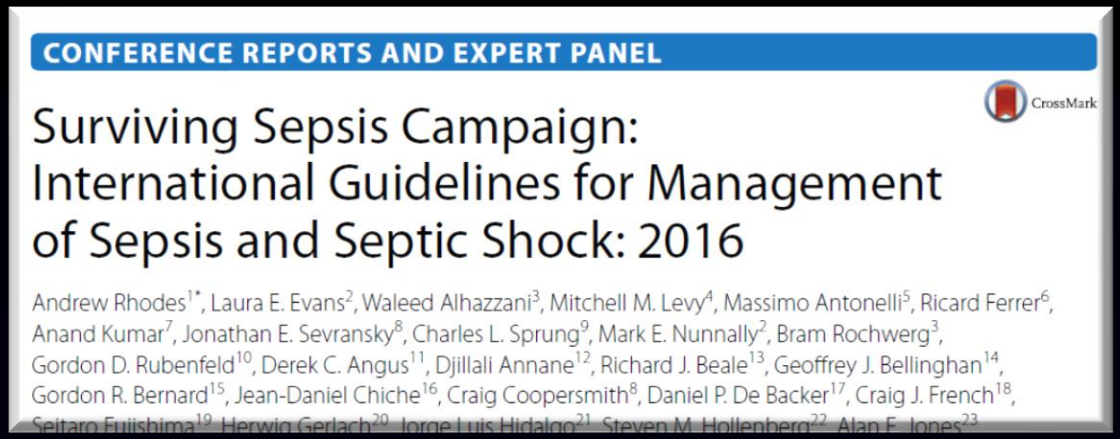
Le sepsis:
Des urgences aux soins intensifs

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

Inspired from….

Rhodes et al
ICM 2017
CCM 2017



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]

- 55 experts
- 5 sections
  - Hemodynamics
  - Infection
  - Adjunctive therapies
  - Metabolic
  - Ventilation

Society of Critical Care Medicine
The Intensive Care Professionals

Surviving Sepsis Campaign

ESICM
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE
The Intensive Connection

JAMA Clinical Guidelines Synopsis

Management of Sepsis and Septic Shock

Michael D. Howell, MD, MPH; Andrew M. Davis, MD, MPH

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-

Le sepsis aux urgences

1. **Comment reconnaître ?**

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

JAMA 315:801; 2016

Sepsis is a life-thretening organ dysfunction caused by a dysregulated host response to infection

Le sepsis: comment reconnaître?

- **Suspecter une infection…**

- **Détecter une dysfonction d'organe…**

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

JAMA 315:801; 2016

Organ dysfunction is characterized clinically by a change in SOFA score ≥2 related to the episode of new infection

Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Sevransky, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

Seymour C et al
JAMA 315:762; 2016

Sepsis = infection + 2 qSOFA points

Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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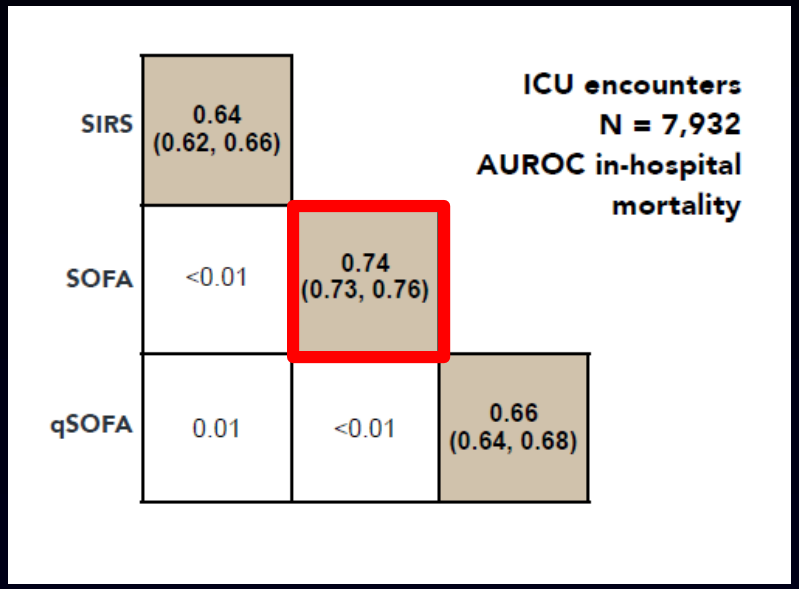
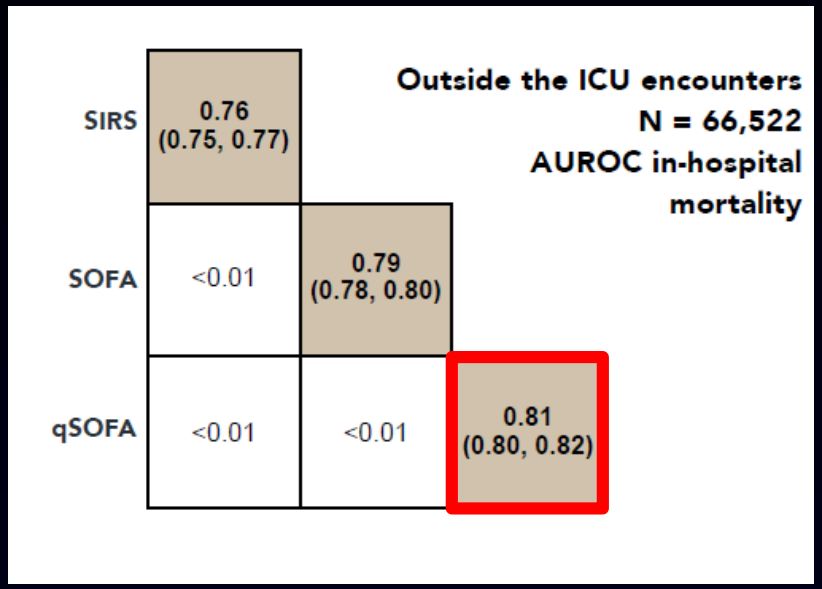
Seymour C et al
JAMA 315:762; 2016





SOFA in the ICU

qSOFA outside the ICU

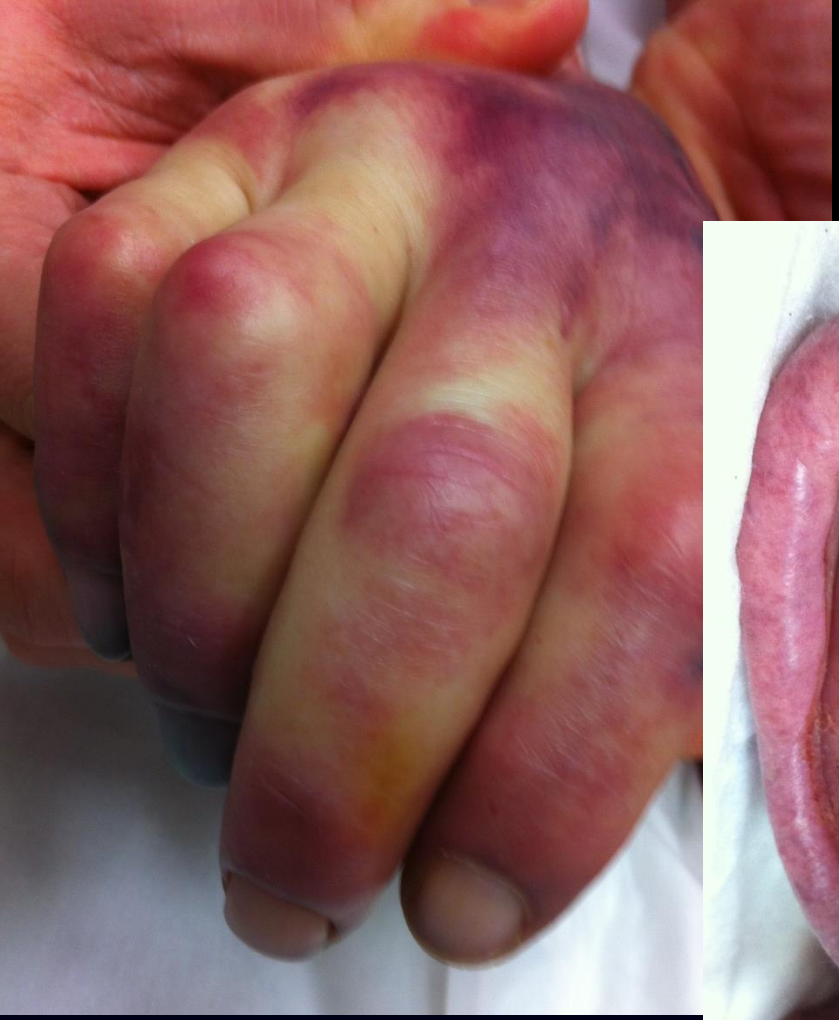
qSOFA

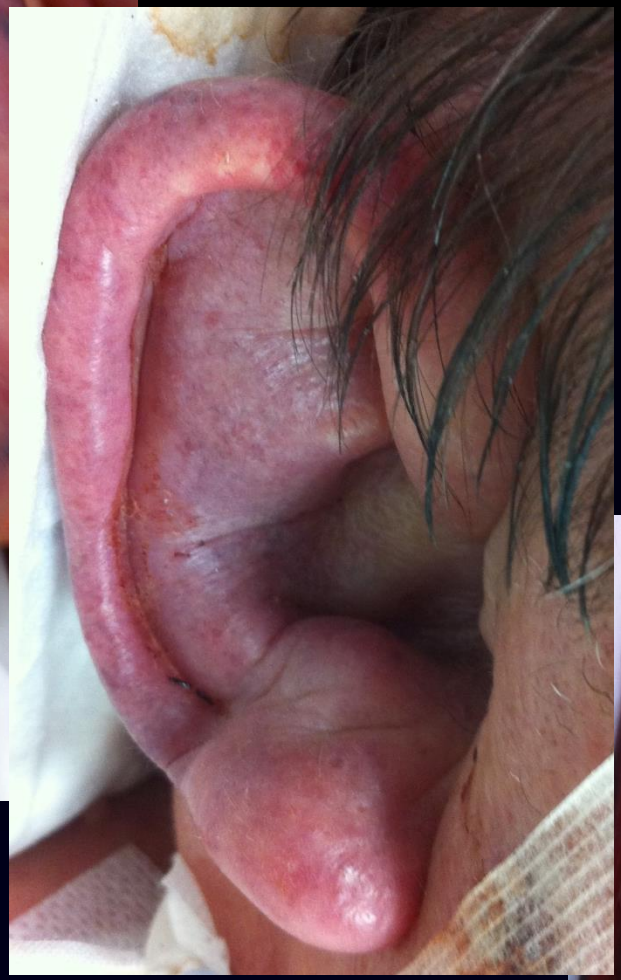
- Respiratory rate ≥ 22 bpm
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg

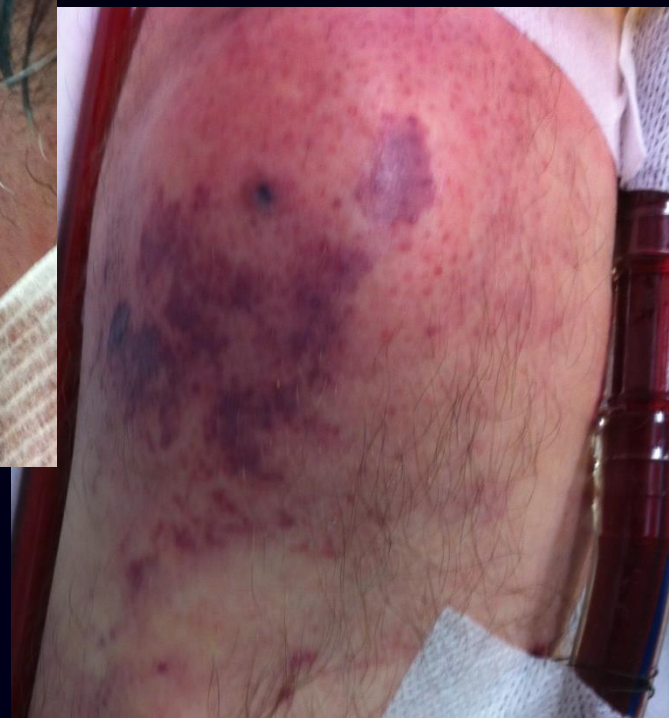
Le sepsis: comment reconnaître?

- **Suspecter une infection…**
  - **Signes cliniques habituels…T°/GB/CRP…**
- **Détecter une dysfonction d'organe…**
  - **qSOFA 2**
  - **2 pts dysfonction d'organe**
  - **Signes biologiques**

Evaluation of skin perfusion

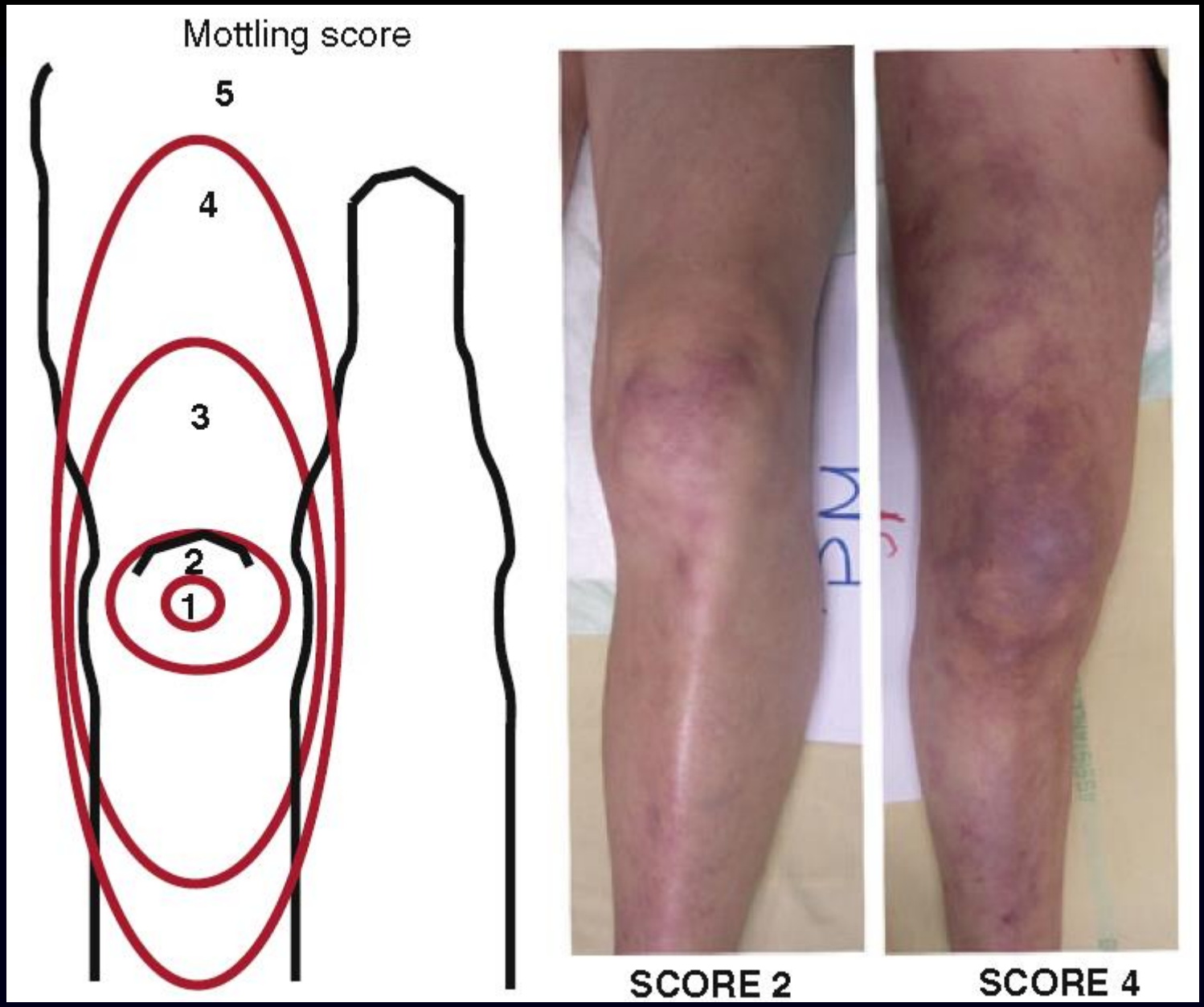






The Mottling Score

Ait Oufella et al
ICM 37:801;2011



The Mottling Score

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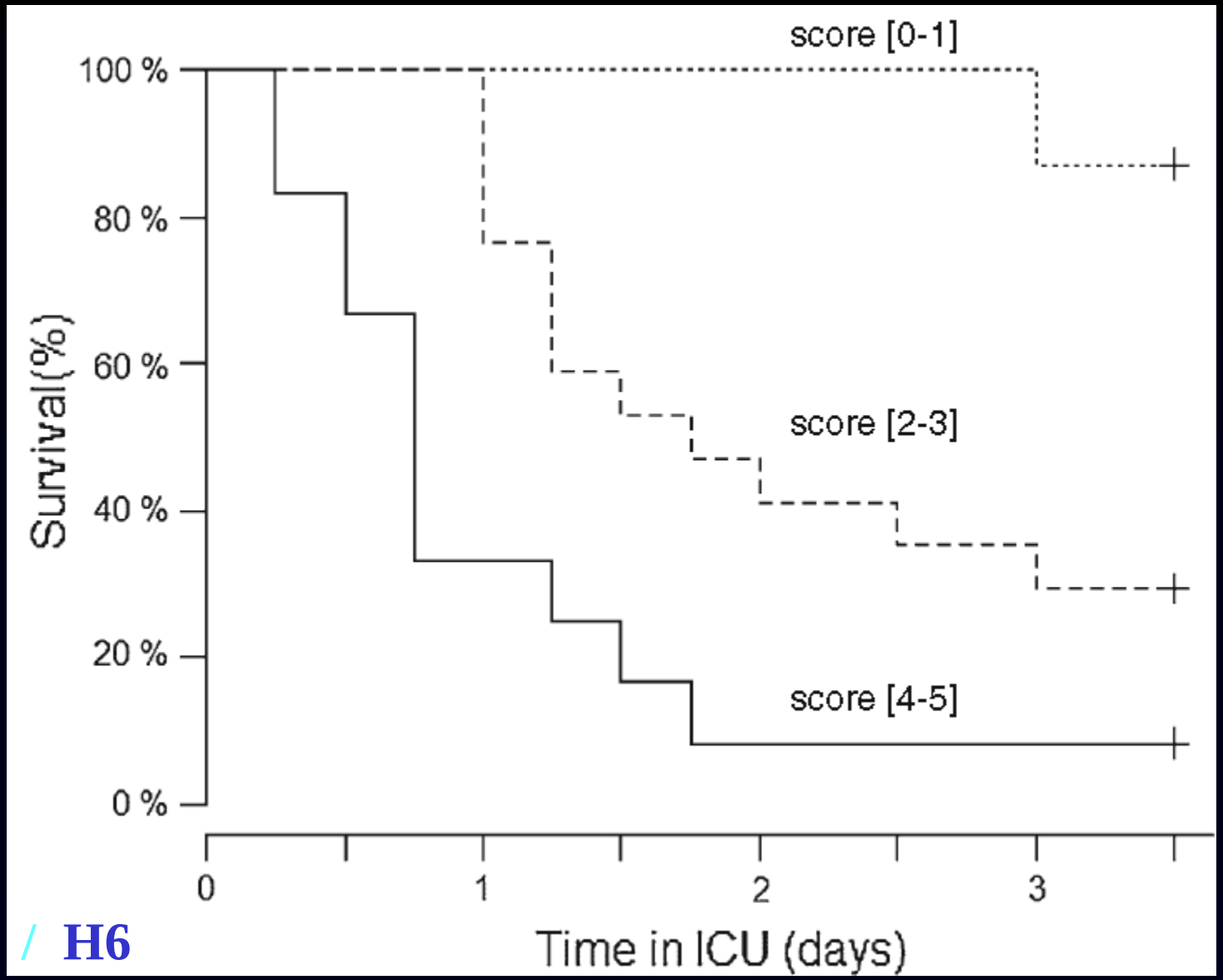
ICM 37:801;2011



N=60 / H6

Le sepsis aux urgences

1. Comment reconnaître ?
2. Prise en charge

Le sepsis aux urgences: Prise en charge

- **Identifier / Contrôler la source**
- **Antibiotiques**

- **Traitement supportif**

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

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).

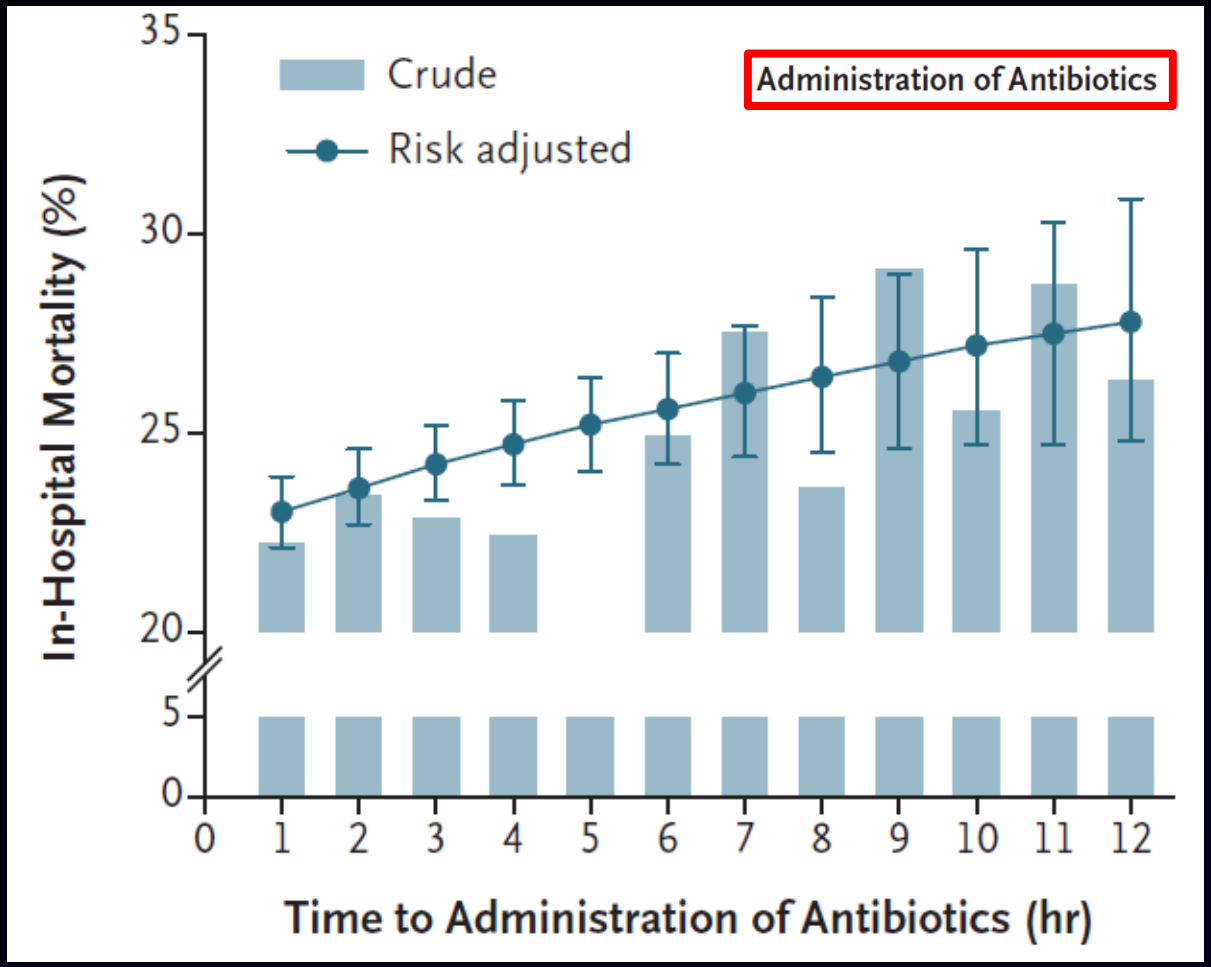
The NEW ENGLAND JOURNAL of MEDICINE

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

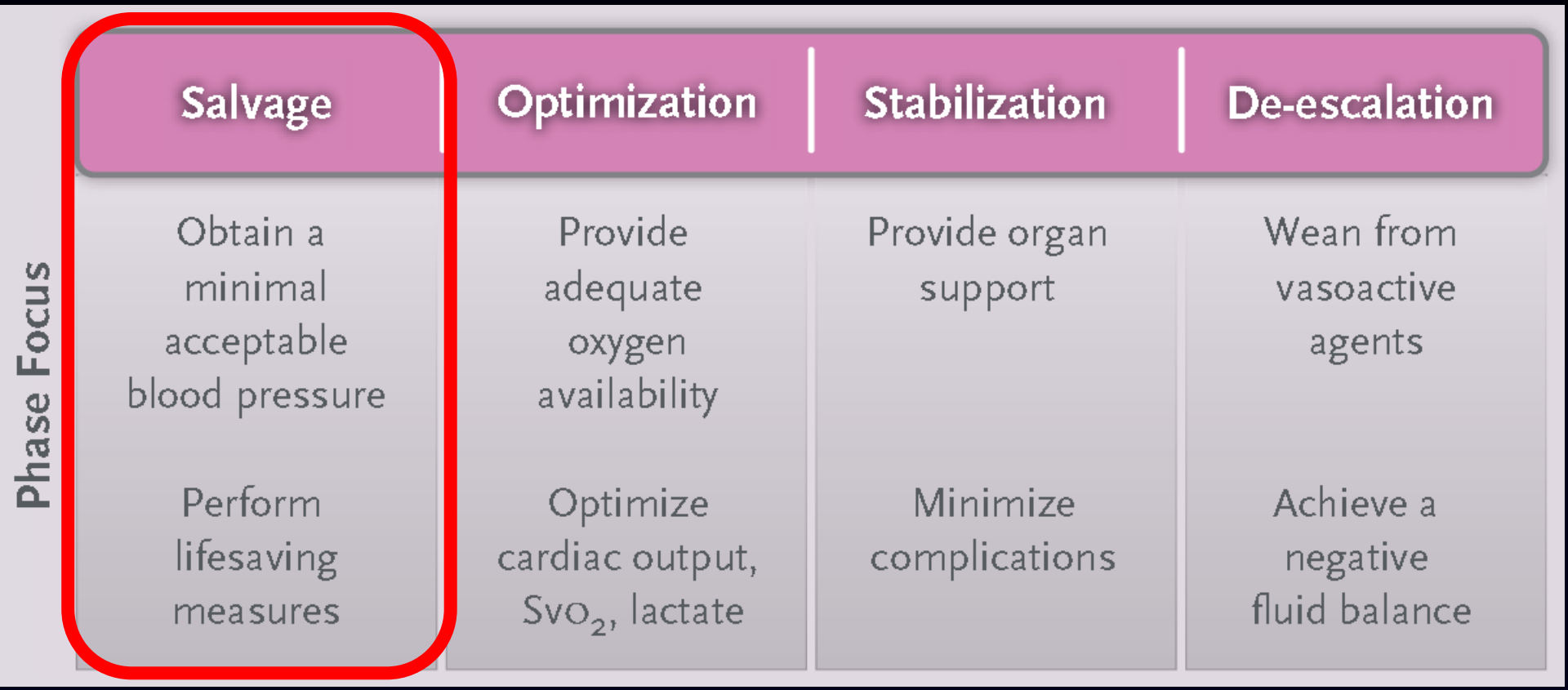


NY state
49331 pts
149 hosp

HEMODYNAMIC RESUSCITATION

Fluids at the different stages of shock

Vincent JL and De Backer D
NEJM 369:1726; 2013



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

CONFERENCE REPORTS AND EXPERT PANEL

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B. Taylor Thompson[47], Sean
Janice L. Zimmerman[51] and

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).

New bundles

Levy-M et al
ICM 2018

SPECIAL EDITORIAL

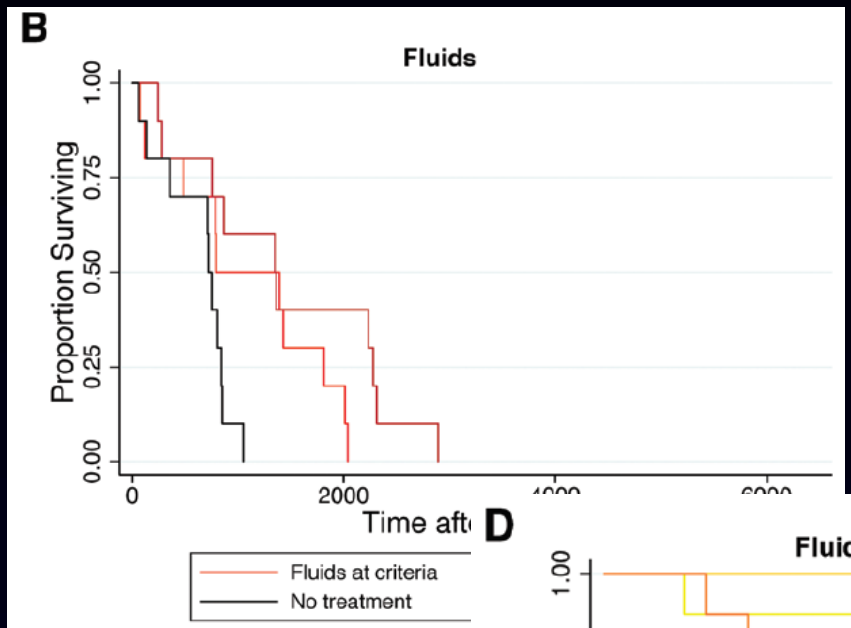
The Surviving Sepsis Campaign Bundle: 2018 update

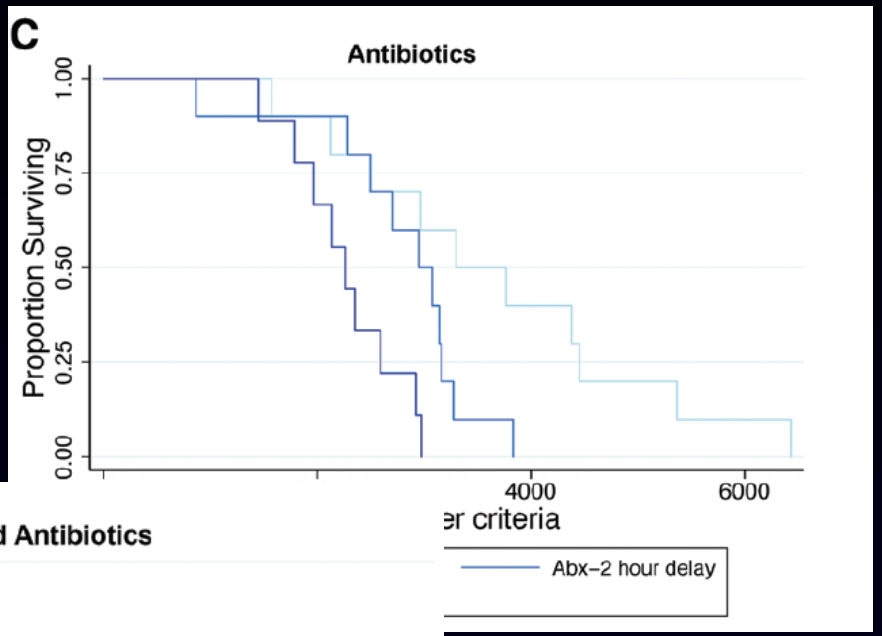
- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

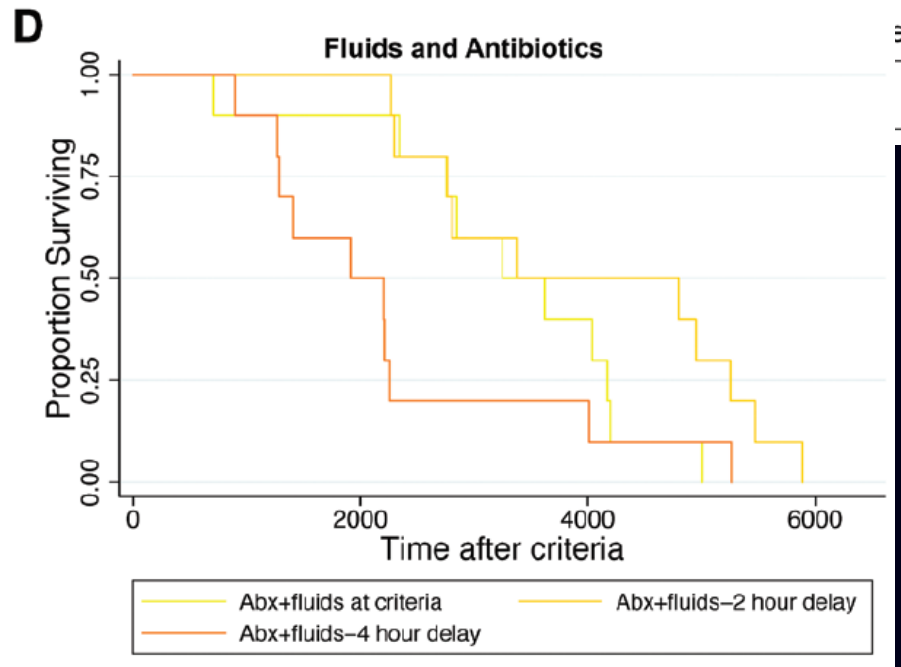
**"Time zero" or "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.*

Fig. 1 Hour-1 Surviving Sepsis Campaign Bundle of Care

Prompt Administration of Antibiotics and Fluids in the Treatment of Sepsis: A Murine Trial*

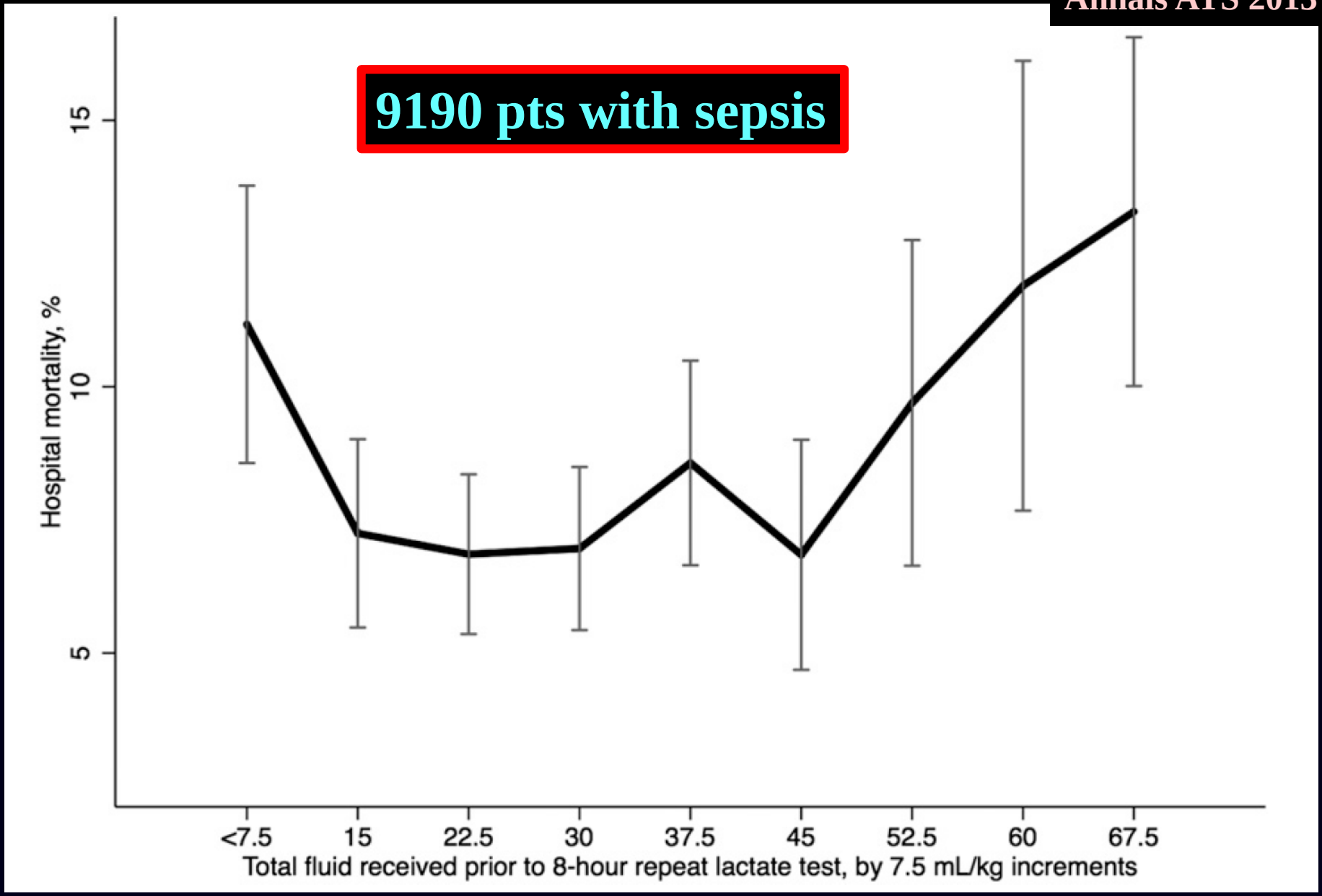






Not too much but also not limited….

Liu V et al
Annals ATS 2013

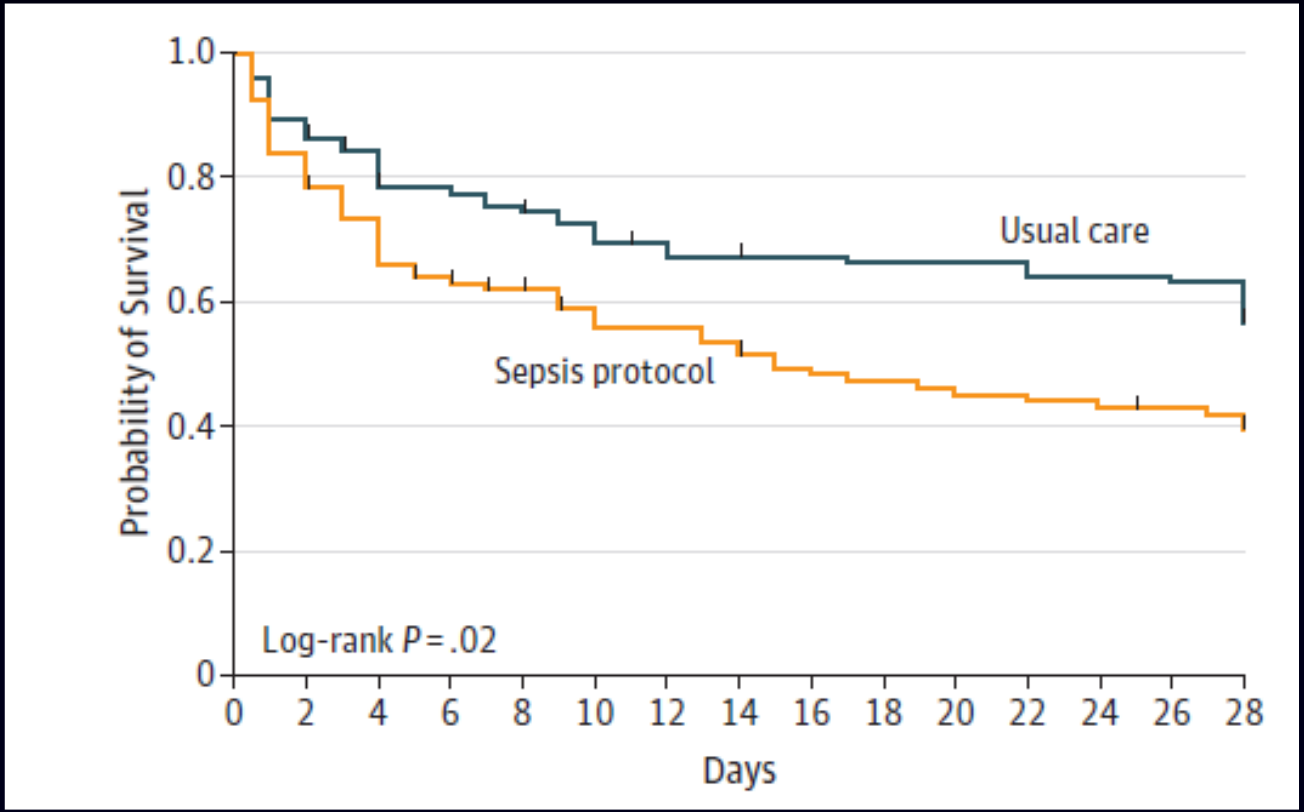


Andrews-B et al
JAMA 2017

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension

A Randomized Clinical Trial



212 patients in Zambia

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of an Early Resuscitation Protocol on In-hospital Mortality Among Adults With Sepsis and Hypotension
A Randomized Clinical Trial

Ben Andrews, MD; Matthew W. Semler, MD, MSc; Levy Muchemwa, MBChB; Paul Kelly, MD, FRCP; Shabir Lakhi, MBChB; Douglas C. Heimburger, MD, MS; Chileshe Mabula, MBChB; Mwango Bwalya, MBChB; Gordon R. Bernard, MD

Jama 2017

Sepsis Protocol Group

Patients randomized to the sepsis protocol received hemodynamic management for the first 6 hours after enrollment. An initial 2-L bolus of intravenous isotonic crystalloid was administered within 1 hour of enrollment, followed by an additional 2 L over the subsequent 4 hours. After each liter of intravenous fluid was administered, an investigator or study nurse measured arterial oxygen saturation, respiratory rate, and JVP (details appear in the eMethods in Supplement 2). If the arterial oxygen saturation decreased by 3%, the respiratory rate increased by 5 breaths per minute, or JVP reached 3 cm or greater above the sternal angle, fluid infusion was discontinued. The sepsis protocol limited intravenous fluid administration to a total of 4 L, including any fluid given in the ED prior to enrollment.

~70 ml/kg

=> Patients were reassessed for tolerance, but not for indication!

Influenza preparedness in low-resource settings: a look at oxygen delivery in 12 African countries

Janeil Belle[1], Hillary Cohen[2], Nahoko Shindo[3], Matthew Lim[4], Adriana Velazquez-Berumen[5], Jean-Bosco Ndihokubwayo[6], Meena Cherian[7]

J Infect Dev Ctries 2010; 4(7):419-424.

[1]*Duke University School of Medicine, Durham, NC, USA*
[2]*Maimonides Medical Center, Department of Emergency Medicine, Brooklyn, NY, USA*
[3-5,7]*World Health Organization Headquarters, Geneva, Switzerland,*
[6]*World Health Organization Regional Office for Africa, Brazzaville, Congo*

	Electricity	Generator	Any oxygen source	Oxygen Cylinder	Oxygen Concentrator	Face mask and tubing
Always available	81 (35.1)	127 (56.7)	99 (43.8)	66 (29.1)	55 (24.6)	75 (34.3)
Sometimes available	112 (48.5)	59 (26.3)	71(31.4)	55 (22.9)	64 (28.6)	79 (37.6)
Not available	38 (16.5)	38 (17.0)	56 (24.8)	109 (48.0)	105 (46.9)	65 (31.0)

The following countries participated in the situational analysis: Ethiopia, The Gambia, Ghana, Kenya, Liberia, Malawi, Mali, Nigeria, Sierra Leone, Sao Tome and Principe, United Republic of Tanzania, and Uganda. Allopathic health facilities, community

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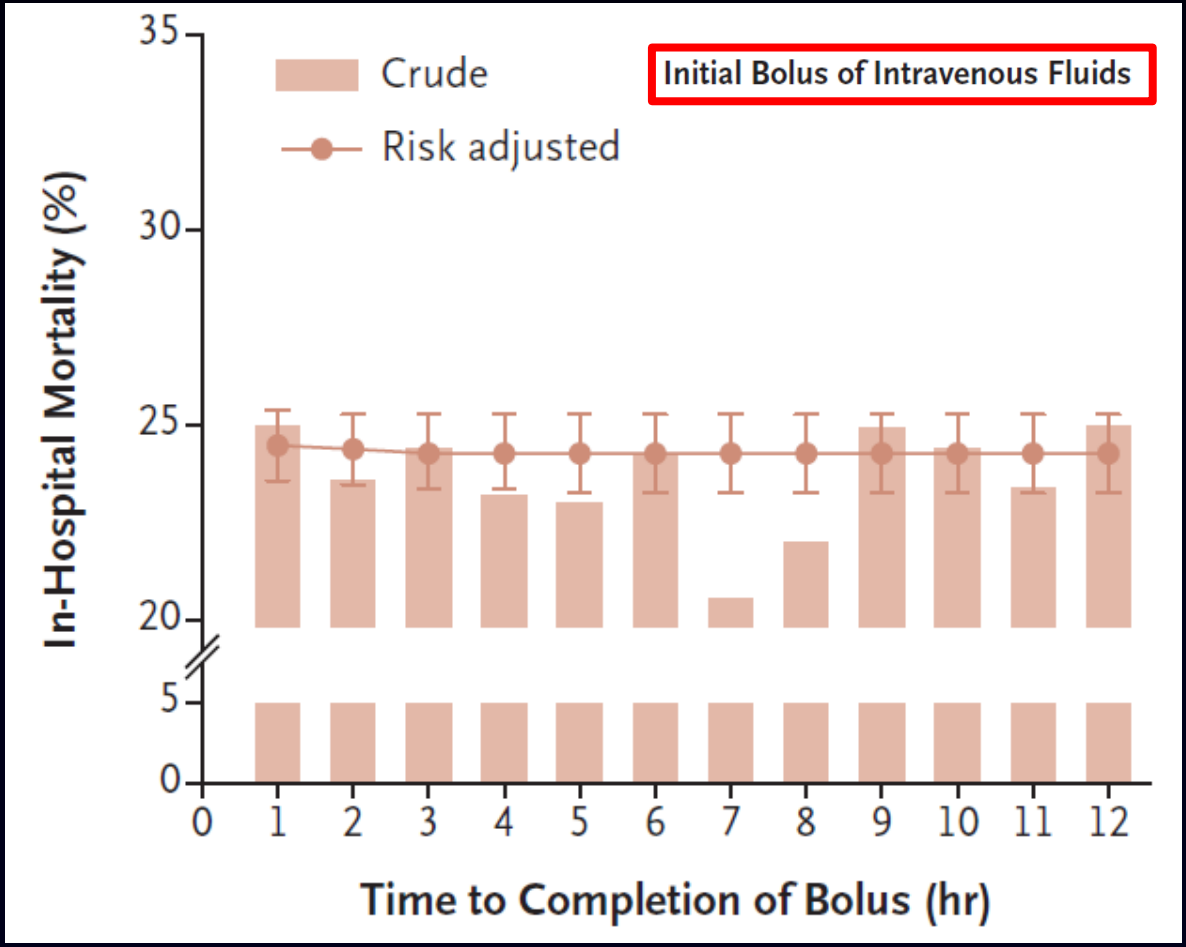
NEJM 2017

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



NY state
49331 pts
149 hosp

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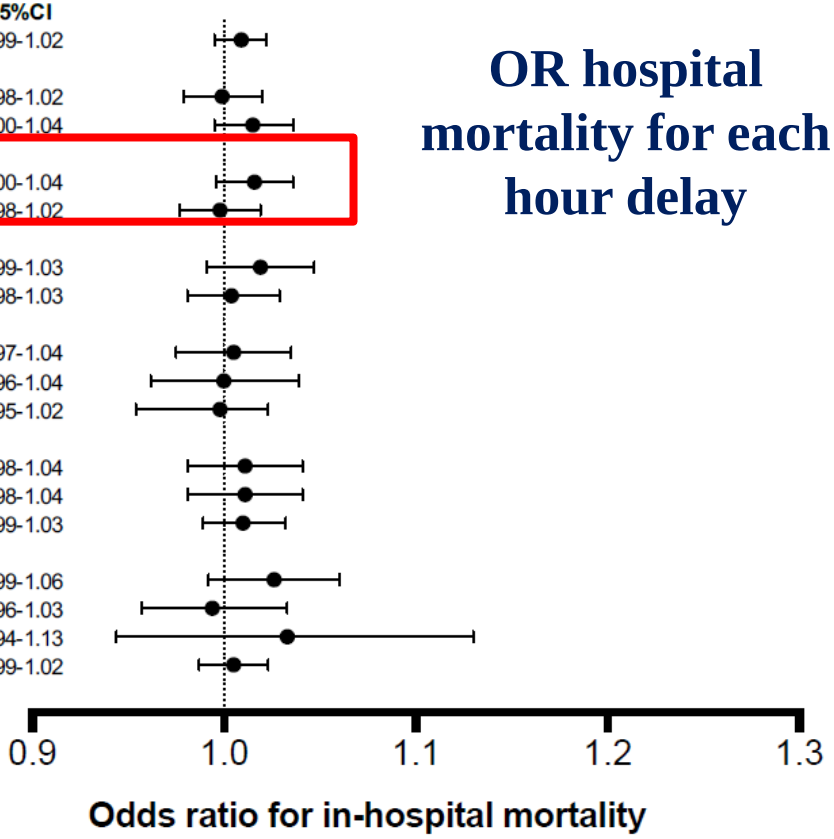
NEJM 2017

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

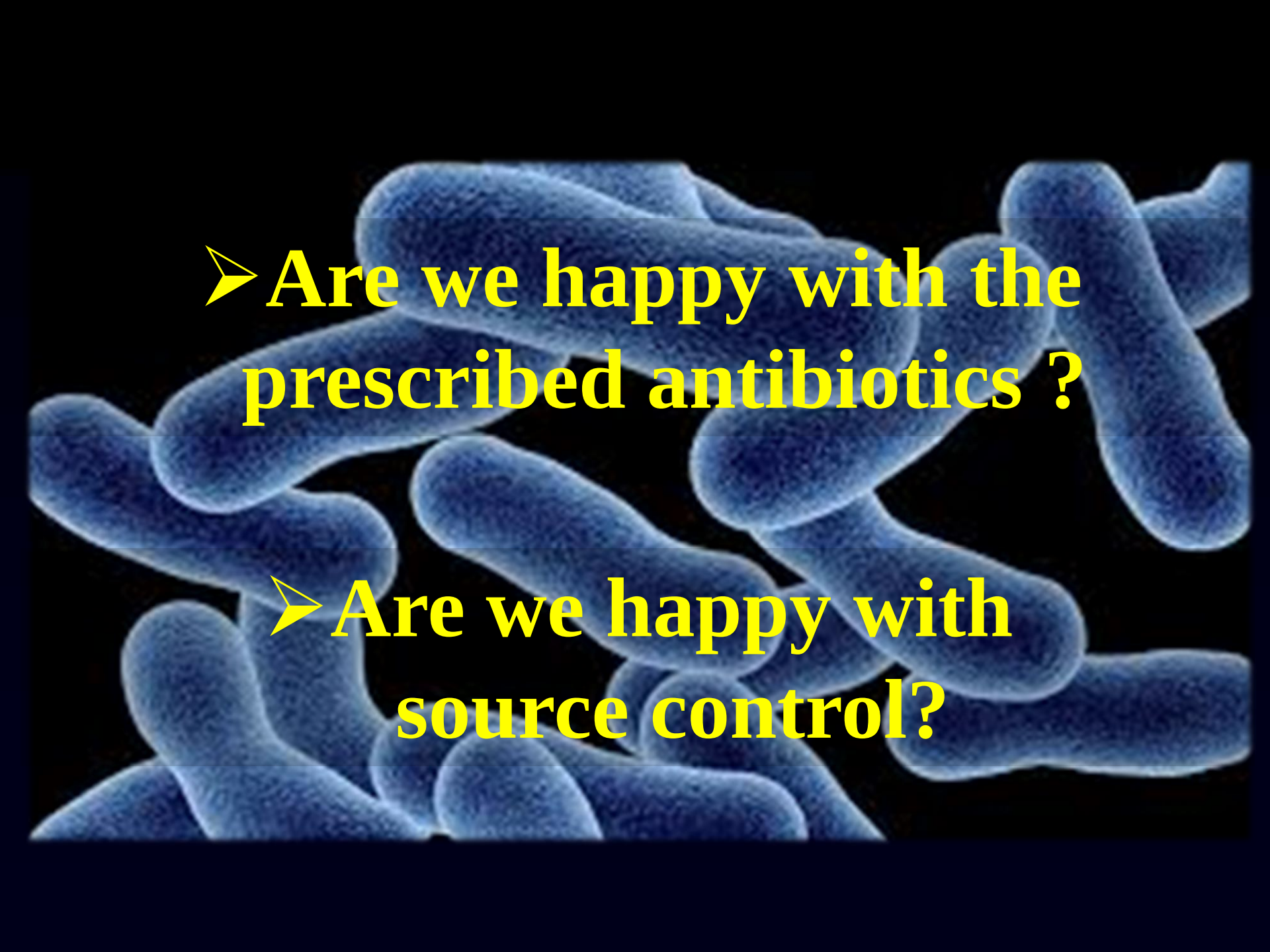


OR hospital mortality for each hour delay

NY state
49331 pts
149 hosp

Le sepsis aux soins intensifs: Prise en charge

- **Identifier / Contrôler la source**
- **Antibiotiques**
- **Traitement supportif**


Are we happy with the prescribed antibiotics ?
Are we happy with source control?

DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?

CID 2014

Jason A. Roberts,[1,2] Sanjoy K. Paul,[3,4] Murat Akova,[5] Matteo Bassetti,[6] Jan J. De Waele,[7] George Dimopoulos,[8] Kirsi-Maija Kaukonen,[9] Despoina Koulenti,[1,8] Claude Martin,[10,11] Philippe Montravers,[12] Jordi Rello,[13] Andrew Rhodes,[14] Therese Starr,[2] Steven C. Wallis,[1] and Jeffrey Lipman;[1,2] for the DALI Study[a]

Table 3. Antibiotic Data for Achievement of Pharmacokinetic/Pharmacodynamic Targets[a] in Critically Ill Patients

	Antibiotic (No. of Patients)				
Dosing and PK/PD Data	Amoxicillin (n = 71)	Ampicillin (n = 18)	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)
Dosage per 24 h[b], g	6.0 (3.5–6.0)	12.0 (8.3–12.0)	3.0 (3.0–4.0)	6.0 (5.0–6.0)	2.0 (2.0–4.0)
50% $f\,T_{>MIC}$ achieved	52.1%	55.6%	100.0%	78.6%	97.0%
50% $f\,T_{>4\times MIC}$ achieved	16.9%	27.8%	50.0%	50.0%	93.9%
100% $f\,T_{>MIC}$ achieved	18.3%	33.3%	78.6%	78.6%	93.9%
100% $f\,T_{>4\times MIC}$ achieved	11.3%	22.2%	14.3%	71.4%	87.9%

D. ANTIMICROBIAL THERAPY

Rhodes et al
ICM 2017
CCM 2017

6. We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock (weak recommendation, low quality of evidence).

Combination therapy	The use of multiple antibiotics (usually of different mechanistic classes) with the specific intent of covering the known or suspected pathogen(s) with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with β-lactams for streptococcal toxic shock) or potential immune modulatory effects (macrolides with a β-lactam for pneumococcal pneumonia).

D. ANTIMICROBIAL THERAPY

Rhodes et al
ICM 2017
CCM 2017

10. We suggest that an antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock (weak recommendation, low quality of evidence).

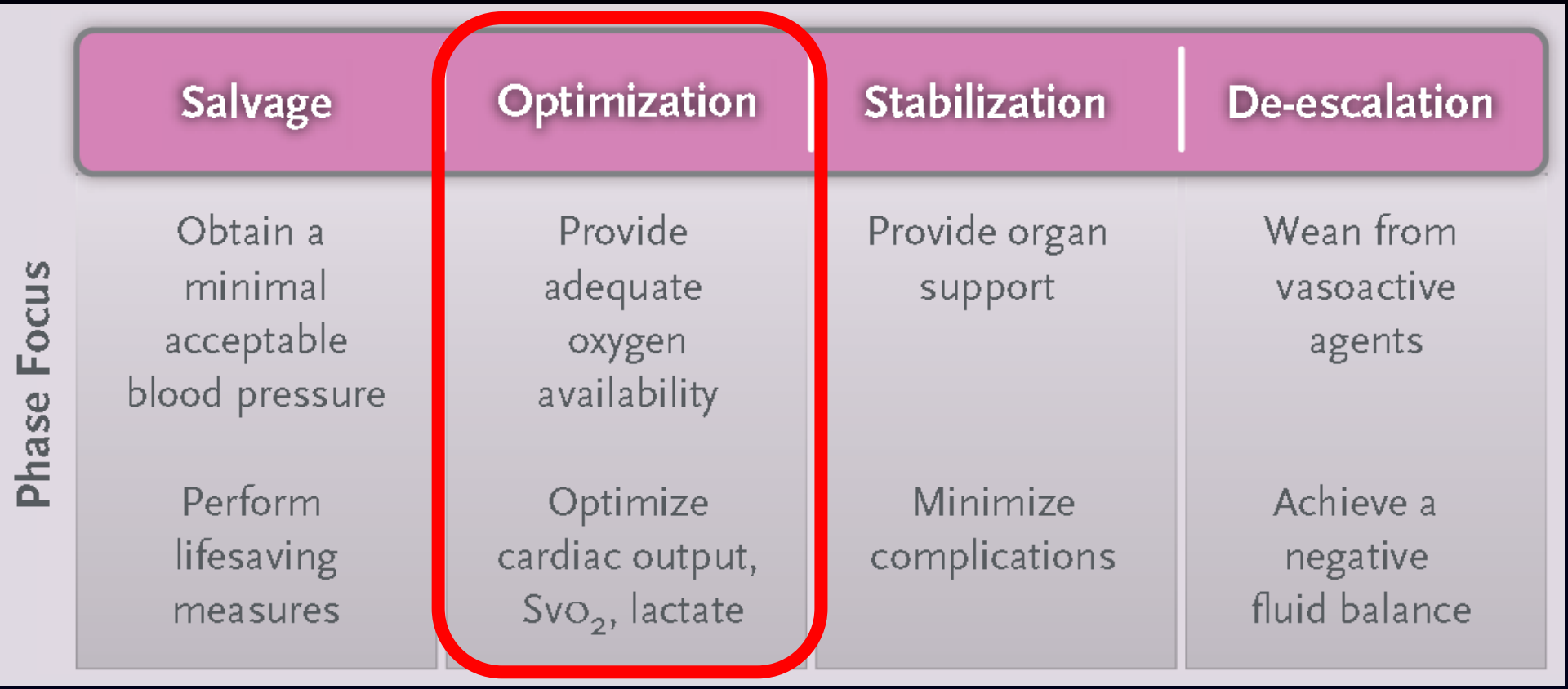
D. ANTIMICROBIAL THERAPY

Rhodes et al
ICM 2017
CCM 2017

13. We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock (BPS).

Resuscitation targets at the different stages of shock

Vincent JL and De Backer D
NEJM 369:1726; 2013



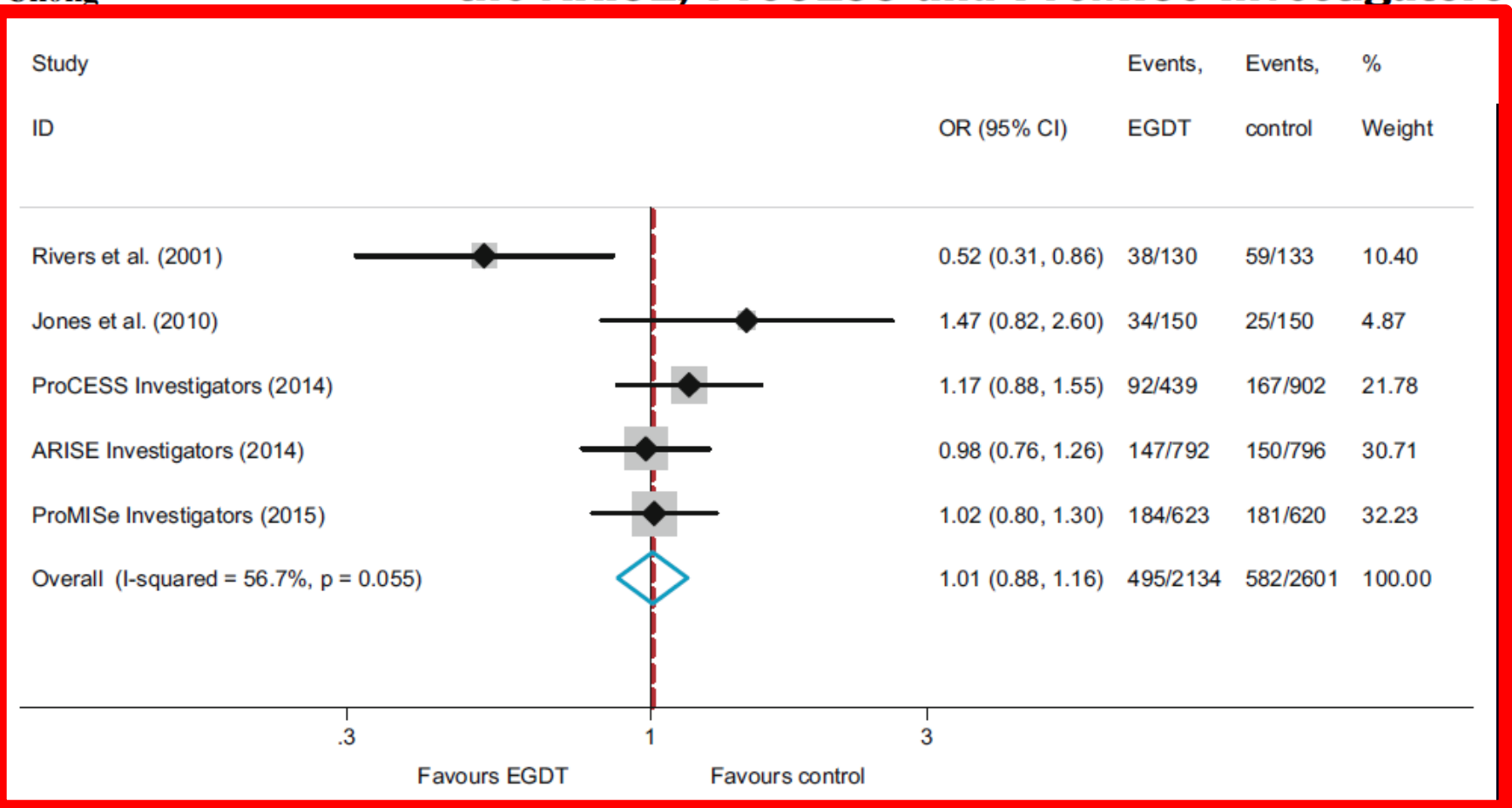
Intensive Care Med
DOI 10.1007/s00134-015-3822-1

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



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

EDITORIAL

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

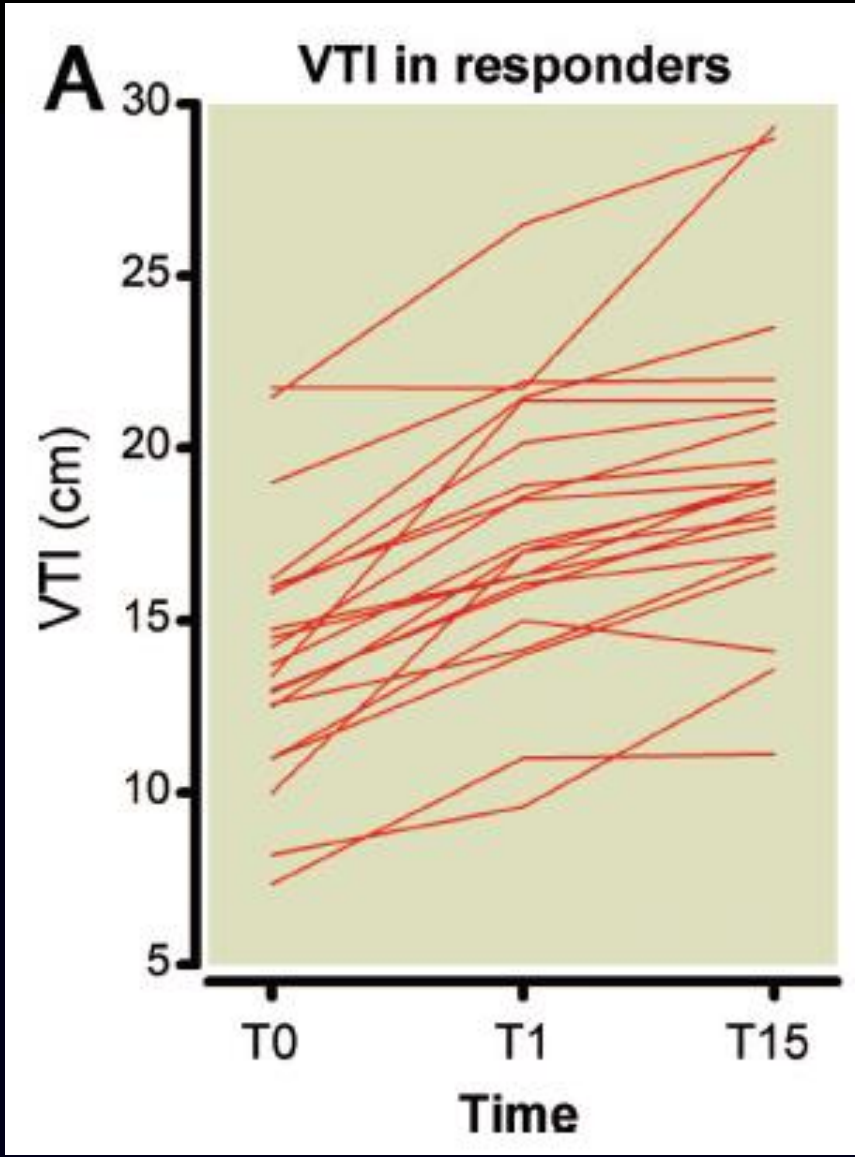
Daniel De Backer[1*] and Jean-Louis Vincent[2]

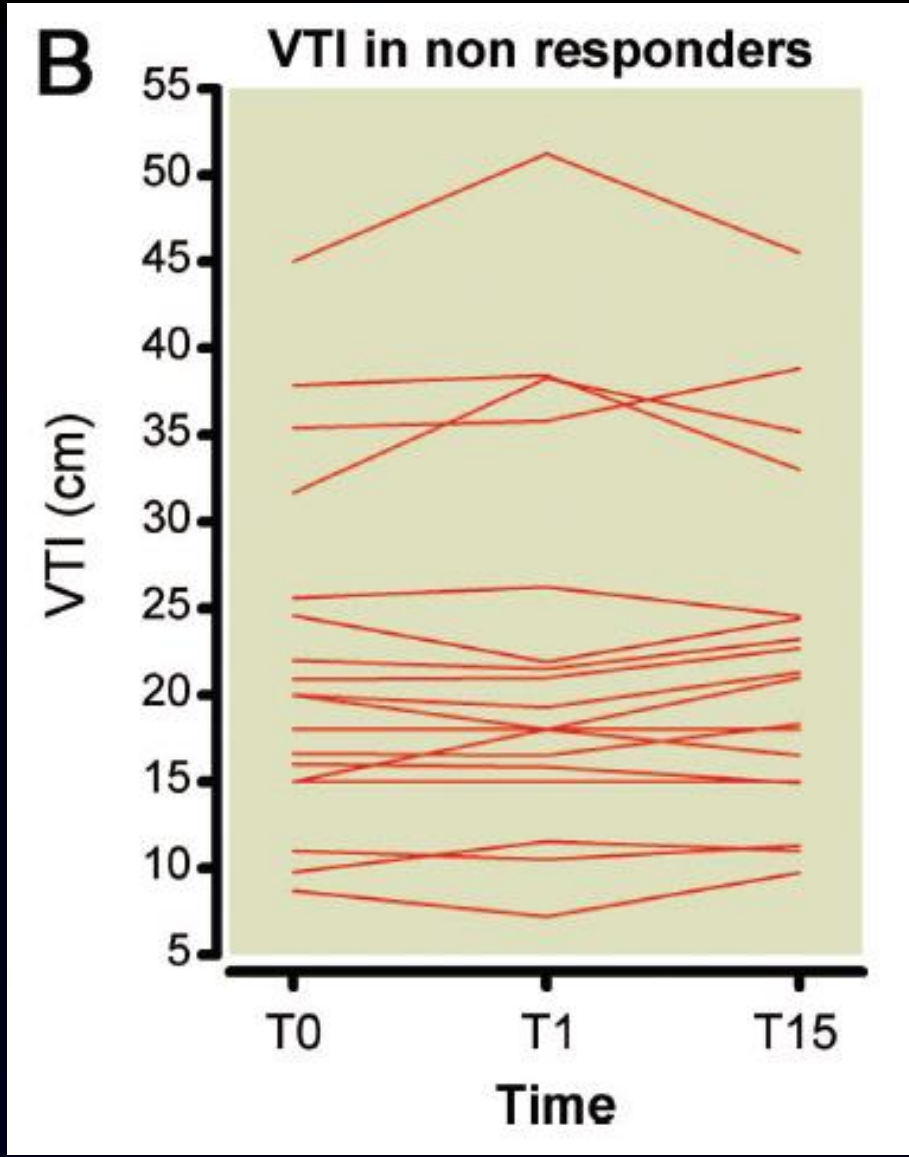
- **The concept remains valid**
- **Patient identification is crucial**
- **The classical EGDT may be applied when better hemodynamic strategies cannot be used**
- **Whenever possible use advance hemodynamic monitoring tools to optimize tissue perfusion**

What is the right amount of fluids <u>after</u> the salvage phase?

Fluids and cardiac output

Muller L et al
Anesthesiology
115:541; 2011

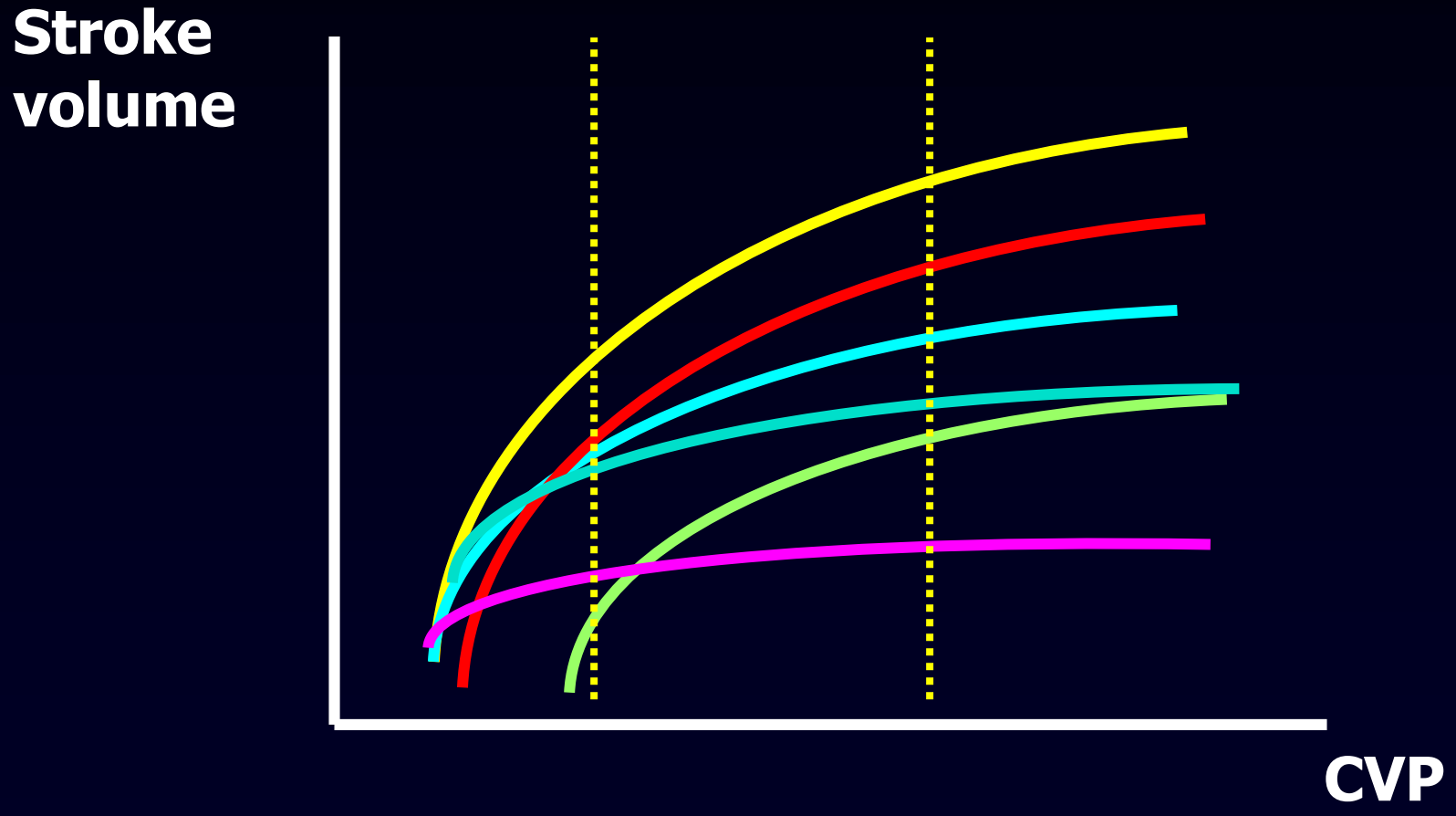




39 critically ill patients

CVP as a target ?

Extreme CVP values provide some information even if a indices of preload poorly predict fluid responsiveness !



DDB USI

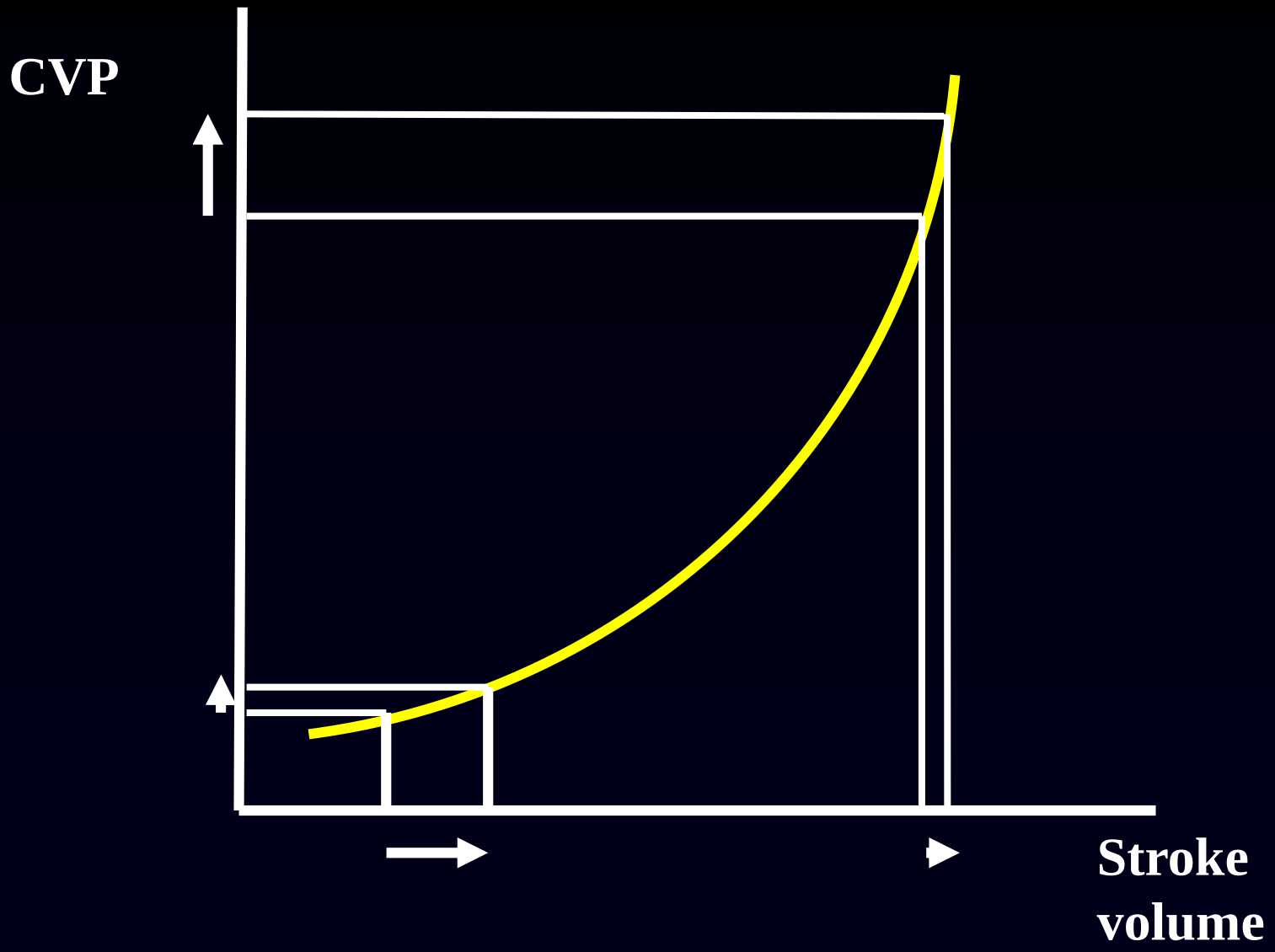
CVP: Never an optimal prediction but still some reasonable guidance if nothing better can be used….

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

The increase in CVP does not indicate the response to fluids



We should individualize fluid therapy !

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

ESICM
EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

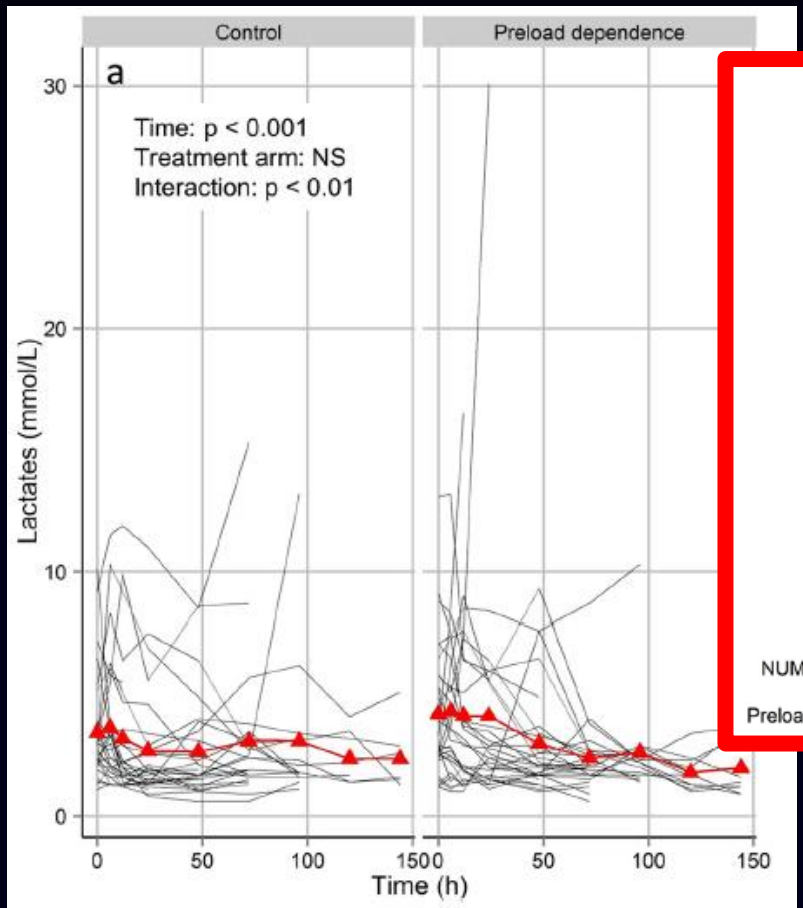
28.	We recommend that commonly used preload measures (such as CVP or PAOP or end diastolic area or global end diastolic volume) alone should not be used to guide fluid resuscitation	Level 1; QoE moderate (B)	Recommendation
29.	We recommend not to target any absolute value of ventricular filling pressure or volume	Level 1; QoE moderate (B)	Recommendation
30.	We recommend that fluid resuscitation should be guided by more than one single hemodynamic variable	Ungraded	Best practice
31.	We recommend using dynamic over static variables to predict fluid responsiveness, when applicable	Level 1; QoE moderate (B)	Recommendation

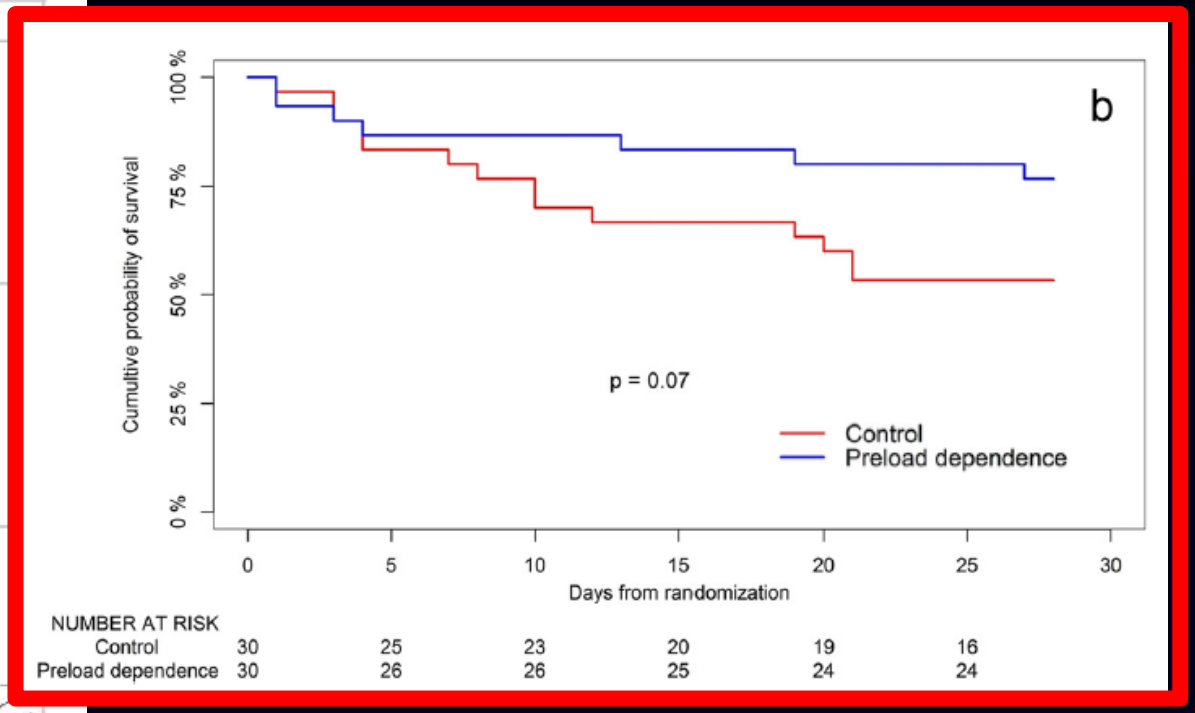
Richard *et al. Critical Care* (2015) 19:5
DOI 10.1186/s13054-014-0734-3

CRITICAL CARE

RESEARCH Open Access

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





The best way to administer fluids

Perfusion issue that may respond to fluids

↓

Prediction of the response to fluids

↓

Fluid challenge to assess response (incl.and tolerance) to fluids

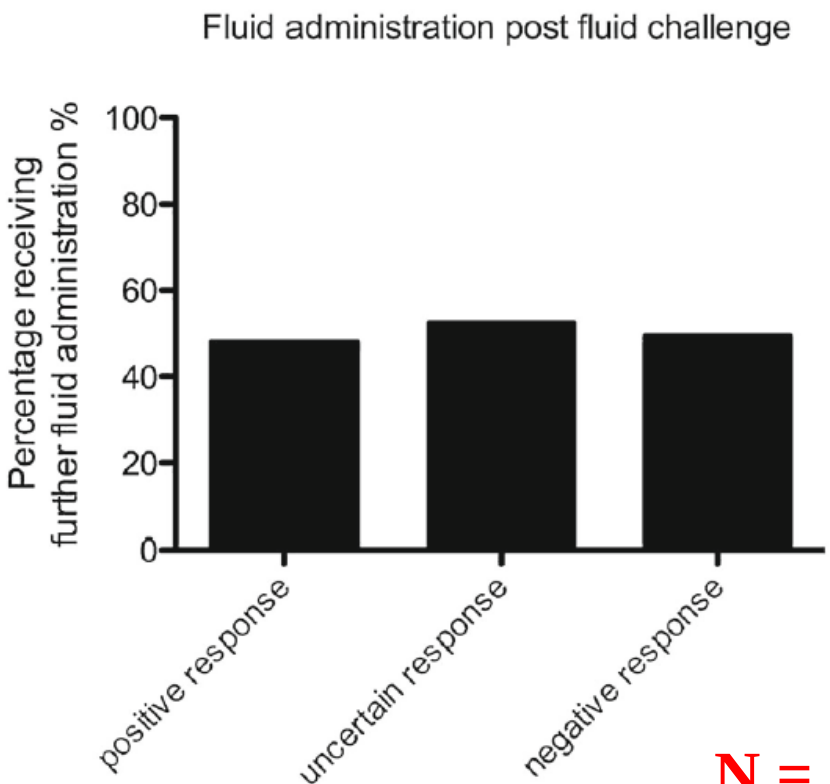
Pay attention to the response of the patient

SEVEN-DAY PROFILE PUBLICATION

ICM 2015

Fluid challenges in intensive care: the FENICE study

A global inception cohor



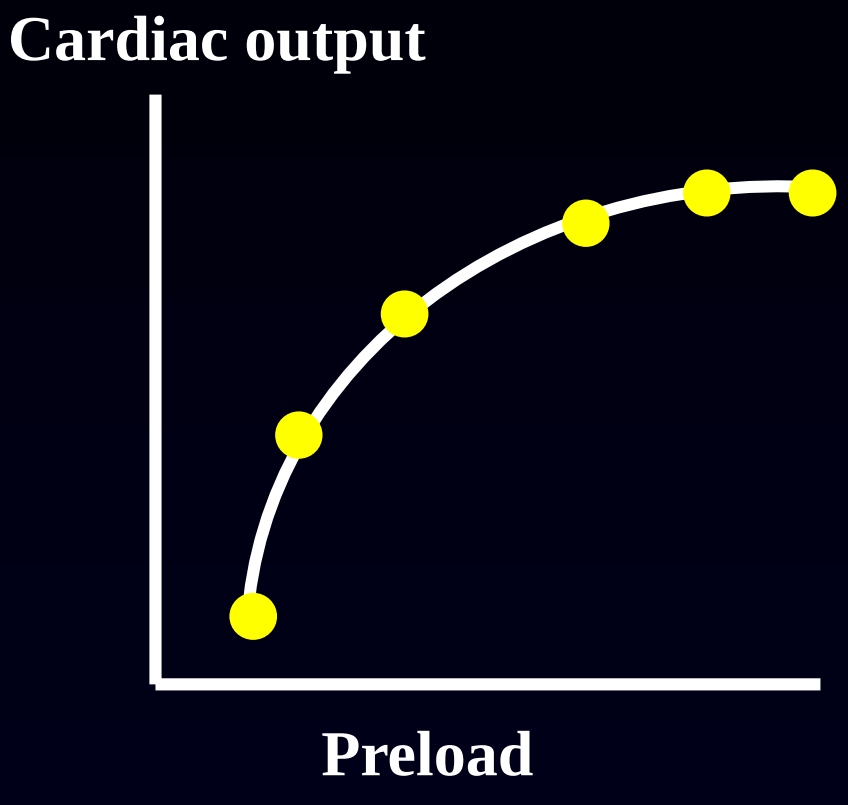
N = 2213

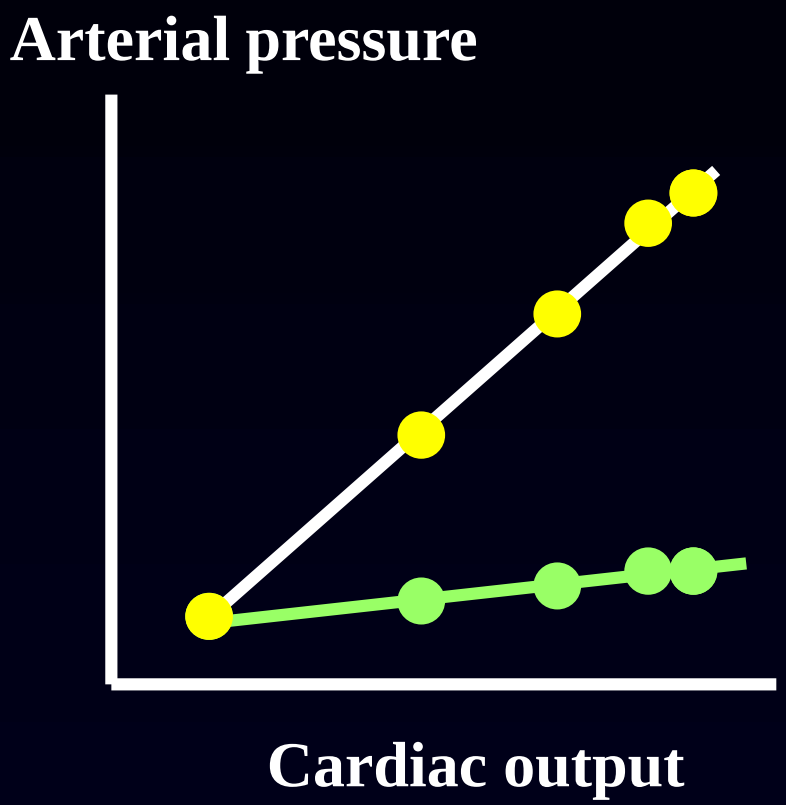
ESICM EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

TRIALS GROUP

Do fluids correct hypotension in septic shock ?

The increase in arterial pressure depends on vascular tone and the impact on cardiac output





In sepsis, the low vascular tone limits the increase in arterial pressure in response to fluids.

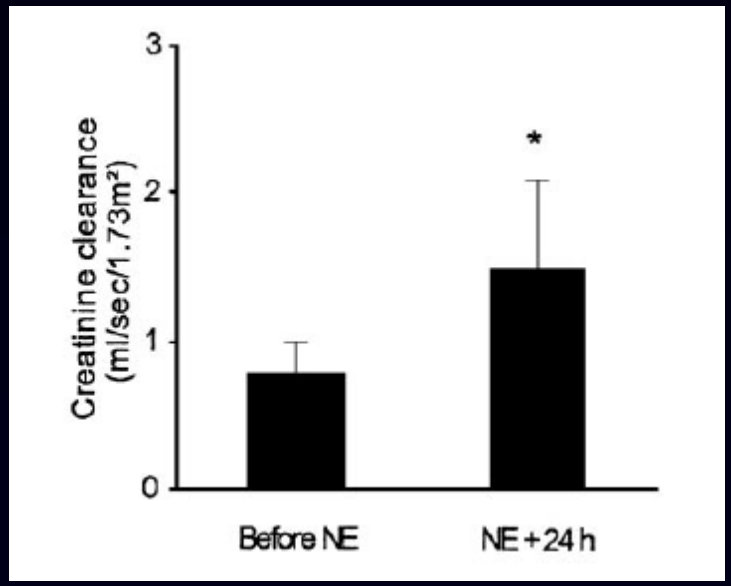
Does correction of hypotension with vasopressors affect tissue perfusion ?

Correction of hypotension improves urine output and renal function in septic patients

Albanese et al
Chest 126:534;2004

Variables	UF		
	Before, mL/h	NE + 2 h, mL/h	NE + 24 h, mL/d
Septic shock (n = 14)	14 ± 13	121 ± 87†	2,450 ± 1,237†

MAP 50 => 78 mmHg



Patients with septic shock (n=14)

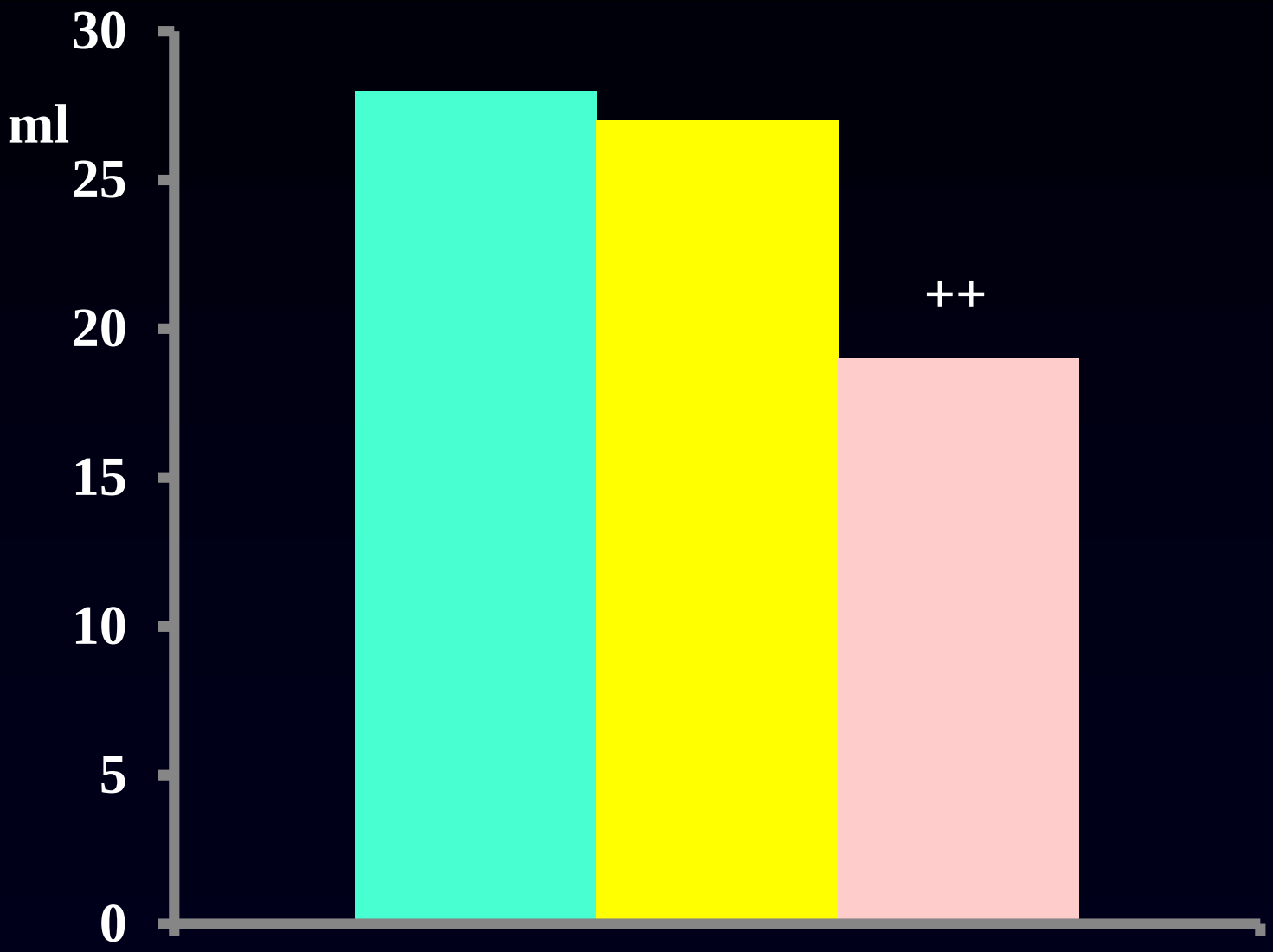
DDB USI

When to introduce vasopressors?

Early introduction of vasopressors may decrease later need for fluids

Early introduction of norepi decreased fluids requirements

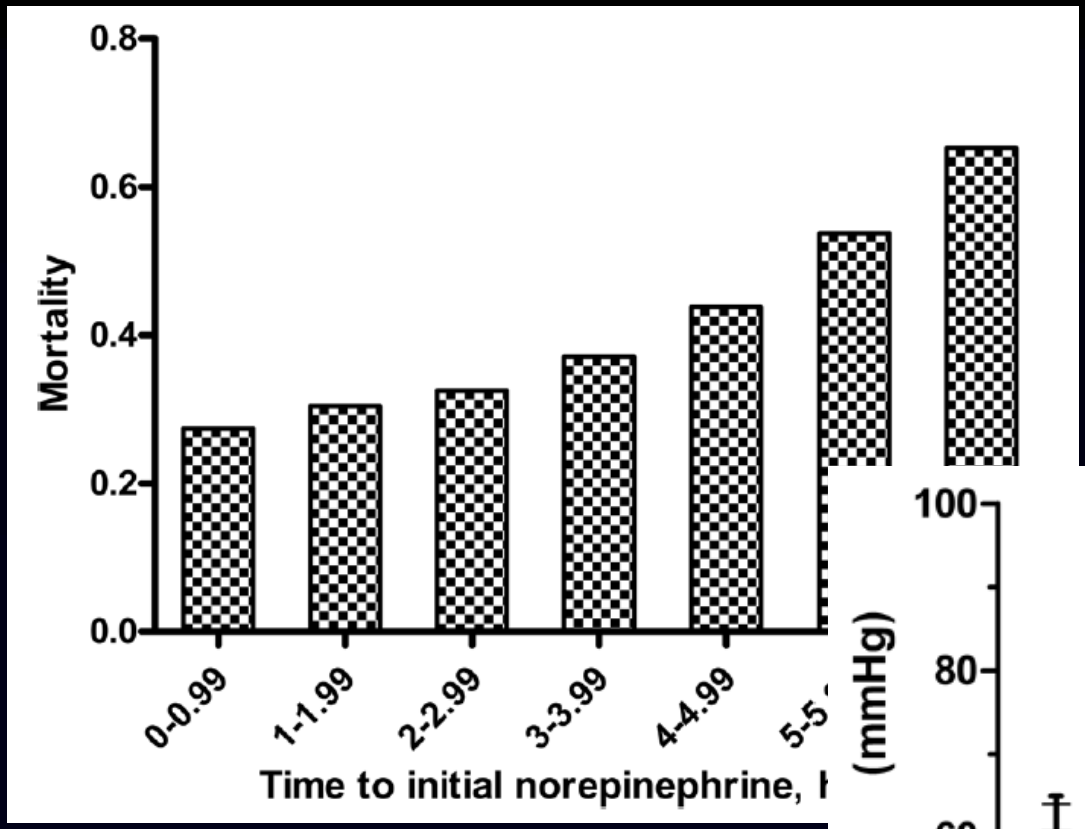
Sennoun N et al
CCM 35:1736;2007

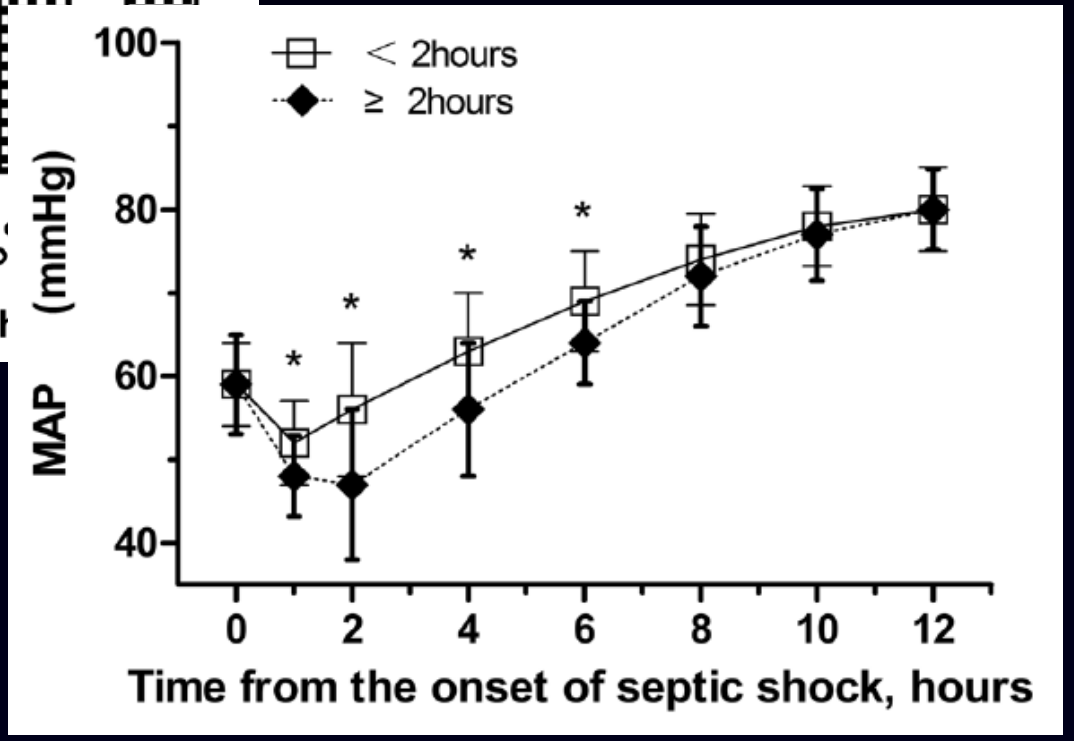


Rats / LPS

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

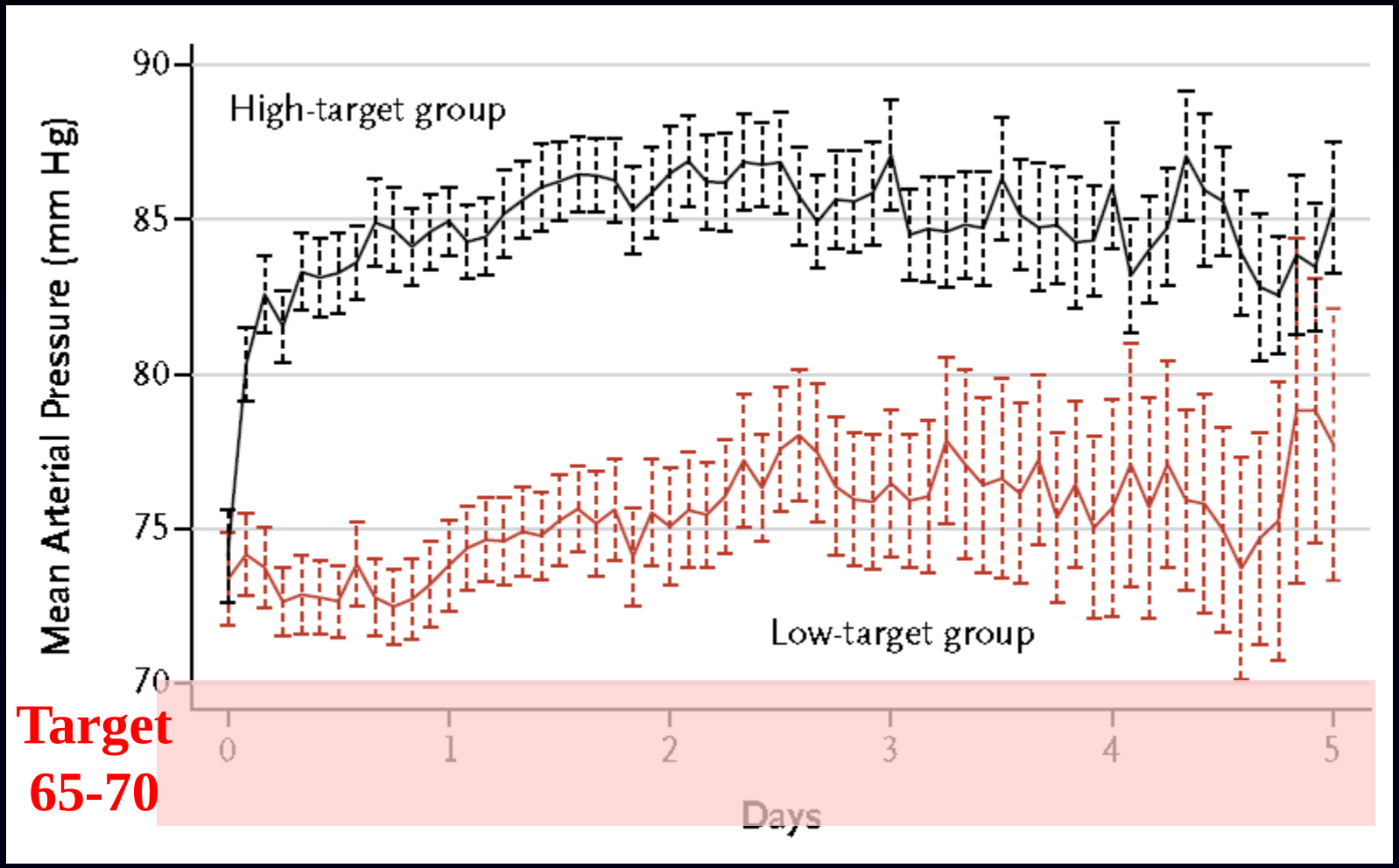
Which blood pressure target ?

DDB USI

High vs Low MAP ?

~~65-70~~ 73-75 VS 80-85 mmHg

Asfar P et al
NEJM 2014

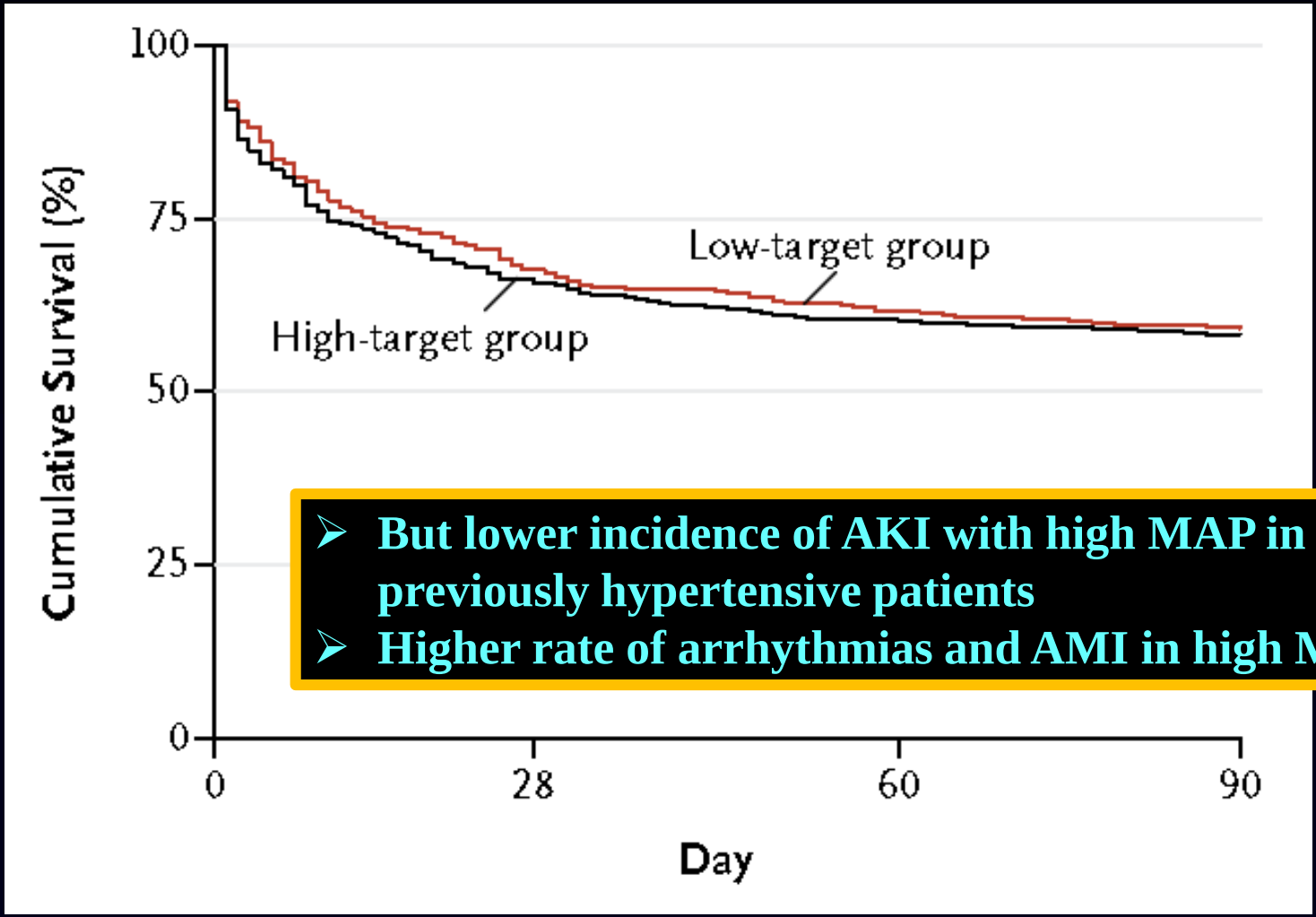


798 pts septic shock

High vs Low MAP ?

65-70 VS 80-85 mmHg

Asfar P et al
NEJM 2014



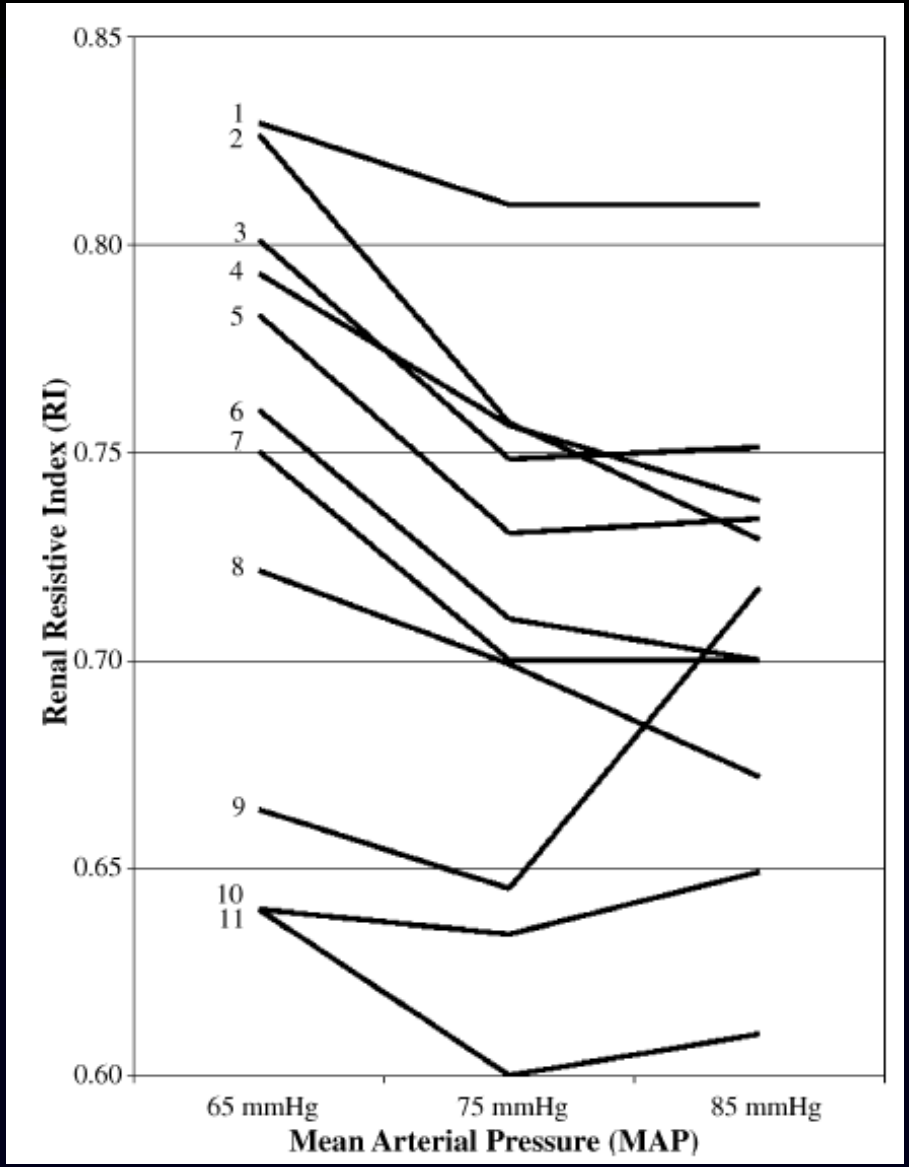
- **But lower incidence of AKI with high MAP in previously hypertensive patients**
- **Higher rate of arrhythmias and AMI in high MAP**

798 pts septic shock

High variablity in response to increase in MAP

Deruddre et al
ICM 33:1557;2007

Renal Doppler



11 pts septic shock

MAP target ?

- **65 mmHg as a starting point**

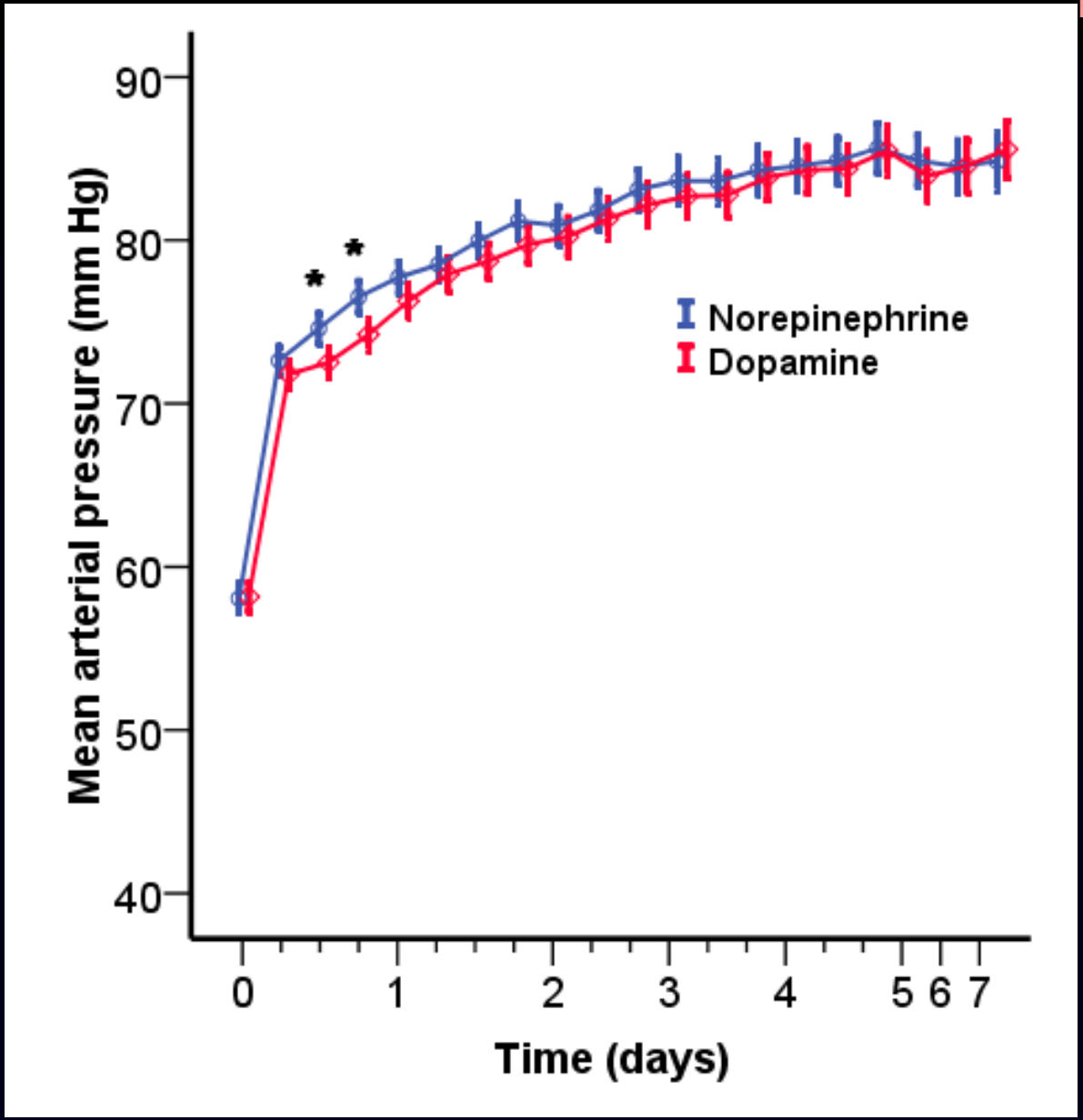
- **Higher levels can be considered in some patients but the response to a higher target level shoud be evaluated**
  => « MAP challenge »

- **However, the « MAP challenge » should take place only after having optimized other aspects of perfusion.**


Select the right vasopressor agent !

Norepinephrine vs Dopamine in shock (SOAP investigators)

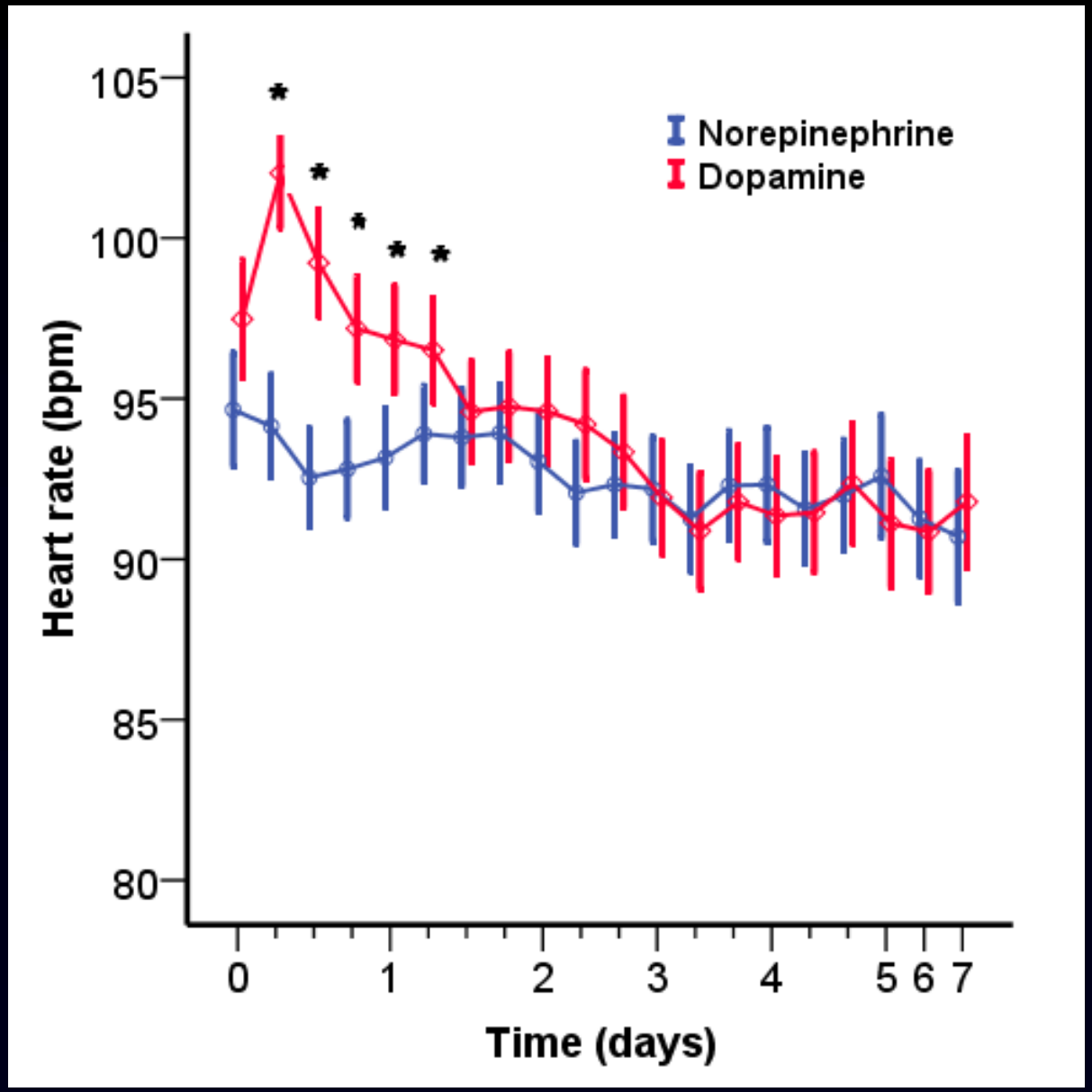
De Backer et al
NEJM 362: 779; 2010



N = 1679

* p<0.05

Norepinephrine vs Dopamine in shock (SOAP investigators)



De Backer et al
NEJM 362: 779; 2010

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Norepinephrine vs Dopamine in shock (SOAP investigators)

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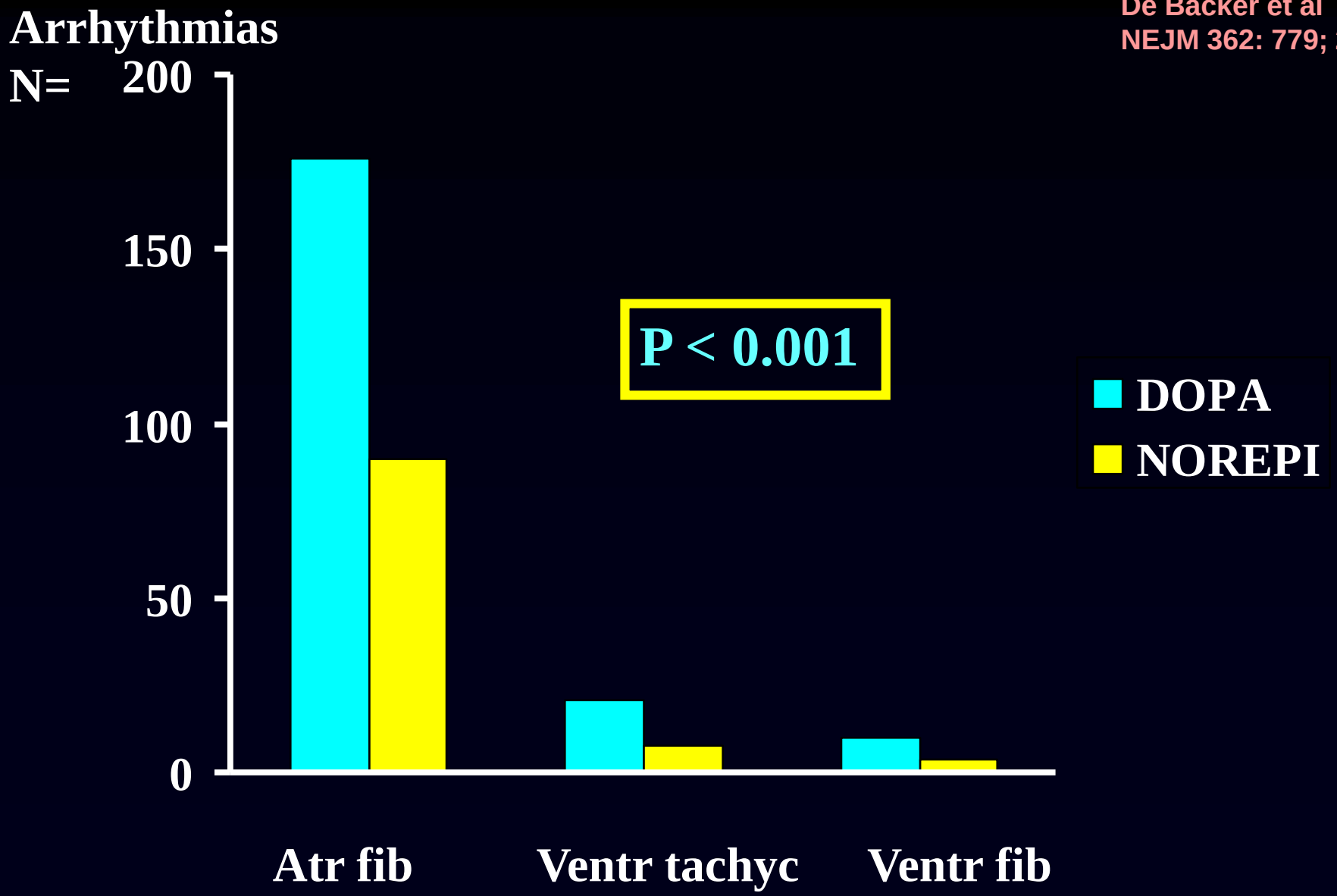
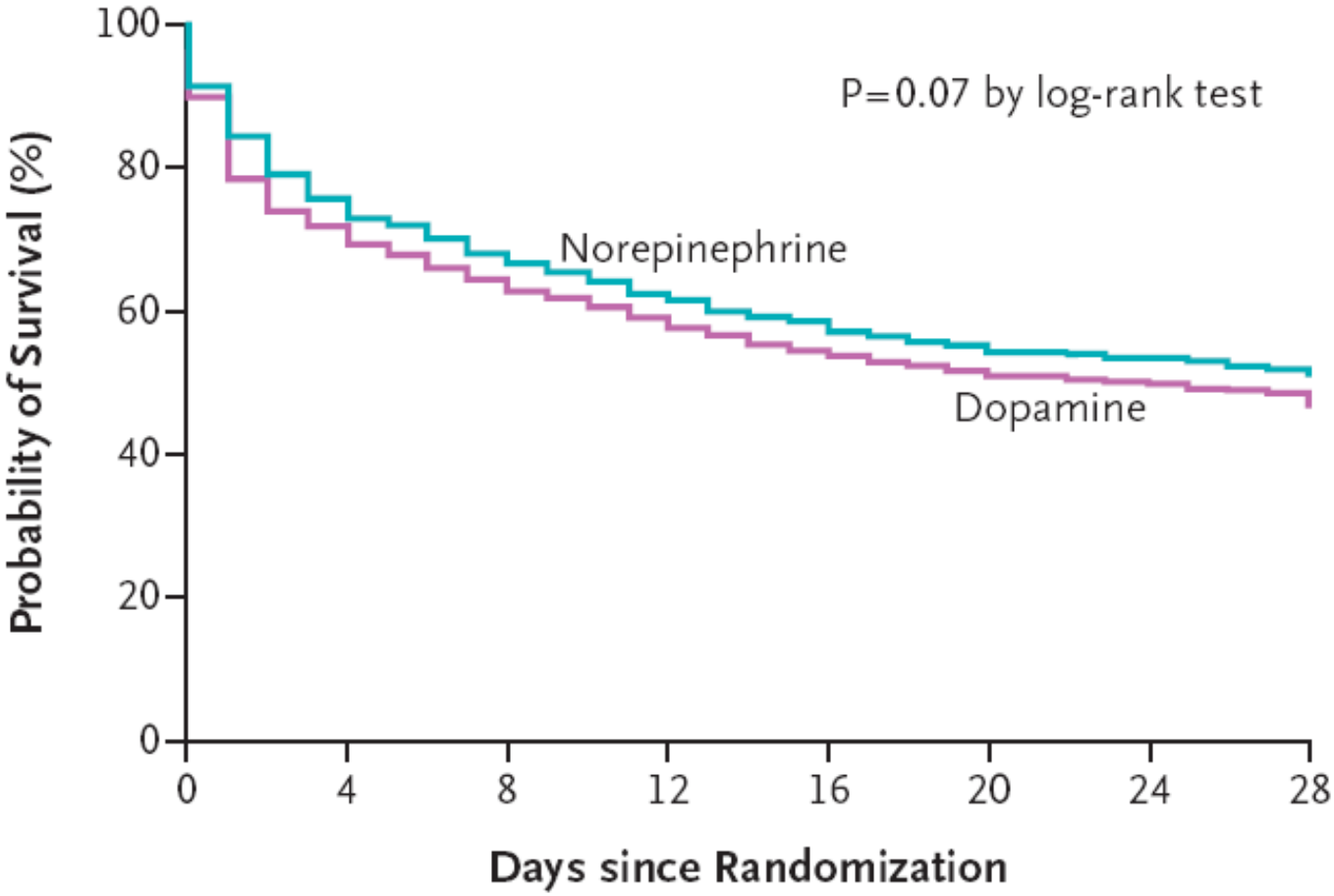


Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010

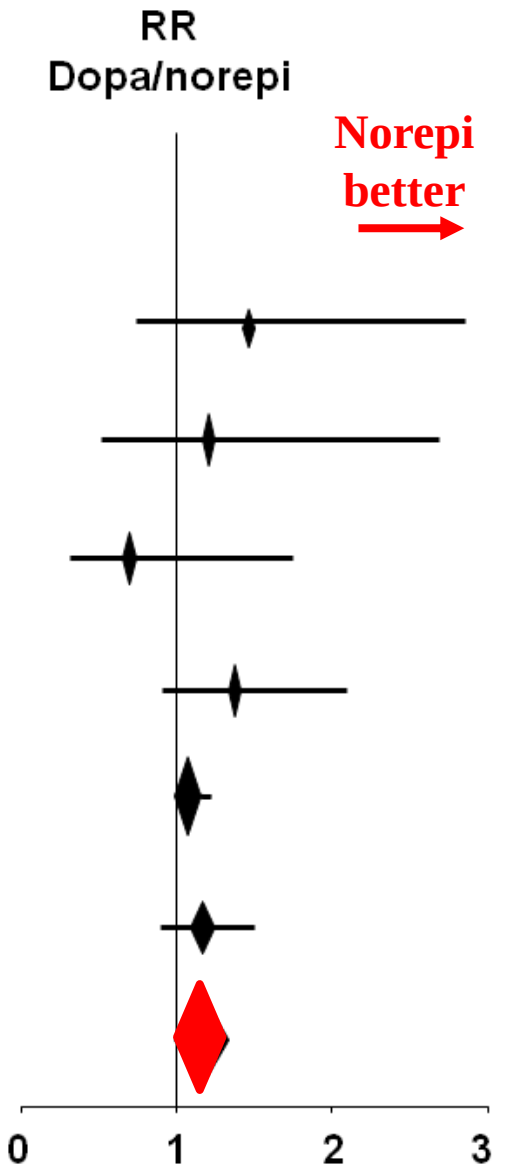


No. at Risk								
Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386

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]**

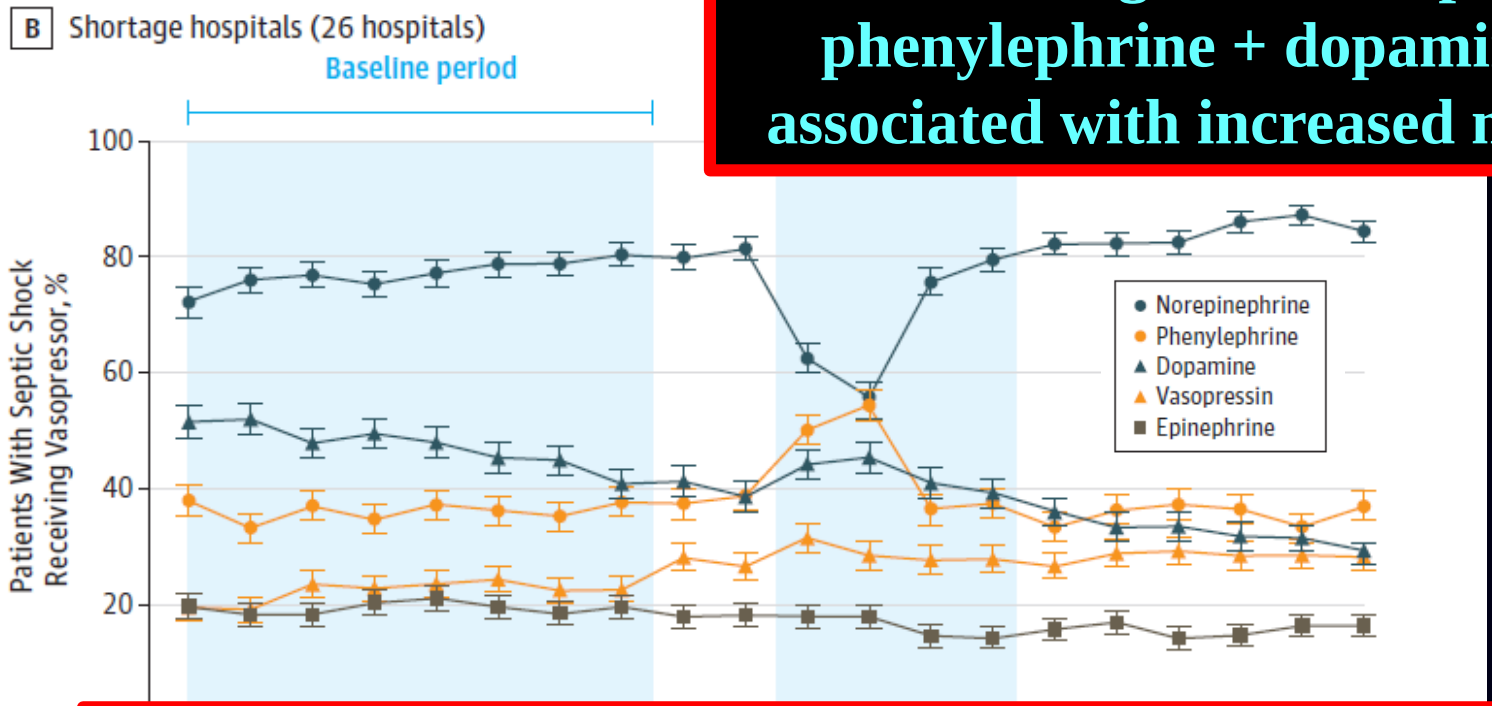


Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

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

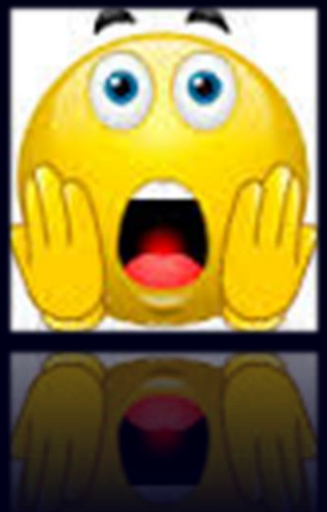
1. We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).

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.

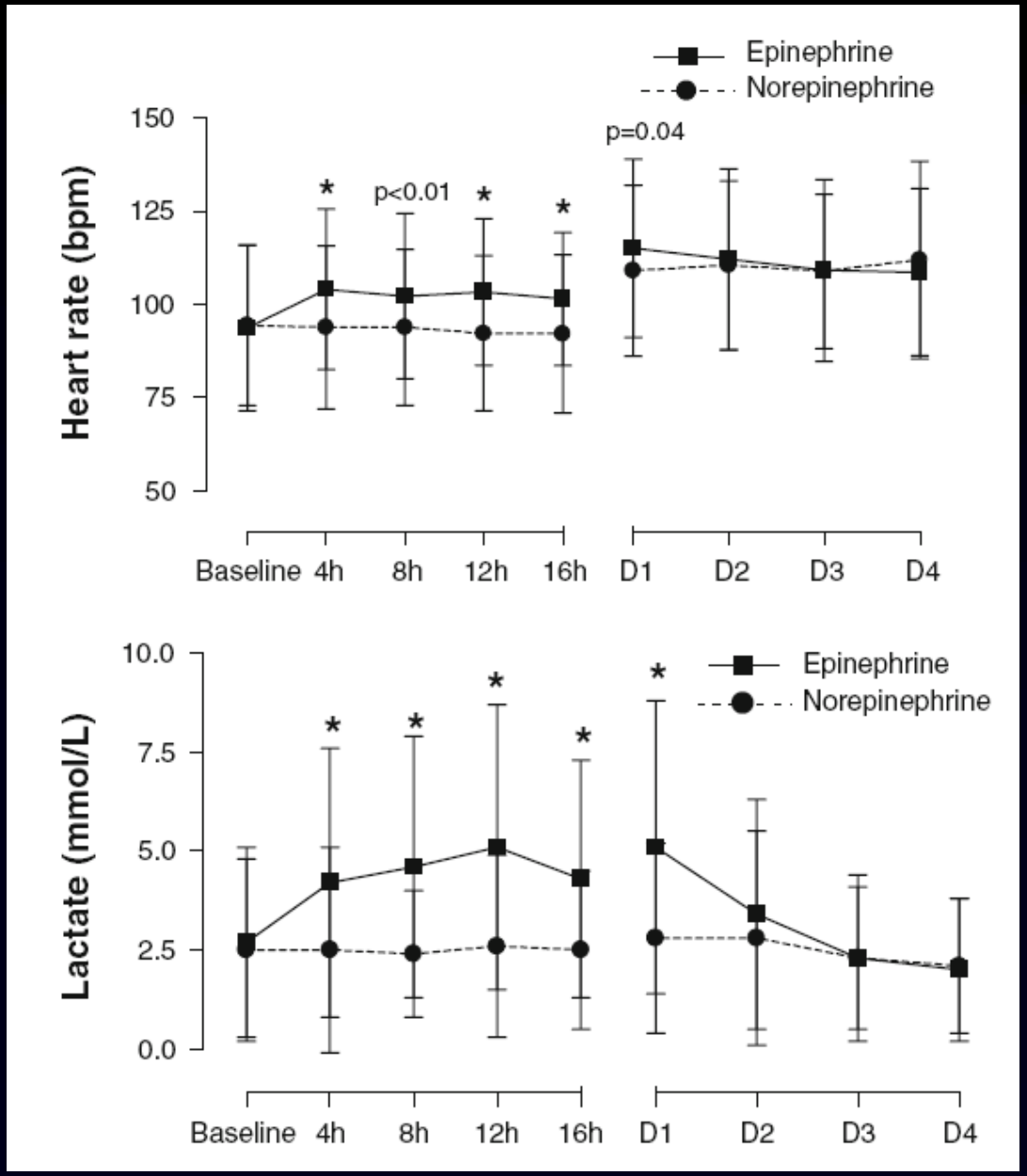
What to do if the patient is not responding to norepinephrine ?

$\alpha = \alpha$

Adding another alpha adrenergic agent (i.e. epinephrine) would not increase blood pressure more than increasing the dose of norepinephrine…

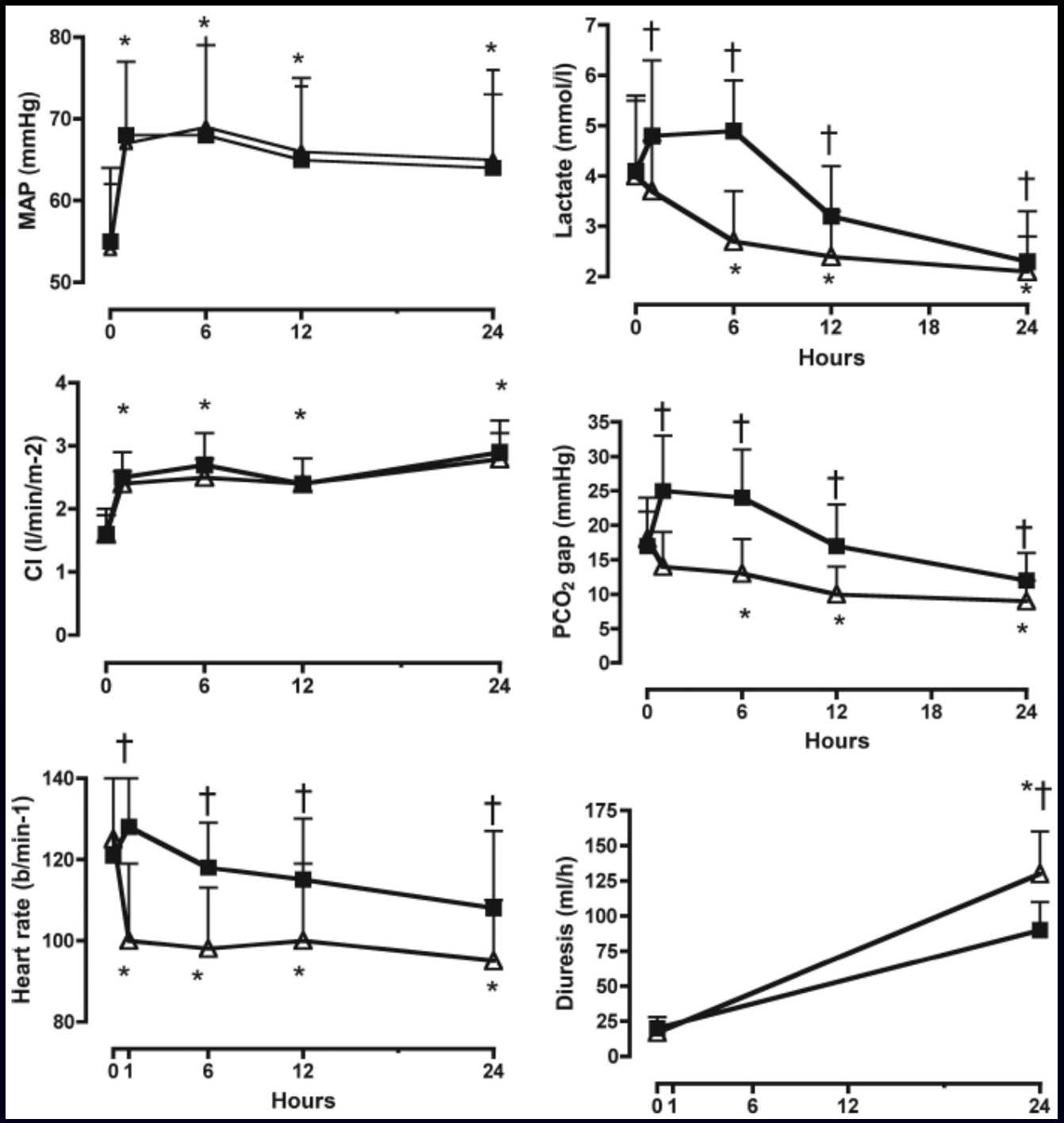


Norepinephrine vs Epinephrine



Myburgh et al
ICM 34:2226;2008

280 pts



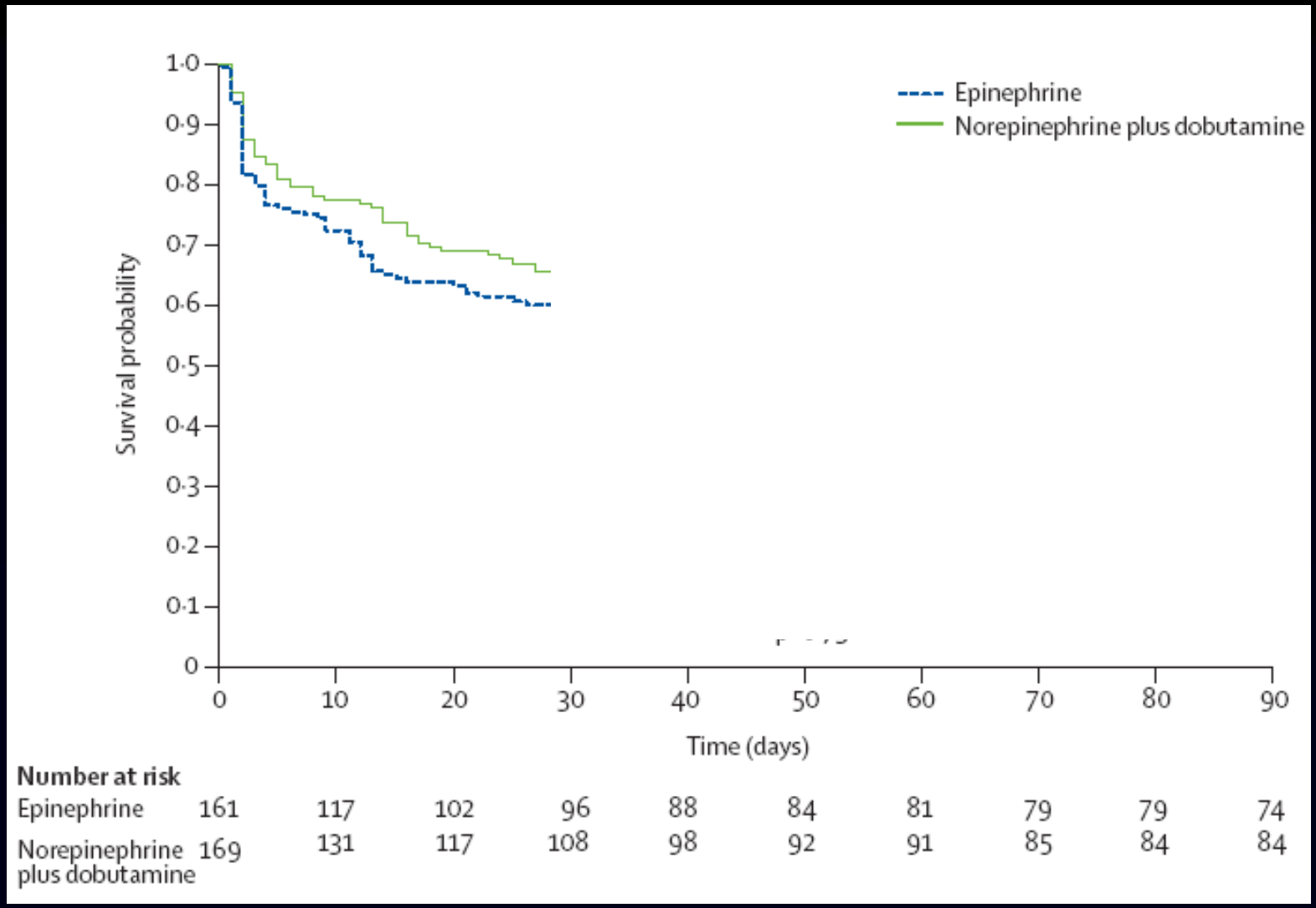
Levy B et al CCM 2011

30 pts cardiogenic shock

Norepi + dobu VS Epi

EPI vs NOREPI (+-DOBU)

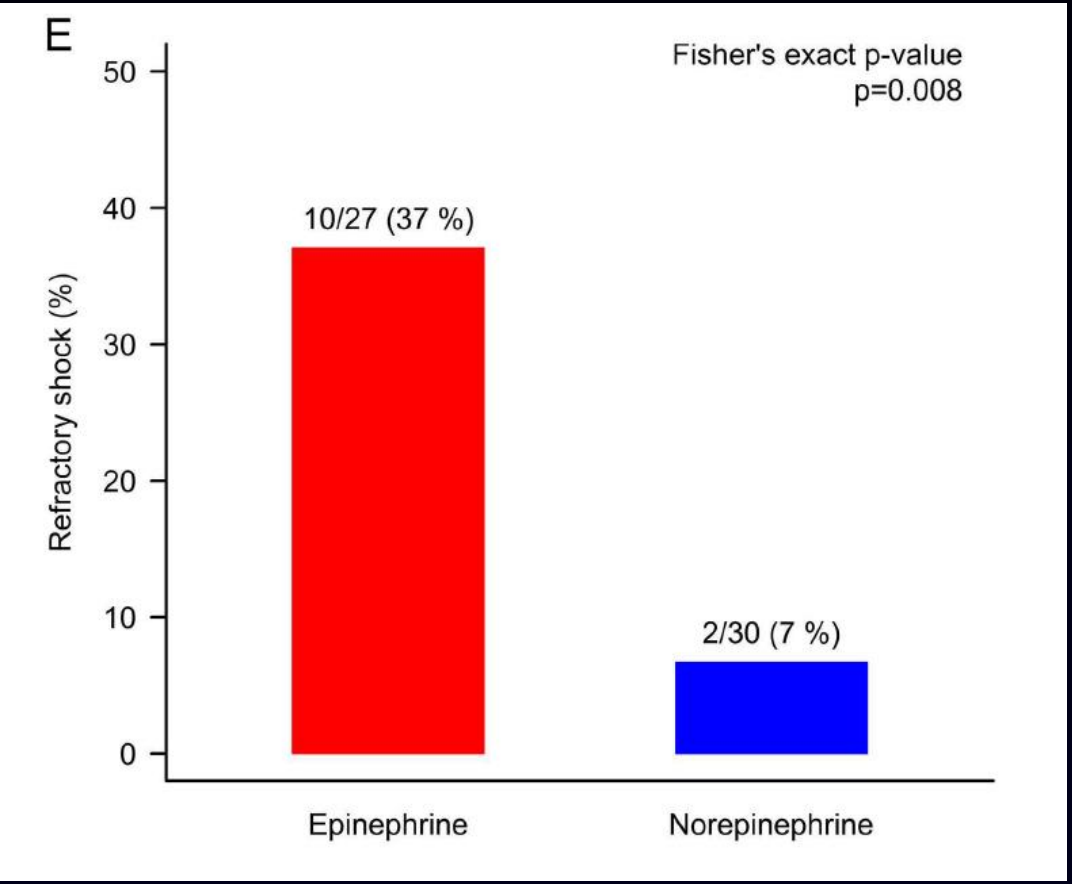
Annane et al
Lancet 370:676;2007



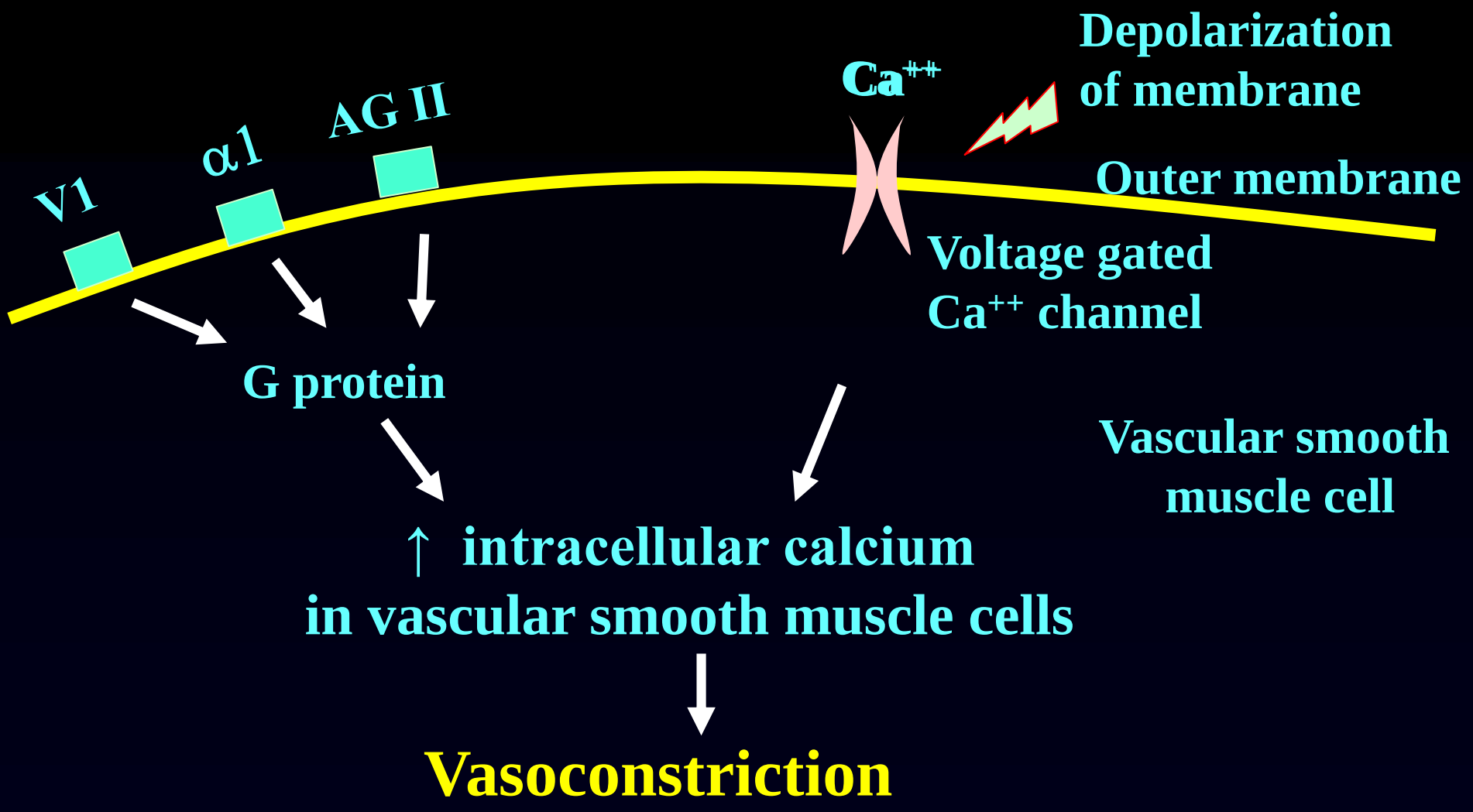
330 pts septic shock

Epinephrine versus norepinephrine in cardiogenic shock after acute myocardial infarction. A double-blind, multicenter randomized study.

Levy B et al JACC 2018



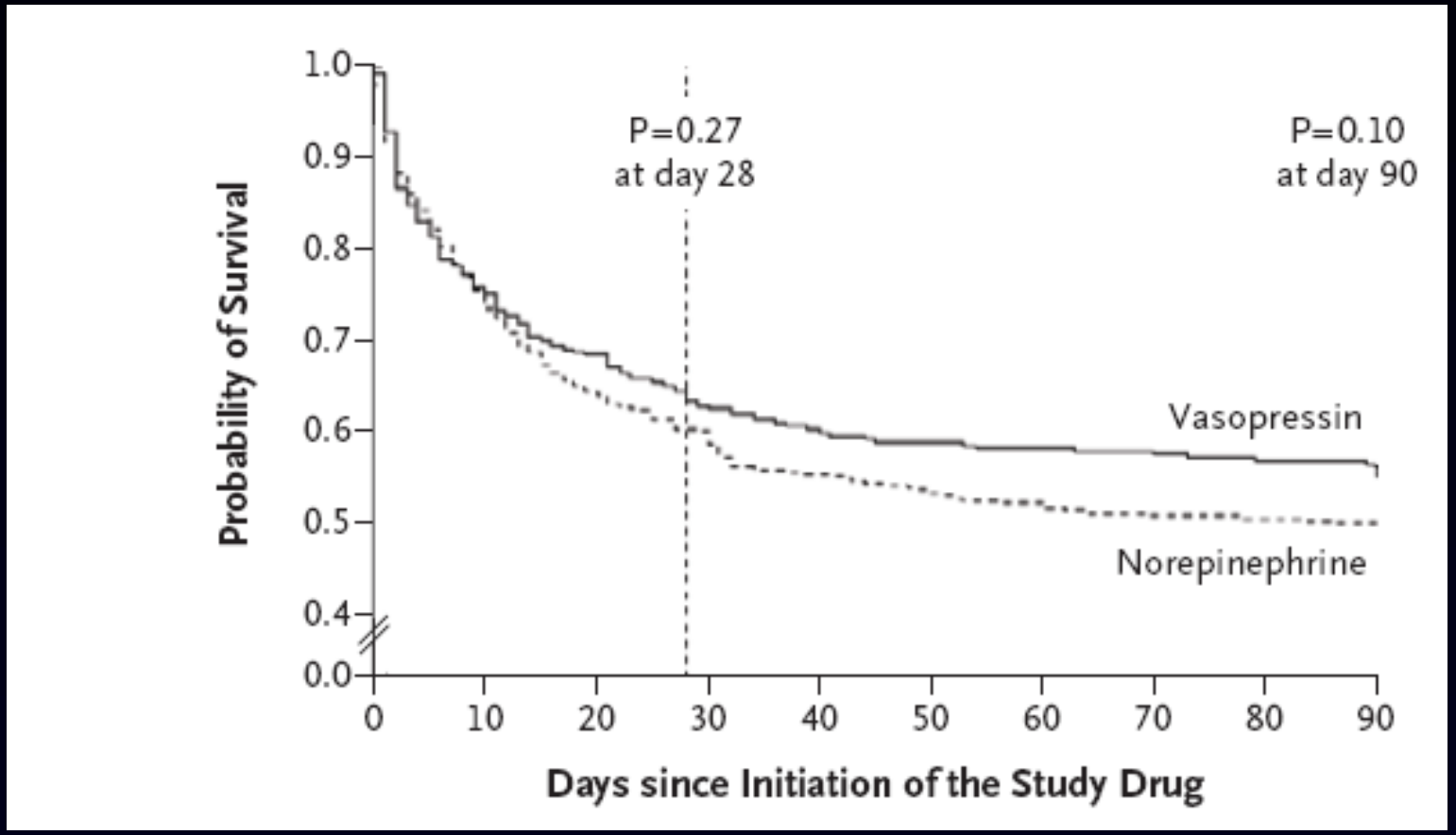
Death rate: 52 % vs 37% p=0.25



Differences arise due to receptor sensitivity and disposition in the vascular system, as well as stimulation of other receptors (beta/V2…)

VASST

Russell et al
NEJM 358:877;2008

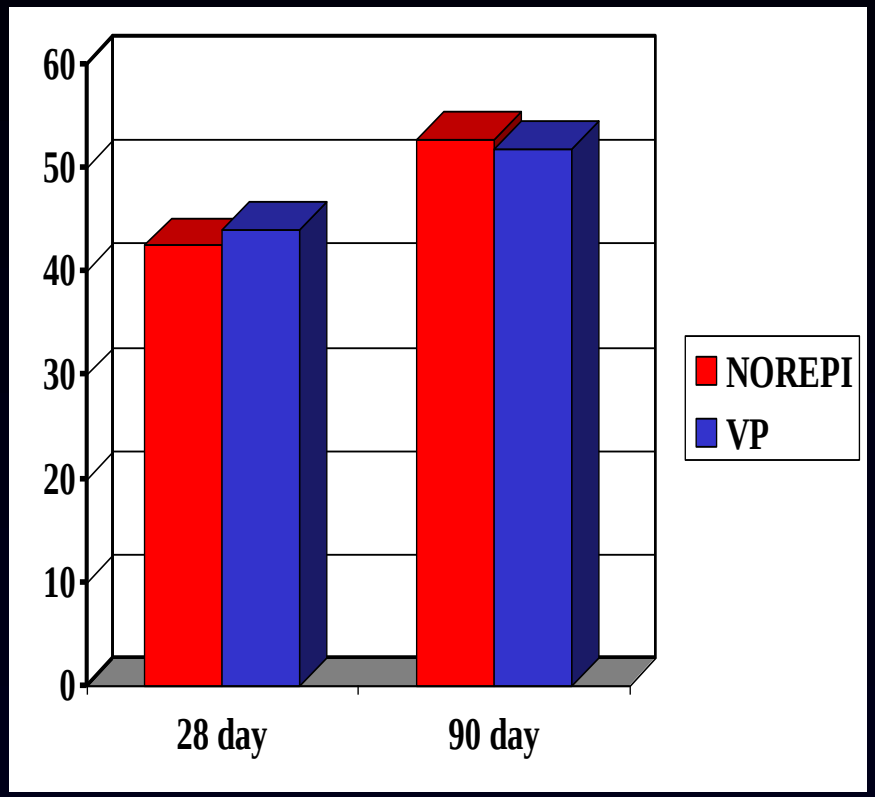


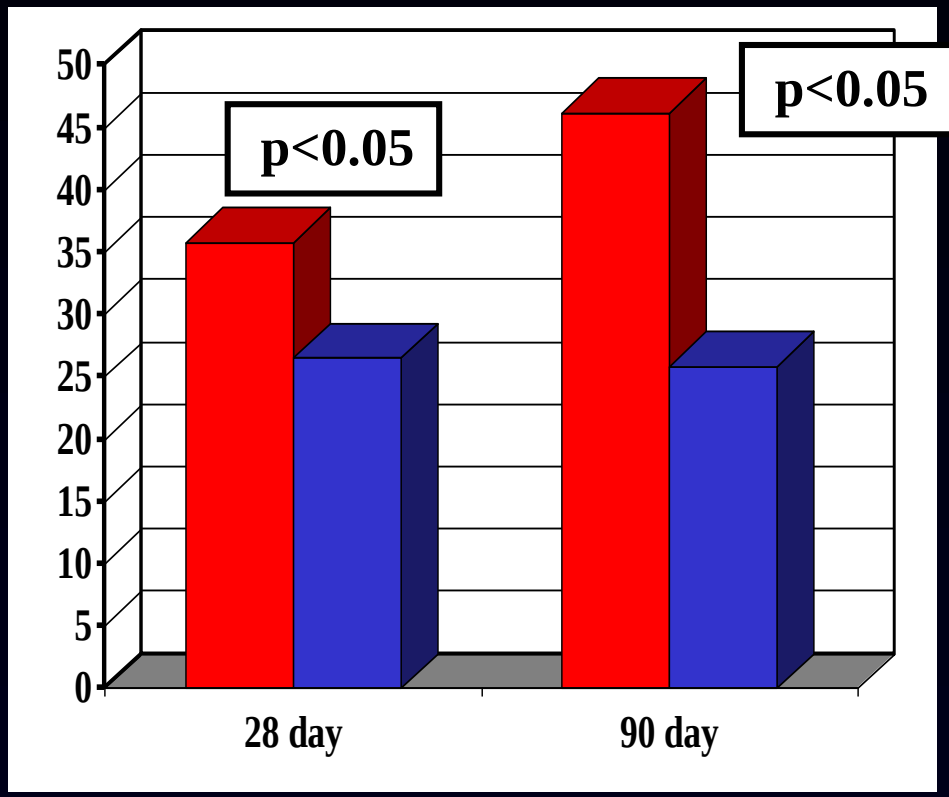
802 septic shock pts

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

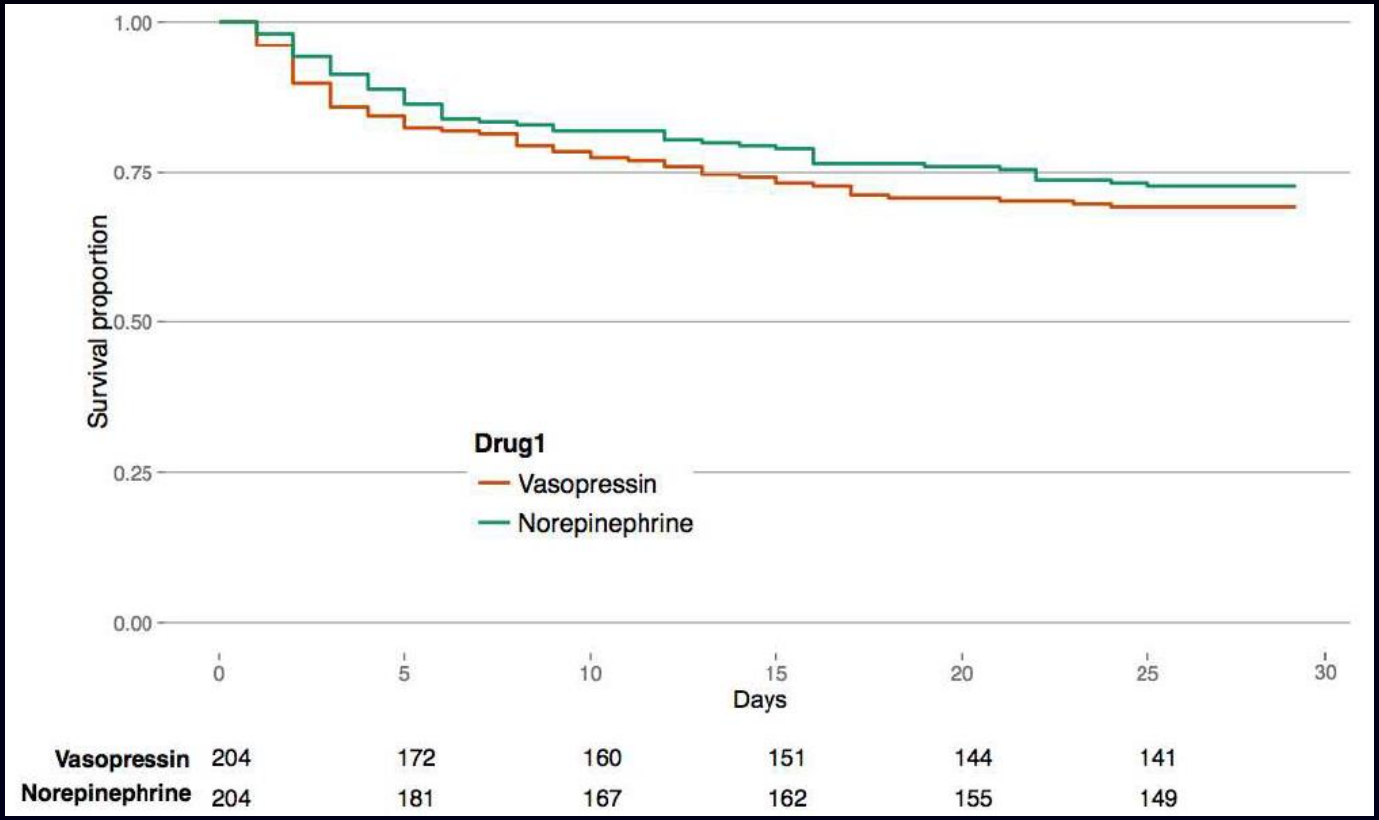
Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock

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

Terlipressin

Half-Life 6h

Bolus 0.5 – 1 mg /8-6h

O’Brien A Singer M Lancet 2002
Lange M et al ICM 2009

Infusion 20 – 160 µg/h

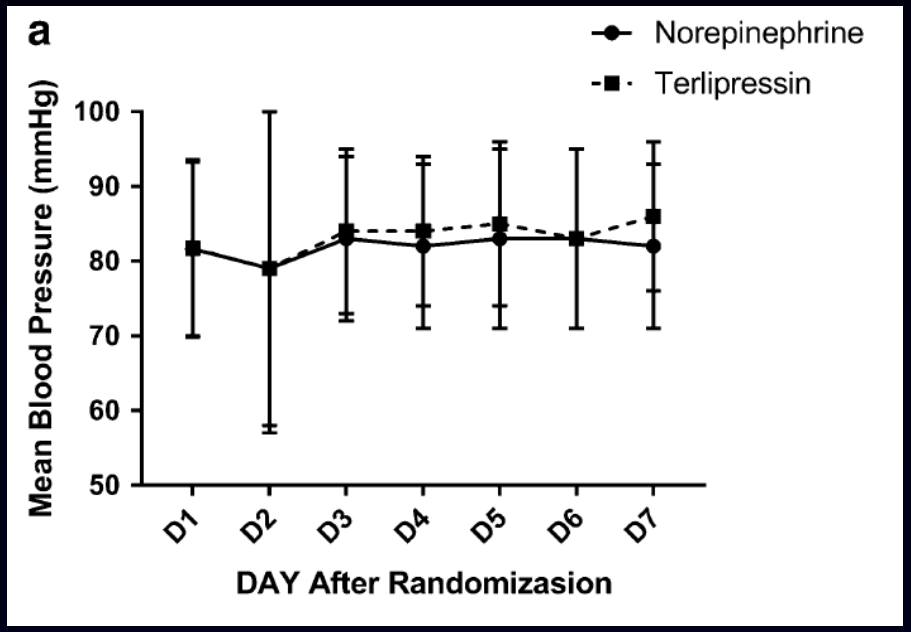
Morelli A Crit Care 2009
Liu Z et al ICM 2018

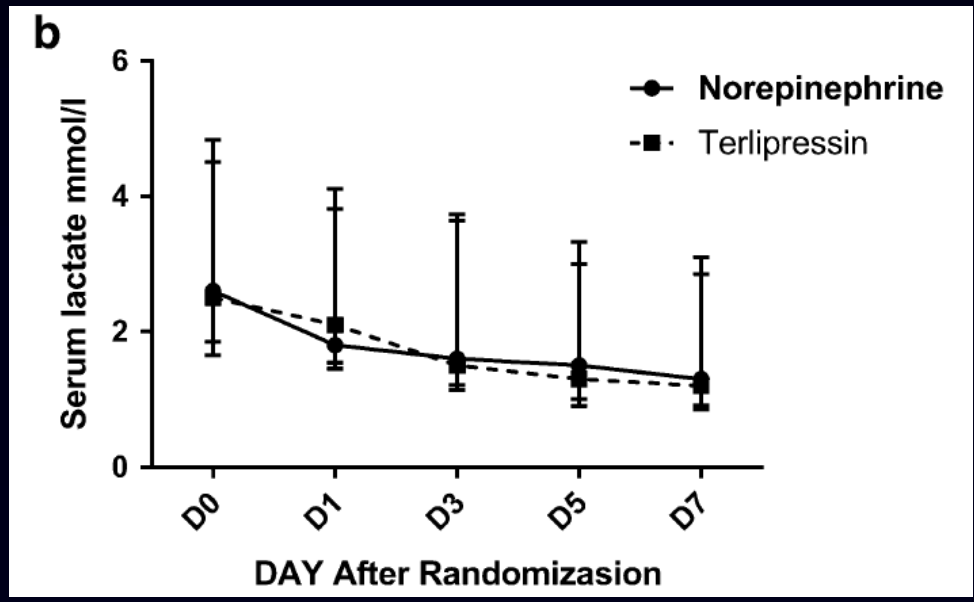
ORIGINAL

Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

Zi-Meng Liu[1], Juan Chen[1], Qiuye Kou[2], Qinhan Lin[3], Xiaobo Huang[4], Zhanhong Tang[5], Yan Kang[6], Ke Li[7], Lixin Zhou[8], Qing Song[9], Tongwen Sun[10], Ling Zhao[11], Xue Wang[12], Xiandi He[13], Chunting Wang[14], Benquan Wu[15], Jiandong Lin[16], Shiying Yuan[17], Qin Gu[18], Kejian Qian[19], Xianqing Shi[20], Yongwen Feng[21], Aihua Lin[22], Xiaoshun He[1], Study Group of investigators and Xiang-Dong Guan[1*]

Liu Z et al
ICM 2018





N=617

ORIGINAL

Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

Zi-Meng Liu[1], Juan Chen[1], Qiuye Kou[2], Qinhan Lin[3], Xiaobo Huang[4], Zhanhong Tang[5], Yan Kang[6], Ke Li[7], Lixin Zhou[8], Qing Song[9], Tongwen Sun[10], Ling Zhao[11], Xue Wang[12], Xiandi He[13], Chunting Wang[14], Benquan Wu[15], Jiandong Lin[16], Shiying Yuan[17], Qin Gu[18], Kejian Qian[19], Xianqing Shi[20], Yongwen Feng[21], Aihua Lin[22], Xiaoshun He[1], Study Group of investigators and Xiang-Dong Guan[1*]

Liu Z et al
ICM 2018

Variable	Norepinephrine group ($N=266$)	Terlipressin group ($N=260$)	p
28-day mortality *N* (%)	101/266 (38%)	104/260 (40%)	0.633
Days alive and free of vasopressor	14.66 ± 11.13	15.50 ± 11.14	0.424
Change of SOFA score from D0 to D7[a]	−6 (−10 to 5)[b]	−7 (−11 to 3)[b]	0.123

Variable *N* (%)	Norepinephrine group ($n=266$)	Terlipressin group ($n=260$)	p
Acute myocardial infarction or ischaemia	4 (1.39%)	2 (0.68%)	0.45
Life-threatening arrhythmia	6 (2.08%)	7 (2.38%)	1.00
Acute mesenteric ischaemia	1 (0.35%)	3 (1.02%)	0.62
Hyponatraemia	18 (6.25%)	25 (8.5%)	0.56
Digital ischaemia	1 (0.35%)	33 (12.6%)	< 0.0001
Diarrhoea	1 (0.35%)	8 (2.72%)	0.037
Overall	31 (11.65%)	78 (30%)	< 0.01

N=617

A role for angiotensin II in septic shock ?

Administration of AGII decreases the need for norepinephrine

Chawla L et al
Crit Care 2014

20 pts distributive shock

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

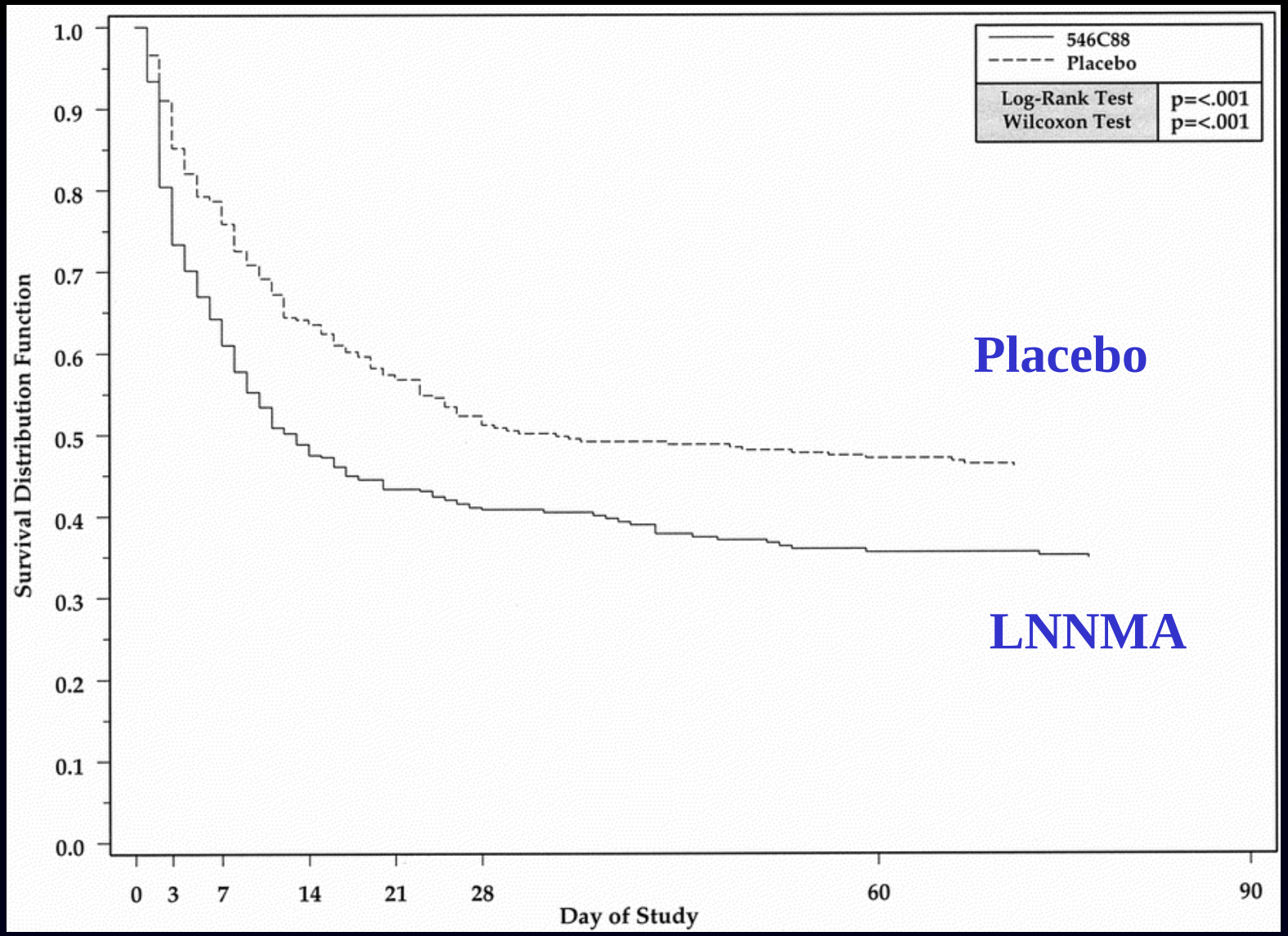
The primary end point was the response with respect to mean arterial pressure at hour 3, with response defined as a mean arterial pressure of 75 mm Hg or higher or an increase in mean arterial pressure from baseline of at least 10 mm Hg, without an increase in the dose of background vasopressors. The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

Nitric oxide inhibition ?

LNNMA IN PATIENTS WITH SEPTIC SHOCK

Lopez et al
CCM 32:21;2004

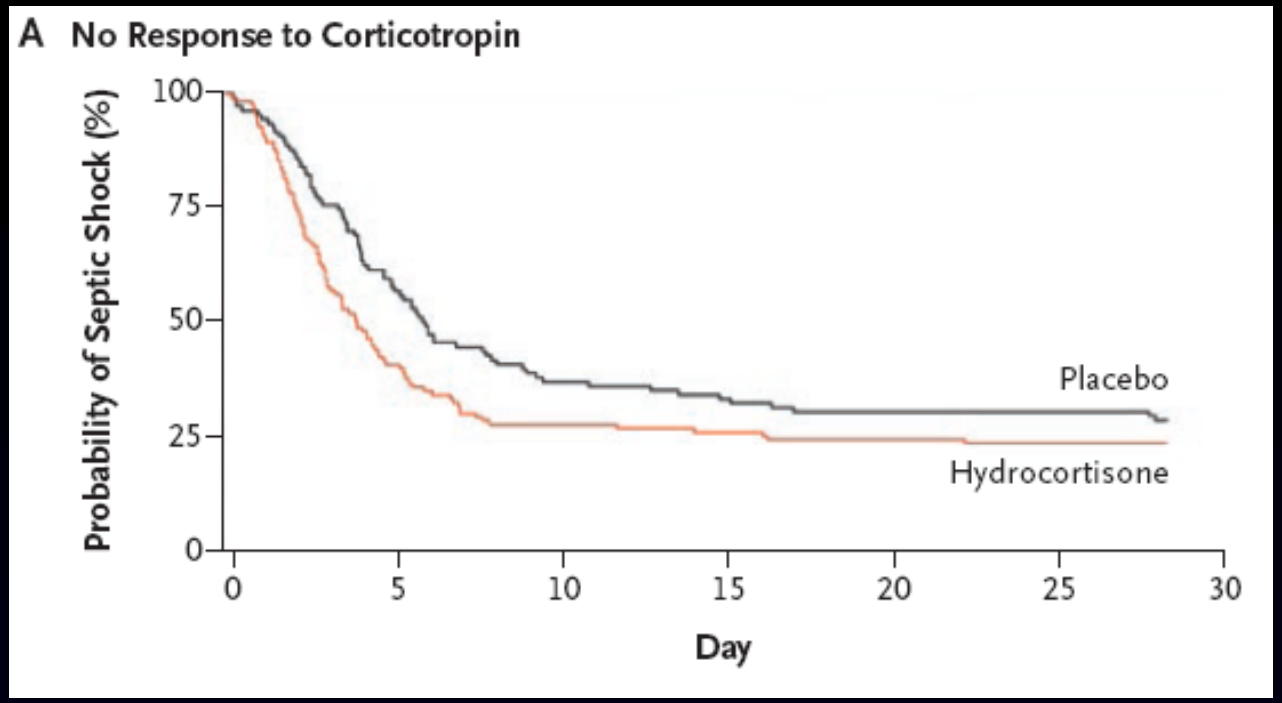


DDB USI

VASOPRESSOR SUPPORT IN SHOCK

- Norepinephrine as the 1st choice agent
- Vasopressin as an alternative.
- Angiotensin appears to be promising in septic shock but more data are needed.
- If one drug seems of limited efficacy, add a second agent of another class rather than another agent of same class.

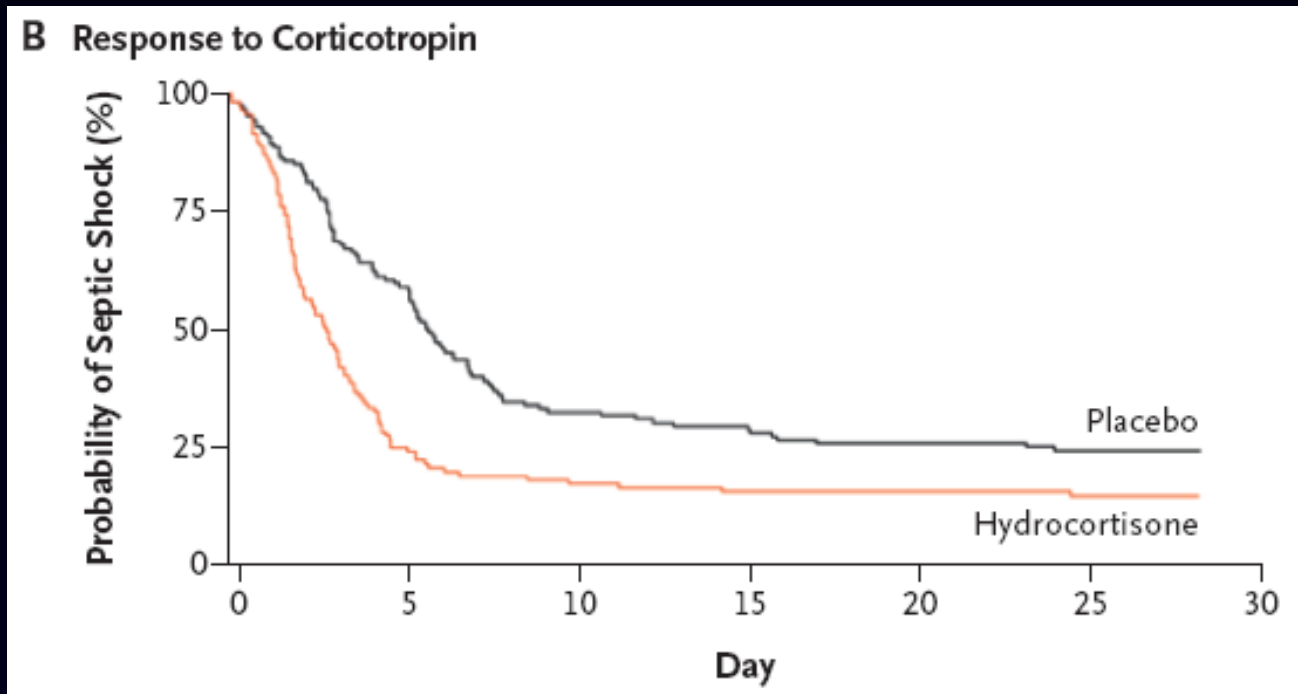
And steroids….



Sprung et al
NEJM 358:111;2008

CORTICUS

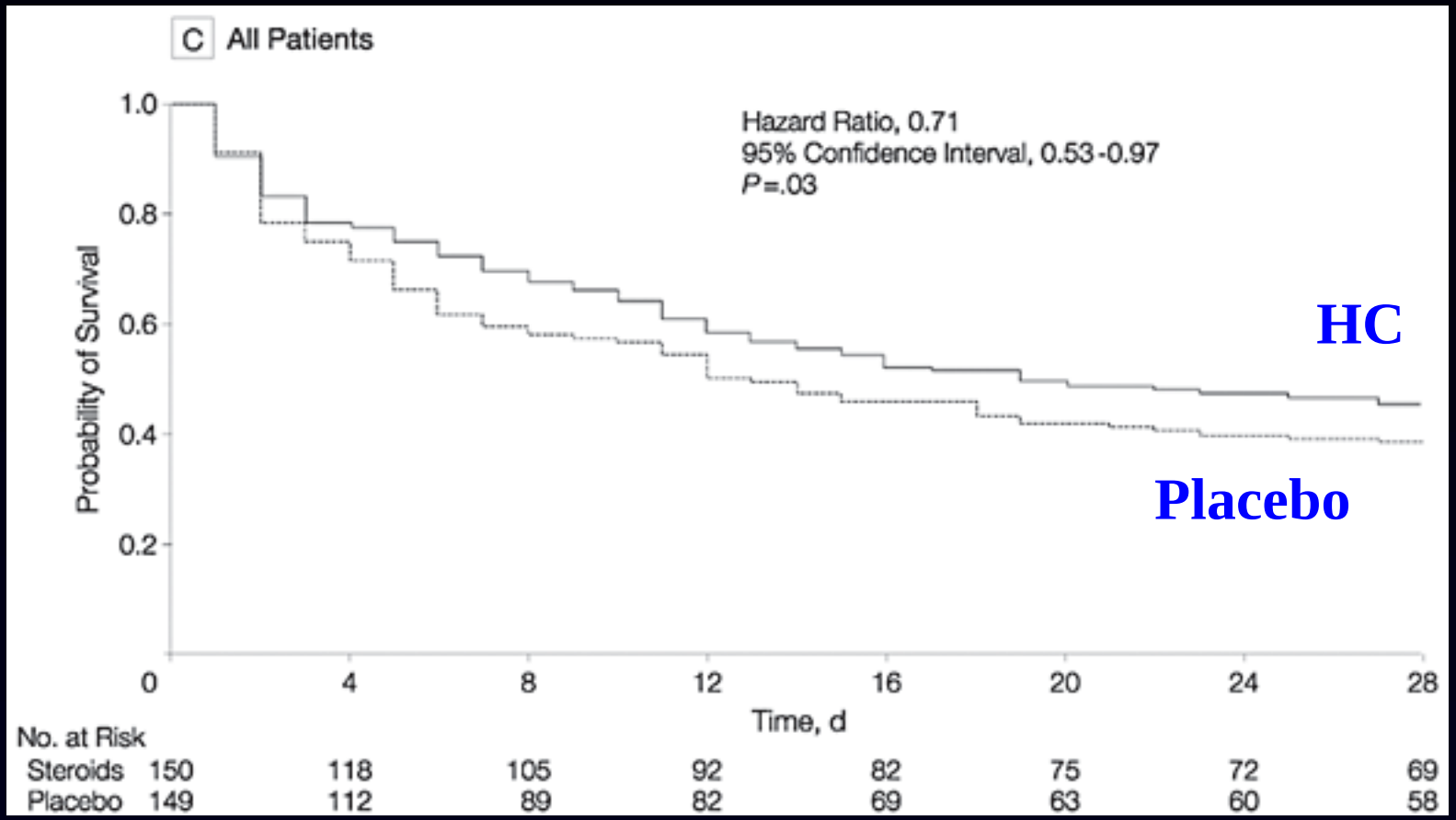
Shock reversal



500 pts septic shock

EFFECT ON OUTCOME

Annane et al
JAMA 288:862; 2001

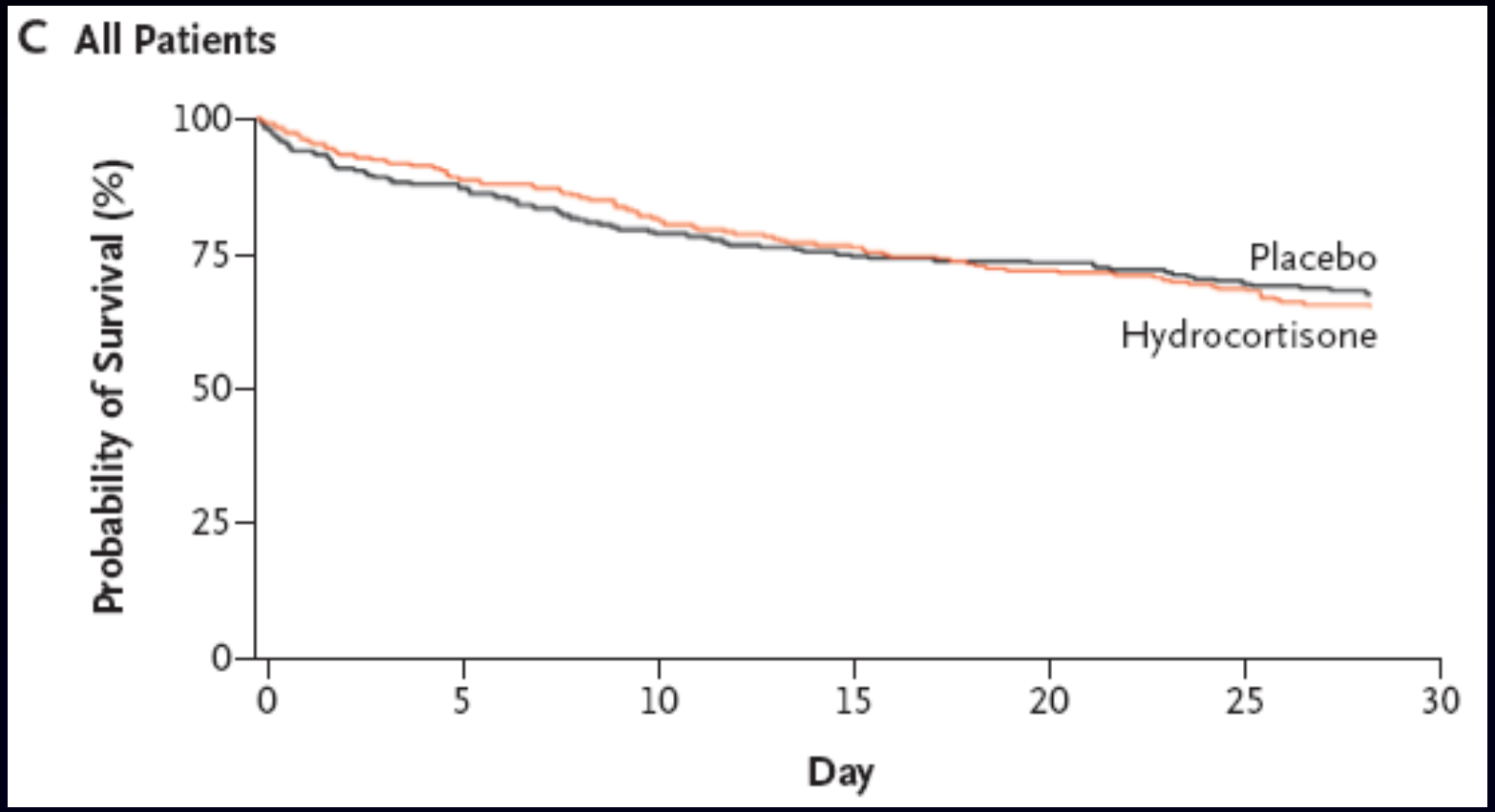


300 Patients in septic shock

CORTICUS

Sprung et al
NEJM 358:111;2008

Outcome

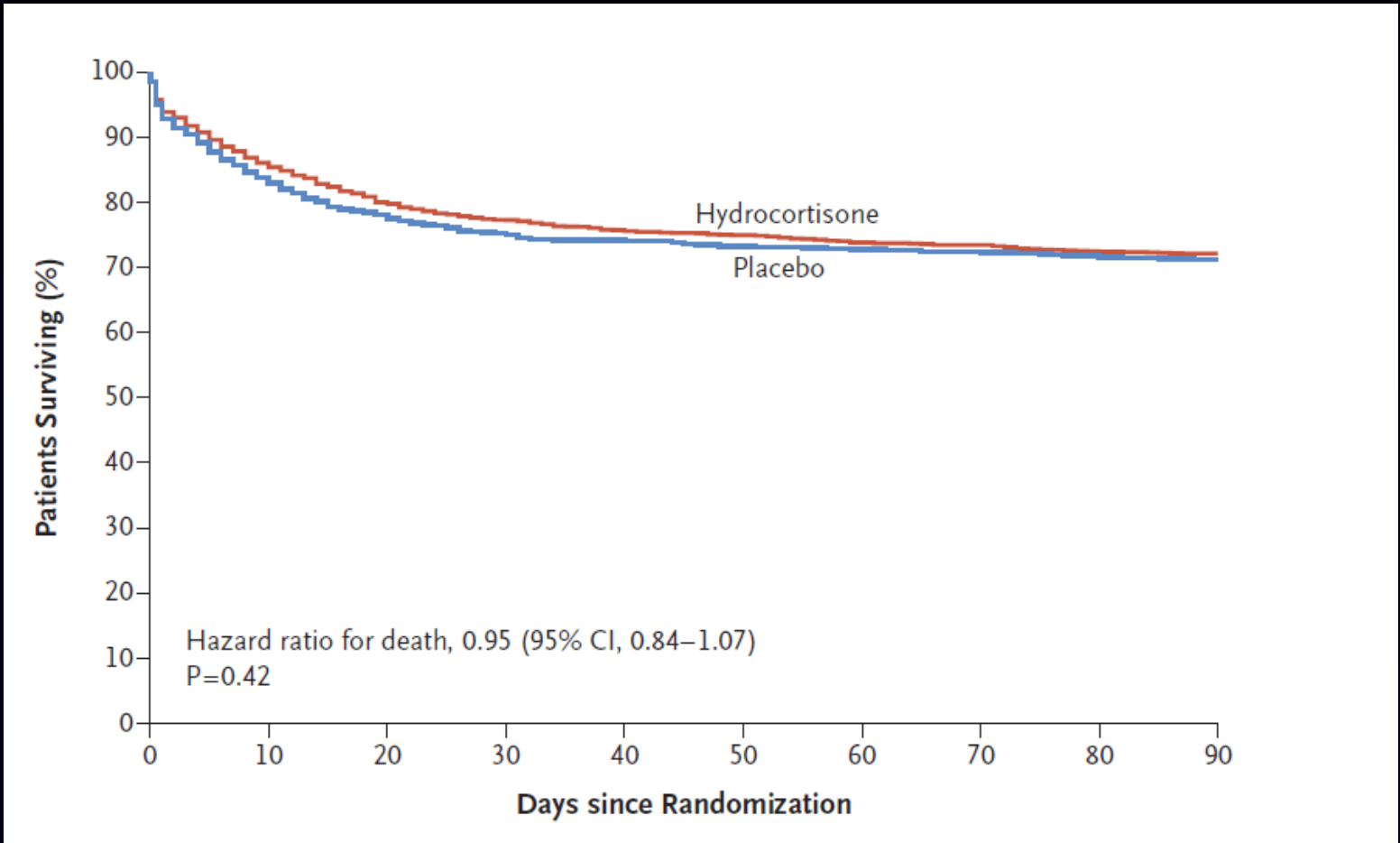


500 pts septic shock

Outcome

ADRENAL

Venkatesh et al
NEJM 378:798;2018

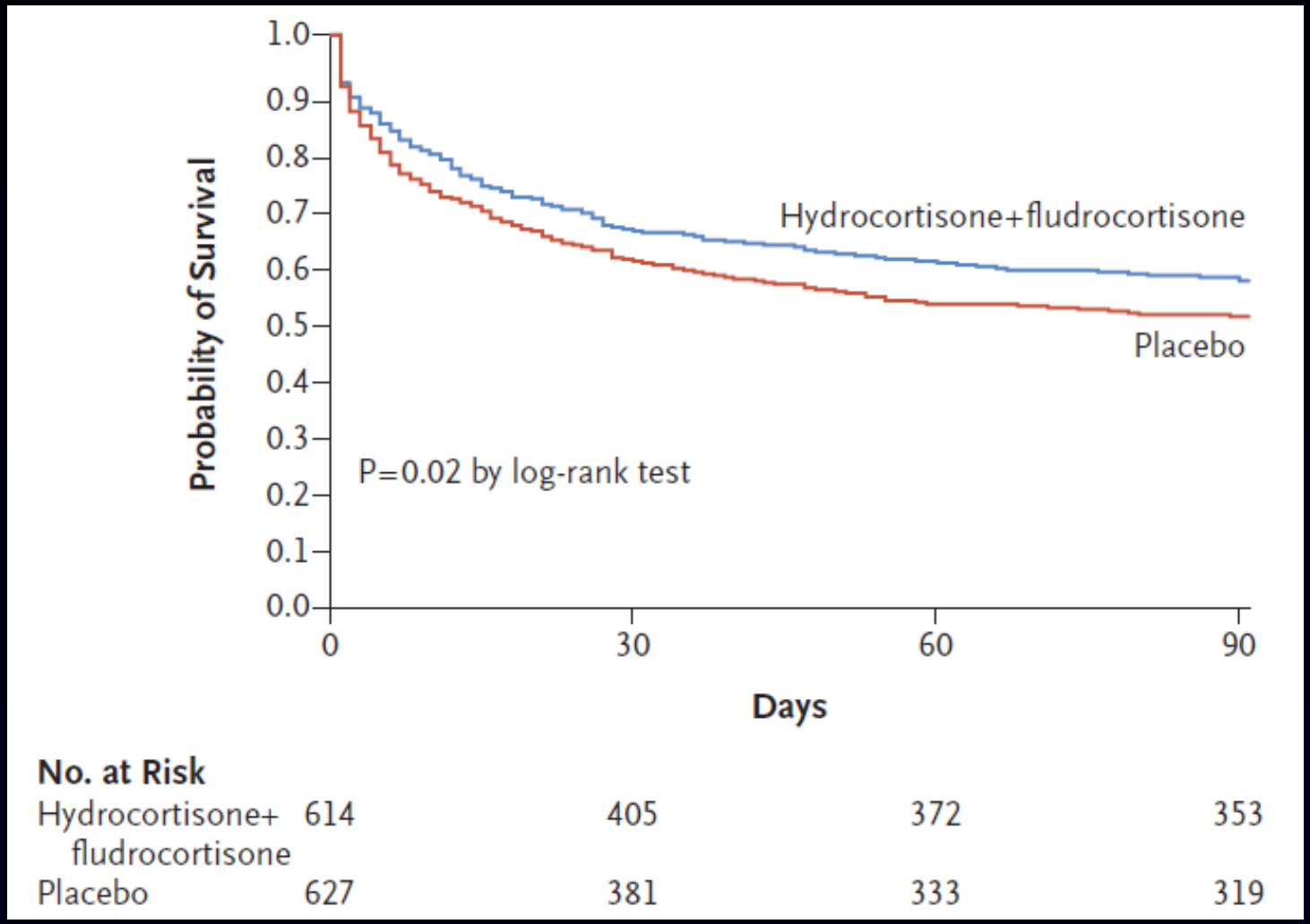


3800 pts septic shock

Outcome

APPROCCHSS

Annane et al
NEJM 378:809;2018



1241 pts septic shock

Norepi (epi) dose at randomization

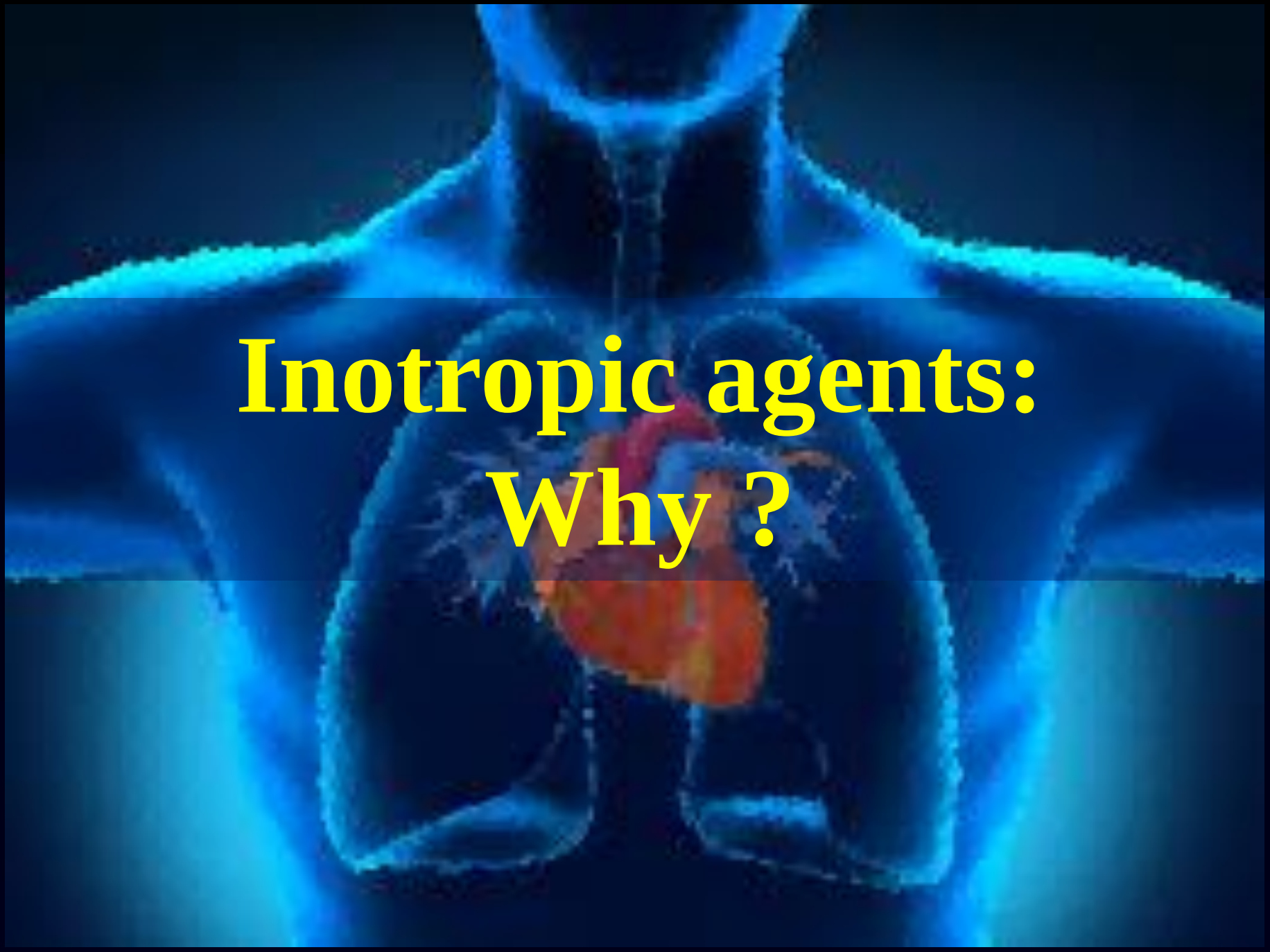
Annane JAMA 2002: **1.1 (0.9) mcg/kg.min**

APPROACHS 2018: **1.2 mcg/kg.min**

CORTICUS 2008: **~0.5 mcg/kg.min**

VANISH 2016: **0.16 [0.10-0.31] mcg/kg.min**

ADRENAL 2018: **50% <0.2 mcg/kg.min**

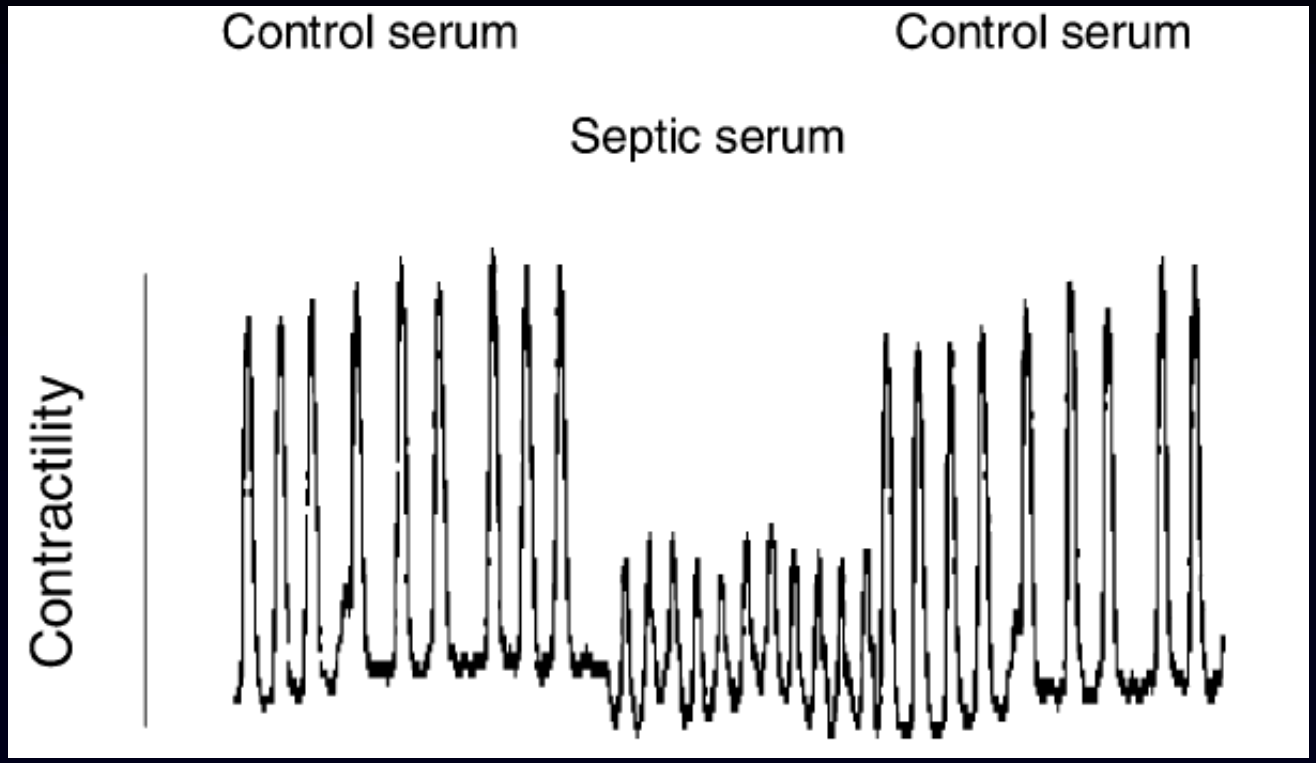


Inotropic agents: Why ?

Myocardial depression in patients with septic shock

Reversible alteration in contractility

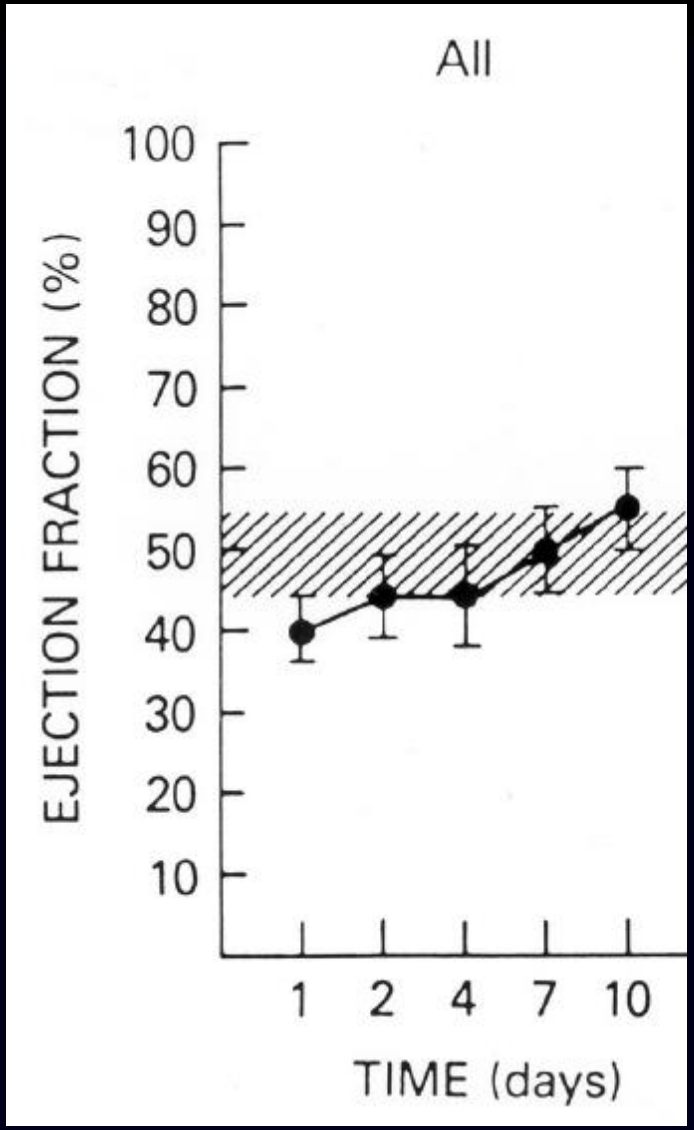
Parillo J et al
JCI 76:1539;1985



In vitro myocardial muscle

Reversible myocardial depression in patients with septic shock

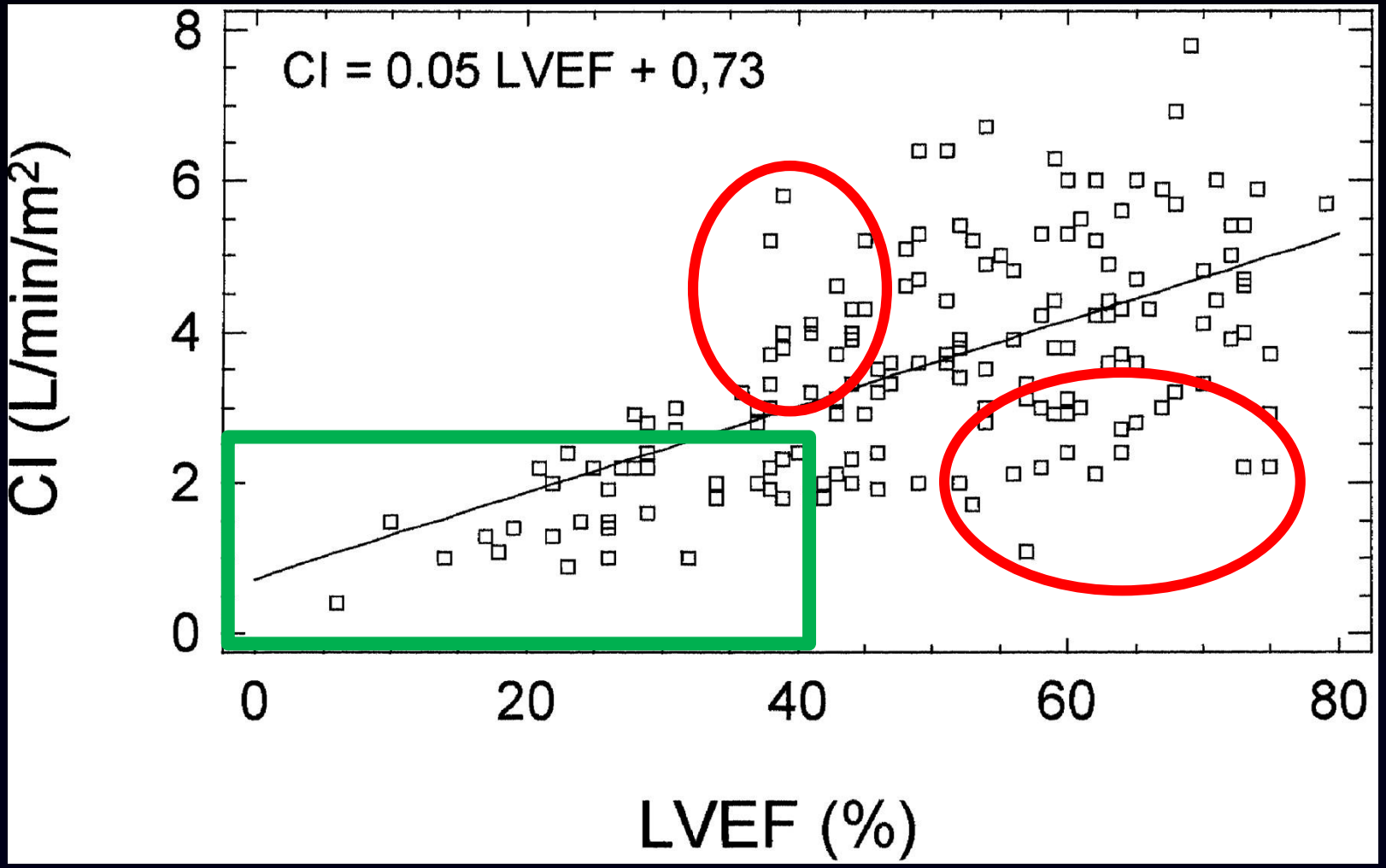
Parker et al. Ann Intern Med 1984: 100; 483-490



DDB USI

Echographic evaluation of LVEF in patients with septic shock

Vieillard-Baron et al
AJRCCM 168:1270;2003

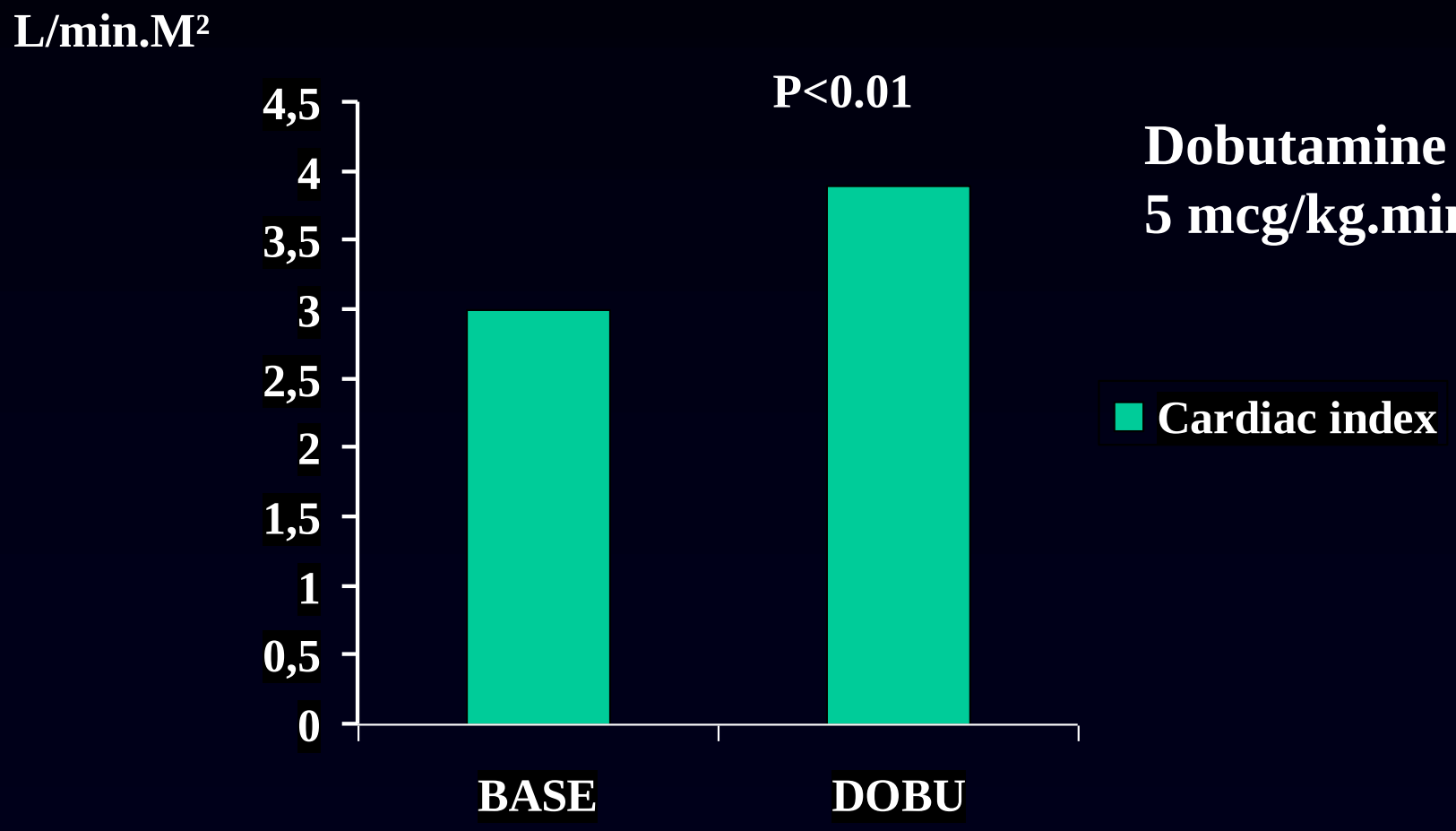


=> Inotropic agents should not be used to correct a low EF

Inotropic agents: Which?

EFFECT OF DOBUTAMINE

Vincent et al
CCM 18:689;1990



DDB USI

An increase in cardiac output is not always achieved by an increased contractility

Jellena et al
CCM 34:2392;2006

	ΔSVI > 10% (n = 5)			ΔSVI ≤ 10% (n = 14)		
	Baseline	Dobu Max	End	Baseline	Dobu Max	End
HR, beats/min	105 (77–114)	103 (83–132)	94 (87–119)	97 (67–123)	116 (76–135)[a]	105 (69–125)
MPAP, mm Hg	30 (27–40)	35 (23–36)	30 (28–40)	27 (16–41)	24 (18–39)	26 (18–44)
PAOP, mm Hg	18 (15–22)	15 (11–23)	18 (15–24)	15 (10–19)	15 (12–19)	14 (10–20)
RAP, mm Hg	12 (8–24)	10 (6–21)	10 (7–20)	12 (7–21)	13 (8–21)	13 (6–18)
SVI, $mL \cdot m^{-2}$	49 (25–55)	56 (31–66)[a]	46 (27–55)	52 (31–80)	44 (26–76)[a]	50 (26–78)
CI, $L \cdot min^{-1} \cdot m^{-2}$	4.3 (2.9–5.6)	5.4 (3.3–7.5)[a]	4.8 (2.5–5.2)	4.4 (2.8–7.7)	4.9 (2.8–6.9)	4.6 (2.8–7.7)
LVSWI, $g \cdot m \cdot m^{-2}$	41 (25–56)	65 (25–75)	46 (26–55)	41 (25–55)	31 (17–57)[a]	36 (17–49)
Sao_2, %	98 (97–99)	97 (96–97)	97 (95–98)	97 (95–99)	96 (93–98)	97 (93–98)
Pvo_2, mm Hg	44 (36–45)	44 (40–48)	42 (36–44)	44 (36–48)	46 (34–57)	46 (32–54)
Svo_2, %	72 (69–77)	79 (74–81)	71 (68–74)	77 (58–83)	76 (60–85)	79 (60–87)
Do_2I, $mL \cdot min^{-1} \cdot m^{-2}$	601 (398–744)	622 (466–979)	571 (430–676)	560 (423–855)	628 (394–977)[a]	630 (485–967)
Vo_2I, $mL \cdot min^{-1} \cdot m^{-2}$	159 (125–179)	143 (125–179)	155 (123–175)	127 (86–263)	141 (100–198)	130 (85–226)
O_2ER, %	27 (21–31)	22 (21–31)	27 (24–32)	22 (16–38)	20 (17–36)	19 (17–36)
DPTI/SPTI	1.02 (0.77–1.2)	0.97 (0.7–1.1)	0.97 (0.63–1.14)	0.96 (0.59–1.46)	0.81 (0.5–1.41)[a]	0.85 (0.59–1.45)
PWI, mL $O_2 \cdot min/100\ g^{-1}$	9.0 (8.0–10.8)	11.9 (8.6–13.3)	9.4 (8.7–10.7)	8.7 (6.1–11.1)	8.5 (6.5–11.8)	8.4 (6.6–11.5)

19 patients with septic shock

EFFECT OF LEVOSIMENDAN

Morelli et al
ICM 31:638;2006

	Levosimendan		Dobutamine	
	Baseline	24 h	Baseline	24 h
EDVI (ml m^{-1})	75.8±23.8	66.2±24.6*,**	84.2±25.1	82.9±26.4
ESVI (ml m^{-1})	46.7±21.9	36.9±19.4*,**	52.4±25.8	50.5±25.3
LVEF (%)	37.1±3.0	45.4±8.4*	37.3±2.6	40.8±11.3

*$p<0.05$ baseline vs. 24 h, **$p<0.05$ levosimendan vs. dobutamine after 24 h

DDB USI

EFFECT OF LEVOSIMENDAN

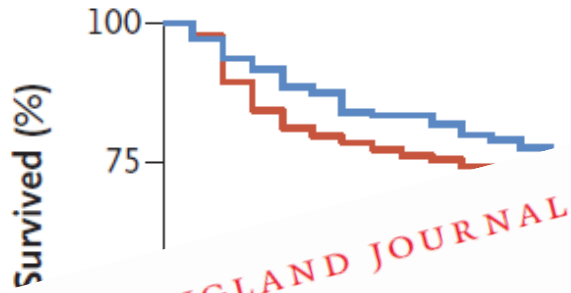
Morelli et al
ICM 31:638;2006

	Levosimendan		Dobutamine	
	Baseline	24 h	Baseline	24 h
HR (bpm)	114±8.3	115±10.5	115±7.3	116±5.8
MAP (mmHg)	76.2±2.8	75.0±3.3	74.7±2.4	73.9±1.7
MPAP (mmHg)	26.2±2.4	23.1±2.4*,***	26.7±1.0	26.6±1.1
RAP (mmHg)	13.5±1.4	12.3±1.5*	12.8±0.7	13.0±0.7
PAOP (mmHg)	16.8±1.2**	12.0±0.6*,***	13.9±0.6	14.4±0.7*
SI (ml m^{-2})	36.6±2.9	39.1±4.1*	37.1±3.7	36.4±2.7
CI (l min^{-1} m^{-2})	4.1±0.2	4.5±0.2*	4.2±0.3	4.2±0.2
SVRI (dyne s^{-1} cm^{-5} m^{-2})	1238±100	1181±114	1160±99	1143±71
PVRI (dyne s^{-1} cm^{-5} m^{-2})	226±56	202±45	233±55	231±47
DO_2I (ml min^{-1} m^{-2})	715±58	746±59*	721±59	718±44
VO_2I (ml min^{-1} m^{-2})	223±36	239±32*	225±23	227±24
LVSWI (g m^{-1} m^{-2})	29.6±2.8	33.9±3.7*,***	28.5±1.4	27.9±1.0
Troponin cTnI (ng/ml)	0.14±0.07	0.13±0.06***	0.14±0.08	0.15±0.06
GMP (%)	–	+55.3±20.1***	–	2.5±4.7
$\Delta P_{g-a}CO_2$ (mmHg)	15.3±1.1**	11.9±1.3*,***	14.2±1.2	14.4±1.2
Arterial lactate (mmol l^{-1})	4.9±1.2	3.7±0.7*,***	5.2±1.1	5.2±1.0
Creatinine clearence (ml min^{-1})	43.9±12.8	72.1±16.2*,***	51.2±17.0	51.3±13.3
Urinary output (ml 24 h^{-1})	–	2028±461***	–	1521±302
Fluid perfused (ml 24 h^{-1})	–	5907±330***	–	4311±136
Norepinephrine rate (µg kg^{-1} min^{-1})	0.22±0.07	0.22±0.06	0.23±0.05	0.23±0.06

*$p<0.05$ baseline vs. 24 h, **$p<0.05$ levosimendan vs. dobutamine at baseline, ***$p<0.05$ levosimendan vs. dobutamine after 24 h

Levosimendan in sepsis

Gordon A et al
NEJM 2016



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levosimendan for the Prevention of Acute Organ ion in Sepsis

A.C. Gordon, G.D. Per
S. Santhakumaran, A.J. Mason, M. Cro
C.L. Nutt, J.J. McNam H. Reschreiter, A. Brec

Adult patients who had septic shock and had received vasopressors for at least 4 hours were eligible for inclusion. Detailed inclusion and ex-

- **No evaluation of cardiac output**
- **No evaluation of contractility**

Select the right hemodynamic tool

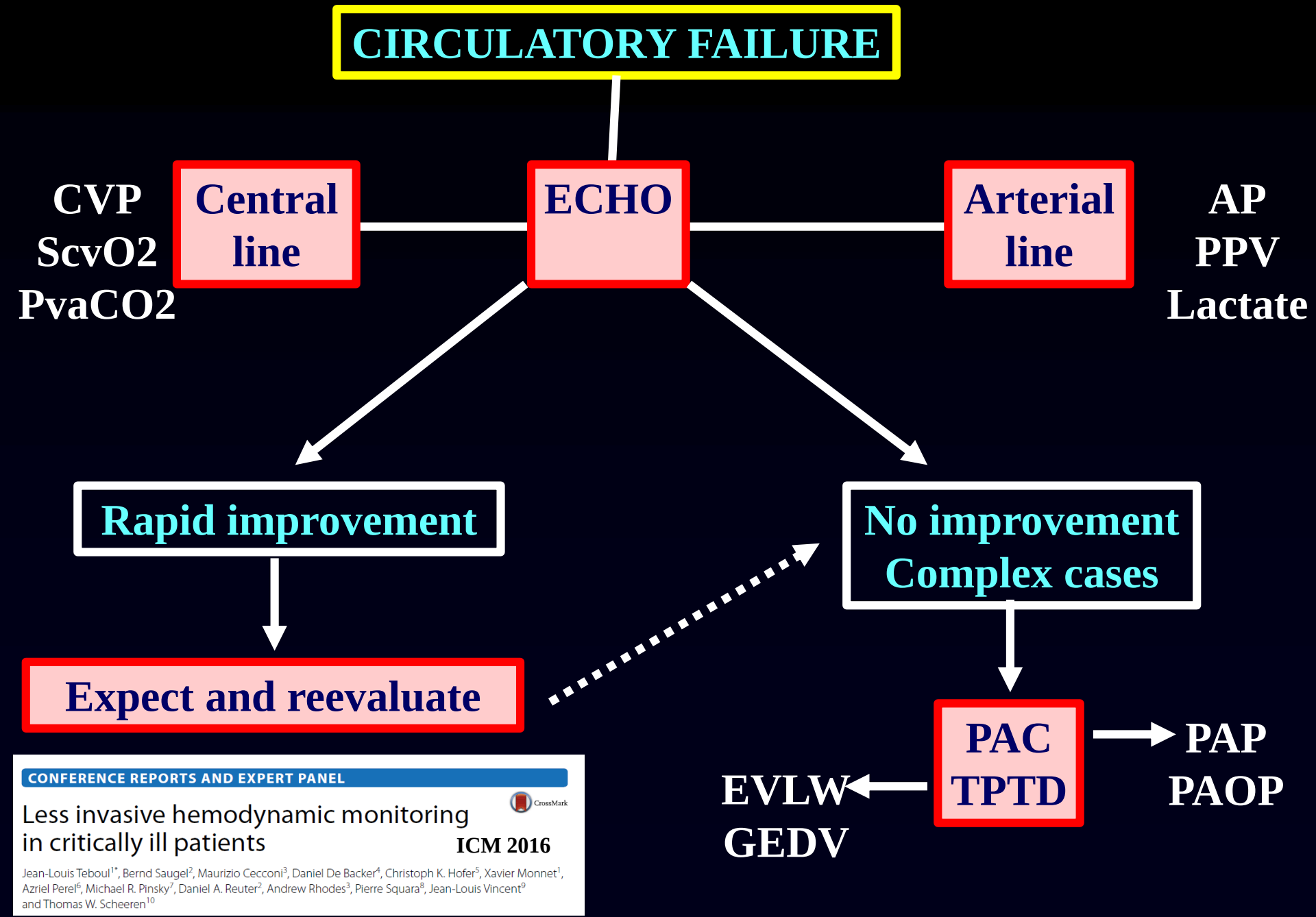
Intensive Care Med (2014) 40:1795–1815
DOI 10.1007/s00134-014-3525-z

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

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

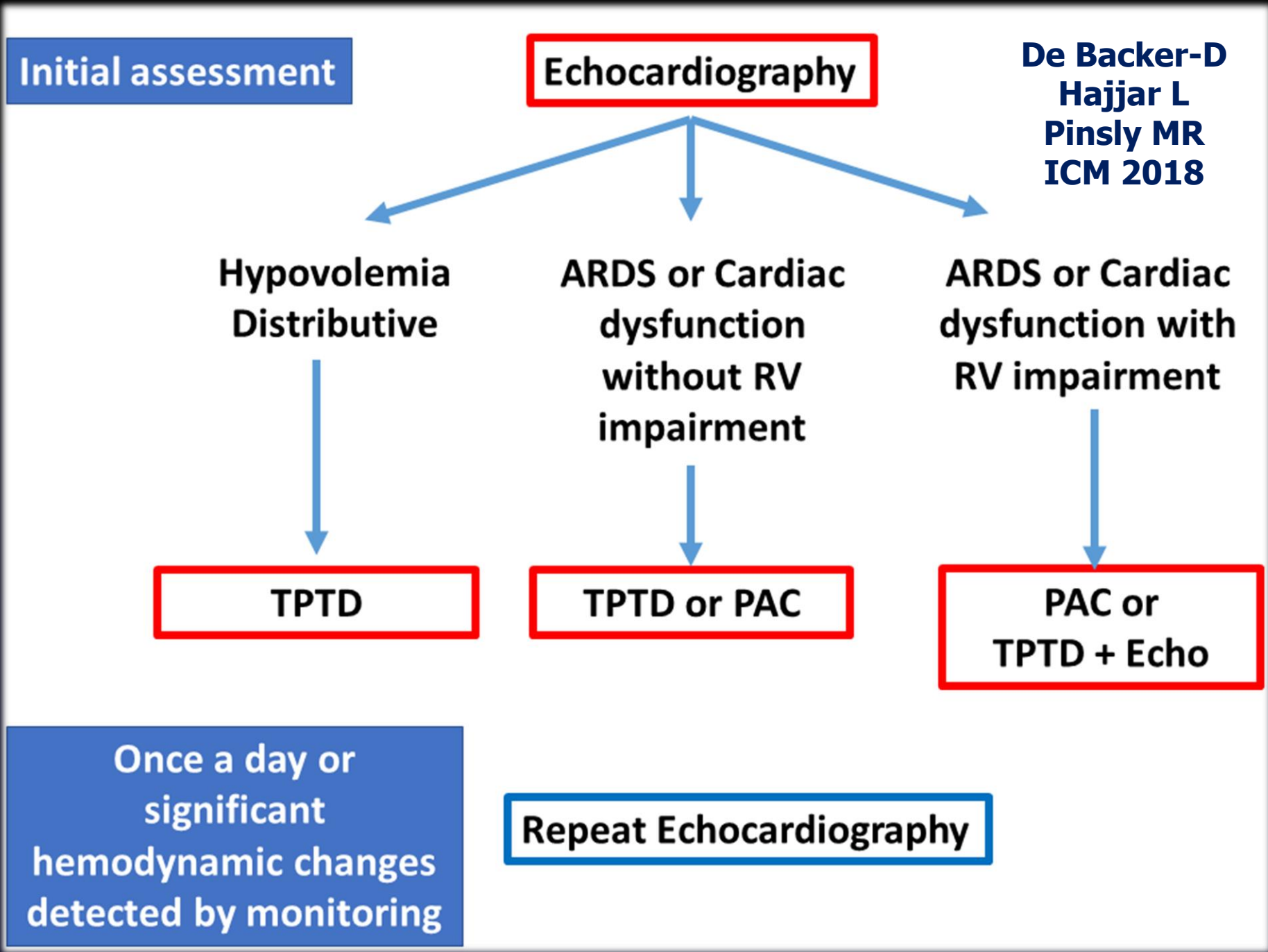


CONFERENCE REPORTS AND EXPERT PANEL

Less invasive hemodynamic monitoring in critically ill patients

ICM 2016

Jean-Louis Teboul[1*], Bernd Saugel[2], Maurizio Cecconi[3], Daniel De Backer[4], Christoph K. Hofer[5], Xavier Monnet[1], Azriel Perel[6], Michael R. Pinsky[7], Daniel A. Reuter[2], Andrew Rhodes[3], Pierre Squara[8], Jean-Louis Vincent[9] and Thomas W. Scheeren[10]


Initial assessment
Echocardiography
De Backer-D
Hajjar L
Pinsly MR
ICM 2018
Hypovolemia
Distributive
ARDS or Cardiac dysfunction without RV impairment
ARDS or Cardiac dysfunction with RV impairment
TPTD
TPTD or PAC
PAC or
TPTD + Echo
Once a day or significant hemodynamic changes detected by monitoring
Repeat Echocardiography

What is the resuscitation goal ?

Early phase

Vincent JL and De Backer D
NEJM 369:1726; 2013

Phase Focus	Salvage	Optimization	Stabilization	De-escalation
	Obtain a minimal acceptable blood pressure	Provide adequate oxygen availability	Provide organ support	Wean from vasoactive agents
	Perform lifesaving measures	Optimize cardiac output, Svo_2, lactate	Minimize complications	Achieve a negative fluid balance

Later stages

Thank you