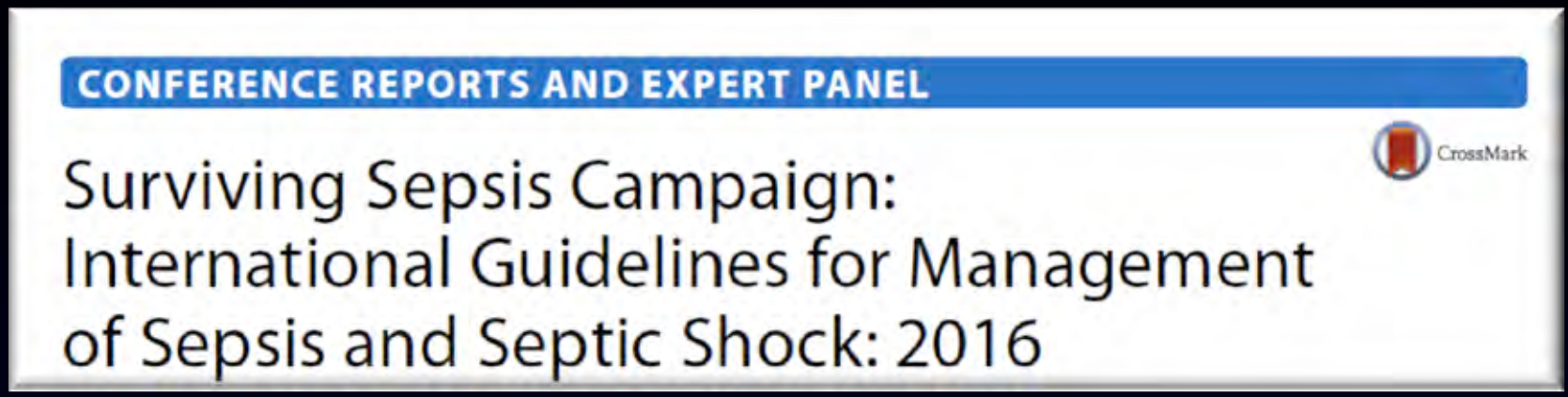
Actualités de la prise en charge hémodynamique initiale



Daniel De Backer

Head Dept Intensive Care, CHIREC hospitals, Belgium
Professor of Intensive Care, Université Libre de Bruxelles
Past- President European Society of Intensive Care Medicine

Intensive Care Med
DOI 10.1007/s00134-017-4683-6

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[27]

Society of Critical Care Medicine

Surviving Sepsis Campaign

ESICM
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

The Intensive Connection

JAMA 2017

VIEWPOINT

Surviving Sepsis Guidelines
A Continuous Move Toward Better Care of Patients With Sepsis

Daniel De Backer, MD
Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium.

Todd Dorman, MD,

Sepsis is a life-threatening condition that affects more than 1 million patients a year in the United States and even more patients around the globe and is one of the leading causes of death. Since the Declaration of Barcelona in 2002, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (SCCM) have launched several initiatives to decrease

cases; for example, those with a history of cardiac dysfunction who develop pneumonia, when the nature of circulatory failure is not always obvious).

Another important advance is that the new guidelines recommend the use of dynamic (ie, pulse or stroke volume variations induced by mechanical ventilation or passive leg raise test) over static variables (in-

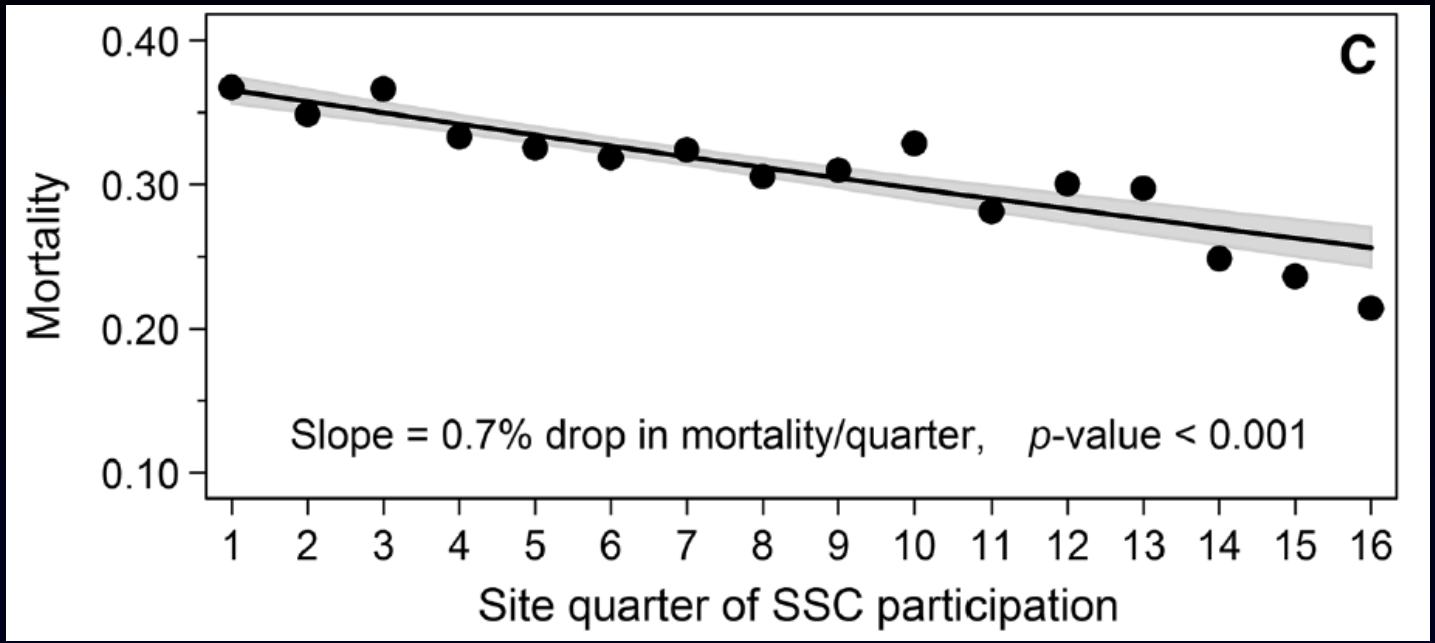
Intensive Care Med
DOI 10.1007/s00134-014-3496-0

ORIGINAL

ICM 2014

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



29470 septic pts

Voluntary submission of data

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

NEJM 2017

Bundle	Eligible	Elements
3-hour	Severe sepsis or septic shock	Administration of antibiotics within 1 hour of protocol initiation *
		Drawing blood cultures prior to administration of antibiotics
		Measurement of blood lactate within 3 hours of protocol initiation
6-hour	Above plus hypotension (SBP<90) or serum lactate ≥4.0 mmol/L	Administration of a 30cc/kg intravenous fluid bolus
		Administration of vasopressors for refractory hypotension
		Re-measurement of serum lactate within 6 hours of protocol initiation

NY state
49331 pts
149 hosp

Mandatory reporting

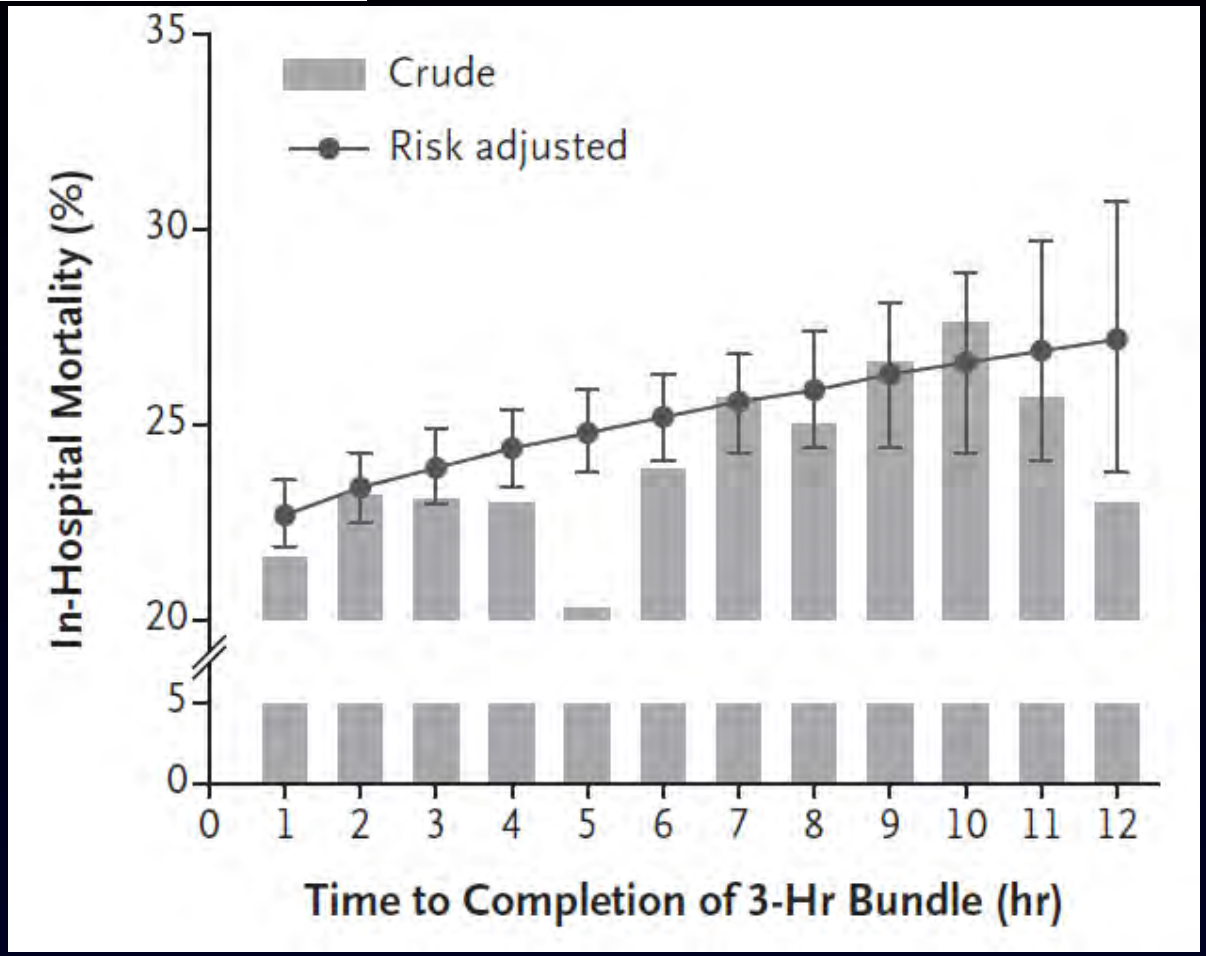
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

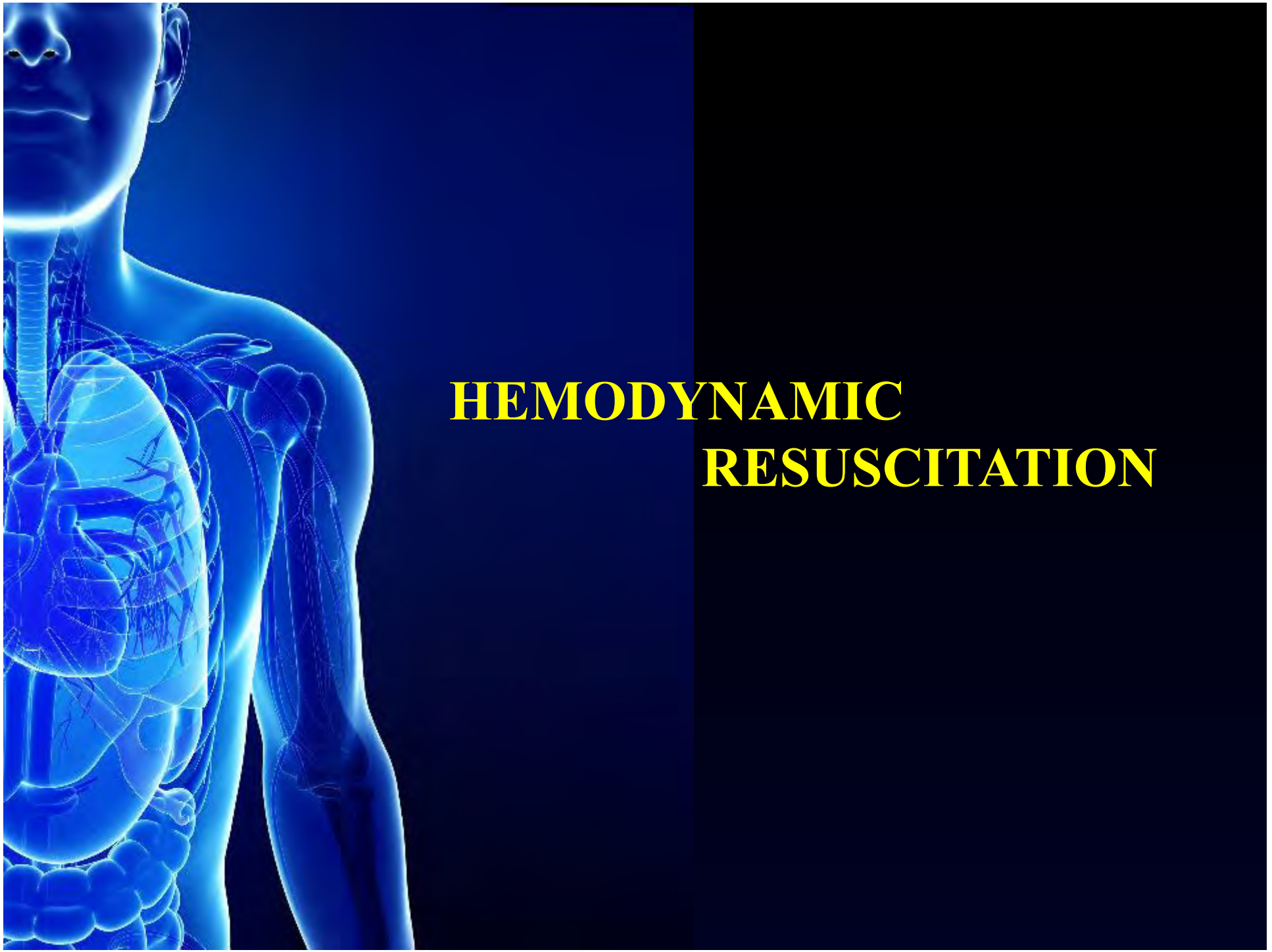
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

NEJM 2017



NY state
49331 pts
149 hosp



HEMODYNAMIC RESUSCITATION

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Rhodes et al
ICM 2017
CCM 2017

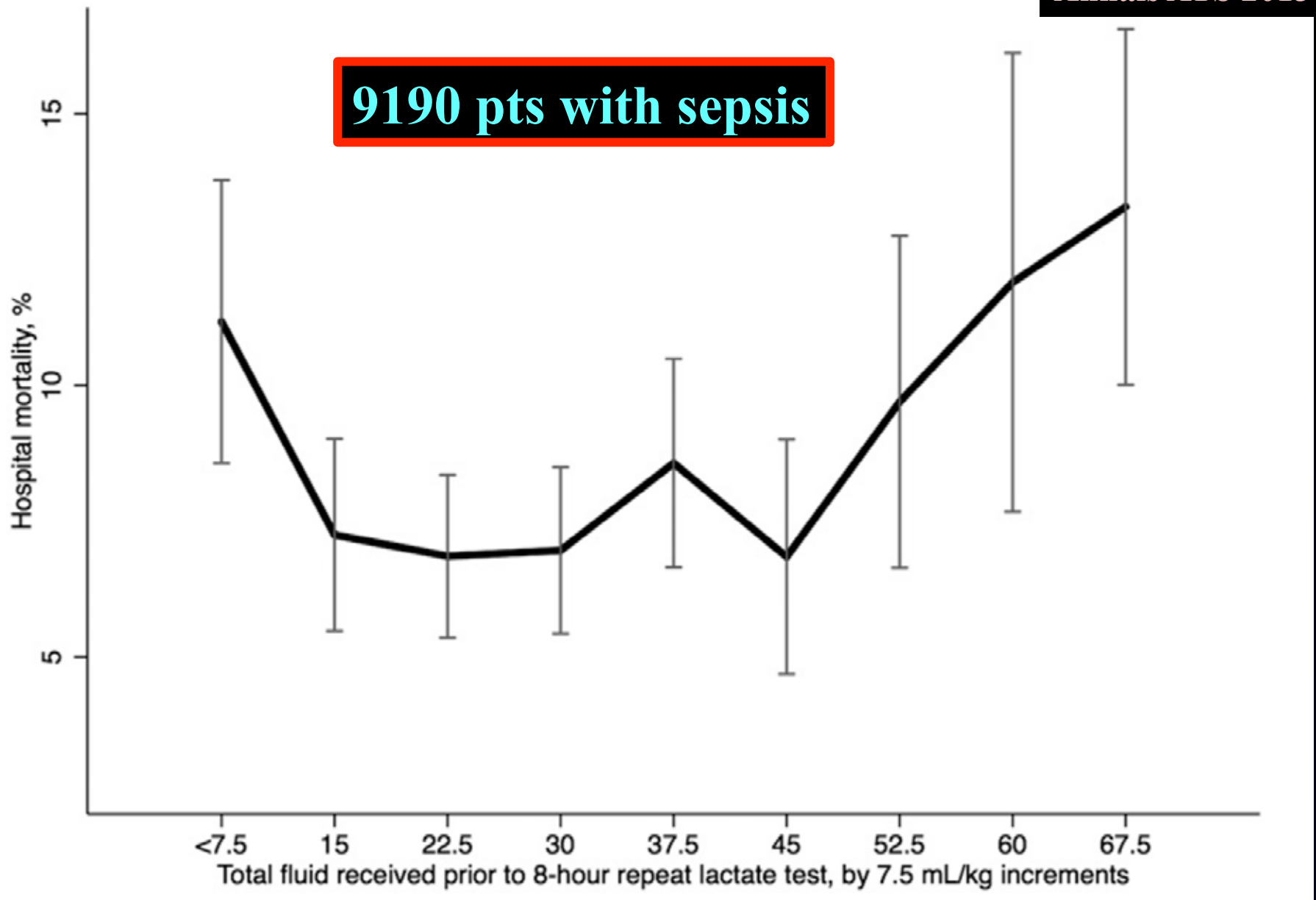
A. INITIAL RESUSCITATION

2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence).

Not too much but also not limited….

Liu V et al
Annals ATS 2013

9190 pts with sepsis



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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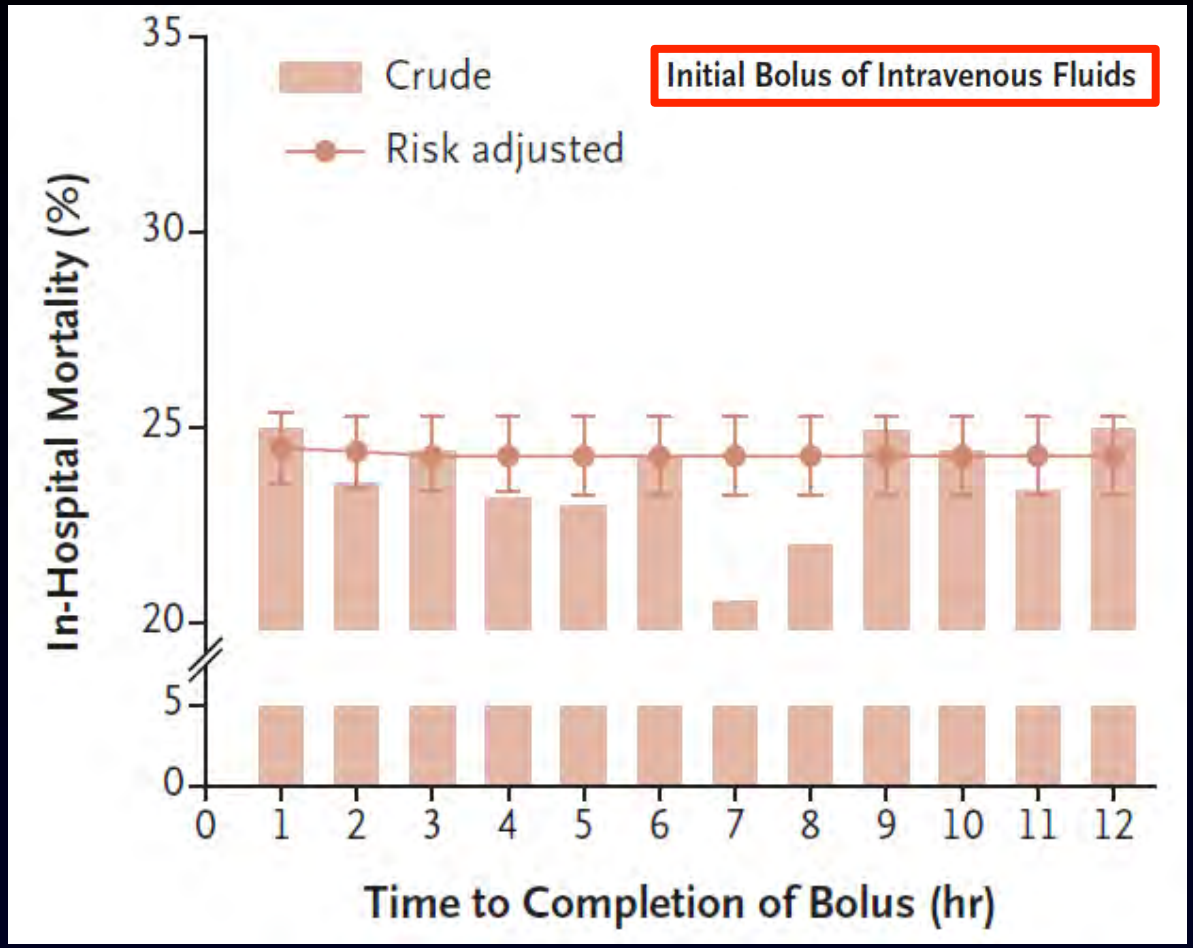
Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

NEJM 2017

Caution: the delay in fluid administration may be related to lower initial severity



NY state
49331 pts
149 hosp

The NEW ENGLAND JOURNAL of MEDICINE

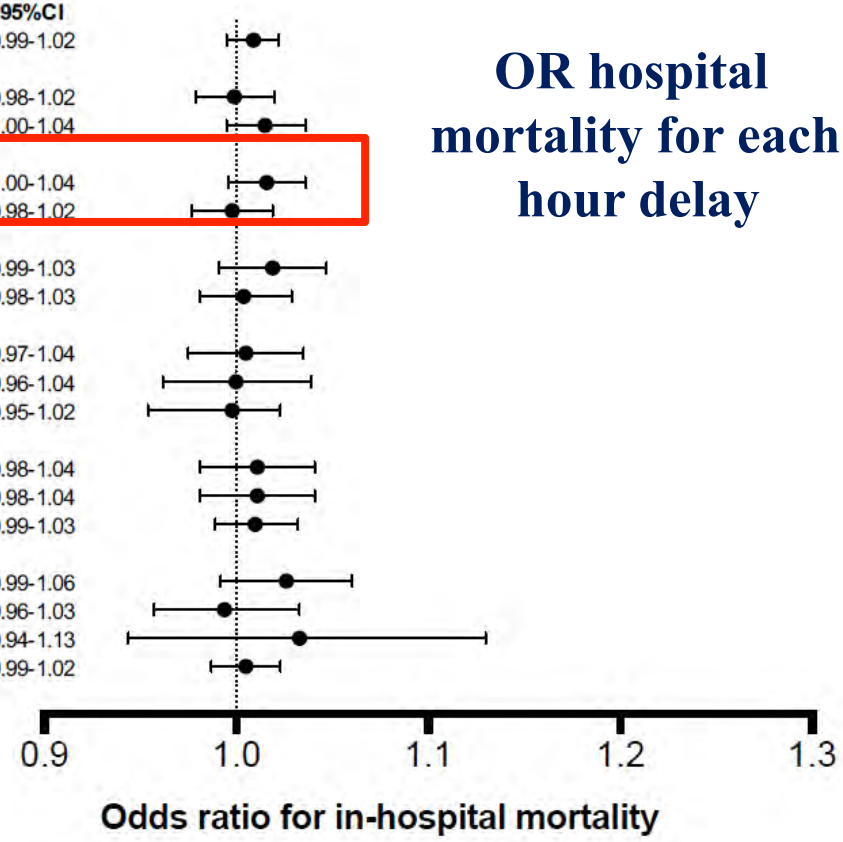
ORIGINAL ARTICLE

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

NEJM 2017

Model	No.	Odds ratio	95%CI
All cases	49,331	1.01	0.99-1.02
Gender			
Male	25,689	1.00	0.98-1.02
Female	23,634	1.02	1.00-1.04
Vasopressors			
Yes	16,721	1.02	1.00-1.04
No	32,610	1.00	0.98-1.02
Admission source			
Home	33,464	1.01	0.99-1.03
Other	15,867	1.00	0.98-1.03
Comorbidities			
Congestive heart failure	10,092	1.00	0.97-1.04
Hemodialysis	5,207	1.00	0.96-1.04
Chronic respiratory failure	5,738	0.99	0.95-1.02
Source of infection			
Respiratory	19,839	1.01	0.98-1.04
Urinary	13,439	1.01	0.98-1.04
Other	16,053	1.01	0.99-1.03
Bacteremia			
Gram positive	7,175	1.03	0.99-1.06
Gram negative	6,431	0.99	0.96-1.03
Other	965	1.03	0.94-1.13
None	34,757	1.00	0.99-1.02



OR hospital mortality for each hour delay

NY state
49331 pts
149 hosp

A. INITIAL RESUSCITATION

Rhodes et al
ICM 2017
CCM 2017

2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence).

The good

- Emphasis on Fluid resuscitation
- Amount in agreement with observational data

The bad

- No strong data
- One size fits all?

The ugly

- Why delaying therapy?

Rhodes et al
ICM 2017
CCM 2017

A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

Surviving Sepsis Campaign

2012 Recommendation for Initial Resuscitation.

We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scvo2 ≥ 70%.

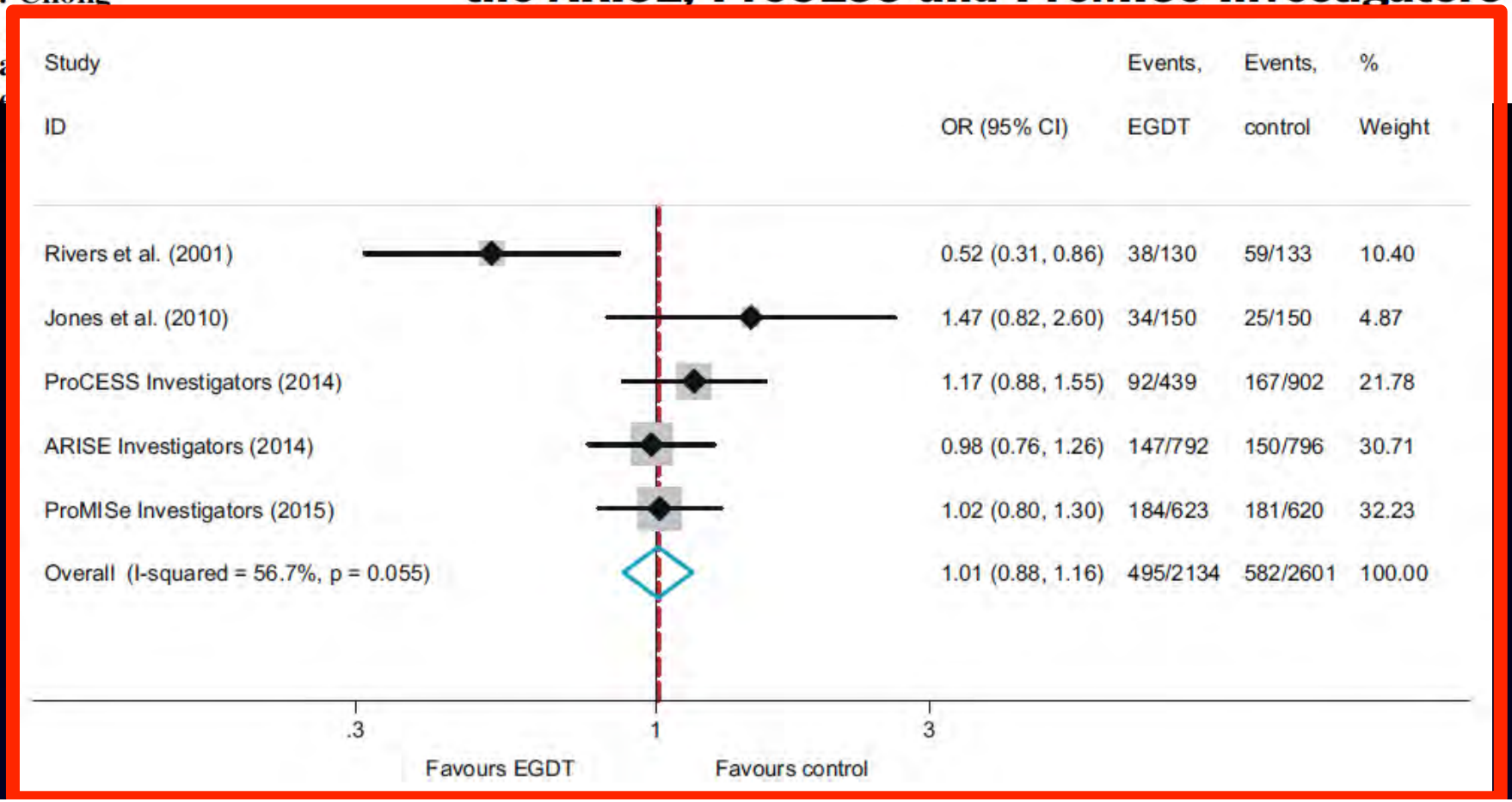
Intensive Care Med
DOI 10.1007/s00134-015-3822-1

SEVEN-DAY PROFILE PUBLICATION

ICM 2015

D. C. Angus
A. E. Barnato
D. Bell
R. Bellomo
C.-R. Chong
T. J.
A. Da
A. De

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



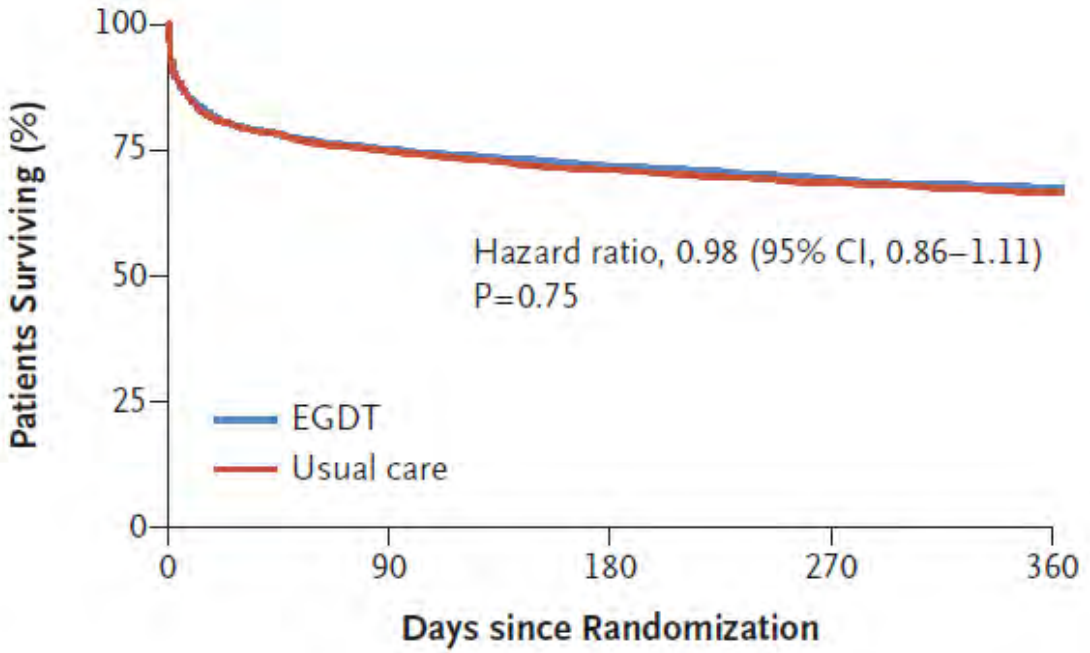
The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2017

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*



No. at Risk					
EGDT	1857	1391	1287	1209	1119
Usual care	1880	1395	1295	1206	1110

Rhodes et al
ICM 2017
CCM 2017

Although this protocol cannot now be recommended from its evidence base, bedside clinicians still need guidance as to how to approach this group of patients who have significant mortality and morbidity. We recommend, therefore, that these patients be viewed as having a medical emergency that necessitates urgent assessment and treatment. As part of this, we recommend that initial

Intensive Care Med
DOI 10.1007/s00134-016-4295-6

EDITORIAL

Early goal-directed therapy: do we have a definitive answer?

Daniel De Backer[1]* and Jean-Louis Vincent[2]

Most patient already reached target ScvO2 values in the recent trials

	Rivers et al	PROCESS	ARISE	PROMISE
ScvO2 %	49	71	73	70

Rivers et al NEJM 2001

Angus D et al NEJM 2014

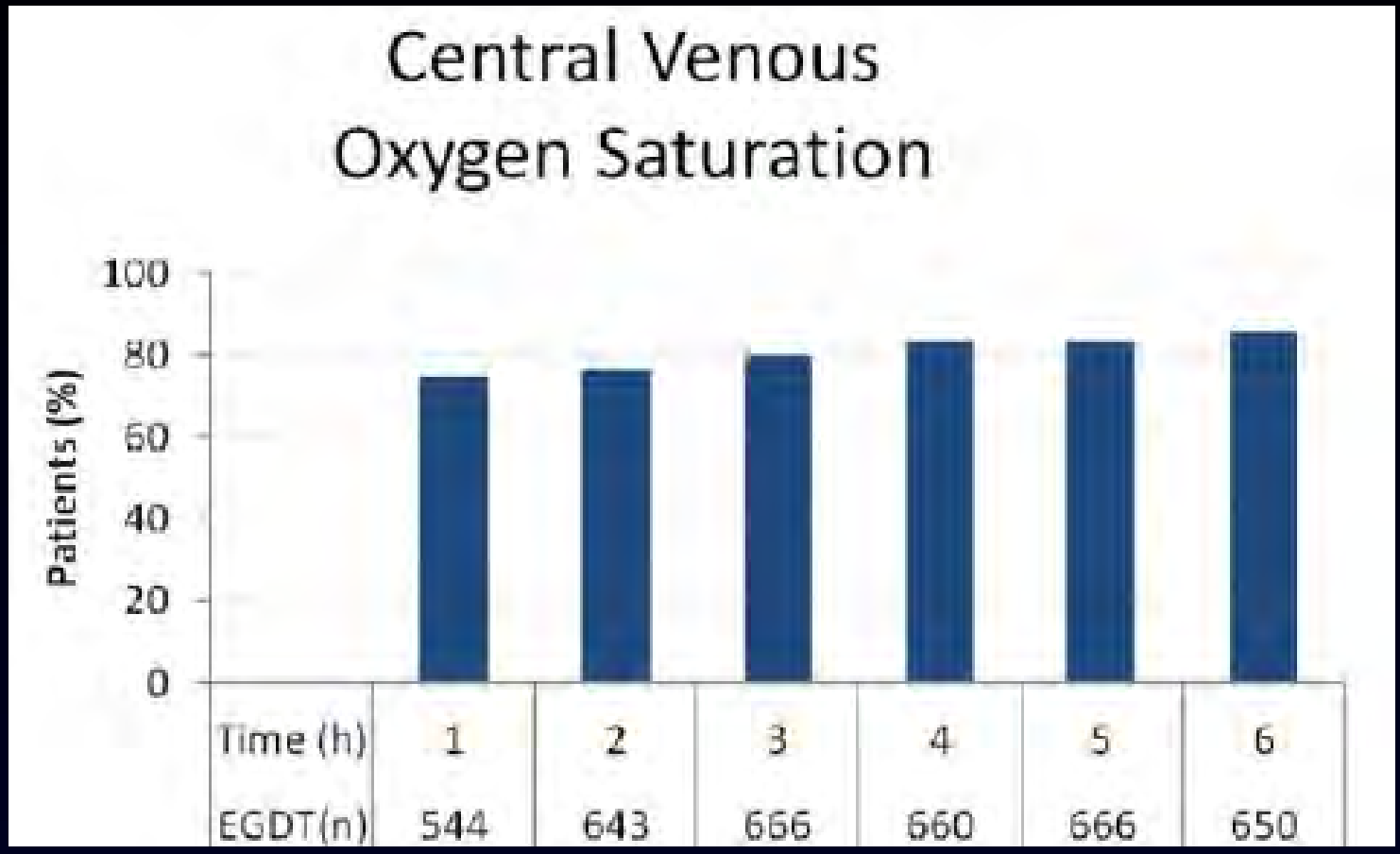
Peake S et al NEJM 2014

Mouncey P et al NEJM 2015

Inclusion: refractory hypotension and/or lactate ≥4 (despite fluids)

Most patients reached ScvO2 goal at inclusion and the proposed protocol was not able to significantly increase this proportion over time !

Peake S et al
NEJM 2014



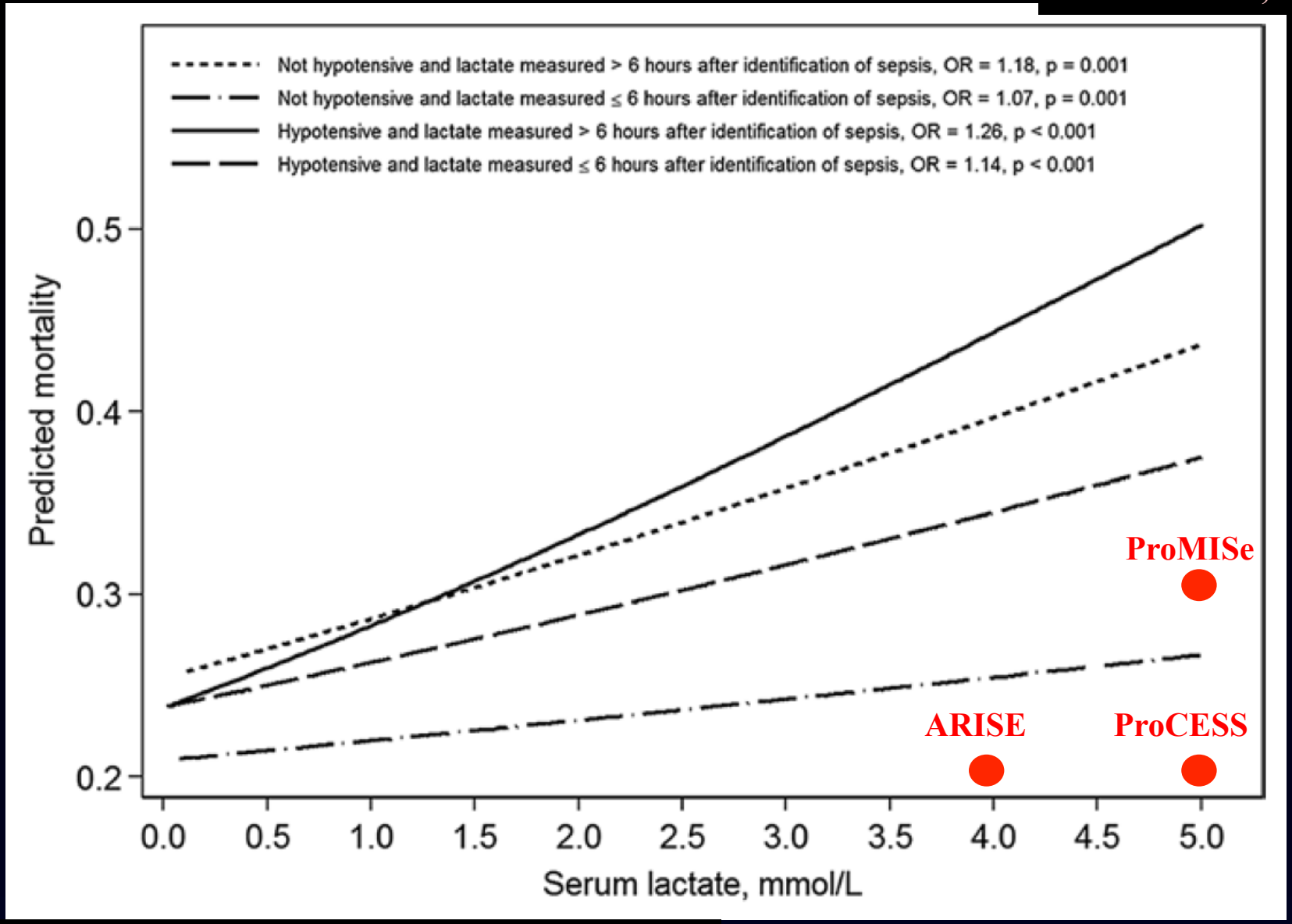
Major differences in mortality in control arm

	Rivers et al	PROCESS	ARISE	PROMISE
Mortality % (ctrl)	50	19	19	29
ScvO2 %	49	71	73	70
	Rivers et al NEJM 2001	Angus D et al NEJM 2014	Peake S et al NEJM 2014	Mouncey P et al NEJM 2015

Inclusion: refractory hypotension and/or lactate ≥4 (despite fluids)

Prognostic value of lacate and impact of time from diagnosis

Casserly B et al
CCM 43:567;20150



28150 pts / 218 sites / SSC database

Inclusion rates ?

Angus D et al
NEJM 2014

- 0.9 Patients/ centre / month (included)
  3.9 Patients/ centre / month (screened)
  (ED with at least 40000 admissions/ year)

Peake S et al
NEJM 2014

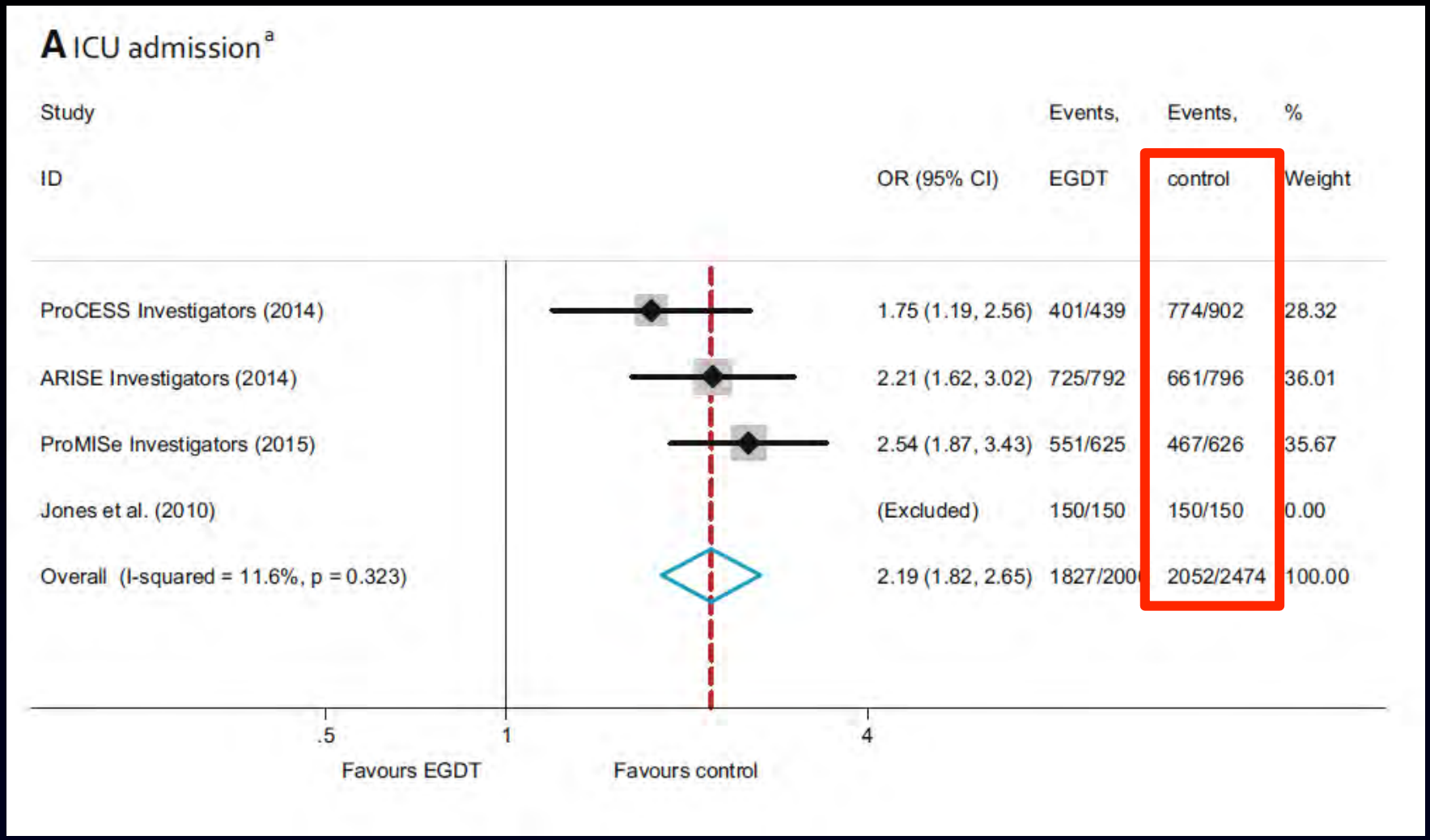
- 0.5 Patients/ centre / month (included)
  1.6 Patients/ centre / month (screened)

Rowan et al
NEJM 2015

- 0.5 Patients/ centre / month (included)
  1.6 Patients/ centre / month (screened)

20 % of these « septic shock » patients were not admitted to the ICU !?

Angus D et al ICM 20145



Inclusion: refractory hypotension and/or lactate ≥4 (despite fluids)

Intensive Care Med
DOI 10.1007/s00134-016-4295-6

EDITORIAL

Early goal-directed therapy: do we have a definitive answer?

Daniel De Backer[1*] and Jean-Louis Vincent[2]

- **The concept remains valid**
- **Patient identification is crucial**
- **The classical EGDT may be applied when better hemodynamic strategies cannot be used**

3. **We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).**
Remarks Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.

Rhodes et al
ICM 2017
CCM 2017

The good

- **Integrates other variables of tissue hypoperfusion to indicate fluids**
- **No rigid follow up of EGDT bundles**

The bad

- **No strong data**
- **Too evasive**

The ugly

- **No clear recommendation**

In practice ?

Rhodes et al
ICM 2017
CCM 2017

A. INITIAL RESUSCITATION

3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

What do you recommend to your junior doctors, ED colleagues, nurses,…?

Variables to use to indicate further fluid administration?

- Heart rate / blood pressure
- Skin mottling
- CVP
- Lactate
- Veno-arterial PCO_2 gradients
- Urine output
- Echo
- Other available hemodynamic measurements

Most of these variables indicate poor tissue perfusion not that the patient will respond to fluids !

Rhodes et al
ICM 2017
CCM 2017

A. INITIAL RESUSCITATION

4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).

Intensive Care Med (2014) 40:1795–1815
DOI 10.1007/s00134-014-3525-z

CONFERENCE REPORTS AND EXPERT PANEL

Maurizio Cecconi
Daniel De Backer
Massimo Antonelli
Richard Beale
Jan Bakker
Christoph Hofer
Roman Jaeschke
Alexandre Mebazaa
Michael R. Pinsky
Jean Louis Teboul
Jean Louis Vincent
Andrew Rhodes

Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

The Intensive Connection

No.	Statement/recommendation	GRADE level of recommendation; quality of evidence	Type of statement
13.	We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis	Ungraded	Best practice
14.	We suggest that, when further hemodynamic assessment is needed, echocardiography is the preferred modality to initially evaluate the type of shock as opposed to more invasive technologies	Level 2; QoE moderate (B)	Recommendation
15.	In complex patients, we suggest to additionally use pulmonary artery catheterization or transpulmonary thermodilution to determine the type of shock	Level 2; QoE low (C)	Recommendation

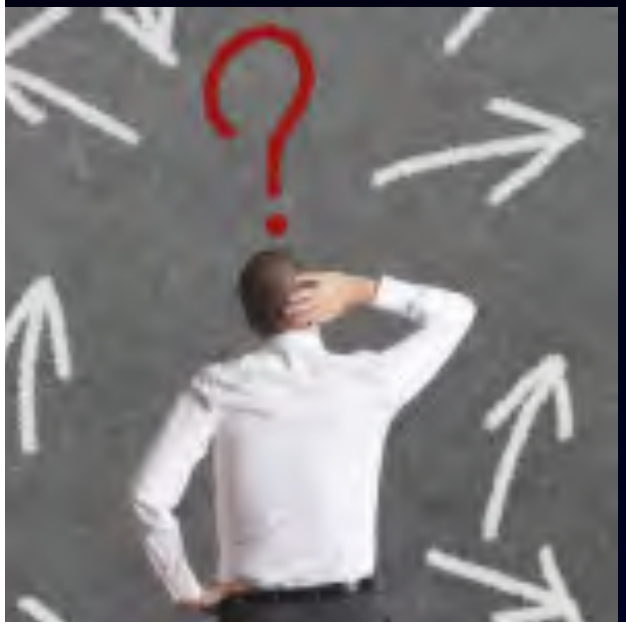
Rhodes et al
ICM 2017
CCM 2017

A. INITIAL RESUSCITATION

5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).

Dynamic variables to predict the response to fluids?

=> Evaluation of preload responsiveness during transient change in preload induced by respiration or external maneuver



Dynamic variables to predict the response to fluids?

Heart-lung interactions

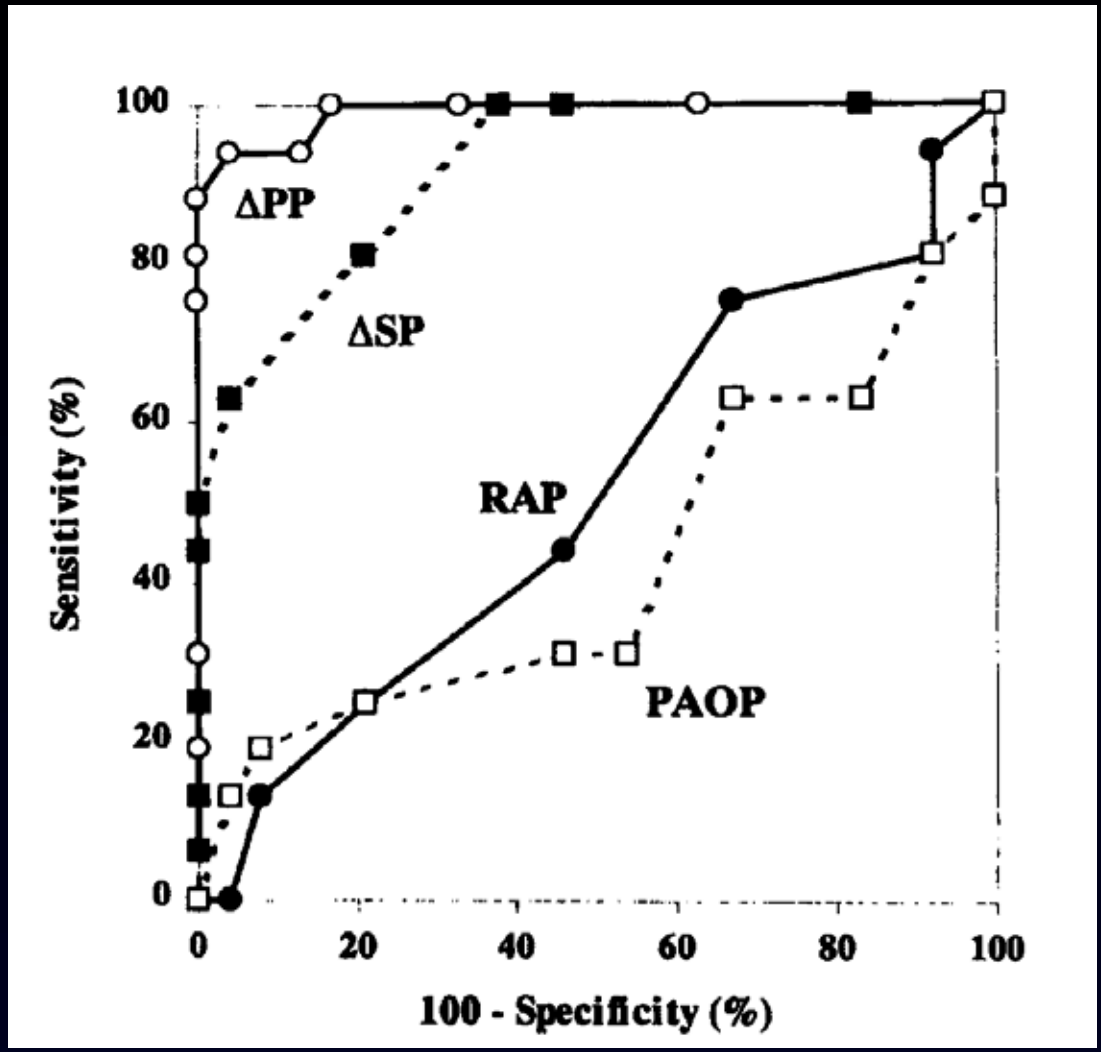
- Respiratory variations in stroke volume
- Respiratory variations in vena cava size
- Expiratory pause

External maneuvers

- Passive leg raising test

SEPSIS

Michard et al
AJRCCM 162:134;2000



N= 40

Cut-off value: 13%

DDB

Rhodes et al
ICM 2017
CCM 2017

Table 12. Pulse pressure variation in predicting fluid responsiveness in patients with sepsis or septic shock

Sensitivity	0.72 (95% CI: 0.61 to 0.81)
Specificity	0.91 (95% CI: 0.83 to 0.95)

Prevalence	40%[5]

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease quality of evidence					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 40%	
True positives (patients with Fluid responsiveness)	5 studies 219 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious	not serious	serious [2]	none	288 (244 to 324)	⊕⊕◯◯ LOW
False negatives (patients incorrectly classified as not having Fluid responsiveness)								112 (76 to 156)	
True negatives (patients without Fluid responsiveness)	5 studies 219 patients	cross-sectional (cohort type accuracy study)	serious [1]	not serious [3]	not serious	serious [4]	none	546 (498 to 570)	⊕⊕◯◯ LOW
False positives (patients incorrectly classified as having Fluid responsiveness)								54 (30 to 102)	

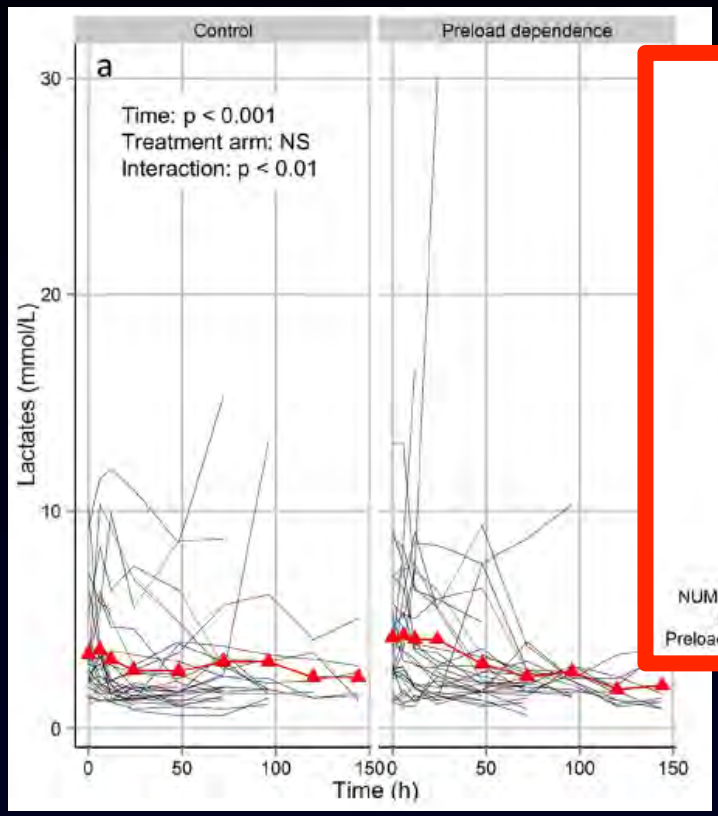
1. We downgraded the quality of evidence for risk of bias by one level, most studies were at high risk of bias with QUADAS Tool
2. We downgraded the quality for imprecision by one level, 112 per 1000 tested patients will have a false negative results, the CI of pooled sensitivity was wide
3. Although the reference test was not a static measure in included studies, we did not downgrade the quality of evidence because we can indirectly compare with other static measures
4. We downgraded the quality of evidence by one level for imprecision, small number of patients and the CI of the pooled specificity included values below the desired threshold
5. Prevalence of fluid responsiveness is estimated to be 40%, data from Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids? JAMA. 2016;316(12):1298-309.

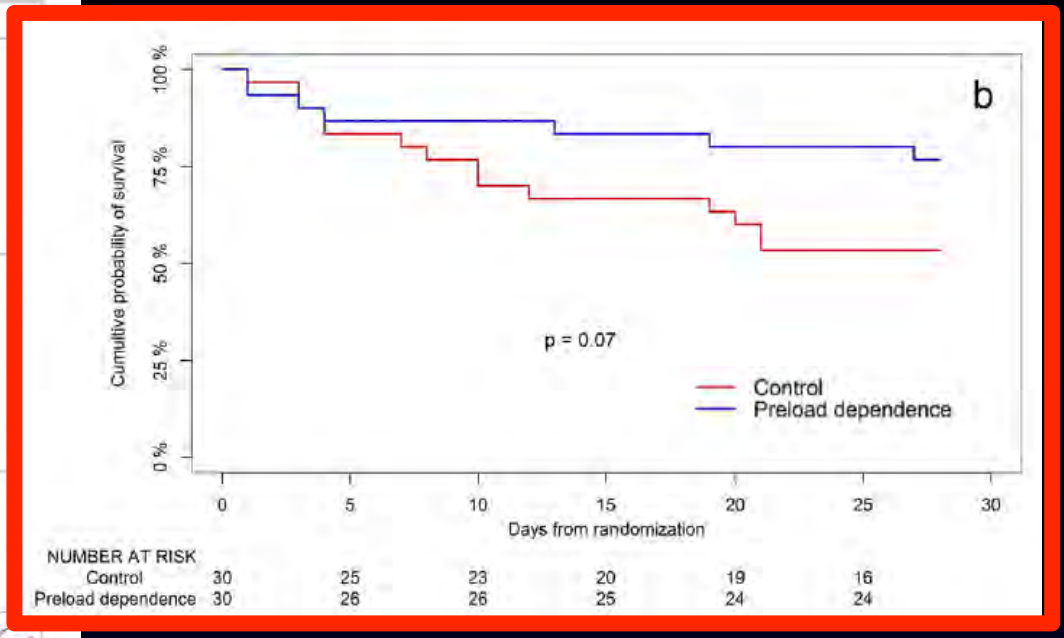
Richard et al. Critical Care (2015) 19:5
DOI 10.1186/s13054-014-0734-3

CRITICAL CARE

RESEARCH Open Access

Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial





CVP: Never an optimal prediction but still some reasonable guidance if nothing better can be used….

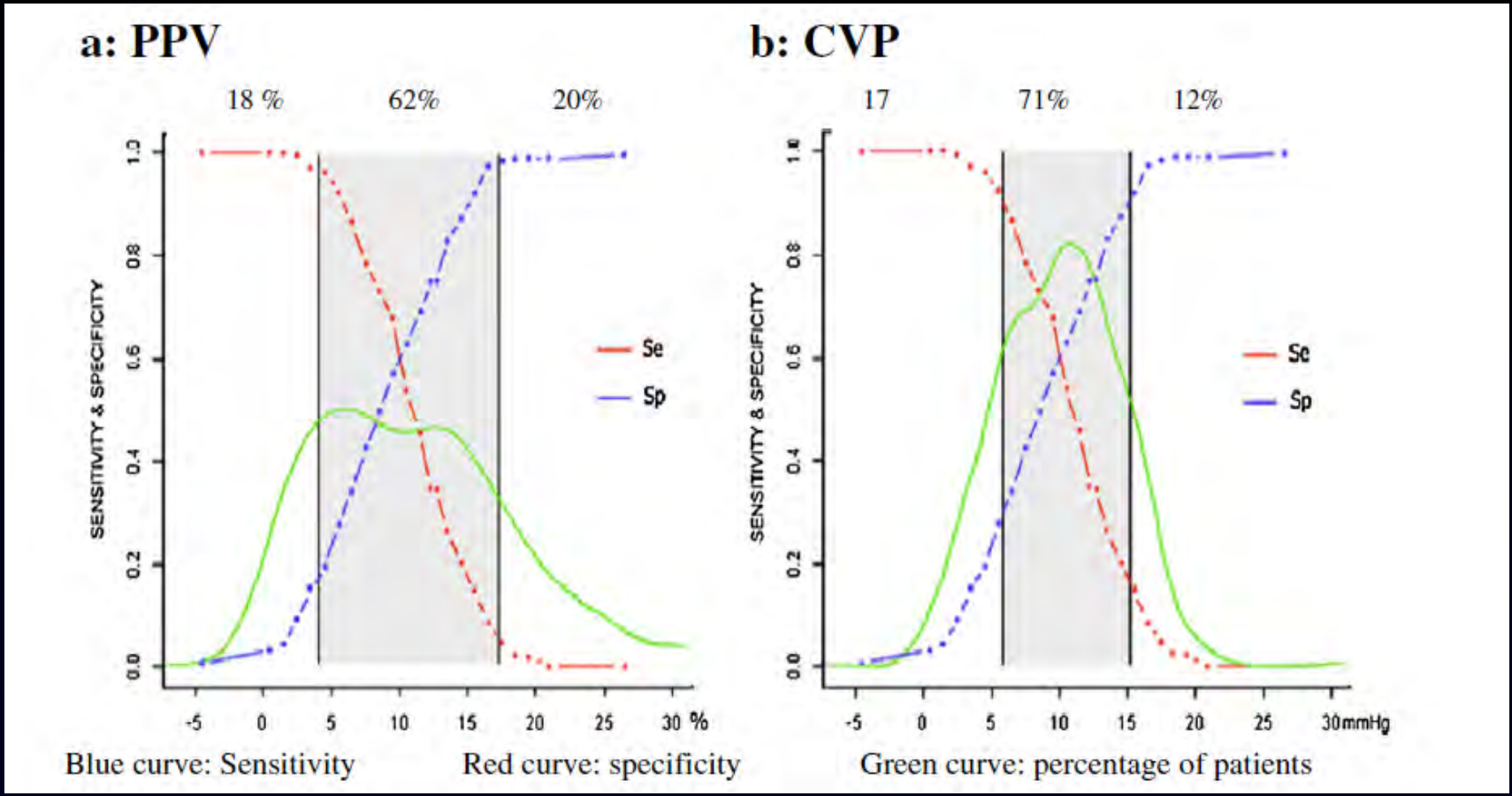
Eskesen et al
ICM 2016

CVP cut-off point (mmHg)	Number of data sets for the CVP ranges given	Positive predictive value	Negative predictive value
0	<2: 72	64 % (39–89)	52 % (49–55)
2	2–3: 125	65 % (54–76)	53 % (50–56)
4	4–5: 163	64 % (57–71)	55 % (52–59)
6	6–7: 177	59 % (54–65)	57 % (54–61)
8	8–9: 187	56 % (52–61)	59 % (56–63)
10	10–11: 161	53 % (50–57)	61 % (56–66)
12	12–13: 108	51 % (47–54)	61 % (55–67)
14	14–15: 79	50 % (47–53)	66 % (58–73)
16	16–17: 39	49 % (46–52)	64 % (54–75)
18	18–19: 22	48 % (45–51)	59 % (44–75)
20	>19: 15	48 % (45–51)	53 % (28–79)

1148 pts

CVP: Never an optimal prediction but still some reasonable guidance if nothing better can be used….

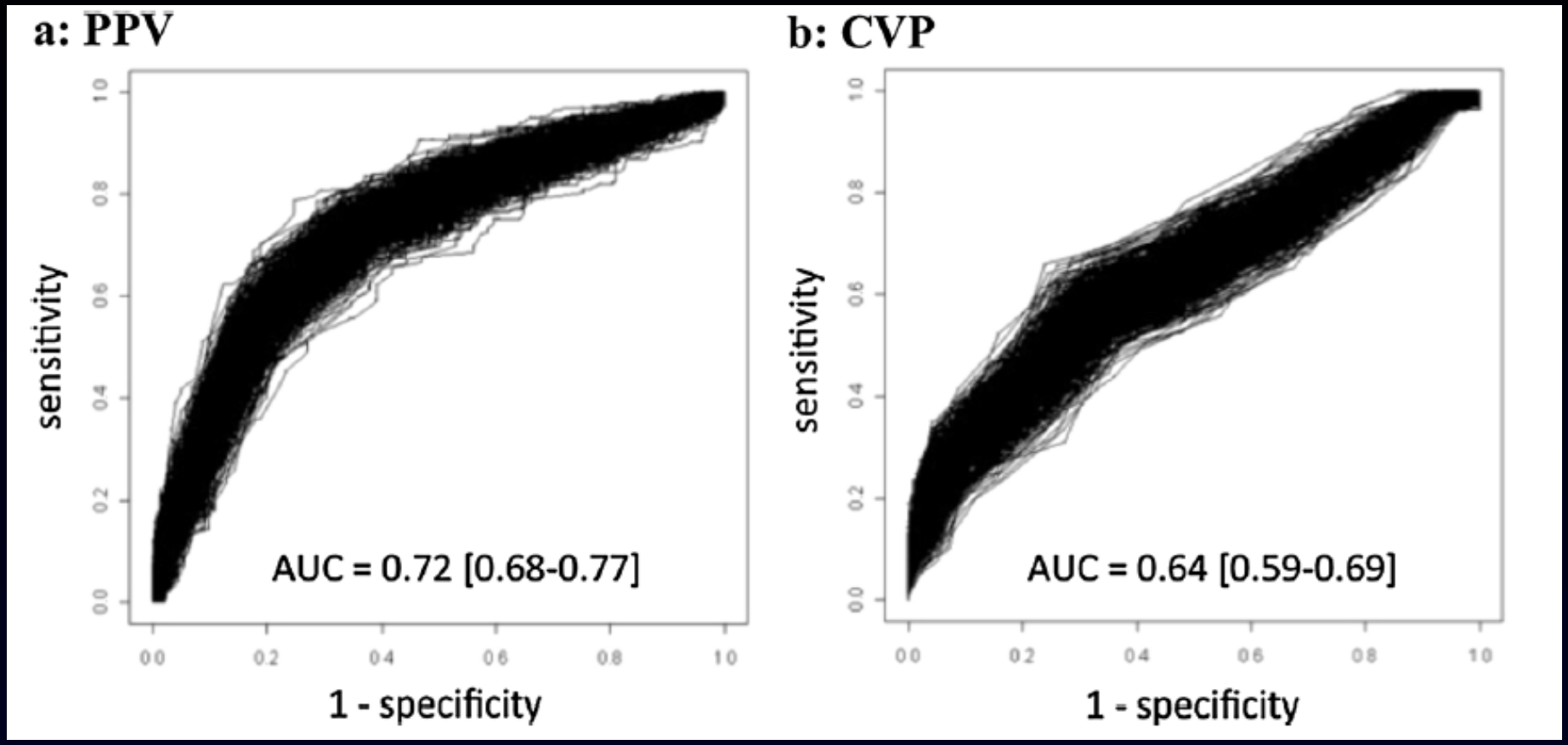
Biais-M et al
Crit Care 2014



556 pts

CVP: Never an optimal prediction but still some reasonable guidance if nothing better can be used….

Biais-M et al
Crit Care 2014



556 pts

F. FLUID THERAPY

Rhodes et al
ICM 2017
CCM 2017

1. We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve (BPS).

Rhodes et al
ICM 2017
CCM 2017

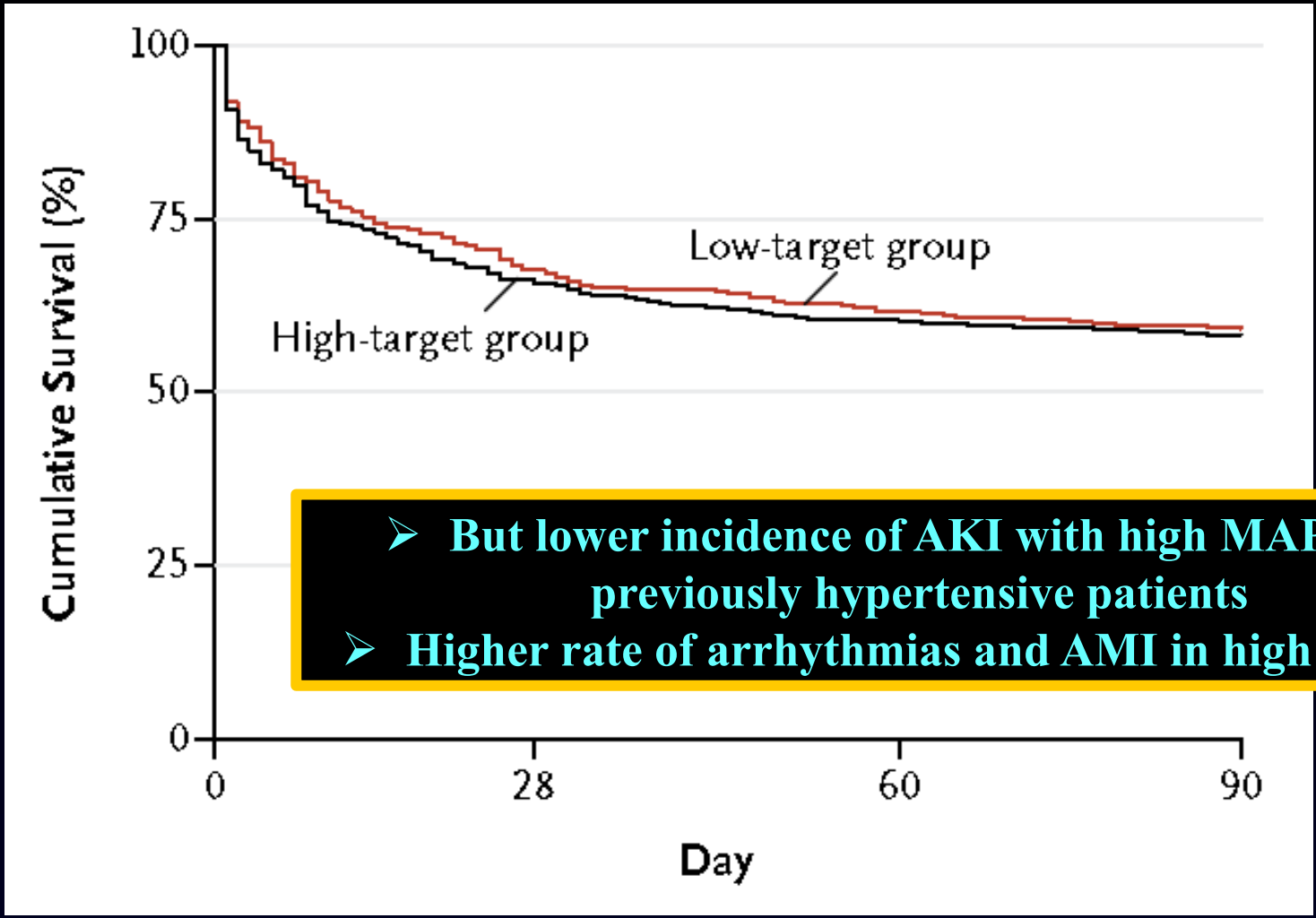
A. INITIAL RESUSCITATION

6. We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).

High vs Low MAP ?

65-70 VS 80-85 mmHg

Asfar P et al
NEJM 2014



- But lower incidence of AKI with high MAP in previously hypertensive patients
- Higher rate of arrhythmias and AMI in high MAP

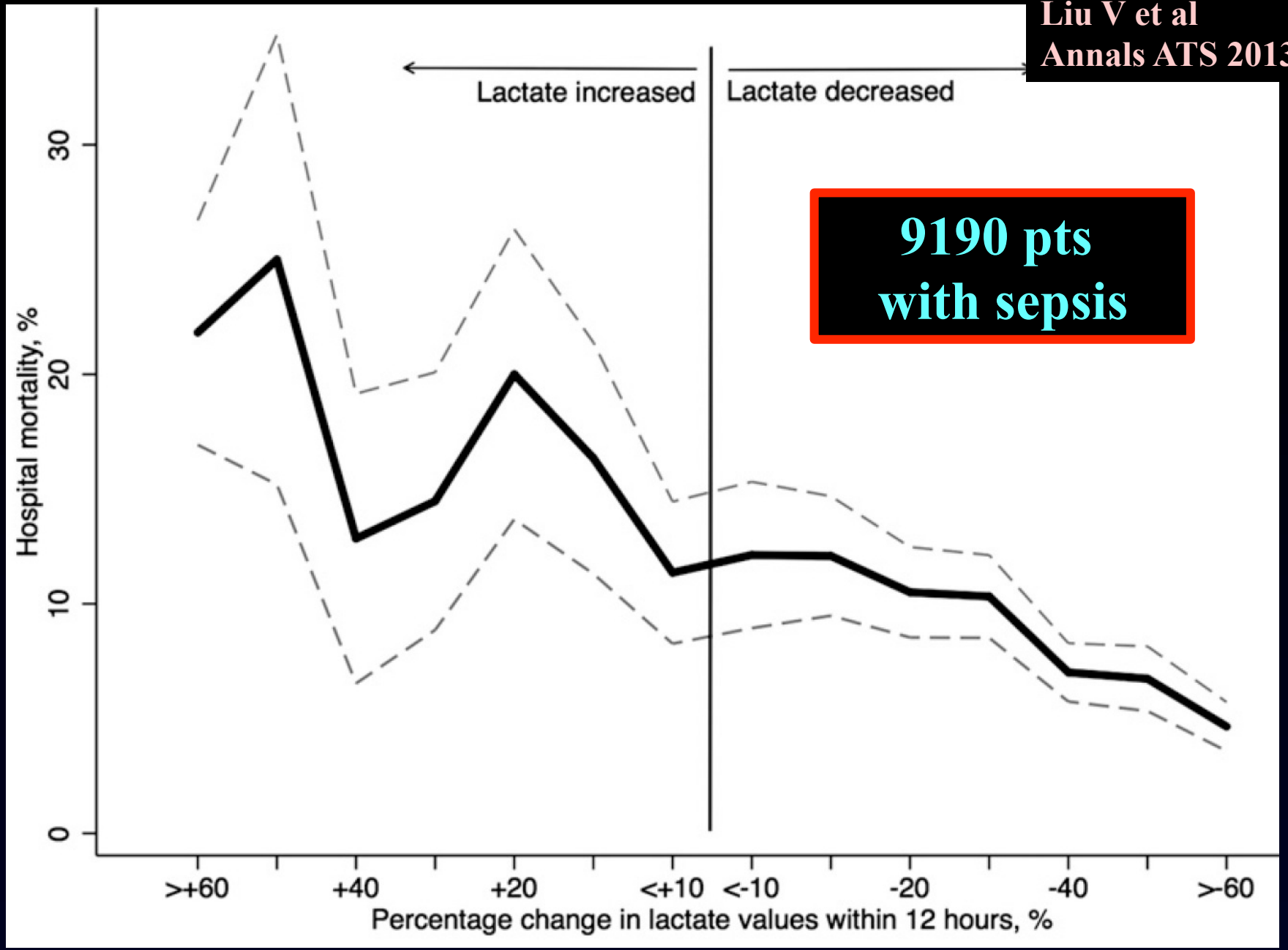
798 pts septic shock

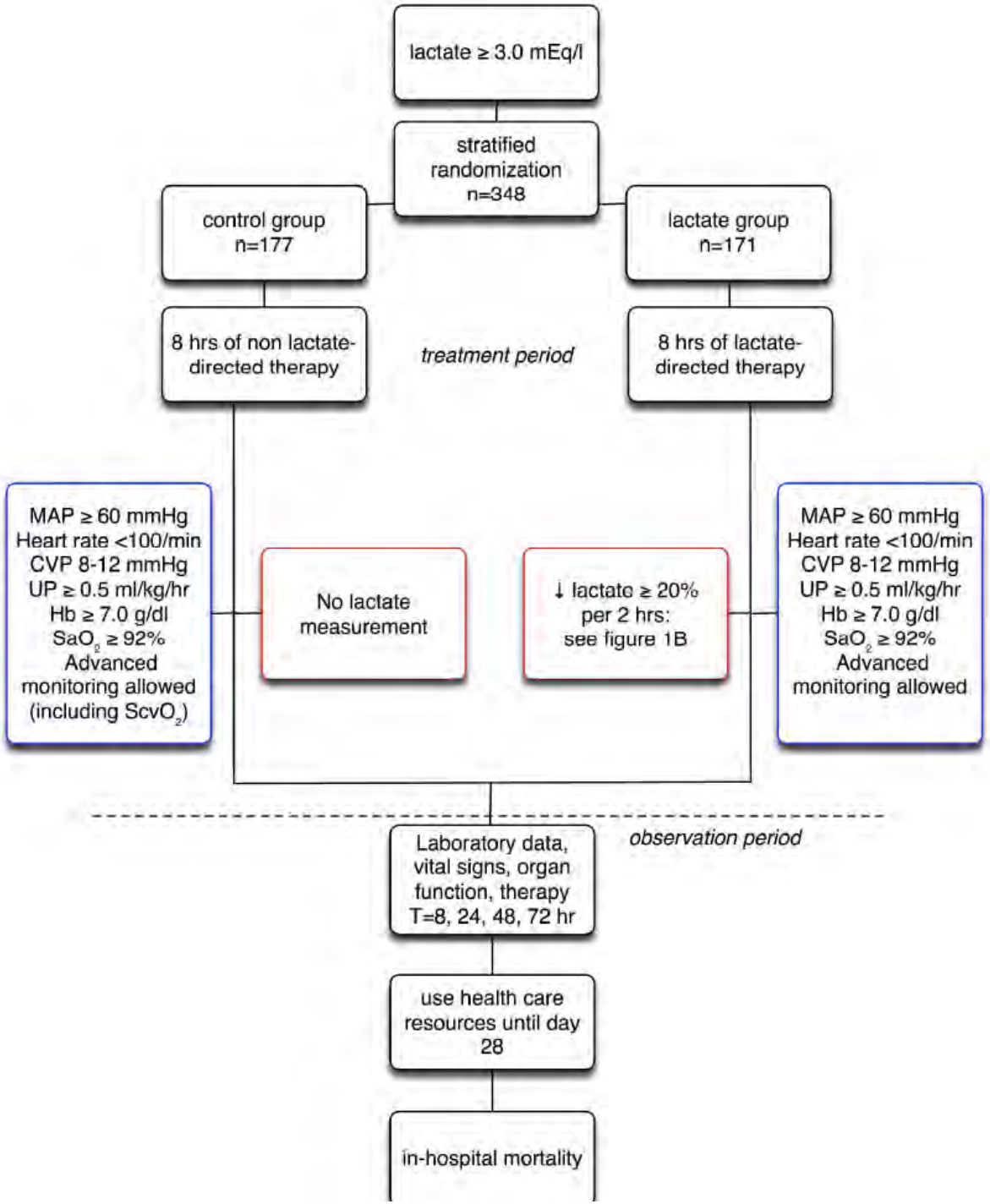
Rhodes et al
ICM 2017
CCM 2017

A. INITIAL RESUSCITATION

7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

Liu V et al
Annals ATS 2013



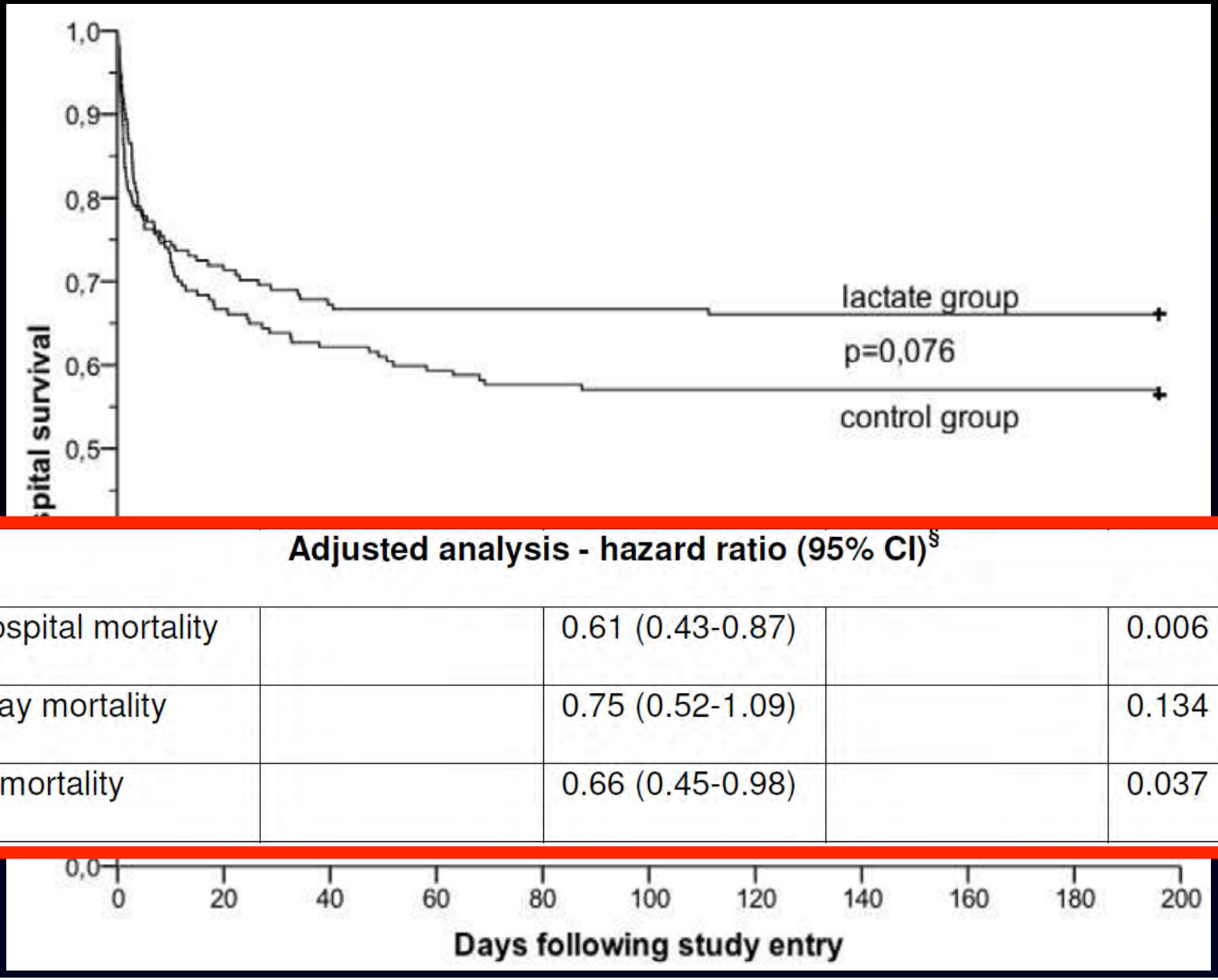


Janssens T et al
AJRCCM 2010

Lactate guided therapy

Lactate guided therapy (-20%/2h for 8h)

Janssens T et al AJRCCM 2010



	Adjusted analysis - hazard ratio (95% CI)[§]		
In-hospital mortality		0.61 (0.43-0.87)	0.006
28-day mortality		0.75 (0.52-1.09)	0.134
ICU-mortality		0.66 (0.45-0.98)	0.037

N=348

Intensive Care Med
DOI 10.1007/s00134-015-3955-2

LETTER

Wan-Jie Gu
Zhongheng Zhang
Jan Bakker

Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials

Accepted: 8 June 2015

the potential to be such a promising goal for quantitative resuscitation. We performed a meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of early lactate clearance-guided therapy on mortality and other outcomes in patients with sepsis.

We searched PubMed, Embase, and Cochrane Central Register of Controlled Trials to identify RCTs that evaluated the effect of early lactate clearance-guided therapy on clinical outcomes in adults with

event proportion obtained from the results of the meta-analysis, and a relative risk reduction of 20 % in all-causes mortality, using standard software TSA version 0.9 Beta (http://www.ctu.dk/tsa).

Four RCTs enrolling 547 patients were included in the meta-analysis [2–5]. The main characteristics of the four included RCTs are presented in Table 1 in the Electronic Supplementary Material (ESM). Assessment of the risk of bias is summarized in Table 2 (ESM). Overall, two RCTs

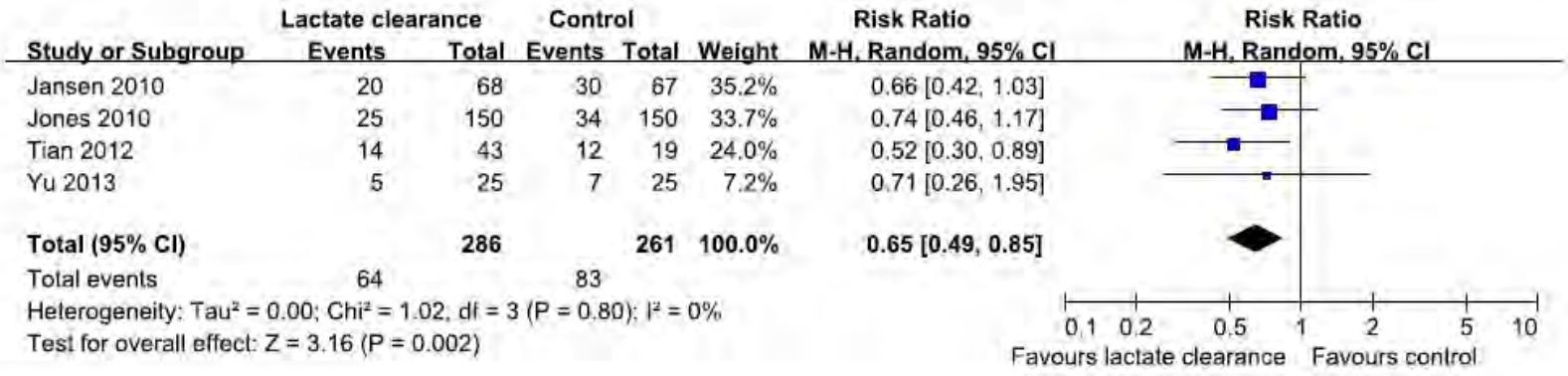


Fig. 1 Forest plot depicting mortality

RESEARCH Open Access

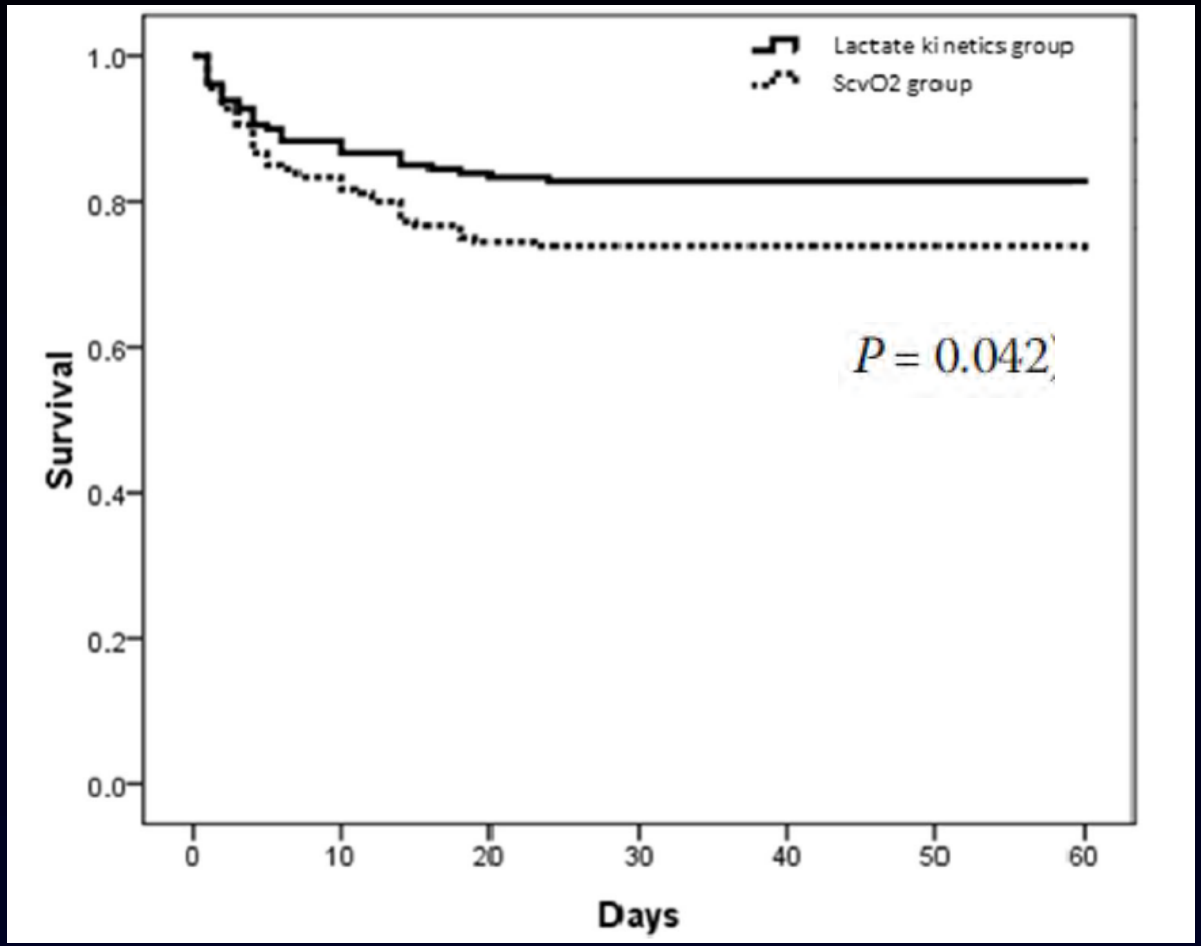
Use of stepwise lactate kinetics-oriented hemodynamic therapy could improve the clinical outcomes of patients with sepsis-associated hyperlactatemia

Xiang Zhou[1], Dawei Liu[1*], Longxiang Su[1], Bo Yao[2], Yun Long[1], Xiaoting Wang[1], Wenzhao Chai[1], Na Cui[1], Hao Wang[1] and Xi Rui[1]

Crit Care 2016

60 day mortality:
28 vs 18%
p=0.033

N=360



Rhodes et al
ICM 2017
CCM 2017

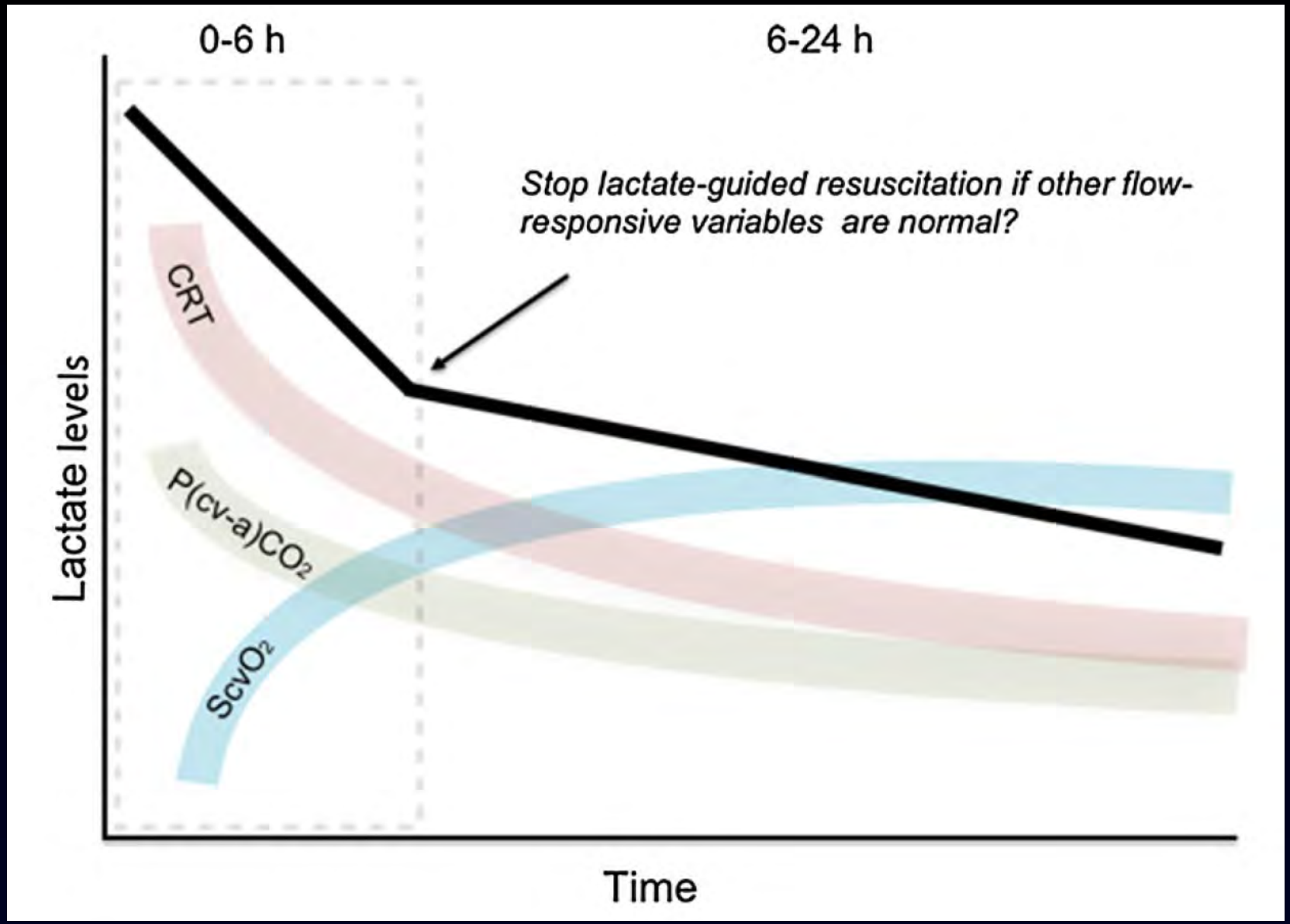
A. INITIAL RESUSCITATION

7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

EDITORIAL

Lactate-guided resuscitation saves lives: we are not sure

Bakker – De Backer -Hernandez
ICM 2016



FLUID THERAPY

F. FLUID THERAPY

Rhodes et al
ICM 2017
CCM 2017

2. We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).
3. We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).

F. FLUID THERAPY

Rhodes et al
ICM 2017
CCM 2017

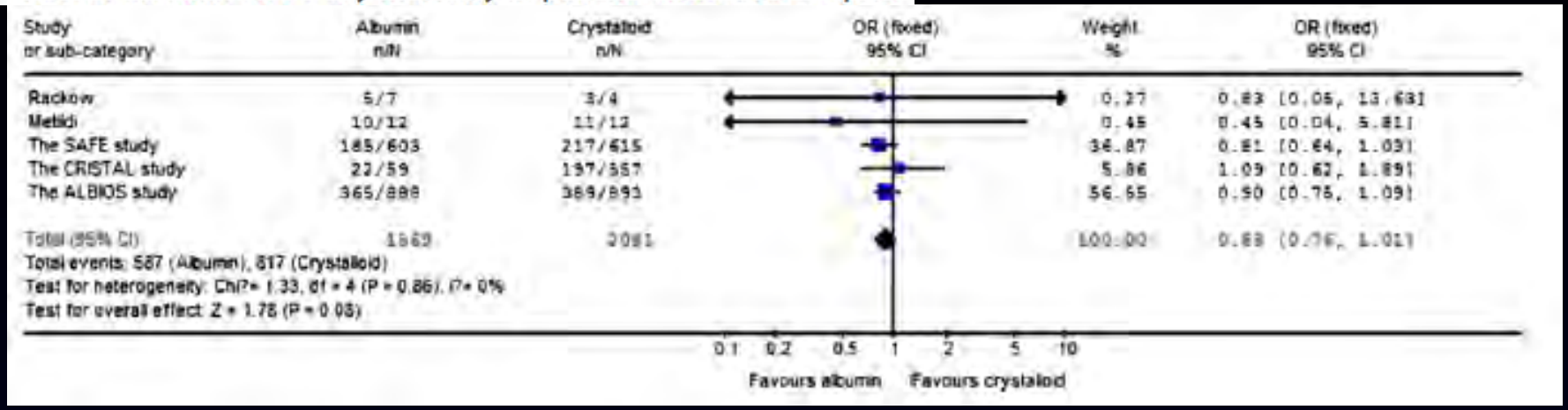
4. We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

RESEARCH Open Access

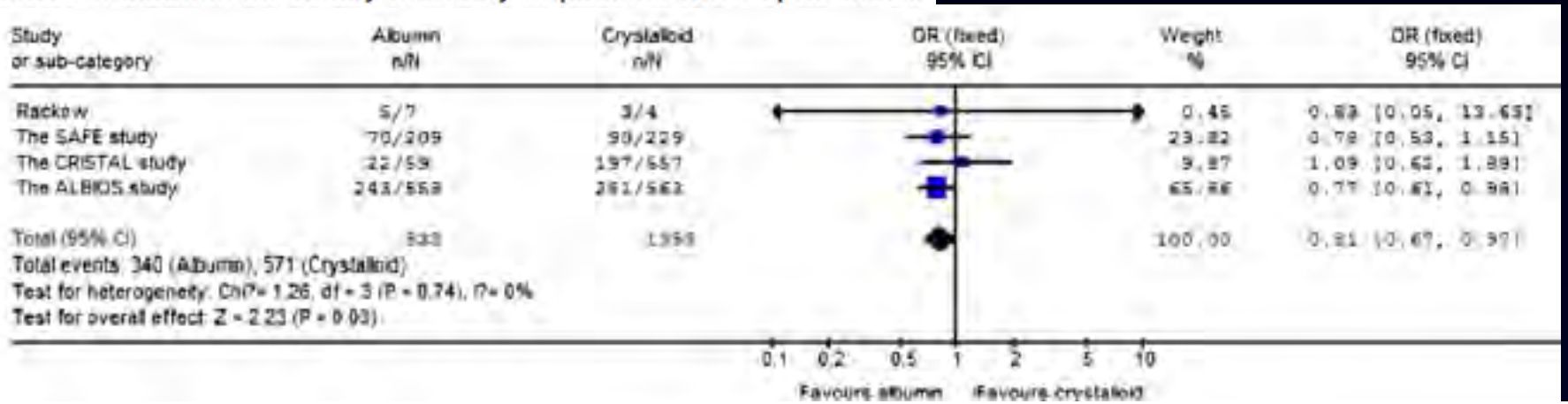
Comparison of the effects of albumin and crystalloid on mortality in adult patients with severe sepsis and septic shock: a meta-analysis of randomized clinical trials

Xu JY et al
Crit Care 2014

The effect of albumin on 90-day mortality in patients with severe sepsis.



The effect of albumin on 90-day mortality in patients with septic shock.



F. FLUID THERAPY

Rhodes et al
ICM 2017
CCM 2017

5. We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
6. We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

VASOPRESSOR SUPPORT

Rhodes et al
ICM 2017
CCM 2017

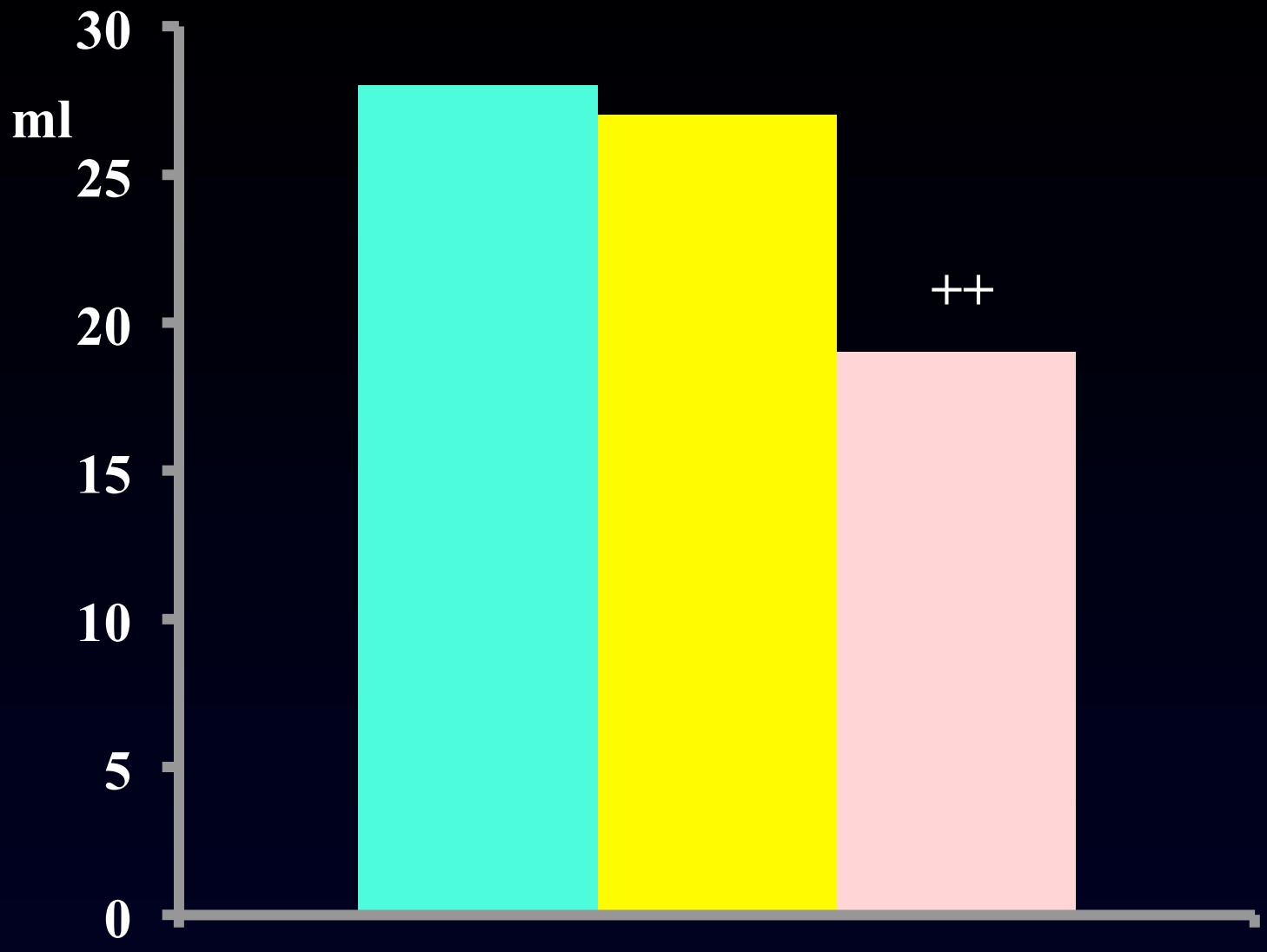
When to introduce vasopressors?

When to introduce vasopressors?

Early introduction of vasopressors may decrease later need for fluids

Early introduction of norepi decreased fluids requirements

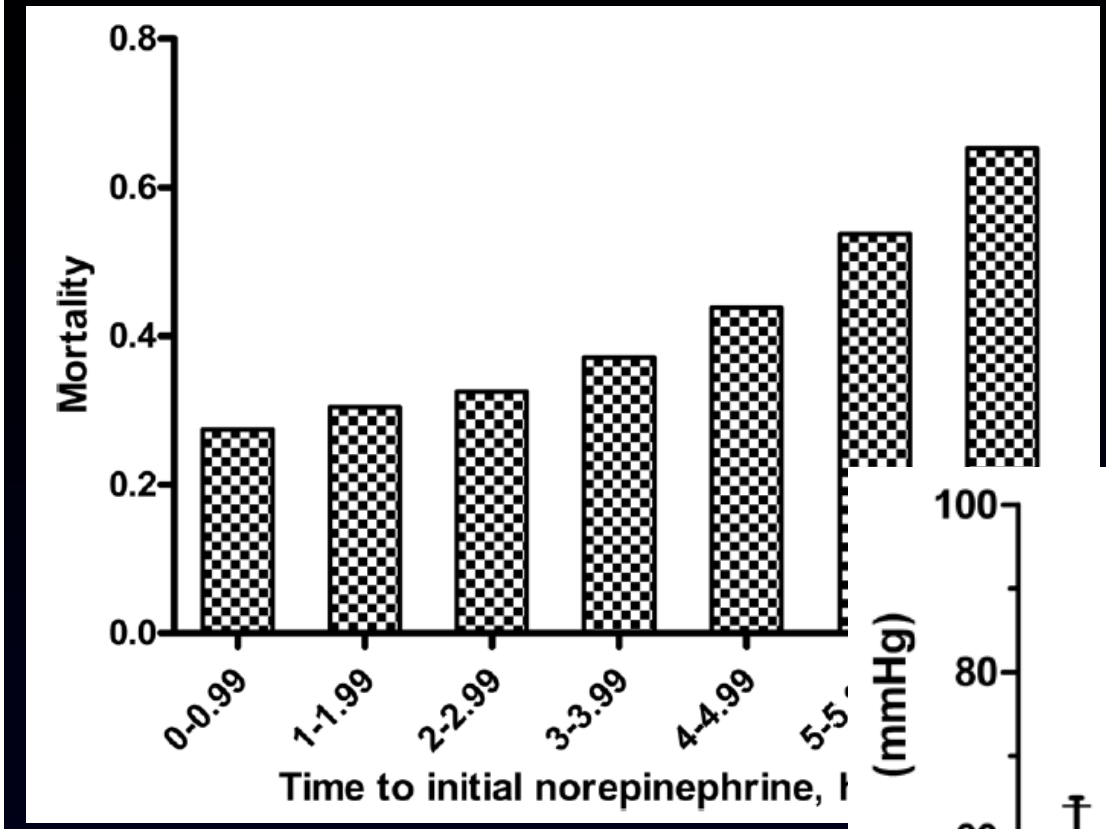
Sennoun N et al
CCM 35:1736;2007

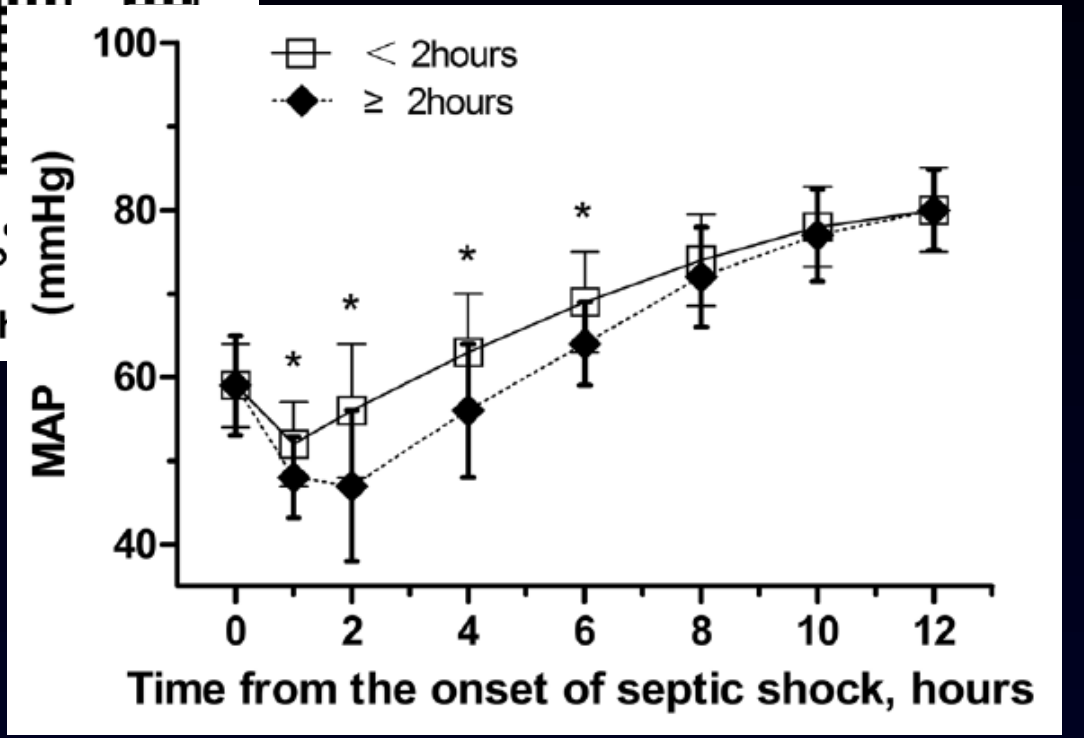


Rats / LPS

Duration of hypotension before initiation of vasopressor agents is associated with poor outcome

Bai X et al
Crit Care 2014





213 pts with septic shock

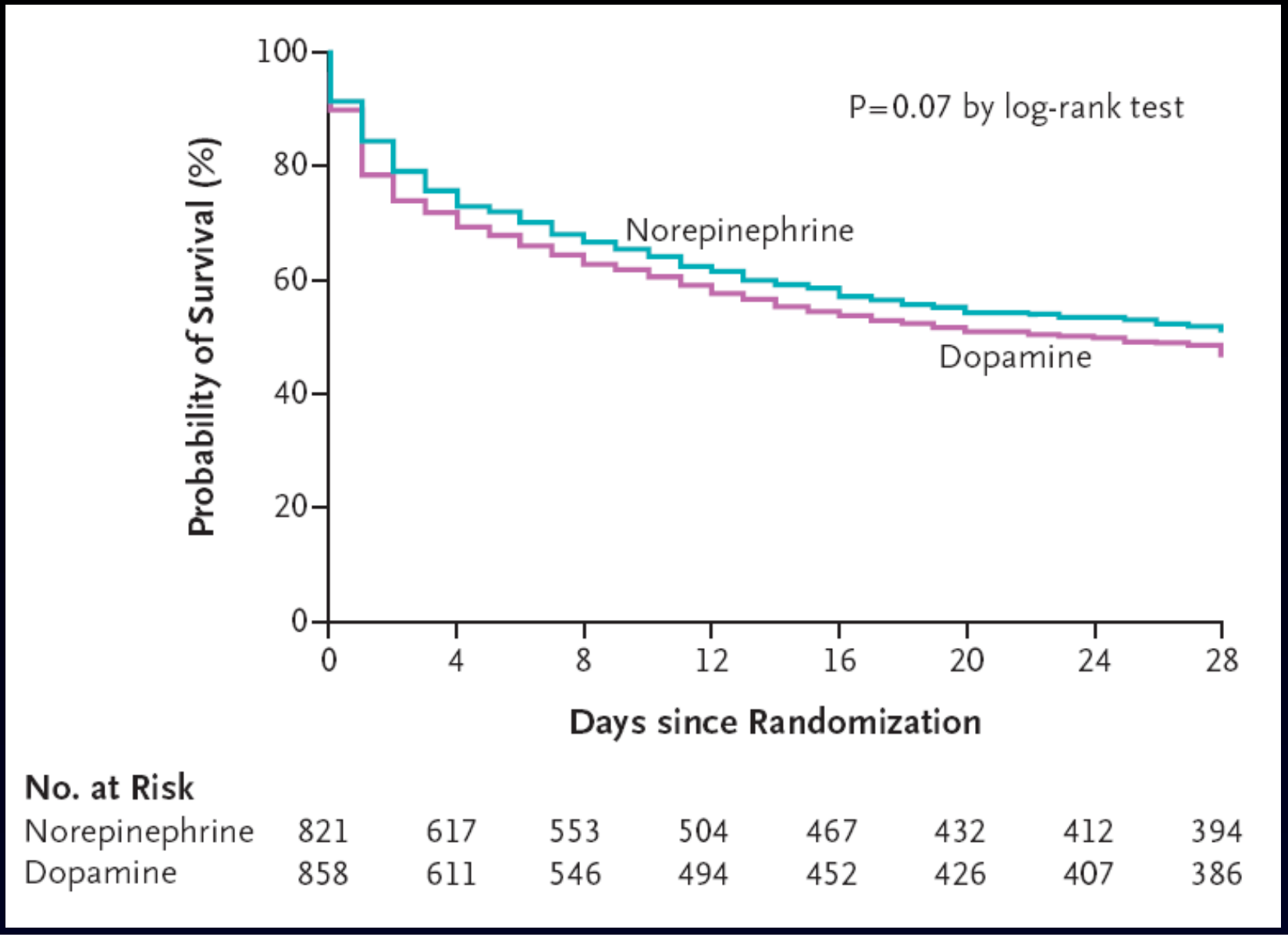
G. VASOACTIVE MEDICATIONS

Rhodes et al
ICM 2017
CCM 2017

1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).

Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010



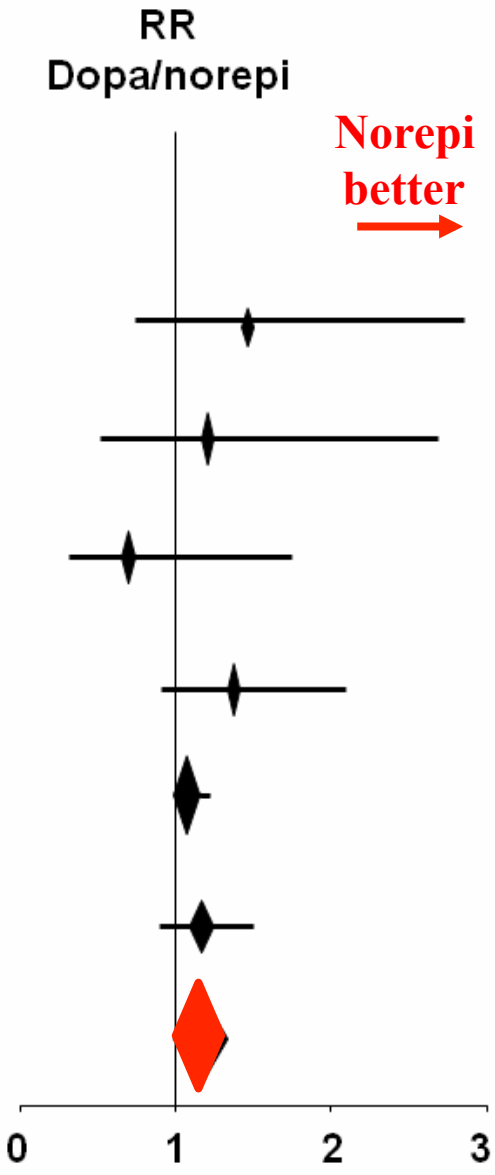
No. at Risk

Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386

Dopamine vs norepinephrine in septic shock
A meta-analysis

De Backer et al
CCM 40:725:2012

Study	Norepinephrine		Dopamine		
	Event	Total	Event	Total	RR [95%CI]
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]**

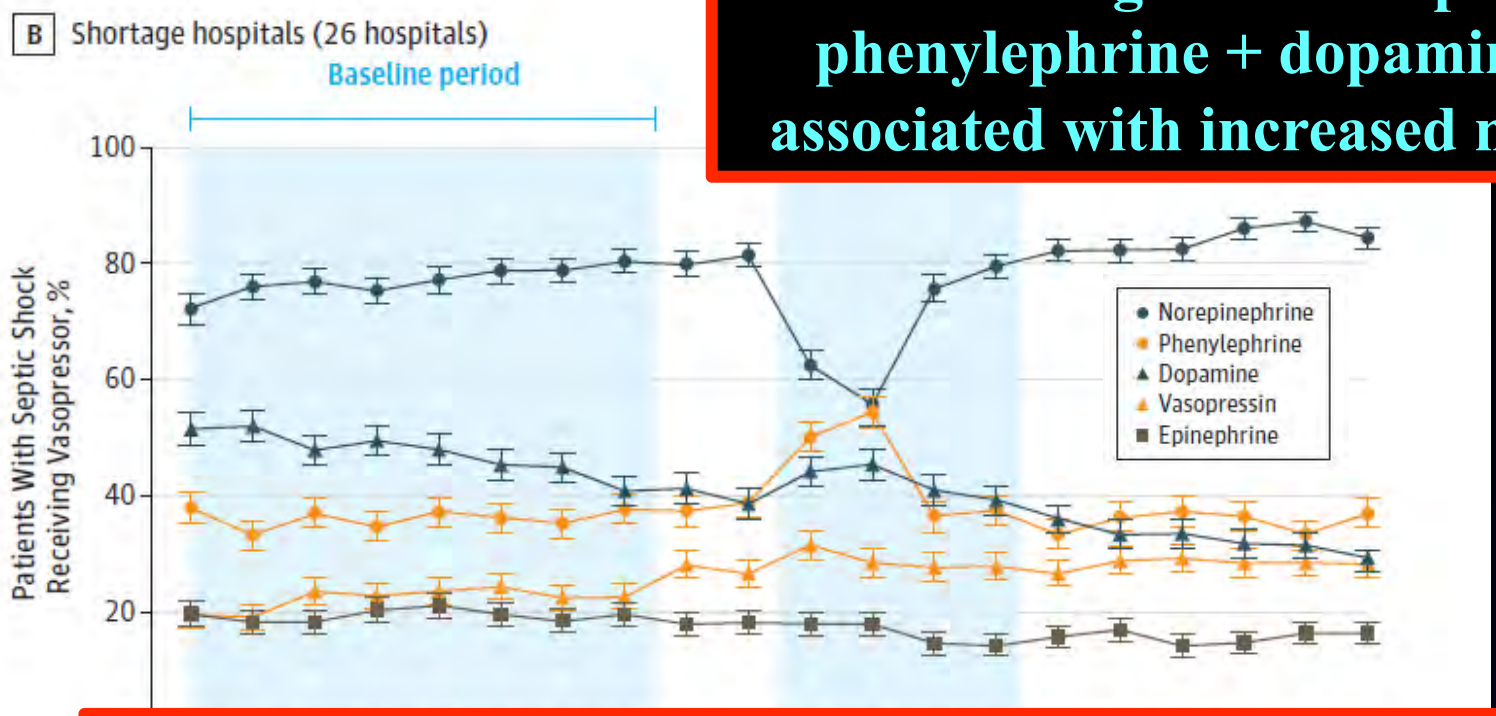


Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

Emily Vail, MD; Hayley B. Gershengorn, MD; May Hua, MD, MSc; Allan J. Walkey, MD, MSc; Gordon Rubenfeld, MD, MSc; Hannah Wunsch, MD, MSc

Vail E et al
JAMA 2017

Shifting from norepi to phenylephrine + dopamine was associated with increased mortality



Cohort	Deaths, No./Total Patients, No. (%)	Absolute Mortality Difference, % (95% CI)[a]	Adjusted Odds Ratio (95% CI)[b]	*P* Value
Patients with septic shock receiving vasopressors				
Primary model[c]				
Admission to shortage hospitals during a nonshortage quarter	9283/25 874 (35.9)	NA	1 [Reference]	
Admission to shortage hospitals during a quarter of 2011 in which norepinephrine use decreased >20% below baseline	777/1961 (39.6)	3.7 (1.5-6.0)	1.15 (1.01-1.30)	.03

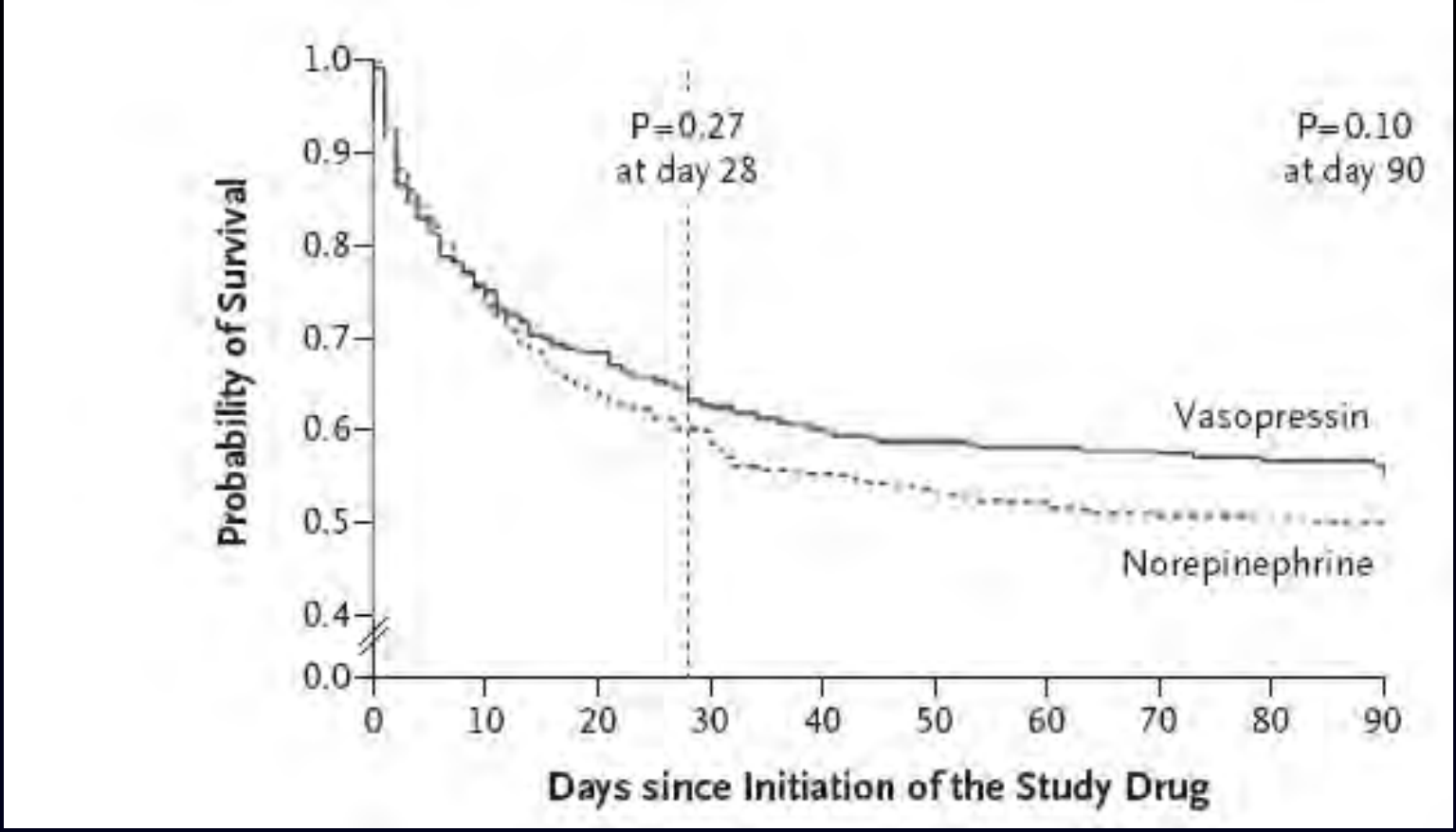
G. VASOACTIVE MEDICATIONS

Rhodes et al
ICM 2017
CCM 2017

2. We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.

VASST

Russell et al
NEJM 358:877;2008

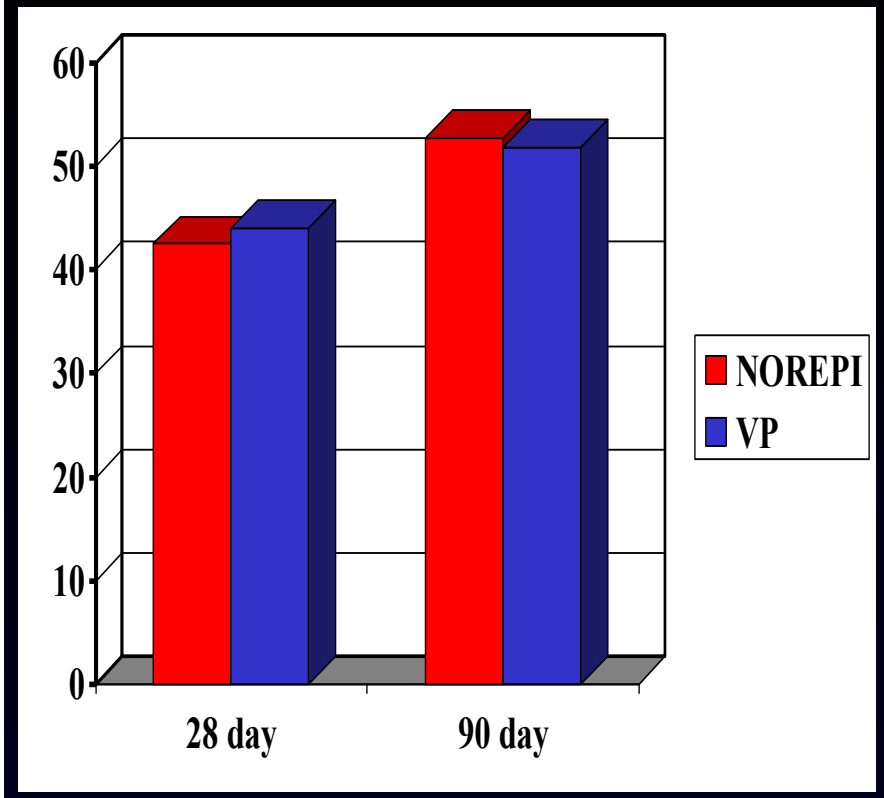


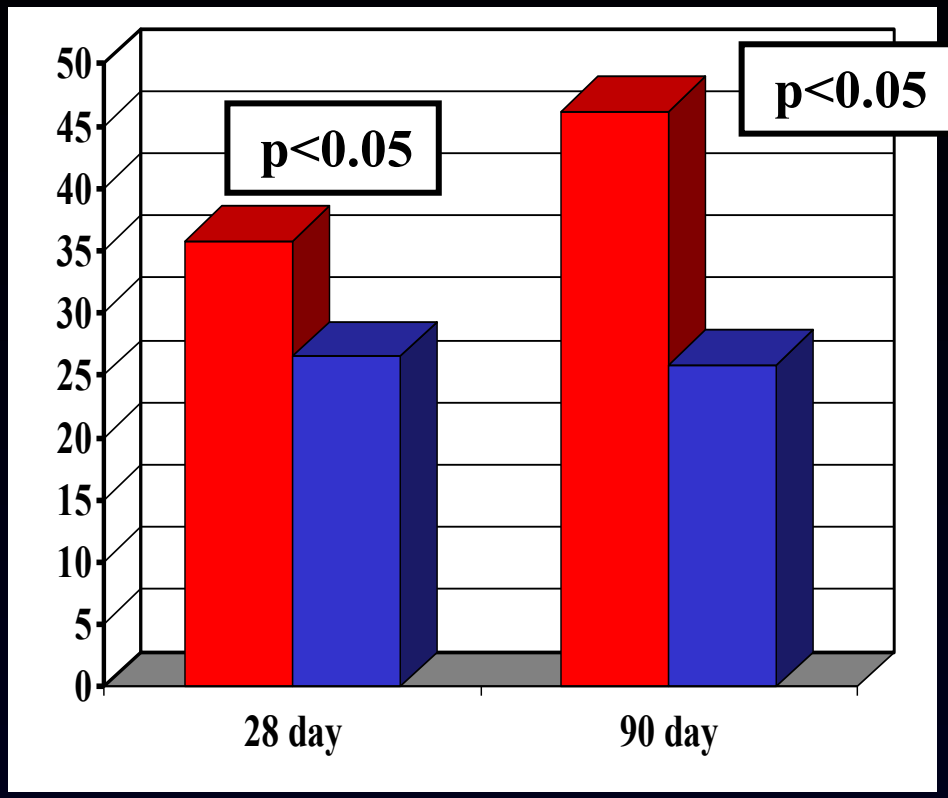
802 septic shock pts

VASST

Russell et al
NEJM 358:877;2008

Mortality (%) according to severity at baseline





More severe n= 400
(NE > 15 mcg/min)

Less severe n= 378
(NE < 15 mcg/min)

(15 mcg/min ~0.19 - 0.21 mcg/kg.min for 80-70kg pts)

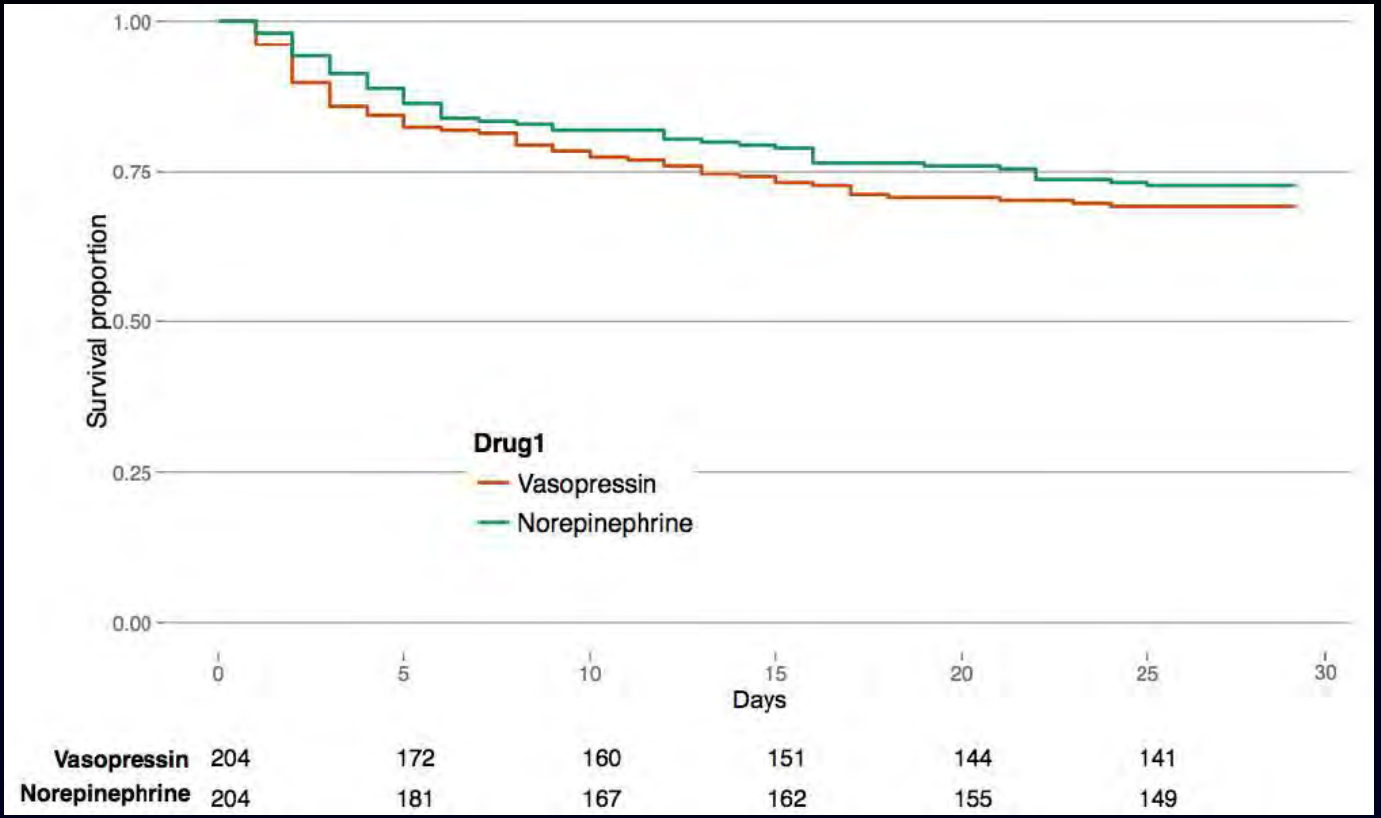
JAMA | Original Investigation

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock
The VANISH Randomized Clinical Trial

Anthony C. Gordon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD; Magda Cepkova, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc; Shalini Santhakumaran, MSc; Deborah Ashby, PhD; Stephen J. Brett, MD; for the VANISH Investigators

Gordon et al JAMA 2016

A double-blind randomised controlled trial of vasopressin (up to 0.06 u/min) vs noradrenaline within 6h of onset of septic shock.



Norepi dose at randomization: 0.16 [0.10-0.31] mcg/kg.min

The NEW ENGLAND JOURNAL of MEDICINE

NEJM 2017

ORIGINAL ARTICLE

Angiotensin II for the Treatme of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S.
Kealy Ham, M.D., James Tumlin, M.D., Harold Szerlip, M.D.,
Laurence W. Busse, M.D., Laith Altaweel, M.D.,
Timothy E. Albertson, M.D., M.P.H., Ph.D., Caleb Mackey, M.D.,
Michael T. McCurdy, M.D., David W. Boldt, M.D., Stefan Chock, M.D.
Ric
Raghavar
Joh
Bal
Ri
L
ar

The primary end point was the response with respect to mean arterial pressure at hour 3, with response defined as a mean arterial pressure of 75 mm Hg or higher or an increase in mean arterial pressure from baseline of at least 10 mm Hg, without an increase in the dose of background vasopressors. The mean values of triplicate deter-

End Point	Angiotensin II (N=163)	Placebo (N=158)	Odds or Hazard Ratio (95% CI)	P Value
Primary efficacy end point: MAP response at hour 3 — no. (%)†	114 (69.9)	37 (23.4)	Odds ratio, 7.95 (4.76–13.3)	<0.001
Secondary efficacy end points				
Mean change in cardiovascular SOFA score at hour 48‡	−1.75±1.77	−1.28±1.65		0.01
Mean change in total SOFA score at hour 48§	1.05±5.50	1.04±5.34		0.49
Additional end points				
Mean change in norepinephrine-equivalent dose from baseline to hour 3¶	−0.03±0.10	0.03±0.23		<0.001
All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12


IMPROVE
-MENT
Thank you