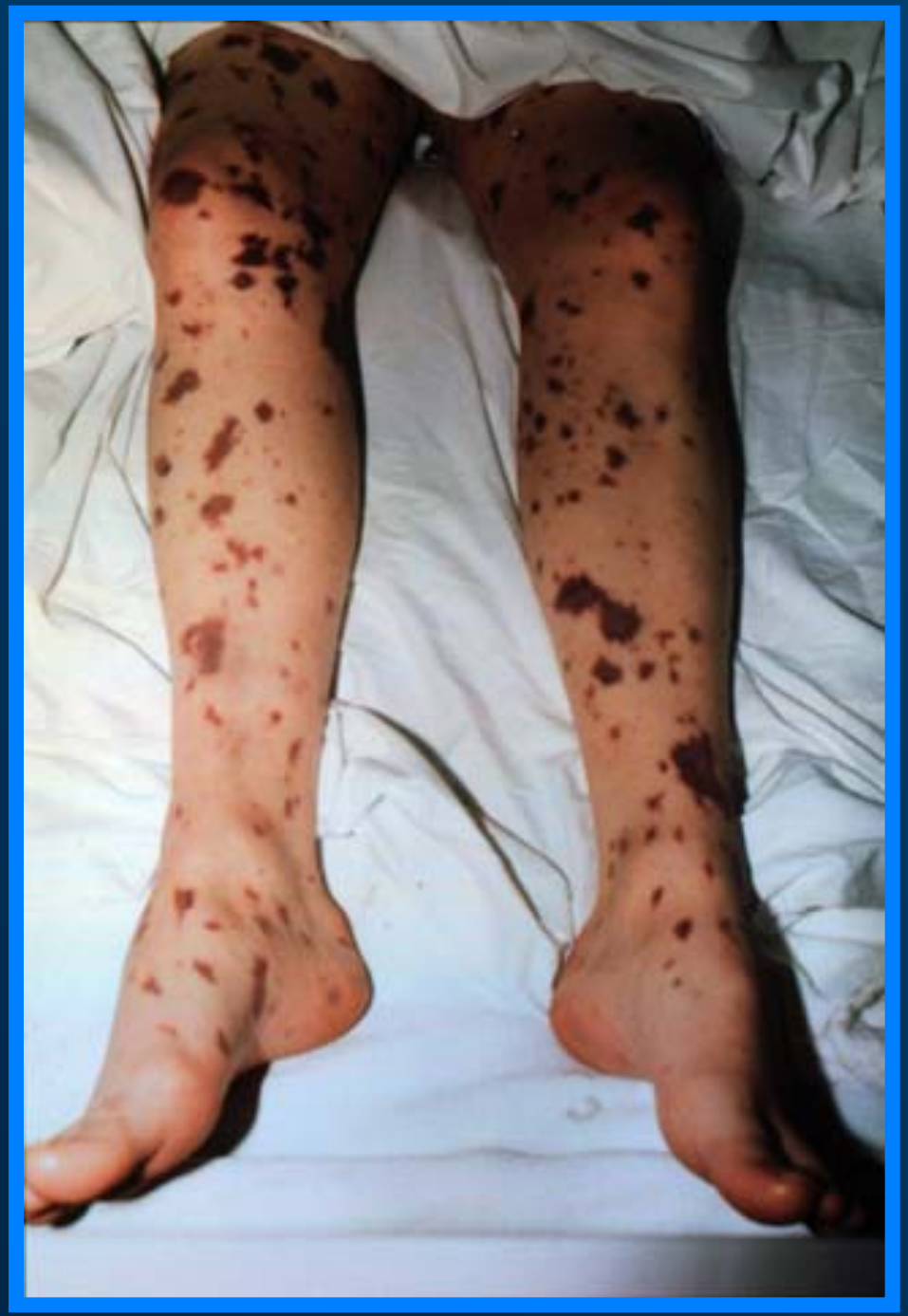
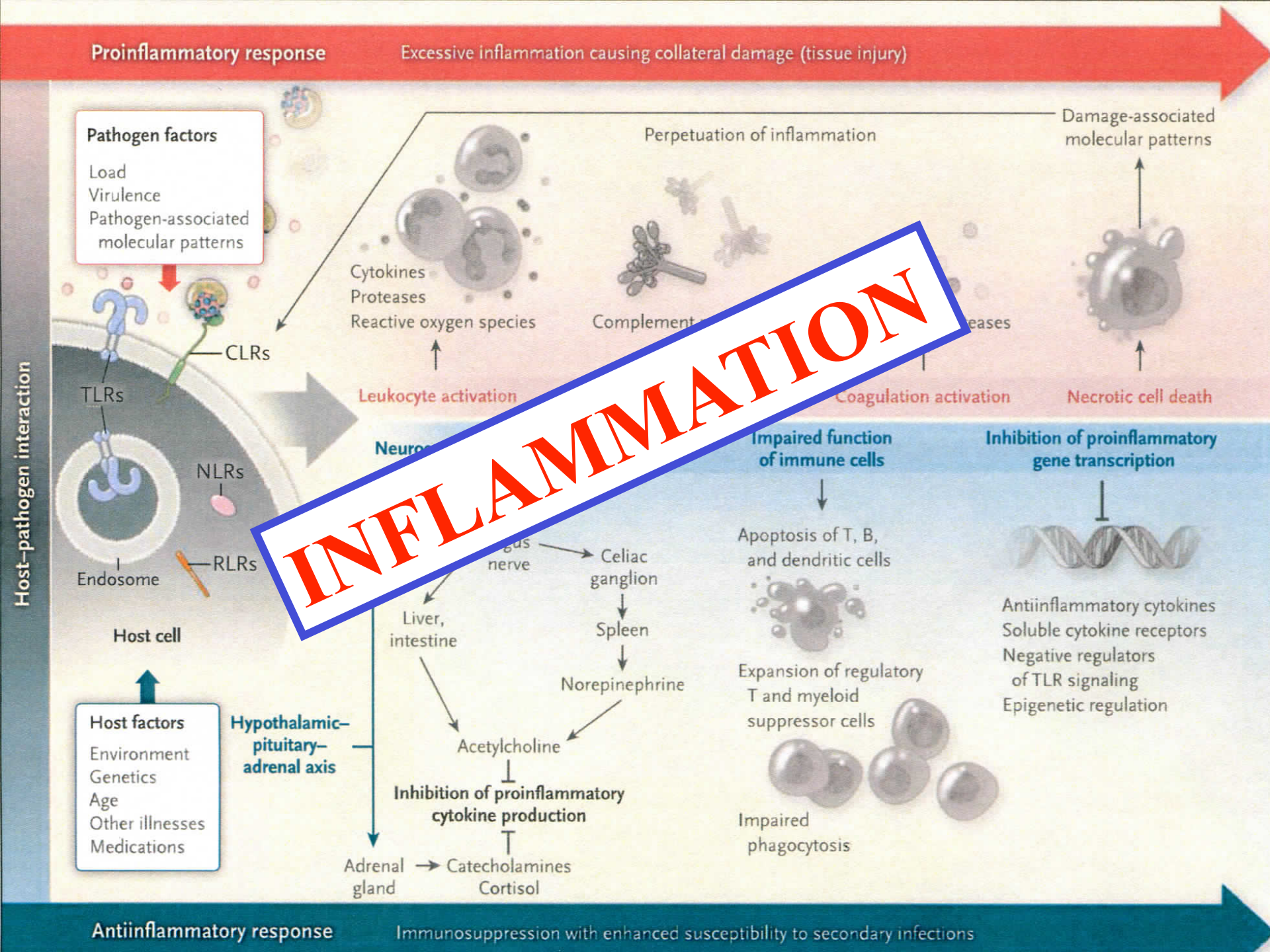
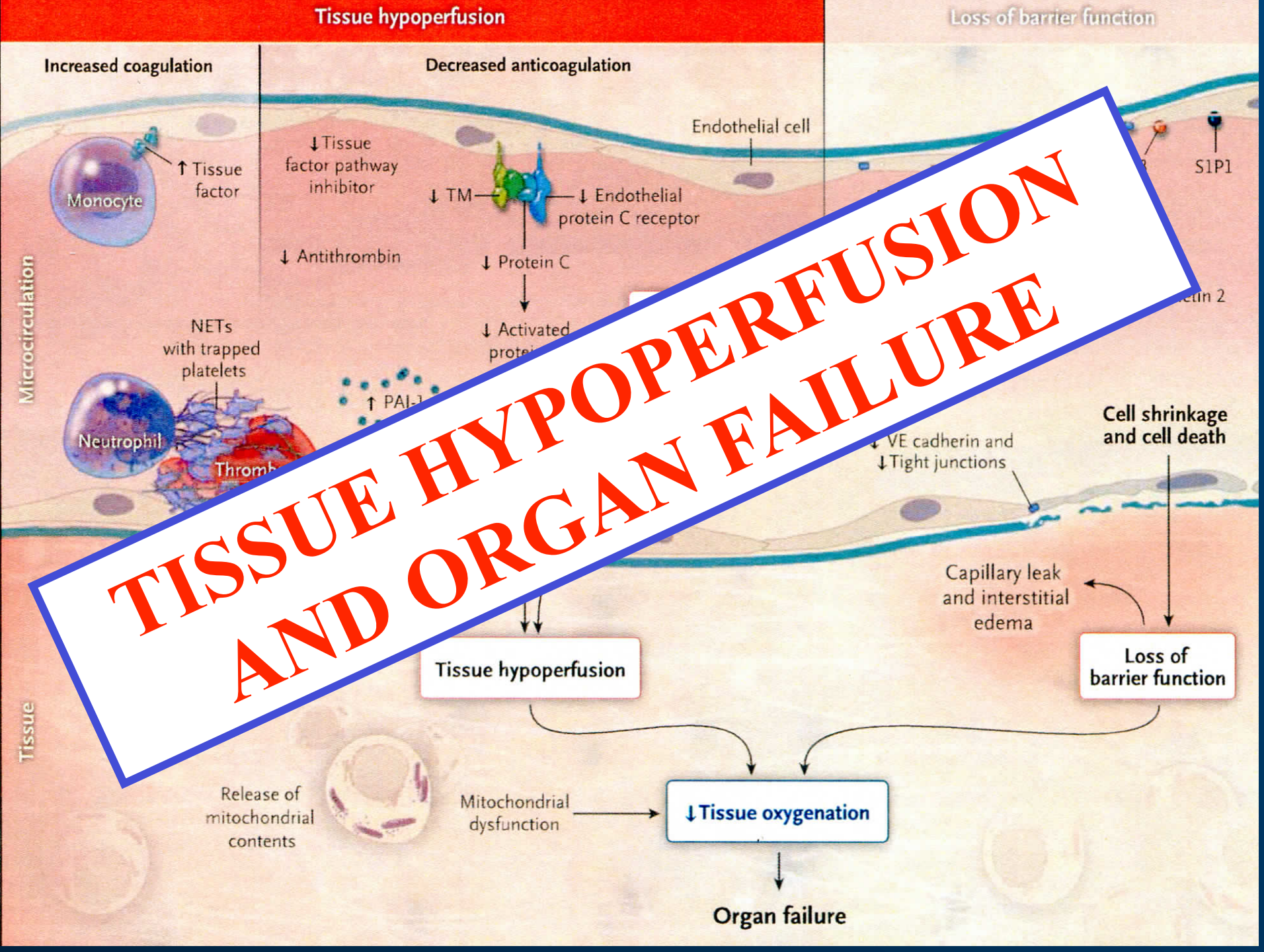



Proinflammatory response
Excessive inflammation causing collateral damage (tissue injury)
Pathogen factors
Load
Virulence
Pathogen-associated molecular patterns
CLRs
TLRs
NLRs
RLRs
Endosome
Host cell
Host–pathogen interaction
Perpetuation of inflammation
Damage-associated molecular patterns
Cytokines
Proteases
Reactive oxygen species
Complement
Leukocyte activation
Coagulation activation
Necrotic cell death
INFLAMMATION
Impaired function of immune cells
Inhibition of proinflammatory gene transcription
Apoptosis of T, B, and dendritic cells
Expansion of regulatory T and myeloid suppressor cells
Impaired phagocytosis
Antiinflammatory cytokines
Soluble cytokine receptors
Negative regulators of TLR signaling
Epigenetic regulation
Celiac ganglion
Spleen
Norepinephrine
Liver, intestine
Acetylcholine
Inhibition of proinflammatory cytokine production
Adrenal gland
Catecholamines
Cortisol
Host factors
Environment
Genetics
Age
Other illnesses
Medications
Hypothalamic–pituitary–adrenal axis
Antiinflammatory response
Immunosuppression with enhanced susceptibility to secondary infections



TISSUE HYPOPERFUSION AND ORGAN FAILURE

Review

Septic Shock
Advances in Diagnosis and Treatment

Christopher W. Seymour, MD, MSc; Matthew R. Rosengart, MD, MPH

IMPORTANCE Septic shock is a clinical emergency that occurs in more than 230 000 US patients each year.

OBSERVATIONS AND ADVANCES In the setting of suspected or documented infection, septic shock is typically defined in a clinical setting by low systolic (≤90 mm Hg) or mean arterial blood pressure (≤65 mm Hg) accompanied by signs of hypoperfusion (eg, oliguria, hyperlactemia, poor peripheral perfusion, or altered mental status). Focused ultrasonography is recommended for the prompt recognition of complicating physiology (eg, hypovolemia or cardiogenic shock), while invasive hemodynamic monitoring is recommended only for select patients. In septic shock, 3 randomized clinical trials demonstrate that protocolized care offers little advantage compared with management without a protocol. Hydroxyethyl starch is no longer recommended, and debate continues about the role of various crystalloid solutions and albumin.

CONCLUSIONS AND RELEVANCE The prompt diagnosis of septic shock begins with obtainment of medical history and performance of a physical examination for signs and symptoms of infection and may require focused ultrasonography to recognize more complex physiologic manifestations of shock. Clinicians should understand the importance of prompt administration of intravenous fluids and vasoactive medications aimed at restoring adequate circulation, and the limitations of protocol-based therapy, as guided by recent evidence.

JAMA. 2015;314(7):708-717. doi:10.1001/jama.2015.7885

Supplemental content at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 725

Author Affiliations: Author affiliations are listed at the end of this article.

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

1. APACHE III admission diagnosis consistent with sepsis:
   A. Sepsis (other than urinary tract infection)
   B. Sepsis of urinary tract infection
   C. Sepsis with shock (other than urinary tract infection)
   D. Sepsis with shock (urinary tract infection)
   E. Severe sepsis: A and B
   F. Septic shock: C and D
2. Infection and organ failure criteria:
   A. APACHE admission diagnosis consistent with infection
   B. At least 1 organ failure within the first 24 hours after ICU admission
   C. Severe sepsis: A and any organ failure in B
   D. Septic shock: A and cardiovascular organ failure in B

101000 Patients
2000-2012
Database prospective
Sepsis dans 1eres 24h
Incidence SS: 10 %

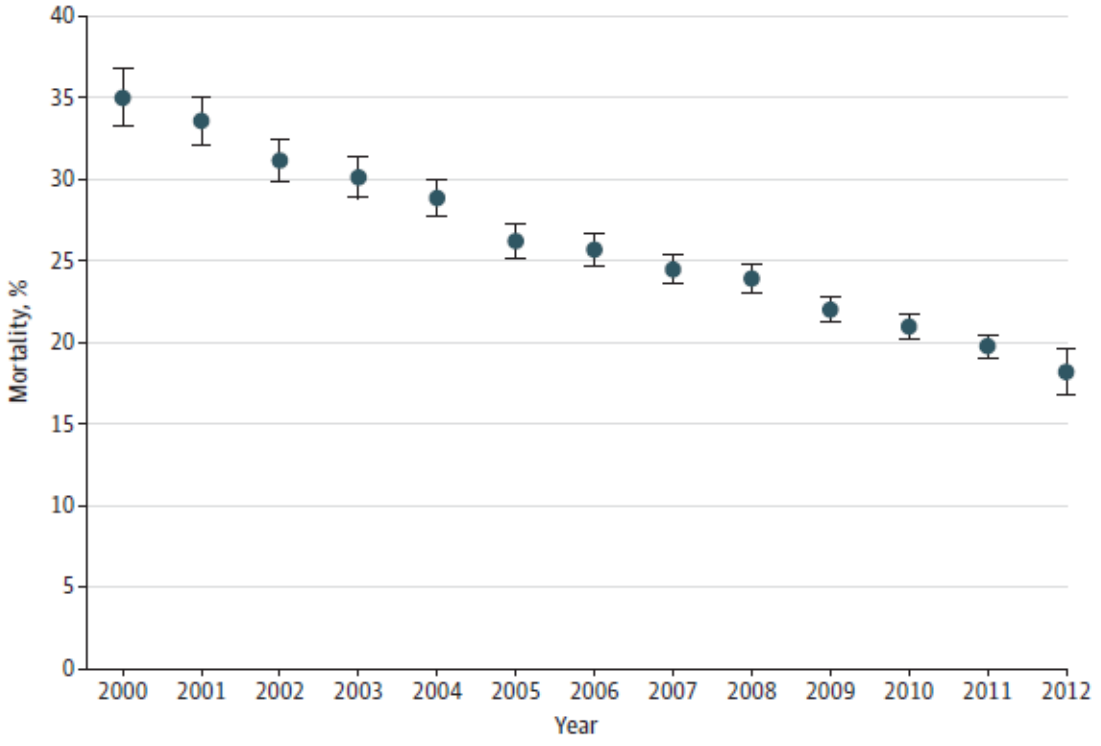
JAMA. 2014;311(13):1308-1316. doi:10.1001/jama.2014.2637
Published online March 18, 2014.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Kirsi-Maija Kaukonen, MD, PhD, EDIC; Michael Bailey, PhD; Satoshi Suzuki, MD; David Pilcher, FCICM; Rinaldo Bellomo, MD, PhD

Figure 1. Mean Annual Mortality in Patients With Severe Sepsis



Error bars indicate 95% CI.

JAMA. 2014;311(13):1308-1316. doi:10.1001/jama.2014.2637
Published online March 18, 2014.

Interaction Between Fluids and Vasoactive Agents on Mortality in Septic Shock: A Multicenter, Observational Study

Jason Waechter, MD[1]; Anand Kumar, MD[2]; Stephen E. Lapinsky, MB, MSc[3]; John Marshall, MD[3]; Peter Dodek, MD, MHSc[4]; Yaseen Arabi, MD[5]; Joseph E. Parrillo, MD[6]; R. Phillip Dellinger, MD[7]; Allan Garland, MD, MA[2]; for the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group

CCM 2014 **USA**

BLE 1. (*Continued*). Characteristics, Interventions, and Outcomes of 2,849 Patients With ptic Shock

ariable	Value	Range
Colloids 0–1 hr (L)	0.03 ± 0.07	0, 0.8
No. (%) who got any	582 (20.4)	
Colloids 1–6 hr (L)	0.09 ± 0.17	0, 2.8
No. (%) who got any	1,267 (44.5)	
Colloids 6–24 hr (L)	0.19 ± 0.29	0, 3.1
No. (%) who got any	1,664 (58.4)	
Total equivalent volume (L)[b]		
0–1 hr after shock onset	1.02 ± 0.91	0, 9.0
1–6 hr	2.10 ± 1.85	0, 13.3
6–24 hr	3.07 ± 2.54	0, 16.8
utcomes		
Hospital mortality (%)	47.4	
ICU length of stay (d)	10.9 ± 13.6	1.0, 215.0
Median (IQR)	6.5 (3.1, 13.0)	
Hospital length of stay (d)	27.2 ± 35.2	1.1, 370.0
Median (IQR)	15.0 (6.0, 32.0)	

Hospital Mortality 47.4 % M

Intensive Care Med (2015) 41:444–451
DOI 10.1007/s00134-014-3638-4

ORIGINAL

ICM March 2015

China

Zhongheng Zhang
Hongying Ni
Zhixian Qian

Effectiveness of treatment based on PiCCO parameters in critically ill patients with septic shock and/or acute respiratory distress syndrome: a randomized controlled trial

Mortality +/- 50 %

Table 2 Comparison of outcomes between PiCCO and control groups

Outcome variables	PiCCO group (n = 168)	Control group (n = 182)	P value
Primary outcome			
28-day mortality	83 (49.4)	90 (49.5)	0.993
Secondary outcomes			
Maximum SOFA	12 (10–14)	12 (9–14)	0.023
14-day mortality	68 (40.5)	75 (41.2)	0.889
Days on vasopressor	4 (2–6)	3 (2–6.5)	0.852
Days on MV	6 (3–12)	5.5 (3–12)	0.897
Days on CRRT	4 (3–7)	4.5 (3–7)	0.586
Length of stay in ICU	9 (5–13)	7.5 (4–15)	0.598
Days free of vasopressor in 14 days	10 (0–12)	9 (0–12)	0.562
Days free of MV in 14 days	1 (0–10)	4 (0–12)	0.127
Days free of CRRT in 14 days	11 (3–14)	14 (4–14)	0.0038
Days free of vasopressor in 28 days	14.5 (0–25)	19 (0–26)	0.676
Days free of MV in 28 days	3 (0–24)	6 (0–25)	0.168
Days free of CRRT in 28 days	15.5 (3–28)	21 (4–28)	0.048

Patients without use of MV, CRRT, or vasopressor were treated as missing variable, instead of zero
MV mechanical ventilation, *ICU* intensive care unit, *IQR* interquartile range, *CRRT* continuous renal replacement therapy

SHOCK, Vol. 44, No. 4, pp. 305–309, 2015

NOREPINEPHRINE: NOT TOO MUCH, TOO LONG

Claude Martin, Sophie Medam, François Antonini, Julie Alingrin, Malik Haddam, Emmanuelle Hammad, Bertrand Meyssignac, Coralie Vigne, Laurent Zieleskiewicz, and Marc Leone

Service d'Anesthésie et de Réanimation, Hôpital Nord, Assistance Publique Hôpitaux de Marseille, and Aix Marseille Université, Marseille, France

Received 12 Mar 2015; first review completed 30 Mar 2015; accepted in final form 8 Jun 2015

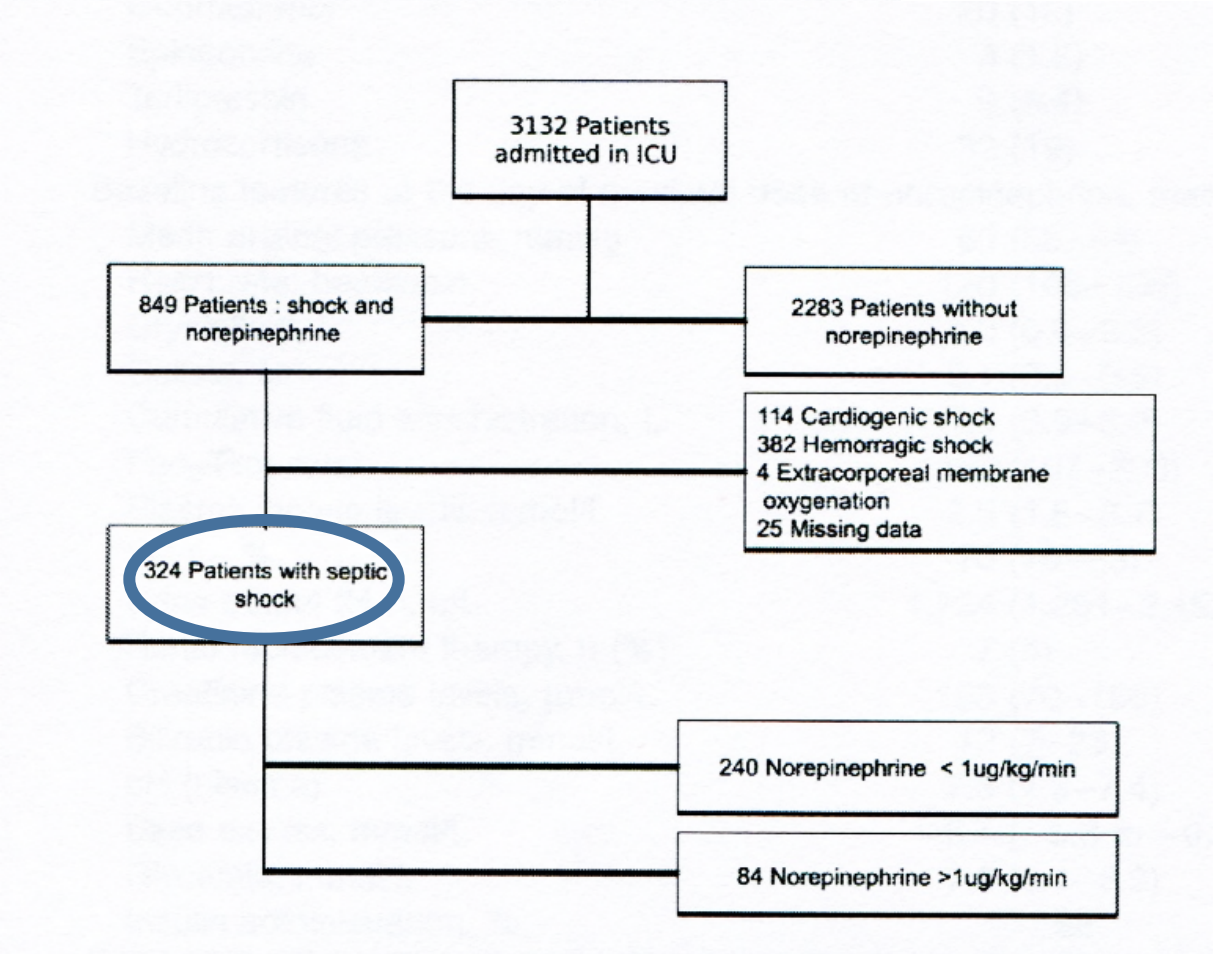


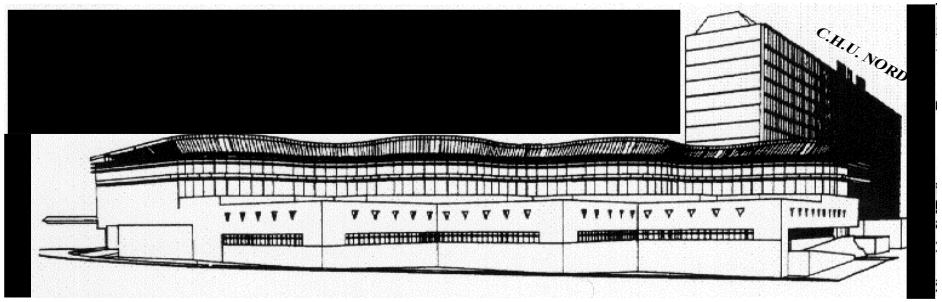
FIG. 1. **Flowchart of inclusion.**

High Dose norepinephrine

C Martin et al Shock in press 2015

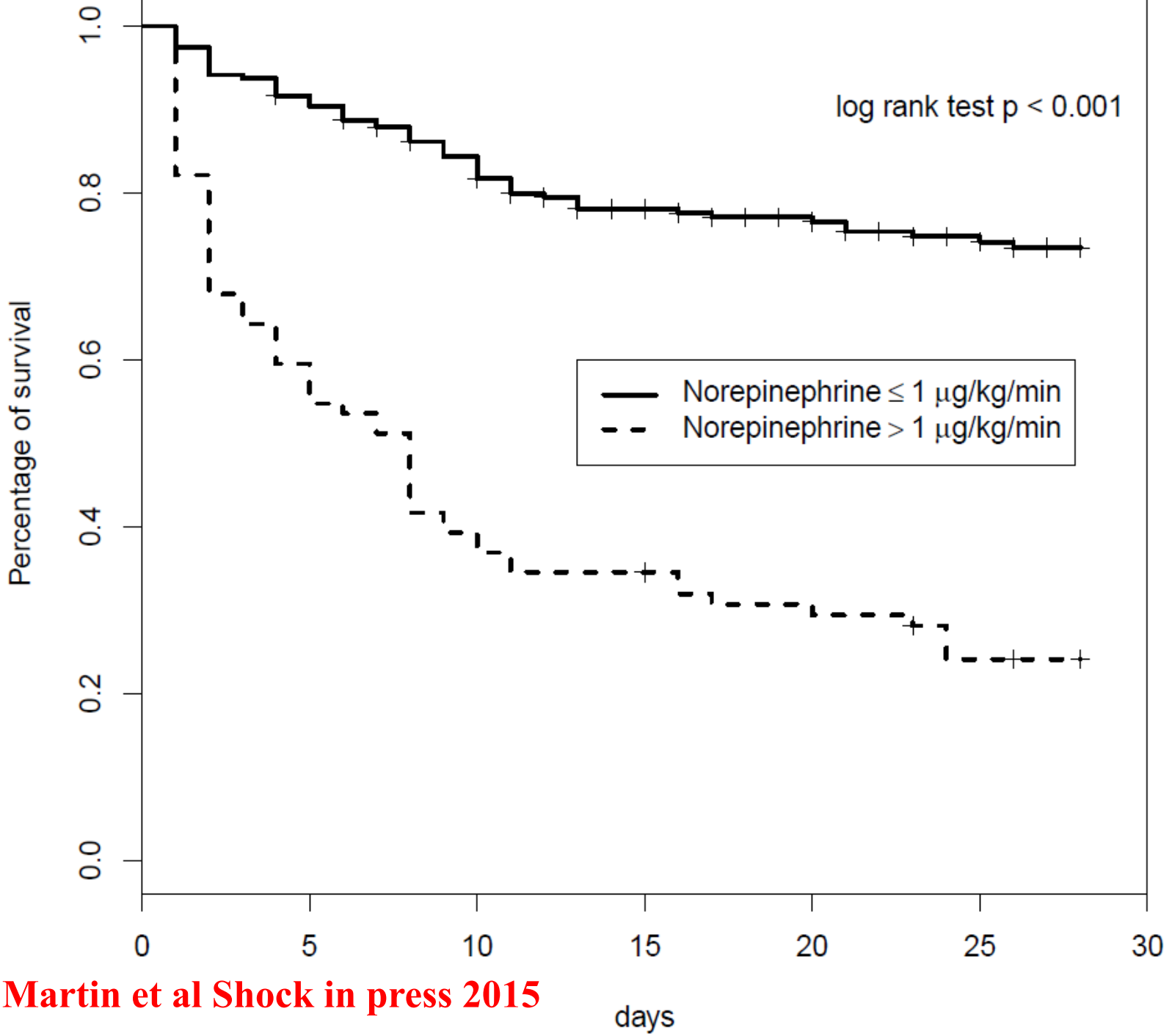
FRANCE

- 348 septic shock patients
- 2011-2013
- Nosocomial infections, mechanicaly ventilated
- ICU stay : 9 days
- **Mortality : 48%**



Faculté de Médecine Marseille

AP HM
Assistance Publique
Hôpitaux de Marseille



C Martin et al Shock in press 2015

Intensive Care Med (2014) 40:1623–1633
DOI 10.1007/s00134-014-3496-0

ORIGINAL

Mitchell M. Levy
Andrew Rhodes
Gary S. Phillips
Sean R. Townsend
Christa A. Schorr
Richard Beale
Tiffany Osborn
Stanley Lemeshow
Jean-Daniel Chiche
Antonio Artigas
R. Phillip Dellinger

Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study

Trans continental

Table 3 Hospital mortality across low- and high-compliance sites for resuscitation management bundles

Characteristic	Low resuscitation compliance			High resuscitation compliance			Total			p^a
	Total (*n*)	Died (*n*)	%	Total (*n*)	Died (*n*)	%	Total (*n*)	Died (*n*)	%	
Overall	11,609	4,475	38.6	17,861	5,185	29.0	29,470	9,660	32.8	<0.001
Location of severe sepsis identification										<0.001
ED	5,984	1,850	30.9	10,465	2,421	23.1	16,449	4,271	26.0	
Ward	3,970	1,800	45.3	5,532	2,032	36.7	9,502	3,832	40.3	
ICU	1,655	825	49.8	1,864	732	39.3	3,519	1,557	44.2	
Site duration										<0.001
<2 years	4,960	1,896	38.2	3,352	992	29.6	8,312	2,888	34.7	
2 to <3 years	1,611	600	37.2	6,557	1,895	28.9	8,168	2,495	30.5	
≥3 years	5,038	1,979	39.3	7,952	2,298	28.9	12,990	4,277	32.9	

Therapeutic Targets and Tools

Vessels :
norepinephrine
epinephrine
dopamine

Volemia :
Fluid challenge

Heart :
dobutamine
norepinephrine

Rescue therapy :
Vasopressin, terlipressin

Microcirculation :
Nitroglycerin ???

Septic Shock

- **Hypovolémie absolue**
- **Hypovolémie relative**
- **Choc distributif**
- **Dysfonction cardiaque**
- **Anomalie de l'extraction de l'oxygène**

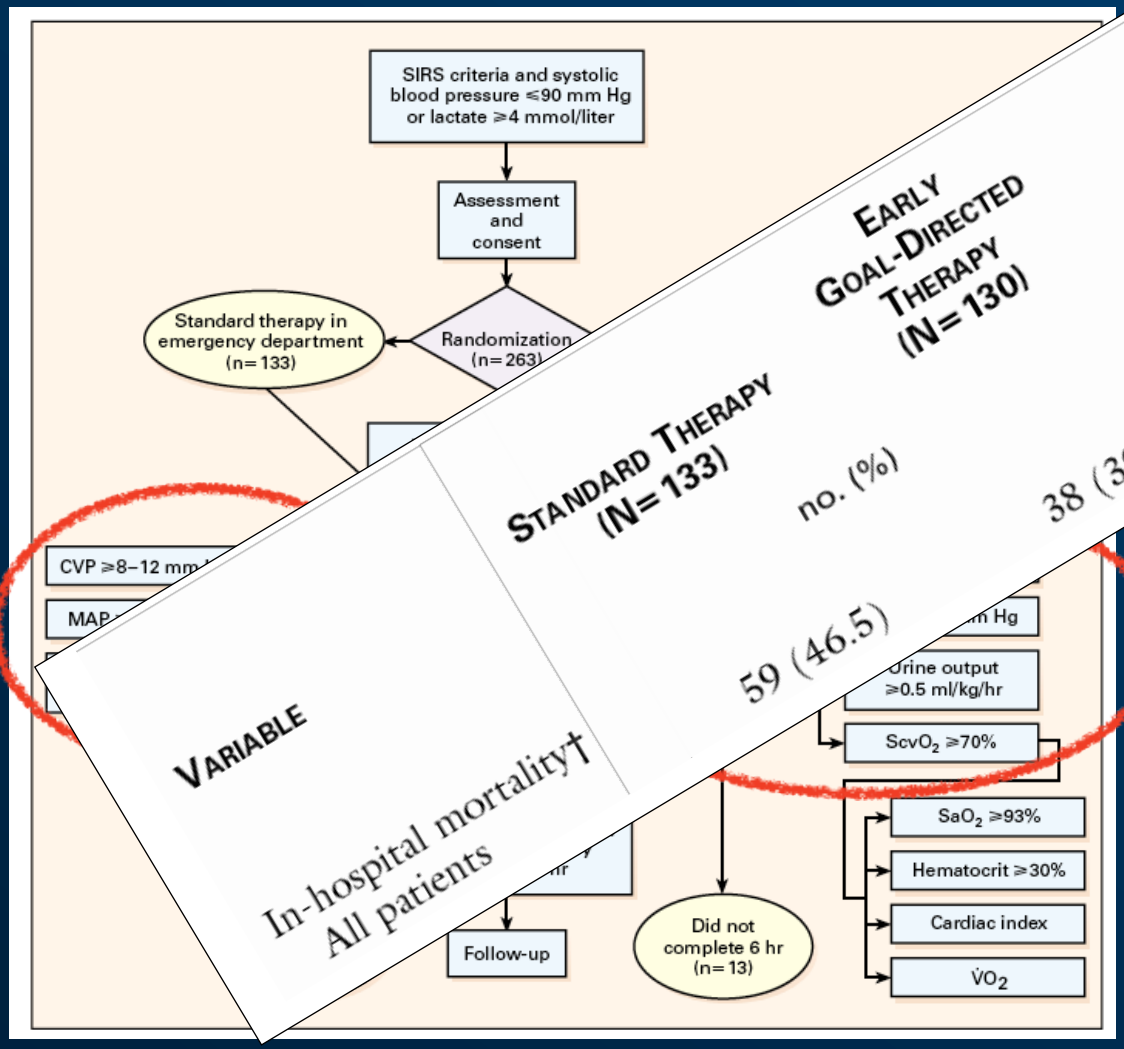
Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SE
AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., J
ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND
FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE



VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†				
All patients	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009

N Engl J Med 2001;345:1368-77.

« Early Goal-directed Therapy »

263 patients :
. Severe sepsis
. Septic shock

ECG, SpO_2, UF
Art cath , CVC

Standard treatment
n = 133

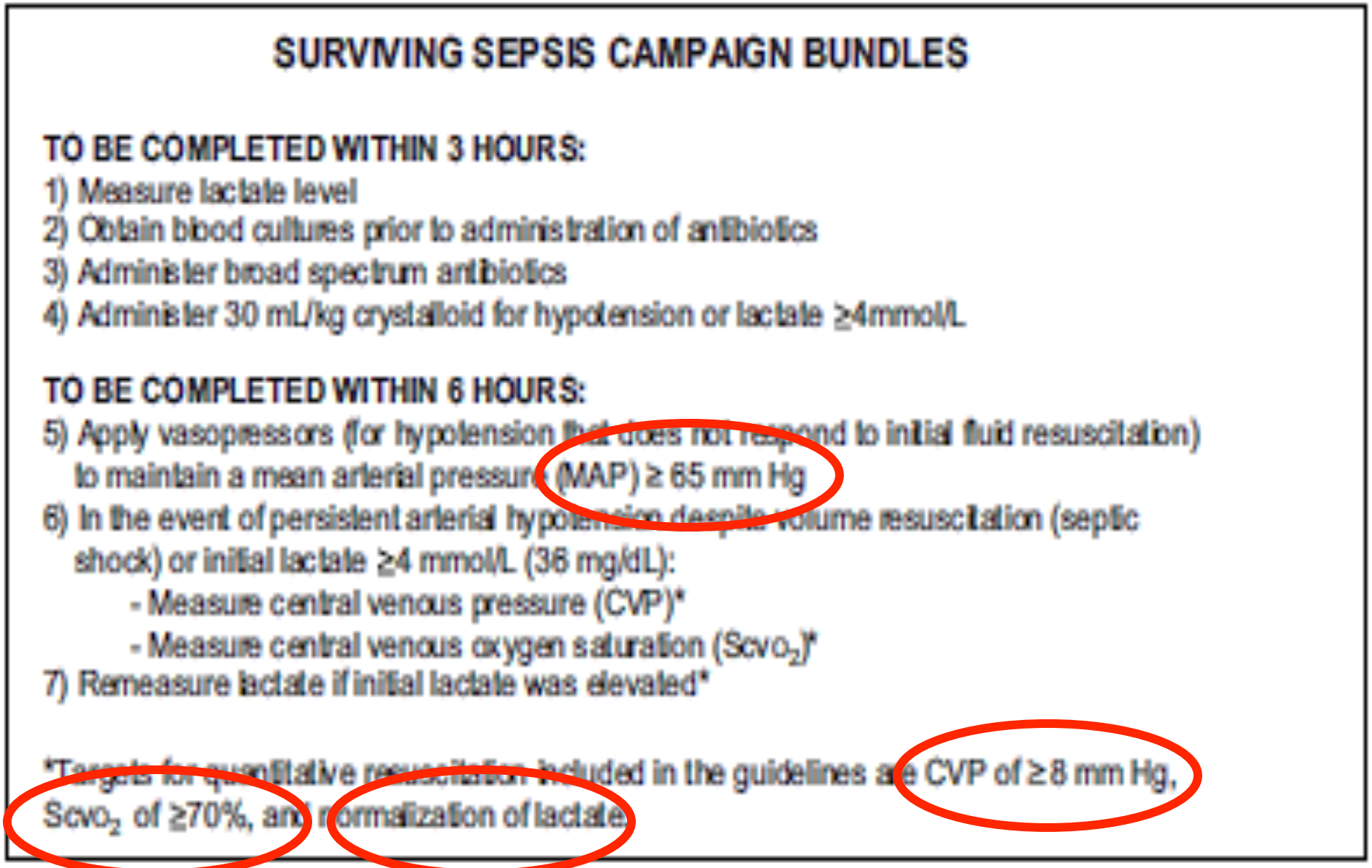
CVP 8 -12 mmHg
MAP ≥ 65 mmHg
UF ≥ 0.5 ml/kg/h

Protocol
n = 130

idem + $ScvO_2 \geq 70\%$
$SaO_2 \geq 93\%$
HT ≥ 30 %

For 6 hrs

Rivers et al NEJM, 2001, 345, 1368-1377



SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

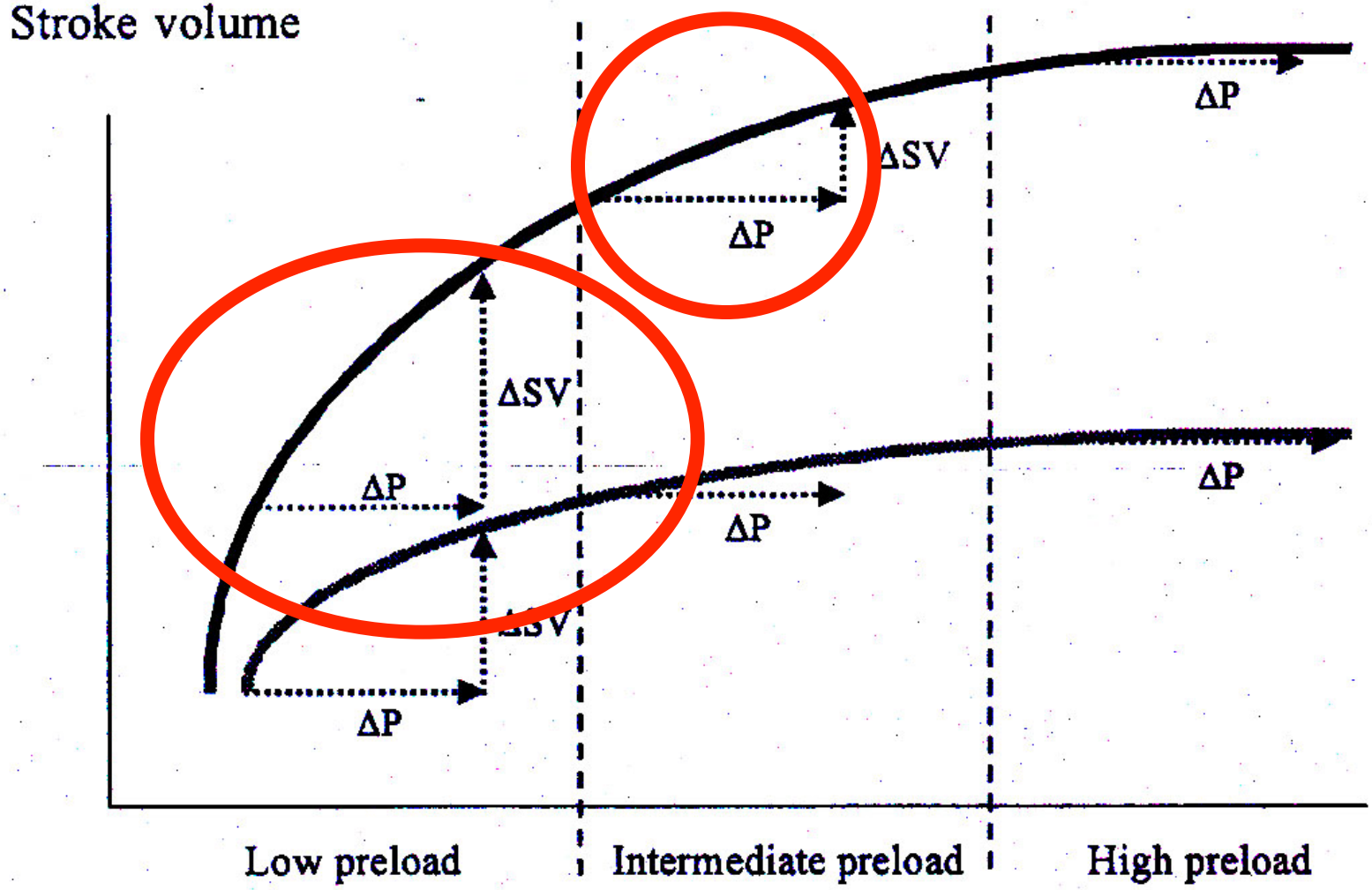
*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.

Réanimation initiale

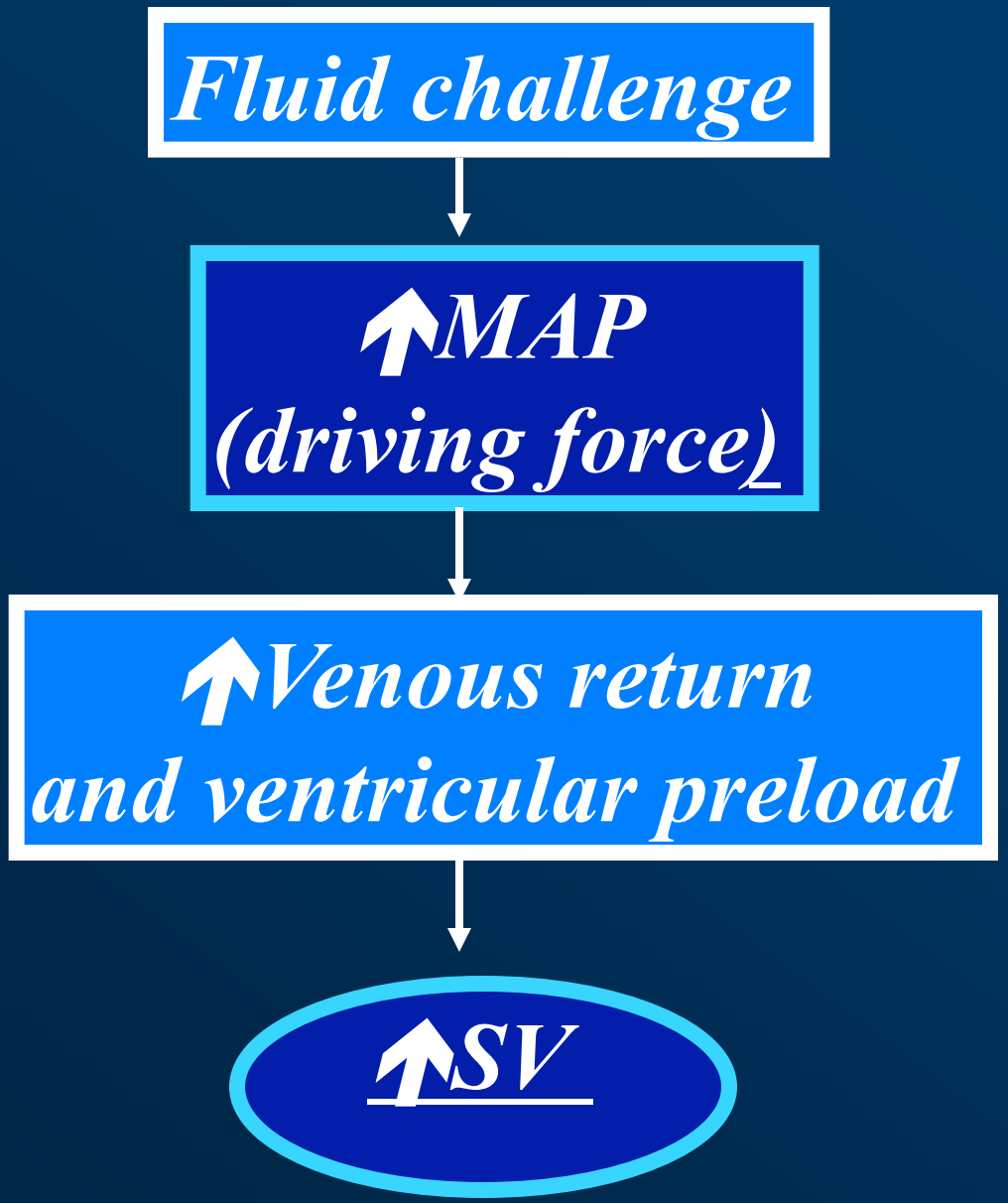
- PAM ≥ 65 mmHg
- PVC 8 - 12 mmHg
- DH ≥ 0.5 $ml.kg^{-1}.hr^{-1}$
- $ScvO_2$ ≥ 70%
- SvO_2 ≥ 65%

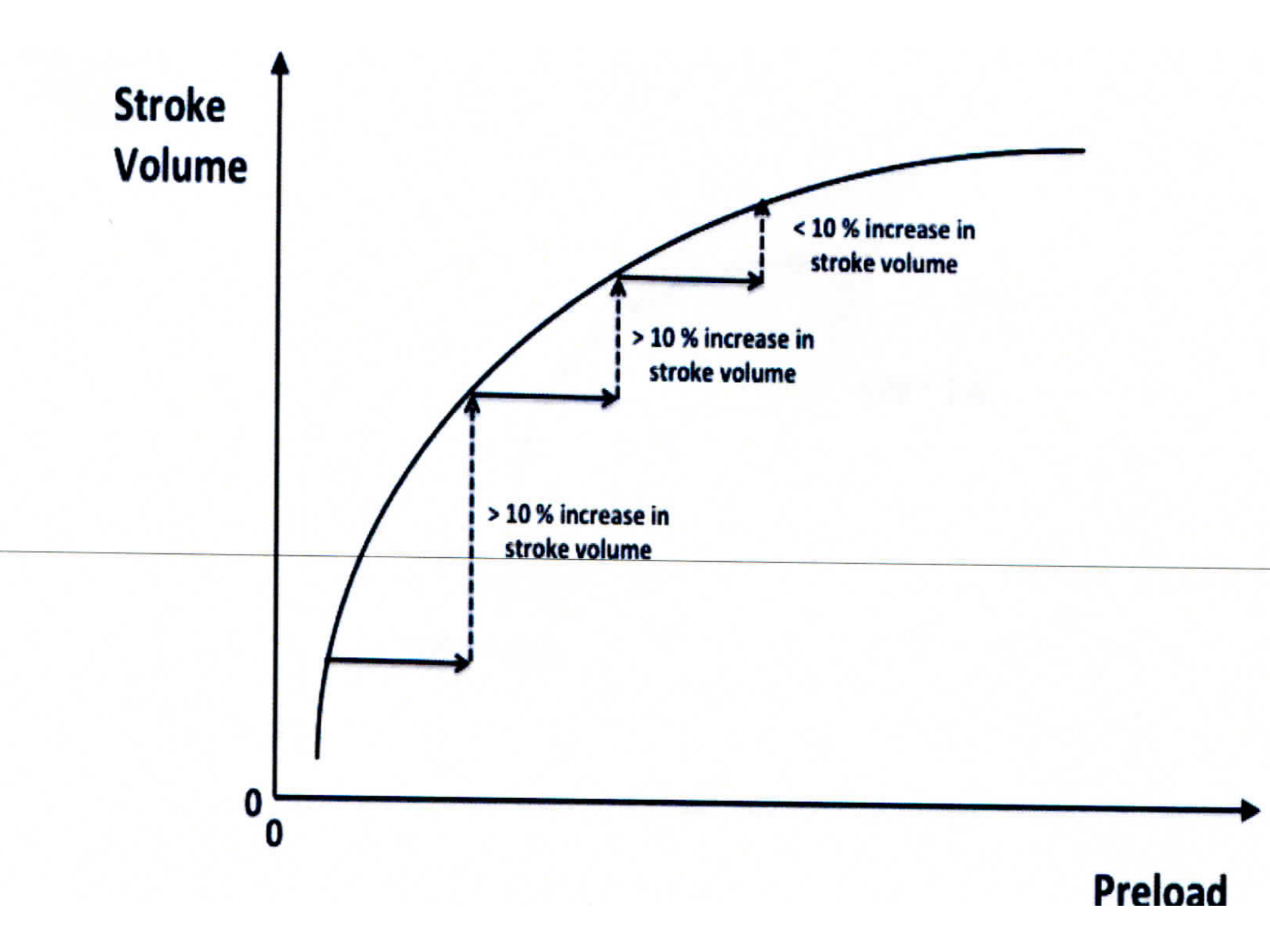
- Retour veineux
- optimal
- ?????????



Schematic representation of the ventricular preload/stroke volume relationship of a normal ventricle (black line) and a failing ventricle (gray line). When preload is low, an increase in preload (ΔP) induces a significant increase in stroke volume (ΔSV) whatever the ventricular function, while when preload is high a significant increase in stroke volume is very unlikely. In contrast, for the intermediate values of preload, the increase in stroke volume depends more on ventricular function (*ie*, on the slope of the curve) than on the preinfusion cardiac preload; therefore, assessing preload may be helpful to predict fluid responsiveness when preload is low or high, but not for intermediate values.

Fluid challenge




Stroke Volume
< 10 % increase in stroke volume
> 10 % increase in stroke volume
> 10 % increase in stroke volume
0
0
Preload

Fluid Challenge

- 500-1000 ml cristalloid
- 300-500 ml colloid
- over 30 min
- control CVP or PAOP and reduce speed/volume accordingly

PVC ?

?

critical care review

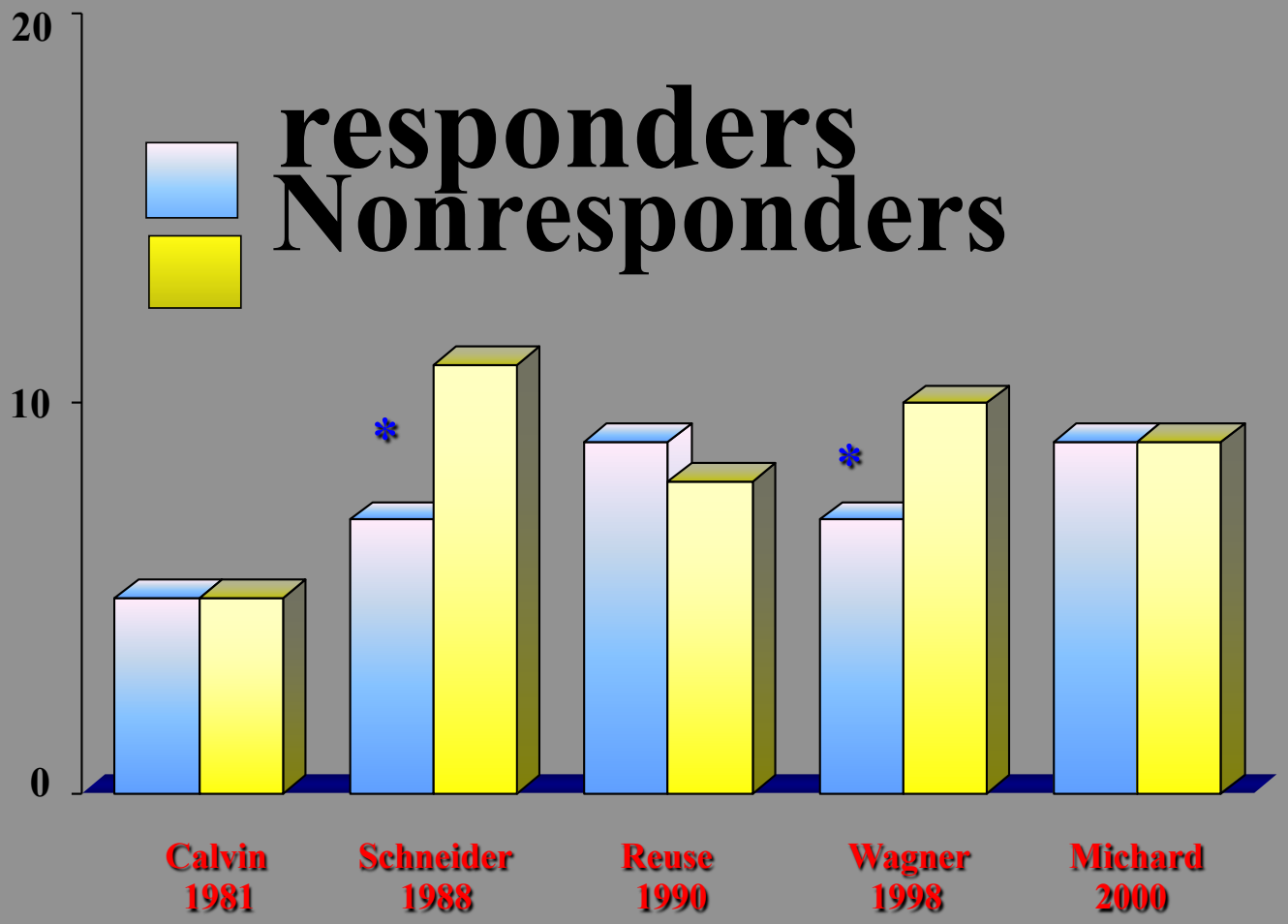
Predicting Fluid Responsiveness in ICU Patients*

A Critical Analysis of the Evidence

Frédéric Michard, MD, PhD; and Jean-Louis Teboul, MD, PhD

Chest 2002, 121:2000-8

RAP *(mmHg)* before volume expansion



	Calvin 1981	Schneider 1988	Reuse 1990	Wagner 1998	Michard 2000
number of pts	28	18	41	25	40
SB pts (%)	54	33	24	6	0

CHEST Special Feature

Does Central Venous Pressure Predict Fluid Responsiveness?*

A Systematic Review of the Literature and the Tale of Seven Mares

Paul E. Marik, MD, FCCP; Michael Baram, MD, FCCP; and Bobbak Vahid, MD

Background: **Central venous pressure (CVP) is used almost universally to guide fluid therapy in hospitalized patients. Both historical and recent data suggest that this approach may be flawed.**
Objective: **A systematic review of the literature to determine the following: (1) the relationship between CVP and blood volume, (2) the ability of CVP to predict fluid responsiveness, and (3) the ability of the change in CVP (ΔCVP) to predict fluid responsiveness.**
Data sources: **MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles.**
Study selection: **Reported clinical trials that evaluated either the relationship between CVP and blood volume or reported the associated between CVP/ΔCVP and the change in stroke volume/cardiac index following a fluid challenge. From 213 articles screened, 24 studies met our inclusion criteria and were included for data extraction. The studies included human adult subjects, healthy control subjects, and ICU and operating room patients.**
Data extraction: **Data were abstracted on study design, study size, study setting, patient population, correlation coefficient between CVP and blood volume, correlation coefficient (or receive operator characteristic [ROC]) between CVP/ΔCVP and change in stroke index/cardiac index, percentage of patients who responded to a fluid challenge, and baseline CVP of the fluid responders and nonresponders. Metaanalytic techniques were used to pool data.**
Data synthesis: **The 24 studies included 803 patients; 5 studies compared CVP with measured circulating blood volume, while 19 studies determined the relationship between CVP/ΔCVP and change in cardiac performance following a fluid challenge. The pooled correlation coefficient between CVP and measured blood volume was 0.16 (95% confidence interval [CI], 0.03 to 0.28). Overall, 56 ± 16% of the patients included in this review responded to a fluid challenge. The pooled correlation coefficient between baseline CVP and change in stroke index/cardiac index was 0.18 (95% CI, 0.08 to 0.28). The pooled area under the ROC curve was 0.56 (95% CI, 0.51 to 0.61). The pooled correlation between ΔCVP and change in stroke index/cardiac index was 0.11 (95% CI, 0.015 to 0.21). Baseline CVP was 8.7 ± 2.32 mm Hg [mean ± SD] in the responders as compared to 9.7 ± 2.2 mm Hg in nonresponders (not significant).**
Conclusions: **This systematic review demonstrated a very poor relationship between CVP and blood volume as well as the inability of CVP/ΔCVP to predict the hemodynamic response to a fluid challenge. CVP should not be used to make clinical decisions regarding fluid management.**
(CHEST 2008; 134:172–178)

Key words: anesthesia; blood volume; central venous pressure; fluid responsiveness; fluid therapy; hemodynamic monitoring; ICU; preload; stroke volume

Abbreviations: AUC = area under the curve; CI = confidence interval; CVP = central venous pressure; ΔCVP = change in central venous pressure; ROC = receiver operator characteristic

2008

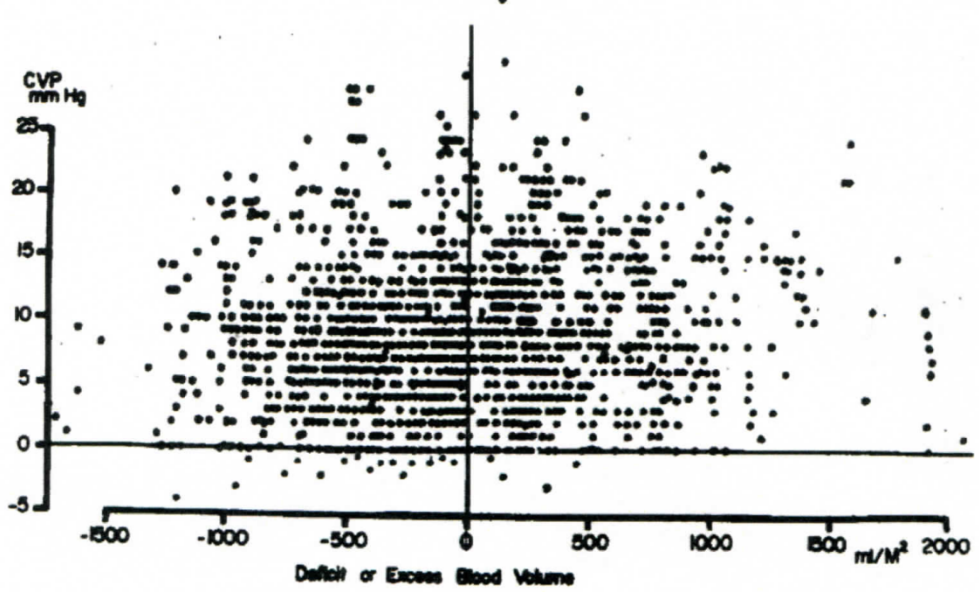


FIGURE 1. Fifteen hundred simultaneous measurements of blood volume and CVP in a heterogenous cohort of 188 ICU patients demonstrating no association between these two variables ($r = 0.27$). The correlation between ΔCVP and change in blood volume was 0.1 ($r^2 = 0.01$). This study demonstrates that patients with a low CVP may have volume overload and likewise patients with a high CVP may volume depleted. Reproduced with permission from Shippy et al.[11]

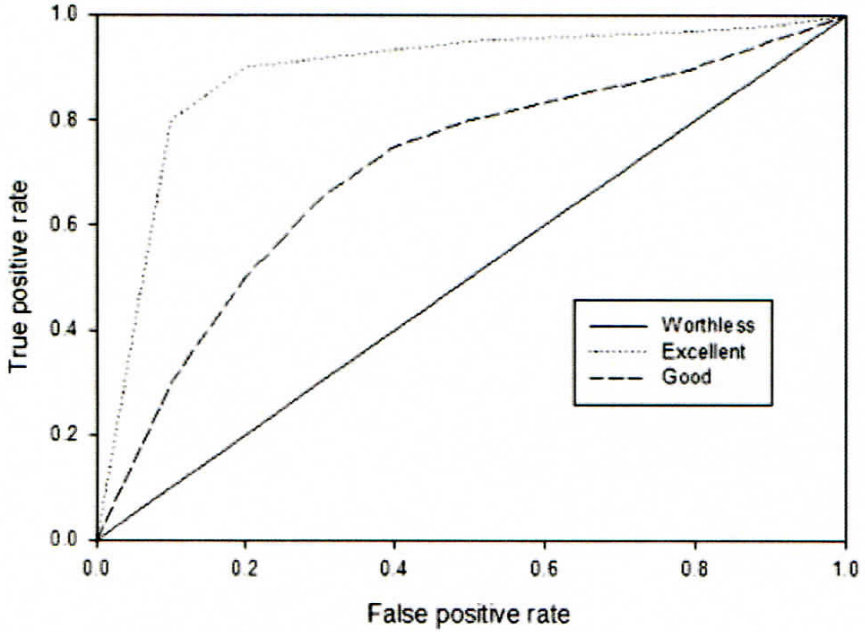


FIGURE 2. Comparison of ROC curves showing tests with

Does the Central Venous Pressure Predict Fluid Responsiveness? An Updated Meta-Analysis and a Plea for Some Common Sense*

Paul E. Marik, MD, FCCM[1]; Rodrigo Cavallazzi, MD[2]

Background: Despite a previous meta-analysis that concluded that central venous pressure should not be used to make clinical decisions regarding fluid management, central venous pressure continues to be recommended for this purpose.

Aim: To perform an updated meta-analysis incorporating recent studies that investigated indices predictive of fluid responsiveness. A priori subgroup analysis was planned according to the location where the study was performed (ICU or operating room).

Data Sources: MEDLINE, EMBASE, Cochrane Register of Controlled Trials, and citation review of relevant primary and review

0.56 (95% CI, 0.54–0.58) for those done in the operating room. The summary correlation coefficient between the baseline central venous pressure and change in stroke volume index/cardiac index was 0.18 (95% CI, 0.1–0.25), being 0.28 (95% CI, 0.16–0.40) in the ICU patients, and 0.11 (95% CI, 0.02–0.21) in the operating room patients.

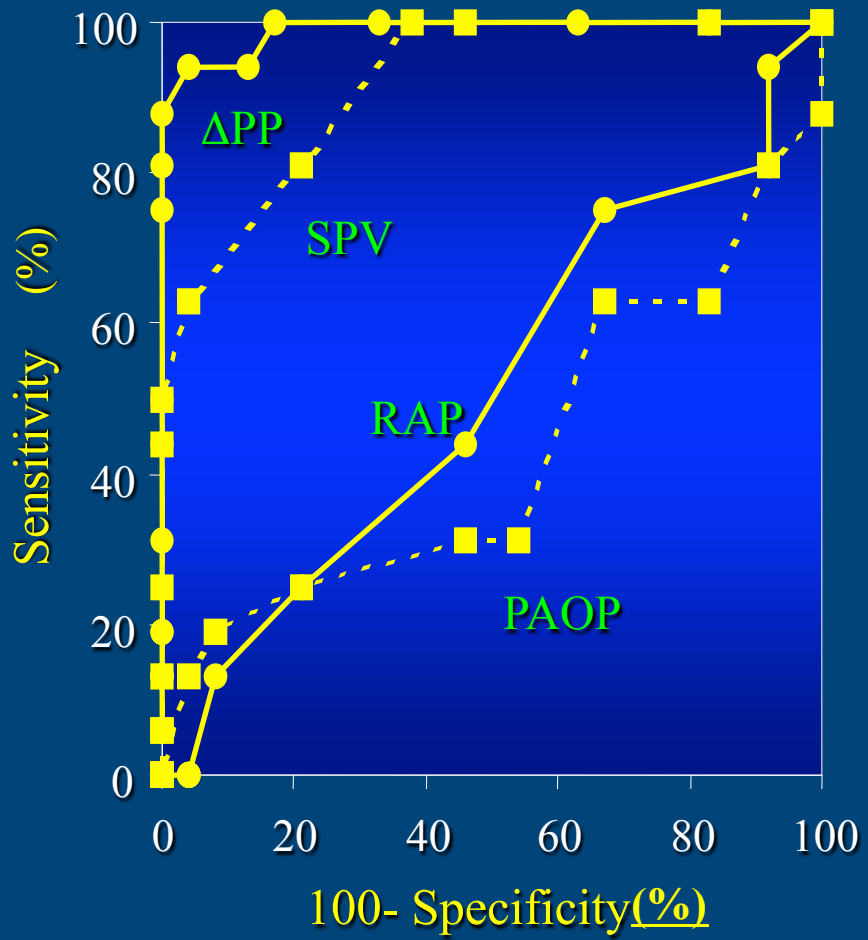
Conclusions: There are no data to support the widespread practice of using central venous pressure to guide fluid therapy. This approach to fluid resuscitation should be abandoned. (*Crit Care Med* 2013; 41:1774–1781)

Inclusion Criteria	Mechanical Ventilation	Other Comparator	Challenge	r-ΔSV	Area Under the Receiver Operator Characteristic Curve
SV > 25%	Y	SVV, PPV	Head up-down	–	0.29
SVI > 12%	Y	PPV, SVV	10 mL/kg Colloid	–	0.57
CI > 15%	Y	SVV	500 cc Colloid	–	0.53
SVI > 15%	Y	SVV/PVI	7 mL/kg Colloid	0.18	0.55
CI < 15%	Y	PVI	10 cm PEEP	–	0.25
CI > 15%	Y	PVI	500 cc Colloid	–	0.48
CI > 15%	Y	SVV	10 mL/kg Colloid	0.11	0.57
SVI > 15%	Y	PVI, PPV	PLR	0.12	0.6
CO > 15%	Y	PPV	500 cc Colloid	–	0.57
	N	Various	3,000 Crystalloid	0.32	

Relation between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure

FRÉDÉRIC MICHARD, SANDRINE BOUSSAT, DENIS CHEMLA, NADIA ANGUEL, ALAIN MERCAT, YVES LECARPENTIER, CHRISTIAN RICHARD, MICHAEL R. PINSKY, and JEAN-LOUIS TEBOUL

Am J Respir Crit Care Med 2000; 162:134-8



Fluid challenge

Respiratory variation under MV	
Parameter	**threshold**
ΔSAP	**10 mmHg or 9%**
Δdown	**5 mmHg**
ΔPP	**12-13 %**
SVV	**9-10%**
CVP	**< 5 mmHg**

French Consensus Conference 2005

Intensive Care Med (2015) 41:444–451
DOI 10.1007/s00134-014-3638-4

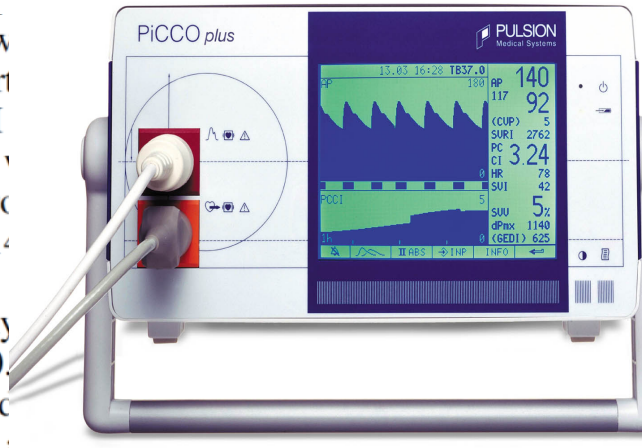
ORIGINAL

Zhongheng Zhang
Hongying Ni
Zhixian Qian

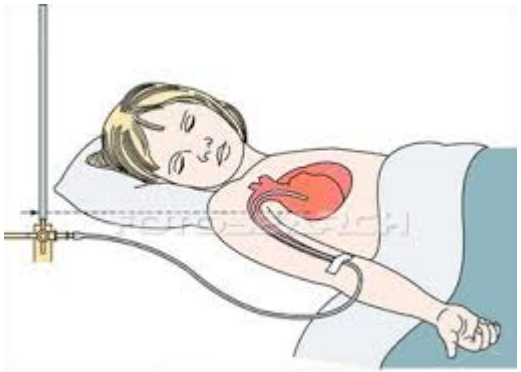
Effectiveness of treatment based on PiCCO parameters in critically ill patients with septic shock and/or acute respiratory distre

Abstract *Purpose:* To compare treatment based on either PiCCO-derived physiological values or central venous pressure (CVP) monitoring, we performed a prospective randomized controlled trial with group sequential analysis. *Methods:* Consecutive critically ill patients with septic shock and/or ARDS were included. The planned total sample size was 715. The primary outcome was 28-day mortality after randomization. Participants underwent stratified randomization according to the classification of ARDS and/or septic shock. Caregivers were not blinded to the intervention, but participants and outcome assessors were blinded to group assignment. *Results:* The study was stopped early because of futility after enrollment of 350 patients including 168 in the PiCCO group and 182 in the control group. There was no loss to follow-up and data from all enrolled participants were analyzed. The result showed that treatment based on PiCCO-derived physiological values w
able to reduce the 28-day mor
risk (odds ratio 1.00, 95 % CI
0.66–1.52; $p = 0.993$). There
difference between the two gr
secondary outcomes such as 1
mortality (40.5 vs. 41.2 %;
$p = 0.889$), ICU length of stay
(median 9 vs. 7.5 days; $p = 0$.
days free of vasopressors (me
14.5 vs. 19 days; $p = 0.676$),
days free of mechanical ventilation
(median 3 vs. 6 days; $p = 0.168$). No
severe adverse event was reported in
both groups. *Conclusion:* On the
basis of our study, PICCO-based fluid
management does not improve out-
come when compared to CVP-based
fluid management.

Keywords Septic shock · PICCO ·
Intensive care unit ·
28-day mortality ·
Acute respiratory distress syndrome ·
Randomized controlled trial

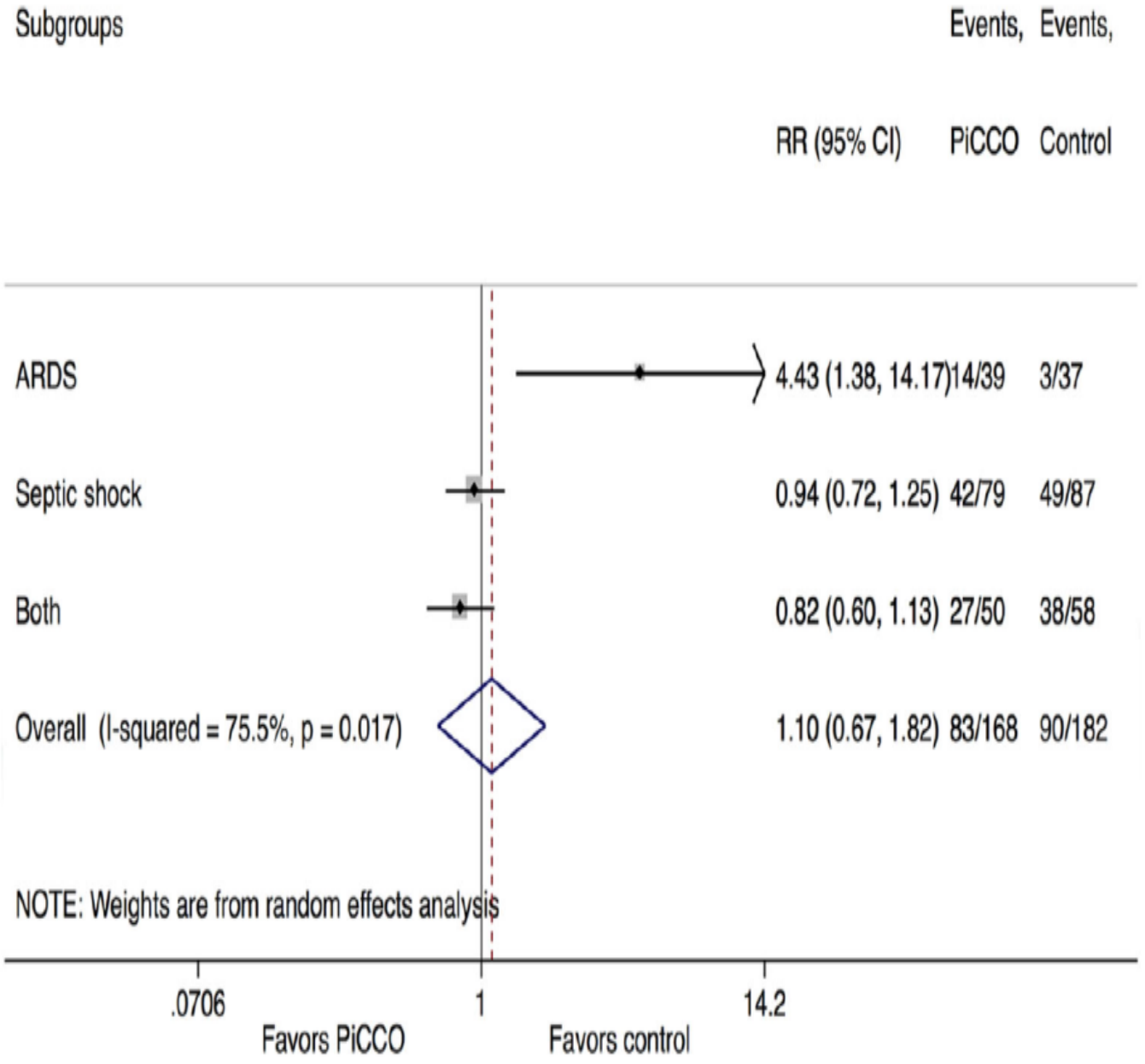


In the control group, volume status was assessed by using central venous pressure (CVP), aiming to maintain a CVP between 8 and 12 mmHg [10]. Patients in the control arm did not receive PiCCO monitoring, but a central venous catheter was routinely inserted (supplemental Fig. 2). If the CVP was less than 8 mmHg, a



The trial stopped early after enrollment of 350 participants because of futility of treatment based on PiCCO-derived physiological values (supplemental Fig. 3). The flow chart of subject enrollment is shown in Fig 1

Fig. 2 Forest plot showing subgroup analysis by the type of patient. Treatment based on PiCCO variables showed a marginal beneficial effect in patients with septic shock (RR 0.94, 95 % CI 0.72–1.25) and both (RR 0.82, 95 % CI 0.60–1.13). However, treatment based on PiCCO variables was harmful in ARDS patients (RR 4.43, 95 % CI 1.38–14.17)



Intensive Care Med (2015) 41:444–451
DOI 10.1007/s00134-014-3638-4

ORIGINAL

ICM March 2015

Zhongheng Zhang
Hongying Ni
Zhixian Qian

Effectiveness of treatment based on PiCCO parameters in critically ill patients with septic shock and/or acute respiratory distress syndrome: a randomized controlled trial

Mortality +/- 50 %

Table 2 Comparison of outcomes between PiCCO and control groups

Outcome variables	PiCCO group (n = 168)	Control group (n = 182)	P value
Primary outcome			
28-day mortality	83 (49.4)	90 (49.5)	0.993
Secondary outcomes			
Maximum SOFA	12 (10–14)	12 (9–14)	0.023
14-day mortality	68 (40.5)	75 (41.2)	0.889
Days on vasopressor	4 (2–6)	3 (2–6.5)	0.852
Days on MV	6 (3–12)	5.5 (3–12)	0.897
Days on CRRT	4 (3–7)	4.5 (3–7)	0.586
Length of stay in ICU	9 (5–13)	7.5 (4–15)	0.598
Days free of vasopressor in 14 days	10 (0–12)	9 (0–12)	0.562
Days free of MV in 14 days	1 (0–10)	4 (0–12)	0.127
Days free of CRRT in 14 days	11 (3–14)	14 (4–14)	0.0038
Days free of vasopressor in 28 days	14.5 (0–25)	19 (0–26)	0.676
Days free of MV in 28 days	3 (0–24)	6 (0–25)	0.168
Days free of CRRT in 28 days	15.5 (3–28)	21 (4–28)	0.048

Patients without use of MV, CRRT, or vasopressor were treated as missing variable, instead of zero
MV mechanical ventilation, *ICU* intensive care unit, *IQR* interquartile range, *CRRT* continuous renal replacement therapy

Ventilation spontannée , VC bas , compliance pulmonaire basse , arythmie

ΔPP

SVV

Non

!!!

- **Passive leg raising**

with > 12% increase

in CO by PiCCO

or oesophageal Döppler

Monnet and Teboul *Critical Care*
DOI 10.1186/s13054-014-0708-5

CRITICAL CARE

EDITORIAL

Passive leg raising: five rules, not a drop of fluid!

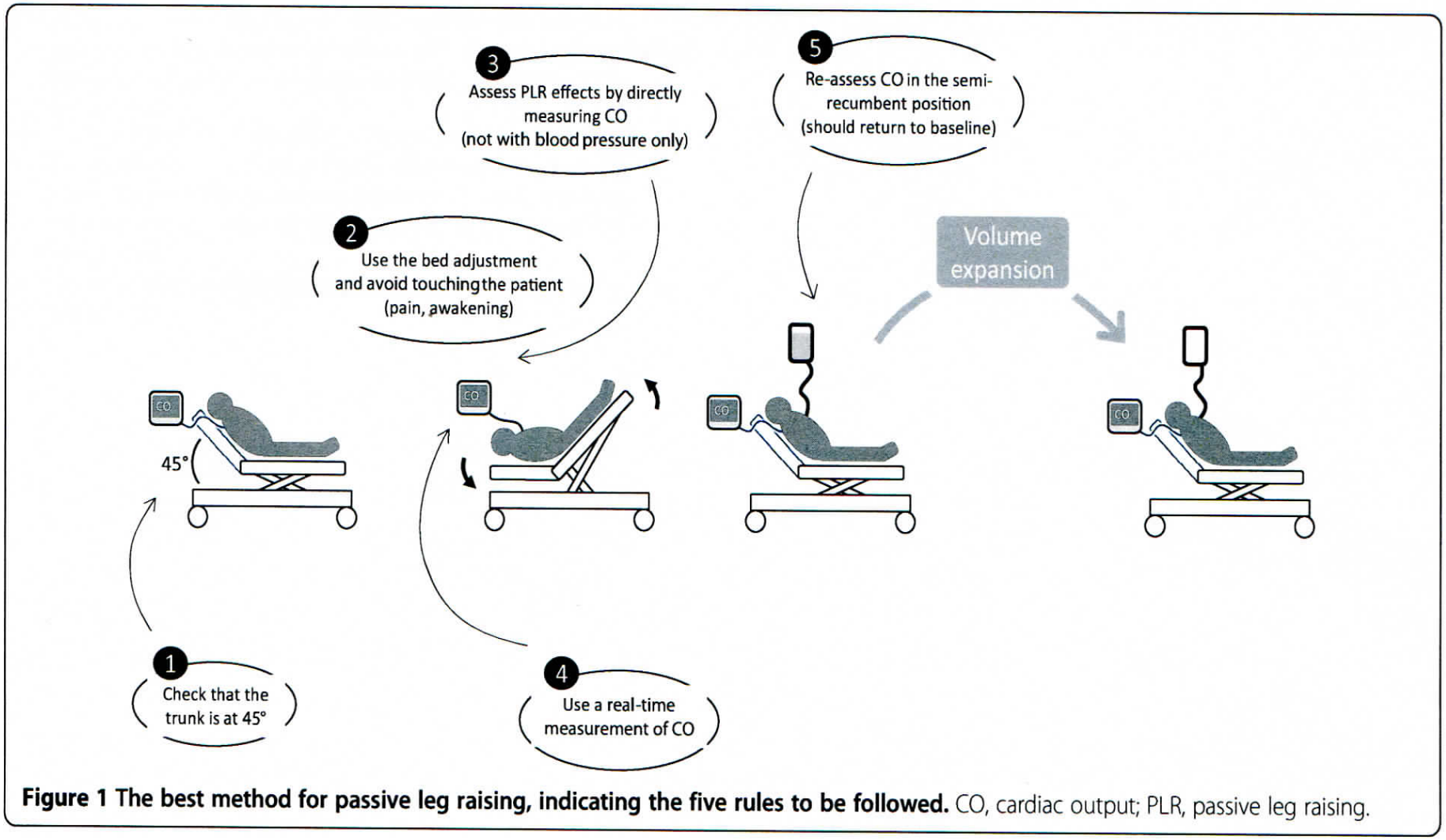


Figure 1 The best method for passive leg raising, indicating the five rules to be followed. CO, cardiac output; PLR, passive leg raising.

Trop

c'est

trop

Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

John H. Boyd, MD, FRCP(C); Jason Forbes, MD; Taka-aki Nakada, MD, PhD; Keith R. Walley, MD, FRCP(C); James A. Russell, MD, FRCP(C)

Objective: To determine whether central venous pressure and fluid balance after resuscitation for septic shock are associated with mortality.

Design: We conducted a retrospective review of the use of intravenous fluids during the first 4 days of care.

Setting: Multicenter randomized controlled trial.

Patients: The Vasopressin in Septic Shock Trial (VASST) study enrolled 778 patients who had septic shock and who were receiving a minimum of 5 μg of norepinephrine per minute.

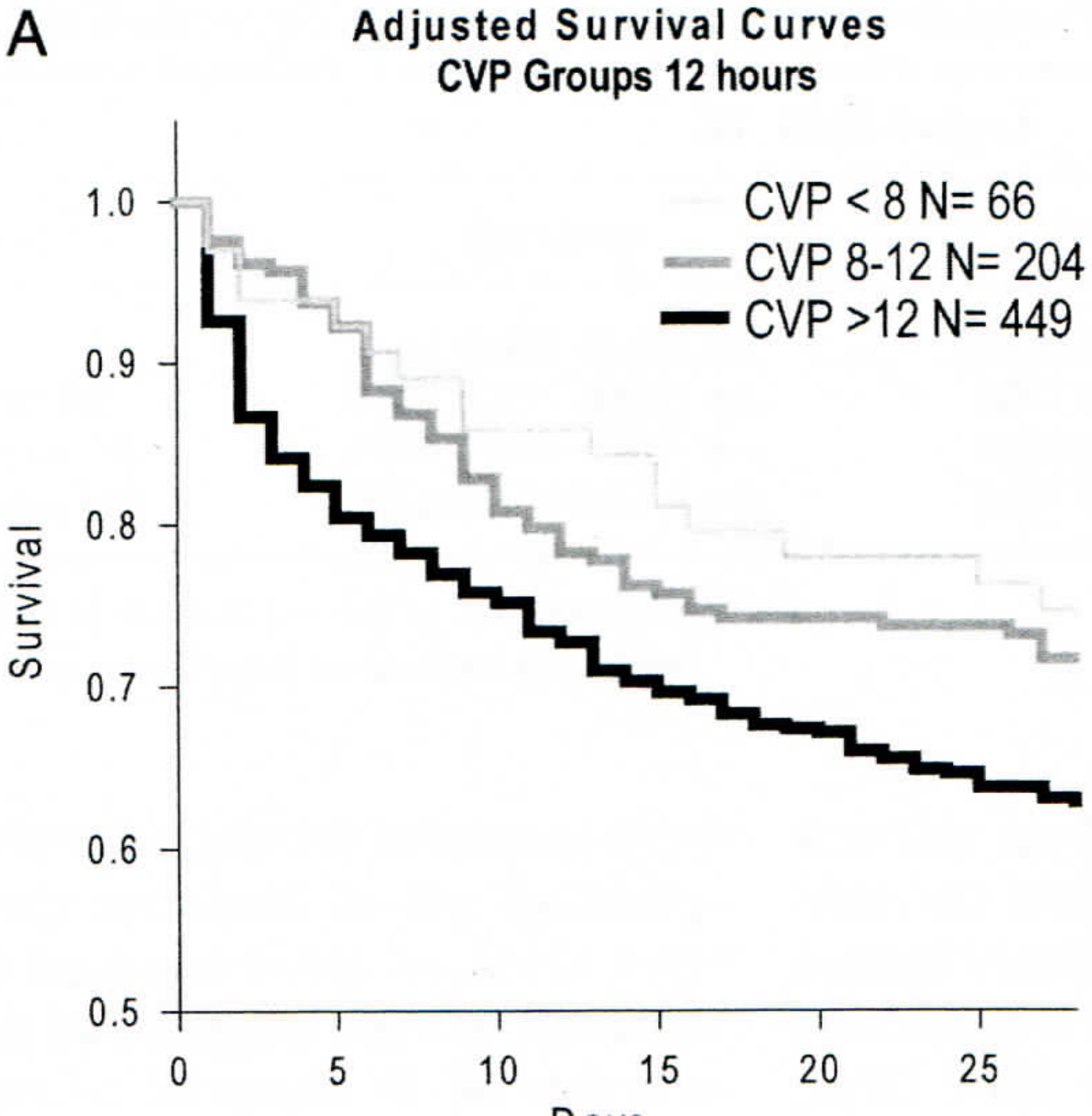
Interventions: None.

Measurements and Main Results: Based on net fluid balance, we determined whether one's fluid balance quartile was correlated with 28-day mortality. We also analyzed whether fluid balance was predictive of central venous pressure and furthermore whether a guideline-recommended central venous pressure of 8–12 mm Hg yielded a mortality advantage. At enrollment, which occurred on average 12 hrs after presentation, the average fluid balance was +4.2 L. By day 4, the cumulative average fluid balance was +11 L. After correcting for age and Acute Physiology and Chronic Health Evaluation II score, a more positive fluid balance at both at 12 hrs and day 4 correlated significantly with increased mortality. Central venous pressure was correlated with fluid balance at 12 hrs, whereas on days 1–4, there was no significant correlation. At 12 hrs, patients with central venous pressure <8 mm Hg had the lowest mortality rate followed by those with central venous pressure 8–12 mm Hg. The highest mortality rate was observed in those with central venous pressure >12 mm Hg. Contrary to the overall effect, patients whose central venous pressure was <8 mm Hg had improved survival with a more positive fluid balance.

Conclusions: A more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Central venous pressure may be used to gauge fluid balance ≤12 hrs into septic shock but becomes an unreliable marker of fluid balance thereafter. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 hrs. (Crit Care Med 2011; 39:259–265)

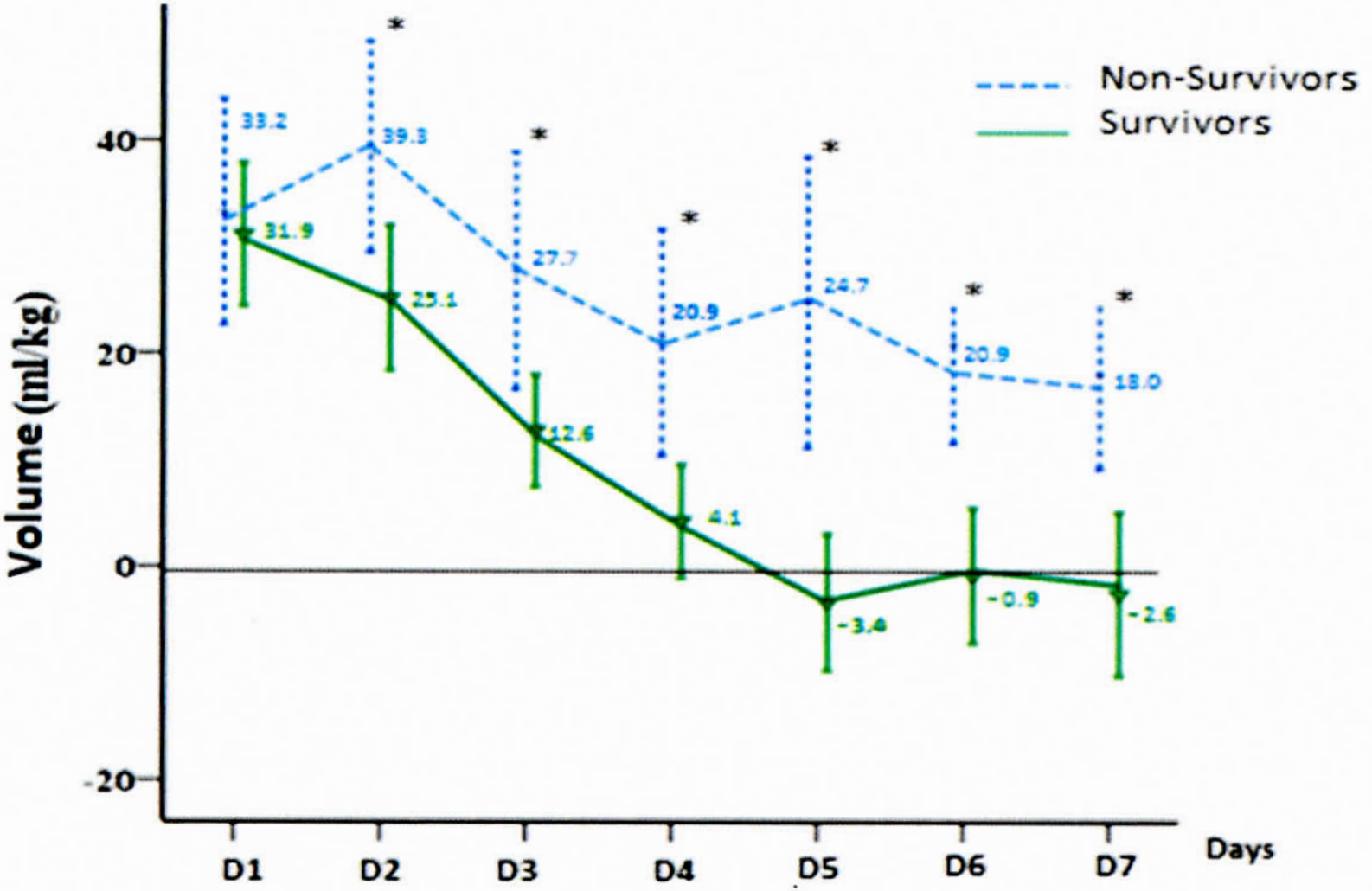
KEY WORDS: sepsis; septic shock; fluid resuscitation

A


Adjusted Survival Curves
CVP Groups 12 hours
CVP < 8 N= 66
CVP 8-12 N= 204
CVP >12 N= 449
Survival
1.0
0.9
0.8
0.7
0.6
0.5
0
5
10
15
20
25

A positive fluid balance i

Angel

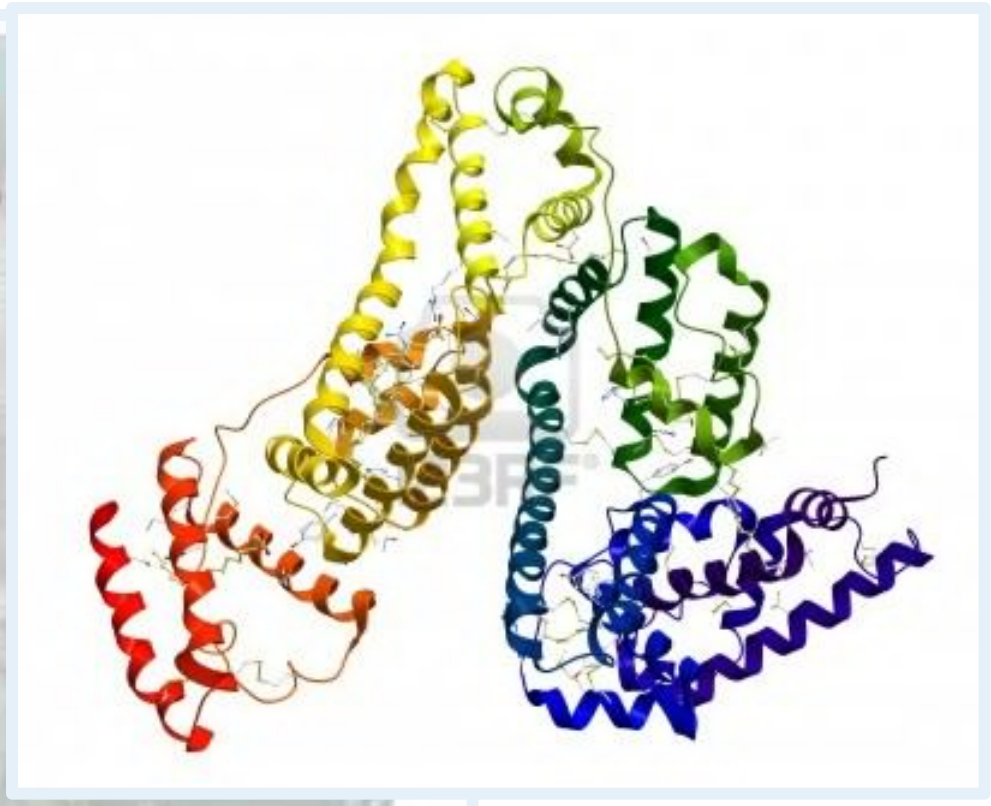


Number of patients per day							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
NS	59	59	59	51	43	38	31
S	114	114	114	96	75	64	49

Les liquides …

- Cristalloïdes / colloïdes…
- Albumine / autres colloïdes
- Equilibrés / non équilibrés


VOLUVEN




Baxter
ALBUMINE HUMAINE
BAXTER BIOSCIENCE
200 g/l
Solution pour perfusion
100 ml

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

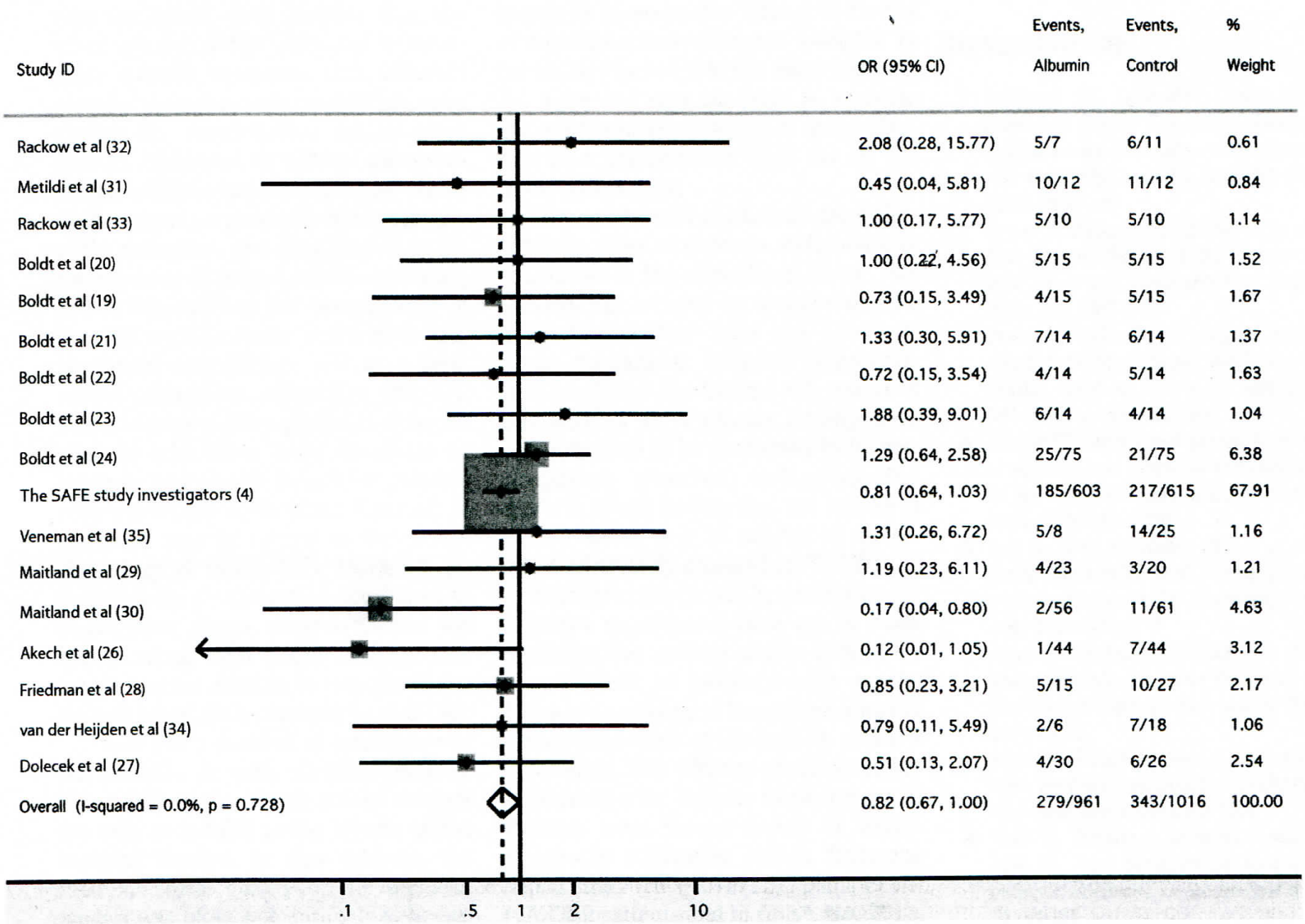


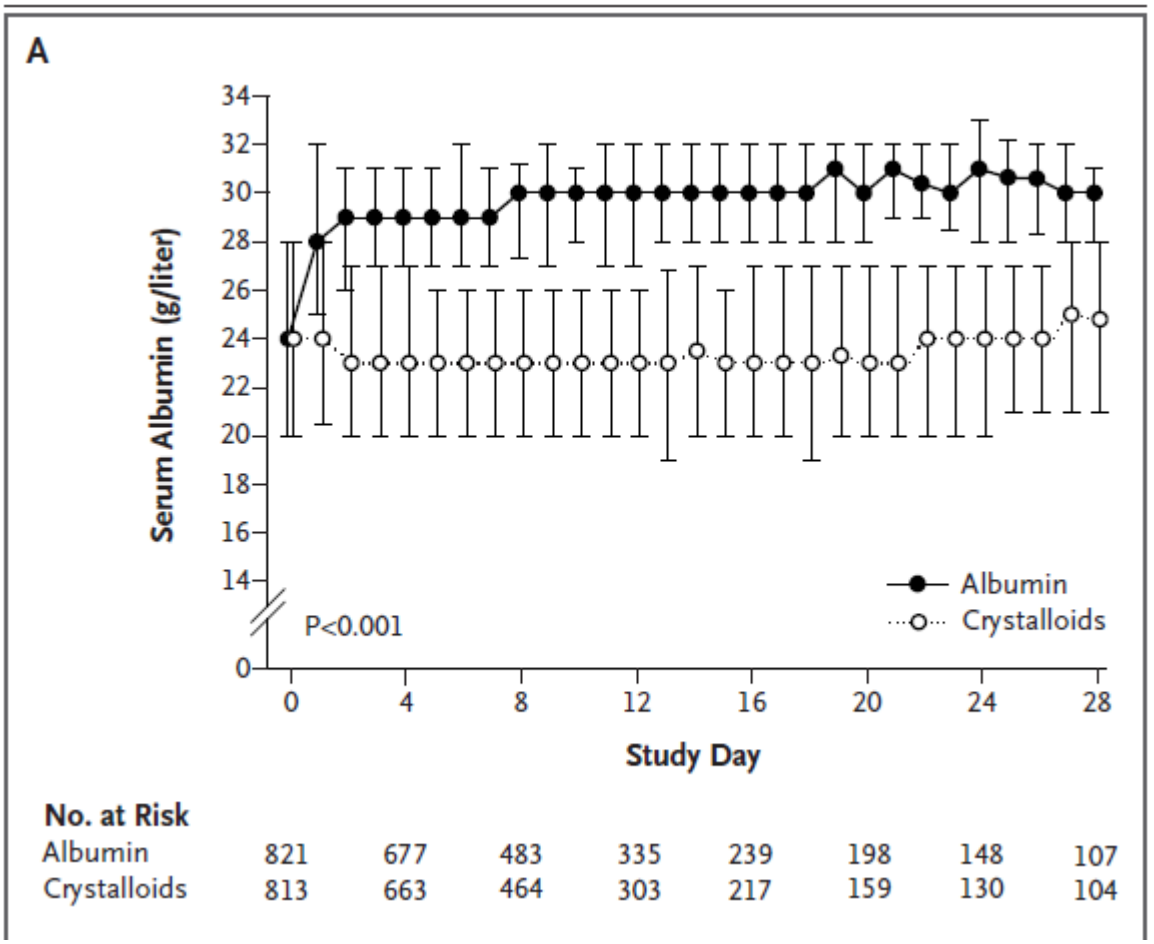
Figure 2. Forrest plot showing the pooled estimate of the effect of resuscitation with albumin-containing solutions on mortality for patients with sepsis. *OR*, odds ratio; *CI*, confidence limit.

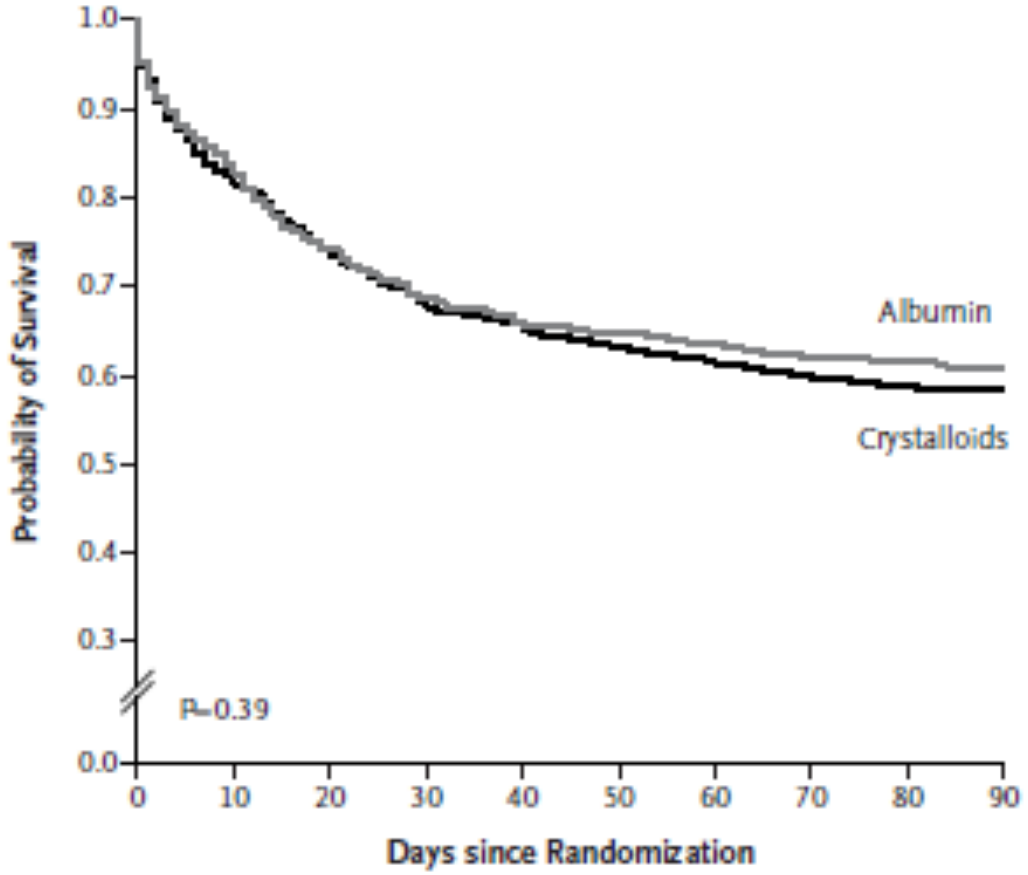
ORIGINAL ARTICLE

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*

1818 patients





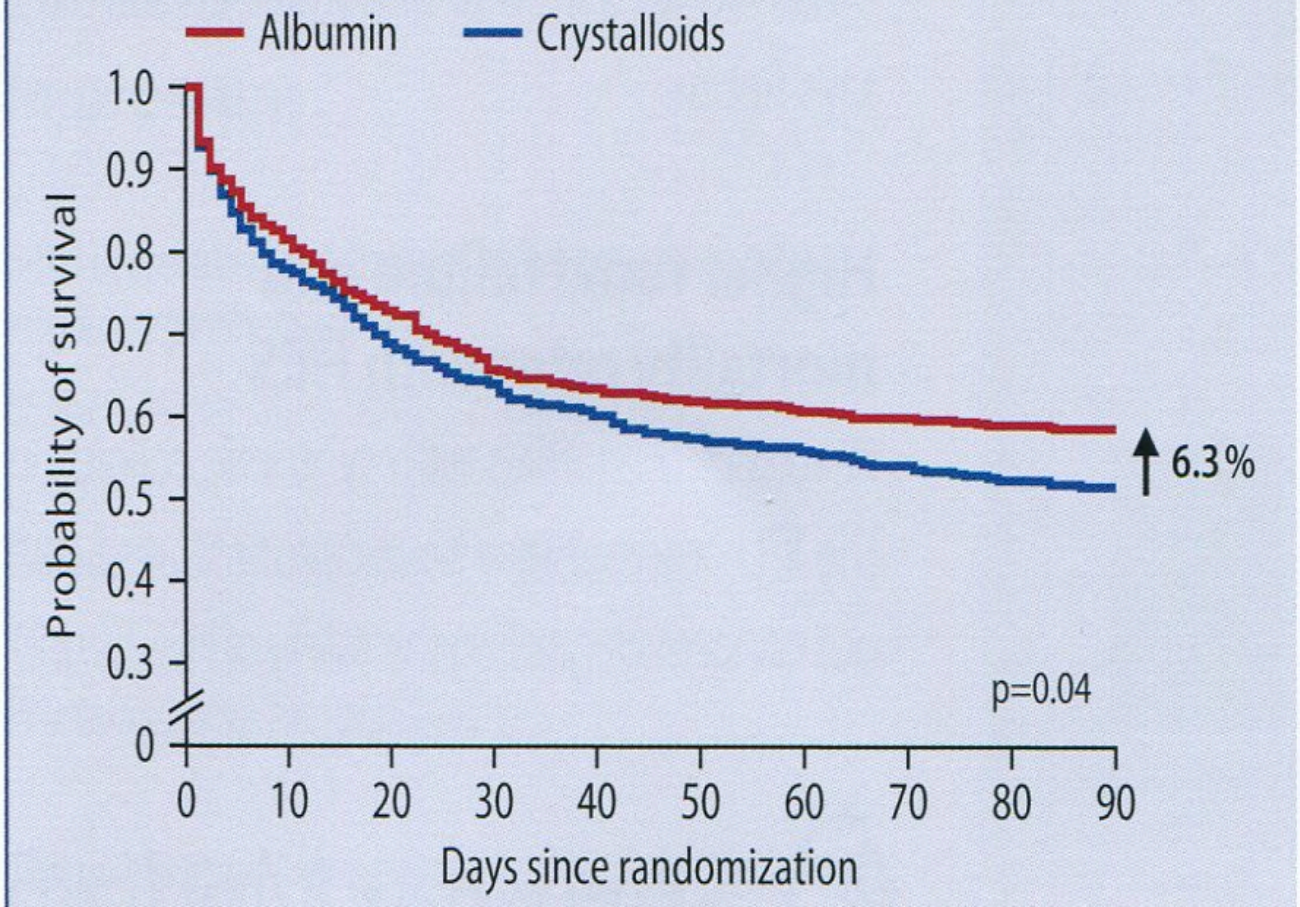
No. at Risk										
Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

Figure 2. Probability of Survival from Randomization through Day 90.

The graph shows the Kaplan–Meier estimates for the probability of survival among patients receiving albumin and crystalloids and among those receiving crystalloids alone. The P value was calculated with the use of the log-rank test.

Conversely, a significant difference was observed in a post hoc subgroup analysis that included 1121 patients with septic shock, as compared with 660 without septic shock, at the time of enrollment (relative risk with septic shock, 0.87; 95% CI, 0.77 to 0.99; relative risk without septic shock, 1.13; 95% CI, 0.92 to 1.39; P=0.03 for heterogeneity) (Fig. S3 in the Supplementary Appendix). Adjustment for baseline covariates did not significantly modify these results (Table S6 in the Supplementary Appendix).

ALBIOS : Septic shock sub-group



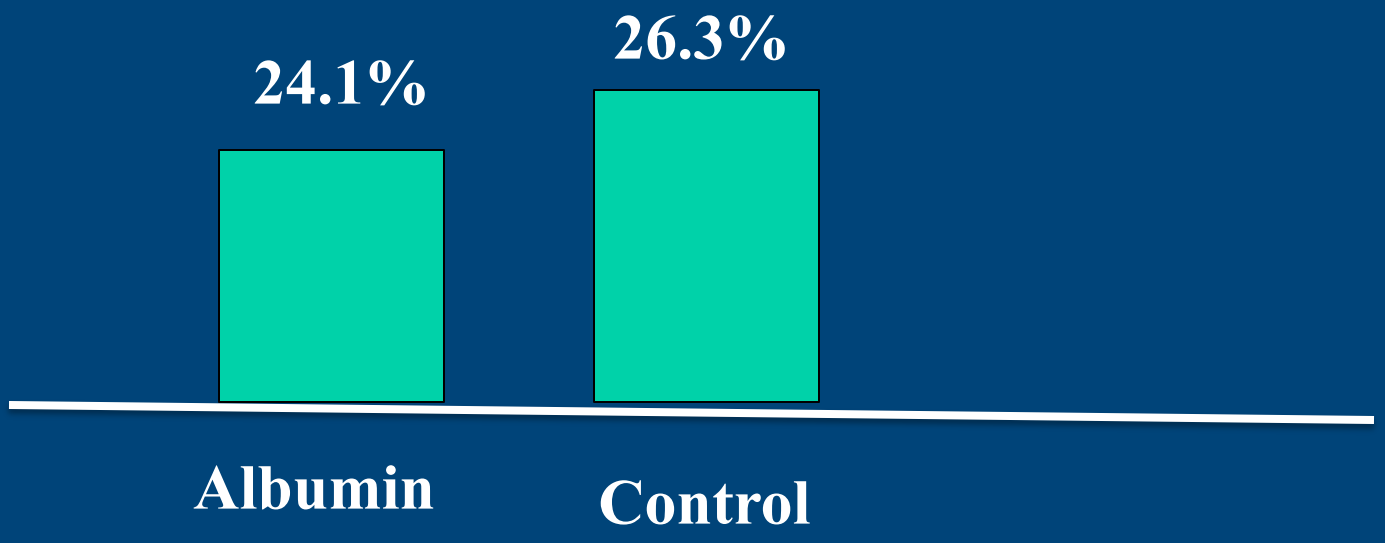
Patients with septic shock as defined according to the SOFA score

modified from Gattioni L, oral presentation at the 34th International Symposium on Intensive Care and Emergency Medicine, March 18-21, 2014, Brussels

Albumin JP Mira et al

- 20 g albumin/normal saline Q 3 for 3 days

Mortality



Charpentier et al ICM 2011 37 Abstract S115

Updated Meta-analysis Wiedermann *et al* 2014

- 14 studies including ALBIOS and EARSS
- 6,353 patients
- **R Ratio of death :**

0.92 (95% CI 0.85- 0.99) fixed model
0.93 (0.86 – 1.00) random model

Vincent *et al. Critical Care* 2014, 18:231
http://ccforum.com/content/18/4/231

CRITICAL CARE

REVIEW

Albumin administration in the acutely ill: what is new and where next?

Jean-Louis Vincent[1*], James A Russell[2], Matthias Jacob[3], Greg Martin[4], Bertrand Guidet[5,6], Jan Wernerman[7], Ricard Ferrer Roca[8], Stuart A McCluskey[9] and Luciano Gattinoni[10]

Abstract

Albumin solutions have been used worldwide for the treatment of critically ill patients since they became commercially available in the 1940s. However, their use has become the subject of criticism and debate in more recent years. Importantly, all fluid solutions have potential benefits and drawbacks. Large multicenter randomized studies have provided valuable data regarding the safety of albumin solutions, and have begun to clarify which groups of patients are most likely to benefit from their use. However, many questions remain related to where exactly albumin fits within our fluid choices. Here, we briefly summarize some of the physiology and history of albumin use in intensive care before offering some evidence-based guidance for albumin use in critically ill patients.

- There is now enough evidence – albeit largely from subgroup analyses – and plausible biological rationale to support use of albumin in patients with septic shock when a colloid is considered

CCM 2014 42 1585

Association Between the Choice of IV Crystalloid and In-Hospital Mortality Among Critically Ill Adults With Sepsis*

Karthik Raghunathan, MD, MPH[1,2]; Andrew Shaw, MB, FRCA, FFICM, FCCM[1]; Brian Nathanson, PhD[3]; Til Stürmer, MD, PhD[4]; Alan Brookhart, PhD[4]; Mihaela S. Stefan, MD[5]; Soko Setoguchi, MD, DrPH[6]; Chris Beadles, MD, PhD[2]; Peter K. Lindenauer, MD, MSc[7]

Objective: Isotonic saline is the most commonly used crystalloid in the ICU, but recent evidence suggests that balanced fluids like Lactated Ringer's solution may be preferable. We examined the association between choice of crystalloids and in-hospital mortality during the resuscitation of critically ill adults with sepsis.

Design: A retrospective cohort study of patients admitted with sepsis, not undergoing any surgical procedures, and treated in an ICU by hospital day 2. We used propensity score matching to control for confounding and compared the following outcomes after resuscitation with balanced versus with no-balanced fluids: in-hospital mortality, acute renal failure with and without dialysis, and hospital and ICU lengths of stay. We also estimated the dose-response relationship between receipt of increasing proportions of balanced fluids and in-hospital mortality.

Setting: Three hundred sixty U.S. hospitals that were members of the Premier Healthcare alliance between November 2005 and December 2010.

Patients: A total of 53,448 patients with sepsis, treated with vasopressors and crystalloids in an ICU by hospital day 2 including 3,396 (6.4%) that received balanced fluids.

Interventions: None.

Measurements and Main Results: Patients treated with balanced fluids were younger and less likely to have heart or chronic renal failure, but they were more likely to receive mechanical ventilation, invasive monitoring, colloids, steroids, and larger crystalloid volumes (median 7 vs 5 L). Among 6,730 patients in a propensity-matched cohort, receipt of balanced fluids was associated with lower in-hospital mortality (19.6% vs 22.8%; relative risk, 0.86; 95% CI, 0.78, 0.94). Mortality was progressively lower among patients receiving larger proportions of balanced fluids. There were no significant differences in the prevalence of acute renal failure (with and without dialysis) or in-hospital and ICU lengths of stay.

Conclusions: Among critically ill adults with sepsis, resuscitation with balanced fluids was associated with a lower risk of in-hospital mortality. If confirmed in randomized trials, this finding could have significant public health implications, as crystalloid resuscitation is nearly universal in sepsis. (*Crit Care Med* 2014; 42:1585–1591)

Conclusions: Among critically ill adults with sepsis, resuscitation with balanced fluids was associated with a lower risk of in-hospital mortality. If confirmed in randomized trials, this finding could have significant public health implications, as crystalloid resuscitation is nearly universal in sepsis. (*Crit Care Med* 2014; 42:1585–1591)

TABLE 1. Association Between Resuscitation With Balanced Fluids and Primary and Secondary Outcomes in Propensity-Matched Cohorts

Outcome	Balanced Fluid–Matched Cohort	No-Balanced Fluid–Matched Cohort	Effect Estimate	95% CI
Absolute in-hospital mortality	19.6% (659 of 3,365)	22.8% (768 of 3,365)	Relative risk, 0.86	0.78, 0.94; $p = 0.001$
ARF with dialysis	4.52% (142 of 3,144)	4.74% (149 of 3,144)	Relative risk, 0.953	0.761, 1.194
ARF without dialysis	7.12% (159 of 2,655)	7.50% (199 of 2,655)	Relative risk, 0.950	0.784, 1.150
Hospital LOS in days (survivors)	11.26	11.37	Absolute difference, −0.11	−0.55, 0.34
ICU LOS in days (survivors)	5.39	5.50	Absolute difference, −0.11	−0.37, 0.15

ARF = acute renal failure, LOS = lengths of stay.

Analyses compare patients initially treated with balanced fluids with patients not treated with any balanced fluids and estimate effects on all outcomes (occurring beyond day 2). Relative risks for in-hospital mortality ($p = 0.001$), ARF (with and without dialysis), and absolute differences in ICU and hospital LOS among survivors are reported. ICU LOS was significantly lower in sensitivity analyses (including outcomes occurring on and beyond day 2), whereas other results remained consistent (eTable 7, Supplemental Digital Content 1, http://links.lww.com/CCM/A929).

Association of Hyperchloremia With Hospital Mortality in Critically Ill Septic Patients

Javier A. Neyra, MD[1]; Fabrizio Canepa-Escaro, MD[2]; Xilong Li, PhD, MS[3]; John Manllo, MD[4]; Beverley Adams-Huet, MS[3]; Jerry Yee, MD[5]; Lenar Yessayan, MD, MS[5,6]; for the Acute Kidney Injury in Critical Illness Study Group

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Objectives: Hyperchloremia is frequently observed in critically ill patients in the ICU. Our study aimed to examine the association of serum chloride (Cl) levels with hospital mortality in septic ICU patients.

Design: Retrospective cohort study.

Setting: Urban academic medical center ICU.

Patients: ICU adult patients with severe sepsis or septic shock who had Cl measured on ICU admission were included. Those with baseline estimated glomerular filtration rate less than 15 mL/min/1.73 m^2 or chronic dialysis were excluded.

Interventions: None.

Measurements and Main Results: Of 1,940 patients included in the study, 615 patients (31.7%) had hyperchloremia (Cl ≥ 110 mEq/L) on ICU admission. All-cause hospital mortality was the dependent variable. Cl on ICU admission (Cl_0), Cl at 72 hours (Cl_{72}), and delta Cl ($\Delta Cl = Cl_{72} - Cl_0$) were the independent variables. Those with Cl_0 greater than or equal to 110 mEq/L were older and had higher cumulative fluid balance, base deficit, and Sequential Organ Failure Assessment scores. Multivariate analysis showed that higher

CCM,2015,43,1938

TABLE 3. Multivariate Analysis of Hospital Mortality as the Dependent Variable Among Hyperchloremic Patients at the Time of ICU Admission ($Cl_0 \geq 110$ mEq/L) for 1) Serum Chloride at the Time of ICU Admission, 2) Serum Chloride at 72 Hours of ICU Stay, and 3) Within-Subject Time-Related Change in Serum Chloride From ICU Admission to 72 Hours (ΔCl)

	Multivariate Model for Cl_0		Multivariate Model for Cl_{72}		Multivariate Model for ΔCl	
Variable	Odds Ratio Hospital Mortality	*p*	Odds Ratio Hospital Mortality	*p*	Odds Ratio Hospital Mortality	*p*
Cl_0 (per 5 mEq/L)	0.84 (0.65–1.07)	0.16	–	–	–	–
Cl_{72} (per 5 mEq/L)	–	–	1.27 (1.02–1.59)	0.03[a]	–	–
ΔCl (per 5 mEq/L)	–	–	–	–	1.37 (1.11–1.69)	0.003[a]

Cl_0 = serum chloride at the time of ICU admission, Cl_{72} = serum chloride at 72 hr of ICU stay, $\Delta Cl = Cl_{72} - Cl_0$.

[a]Statistically significant, $p < 0.05$.

Multivariate models adjusted for age, gender, hypertension, acute kidney injury (Kidney Disease Improving Global Outcomes serum creatinine–based criteria), oliguria, cumulative fluid balance, vasopressor or inotrope requirements, mechanical ventilation, Sequential Organ Failure Assessment (SOFA) score, and base deficit. Multivariate models included all variables associated with hospital mortality on univariate analysis at $p < 0.10$. Acute Physiology and Chronic Health Evaluation II was not included in the multivariate model because of collinearity with the SOFA score.

Conclusions: In critically ill septic patients manifesting hyperchloremia (Cl ≥ 110 mEq/L) on ICU admission, higher Cl levels and within-subject worsening hyperchloremia at 72 hours of ICU stay were associated with all-cause hospital mortality. These associations were independent of base deficit, cumulative fluid balance, acute kidney injury, and other critical illness parameters. (*Crit Care Med* 2015; 43:1938–1944)

REVIEW

Are all fluids bad for the kidney?

Johan Mårtensson[a,b] *and Rinaldo Bellomo*[a,c]

Purpose of review
To describe the harmful effects of intravenous fluids on kidney structure and function and summarize recent comparisons between different fluids and their effect on kidney outcome.

Recent findings
Administration of intravenous fluids may contribute to the development and sustention of acute kidney injury. In excess, fluids cause kidney interstitial edema and venous congestion, which prevents renal blood flow and glomerular filtration rate. In contrast to balanced crystalloids, chloride-rich solutions impair renal blood flow via autoregulatory mechanisms. Synthetic colloids, such as hydroxyethyl starches, gelatins, and dextrans are potentially nephrotoxic because they can cause osmotic nephrosis, which, in susceptible patients, might precede permanent kidney damage. Albumin solutions appear well tolerated to use in septic patients, although their renal efficacy over balanced crystalloids is not established. In contrast, administration of albumin solutions to patients with decompensated liver failure effectively prevents and ameliorates hepatorenal syndrome.

Summary
Being nephrotoxic, synthetic colloids should be avoided in patients with reduced renal reserve, such as in critically ill patients and in patients with preexisting renal dysfunction. Suggested adverse effects with chloride-rich solutions need confirmation from ongoing trials. Albumin solutions are well tolerated in patients with sepsis and/or liver failure and improve outcomes in the latter.

Keywords
acute kidney injury, colloids, crystalloids, dextrans, gelatins, hydroxyethyl starches

Table 1. Electrolyte composition and osmolality of human plasma and widely available crystalloid solutions

	Human plasma	0.9% saline	Ringer's lactate[a]	Ringer's acetate[b]	Plasmalyte[c]	Jonosteril[b]	Sterofundin[a]
Sodium (mmol/l)	142	154	130	131	140	137	145
Potassium (mmol/l)	4.5		4	4	5	4	4
Calcium (mmol/l)	2.5		3	2		1.7	2.5
Magnesium (mmol/l)	1.25			1	1.5	1.3	1
Chloride (mmol/l)	103	154	110	110	98	110	127
Bicarbonate (mmol/l)	24						
Lactate (mmol/l)	1.5		28				
Acetate (mmol/l)				30	27	37	24
Gluconate (mmol/l)					23		
Malate (mmol/l)							5
Osmolality[d] (mosm/kg) H_2O	290	308	275	270	295	291	309

[a]B Braun (Melsungen, Germany).
[b]Fresenius Kabi (Bad Homburg, Germany).
[c]Baxter International (Deerfield, Illinois, USA).
[d]Calculated osmolality for the different solutions. Actual osmolality is lower.

Table 2. Saline compared to balanced solutions and kidney outcome

Reference	Design	Population	N	Balanced fluid	Chloride rich	Kidney outcome
[24]	Before-and-after	General ICU	1533	Chloride-poor	Chloride-rich	Lower AKI incidence and lower need for RRT during chloride-poor period
[5]	RCT	Healthy volunteers	12	Plasmalyte	0.9% saline	Reduced kidney perfusion and urine output with saline
[25]	Retrospective	DKA	23	Plasmalyte	0.9% saline	Lower urine output with saline. Similar changes in serum creatinine
[26]	Retrospective	Major abdominal surgery	3704	Plasmalyte	0.9% saline	Increased need for RRT with saline
[27]	RCT	DKA	54	Ringer's lactate	0.9% saline	Similar changes in serum creatinine
[28]	RCT	Kidney transplantation	74	Ringer's lactate	0.9% saline	Higher postoperative serum creatinine with saline. Similar urine output
[29]	Observational	Dehydration due to diarrhea	40	Ringer's lactate	0.9% saline	Similar changes in serum creatinine
[30]	RCT	Kidney transplantation	60	Plasmalyte	0.9% saline	Postoperative serum creatinine, urine output and incidence of graft failure were similar
[31▪]	RCT	Trauma	65	Plasmalyte	0.9% saline	Nonsignificant trend towards higher urine output in the first 6 h and lower delta creatinine within the first 5 days with Plasmalyte
[32▪▪]	Retrospective	Sepsis	6730	Balanced crystalloid + 0.9% saline	0.9% saline	Similar incidence of acute renal failure with or without need for dialysis. Balanced fluids associated with lower in-hospital mortality

AKI, acute kidney injury; DKA, diabetic ketotic acidosis; RCT, randomized controlled trial; RRT, renal replacement therapy.

Table 1. Commonly used crystalloid solutions (all concentrations in mmol/l)

	0.9% sodium chloride	Compound sodium lactate (Hartmann's)	Ringer's acetate	0.18% sodium chloride and 4% glucose	Plasma-Lyte
Na	154	130	145	30	140
K		4	4		5
Cl	154	109	127	30	98
Ca		2.7	2.5		
Mg			1		1.5
Glucose				222	
Lactate		28			
Malate			5		
Acetate			24		27
Gluconate					23
pH	4.5–7.0	5.0–7.0	5.1–5.9	3.5–6.5	4.0–6.5
Osmolality (mOsmol/kg water)	308	273	309	282	294
Cost (per 1 l in Australian dollars)	$1.14	$1.12	[a]	$1.88	$2.39
Storage conditions	Below 25 °C	Below 25 °C	Below 30 °C	Below 30 °C	Below 30 °C

[a]Cost not available in Australian dollars (original).

Plasma Lyte

Baxter

Isofundine

Sterofundin

BBraun


One Litre Single-Dose Container No.1583WC
NORMAL SALINE
(SODIUM CHLORIDE INJECTION)


Baxter
FE0324
Viaflo
1000 ml
Plasma–Lyte 148 (pH 7.4)
Plasma–Lyte 148 (pH 7.4)
Solution for Infusion
Solution for infusion
Single Dose
Isotonic
pH 6.5 – 8.0
Osmolarity 295 mOsm/l (approx)
Sterile free from bacterial endotoxins
Formula per 1000 ml
Sodium Chloride 5.26 g
Potassium Chloride 0.37 g
Magnesium Chloride hexahydrate 0.30 g
Sodium Acetate trihydrate 3.68 g
Sodium Gluconate 5.02 g
Water for Injections qs
Sodium hydroxide qs pH
mmol per 1000 ml (approx)
Sodium 140 Chloride 98
Potassium 5 Acetate 27
Magnesium 1.5 Gluconate 23
For intravenous administration
Rapid infusion may be harmful
Store out of reach and sight of children
Do not use unless solution is clear without visible particles and container undamaged
Check additive compatibility with both the solution and container prior to use
Thorough and careful aseptic mixing of any additive is mandatory
Do not remove from overwrap until ready for use
Discard any unused portion after first use
Do not reconnect partially used bags
For use under medical supervision
POM
PL0116/0332
UN-35-01-383
Baxter Healthcare Ltd
Thetford Norfolk
IP24 3SE
United Kingdom
5 413760 228242
Lot
Expiry


Sterofundin ISO 1/1 E
1000 ml
B BRAUN
Sterofundin ISO


Baxter
ALBUMINE HUMAINE
BAXTER BIOSCIENCE
200 g/l
Solution pour perfusion
100 ml

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

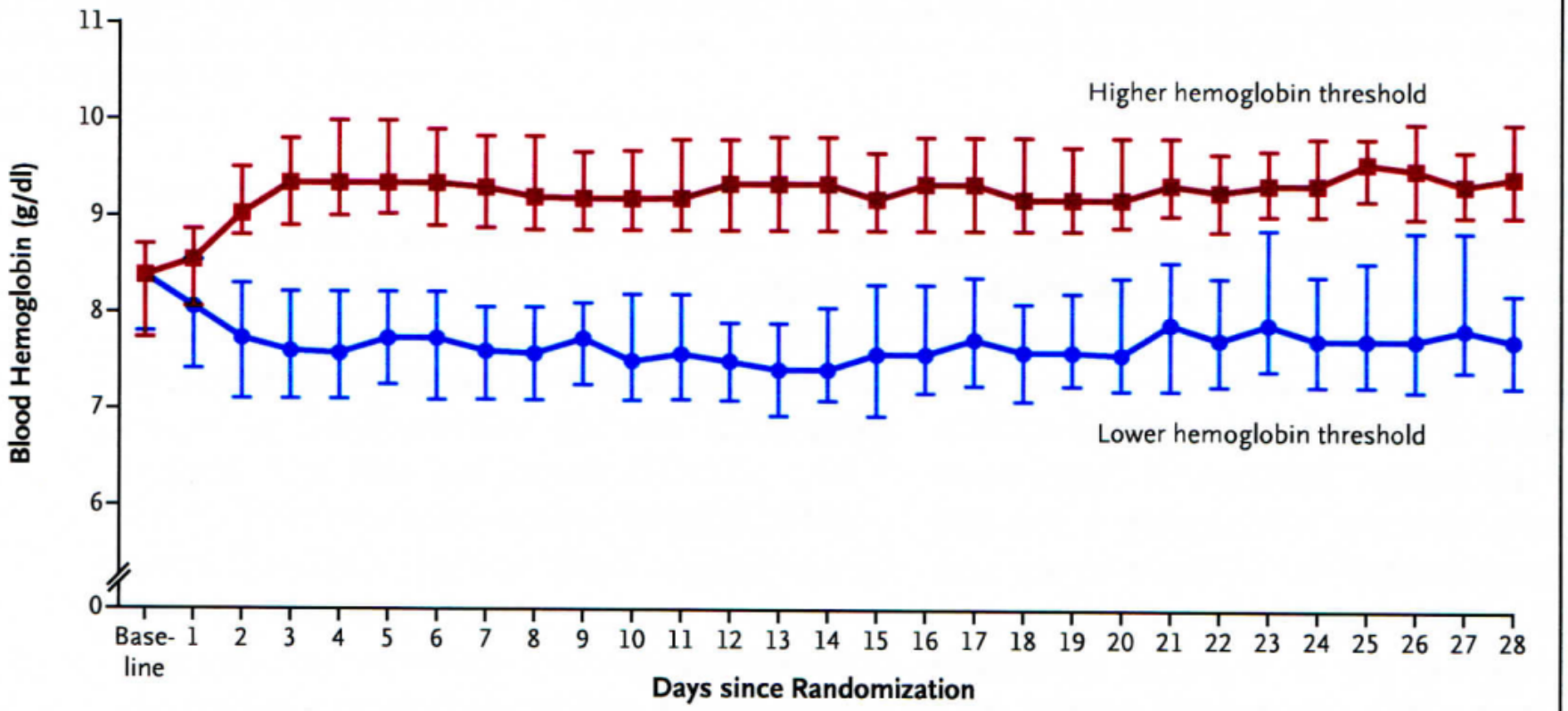
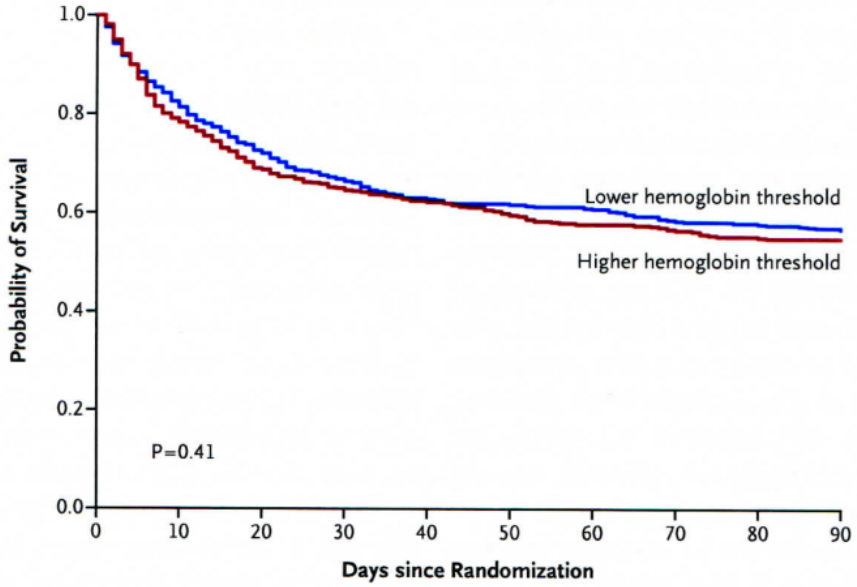


Figure 2. Blood Hemoglobin Levels in Patients in the ICU at Baseline and after Randomization.

The graphs show the median daily lowest levels of blood hemoglobin in the lower-threshold group and the higher-threshold group. Baseline values were the lowest blood hemoglobin level measured in the 24 hours before randomization. Day 1 was defined as the time of randomization to the end of that day and lasted a median of 15 hours in the lower-threshold group and 14 hours in the higher-threshold group. The I bars indicate the 25th and 75th percentiles.

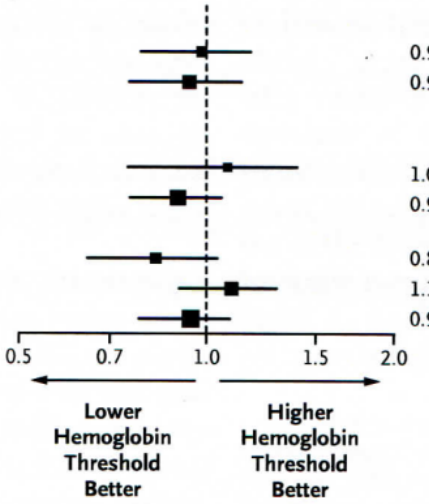
A Time to Death



No. at Risk				
Lower hemoglobin threshold	502	334	306	286
Higher hemoglobin threshold	496	321	287	273

B Relative Risk of the Primary Outcome

Subgroup	Lower Hemoglobin Threshold	Higher Hemoglobin Threshold	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. of patients in subgroup			
Age				0.85
>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				0.25
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				0.06
>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)	



VASOPRESSEURS

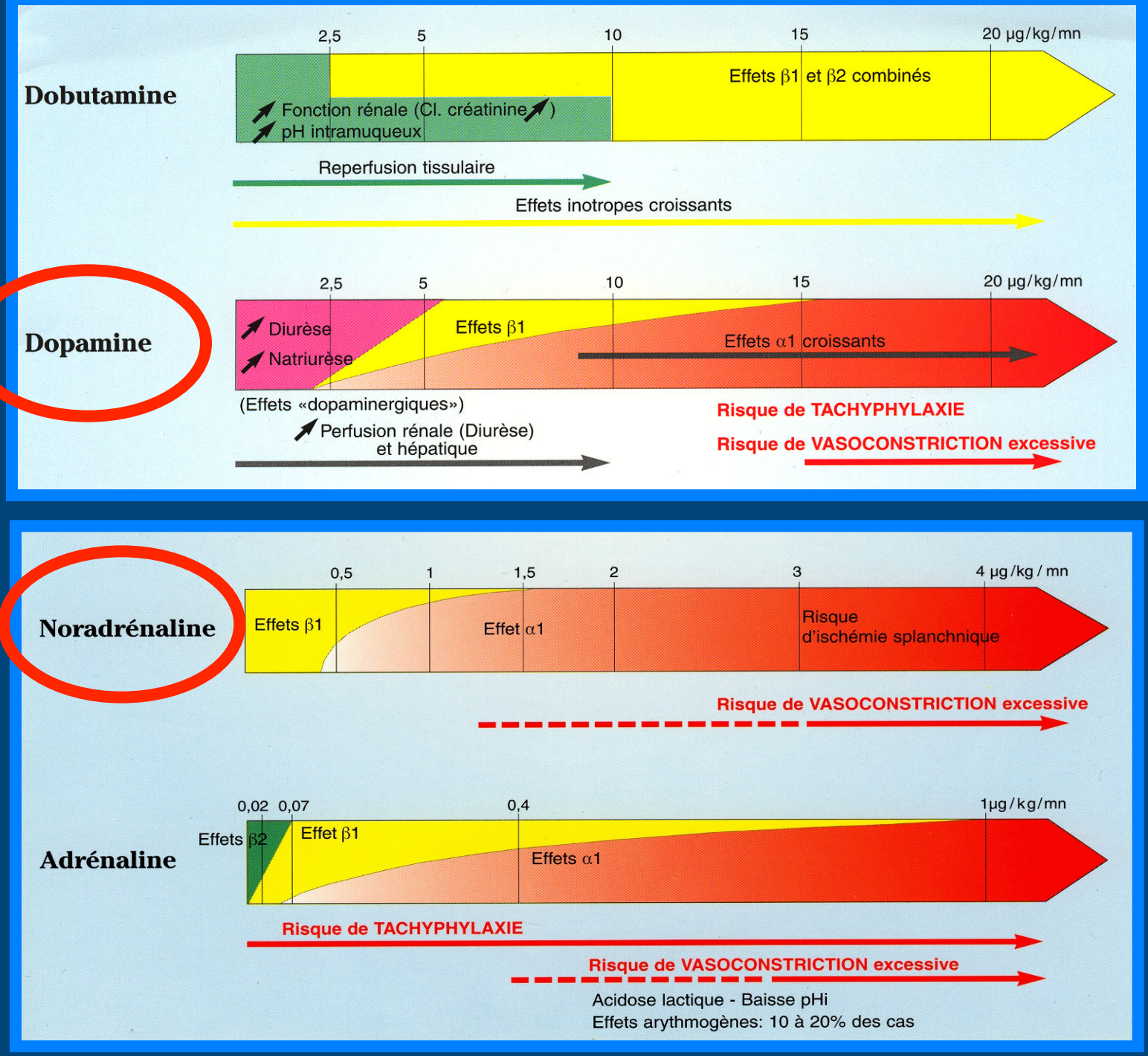
Dopamine

Epinephrine

Norepinephrine

Vasopressine

Terlipressine


Dobutamine
2,5
5
10
15
20 µg/kg/mn
Effets β1 et β2 combinés
Fonction rénale (Cl. créatinine)
pH intramuqueux
Reperfusion tissulaire
Effets inotropes croissants
Dopamine
2,5
5
10
15
20 µg/kg/mn
Diurèse
Natriurèse
Effets β1
Effets α1 croissants
(Effets «dopaminergiques»)
Perfusion rénale (Diurèse)
et hépatique
Risque de TACHYPHYLAXIE
Risque de VASOCONSTRICTION excessive
Noradrénaline
0,5
1
1,5
2
3
4 µg/kg/mn
Effets β1
Effet α1
Risque
d'ischémie splanchnique
Risque de VASOCONSTRICTION excessive
Adrénaline
0,02
0,07
0,4
1µg/kg/mn
Effets β2
Effet β1
Effets α1
Risque de TACHYPHYLAXIE
Risque de VASOCONSTRICTION excessive
Acidose lactique - Baisse pHi
Effets arythmogènes: 10 à 20% des cas

Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis

Daniel De Backer, MD, PhD; Cesar Aldecoa, MD; Hassane Njimi, MSc, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Objectives: There has long-been controversy about the possible superiority of norepinephrine compared to dopamine in the treatment of shock. The objective was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock.

Data Sources: A systematic search of the MEDLINE, Embase, Scopus, and CENTRAL databases, and of Google Scholar, up to June 30, 2011.

Study Selection and Data Extraction: All studies providing information on the outcome of patients with septic shock treated with dopamine compared to norepinephrine were included. Observational and randomized trials were analyzed separately. Because time of outcome assessment varied among trials, we evaluated 28-day mortality or closest estimate. Heterogeneity among trials was assessed using the Cochrane Q homogeneity test. A Forest plot was constructed and the aggregate relative risk of death was computed. Potential publication bias was evaluated using funnel plots.

Methods and Main Results: We retrieved five observational (1360 patients) and six randomized (1408 patients) trials, totaling 2769 patients (1474 who received norepinephrine and 1295 who received dopamine). In observational studies, among which there was significant heterogeneity ($p < .001$), there was no difference in mortality (relative risk, 1.09; confidence interval, 0.84–1.41; $p = .72$). A sensitivity analysis identified one trial as being responsible for the heterogeneity; after exclusion of that trial, no heterogeneity was observed and dopamine administration was associated with an increased risk of death (relative risk, 1.23; confidence interval, 1.05–1.43; $p < .01$). In randomized trials, for which no heterogeneity or publication bias was detected ($p = .77$), dopamine was associated with an increased risk of death (relative risk, 1.10; confidence interval, 1.01–1.20; $p = .035$). In the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (relative risk, 2.34; confidence interval, 1.46–3.77; $p = .001$).

Conclusions: In patients with septic shock, dopamine administration is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration. (Crit Care Med 2012; 40:000–000)

KEY WORDS: ●●●

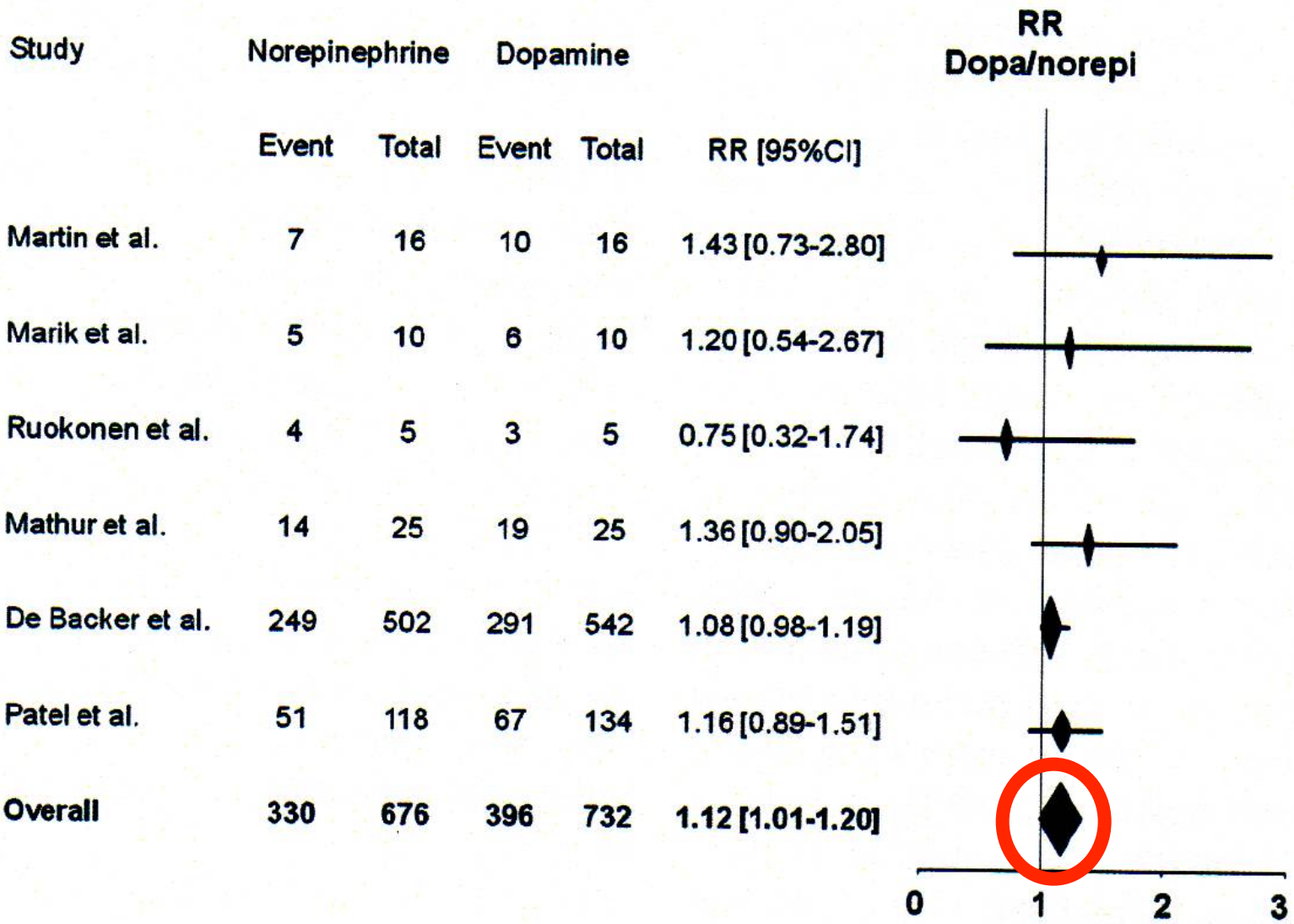


Figure 3. Forest plot of risk ratio (*RR*) of death (28 days or nearest estimate) in interventional trials. The p value for aggregate RR of dopamine (*dopa*) compared to norepinephrine (*norepi*) in interventional studies was .035. Relative weights of the different trials in the analysis: Martin et al (27) 2%; Marik et al (30) 1%; Ruokonen et al (29) 1%; Mathur et al (25) 4%; De Backer et al (15) 81%; and Patel et al (16) 10%. No heterogeneity was observed ($p = .77$; $I^2 = 0$; confidence interval, 0%–25%).

Physicians no longer should consider dopamine for septic shock!*

The 2008 Surviving Sepsis campaign recommended the use of dopamine or norepinephrine as the first vasopressor to be used in patients with fluid refractory sepsis (1). These recommendations were based on theoretical considerations and observations from cohort studies or small controlled trials. Nevertheless, if one considers that in most cases fluid-resuscitated septic shock is characterized by high cardiac index and low peripheral vascular resistance (2), one would admit that correction of vasodilatation may be much more important than increasing further cardiac index. In addition, in the intensive care unit, sepsis is one of the main conditions independently associated with an increased risk for life-threatening arrhythmias (3), a complication that is aggravated by β-adrenergic drugs. Then, theoretically α-agonists should be preferred to β-agonists. Norepinephrine is a more powerful α-agonist than dopamine and has much less β-agonist activity. In practice, recently, two relatively large trials reported nonsignificant lower 28-day mortality risk with norepinephrine compared to dopamine (risk difference −0.04; 95% confidence interval [CI] −0.09 to 0.01; and relative risk 0.07; 95% CI −0.19 to 0.06, respectively) (4, 5). In these trials, there were significantly lower risks of supraventricular arrhythmias (risk difference −0.10; 95% CI −0.13 to −0.06; and risk difference 0.30; 95% CI −0.39 to −0.20, respectively). Likewise the risk difference for ventricular arrhythmias favored norepinephrine (risk difference −0.02; 95% CI −0.04 to −0.01; and risk difference 0.05; 95% CI −0.09 to −0.01, respectively). In this issue of *Critical Care Medicine*, Dr. De Backer and colleagues combined information from five observational (n = 1360) and six randomized (n = 1408) trials of dopamine vs. norepinephrine (6). Then, there was no significant difference in mortality between dopamine and norepinephrine (relative risk, 1.11; 95% CI 0.97–1.27). However, when pooling only the six randomized trials, the relative risk of death was 0.91 (95% CI 0.83–0.99) in favor of norepinephrine, with no heterogeneity across studies (I_2 = 0%). Sensitivity analyses removing the trial from Dr. De Backer and colleagues, which included septic shock and nonseptic shock, or the trial by Patel et al (5), which was not blinded, yielded larger CIs but similar point estimates (0.84; 95% CI 0.68–1.02; and 0.91; 95% CI 0.83–1.00). In addition, data for the risk of arrhythmias were available only for two trials (4, 5). The relative risk of supraventricular and ventricular arrhythmias was 0.36 (95% CI 0.15–0.85) and 0.37 (95% CI 0.20–0.69), respectively, in favor of norepinephrine. Finally, there is some evidence that β-1 adrenergic drugs may increase circulating levels of proinflammatory cytokines, an effect not seen with norepinephrine (7). In practice, physicians should take into account the evidence accumulated from the six randomized trials (6) and should consider using norepinephrine as the first-choice vasopressor for sepsis.

There are insufficient data to draw conclusion against the use of dopamine in children with septic shock. In theory, by activating β-adrenergic receptors, dopamine may improve systolic function. In fact, dopamine dose-dependently improved chronotropy, inotropy, and lusitropy of septic rat hearts (8). Then, physicians may still use dopamine in patients with septic shock and a cardiac index of <2.5L/min/m^2, and/or inappropriately low heart rate, i.e., heart rate <90 beats per minutes while systolic blood pressure is <90 mm Hg. Finally, in rare cases in which a central venous line is not in place, infusion via a peripheral vein is safer for dopamine than for norepinephrine.

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*See also p. 725.

Key Words: arrhythmias; evidence-based medicine; mortality; sepsis; vasopressors

The author has not disclosed any potential conflicts of interest.

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PAM :

65-75-85

mmHg ???

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

ABSTRACT

BACKGROUND

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

METHODS

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

RESULTS

At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; P=0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; P=0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; P=0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

CONCLUSIONS

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Asfar at the Department of Medical Intensive Care and Hyperbaric Medicine, University Hospital of Angers, 4 rue Larrey, F-49933 Angers Cedex 9, France, or at piasfar@chu-angers.fr.

*Additional investigators in the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial are listed in the Supplementary Appendix, available at NEJM.org.

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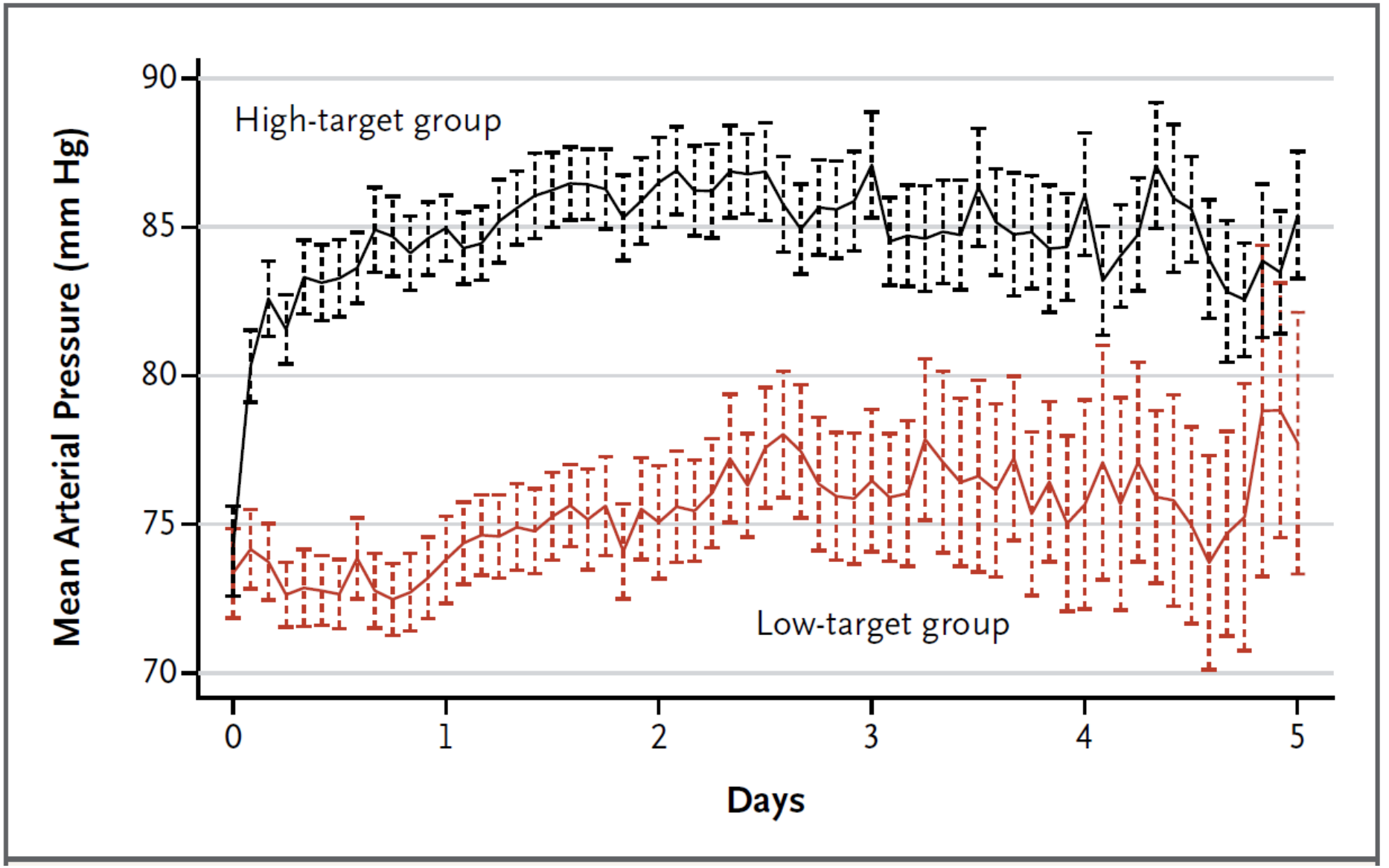
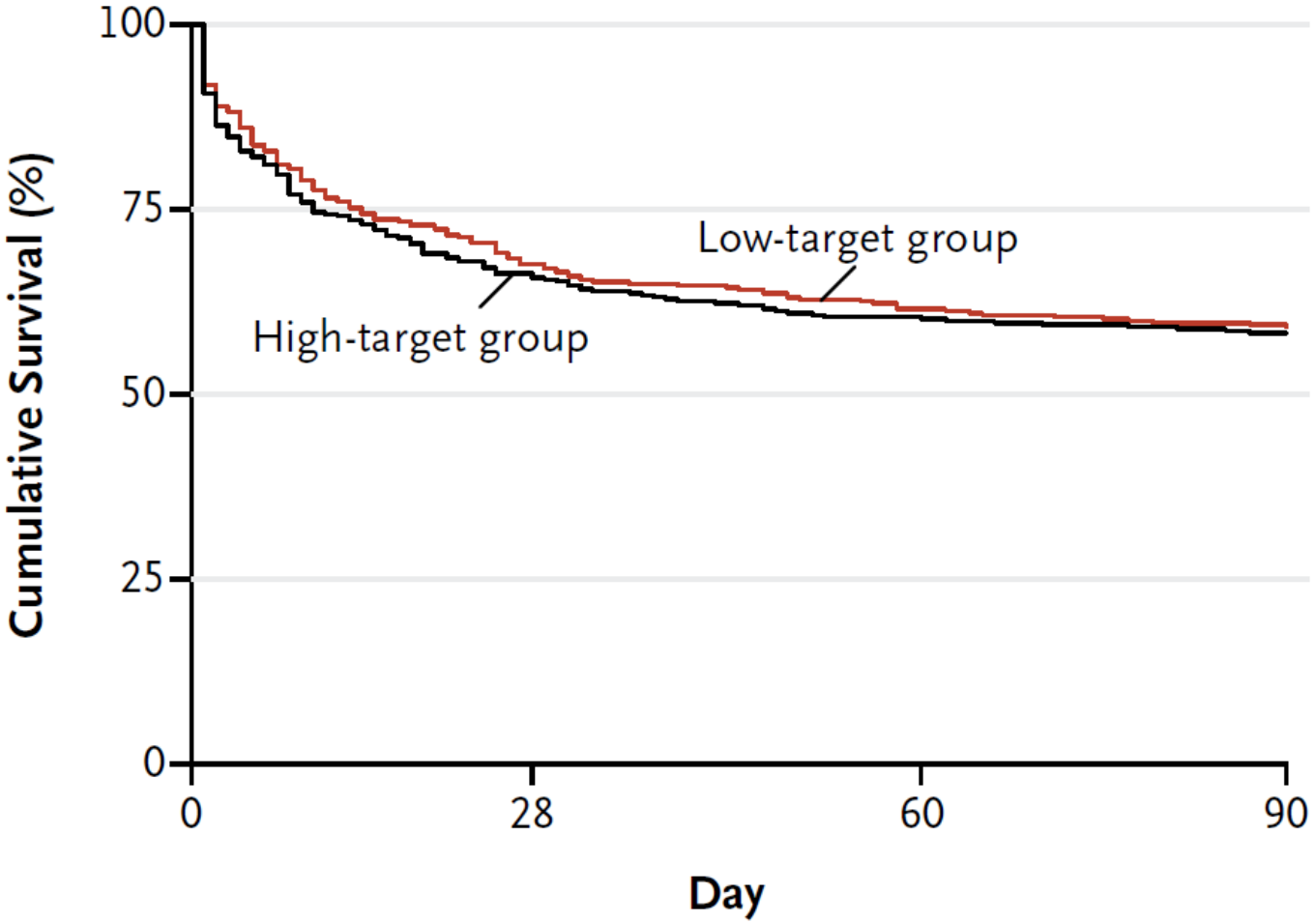

Mean Arterial Pressure (mm Hg)
90
85
80
75
70
High-target group
Low-target group
0
1
2
3
4
5
Days



No. at Risk

Low target	379	256	233	225
High target	375	249	227	219

ABSTRACT

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RESULTS

At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; P=0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; P=0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; P=0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

CONCLUSIONS

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*Additional investigators in the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial are listed in the Supplementary Appendix, available at NEJM.org.

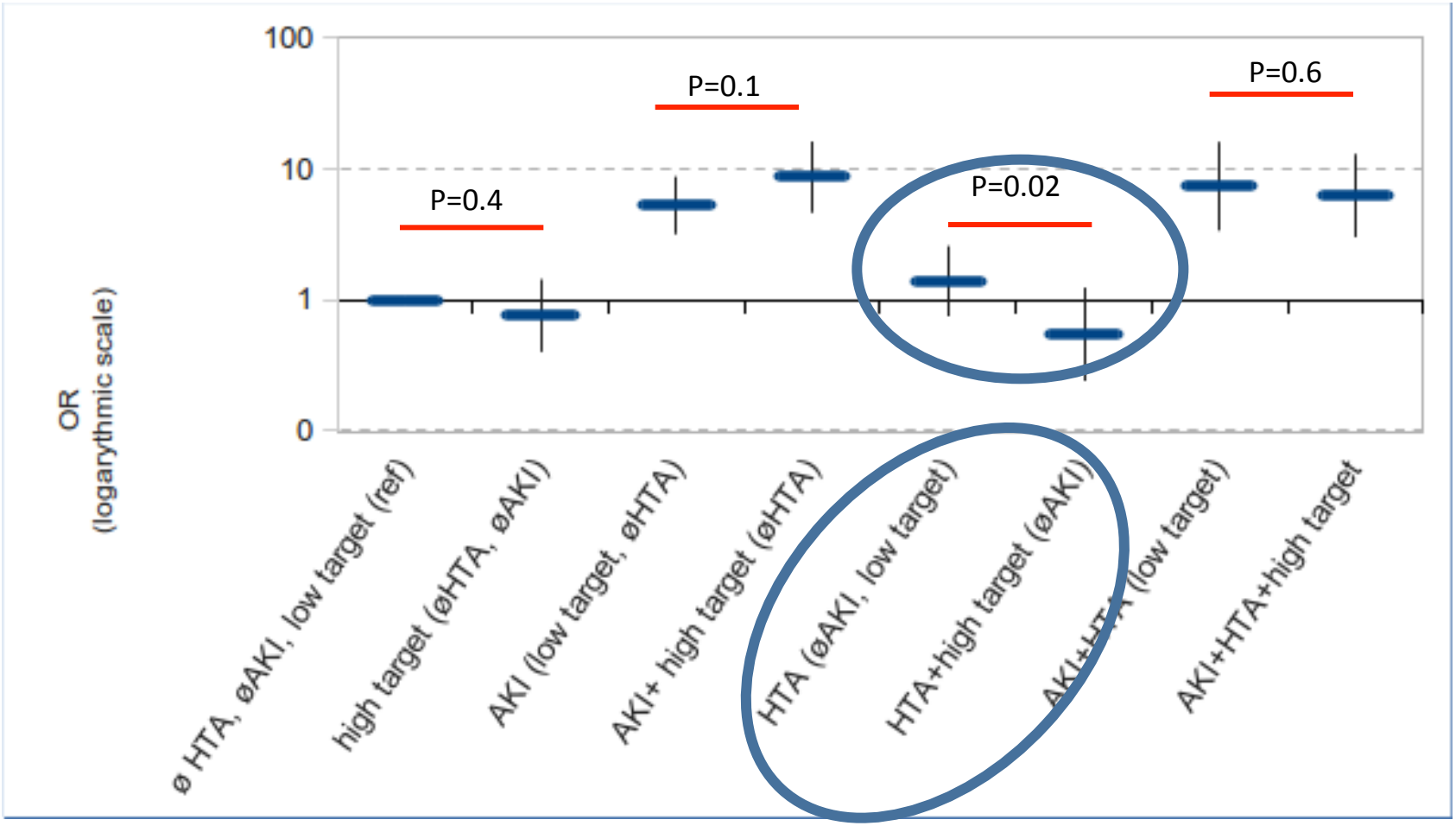
This article was published on March 18, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1312173

NS mortality

Serious adverse events — no. (%)	Lower	Higher	
Any	69 (17.8)	74 (19.1)	0.64
Acute myocardial infarction§	2 (0.5)	7 (1.8)	0.18
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02
Ventricular fibrillation or tachycardia	15 (3.9)	22 (5.7)	0.24
Digital ischemia	9 (2.3)	10 (2.6)	0.82
Mesenteric ischemia	9 (2.3)	9 (2.3)	1.00
Bleeding	42 (10.8)	31 (8.0)	0.22

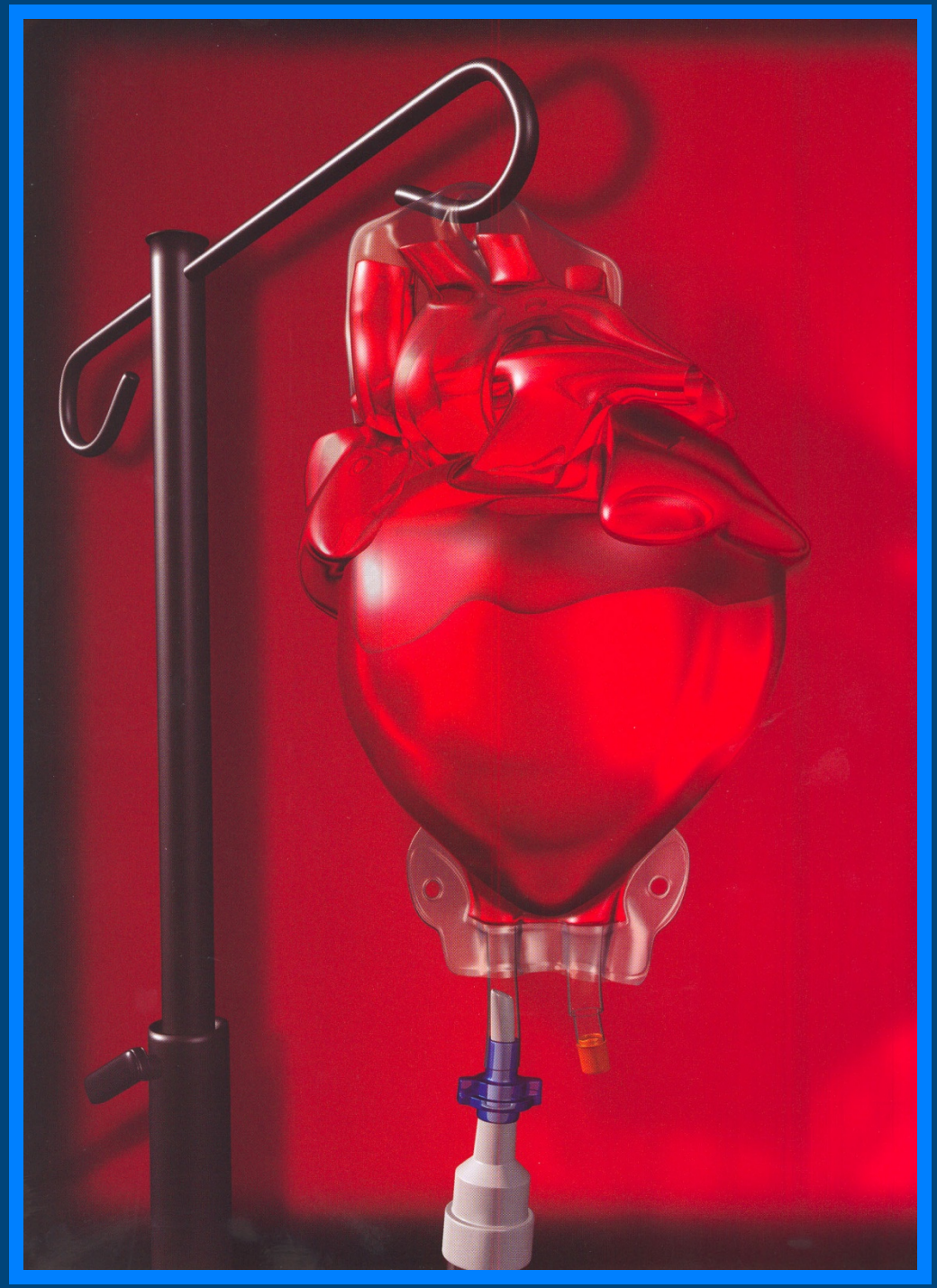
Risk of renal replacement requirement between inclusion Day 7 according to MAP, chronic hypertension and renal failure (renal SOFA≥2) at inclusion.



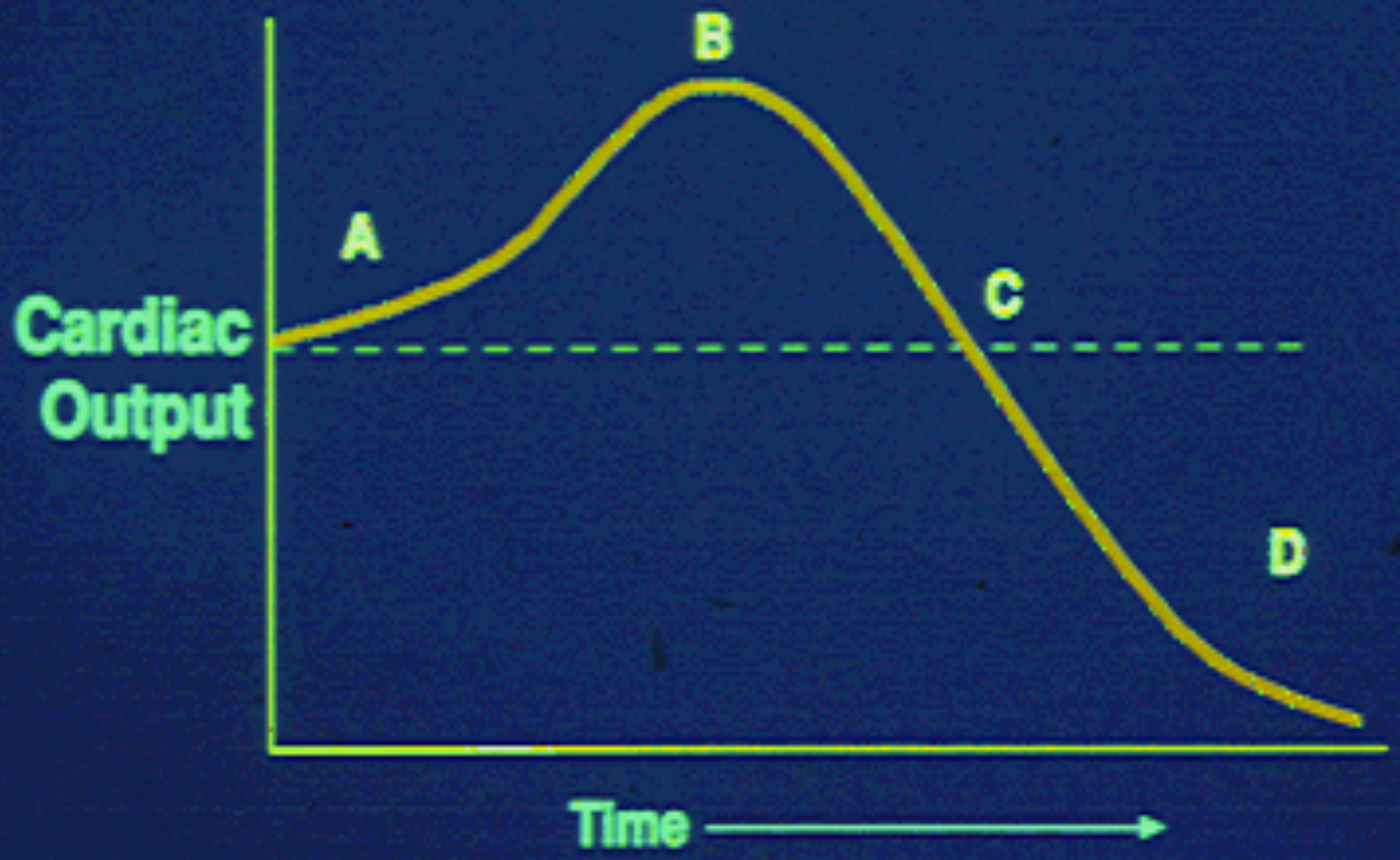
Personal data

PAM :

65 mmHg



Natural History of Septic Hemodynamics



Septic shock. Inotropic Therapy

. **Dobutamine** is the first choice for patients with **low CO (< 2.5 l/min/m2)**

- ➔ after fluid resuscitation
- ➔ after an adequate MAP

. Dobutamine may cause **hypotension** and /or **tachycardia in some patients:**

- ➔ especially those with low filling pressure

Task Force of the SCCM. Crit. Care Med 2004,32,1928-1948

Initial Resuscitation

- PAM ≥ 65 mmHg
- PVC 8-12 mmHg

DH ≥ 0,5 $ml.kg^{-1}.hr^{-1}$

- $ScvO_2 \geq 70\%$
- $SvO_2 \geq 65\%$

LACTATE

OU

SvO2

????????

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

A Randomized Clinical Trial

Alan E. Jones, MD
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Stephen Trzeciak, MD, MPH
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for the Emergency Medicine Shock Research Network (EMShockNet) Investigators

Context Goal-directed resuscitation for severe sepsis and septic shock has been reported to reduce mortality when applied in the emergency department.

Objective To test the hypothesis of noninferiority between lactate clearance and central venous oxygen saturation ($ScvO_2$) as goals of early sepsis resuscitation.

Design, Setting, and Patients Multicenter randomized, noninferiority trial involving patients with severe sepsis and evidence of hypoperfusion or septic shock who were admitted to the emergency department from January 2007 to January 2009 at 1 of 3 participating US urban hospitals.

Interventions We randomly assigned patients to 1 of 2 resuscitation protocols. The $ScvO_2$ group was resuscitated to normalize central venous pressure, mean arterial pressure, and $ScvO_2$ of at least 70%; and the lactate clearance group was resuscitated to normalize central venous pressure, mean arterial pressure, and lactate clearance of at least 10%. The study protocol was continued until all goals were achieved or for up to 6 hours. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment.

Main Outcome Measure The primary outcome was absolute in-hospital mortality rate; the noninferiority threshold was set at Δ equal to −10%.

Results Of the 300 patients enrolled, 150 were assigned to each group and patients were well matched by demographic, comorbidities, and physiological features. There were no differences in treatments administered during the initial 72 hours of hospitalization. Thirty-four patients (23%) in the $ScvO_2$ group died while in the hospital (95% confidence interval [CI], 17%-30%) compared with 25 (17%; 95% CI, 11%-24%) in the lactate clearance group. This observed difference between mortality rates did not reach the [illegible] (intent-to-treat analysis: 95% CI for the 6% difference, −3% to 15%). There were no differences in treatment-related adverse events between the groups.

Conclusion Among patients with septic shock who were treated to normalize central venous and mean arterial pressure, additional management to normalize lactate clearance compared with management to normalize $ScvO_2$ did not result in significantly different in-hospital mortality.

Trial Registration clinicaltrials.gov Identifier: NCT00372502

THE RATE OF SEVERE SEPSIS HOSpitalizations has doubled during the last decade with estimates indicating that at least 750 000 persons are affected annually in the United States.[1-3] Approximately, 500 000 patients with severe sepsis in the United States annually are initially treated in emergency departments.[4] The Surviving Sepsis Campaign international consensus guidelines recommend protocol-driven treatment that uses quantitative resuscitation for emergency department patients with severe sepsis and septic shock.[5]

Quantitative resuscitation refers to the use of an explicit protocol that targets predefined physiological or laboratory goals to be achieved within the first several hours. This concept was

Table 5. Hospital Mortality and Length of Stay

Variable	Lactate Clearance Group (n = 150)	$ScvO_2$ Group (n = 150)	Proportion Difference (95% Confidence Interval)	*P* Value[b]
In-hospital mortality, No. (%)[a]				
Intent to treat	25 (17)	34 (23)	6 (–3 to 15)	
Per protocol	25 (17)	33 (22)	5 (–3 to 14)	
Length of stay, mean (SD), d				
ICU	5.9 (8.46)	5.6 (7.39)		.75
Hospital	11.4 (10.89)	12.1 (11.68)		.60
Hospital complications				
Ventilator-free days, mean (SD)	9.3 (10.31)	9.9 (11.09)		.67
Multiple organ failure, No. (%)	37 (25)	33 (22)		.68
Care withdrawn, No. (%)	14 (9)	23 (15)		.15

Abbreviations: ICU, intensive care unit; $ScvO_2$, central venous oxygen saturation.
[a] Primary study end point.
[b] Continuous data are compared using an unpaired *t* test; categorical variables, using the χ^2 test.

Critical Care

CRITICAL CARE

Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation

Critical Care 2011, **15**:R229 doi:10.1186/cc10469

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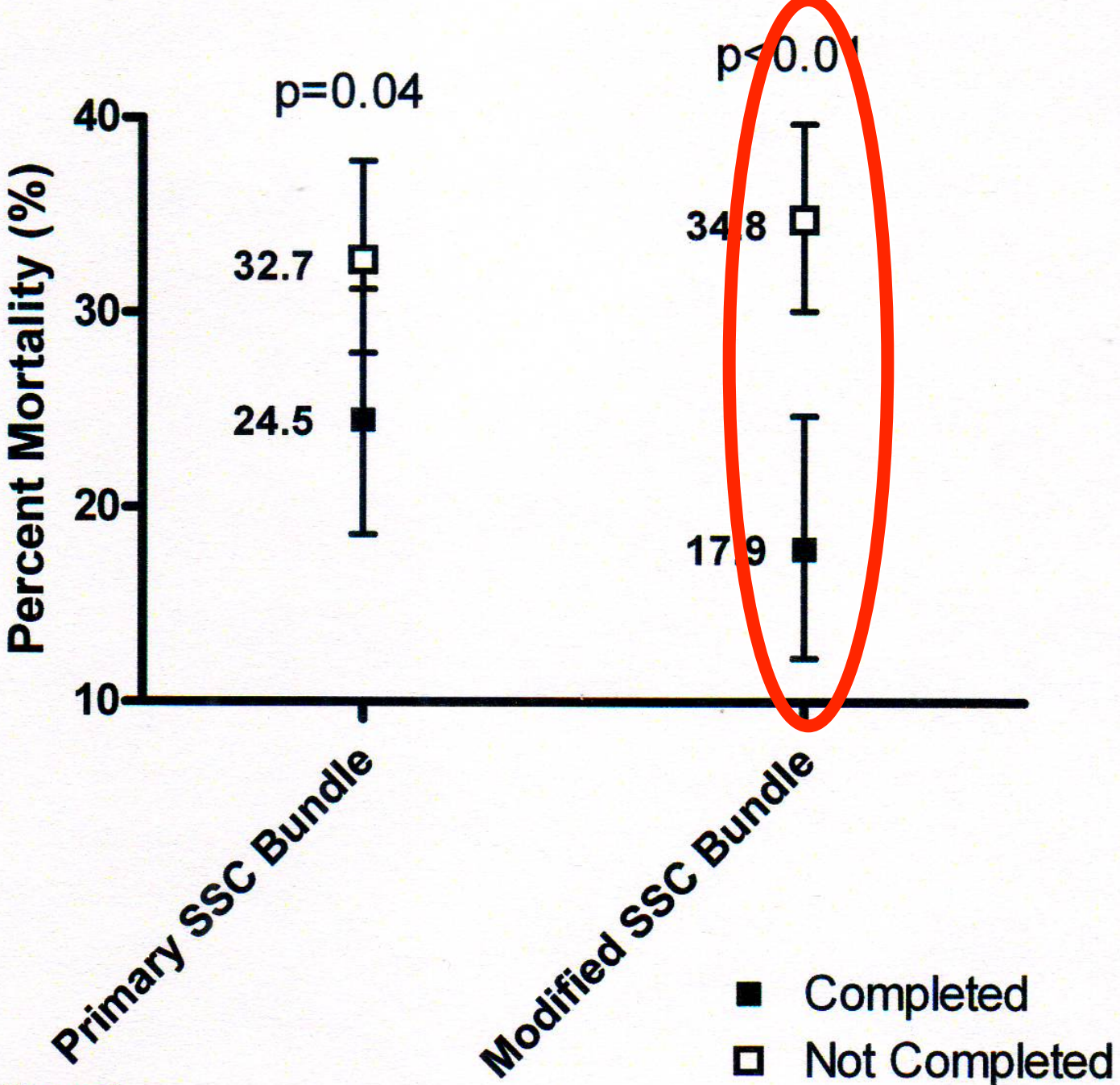

p=0.04
p<0.01
Percent Mortality (%)
40
30
20
10
32.7
24.5
34.8
17.9
Primary SSC Bundle
Modified SSC Bundle
Completed
Not Completed

Figure 2

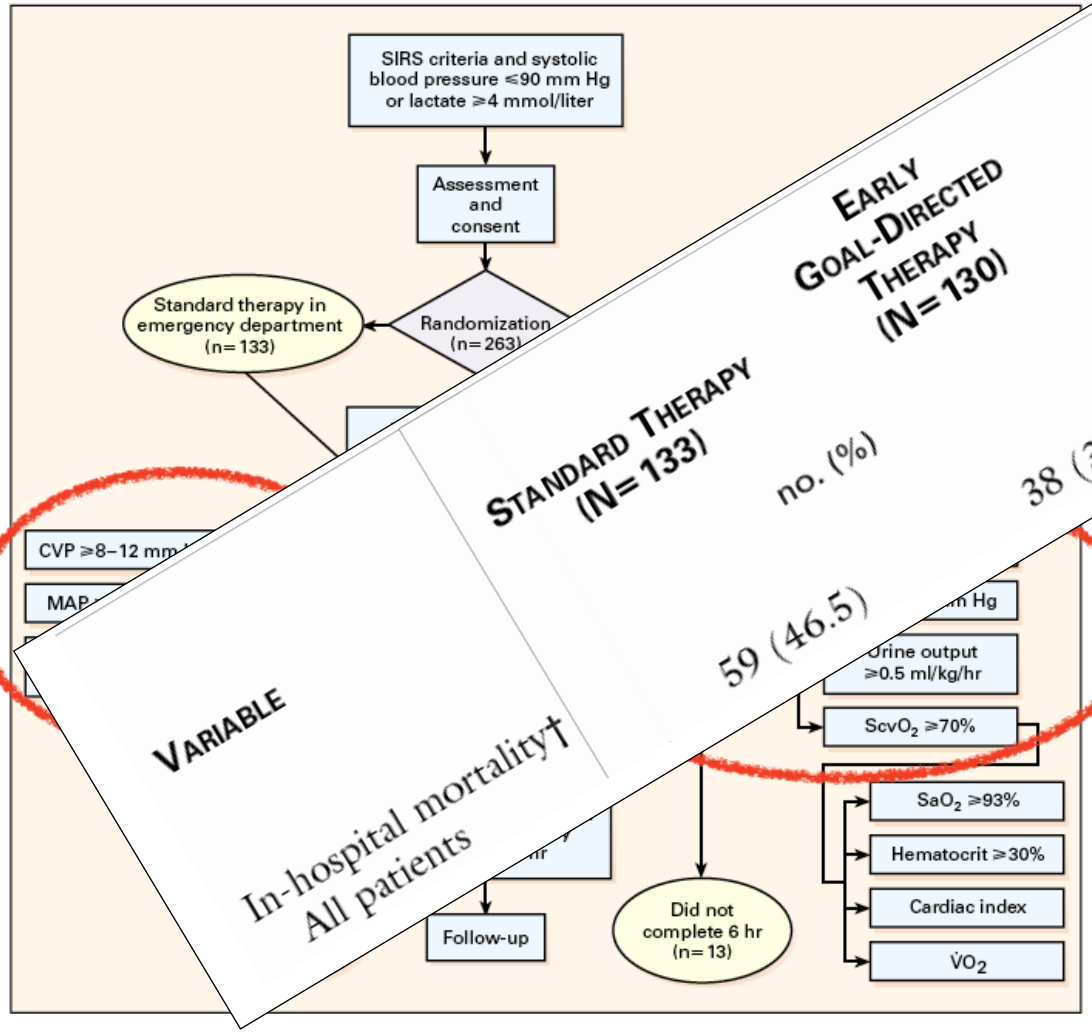
LACTATE

ou

SvO2

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE S
AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., J
ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND
FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE



VARIABLE	STANDARD THERAPY (N=133)	EARLY GOAL-DIRECTED THERAPY (N=130)	RELATIVE RISK (95% CI)	P VALUE
	no. (%)			
In-hospital mortality†	59 (46.5)	38 (30.5)	0.58 (0.38–0.87)	0.009
All patients				

N Engl J Med 2001;345:1368-77.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The ProCESS Investigators*

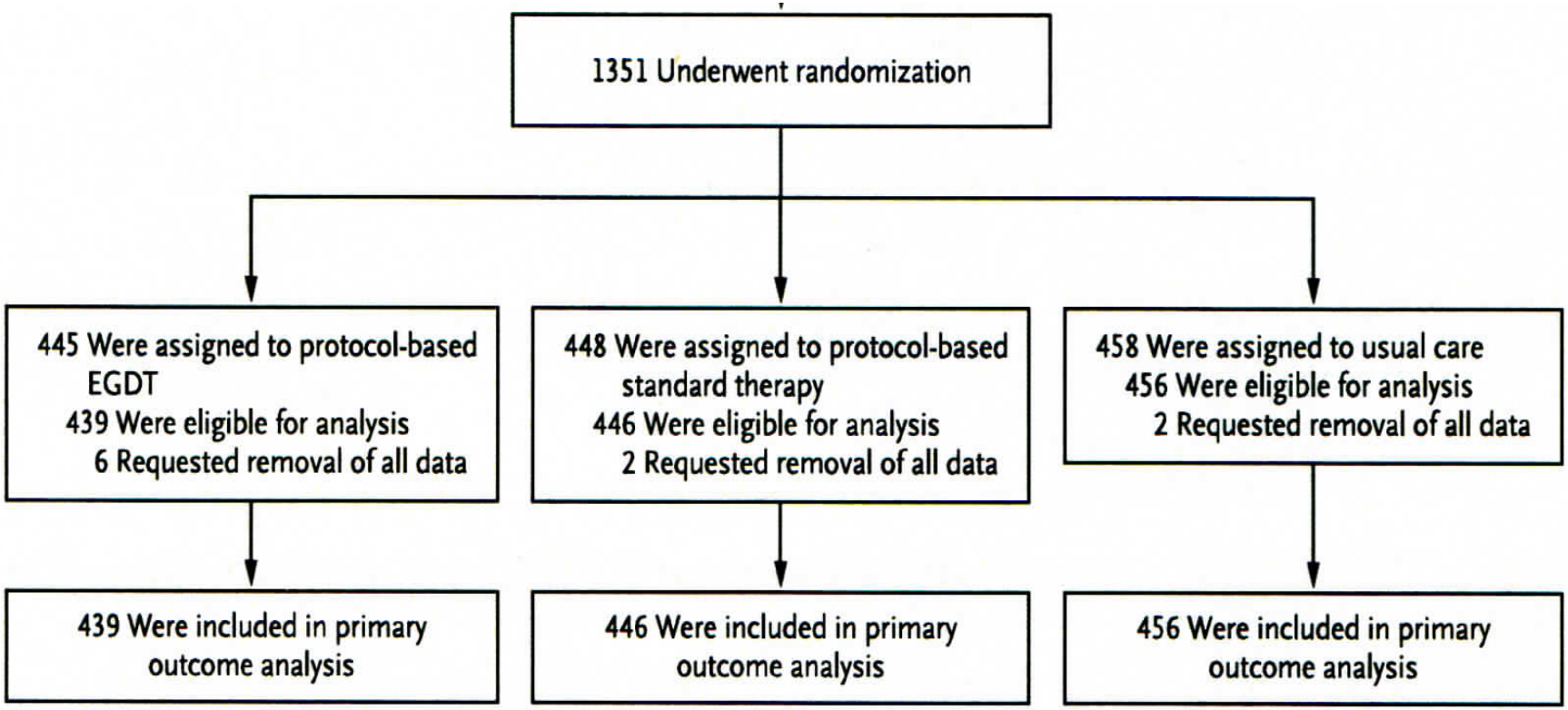


Figure 1. Screening, Randomization, and Follow-up.

EGDT denotes early goal-directed therapy, LAR legally authorized representative, and SIRS systemic inflammatory response syndrome.

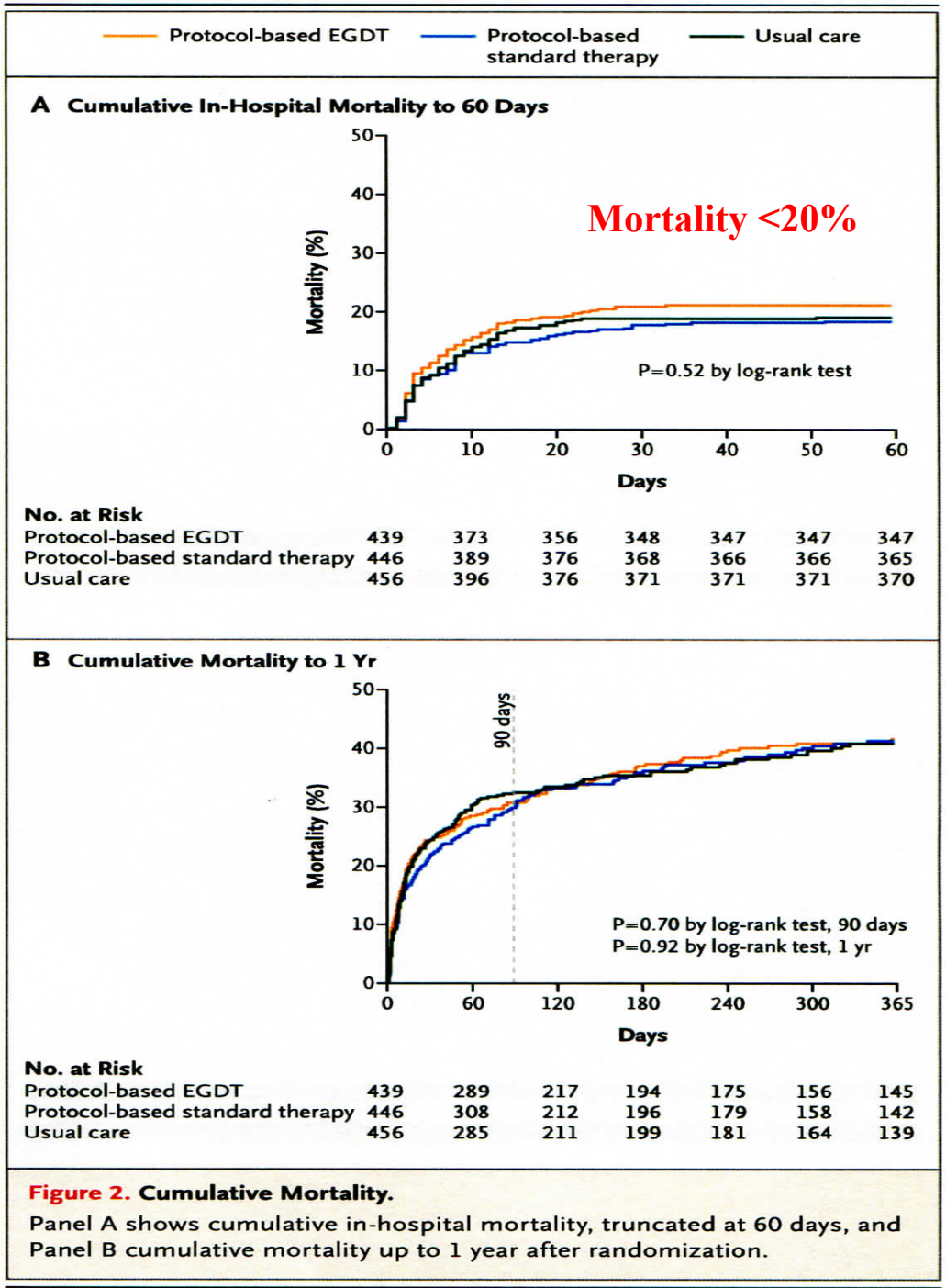


Figure 2. Cumulative Mortality.

Panel A shows cumulative in-hospital mortality, truncated at 60 days, and Panel B cumulative mortality up to 1 year after randomization.

36 %ventilated

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

ARISE Trial October 2014

The ARISE Investigators and the ANZICS Clinical Trials Group*

ABSTRACT

BACKGROUND

Early goal-directed therapy (EGDT) has been endorsed in the guidelines of the Surviving Sepsis Campaign as a key strategy to decrease mortality among patients presenting to the emergency department with septic shock. However, its effectiveness is uncertain.

METHODS

In this trial conducted at 51 centers (mostly in Australia or New Zealand), we randomly assigned patients presenting to the emergency department with early septic shock to receive either EGDT or usual care. The primary outcome was all-cause mortality within 90 days after randomization.

RESULTS

Of the 1600 enrolled patients, 796 were assigned to the EGDT group and 804 to the usual-care group. Primary outcome data were available for more than 99% of the patients. Patients in the EGDT group received a larger mean (±SD) volume of intravenous fluids in the first 6 hours after randomization than did those in the usual-care group (1964±1415 ml vs. 1713±1401 ml) and were more likely to receive vasopressor infusions (66.6% vs. 57.8%), red-cell transfusions (13.6% vs. 7.0%), and dobutamine (15.4% vs. 2.6%) ($P<0.001$ for all comparisons). At 90 days after randomization, 147 deaths had occurred in the EGDT group and 150 had occurred in the usual-care group, for rates of death of 18.6% and 18.8%, respectively (absolute risk difference with EGDT vs. usual care, −0.3 percentage points; 95% confidence interval, −4.1 to 3.6; $P=0.90$). There was no significant difference in survival time, in-hospital mortality, duration of organ support, or length of hospital stay.

CONCLUSIONS

In critically ill patients presenting to the emergency department with early septic shock, EGDT did not reduce all-cause mortality at 90 days. (Funded by the National Health and Medical Research Council of Australia and the Alfred Foundation; ARISE ClinicalTrials.gov number, NCT00975793.)

The members of the writing committee (Sandra L. Peake, M.D., Ph.D., Anthony Delaney, M.D., Ph.D., Michael Bailey, Ph.D., Rinaldo Bellomo, M.D., Peter A. Cameron, M.D., D. James Cooper, M.D., Alisa M. Higgins, M.P.H., Anna Holdgate, M.D., Belinda D. Howe, M.P.H., Steven A.R. Webb, M.D., Ph.D., and Patricia Williams, B.N.) assume responsibility for the overall content and integrity of the article. Address reprint requests to Ms. Belinda Howe at the Australian and New Zealand Intensive Care Research Centre, Alfred Centre, Level 6 (Lobby B), 99 Commercial Rd., Melbourne, VIC 3004, Australia, or at anzicrc@monash.edu.

*The Australasian Resuscitation in Sepsis Evaluation (ARISE) study is a collaboration of the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, the Australasian College for Emergency Medicine, and the Australian and New Zealand Intensive Care Research Centre. The affiliations of the writing committee members are listed in the Appendix. A complete list of investigators in the ARISE study is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 1, 2014, at NEJM.org.

DOI: 10.1056/NEJMoa1404380

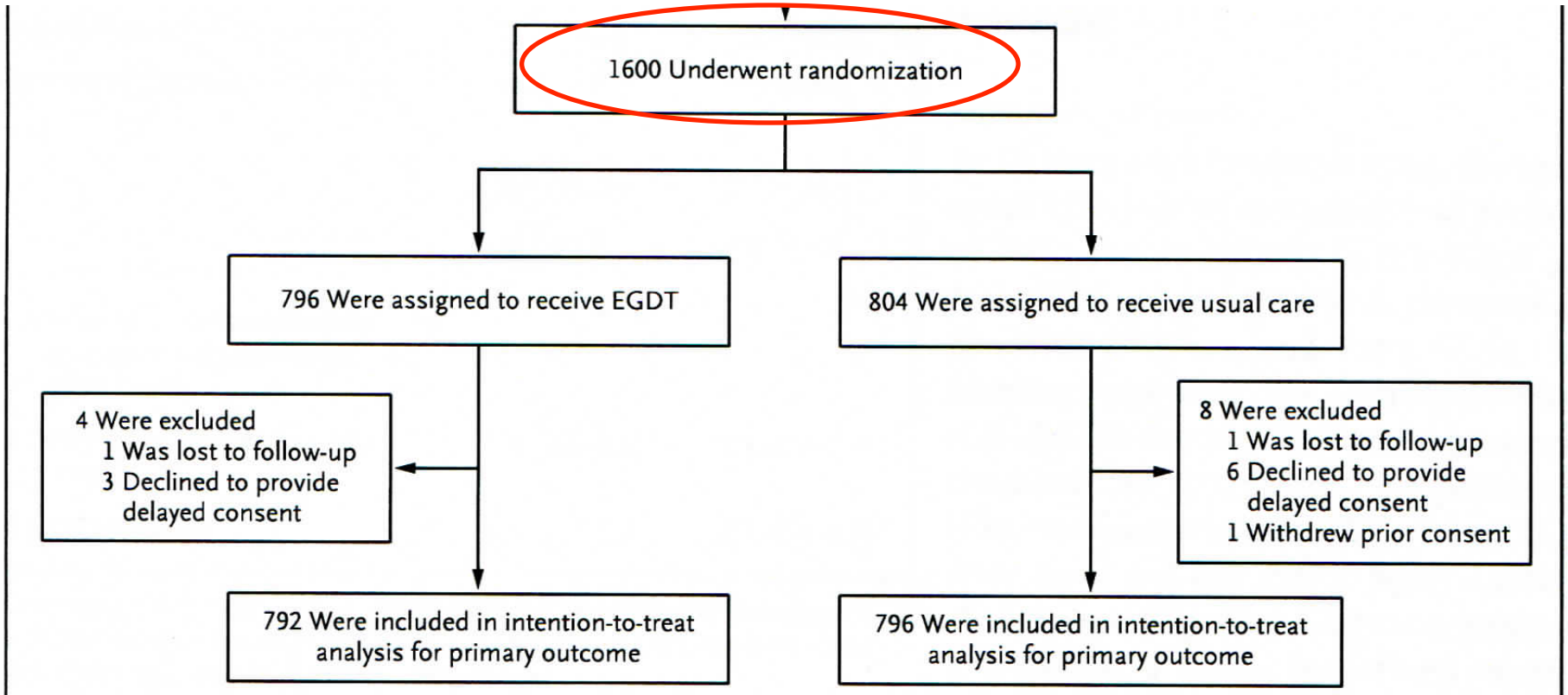
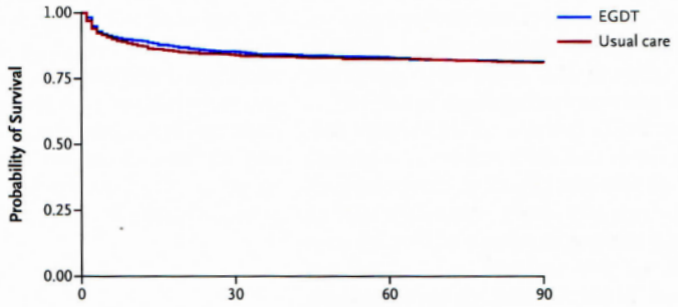


Figure 1. Enrollment and Outcomes.

CVC denotes central venous catheter, and EGDT early goal-directed therapy.

A Survival



No. at Risk				
EGDT	792	677	660	646
Usual care	796	670	657	646

B Subgroup Analyses

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	

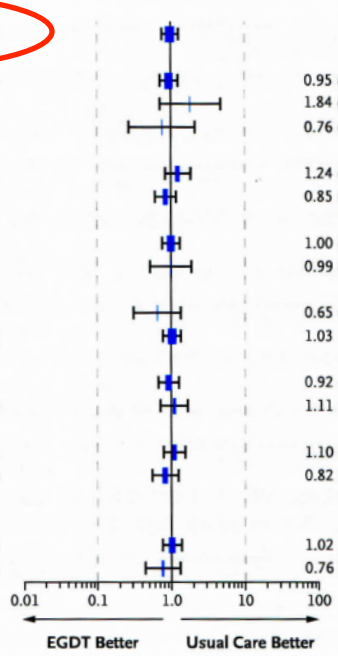


Figure 2. Probability of Survival and Subgroup Analyses of the Risk of Death at 90 Days.

Panel A shows Kaplan–Meier estimates of the probability of death at 90 days for patients with septic shock receiving either early goal-directed therapy (EGDT) or usual care for 6 hours ($P=0.82$ by the log-rank test for the between-group difference). Panel B shows the odds ratio for death at 90 days in the EGDT group, as compared with the usual-care group, among all patients and in predefined subgroups. The size of the squares representing odds ratios corresponds to the relative size of the subgroup. The horizontal bars represent 95% confidence intervals. Scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. IV denotes intravenous.

Mortality 18%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

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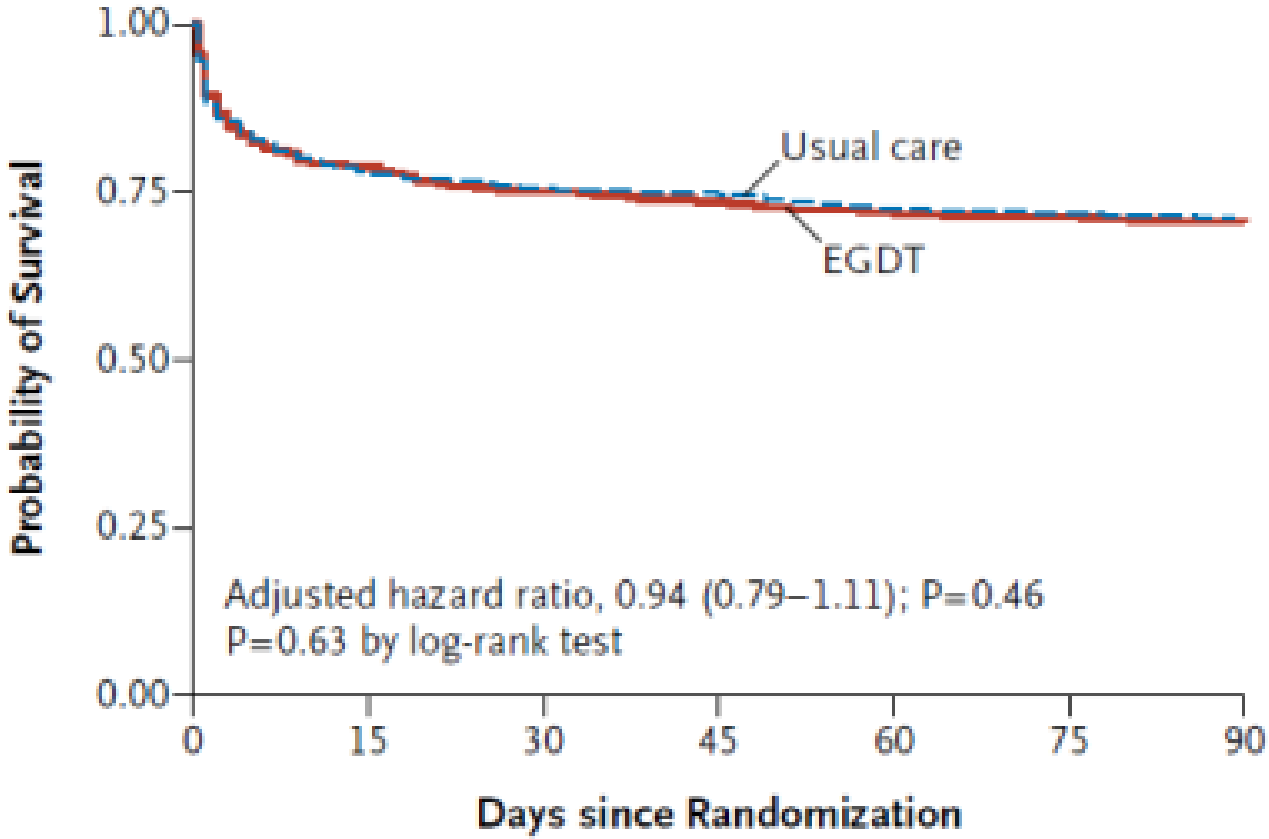
ProMISe Trial

March 2015



No. at Risk							
EGDT	625	492	470	461	449	445	440
Usual care	626	487	469	464	448	445	439

Figure 2. Kaplan–Meier Survival Estimates.

Shown is the probability of survival for patients with severe sepsis receiving early, goal-directed therapy (EGDT) and those receiving usual care at 90 days.

Median total intravenous fluids (IQR) — ml†	2000 (1150–3000)	1784 (1075–2775)	3623 (1800–6060)	3981 (1895–6291)
Intravenous colloids				
Patients — no./total no. (%)†	197/623 (31.6)	180/625 (28.8)	171/603 (28.4)	150/603 (24.9)
Median volume (IQR) — ml	1000 (500–1500)	750 (500–1000)	750 (500–1750)	750 (500–1500)
Intravenous crystalloids				
Patients — no./total no. (%)†	584/623 (93.7)	597/625 (95.5)	537/603 (89.1)	543/603 (90.0)
Median volume (IQR) — ml	[illegible]	[illegible]	3403 (1576–5647)	3694 (1832–5911)
Vasopressor — no./total no. (%)	332/623 (53.3)	291/625 (46.6)	349/603 (57.9)	317/603 (52.6)
Dobutamine — no./total no. (%)	113/623 (18.1)	24/625 (3.8)	107/603 (17.7)	39/603 (6.5)

Median length of stay in emergency department (IQR) — hr	1.5 (0.4 to 3.1)	1.3 (0.4 to 2.9)		0.34
Median length of stay in ICU (IQR) — days	2.6 (1.0 to 5.8)	2.2 (0.0 to 5.3)		0.005
Median length of stay in hospital (IQR) — days	9 (4 to 21)	9 (4 to 18)		0.46
Death from any cause — no./total no. (%)				
At 28 days	155/625 (24.8)	152/621 (24.5)	1.01 (0.83 to 1.23)¶ 0.95 (0.73 to 1.25)**	0.90† 0.73
At hospital discharge	160/625 (25.6)	154/625 (24.6)	1.04 (0.86 to 1.26)¶ 0.98 (0.75 to 1.29)**	0.74† 0.90

Ces études évaluent beaucoup de patients de gravité faible

Sub group Analysis

D Angus ESICM 2015

Intensive Care Med
DOI 10.1007/s00134-015-3822-1

SEVEN-DAY PROFILE PUBLICATION

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A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

Table 1 Characteristics of included studies for the primary and secondary objectives

Author	Region	No. of sites	Population	Source	Control(s)	No. of patients	Primary outcome
Primary objective							
Rivers et al. [1]	USA	1	Adult	ED	Usual care	263	In-hospital
Jones et al. [19]	USA	3	Adult	ED	Lactate clearance[c]	300	In-hospital
ProCESS Investigators [8]	USA	31	Adult	ED	Usual care or protocol-based standard therapy[d]	1341	In-hospital[h]
ARISE Investigators [10]	Australasia[a]	51	Adult	ED	Usual care	1600	90-day
ProMISe Investigators [12]	England	56	Adult	ED	Usual care	1260	90-day
Secondary objective							
Wang et al. [21]	China	1	Adult	Unknown[b]	Usual care	33	14-day
De Oliviera et al. [20]	Brazil	2	Paediatric	ED, ward, ICU	ACCM/PALS guidelines[e]	102	28-day
EGDT Collaborative [22]	China	8	Adult	Unknown[b]	Usual care	314	28-day
Tian et al. [23]	China	1	Adult	Unknown[b]	10 or 30 % lactate clearance	71	28-day
Yu et al. [24]	China	1	Adult	Unknown[b]	Lactate clearance $\geq$10 %[f]	50	28-day
Lu et al. [25]	China	1	Adult	Unknown[b]	PiCCO-guided resuscitation[g]	82	In-hospital

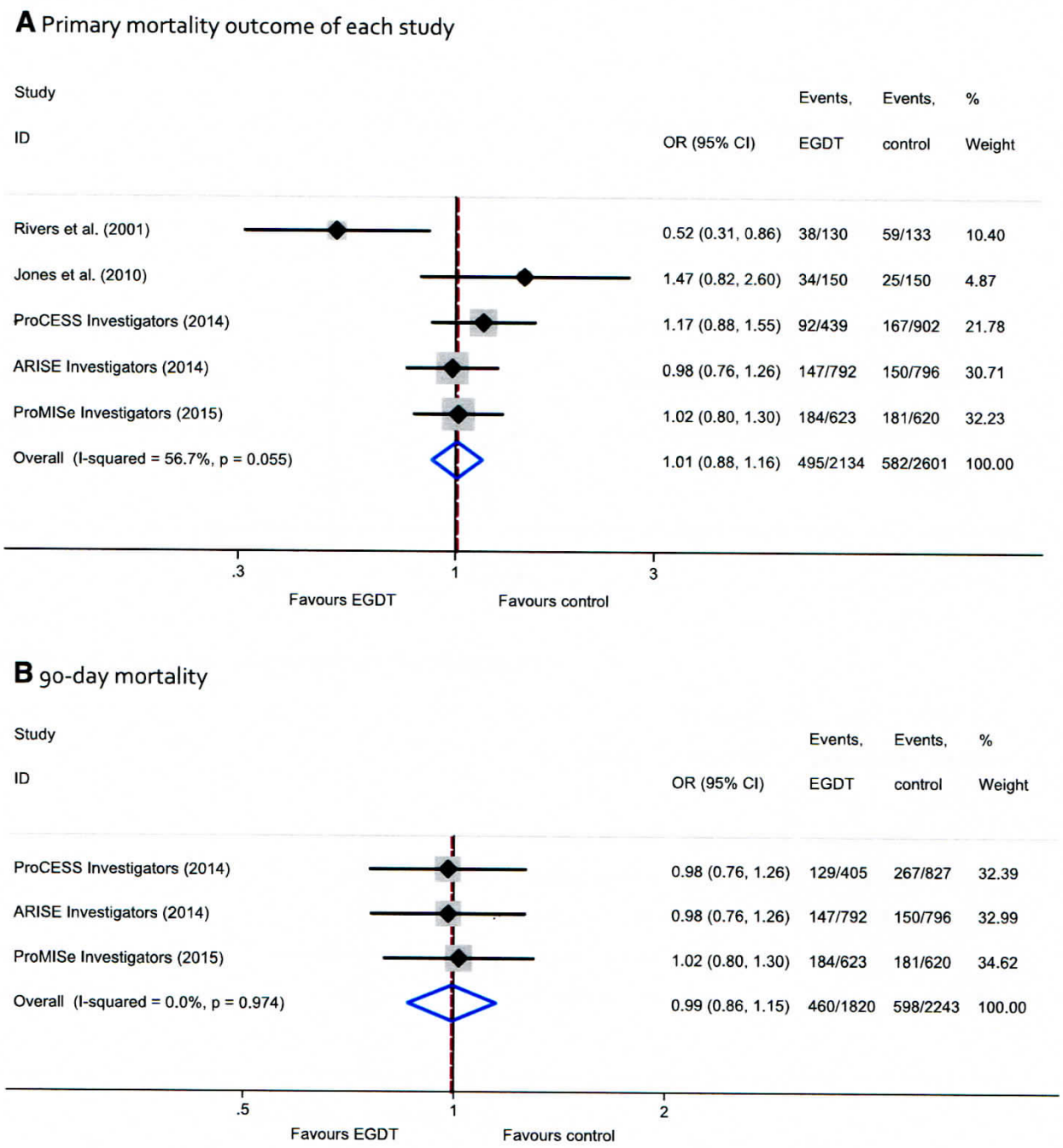

Fig. 2 Effect of EGDT on mortality in patients presenting to the emergency department with septic shock. **a** Primary mortality outcome of each study. **b** 90-day mortality. *EGDT* early goal-directed therapy, *OR* odds ratio, *CI* confidence interval. The control was usual care or another non-EGDT resuscitation strategy. Fixed-effect model: the *individual points* denote the OR of each study and the *lines* either side the 95 % confidence intervals. The *vertical lines* denote the null effect. The control for the ProCESS trial [8] includes both usual care and protocol-based standard therapy groups combined. Analysis comparing EGDT with the ProCESS usual care group only and excluding the Jones trial (control group lactate clearance) [19] did not change the result (OR 0.97 [95 % CI 0.84–1.12; I^2 56.5, $P = 0.08$]

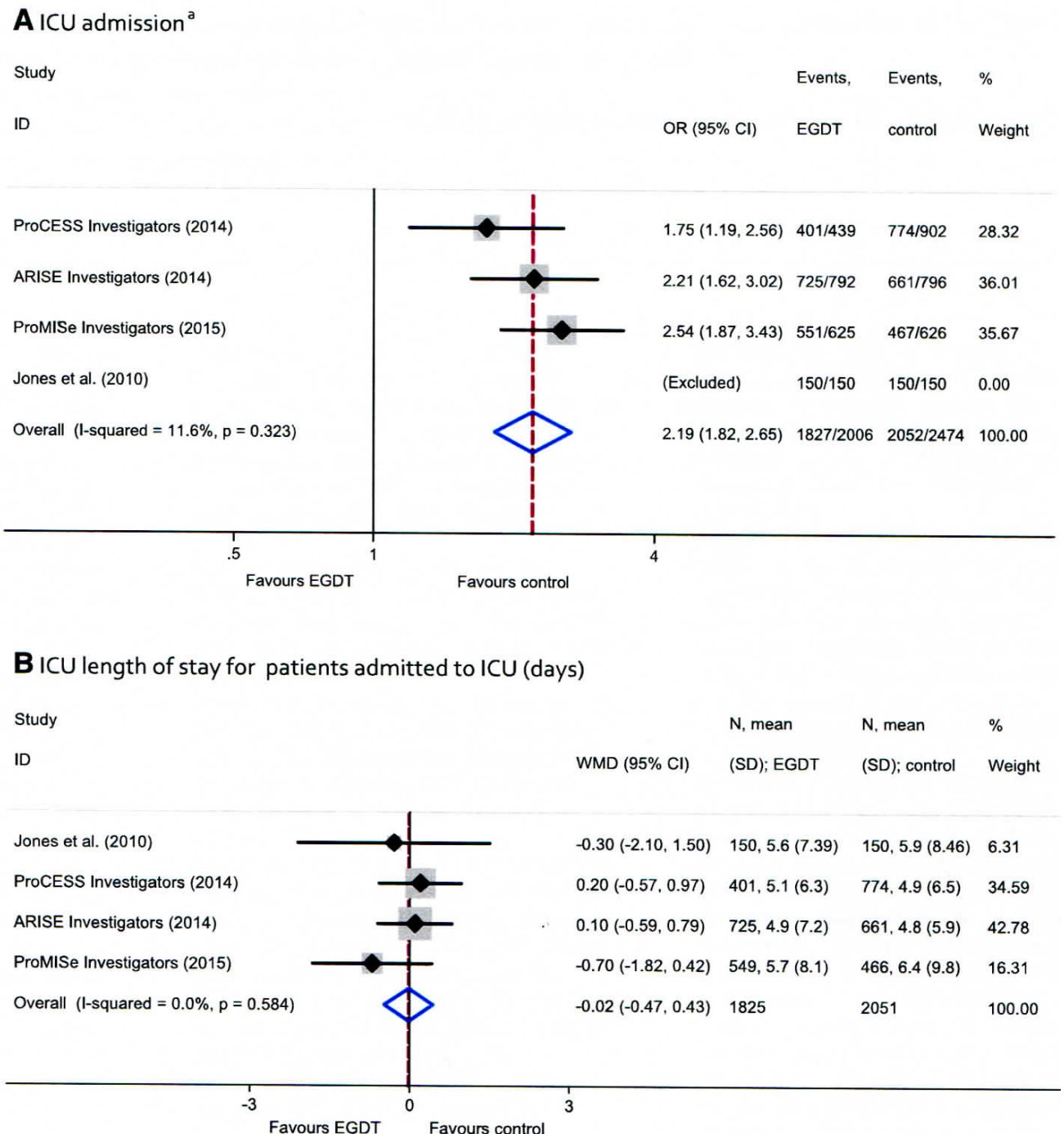

Fig. 3 Effect of EGDT on ICU utilisation in patients presenting to the emergency department with septic shock. **a** ICU admission[a]. **b** ICU length of stay for patients admitted to ICU (days). *ICU* intensive care unit, *EGDT* early goal-directed therapy, *OR* odds ratio, *CI* confidence interval, *WMD* weighted mean difference, *SD* standard deviation. The control was usual care or another non-EGDT resuscitation strategy. Fixed-effect model: the *individual points* denote the OR or WMD of each study and the *lines* either side the 95 % confidence intervals. The control for the ProCESS trial [8] includes both usual care and protocol-based standard therapy groups combined. [a]"Favours EGDT" denotes lower ICU admission rate for the EGDT group and "Favours control" denotes higher ICU admission rate for the EGDT group

Cathéter veineux central

- **Accès veineux sécurisé**
- **Très peu de complications**
- **+/- 100% de succès par échoguidage**
- **Multilumières**
- **Perfusion sécurisée de vasopresseurs**
- **Utilisable plus de 4 jours**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intravascular Complications of Central Venous Catheterization by Insertion Site

Jean-Jacques Parienti, M.D., Ph.D., Nicolas Mongardon, M.D., Bruno Mégarbane, M.D., Ph.D., Jean-Paul Mira, M.D., Ph.D., Pierre Kalfon, M.D., Ph.D., Antoine Gros, M.D., Sophie Marqué, M.D., Marie Thuong, M.D., Véronique Pottier, M.D., Michel Ramakers, M.D., Benoît Savary, M.D., Amélie Seguin, M.D., Xavier Valette, M.D., Nicolas Terzi, M.D., Ph.D., Bertrand Sauneuf, M.D., Vincent Cattoir, Pharm.D., Ph.D., Leonard A. Mermel, D.O., and Damien du Cheyron, M.D., Ph.D., for the 3SITES Study Group*

September 24,2015

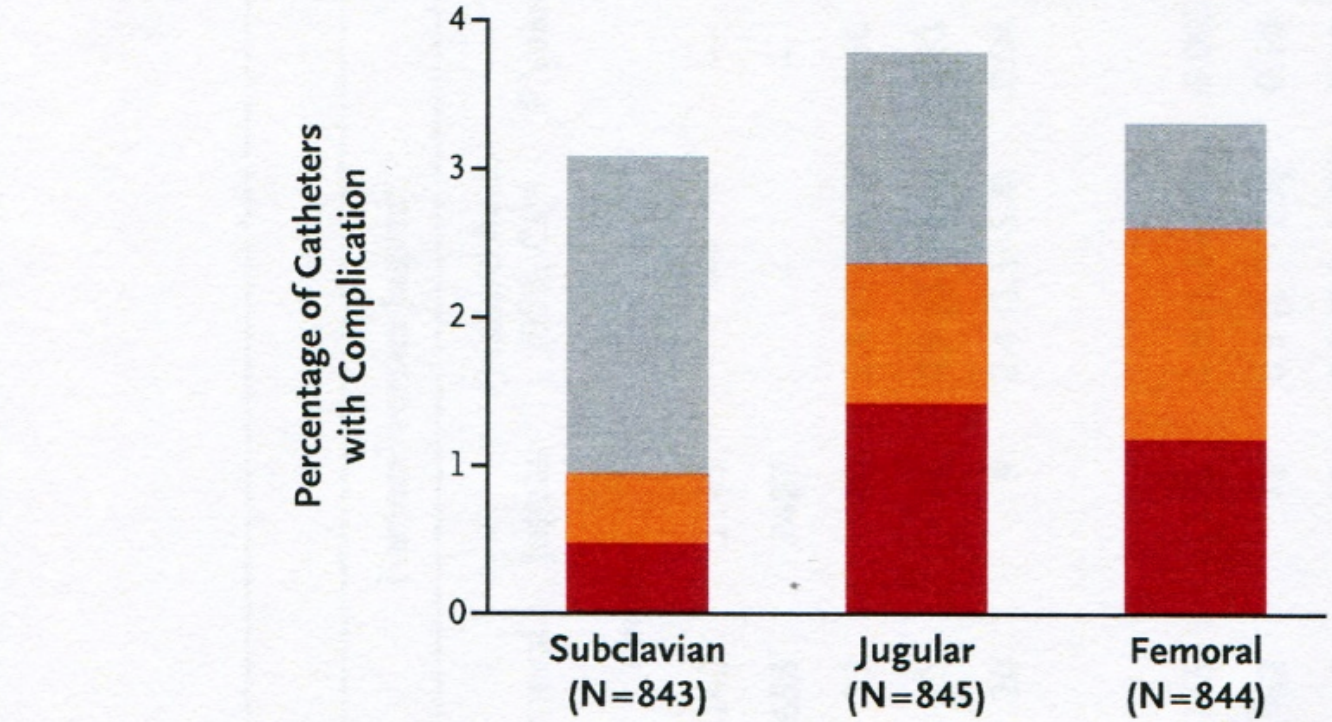

Figure 2. Complications in the Three-Choice Comparison, According to Insertion-Site Group.

The primary end point (the composite of symptomatic deep-vein thrombosis and bloodstream infection) differed significantly among the insertion-site groups (P=0.02 by the log-rank test), as did the principal safety secondary end point (mechanical complications) (P=0.047 by the chi-square test).

Cathéter veineux central

- **Accès veineux sécurisé**
- **Très peu de complications**
- **+/- 100% de succès par échoguidage**
- **Multilumières**
- **Perfusion sécurisée de vasopresseurs**
- **Utilisable plus de 4 jours**

- **Pourquoi ne pas prélever un échantillon pour mesurer la ScVO2 ????**

Messages 1

- Eviter le sur-remplissage
- Solutions balancées et albumine
- Noradrénaline
- PAM 60-65 mmHg
- Controler le lactate

Messages 2

- Aux urgences pas de CVC
- Aux urgences pas de ScVO2
- En réanimation ou en cas de choc évolué non stabilisé:

  Monitorage invasif

  ScVO2 et lactate

Dynamic Aspect

1st hour

- blood gas
- lactate
- cultures
- ATB
- peripheral IV
- vasopressor
- fluid

2nd hour

- MAP 65 mmHg
- arterial line
- DPP
- CVC $ScvO_2$
- lactate

6th hour

- ScvO2 > 70%
- SvO2 > 65 %
- Lactate ⇓
- plateau pressure < 30 mmHg