

Pulmonary Medicine

Grand Rounds

1/18/02

“Coagulopathies in Intensive
Care Medicine”

Marcus E. Carr, Jr., MD, PhD

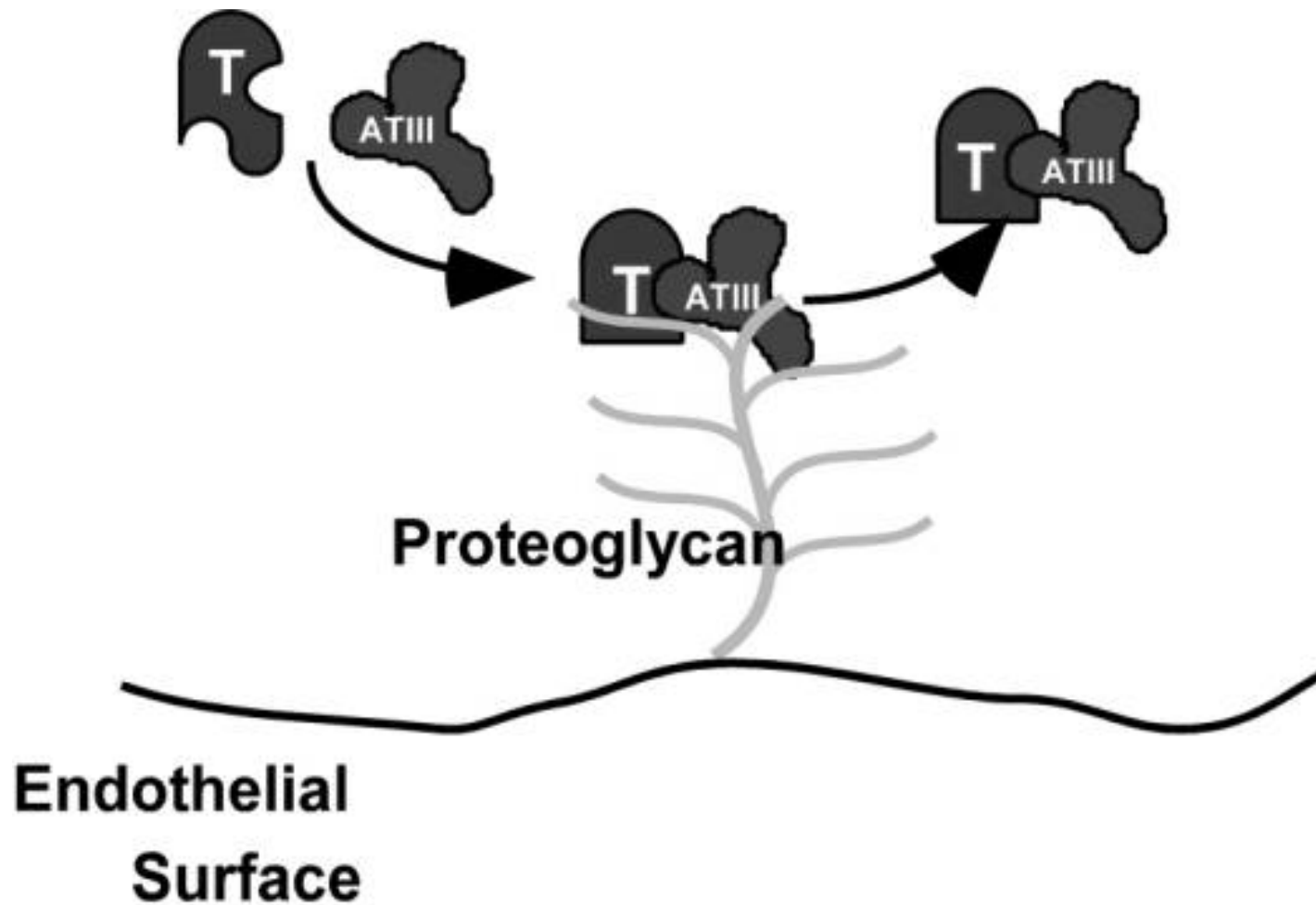
“Coagulopathies in Intensive Care Medicine”

Activated Recombinant

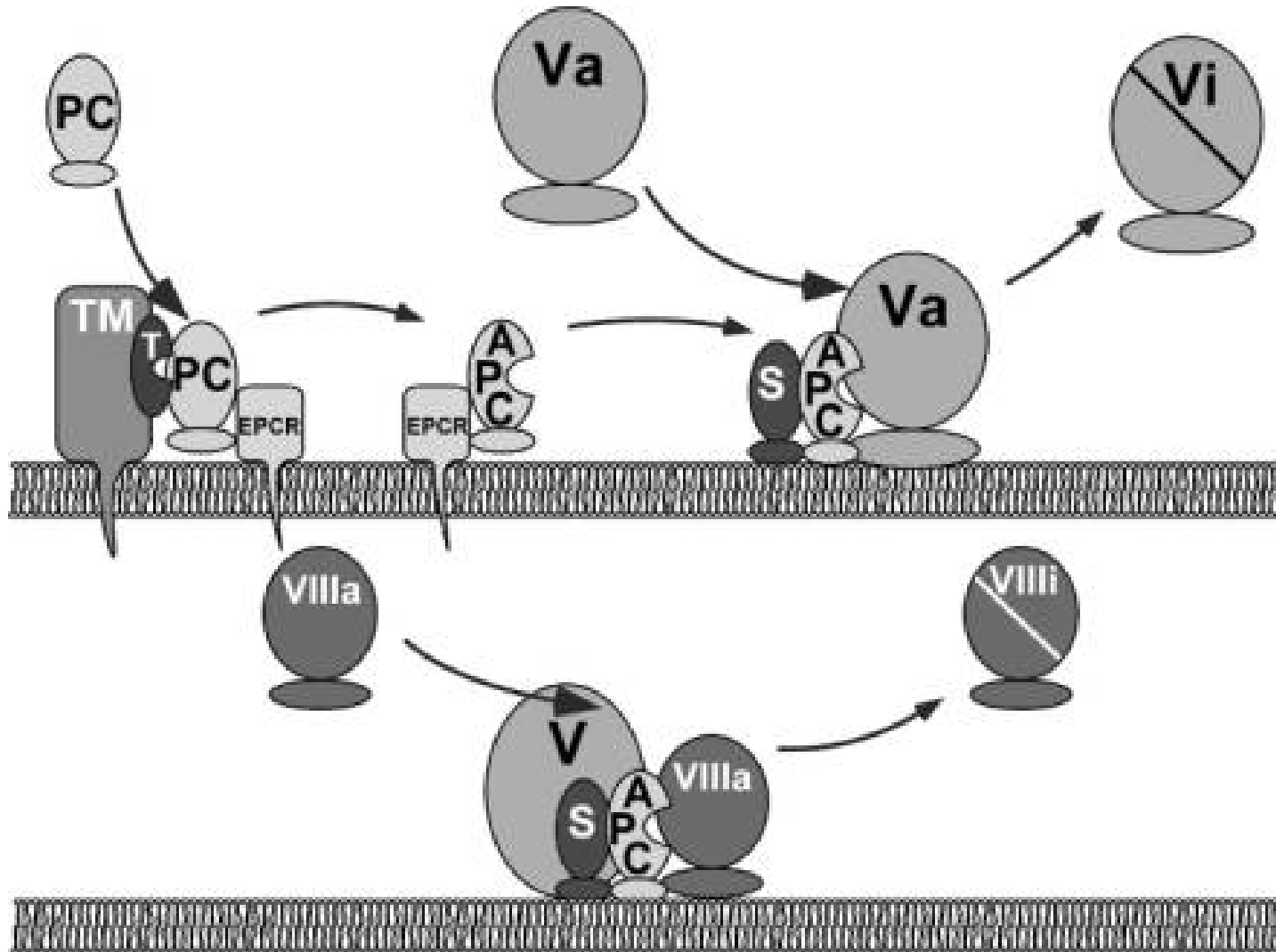
Protein C for

Control of Acute, Systemic
Inflammation and Coagulation

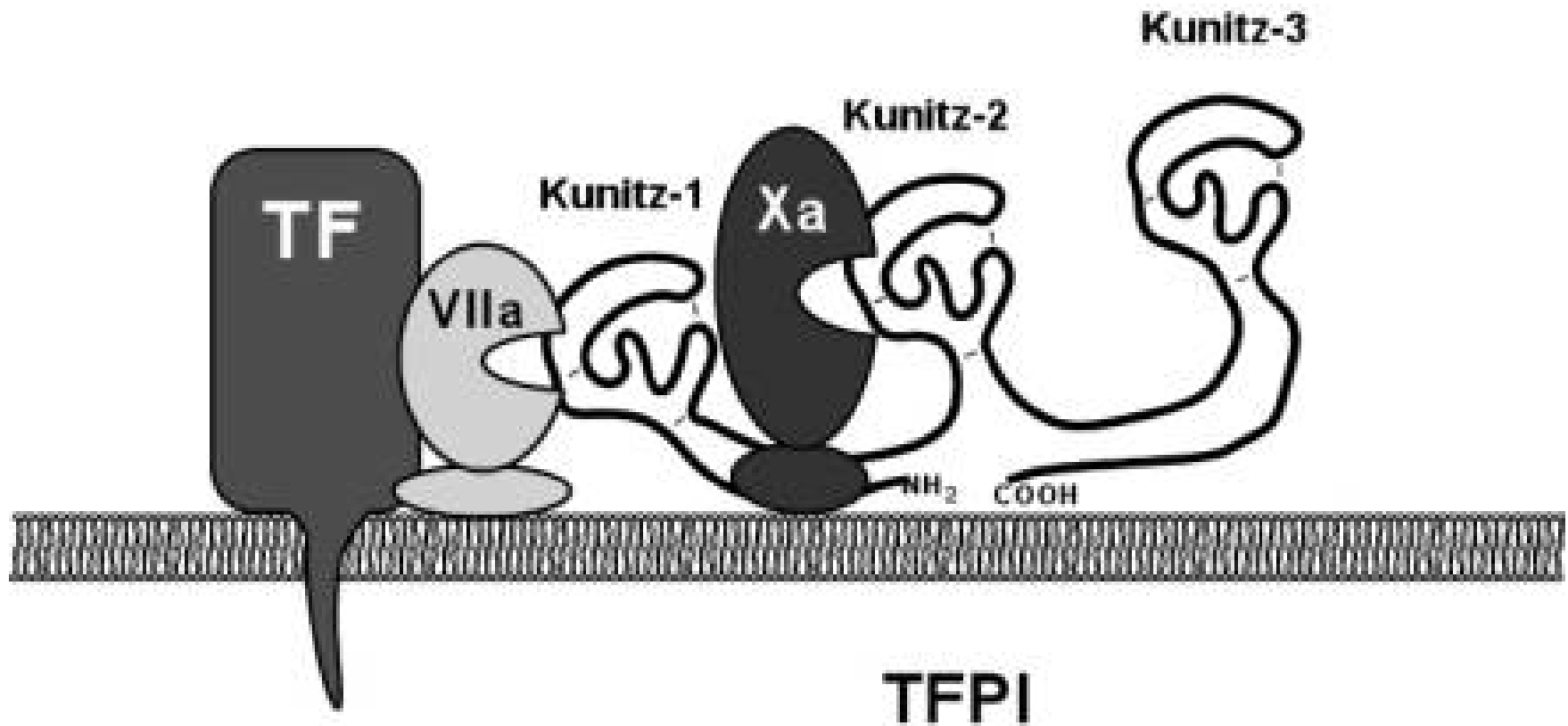
Mechanism of Action of ATIII



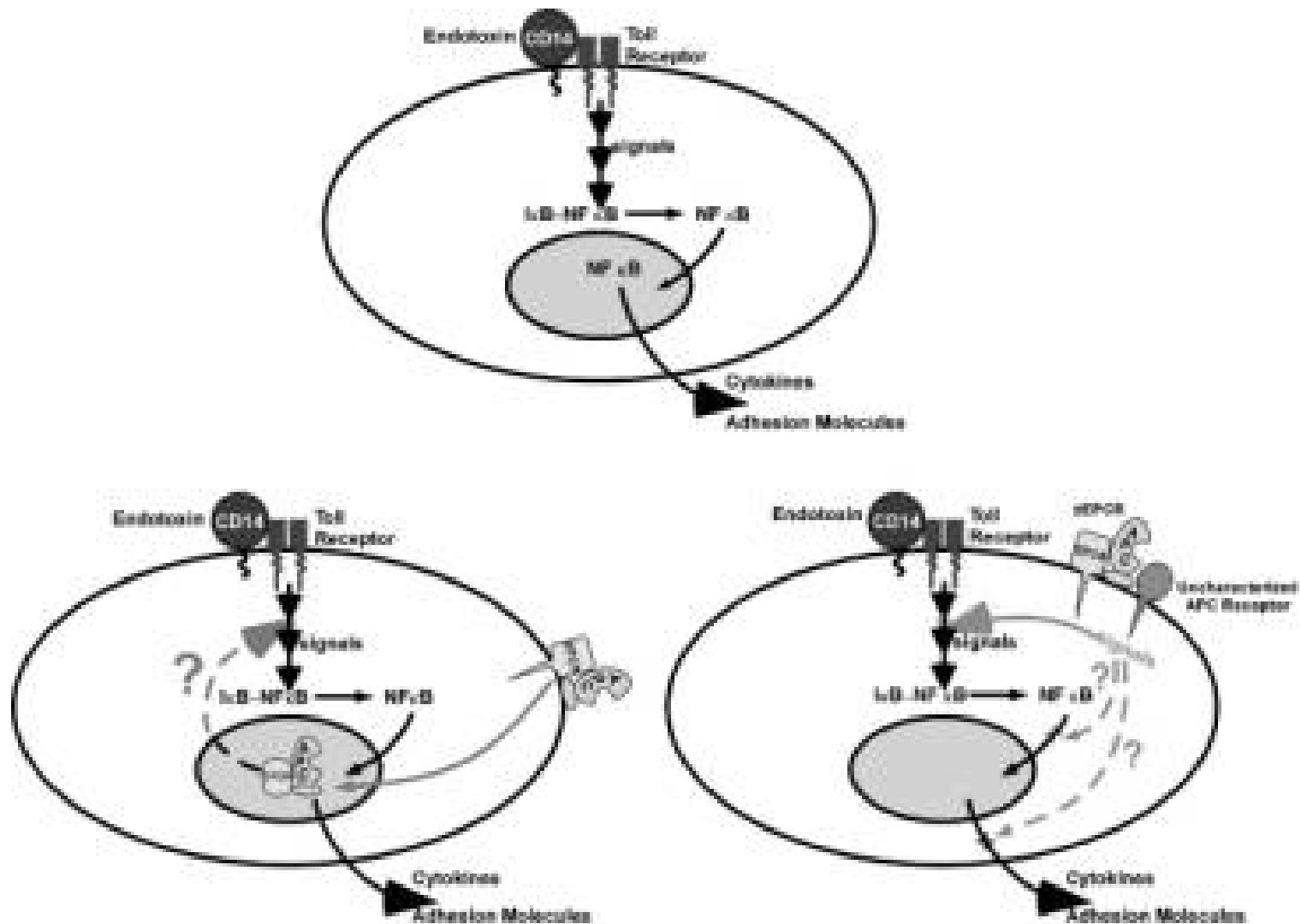
Protein C Pathway



Tissue Factor Pathway Inhibitor



Inhibition of Inflammation by APC



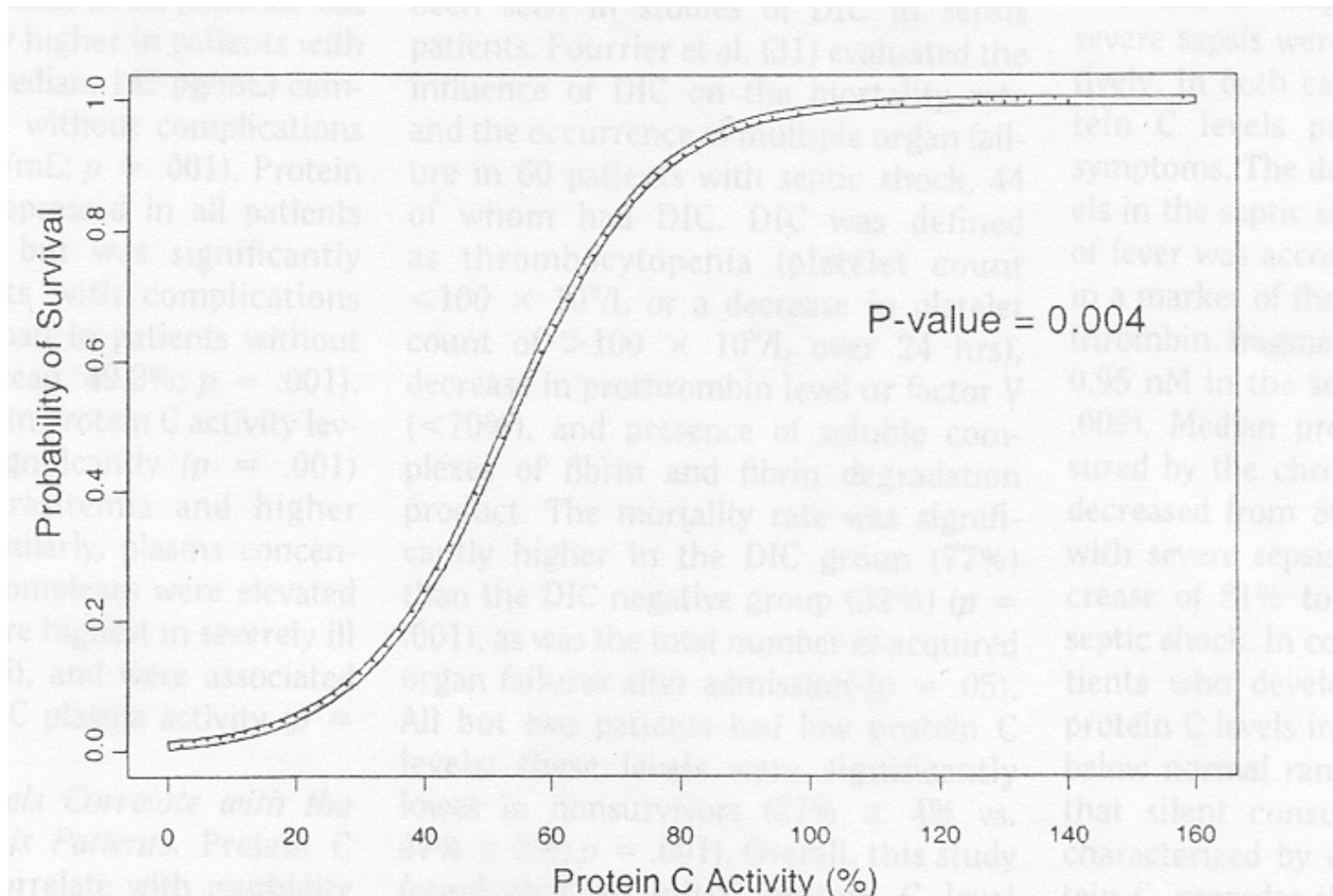
Indication of Prognostic Significance

Protein C Levels as a prognostic indicator of
outcome in sepsis and related diseases.

Charles J. Fisher, Jr., MD, S. Betty Yan, PhD

Crit. Care Med 2000, VOL 28, No. 9 (Suppl) S49-56

Correlation of Protein C Activity and Probability of Survival



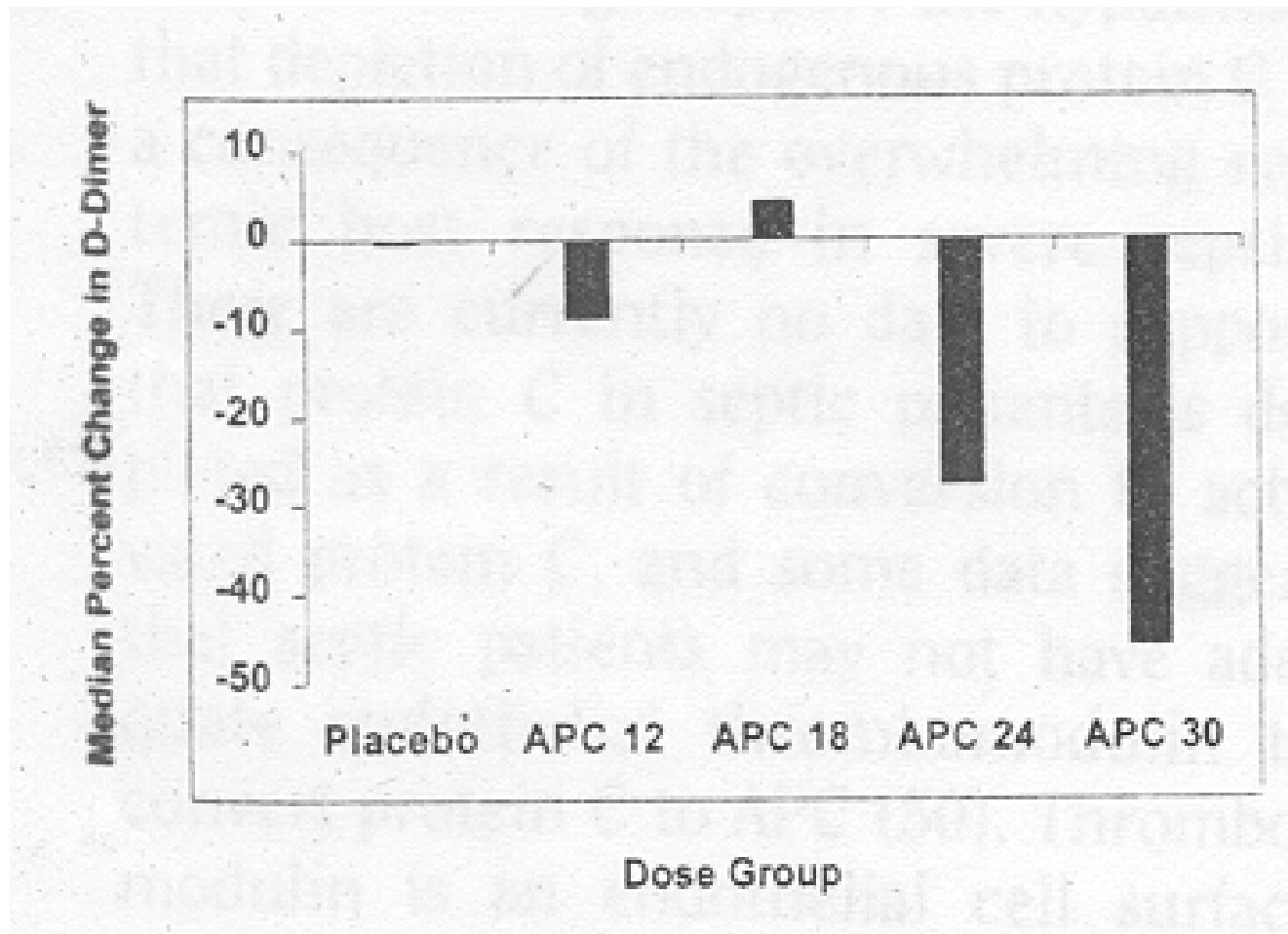
Phase I Safety Trial

Safety and dose relationship of recombinant human activated protein C for coagulopathy in severe sepsis

Gordon R. Bernard, E. Wesley Ely, Theresa J. Wright, Joseph Fraiz, Jerome E. Stasek Jr., ;James A. Russell, Irvin Mayers, Brian A. Rosenfeld, Peter E. Morris, S. Betty Yan, Jeffery D. Helderbrand, (rhAPC Sepsis Study Group

Crit Care Med 2001 Vol 29, Pages 2051-59

Dose Dependent Reduction of D-Dimer by APC



Phase III Trial Showing Efficacy of Activated Protein C in Sepsis

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

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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*

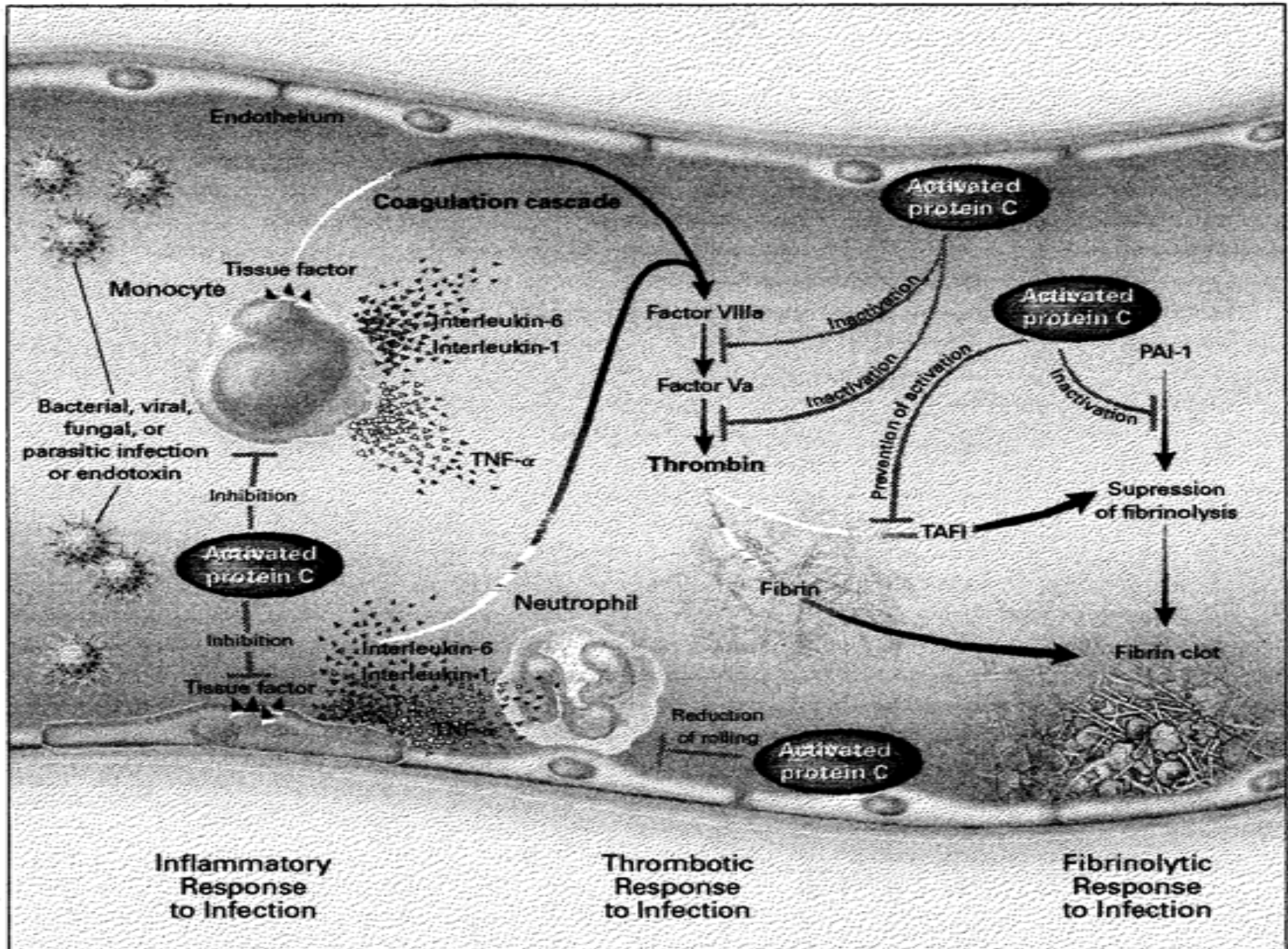


Figure 1. Proposed Actions of Activated Protein C in Modulating the Systemic Inflammatory, Procoagulant, and Fibrinolytic Host Responses to Infection.

**Patients Were
Older (>60
yrs), Had High
APACHE II
scores (25+),
and Had Multi-
organ
dysfunction**

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO GROUP (N=840)	DROTRECOPIN ALFA ACTIVATED GROUP (N=850)
Age (yr)	60.6±16.5	60.5±17.2
Age (%)		
<60 yr	43.6	44.1
<65 yr	53.5	51.4
<75 yr	78.5	75.9
Male sex (%)	58.0	56.1
White race (%)	82.0	81.8
Prior or preexisting conditions (%)		
Hypertension	35.0	38.2
Myocardial infarction	14.4	12.1
Congestive cardiomyopathy	9.0	6.4
Diabetes	22.4	20.7
Pancreatitis	3.9	3.4
Liver disease	2.6	2.1
COPD	26.1	22.2
Cancer	18.8	17.1
Recent trauma	5.1	3.3
Recent surgical history (%)		
Elective surgery	6.2	5.8
Emergency surgery	21.2	20.7
No history of surgery	72.6	73.5
APACHE II score	25.0±7.8	24.6±7.6
Other indicators of disease severity (%)		
Mechanical ventilation	77.6	73.3
Shock	71.7	70.4
Use of any vasopressor	75.5	71.8
Use of dobutamine	13.5	13.9
No. of dysfunctional organs or systems (%)		
0	0	0.1
1	24.2	25.3
2	32.5	31.8
3	26.0	25.2
4	13.8	14.0
5	3.6	3.6
Time from first organ dysfunction to start of drug infusion (hr)	17.4±9.1	17.5±12.8

*Plus-minus values are means ±SD. COPD denotes chronic obstructive pulmonary disease, and APACHE II Acute Physiology and Chronic Health Evaluation II. Because of rounding, not all percentages total 100.

Infections
 Where Primarily
 Pulmonary and
 the Vast
 Majority Were
 Bacterial (Staph,
 Strep, E. Coli)

TABLE 2. SITES AND CAUSES OF INFECTION IN PATIENTS WITH SEVERE SEPSIS.

VARIABLE	PLACEBO GROUP	DROTRECOCIN
	(N=840)	ALFA ACTIVATED GROUP (N=850)
	percent	
Site of infection*		
Lung	53.6	53.6
Abdomen	19.9	20.0
Urinary tract	10.2	10.0
Other†	16.3	16.4
Positive blood culture	32.5	32.7
Results of Gram's staining of bacterial pathogen		
Purely gram-negative	23.3	21.8
Purely gram-positive	25.1	25.8
Mixed	13.9	15.6
Unconfirmed	5.4	3.3
Culture negative or not obtained	32.3	33.5
Type of organism‡		
Gram-positive		
<i>Staphylococcus aureus</i>	14.4	14.1
Other staphylococcus species	6.2	7.1
<i>Streptococcus pneumoniae</i>	11.3	12.5
Other streptococcus species	9.2	8.6
Enterococcus species	6.5	7.4
Other gram-positive	3.0	3.9
Gram-negative		
<i>Escherichia coli</i>	17.4	15.5
Klebsiella species	6.8	5.5
Pseudomonas species	5.1	6.6
Enterobacter species	4.2	4.8
<i>Haemophilus influenzae</i>	4.2	3.1
Bacteroides species	3.0	3.6
Other gram-negative	10.2	9.5
Fungus		
<i>Candida albicans</i>	1.7	2.0
Other candida species	5.0	4.5
Yeast	1.1	1.1
Other fungus	0.8	0.8

*The site of infection was either documented or presumed on the basis of clinical findings.

†Other sites of infection included the blood, skin, central nervous system, bones and joints, cardiac system, and reproductive organs.

‡Patients may have had more than one organism cultured.

Baseline D-Dimer and IL-6 Levels Were Elevated and Protein C levels Were Down

TABLE 3. BASE-LINE LEVELS OF INDICATORS OF COAGULATION AND INFLAMMATION.*

VARIABLE	PLACEBO GROUP	DROTRECOGIN ALFA ACTIVATED GROUP
Plasma D-dimer		
No. of patients	758	792
Median level ($\mu\text{g}/\text{ml}$)	4.15	4.22
Interquartile range ($\mu\text{g}/\text{ml}$)	2.18-8.65	2.28-8.11
Serum interleukin-6		
No. of patients	808	827
Median level (pg/ml)	484	497
Interquartile range (pg/ml)	129-2540	153-2701
Plasma protein C activity		
No. of patients	775	799
Median level (%)	50	47
Interquartile range (%)	33-68	30-63
Protein C deficiency (% of patients)		
Yes	79.8	83.4
No	12.5	10.6
Unknown	7.7	6.0

*The normal range of D-dimer levels is 0.0 to 0.39 μg per milliliter. The normal range of interleukin-6 levels is 0.38 to 10.09 pg per milliliter. The normal range of protein C activity is 81 percent to 173 percent. A deficiency of protein C was defined as an activity level of less than 81 percent.

Septic Patients on rAPC Had Lower D-Dimer Levels

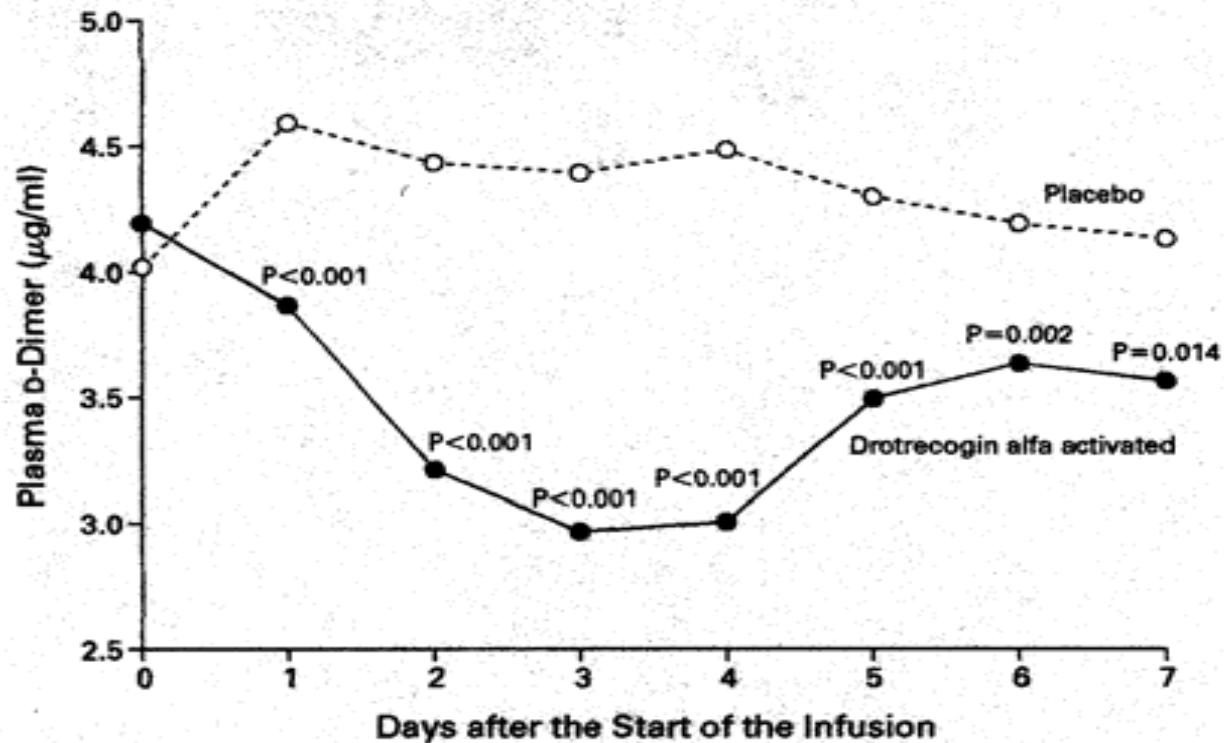


Figure 3. Changes in Median Plasma D-Dimer Levels in 770 Patients with Severe Sepsis in the Drotrecogin Alfa Activated Group and 729 Patients in the Placebo Group.

Only patients with base-line values and at least one subsequent value were included in the analysis. The P values are for the comparison with the placebo group.

Study Was Stopped Due to Survival Advantage in Treated Group

TABLE 4. ANALYSIS OF THE RATES AND RISKS OF DEATH FROM ANY CAUSE AT 28 DAYS.*

VARIABLE	PLACEBO GROUP	DROTRECOGIN ALFA ACTIVATED GROUP	P VALUE†	RELATIVE RISK OF DEATH (95% CI)‡	ABSOLUTE REDUCTION IN RISK (95% CI)§
	no./total no. (%)				%
Treated patients					
Nonstratified analysis	259/840 (30.8)	210/850 (24.7)	0.005	0.80 (0.69 to 0.94)	6.1 (1.9 to 10.4)
Stratified analysis¶			0.005	0.81 (0.70 to 0.93)	6.2 (1.6 to 10.8)
Protein C deficiency					
Yes	215/670 (32.1)	182/709 (25.7)	0.009	0.80 (0.68 to 0.95)	6.4 (1.6 to 11.2)
No	28/105 (26.7)	14/90 (15.6)	0.06	0.58 (0.33 to 1.04)	11.1 (-0.4 to 22.6)
Unknown	16/65 (24.6)	14/51 (27.5)	0.73	1.12 (0.60 to 2.07)	-2.8 (-19.0 to 13.4)
Randomized patients¶					
Nonstratified analysis	268/857 (31.3)	216/871 (24.8)	0.003	0.79 (0.68 to 0.92)	6.5 (2.2 to 10.7)

*Patients were analyzed in the treatment group to which they were assigned at randomization. CI denotes confidence interval.

†Two-sided P values for the nonstratified and subgroup analyses are based on Pearson's chi-square tests, and the P value for the primary stratified analysis is based on the Cochran-Mantel-Haenszel test.

‡The relative risk of death is calculated as the mortality rate in the drotrecogin alfa activated group divided by the mortality rate in the placebo group.

§For the stratified analysis, the absolute reduction in risk was estimated with use of the average of the absolute reduction in risk within strata.

¶In the prospectively defined stratified analysis, the relative risk of death was calculated after an adjustment for the base-line APACHE II quartile, age, and protein C activity.

¶This analysis included 38 patients who were randomly assigned to treatment but who never received the study drug.

rAPC Treated
Group Had
More
Bleeding but
Less
Thrombosis

TABLE 5. INCIDENCE OF SERIOUS ADVERSE EVENTS.

VARIABLE	PLACEBO	DROTRECOGIN	P VALUE
	GROUP (N=840)	ALFA ACTIVATED GROUP (N=850)	
	no. of patients (%)		
At least one serious adverse event	102 (12.1)	106 (12.5)	0.84
Serious bleeding event*	17 (2.0)	30 (3.5)	0.06
Gastrointestinal	9 (1.1)	9 (1.1)	
Intraabdominal	4 (0.5)	3 (0.4)	
Intrathoracic	1 (0.1)	6 (0.7)	
Retroperitoneal	0	4 (0.5)	
Intracranial	1 (0.1)	2 (0.2)	
Skin or soft tissue	0	2 (0.2)	
Genitourinary	0	2 (0.2)	
Source unidentified†	2 (0.2)	2 (0.2)	
Thrombotic events	25 (3.0)	17 (2.0)	0.20

*A serious bleeding event was defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of 3 units of packed red cells on two consecutive days.

†These patients received 3 units of packed red cells on two consecutive days but had no identifiable source of bleeding.