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

CCM 2014 **USA**

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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

TABLE 1. (Continued). Characteristics, Interventions, and Outcomes of 2,849 Patients With Septic Shock

Hospital Mortality 47.4 % M

Variable	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
Outcomes		
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)	

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
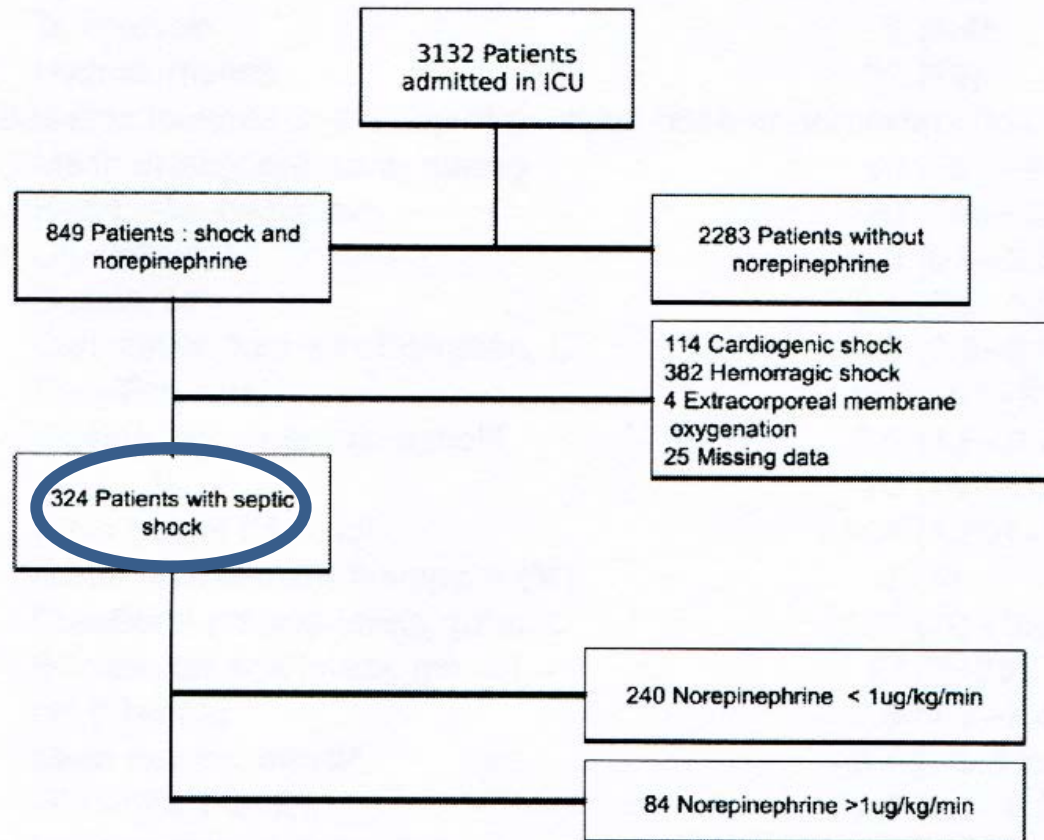Aix Marseille Université, Marseille, France*

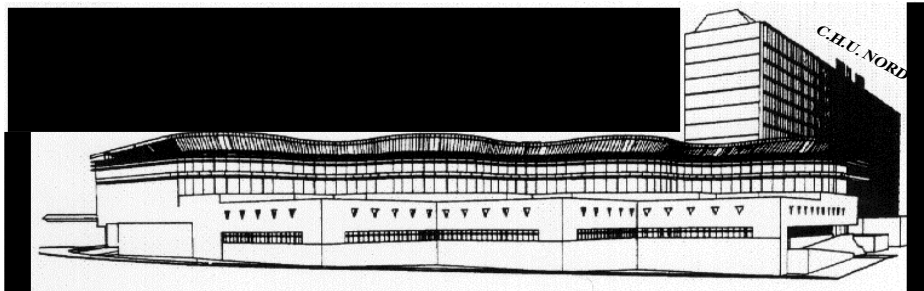FIG. 1. **Flowchart of inclusion.**

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%**

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 compliance resuscitation			High compliance resuscitation			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	

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

Box 3. New Terms and Definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.

  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.

  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.

- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.

- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

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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 ≥ 4 mmol/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 $\geq 70\%$, and normalization of lactate

Figure 1. Surviving Sepsis Campaign Care Bundles.

SURVIVING SEPSIS CAMPAIGN BUNDLES

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...stent arterial hypotension despite volume resuscitation (septic ...le 24 mmol/l (36 mg/dl)

7) ...

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate

Figure 1. Surviving Sepsis Campaign Care Bundles.

MAP > 65 mmHg

ScvO2 >70%

Normalisation of lactate

CVP > 8 mmHg

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.

This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

Does pulse pressure variation predict fluid responsiveness in critically ill patients? A systematic review and meta-analysis

Xiaobo Yang (want.tofly@aliyun.com)
Bin Du (dubin98@gmail.com)

○	Observed Data
◆	Summary Operating Point SENS = 0.88 [0.81 - 0.92] SPEC = 0.89 [0.84 - 0.92]
—	SROC Curve AUC = 0.94 [0.91 - 0.95]
—	95% Confidence Contour
⋯	95% Prediction Contour
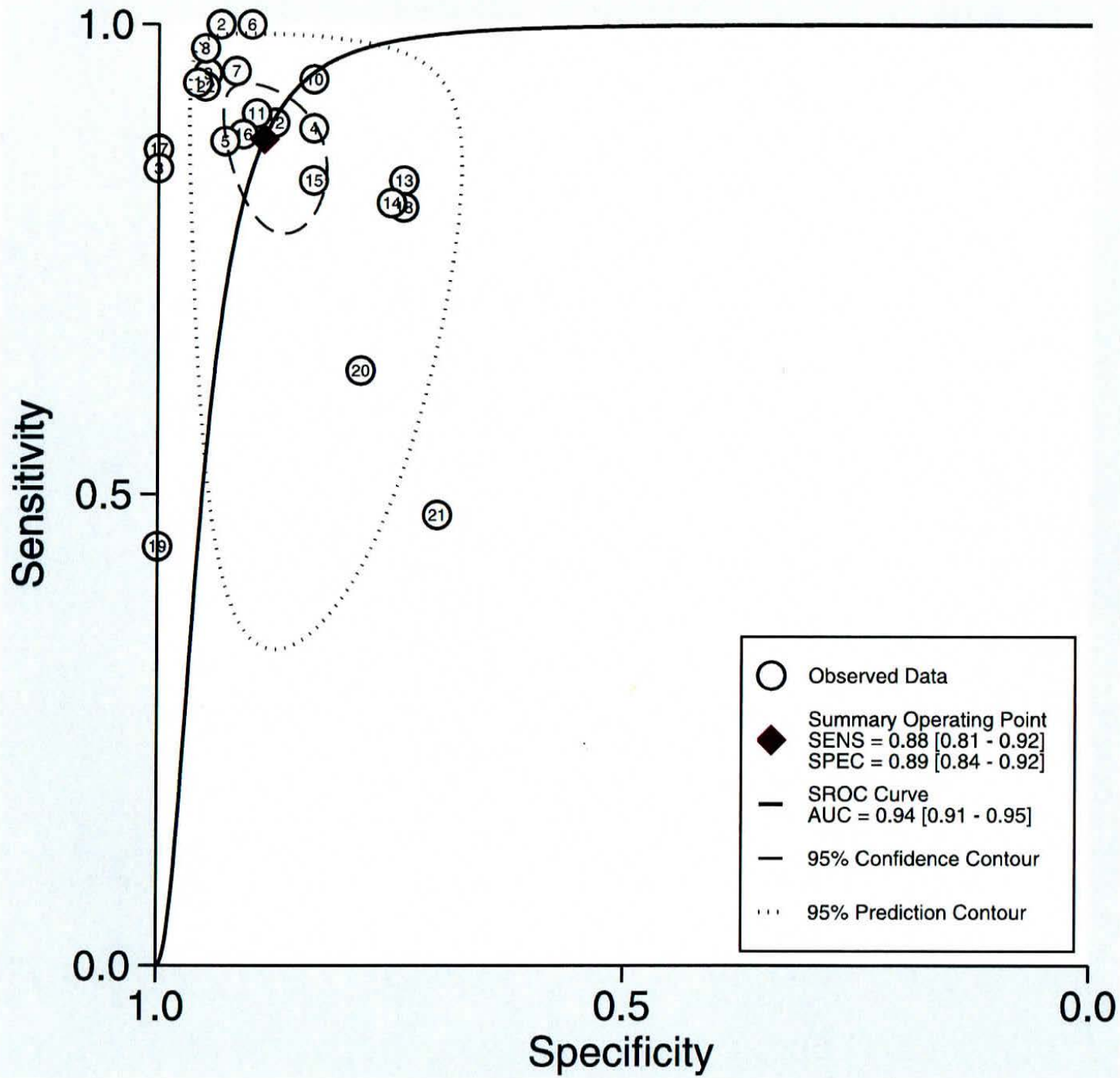
Conclusions

PPV is an accurate predictor of fluid responsiveness in critically ill patients passively ventilated with tidal volume >8 ml/kg and without cardiac arrhythmia.

Key messages

- A significant threshold effect existed while using pulse pressure variation to determine a responder (or non-responder) to volume expansion.
- Pulse pressure variation is an accurate predictor of fluid responsiveness in critically ill patients ventilated with relative large tidal volume and without spontaneous breathing and cardiac arrhythmia.

Fluid Responsiveness in Spontaneously Breathing Patients

ΔPP
SVV

No
!!!

Teboul JL 8th Int. Consensus Conference ATS/SRLF/ERS/SCC/Esicm, Paris 27-28 April 2006
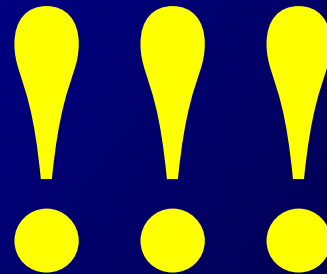
- **Passive leg raising with > 12% increase in CO by PiCCO or oesophageal Döppler**

CRITICAL CARE

Passive leg raising: five rules, not a drop of fluid!
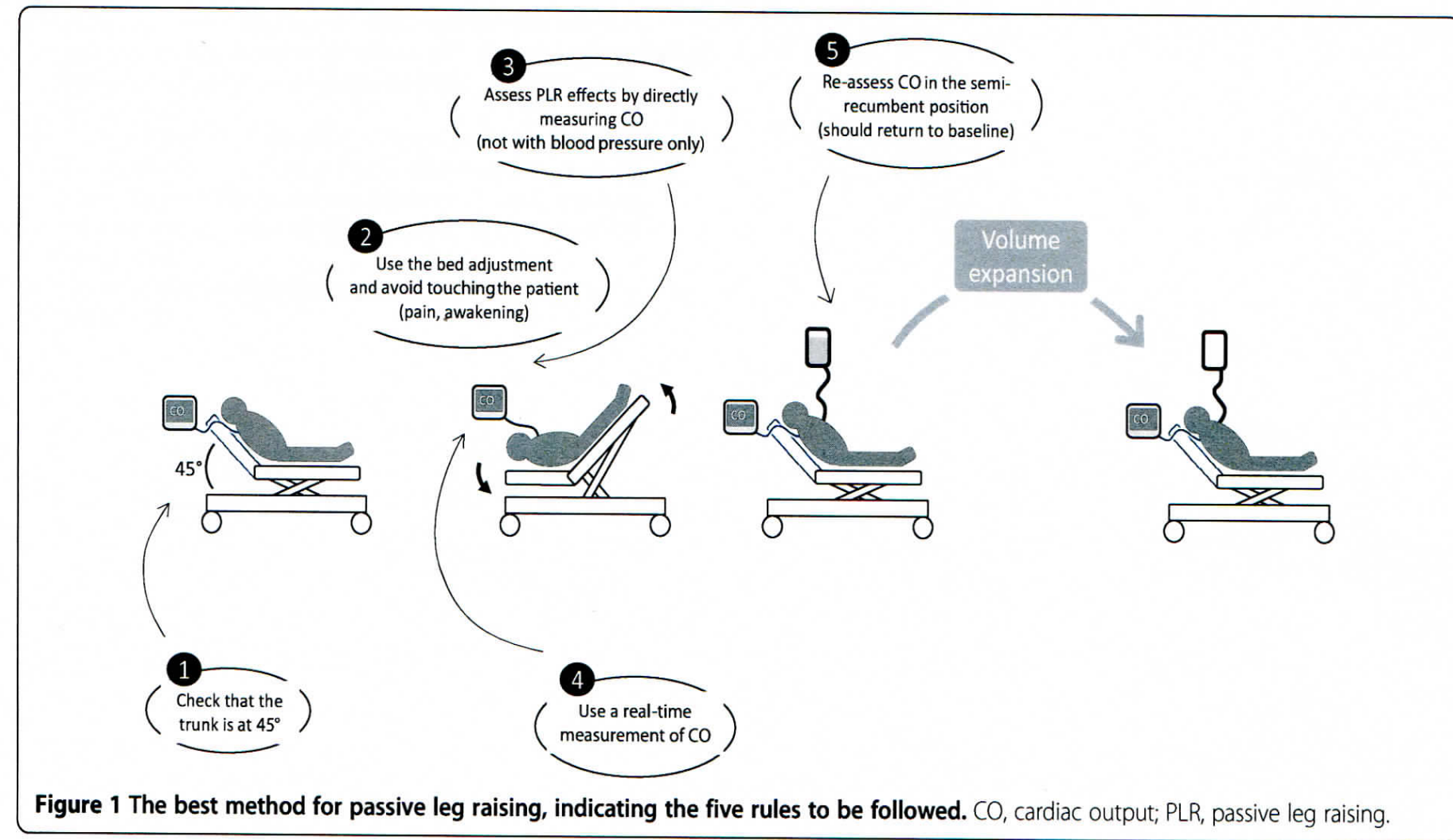
Figure 1 The best method for passive leg raising, indicating the five rules to be followed. CO, cardiac output; PLR, passive leg raising.

ORIGINAL

CrossMark

Xavier Monnet
Paul Marik
Jean-Louis Teboul

Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis

Q = 41.4
I^2 = 10% (95%CI: 0% - 49%)

Monnet et al. (2006) (9)
Lafanechère et al. (31)
Lamia et al. (32)
Maizel et al. (37)
Monnet et al. (2009) (34)
Préau et al. (36)
Benomar et al. (22)
Guinot et al. (16)
Monnet et al. (2012) (18)
Brun et al. (19)
Monge-Garcia et al. (15)
Kupersztych-Hagège et al. (13)
Silva et al. (14)
Monnet et al. (2013) (17)

Total (fixed effects)
Total (random effects)

Correlation coefficient

Sensitivity

AUC = 0.95±0.01

I^2 = 34% (95%CI: 0 − 44%)

1-specificity

ORIGINAL

CrossMark

Xavier Monnet
Paul Marik
Jean-Louis Teboul

Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis

minimized.
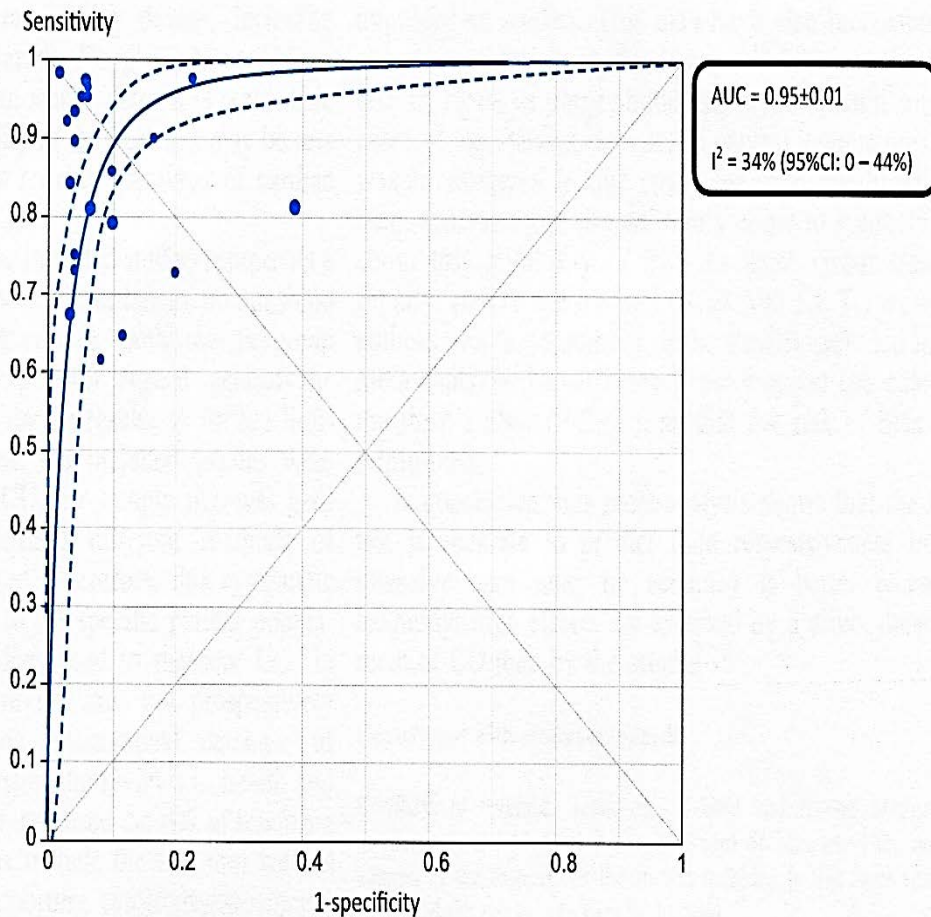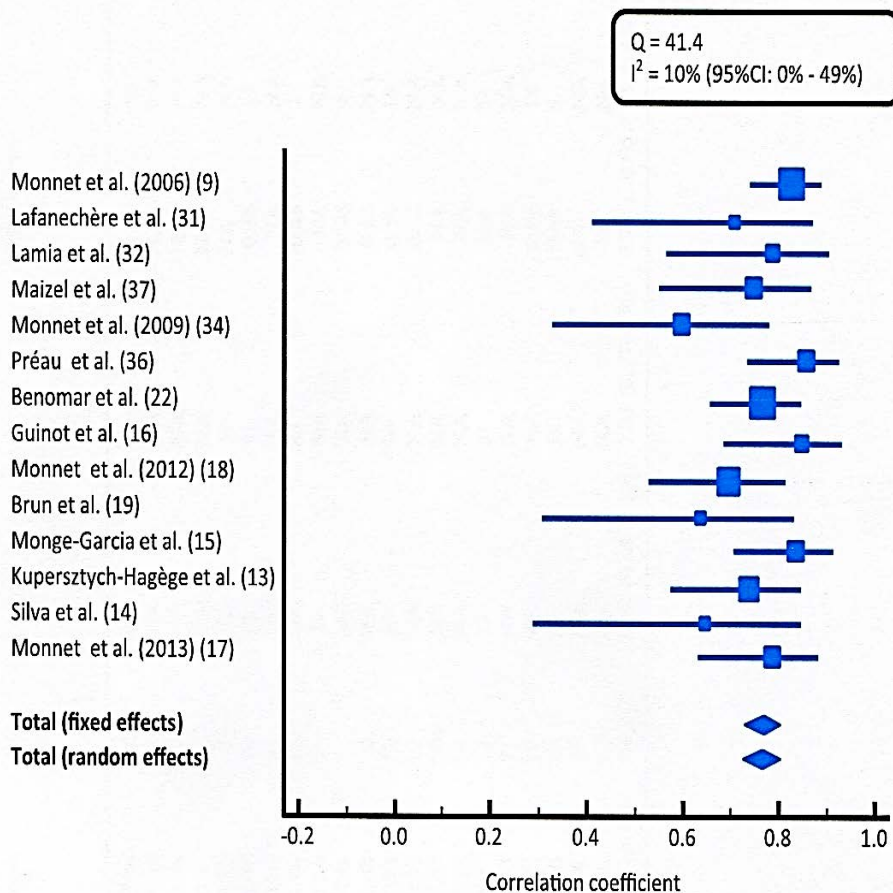
In conclusion, this meta-analysis shows that the PLR test is accurate to predict fluid responsiveness in the intensive care unit. Its accuracy is better when its haemodynamic effects are assessed by a direct measurement of CO than by the arterial PP.

A positive fluid balance i

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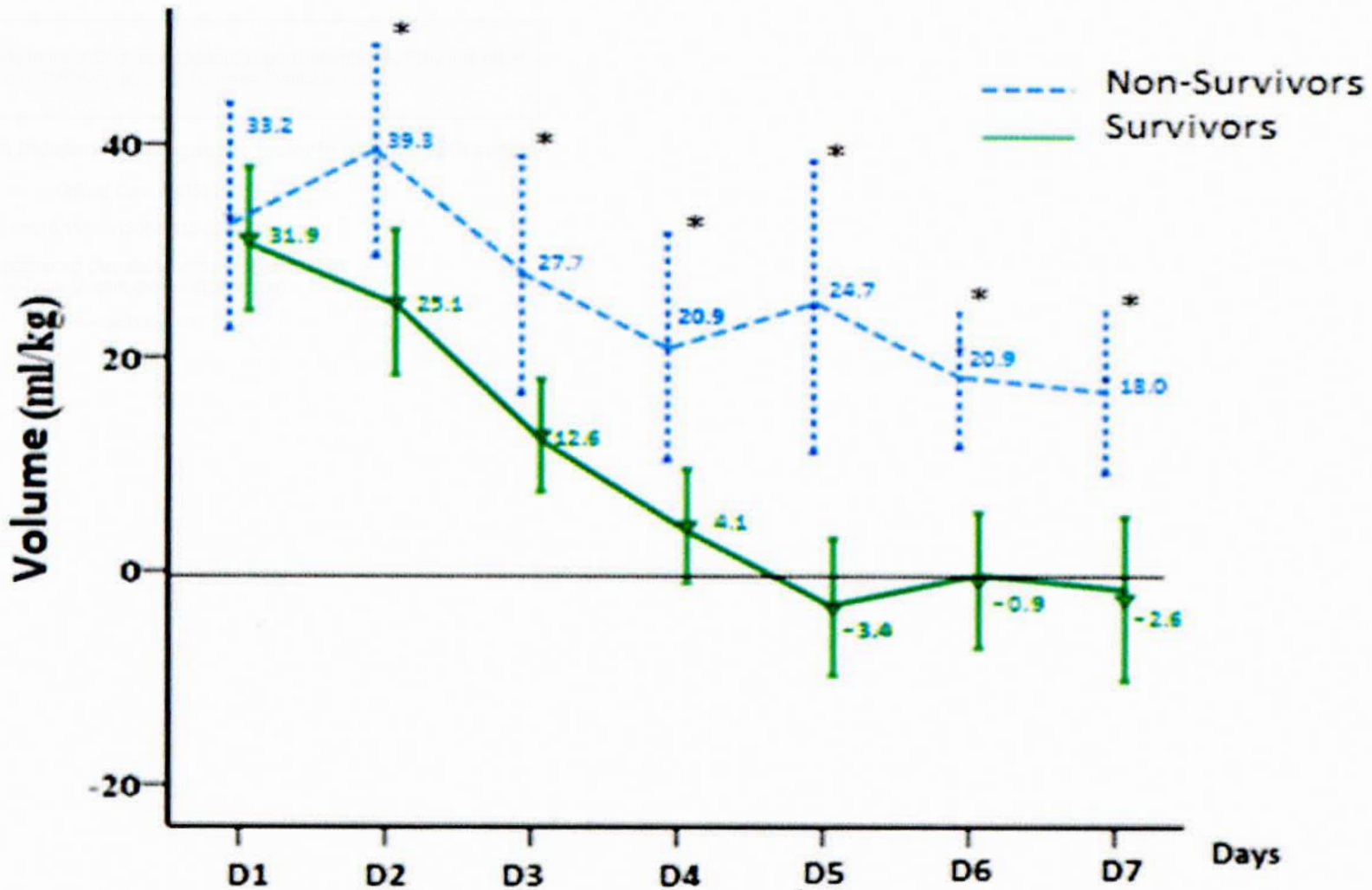
Number of patients per day							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
NS	59	59	59	51	43	38	31
S	114	114	114	96	75	64	49
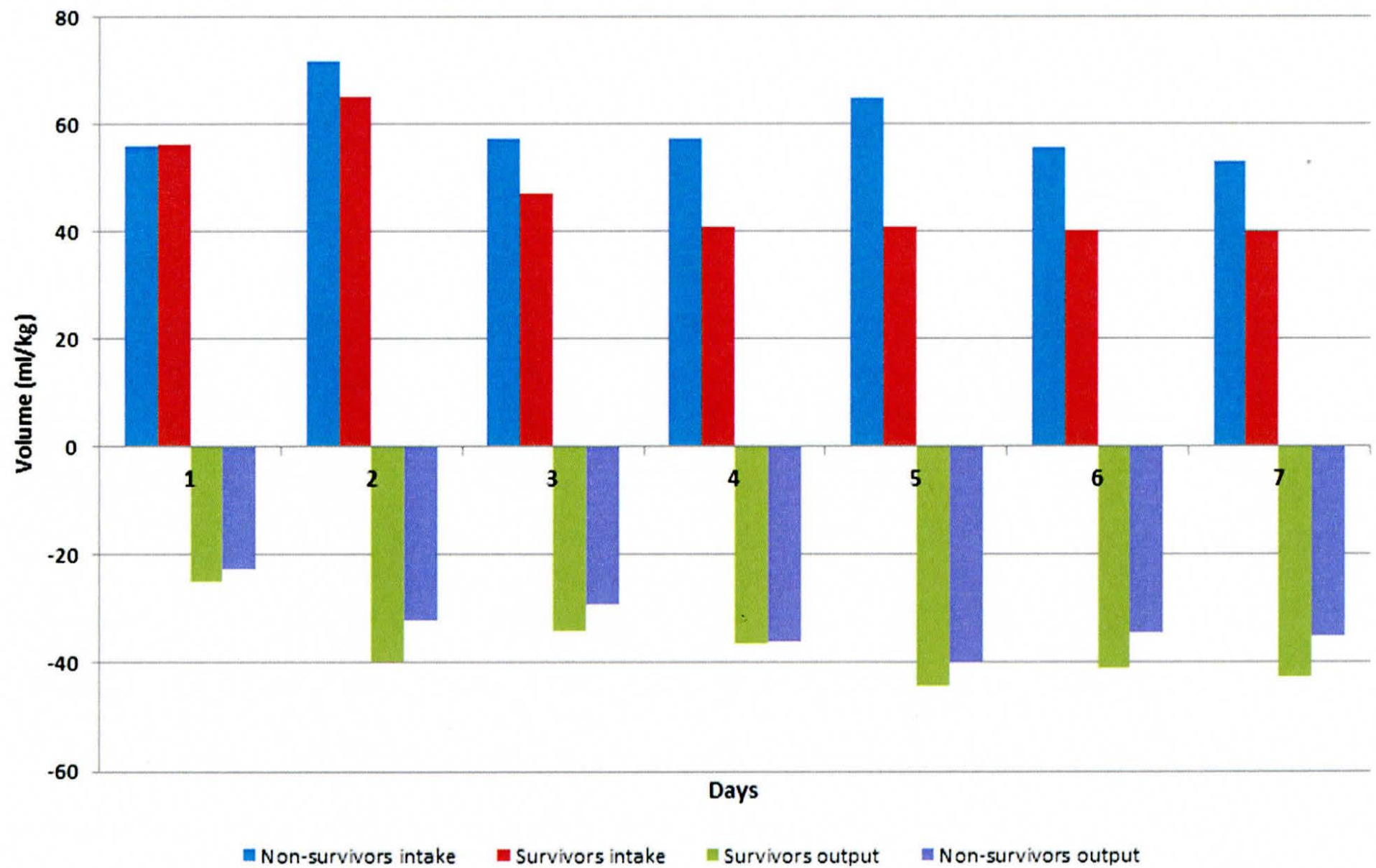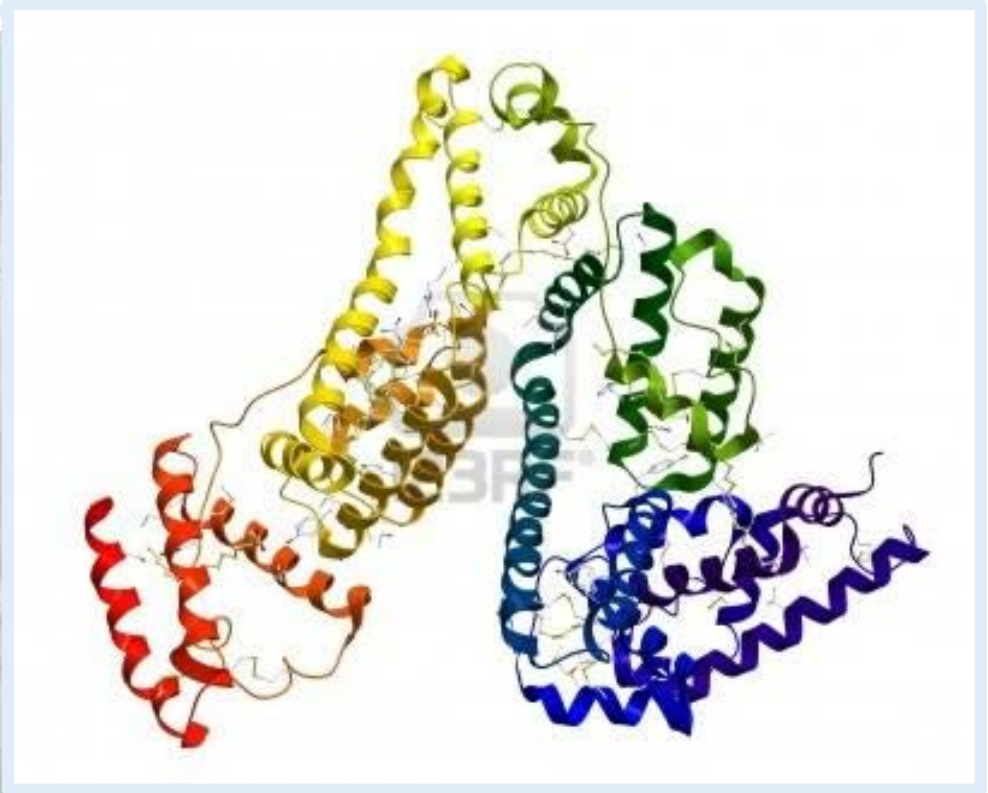
ORIGINAL ARTICLE

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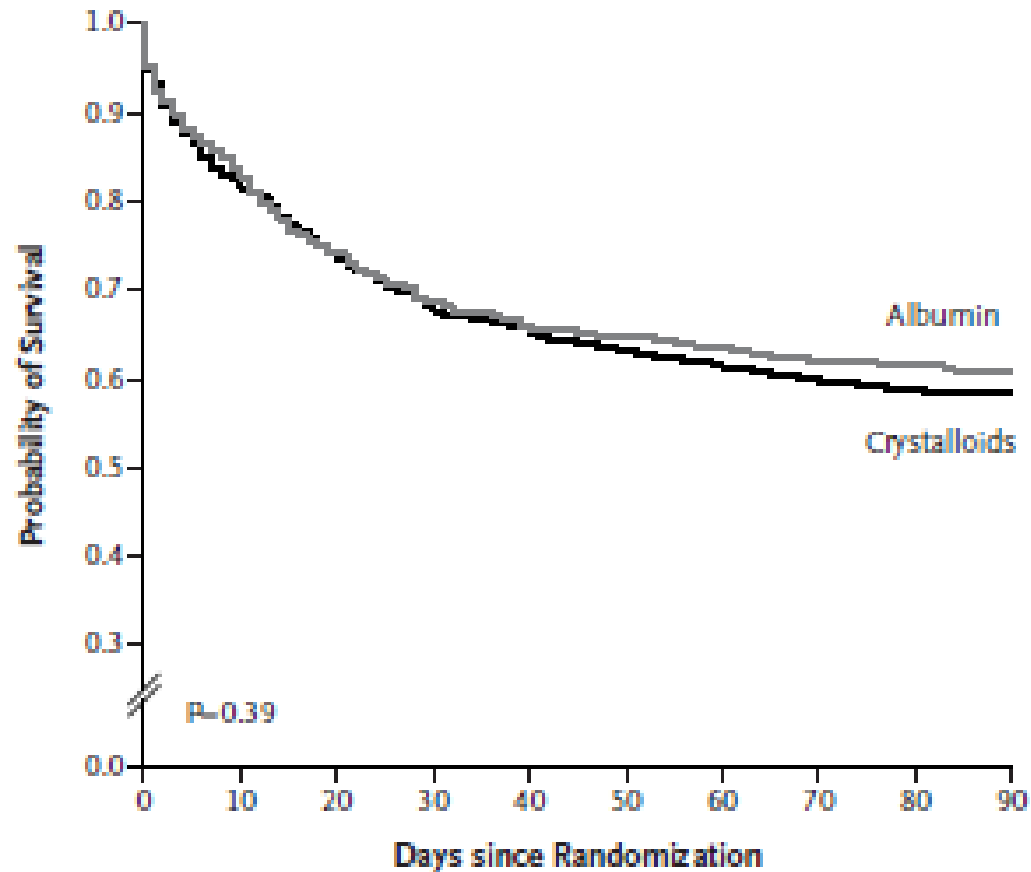
Figure 2. Probability of Survival from Randomization through Day 90.

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.

23

ALBIOS : Septic shock sub-group
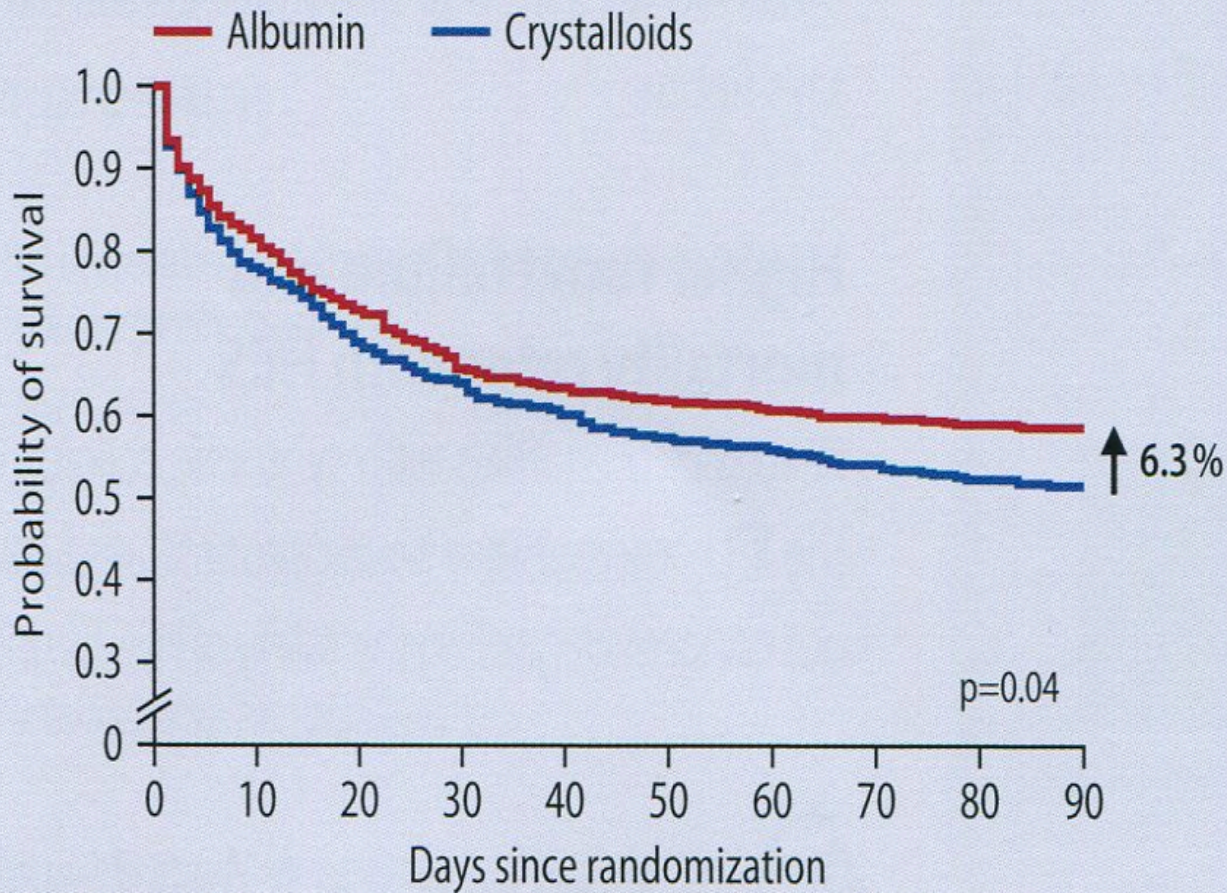
This Provisional PDF corresponds to the article as it appeared upon acceptance. Fully formatted PDF and full text (HTML) versions will be made available soon.

Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials

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Study or sub-category	Albumin n/N	Crystalloid n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Rackow	5/7	3/4		0.27	0.83 [0.05, 13.63]
Metidi	10/12	11/12		0.45	0.45 [0.04, 5.81]
The SAFE study	185/603	217/615		36.87	0.81 [0.64, 1.03]
The CRISTAL study	22/59	197/557		5.86	1.09 [0.62, 1.89]
The ALBIOS study	365/888	389/893		56.55	0.90 [0.75, 1.09]
Total (95% CI)	1569	2081		100.00	0.88 [0.76, 1.01]

Total events: 587 (Albumin), 817 (Crystalloid)
Test for heterogeneity: Chi² = 1.33, df = 4 (P = 0.86), I² = 0%
Test for overall effect: Z = 1.78 (P = 0.08)

0.1 0.2 0.5 1 2 5 10
Favours albumin   Favours crystalloid

Severe Sepsis p = 0.08

Study or sub-category	Albumin n/N	Crystalloid n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Rackow	5/7	3/4		0.45	0.83 [0.05, 13.63]
The SAFE study	70/209	90/229		23.82	0.78 [0.53, 1.15]
The CRISTAL study	22/59	197/557		9.87	1.09 [0.62, 1.89]
The ALBIOS study	243/558	281/563		65.86	0.77 [0.61, 0.98]
Total (95% CI)	833	1353		100.00	0.81 [0.67, 0.97]

Total events: 340 (Albumin), 571 (Crystalloid)
Test for heterogeneity: Chi² = 1.26, df = 3 (P = 0.74), I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

0.1 0.2 0.5 1 2 5 10
Favours albumin   Favours crystalloid

Septic Shock p = 0.03

Albumin Replacement in Severe Sepsis or Septic Shock

TO THE EDITOR: The Albumin Italian Outcome Sepsis study conducted by Caironi et al. (April 10 issue)[1] is the third large-scale, randomized trial to compare albumin with crystalloids in adult pati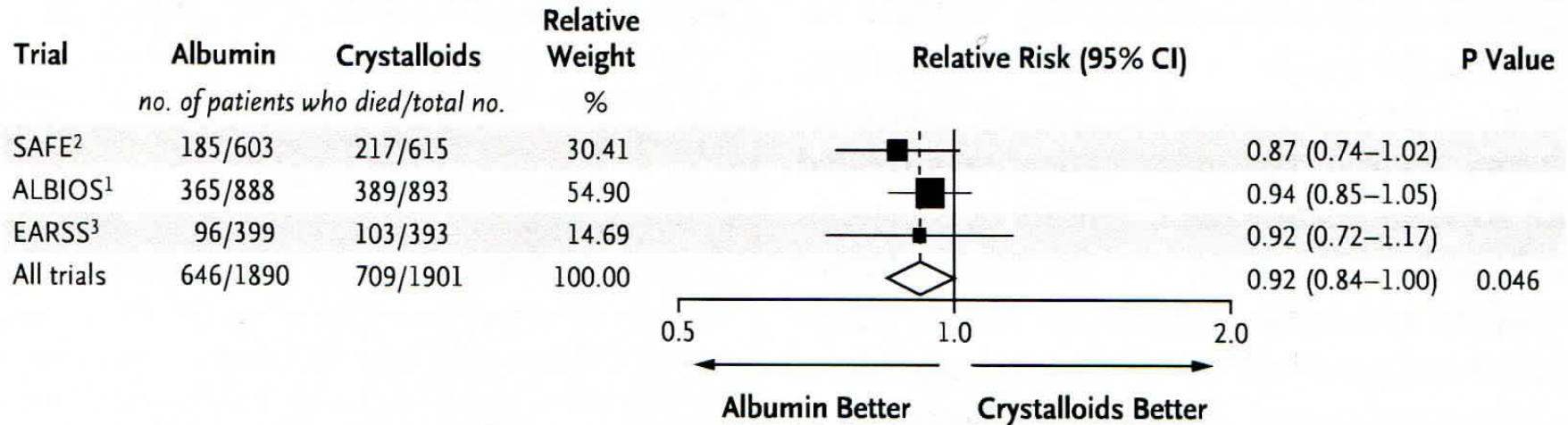ents with severe sepsis. The first such trial was the Saline versus Albumin Fluid Evaluation study.[2] In addition, the Early Albumin Resuscitation during Septic Shock study has been completed and its mortality results published.[3]

portant pathophysiological features with severe sepsis.[5]

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Trial	Albumin	Crystalloids	Relative Weight	Relative Risk (95% CI)		P Value
	no. of patients who died/total no.		%			
SAFE[2]	185/603	217/615	30.41		0.87 (0.74–1.02)	
ALBIOS[1]	365/888	389/893	54.90		0.94 (0.85–1.05)	
EARSS[3]	96/399	103/393	14.69		0.92 (0.72–1.17)	
All trials	646/1890	709/1901	100.00		0.92 (0.84–1.00)	0.046

0.5   1.0   2.0

Albumin Better   Crystalloids Better

Figure 1. Meta-Analysis of Mortality in Large-Scale Randomized Trials Comparing Albumin with Crystalloids in Adult Patients with Severe Sepsis.

A fixed-effect model was used in the analysis. The size of the squares indicates the data points from the individual trials scaled according to the percentage of total weight (with individual trial weight equaling the proportion of total patients receiving albumin multiplied by the number of deaths in the crystalloids group), and the diamond indicates the pooled findings. The dashed line indicates the pooled relative risk. The proportion of variation attributable to heterogeneity (I^2) was 0% (P=0.71). ALBIOS denotes Albumin Italian Outcome Sepsis, CI confidence interval, EARSS Early Albumin Resuscitation during Septic Shock, and SAFE Saline versus Albumin Fluid Evaluation.

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*

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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)

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

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 m² 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 $\geq$ 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)

Variable	Multivariate Model for Cl_0		Multivariate Model for Cl_{72}		Multivariate Model for ΔCl	
	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.

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Plasma–Lyte 148 (pH 7.4)

Plasma–Lyte 148 (pH 7.4)
Solution for Infusion

Solution for infusion   Isotonic
Single Dose   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

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5 413760 228242

Lot   Expiry

Sterofundin ISO   solution for infusion

**Sterofundin
ISO   1/1 E**

Each 1000 ml contains: mmol
Electrolytes   145
Sodium   4.0
Potassium   2.5
Calcium   1.0
Magnesium   5.0
Malate
Chloride   127
Acetate   24

Sodium Chloride   6.80 g
Potassium Chloride   0.30 g
Calcium Chloride
Dihydrate   0.37 g
Magnesium Chloride
trihydrate   0.20 g

1000 ml

2C 16/53

22.10.2012
12431B151
21.10.2015

Sodium Acetate
Trihydrate   3.27 g
Malic Acid   0.67 g
Water for Injections

Osmolarity   309 mOsm/l
pH   5.1 – 5.9

For intravenous use.
Do not use if container or
closure is damaged.
For single use only.
Discard any unused
contents.
Keep out of the reach and
sight of children.
See Directions for Use inside
carton.
Do not store above 25°C.
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VASOPRESSEURS
Dopamine
Epinephrine
Norepinephrine
Vasopressine
Terlipressine

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)
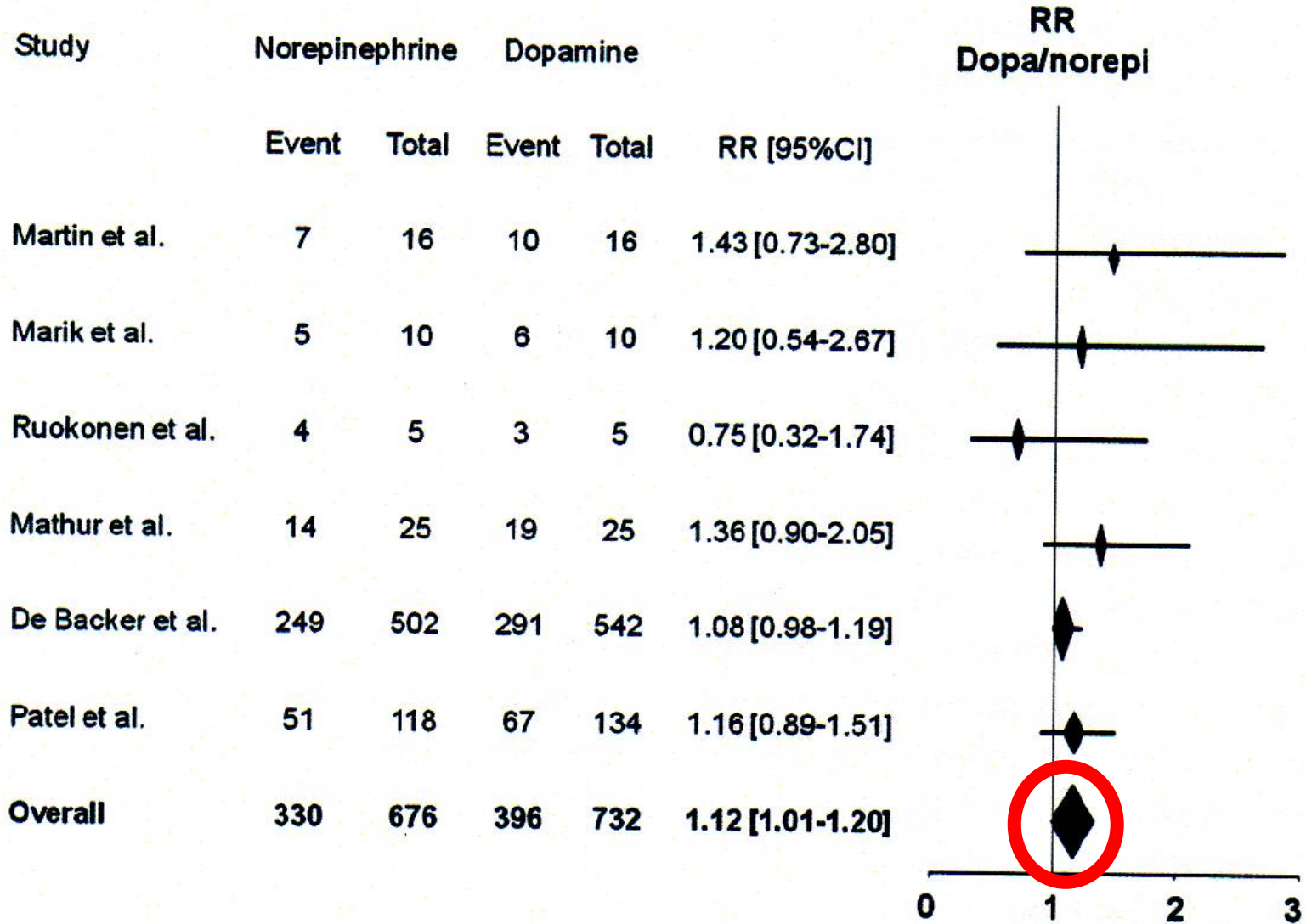
KEY WORDS: ●●●

Study	Norepinephrine		Dopamine		RR [95%CI]
	Event	Total	Event	Total	
Martin et al.	7	16	10	16	1.43 [0.73-2.80]
Marik et al.	5	10	6	10	1.20 [0.54-2.67]
Ruokonen et al.	4	5	3	5	0.75 [0.32-1.74]
Mathur et al.	14	25	19	25	1.36 [0.90-2.05]
De Backer et al.	249	502	291	542	1.08 [0.98-1.19]
Patel et al.	51	118	67	134	1.16 [0.89-1.51]
Overall	330	676	396	732	1.12 [1.01-1.20]

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%).

PAM : 65-75-85 mmHg ???

ORIGINAL ARTICLE

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

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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.,
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Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D.,
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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*
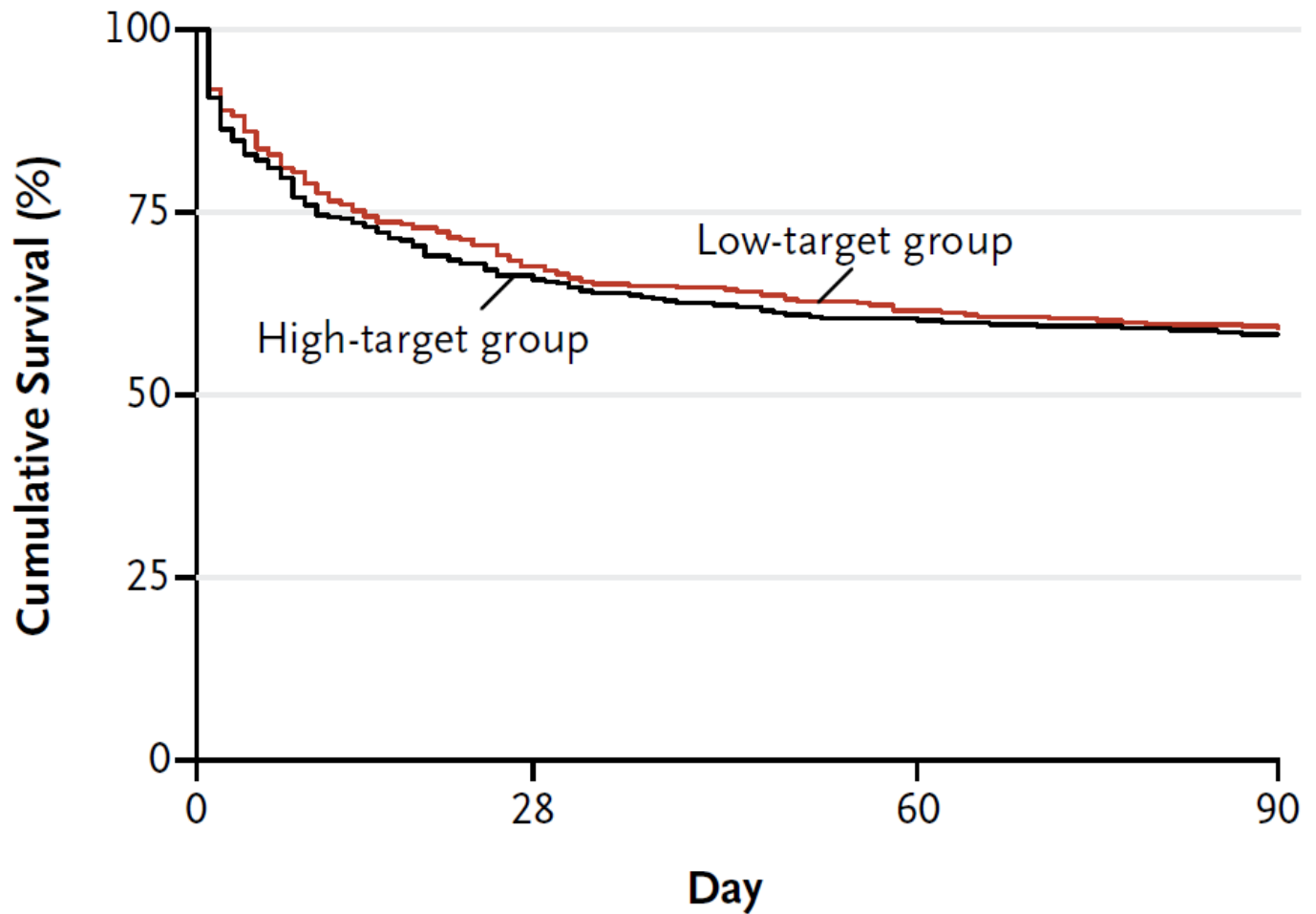
No. at Risk				
Low target	379	256	233	225
High target	375	249	227	219

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.
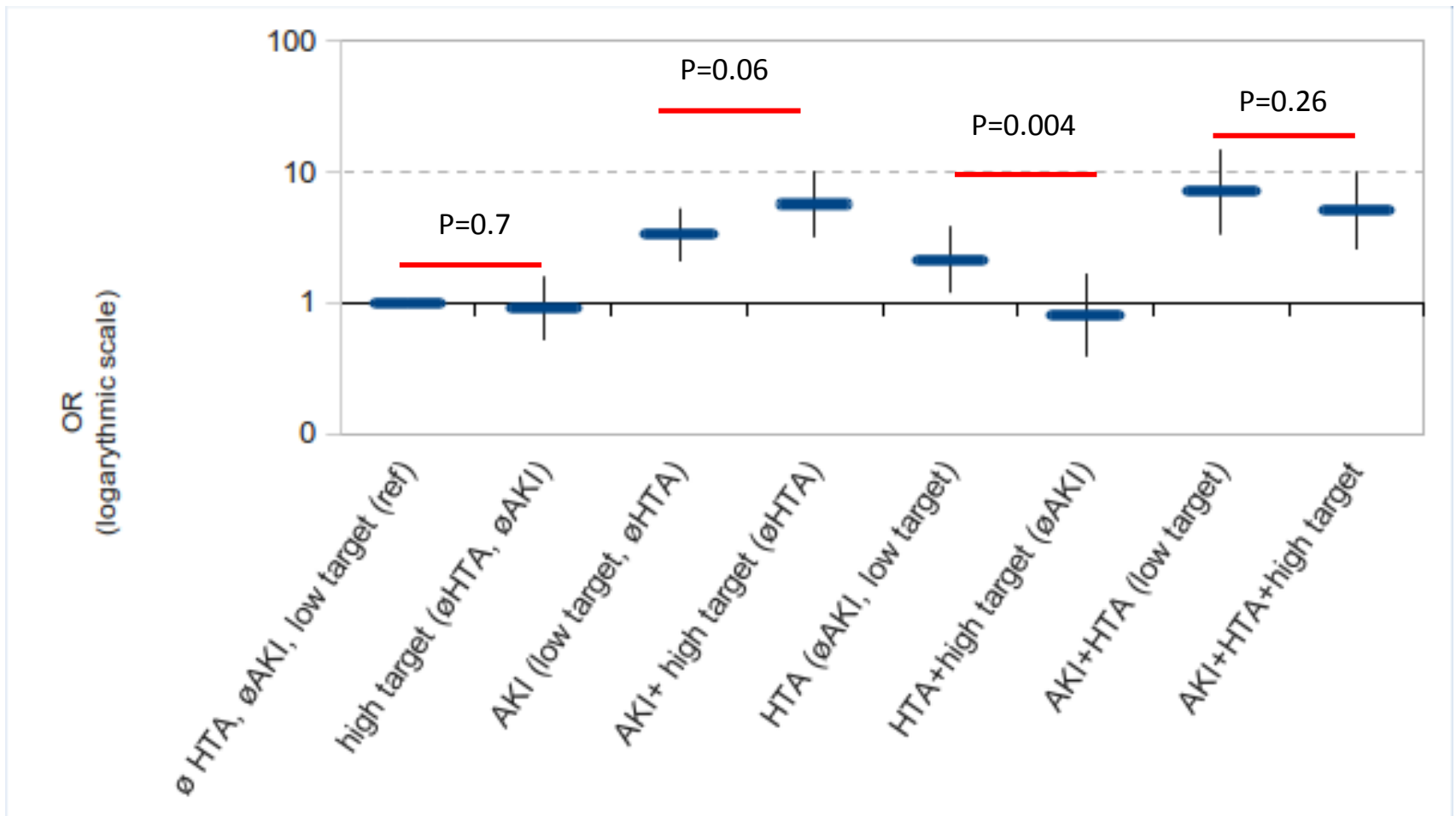
NS mortality

Sub Group Analysis
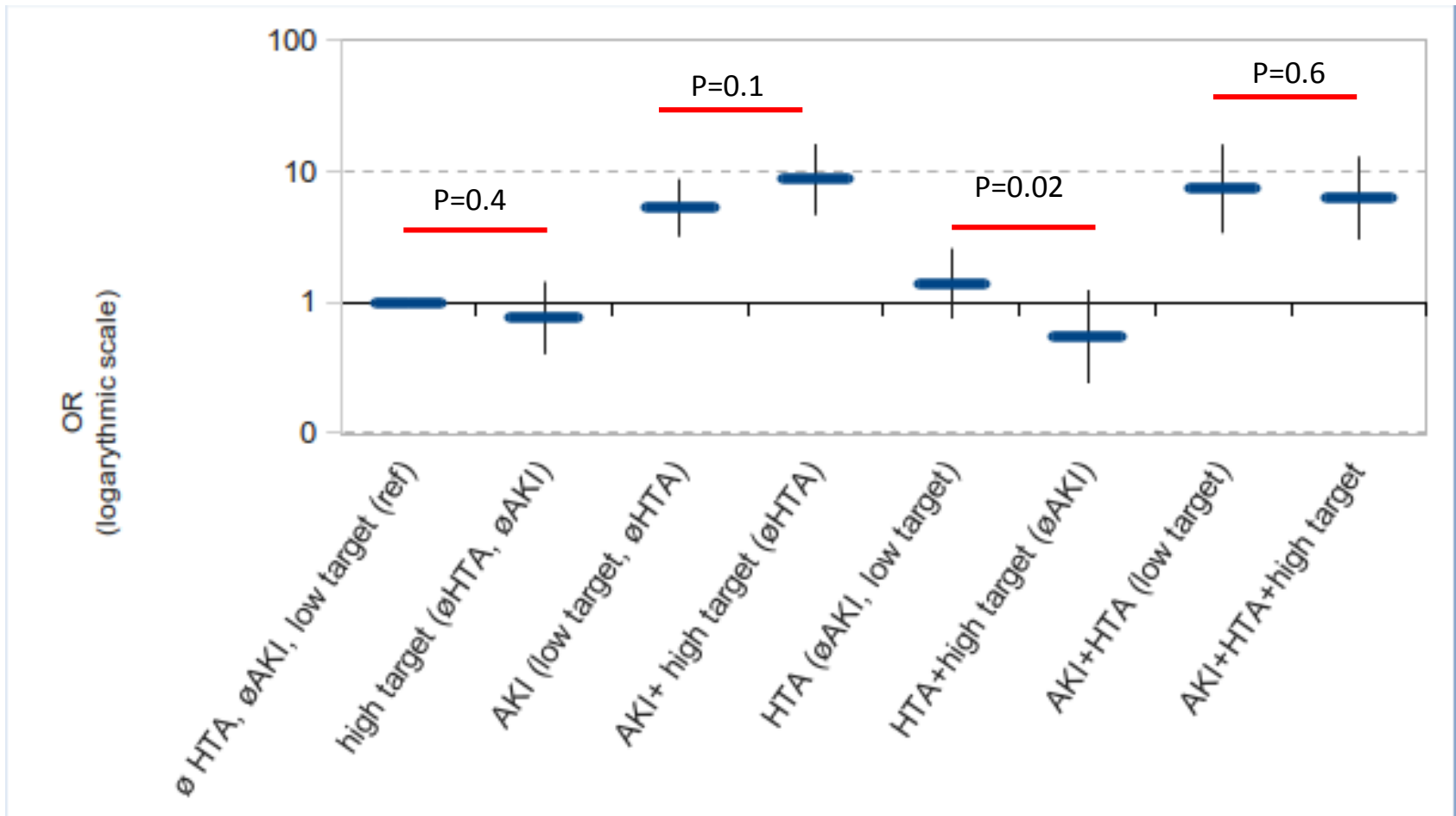
Less RRT in formerly hypertensive patients

P< 0.43

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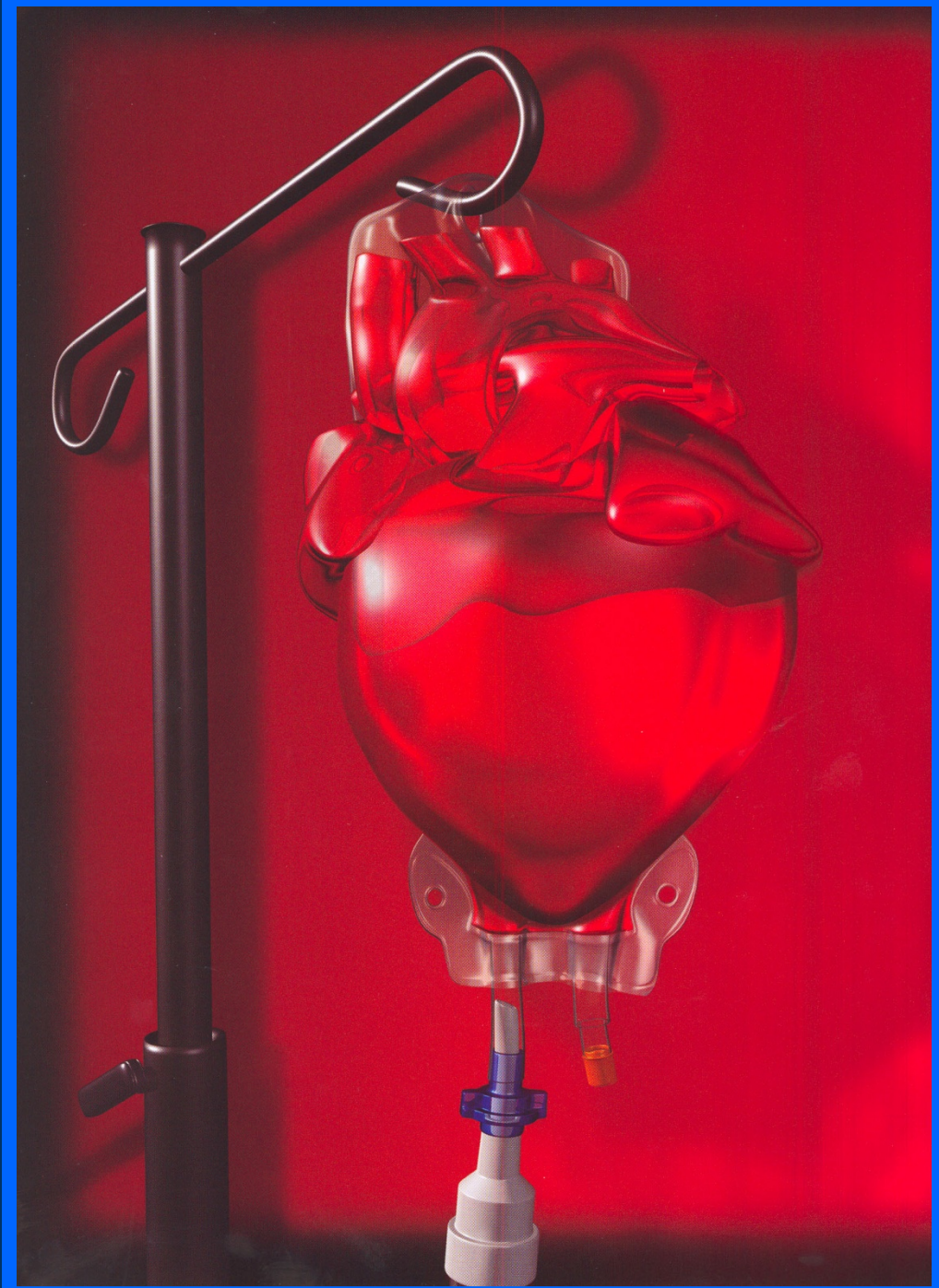
Risk of renal replacement requirement between inclusion Day 7 according to MAP, chronic hypertension and renal failure (renal SOFA≥2) at inclusion.

PAM :
65 mmHg

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

◆ MAP ≥ 65 mmHg

◆ CVC 8-12 mmHg

UH ≥ 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

Nathan I. Shapiro, MD, MPH

Stephen Trzeciak, MD, MPH

Ryan C. Arnold, MD

Heather A. Claremont, BFA

Jeffrey A. Kline, MD

for the Emergency Medicine Shock
Research Network (EMShockNet)
Investigators

THE RATE OF SEVERE SEPSIS HOS-pitalizations 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

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~~ ~~~~~~ (intent-to-treat analysis: 95% C~~I for~~ ~~the~~ 6% difference, −3% to 15%). There were no difference in ~~tre~~atment-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

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

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

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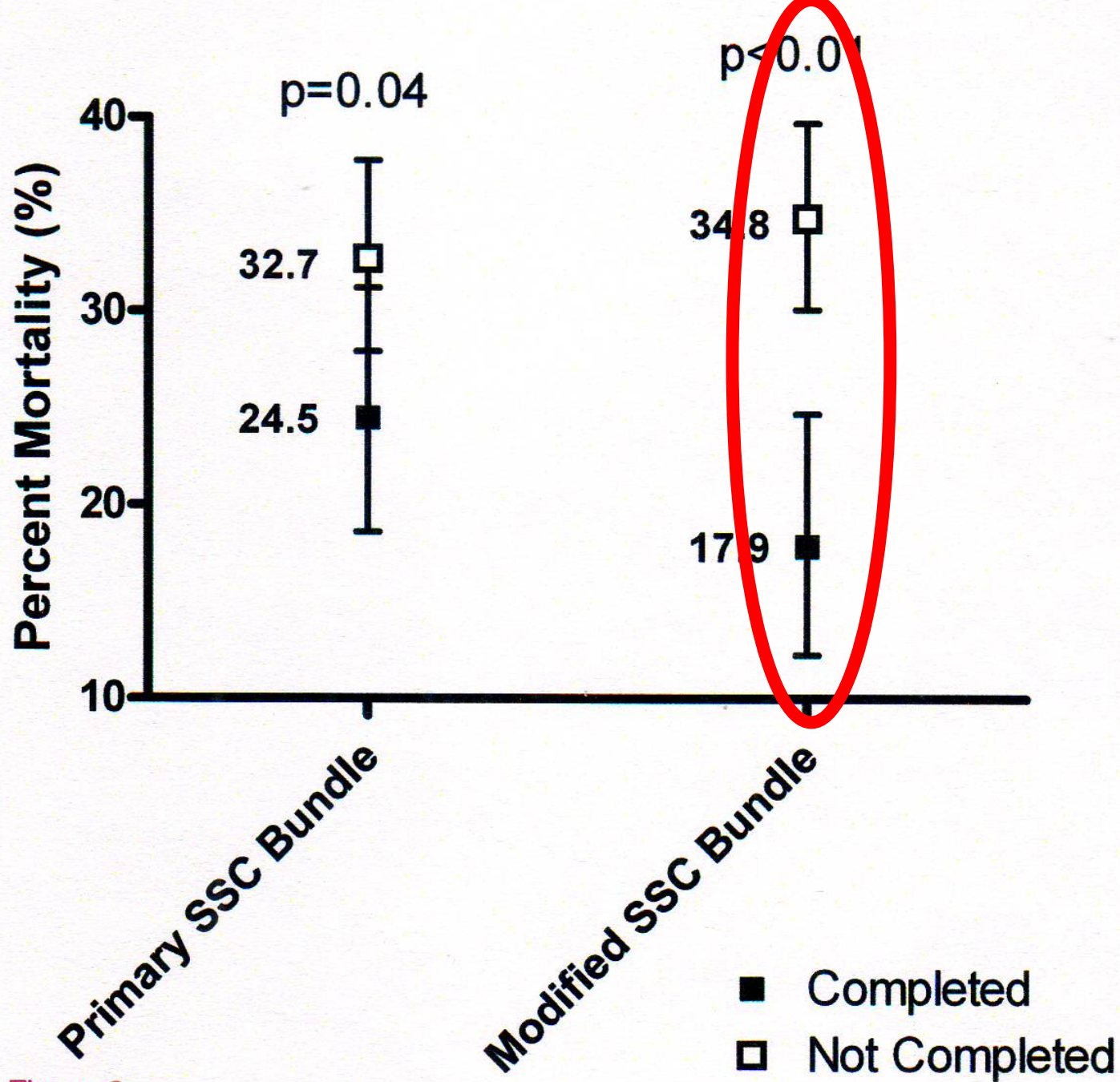Atlas Investigators (kuanws@gmail.com)

Figure 2

LACTATE
OR
SvO2
???????

LACTATE
and
SvO2

ORIGINAL ARTICLE

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

The ProCESS Investigators*

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

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

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Delaney, M.D., Ph.D., Michael Bail
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Alisa M. Higgins, M.P.H., Anna Ho
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*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.

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ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

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

- ARISE , ProCESS and ProMISe do not reflect the totality of septic patients

- Mortality may be very high in the most severe patients

Sub group Analysis

D Angus ESICM 2015
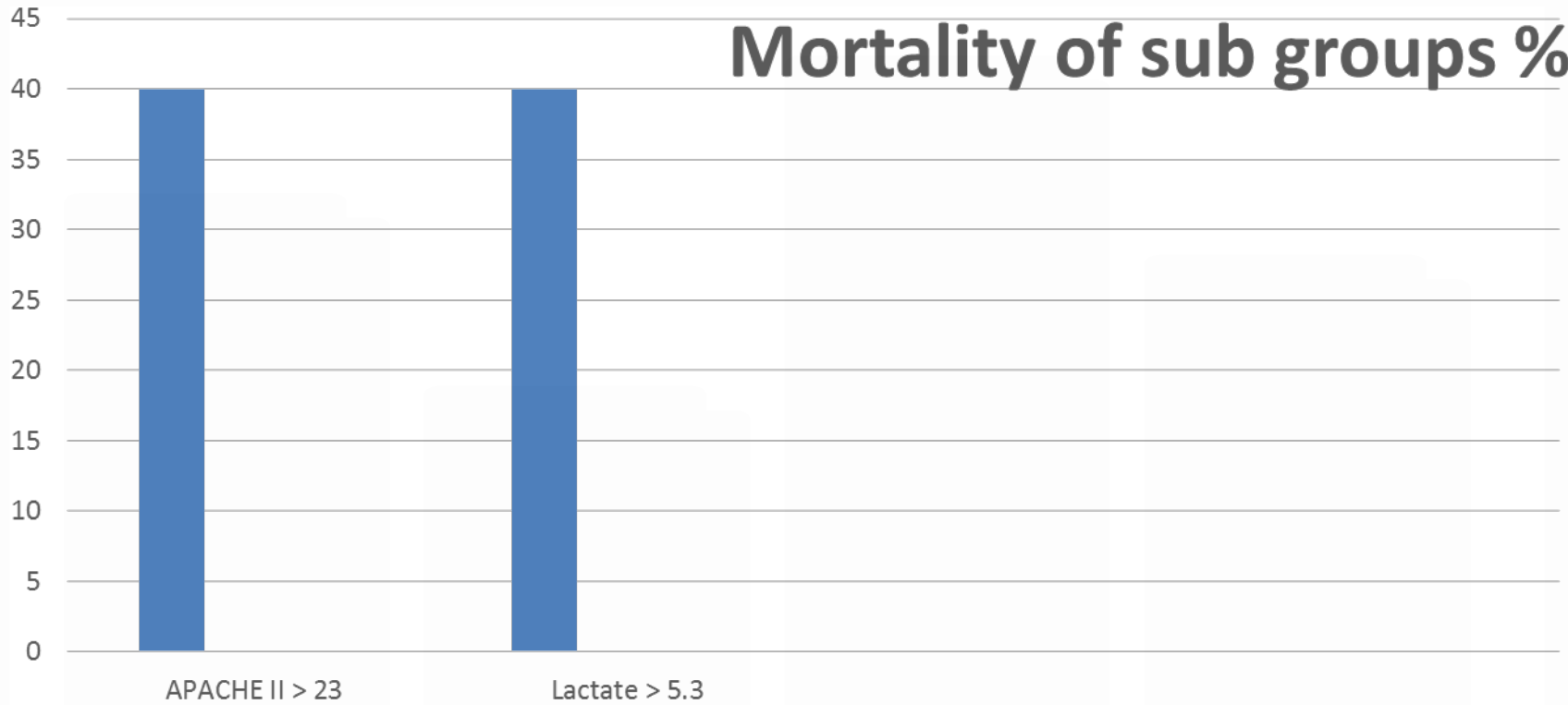
Table 1. Baseline haemodynamic variables at enrolment of intervention trials

	Refractory hypotension (%)	Lactate >4 mmol/l (%)	ScvO$_2$ (%)	Lactate (mmol/l)	Hospital mortality (%)
EGDT [5][a]	51.1–54.6	79–80	48.6–49.2	6.9–7.7	30.5–46.5
Holst et al. [58■■]	All	n/a	68–69	2.4–2.7	43–45
ProCESS [7■■][b]	53.5–55.6	59.0–60.7	71	4.8–5.0	18.2–21.0
ARISE [9■■][b]	69.8–70.0	46.3–46.5	72.7	4.2–4.4	14.5–15.7
ProMISE [8■■][b]	54.1–55.6	63.7–65.4	70.1	5.1–5.2	24.0–25.0
Jones et al. [59][a]	74–82	39	74	3.9–4.2	16.7–22.0

ARISE, Australasian Resuscitation in Sepsis Evaluation; EGDT, early goal-directed therapy; n/a, not available; ProCESS, Protocolised Care for Early Septic Shock; ProMISE, Protocolised Management in Sepsis.
[a]Refractory hypotension to 20–30 ml/kg of intravenous fluids.
[b]Refractory hypotension to 1 l bolus of intravenous fluids.

CrossMark

D. C. Angus
A. E. Barnato
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R. Bellomo
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M. Singer
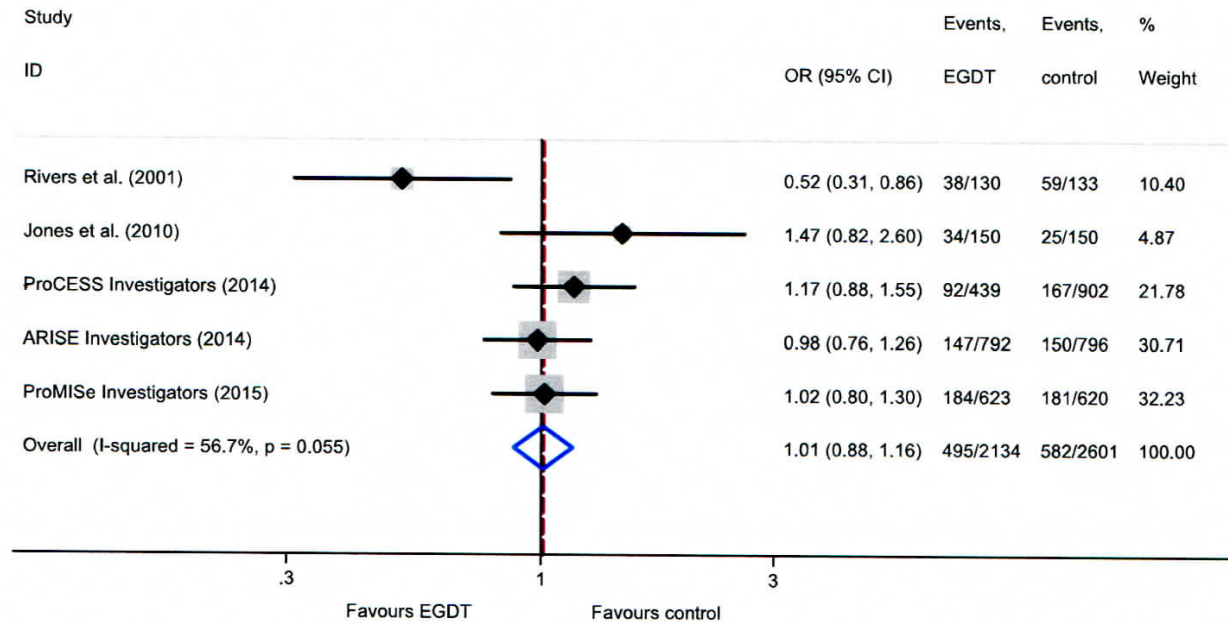S. A. R. Webb
L. A. Weissfeld
D. M. Yealy
J. D. Young

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

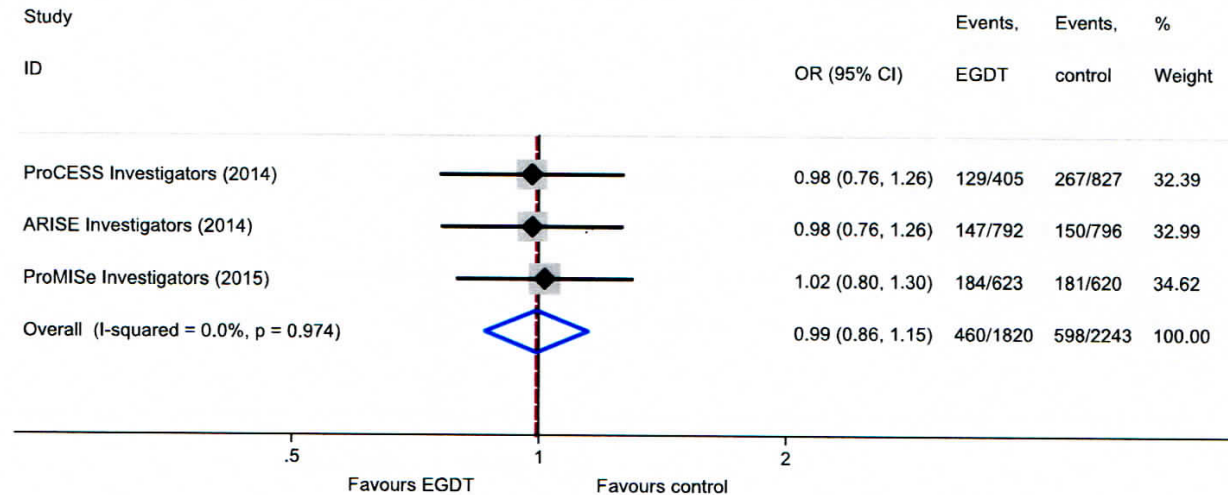**Table 1** Characteristics of included studies for the primary and secondary objectives

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 ≥ 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, $P = 0.08$]
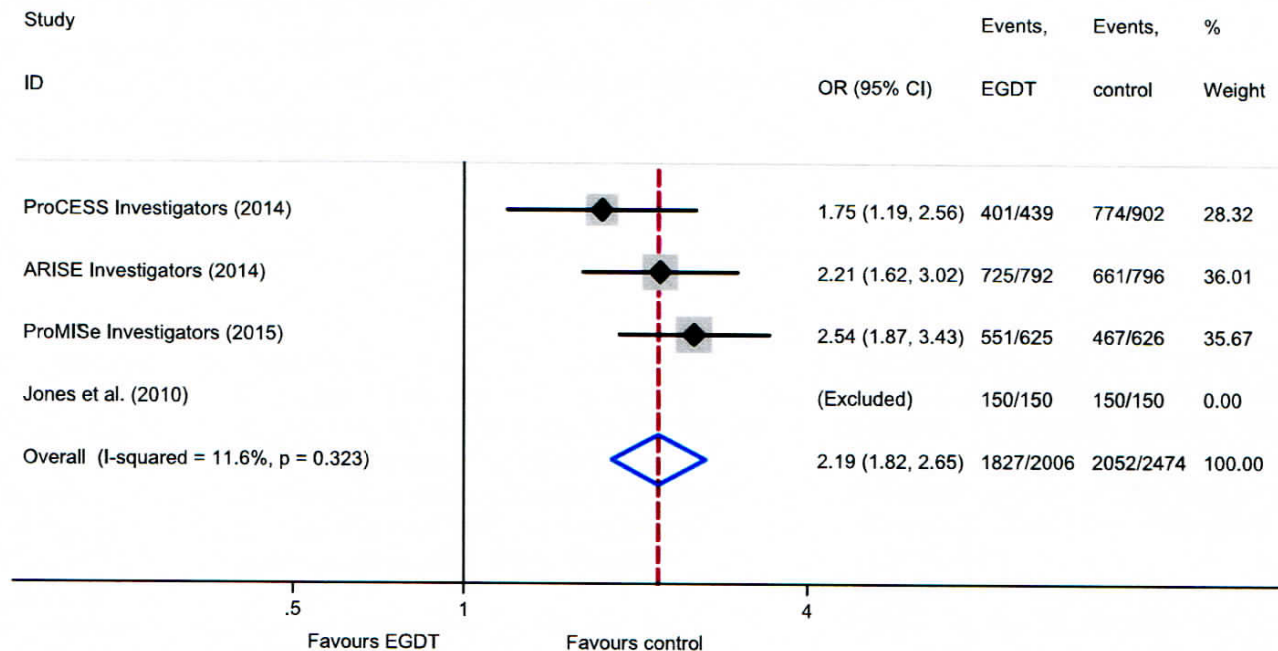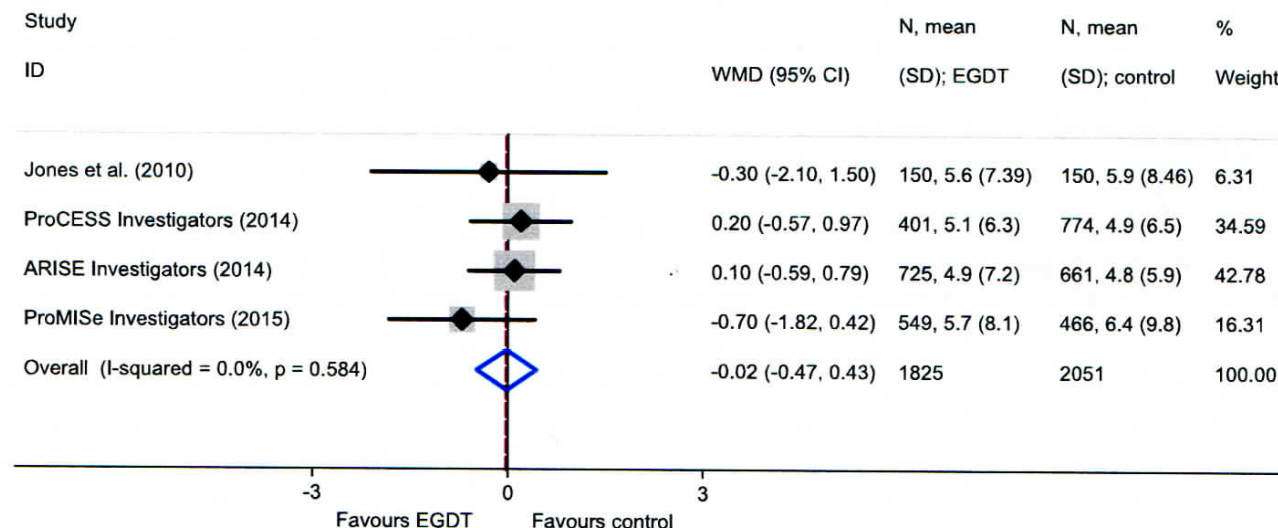
Fig. 3 Effect of EGDT on ICU utilisation in patients presenting to the emergency department with septic shock. **a** ICU admission[a]. **b** ICU length of stay for patients admitted to ICU (days). *ICU* intensive care unit, *EGDT* early goal-directed therapy, *OR* odds ratio, *CI* confidence interval, *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

A ICU admission[a]

Study ID	OR (95% CI)	Events, EGDT	Events, control	% Weight
ProCESS Investigators (2014)	1.75 (1.19, 2.56)	401/439	774/902	28.32
ARISE Investigators (2014)	2.21 (1.62, 3.02)	725/792	661/796	36.01
ProMISe Investigators (2015)	2.54 (1.87, 3.43)	551/625	467/626	35.67
Jones et al. (2010)	(Excluded)	150/150	150/150	0.00
Overall (I-squared = 11.6%, p = 0.323)	2.19 (1.82, 2.65)	1827/2006	2052/2474	100.00

.5   1   4

Favours EGDT   Favours control

B ICU length of stay for patients admitted to ICU (days)

Study ID	WMD (95% CI)	N, mean (SD); EGDT	N, mean (SD); control	% Weight
Jones et al. (2010)	-0.30 (-2.10, 1.50)	150, 5.6 (7.39)	150, 5.9 (8.46)	6.31
ProCESS Investigators (2014)	0.20 (-0.57, 0.97)	401, 5.1 (6.3)	774, 4.9 (6.5)	34.59
ARISE Investigators (2014)	0.10 (-0.59, 0.79)	725, 4.9 (7.2)	661, 4.8 (5.9)	42.78
ProMISe Investigators (2015)	-0.70 (-1.82, 0.42)	549, 5.7 (8.1)	466, 6.4 (9.8)	16.31
Overall (I-squared = 0.0%, p = 0.584)	-0.02 (-0.47, 0.43)	1825	2051	100.00

-3   0   3

Favours EGDT   Favours control

Central Venous Catheter

- **Secured IV access**

- **Very low rate of complications**

- **+/- 100% success with echo-guidance**

- **Multilumens**

- **Secured infusion of potent vasopressors**

- **Used for more than 4 days**

•Why not draw samples for ScVO2 ???

Take Home Messages 1

❖Avoid fluid overload

❖Balanced solutions and albumin

❖Norepinephrine

❖Target MAP 60-65 mmHg

❖Control lactate

Take Home Messages 2

❖In the ED no central venous access

❖In the ED no ScVO2

❖In the ICU ,in case of late septic shock :

Invasive monitoring

ScVO2 and lactate

Initial Resuscitation

- ◆ MAP $\geq$ 65 mmHg ??
- ◆ ~~CVP 8 - 12 mmHg~~
- ◆ UF $\geq$ 0.5 ml.kg^{-1}.hr^{-1}
- ◆ ScvO$_2$ $\geq$ 70% $\leq$ 80%
- ◆ ~~SvO$_2$ $\geq$ 65%~~
- ◆ ↓ Lactate

Aspects Dynamiques

1ere heure

- ◆ gazométrie
- ◆ lactate
- ◆ cultures
- ◆ ATB
- ◆ IV périph
- ◆ vasopresseur
- ◆ fluides

2eme heure

- ◆ PAM 65 mmHg
- ◆ artère
- ◆ DPP SVV
- ◆ PVC SvO_2
- ◆ lactate

6eme heure

- ◆ ScvO2 > 70%
- ◆ SvO2 > 65 %????
- ◆ Lactate ↘
- ◆ Pression plateau < 30 mmHg

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