Adjuvent and New therapeutic interventions in Septic Shock ?

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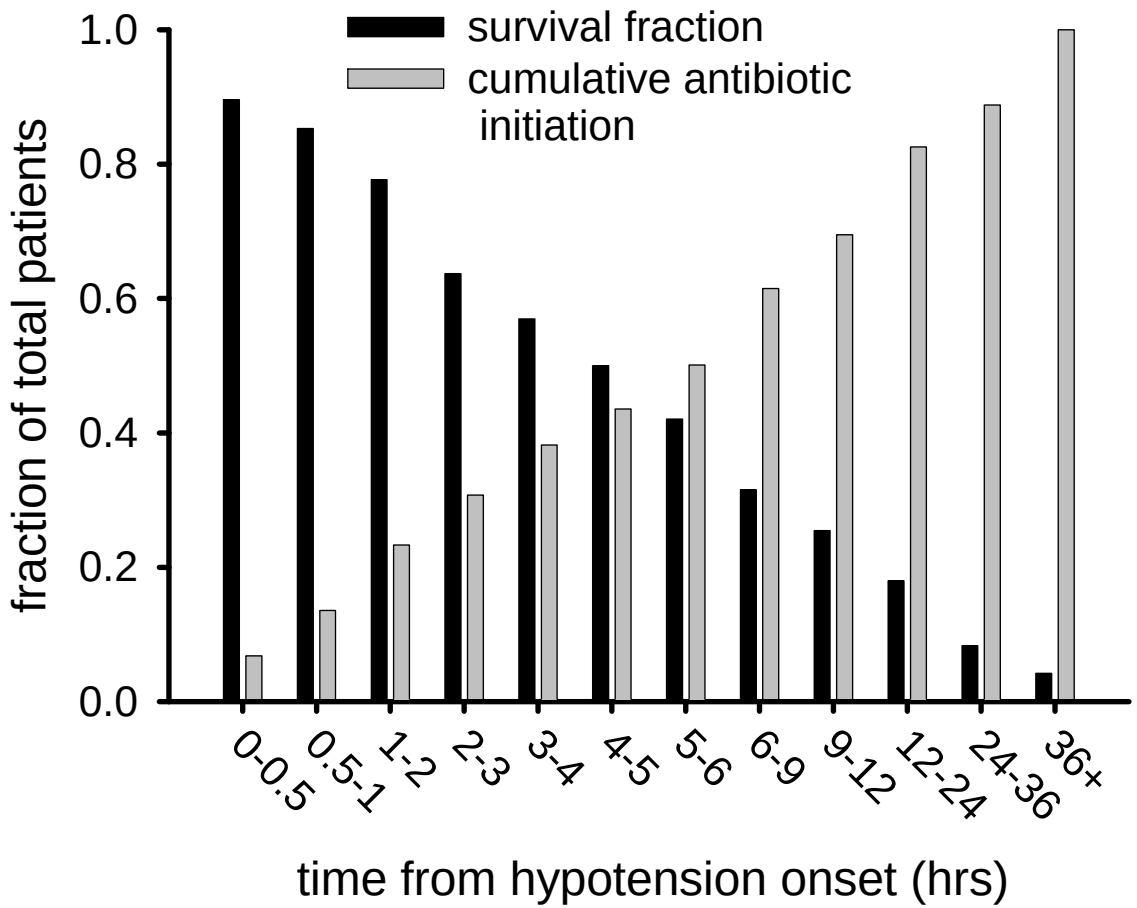
Cumulative Initiation of Effective Antimicrobial Therapy and Survival in Septic Shock



Kumar et al, CCM

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*

Michael A. Puskarich, MD; Stephen Trzeciak, MD; Nathan I. Shapiro, MD; Ryan C. Arnold, MD; James M. Horton, MD; Jonathan R. Studnek, PhD; Jeffrey A. Kline, MD; Alan E. Jones, MD; on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET)

Crit Care Med 2011 Vol. 39, No. 9

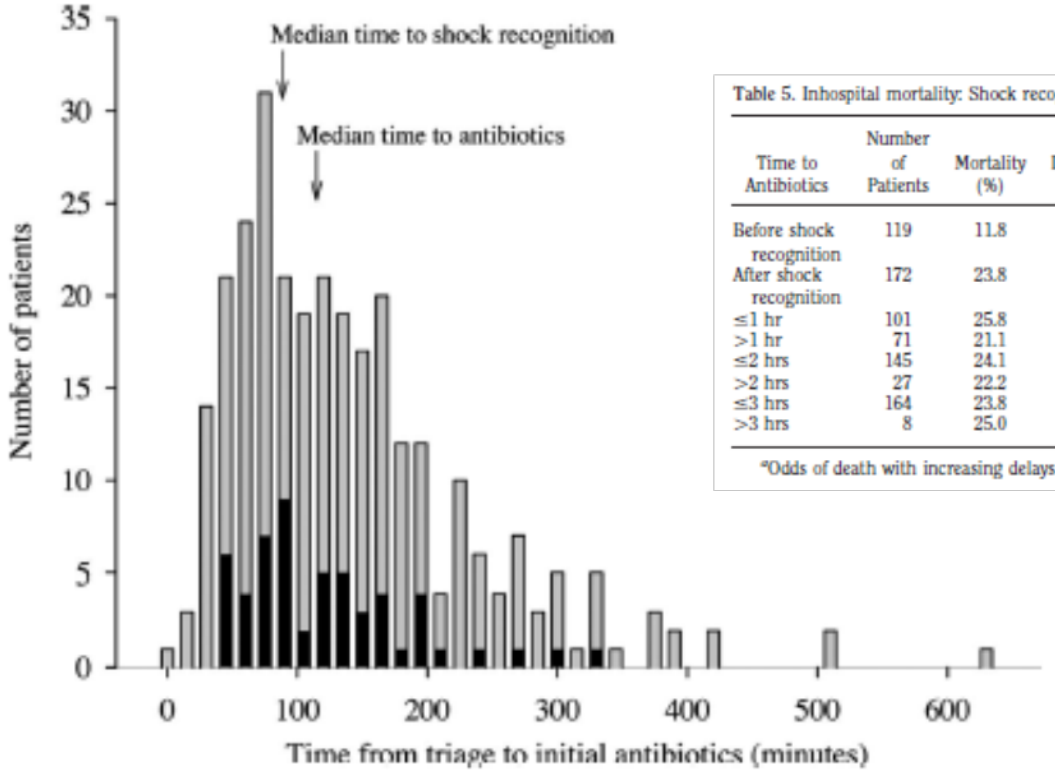


Figure 1. Graphic depiction of the time from triage to initial antibiotics in the entire cohort stratified by final hospital outcome. Gray bars represent patients who survived the hospitalization and black bars represent patients who died in the hospital.

Table 5. Inhospital mortality: Shock recognition to initial antibiotics

Time to Antibiotics	Number of Patients	Mortality (%)	Difference (%)	Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
Before shock recognition	119	11.8	12	2.35	1.12–4.53	2.59	1.17–5.74
After shock recognition	172	23.8					
≤1 hr	101	25.8	−4.7	1.29	0.63–2.67	0.93	0.41–2.12
>1 hr	71	21.1					
≤2 hrs	145	24.1	−1.9	1.11	0.42–2.98	0.69	0.21–2.22
>2 hrs	27	22.2					
≤3 hrs	164	23.8	1.2	0.94	0.18–4.82	0.84	0.13–5.52
>3 hrs	8	25.0					

[a]Odds of death with increasing delays in antibiotic administration.

Intensive Care Med (2009) 35:847–853
DOI 10.1007/s00134-008-1373-4

ORIGINAL

Alexandre Boyer
Frederic Vargas
Fanny Coste
Elodie Saubusse
Yves Castaing
Georges Gbikpi-Benissan
Gilles Hilbert
Didier Gruson

Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management

Table 4 Results of multivariate analysis of hospital mortality in patients with severe NSTI

Variables	Adjusted OR	95% CI	*P* value
SAPS II	1.15	1.04–1.26	0.02
Cardiovascular disease			
No	1	–	
Yes	13.9	1.8–106	0.01
Localization			
Extremities	1	–	
Abdominoperineal	15.1	1.5–149	0.002
Time from first signs to diagnosis; $n = 99$[a]			
>72 h	1	–	
≤72 h	0.09	0.01–0.68	0.02
Time from diagnosis to surgery in patients with septic shock; $n = 33$[b]			
≤14 h	1	–	
>14 h	34.5	2.05–572	0.007

NSTI necrotizing soft tissue infection, *SAPS* simplified acute physiology score

[a] Information available for 99 patients out of the 106 studied

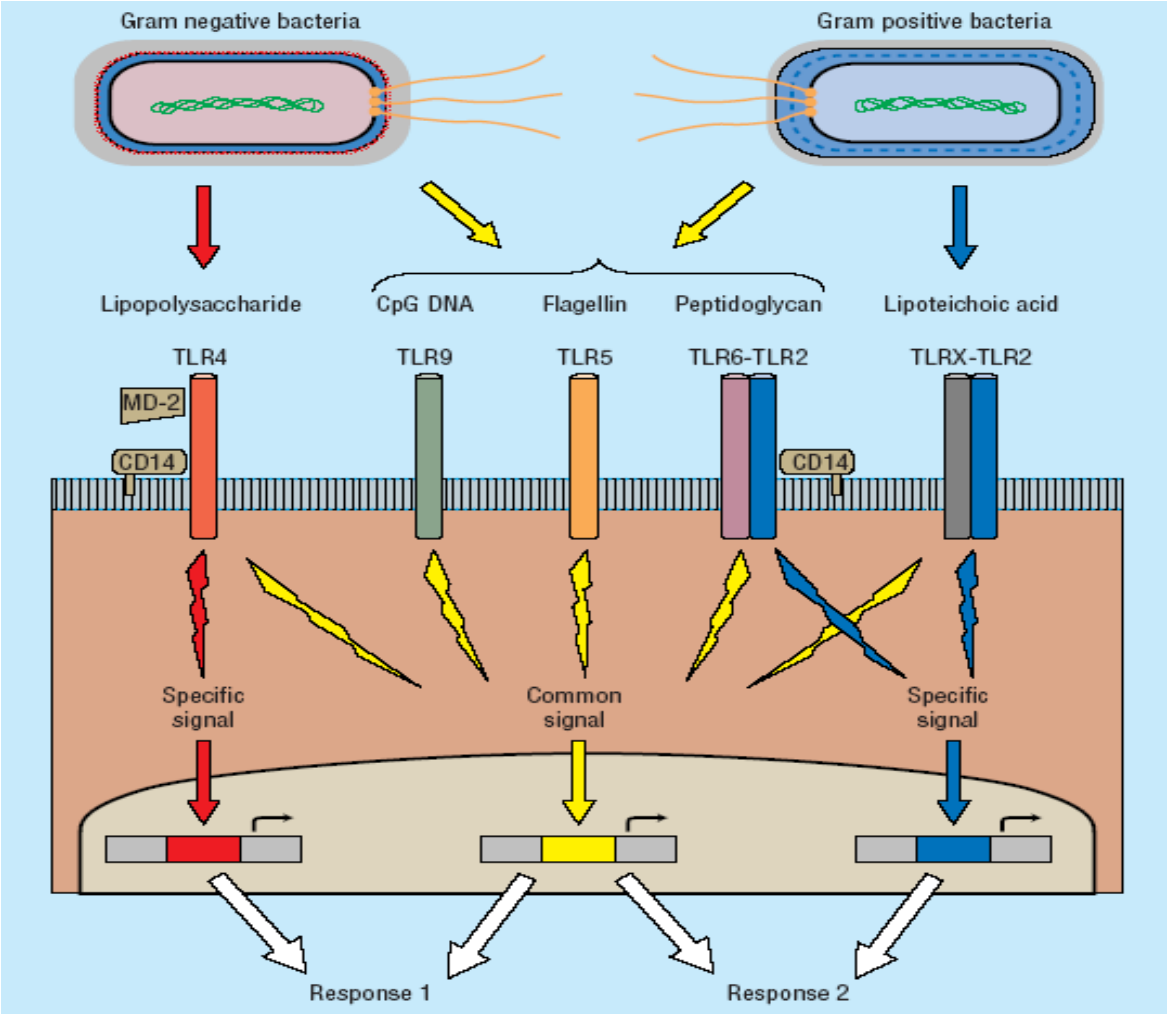
[b] Information available for 33 patients out of the 43 patients with septic shock

Hypothesis ?

- **Host response is excessive in sepsis and blocking or suppressing this response should improve outcome ?**

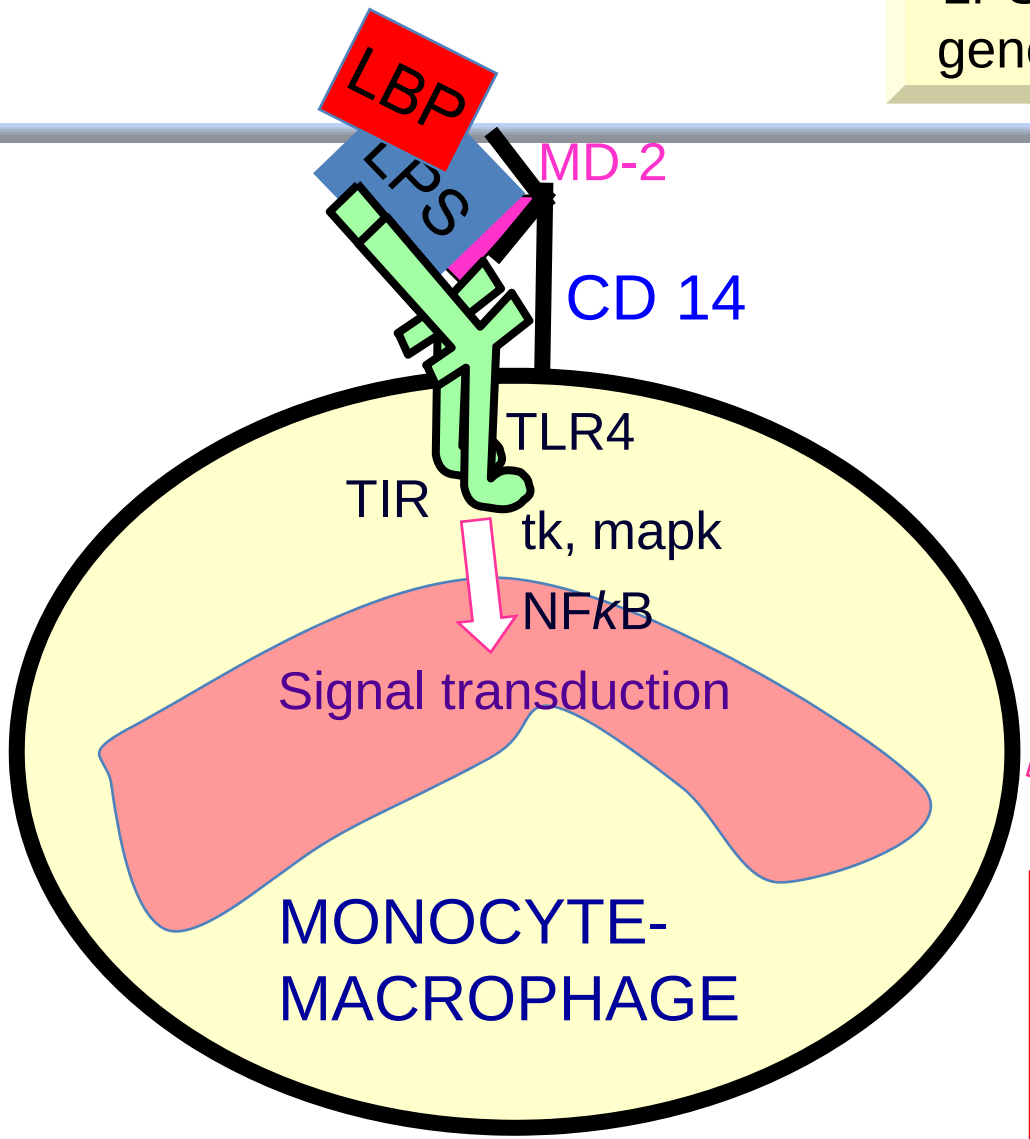
- **Host response represents a final common pathway whatever the source of infection and modulating the response should work ?**

Interaction between bacterial products and pattern recognition receptors



Bochud PY, Calandra T, *BMJ* 2003;326:262-6

LPS-mediated gene induction

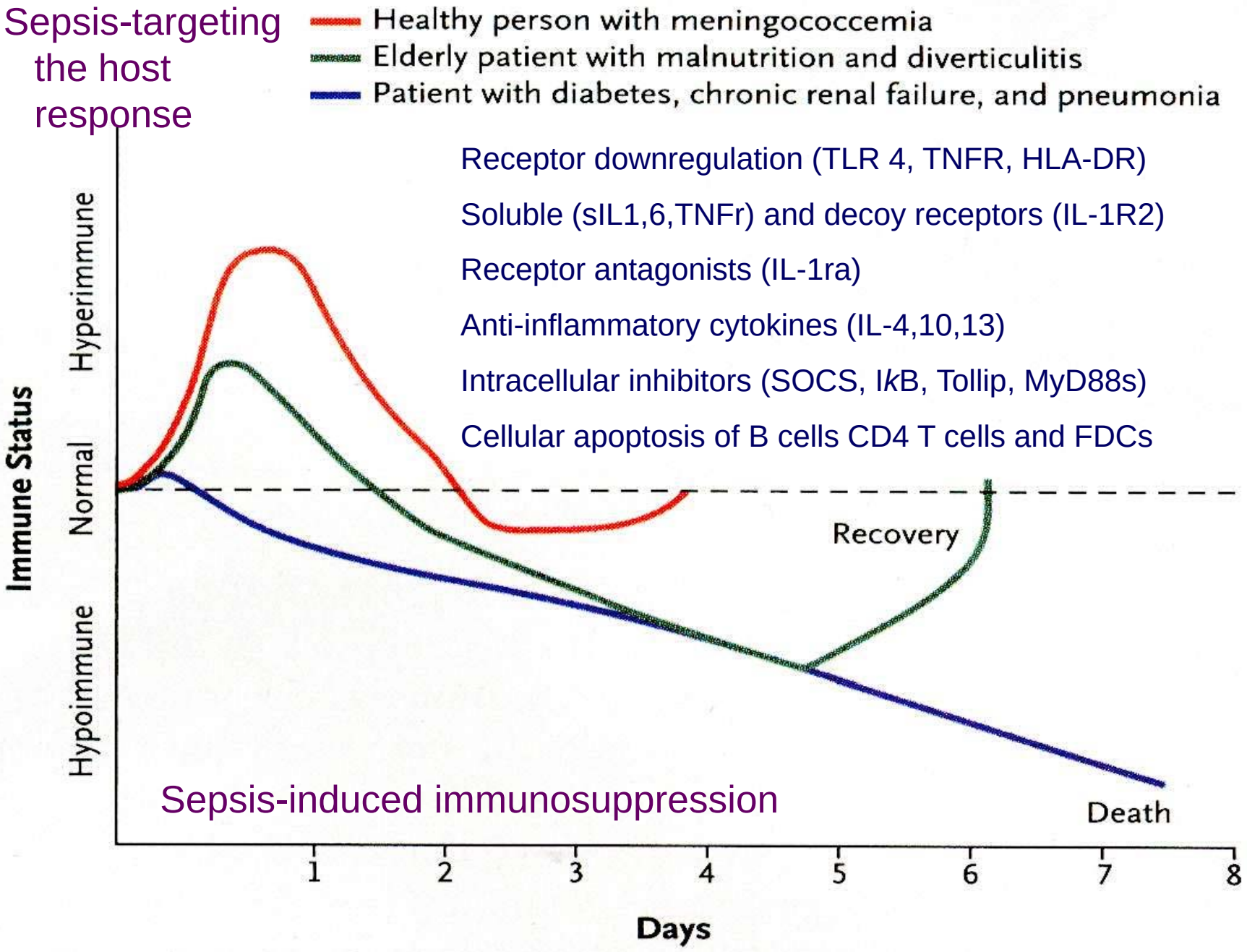


3714 genes (12% of the human transcriptome) is altered over 24 hours upon exposure to LPS

Cytokines
Chemokines
Nitric oxide
Acute phase proteins
Pro-coagulants

Lowry et al. Nature 2005;437:1032-7

Sepsis-targeting the host response

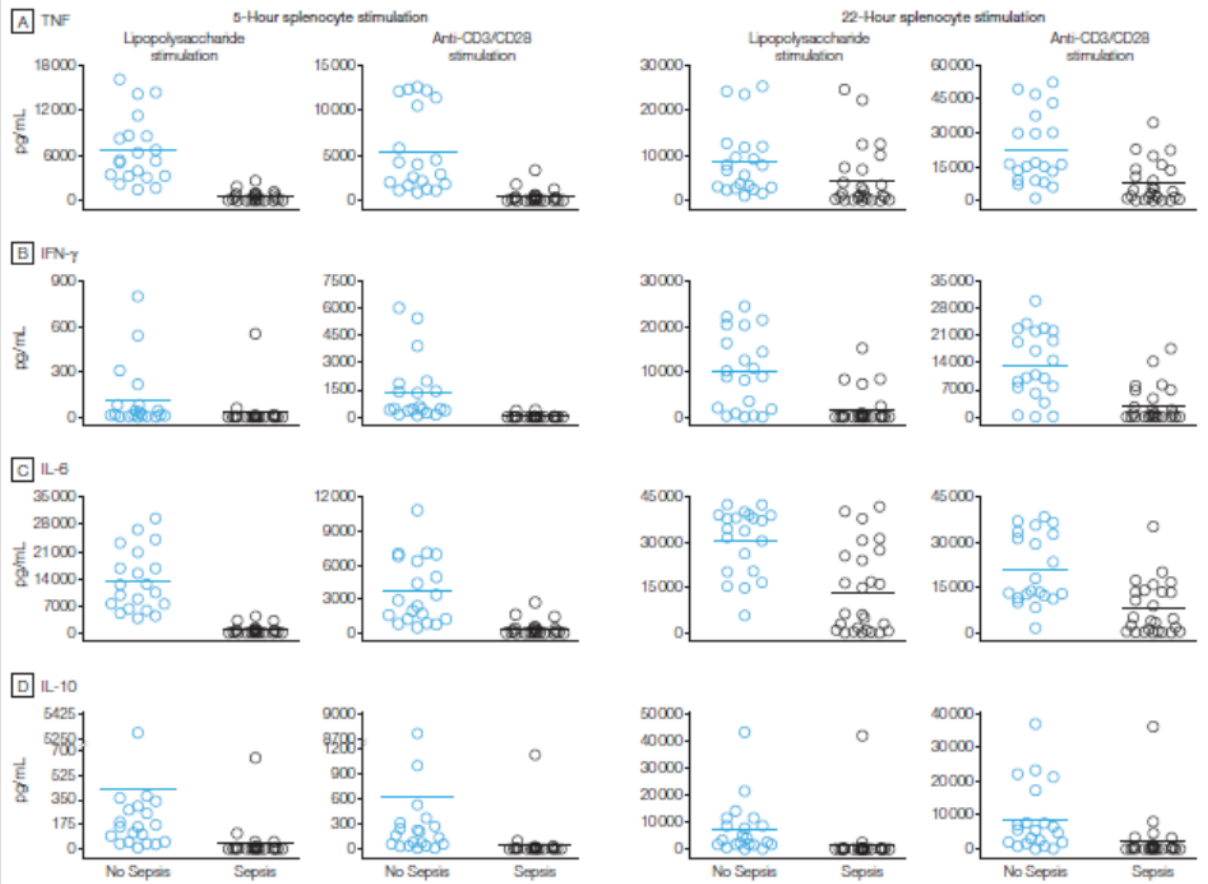


Hotchkiss and Karl NEJM 2003;348:138

Immunosuppression of patients who die from sepsis and MOF

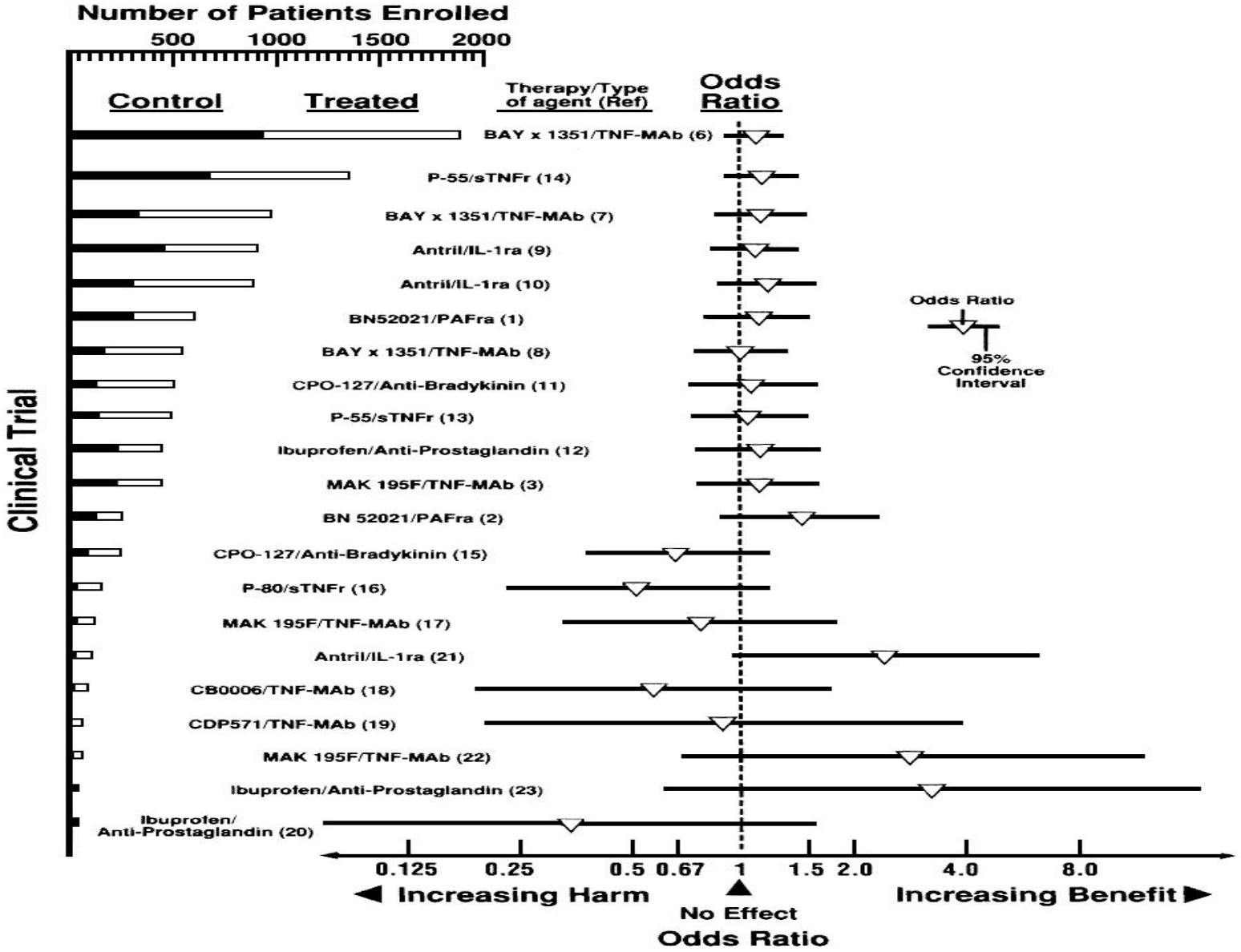
JS Boomer et al. JAMA. 2011;306(23):2594-2605

Figure 1. Cytokine Secretion in Stimulated Splenocytes



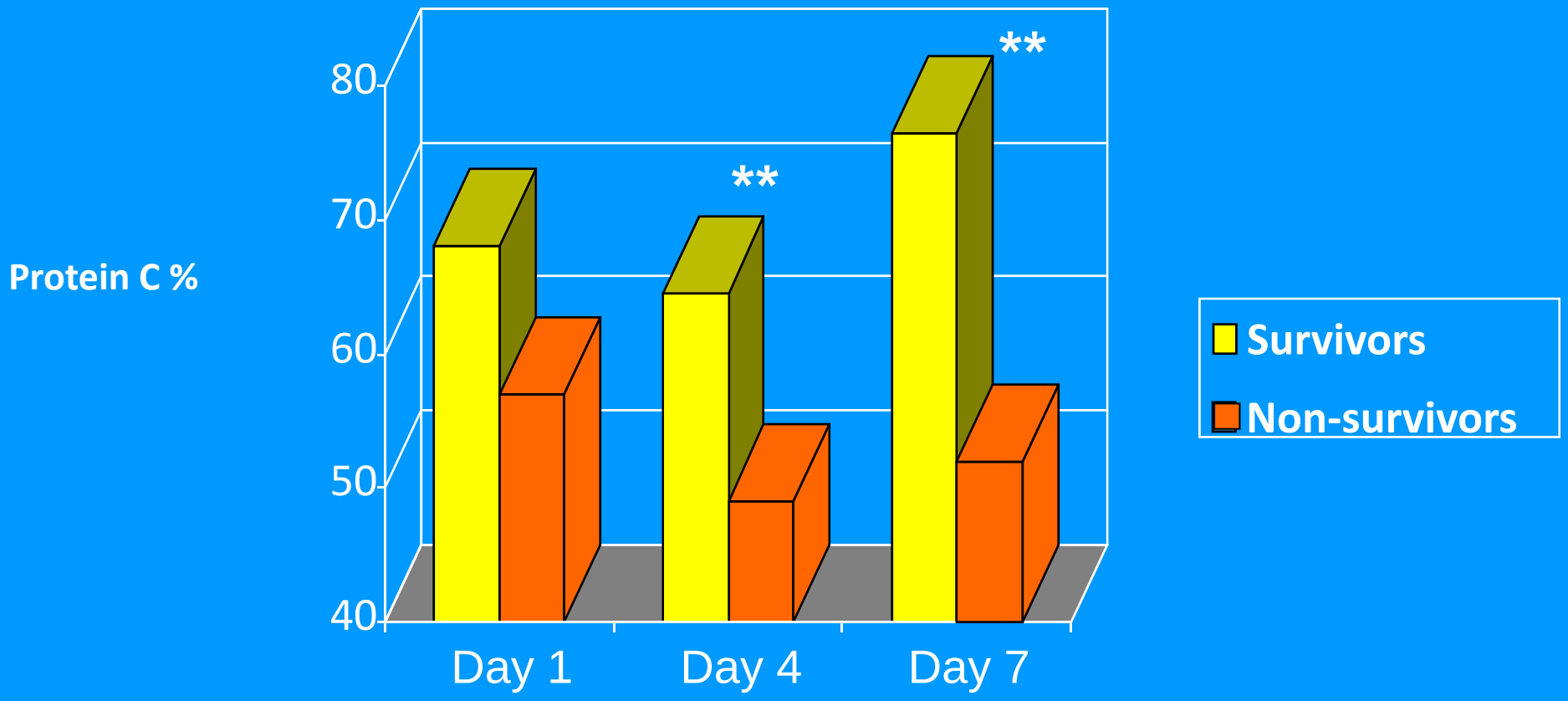
Spleens were harvested from patients who died of sepsis (n=24-26) or nonsepsis etiologies (n=20-21). Cells were dissociated and washed and viability determined by trypan blue exclusion. Viable splenocytes (1×10^6) were stimulated with lipopolysaccharide or anti-CD3/anti-CD28 antibody. Supernatants were harvested at 5 and 22 hours and tumor necrosis factor (TNF), interferon γ (IFN-γ), and interleukins (IL) 6 and 10 were measured by enzyme-linked immunosorbent assay. There was a marked decrease in cytokine secretion in sepsis patients vs nonsepsis controls. Data were analyzed by 2-tailed nonparametric *t* test (Mann-Whitney *U* test). Each data marker represents an individual patient. Horizontal lines represent mean values. $P<.001$ for all plots, except $P<.01$ for TNF with lipopolysaccharide stimulation at 22 hours.

Anti-Inflammatory Sepsis Trials
Apparent Benefit and Confidence Intervals



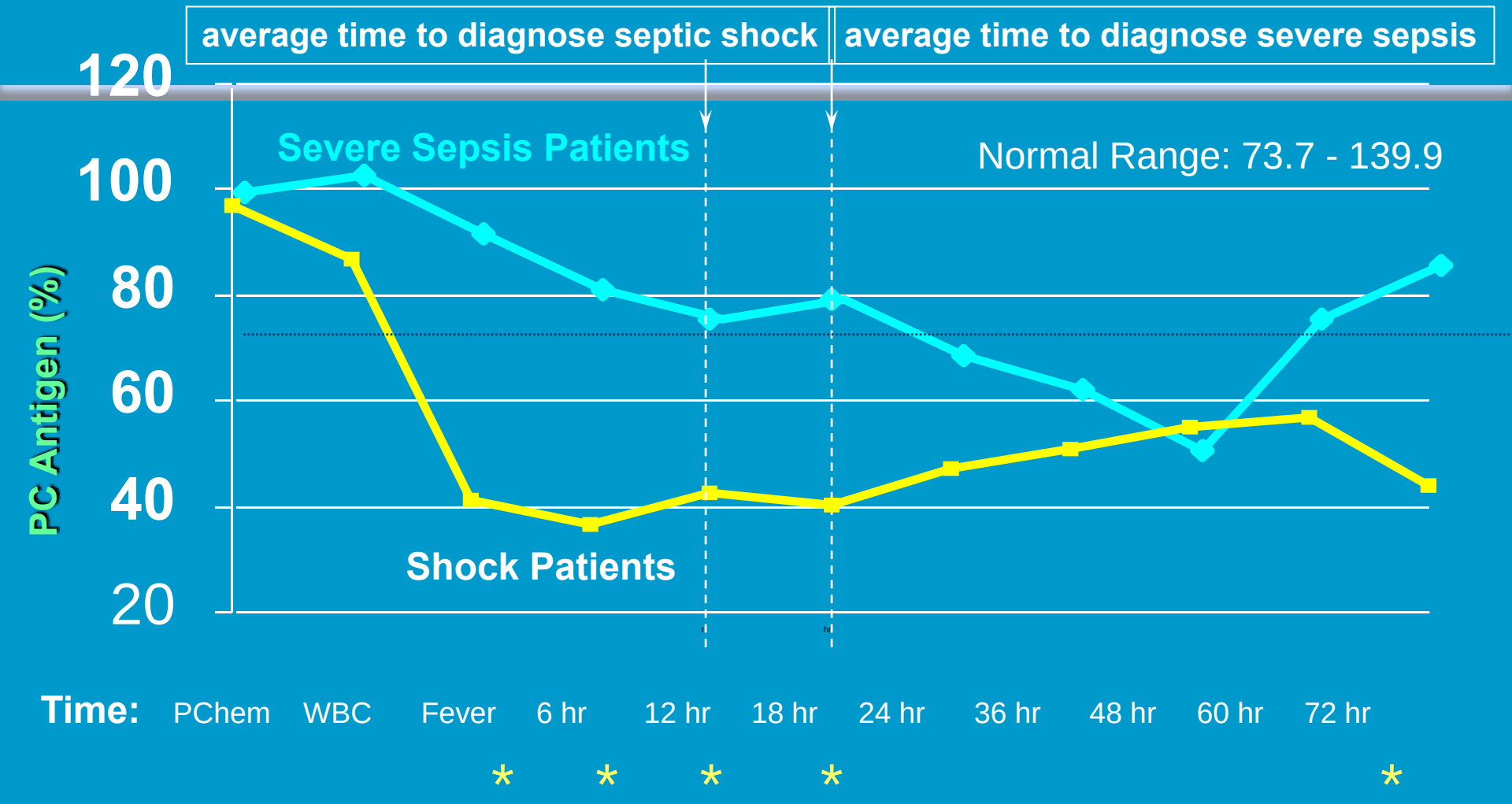
Natanson et al. Crit Care Med 26:1927-1931,1998

Protein C deficiency is associated with an increased mortality



** p < 0.05 for the comparison of survivors with nonsurvivors

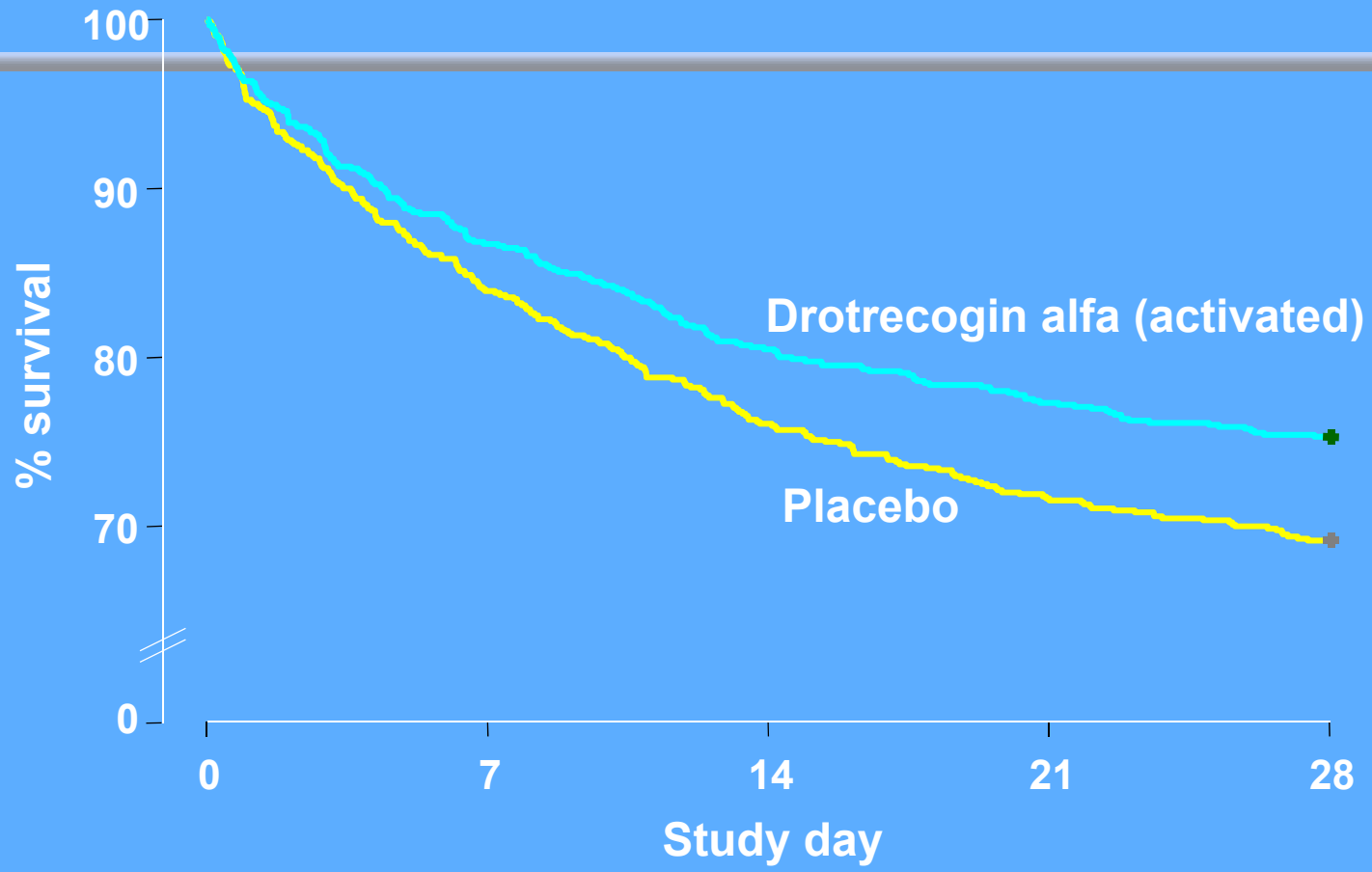
Lorente, Chest 1993



* **Denotes Statistical Significance at two-sided 0.05 level**

Hartman DL., Meister R, Yan SB, et al Chest, 1997

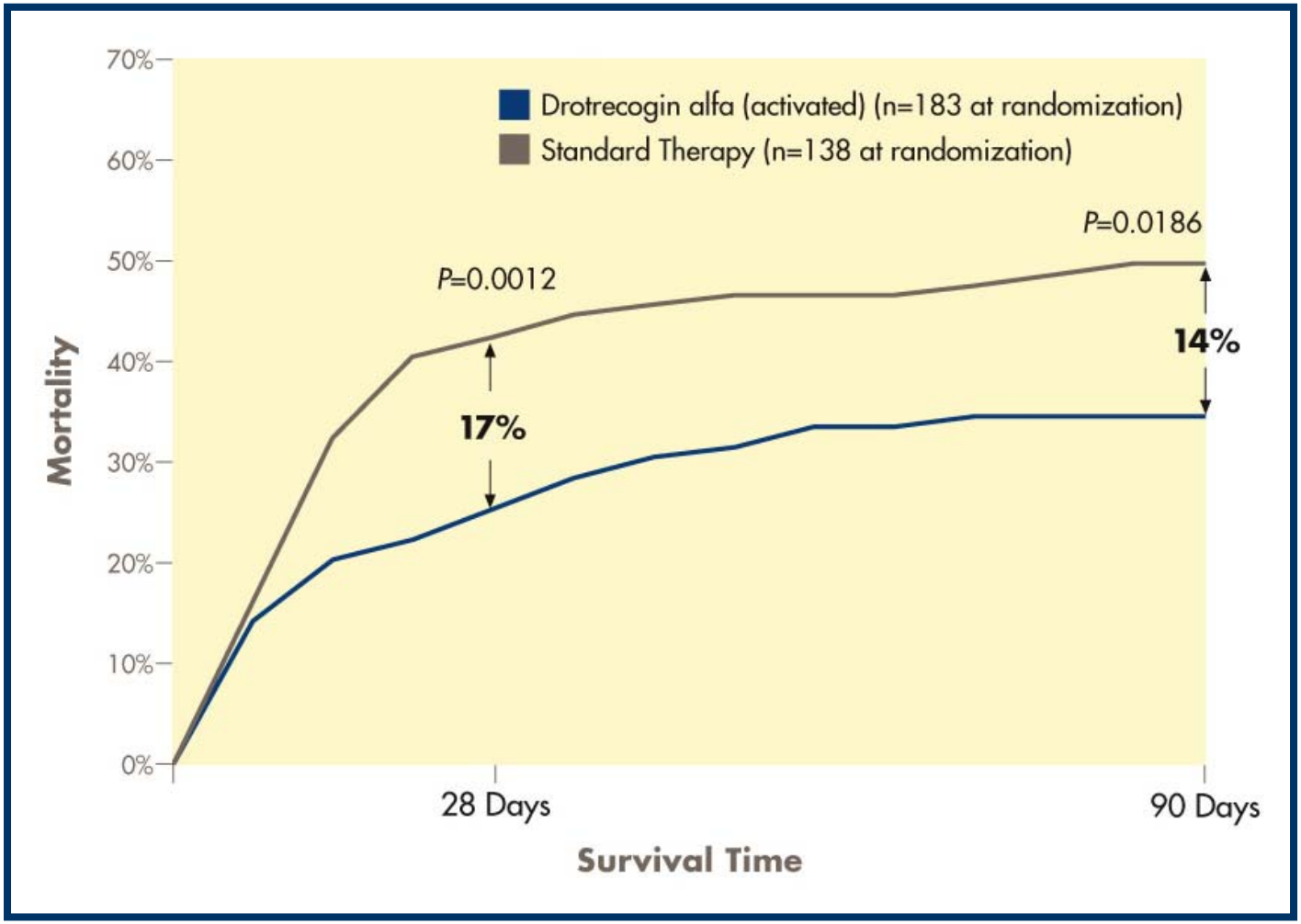
PROWESS 28-day results



- N=1690
  - 6.1% absolute mortality reduction (p=0.006)
  - Largest reduction in 'high risk' subgroups

Bernard et al. NEJM 2001

Survival in Patients With CAP-Induced High-Risk Severe Sepsis



PROWESS Shock ?

- **N= 1,696**

- Placebo mortality : 24,2%
- Drotrecogin : 26,4%

- **Negative trial : withdrawal from the market…..**

Sample Size

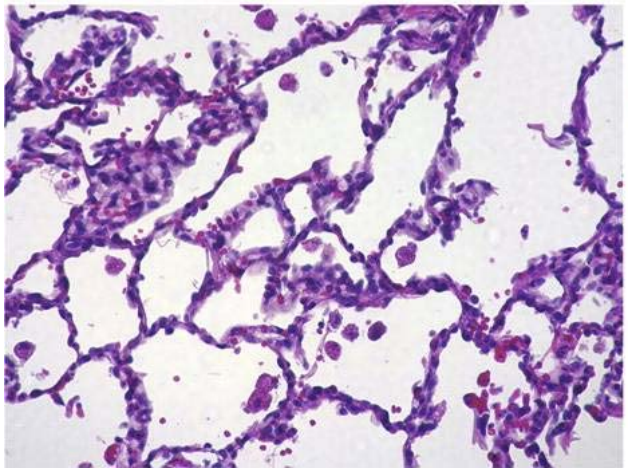
- 1500 patients
- 80% power at an alpha level of .05
- Assumptions:
  - Placebo mortality rate of 35%
  - Treatment with drotrecogin alfa (activated) is associated with a 20% relative risk reduction
  - Drotrecogin alfa (activated) mortality rate of 28%

PROWESS Shock ?

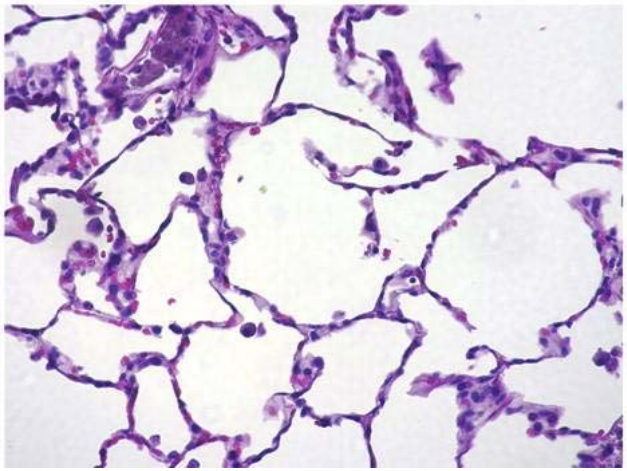
- **Why did it fail ?**
  - **Severity :** Placebo mortality 24.2% **??..initial assumption was a 35% mortality rate**
    - **Lack of severity ?**
    - **Dramatic improvement in sepsis treatment ?**
  - Severe bleeding **: no difference ? (only trial !) is this a witness of low severiry ?**

Blockade of Tissue Factor — Factor X Binding Attenuates Sepsis-induced Lung Injury

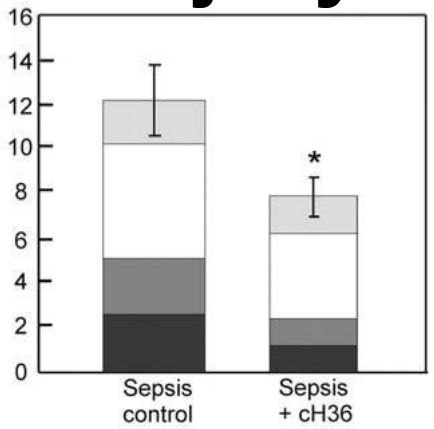
Control



TF blockade

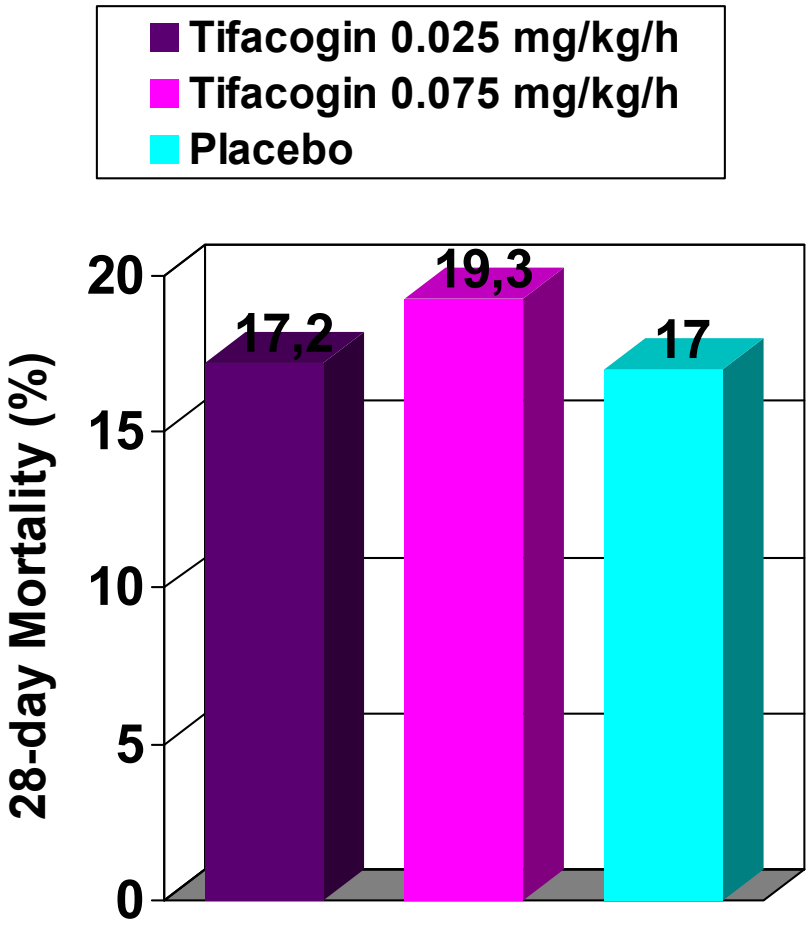


Lung injury

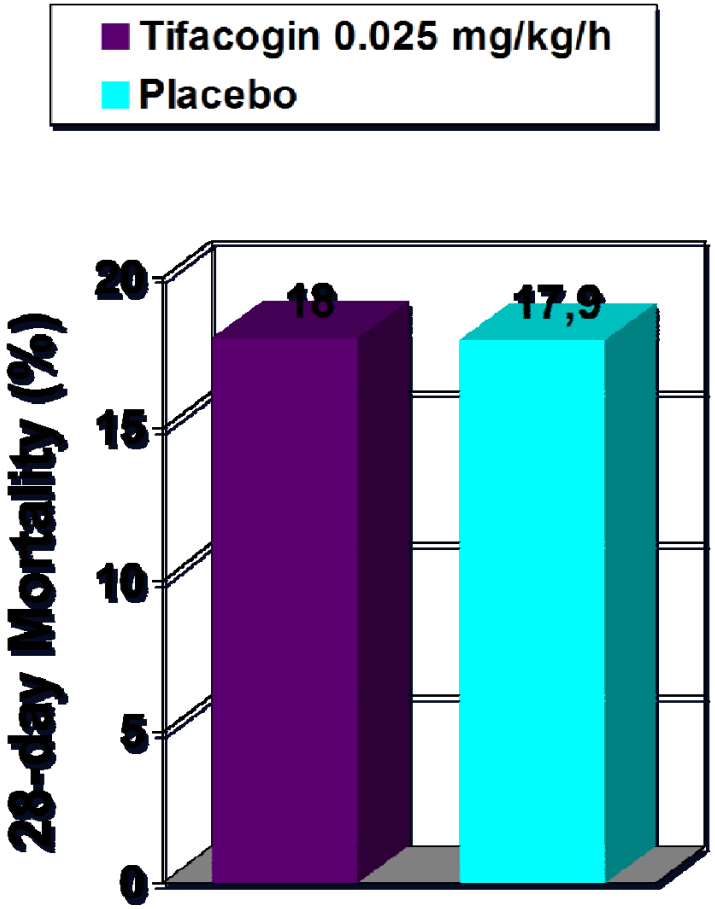


Welty-Wolf KE. *Am J Physiol Lung Cell Mol Physiol*. 2006;290:L21

28-day All-cause Mortality (ITT population)

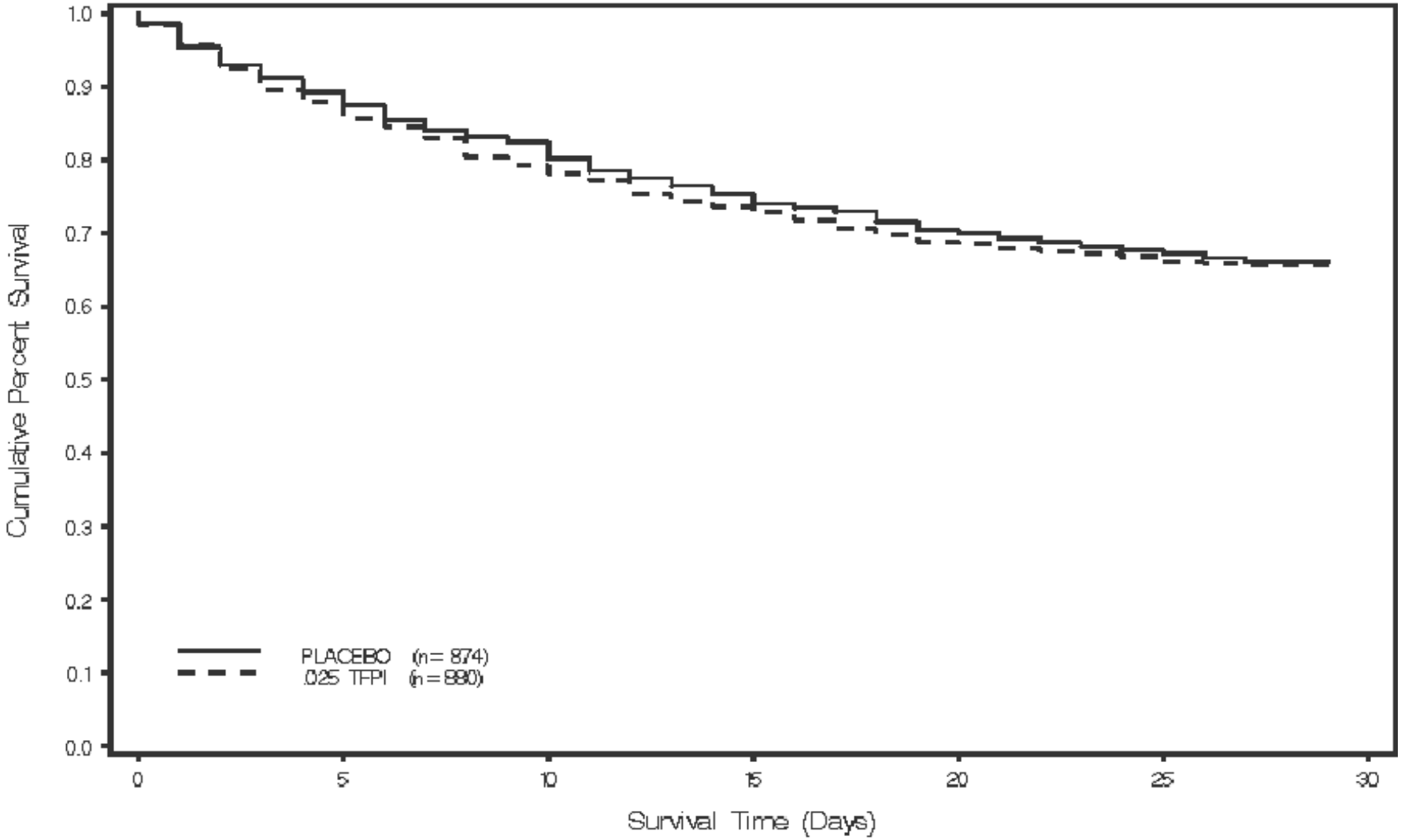


After 1st Interim Analysis



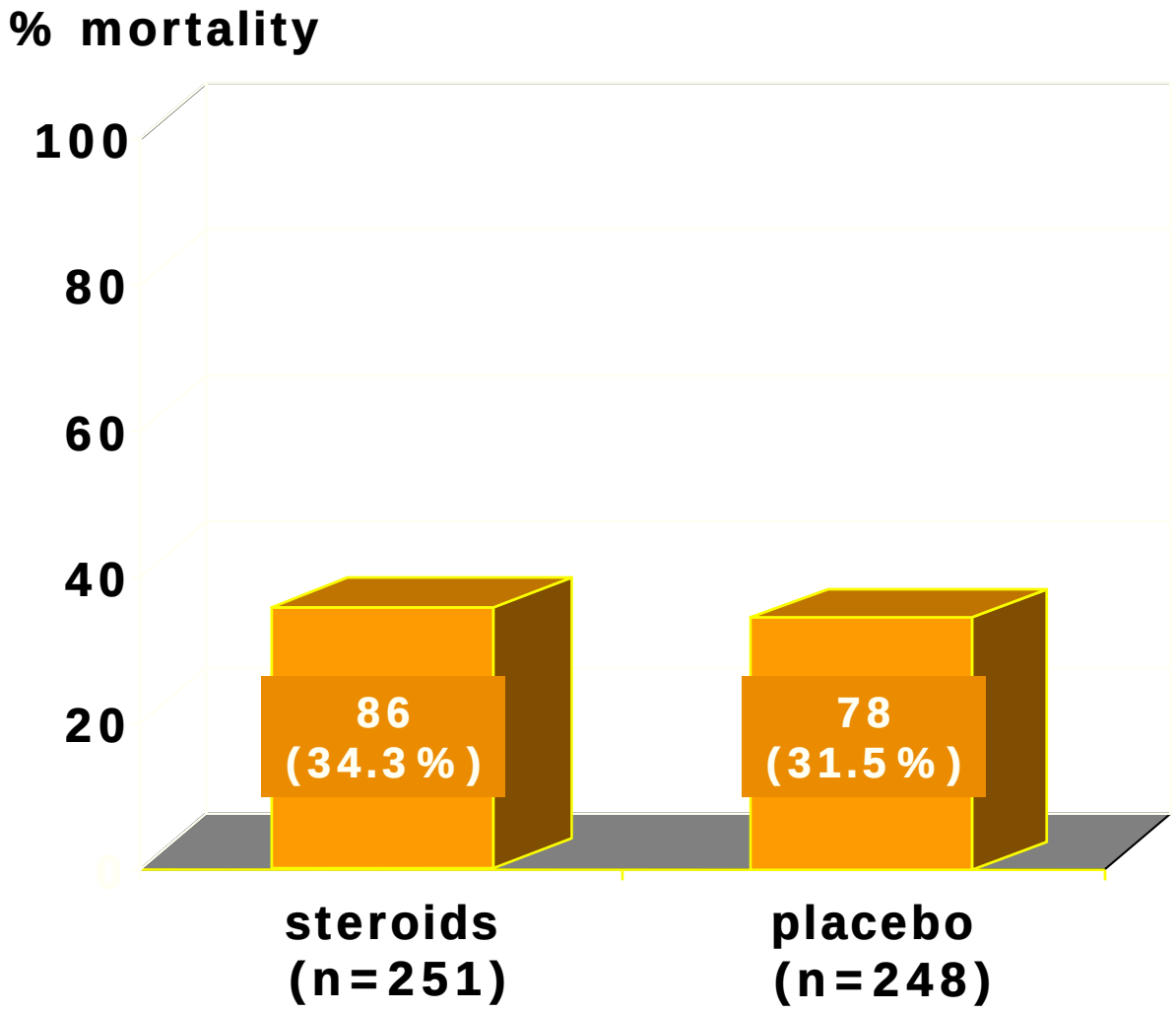
Overall

28 Day All-Cause Mortality, INR ≥ 1.2 TFPI versus Placebo



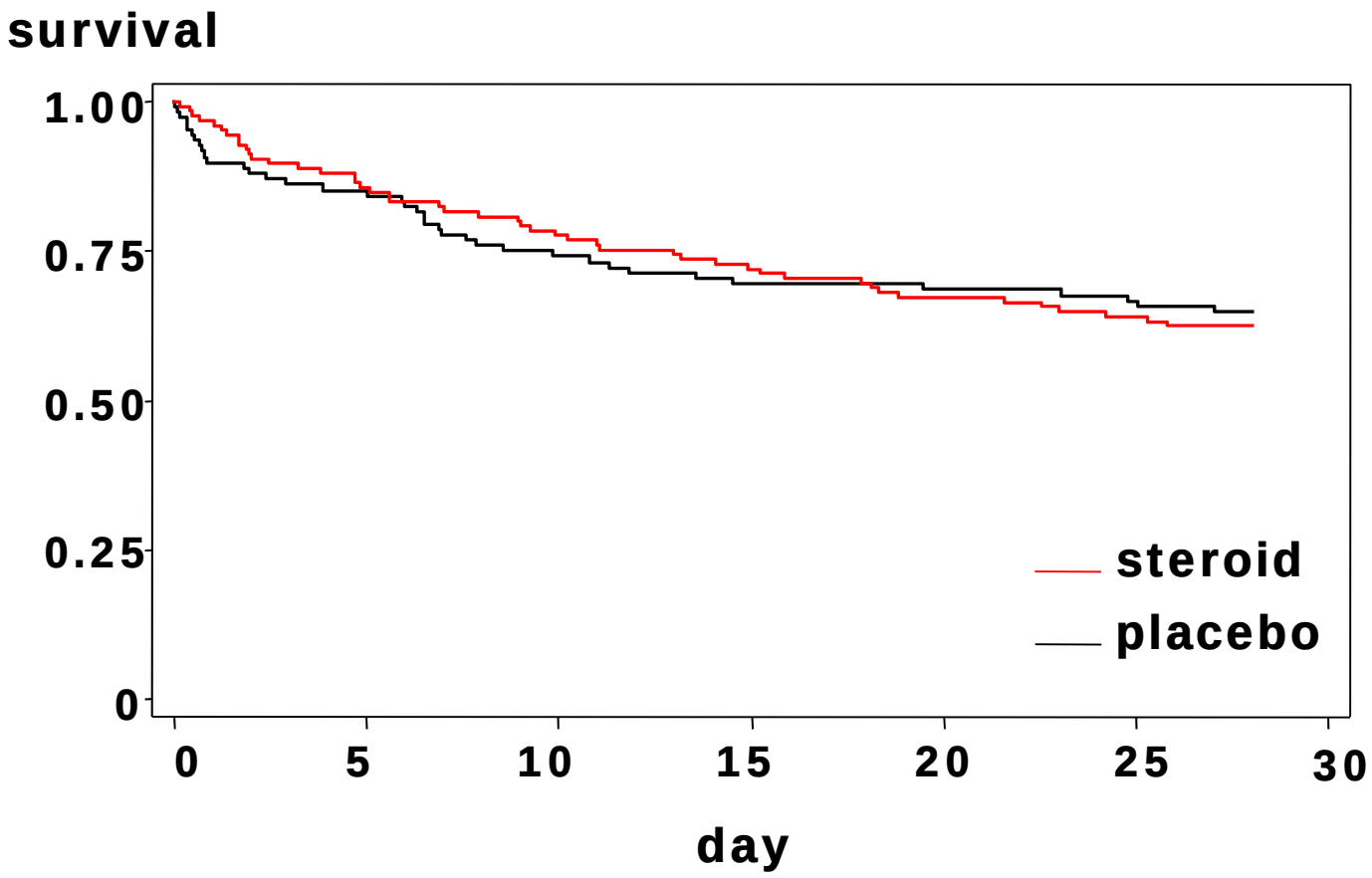
Corticus

RESULTS: 28-day mortality - all patients



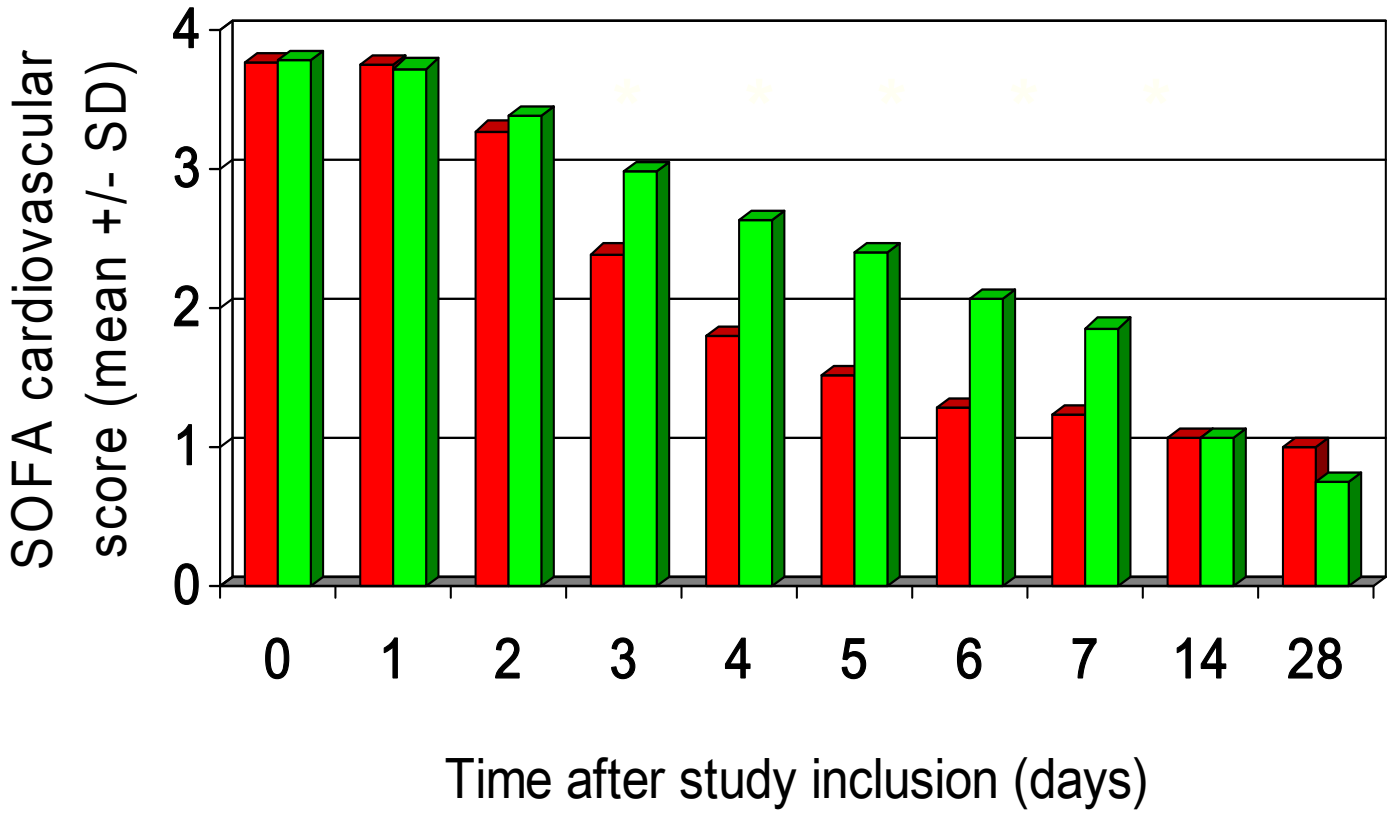
P = 0.51

RESULTS: 28 day survival curves - ACTH non-responders



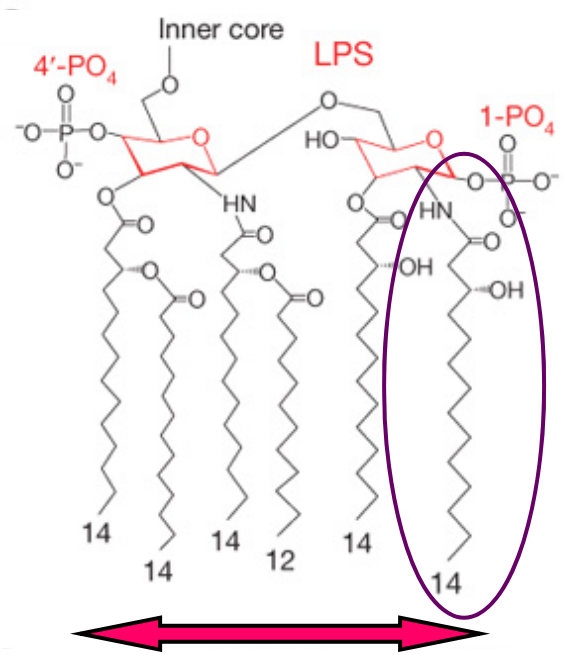
P value for log rank test: 0.786

SOFA cardiovascular score

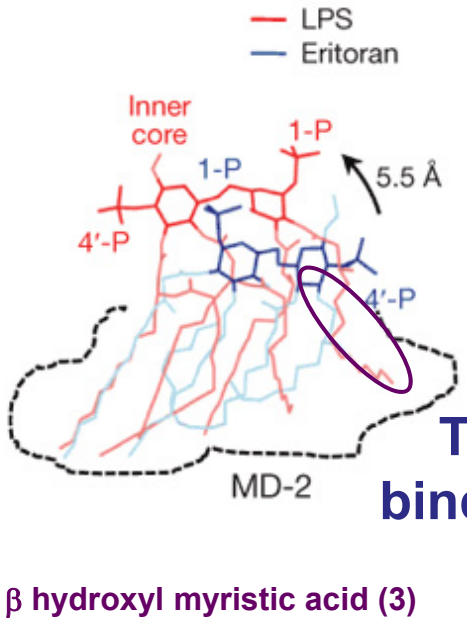


(* p < 0.05)

E. coli Lipid A Versus Eritoran (E5564) as a Lipid A Antagonist

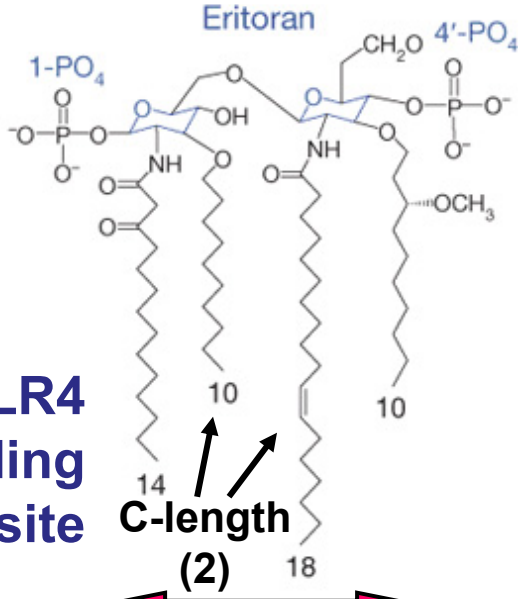


Hexa-acyl format



β hydroxyl myristic acid (3)

TLR4 binding site



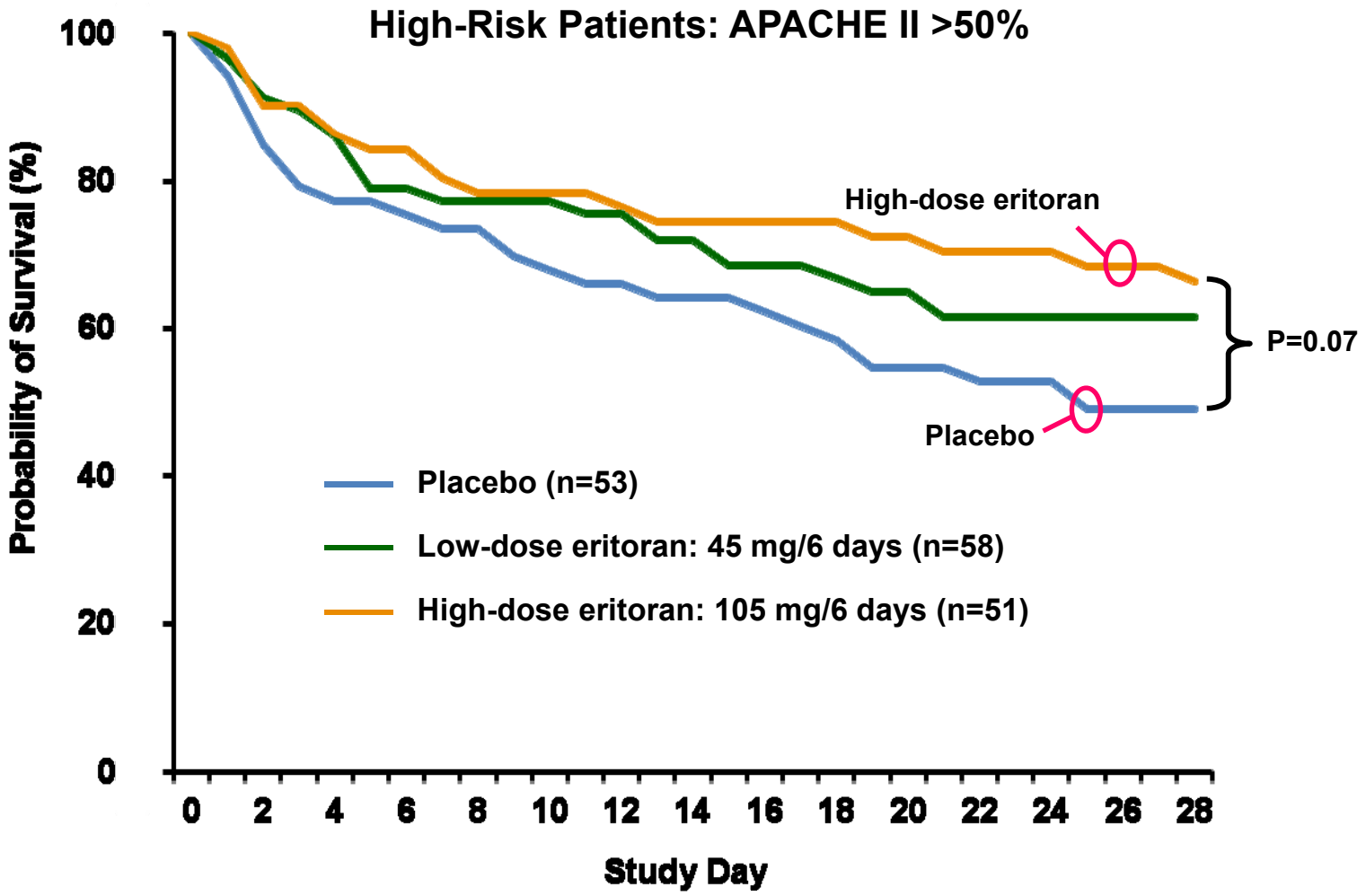
C-length (2)

Tetra-acyl format (1)

E. coli **lipid A**

Park et al. *Nature* 2009;7830:1-5

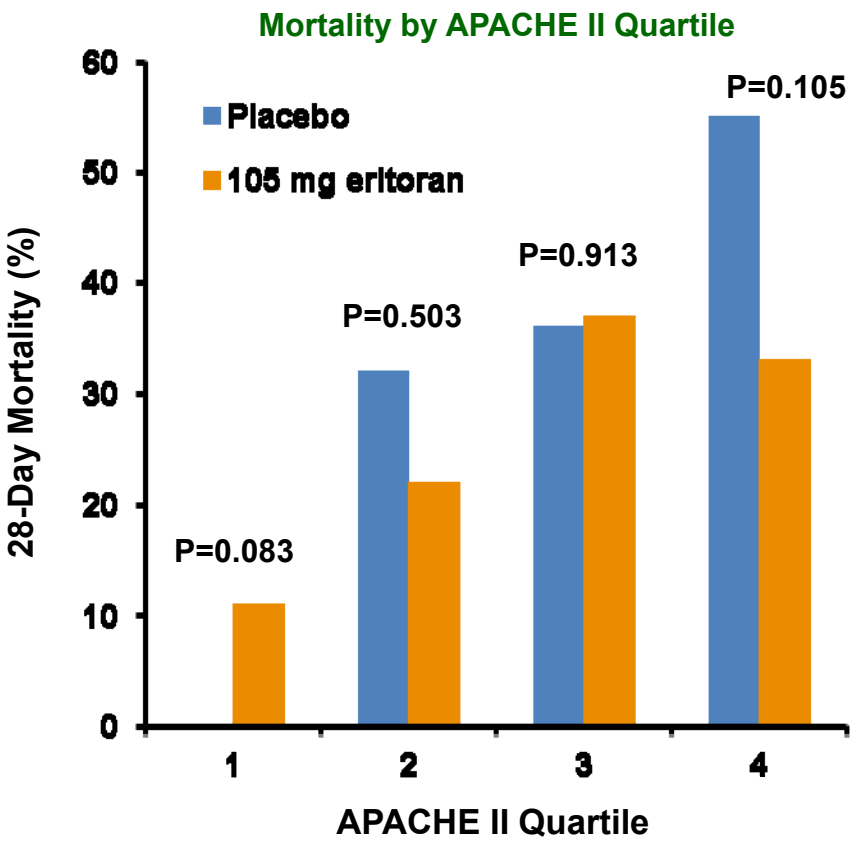
Eritoran Phase II Clinical Trial

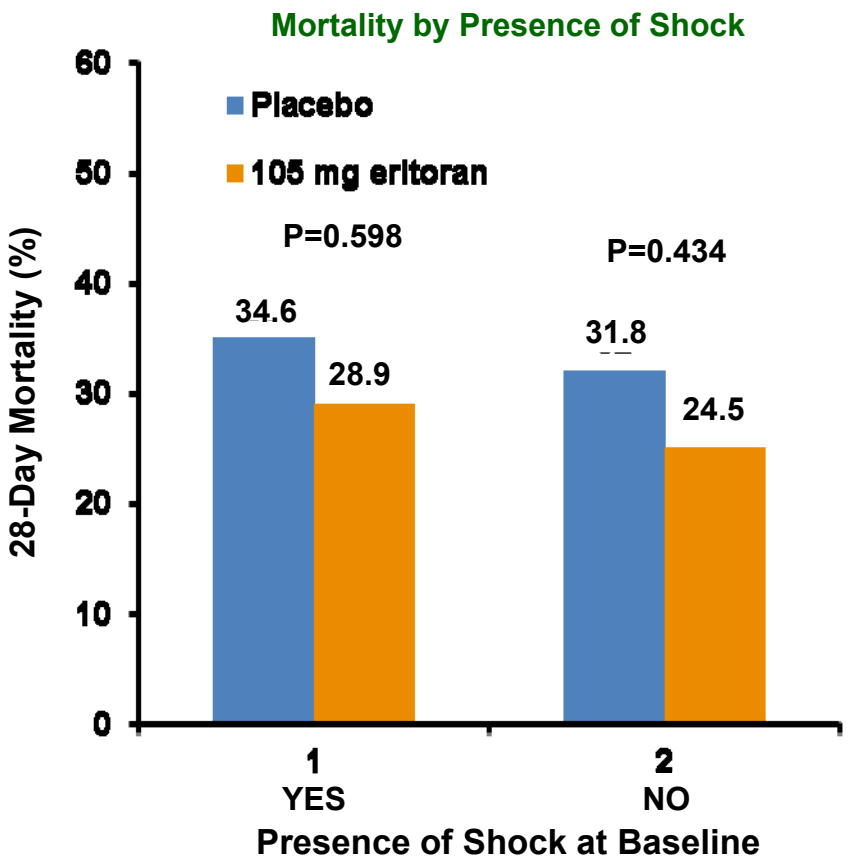


Tidswell et al. *Crit Care Med* 2010;38:72-83

Eritoran Phase II Clinical Trial

Prospectively Defined Subgroups





Tidswell et al. *Crit Care Med* 2010;38:72-83

Endotoxin in Critically Ill

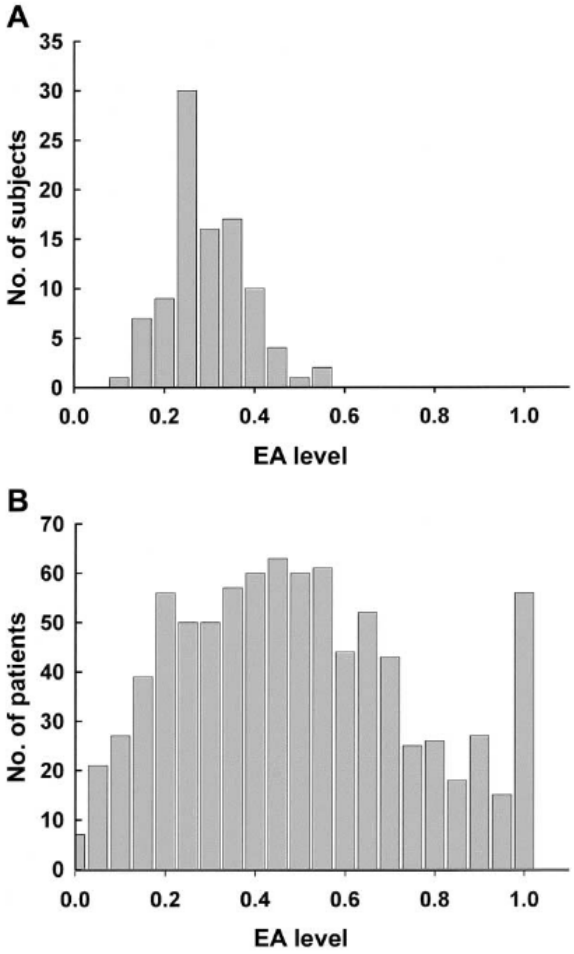


Figure 1. Endotoxin activity (EA) in blood from healthy volunteers and from critically ill patients in the intensive care unit (ICU). *A,* EA in whole-blood samples obtained from 97 healthy volunteers. Low-level activity was evident in the majority of subjects, although in none was the level >0.60 EA units. *B,* Distribution of EA levels in the 857 patients studied, on the day of their admission to the ICU.

ACCESS Trial

A Controlled Comparison of Eritoran Tetrasodium and Placebo in Patients with Severe Sepsis

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Eritoran Tetrasodium in Patients with Severe Sepsis: Can Inhibition of TLR-4 Improve All-Cause Mortality in Patients with Severe Sepsis?

- **159 worldwide study locations**
- **Just under 2000 patients enrolled in trial**

Disease Severity and Characteristics

Variables at baseline	Placebo (N=657)	Eritoran (N=1304)
APACHE II Mean (+/-SD)	27.3 (4.52)	27.2 (4.50)
21 to 24	209 (31.8%)	441 (33.8%)
25 to 26	122 (18.6%)	219 (16.8%)
27 to 31	194 (29.5%)	371 (28.5%)
32 to 37	128 (19.5%)	265 (20.3%)
All Organ Dysfunctions, n (%)		
ALI/ARDS	164 (25.0%)	296 (22.7%)
Thrombocytopenia	102 (15.5%)	221 (16.9%)
Lactic acidosis	333 (50.7%)	625 (47.9%)
Shock	533 (81.1%)	1070 (82.1%)
AKI	226 (34.4%)	472 (36.2%)
Number of Organ Failures, n (%)		
1	223 (33.9%)	449 (34.4%)
2	234 (35.6%)	443 (34.0%)
3	138 (21.0%)	299 (22.9%)
4 or 5	62 (9.5%)	110 (8.4%)

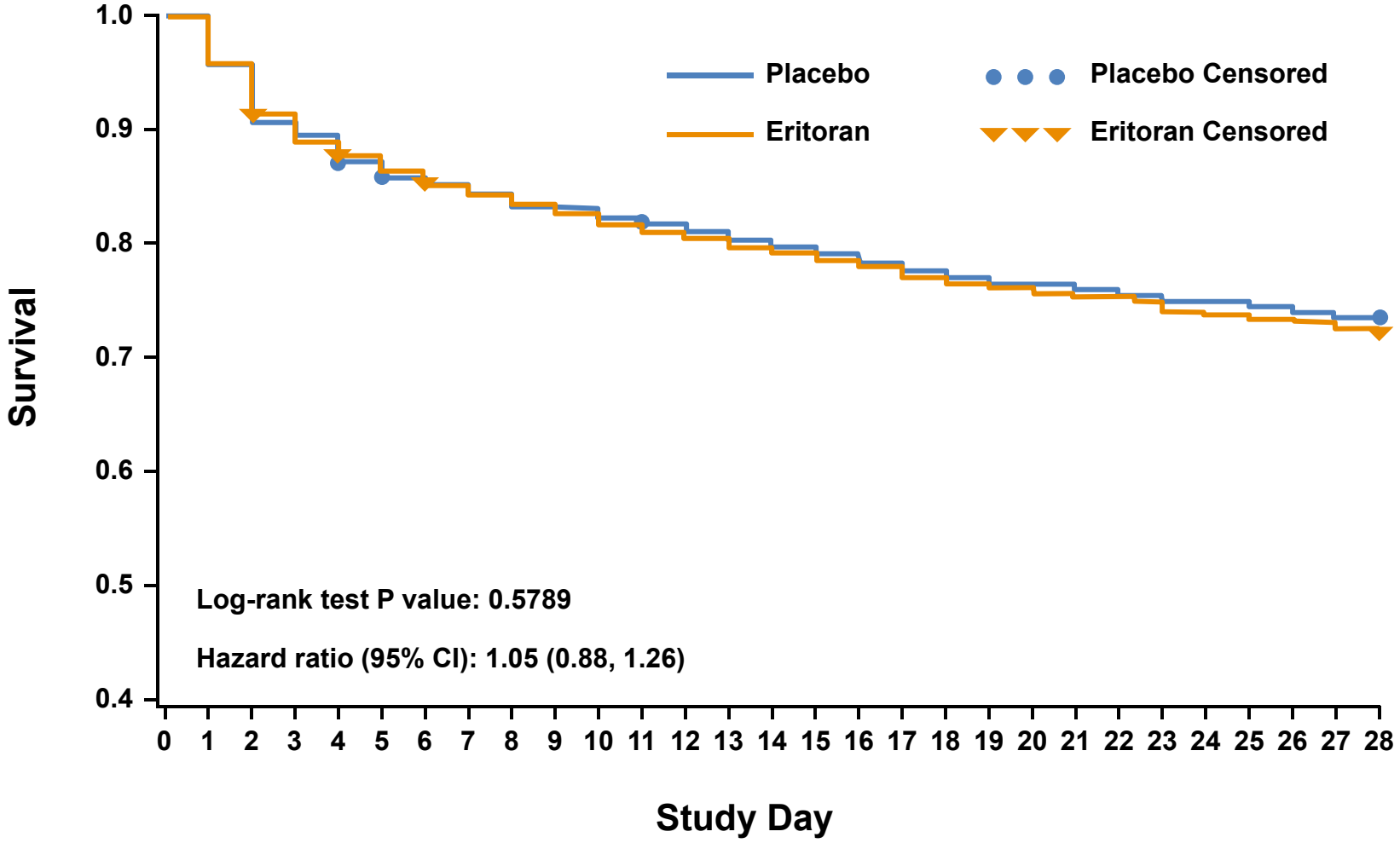
Disease Characteristics: Adjudicated by CEC

Variable (Site and type of infection)	Placebo (N=657)	Eritoran (N=1304)
Lung	254 (38.7%)	519 (39.8%)
Genitourinary	106 (16.1%)	185 (14.2%)
Intra-abdominal/GYN	163 (24.8%)	300 (23.0%)
Catheter-related blood	6 (0.9%)	24 (1.8%)
Skin/soft tissue	50 (7.6%)	91 (7.0%)
CNS	12 (1.8%)	27 (2.1%)
Endovascular	6 (0.9%)	24 (1.8%)
Bone/joint	10 (1.5%)	22 (1.7%)
Type of Infection		
Gram negative bacteria	215 (32.7%)	421(32.3%)
Gram positive bacteria	182 (27.7%)	349 (26.8%)
Mixed gram+ and gram− bacteria	76 (11.6%)	136 (10.4%)
Fungal / Mixed bacterial and fungal	4 (0.6%)/ 15 (2.3%)	19 (1.5%)/ 34(2.6%)
Unknown	143 (21.8%)	299 (22.9%)

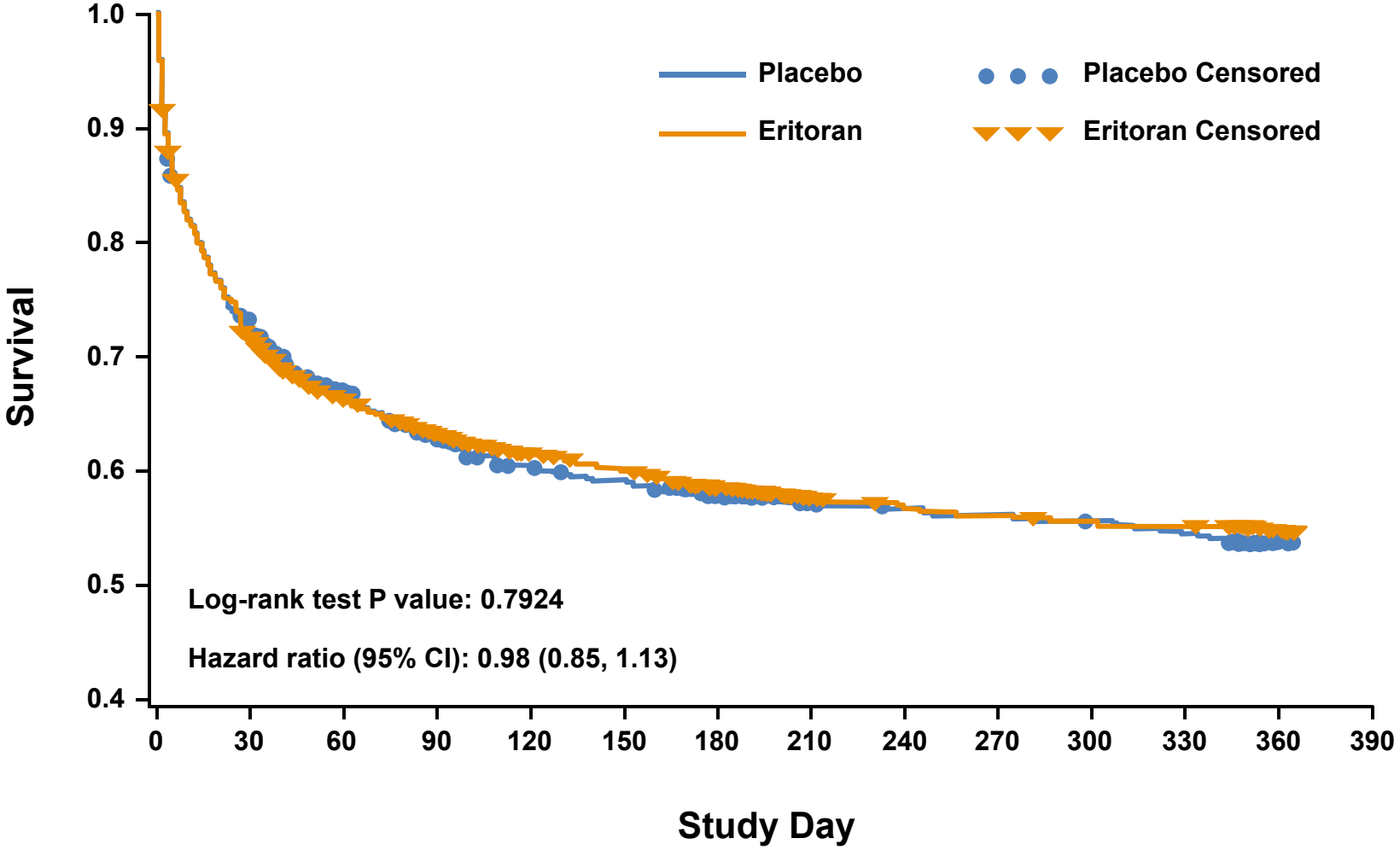
Sepsis Treatment Adjudicated by CEC

Sepsis Treatment	Placebo (N=657)	Eritoran (N=1304)
Source Control-Adequate	238 (36.2%)	454 (34.8%)
Source Control- Inadequate	39 (5.9%)	84 (6.4%)
N/A	380 (57.8%)	766 (58.7%)
Antimicrobial Therapy Type		
Targeted	487 (74.1%)	952 (73.0%)
Empiric	148 (22.5%)	307 (23.5%)
Appropriate Antimicrobial Therapy		
YES	612 (93.2%)	1199 (91.9%)
NO	23 (3.5%)	59 (4.5%)
Time to Appropriate Antimicrobial Rx		
< 0 hour	270 (41.1%)	517 (39.6%)
0 to 4 hours	207 (31.5%)	383 (29.4%)
4 < to 8 hours	52 (7.9%)	125 (9.6%)
8 < to 12 hours	21 (3.2%)	39 (3.0%)
12 < to 24 hours	11 (1.7%)	37 (2.8%)
> 24 hours	51 (7.8%)	98 (7.5%)
Appropriate Antimicrobial Duration	604 (91.9%)	1161 (89.0%)

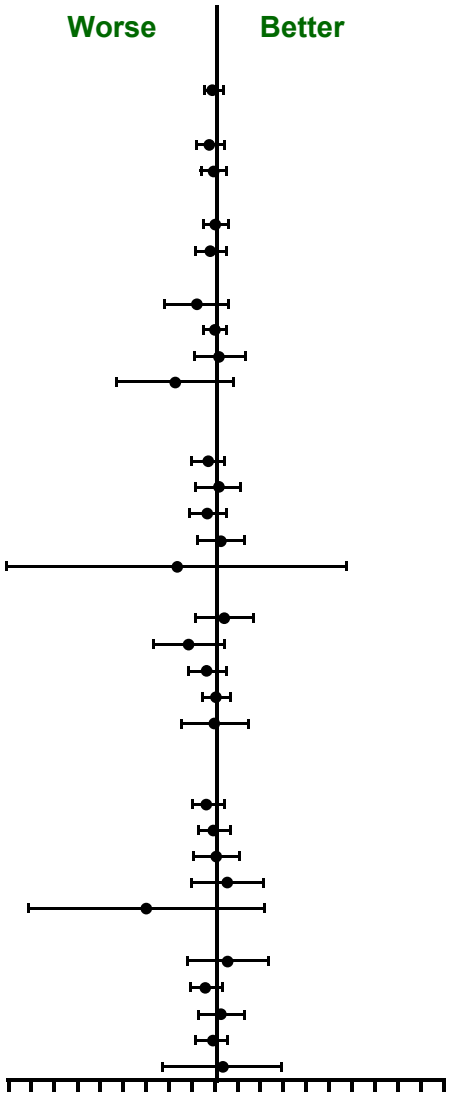
28-Day Mortality



1-Year Mortality (Secondary Endpoint)

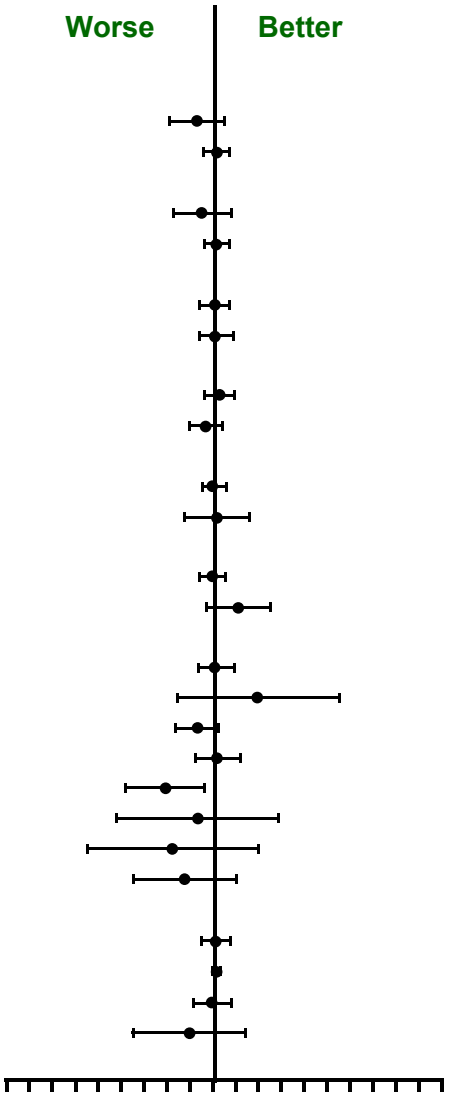


28-Day Mortality Subgroup Analysis (1)



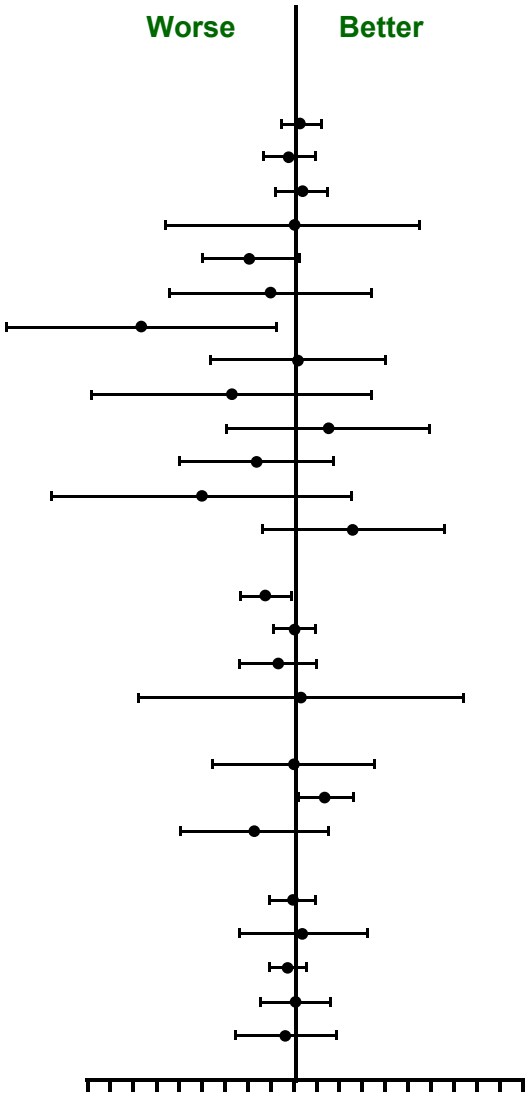
	N	Mortality (%) Placebo	Eritoran	Difference (95% CI)
Overall	1961	26.9	28.1	−1.1 (−5.3, 3.1)
Age Categorized				
Age 18 − 64 yr	814	20.7	23.0	−2.2 (−8.3, 3.8)
Age ≥ 65 yr	1147	31.3	31.7	−0.4 (−6.1, 5.2)
Gender				
Male	1145	26.1	26.5	−0.4 (−5.8, 5.0)
Female	816	28.1	30.3	−2.2 (−8.8, 4.4)
Race				
Black	120	11.6	19.5	−7.9 (−21.8, 6.1)
White	1544	28.7	29.0	−0.3 (−5.1, 4.5)
Asian	239	25.3	23.7	1.6 (−9.8, 13.0)
Other	58	21.1	38.5	−17.4 (−43.1, 8.3)
APACHE II Group				
< 21	5		0.0	
≥ 21 − ≤ 24	650	19.1	22.4	−3.3 (−10.1, 3.4)
> 24 − ≤ 26	341	29.5	28.3	1.2 (−8.8, 11.2)
> 26 − ≤ 31	565	25.8	29.1	−3.3 (−11.1, 4.5)
> 31 − ≤ 37	393	38.3	35.8	2.4 (−7.7, 12.6)
> 37	7	50.0	66.7	−16.7 (−90.7, 57.4)
Qualifying Organ Dysfunction				
Lung injury/respiratory distress	189	25.4	21.4	4.0 (−8.7, 16.6)
Thrombocytopenia	157	19.1	30.9	−11.8 (−27.0, 3.5)
Lactic acidosis	500	28.4	32.0	−3.6 (−12.2, 4.9)
Shock	959	28.4	28.0	0.4 (−5.6, 6.4)
Acute renal failure	153	21.3	21.7	−0.4 (−14.5, 13.7)
Number of Organ Dysfunctions				
0	3		0.0	
1	672	21.5	24.9	−3.4 (−10.3, 3.4)
2	677	23.5	24.2	−0.6 (−7.4, 6.1)
3	437	35.5	35.1	0.4 (−9.2, 10.0)
4	155	42.1	36.7	5.4 (−10.5, 21.3)
5	17	20.0	50.0	−30.0 (−81.3, 21.3)
Time to First Dose of Study Drug from Recognition of Qualifying Organ Dysfunction				
> 0 − ≤ 4 hours	118	31.6	26.3	5.3 (−12.0, 22.7)
> 4 − ≤ 8 hours	653	25.0	29.1	−4.1 (−11.4, 3.1)
> 8 − ≤ 10 hours	384	31.0	28.7	2.3 (−7.6, 12.2)
> 10 − ≤ 12 hours	743	25.1	26.4	−1.3 (−8.0, 5.3)
> 12	60	40.0	37.5	2.5 (−23.6, 28.6)

28-Day Mortality Subgroup Analysis (2)



	N	Mortality (%) Placebo	Eritoran	Difference (95% CI)
SOFA Scores − Cardiovascular				
0 − 1	301	20.4	27.6	−7.2 (−17.7, 3.3)
2 − 4	1658	28.0	28.2	−0.1 (−4.7, 4.4)
SOFA Scores − Respiratory				
0 − 1	268	21.3	26.4	−5.2 (−16.0, 5.6)
2 − 4	1647	28.1	28.0	0.1 (−4.5, 4.7)
SOFA Scores − CNS				
0 − 1	1047	24.3	25.1	−0.8 (−6.3, 4.7)
2 − 4	866	29.9	30.1	−0.2 (−6.8, 6.3)
SOFA Scores − Renal				
0 − 1	905	21.5	20.6	0.9 (−4.7, 6.6)
2 − 4	1029	30.8	34.8	−4.0 (−10.0, 2.0)
SOFA Scores − Coagulation				
0 − 1	1282	23.7	24.8	−1.1 (−6.0, 3.9)
2 − 4	286	36.8	36.6	0.2 (−11.7, 12.1)
SOFA Scores − Hepatic				
0 − 1	1639	25.9	27.5	−1.6 (−6.2, 2.9)
2 − 4	255	33.7	25.6	8.2 (−3.6, 19.9)
Infection Site				
Lung	1000	29.5	29.8	−0.3 (−6.4, 5.7)
Primary bloodstream	50	41.7	26.3	15.4 (−14.4, 45.1)
Genitourinary	417	16.8	23.9	−7.1 (−15.3, 1.1)
Abdomen	464	29.6	29.2	0.4 (−8.3, 9.1)
Skin/soft tissue	177	16.4	35.2	−18.9 (−33.4, −4.4)
CNS	45	28.6	35.5	−6.9 (−36.7, −22.8)
Catheter-related bacteremia	46	18.2	34.3	−16.1 (−47.3, 15.1)
Other	113	22.6	34.1	−11.6 (−30.7, 7.5)
Primary Care Status				
Medical	1163	28.5	28.8	−0.3 (−5.9, 5.2)
Burn	6	0.0	0.0	0.0 (0.0, 0.0)
Surgical	741	26.2	27.9	−1.7 (−8.4, 5.0)
Trauma	51	6.7	16.7	−10.0 (−30.7, 10.7)

28-Day Mortality Subgroup Analysis (3)



	N	Mortality (%) Placebo	Eritoran	Difference (95% CI)
Primary Focus of Infection				
Lung	773	29.9	27.4	2.6 (−4.2, 9.3)
Genitourinary	291	13.2	14.6	−1.4 (−9.7, 6.9)
Intra-abdominal or GYN	463	30.7	28.3	2.3 (−6.3, 11.0)
Catheter-related, bloodstream	30	33.3	33.3	0.0 (−42.2, 42.2)
Skin or soft tissue	141	22.0	36.3	−14.3 (−30.2, 1.7)
CNS (brain or spinal cord)	39	33.3	40.7	−7.4 (−40.5, 25.7)
Endovascular infection	30	16.7	66.7	−50.0 (−94.3, −5.7)
Bone/joint	32	20.0	18.2	1.8 (−27.4, 31.0)
Head/ear/nose/throat	13	0.0	20.0	−20.0 (−66.6, 26.6)
Pleural	17	20.0	8.3	11.7 (−21.9, 45.3)
None	63	28.6	40.5	−11.9 (−37.1, 13.3)
Other	23	20.0	50.0	−30.0 (−79.1, 19.1)
Unknown	46	56.3	36.7	19.6 (−10.5, 49.7)
Infection Type				
Gram positive	531	24.7	33.8	−9.1 (−17.4, −0.8)
Gram negative	636	22.3	21.9	0.5 (−6.3, 7.3)
Gram+/gram− bacteria	212	27.6	32.4	−4.7 (−17.7, 8.2)
Fungal	23	50.0	47.4	2.6 (−51.2, 56.5)
Viral	1	0.0	100.0	
Bacterial/fungal/other	49	26.7	26.5	0.2 (−26.6, 27.0)
Unknown	442	35.7	25.1	10.6 (1.6, 19.6)
No evidence of infection	67	27.3	40.0	−12.7 (−37.2, 11.7)
Region				
North America	611	29.0	29.2	−0.2 (−7.8, 7.4)
Latin America	112	53.1	50.0	3.1 (−17.4, 23.6)
Europe	895	23.4	25.2	−1.8 (−7.7, 4.2)
Asia	214	23.4	22.6	0.7 (−11.0, 12.5)
Rest of World	129	28.6	31.0	−2.5 (−19.4, 14.5)

What Went Wrong?

Is the LPS signaling pathway still a viable target for therapeutic intervention?

- **In addition to the usual challenges with large sepsis trials (patient heterogeneity, myriad of pathogens and infection sites, different practice patterns, etc), what other factors should be considered?**
- **Once septic shock has begun, is it too late to intervene with an MD2:TLR4 inhibitor? (LPS re-programming, sepsis-induced immune suppression)**
- **Was the selected study population too sick? Not sick enough? Did they not have LPS-LBP-CD14-MD2:TLR4 dependent sepsis? Was eritoran timing and dosing appropriate?**
- **Are there better ways to inhibit TLR4? (Combinations? Intracellular signaling inhibitors?)**
- **Why was the placebo mortality so low? Was the study not powered due to the low placebo mortality?**

Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

JAMA, June 17, 2009—Vol 301

Table 1. Baseline Characteristics of the Treatment Groups[a]

Characteristics	Mean (95% Confidence Interval)		*P* Value
	Polymyxin B Hemoperfusion (n = 34)	Conventional Therapy (n = 30)	
Age, y	61 (57-66)	67 (61-72)	.09
Male sex, No. (%)	24 (71)	18 (60)	.53
APACHE II score	21 (19-23)	20 (18-23)	.86
SOFA score	11 (10-12)	9 (8-11)	.07
Mean arterial pressure, mm Hg	76 (72-80)	74 (70-78)	.40
Noradrenaline, µg/kg/min	0.27 (0.17-0.36)	0.24 (0.13-0.36)	.70
Dopamine, µg/kg/min	3.1 (1.7-4.4)	4.6 (2.9-5.6)	.13
Inotropic score	29.9 (20.4-39.4)	28.6 (16.6-40.7)	.85
Vasopressor dependency index, mm Hg^{-1}	4.3 (2.7-5.9)	4.1 (2.3-6.0)	.87
White blood cell count, 1000/µL	13.7 (11.4-16.0)	11.4 (9.0-13.8)	.12
PaO_2/FIO_2	235 (206-265)	217 (188-247)	.53
Diuresis, mL/h	66 (50-90)	87 (59-116)	.22
Creatinine, mg/dL	2.3 (1.7-2.9)	1.7 (1.3-2.2)	.18
Renal replacement therapy, No. (%)	13 (38)	6 (20)	.17

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The EUPHAS Randomized Controlled Trial

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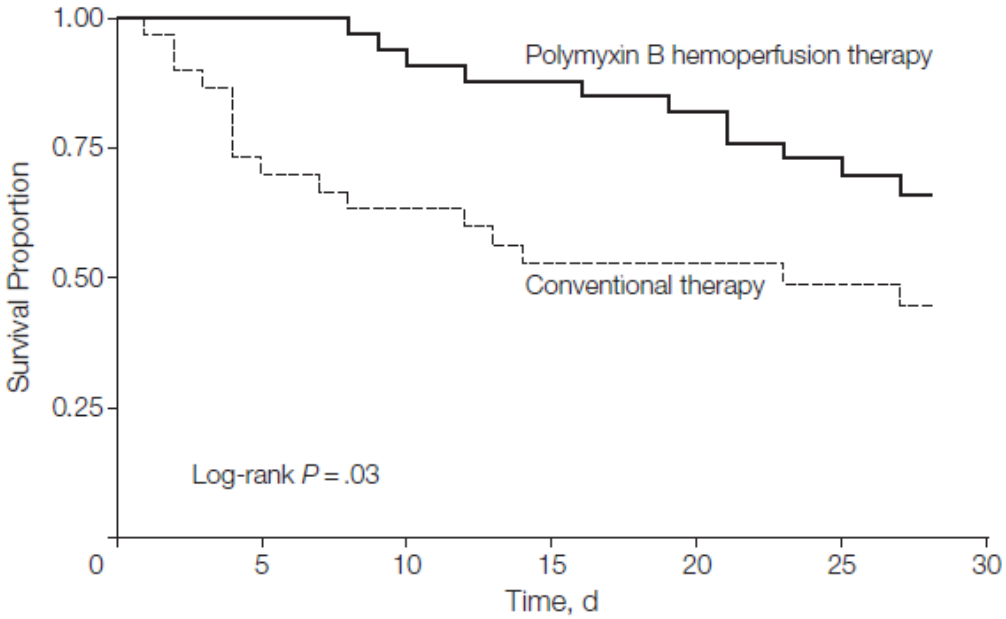
Figure 3. Estimation of Survival Rate According to Treatment Group

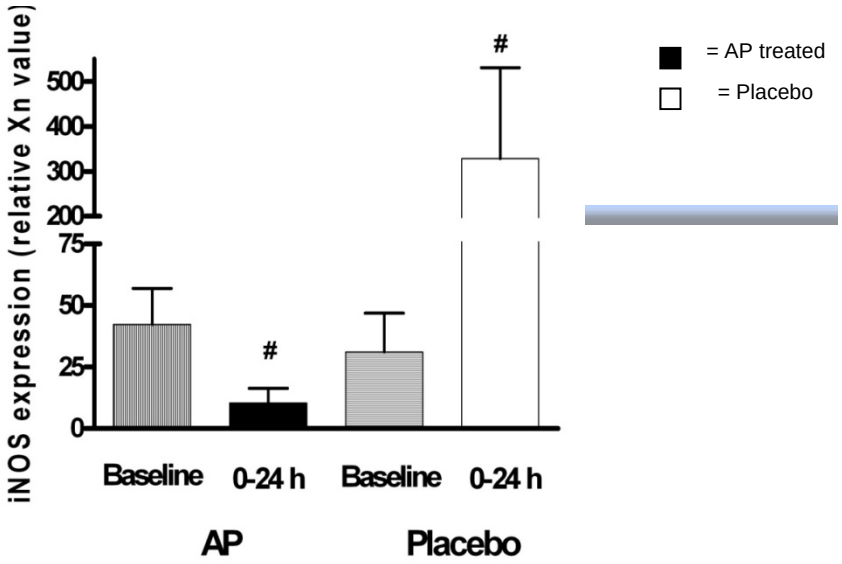


No. at risk							
Polymyxin B hemoperfusion therapy	34	34	32	30	27	22	18
Conventional therapy	30	22	19	15	15	12	11

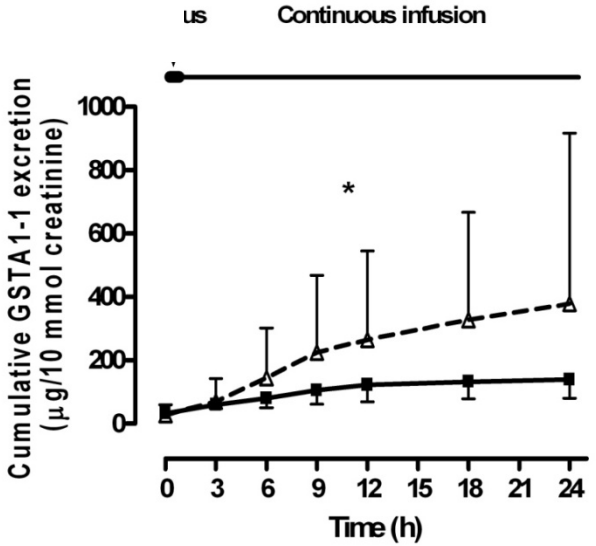
Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

Anti-Inflammatory Effect of AP Prevents further Renal Damage (APSFP)

Inflammation (Induction of iNOS) is reduced in AP treated patients



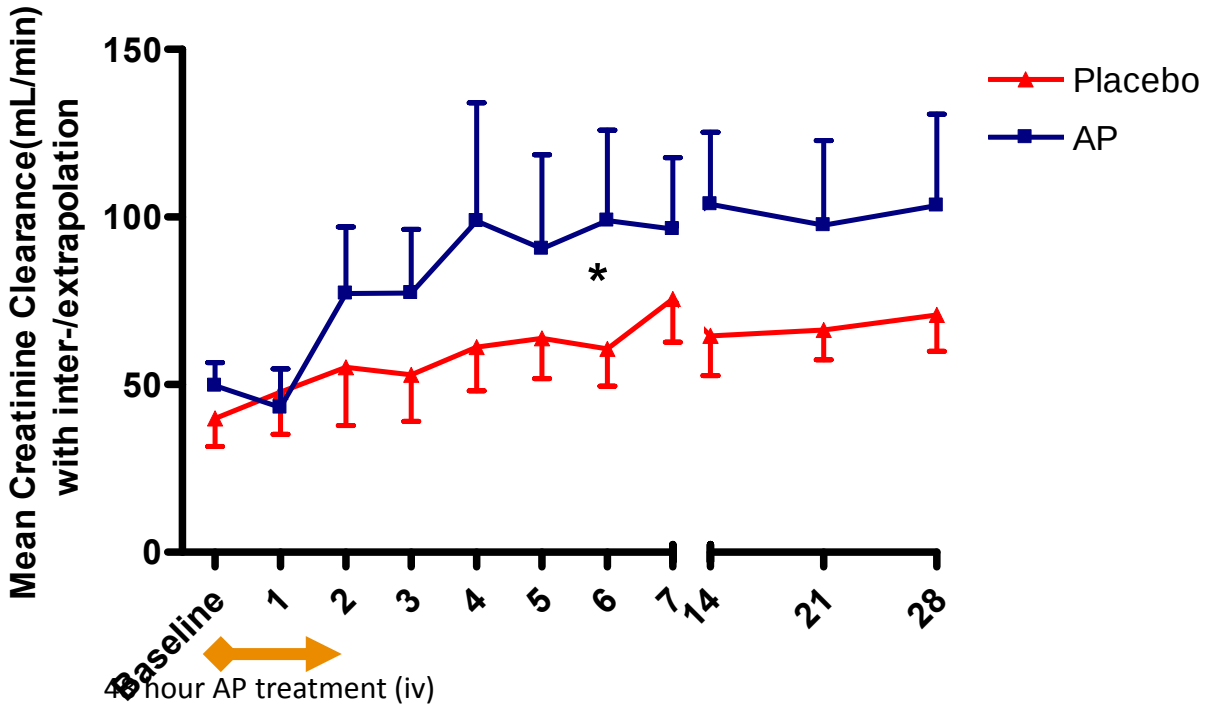
Proximal tubular renal damage (GSTA1-1) is reduced in AP treated patients



CCM 2009

AP-Treatment Improved Renal Creatinine Clearance is Sustained During Study Period

Renal Creatinine Clearance remains higher for the treatment group and impaired for the placebo group during the study period (FAS)



Clearance with linear inter/extrapolation for missing values

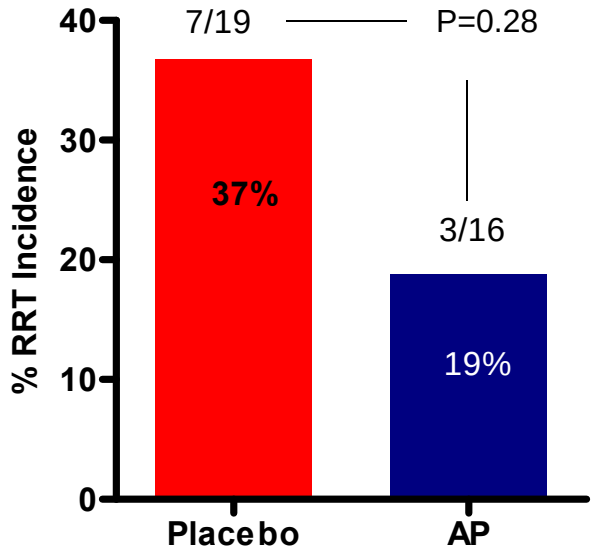
*** p<0.02 two-way Anova repeated measures**

AP Treatment Reduces Dialysis Requirement

AP-treatment reduces need for dialysis and relative dialysis duration

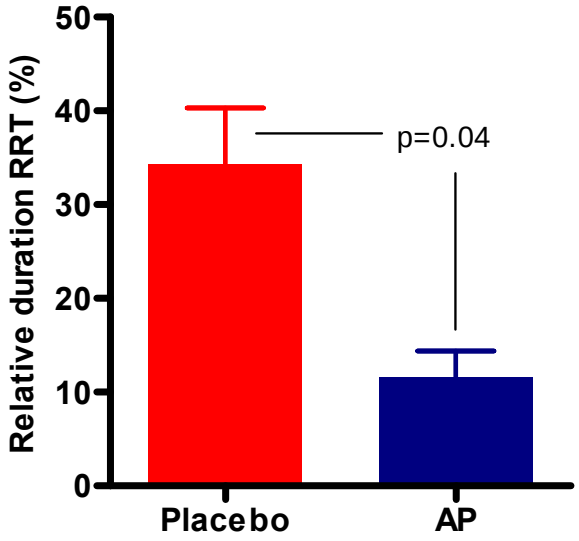
Dialysis Requirement (ITT)

Yes/no dialysis requirement during 28 days



Relative Dialysis Duration in % (ITT)

Total dialysis duration for dialysis patients / Time (d) in the study

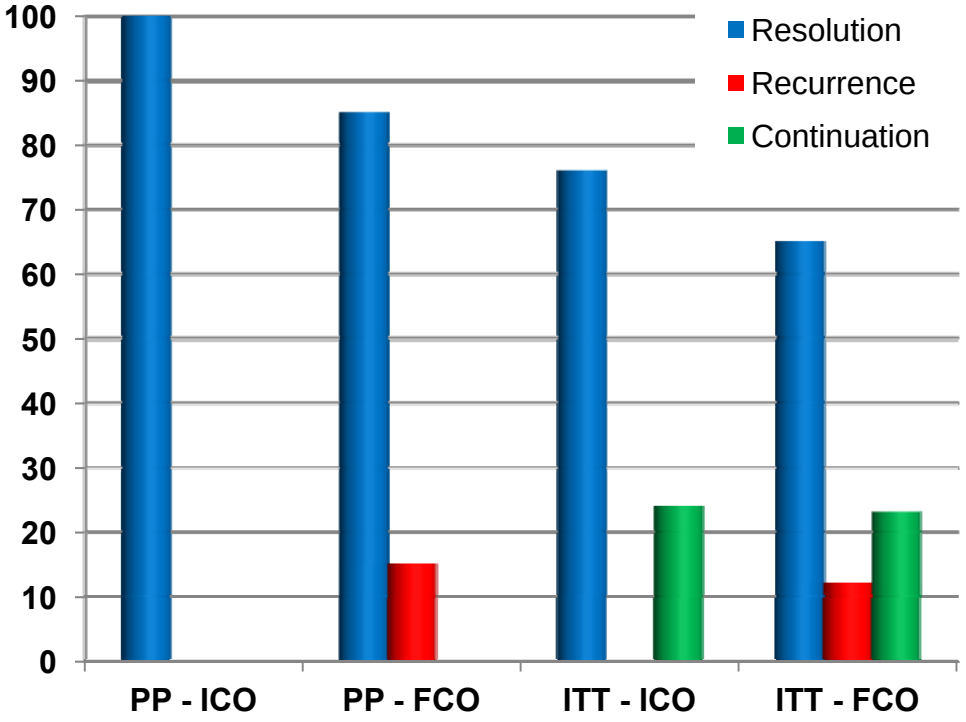


EMA advises: reduced dialysis requirement will be pivotal primary endpoint

PANOBACUMAB: Phase IIa

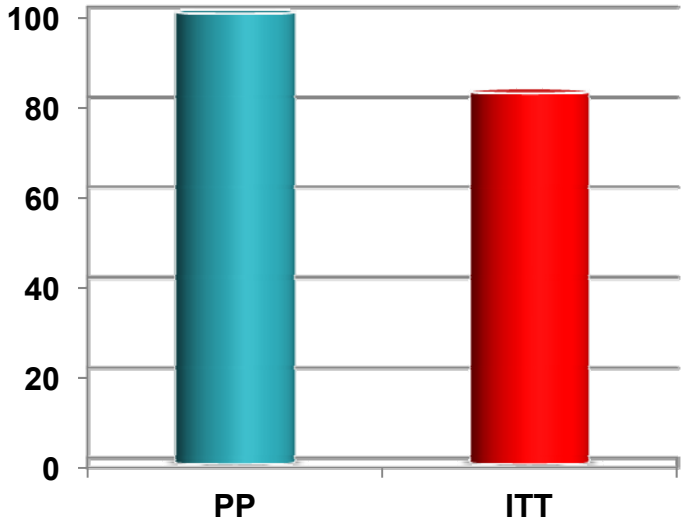
fully human monoclonal antibody (IgM

ITT: 17 P.a. O11 patients treated with Panobacumab VAP: 14 - HAP: 3	
PP: 13 pts (3 doses) VAP: 12 - HAP: 1	4 pts with 1 dose VAP: 2 - HAP: 2



ICO: Initial clinical outcome
FCO: Final clinical outcome

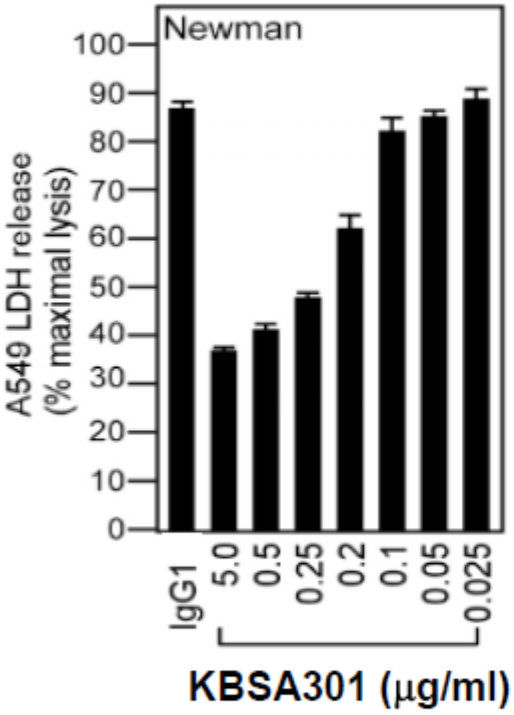
SURVIVAL (D-30)	
PP	**ITT**



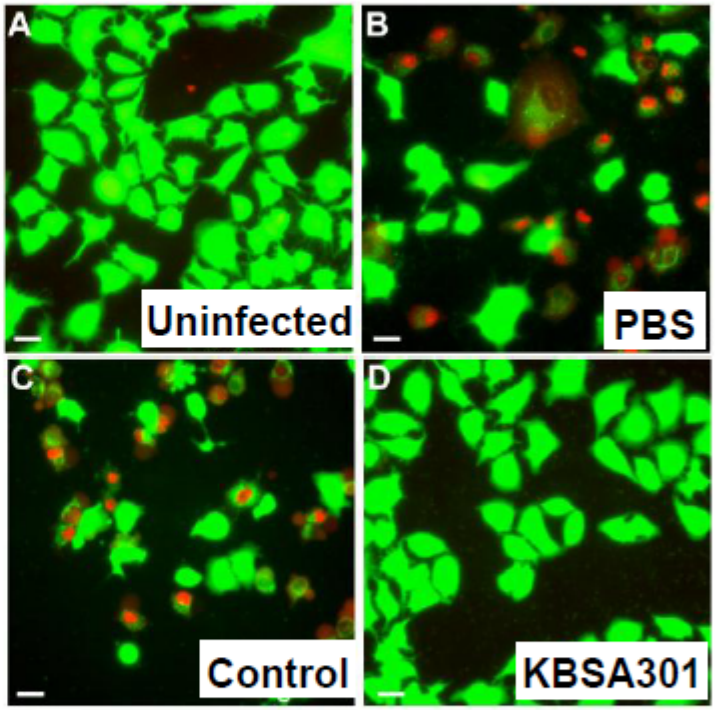
Laterre. ECCMID 2010

Protection of human alveolar epithelial cells from αToxin induced lysis using KBSA301

LDH ELISA



Microscoping imaging

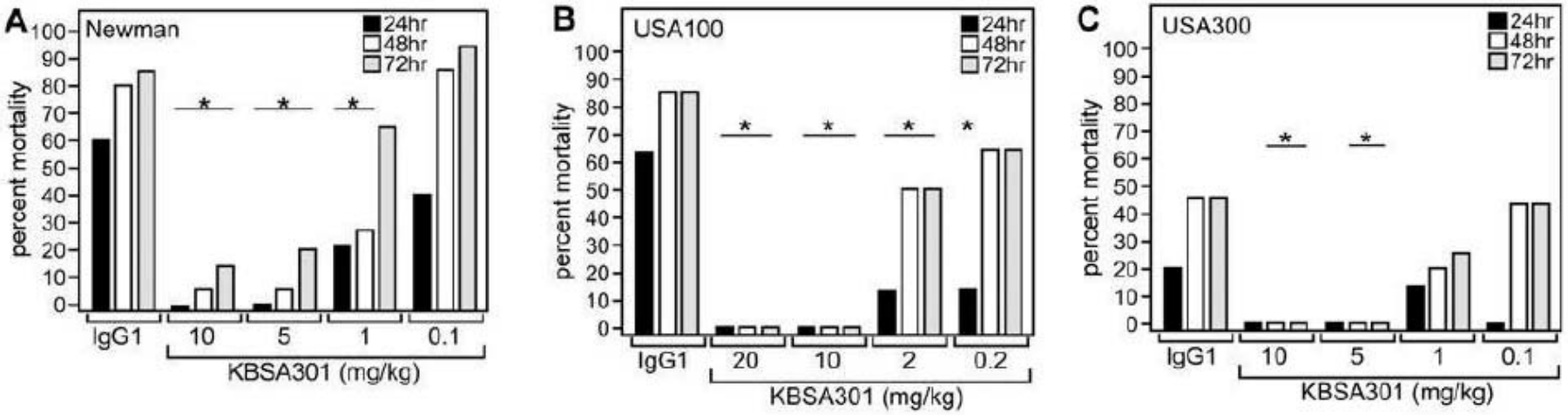


green = live cells; red = dead cells

- Human alveolar epithelial cells (A549) are incubated with *S. aureus* culture supernatant
- Cells are protected from lysis by application of KBSA301

kenta BIOTECH

In vivo functionality of KBSA301 in a prophylactic mouse lung challenge model

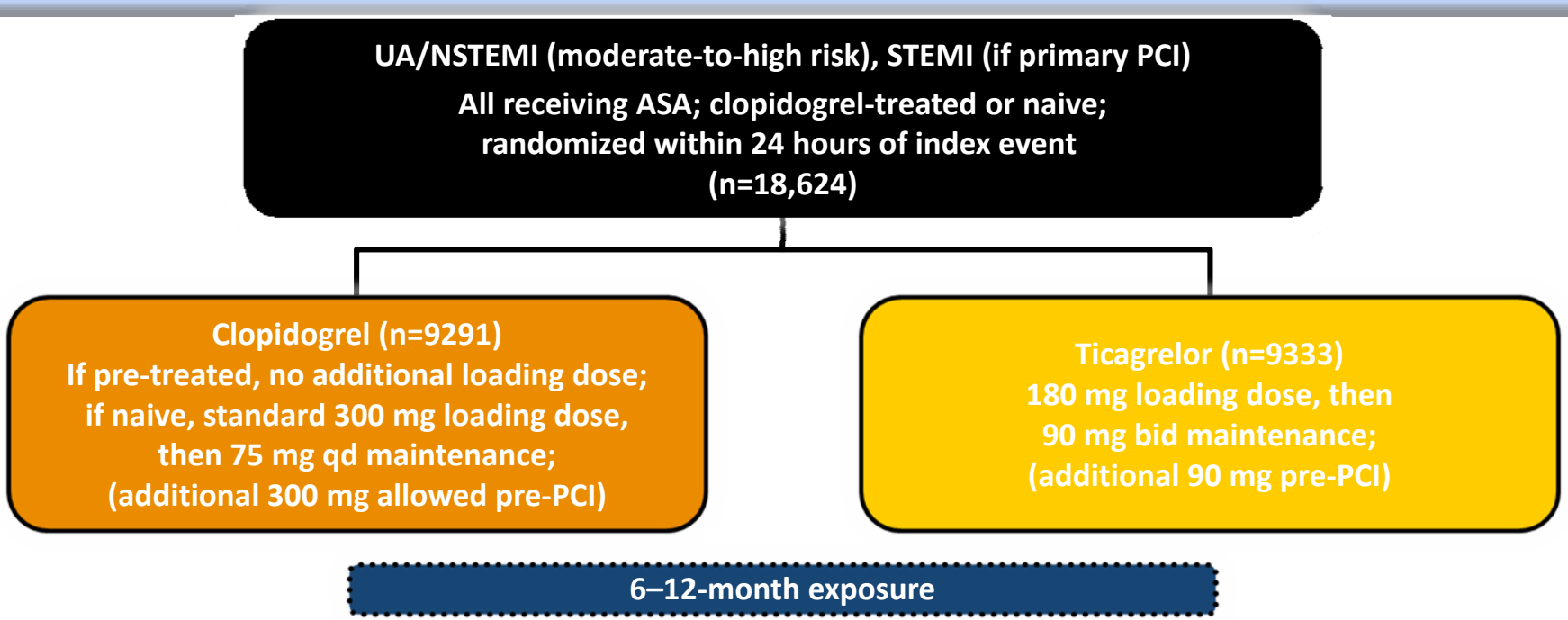


- Prophylactic administration of KBSA301 resulted in dose dependent protection against MSSA (A), HA-MRSA (B) and CA-MRSA (C) strains of highest incidence
- Statistical significance ($P < 0.05$) to the isotype control group is indicated by an asterisk

New developments

- V1a agonist FE 202158 (Ferring)
  - Vasopressin analog
  - Treatment of septic shock
- Polyclonal anti-TNF antibody
  - Phase II trial completed (results pending)
  - Phase III trial ?

PLATO: Study design



Primary endpoint:
- CV mortality, MI or stroke

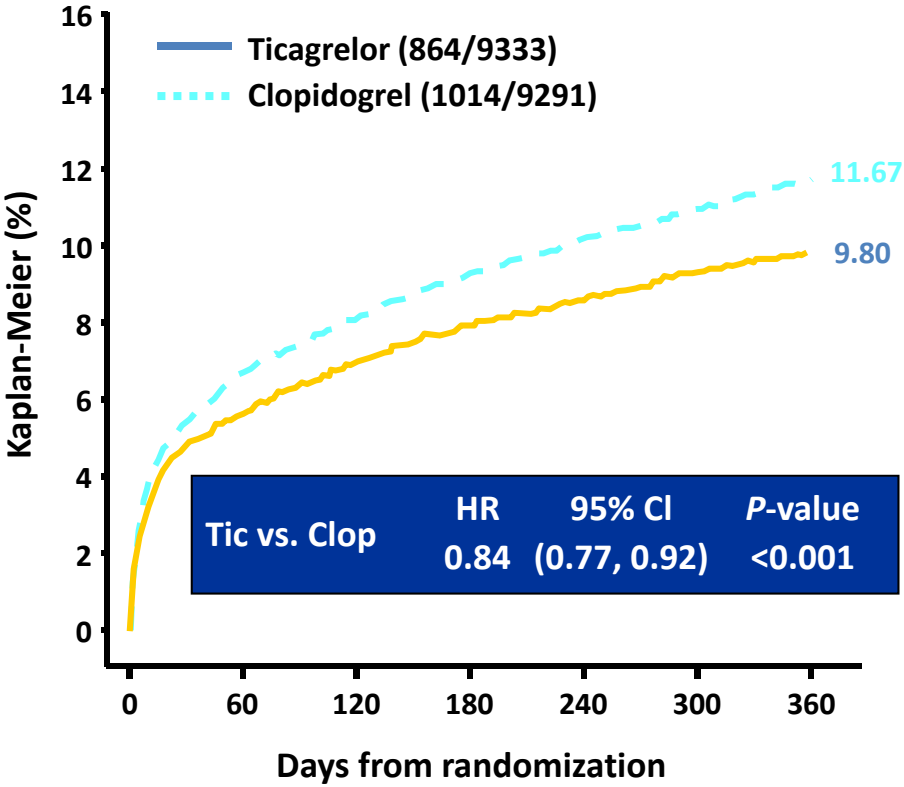
Key secondary:
- CV mortality, MI or stroke in patients intended for invasive management
- Total mortality or MI + stroke
- CV mortality, MI, stroke, recurrent ischemia, TIA or arterial thrombotic events
- MI alone/CV mortality alone/stroke alone/total mortality alone

Primary safety:
- Total major bleeding (PLATO definition)

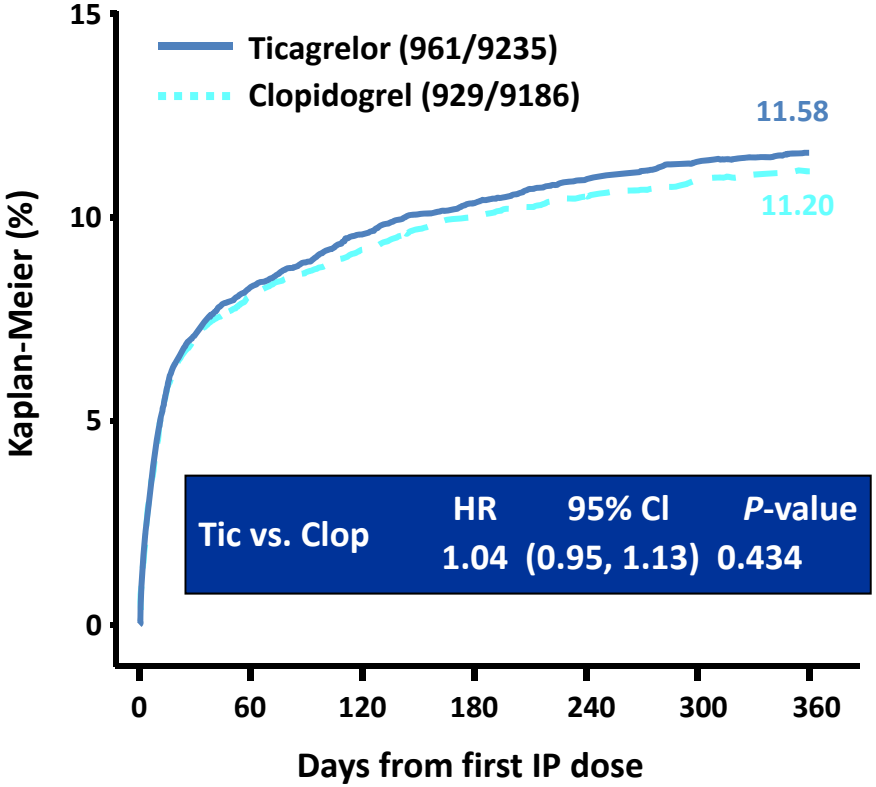
James S *et al*. *Am Heart J* 2009;157:599–605; Wallentin L *et al*. *N Engl J Med* 2009;361:1045–1057

PLATO: Main efficacy/safety results

Primary efficacy endpoint: CV death + MI + stroke

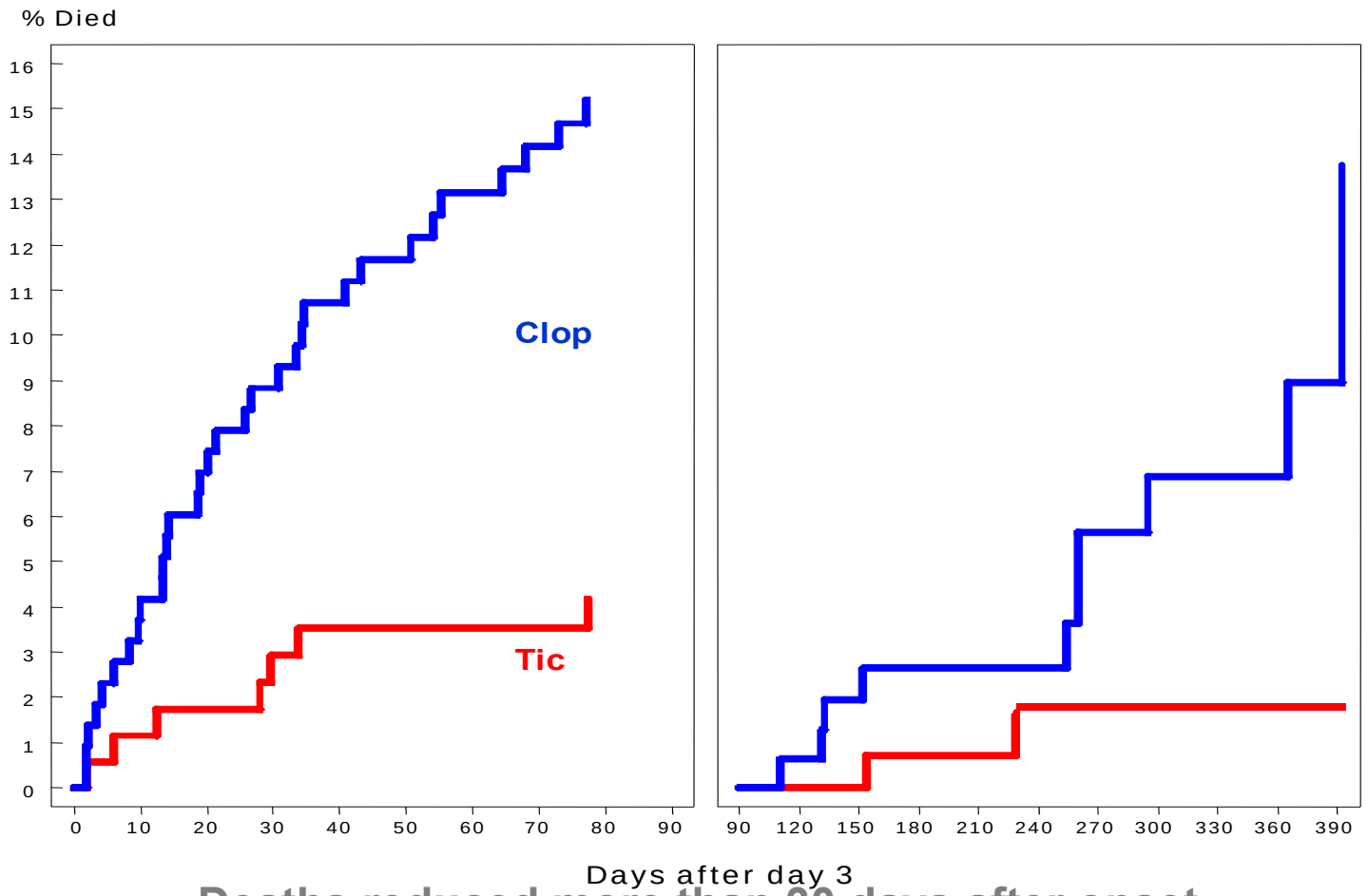


Primary safety endpoint: Total major bleeding



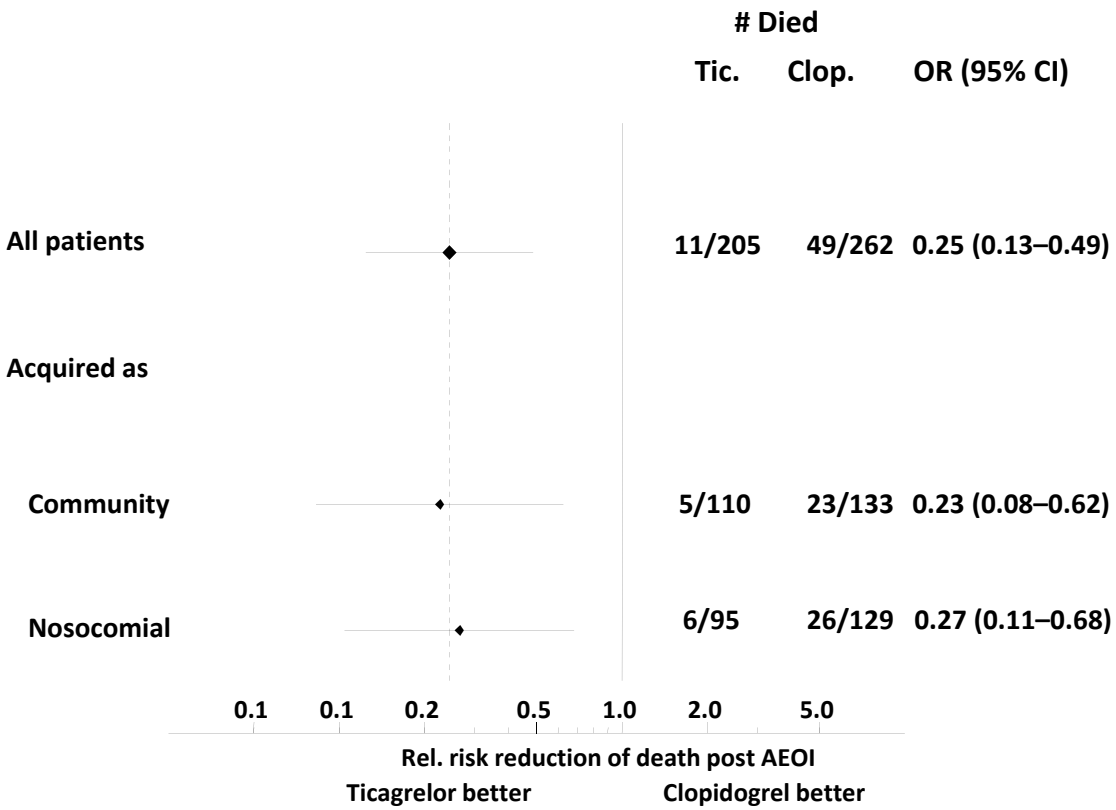
- Non-CABG major and non-procedural major/minor bleeding were significantly higher with ticagrelor versus clopidogrel, along with discontinuations due to bleeding

PLATO: Landmark Analysis of time to death following pneumonia



Deaths reduced more than 30 days after onset

PLATO: Death by CAP vs HAP: Patients with pneumonia AEs on study drug 3 days after AE onset



'Nosocomial' is 2+ days post admit and <7 days post discharge
Pneumonia preferred terms (broad)

Clinical trials of potential therapies in severe sepsis

- **Preclinical animal : too simplistic ?**
  - **Animals good health and no comorbidities**
  - **Insult often LPS, or CLP, or live bacteria**
  - **Often no antibiotics**
  - **No supportive care**

- **Patient selection : severe sepsis as syndrome**
  - **OD sepsis-induced ?**
  - **Infection present ?**

Conclusions

- **Back to basics**
- **Understanding of pathophysiology to be revisisted**
- **Potential therapies to be redifined**
- **Patients selection**
  - **Other criteria or markers ?**
  - **More homogenous populations**
  - **Different endpoints ?**
  - **Increase sample size if survival has improved ?**
  - **Limit variability : CCC and less sites with more patients per site ?**