Update in Sepsis Management

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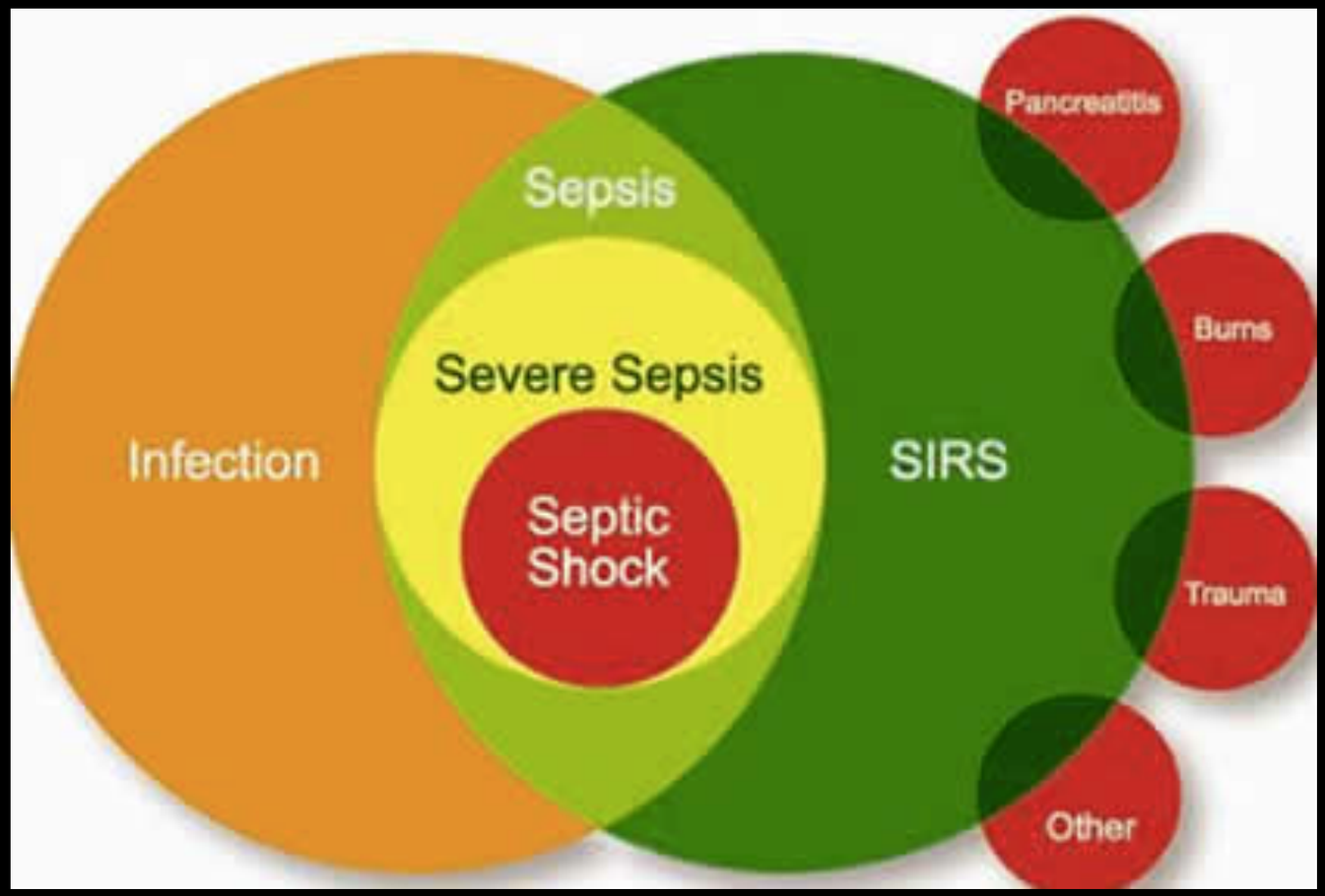
Content

- Definition
- Impact and epidemiology
- Update management

Classification

- Sepsis
- Severe Sepsis
- Septic Shock



SIRS

Infection

Sepsis

Definition of Sepsis

- Clinical syndrome responses to infection and result in systemic inflammatory responses.

Systemic Inflammatory Responses (SIRS)

- 1. Body Temperature > 37.4c or < 36.0
- 2. Respiratory rate > 20 /min
- 3. Pulse rate > 90 /min
- 4. WBC count > 12,000 or < 4,000 or bandemia > 10%

Sepsis

- Infection with
  - general variables
  - inflammatory variables
  - hemodynamic variables
  - organ dysfunction variables
  - tissue perfusion variables

sepsis

general variables	inflammatory variable	hemodynamic variable	organ dysfunction variable	tissue perfusion variables
•Temperature >38.3 or <36°C •Heart rate >90 beats/min or more than two standard deviations above the normal value for age •Tachypnea, respiratory rate >20 breaths/min •Altered mental status •Significant edema or positive fluid balance (>20 mL/kg over 24 hours) •Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes	•Leukocytosis (WBC count >12,000 microL–1) or leukopenia (WBC count <4000 microL–1) •Normal WBC count with greater than 10 percent immature forms •Plasma C-reactive protein more than two standard deviations above the normal value •Plasma procalcitonin more than two standard deviations above the normal value	•Arterial hypotension (systolic blood pressure SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or less than two standard deviations below normal for age)	•Arterial hypoxemia (arterial oxygen tension [PaO2]/fraction of inspired oxygen [FiO2] <300) •Acute oliguria (urine output <0.5 mL/kg/hr for at least two hours despite adequate fluid resuscitation) •Creatinine increase >0.5 mg/dL or 44.2 micromol/L •Coagulation abnormalities (international normalized ratio [INR] >1.5 or activated partial thromboplastin time [aPTT] >60 seconds) •Ileus (absent bowel sounds) •Thrombocytopenia (platelet count <100,000 microL–1) •Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 micromol/L)	•Hyperlactatemia (>1 mmol/L) •Decreased capillary refill or mottling

Severe Sepsis
Sepsis with organ dysfunction

- Sepsis-induced hypotension
- Lactate above upper limits of laboratory normal
- Urine output <0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation
- Acute lung injury with PaO2/FIO2 <250 in the absence of pneumonia as infection source
- Acute lung injury with PaO2/FIO2 <200 in the presence of pneumonia as infection source
- Creatinine >2 mg/dL (176.8 micromol/L)
- Bilirubin >4 mg/dL (34.2 micromol/L)
- Platelet count <100,000 microL–1
- Coagulopathy (INR >1.5)

Septic Shock

- Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, which may be defined as infusion of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent)

- Septic induced hypotension = MAP < 70 mmHg

Epidemiology

Incidence of Sepsis

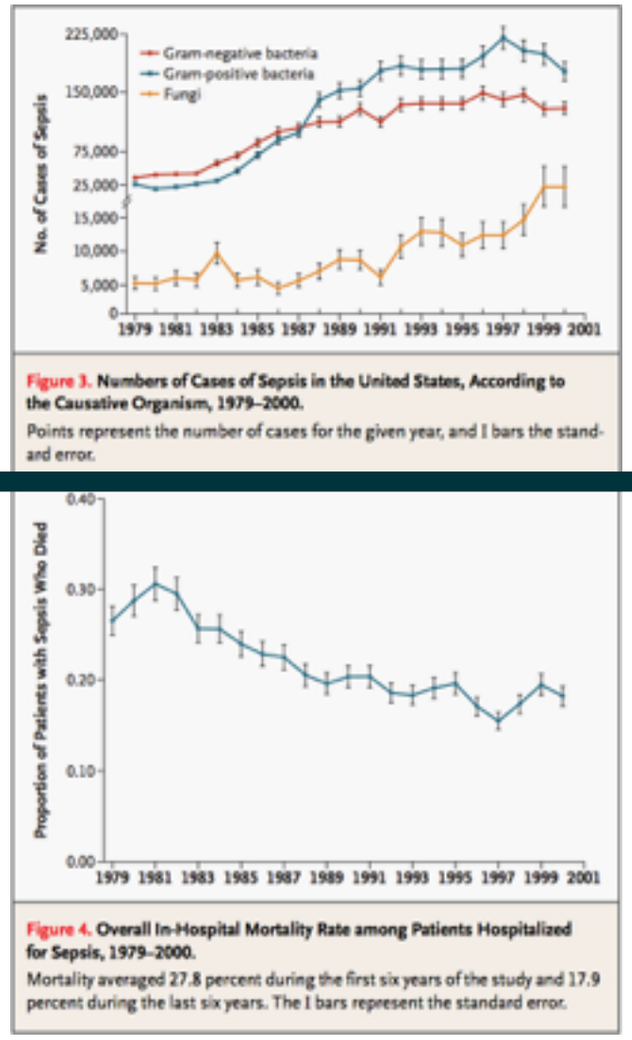
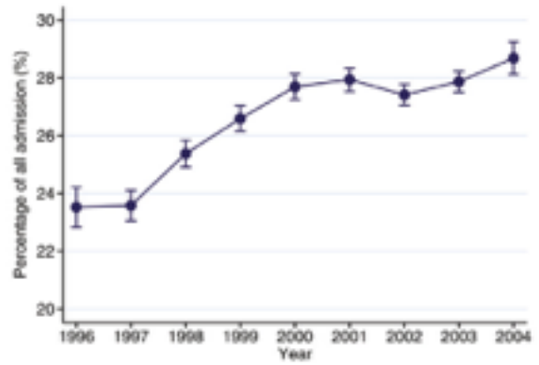


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the stand- and error.

[1993-2001]...a **75% increase** in... severe sepsis...

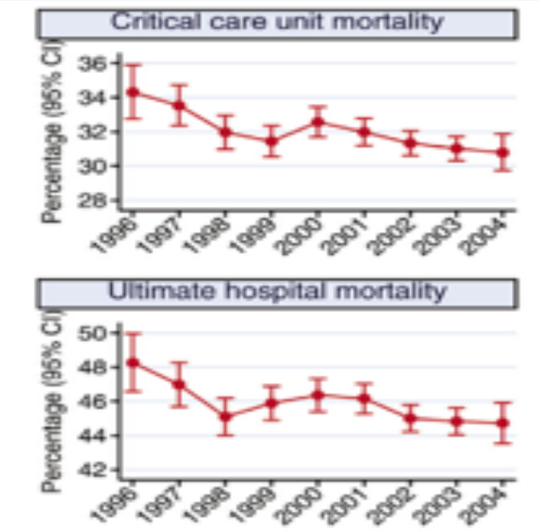


Mortality of Sepsis

Figure 4. Overall In-Hospital Mortality Rate among Patients Hospitalized for Sepsis, 1979–2000.

Mortality averaged 27.8 percent during the first six years of the study and 17.9 percent during the last six years. The I bars represent the standard error.

[1993 - 2001]...a **17% reduction** in mortality.



Martin, G. S., Mannino, D. M., Eaton, S., & Moss, M. (2003). The epidemiology of sepsis in the United States from 1979 through 2000. *New England Journal of Medicine*, *348*(16), 1546–1554.

Brun-Buisson, C., Meshaka, P., Pinton, P., Vallet, B., EPISEPSIS Study Group. (2004). EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Medicine*, *30*(4), 580–588.

Harrison, D. A., Welch, C. A., & Eddleston, J. M. (2006). The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Critical Care*, 10(2), R42.

ORIGINAL ARTICLE

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

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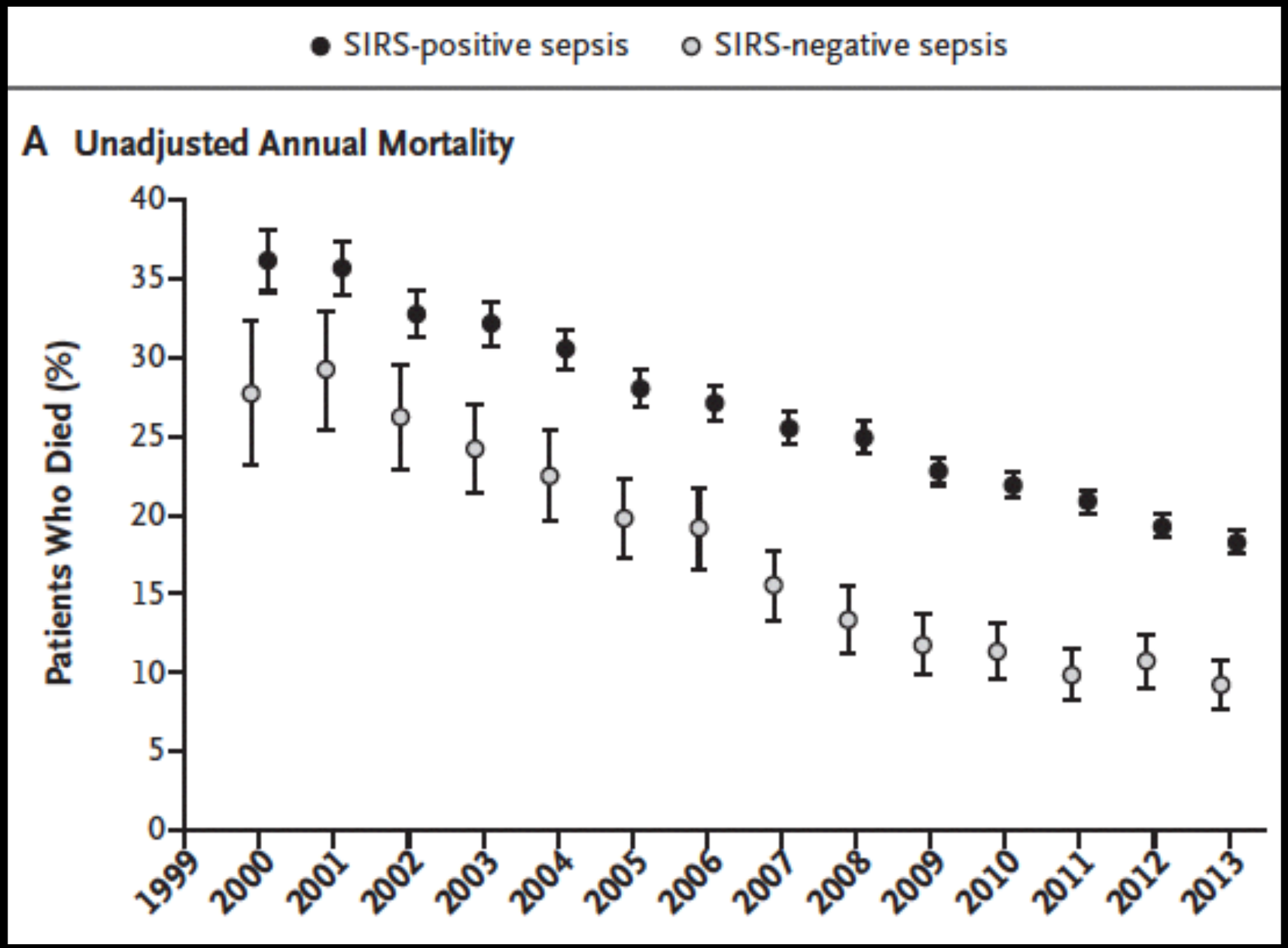

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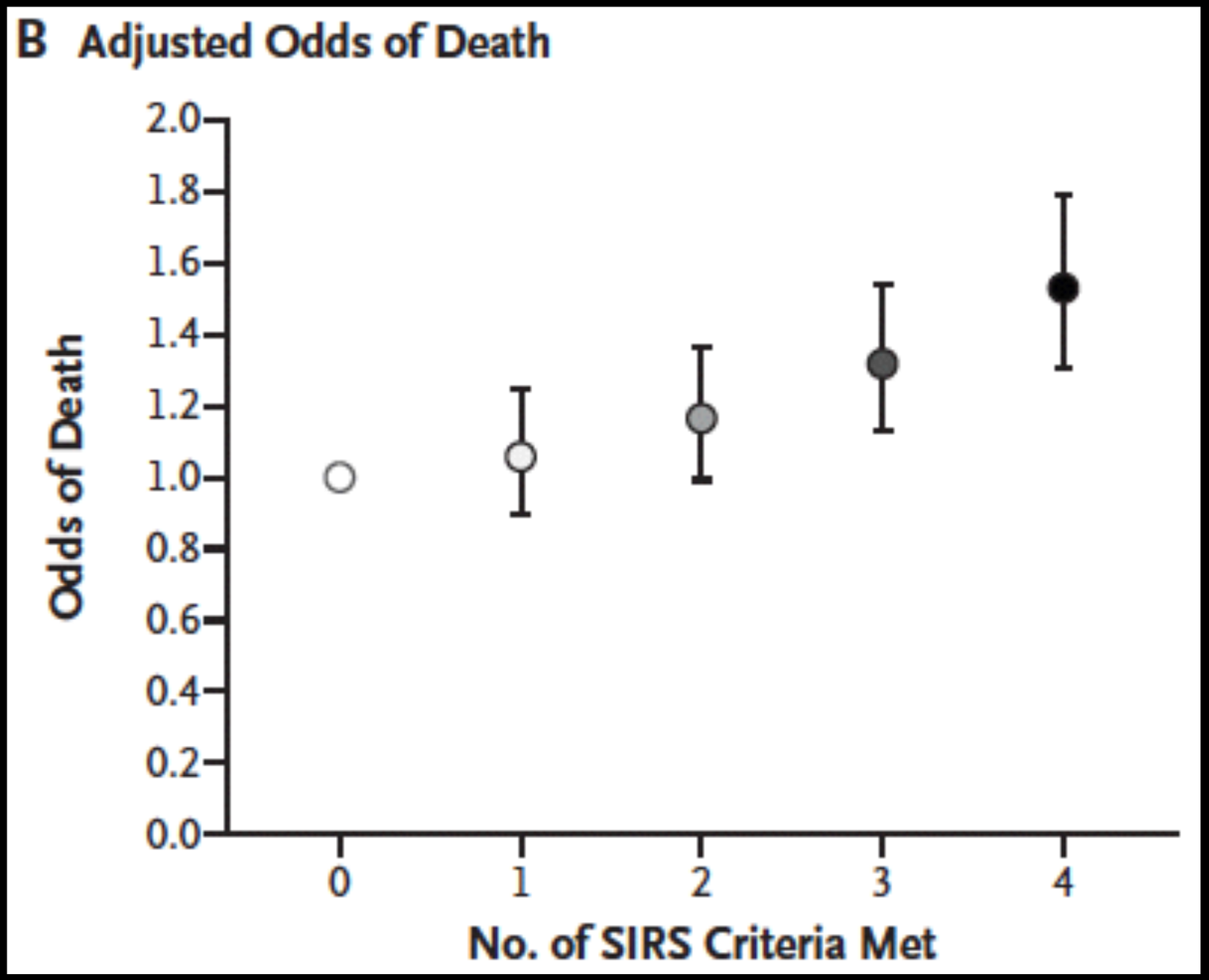
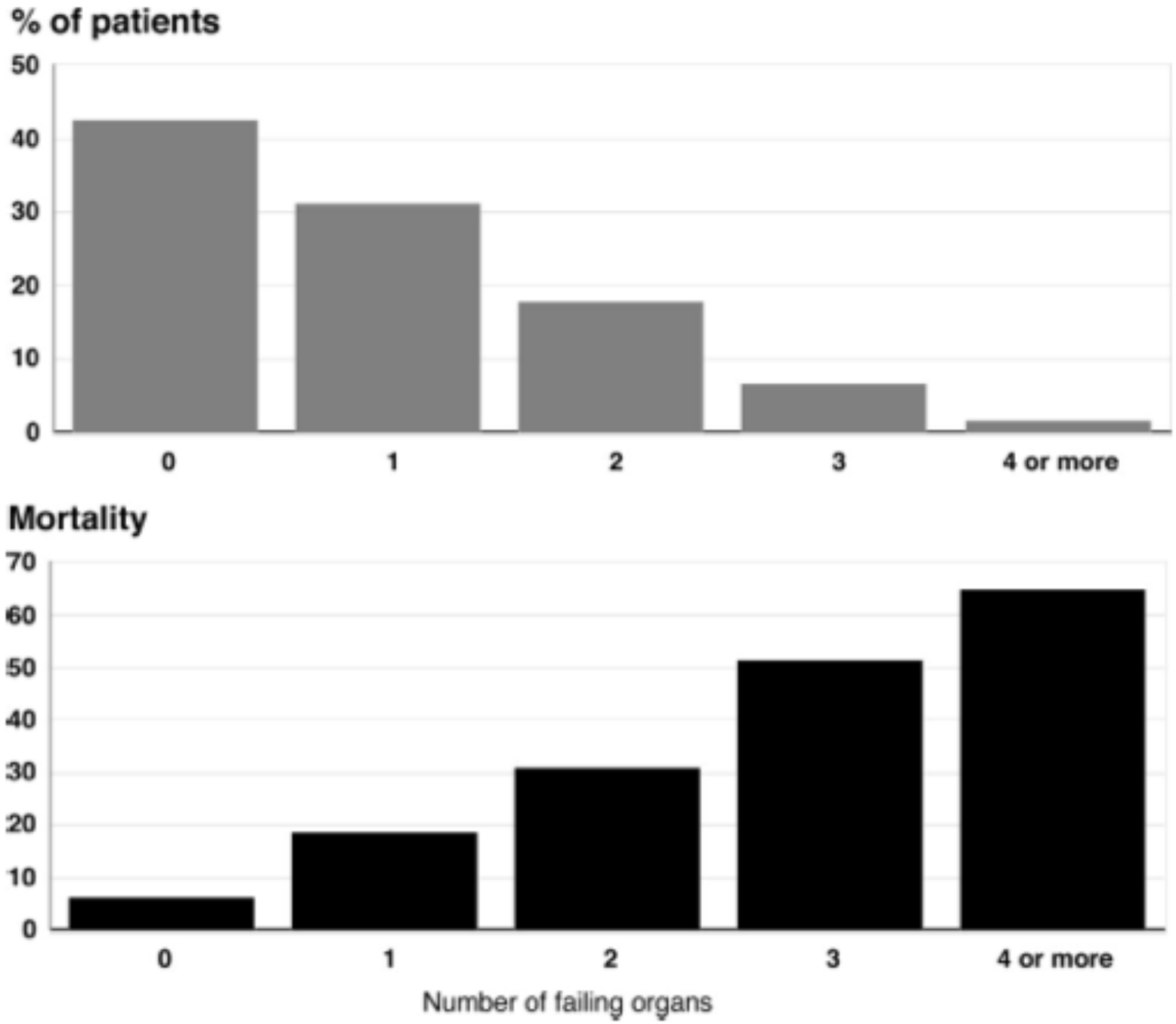


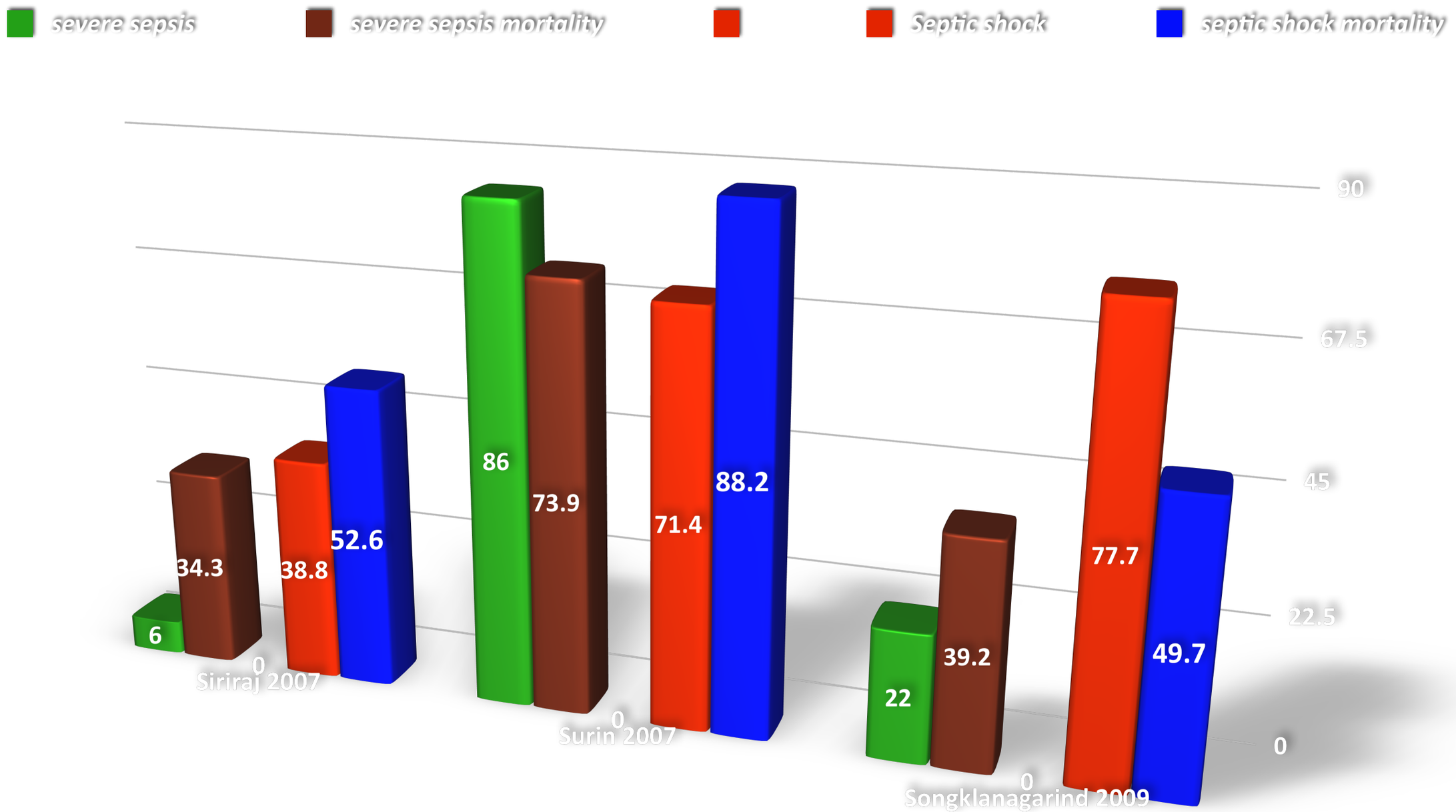
Organ failure in sepsis



P/F
Platelets
Bili
BP
GCS
Cr/UOP

Vincent, J.-L., Sakr, Y., Sprung, C. L., Ranieri, V. M., Reinhart, K., Gerlach, H., Moreno, R., et al. (2006). Sepsis in European intensive care units: results of the SOAP study. *Critical Care Medicine*, *34*(2), 344–353.

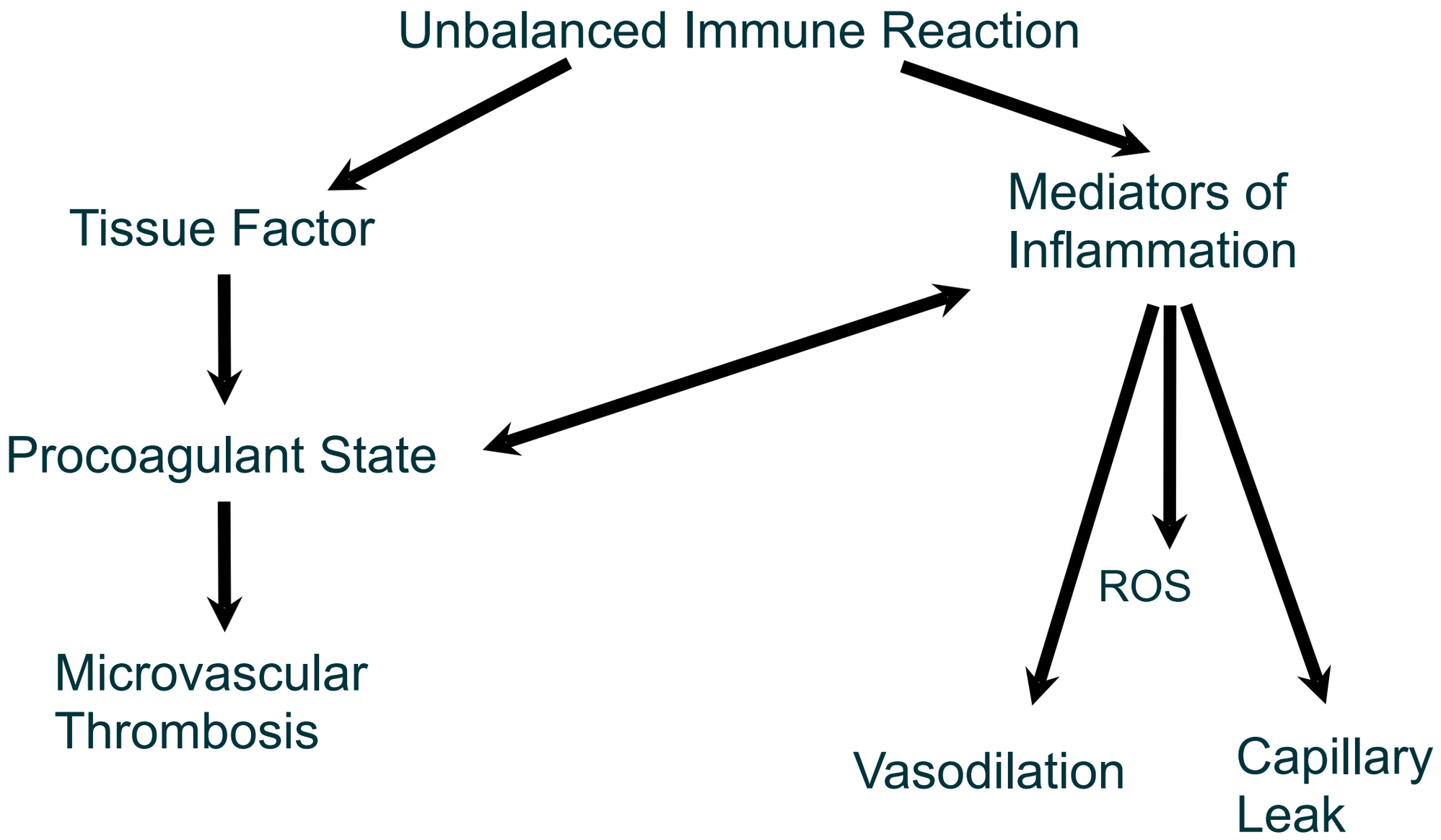
incidence and mortality of severe sepsis and septic shock in Thailand



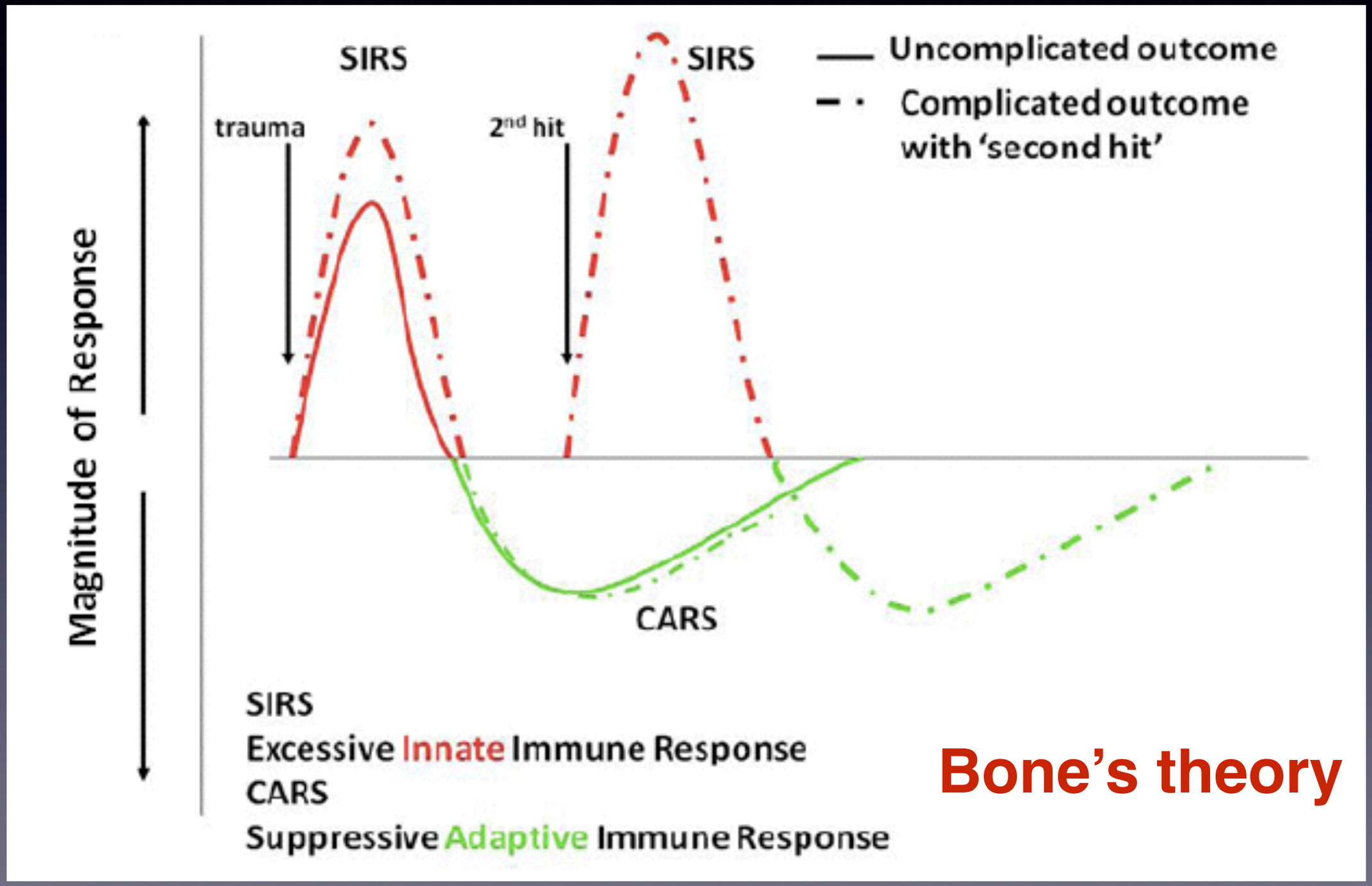
Angkasekwinai. JMAT 2007
Chuesakoolvanich. JMAT 2007.
Khwannimit. Epidemiol Infect 2009.

Pathophysiology of Sepsis

Sepsis Pathogenesis

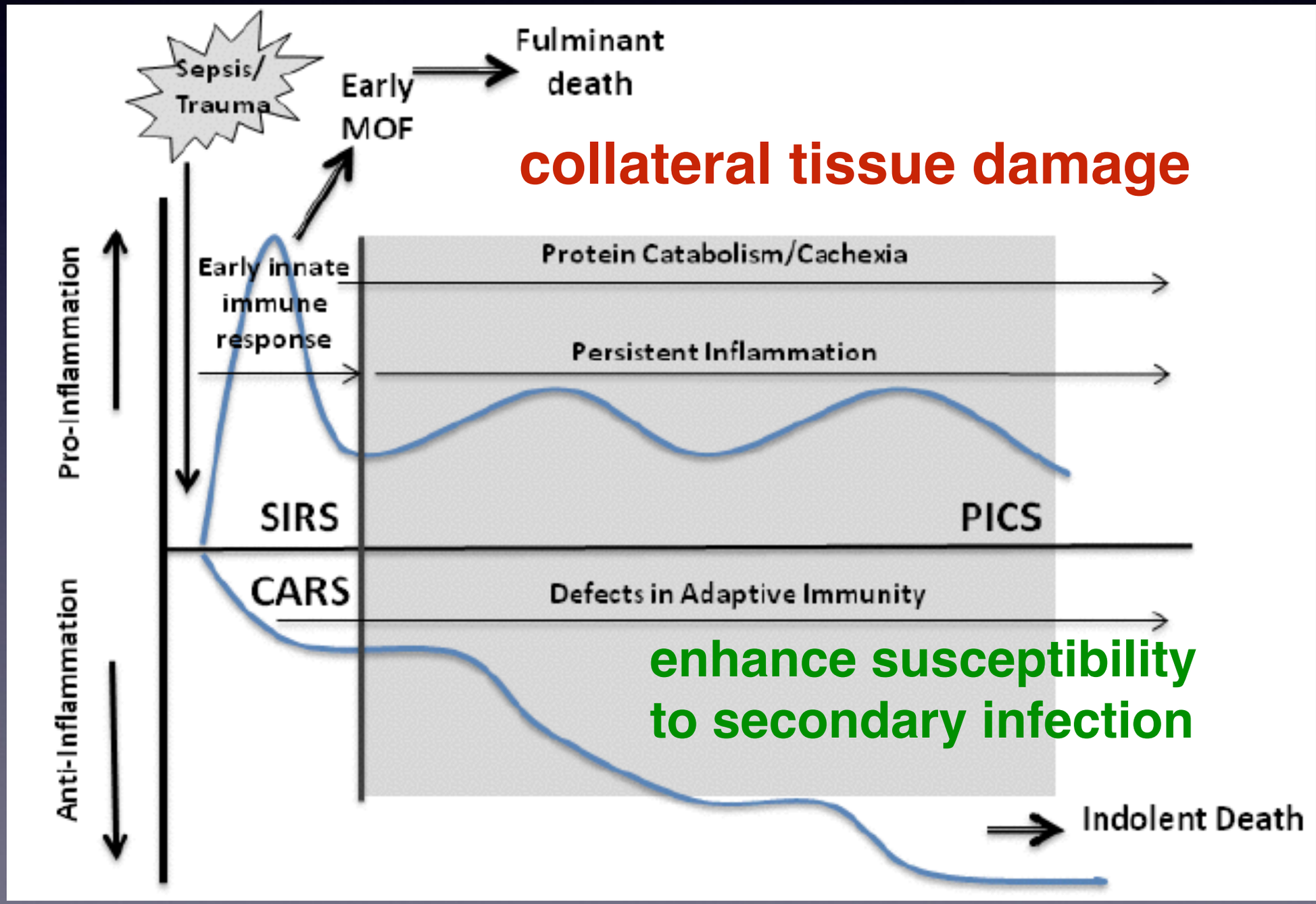


Host response in sepsis

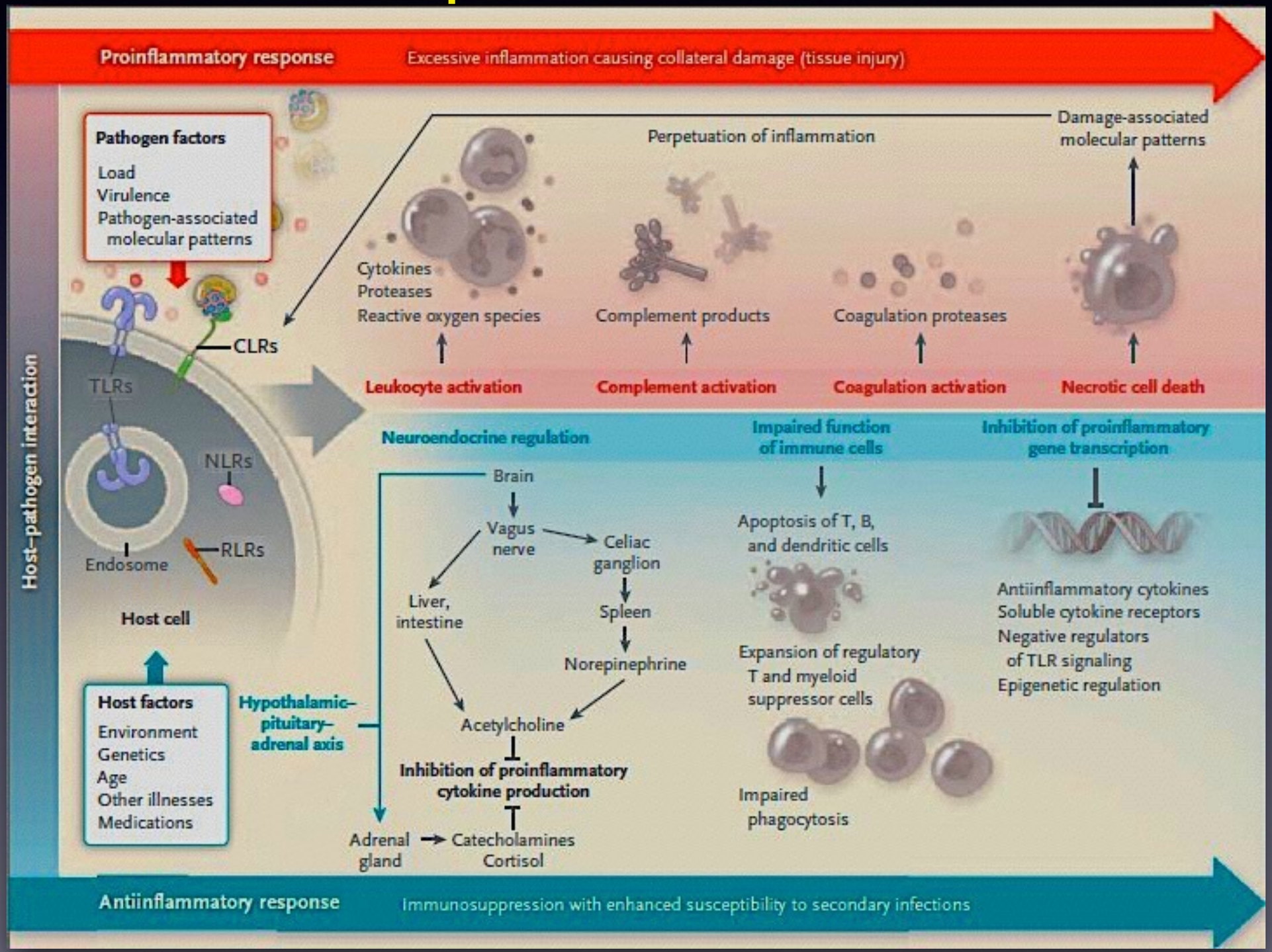


Bone's theory

Host responses in sepsis

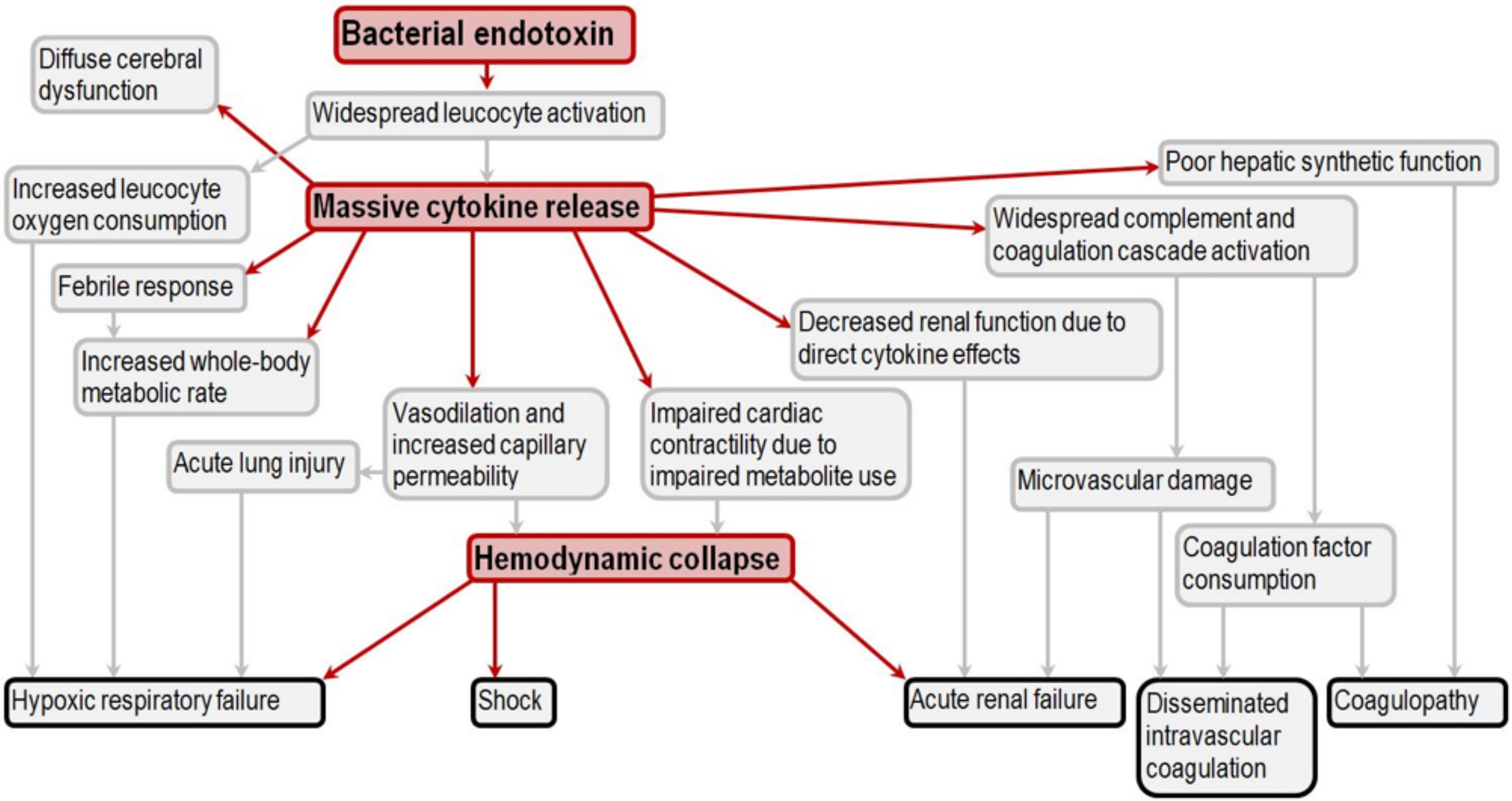


Pathophysiology of sepsis/ septic shock



Circulatory dysfunction

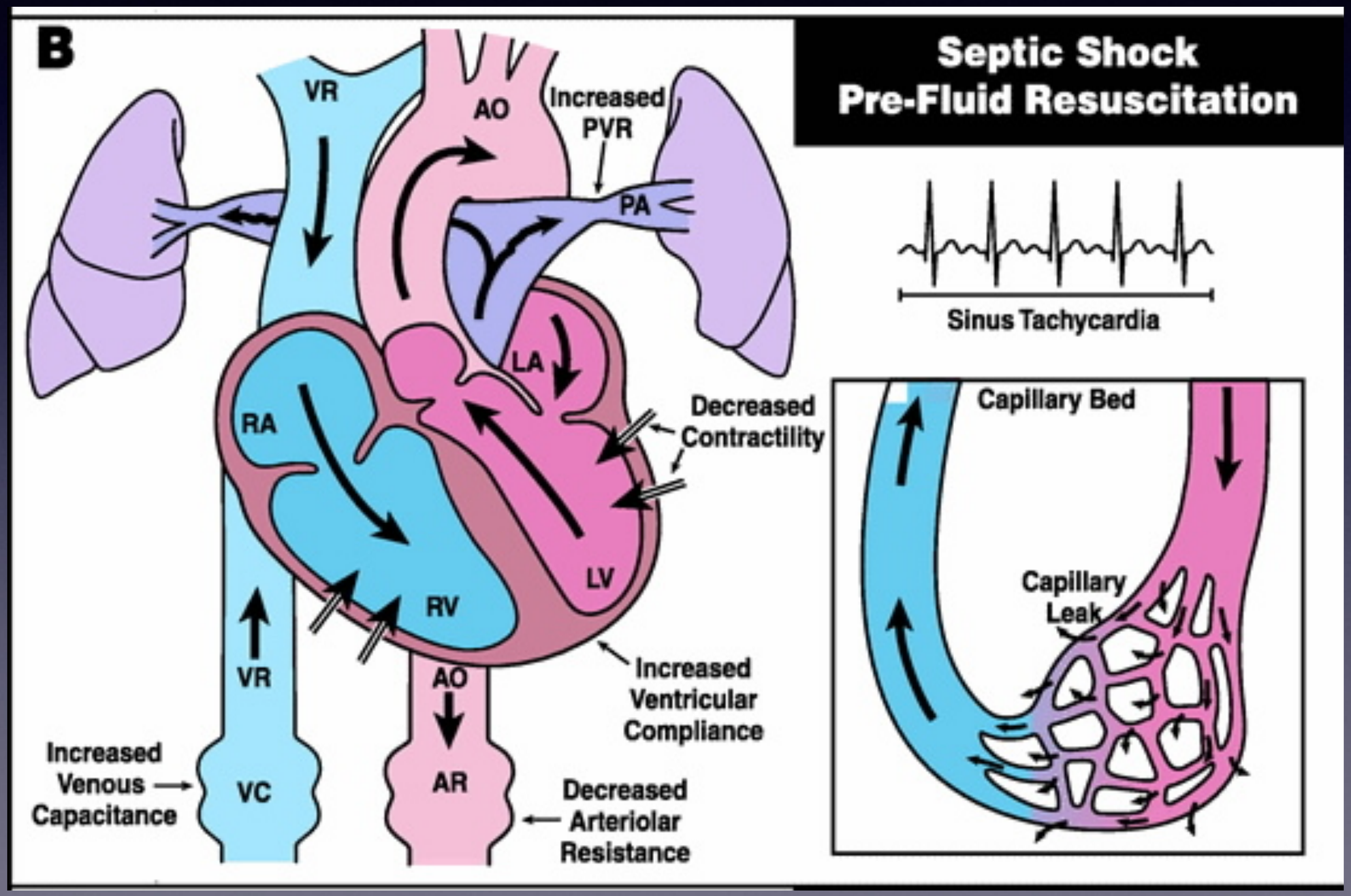
Circulatory dysfunction in septic shock



Circulatory dysfunction in septic shock

- Macrovascular dysfunction
- Microvascular dysfunction

Macrovascular in septic shock



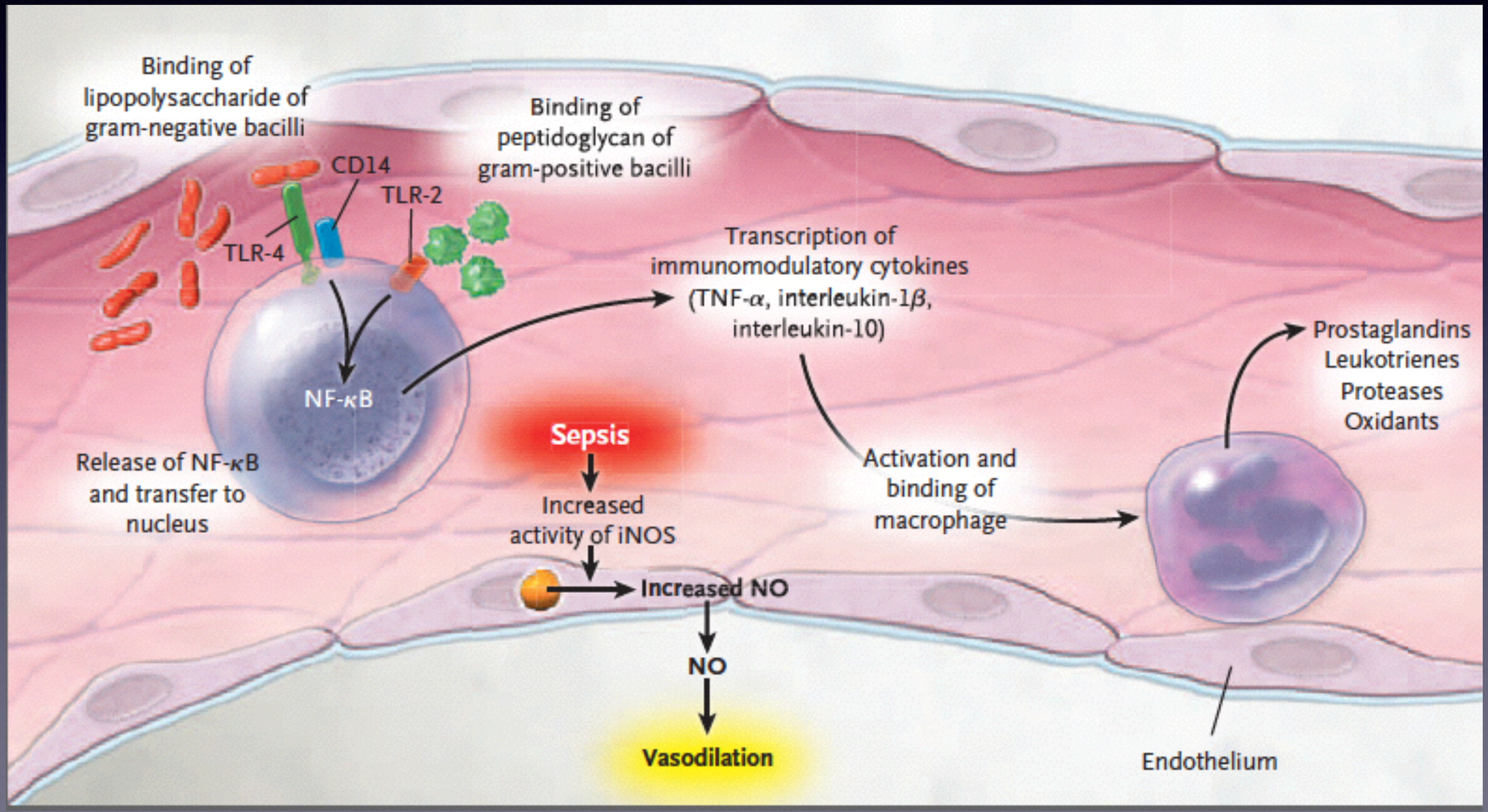
Macrocirculation on septic shock

Blood pressure

preload x cardiac contractility x afterload

- Preload: venodilatation, relative hypovolemia
- Cardiac: myocardial suppression
- Afterload: arteriolar dilatation

Macrocirculation on septic shock

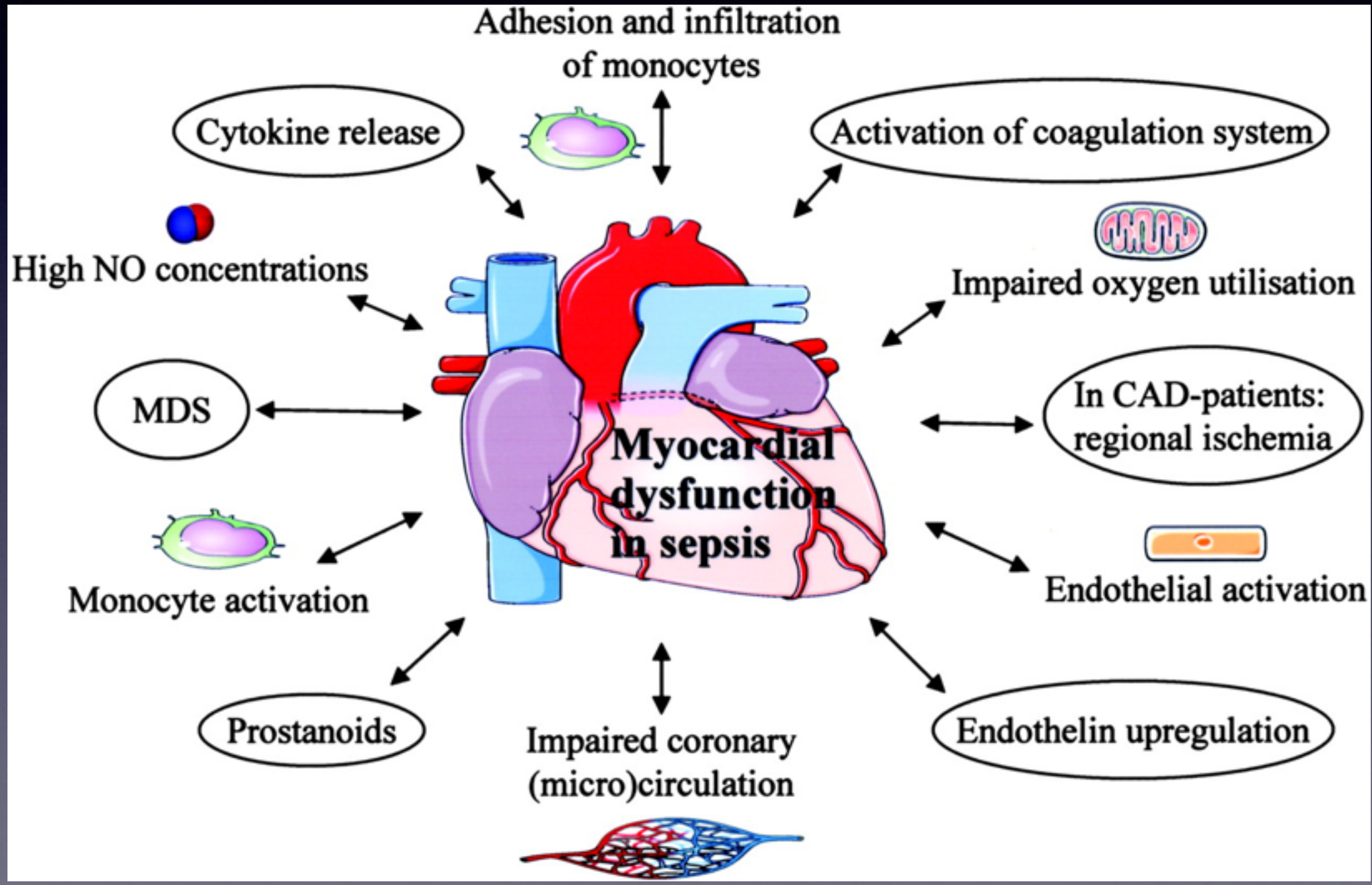


Cardiac dysfunction in septic shock

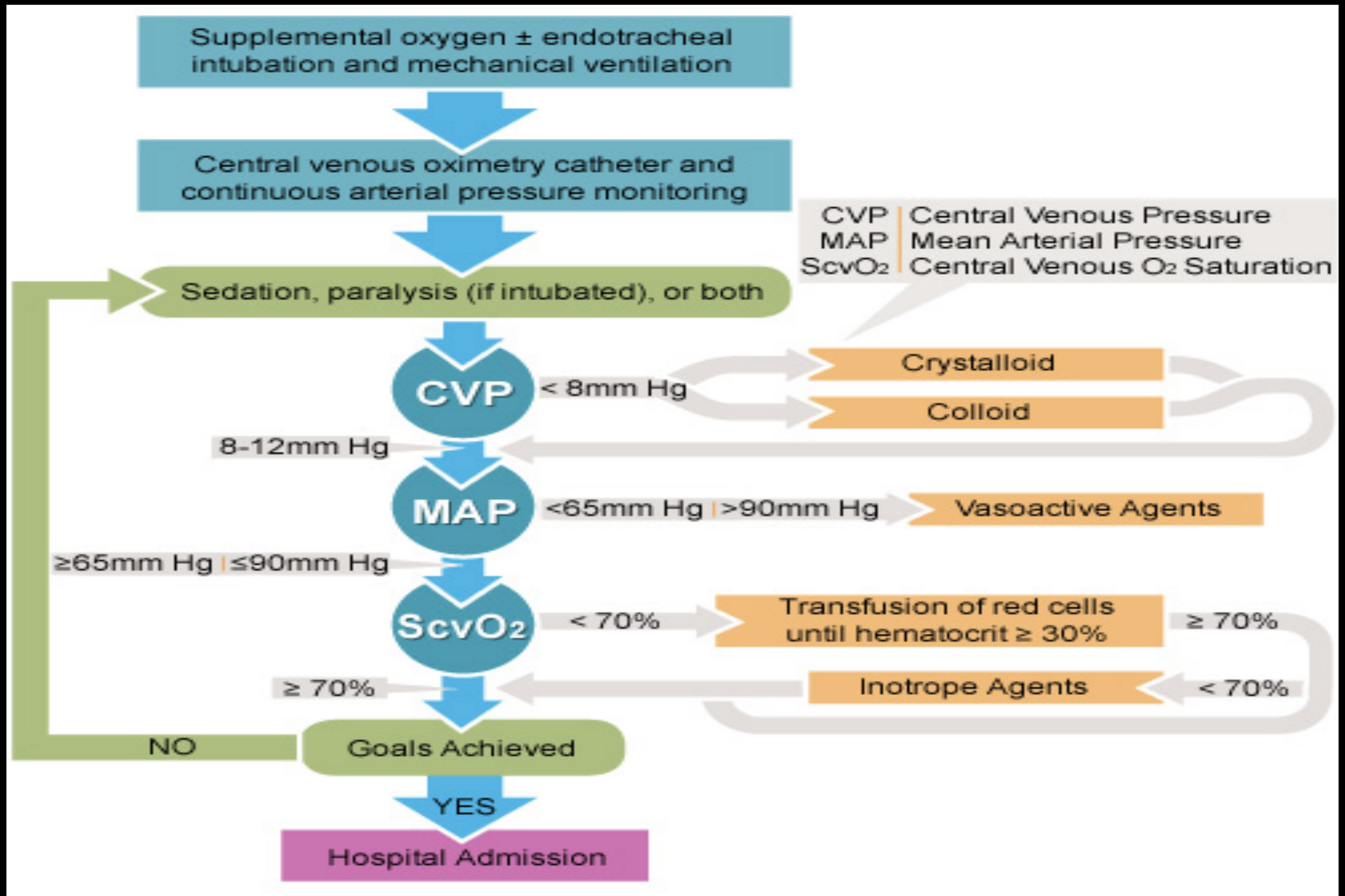
Cardiac dysfunction in septic shock

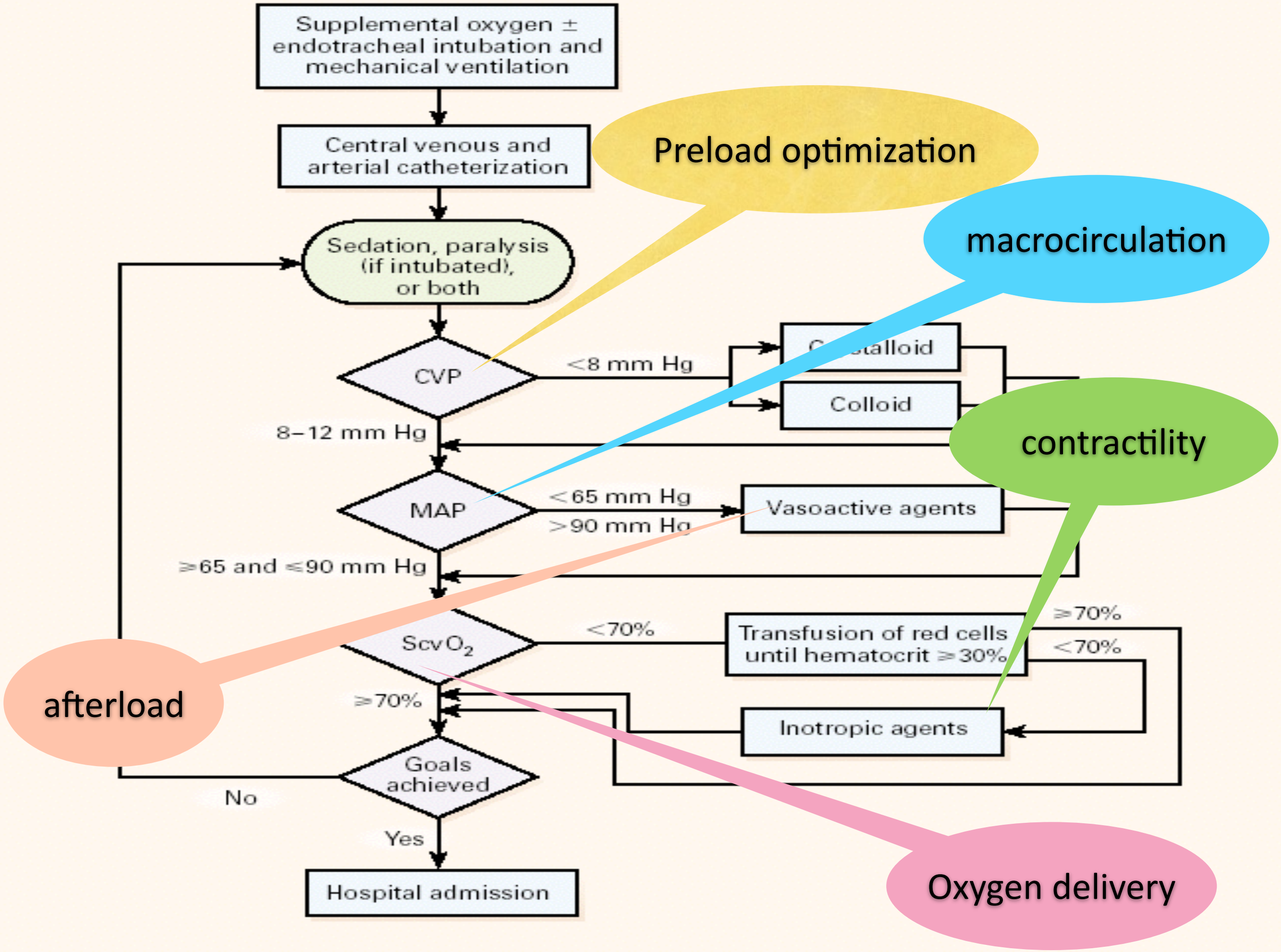
- one of the major predictors of mortality and morbidity in sepsis
- represent more than 40% of cases
- increase mortality up to 70%
- mostly reversible
- occurred in both LV and RV systolic dysfunction
- Diastolic dysfunction is also noted

Cardiac dysfunction in septic shock



Early Goal Directed Therapy

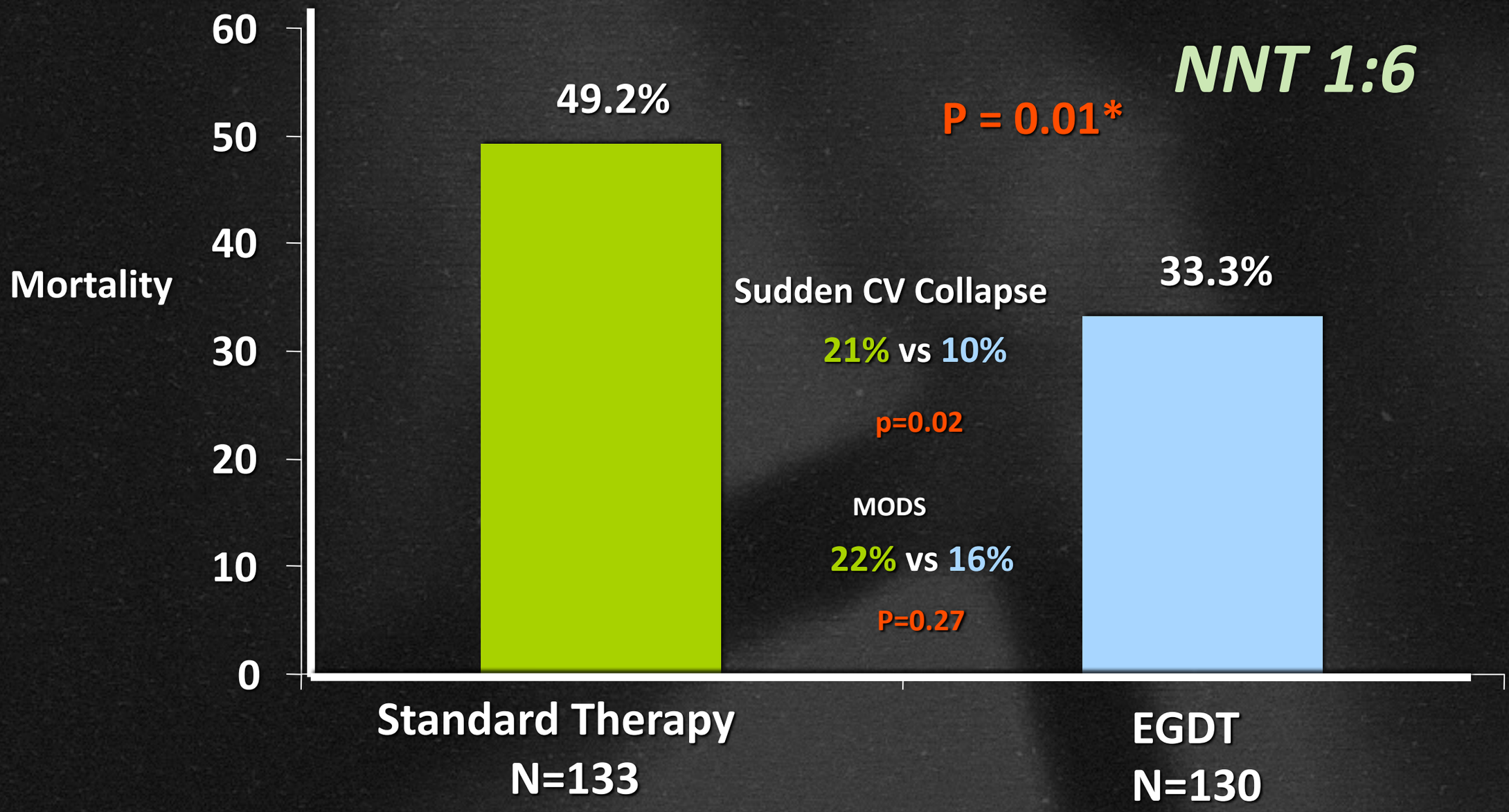



Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO2
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission
Preload optimization
macrocirculation
contractility
afterload
Oxygen delivery

Goal of Rivers' EGDT

1. central venous pressure (CVP) > 8 mmHg
2. mean arterial blood pressure (MAP) > 65 mmHg
3. $ScvO_2$ > 70% : indicate as a endpoint of resuscitation

Early Goal-Directed Therapy Results: 28 Day Mortality



Hemodynamic management

Summary of Trials

	Rivers 2001 RCT	Sebat 2005 Before-After	Nguyen 2007 Complete or Not	Thiel 2009 Before-After	Levy 2011 Before-After
Goals	*CVP >8* ***MAP > 65*** ScVO2 >70% HCT >30	***MAP > 70*** *SaO2 > 92* UOP > 30ml/h SvO2 > 60 CI > 2.5	*ABX in 4 h* *CVP > 8,* ***MAP > 65***, ScVO2 > 70%, HCT > 30 Check Lactate Steroids	Appropriate ABX in 4 h, CVP > 8, **MAP > 65,** ScVO2 > 70%	Early ABX, Blood Cultures, Appropriate ABX, CVP > 8, **MAP > 65**, SvO2 > 70%
Specific Interventions	**Fluids**, Blood, **Pressors**	**ABX, Fluids Pressors**	**ABX, Fluids**, Blood, **Pressors**	**ABX, Fluids**, **Pressors**, Steroids, Xigris, Other Supportive Care	**ABX, Fluids**, **Pressors**, Steroids, Xigris, Other Supportive Care
System Interventions	ED-based Sepsis Team	Screening, Education, Shock Team, Protocols	Education, In-services, Protocols	Education, In-services, Order Set, Protocols	Screening, Education, Order Sets
Absolute Change in Mortality	**-16%**	**-12%**	**-19%**	**-16%**	**-7%**

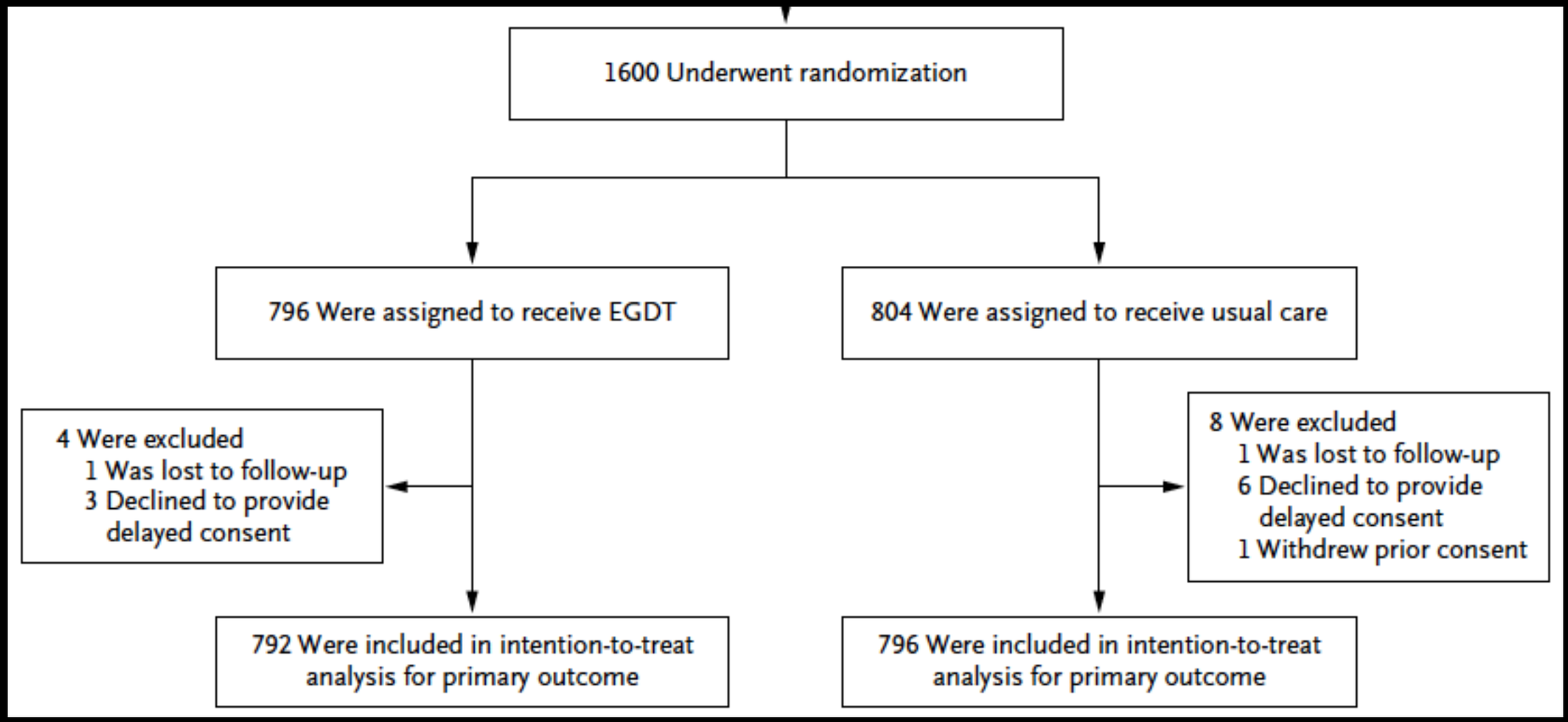
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

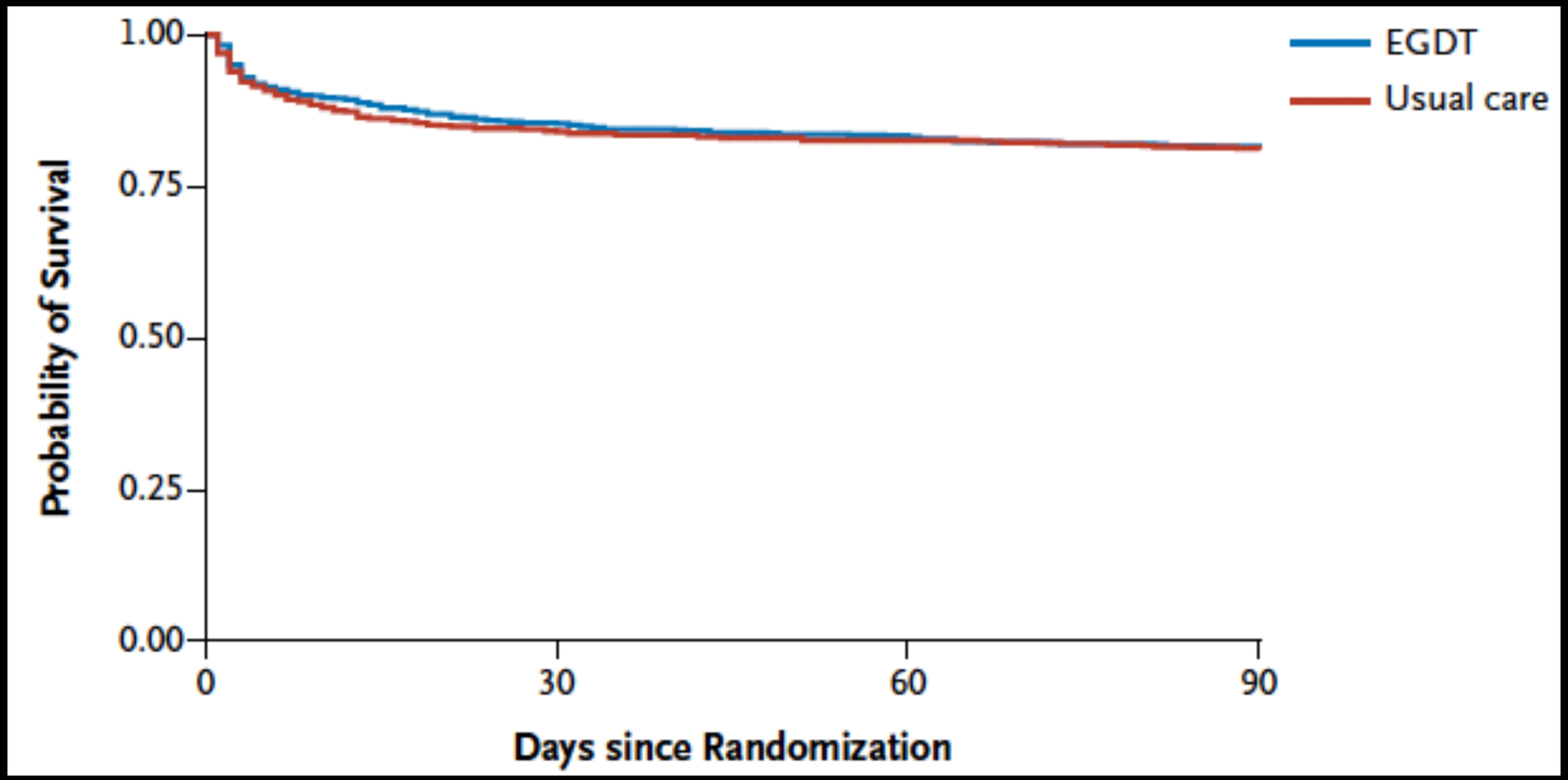
Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

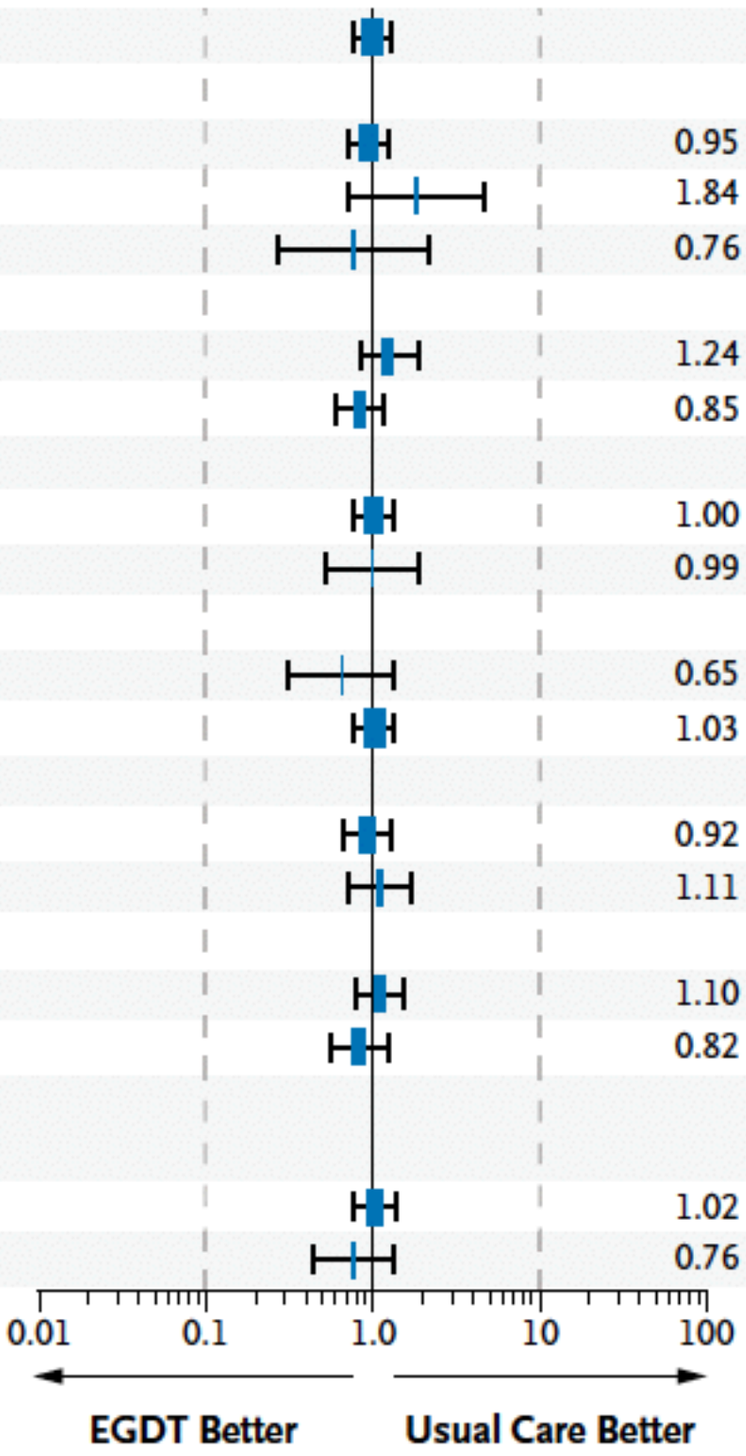
ARISE


1600 Underwent randomization
796 Were assigned to receive EGDT
804 Were assigned to receive usual care
4 Were excluded
1 Was lost to follow-up
3 Declined to provide delayed consent
8 Were excluded
1 Was lost to follow-up
6 Declined to provide delayed consent
1 Withdrew prior consent
792 Were included in intention-to-treat analysis for primary outcome
796 Were included in intention-to-treat analysis for primary outcome

ARISE


1.00
0.75
0.50
0.25
0.00
Probability of Survival
0
30
60
90
Days since Randomization
EGDT
Usual care

Subgroup	EGDT	Usual Care	Odds Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no. (%)				
Overall	147/792 (18.6)	150/796 (18.8)			
Country					0.38
Australia	126/677 (18.6)	132/679 (19.4)	0.95 (0.72–1.24)	0.70	
New Zealand	13/67 (19.4)	8/69 (11.6)	1.84 (0.71–4.76)	0.21	
Other	8/48 (16.7)	10/48 (20.8)	0.76 (0.27–2.13)	0.60	
Age					0.15
<65 yr	61/393 (15.5)	50/387 (12.9)	1.24 (0.83–1.85)	0.30	
≥65 yr	86/399 (21.6)	100/409 (24.4)	0.85 (0.61–1.18)	0.33	
APACHE II					0.98
<25	114/720 (15.8)	114/718 (15.9)	1.00 (0.75–1.32)	0.98	
≥25	33/72 (45.8)	36/78 (46.2)	0.99 (0.52–1.88)	0.97	
Invasive mechanical ventilation					0.25
Yes	19/71 (26.8)	23/64 (35.9)	0.65 (0.31–1.36)	0.25	
No	128/721 (17.8)	127/732 (17.3)	1.03 (0.78–1.35)	0.84	
Refractory hypotension					0.50
Yes	90/554 (16.2)	97/557 (17.4)	0.92 (0.67–1.26)	0.60	
No	57/238 (23.9)	53/239 (22.2)	1.11 (0.72–1.69)	0.65	
Hypofusion					0.27
Yes	99/365 (27.1)	93/369 (25.2)	1.10 (0.79–1.54)	0.55	
No	48/427 (11.2)	57/427 (13.3)	0.82 (0.55–1.24)	0.35	
IV fluid volume before randomization					0.41
≥20 ml/kg	106/574 (18.5)	104/572 (18.2)	1.02 (0.76–1.37)	0.90	
<20 ml/kg	28/181 (15.5)	35/181 (19.3)	0.76 (0.44–1.32)	0.33	



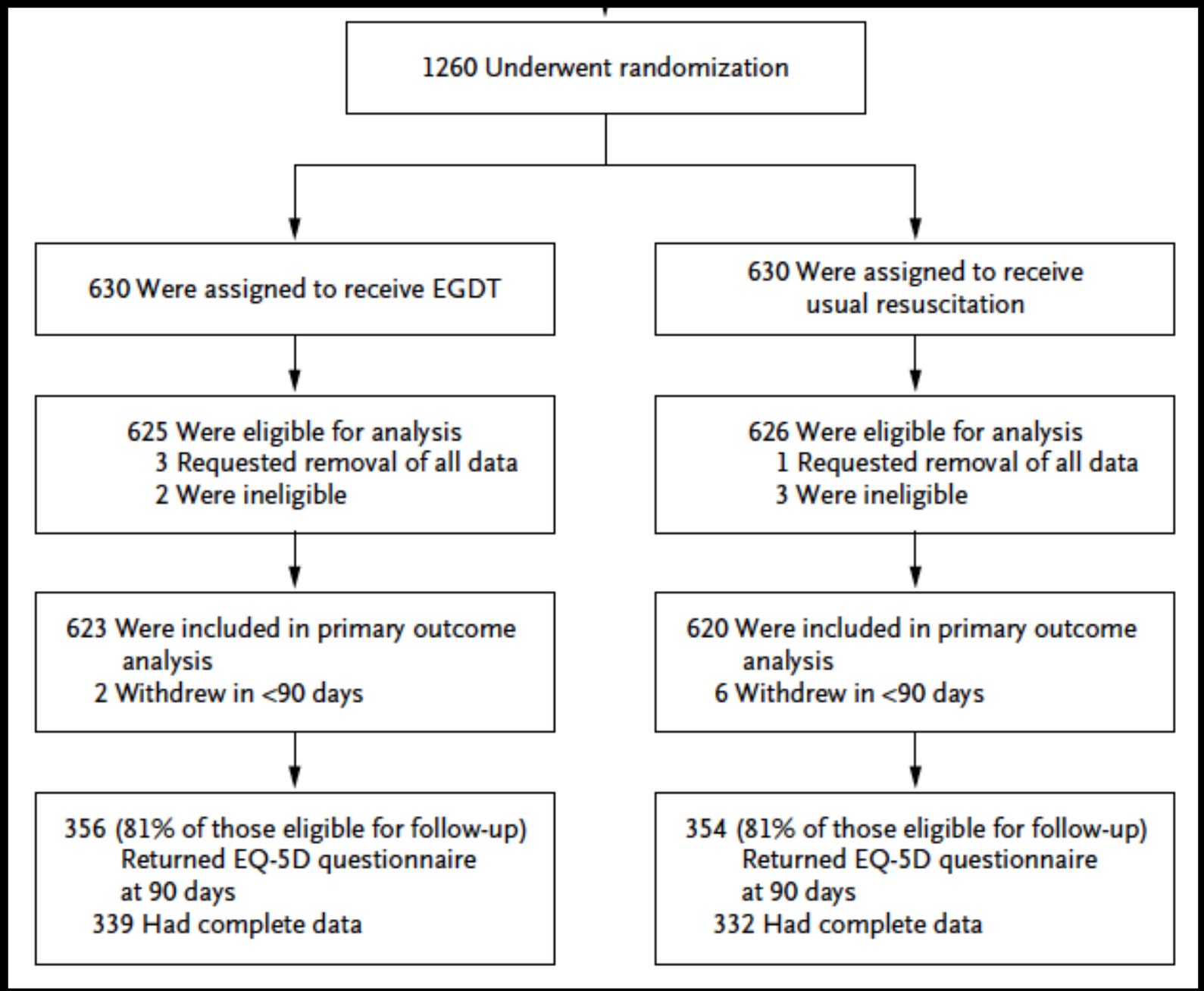
ProMiSe

ORIGINAL ARTICLE

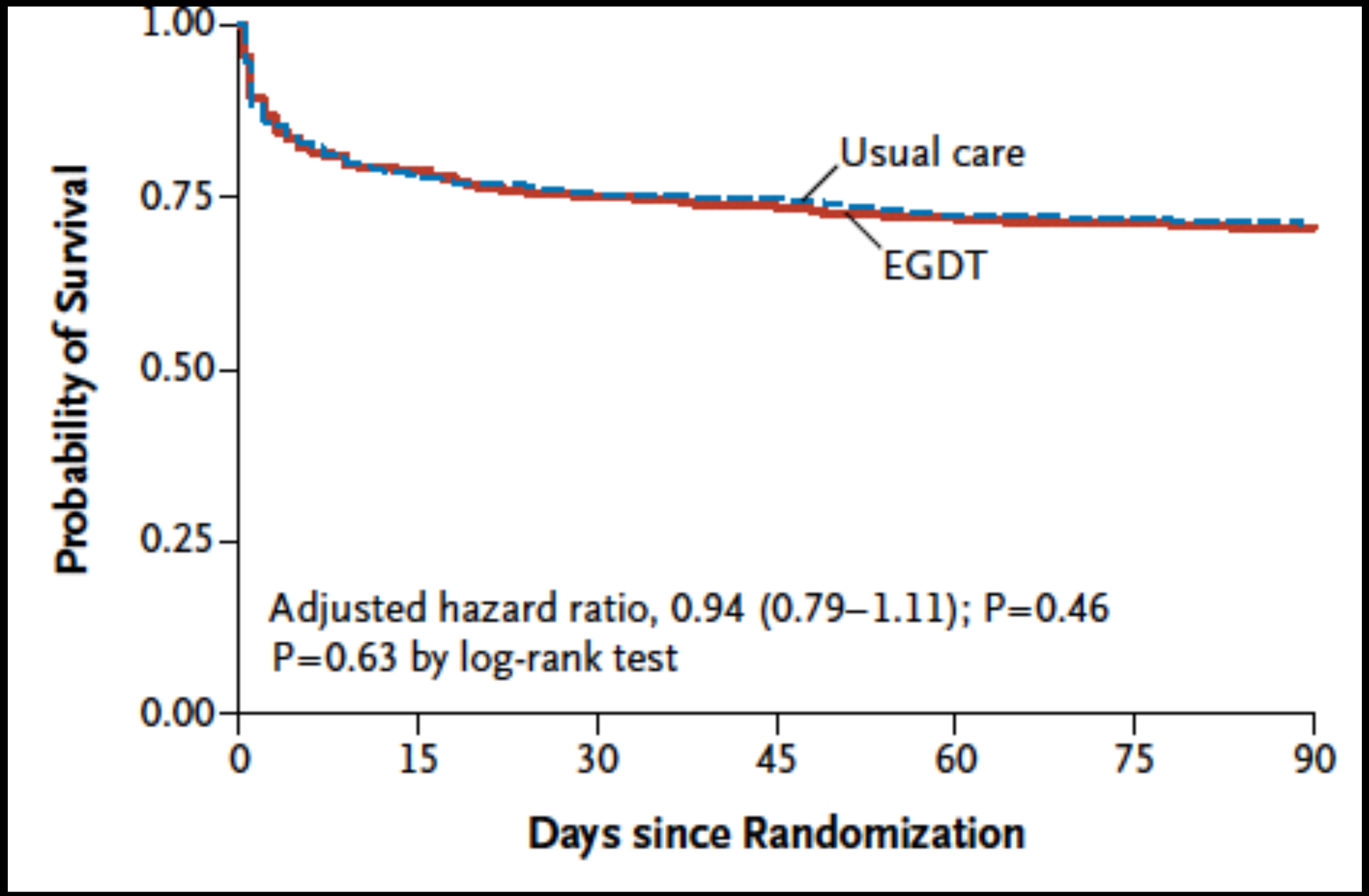
Trial of Early, Goal-Directed Resuscitation for Septic Shock

Paul R. Mouncey, M.Sc., Tiffany M. Osborn, M.D., G. Sarah Power, M.Sc., David A. Harrison, Ph.D., M. Zia Sadique, Ph.D., Richard D. Grieve, Ph.D., Rahi Jahan, B.A., Sheila E. Harvey, Ph.D., Derek Bell, M.D., Julian F. Bion, M.D., Timothy J. Coats, M.D., Mervyn Singer, M.D., J. Duncan Young, D.M., and Kathryn M. Rowan, Ph.D., for the ProMISe Trial Investigators*

ProMiSe


1260 Underwent randomization
630 Were assigned to receive EGDT
630 Were assigned to receive usual resuscitation
625 Were eligible for analysis
3 Requested removal of all data
2 Were ineligible
626 Were eligible for analysis
1 Requested removal of all data
3 Were ineligible
623 Were included in primary outcome analysis
2 Withdrew in <90 days
620 Were included in primary outcome analysis
6 Withdrew in <90 days
356 (81% of those eligible for follow-up) Returned EQ-5D questionnaire at 90 days
339 Had complete data
354 (81% of those eligible for follow-up) Returned EQ-5D questionnaire at 90 days
332 Had complete data

ProMiSe


1.00
0.75
0.50
0.25
0.00
Probability of Survival
Usual care
EGDT
Adjusted hazard ratio, 0.94 (0.79–1.11); P=0.46
P=0.63 by log-rank test
0
15
30
45
60
75
90
Days since Randomization

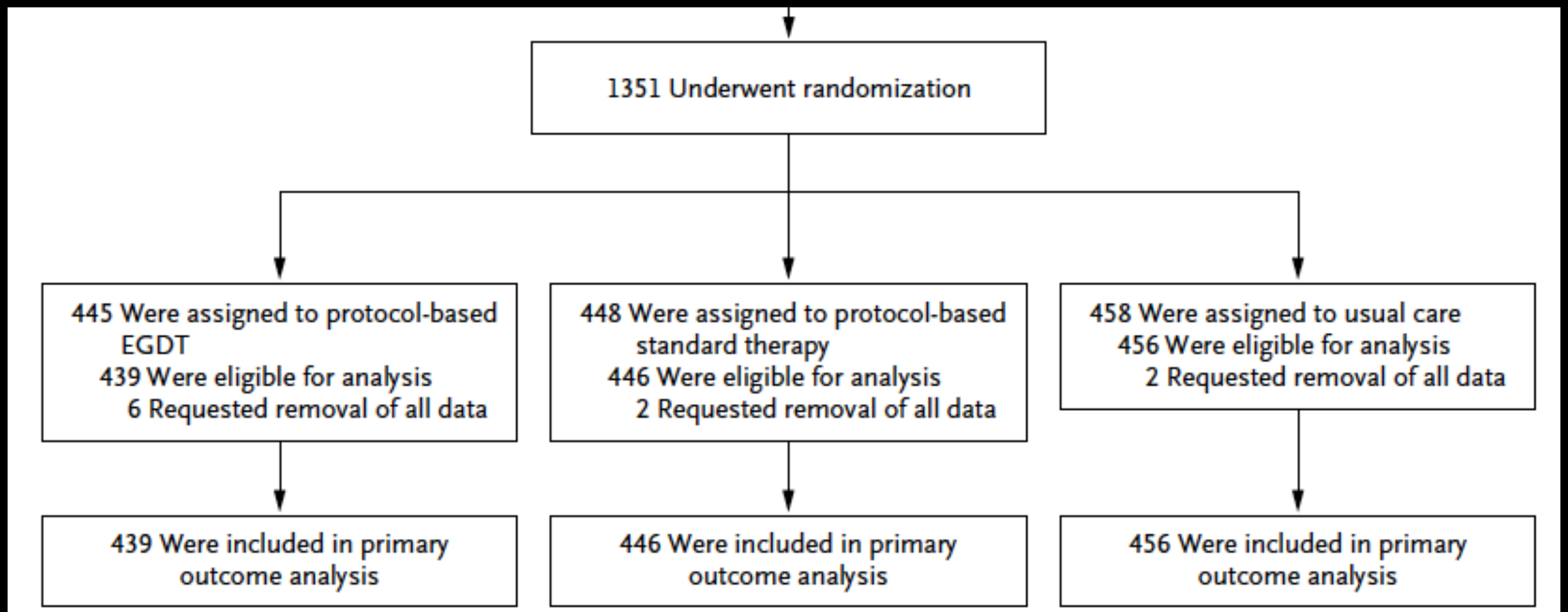
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 1, 2014 VOL. 370 NO. 18

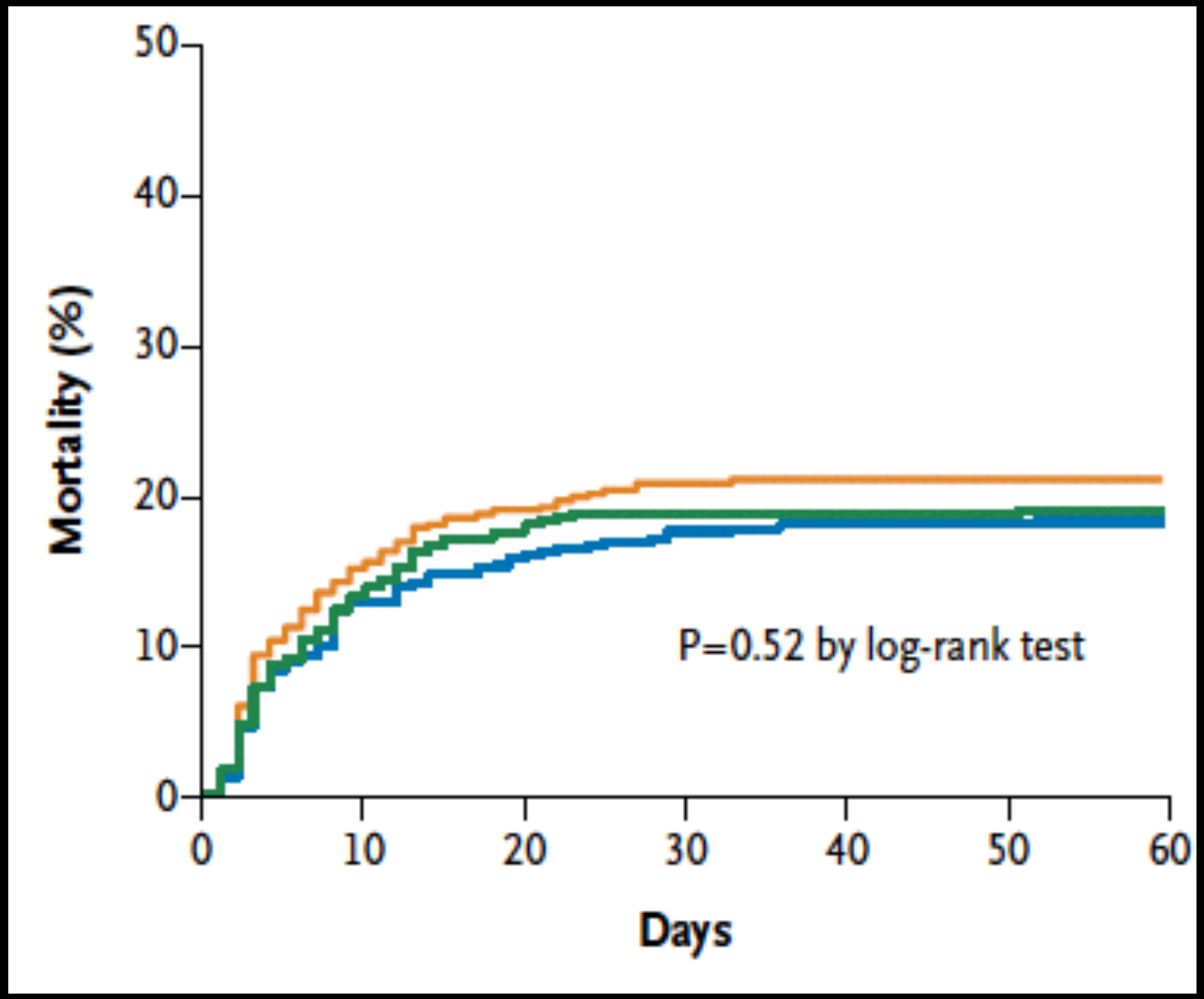
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

ProCESS

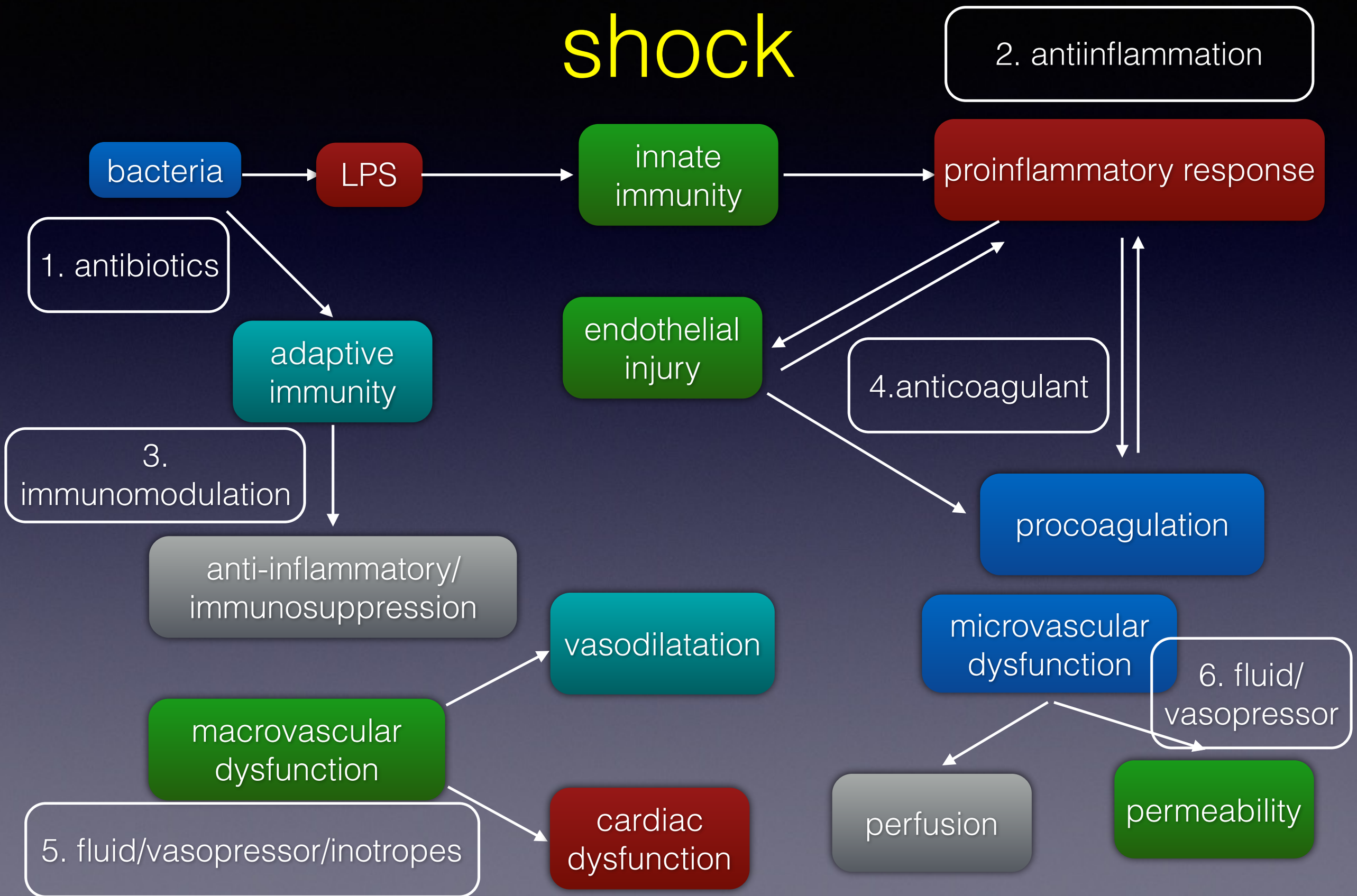

1351 Underwent randomization
445 Were assigned to protocol-based EGDT
439 Were eligible for analysis
6 Requested removal of all data
448 Were assigned to protocol-based standard therapy
446 Were eligible for analysis
2 Requested removal of all data
458 Were assigned to usual care
456 Were eligible for analysis
2 Requested removal of all data
439 Were included in primary outcome analysis
446 Were included in primary outcome analysis
456 Were included in primary outcome analysis

ProCESS


50
40
30
20
10
0
Mortality (%)
0
10
20
30
40
50
60
Days
P=0.52 by log-rank test

pathophysiology-based management

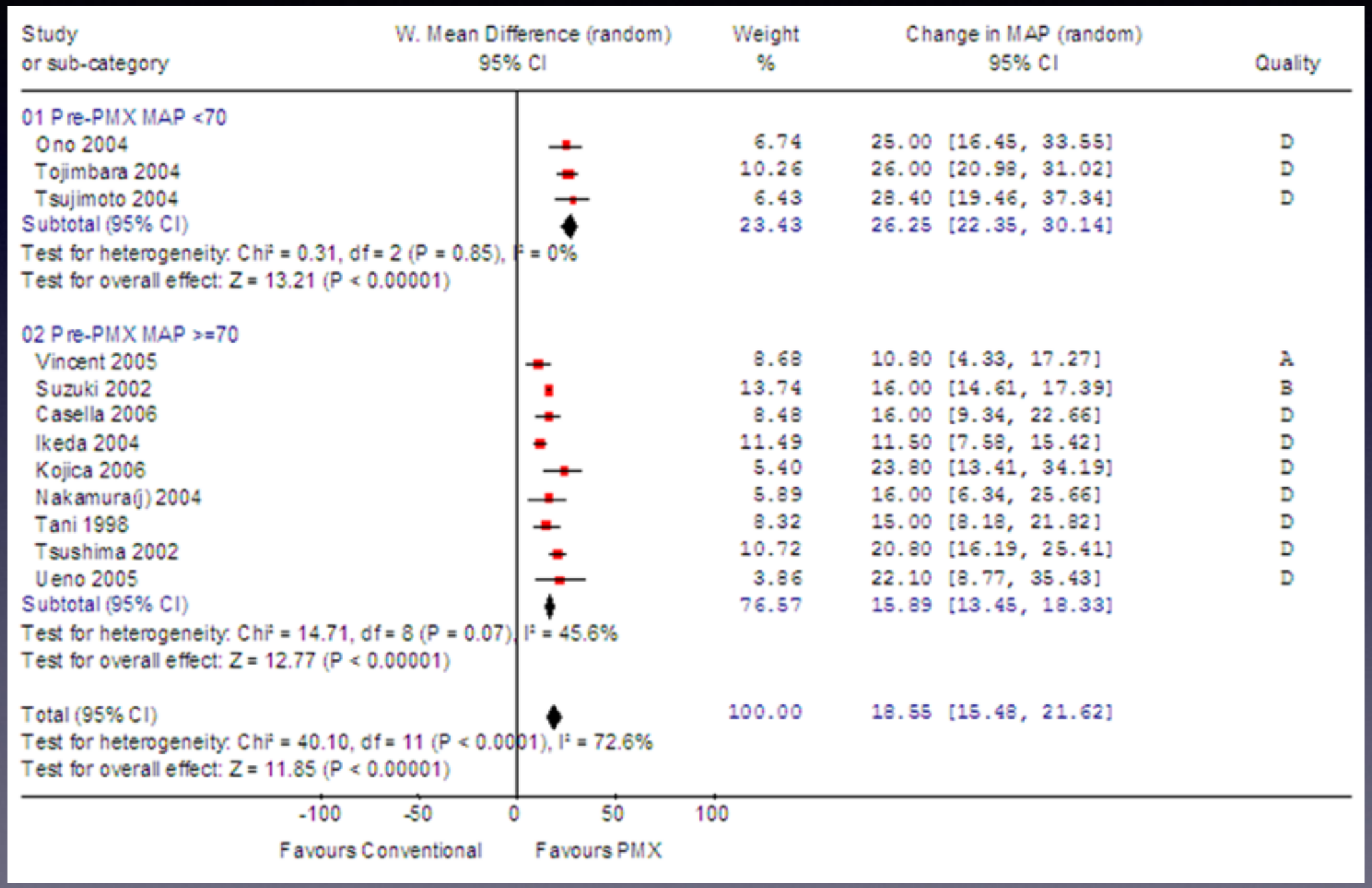
Pathophysiology of septic shock



microorganism management

- given broad spectrum antibiotics after microbiological culture within 1-3 hours
- deescalation after microbiological result turn up
- source of infection must be controlled within 6 hours
- remove microorganism and its chemokines

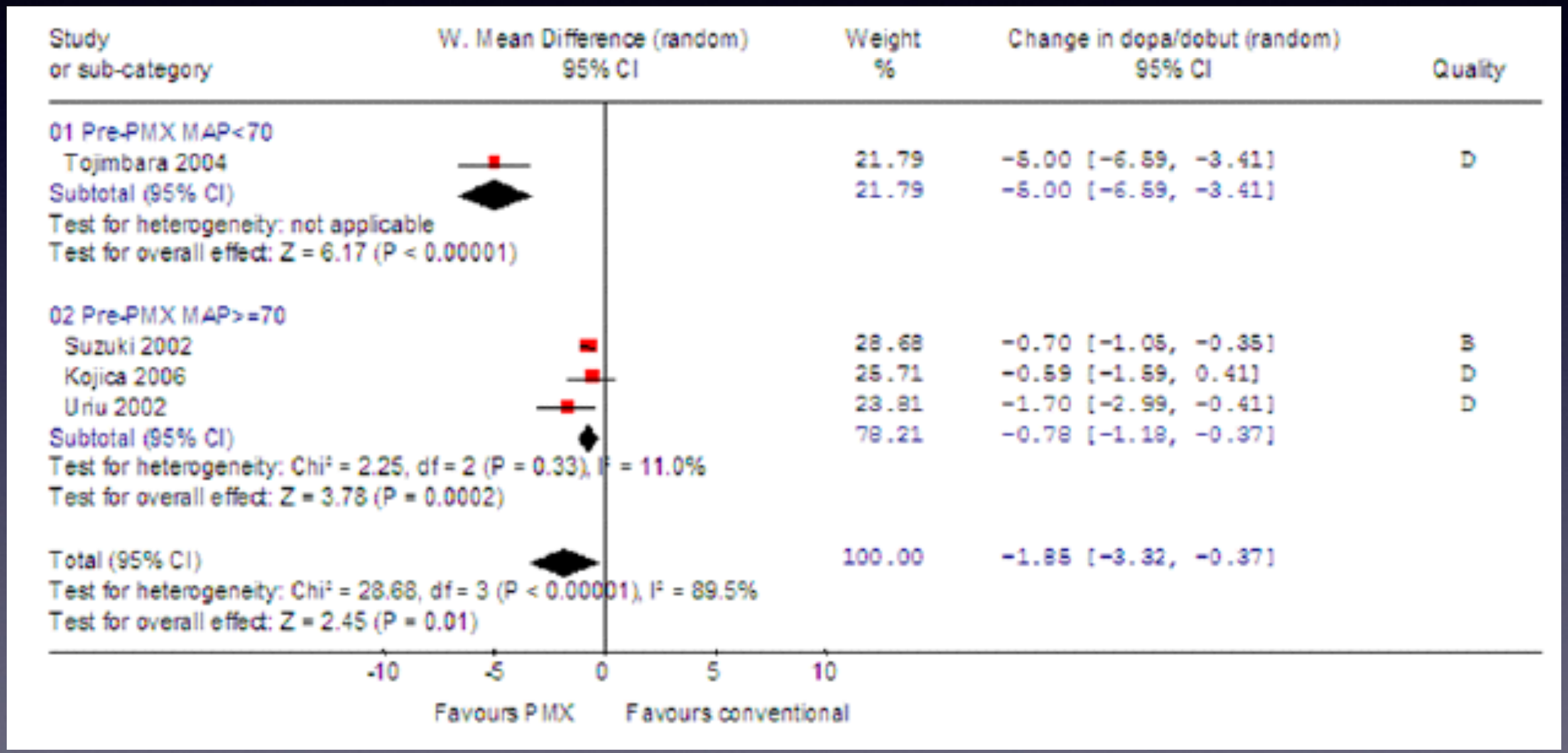
blood purification system



Cruz. CC2007.

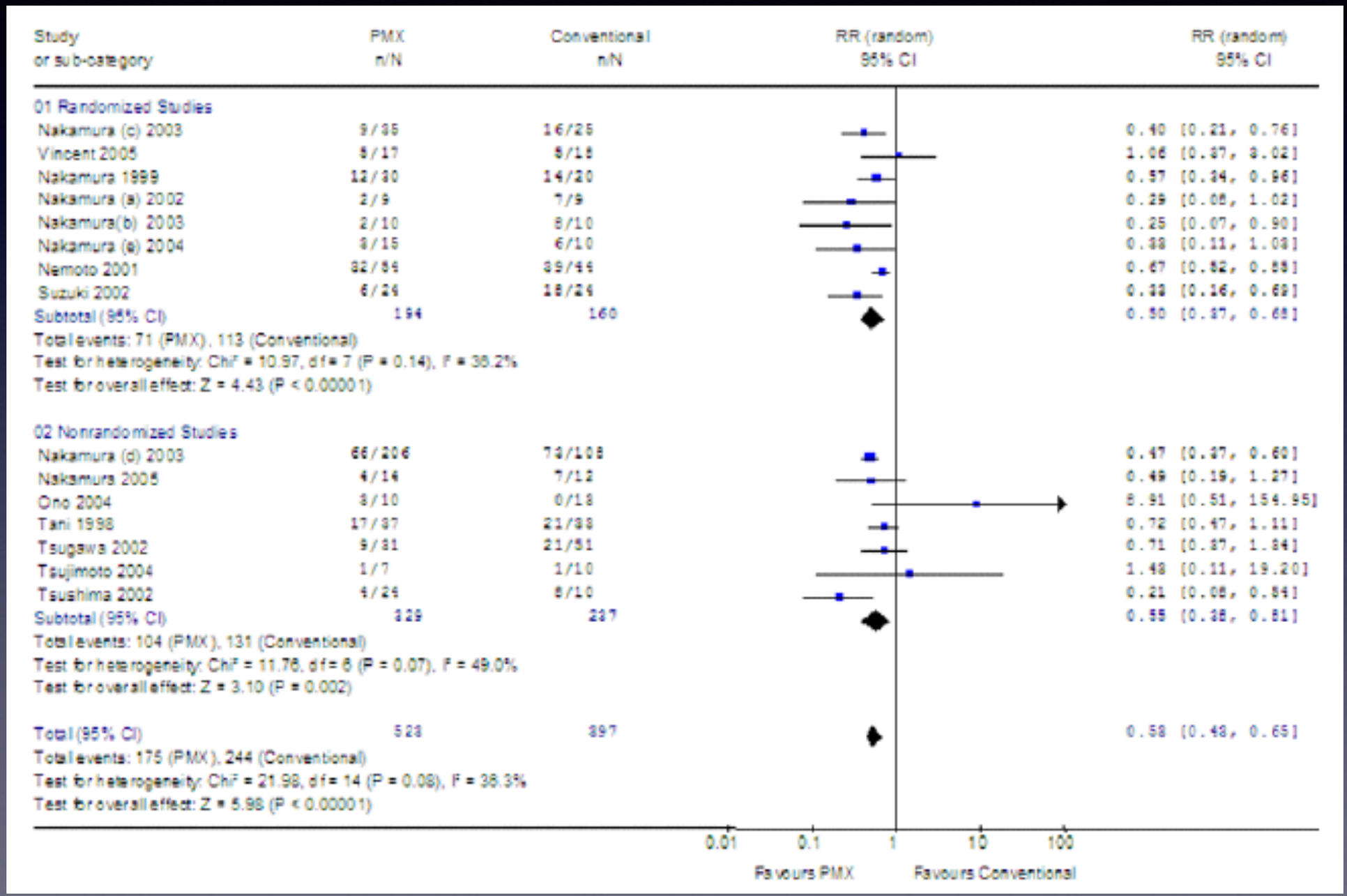
Better MAP

blood purification system



reduce dopamine/dobutamine used **Cruz. CC2007.**

blood purification system



reduce mortality

Cruz. CC2007.

Target of BP

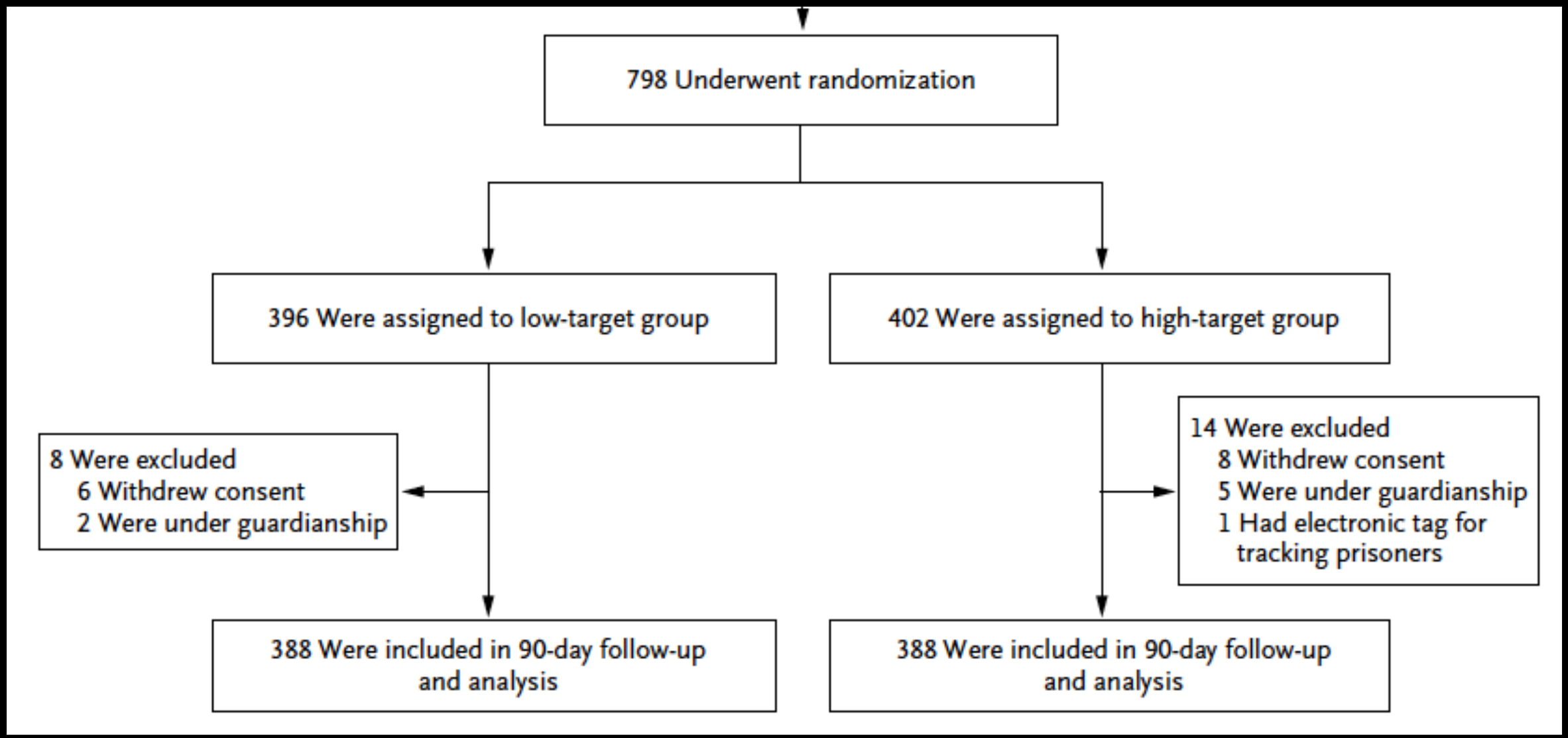
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

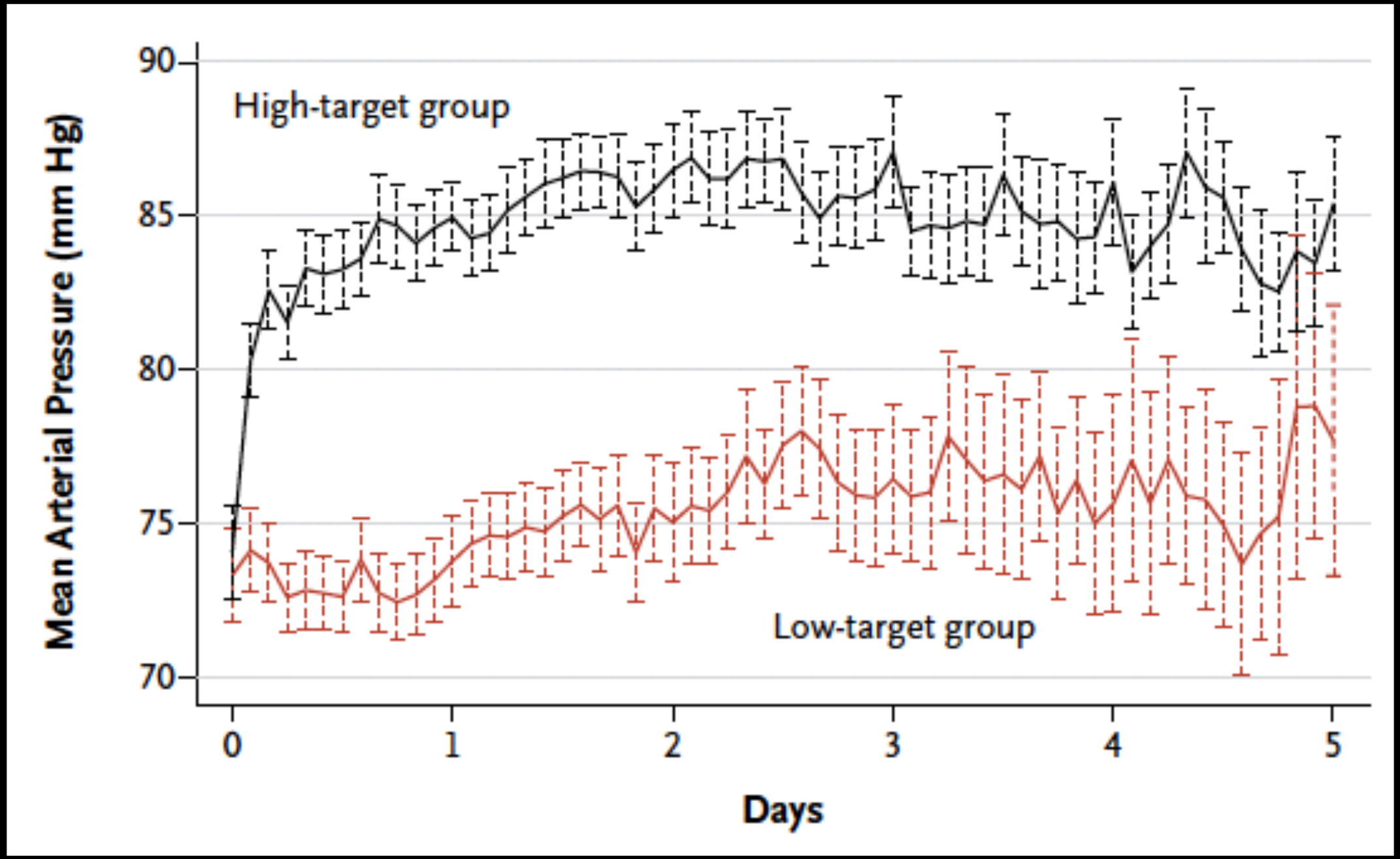
High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D., for the SEPSISPAM Investigators*

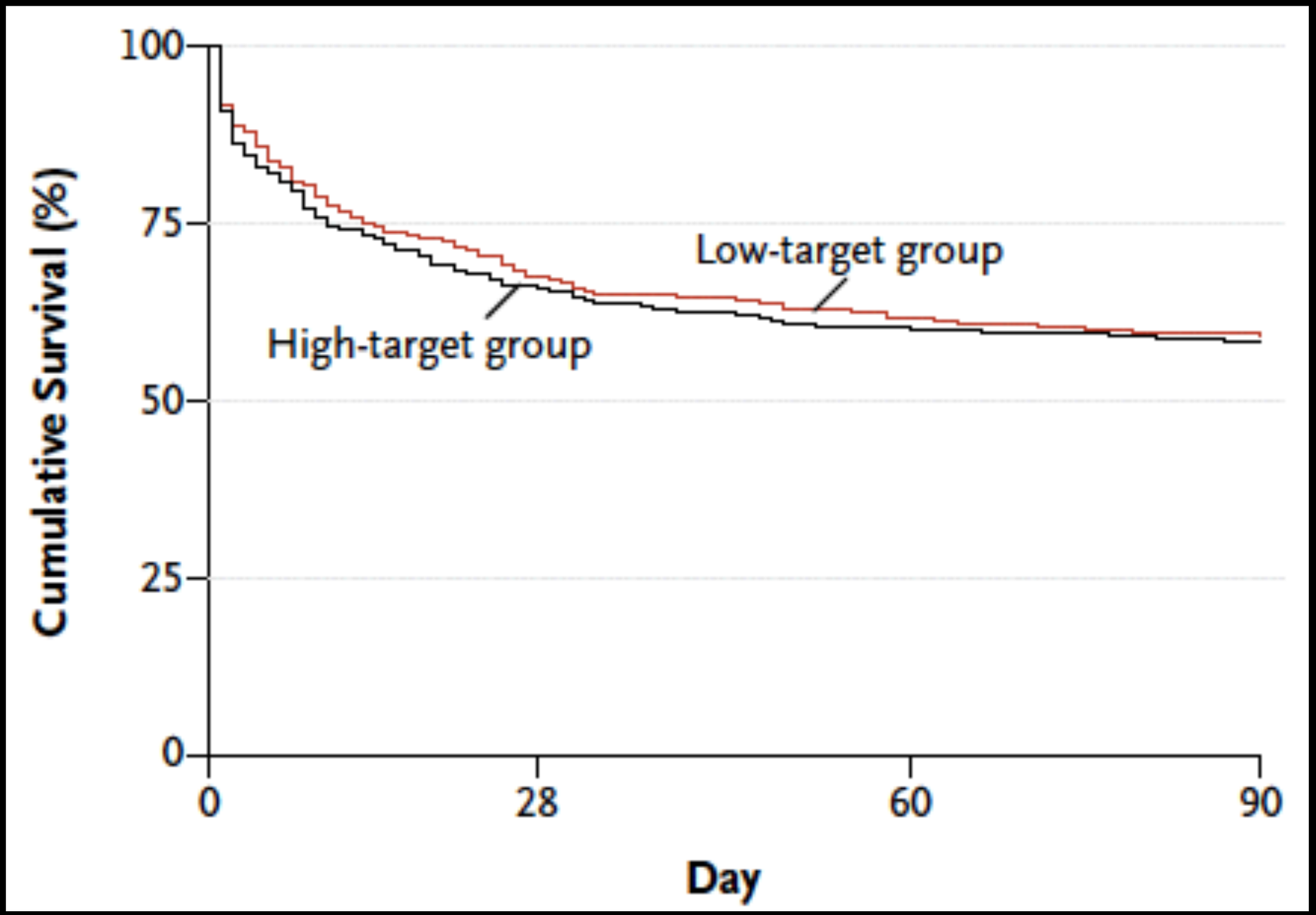
SEPSISSPAM


798 Underwent randomization
396 Were assigned to low-target group
402 Were assigned to high-target group
8 Were excluded
6 Withdrew consent
2 Were under guardianship
14 Were excluded
8 Withdrew consent
5 Were under guardianship
1 Had electronic tag for tracking prisoners
388 Were included in 90-day follow-up and analysis
388 Were included in 90-day follow-up and analysis

MAP: SEPSISSPAM



Survival: SEPSISSPAM



General Management of Shock

	Salvage	Optimization	Stabilization	De-escalation
Phase Focus	Obtain a minimal acceptable blood pressure Perform lifesaving measures	Provide adequate oxygen availability Optimize cardiac output, SvO_2, lactate	Provide organ support Minimize complications	Wean from vasoactive agents Achieve a negative fluid balance

Management of shock

V
- **ventilation**

- Oxygen supplement
- PEEP

I
- **infusion**

- Fluid resuscitation
- Blood transfusion

P
- **pump**

- Vasopressor
- Inotrope
- devices

Management of shock

BP = Preload x Contractility x Afterload

- Preload management and monitoring
- Cardiac function management
- Afterload management

Preload/fluid

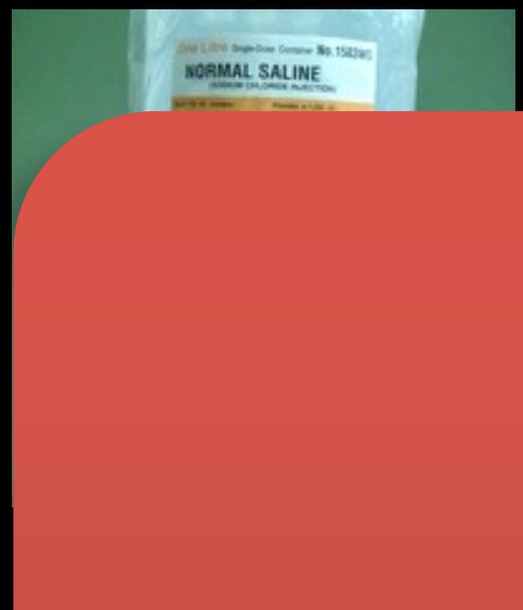
type

amount

monitor

speed

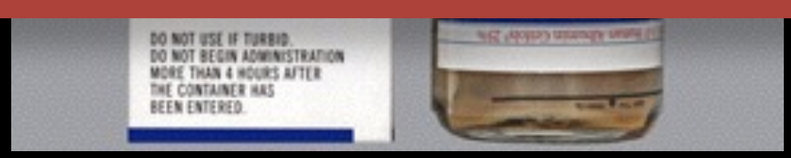
Preload: fluid types?

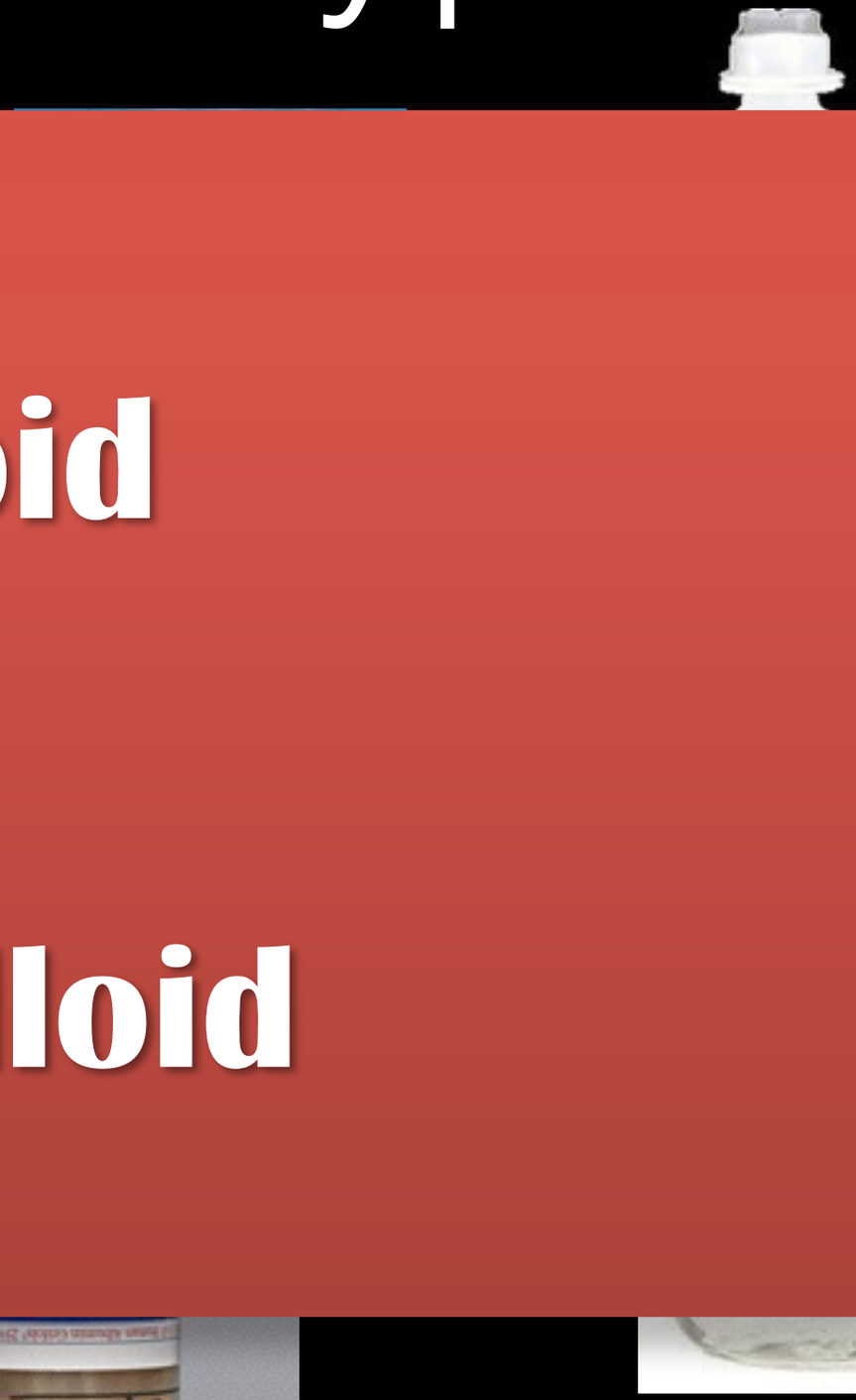


Colloid

vs

crystalloid

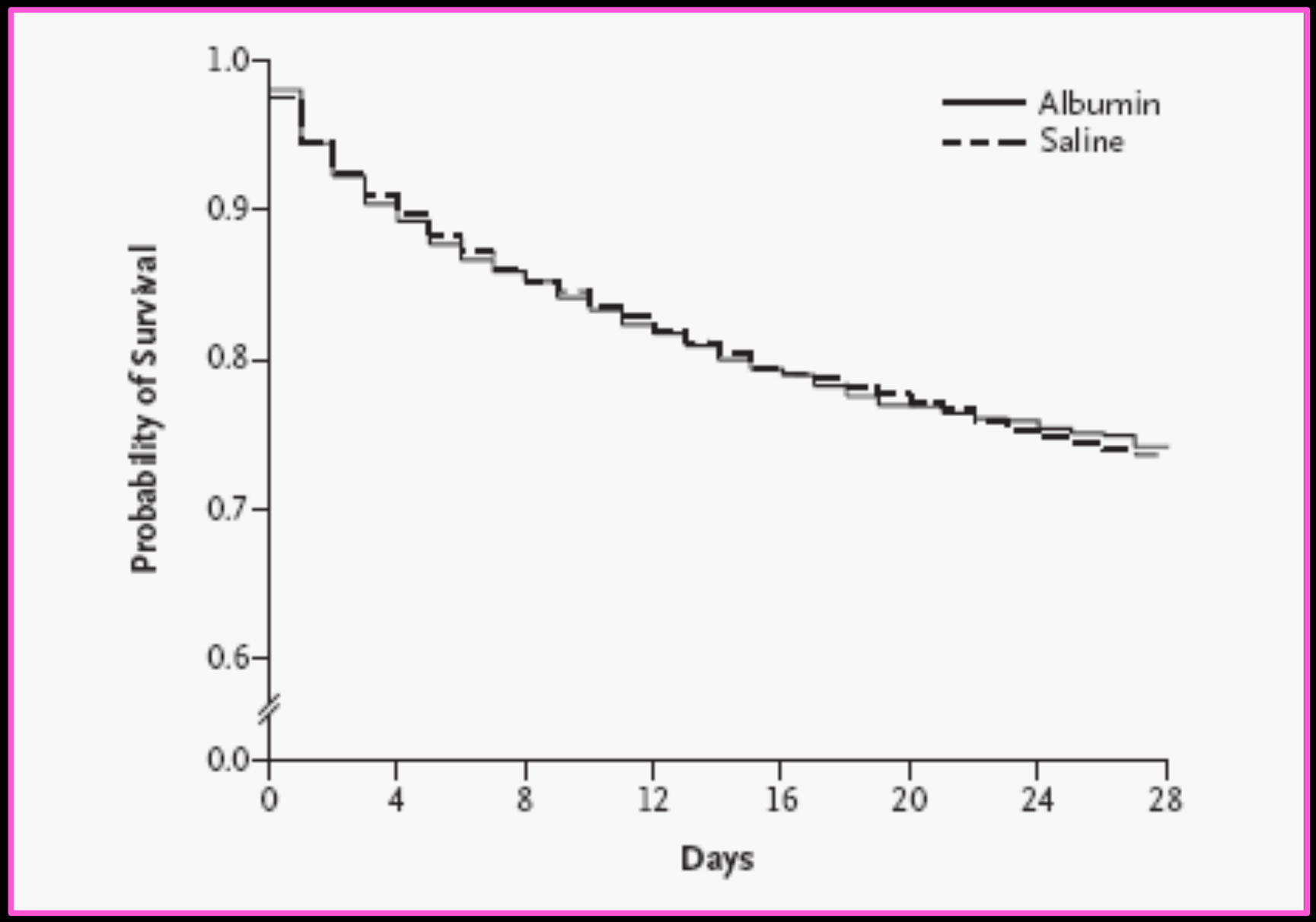




Fluid: type

	ชนิดสารน้ำ								
	สารละลาย albumin		starches	dextrans		Gelatins	crystalloids		
	5%	20%	6% hetastarch	Dextran-40	Dextran-70	Gelofusin Haemaccel	NSS	RLS	RAS
Molecular weight (kD)	69	69	450	40	70	30-35	0	0	0
Osmolarity (mOsm/L)	290	310	300	280-324	280-324	300-350	285-308	250-273	250-273
Colloidal osmotic pressure (mmHg)	20-30	70-100	23-50	20-60	20-60	25-42	0	0	0
Duration of volume expansion (h)	12-24	12-24	8-36	1-2	8-24	4-6	1-4	1-4	1-4
Plasmatic half-life (h)	16-24	16-24	50	4-6	12	2-9	0.5	0.5	0.5
Potential adverse reactions	+	+	++	+++	+++	++	+	+	+
Possible side effect	Allergy Infection	Allergy Infection	Coagulopathy Renal failure	Allergy Anaphylactoid	Allergy Anaphylactoid	anaphylactoid	Hyperchloremic acidosis	hyperkalemia	hyperkalemia

Type of fluid



There is no mortality risk for albumin resuscitation in critically ill.

SAFE. NEJM 2004;350:2247-56.

Type of fluid

Clinical Outcomes in Saline versus Albumin Fluid Evaluation[22,a]

Outcome	Albumin Group ($n = 3497$)	NS Group ($n = 3500$)
Mortality (%)	20.9	21.1
Mean ± S.D. ICU length of stay (days)	6.5 ± 6.6	6.2 ± 6.2
Mean ± S.D. hospital length of stay (days)	15.3 ± 9.6	15.6 ± 9.6
Mean ± S.D. duration of mechanical ventilation (days)	4.5 ± 6.1	4.3 ± 5.7
Mean ± S.D. duration of renal replacement therapy (days)	0.48 ± 2.28	0.39 ± 2.0
Degree of new organ failure (%)		
No failure	52.7	53.3
1 organ	30.0	29.8
≥2 organs	17.3	16.9

[a]Differences between groups were not statistically significant. NS = 0.9% sodium chloride injection, ICU = intensive care unit.

Serum albumin 2.7 +/- 7 gm/dl

SAFE. NEJM 2004;350:2247-56.

Type of fluid

Mortality in Selected Subgroups of Patients in Saline versus Albumin Fluid Evaluation[22,a]

Subgroup	Mortality Rate (%)			
	Albumin Recipients	NS Recipients	RR (95% CI)	*p*
Trauma (*n* = 1186)	13.6	10.0	1.36 (0.99–1.86)	0.06
With head injury (*n* = 492)	24.5	15.1	1.62 (1.12–2.34)	0.01
Without head injury (*n* = 694)	6.2	6.2	1.00 (0.56–1.79)	1.00
Severe sepsis (*n* = 1218)	30.7	35.3	0.87 (0.74–1.02)	0.09
ARDS (*n* = 127)	39.3	42.4	0.93 (0.61–1.41)	0.72

[a]RR = risk ratio, CI = confidence interval, ARDS = acute respiratory distress syndrome.

SAFE. NEJM 2004;350:2247-56.

Fluid: type

The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis*

Anthony P. Delaney, MD, FCICM; Arina Dan, MD, FCICM; John McCaffrey, MD, FCICM; Simon Finfer, MD, FCICM

Objective: To assess whether resuscitation with albumin-containing solutions, compared with other fluids, is associated with lower mortality in patients with sepsis.

Data Sources: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, the metaRegister of Controlled Trials, and the Medical Editors Trial Amnesty Register.

Study Selection: Prospective randomized clinical trials of fluid resuscitation with albumin-containing solutions compared with other fluid resuscitation regimens, which included a population or subgroup of participants with sepsis, were included.

Data Extraction: Assessment of the validity of included studies and data extraction were conducted independently by two authors.

Data Synthesis: For the primary analysis, the effect of albumin-containing solutions on all-cause mortality was assessed by using a fixed-effect meta-analysis.

Results: Seventeen studies that randomized 1977 participants were included in the meta-analysis. There were eight studies that included only patients with sepsis and nine where patients with sepsis were a subgroup of the study population. There was no evidence of heterogeneity, $I^2 = 0\%$. The use of albumin for resuscitation of patients with sepsis was associated with a reduction in mortality with the pooled estimate of the odds ratio of 0.82 (95% confidence limits 0.67–1.0, $p = .047$).

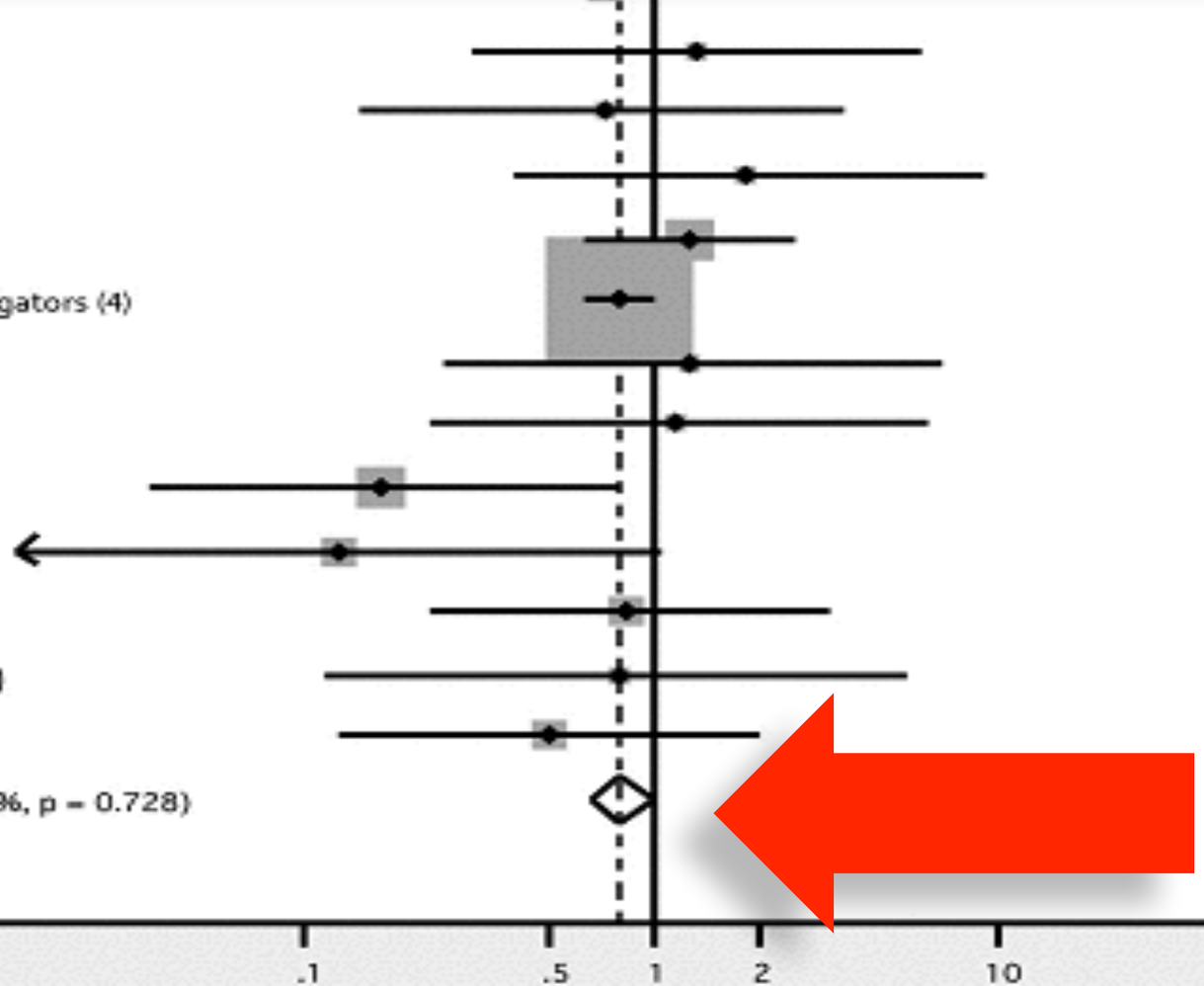
Conclusions: In this meta-analysis, the use of albumin-containing solutions for the resuscitation of patients with sepsis was associated with lower mortality compared with other fluid resuscitation regimens. Until the results of ongoing randomized controlled trials are known, clinicians should consider the use of albumin-containing solutions for the resuscitation of patients with sepsis. (Crit Care Med 2011; 39:386–391)

KEY WORDS: sepsis; resuscitation; albumin-containing solutions; meta-analysis

Fluid: type

Albumin contained fluid resuscitation may reduce mortality in septic population

Study ID		Events, Albumin	Events, Control	% Weight
Rackow et al (32)	,77)	5/7	6/11	0.61
Metildi et al (31)	1)	10/12	11/12	0.84
Rackow et al (33)	7)	5/10	5/10	1.14
Boldt et al (20)	56)	5/15	5/15	1.52
Boldt et al (19)	0.73 (0.15, 3.49)	4/15	5/15	1.67
Boldt et al (21)	1.33 (0.30, 5.91)	7/14	6/14	1.37
Boldt et al (22)	0.72 (0.15, 3.54)	4/14	5/14	1.63
Boldt et al (23)	1.88 (0.39, 9.01)	6/14	4/14	1.04
Boldt et al (24)	1.29 (0.64, 2.58)	25/75	21/75	6.38
The SAFE study investigators (4)	0.81 (0.64, 1.03)	185/603	217/615	67.91
Veneman et al (35)	1.31 (0.26, 6.72)	5/8	14/25	1.16
Maitland et al (29)	1.19 (0.23, 6.11)	4/23	3/20	1.21
Maitland et al (30)	0.17 (0.04, 0.80)	2/56	11/61	4.63
Akech et al (26)	0.12 (0.01, 1.05)	1/44	7/44	3.12
Friedman et al (28)	0.85 (0.23, 3.21)	5/15	10/27	2.17
van der Heijden et al (34)	0.79 (0.11, 5.49)	2/6	7/18	1.06
Dolecek et al (27)	0.51 (0.13, 2.07)	4/30	6/26	2.54
Overall (I-squared = 0.0%, p = 0.728)	0.82 (0.67, 1.00)	279/961	343/1016	100.00



Journal of Pathology
J Pathol 2012; **226:** 562–574
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.3964

INVITED REVIEW

Endothelial glycocalyx dysfunction in disease: albuminuria and increased microvascular permeability

Andrew HJ Salmon[1,2] and Simon C Satchell[1]*

British Journal of Anaesthesia **108** (3): 384–94 (2012)
Advance Access publication 29 January 2012 · doi:10.1093/bja/aer515

BJA

Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy

T. E. Woodcock[1*] and T. M. Woodcock[2]

Basic Res Cardiol (2010) 105:687–701
DOI 10.1007/s00395-010-0118-z

INVITED REVIEW

Endothelial glycocalyx and coronary vascular permeability: the fringe benefit

Bernhard F. Becker · Daniel Chappell · Matthias Jacob

Cardiovascular Research (2010) **87**, 300–310
doi:10.1093/cvr/cvq137

SPOTLIGHT REVIEW

Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential†

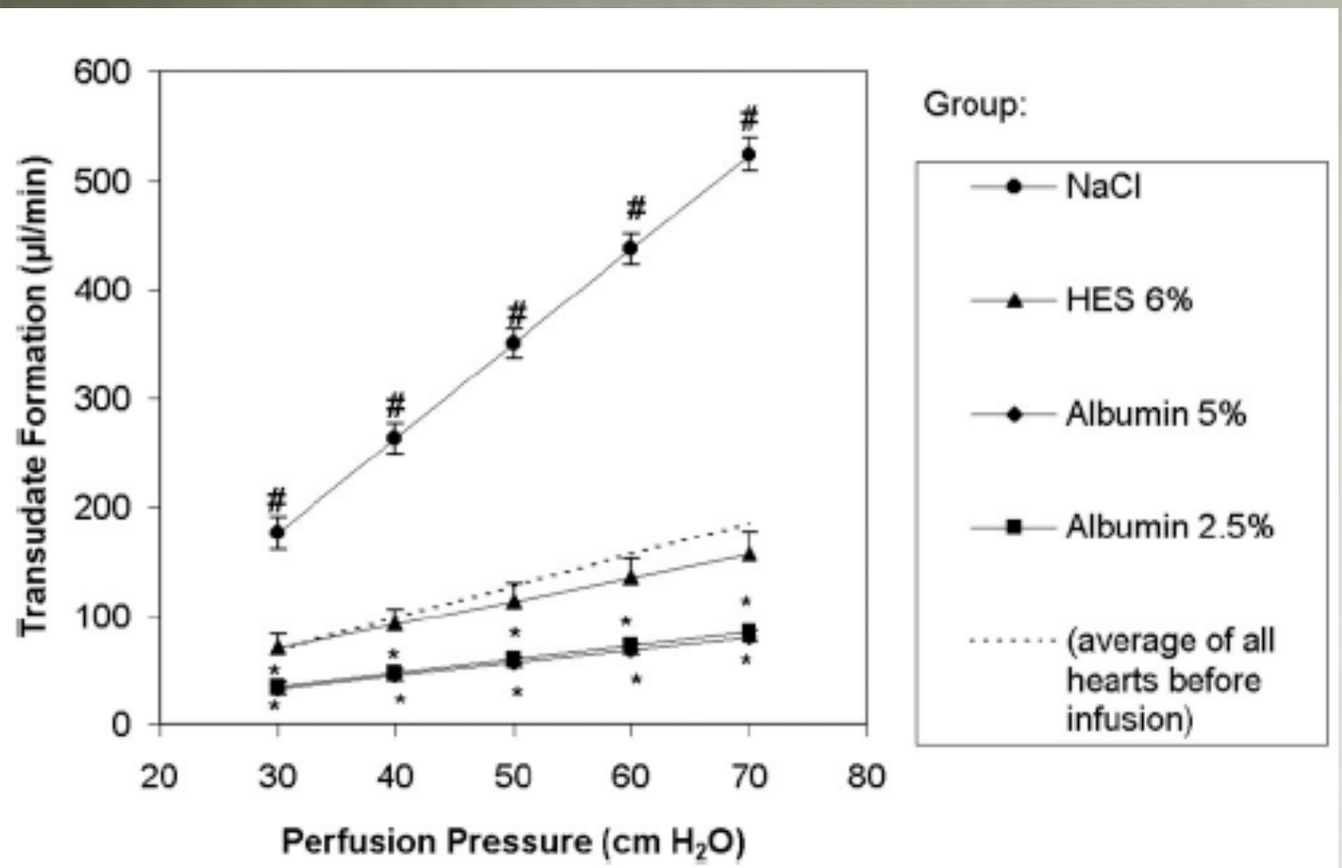
Bernhard F. Becker[1]*, Daniel Chappell[2], Dirk Bruegger[2], Thorsten Annecke[1,2], and Matthias Jacob[2]

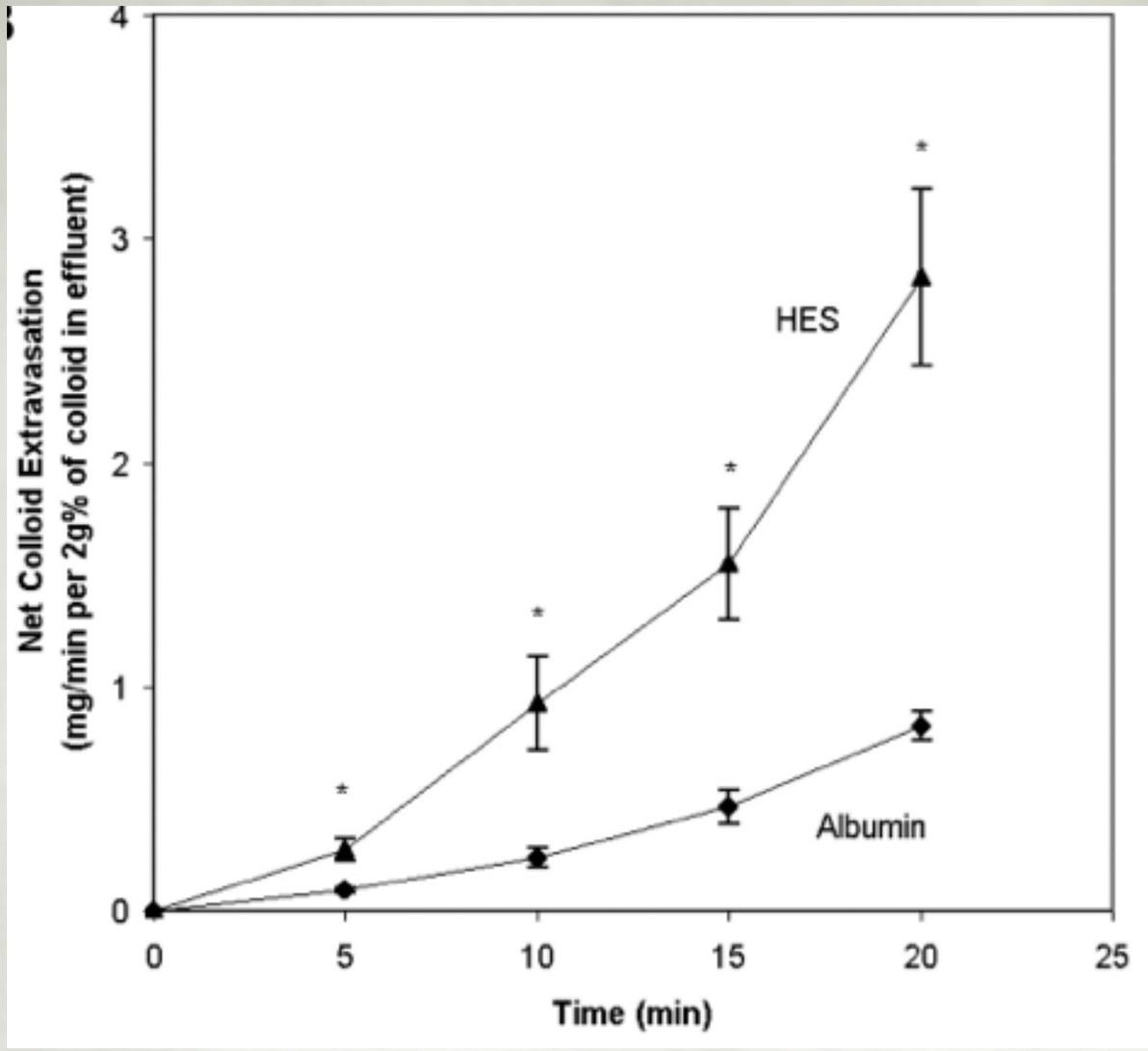
Infusion of human plasma albumin (to maintain mechanical & chemical stability of the endothelial surface layer) seems the easiest treatment to implement

Anesthesiology 2006; 104:1223–31
© 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Contrasting Effects of Colloid and Crystalloid Resuscitation Fluids on Cardiac Vascular Permeability

Matthias Jacob, M.D.,* Dirk Bruegger, M.D.,* Markus Rehm, M.D.,† Ulrich Welsch, M.D., Ph.D.,‡
Peter Conzen, M.D.,§ Bernhard F. Becker, M.D., Ph.D.‖





Anesthesiology 2006; 104:1223–31
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Contrasting Effects of Colloid and Crystalloid Resuscitation Fluids on Cardiac Vascular Permeability

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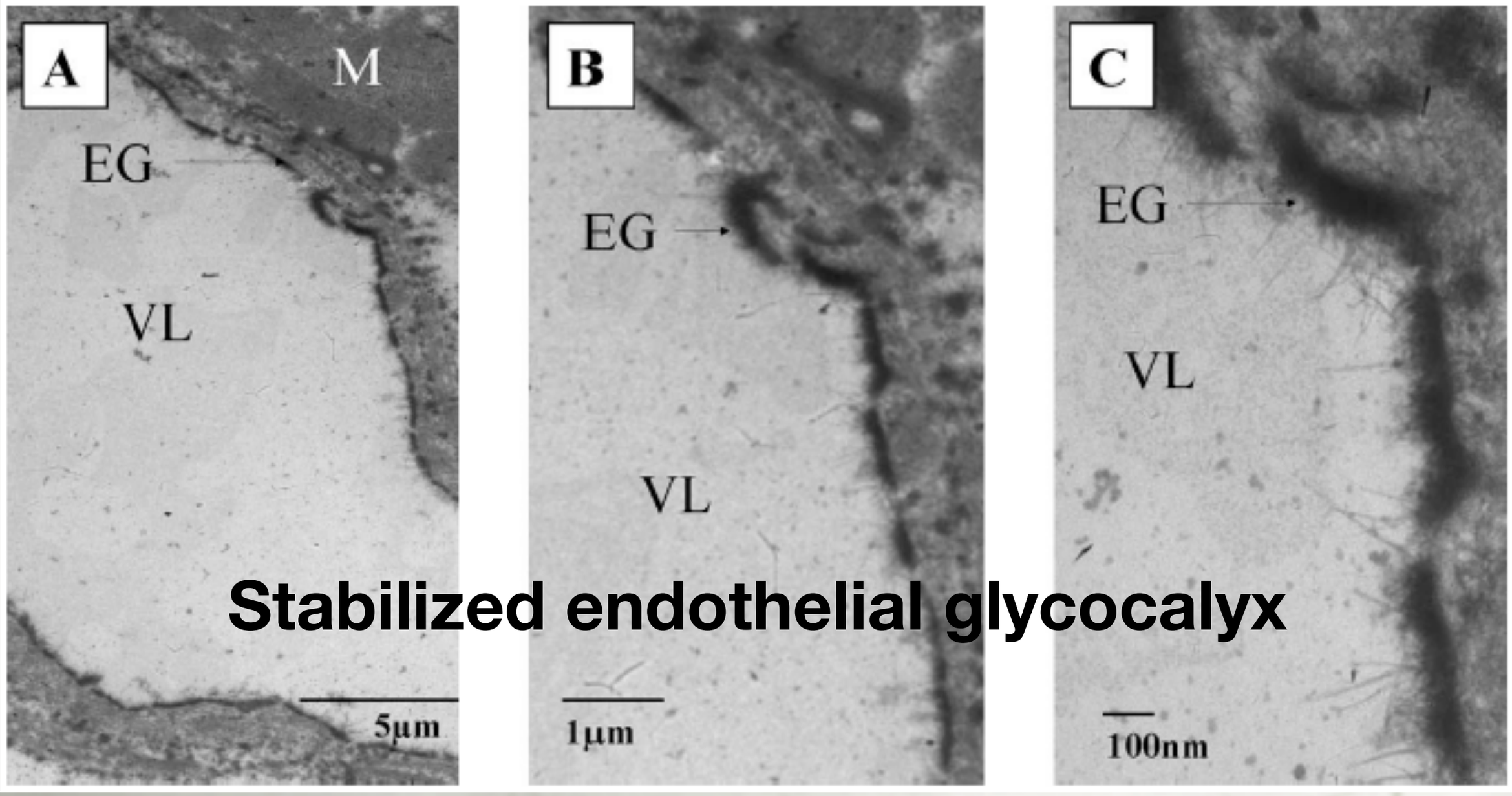

Stabilized endothelial glycocalyx

Anesthesiology 2006; 104:1223–31
© 2006 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Contrasting Effects of Colloid and Crystalloid Resuscitation Fluids on Cardiac Vascular Permeability

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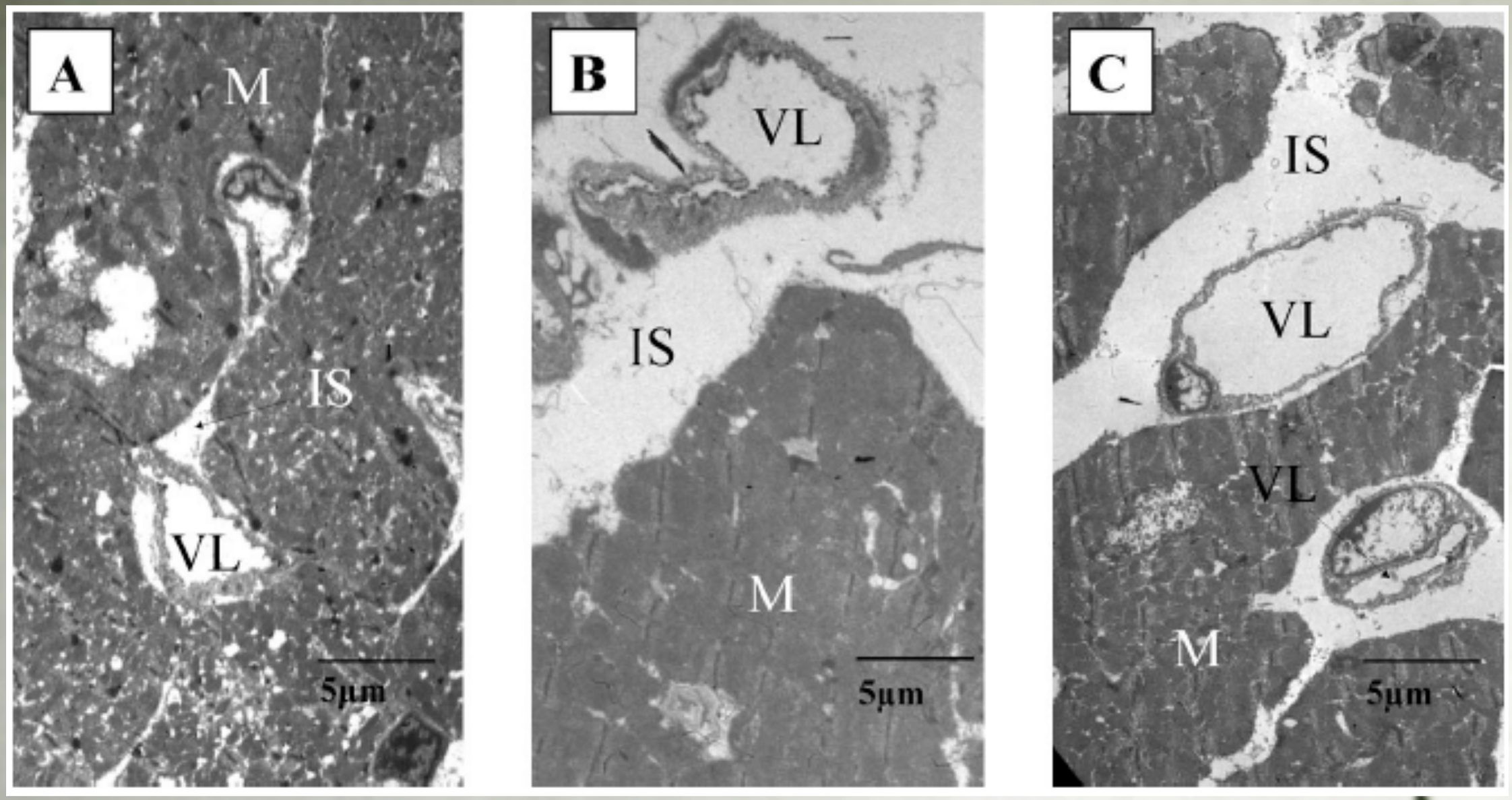


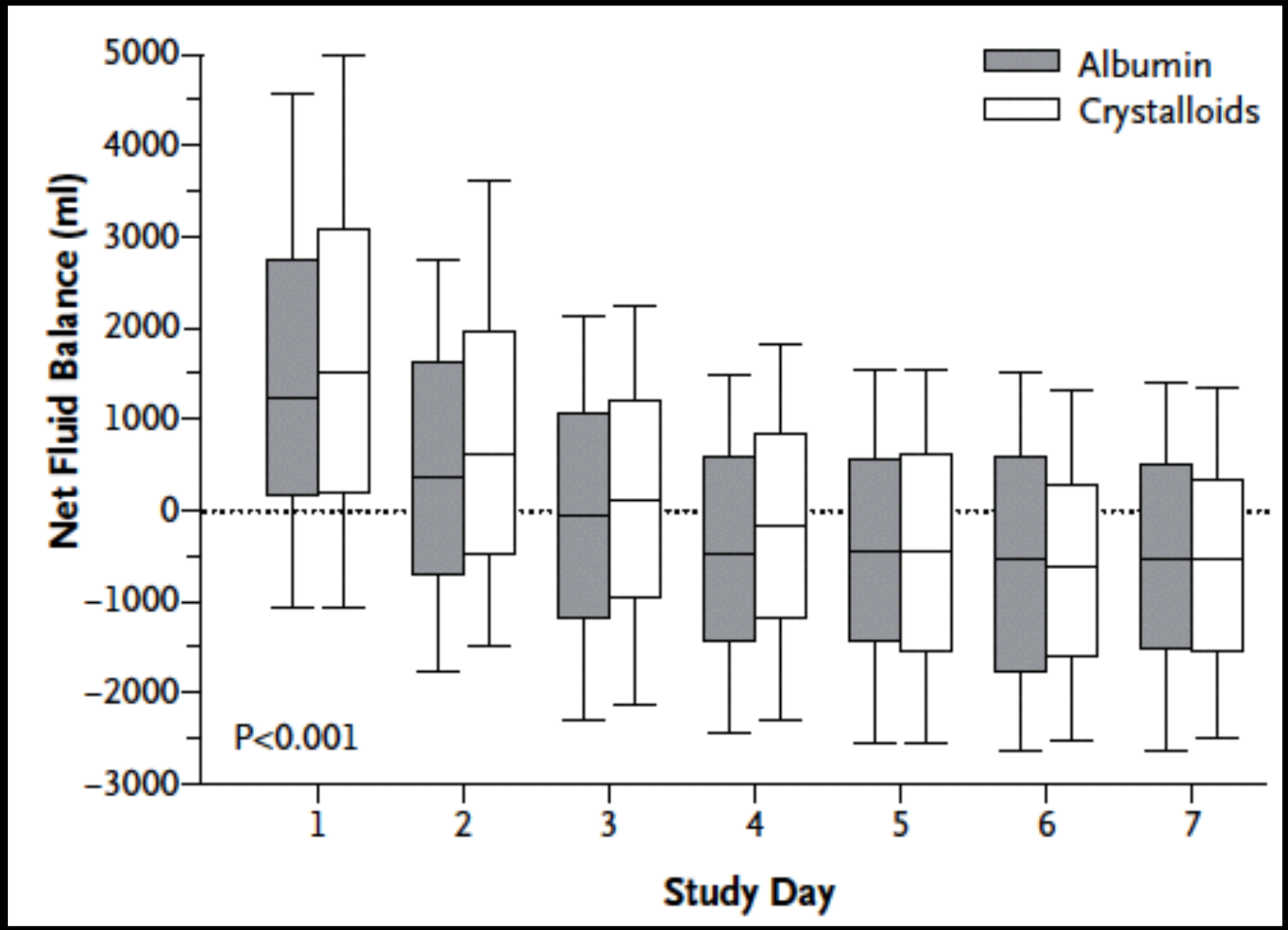
Albumin HES NSS

ORIGINAL ARTICLE

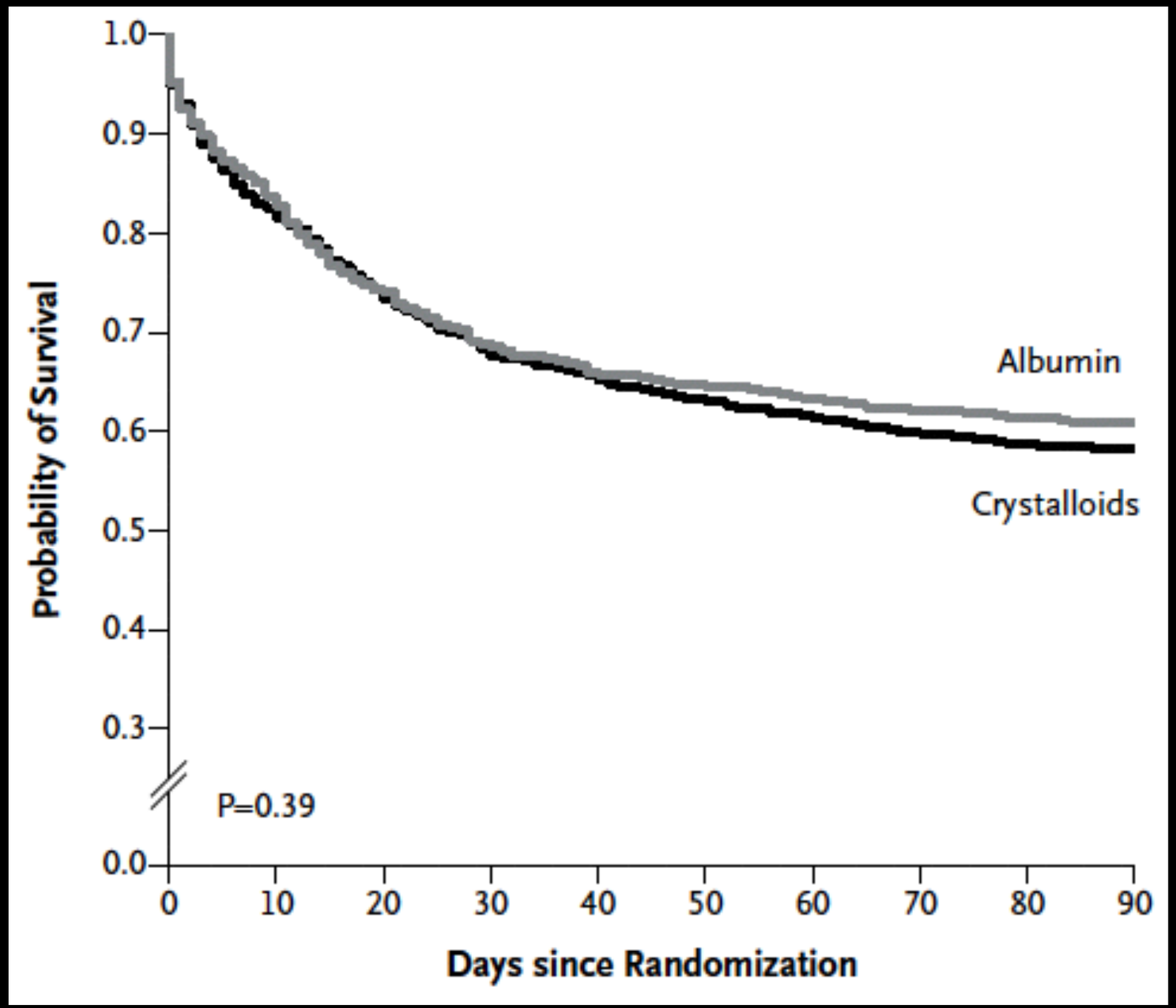
Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

ALBIOS:net volume



ALBIOS:MR

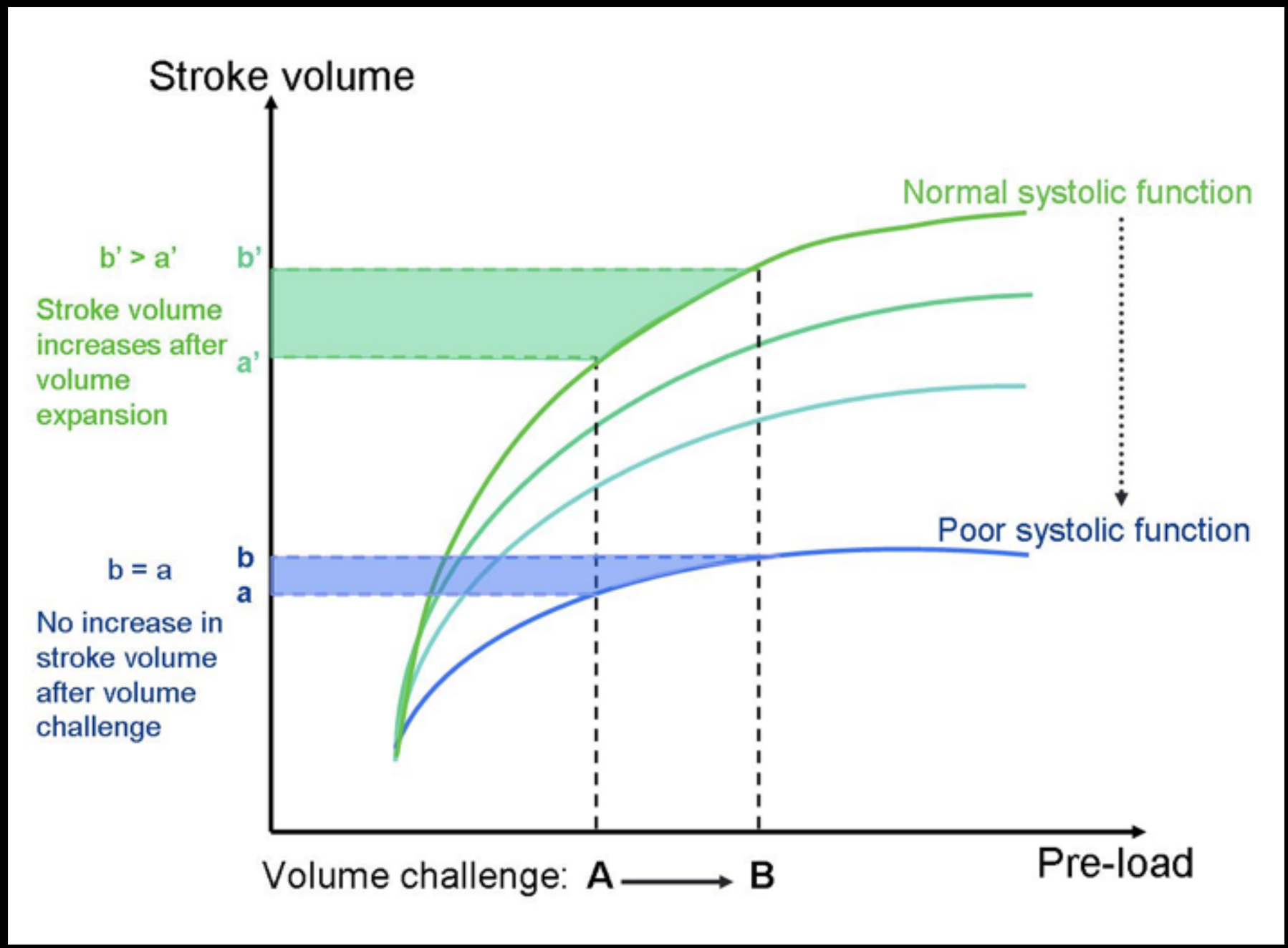

1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.0
Probability of Survival
Albumin
Crystalloids
P=0.39
0
10
20
30
40
50
60
70
80
90
Days since Randomization

Fluid: type

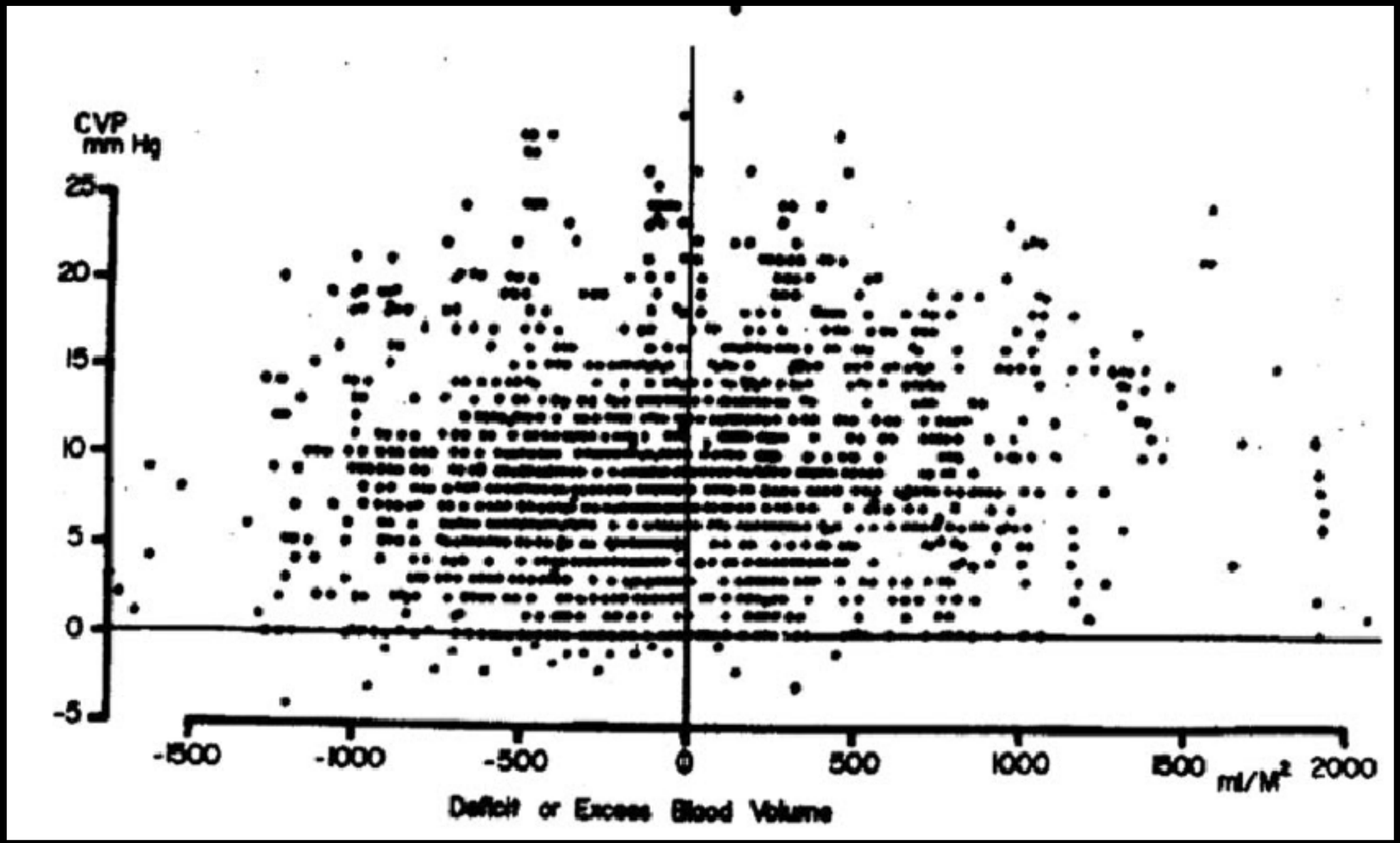
- There has been no significant medical data of the mortality benefit between colloid and crystalloid in shock resuscitation

Fluid responsive?

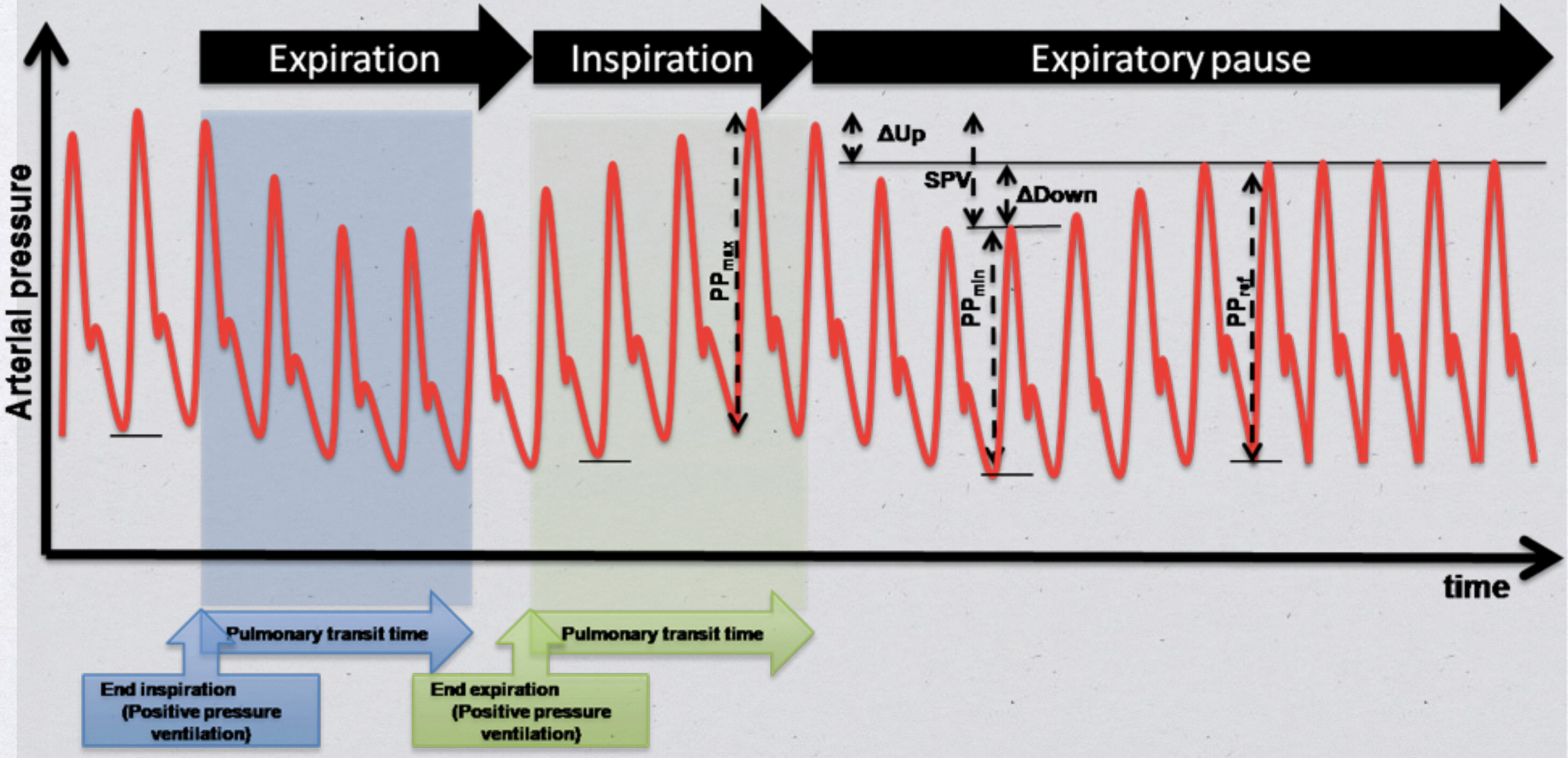
Fluid Response



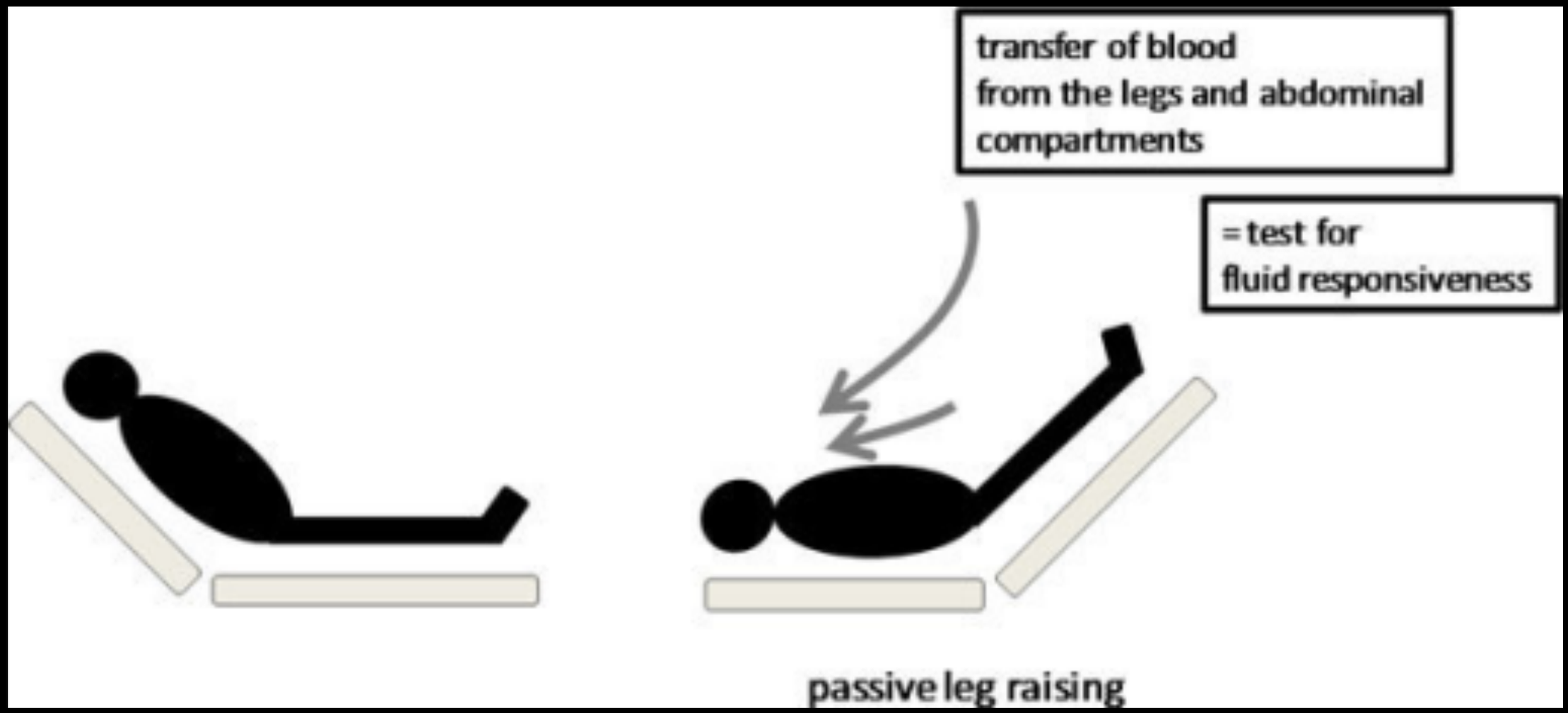
CVP as volume measurement



Arterial pressure variation during positive pressure ventilation without spontaneous effort.

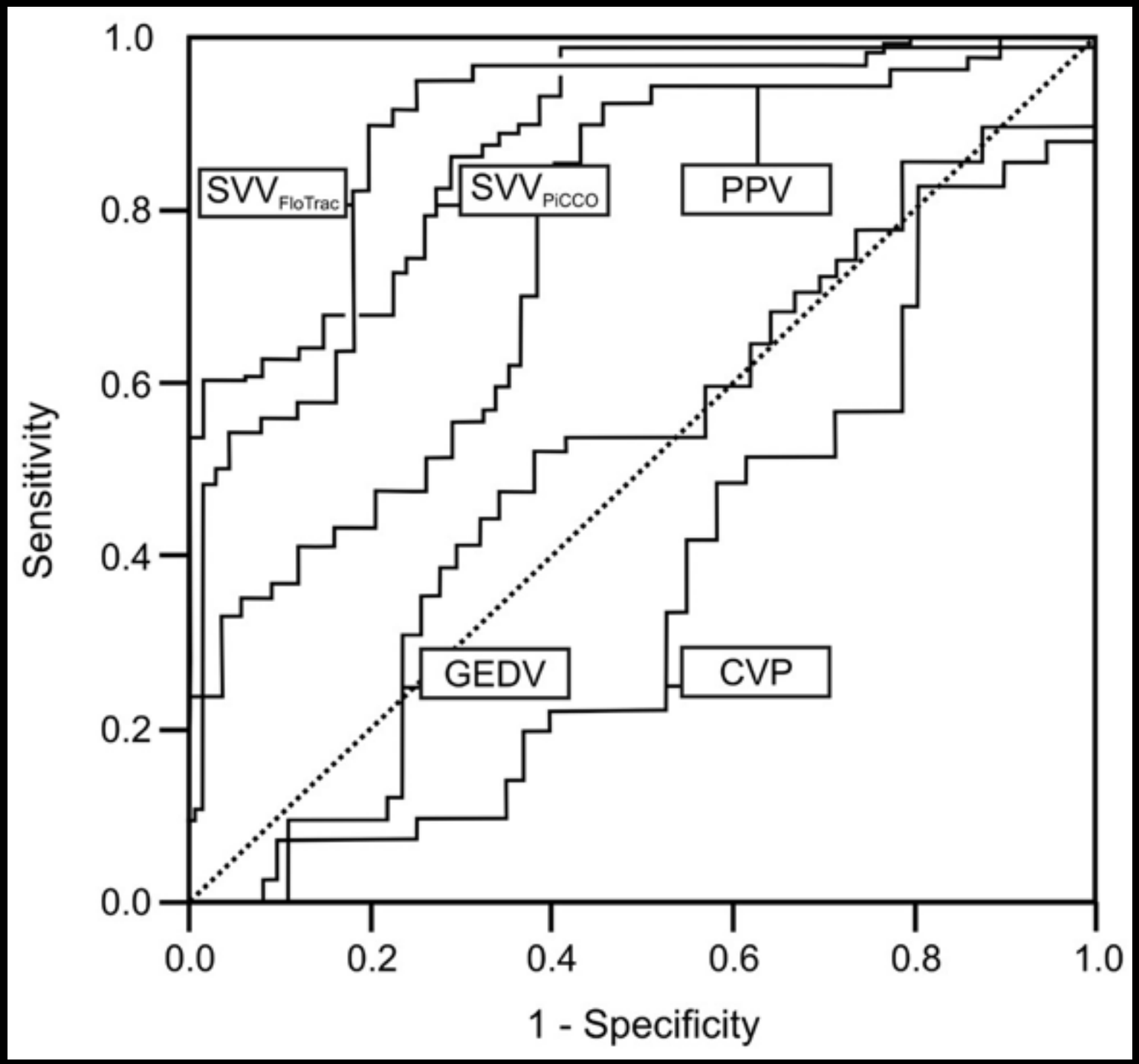


Passive Leg Raising



PLR as Roller Coaster

Fluid responses



Fluid challenge test (new concept)

T
- **Type of fluid**

R
- **Rate of administration**

O
- **Objective of resuscitation**

L
- **Limitation/safety**

Vincent. CCM 2006.

TROL resuscitation

Current V/S: BP 70/40mmHg, MAP 50 mmHg, CVP 8 mmHg

T
- **NSS**

R
- **500 ml iv drip in 30 minutes**

O
- **Keep MAP > 65 mmHg**

L
- **CVP < 15 mmHg**

TROL resuscitation

10th min
- MAP 60 mmHg
- CVP 10 mmHg

20th min
- MAP 62mmHg
- CVP 12 mmHg

30th min
- MAP 70 mmHg
- CVP 15 mmHg

10th min
- MAP 60 mmHg
- CVP 10 mmHg

20th min
- MAP 68mmHg
- CVP 12 mmHg

10th min
- MAP 60 mmHg
- CVP 20 mmHg

Hemodynamic Drugs

Vasoactive agents

- Adrenergic agents to maintain hemodynamic and perfusion
- Adrenergic receptor agonist

α

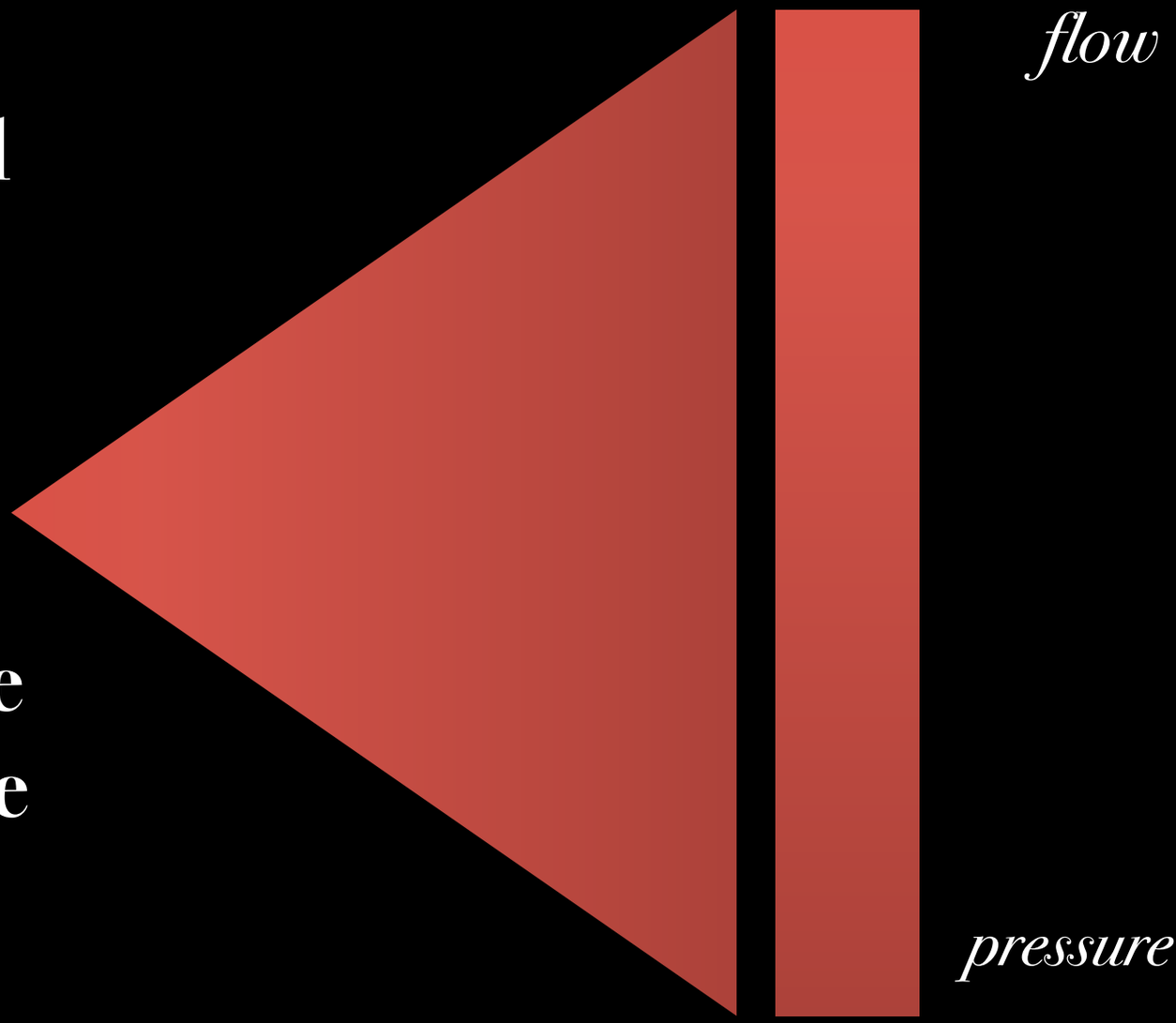
β

Inotropes and vasopressors

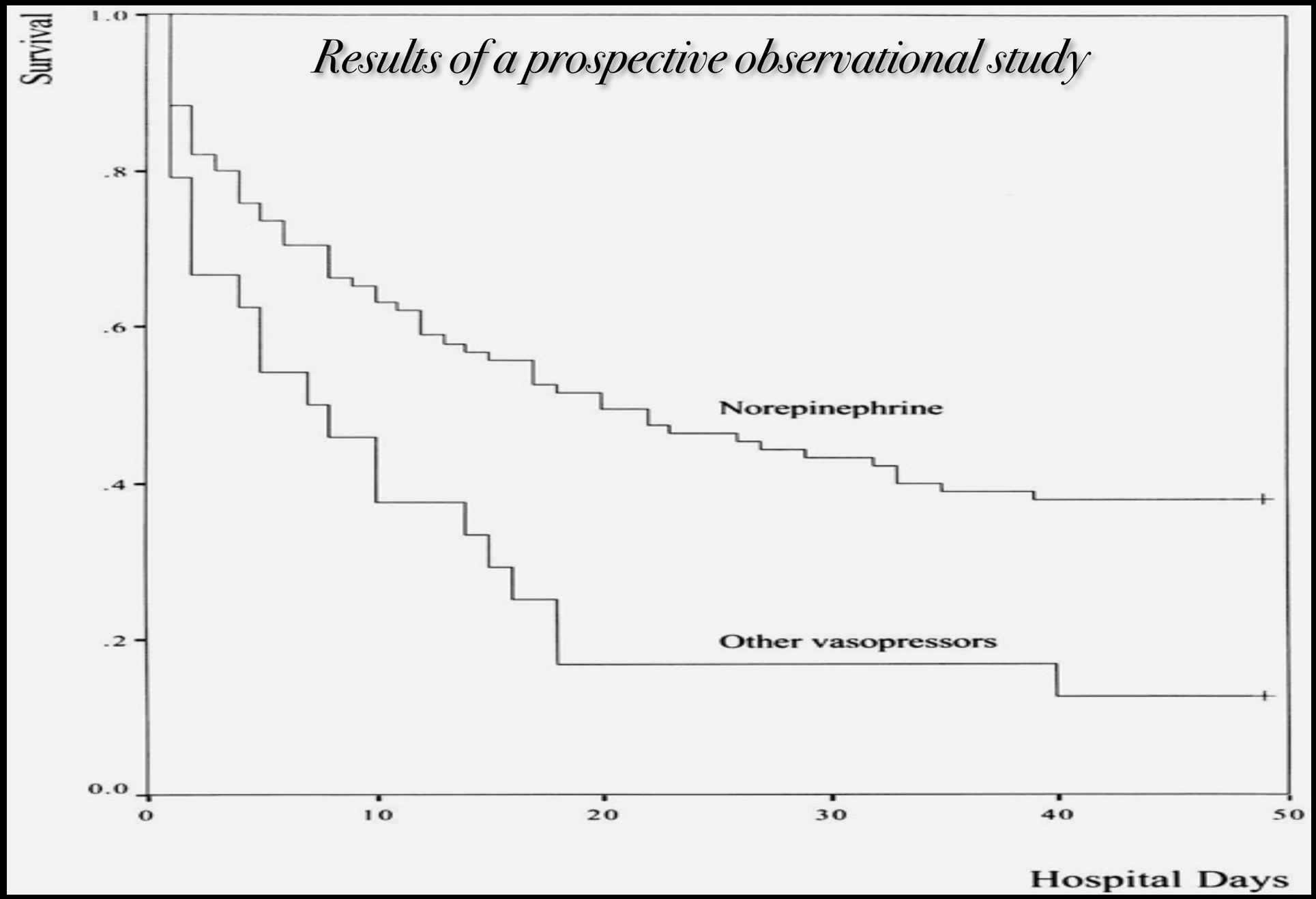
Adrenergic agent	Receptor	action
Noradrenaline	α+β1	Vasoconstrict
Adrenaline	α+β1+β2	Vasoconstrict and tachycardia
Dopamine(low)	dopaminergic	Increase RBF
Dopamine(high)	α+β1+DA	As adrenaline
Dobutamine	β1+β2	Chronotrope

Inotrope and vasopressor

isoproterenol
dobutamine
PDI-III
adrenaline
dopamine
noradrenaline
phenylephrine



Norepinephrine vs. Dopamine +/_ Epinephrine in Septic Shock



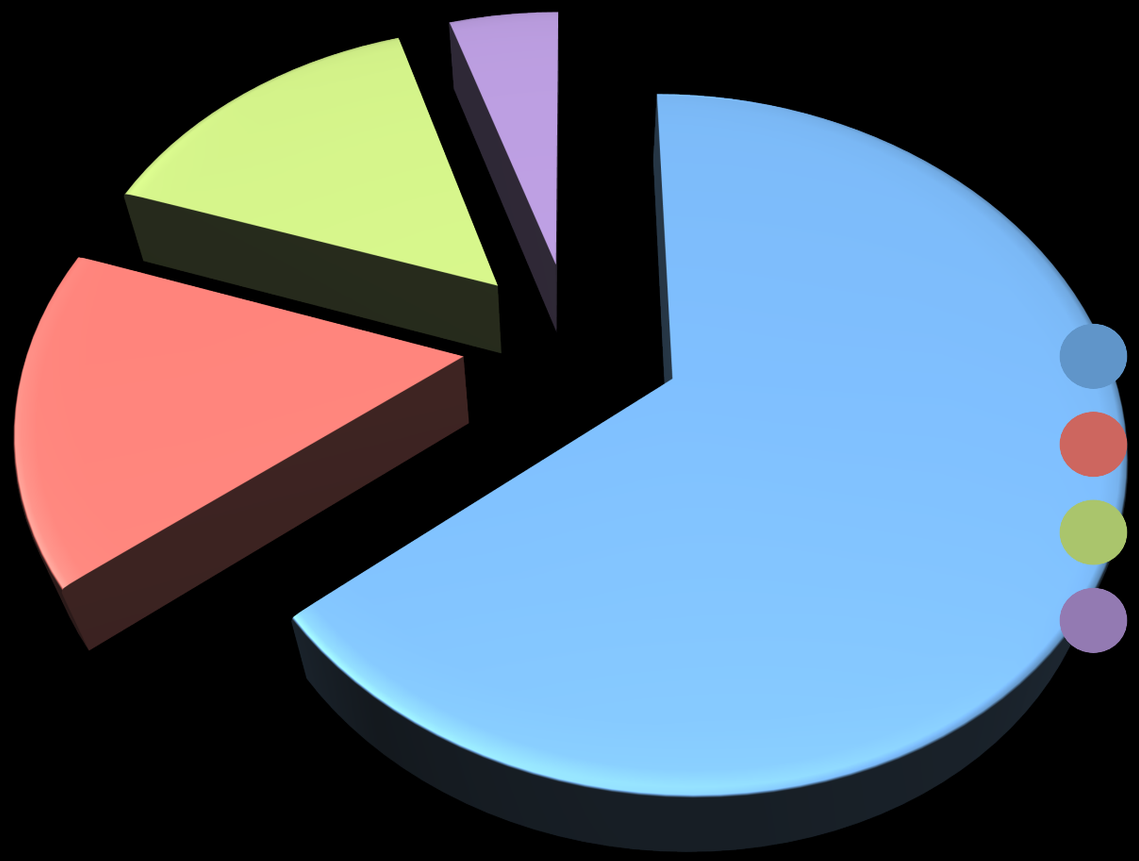
Claude, Critical Care Med 2000;28:2758

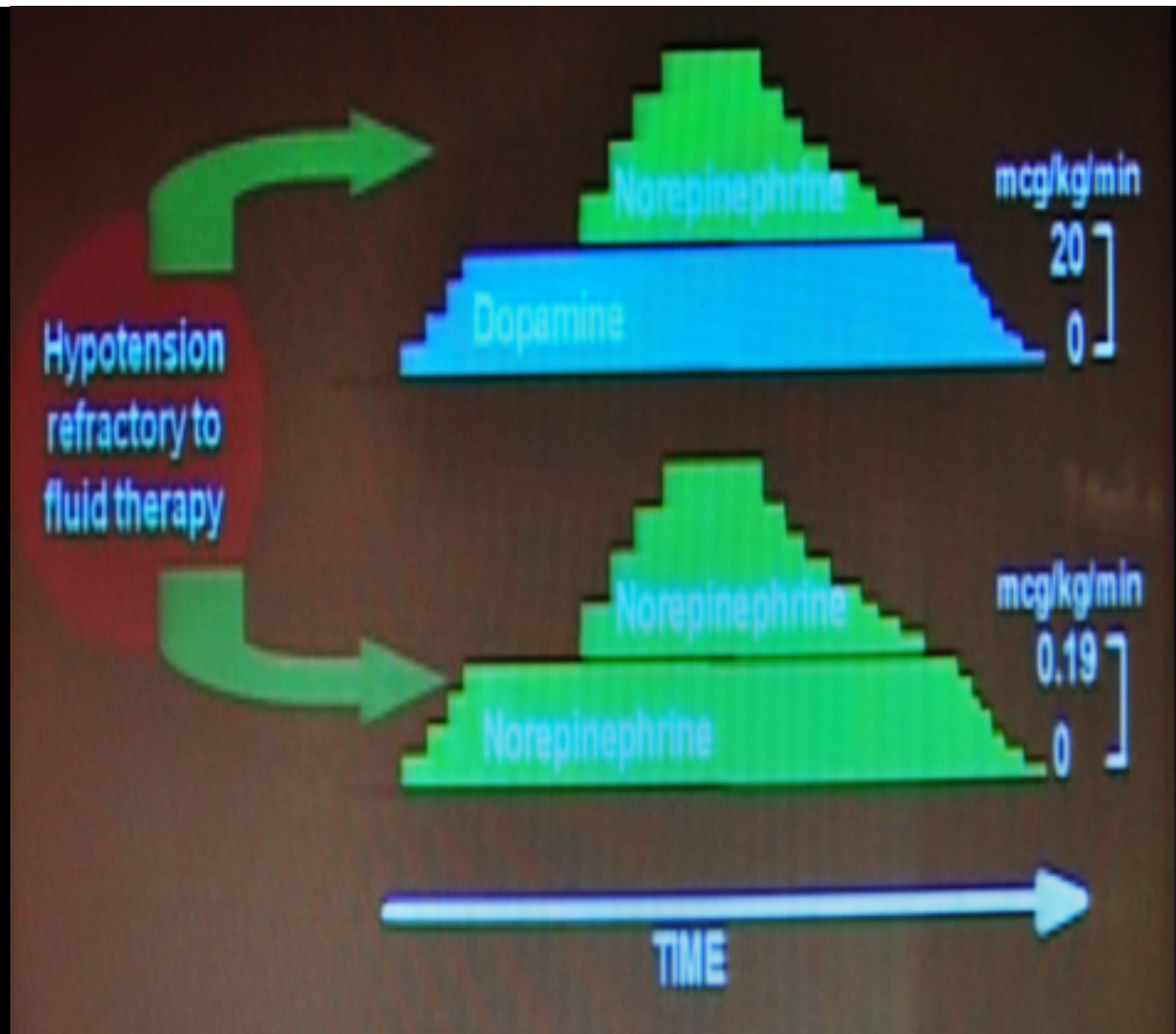
The NEW ENGLAND JOURNAL of MEDICINE

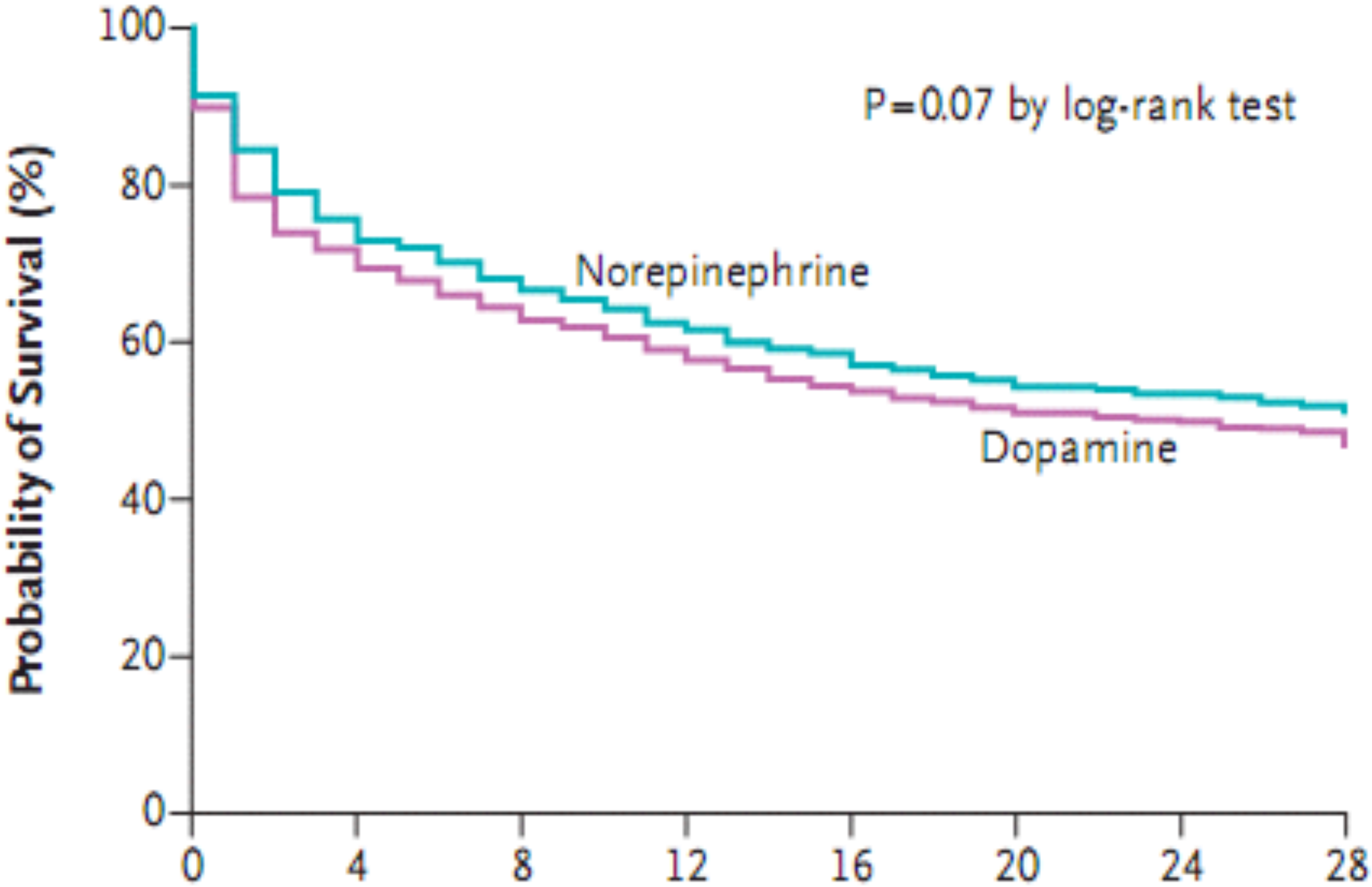
ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

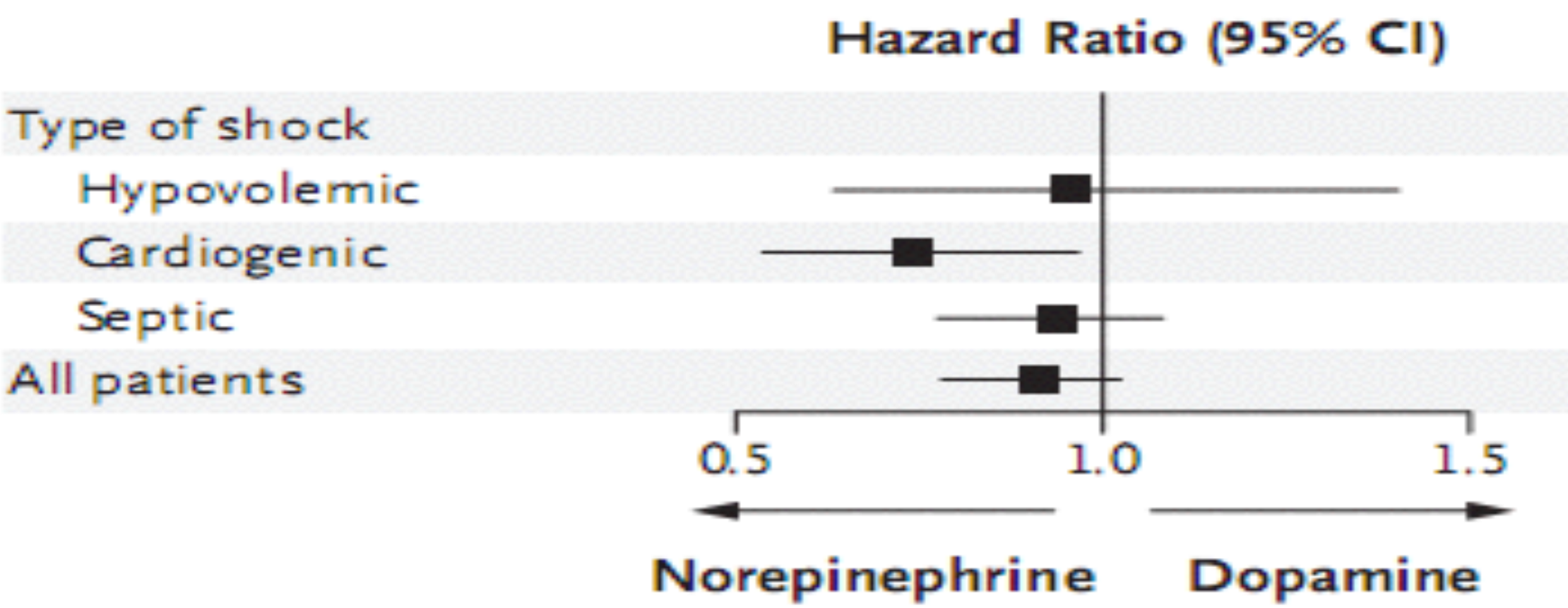
Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*







No. at Risk								
Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386



Adverse events			
Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	

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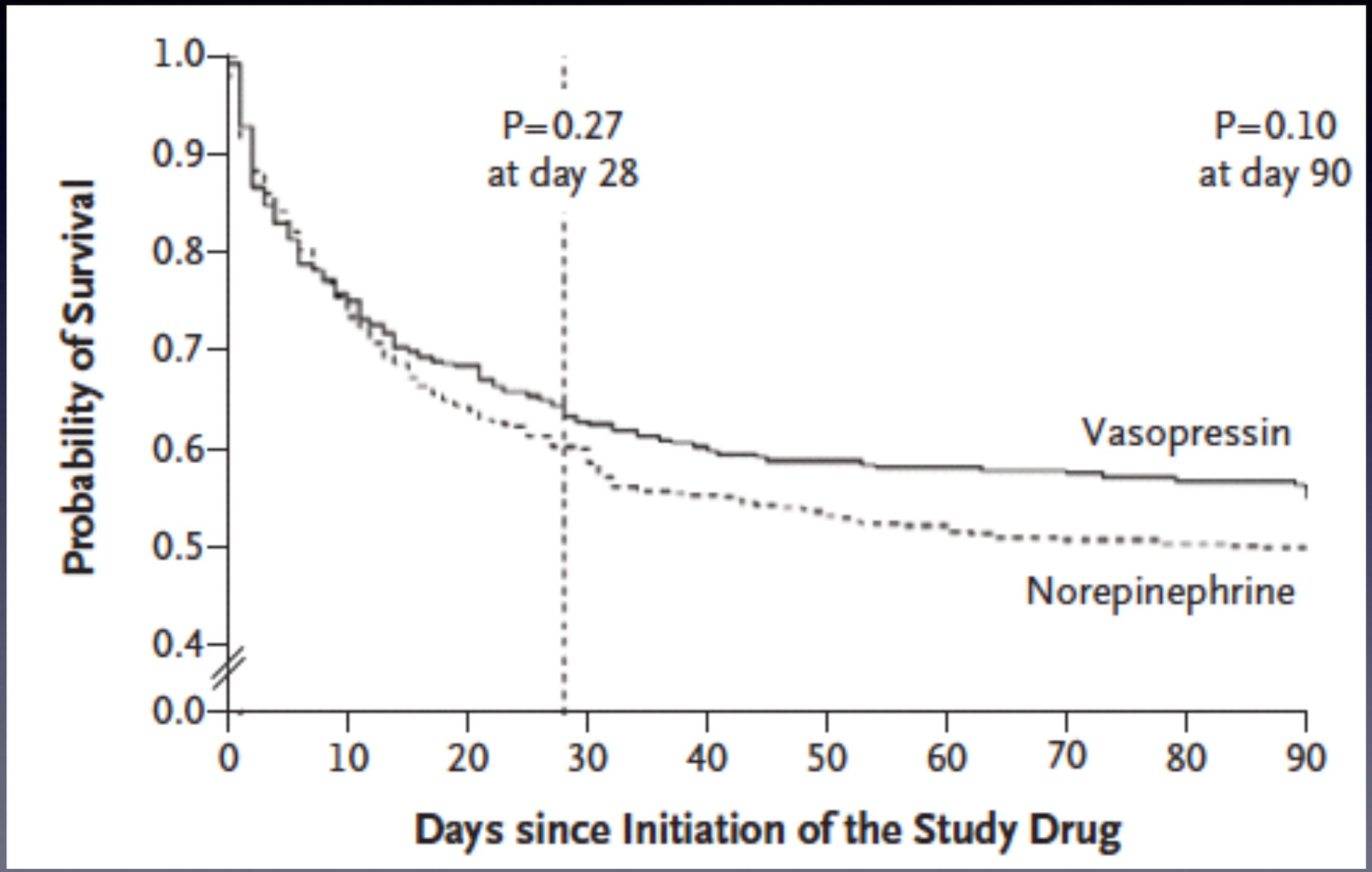
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

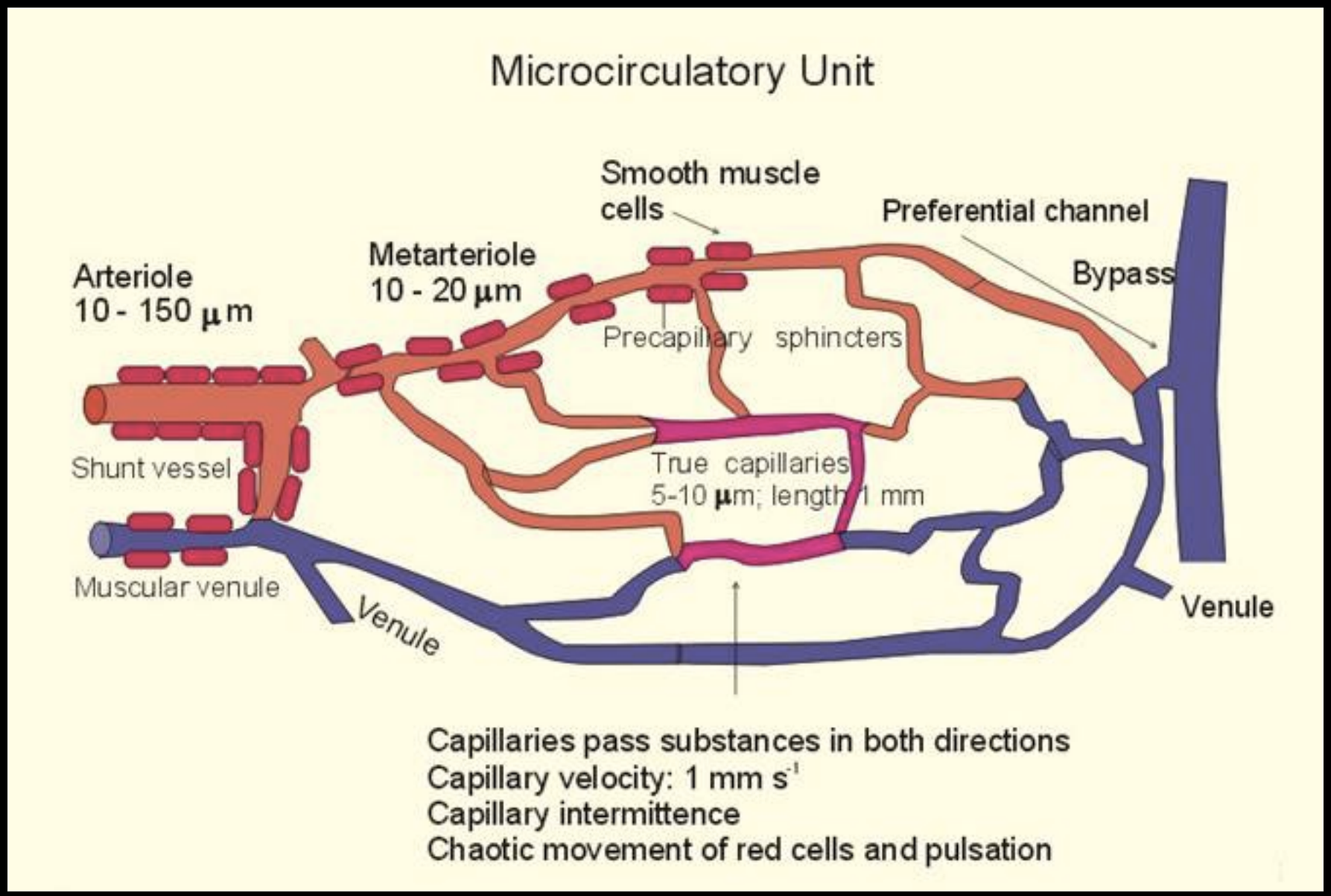
VASST



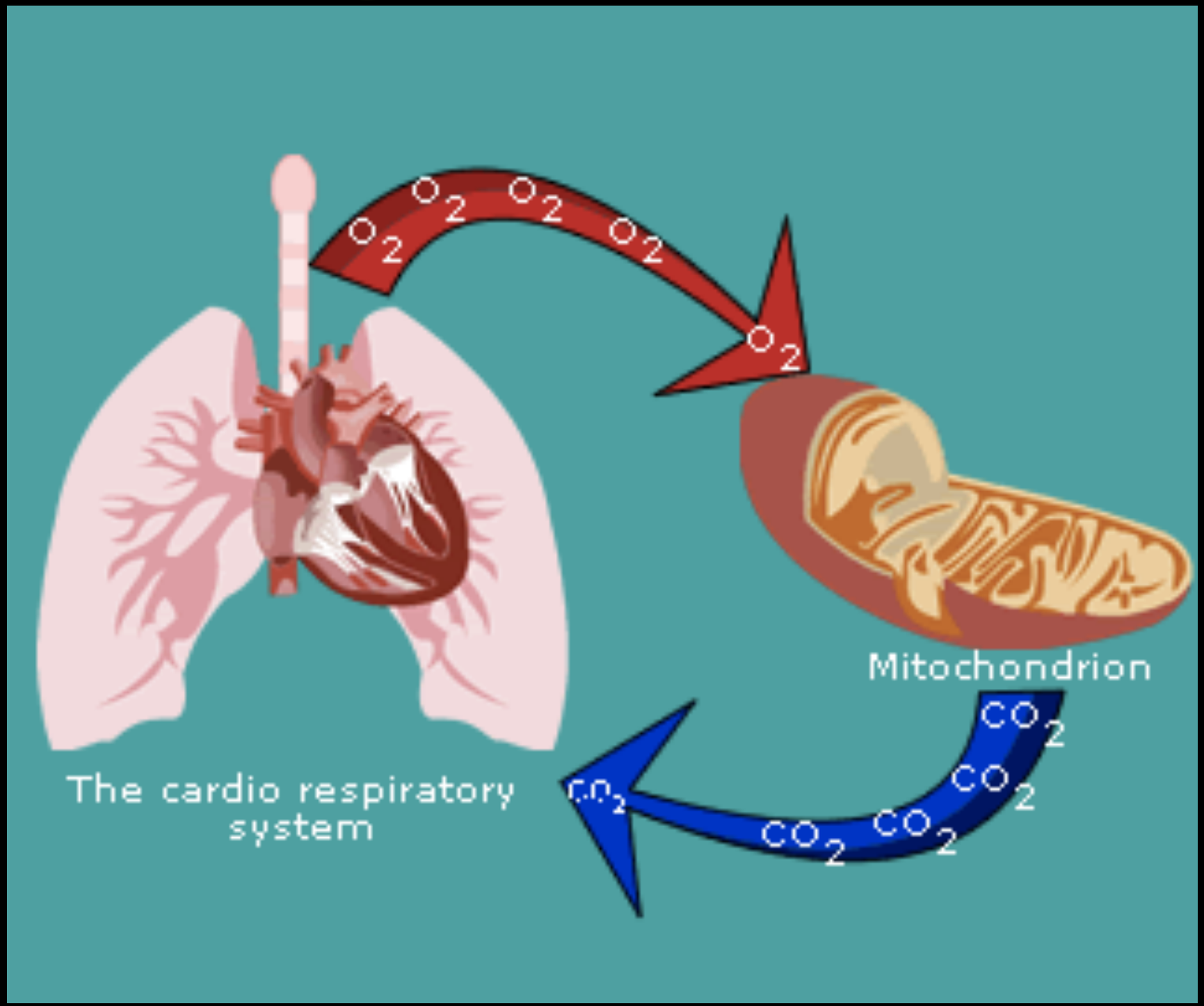
Russel. NEJM 2008

Microcirculation

microcirculation



Oxygen delivery

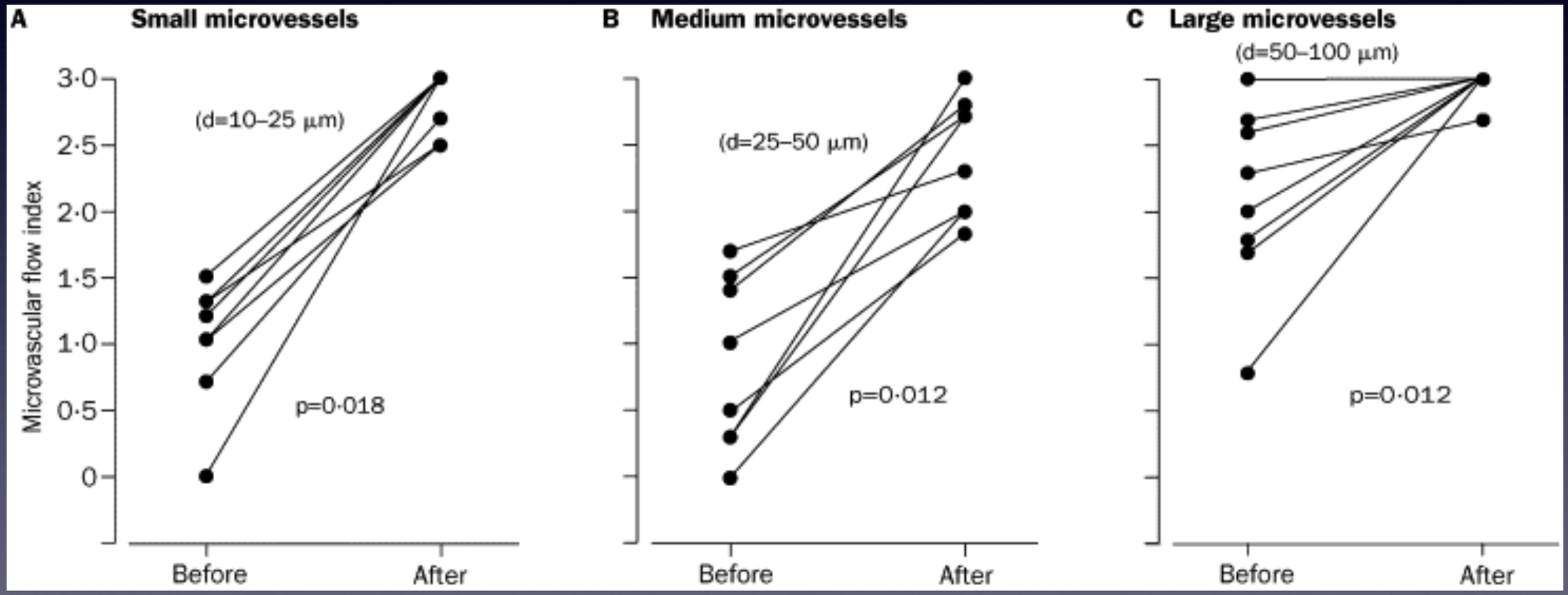


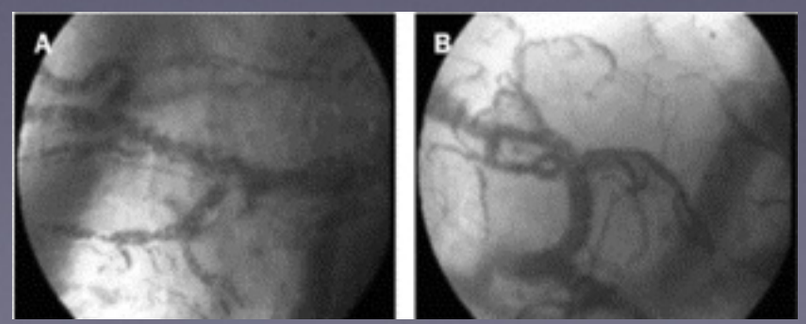
Oxygen delivery

- depend on
  - cardiac output
  - oxygen content
    - Hb level
    - SaO2

Vasodilator in septic shock

Nitroglycerine bolus 0.5 mg in well resuscitate patients





Spronk. Lancet 2002.

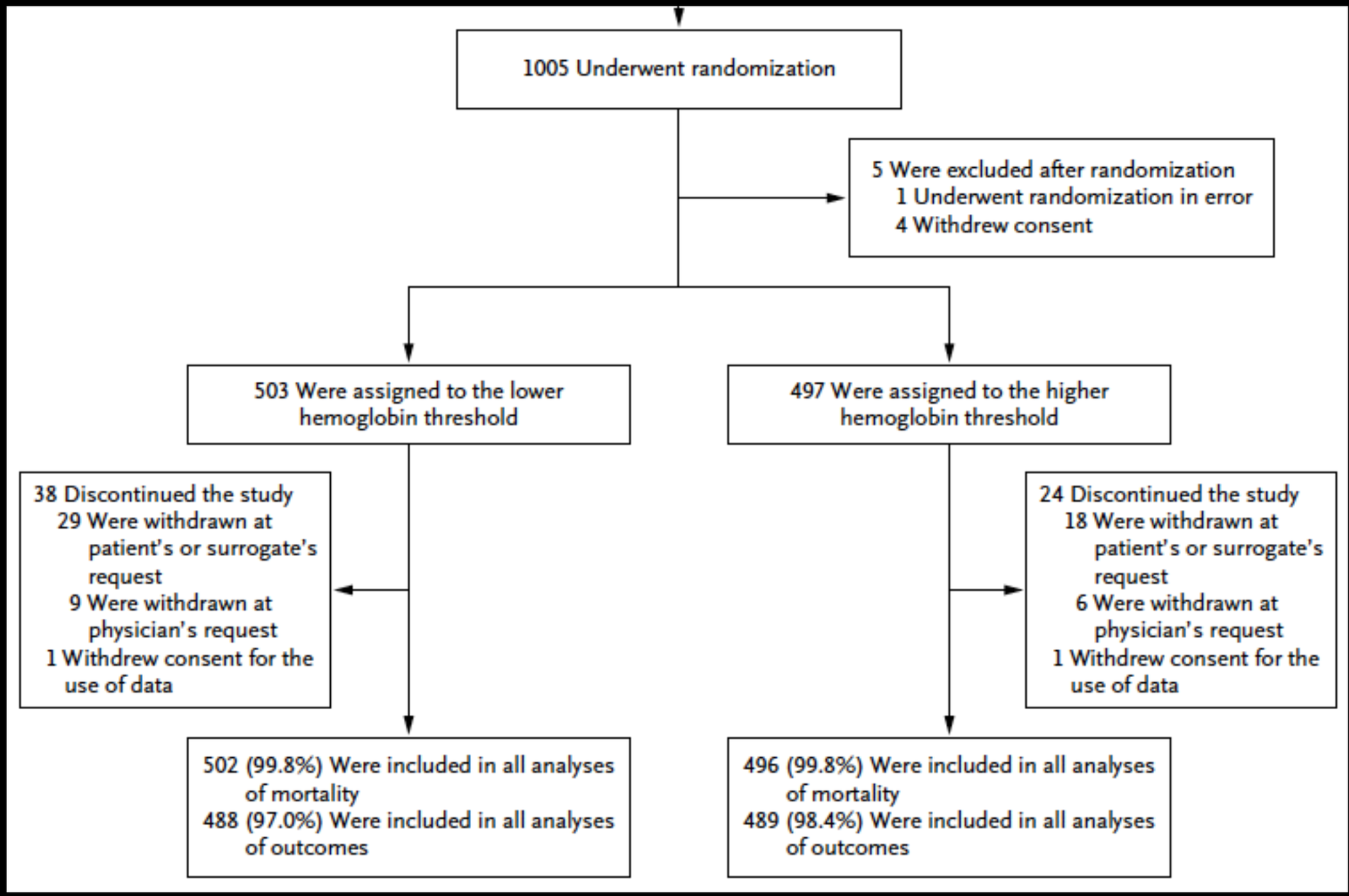
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 9, 2014 VOL. 371 NO. 15

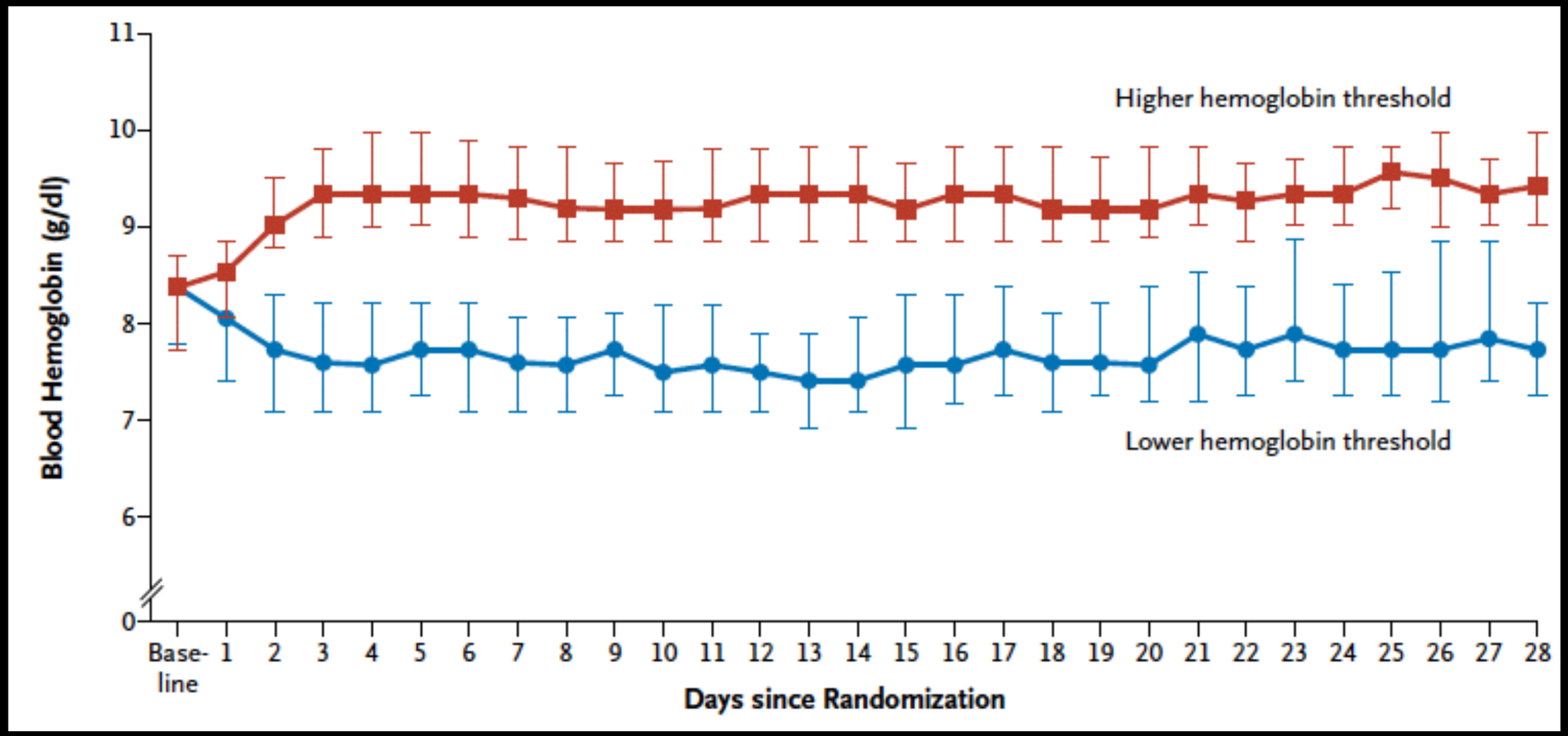
Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D., Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D., Anders Åneman, M.D., Ph.D., Marianne L. Vang, M.D., Robert Winding, M.D., Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D., Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D., Ville Pettilä, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D., Ulf G. Pedersen M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D., Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Møller, M.D., Ph.D., Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N., Suzanne Odeberg-Wernerman, M.D., Ph.D., Brit Sjøbø, R.N., Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D., Rikke Mærkedahl, M.D., Carsten Albeck, M.D., Dorte Illum, M.D., Mary Kruse, M.D., Per Winkel, M.D., D.M.Sci., and Anders Perner, M.D., Ph.D., for the TRISS Trial Group* and the Scandinavian Critical Care Trials Group

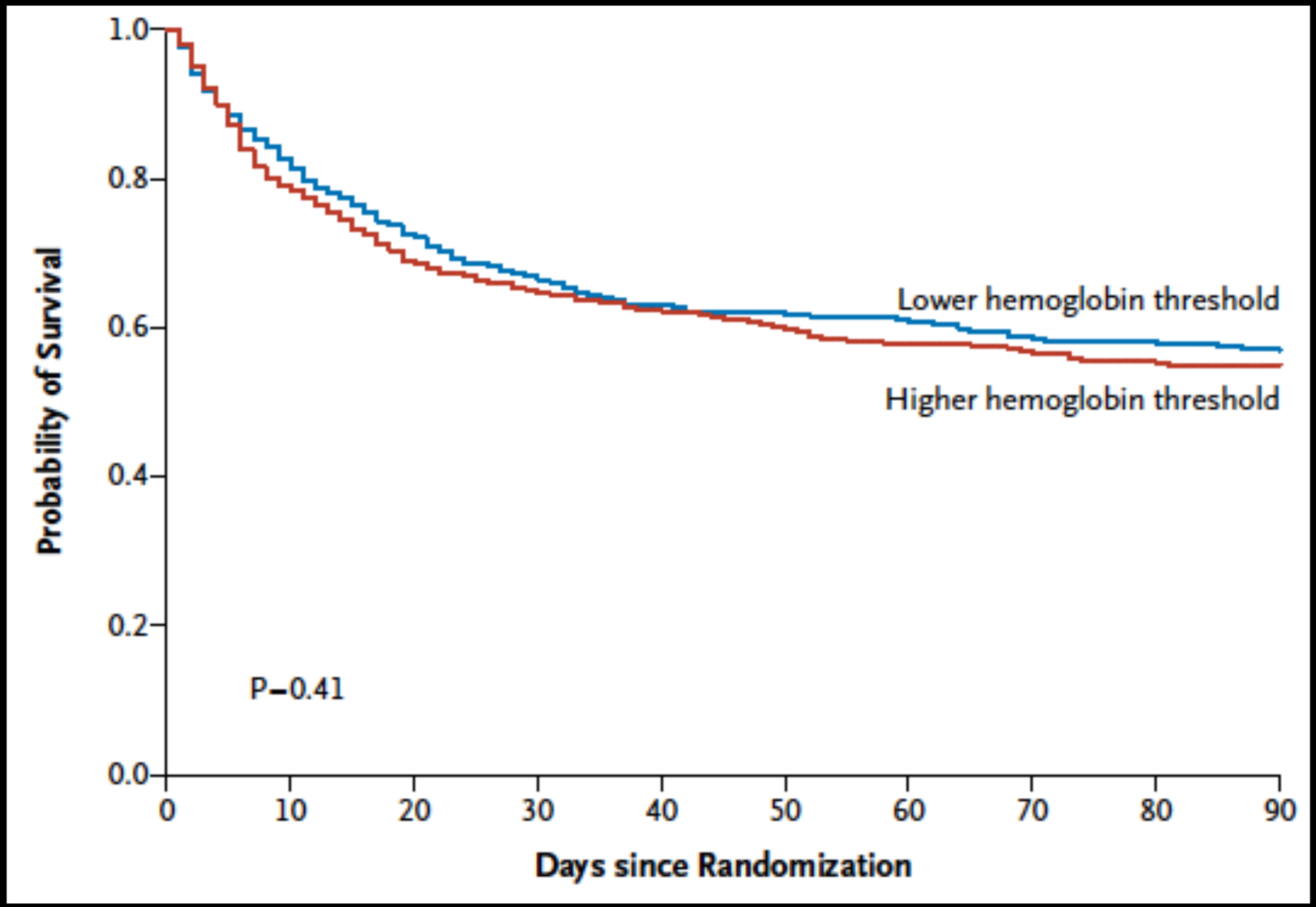
TRICC: randomization



TRICC: Hb

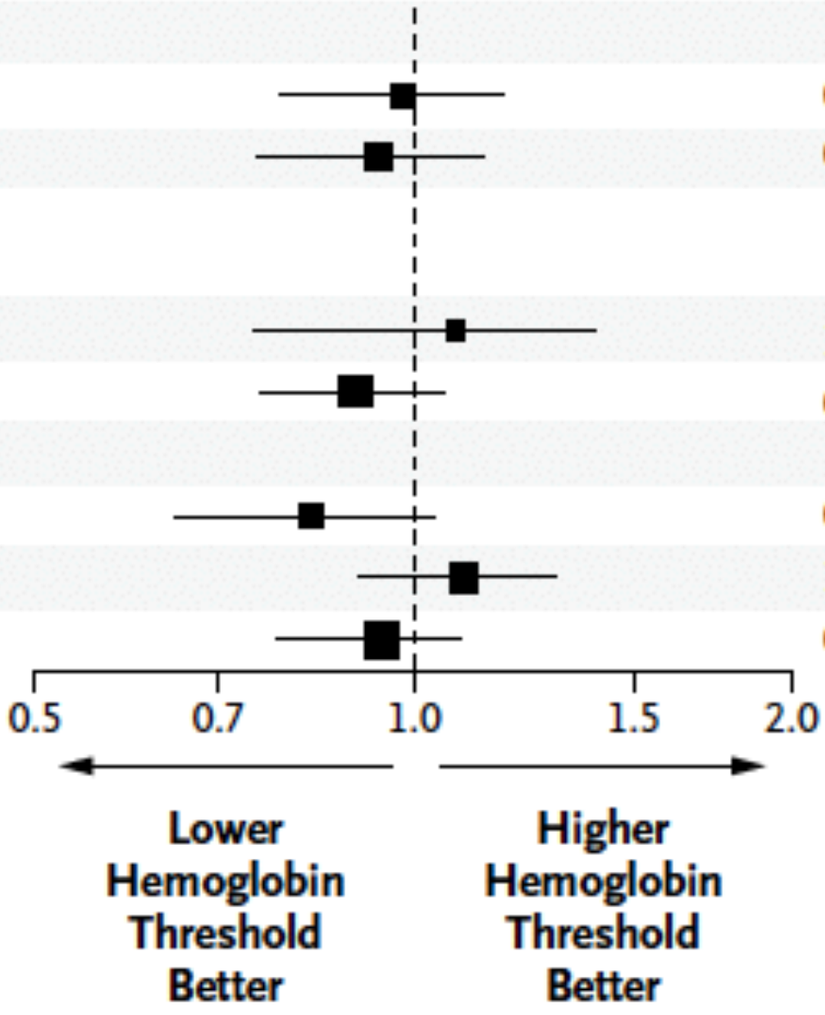

Higher hemoglobin threshold
Lower hemoglobin threshold
Blood Hemoglobin (g/dl)
11
10
9
8
7
6
0
Base-line
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
Days since Randomization

TRICC: MR


1.0
0.8
0.6
0.4
0.2
0.0
Probability of Survival
Lower hemoglobin threshold
Higher hemoglobin threshold
P=0.41
0
10
20
30
40
50
60
70
80
90
Days since Randomization

TRICC:subgroup

Subgroup	Lower Hemoglobin Threshold	Higher Hemoglobin Threshold	Relative Risk (95% CI)
	no. of events/no. of patients in subgroup		
Age			
>70 yr	93/173	98/185	0.98 (0.79–1.18)
≤70 yr	123/329	125/311	0.94 (0.75–1.14)
Chronic cardiovascular disease			
Yes	42/75	33/66	1.08 (0.75–1.40)
No	174/427	190/430	0.90 (0.75–1.06)
SAPS II at baseline			
>53	112/207	139/226	0.83 (0.64–1.04)
≤53	104/295	84/270	1.10 (0.91–1.30)
All patients	216/502	223/496	0.94 (0.78–1.09)



Anti-inflammation

Anti-inflammation

- almost anti-inflammatory agent revealed negative results e.g. anti-TNF, IL1-receptor antagonist, IL-6 antagonist, Ibuprofen, high dose steroid, bradykinin antagonist, antioxidant, fish oil, nitric oxide synthase inhibitor

Russel. NEJM 2006.

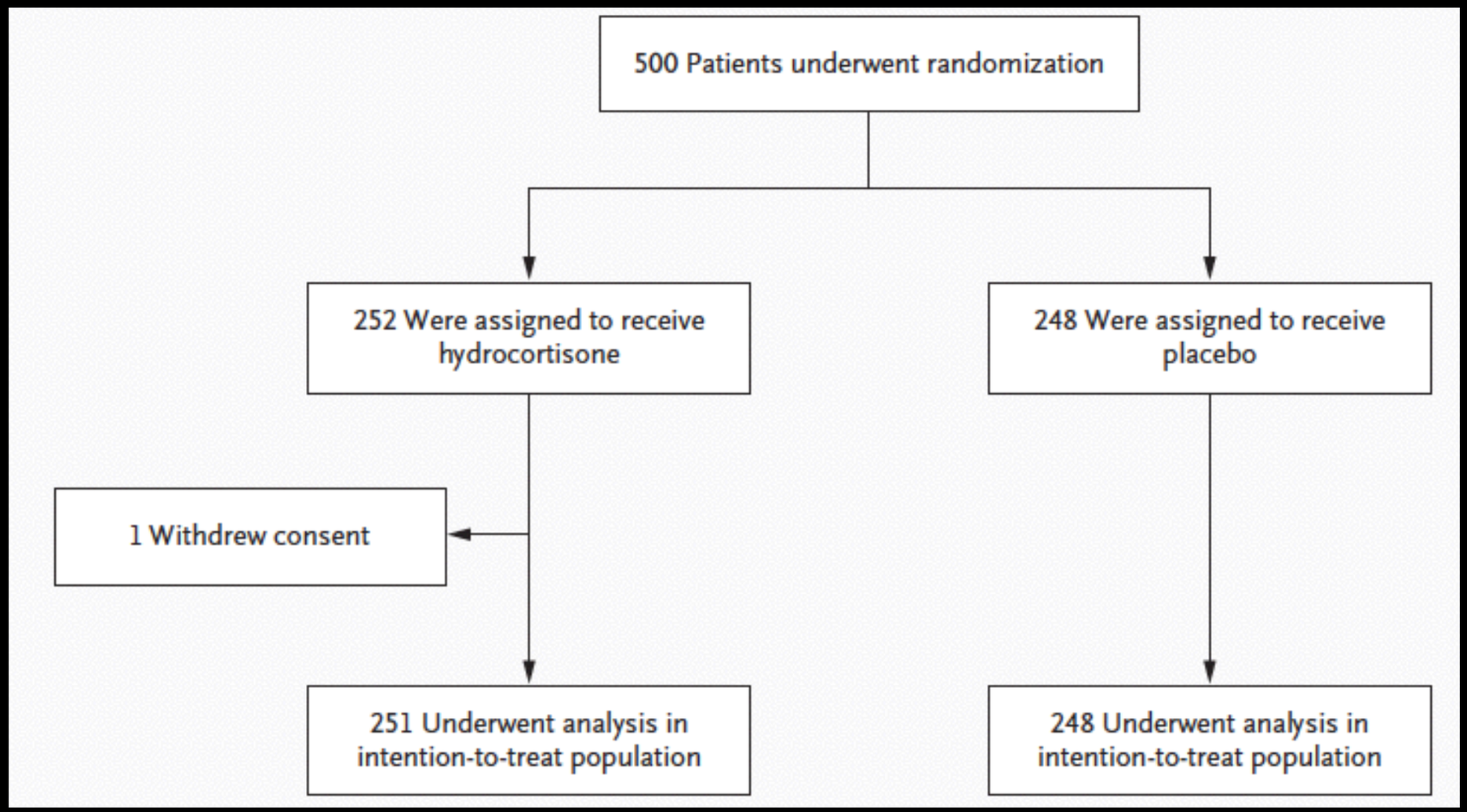
The NEW ENGLAND JOURNAL of MEDICINE

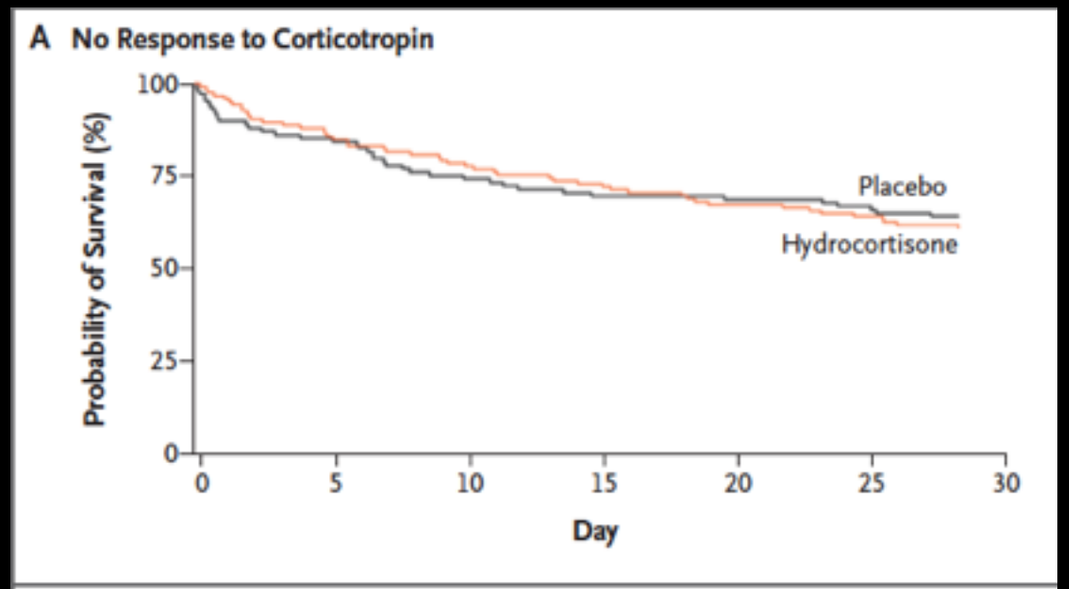
ESTABLISHED IN 1812 JANUARY 10, 2008 VOL. 358 NO. 2

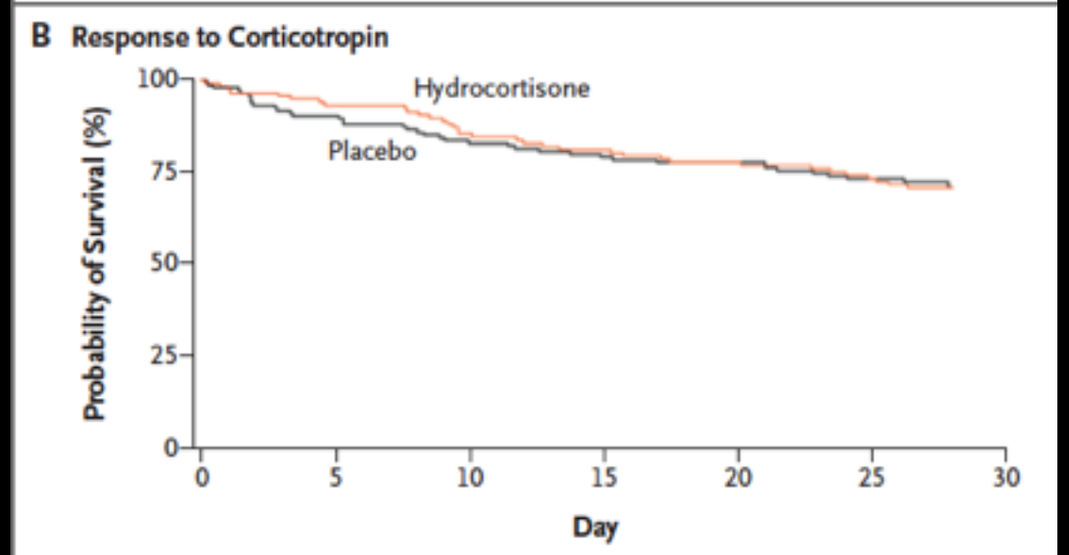
Hydrocortisone Therapy for Patients with Septic Shock

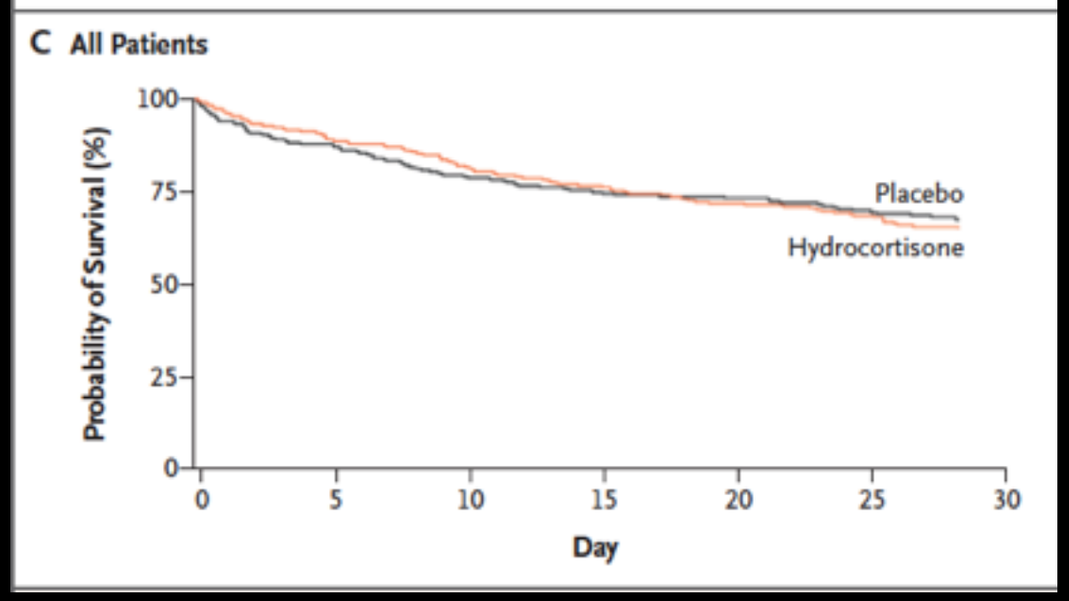
Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

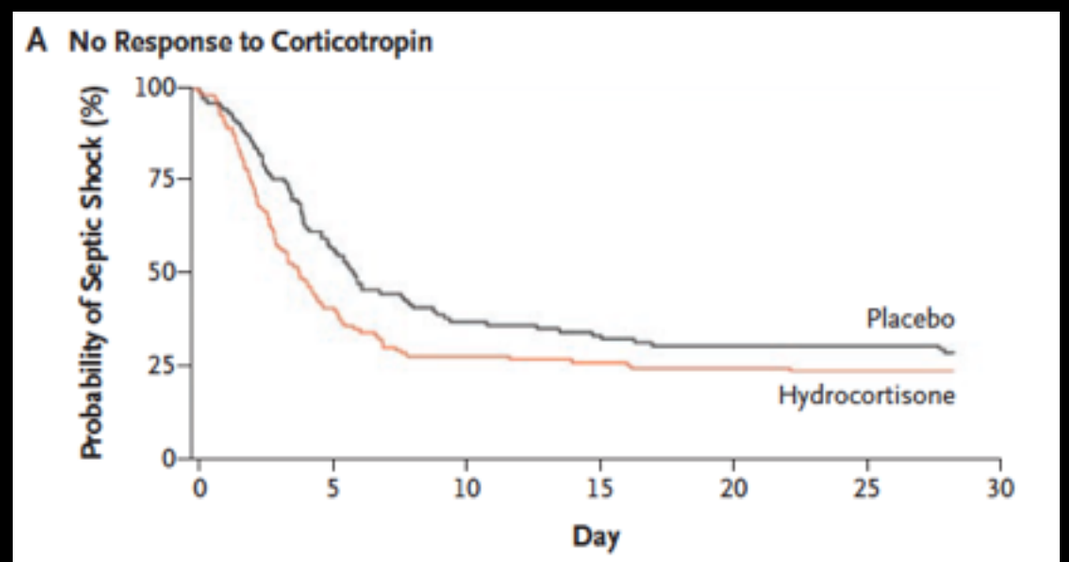
CORTICUS: random

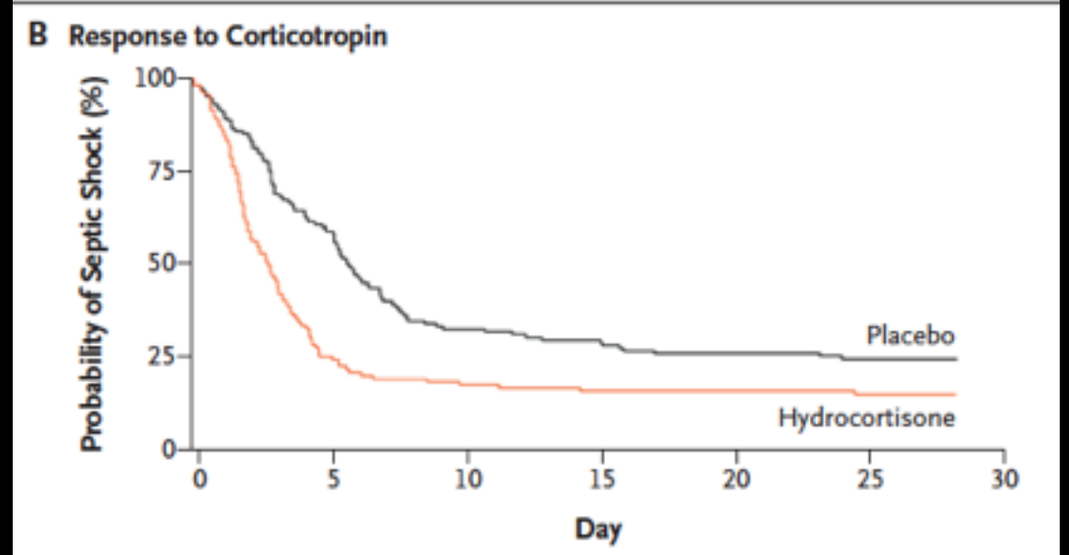


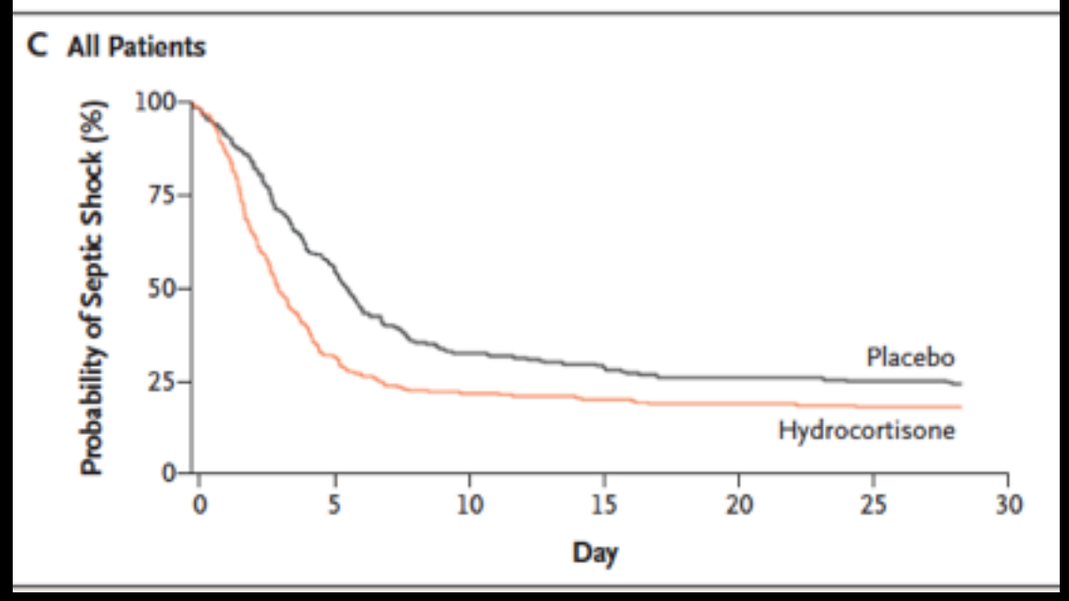

A No Response to Corticotropin
Probability of Survival (%)
100
75
50
25
0
Placebo
Hydrocortisone
0
5
10
15
20
25
30
Day


B Response to Corticotropin
Probability of Survival (%)
100
75
50
25
0
Hydrocortisone
Placebo
0
5
10
15
20
25
30
Day


C All Patients
Probability of Survival (%)
100
75
50
25
0
Placebo
Hydrocortisone
0
5
10
15
20
25
30
Day


A No Response to Corticotropin
Probability of Septic Shock (%)
100
75
50
25
0
Placebo
Hydrocortisone
0
5
10
15
20
25
30
Day


B Response to Corticotropin
Probability of Septic Shock (%)
100
75
50
25
0
Placebo
Hydrocortisone
0
5
10
15
20
25
30
Day

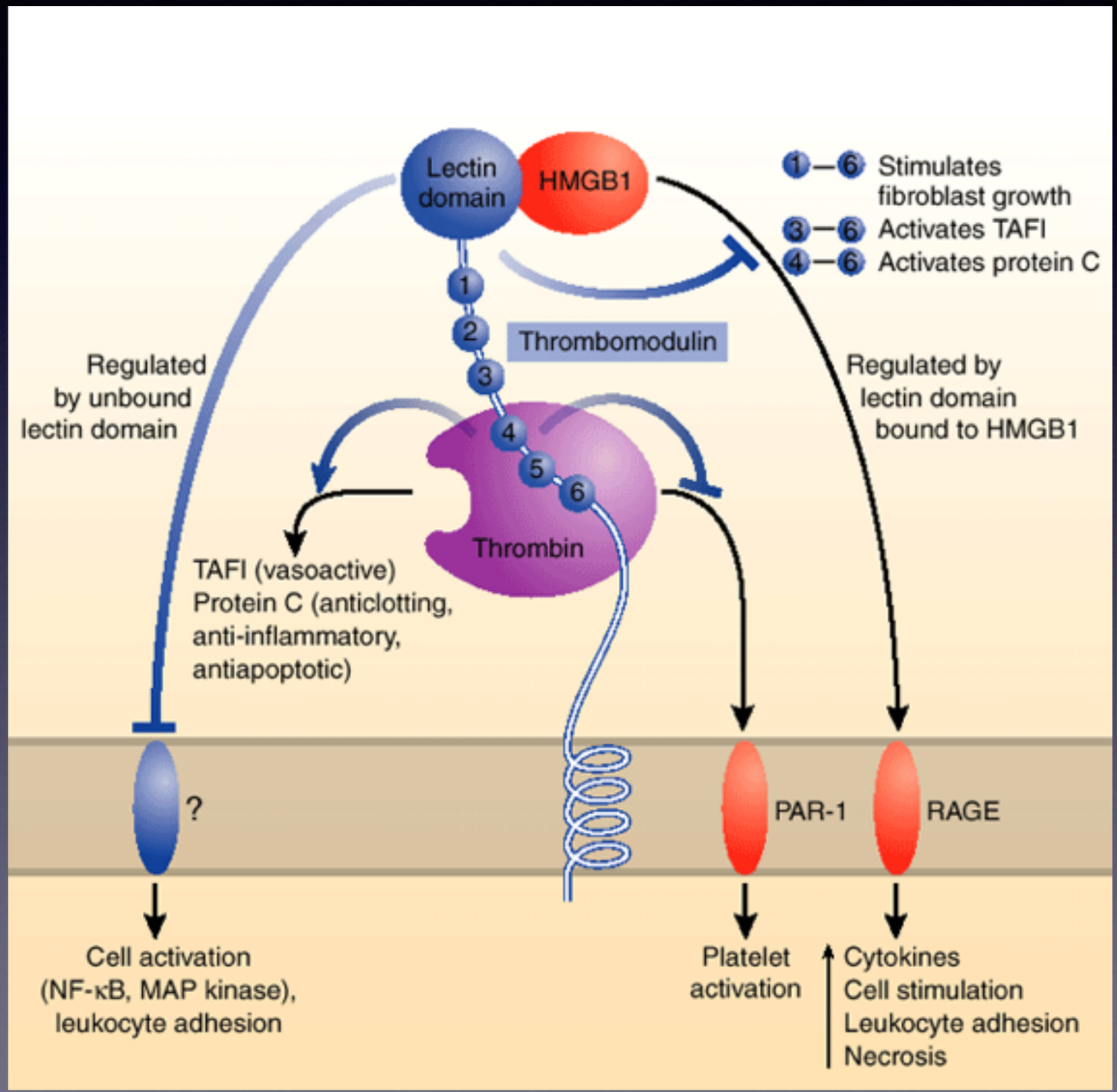

C All Patients
Probability of Septic Shock (%)
100
75
50
25
0
Placebo
Hydrocortisone
0
5
10
15
20
25
30
Day

anticoagulant

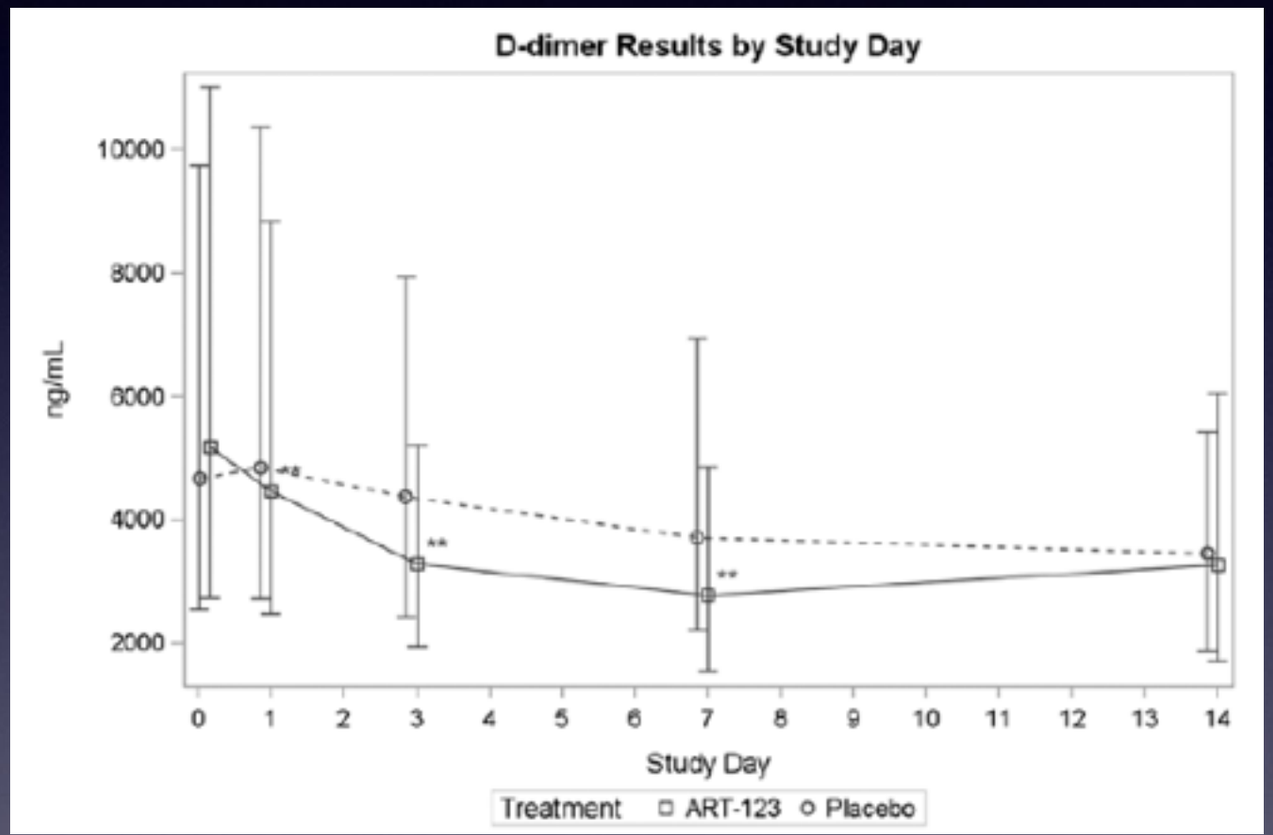
A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Safety and Efficacy of Recombinant Human Soluble Thrombomodulin, ART-123, in Patients With Sepsis and Suspected Disseminated Intravascular Coagulation*

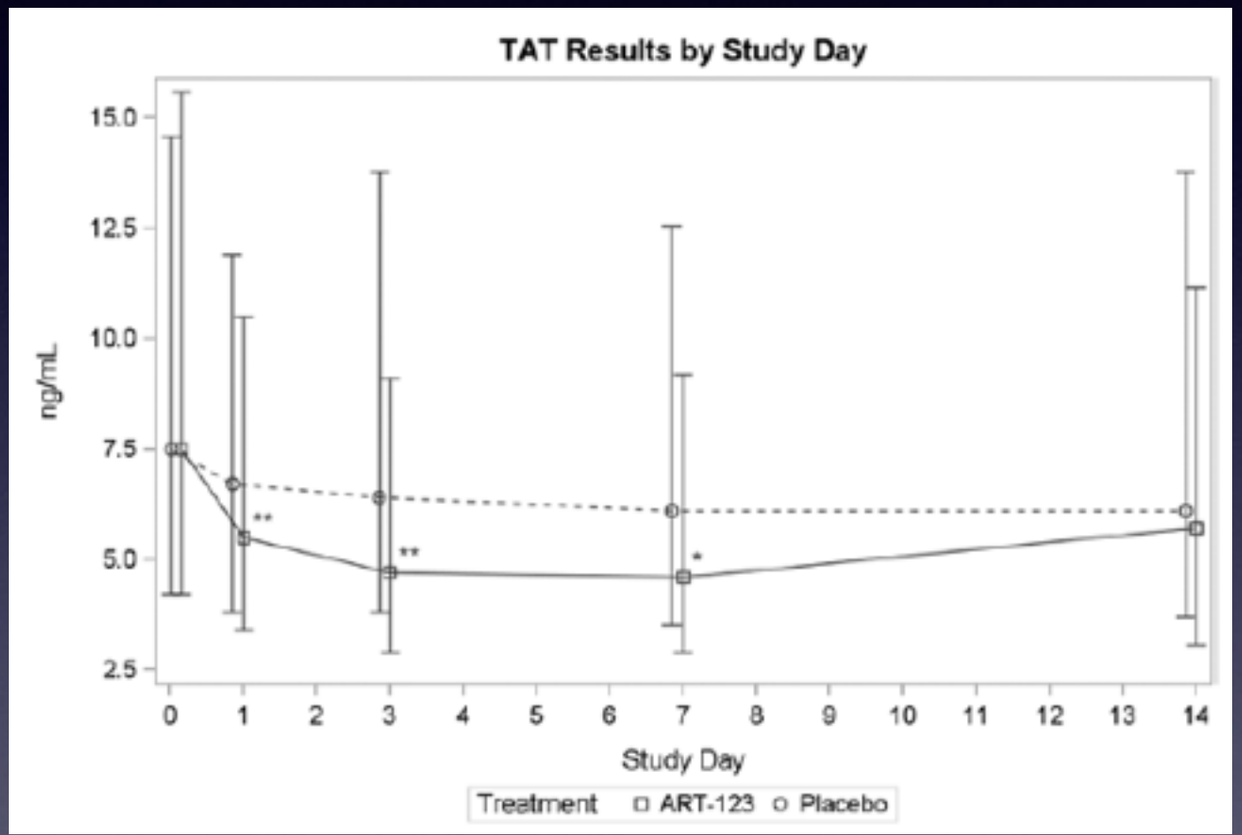
Jean-Louis Vincent, MD, PhD, FCCM[1]; Mayakonda K. Ramesh, MS[2]; David Ernest, MBBS[3]; Steven P. LaRosa, MD[4]; Jan Pachl, MD, PhD[5]; Naoki Aikawa, MD, DMSc, FACS[6]; Eric Hoste, MD, PhD[7]; Howard Levy, MB, BCh, PhD[8]; Joe Hirman, PhD[9]; Marcel Levi, MD, PhD[10]; Mradul Daga, MD, FCCP[11]; Demetrios 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]

ART-123 (Thrombomodulin)



ART123

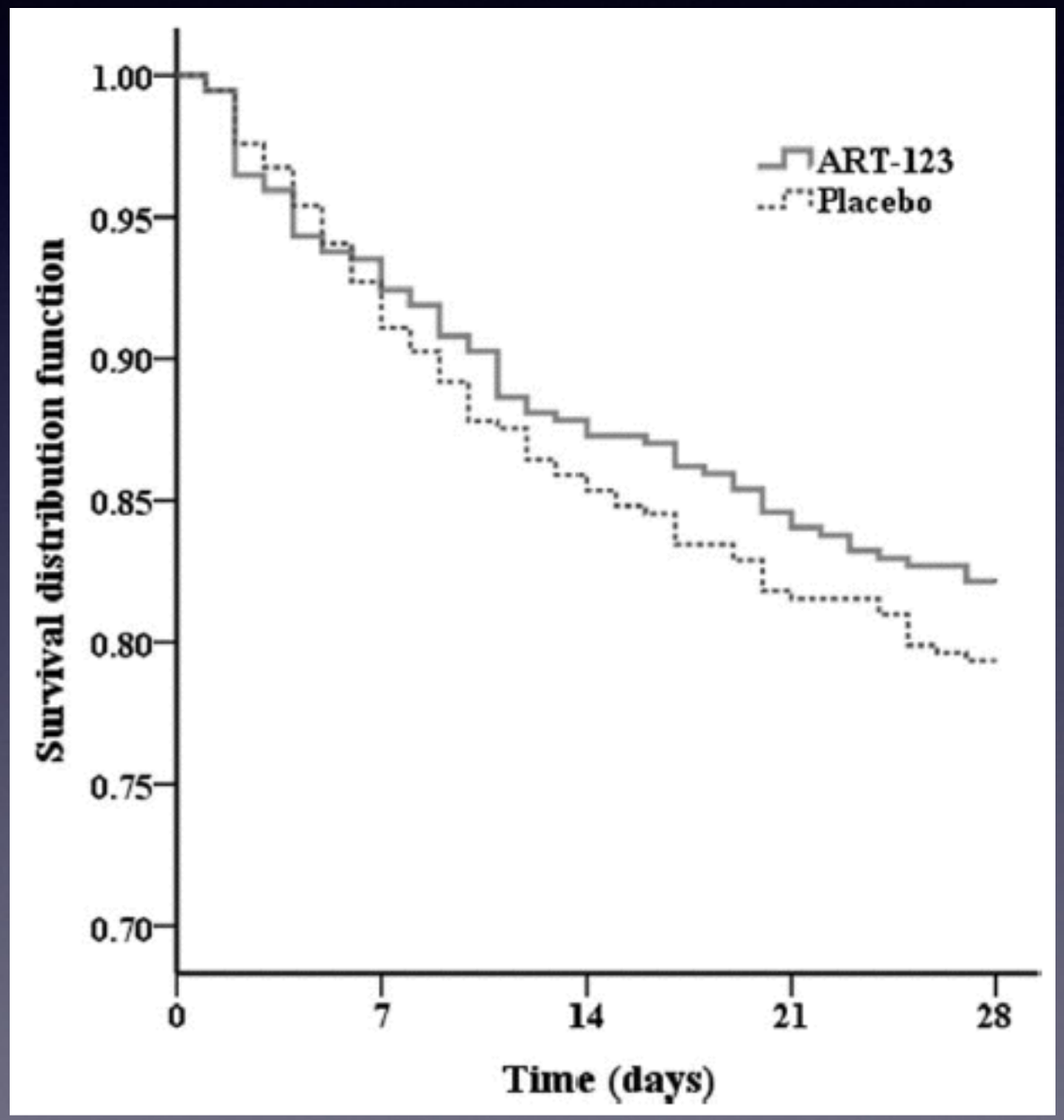




significant lower D-dimer, $p < 0.05$ and lower TAT, $p<0.001$

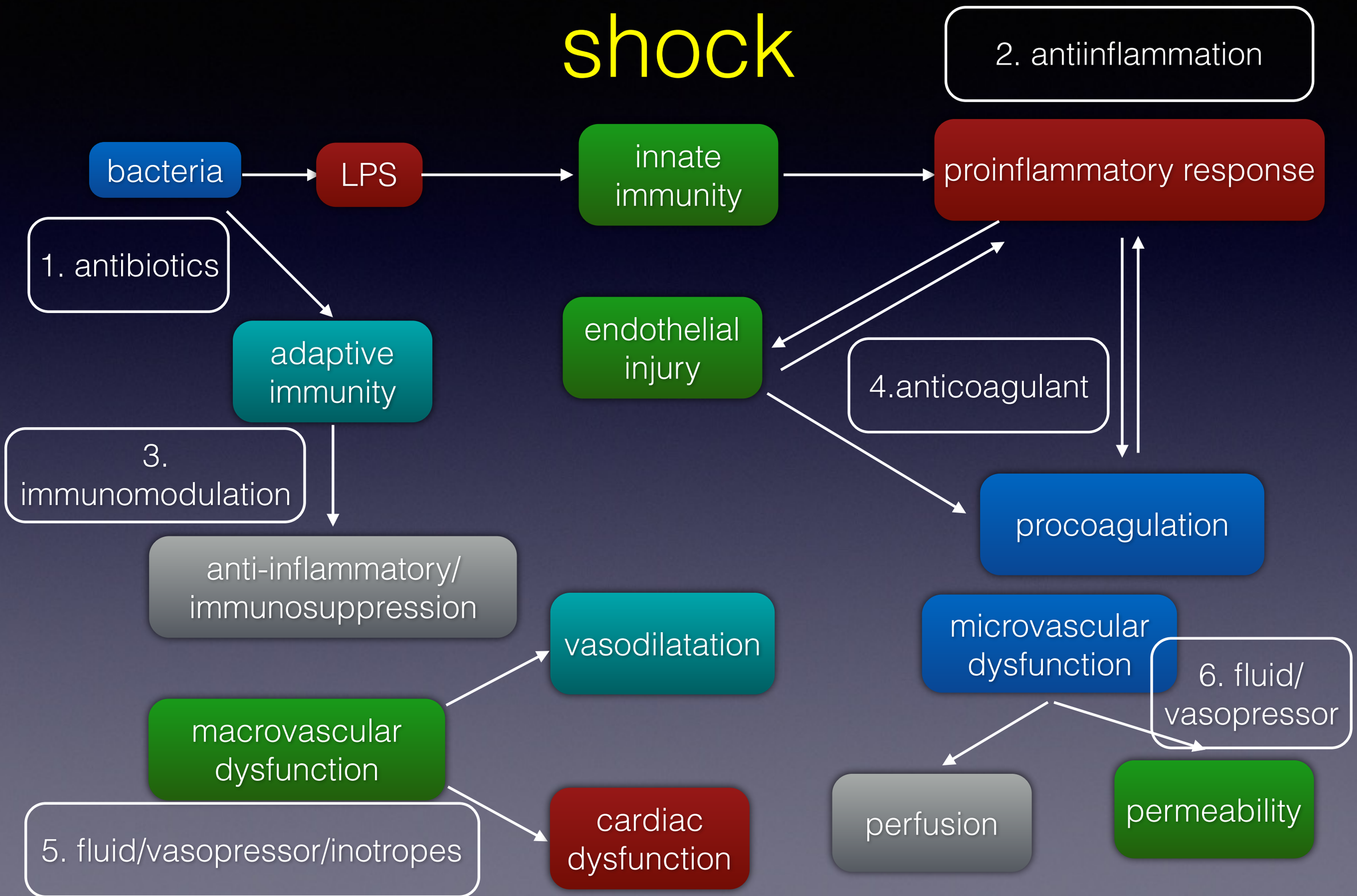
Vincent. CCM 2013

ART123



No mortality benefit;
p =0.17

Vincent. CCM 2013

Conclusion

Pathophysiology of septic shock