Catecholamines in septic shock

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Norepinephrine Dobutamine

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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],

Intensive Care Med (2017) 43:304–377

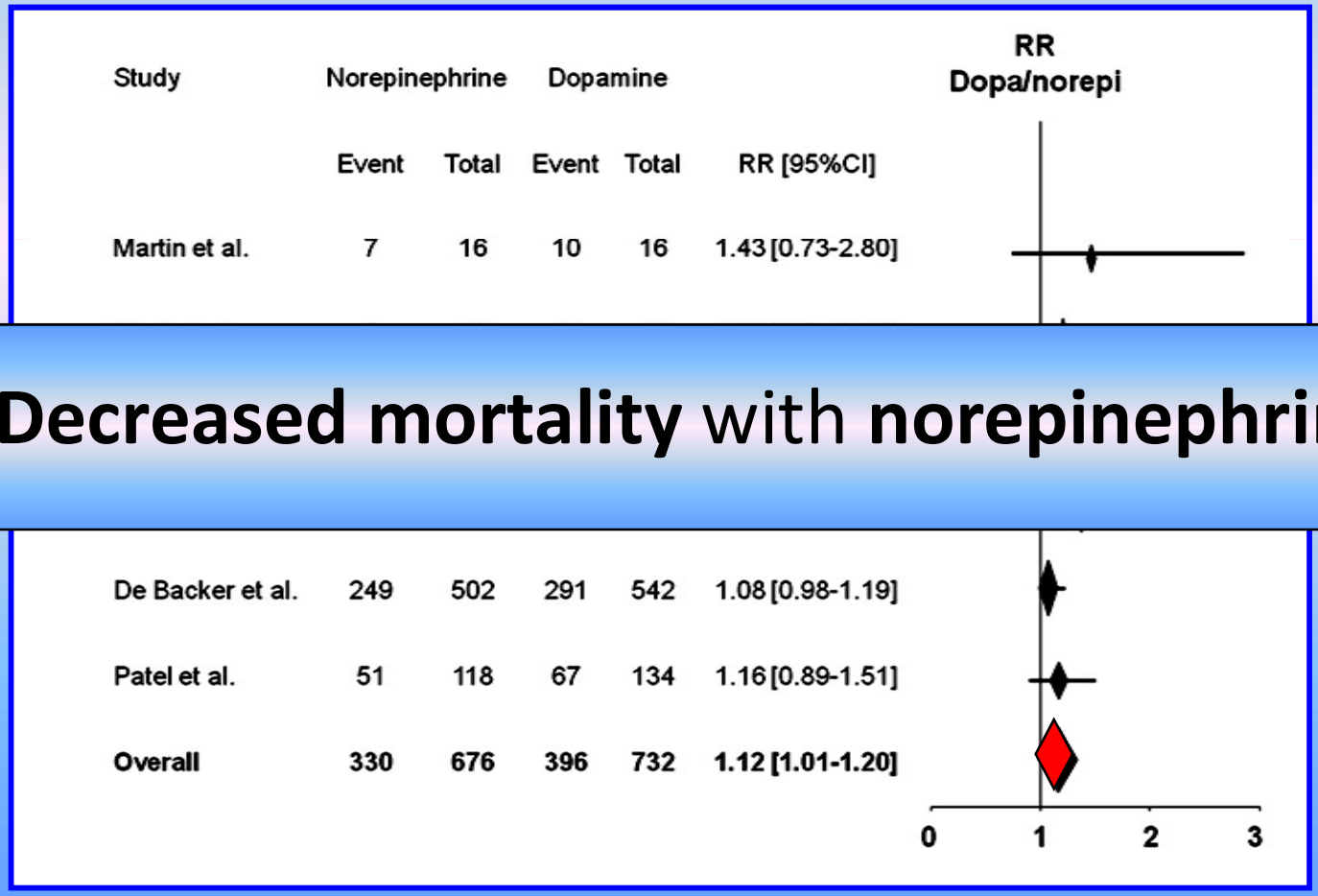
We **recommend** **norepinephrine** as the first-choice vasopressor

(strong recommendation, moderate quality of evidence)

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

Crit Care Med 2012; 40:725–730



Decreased mortality with **norepinephrine**

Norepinephrine in septic shock

1- Why?

2- When to start?

3- Which target?

4- What to do in cases of refractory hypotension?

Why do we **use** vasopressors in septic shock?

1- Septic shock is characterized by a **decreased vascular tone**

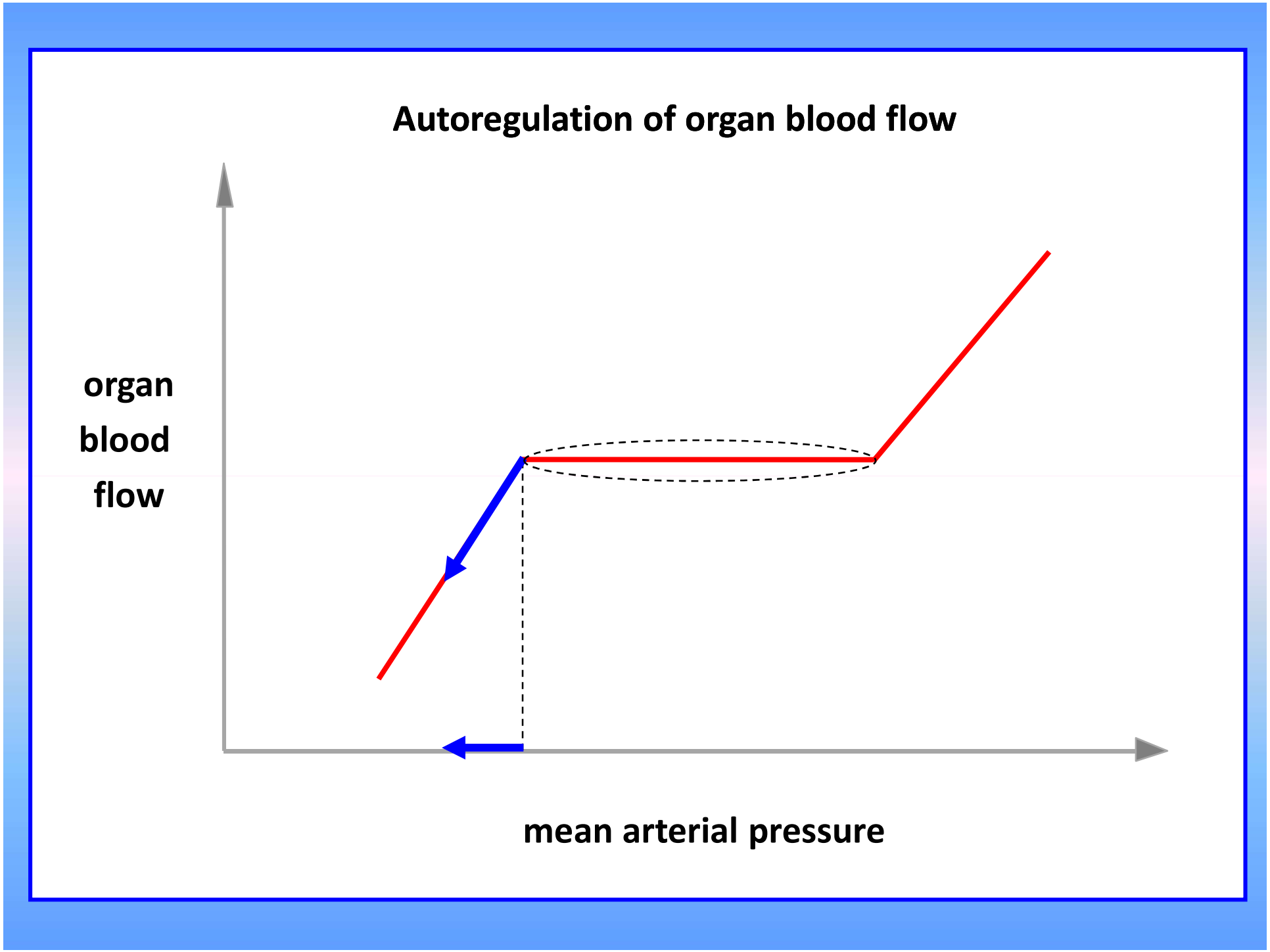
(inducible NO synthase activation, etc)

⬇

Hypotension

⬇

Worsening of hypoperfusion


Autoregulation of organ blood flow
organ
blood
flow
mean arterial pressure

Why do we **use** vasopressors in septic shock?

1- Septic shock is characterized by a decreased vascular tone

(inducible NO synthase activation, etc)

2- Profound **hypotension** worsens **organ hypoperfusion**

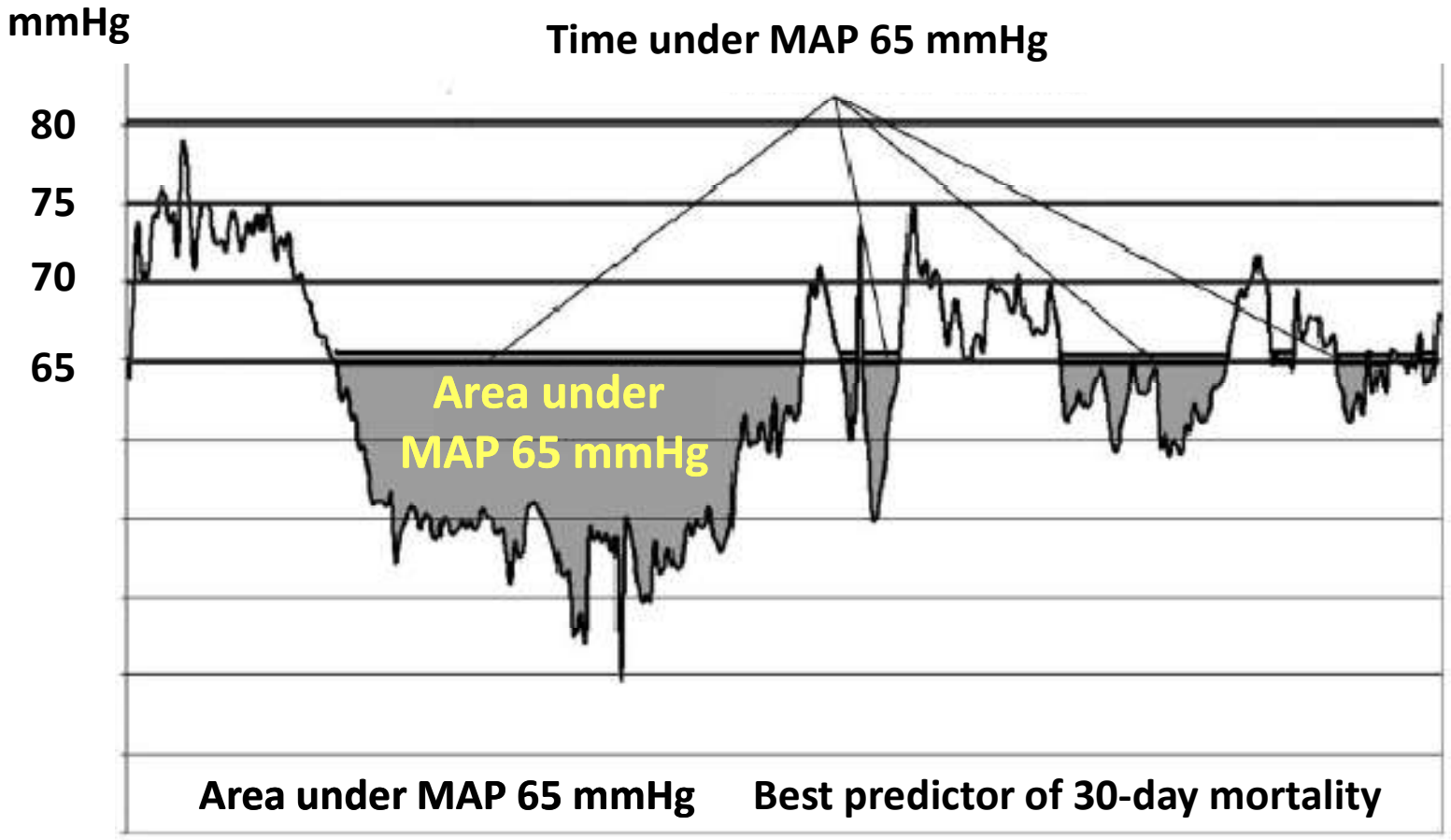
…… and represents an **independent risk of death**

Intensive Care Med (2005) 31:1066–1071

ORIGINAL

Marjut Varpula
Minna Tallgren
Katri Saukkonen
Liisa-Maria Voipio-Pulkki
Ville Pettilä

Hemodynamic variables related to outcome in septic shock



Why do we **use** vasopressors in septic shock?

1- Septic shock is characterized by a decreased vascular tone

(inducible NO synthase activation, etc)

2- Profound hypotension worsens organ hypoperfusion

…… and represents an independent risk of death

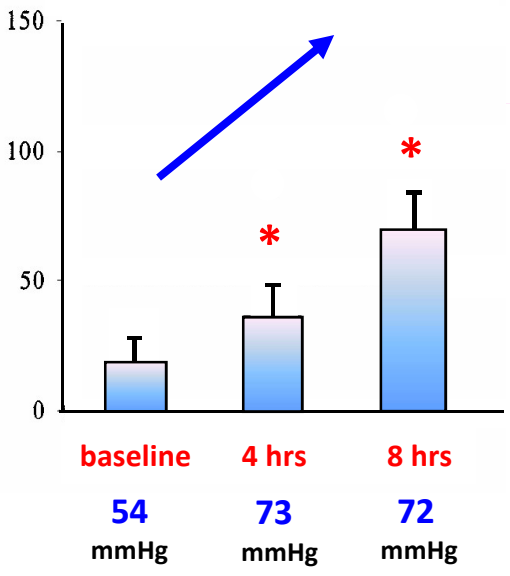
3- **Correction** of **hypotension** with a vasopressor allows **improving organ perfusion**

Terlipressin or norepinephrine in hyperdynamic septic shock: A prospective, randomized study*

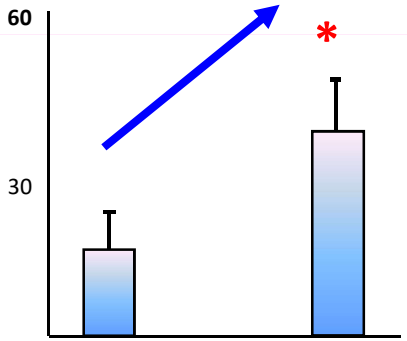
Jacques Albanèse, MD; Marc Leone, MD; Anne Delmas, MD; Claude Martin, MD, FCCM

Probable "**arterial pressure**" effect

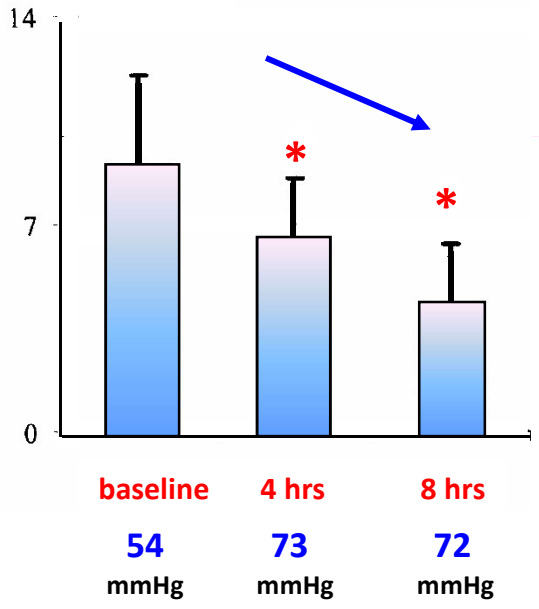
Urine flow (ml/h)



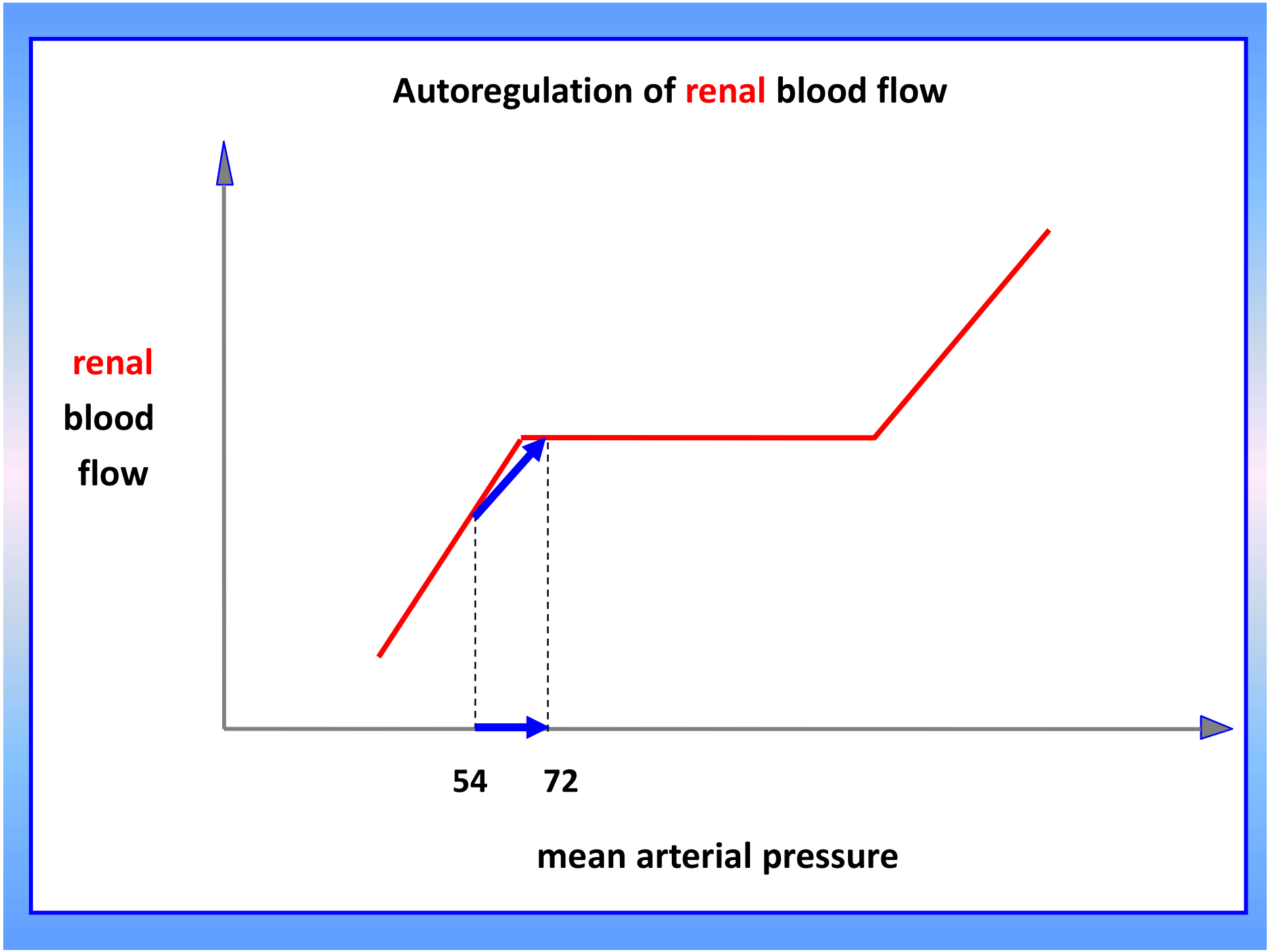
Creatinine clearance



Blood lactate (meq/l)



while cardiac output did not change


Autoregulation of renal blood flow
renal
blood
flow
54
72
mean arterial pressure

Norepinephrine in septic shock

1- Why?

2- When to start?

3- Which target?

4- What to do in cases of refractory hypotension?

Arguments to initiate norepinephrine early

1- Duration and **degree** of hypotension associated with **increased mortality**

Intensive Care Med (2005) 31:1066–1071

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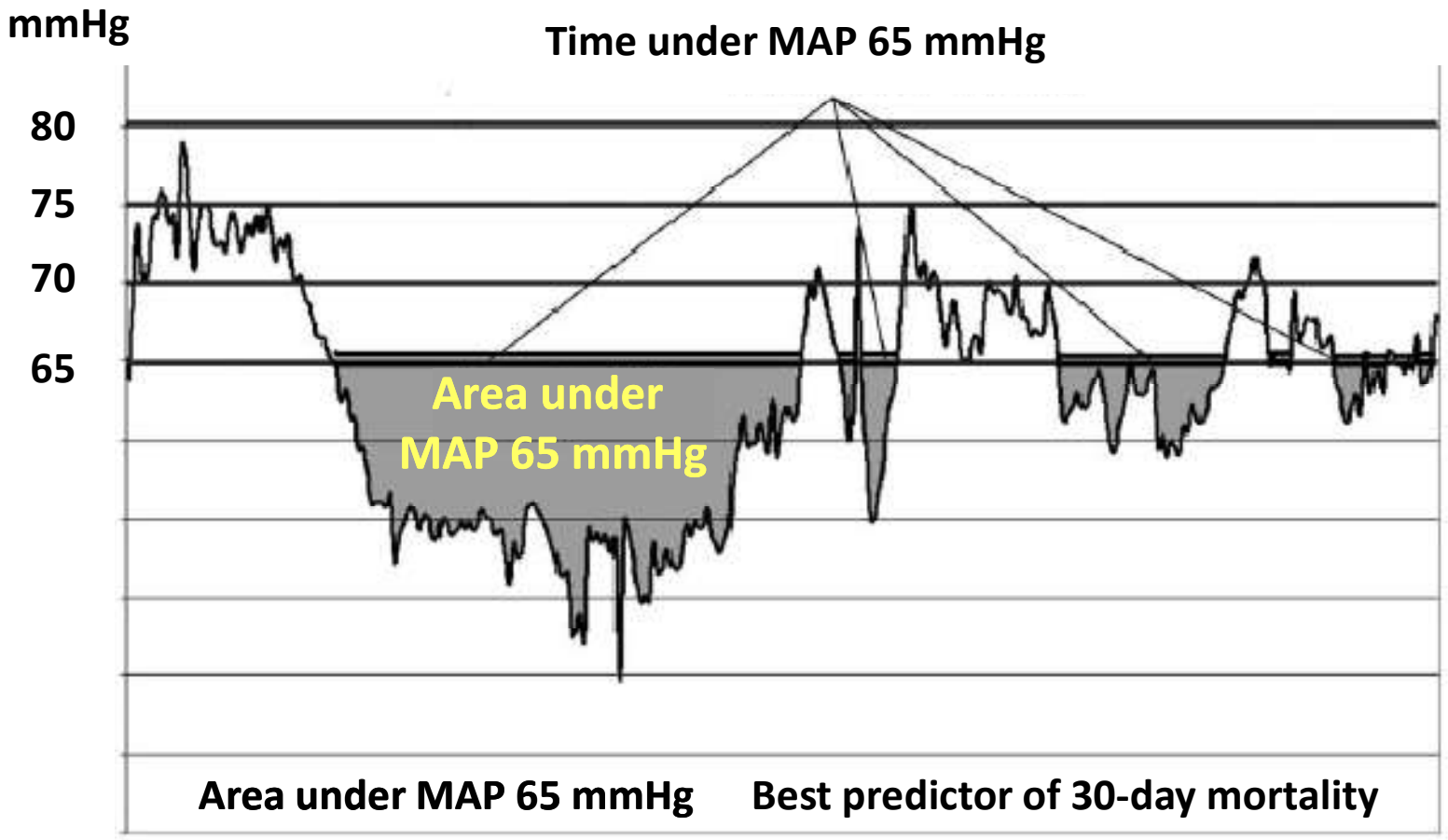


Arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

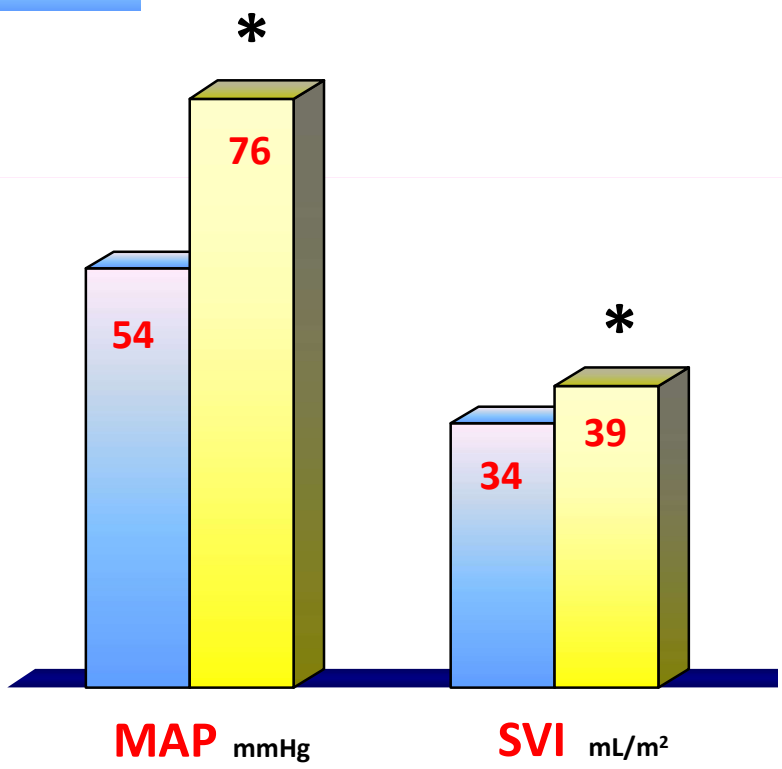
2- NE increases cardiac output, when initiated **early**

Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension

Olfa Hamzaoui, Jean-François Georger, Xavier Monnet, Hatem Ksouri, Julien Maizel, Christian Richard, Jean-Louis Teboul*

Critical Care 2010, **14**:R142

105 pts



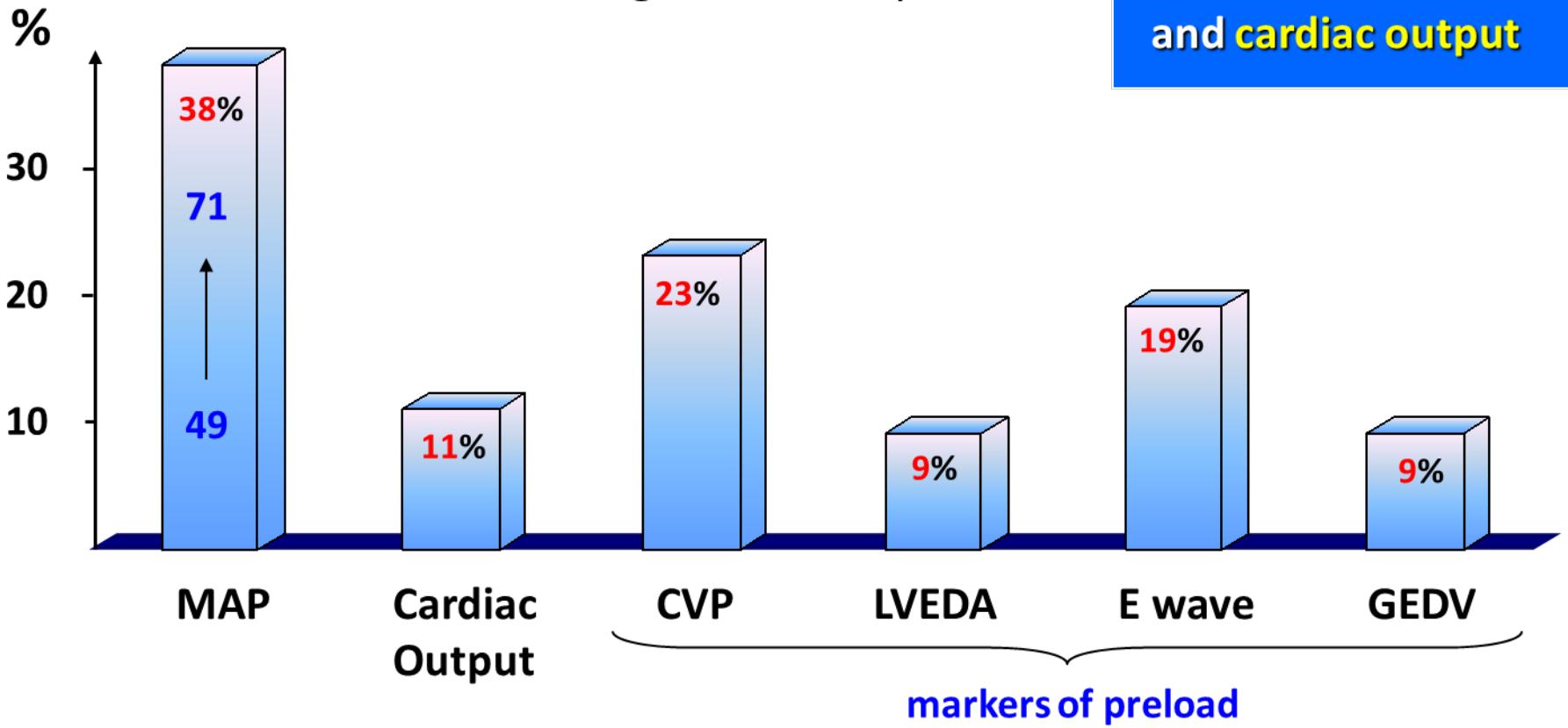
Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients*

Xavier Monnet, MD, PhD; Julien Jabot, MD; Julien Maizel, MD; Christian Richard, MD; Jean-Louis Teboul, MD, PhD

Crit Care Med 2011; 39:689–694

Changes induced by **NE**

NE ↗ cardiac preload and cardiac output



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Messages of these two studies

- NE increases **cardiac preload** … as **fluid** infusion does
- NE **increases CO** in **preload-dependent** patients
- **NE reduces** the degree of **preload-dependency**

How does **NE impact** the **venous circulation**?

by blood **redistribution**
from **unstressed** to **stressed** volume?

Effects of norepinephrine on mean systemic pressure and venous return in human septic shock*

Romain Persichini, MD; Serena Silva, MD; Jean-Louis Teboul, MD, PhD; Mathieu Jozwiak, MD; Denis Chemla, MD, PhD; Christian Richard, MD; Xavier Monnet, MD, PhD

Crit Care Med 2012; 40:3146–3153

In spite of an increase in venous resistance,

venous return increases with **NE**

through an **increase** in **Mean Systemic Pressure**

related to blood **redistribution**

from unstressed to stressed volume

This is **fine**

since **unstressed volume** is **abnormally increased**

during sepsis and further **overfilled** by fluid loading

Arguments to initiate norepinephrine early in septic shock

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- **NE increases cardiac output**, when initiated **early**

3- **Early** initiation of **NE increases cardiac contractility**

CLINICAL INVESTIGATION

Norepinephrine exerts an inotropic effect during the early phase of human septic shock

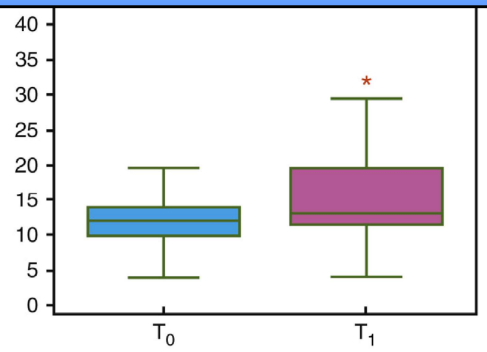
O. Hamzaoui[1,*], M. Jozwiak[2], T. Geffriaud[2], B. Sztrymf[1], D. Prat[1], F. Jacobs[1], X. Monnet[2], P. Trouiller[1], C. Richard[2] and J.L. Teboul[2]

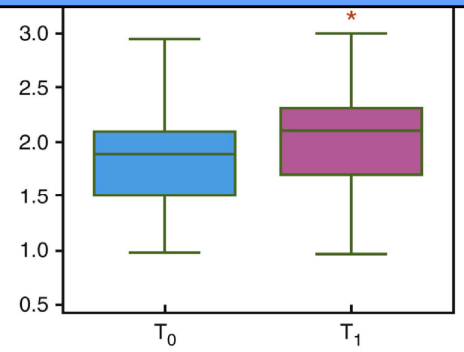
British Journal of Anaesthesia, 120 (3): 517–524 (2018)

In spite of the increase in blood pressure (LV afterload),

all the indices of cardiac systolic function improved with **NE**

suggesting an **improved cardiac contractility**





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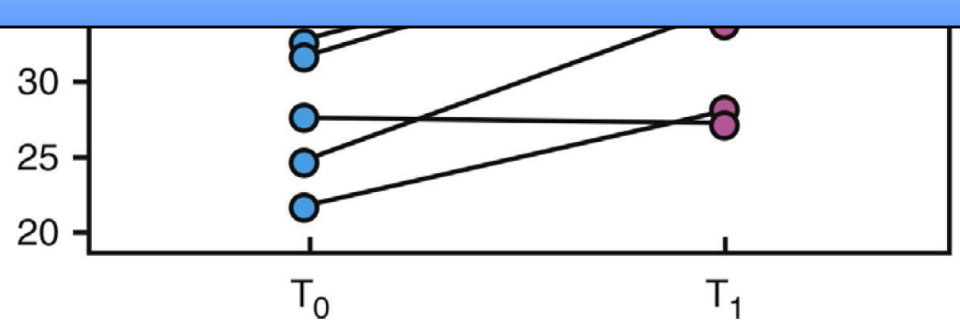
British Journal of Anaesthesia, 120 (3): 517–524 (2018)

Potential **mechanisms**:

- Effect on myocardial **β_1 receptors not** yet **down-regulated** at the **early** phase
- Increase in **coronary perfusion pressure** (through increase in DAP)



Arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- **NE increases cardiac output**, when initiated **early**

3- **Early** initiation of **NE increases cardiac contractility**

4- NE improves microcirculation, when initiated **early**

Intensive Care Med (2010) 36:1882–1889

ORIGINAL

Jean-François Georger
Olfa Hamzaoui
Anis Chaari
Julien Maizel
Christian Richard
Jean-Louis Teboul

Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients

MAP mmHg 54± 8 77± 9

MAP mmHg 54± 8 77± 9

StO_2 %

$p < 0.05$

StO_2 recovery slope (%/s)

90
85
80
75
70
65
60
55

before NE with NE

before NE with NE

Restoration of a "good" MAP with NE

resulted in recruitment

of microvessels and better tissue oxygenation

Arguments to initiate norepinephrine early

1- **Duration** and **degree** of hypotension associated with **increased mortality**

2- **NE increases cardiac output**, when initiated **early**

3- **Early** initiation of **NE increases cardiac contractility**

4- **NE improves microcirculation,** when initiated **early**

5- Early initiation of **NE prevents** harmful fluid **overload**

Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators

Crit Care Med 2006; 34:344–353

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

	OR (95% CI)	*p* Value
SAPS II score[a] (per point increase)	1.0 (1.0–1.1)	<.001
Cumulative fluid balance[b] (per liter increase)	1.1 (1.0–1.1)	.001
Age (per year increase)	1.0 (1.0–1.0)	.001
Initial S		.002
Blood s		.004
Cirrhos		.008
Pseudo		.017
Medical		.049
Female		.044

Positive cumulative **fluid balance**

is an **independent** factor associated with **mortality**

Early versus delayed administration of norepinephrine in patients with septic shock

Xiaowu Bai, Wenkui Yu*, Wu Ji, Zhiliang Lin, Shanjun Tan, Kaipeng Duan, Yi Dong, Lin Xu and Ning Li*

Critical Care 2014, **18**:532

Characteristic	<2 hours (number = 86)	≥2 hours (number = 127)	*P* value
24-hour norepinephrine administration (mg)	29.4 ± 9.7	32.8 ± 10.0	0.013
Time to initial antimicrobial treatment (h)	1.6 ± 1.4	1.7 ± 1.5	0.126
Volume of intravenous fluids within 6 h (L)	3.1 ± 0.9	3.3 ± 0.8	0.092
Volume of intravenous fluids within 24 h (L)	6.2 ± 0.6	6.9 ± 0.7	<0.001

When **NE** is initiated **early:**

- **Less fluids** are infused
- The **total dose** of **NE during** the first 24h is **lower**
- The **duration** of **NE** infusion is **shorter** (2.6 *vs.* 2.9 days)

Arguments to initiate norepinephrine early

1- Duration and **degree** of hypotension associated with **increased mortality**

2- NE increases cardiac output, when initiated **early**

3- Early initiation of **NE increases cardiac contractility**

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5- Early initiation of **NE prevents** harmful fluid **overload**

Does **early** initiation of **NE improve outcome**?

Early versus delayed administration of norepinephrine in patients with septic shock

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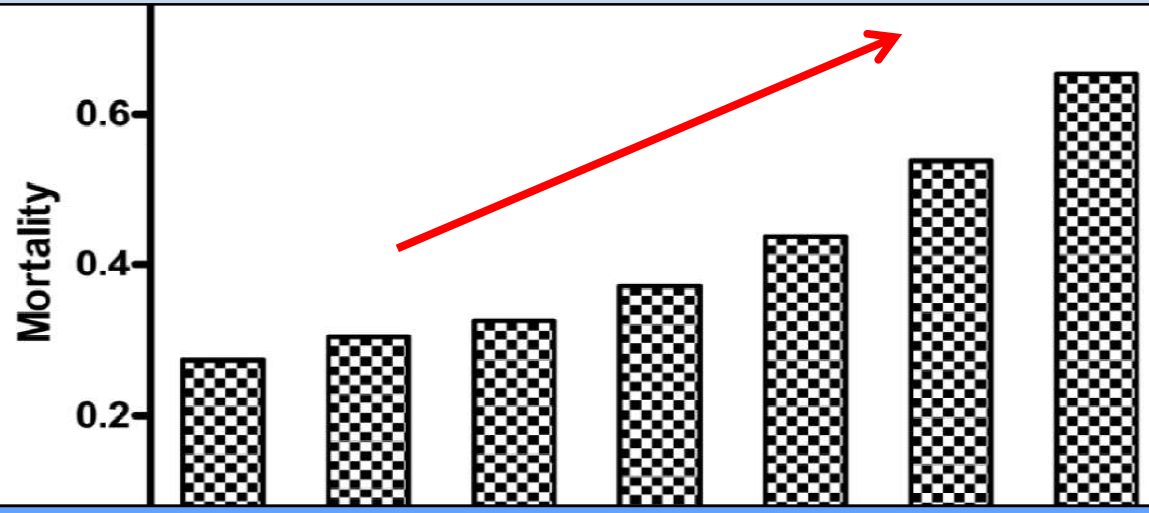
Critical Care 2014, **18**:532

The **later NE** was **initiated**, the **higher** the **mortality** rate



Time to **initial NE** administration: **independent** predictor of **mortality**

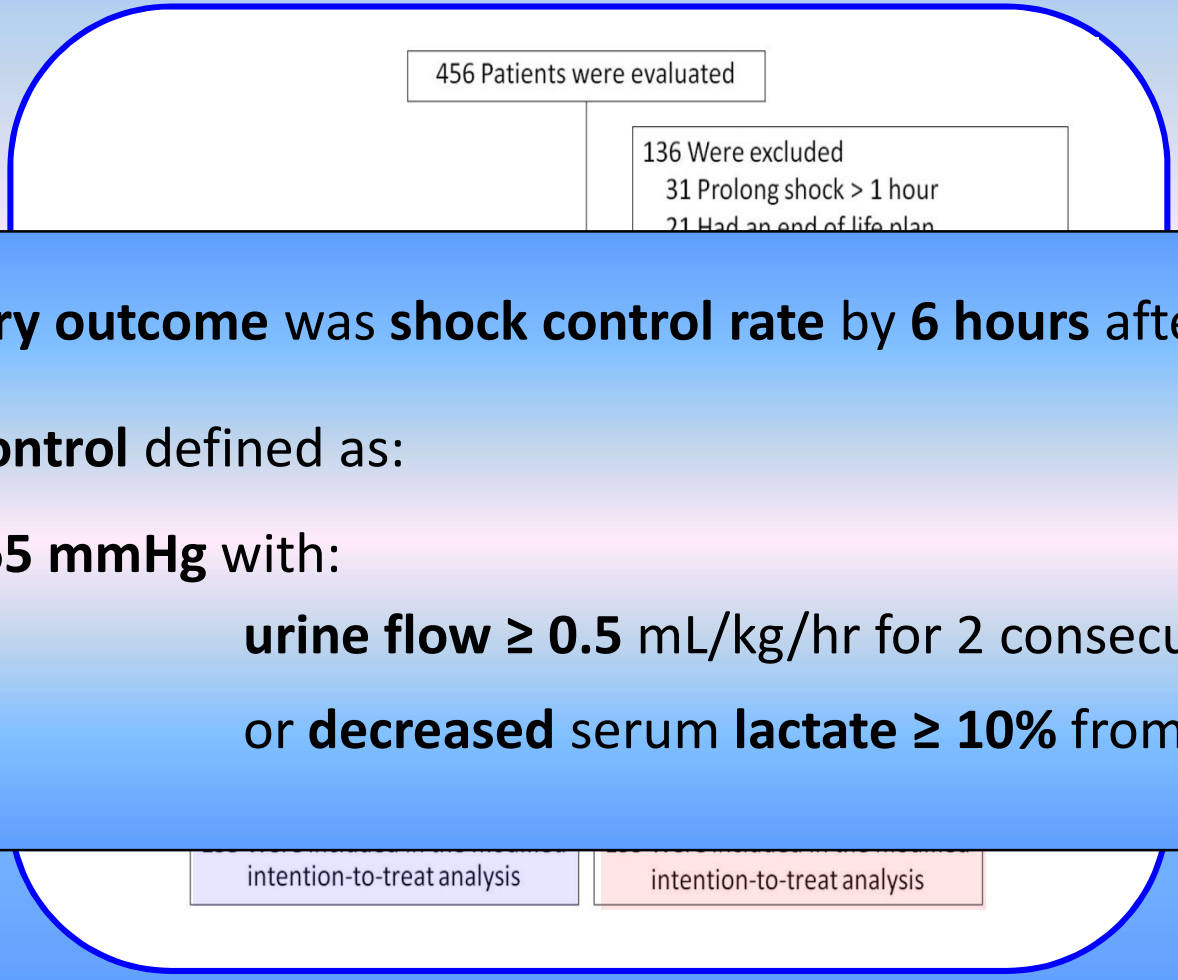
…. the **later**, the **worse**

Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER)

A Randomized Trial

Chairat Permpikul[1], Surat Tongyoo[1], Tanuwong Viarasilpa[1], Thavinee Trainarongsakul[1], Tipa Chakorn[2], and Suthipol Udompanturak[3]

Am J Respir Crit Care Med 2019; 199: 1097-1105



The **primary outcome** was **shock control rate** by **6 hours** after diagnosis

Shock control defined as:

MAP ≥ 65 mmHg with:

urine flow ≥ 0.5 mL/kg/hr for 2 consecutive hours

or **decreased** serum **lactate ≥ 10%** from baseline

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Outcome	Nore arly nephrine (N 155)	Standard Treatment (N 155)	Od ls Re a 3
Primary outcome, No. (%)			C c
Achieved target mABP + tissue p usion			

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Outcome	Early Norepinephrine	Standard Treatment	Odds Ratio
Secondary outcomes		Relative Risk	
Mortality at 28 days, No. (%)	24 (15.5)	34 (21.9)	0.79 (0.53–1.11)	0.15
Hospital mortality, No. (%)	35 (22.6)	38 (24.5)	0.95 (0.72–1.24)	0.69
Time from initial treatment to achieving target mABP + tissue perfusion goal, median (IQR), h:min	4:45 (3:30–5:56)	6:02 (4:20–9:18)		<0.001

Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER)

A Randomized Trial

Chairat Permp… and
Suthipol Udon…

…097-1105

Early NE group: **lower incidence** of:

- **cardiogenic pulmonary edema**
- new onset of **cardiac arrhythmia**

Events	Norepinephrine (N=155)	Treatment (N=155)	Relative Risk (95%CI)	P Value
Adverse events, No. (%)				
Cardiogenic pulmonary edema	22 (14.4)	43 (27.7)	0.70 (0.56–0.87)	0.004
Acute respiratory distress syndrome	17 (11)	14 (9)	1.12 (0.75–1.68)	0.56
New-onset cardiac arrhythmia	17 (11)	31 (20)	0.74 (0.56–0.94)	0.03
Hospital-acquired infection	22 (14.5)	21 (13.7)	1.03 (0.74–1.43)	0.85
Upper gastrointestinal hemorrhage	6 (3.9)	5 (3.2)	1.12 (0.58–2.15)	0.73
Acute limb and/or intestinal ischemia	5 (3.2)	3 (1.9)	1.35 (0.55–3.32)	0.47
Skin necrosis	1 (0.6)	1 (0.6)	1.0 (0.25-4.02)	1.0

Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER)

A Randomized Trial

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What This Study Adds to the Field: In this double-blind, randomized, controlled trial that enrolled 310 adults with sepsis with hypotension, early norepinephrine administration resulted in a significantly higher shock control rate than standard treatment (76.1% vs. 48.4%, respectively). The findings of this study support the benefit of early administration of norepinephrine at the initiation of sepsis with hypotension resuscitation, together with fluid therapy.

Current use of vasopressors in septic shock

Thomas W. L. Scheeren[1*], Jan Bakker[2,3,4,5], Daniel De Backer[6], Djillali Annane[7], Pierre Asfar[8], E. Christiaan Boerma[9], Maurizio Cecconi[10], Arnaldo Dubin[11], Martin W. Dünser[12], Jacques Duranteau[13], Anthony C. Gordon[14], Olfa Hamzaoui[15], Glenn Hernández[16], Marc Leone[17], Bruno Levy[18], Claude Martin[17], Alexandre Mebazaa[19], Xavier Monnet[20,21], Andrea Morelli[22], Didier Payen[23], Rupert Pearse[24], Michael R. Pinsky[25], Peter Radermacher[26], Daniel Reuter[27], Bernd Saugel[28], Yasser Sakr[29], Mervyn Singer[30], Pierre Squara[31], Antoine Vieillard-Baron[32,33], Philippe Vignon[34], Simon T. Vistisen[35], Iwan C. C. van der Horst[36], Jean-Louis Vincent[37] and Jean-Louis Teboul[38]

Ann. Intensive Care (2019) 9:20

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Ann. Intensive Care (2019) 9:20

Table 4 Summary of the expert's recommendations and its degree of consensus and grade of recommendation

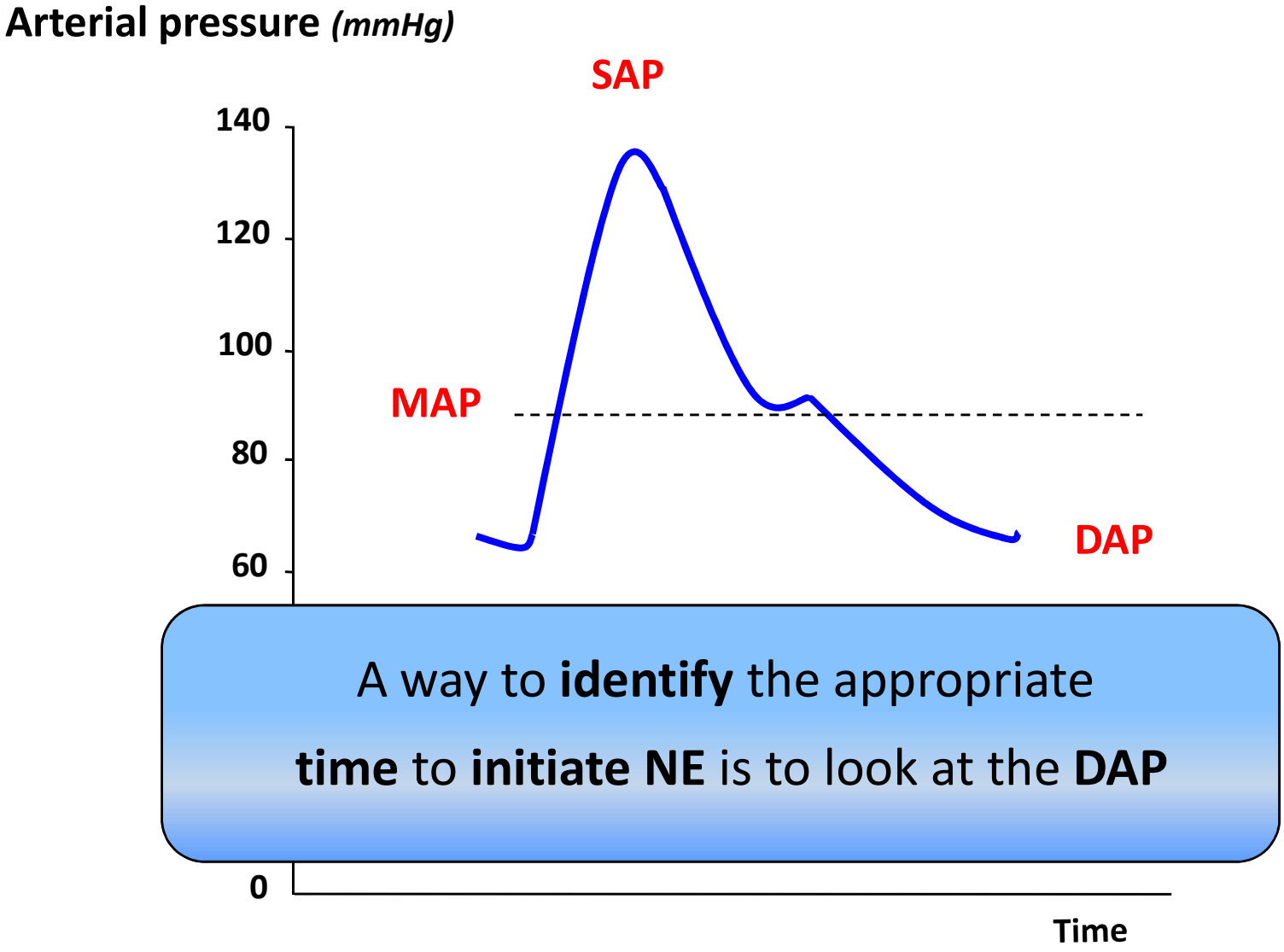
Statement	Degree of consensus	Grade of recommendation
Blood pressure monitoring		
1. In patients with shock, arterial blood pressure should be monitored invasively and continuously via an arterial catheter	Perfect	Strong
Ideal moment to start vasopressor therapy in treating circulatory shock		
2. Vasopressors should be started early, before (complete) completion of fluid resuscitation	Reasonable	Conditional
Treatment options in refractory hypotension		
7. Adding a second vasopressor in case of refractory hypotension	Good	Strong
8. Using vasopressin or terlipressin as second vasopressor	Good	Strong
Reason to stop vasopressor treatment		
9. Vasopressor treatment should be reduced/stopped when the patient improves clinically, when side effects occur, or in case of ineffectiveness	Perfect	Strong
Use of steroids to reach target		
10. Steroids should be considered in septic shock	Good	Strong

Definitions of degree of consensus and grades of recommendations based on the RAND algorithm. All 34 experts in agreement defined a perfect consensus and experts ≥ 80% agreement defined good consensus; both were considered as strong recommendation. Reasonable consensus was defined as 70–80% agreement among experts, and the recommendation was considered to be conditional

Vasopressors should be started **early** **before completion** of **fluid** resuscitation

Reasonable consensus

(70-80% experts agreed)


Arterial pressure (mmHg)
SAP
140
120
100
MAP
80
DAP
60
A way to identify the appropriate
time to initiate NE is to look at the DAP
0
Time

Norepinephrine in septic shock

1- Why?

2- When to start?

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Intensive Care Med (2005) 31:1066–1071
DOI 10.1007/s00134-005-2688-z

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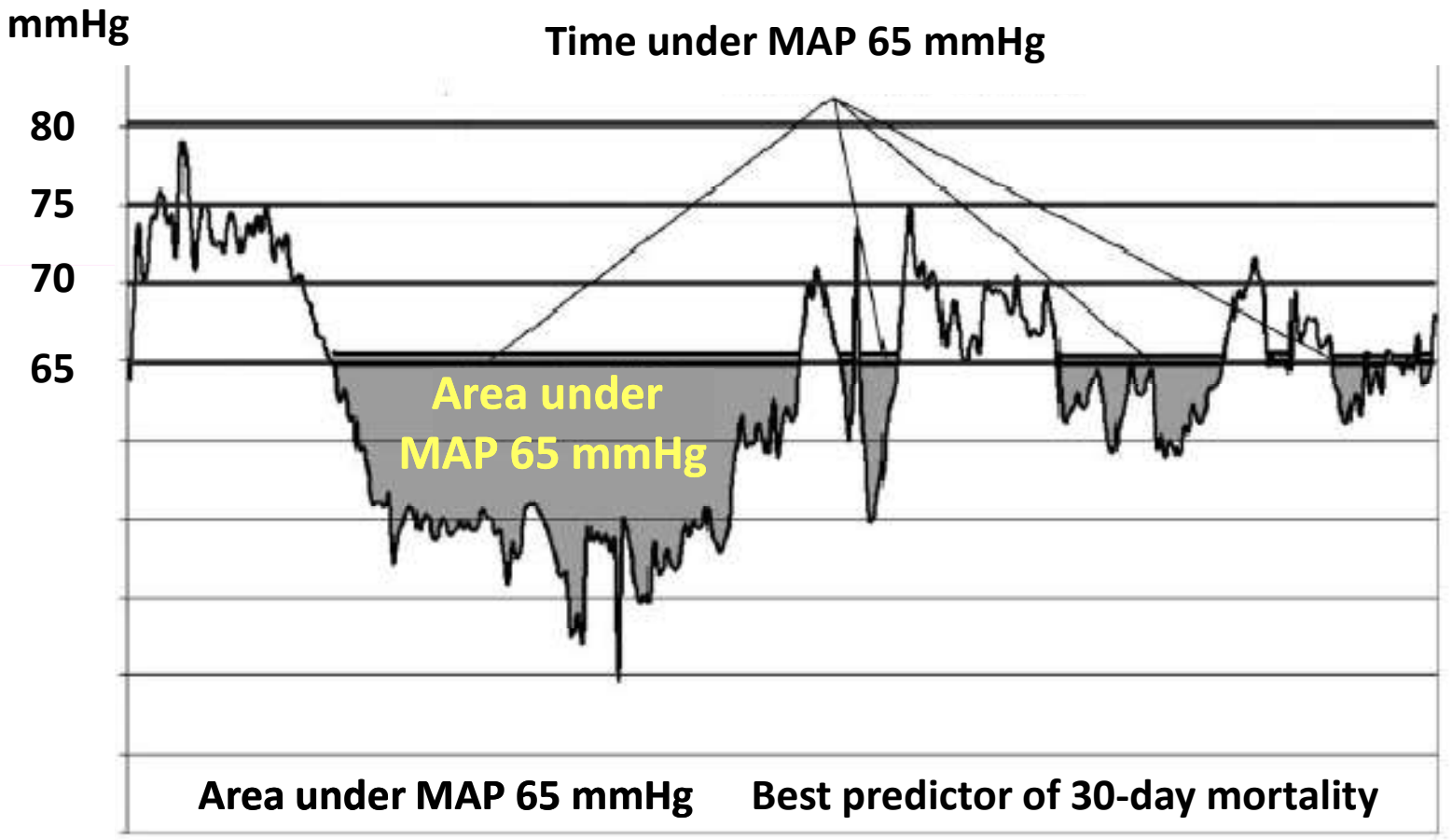

CONFERENCE REPORTS AND EXPERT PANEL

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Intensive Care Med (2017) 43:304–377

We **recommend** an initial target **MAP** of **65 mmHg** in patients with septic shock requiring vasopressors *(strong recommendation, moderate quality of evidence)*

Is it **dangerous** to **target a MAP** value

up to **“normal values”** (around 85 mmHg)

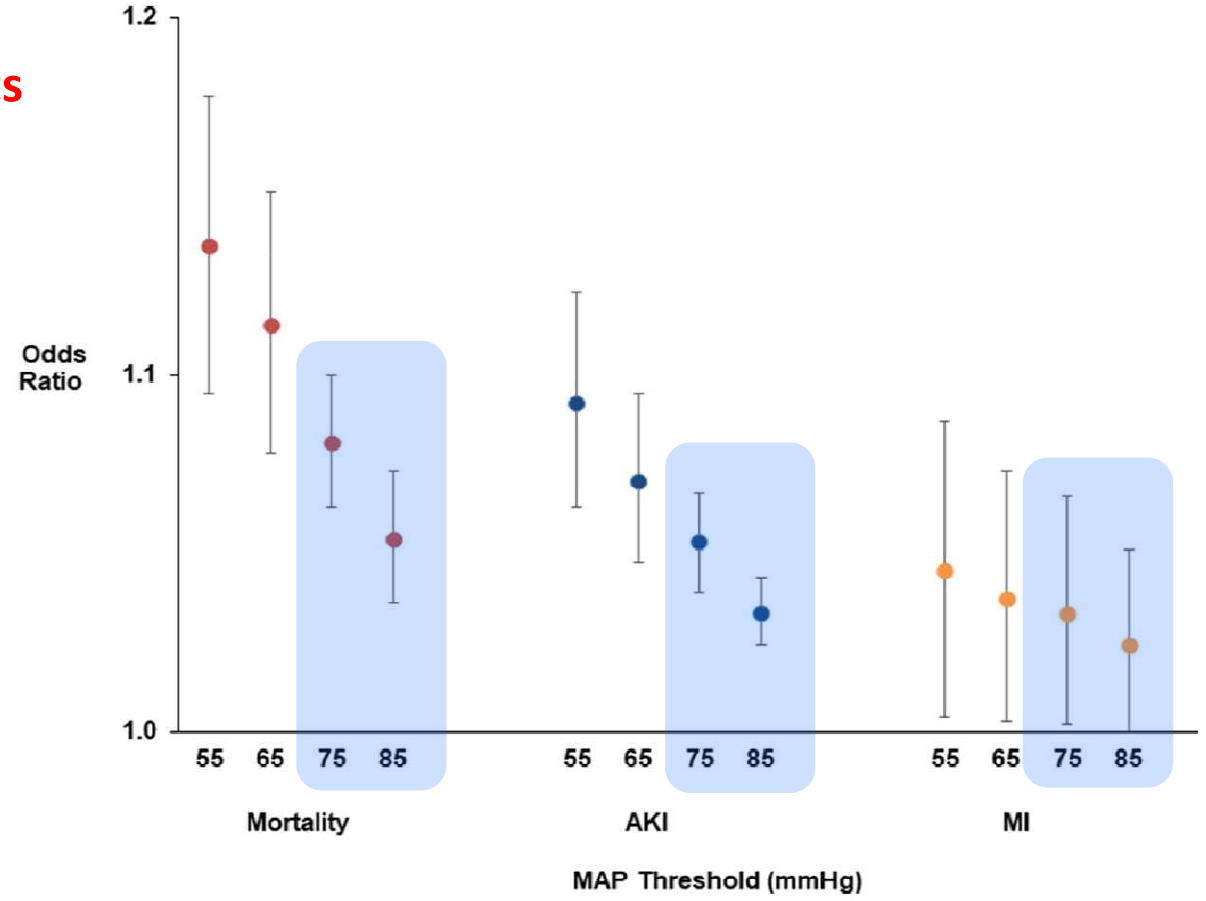
in **septic** shock?

The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients

Kamal Maheshwari[1,7*], Brian H. Nathanson[2], Sibyl H. Munson[3], Victor Khangulov[3], Mitali Stevens[4], Hussain Badani[3], Ashish K. Khanna[5] and Daniel I. Sessler[6]

Intensive Care Med (2018) 44:857–867

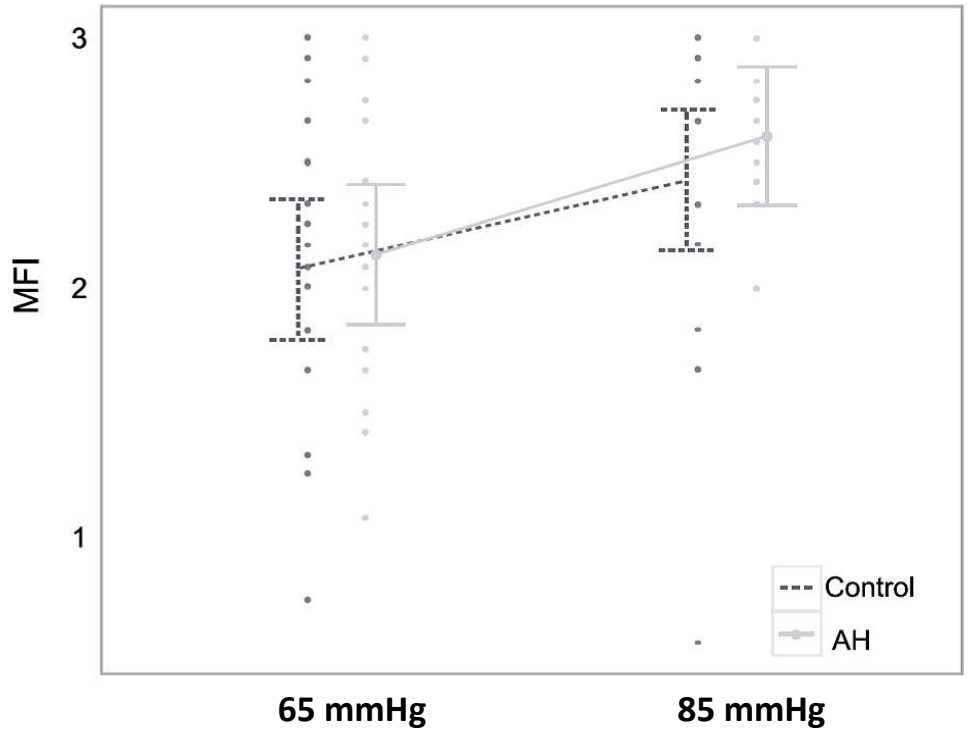
8782 pts



Effect of Increasing Blood Pressure With Noradrenaline on the Microcirculation of Patients With Septic Shock and Previous Arterial Hypertension

Karla Tuanny Fiorese Coimbra, MD; Flávio Geraldo Rezende de Freitas, MD, PhD; Antônio Tonete Bafi, MD; Tuanny Teixeira Pinheiro, MSc; Nathaly Fonseca Nunes, MD, MSc; Luciano César Pontes de Azevedo, MD, PhD; Flávia Ribeiro Machado, MD, PhD

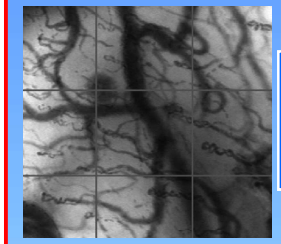
Crit Care Med 2019; 47:1033–1040



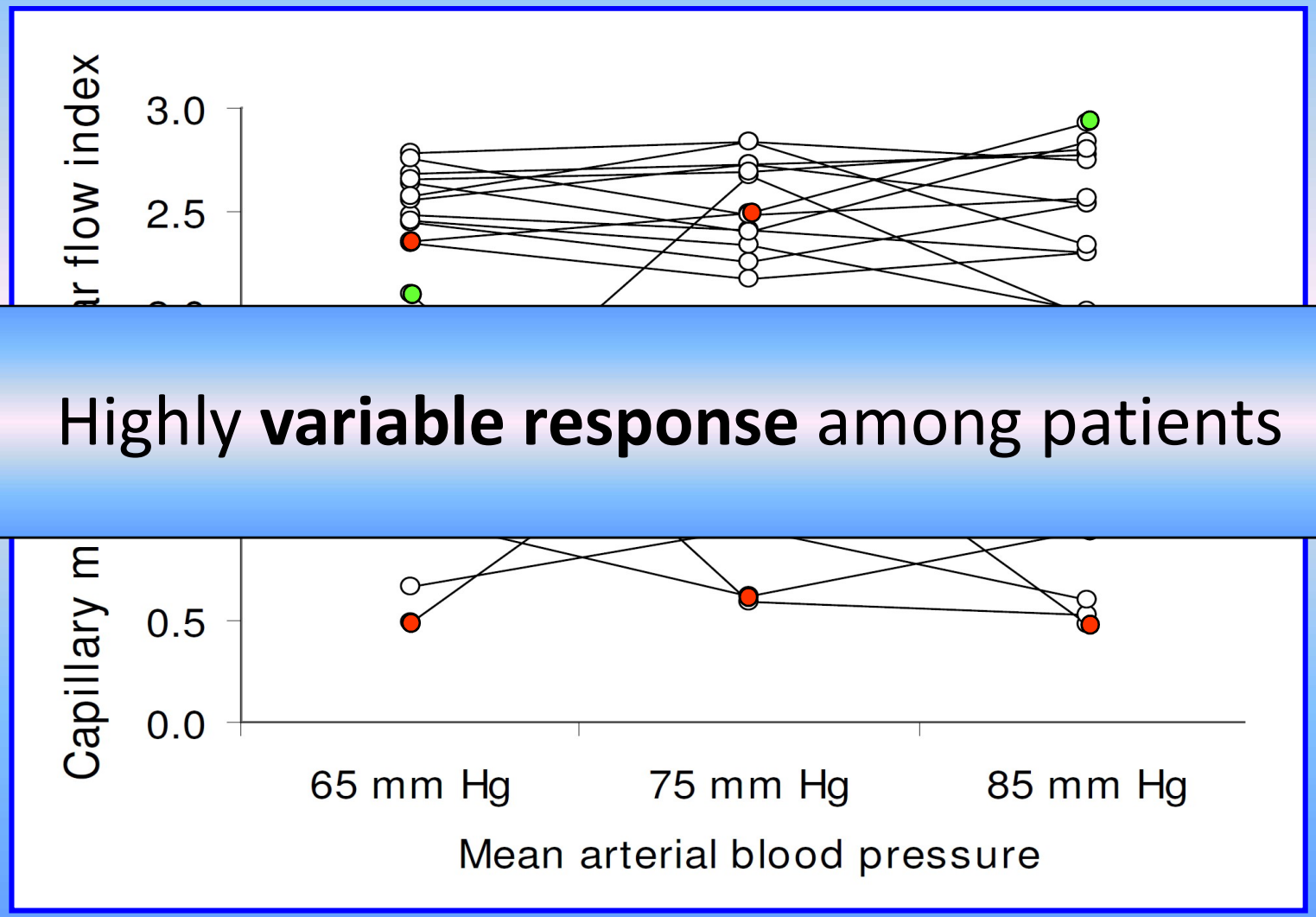
Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study

Arnaldo Dubin[1,2], Mario O Pozo[3], Christian A Casabella[1], Fernando Pálizas Jr[3], Gastón Murias[3], Miriam C Moseinco[1], Vanina S Kanoore Edul[1,2], Fernando Pálizas[3], Elisa Estenssoro[4] and Can Ince[5]

Critical Care 2009, **13**:R92



20 pts with septic shock



Highly **variable response** among patients

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],

Intensive Care Med (2017) 43:304–377

We **recommend** an initial target **MAP** of **65 mmHg** in patients with septic shock requiring vasopressors

Strong recommendation, moderate quality of evidence

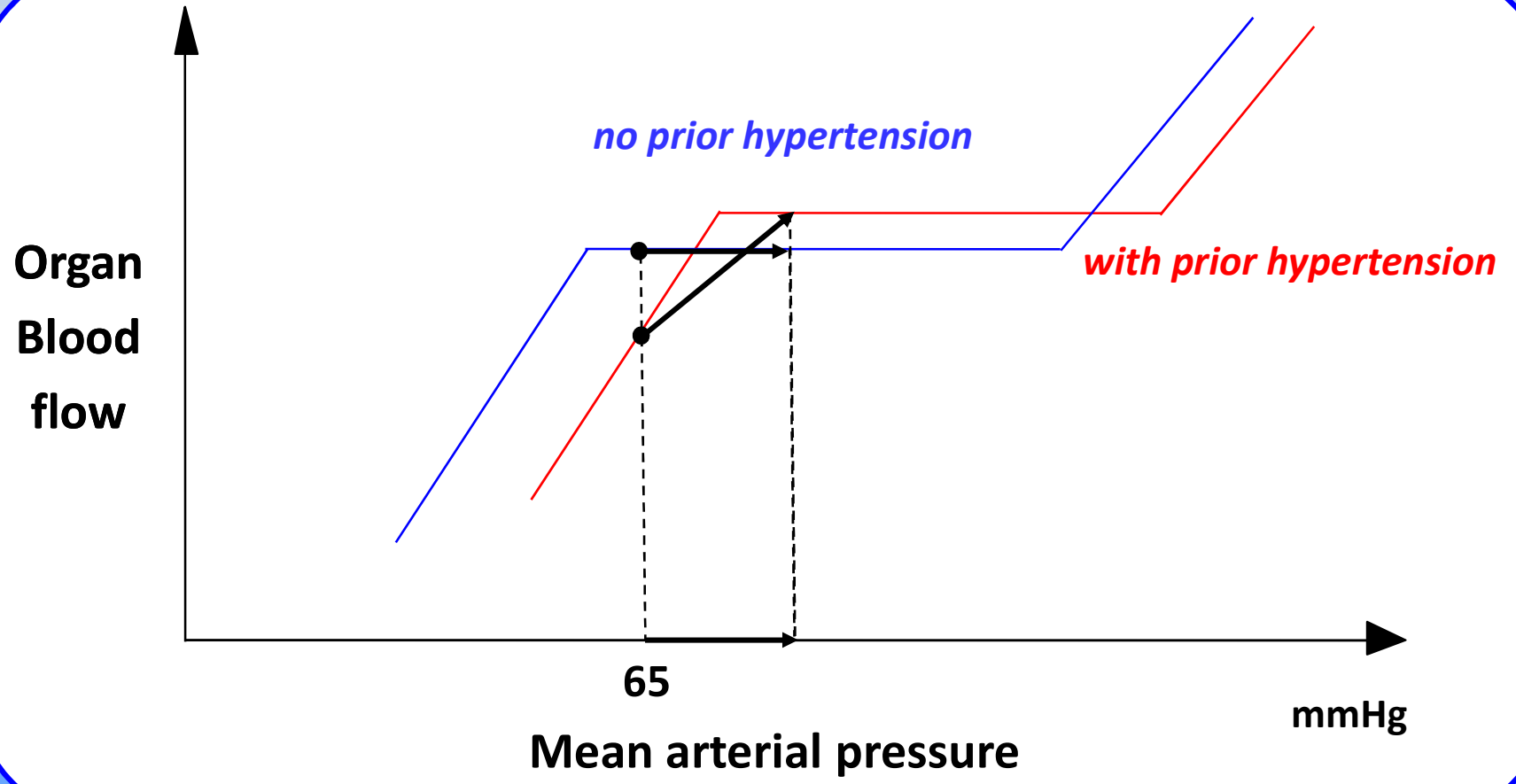
Probably **higher target value** if:

- **History of chronic hypertension**

Norepinephrine in septic shock: when and how much?

Olfa Hamzaoui[a], Thomas W.L. Scheeren[b], and Jean-Louis Teboul[c,d]

Curr Opin Crit Care 2017, 23:000–000



65-70 mmHg

80-85 mmHg

The NEW ENGLAND JOURNAL of MEDICINE

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

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

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

388 pts

388 pts

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Table 2. Clinical Results, Primary and Secondary Outcomes, and Serious Adverse Events.

Variable	Low-Target Group (N = 388)	High-Target Group (N = 388)	P Value
Primary outcome: death at day 28 — no. (%)*	132 (34.0)	142 (36.6)	0.57
Secondary outcomes — no./total no. (%)			
Death at day 90†	164 (42.3)	170 (43.8)	0.74
Survival at day 28 without organ support‡	241 (62.1)	235 (60.6)	0.66
Doubling of plasma creatinine	161 (41.5)	150 (38.7)	0.42
No chronic hypertension	71/215 (33.0)	85/221 (38.5)	0.32
Chronic hypertension	90/173 (52.0)	65/167 (38.9)	0.02
Renal-replacement therapy from day 1 to day 7	139 (35.8)	130 (33.5)	0.50
No chronic hypertension	66/215 (30.7)	77/221 (34.8)	0.36
Chronic hypertension	73/173 (42.2)	53/167 (31.7)	0.046

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Table 2. Clinical Results, Primary and Secondary Outcomes, and Serious Adverse Events.

Variable	Low-Target Group (N = 388)	High-Target Group (N = 388)	P Value
Serious adverse events — no. (%)			
Any	69 (17.8)	74 (19.1)	0.64
Acute myocardial infarction§	2 (0.5)	7 (1.8)	0.18
Atrial fibrillation	11 (2.8)	26 (6.7)	0.02
Ventricular fibrillation or tachycardia	15 (3.9)	22 (5.7)	0.24
Digital ischemia	9 (2.3)	10 (2.6)	0.82
Mesenteric ischemia	9 (2.3)	9 (2.3)	1.00
Bleeding	42 (10.8)	31 (8.0)	0.22

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		Low MAP	High
	Chronic hypertension +	0 (0)	4 (2
AF — no. (%)	All	11 (2.8)	26 (

65-70 mmHg

80-85 mmHg

The NEW ENGLAND JOURNAL of MEDICINE

No difference in **mortality** (34% *vs.* 37%)

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

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-Francois Hamel, M.D., Fabien Grelon, M.D.,

Benefits in terms of **kidney function** with a **high MAP** target in patients with **chronic hypertension**

Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D.,

388 pts

388 pts

CONFERENCE REPORTS AND EXPERT PANEL

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

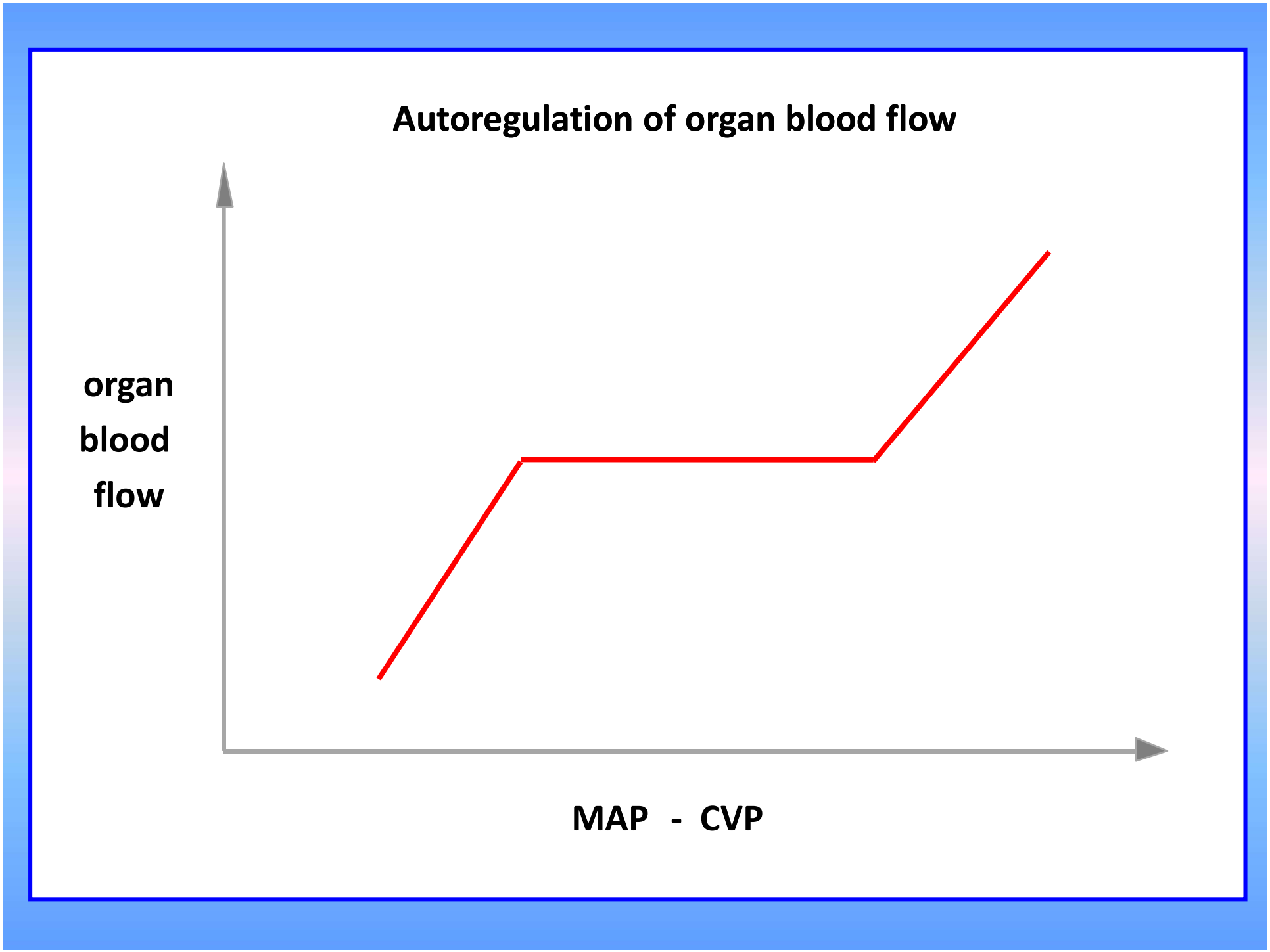
Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6],

Intensive Care Med (2017) 43:304–377

We **recommend** an initial target **MAP** of **65 mmHg** in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence)

Probably **higher target value** if:

- History of chronic hypertension
- **Increased CVP**


Autoregulation of organ blood flow
organ
blood
flow
MAP - CVP

Low mean perfusion pressure is a risk factor for progression of acute kidney injury in critically ill patients – A retrospective analysis

Marlies Ostermann[1*], Anna Hall[2] and Siobhan Crichton[3]

BMC Nephrology (2017) 18:151

Mean perfusion pressure (MPP = MAP-CVP) but **not MAP**

was an independent factor associated with **AKI progression**.

A value of **MPP** of **60 mmHg** was found as a cutoff.

Intensive Care Med (2014) 40:1795–1815

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

Target blood pressure in circulatory shock

- We recommend **individualizing** the target blood pressure during shock resuscitation.

  Recommendation Level 1: QoE moderate (B)

- We recommend to **initially target a MAP of ≥ 65 mmHg.**

  Recommendation: Level 1; QoE low (C)

- We suggest a **higher MAP** in septic patients with a **history of hypertension.**

  Recommendation: Level 2; QoE low (B)

Norepinephrine in septic shock

1- Why?

2- When to start?

3- Which target?

4- What to do in cases of refractory hypotension?

What to do in the case of

refractory hypotension?

There is **no** consensual **definition** of refractory hypotension

For some experts (… but not all), it is defined by inability of **1 µg/kg/min NE** to reach 65 mmHg MAP

Auchet et al. Ann. Intensive Care (2017) 7:43
DOI 10.1186/s13613-017-0261-x

Annals of Intensive Care

RESEARCH Open Access

Outcome of patients with septic shock and high-dose vasopressor therapy

Thomas Auchet[1,2], Marie-Alix Regnier[3], Nicolas Girerd[4] and Bruno Levy[1,2,5*]

40% of patients who received **NE** at dose **> 1 µg/kg/min**

were discharged **alive**

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],

Intensive Care Med (2017) 43:304–377

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

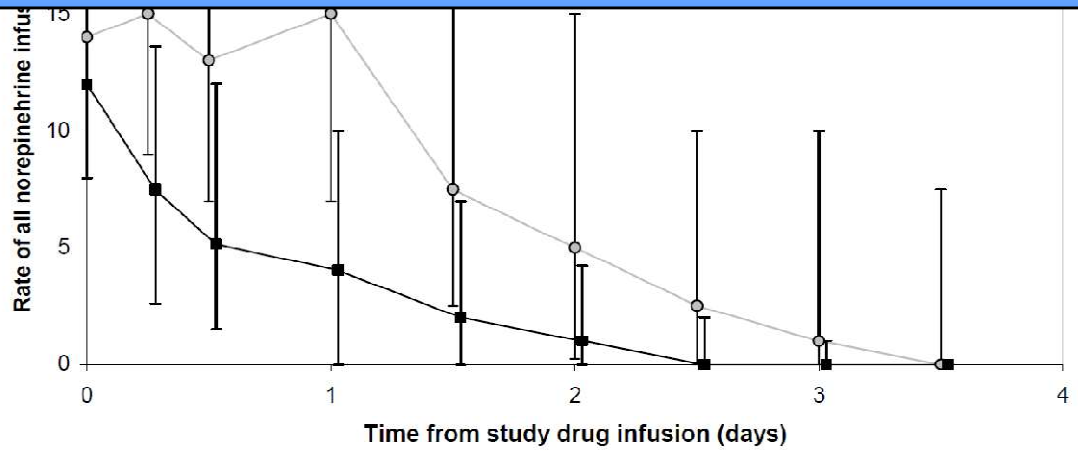
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

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

N Engl J Med 2008;358:877-87.

Adding **vasopressin** for the **same MAP** target

results in a **lower dose** of **NE**



JAMA | Original Investigation

Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock

A Systematic Review and Meta-analysis

William F. McIntyre, MD; Kevin J. Um, BA; Waleed Alhazzani, MD, MSc; Alexandra P. Lengyel; Ludhmila Hajjar, MD; Anthony C. Gordon, MD; François Lamontagne, MD, MSc; Jeff S. Healey, MD, MSc; Richard P. Whitlock, MD, PhD; Emilie P. Belley-Côté, MD, MSc

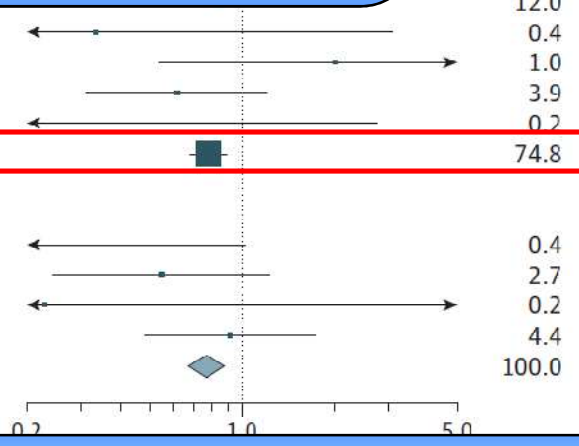
JAMA. 2018;319(18):1889-1900.

Less atrial fibrillation when **vasopressin** is **added** to NE compared to **NE alone**

Source						Weight, %
Abdullah et al,						
Capoletto et al,[38]						12.0
Choudhury et al,[29] 2016	1	42	3	42	0.33 (0.04-3.08)	0.4
Clem et al,[30] 2016	6	41	3	41	2.00 (0.54-7.46)	1.0
Dünser et al,[39] 2003	8	24	13	24	0.62 (0.31-1.21)	3.9
Gordon et al,[20] 2016	0	205	3	204	0.14 (0.01-2.73)	0.2
Hajjar et al,[18] 2017	95	149	124	151	0.78 (0.67-0.89)	74.8
Lauzier et al,[21] 2006	0	13	0	13	Not estimable	
Malay et al,[33] 1999	0	5	0	5	Not estimable	
Morelli et al,[35] 2009	1	30	4	15	0.13 (0.02-1.02)	0.4
Russell et al,[22] 2008	7	44	14	48	0.55 (0.24-1.23)	2.7
Russell et al,[23] 2017	0	31	1	21	0.23 (0.01-5.37)	0.2
Svoboda et al,[37] 2012	7	13	10	17	0.92 (0.48-1.74)	4.4
Total events (95% CI)	159	739	215	723	0.77 (0.67-0.88)	100.0

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_9 = 9.10$ ($P = .43$); $I^2 = 1\%$

Overall effect: $z = 3.79$ ($P < .001$)



But this result is driven by one study in post-surgery (Hajjar et al)

JAMA | Original Investigation

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JAMA. 2018;319(18):1889-1900.

No difference when only **sepsis** is taken into account

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
1.11.1 Sepsis						
Abdullah 2012 [3]	0	17	0	17		Not estimable
Capoletto 2017 [7]	34	125	40	125	10.6%	0.85 [0.58, 1.25]
Choudhury 2016 [9]	1	42	3	42	0.3%	0.33 [0.04, 3.08]
Clem 2016 [10]	6	41	3	41	0.9%	2.00 [0.54, 7.46]
Dünser 2003 - Sepsis [11]	4	14	6	15	1.5%	0.71 [0.25, 2.01]
Gordon 2016 [13]	0	205	3	204	0.2%	0.14 [0.01, 2.73]
Lauzier 2006 [17]	0	13	0	13		Not estimable
Malay 1999 [18]	0	5	0	5		Not estimable
Morelli 2009 [19]	1	30				
Russell 2008 [23]	7					
Russell 2017 [24]	0					
Svoboda 2012 [25]						
Subtotal (95% CI)		58				
Total events	60					
Heterogeneity: Tau² = 0.02; Chi² = 8.68, df = 8 (P = 0.37); I² = 8						
Test for overall effect: Z = 1.67 (P = 0.09)						
1.11.2 Cardiac Surgery						
Dünser 2003 - Postcardiotomy [11]	4	10	7	9	2.2%	0.51 [0.22, 1.19]
Hajjar 2017 [14]	95	149	124	151	77.6%	0.78 [0.67, 0.89]
Subtotal (95% CI)		**159**		**160**	**79.8%**	**0.77 [0.67, 0.88]**
Total events	99		131			
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 3.70 (P = 0.0002)						

0.76 [0.55, 1.05]

ORIGINAL

Terlipressin versus norepinephrine as infusion in patients with septic shock multicentre, randomised, double-blind

Zi-Meng Liu[1], Juan Chen[1], Qiuye Kou[2], Qinhan Lin[3], Xiaobo Huang[4], Zhanhong Tang[5], Yan Lixin Zhou[8], Qing Song[9], Tongwen Sun[10], Ling Zhao[11], Xue Wang[12], Xiandi He[13], Chunting

Intensive Care Med (2018) 44:1816–1825

Multicentre, double-blinded RCT including **617 pts**

- **No difference in** terms of **incidence** of **AF** between
  - **Terlipressin** (2%)
  - **NE** (2%)

JAMA | Original Investigation

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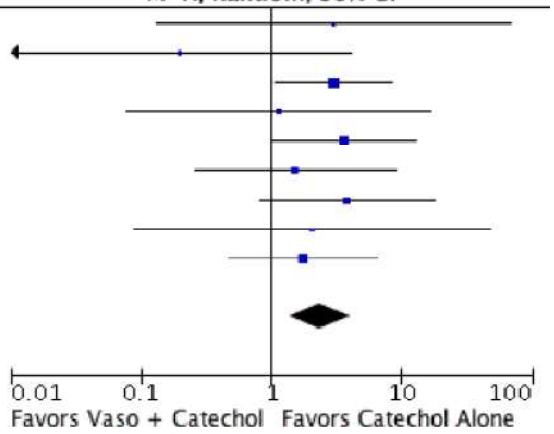
JAMA. 2018;319(18):1889-1900.

Digital Ischemia – All Studies[a,b]

Study or Subgroup	Vaso + Catecholamine Events	Vaso + Catecholamine Total	Catecholamine Alone Events	Catecholamine Alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Barzegar 2014 [6]	1	15	0	15	3.1%	3.00 [0.13, 68.26]
Capoletto 2017 [7]	0	125	2	125	3.3%	0.20 [0.01, 4.12]
Choudhury 2016 [9]	12	42	4	42	27.5%	3.00 [1.05, 8.55]
Fonseca Ruiz 2013 [12]	1	14	1	16	4.2%	1.14 [0.08, 16.63]
Gordon 2016 [13]	11	205	3	204	19.0%	3.65 [1.03, 12.89]
Hajjar 2017 [14]	3	149	2	151	9.6%	1.52 [0.26, 8.97]
Russell 2008 [23]	8	396	2	382	12.7%	3.86 [0.82, 18.05]
Russell 2017 [24]	1	31	0	21	3.0%	2.06 [0.09, 48.34]
Svoboda 2012 [25]	4	13	3	17	17.6%	1.74 [0.47, 6.47]
Total (95% CI)		**990**		**973**	**100.0%**	**2.38 [1.37, 4.12]**
Total events	41		17			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.36$, df = 8 (P = 0.82); $I^2 = 0\%$

Test for overall effect: Z = 3.09 (P = 0.002)



< 2 % of cases…!!

Risk of bias legend

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

JAMA. 2016;316(5):509-518.

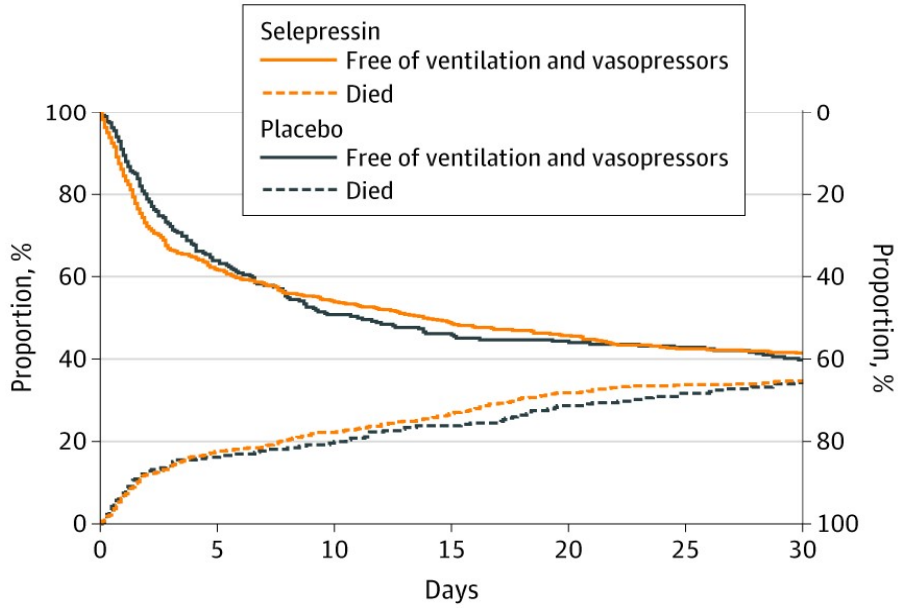
CONCLUSIONS AND RELEVANCE Among adults with septic shock, the early use of vasopressin compared with norepinephrine did not improve the number of kidney failure–free days. Although these findings do not support the use of vasopressin to replace norepinephrine as initial treatment in this situation, the confidence interval included a potential clinically important benefit for vasopressin, and larger trials may be warranted to assess this further.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock
The SEPSIS-ACT Randomized Clinical Trial

Pierre-Francois Laterre, MD; Scott M. Berry, PhD; Allan Blemings, MS; Jan E. Carlsen, MD; Bruno François, MD; Todd Graves, PhD; Karsten Jacobsen, MD; Roger J. Lewis, MD, PhD; Steven M. Opal, MD; Anders Perner, MD, PhD; Peter Pickkers, MD, PhD; James A. Russell, MD; Nis A. Windeløv, MD, PhD; Donald M. Yealy, MD; Pierre Asfar, MD; Morten H. Bestle, MD, PhD; Grégoire Muller, MD; Cédric Bruel, MD; Noëlle Brulé, MD; Johan Decruyenaere, MD; Alain-Michel Dive, MD, PhD; Thierry Dugernier, MD, PhD; Kenneth Krell, MD; Jean-Yves Lefrant, MD; Bruno Megarbane, MD, PhD; Emmanuelle Mercier, MD; Jean-Paul Mira, MD, PhD; Jean-Pierre Quenot, MD; Bodil Steen Rasmussen, MD, PhD; Hans-Christian Thorsen-Meyer, MD; Margot Vander Laenen, MD; Marianne Lauridsen Vang, MD; Philippe Vignon, MD, PhD; Isabelle Vinatier, MD; Sine Wichmann, MD, PhD; Xavier Wittebole, MD; Anne Louise Kjølbye, MS, PhD; Derek C. Angus, MD, MPH; for the SEPSIS-ACT Investigators

JAMA. 2019;322(15):1476-1485.



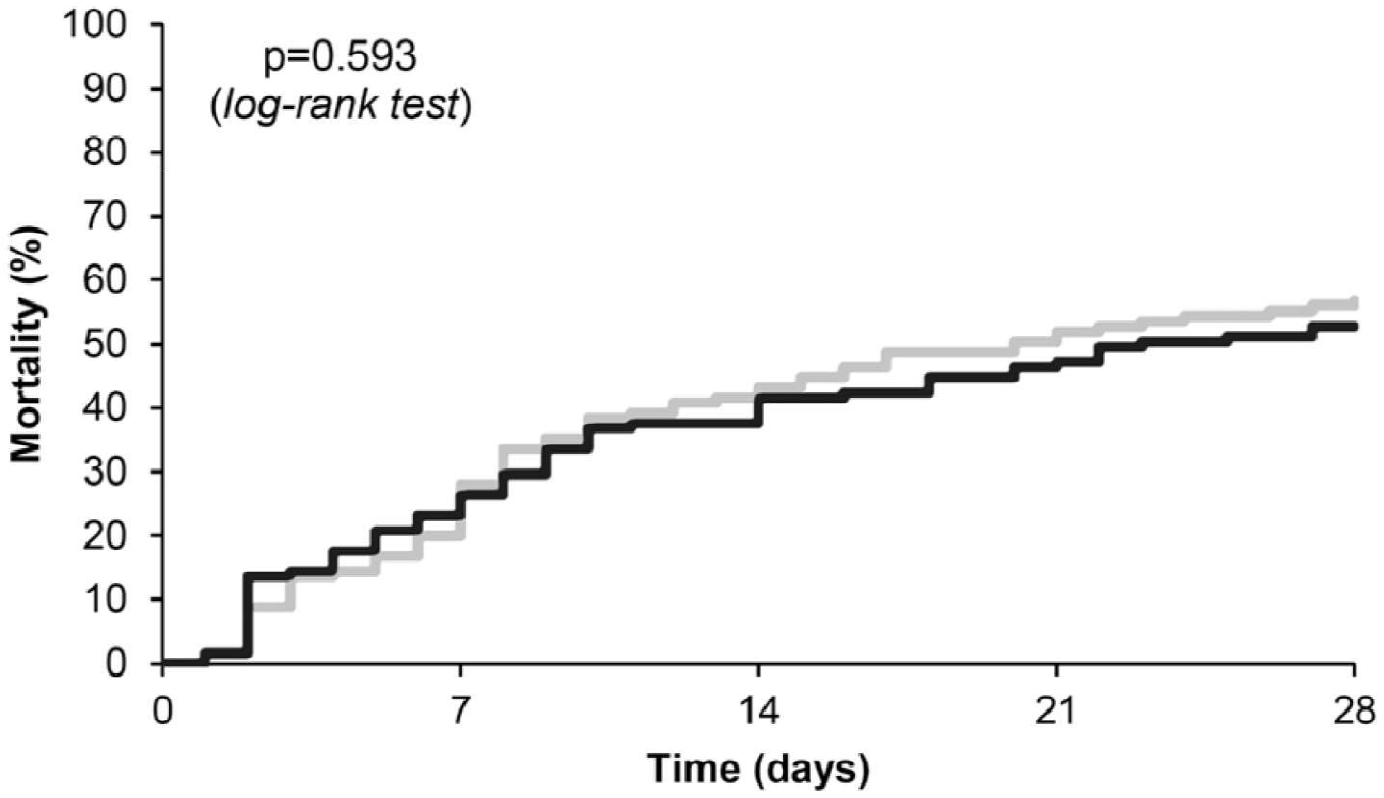
No. at risk

Selepressin	562	460	433	406	376	365	359
Placebo	266	223	213	203	190	183	174

Vasopressin Versus Norepinephrine for the Management of Septic Shock in Cancer Patients: The VANCS II Randomized Clinical Trial*

Ludhmila Abrahão Hajjar, PhD[1,2]; Cristiane Zambolim, MD[1]; Alessandro Belletti, MD[3]; Juliano Pinheiro de Almeida, MD[1]; Anthony C. Gordon, MD[4]; Gisele Oliveira, MD[1]; Clarice Hyesuk Lee Park, MD[1]; Julia Tizue Fukushima, MSc[1]; Stephanie Itala Rizk, MD[1]; Tais Felix Szeles, MD[1]; Nestor Cordeiro dos Santos Neto, MD[1]; Roberto Kalil Filho, MD[1,2]; Filomena Regina Barbosa Gomes Galas, MD[1]; Giovanni Landoni, MD[3,5]

Crit Care Med 2019; 47:1743–1750



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],

Intensive Care Med (2017) 43:304–377

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

- We suggest adding **vasopressin** (up to 0.03 U/min) to NE *(weak recommendation, moderate quality of evidence)* with the intent to **raising MAP** to target or to **decrease NE dosage**

: al. Critical Care (2016)

RESEARCH Open Access

Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury

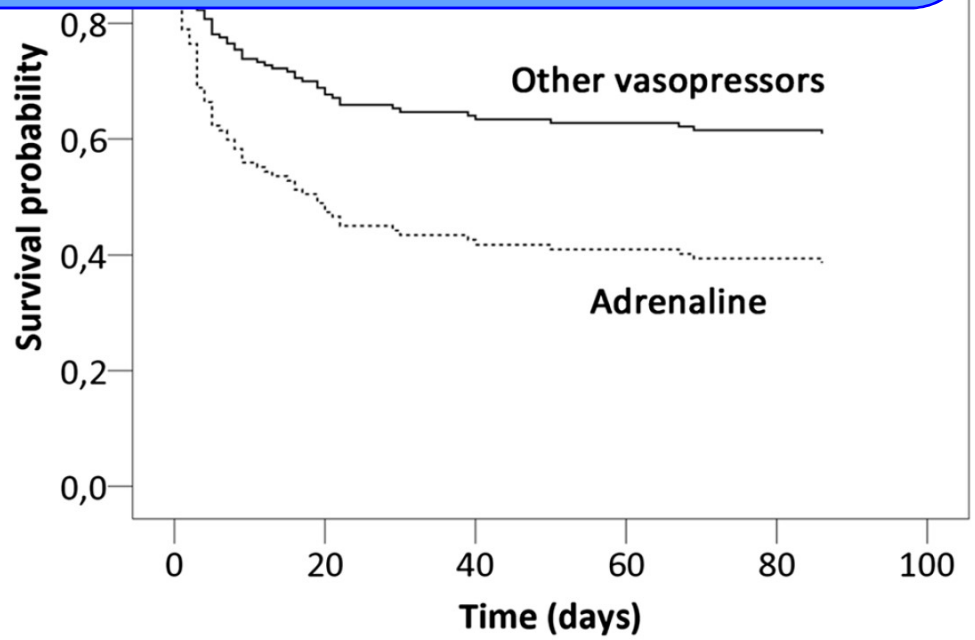
In multivariable logistic regression, only **adrenaline**

was **independently associated** with **increased** 90-day **mortality**

(OR 5.2, 95 % CI 1.88, 14.7,p = 0.002)

NE in **75%** pts
Dopamine in **26%** pts
Adrenaline in **21%** pts

Dobutamine in **49%** pts
Levosimendan in **24%** pts

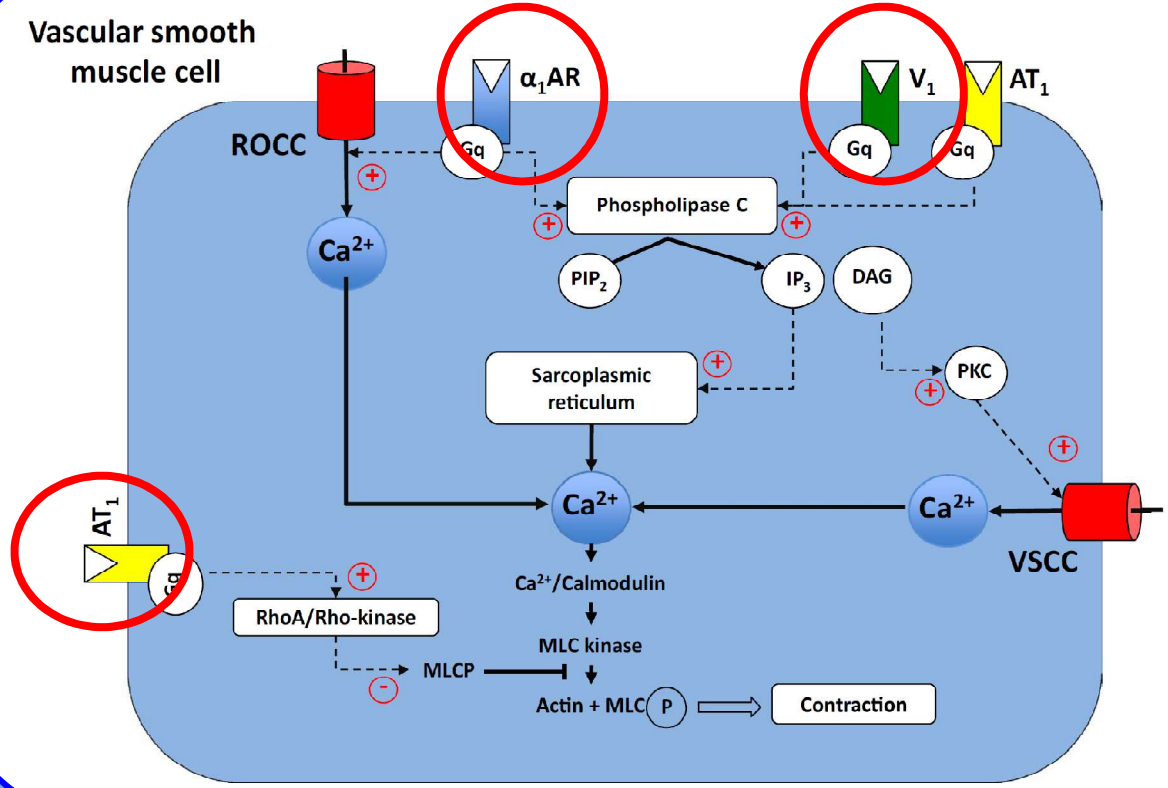


Intensive Care Med **2017**

WHAT'S NEW IN INTENSIVE CARE

Intensive care medicine in 2050: vasopressors in sepsis

Jean-Louis Teboul[1*], Jacques Duranteau[2] and James A. Russell[3]



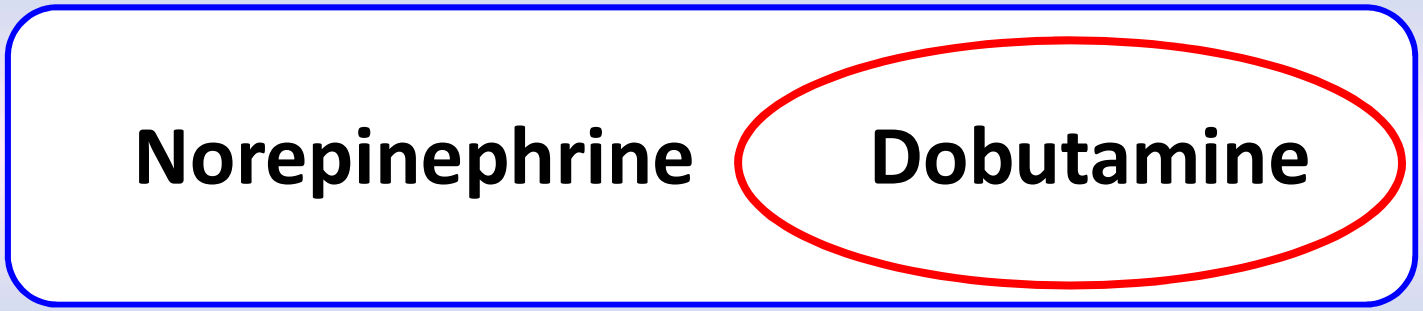
Intensive Care Med 2018; 44:1130-2

WHAT'S NEW IN INTENSIVE CARE

Intensive care medicine in 2050: vasopressors in sepsis

Jean-Louis Teboul[1*], Jacques Duranteau[2] and James A. Russell[3]

Optimal vasopressor therapy could then be a combination of agents acting on different receptors (Fig. 1) with minimizing doses of each agent and perhaps increasing safety.

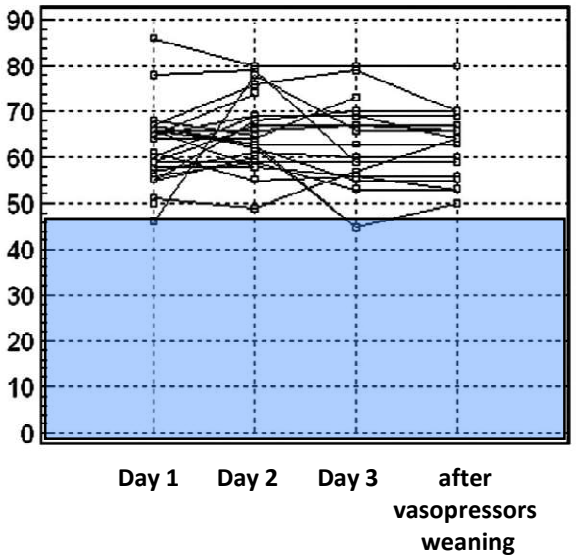

Norepinephrine
Dobutamine

Actual incidence of global left ventricular hypokinesia in adult septic shock

Antoine Vieillard-Baron, MD; Vincent Caille, MD; Cyril Charron, MD; Guillaume Belliard, MD; Bernard Page, MD; François Jardin, MD

Crit Care Med 2008; 36:1701–1706

LV EF %



40% of pts

40% of pts

20% of pts

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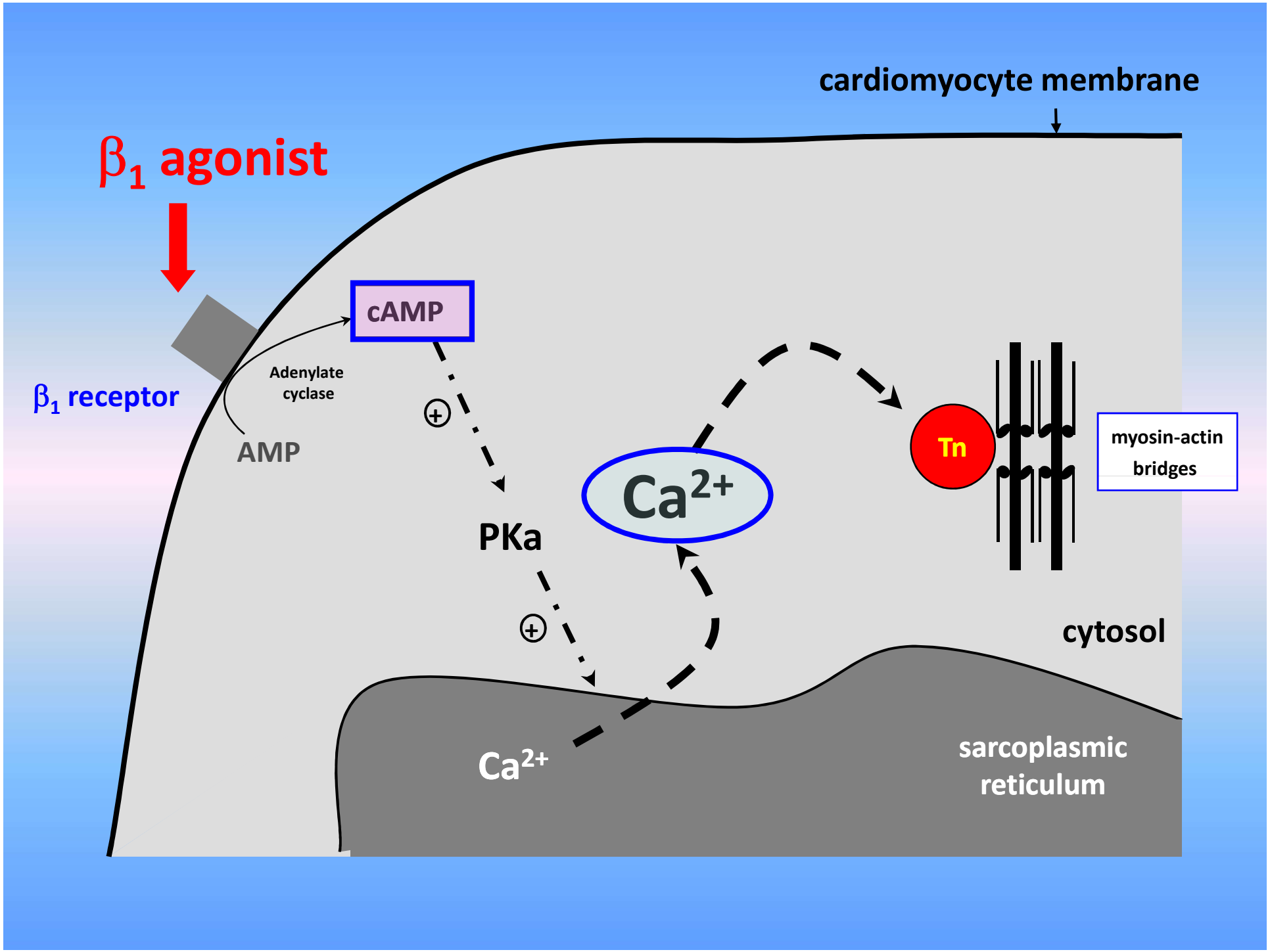
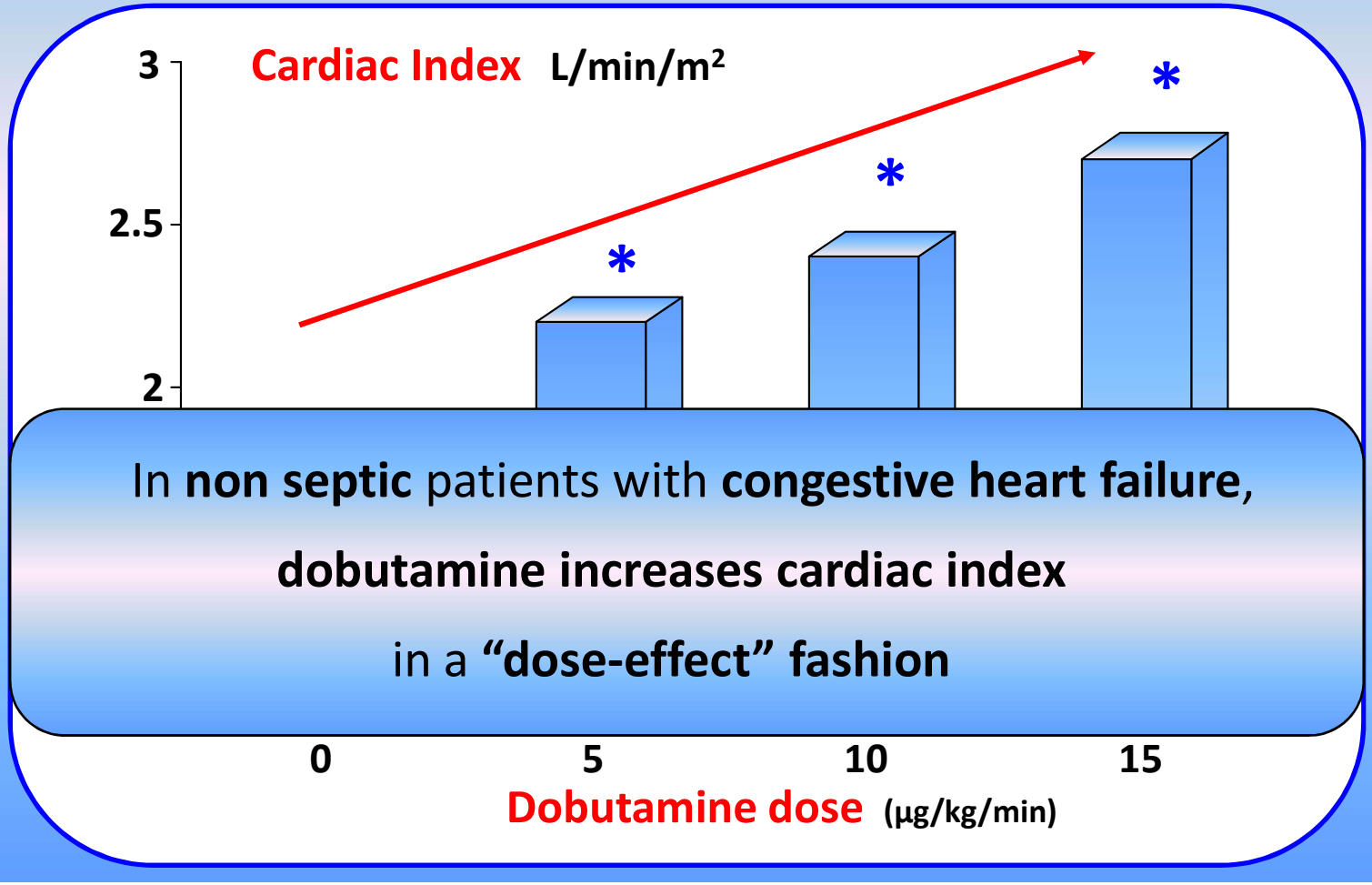
5. We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).


cardiomyocyte membrane
β1 agonist
β1 receptor
Adenylate cyclase
AMP
cAMP
PKa
Ca2+
Tn
myosin-actin bridges
cytosol
Ca2+
sarcoplasmic reticulum

Cardiac Index vs Oxygen-Derived Parameters for Rational Use of Dobutamine in Patients With Congestive Heart Failure*

Jean-Louis Teboul, M.D.; Laïd Graini, M.D.; Rafik Boujdaria, M.D.; Christine Berton, M.D.; and Christian Richard, M.D.

Chest 1993; 103:81-85



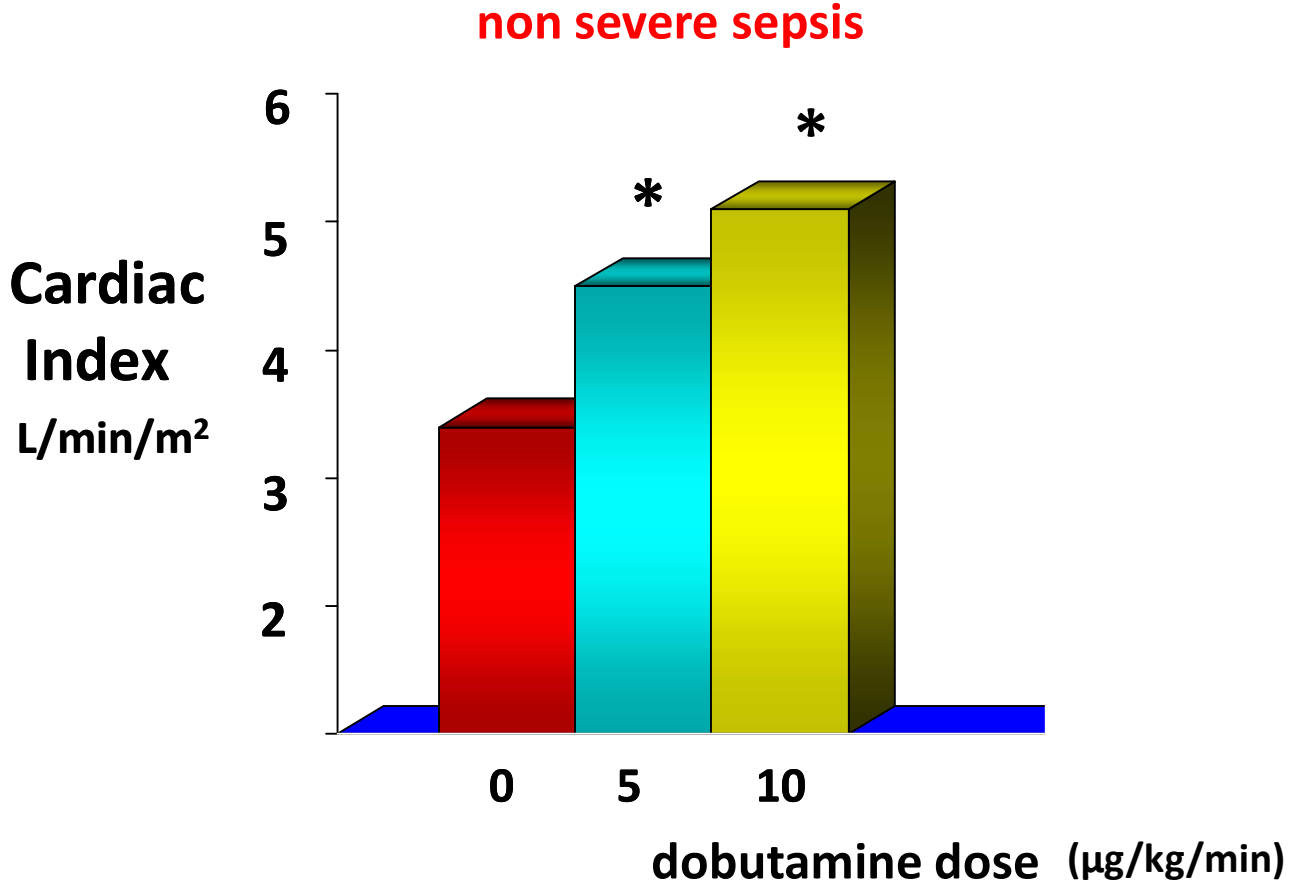
In **non septic** patients with **congestive heart failure,**

dobutamine increases cardiac index

in a **"dose-effect" fashion**

In **septic shock** patients

dobutamine does **not increase cardiac index**

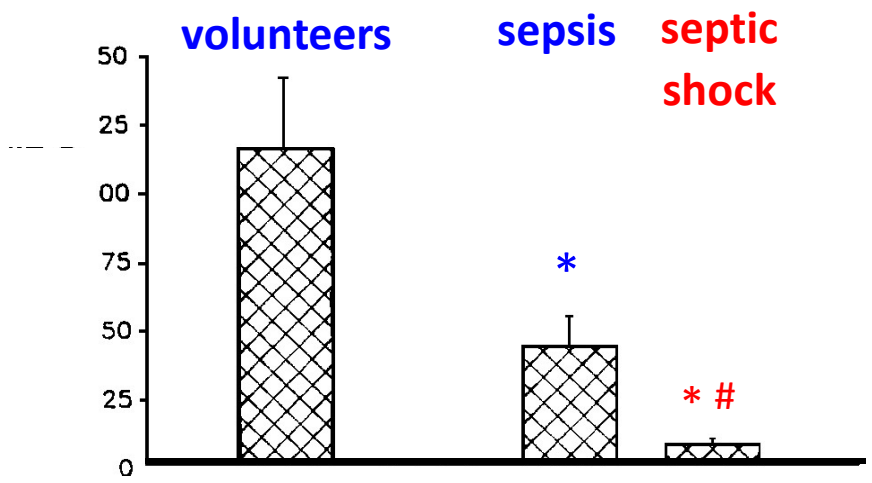


Impaired β-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: Association with myocardial hyporesponsiveness to catecholamines

HENRY J. SILVERMAN, MD; RUBEN PENARANDA, MD; JONATHAN B. ORENS, MD; NORMAN H. LEE, PHD

Crit Care Med 1993; 21:31-39

cAMP response to isoproterenol



impairment of
β_1-adrenergic receptor responsiveness
in **sepsis,**
and even **more** in **septic shock**

This results in a decreased efficacy of β_1-adrenergic agents such as dobutamine in patients with septic shock

CONFERENCE REPORTS AND EXPERT PANEL

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Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6],

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5. We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

but

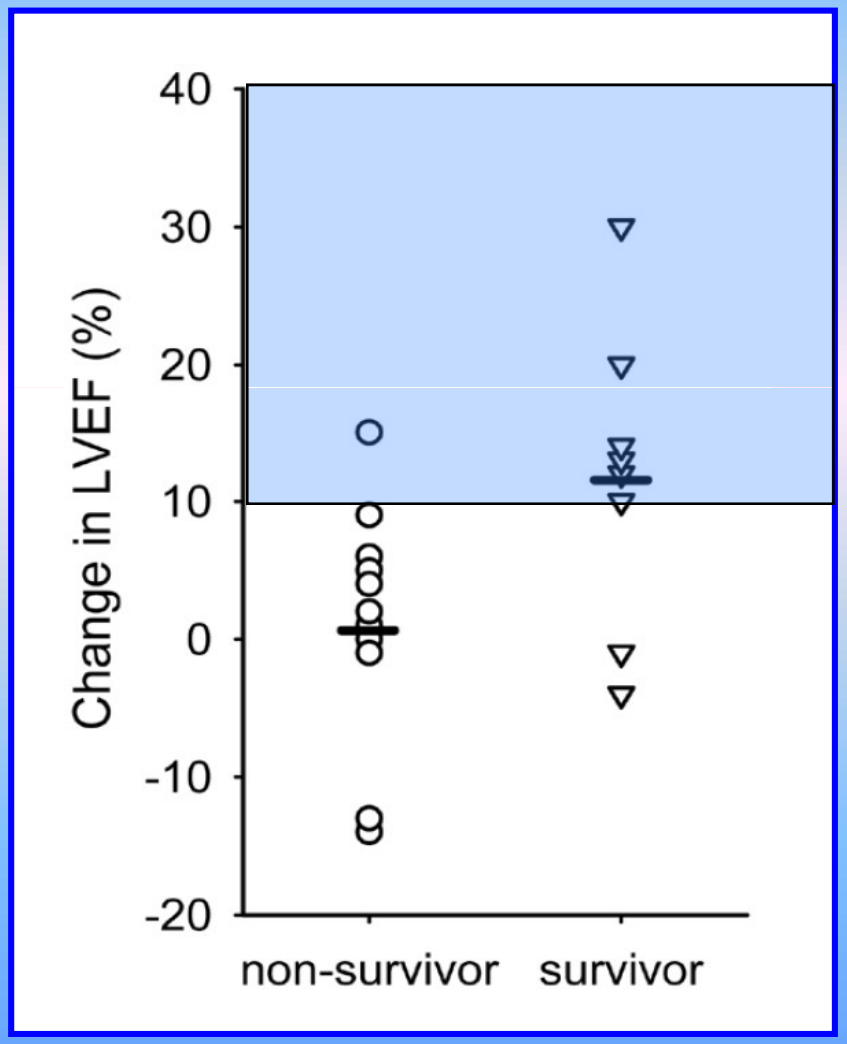
- **beneficial effects of dobutamine are unpredictable**

(potential decreased efficacy)

Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock

Anand Kumar[1,2], Elizabeth Schupp[3], Eugene Bunnell[3], Amjad Ali[4], Barry Milcarek[2] and Joseph E Parrillo[2]

Critical Care 2008, **12**:R35



Dobutamine increased LVEF

by more than 10%

only in 35% of pts

Dobutamine and septic myocardial dysfunction

- **beneficial** effects are **unpredictable** (potential decreased efficacy)
- **detrimental** effects may occur (arrhythmias, vasodilation, etc)

administration of dobutamine should be restricted to patients:

- with persisting shock
- → **test the response to dobutamine**
- **before any prolonged administration**
- despite fluid resuscitation and vasopressors

Treatment of sepsis-related cardiac dysfunction

Alternatives to dobutamine?

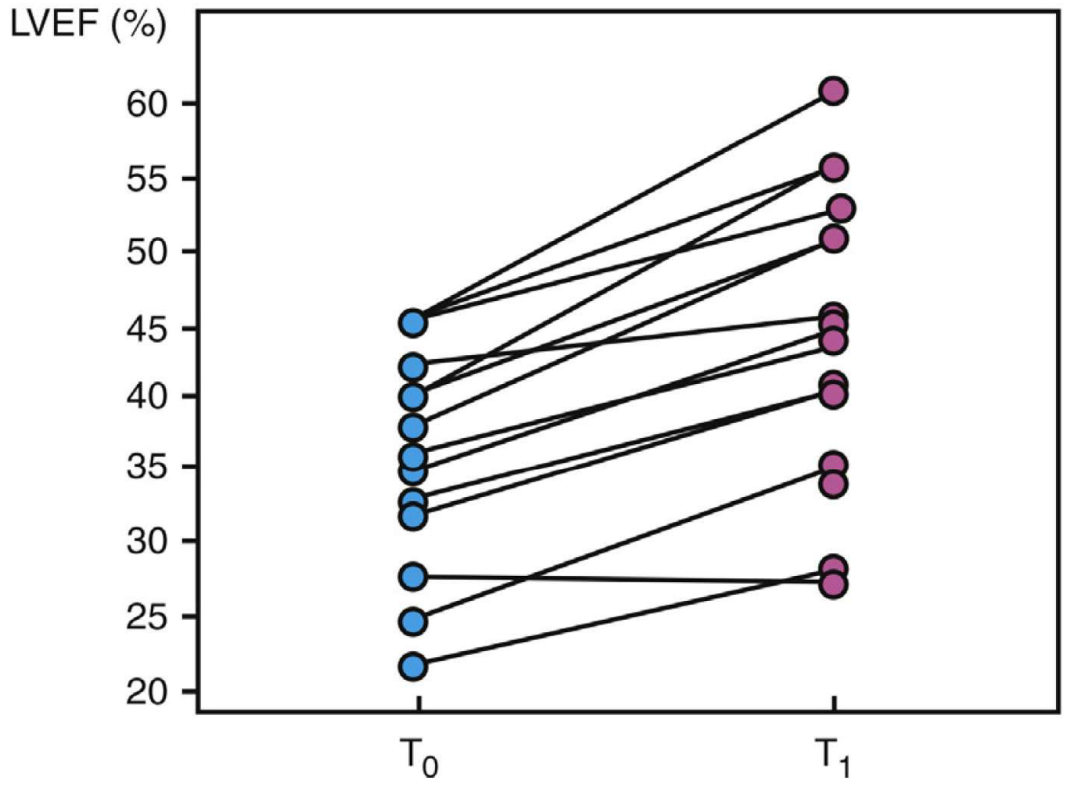
Norepinephrine?

CLINICAL INVESTIGATION

Norepinephrine exerts an inotropic effect during the early phase of human septic shock

O. Hamzaoui[1,*], M. Jozwiak[2], T. Geffriaud[2], B. Sztrymf[1], D. Prat[1], F. Jacobs[1], X. Monnet[2], P. Trouiller[1], C. Richard[2] and J.L. Teboul[2]

British Journal of Anaesthesia, 120 (3): 517–524 (2018)

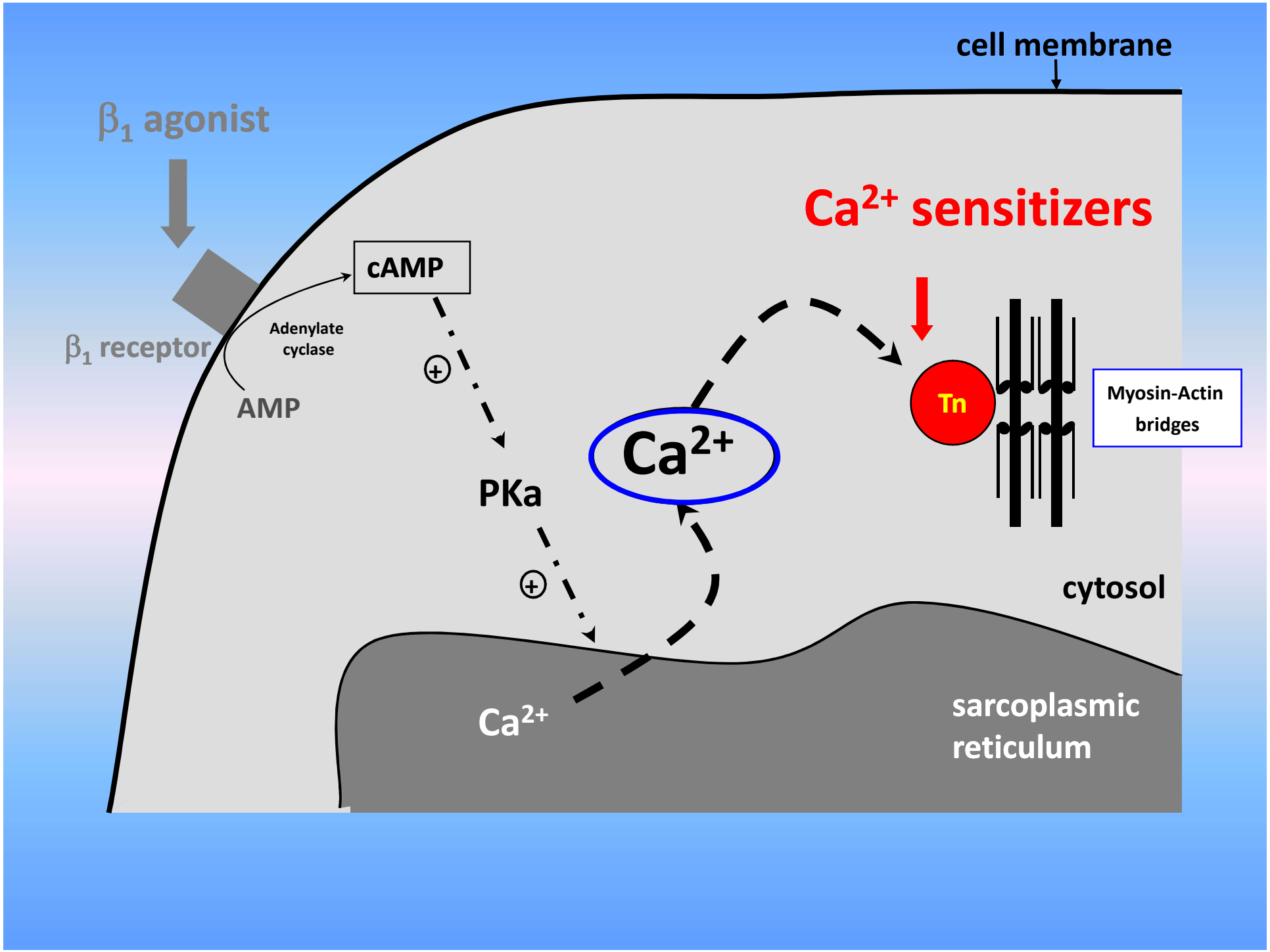


Treatment of sepsis-related cardiac dysfunction

Alternatives to dobutamine?

Norepinephrine?

Levosimendan?

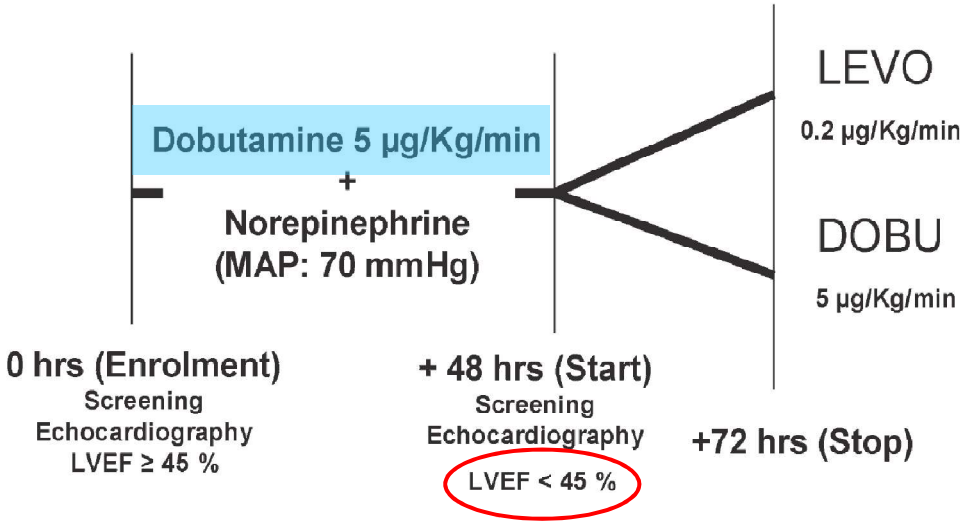

cell membrane
β1 agonist
β1 receptor
Adenylate cyclase
AMP
cAMP
PKa
Ca2+
Ca2+ sensitizers
Tn
Myosin-Actin bridges
cytosol
Ca2+
sarcoplasmic reticulum

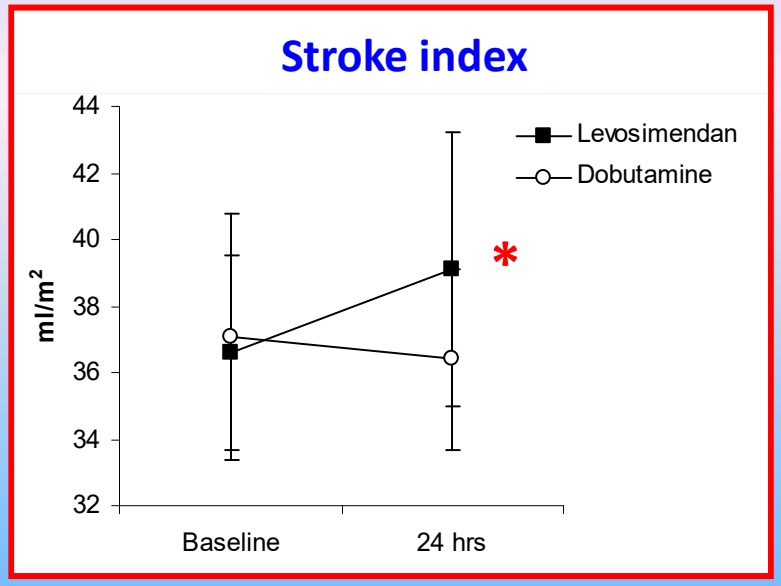
Intensive Care Med (2005) 31:638–644

ORIGINAL

Andrea Morelli
Stefano De Castro
Jean-Louis Teboul
Mervyn Singer
Monica Rocco
Giorgio Conti
Leonardo De Luca
Emanuele Di Angelantonio
Alessandra Orecchioni
Natesa G. Pandian
Paolo Pietropaoli

Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression





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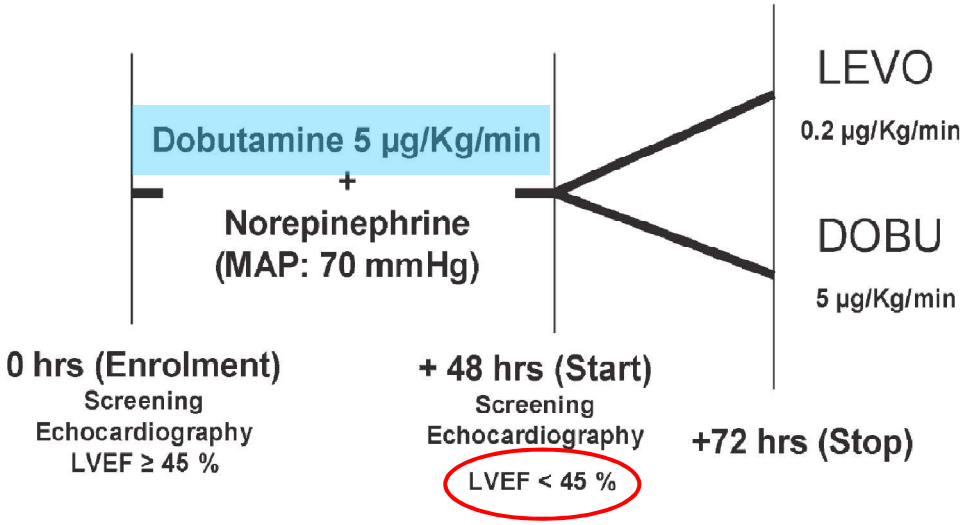
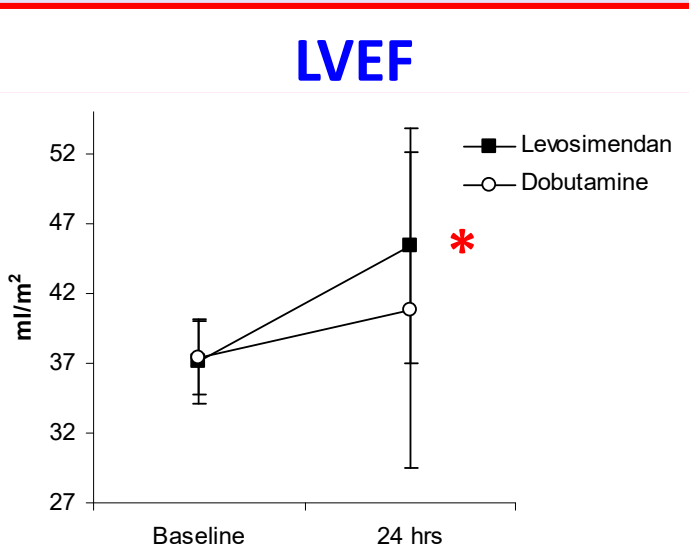
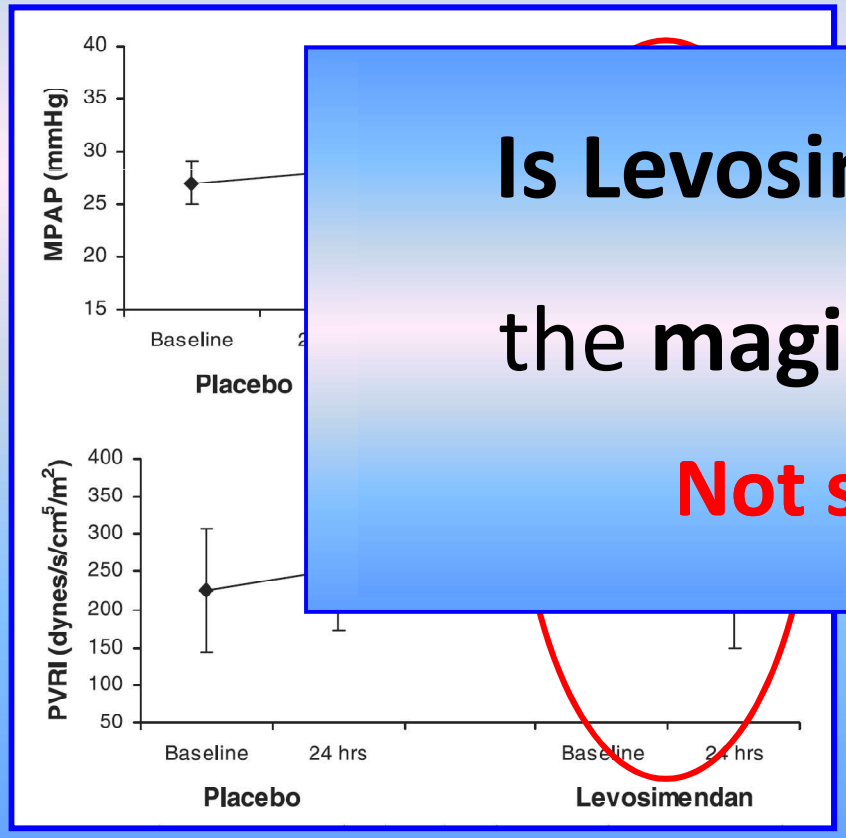




Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study*

Andrea Morelli, MD; Jean-Louis Teboul, MD, PhD; Salvatore Maurizio Maggiore, MD, PhD; Antoine Vieillard-Baron, MD; Monica Rocco, MD; Giorgio Conti, MD; Andrea De Gaetano, MD, PhD; Umberto Picchini, Dr in statistics; Alessandra Orecchioni, MD; Iacopo Carbone, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Martin Westphal, MD

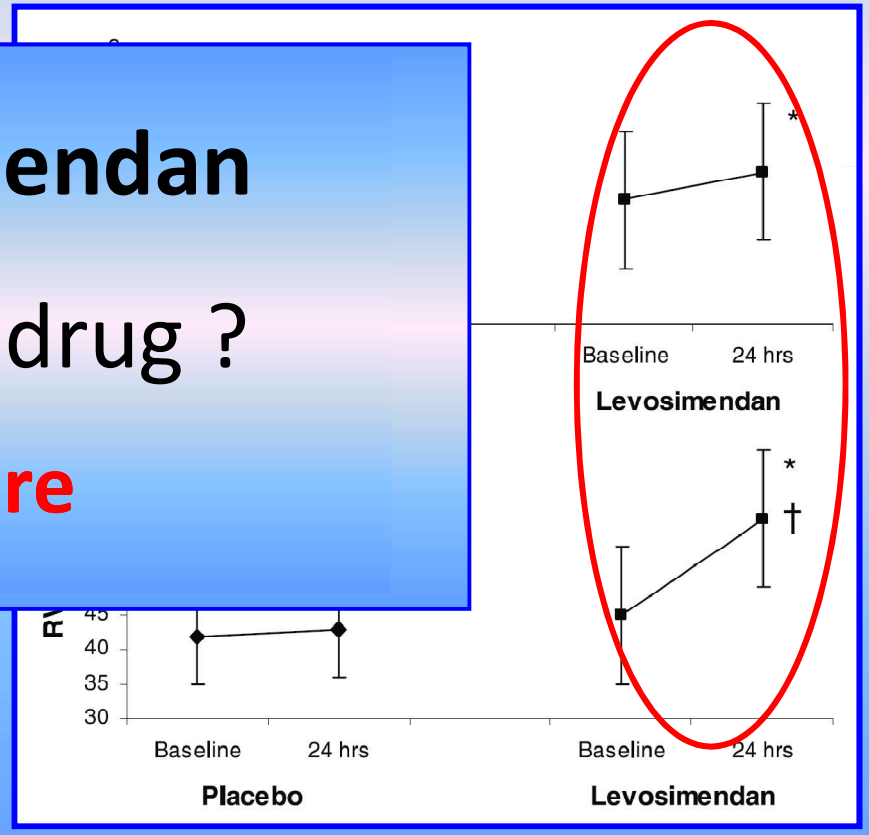
Crit Care Med 2006; 34:2287–2293



Is Levosimendan

the **magic** drug ?

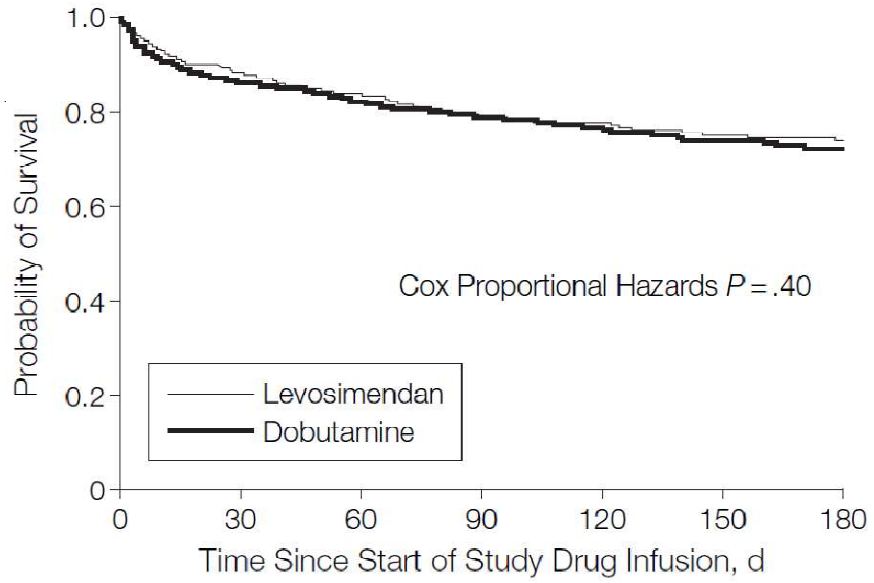
Not sure



Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

Alexandre Mebazaa, MD, PhD
Markku S. Nieminen, MD, PhD
Milton Packer, MD
Alain Cohen-Solal, MD, PhD
Franz X. Kleber, MD
Stuart J. Pocock, PhD
Roopal Thakkar, MD
Robert J. Padley, MD
Pentti Põder, MD, PhD
Matti Kivikko, MD, PhD
for the SURVIVE Investigators



Treatment of sepsis-related cardiac dysfunction

Alternatives to dobutamine?

- Make sure that the patient **is not** still **hypovolemic**

  → assess **fluid responsiveness**

  using dynamic indices of **preload responsiveness**

- Make sure that **hypotension** is **corrected**

In any case, before giving inotropes

شكرا

Thank you

Merci