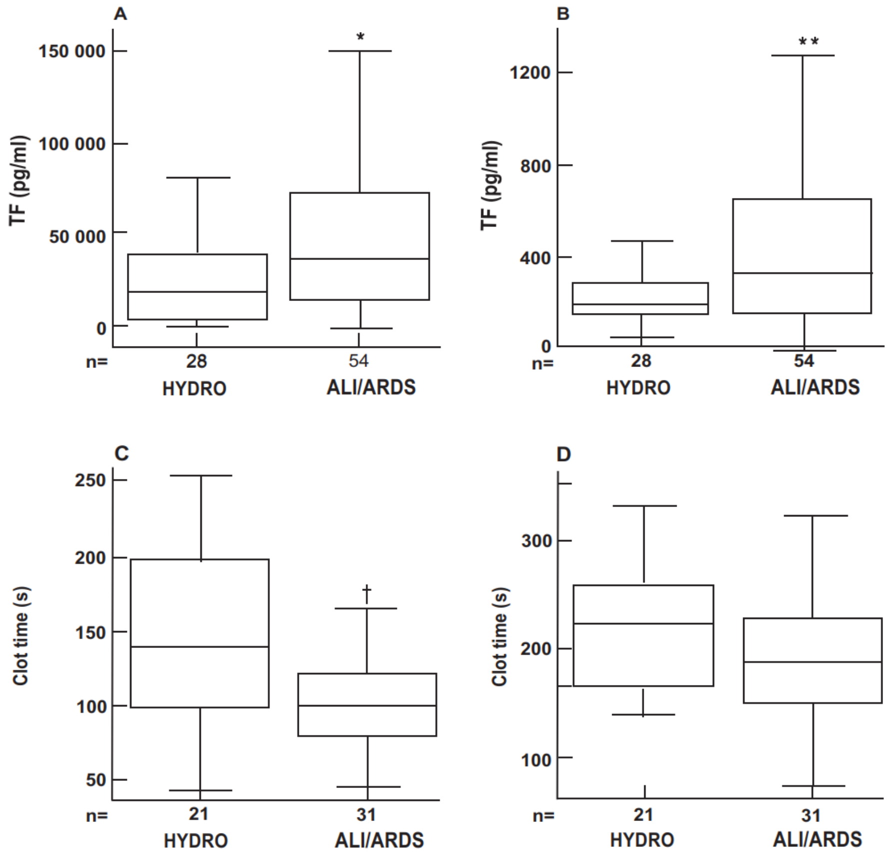
Cytomix: tumor necrosis factor α, interleukin 1β, interferon γ



Thorax 2007;62:608-16

Plasma and pulmonary edema fluid levels of TF and clot time

Edema fluid

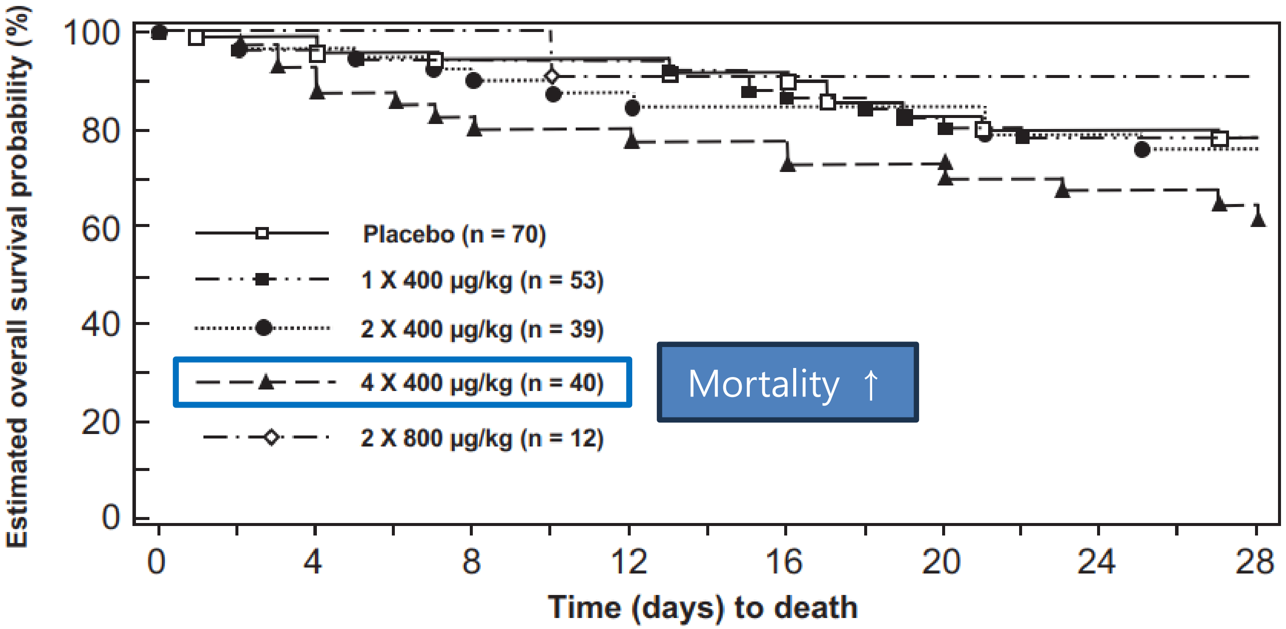


Plasma

Thorax 2007;62:608-16

Inactivated recombinant factor VIIa

A multicenter, randomized, double-blind, placebo-controlled, dose-escalation trial assessing safety and efficacy of active site inactivated recombinant factor VIIa in subjects with acute lung injury or acute respiratory distress syndrome*



TF blockade in sepsis and ARDS – OPTIMIST trial

Efficacy and Safety of Tifacogin (Recombinant Tissue Factor Pathway Inhibitor) in Severe Sepsis
A Randomized Controlled Trial

Study enrolled 1,754 patients, 86% of whom had evidence of ARDS as measured by PaO_2:FiO_2 ratio < 300

Figure 2. Cumulative Proportion of 28-Day All-Cause Mortality of TFPI and Placebo for Patients With High and Low INR

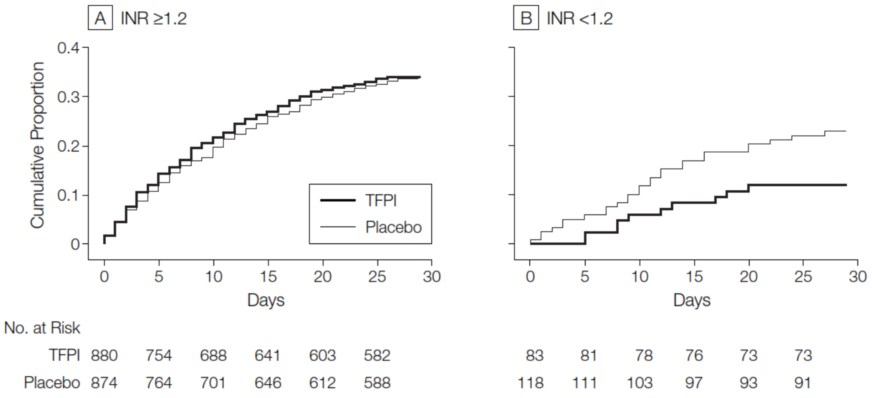


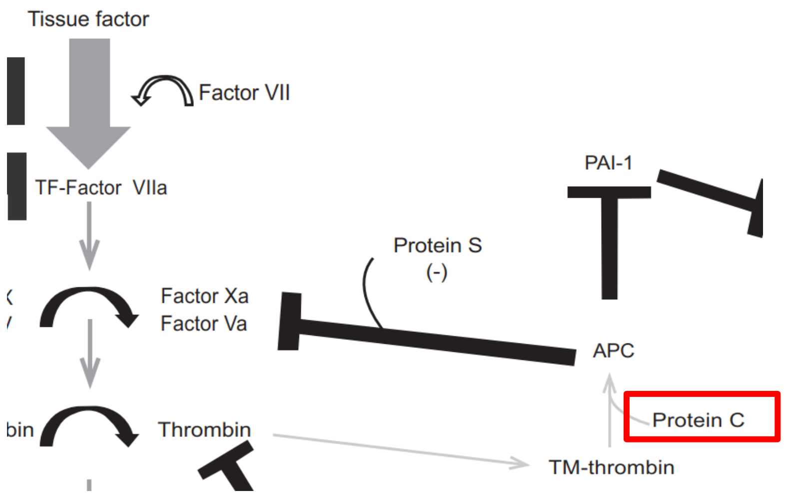
Table 2. 28-Day Mortality Overall and in Prespecified Subpopulations

Population	No. of Patients		28-Day Mortality Rate, No. (%)		Relative Risk (95% Confidence Interval)
	Placebo	Tifacogin	Placebo	Tifacogin	
Primary efficacy (baseline INR ≥1.2)	874	880	296 (33.9)	301 (34.2)	1.01 (0.89-1.15)
Baseline INR ≥1.5 and coagulation organ dysfunction score <4	149	125	68 (45.6)	52 (41.6)	0.91 (0.69-1.20)
Baseline INR <1.5 or coagulation organ dysfunction score ≥4	724	753	228 (31.5)	248 (32.9)	1.05 (0.90-1.21)
Shock at baseline					
No	208	245	62 (29.8)	70 (28.6)	0.96 (0.72-1.28)
Yes	666	635	234 (35.1)	231 (36.4)	1.04 (0.90-1.20)
Baseline APACHE II score					
<20	207	188	45 (21.7)	33 (17.6)	0.81 (0.54-1.21)
≥20	665	689	249 (37.4)	267 (38.8)	1.03 (0.90-1.19)
Baseline PaO_2/FiO_2 ratio <300	767	752	264 (34.4)	263 (35.0)	1.02 (0.89-1.17)
Baseline PaO_2/FiO_2 ratio ≥300	107	127	32 (29.9)	38 (29.9)	1.00 (0.67-1.48)

JAMA 2003;290:238-47

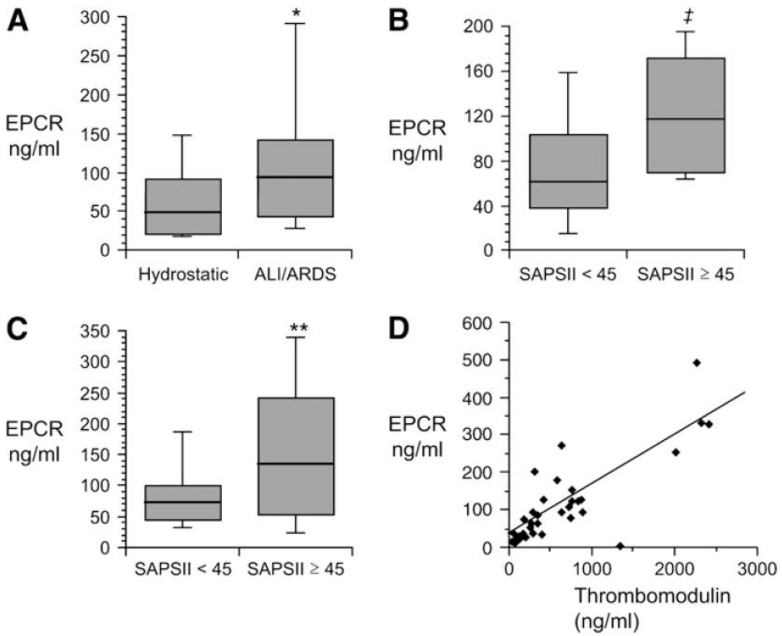
Protein C (PC)

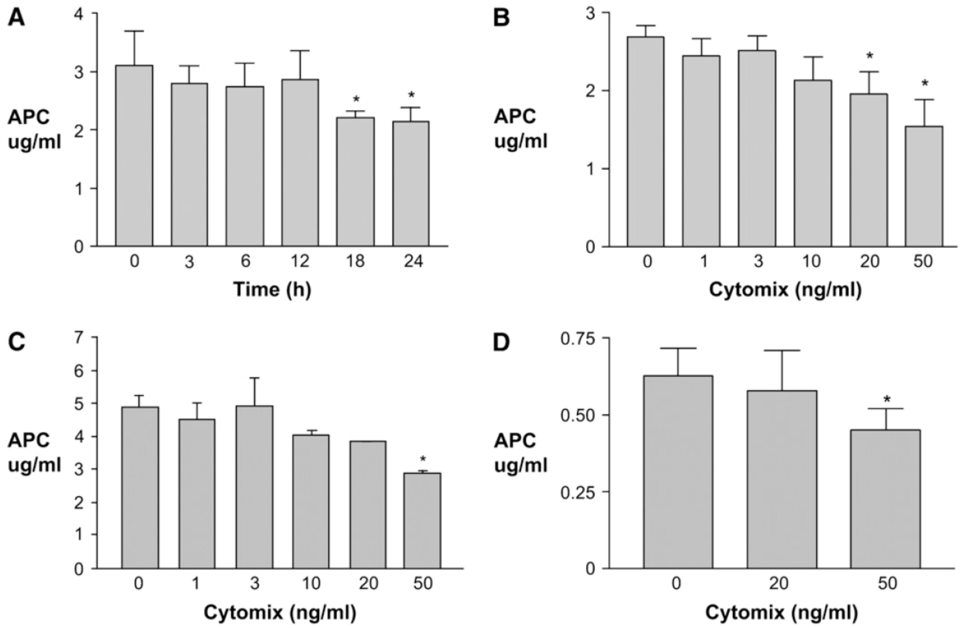
- Vitamin K-dependent plasma glycoprotein that is synthesized by liver and circulates as two-chain biologically inactive zymogen
- Transformed to activated PC (APC) by thrombomodulin (TM)-thrombin complex
- APC suppresses thrombin formation by inactivating coagulation factors Va and VIIIa
- PC activation is further enhanced when bound on cell surface to endothelial cell PC receptor (EPCR)
- APC also has anti-inflammatory properties



Lung epithelial cells modulate protein C pathway

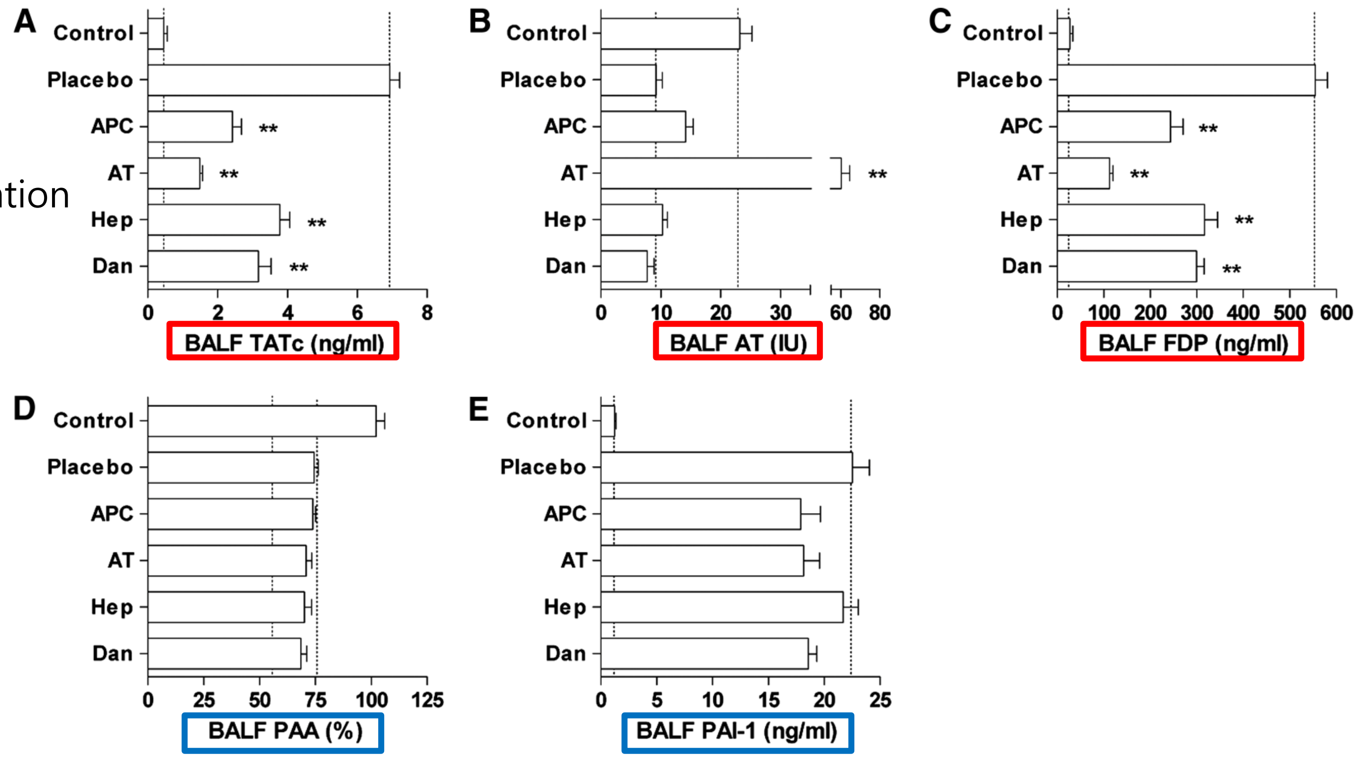
Cytomix: tumor necrosis factor α, interleukin 1β, interferon γ





Nebulized anticoagulants

Nebulization



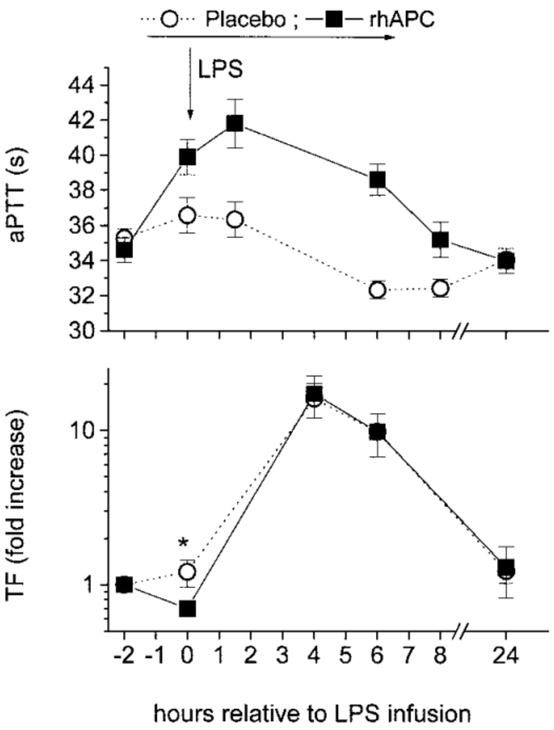
J Aerosol Med Pulm Drug Deliv 2010;23:105-11

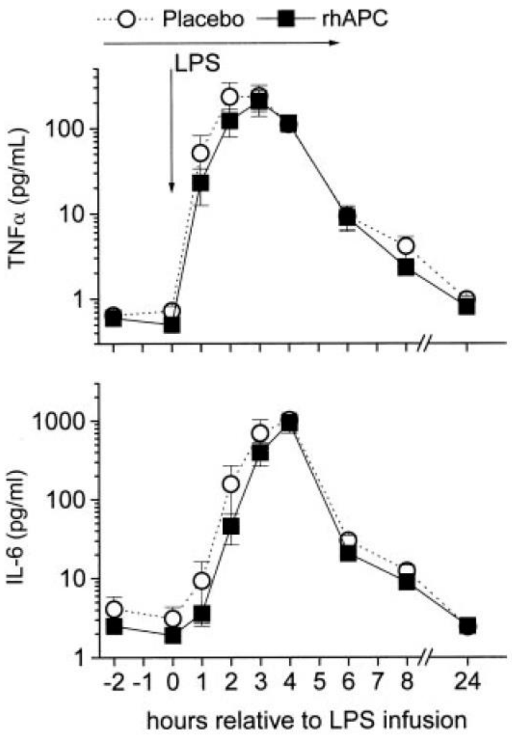
PC administration in human endotoxemia

Recombinant human activated protein C (rhAPC; drotrecogin alfa [activated]) has minimal effect on markers of coagulation, fibrinolysis, and inflammation in acute human endotoxemia

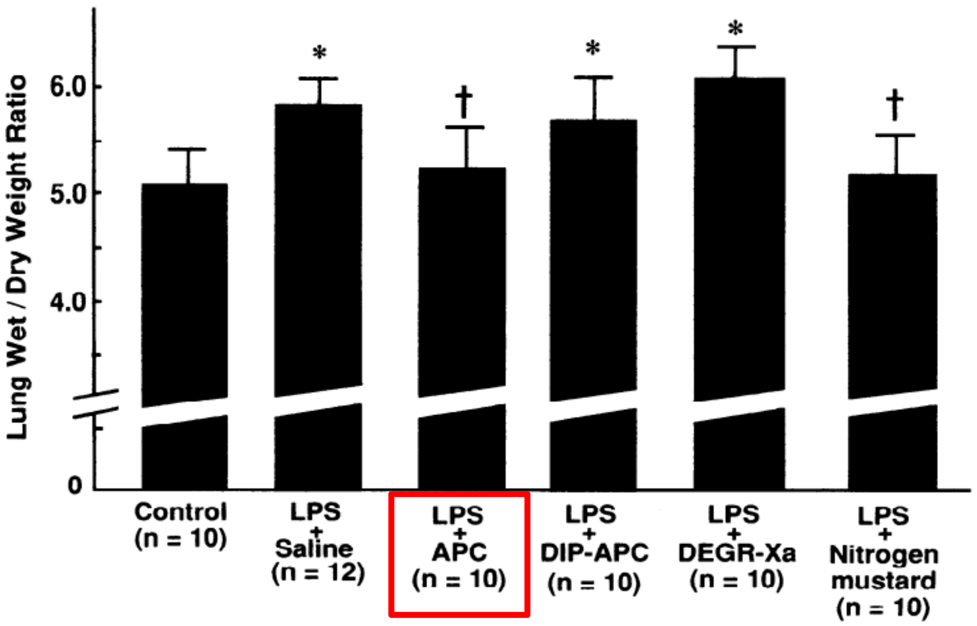
Ulla Derhaschnig, Rosemarie Reiter, Paul Knöbl, Magdalena Baumgartner, Priska Keen, and Bernd Jilma

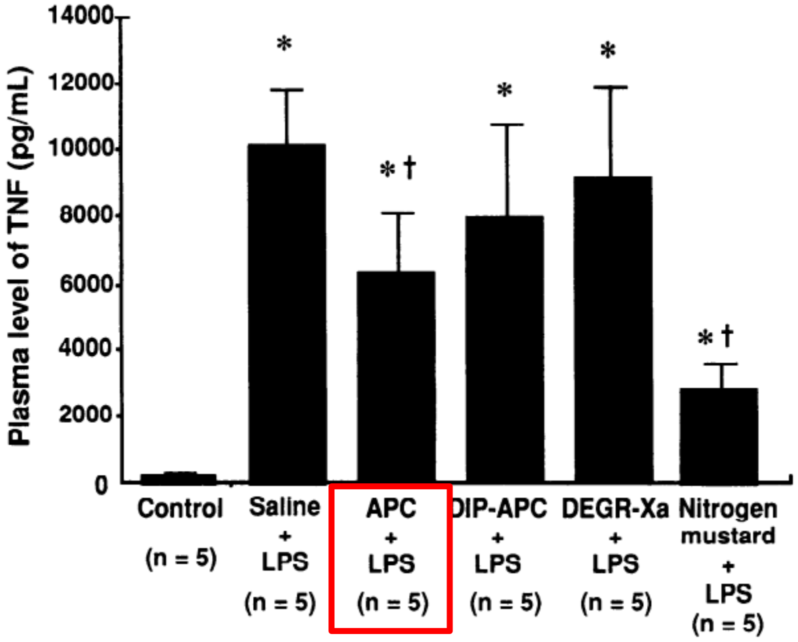
Randomized normal controls to receive infusion of APC or placebo for 2 h prior to and 6 h after receiving intravenous injection of LPS





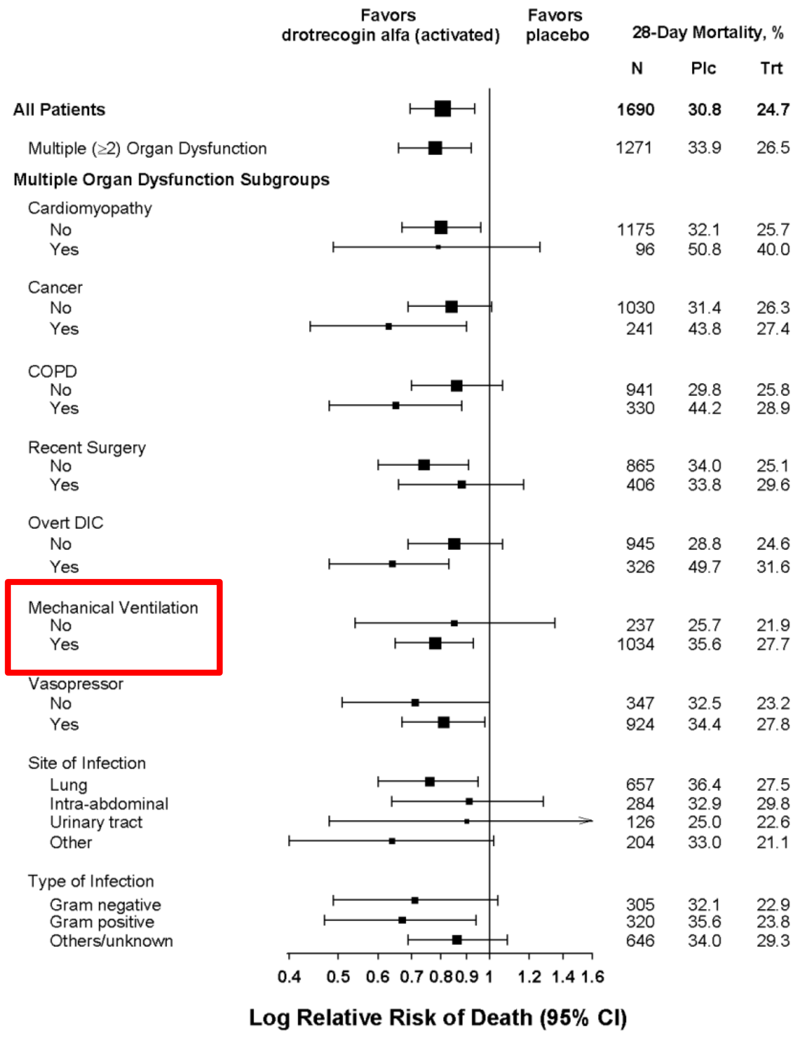
APC has anti-inflammatory effect





Am J Physiol 1997;272(2 Pt 1):L197-202

Secondary analysis of PROWESS study

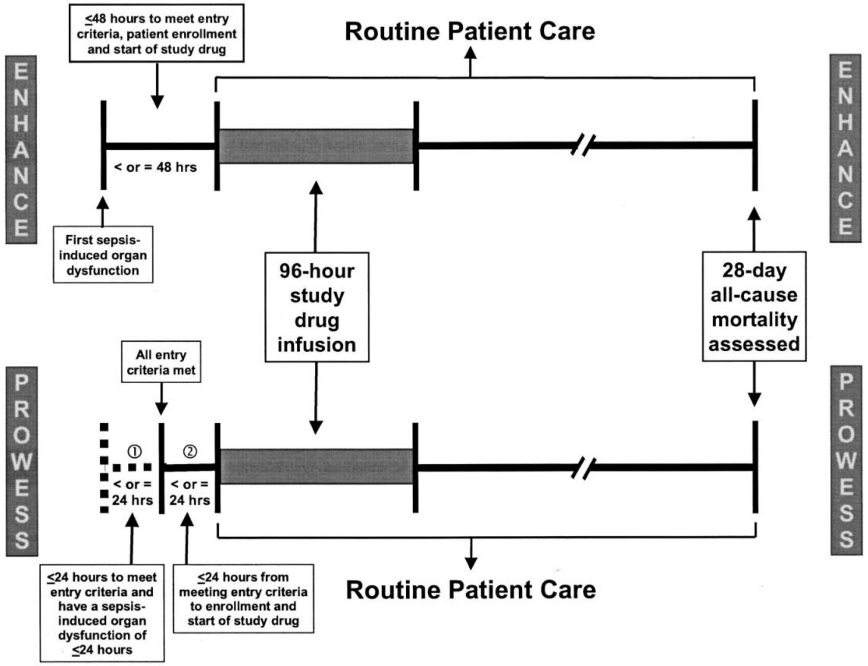


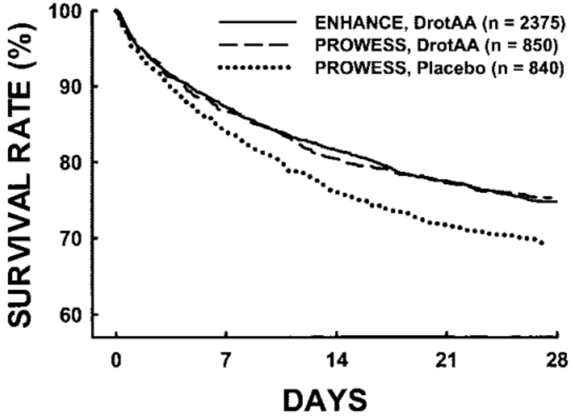
Intensive Care Med 2003;29:894-903

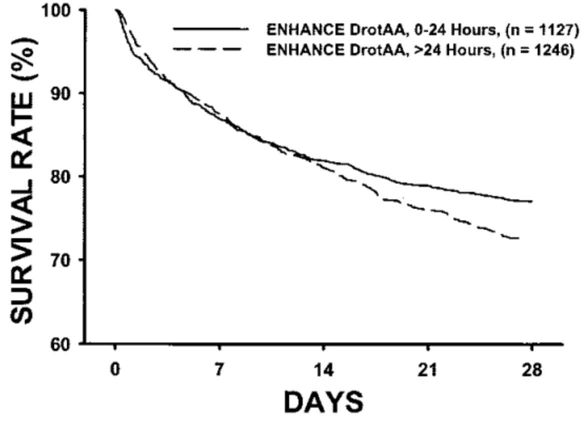
ENHANCE trial

Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment*

Jean-Louis Vincent, MD, PhD, FCCM; Gordon R. Bernard, MD; Richard Beale, MD; Christopher Doig, MD; Christian Putensen, MD, PhD; Jean-Francois Dhainaut, MD, PhD; Antonio Artigas, MD, PhD; Roberto Fumagalli, MD; William Macias, MD, PhD; Theressa Wright, MD; Kar Wong, PhD; David P. Sundin, PhD; Mary Ann Turlo, RN, MSc; Jonathan Janes, MRCP; for the ENHANCE Study Group







ADDRESS trial

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

Edward Abraham, M.D., Pierre-François Laterre, M.D., Rekha Garg, M.D., Howard Levy, M.D., Ph.D., Deepak Talwar, M.D., Benjamin L. Trzaskoma, M.S., Bruno François, M.D., Jeffrey S. Guy, M.D., Martina Brückmann, M.D., Álvaro Rea-Neto, M.D., Rolf Rossaint, M.D., Dominique Perrotin, M.D., Armin Sablotzki, M.D., Ph.D., Nancy Arkins, R.N., Barbara G. Utterback, M.S., M.B.A., and William L. Macias, M.D., for the Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group*

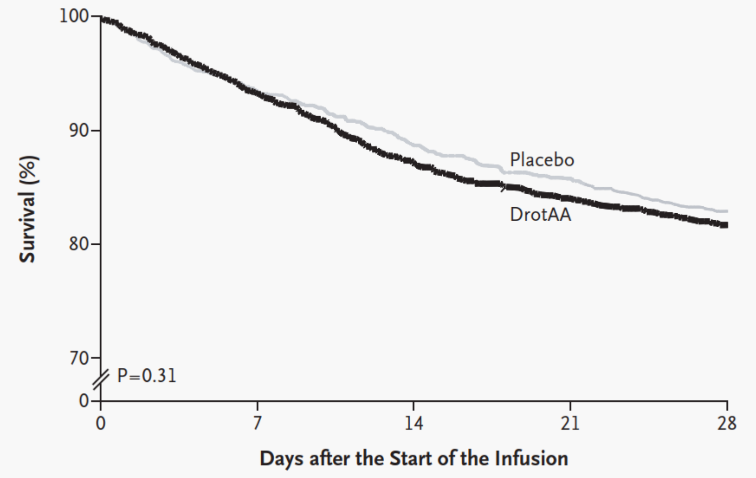


Figure 2. Kaplan–Meier Estimates of Survival among 1316 Patients with Severe Sepsis in the Drotrecogin Alfa (Activated) (DrotAA) Group and 1297 Patients in the Placebo Group.
There was no significant difference between the treatment groups in survival at 28 days (P=0.31 by the log-rank test).

Table 3. Adverse Events.*

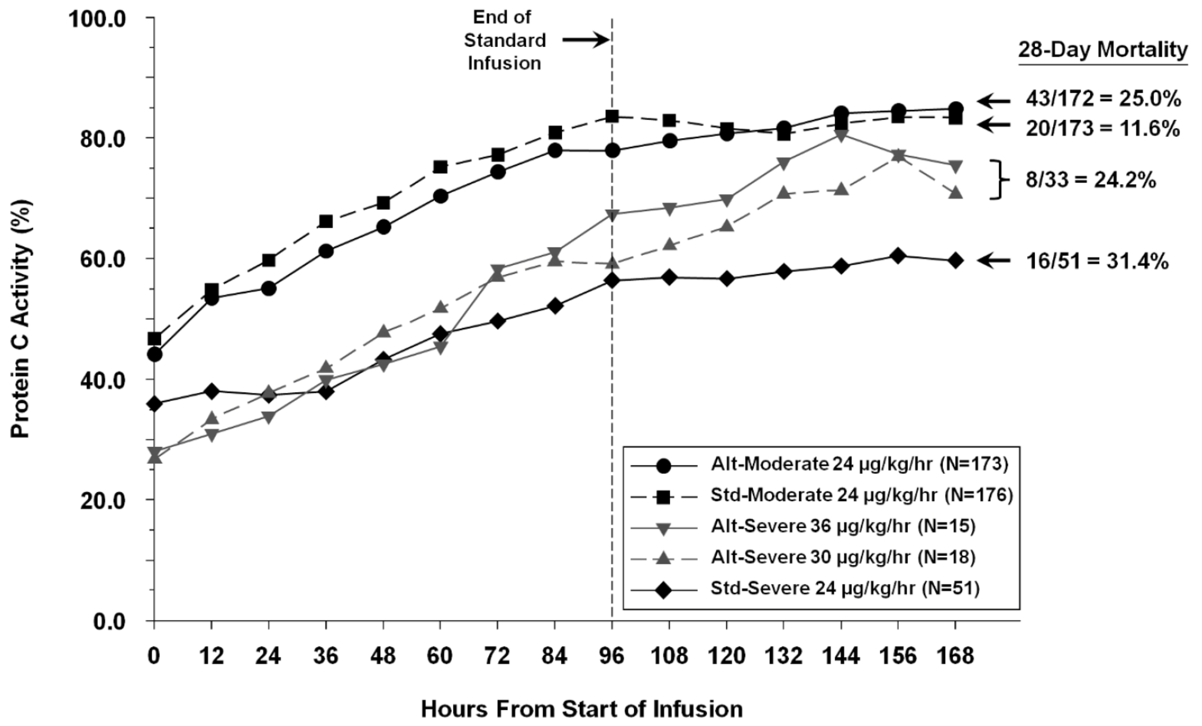
Event	Placebo (N=1293)	DrotAA (N=1317)	P Value
	no. (%)		
Days 0–6 (infusion period)			
Any serious adverse event	78 (6.0)	75 (5.7)	0.71
Serious bleeding events	15 (1.2)	31 (2.4)	0.02
Bleeding involving the central nervous system	3 (0.2)	4 (0.3)	0.72
Serious nonbleeding events	66 (5.1)	46 (3.5)	0.04
Days 0–28			
Any serious adverse event	183 (14.2)	182 (13.8)	0.81
Serious bleeding events	28 (2.2)	51 (3.9)	0.01
Bleeding involving the central nervous system	5 (0.4)	6 (0.5)	0.79
Any bleeding event leading to transfusion	44 (3.4)	90 (6.8)	<0.001
Serious nonbleeding events	168 (13.0)	143 (10.9)	0.09

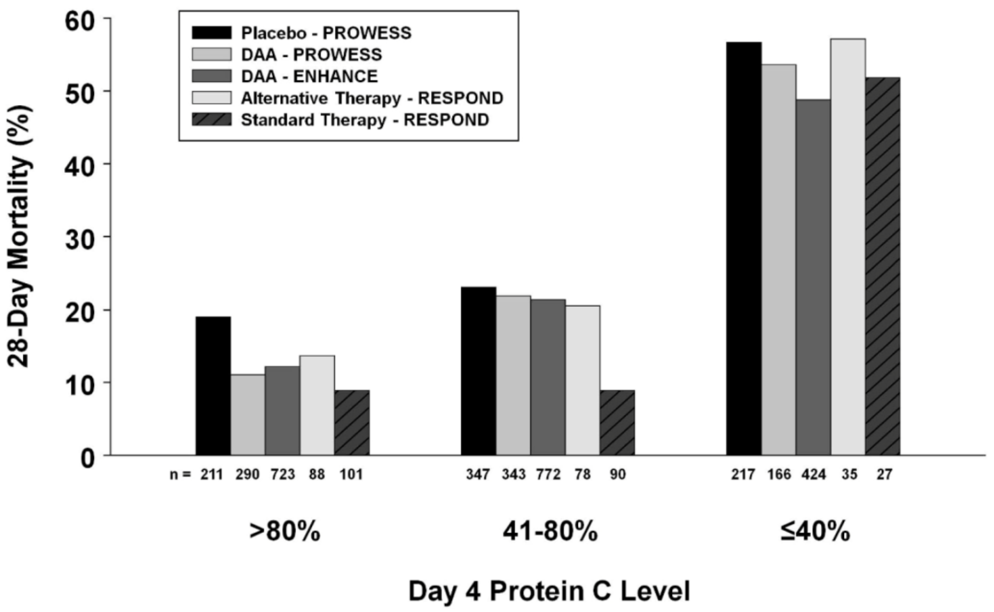
N Engl J Med 2005;353:1332-41

RESPOND trial

Randomized trial evaluating serial protein C levels in severe sepsis patients treated with variable doses of drotrecogin alfa (activated)

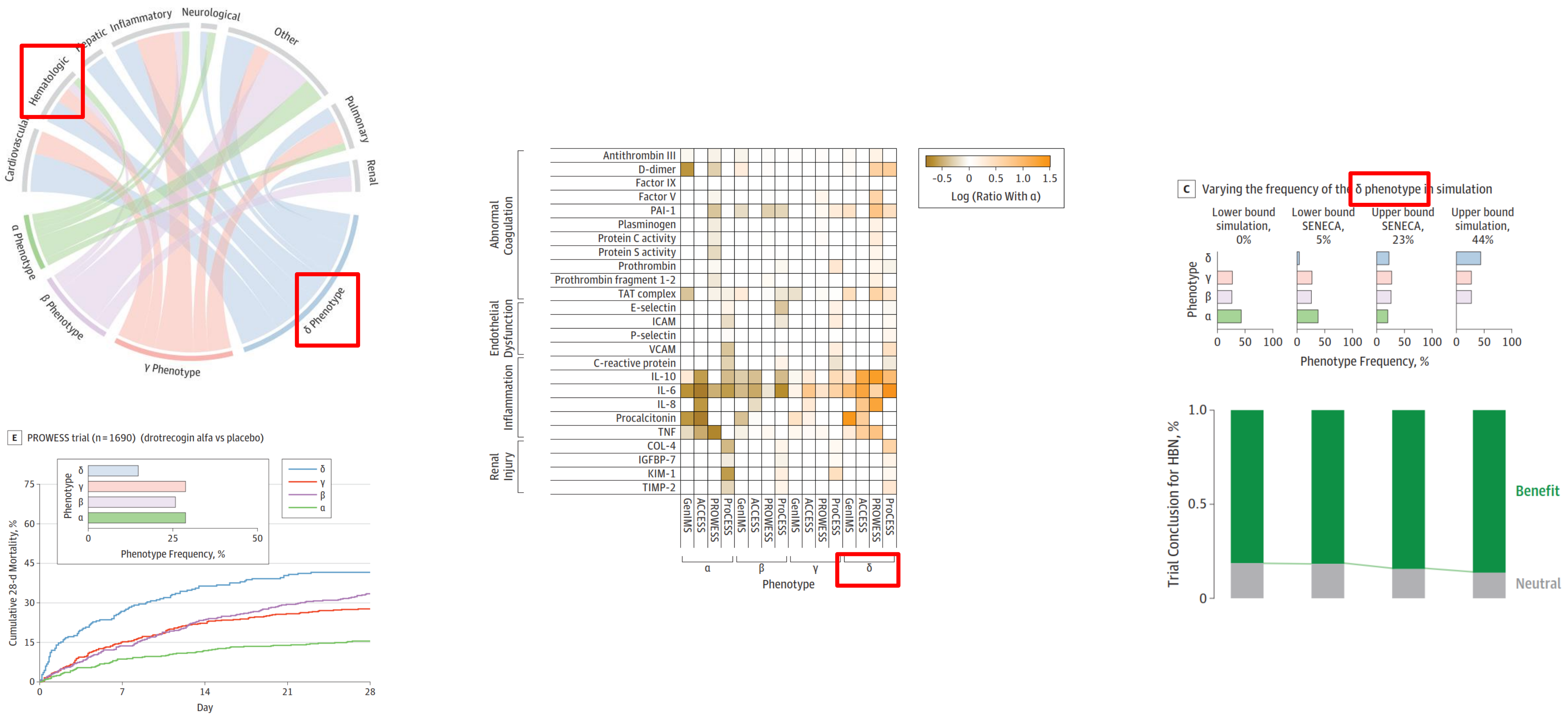
Andrew F Shorr[1*], Jonathan M Janes[2], Antonio Artigas[3], Jyrki Tenhunen[4], Duncan LA Wyncoll[5], Emmanuelle Mercier[6], Bruno Francois[7], Jean-Louis Vincent[8], Burkhard Vangerow[2], Darell Heiselman[2], Amy G Leishman[2], Yajun E Zhu[2], Konrad Reinhart[9], for the RESPOND investigators





Crit Care 2010;14:R229

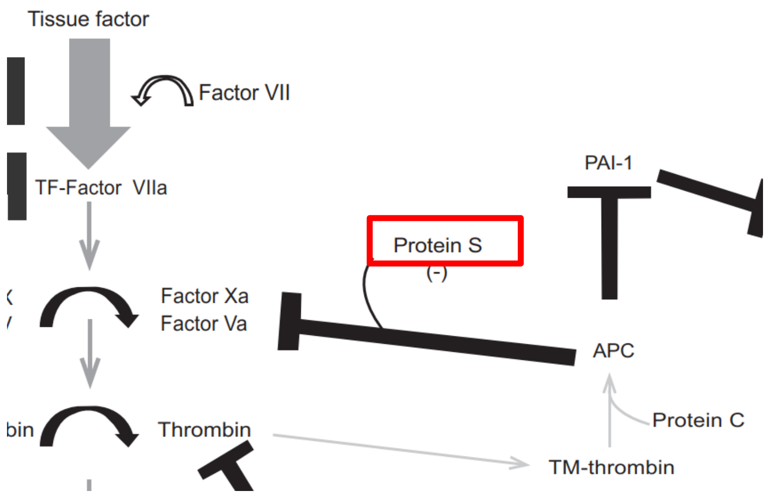
Clinical phenotypes for sepsis by machine learning



JAMA 2019;321:2003-17

Protein S

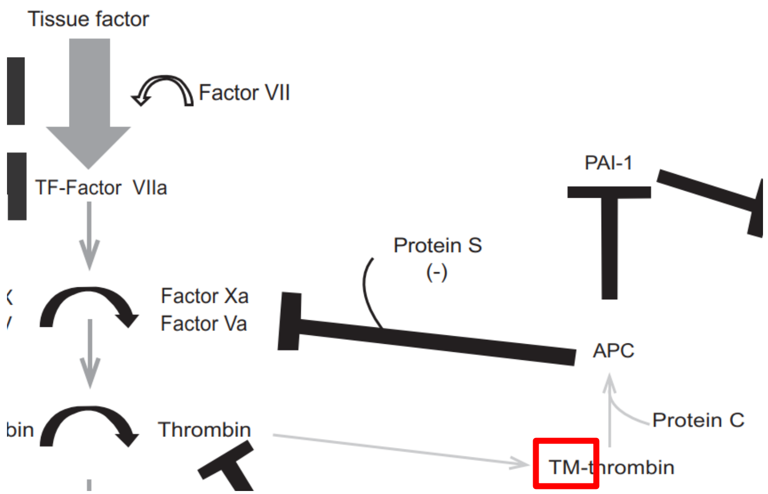
- Acts as cofactor for APC, enhancing APC activity by several-fold
- Ameliorates LPS-mediated lung injury in mouse model
- IP injection of protein S alone or in combination with APC followed by IT instillation of LPS → reduction in lung cytokines and chemokines
- Protein S did not alter thrombin-antithrombin complex measurements



Curr Pharm Biotechnol 2011;12:1481-96

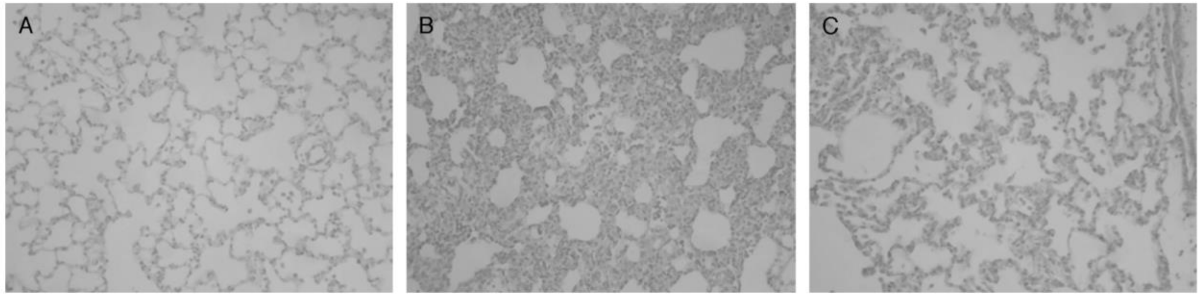
TM

- Transmembrane protein responsible for binding thrombin and APC
- Modulates inflammation and acute lung injury: patients with sepsis and ARDS have elevated plasma levels of soluble TM → worse clinical outcomes and multiple organ dysfunction
- Soluble TM < less effective inhibitor of platelet and fibrinogen activation compared to full-length TM

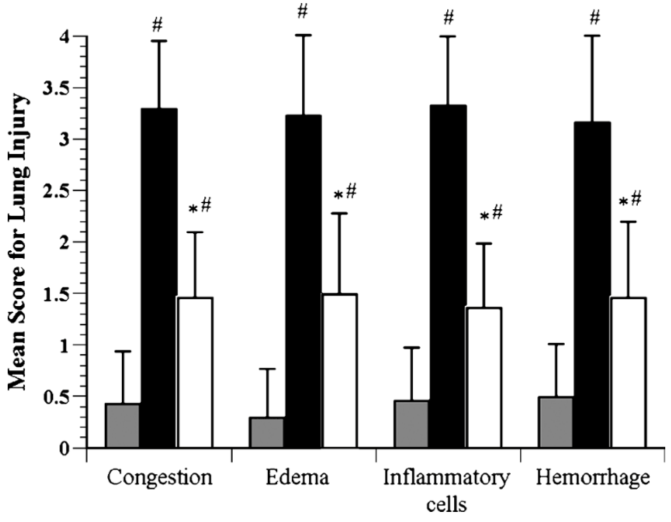


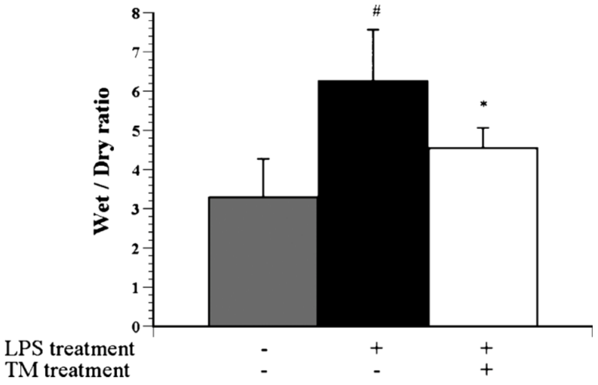
Curr Pharm Biotechnol 2011;12:1481-96

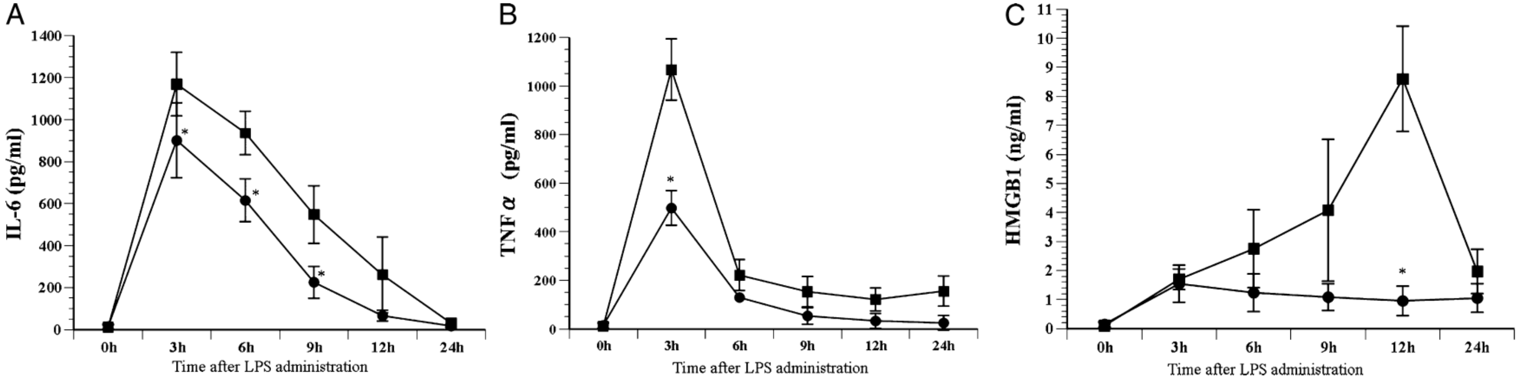
Recombinant TM in LPS-induced sepsis



Saline | LPS | TM + LPS







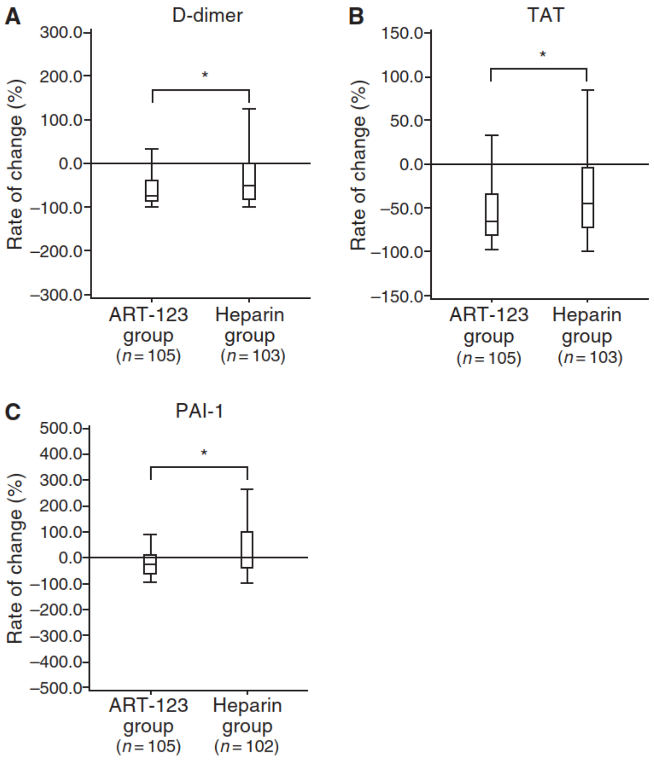
Shock 2010;33:282-8

ART-123

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***

	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)



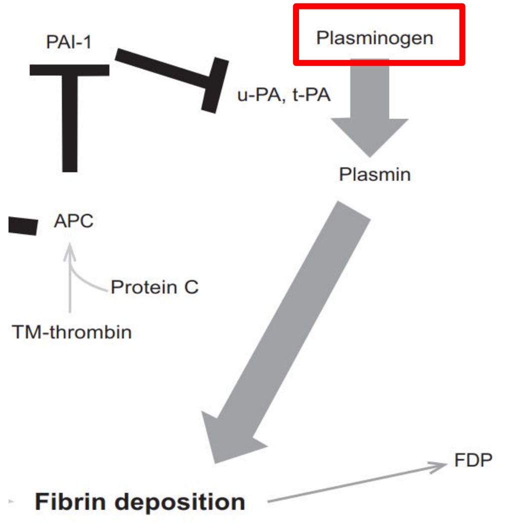
Plasminogen activator (PA)

- Fibrin formation via TF and PC pathways is normally balanced by fibrin degradation through plasminogen system

- Sepsis and ARDS → inhibition of fibrinolysis through increase in PA inhibitor (PAI-1) activity

- PA is present in two forms: urokinase-type (uPA) and tissue-type (tPA)

- uPA must bind to PA receptor for activation, tPA does not require binding to cell surface receptor for activation



Imbalance between coagulation and fibrinolysis

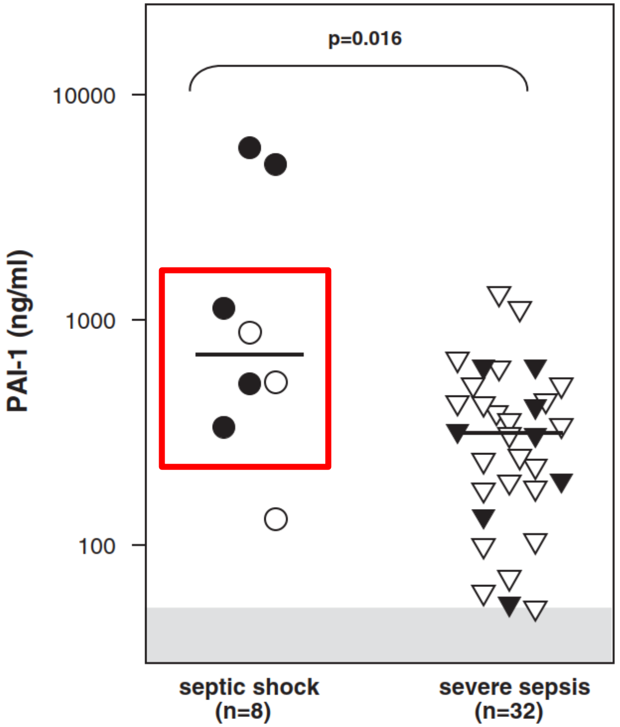


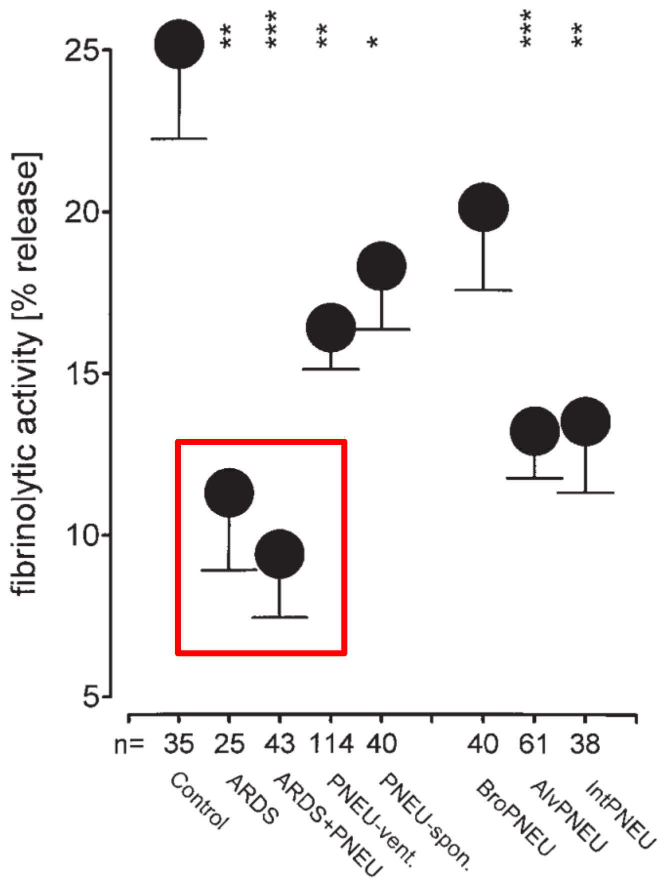
Table 2 Correlations of TAFI and PAI-1 with coagulation and fibrinolysis parameters

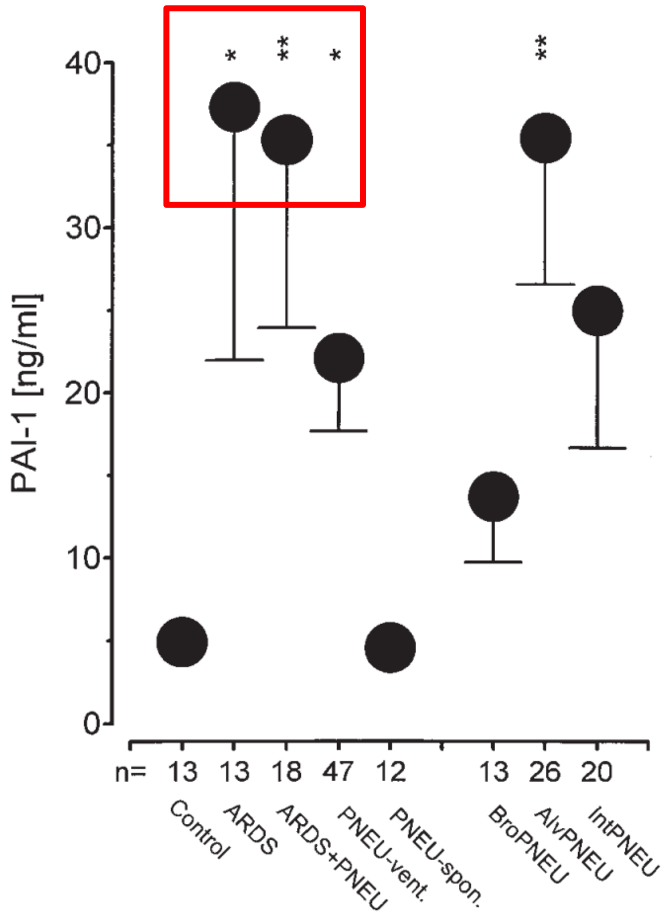
	TAFI		PAI-1	
	r	*p*	*r*	*p*
TAT	−0.126	0.436	0.660	<0.0001
PAP	0.137	0.397	0.046	0.777
$R_{(TAT / PAP)}$	−0.222	0.168	0.550	<0.0001
Fbg	0.429	0.006	−0.402	0.010
FII:C	0.670	<0.0001	−0.381	0.015
FXI:C	0.520	<0.0001	−0.323	0.043

TAFI: thrombin-activatable fibrinolysis inhibitor, PAI-1: plasminogen activator inhibitor type 1, TAT: thrombin–antithrombin complexes, PAP: plasmin–α_2-antiplasmin-complexes, $R_{(TAT / PAP)}$: (TAT / PAP) * 100, Fbg: fibrinogen, FII:C: factor II clotting activity; *r*: Spearman rank coefficient of correlation (corrected for multiple testing using Bonferroni corrections), $p<0.01$ denotes statistical significance.

Thromb Res 2006;118:205-12

BALF fibrinolytic activity

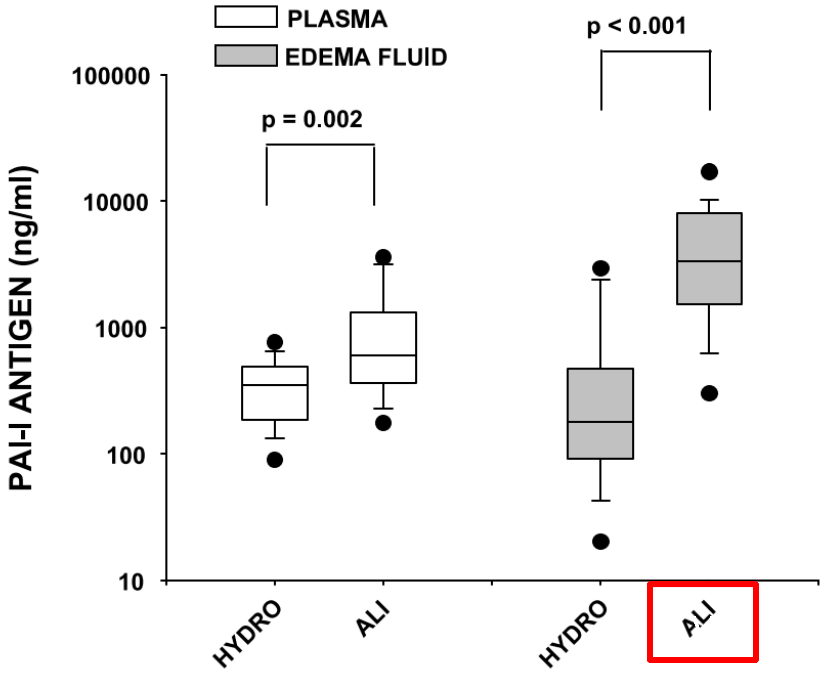


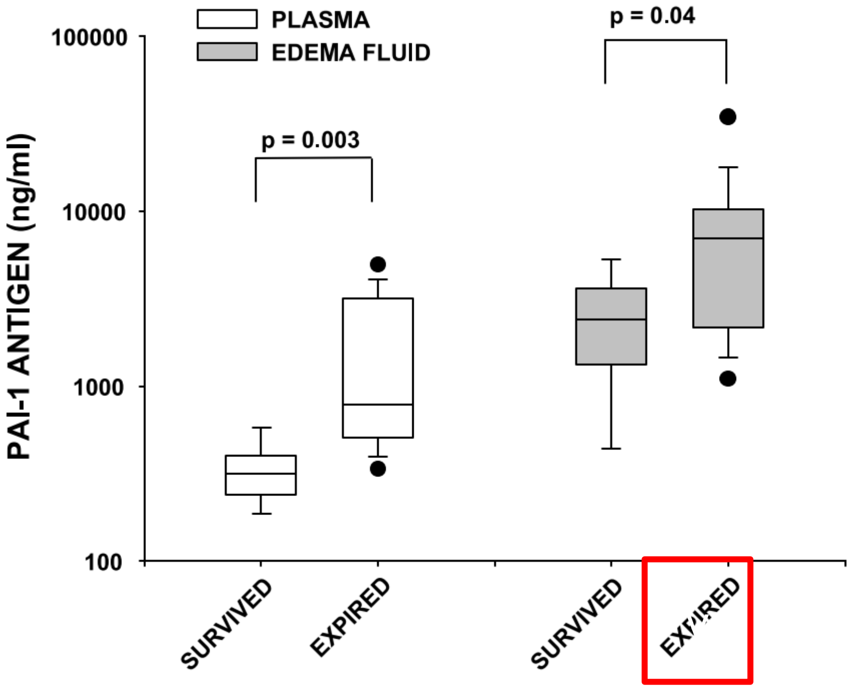


Am J Respir Crit Care Med 2000;161(2 Pt 1):454-62

중앙대학교병원
CHUNG-ANG UNIVERSITY HOSPITAL

PAI-1 in pulmonary edema fluid





Am J Physiol Lung Cell Mol Physiol 2003;285:L20-8

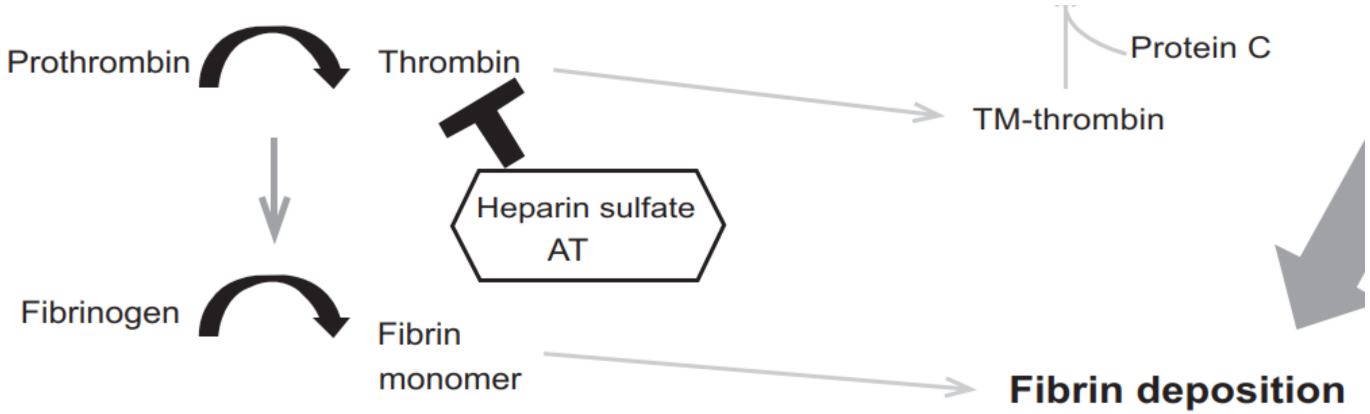
중앙대학교병원
CHUNG-ANG UNIVERSITY HOSPITAL

Thrombin and fibrin formation

- Normal coagulation and fibrinolytic homeostasis is altered in sepsis and ARDS, favoring **procoagulant**, **antifibrinolytic** state

- Results in formation and accumulation of thrombin and fibrin in microvasculature → development of multiorgan failure and shock

- One potential strategy: inhibit thrombin formation → halt formation of fibrin



Antithrombin (AT)

- Endogenous protease inhibitor that binds to proteoglycans and glycosaminoglycans (heparins and heparin sulfates) on cell surface of endothelial cells

- AT neutralizes thrombin and several other proteinases of coagulation pathway

- Intravenous high-dose AT prevented endotoxin-mediated inflammation, lung vascular injury and coagulation abnormalities (reduced platelet count and plasma fibrinogen levels)

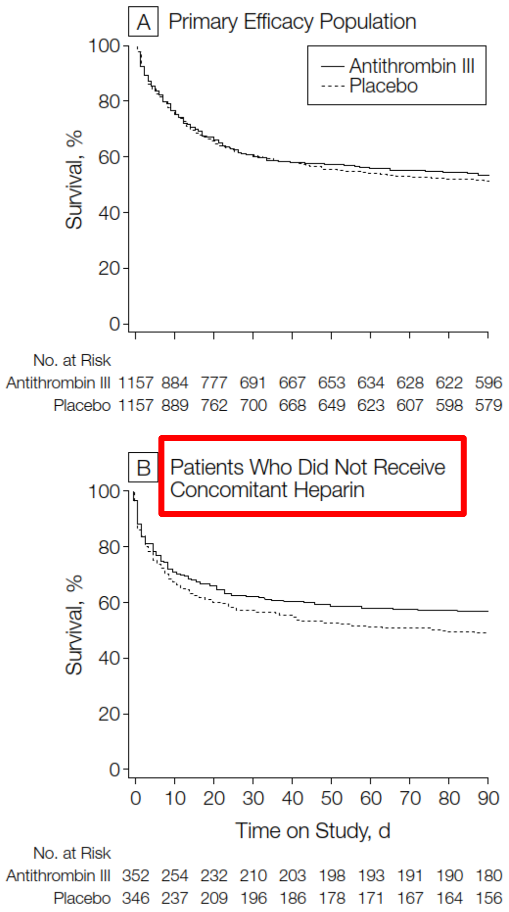
- Intravenous AT has also been demonstrated to decrease vascular injury and permeability

- In patients with sepsis, low plasma levels of AT have been shown to be associated with development of ARDS

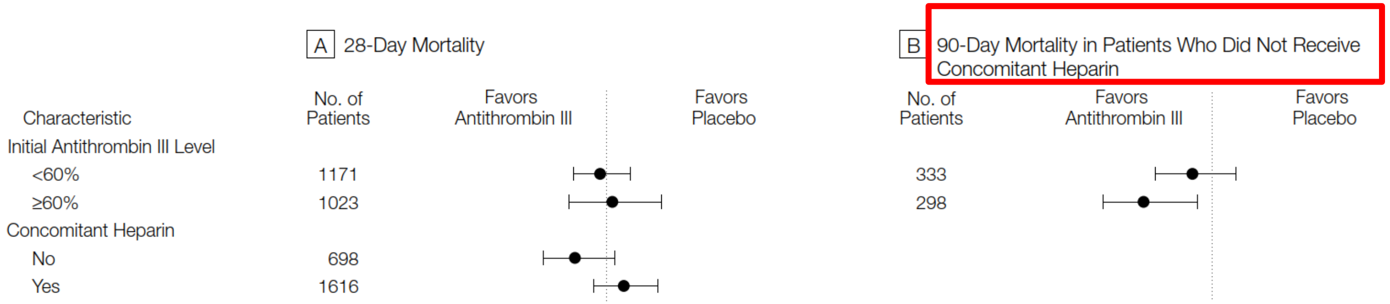
KyberSept trial

High-Dose Antithrombin III in Severe Sepsis

A Randomized Controlled Trial



28 day mortality in AT III group was 38.9 vs 38.7% in placebo group (p = 0.94)



JAMA 2001;286:1869-78

KyberSept trial – subgroup analysis

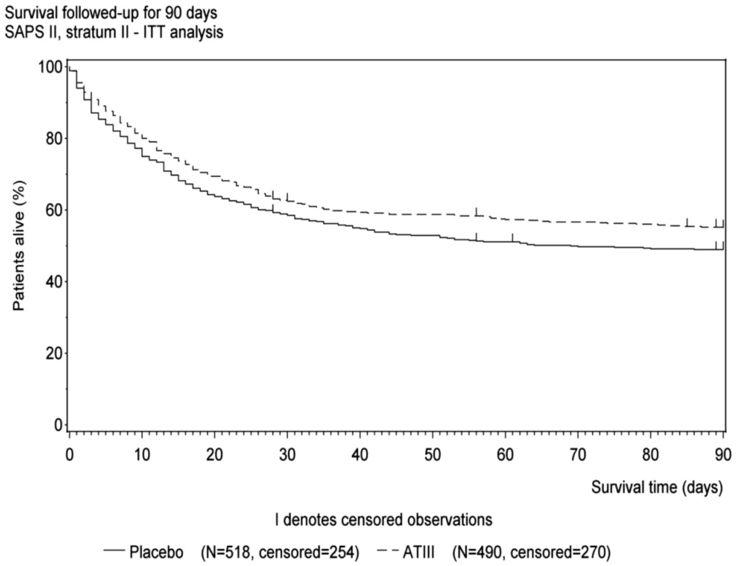


Table 3. Mortality per treatment group in different Simplified Acute Physiology Score (SAPS) II strata (intention-to-treat [ITT] population)

End Point	SAPS II Stratum[a]	Placebo, No. (%)	ATIII, No. (%)	Risk ratio: ATIII/Placebo (95% CI[b])
28 days	I: Moderate risk (<30%)[c]	61/318 (19.2)	73/334 (21.9)	1.139 (0.841–1.543)
	II: High risk (30–60%)[d]	211/518 (40.7)	181/490 (36.9)	0.907 (0.776–1.059)
	III: Very high risk (>60%)[e]	176/321 (54.8)	196/333 (58.9)	1.074 (0.939–1.227)
	Overall	448/1,157 (38.7)	450/1,157 (38.9)	1.004 (0.907–1.113)[f]
56 days	I: Moderate risk (<30%)[c]	73/313 (23.3)	87/327 (26.6)	1.141 (0.871–1.493)
	II: High risk (30–60%)[d]	252/516 (48.8)	204/486 (42.0)	0.859 (0.750–0.985)
	III: Very high risk (>60%)[e]	193/321 (60.1)	207/331 (62.5)	1.040 (0.921–1.175)
	Overall	518/1,150 (45.0)	498/1,144 (43.5)	0.966 (0.882–1.059)[f]
90 days	I: Moderate risk (<30%)[c]	84/310 (27.1)	94/324 (29.0)	1.071 (0.834–1.374)
	II: High risk (30–60%)[d]	264/512 (51.6)	220/483 (45.5)	0.883 (0.777–1.005)
	III: Very high risk (>60%)[e]	206/321 (64.2)	213/330 (64.5)	1.006 (0.897–1.128)
	Overall	554/1,143 (48.5)	527/1,137 (46.4)	0.956 (0.877–1.043)[f]

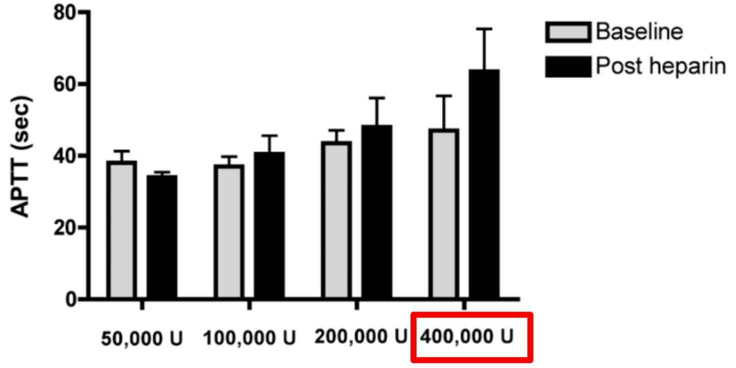
Heparin

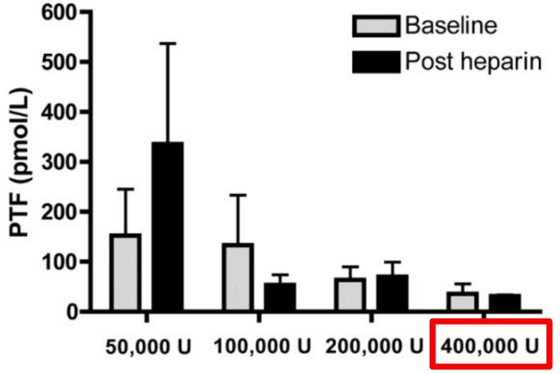
- Glycosaminoglycans that possess anti-inflammatory and anticoagulant effects
- Both endogenous (lung, blood) and exogenous heparin prevent formation of clots and extension of existing clots
- Exogeneous heparin inhibited eosinophil infiltration into lungs of sensitized guinea pigs
- LPS-induced inflammatory cell lung recruitment and serum cytokine markers → reduced with IV heparin or low-molecular weight heparin (LMWH)
- LMWH also attenuated lung injury in LPS-induced models in rats or sheep

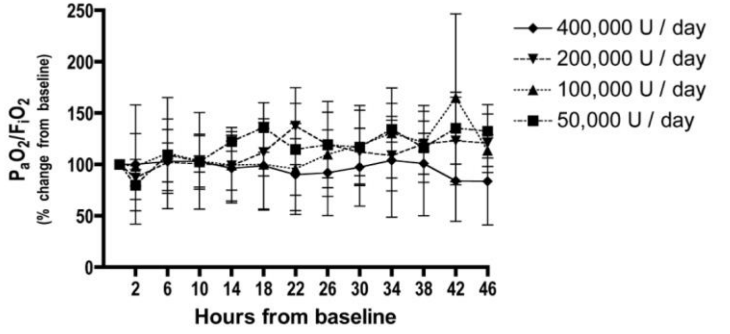
Nebulized heparin

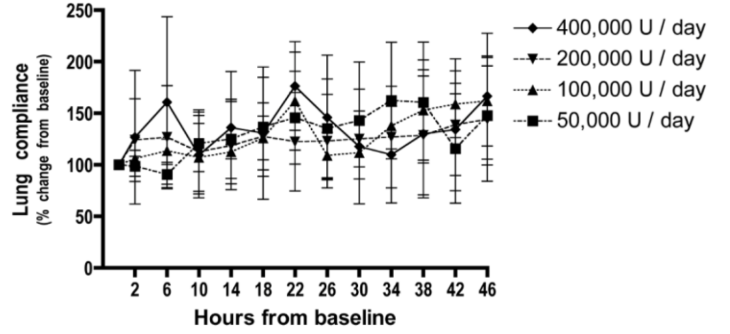
A phase 1 trial of nebulised heparin in acute lung injury

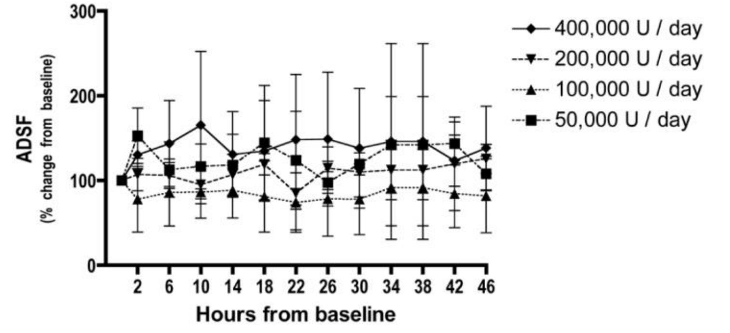
Barry Dixon[1], John D Santamaria[1] and Duncan J Campbell[2]











Clinical data of heparin in sepsis

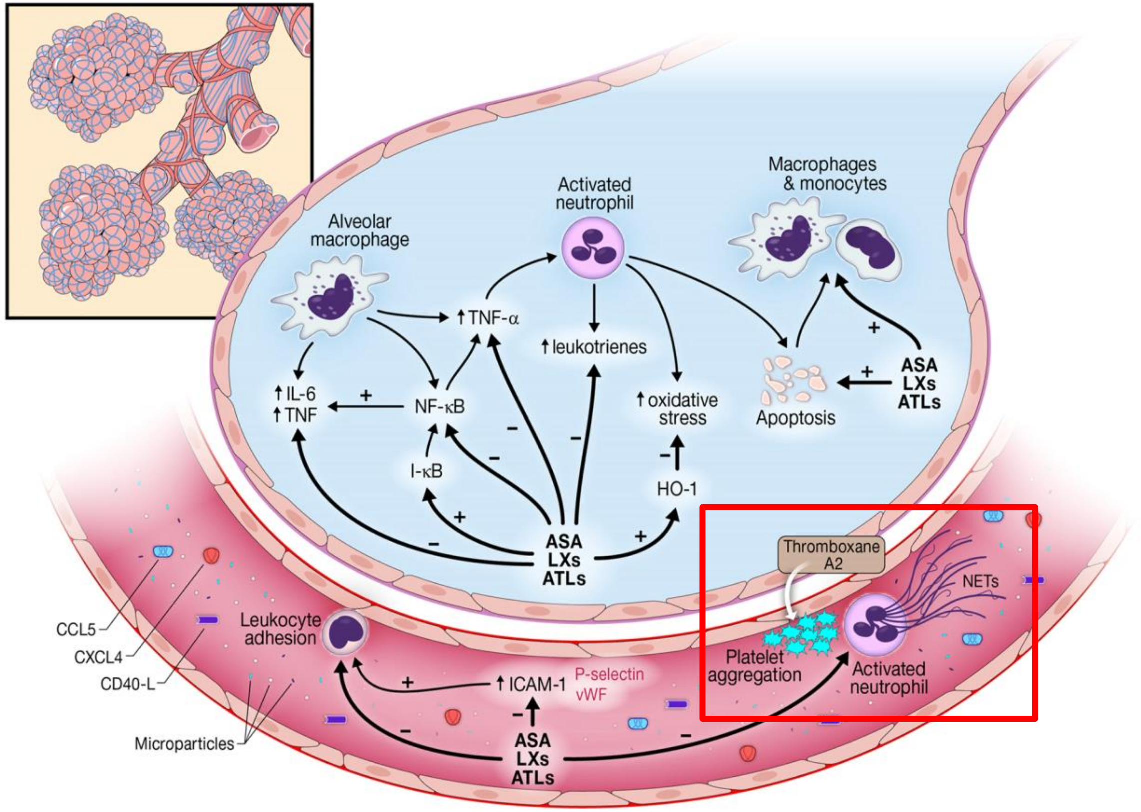
References	Year	Inclusion criteria	*n*	Design	Therapy	Primary outcome	Heparin	Control	*P* Value
Warren et al. (34) (KyberSept)	2001	Severe sepsis (sepsis 1.0)	2314/1155 in control group	Phase 3 RCT	Prophylactic treatment with UFH or LMWH (≤ 10 000 IU subcutaneous per day), and heparin flushes (IV of ≤ 2 IU/kg per hour)	28-day mortality	Control subgroup 38.7% **Heparin** 36.6%	**Non-heparin** 43.6%	0.94
Bernard et al. (26) (PROWESS)	2001	Severe sepsis (sepsis 1.0)	1690/840 in control group	Phase 3 RCT	Prophylactic treatment with a dose of UFH of up to 15,000 U per day	28-day mortality	Control subgroup **Heparin** 28%	**Non-heparin** 39%	0.005
Abraham et al. (30) (OPTIMIST)	2003	Severe sepsis (sepsis 1.0)	1754/992 in control group	Phase 3 RCT	At least 1 dose of UFH or LMWH	28-day mortality	Control subgroup **Heparin** 29.8%	**Non-heparin** 42.7%	0.88
Peng et al. (51)	2022	Sepsis-induced coagulopathy (sepsis 3.0)	1820	Retrospective analysis	UFH	28-day mortality	16.9%	37.7%	<0.001
Zou et al. (52)	2022	Sepsis (sepsis 3.0)	6646	Retrospective cohort study	Prophylactic use of UFH or enoxaparin 5000 IU subcutaneously	In-hospital mortality	14.9%	18.3%	<0.001

Front Immunol 2024;15:1495260

Neutrophil extracellular traps (NET)

- Playing important role in platelet-neutrophil interaction during immunothrombosis
- Released from neutrophil on contact with bacteria under certain circumstances (interaction with activated platelets or inflammatory stimuli)
- Platelet activation and aggregation → activation of coagulation pathway
- In septic patients, TF enclosed in NETs is released → thrombin generation
- NETs bind fXII → activation to intrinsic coagulation cascade

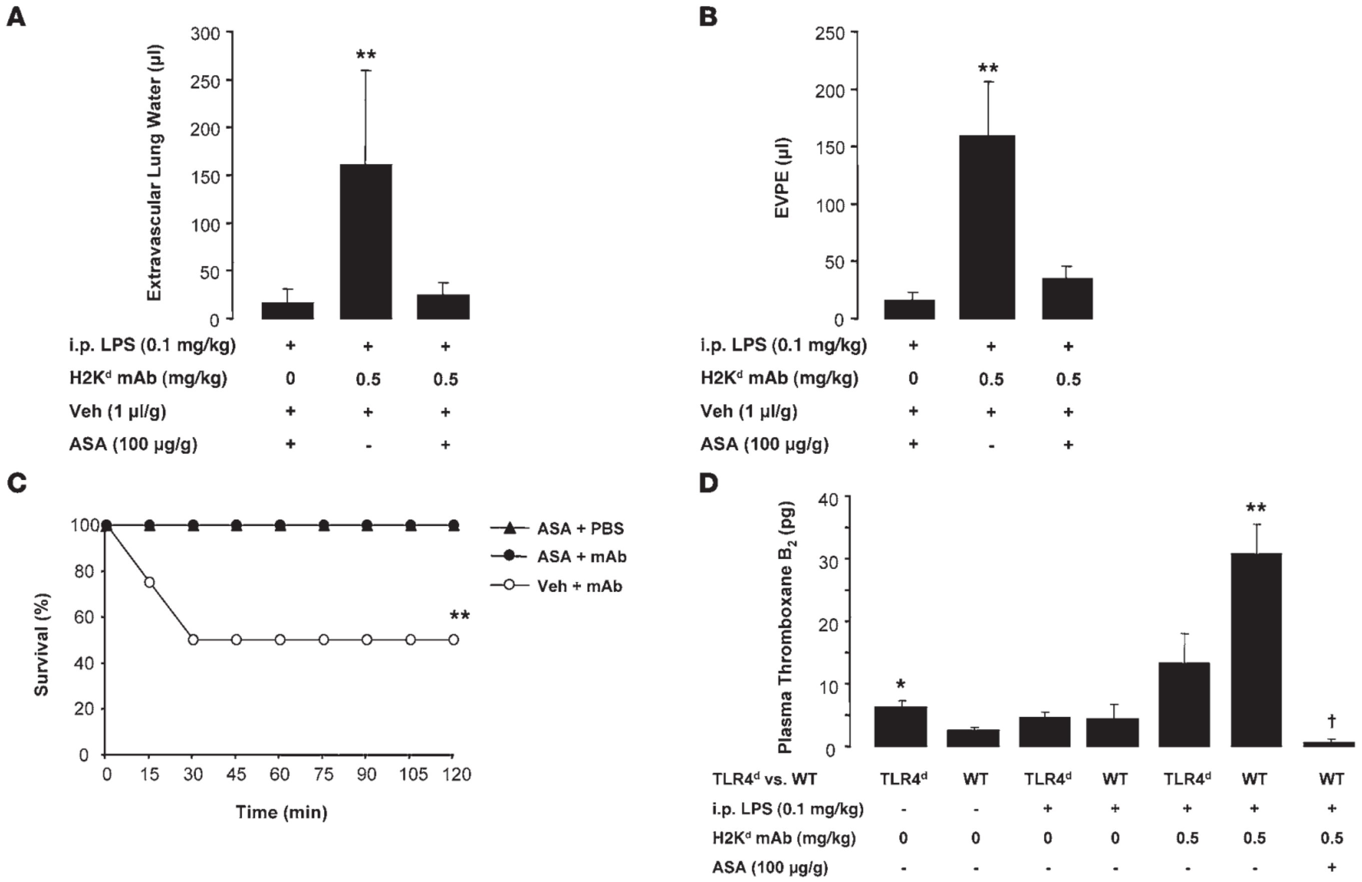
Platelets in pathogenesis of ARDS



In ARDS, platelets participate in NET activation through TLR4 engagement. Consequently, neutrophils are activated, with subsequent release of NETs in pulmonary capillaries, resulting in severe lung injury

Am J Physiol Lung Cell Mol Physiol 2015;309:L915-23

Aspirin in transfusion-related acute lung injury



J Clin Invest 2009;119:3450-61

Prehospitalization aspirin in ARDS

Association of prehospitalization aspirin therapy and acute lung injury: Results of a multicenter international observational study of at-risk patients*

Daryl J. Kor, MD; Jason Erlich, MD; Michelle N. Gong, MD; Michael Malinchoc, MS; Rickey E. Carter, PhD; Ognjen Gajic, MD; Daniel S. Talmor, MD; on behalf of U.S. Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG–LIPS)

Table 2. Univariate analysis of patient outcome by the presence or absence of aspirin administration

Outcome	Aspirin (n = 976)	No Aspirin (n = 2879)	*p*
Acute lung injury[a]	44 (4.5)	196 (6.8)	.010
Intensive care unit mortality[a]	39 (4.0)	134 (4.7)	.391
Hospital mortality[a]	63 (6.5)	180 (6.3)	.822
Intensive care unit length of stay[b]	2 (0–5)	2 (0–5)	.132
Hospital length of stay[b]	5 (4–9)	5 (3–10)	.930

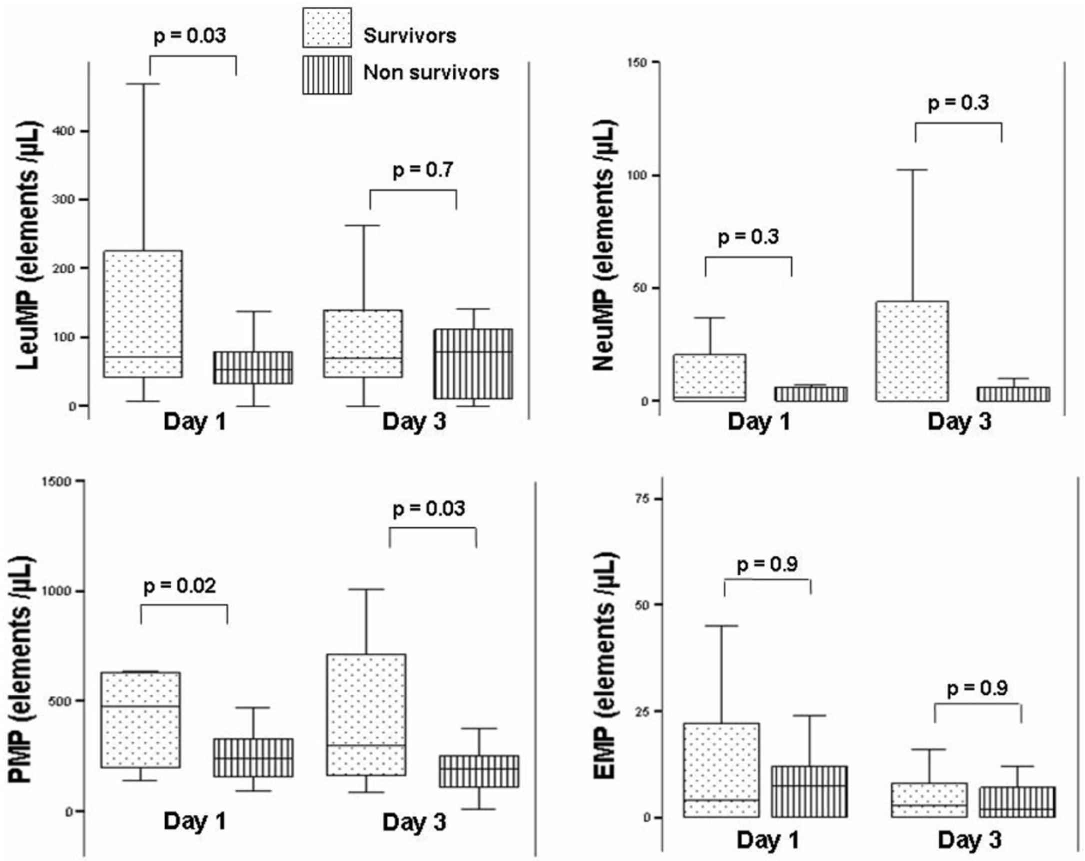
Table 4. Adjusted analyses evaluating the association between prehospitalization aspirin therapy and development of acute lung injury after stratifying by decile of aspirin propensity

Strata	Propensity Score Range[a]	Proportion Develop Acute Lung Injury on Aspirin	Proportion Develop Acute Lung Injury Without Aspirin	Odds Ratio	95% Confidence Interval	*p*
1 (n = 380)	0.019 to 0.035	0/3 (0%)	20/377 (5.0%)	N/A	N/A	—
2 (n = 382)	0.035 to 0.055	1/7 (14.3%)	23/375 (6.1%)	2.55	0.29 – 22.09	—
3 (n = 382)	0.055 to 0.080	1/16 (6.3%)	34/366 (9.3%)	0.65	0.08 – 5.08	—
4 (n = 381)	0.080 to 0.110	1/27 (3.7%)	26/354 (7.3%)	0.49	0.06 – 3.72	—
5 (n = 382)	0.111 to 0.159	2/56 (3.6%)	29/326 (8.9%)	0.38	0.09 – 1.64	—
6 (n = 382)	0.159 to 0.241	6/103 (5.8%)	18/279 (6.5%)	0.90	0.35 – 2.33	—
7 (n = 381)	0.241 to 0.333	4/122 (3.3%)	17/259 (6.6%)	0.48	0.16 – 1.47	—
8 (n = 381)	0.334 to 0.464	10/163 (6.1%)	7/218 (3.2%)	1.97	0.73 – 5.29	—
9 (n = 382)	0.464 to 0.627	4/211 (1.9%)	12/171 (7.0%)	0.26	0.08 – 0.81	—
10 (n = 381)	0.628 to 0.955	15/251 (6.0%)	9/130 (6.9%)	0.85	0.36 – 2.01	—
Overall (n = 3814)[b]	—	—	—	0.70	0.48 – 1.03	.072

Microparticles (MPs)

- Small vehicles modulating intracellular communication that participate in immunothrombosis
- Generated from many cell types: platelets, endothelial cells, polymorphonuclear neutrophils and lymphocytes
- Shed from precursor cells after triggering factors, mediators are secreted by MPs towards various target cells → intracellular information change
- Biomarkers and regulators of cell interactions in sepsis and multiorgan dysfunction syndrome
- In ARDS, MPs are implicated in inflammatory and coagulation response → conveying **beneficial** and **detrimental** effects

Circulating leukocyte MPs in ARDS



Sepsis-induced coagulopathy (SIC)

- Patients with overt DIC may have illness progression no longer amenable from anticoagulant therapy

- Hallmark: excessive suppression of fibrinolysis caused by overproduction of PAI-1

- Organ dysfunction often develops in SIC due to reduced tissue perfusion, while systemic bleeding is more common feature in non-sepsis DIC

- Hypofibrinogenemia is not common in sepsis and elevation in fibrin-related markers (FDP/D-dimer) is not associated with sepsis severity

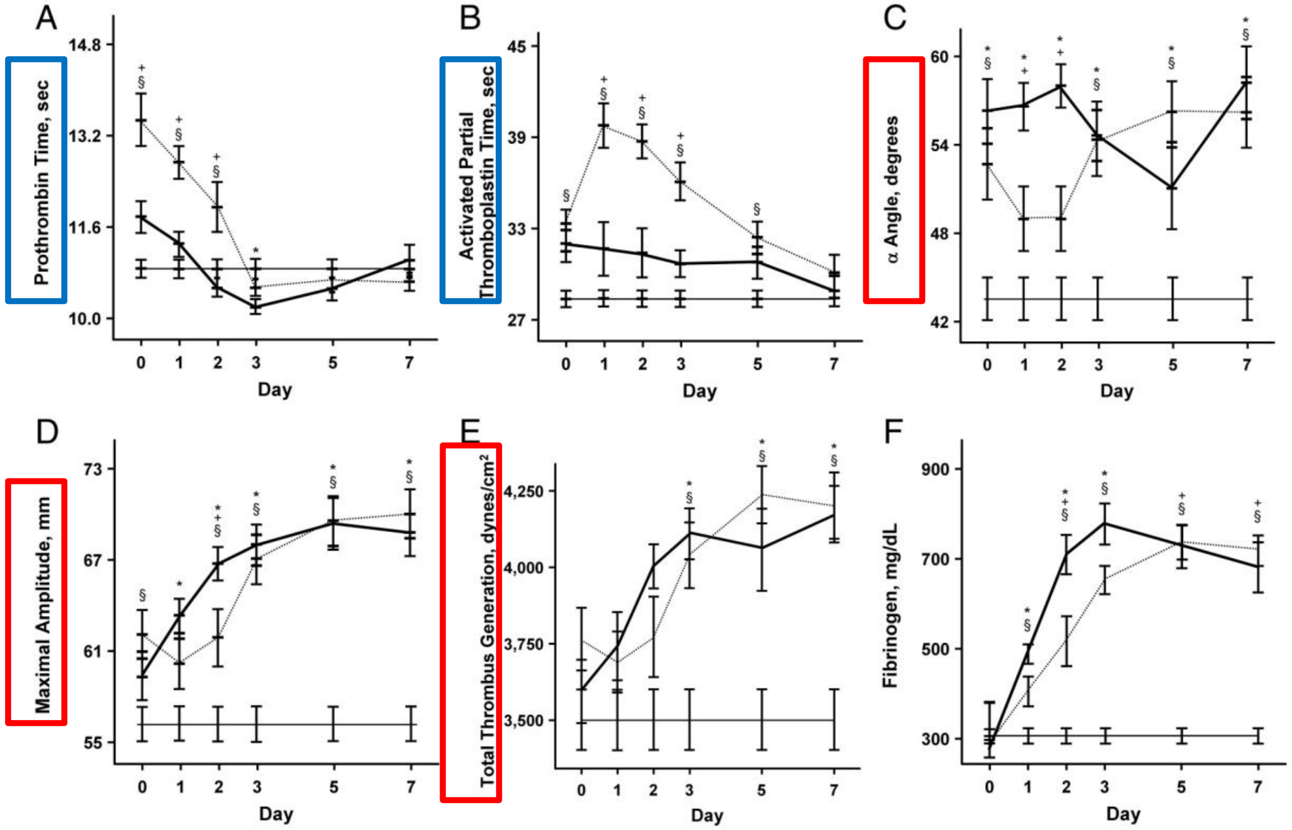
- In contrast, platelet count declines and PT prolongation are correlated with increased mortality

ISTH overt DIC and SIC scoring systems

		ISTH overt DIC	SIC
Item	Score	Range	Range
Platelet count (−10^9/L)	2	<50	< 100
	1	≧50, <100	≧100, <150
FDP/D-dimer	3	Strong increase	—
	2	Moderate increase	—
Prothrombin time (PT ratio)	2	≧6 s	(>1.4)
	1	≧3 s, <6 s	(>1.2, ≦1.4)
Fibrinogen (g/mL)	1	<100	—
SOFA score	2	—	≧2
	1	—	1
Total score for DIC or SIC		≧5	≧4

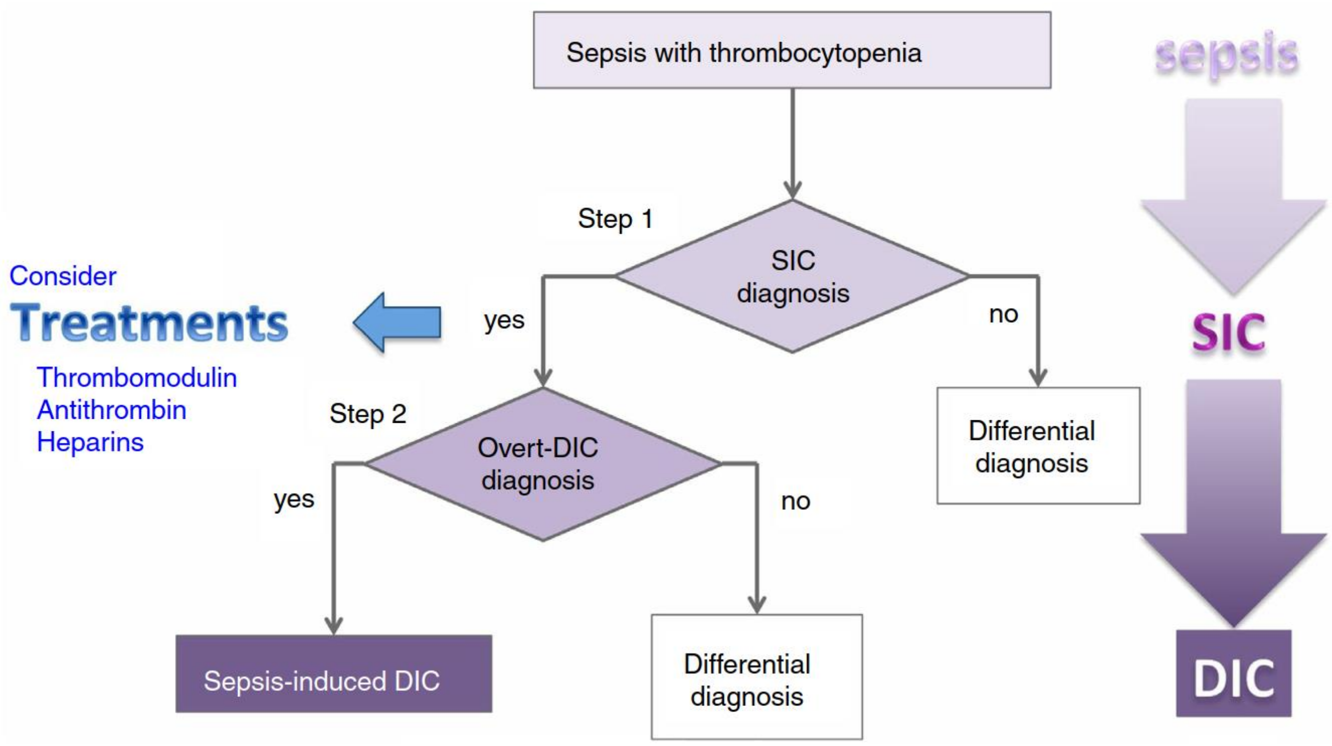
J Thromb Haemost 2019;17:1989-94

Thromboelastography (TEG)



J Trauma 2009;67:266-75

Two-step diagnosis for SIC



J Thromb Haemost 2019;17:1989-94

Take home message

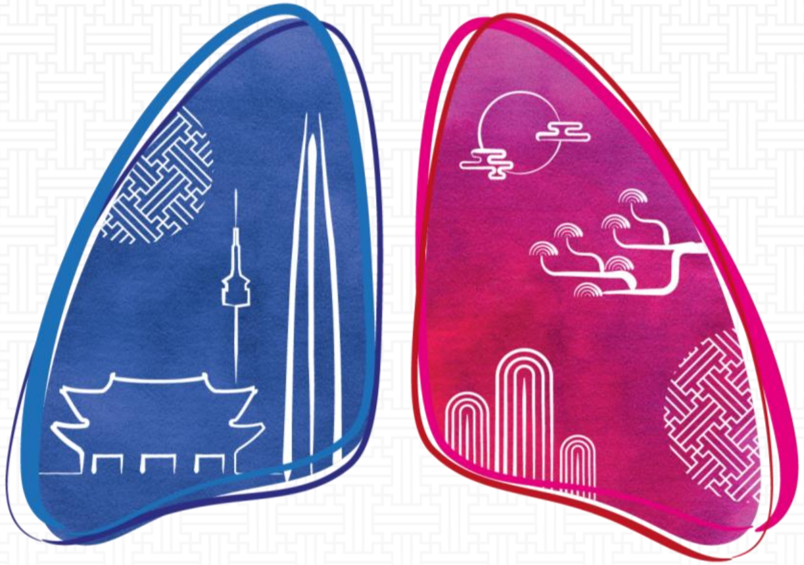
- ARDS and sepsis are characterized by profound imbalances between coagulation and fibrinolysis

- Potential therapeutic strategies could be aimed at reducing TF activity and enhancing fibrinolysis through use of various recombinant proteins

- In spite of improved outcomes in animal studies, there have been few successes in clinical trials

- Heterogenous populations, insufficient understanding of drug activity, interactions and metabolism in humans, optimization of timing, doses and duration of therapy, adverse effects

The Korean Academy of
Tuberculosis and Respiratory Diseases



KATRD

INTERNATIONAL CONFERENCE 2025

The 140th Congress of the Korean Academy of Tuberculosis and Respiratory Diseases

Where Lungs Meet Science

DATE **October 29**(Wed) ~ **31**(Fri), 2025

VENUE **LOTTE HOTEL WORLD,** Seoul, Korea

/ SAVE THE DATE /

KSCCM-ACCC 2026

April 30(Thu.) - **May 1**(Fri.), 2026

BEXCO Busan, Convention Hall

ACCC 2026 Acute and Critical Care Conference

The Korean Society of Critical Care Medicine

Thank you for your attention !!!