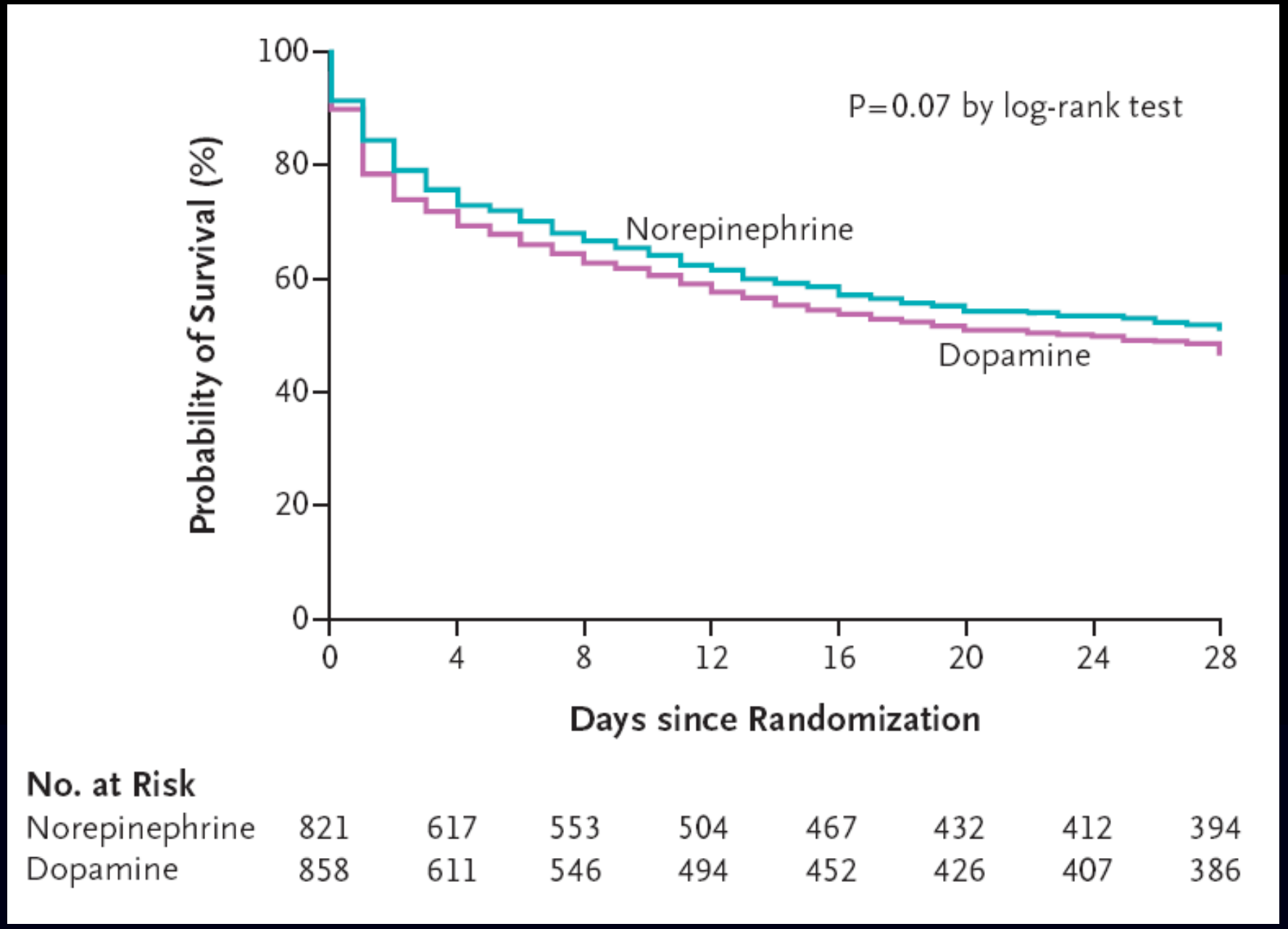
Quelle place pour la vasopressine et les bêta-bloquants?

Daniel De Backer

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

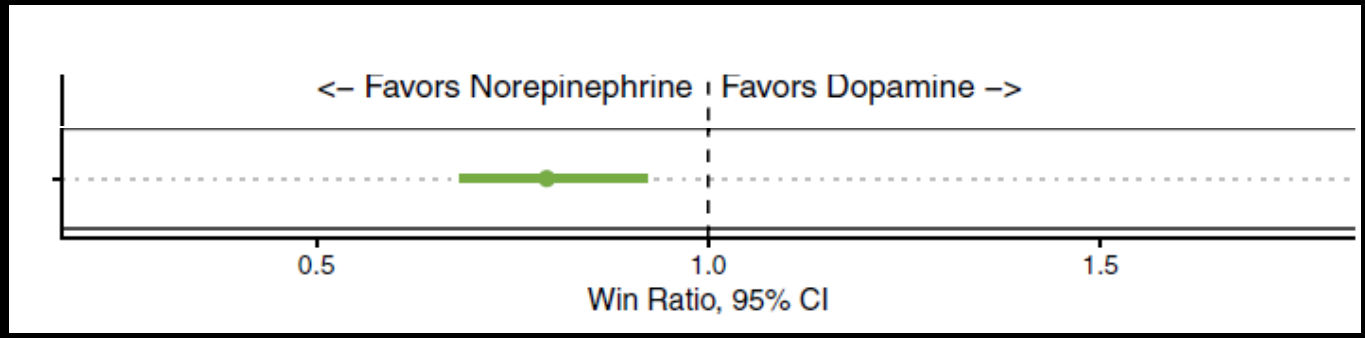
Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et al
NEJM 362: 779; 2010

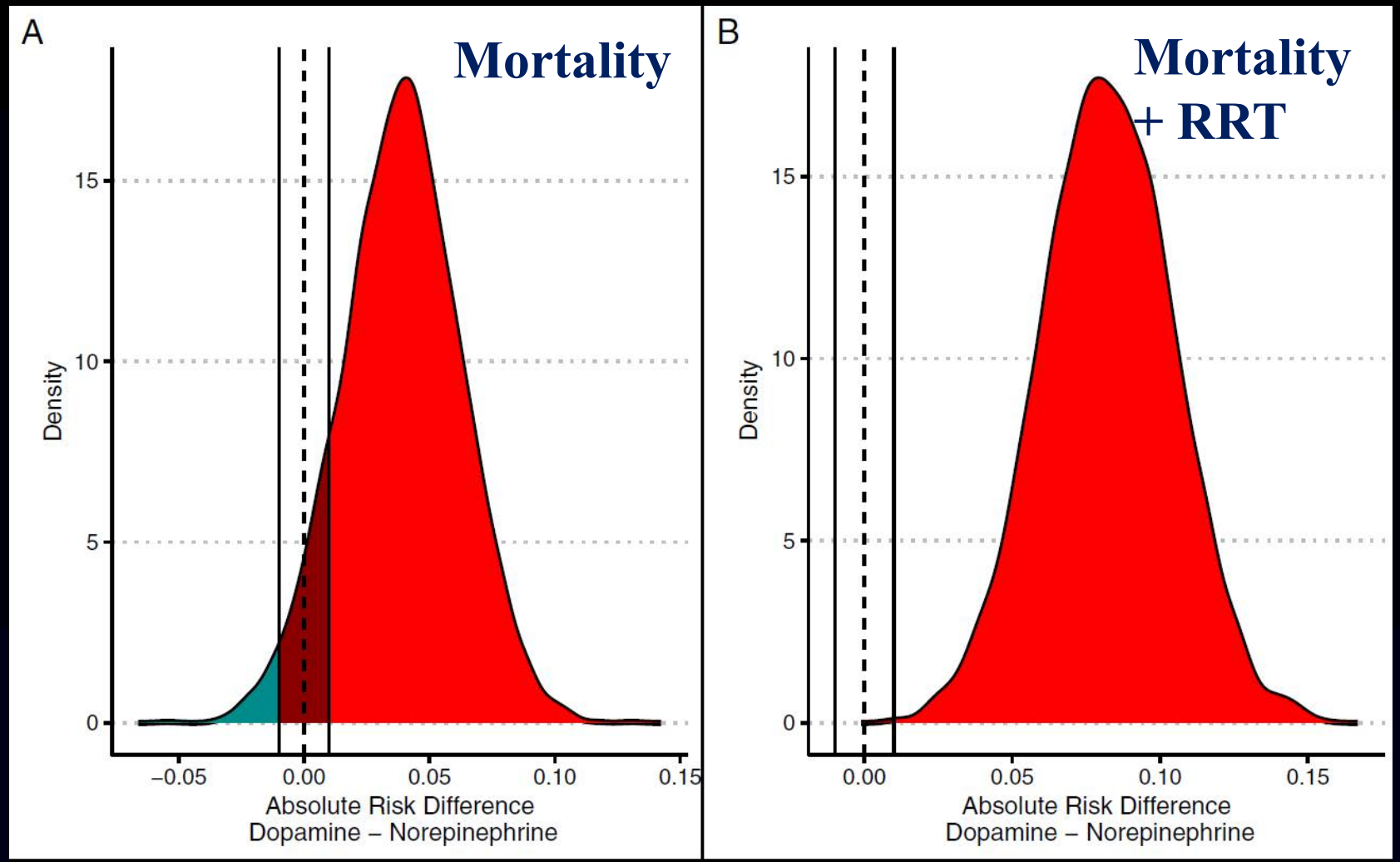


No. at Risk								
Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386

Exploration of different statistical approaches in the comparison of dopamine and norepinephrine in the treatment of shock: SOAP II



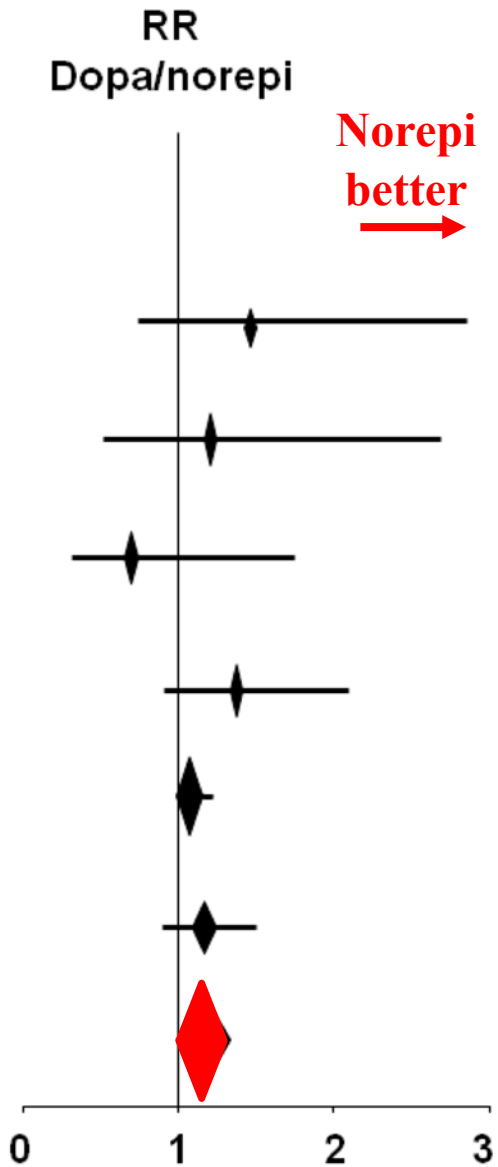
Zampieri F et al
Crit Care 2024



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]**

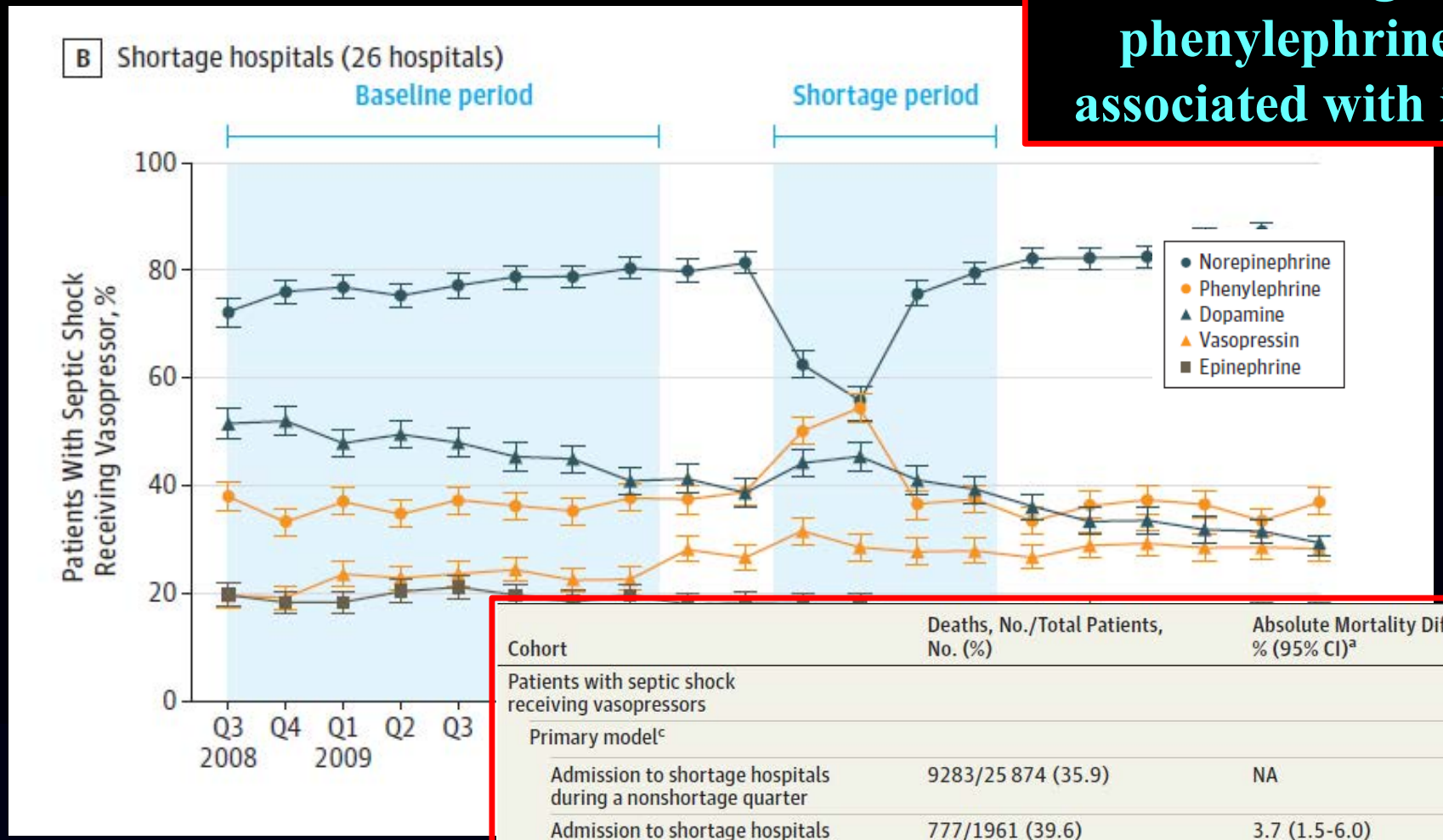


Association Between US Norepinephrine Shortage and Mortality Among Patients With Septic Shock

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



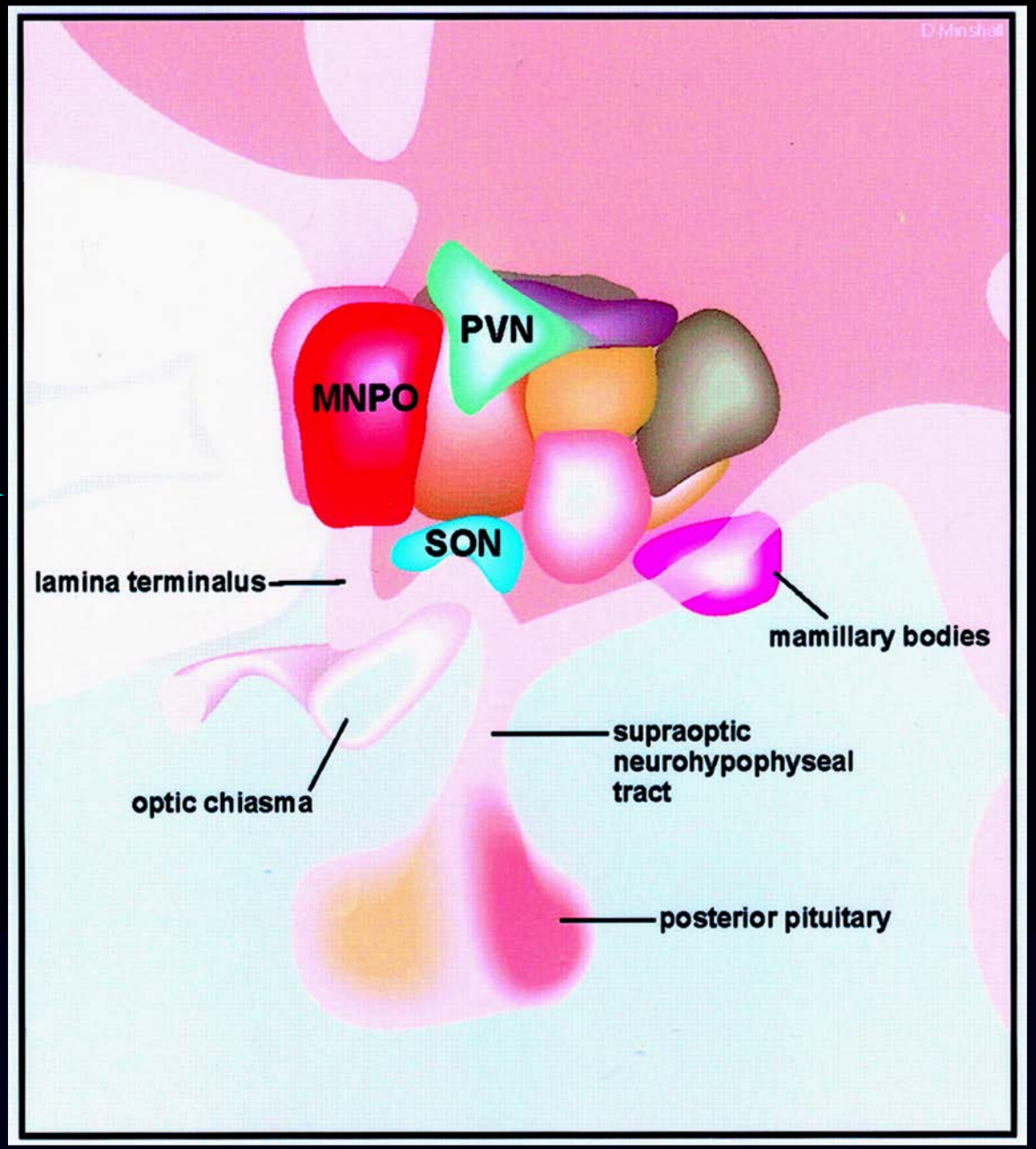
Cohort	Deaths, No./Total Patients, No. (%)	Absolute Mortality Difference, % (95% CI)[a]	Adjusted Odds Ratio (95% CI)[b]	*P* Value
Patients with septic shock receiving vasopressors				
Primary model[c]				
Admission to shortage hospitals during a nonshortage quarter	9283/25 874 (35.9)	NA	1 [Reference]	
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


Vasopressin as an alternative?

VASOPRESSIN

Holmes et al
Chest 120:989;2001

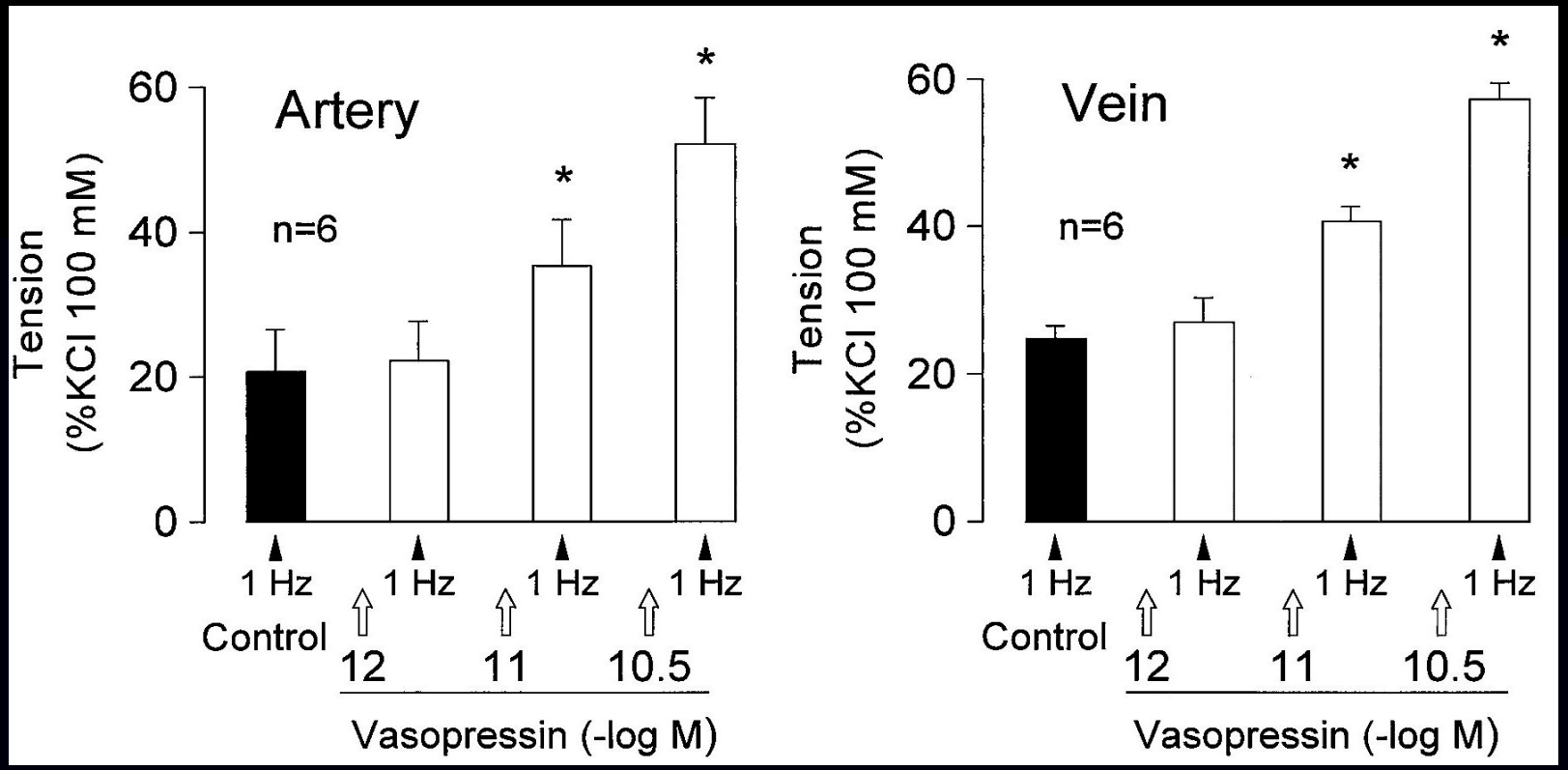
- Nonapeptide hormone synthetized in supraoptic and paraventricular nuclei of the hypothalamus
- Transported and stored in the posterior pituitary



Physiologic effects of vasopressin:

Segarra et al
J Pharm Exp Ther
286: 1315; 1998

Pressure regulation



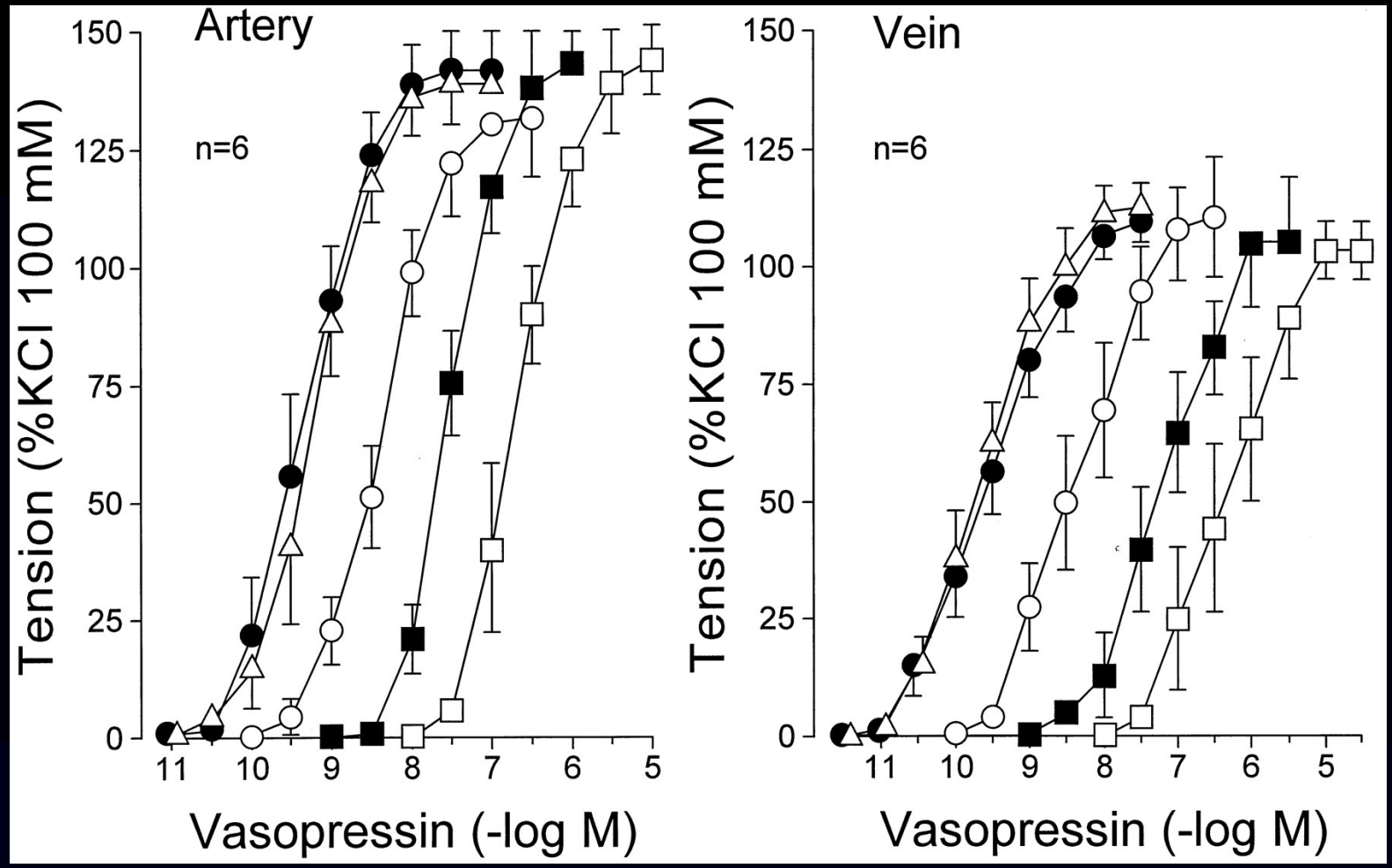
Vasopressin induces arterial and venous constriction

DDB USI

Physiologic effects of vasopressin:

Segarra et al
J Pharm Exp Ther
286: 1315; 1998

V1 receptor receptors are implicated in vasopressin induced vasoconstriction

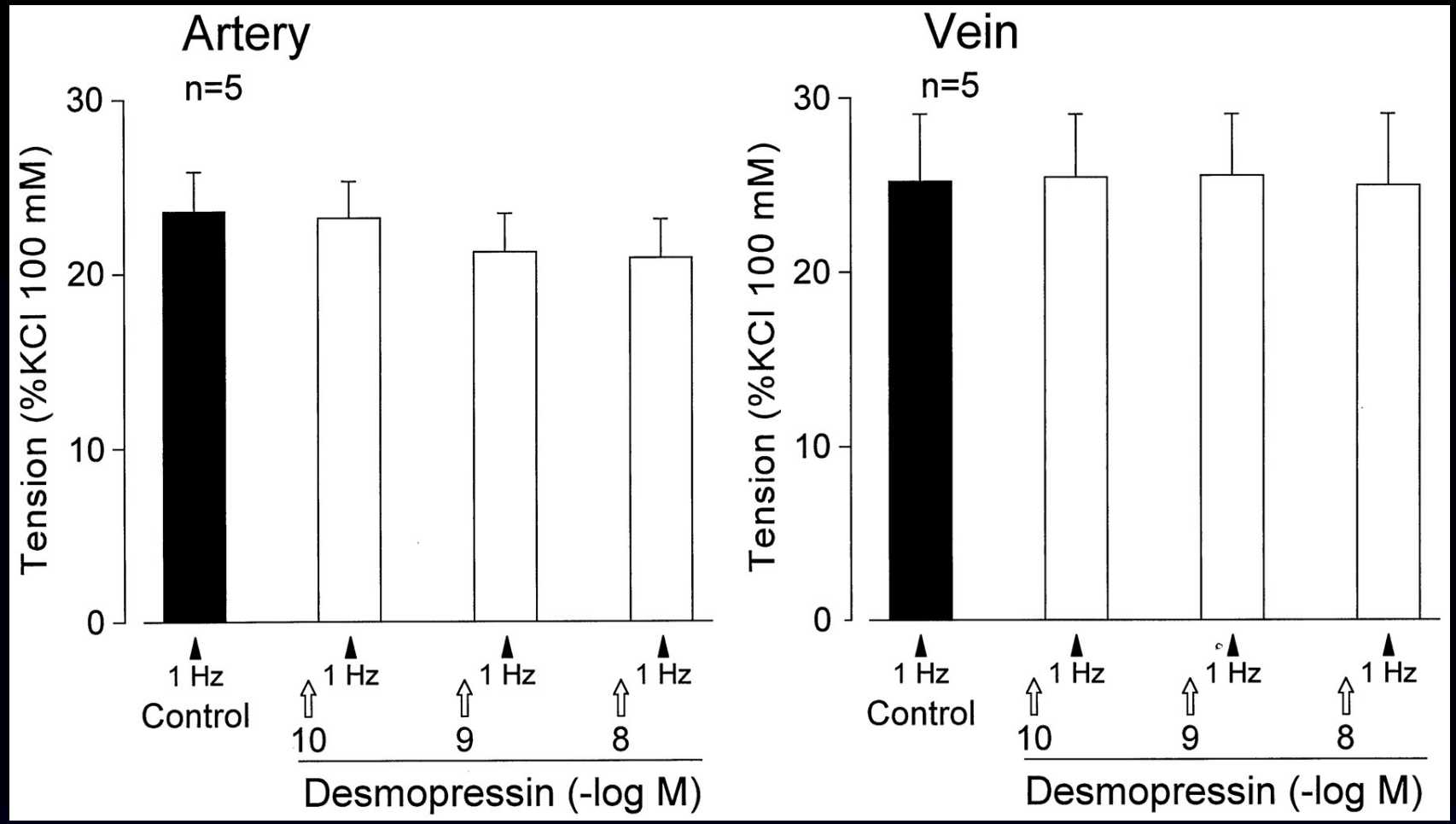


ctrl ==> increasing dose of V1 antagonist

DDB USI

Physiologic effects of vasopressin:

Segarra et al
J Pharm Exp Ther
286: 1315; 1998



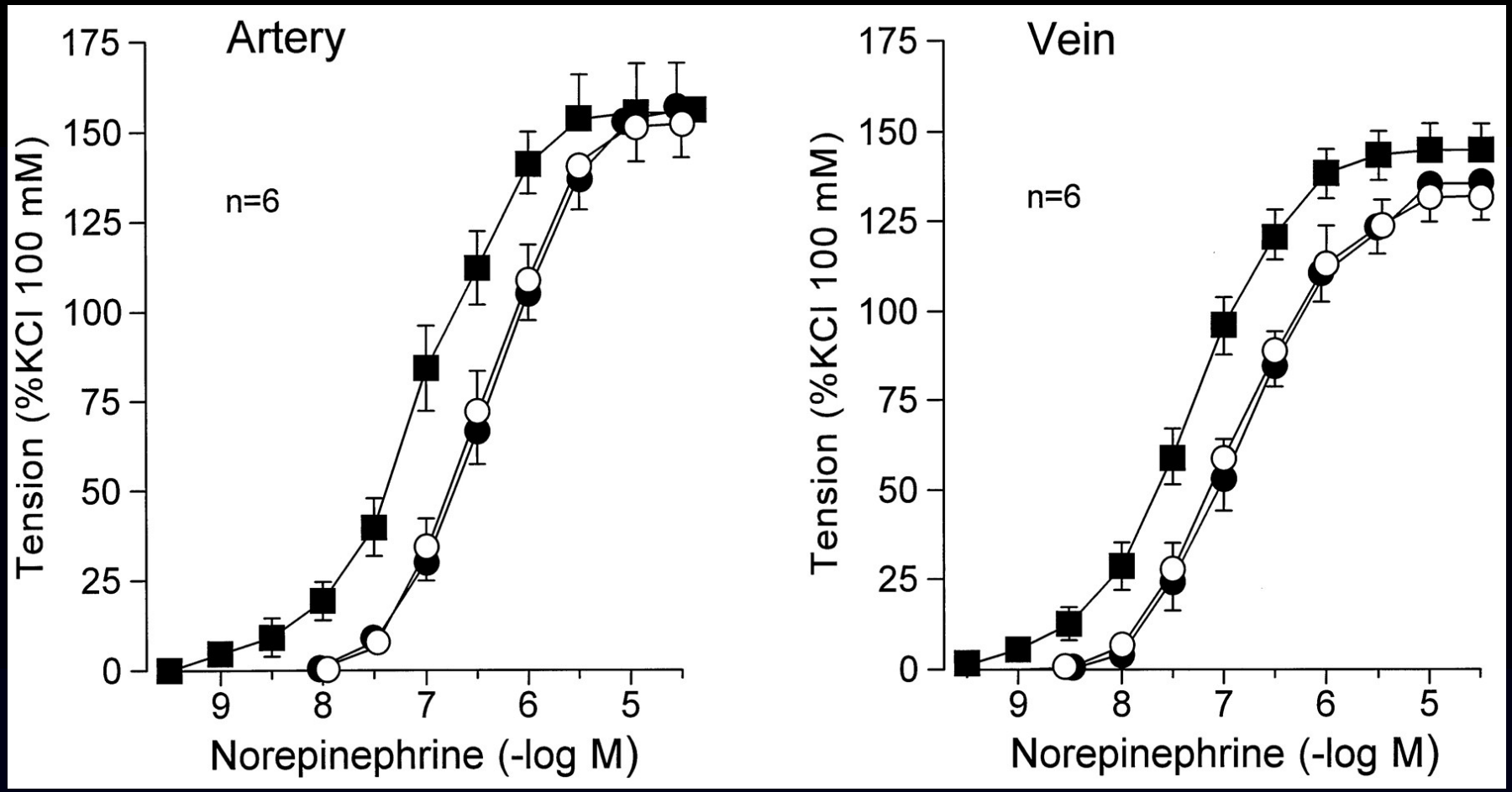
V1 but not V2 receptor stimulation induces arterial and venous constriction

DDB USI

Physiologic effects of vasopressin:

V1 receptor stimulation potentiates the pressor effects of alpha adrenergic agents

Segarra et al
J Pharm Exp Ther
286: 1315; 1998



ctrl Vasopressin antag vasopressin

DDB USI

Physiologic effects of vasopressin:

- **V1 receptor => vasoconstriction**
  - **vascular smooth muscle**
  - **kidney, platelets, uterus**
- **V2 receptor**
  - **renal collecting duct (cAMP)**
  - **=> antidiuretic action**
  - **endothelium => dilation (NO)**
  - **platelets => aggregation**
- **V3 receptor**
  - **pituitary => ACTH release**
- **OTR receptor**
  - **uterus => vasoconstriction**
  - **endothelium => vasodilation (NO)**

VASOPRESSIN

Vasopressin deficiency in (septic) shock

- **Depletion of neurohypophysal stores**
  excessive stimulation (hypoxia, acidosis, hypotension)
  only 20% VP pool can be released

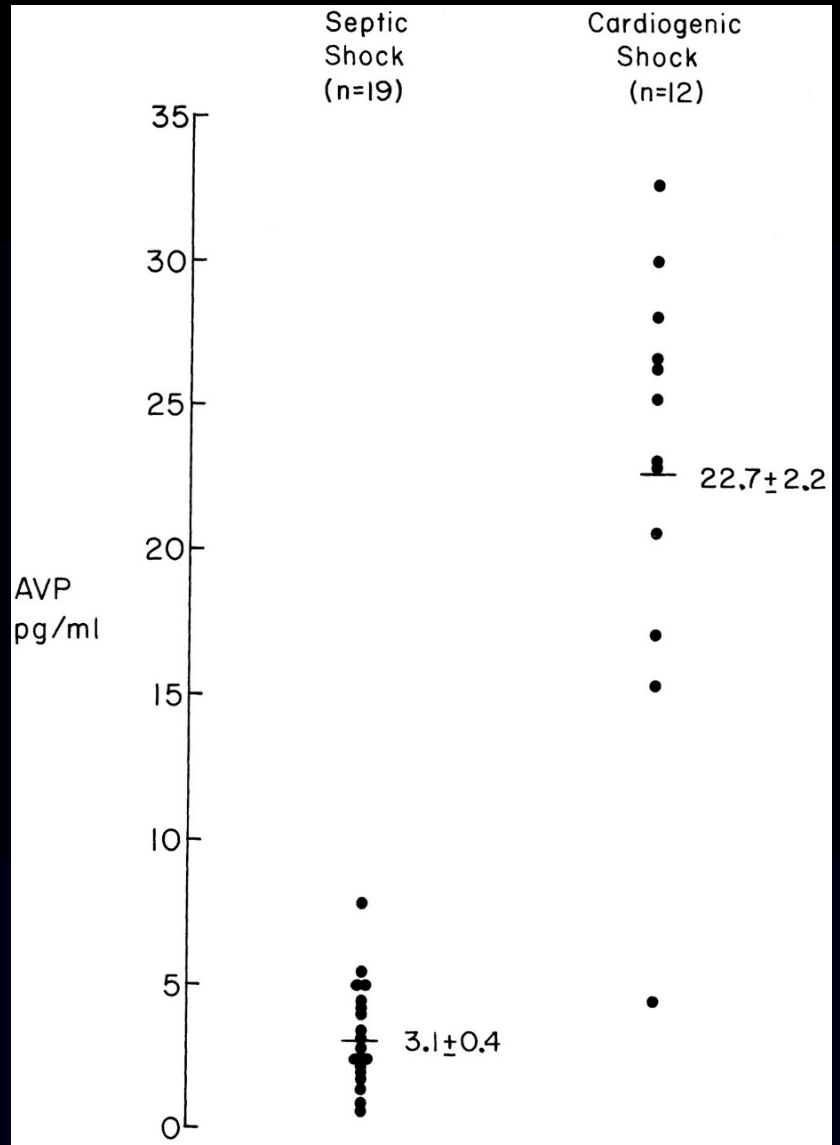
- **Decreased stimulation of VP release**
  impaired autonomic reflexes
  inhibition by atrial stretch receptor (volume loading, mech vent)

- **Inhibition of VP release**
  high NO and norepinephrine levels inhibit VP release

VASOPRESSIN

Vasopressin deficiency in septic shock

Landry et al
Circ 95:1122;1997

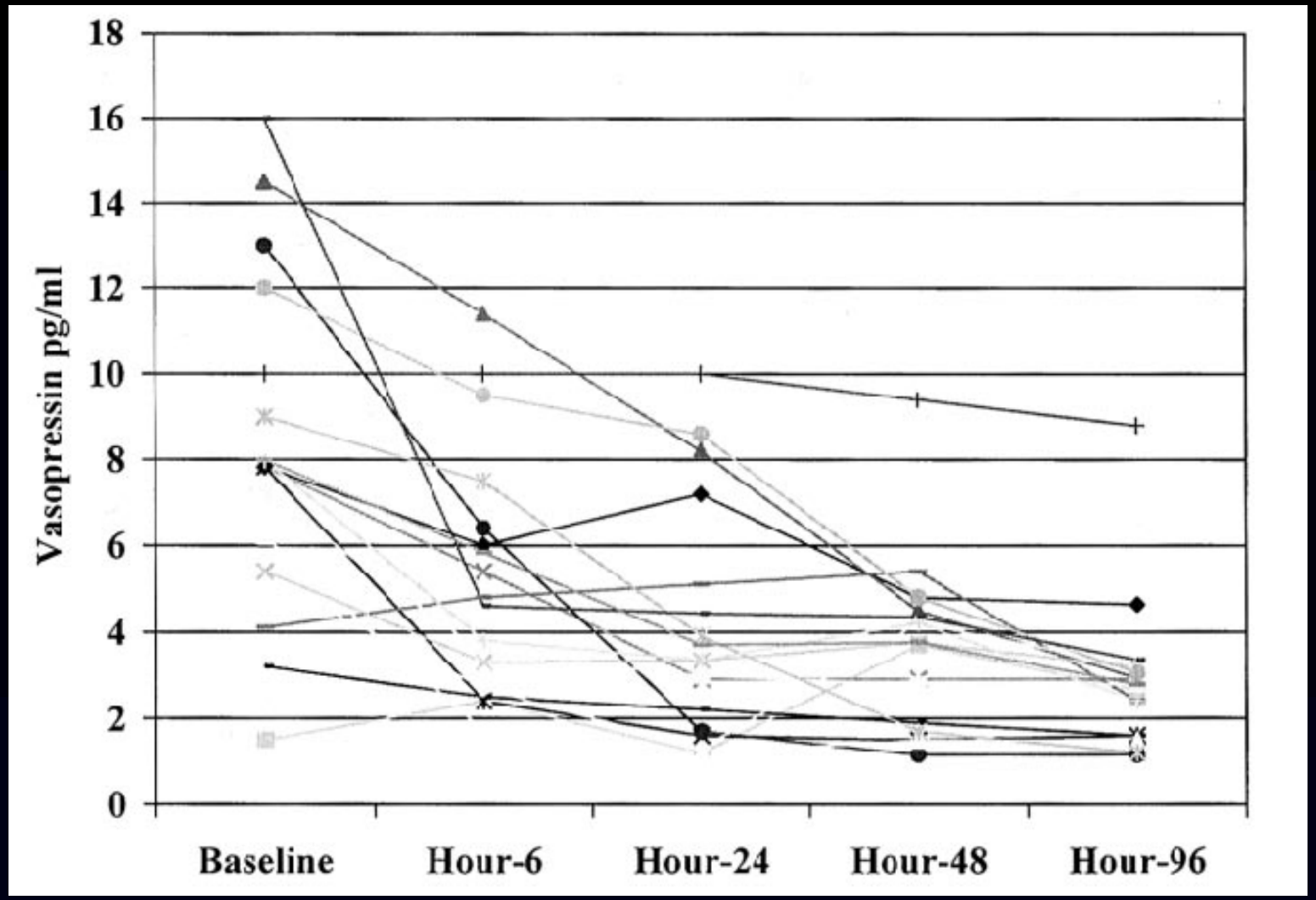


DDB USI

Vasopressin levels in septic shock

Sharshar et al
CCM 31:1752;2003

VP levels decrease with time



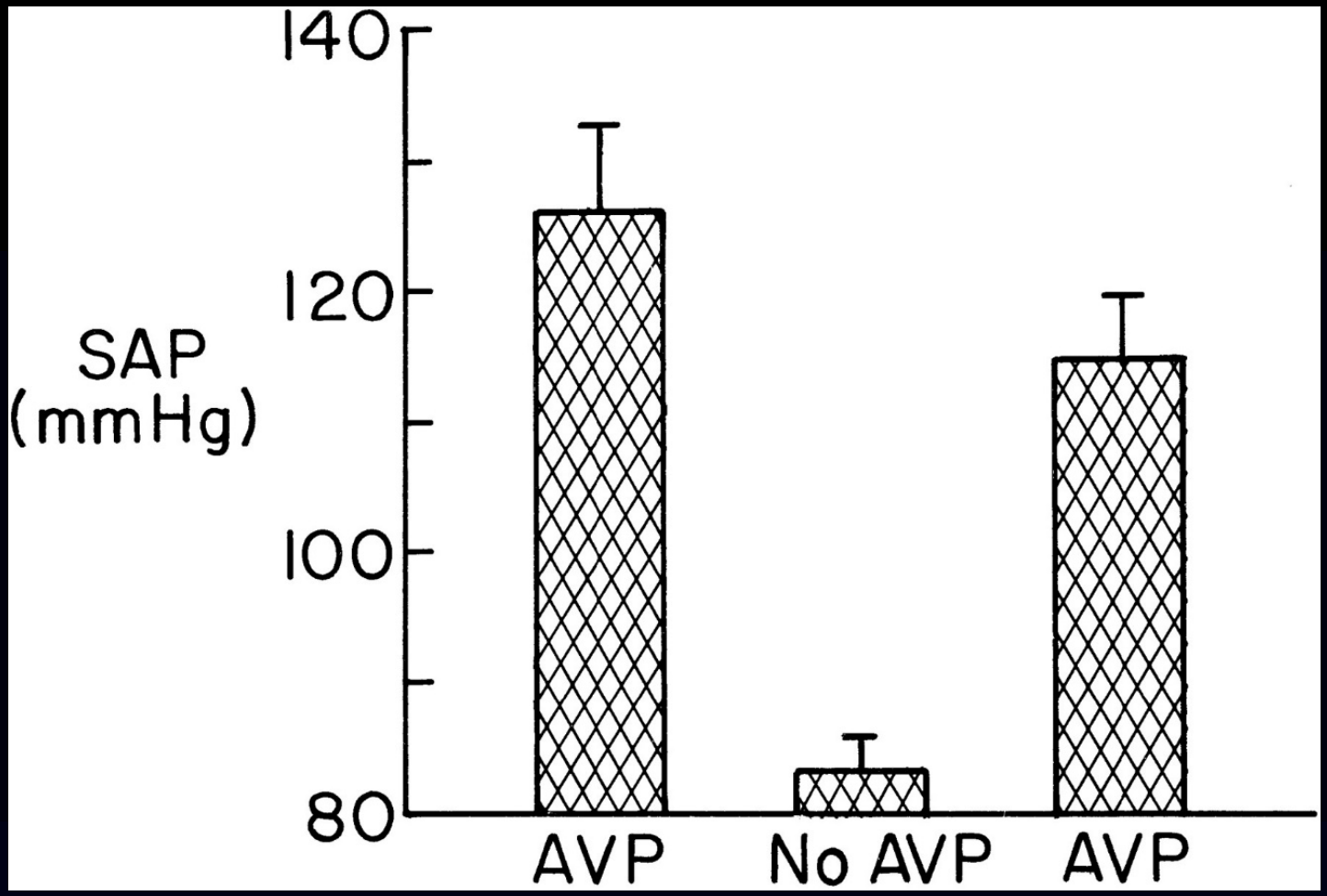
Septic shock n=18

DDB USI

VASOPRESSIN

Vasopressin deficiency in septic shock

Landry et al
Circ 95:1122;1997

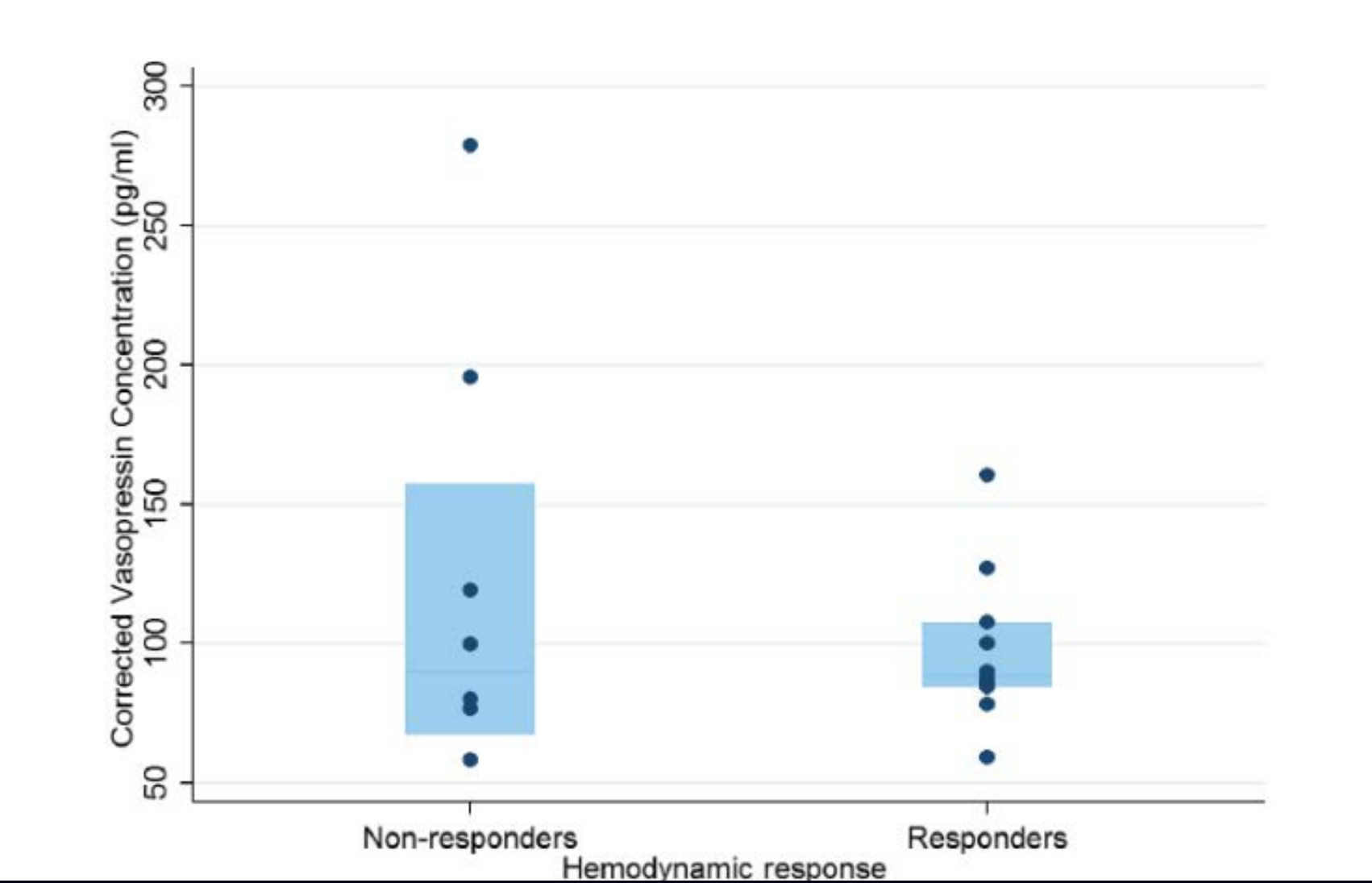


=> restoration of blood pressor by the administration of a small dose of vasopressin (0.04 u/min) normalizing VP levels

DDB USI

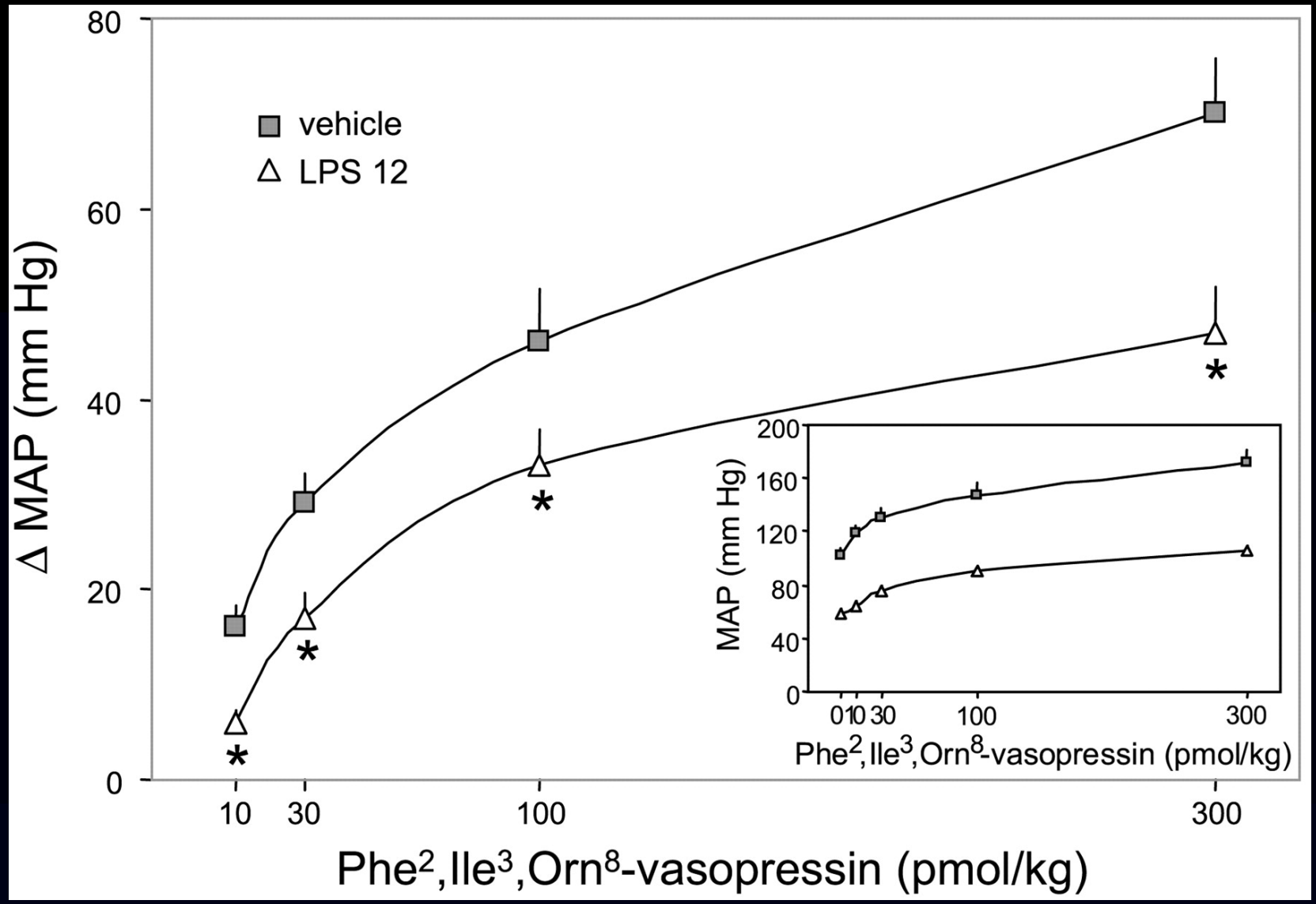
Vasopressin Plasma Concentrations Are Not Associated with Hemodynamic Response to Exogenous Vasopressin for Septic Shock

Yerke J et al
Pharmacotherapy
2020



DOWN REGULATION OF VASOPRESSIN RECEPTORS

Bucher et al
AJP 282:R979;2002

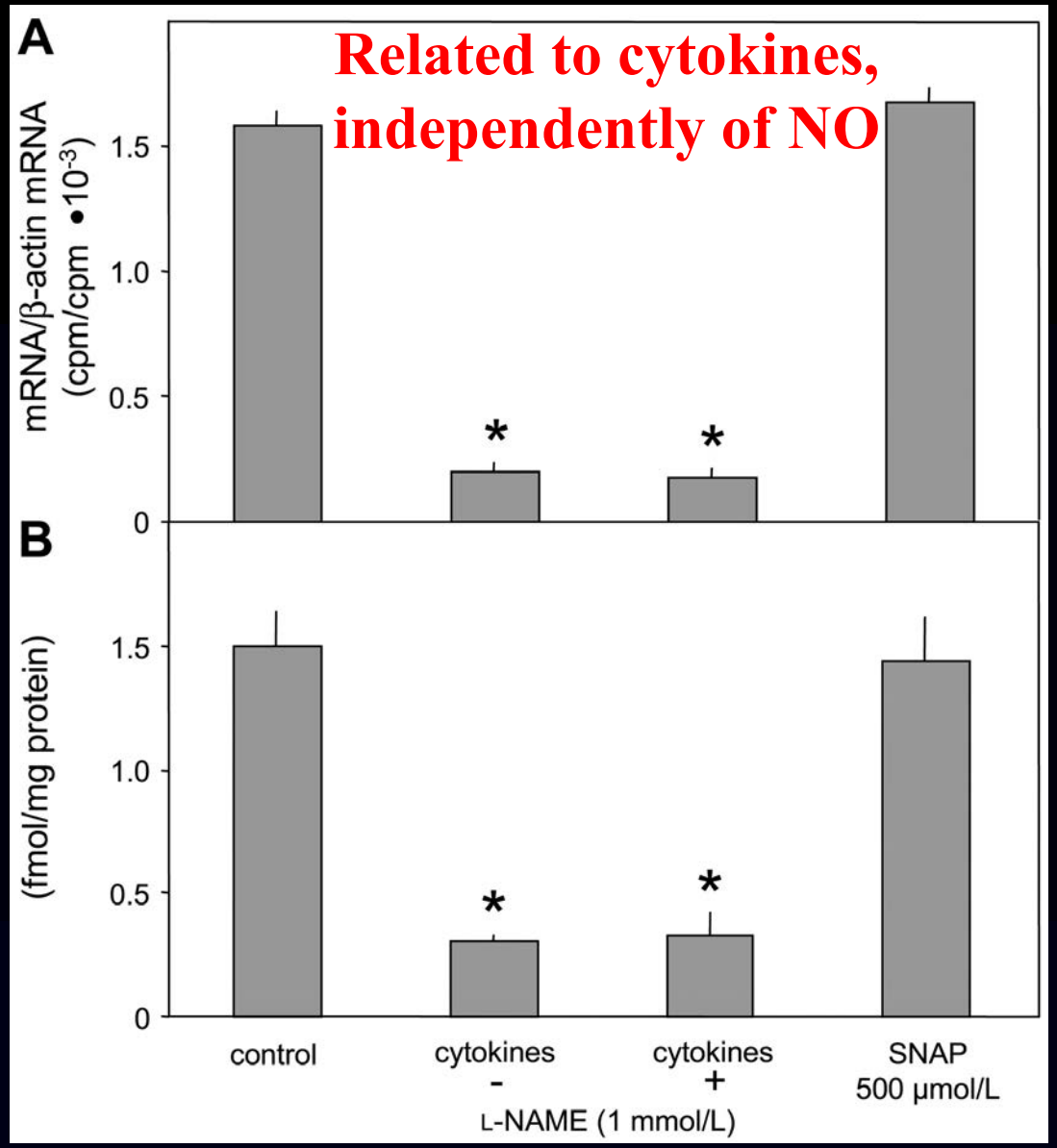


=> decreased sensibility to vasopressin in sepsis

DDB USI

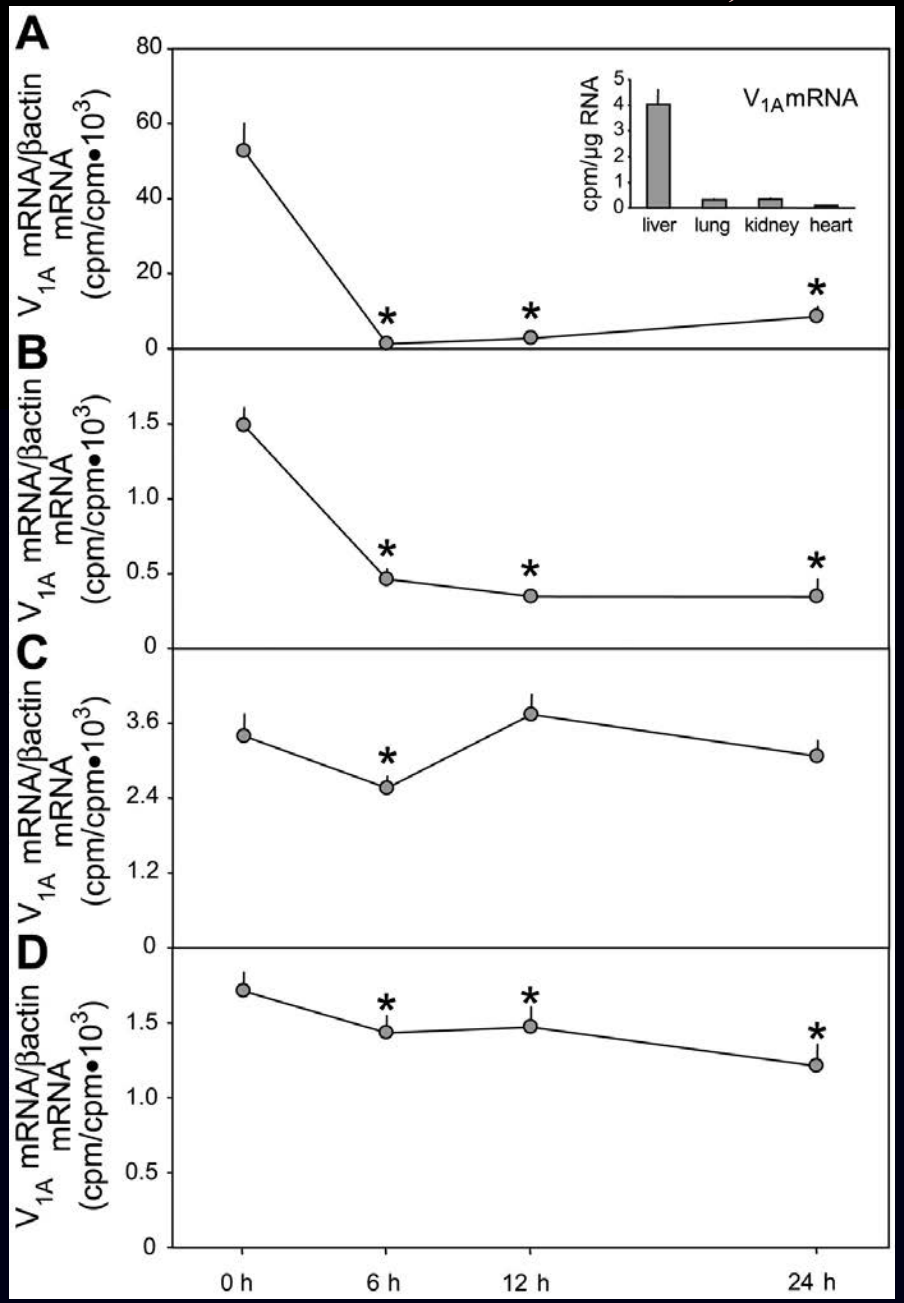
DOWN REGULATION OF VASOPRESSIN RECEPTORS

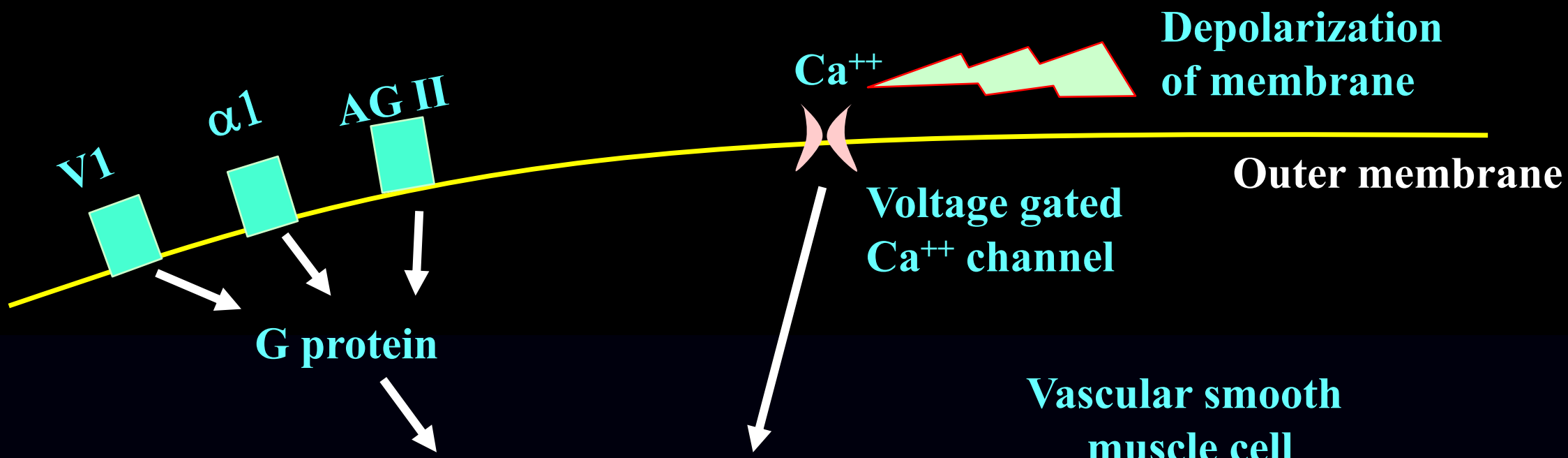
Bucher et al
AJP 282:R979;2002



Related to cytokines, independently of NO

Rapid decrease in V1 receptor mRNA transcription in various organs





Vascular smooth muscle cell

↑ intracellular calcium in vascular smooth muscle cells

Vasoconstriction

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

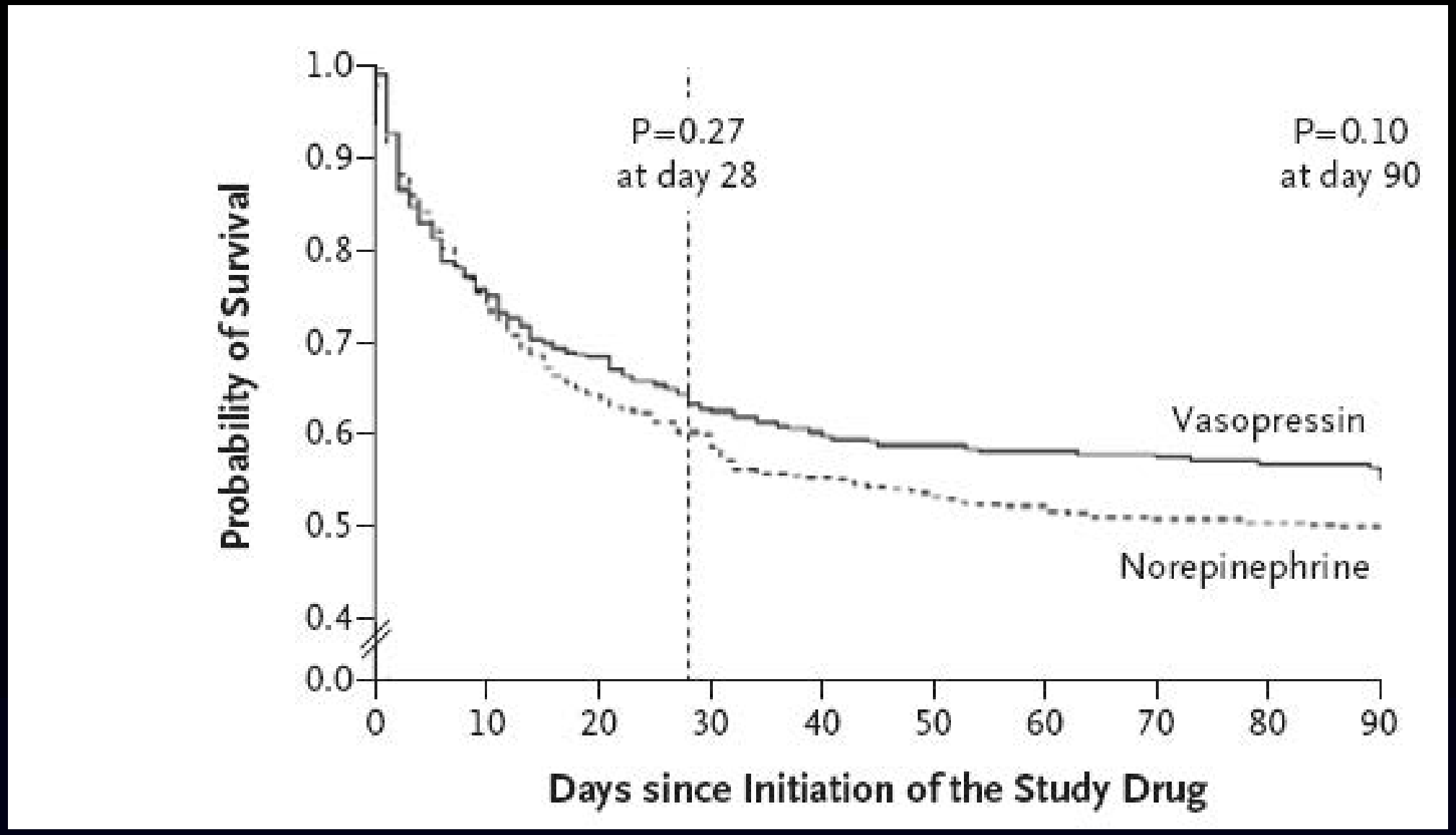
Evans et al
ICM 2021
CCM 2021

MODERATE

38 For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine.

VASST

Russell et al
NEJM 358:877;2008

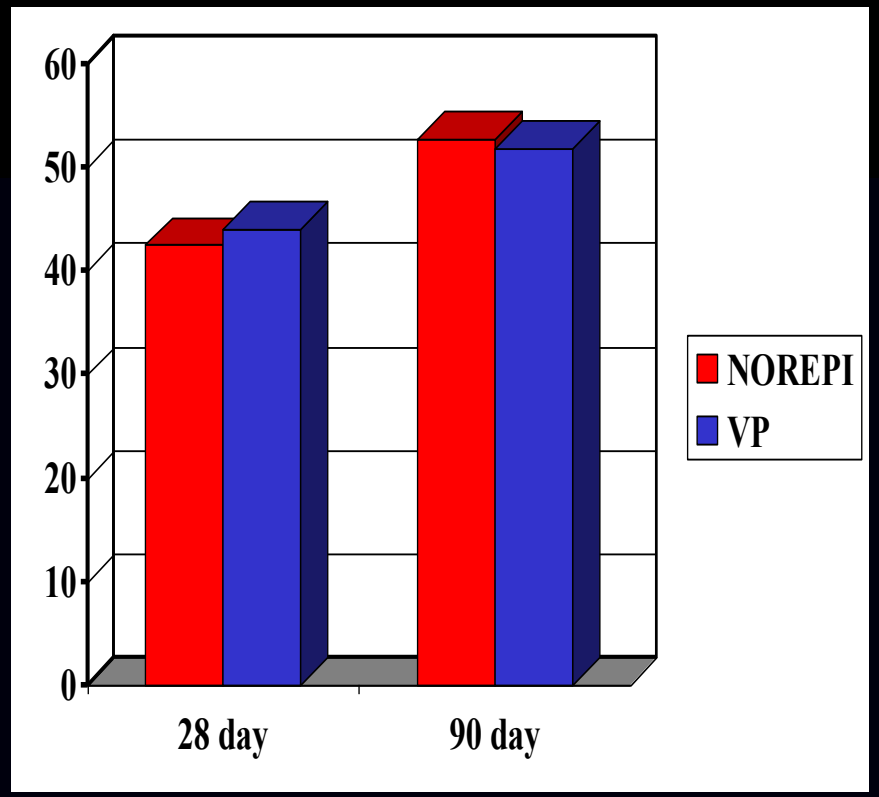


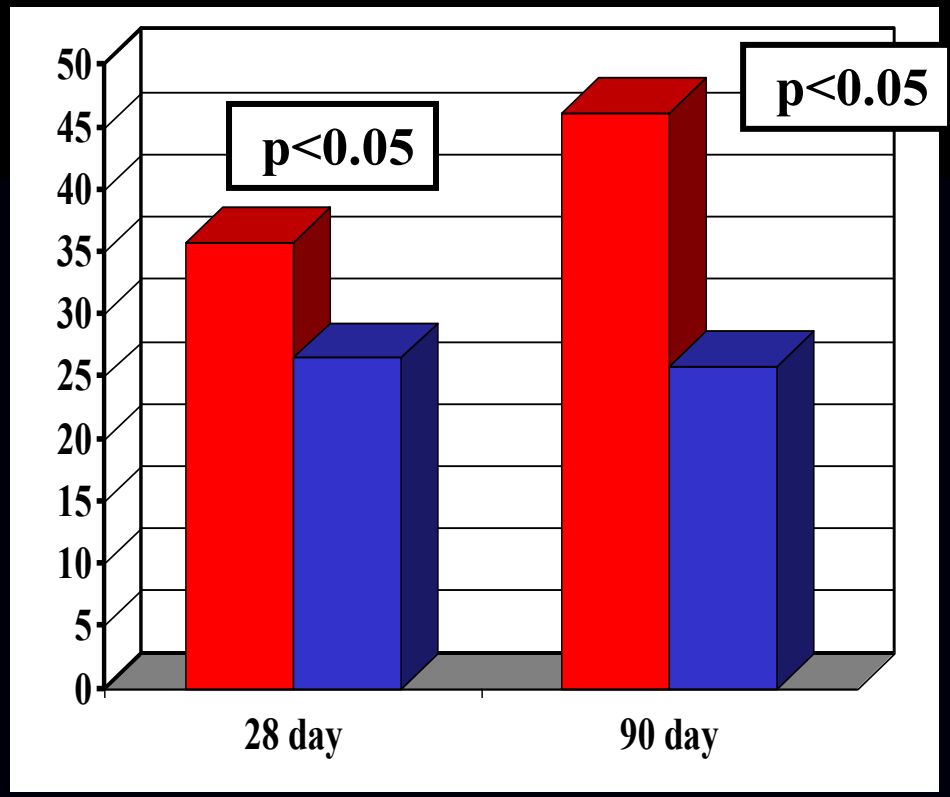
802 septic shock pts

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)

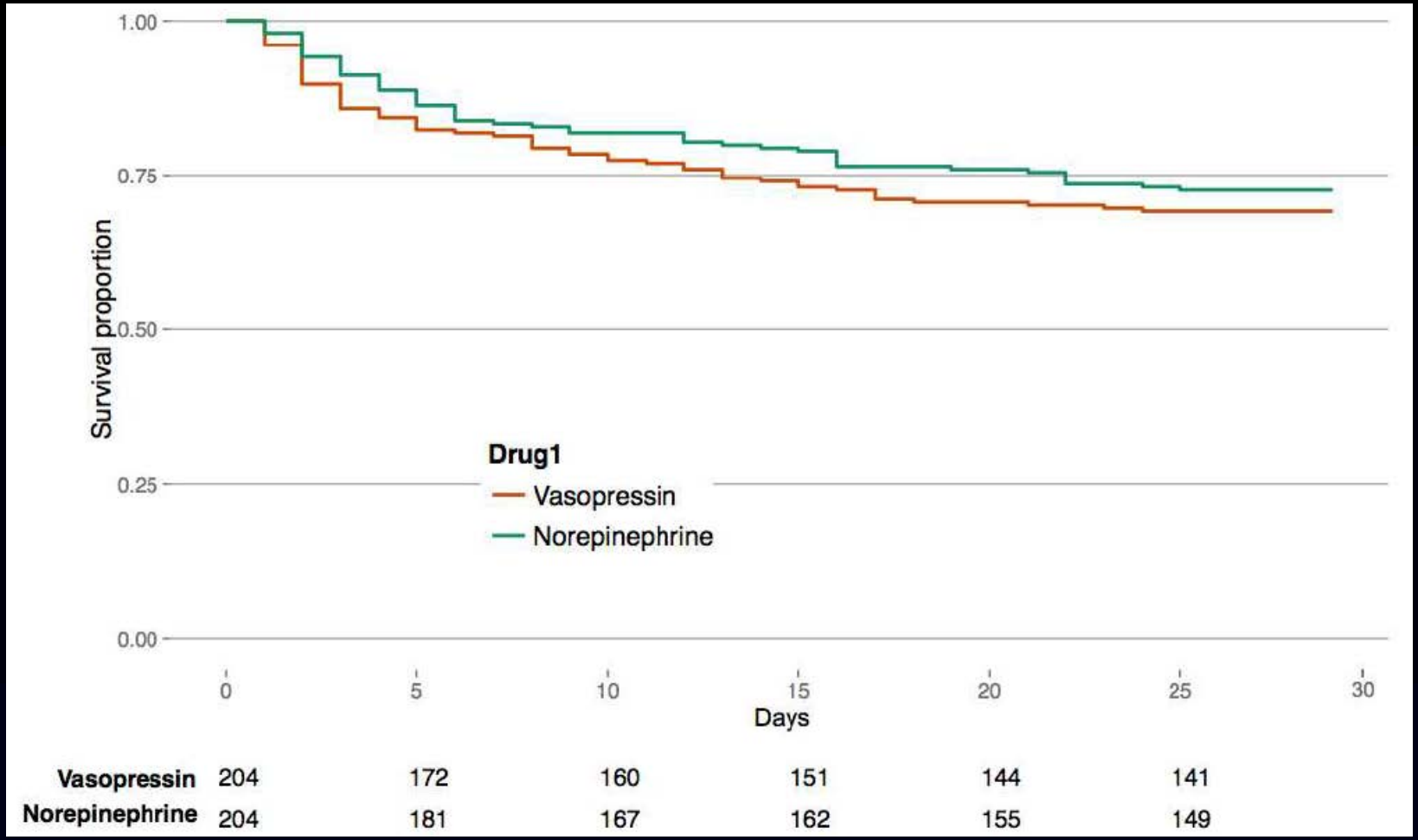
JAMA | Original Investigation

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

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

Gordon et al JAMA 2016



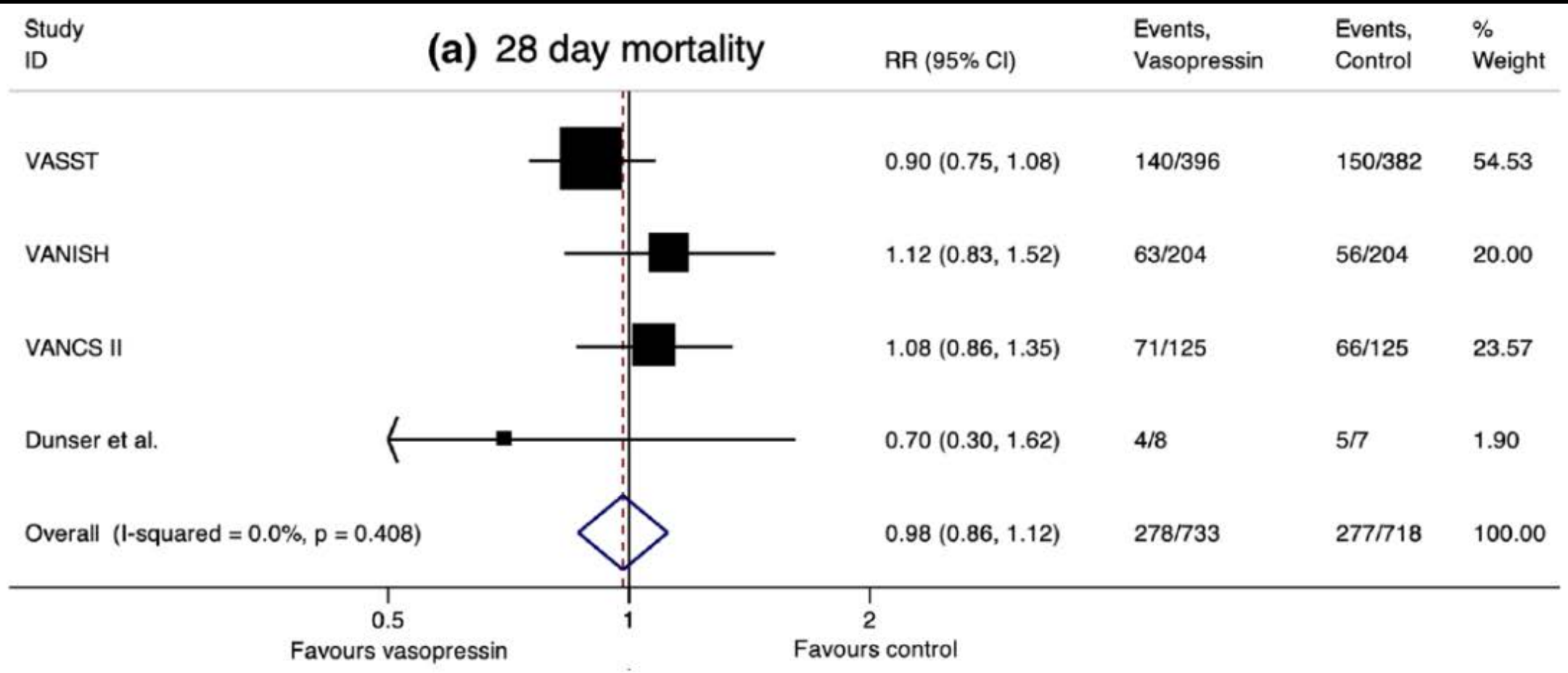
Norepi dose at randomization: 0.16 [0.10-0.31] mcg/kg.min

SYSTEMATIC REVIEW

Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials

Myura Nagendran[1], James A. Russell[2], Keith R. Walley[2], Stephen J. Brett[1,3], Gavin D. Perkins[4], Ludhmila Hajjar[5], Alexina J. Mason[6], Deborah Ashby[7] and Anthony C. Gordon[1,3*]

ICM 2019



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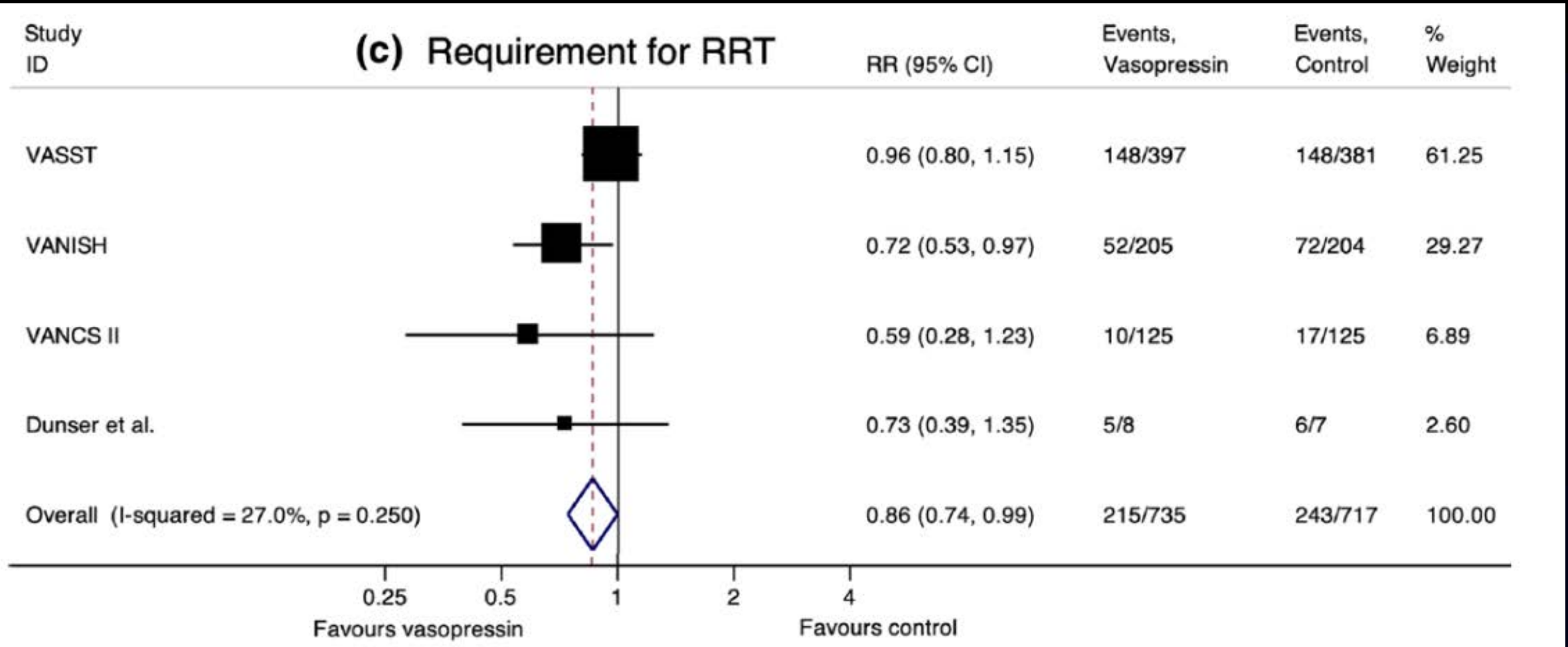


JAMA | Original Investigation

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

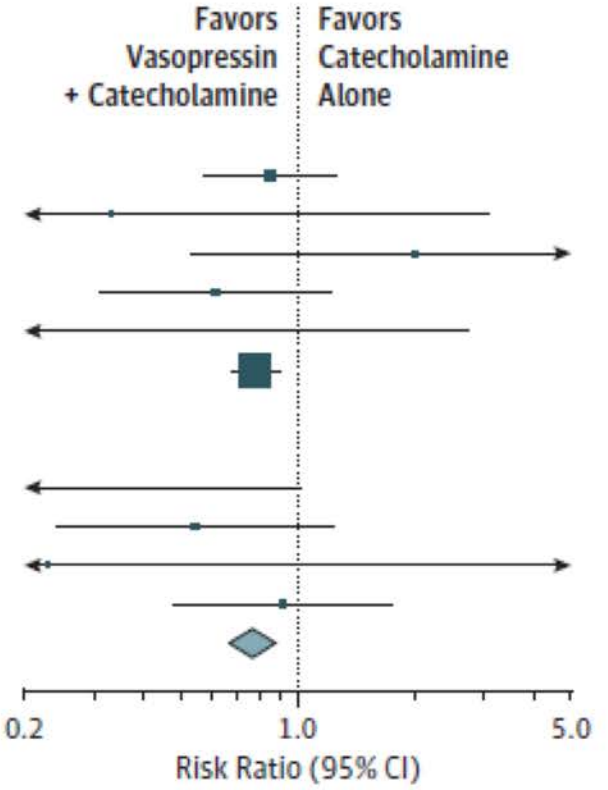
23 studies

A Atrial fibrillation

Source	Vasopressin + Catecholamine[a] No. With Events	Vasopressin + Catecholamine[a] Total No. of Patients	Catecholamine Alone No. With Events	Catecholamine Alone Total No. of Patients	Risk Ratio (95% CI)	Weight, %
Abdullah et al,[25] 2012	0	17	0	17	Not estimable	
Capoletto et al,[38] 2017	34	125	40	125	0.85 (0.58-1.25)	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: $z = 3.79$ ($P < .001$)



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

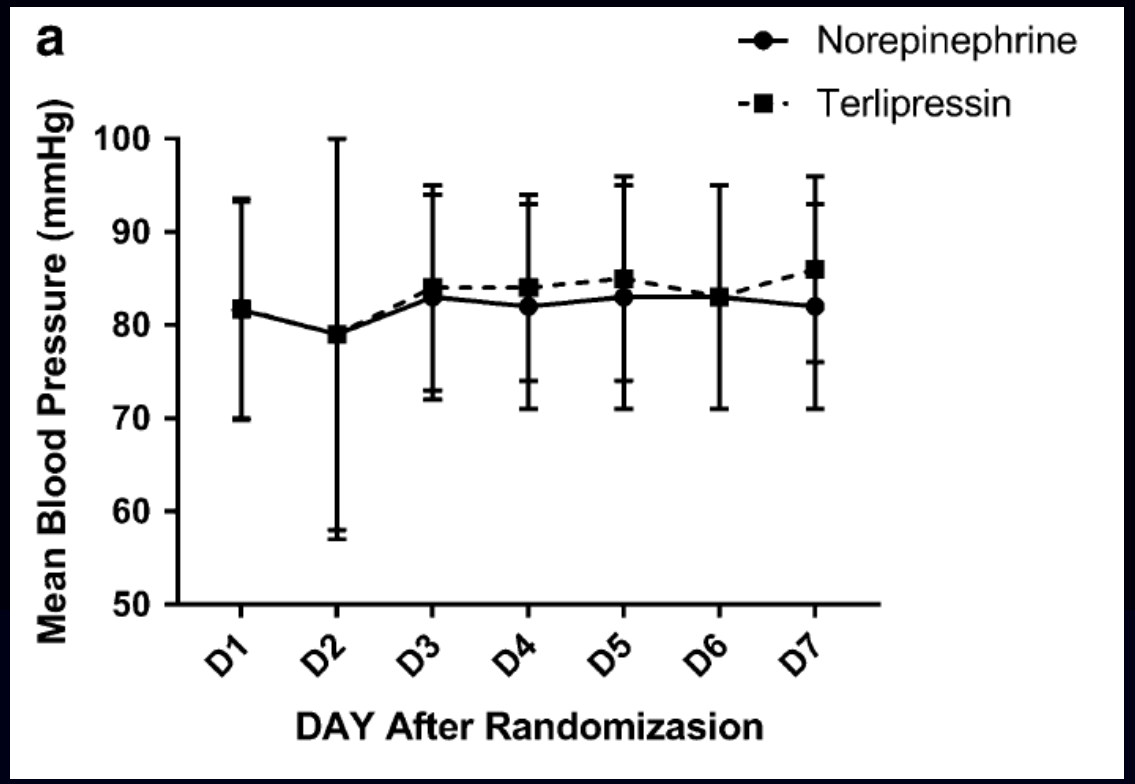
Morelli A Crit Care 2009
Liu Z et al ICM 2018

ORIGINAL

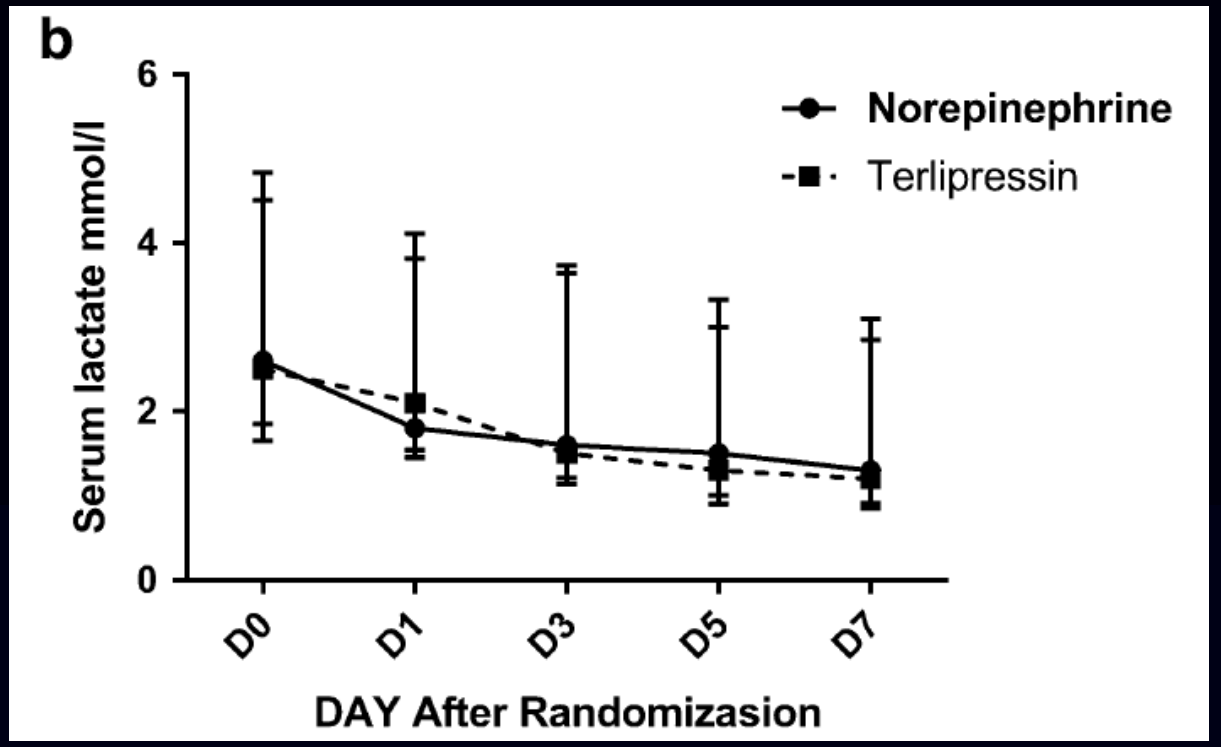
Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

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



Evans et al
ICM 2021
CCM 2021

?

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Liu Z et al
ICM 2018

N=617

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

Variable *N* (%)	Norepinephrine group (*n* = 266)	Terlipressin group (*n* = 260)	*p*
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Overall	31 (11.65%)	78 (30%)	< 0.01

Liu Z et al
ICM 2018

of 65–75 mmHg [367]. The primary outcome was death from any cause at 28 days. The 28-day mortality in the two groups was 40% for terlipressin and 38% for norepinephrine (OR 0.93; 95% CI 0.55–1.56, $p = 0.80$), and there were no differences in SOFA score at day 7 or vasopressor free days. More patients who received terlipressin had serious adverse events; 33 of 260 (12%) patients experienced digital ischaemia after receiving terlipressin, versus only one patient who received norepinephrine ($p < 0.0001$); diarrhea was also more common in the terlipressin group (2.7% versus 0.35%, $p = 0.037$). There were three cases of mesenteric ischae
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Any difference between vasopressin and terlipressin?

Evans L et al
ICM 2021
CCM 2021

Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials **ICM 2019**

Myura Nagendran[1], James A. Russell[2], Keith R. Walley[2], Stephen J. Brett[1,3], Gavin D. Perkins[4], Ludhm
Alexina J. Mason[6], Deborah Ashby[7] and Anthony C. Gordon[1,3*]

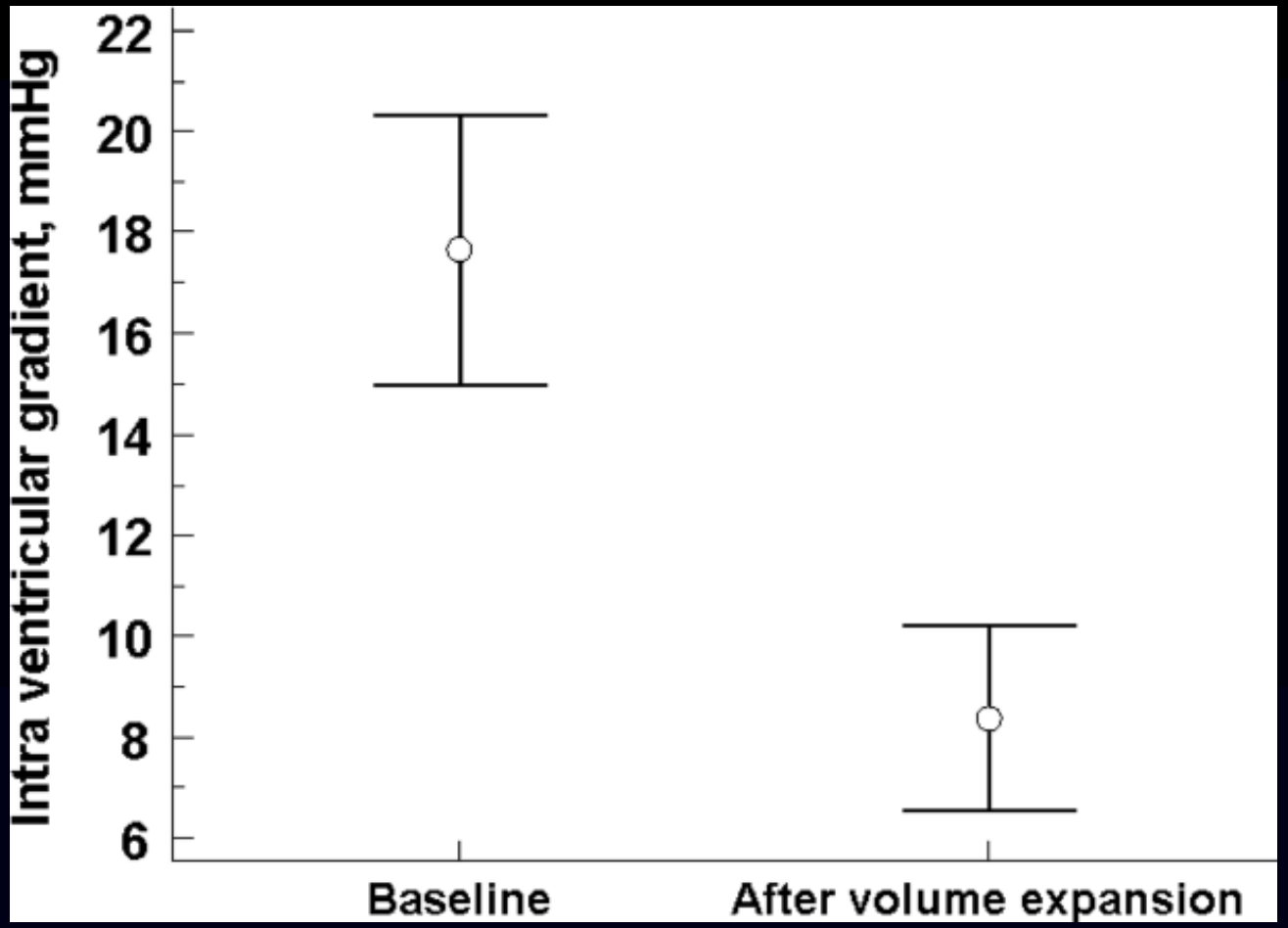
Outcome	Vasopressin	Norepinephrine	ARD[a] (95% CI)
Serious adverse events, no./total (%)	124/735 (16.9)	120/718 (16.7)	0.2 (– 3.7 to 4.0)
Digital ischaemia	21/735 (2.9)	8/718 (1.1)	1.7 (0.3–3.2)
Mesenteric ischaemia[b]	14/727 (1.9)	18/711 (2.5)	– 0.6 (– 2.1 to 0.9)
Acute coronary syndrome	18/735 (2.5)	17/718 (2.4)	0.1 (– 1.5 to 1.7)
Arrhythmia	39/735 (5.3)	58/718 (8.1)	– 2.8 (– 0.2 to – 5.3)

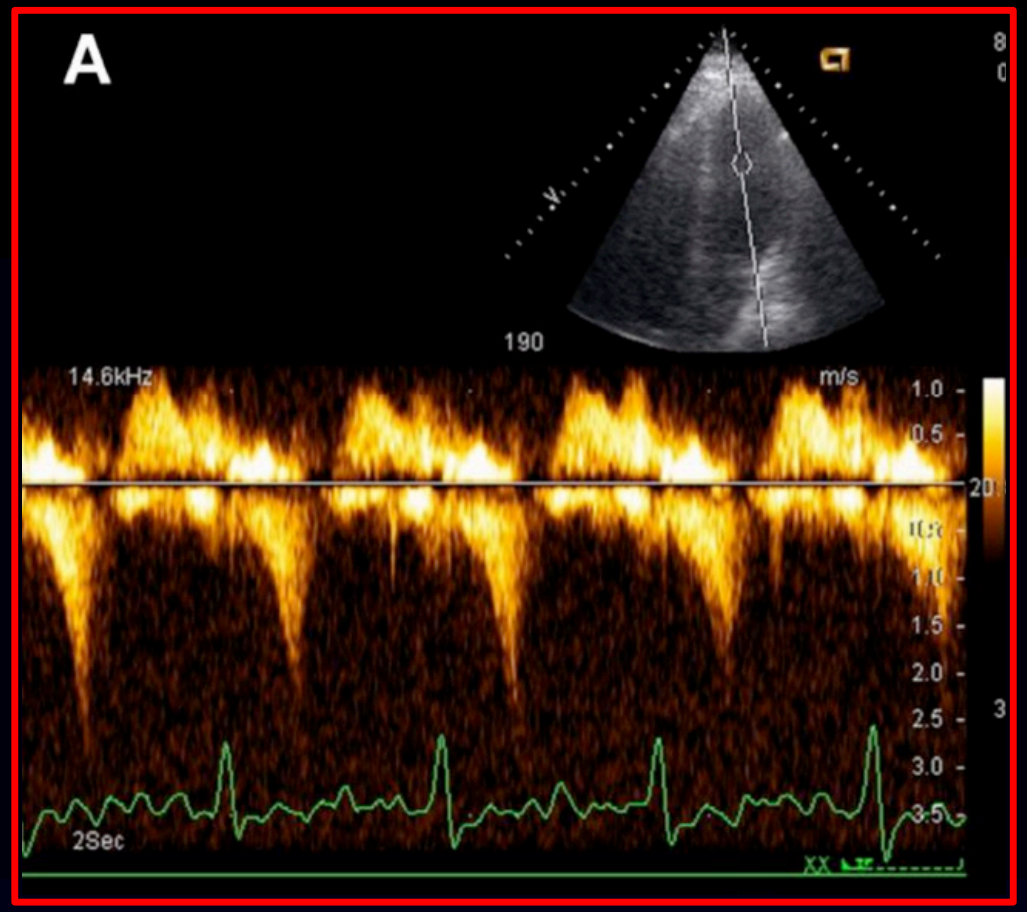
Vasopressin in specific situations ?

Look carefully for LVOT obstruction !

Chauvet JL et al
Crit Care 2015

218 pts septic shock
=> 47 pts with LVOT





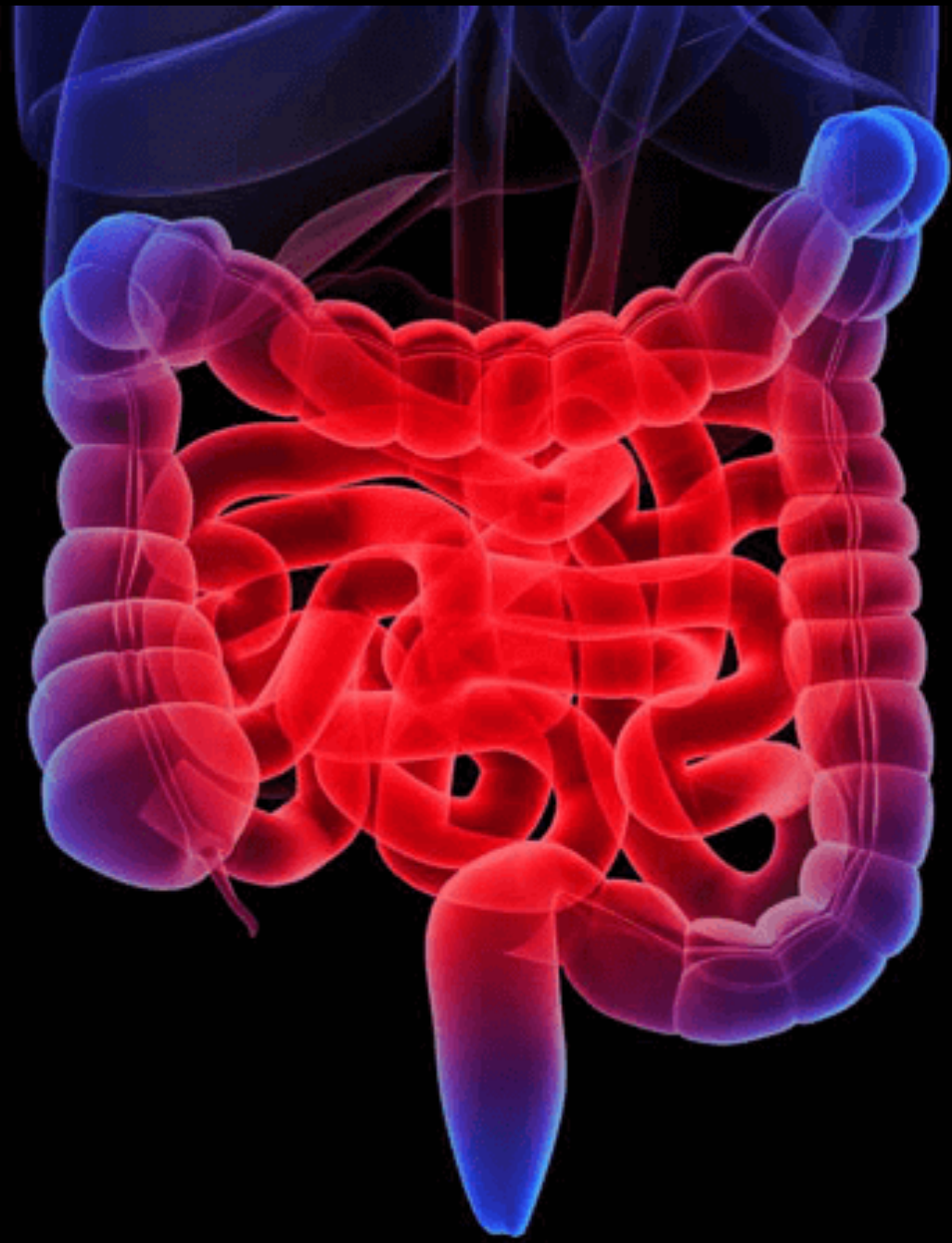
Vasopressin in Patients with Septic Shock and Dynamic Left Ventricular Outflow Tract Obstruction

Balik M et al
Cardiovasc Drug Ther
2020

Parameter	LVOT CW gradient [mmHg]	MR [0–4 scale]	SAM [present /all]	NE dosage [μg/kg.min]	HR [b/min]	Lactate arterial [mmol/l]	paO_2/FiO_2 [mmHg]
Pre AVP	78 [56–123]	3 [2–4]	10/10	0.58 [0.40–0.78]	98 [90–120]	2.5 [2.1–4.6]	103 [88–128]
Post AVP	35 [24–60] *	2 [1–2] *	3/10	0.18 [0.14–0.30] *	93 [82–100]	1.7 [1.5–2.2] *	174 [125–213] *

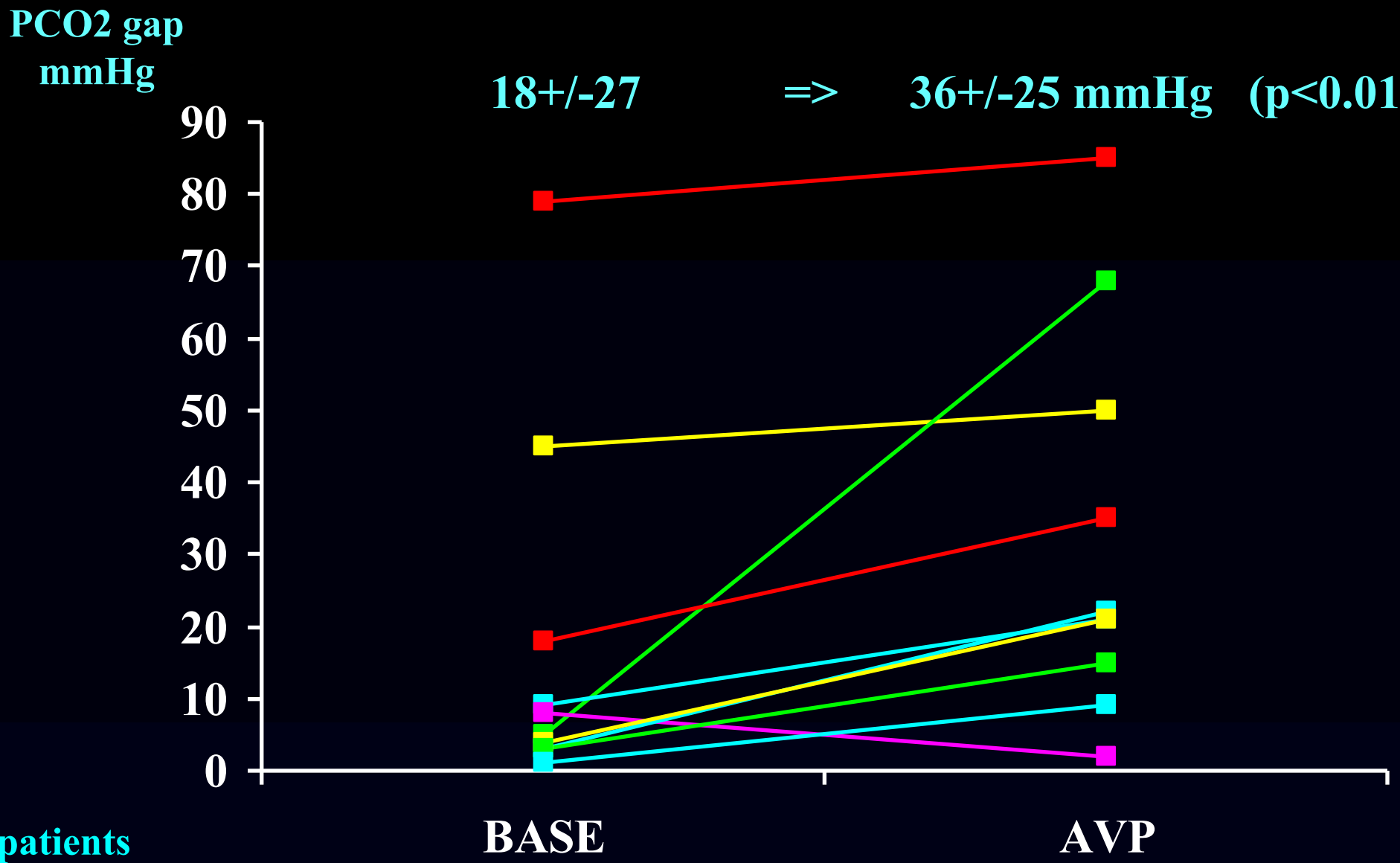
10 septic shock pts with severe LVOTO
(among 527 pts with septic shock over 29 months)

Vasopressin and splanchnic ischemia ?



VASOPRESSIN AND SPLANCHNIC PERFUSION

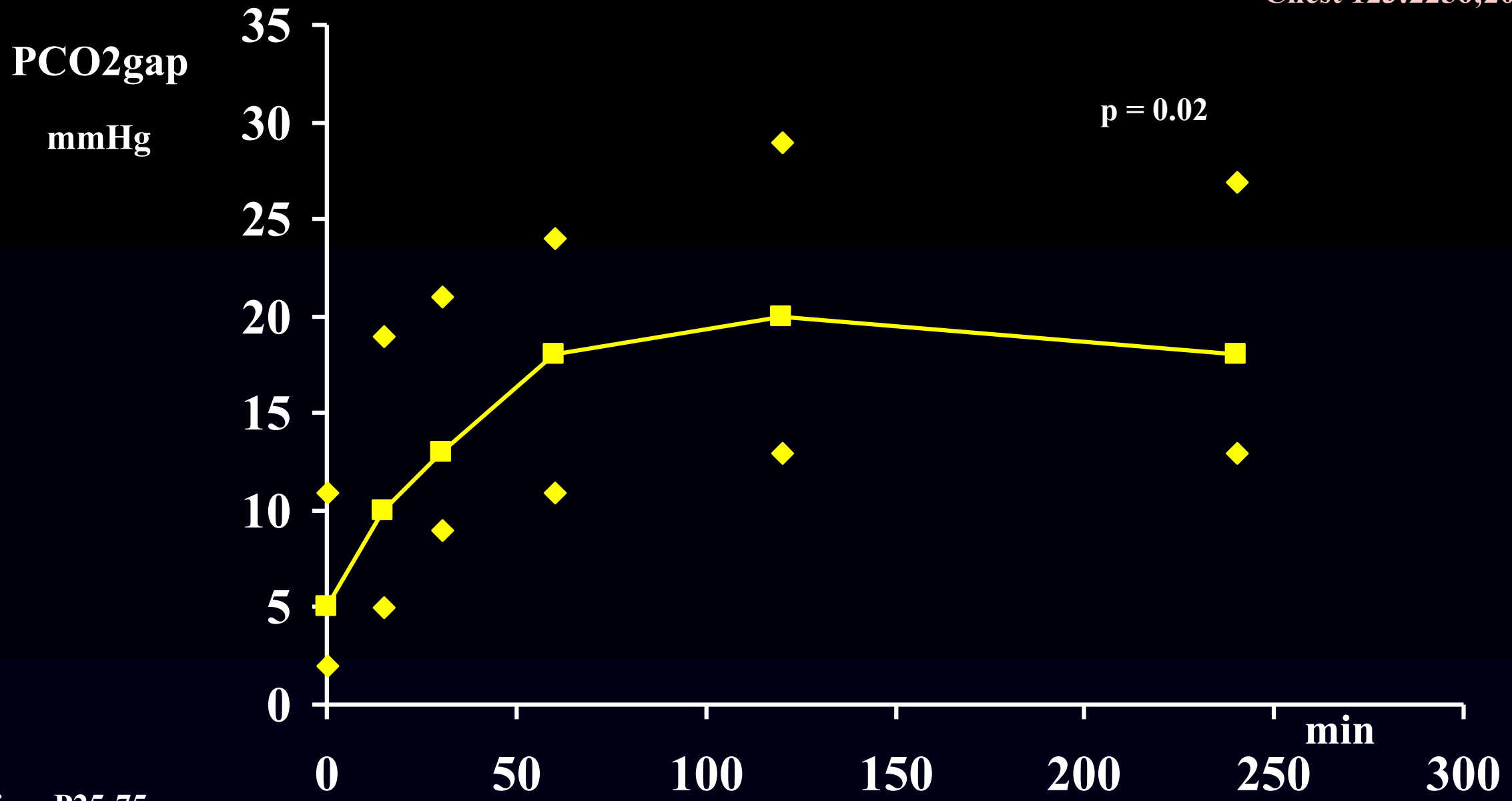
Klinzing et al
CCM 31:2646;2003



12 septic shock patients
NE 0.56 µg/kg.min => AVP 0.47 u/min

VASOPRESSIN AND SPLANCHNIC PERFUSION

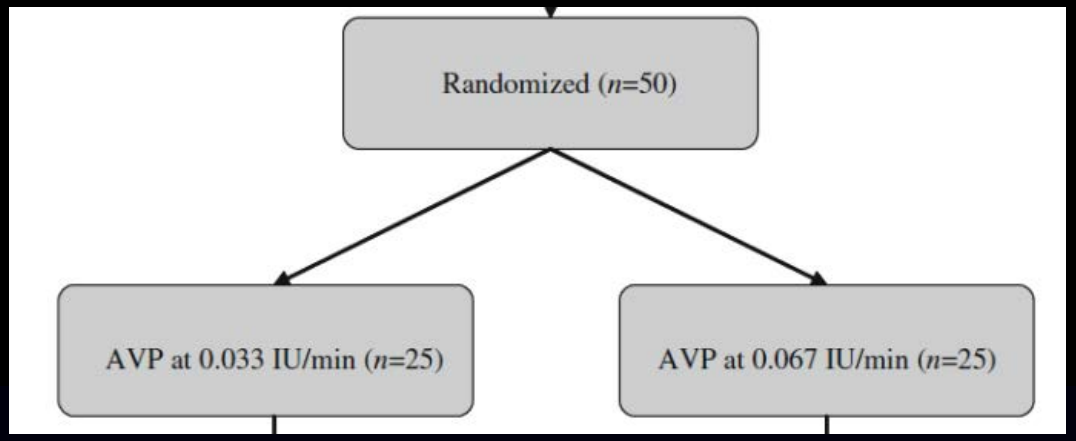
Van Haren et al
Chest 123:2256;2003



Median, P25-75

Comparing two different arginine vasopressin doses in advanced vasodilatory shock: a randomized, controlled, open-label trial

Torgersen C et al
ICM 36:57;2010



	0.033 IU/min	0.067 IU/min	*P*-value
Decrease in cardiac index, *n* (%)	4 (25)	7 (50)	0.26
Increase in serum transaminases, *n* (%)	10 (47.6)	15 (65.2)	0.36
Increase in total bilirubin, *n* (%)	4 (19)	6 (26.1)	0.72
Decrease in platelet count, *n* (%)	15 (71.4)	17 (73.9)	1

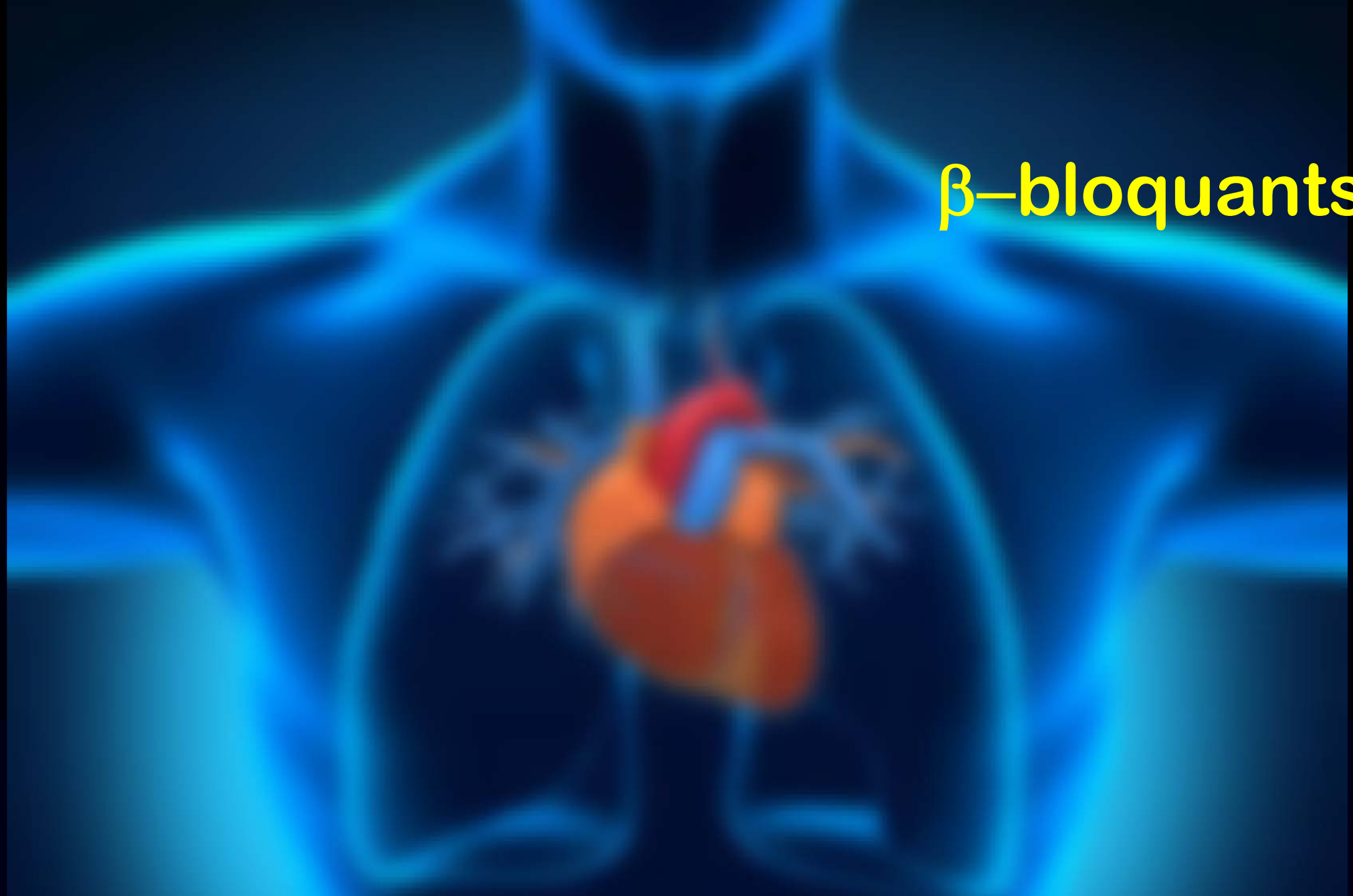
The higher dose of VP increased more blood pressure but it was associated with more adverse effects compared to the lower dose

Putting all together

Vasopressin in septic shock

- Norepinephrine as first line vasopressor agent. It is usually well tolerated and is associated with favorable hemodynamic effects.

- Vasopressin derivatives are excellent adjunctive and in some cases alternative to norepinephrine
- Caution in hepatosplanchnic ischemia
- Benefits in AKI and AF


β–bloquants?

2024

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/jointm

Viewpoint

The pros and cons of beta-blockers in sepsis: Where do we stand in 2024?

Daniel De Backer[1,*], Dechang Chen[2]

[1] *Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels B-1160, Belgium*
[2] *Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

The different Beta-blockers

Floria M et al
Pharmaceutics 2024

Property	Landiolol [26]	Esmolol [26]	Metoprolol [27]	Nebivolol [28]	Bisoprolol [28]	Atenolol [29]	Carvedilol [30]	Propranolol [31]
Drug class	Ultra-short-acting selective β-1 blocker	Short-acting selective β-1 blocker	Selective β-1 blocker	Highly cardio selective β-1 blocker with vasodilator properties	Highly cardio-selective β-1 blocker	Cardio selective β-1 blocker	Non-selective β blocker with alpha-1 blocking activity	Non-selective β blocker
Half-life	Very short (about 4 min)	Very short (about 9 min)	3–7 h	10–12 h	10–12 h	6–7 h	7–10 h	4–6 h
Pharmaco-kinetics	Rapid onset and offset of action	Rapid onset and offset of action	Rapidly and completely absorbed	Absorbed rapidly and extensively metabolized	Slowly and completely absorbed	Absorbed slowly but almost completely	Extensive l y metabolized	Rapidly and completely absorbed

Differ by half-life and β1selectivity

Comparison of the β-Adrenergic Receptor Antagonists Landiolol and Esmolol: Receptor Selectivity, Partial Agonism, and Pharmacochaperoning Actions

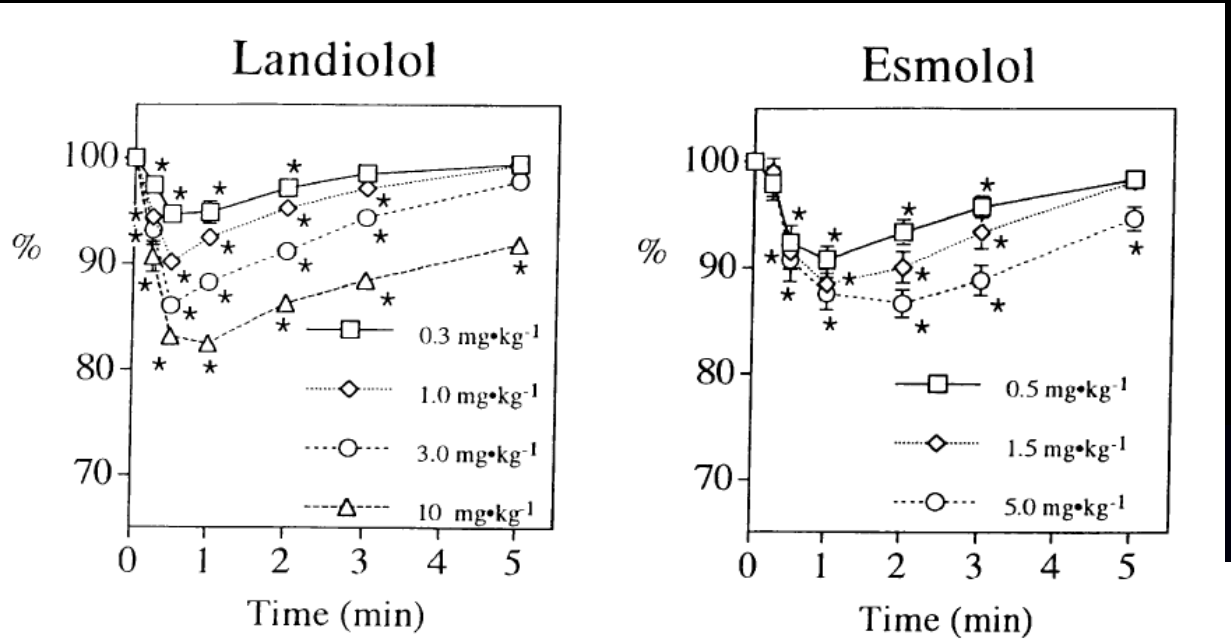
Nasrollahi-Shirazi S et al
J Pharm Exp Ther 2016

	human β_1-receptor	human β_2-receptor	Selectivity ratio (K_i β_2/K_i β_1)
landiolol	90 ± 16 nM	19.4 ± 5.5 µM	216
esmolol	194 ± 7 nM	5.8 ± 2.1 µM	30

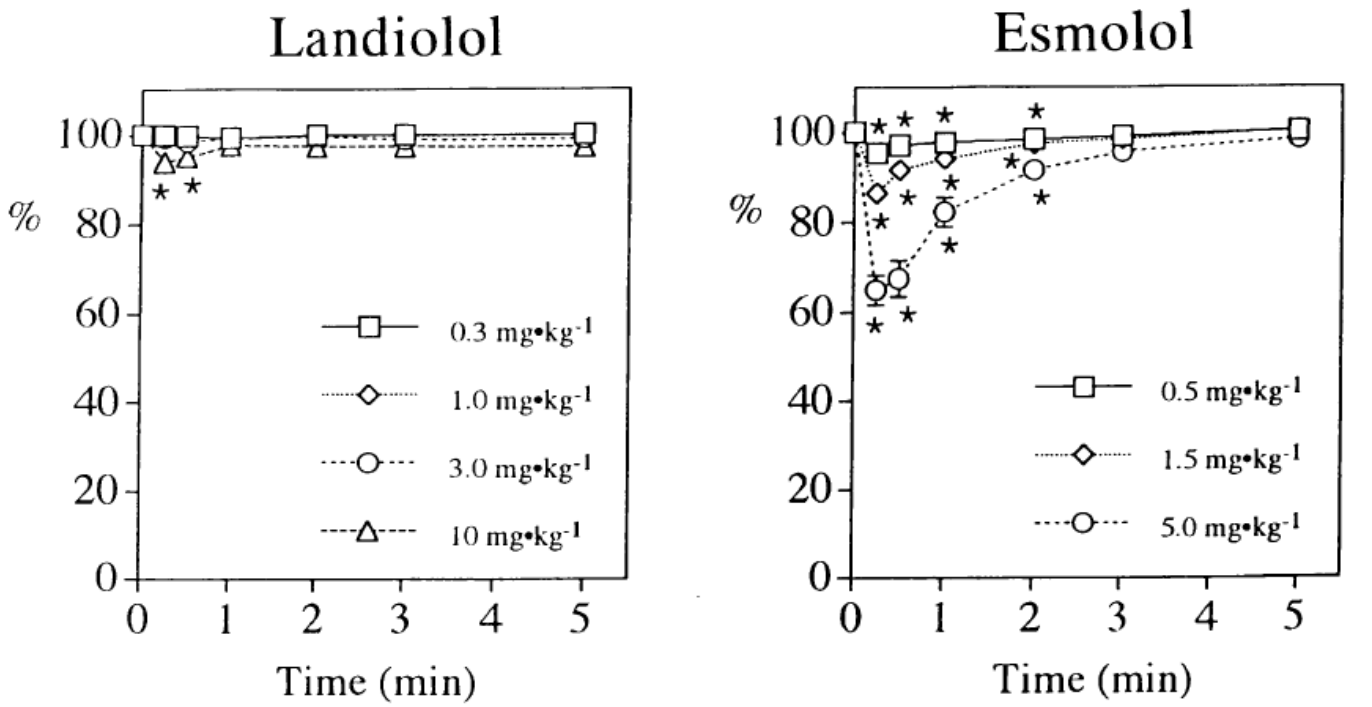
Heart Rate

Sasso J et al
Can J Anesth 2001

Differences between selective β1 Beta-blockers



Mean Arterial Pressure

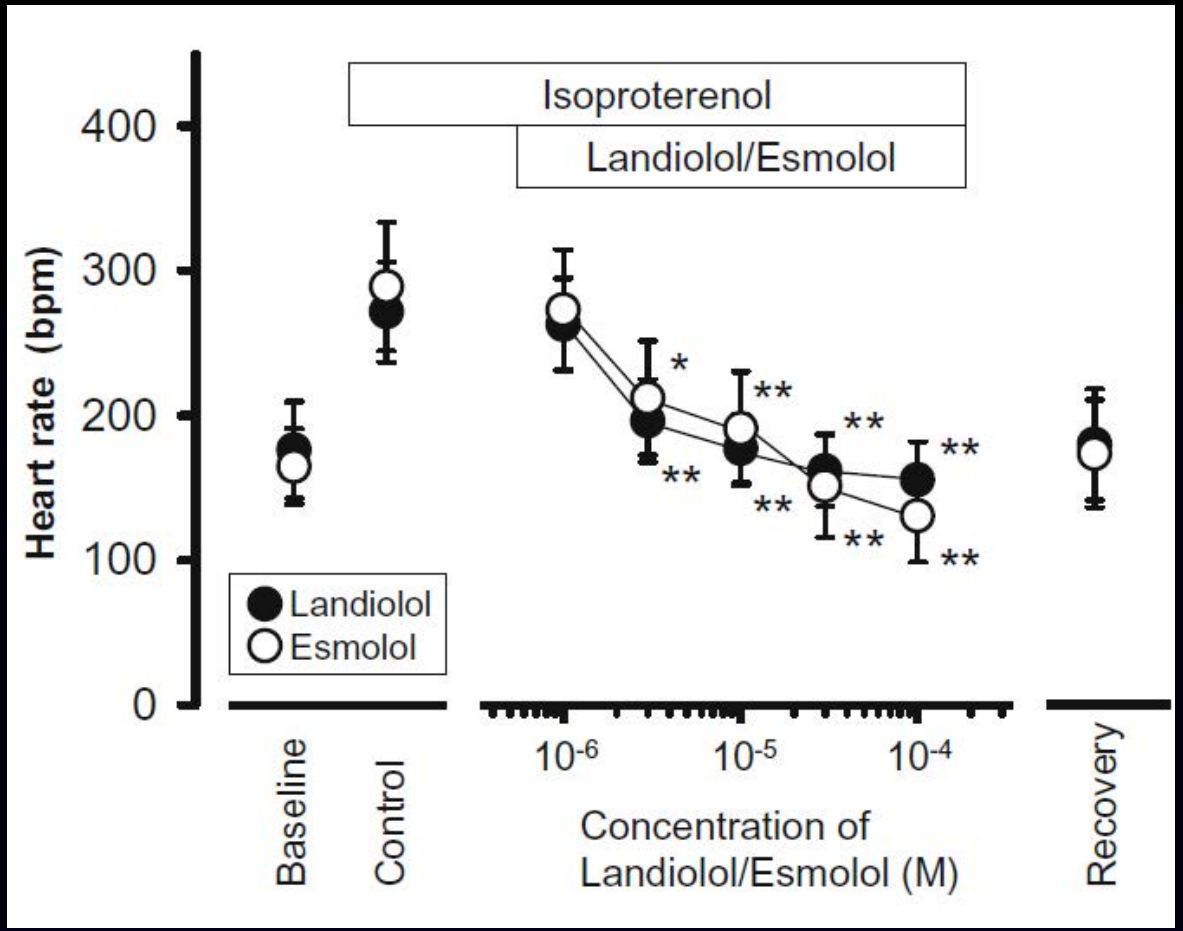


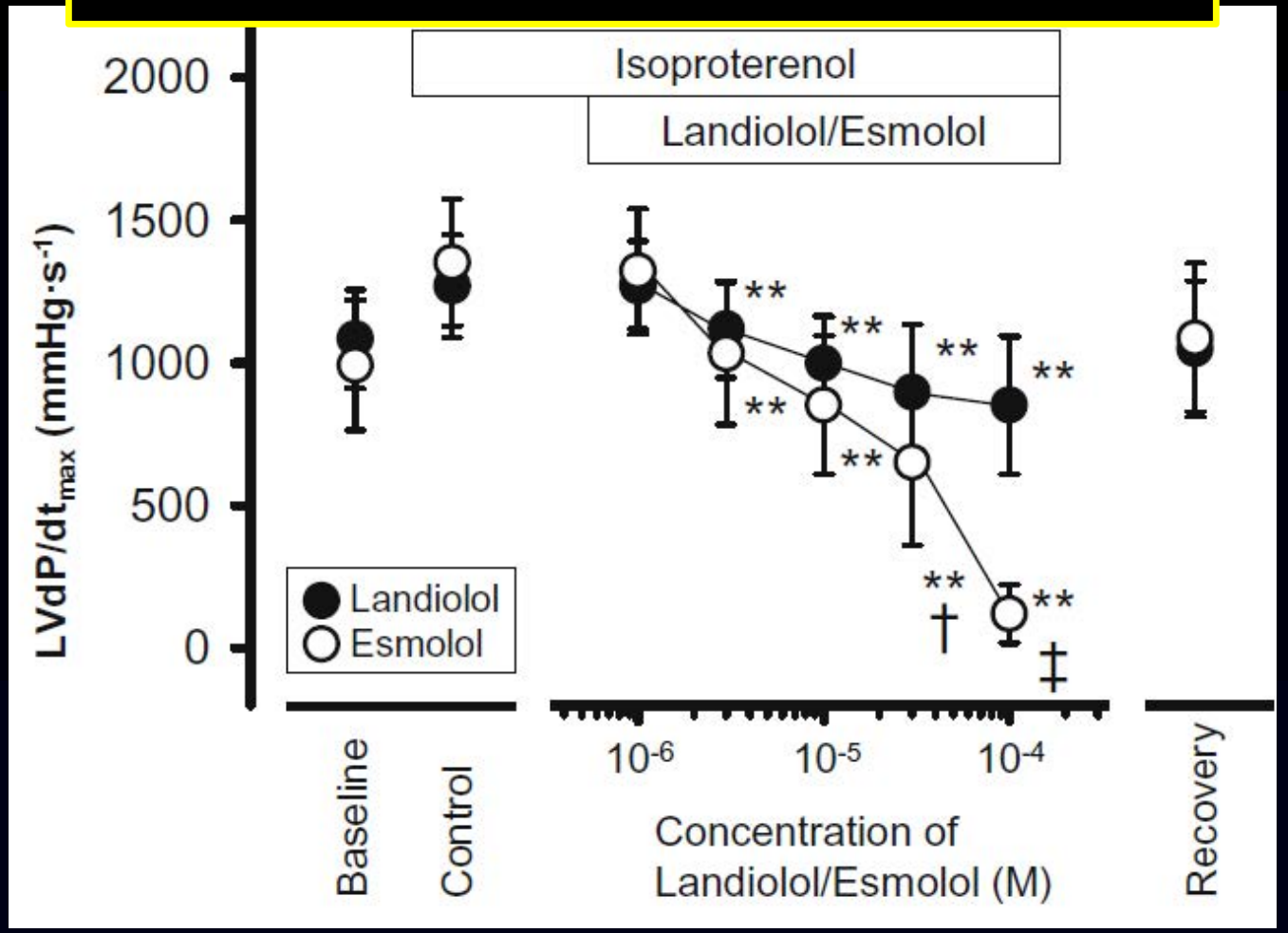
Bolus
Rabbits

Landiolol has a less potent negative inotropic effect than esmolol in isolated rabbit hearts

Sasso J et al
J Anesthia 2001

Decreased contractility with esmolol but not with landiolol for similar heart rate control

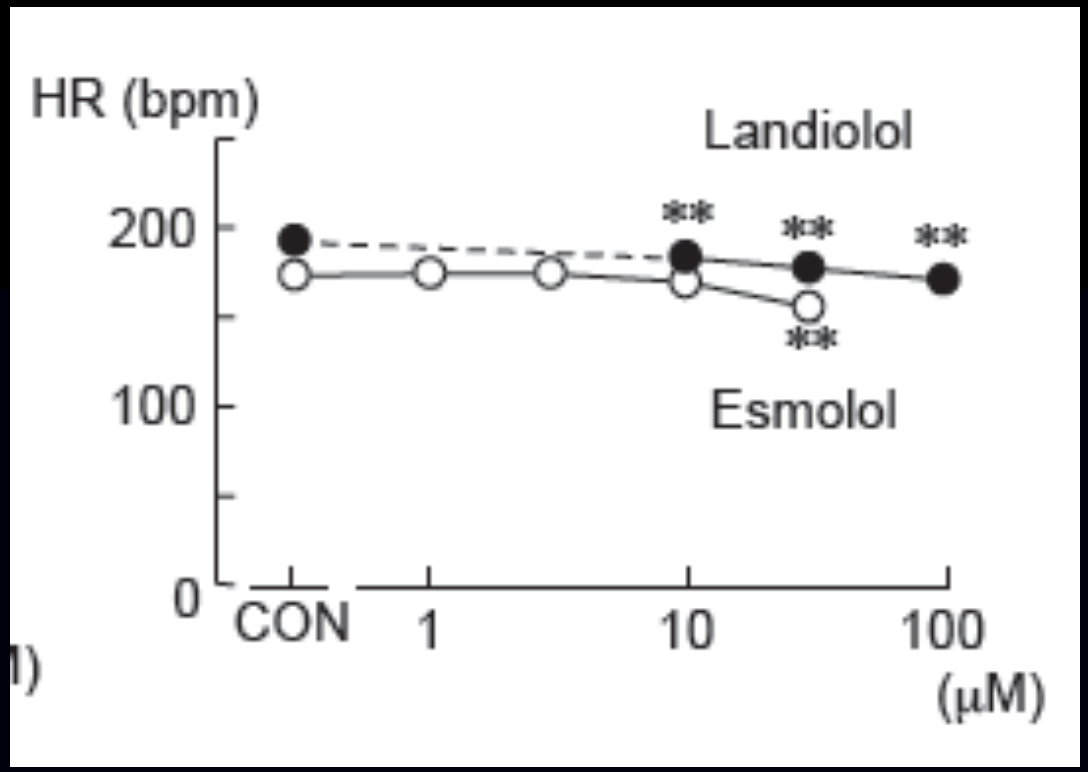




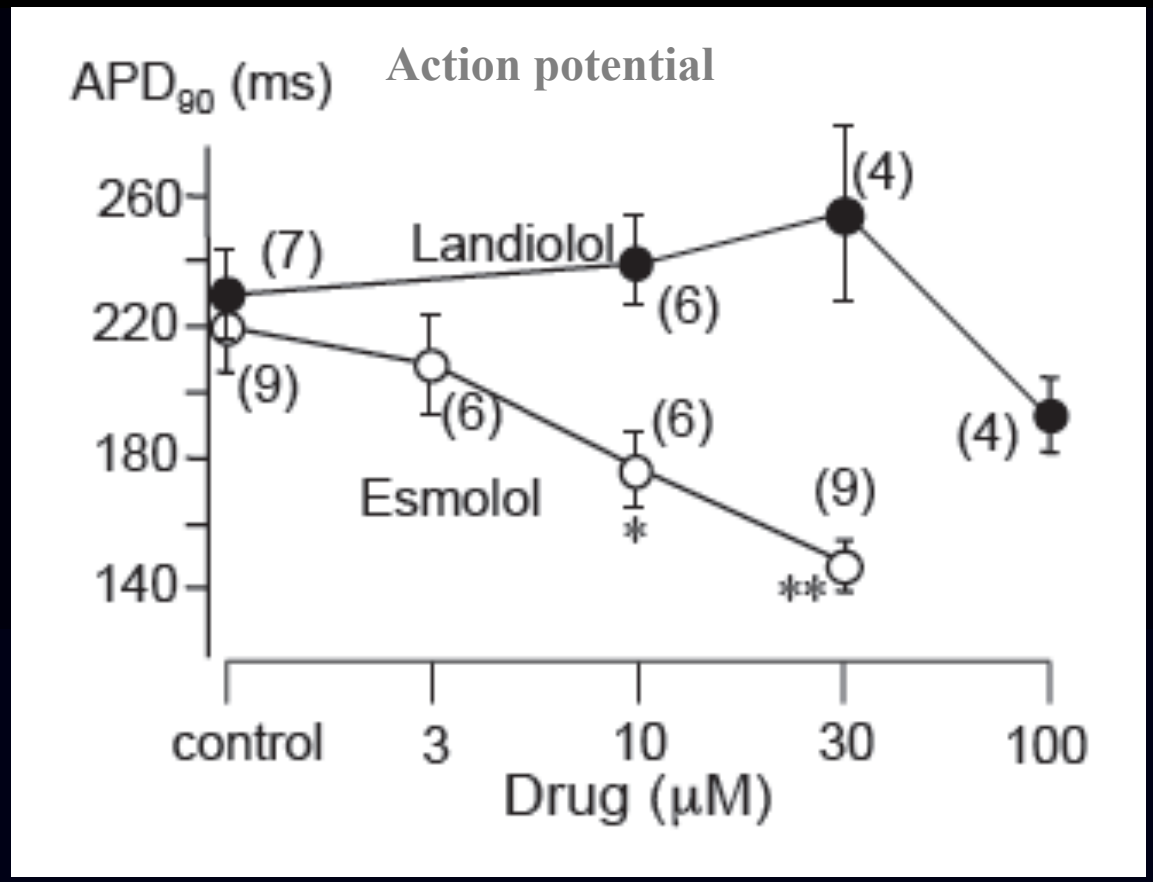
Rabbits

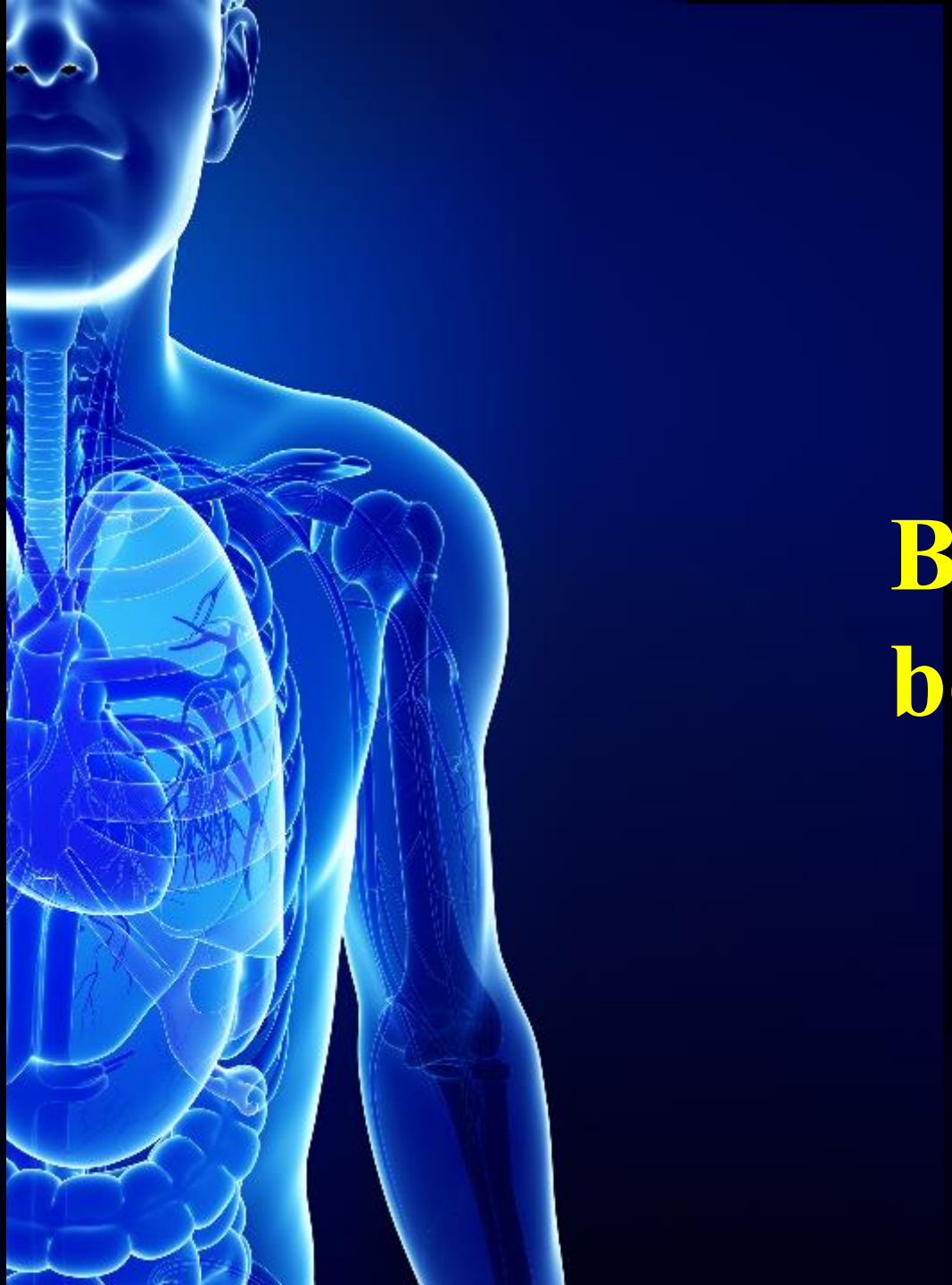
Direct Effects of Esmolol and Landiolol on Cardiac Function, Coronary Vasoactivity, and Ventricular Electrophysiology in Guinea-Pig Hearts

Shibata S et al
J Pharmacol Sci 2012



Decreased contractility with esmolol for similar heart rate control

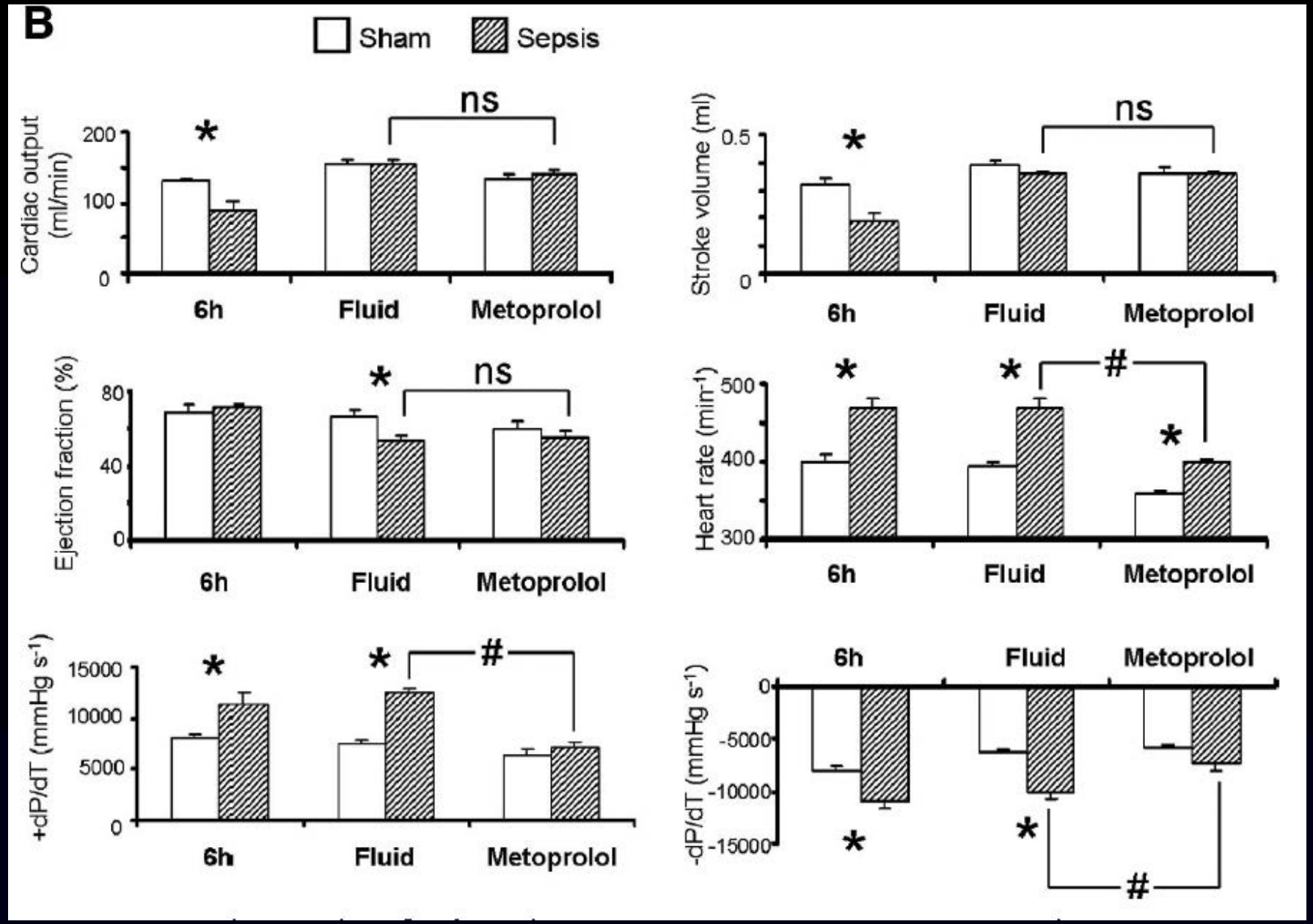




Beta-blockers may have beneficial effects in sepsis

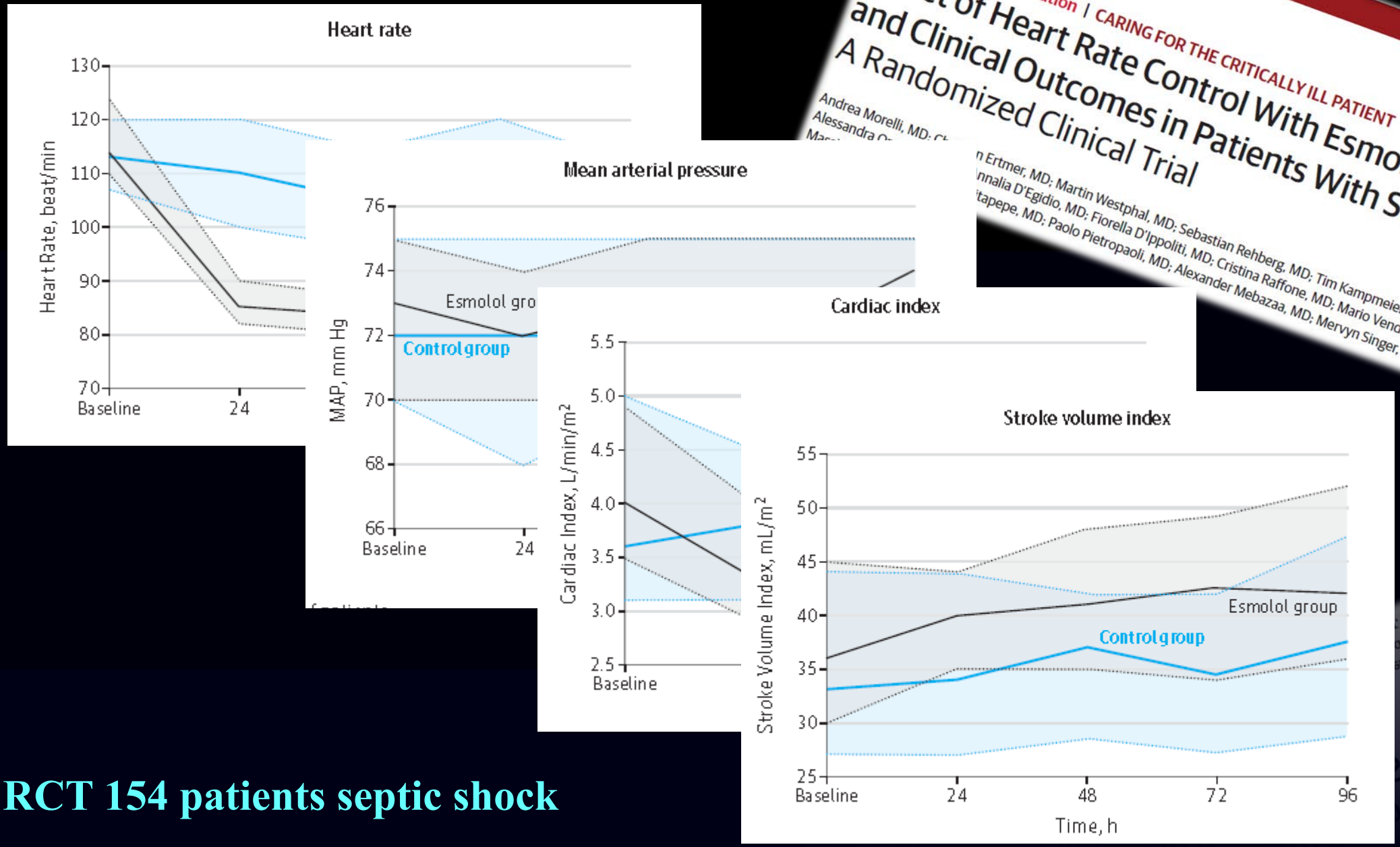
β1-adrenoceptor blockade in septic rats

Ackland G et al
CCM 38:388; 2010



Beta-blockers in septic shock

Morelli et al
JAMA 2013



Preliminary Communication / CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock

A Randomized Clinical Trial

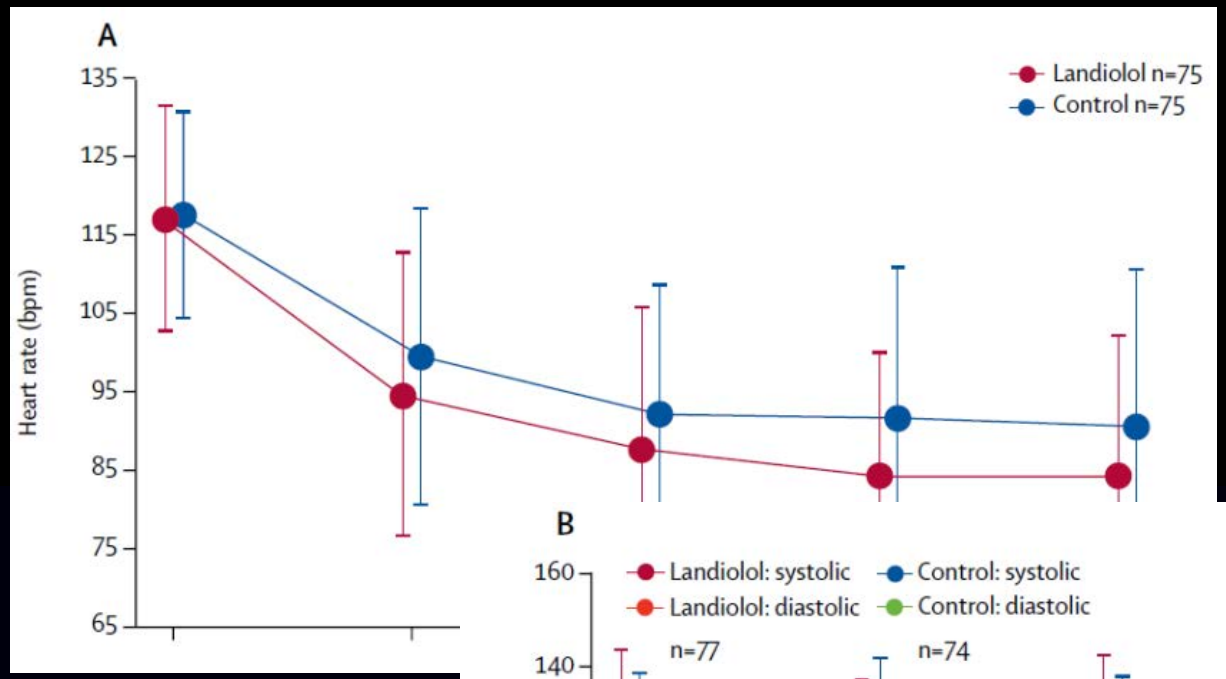
Andrea Morelli, MD; ... n Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; ... nnalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; ... tapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP

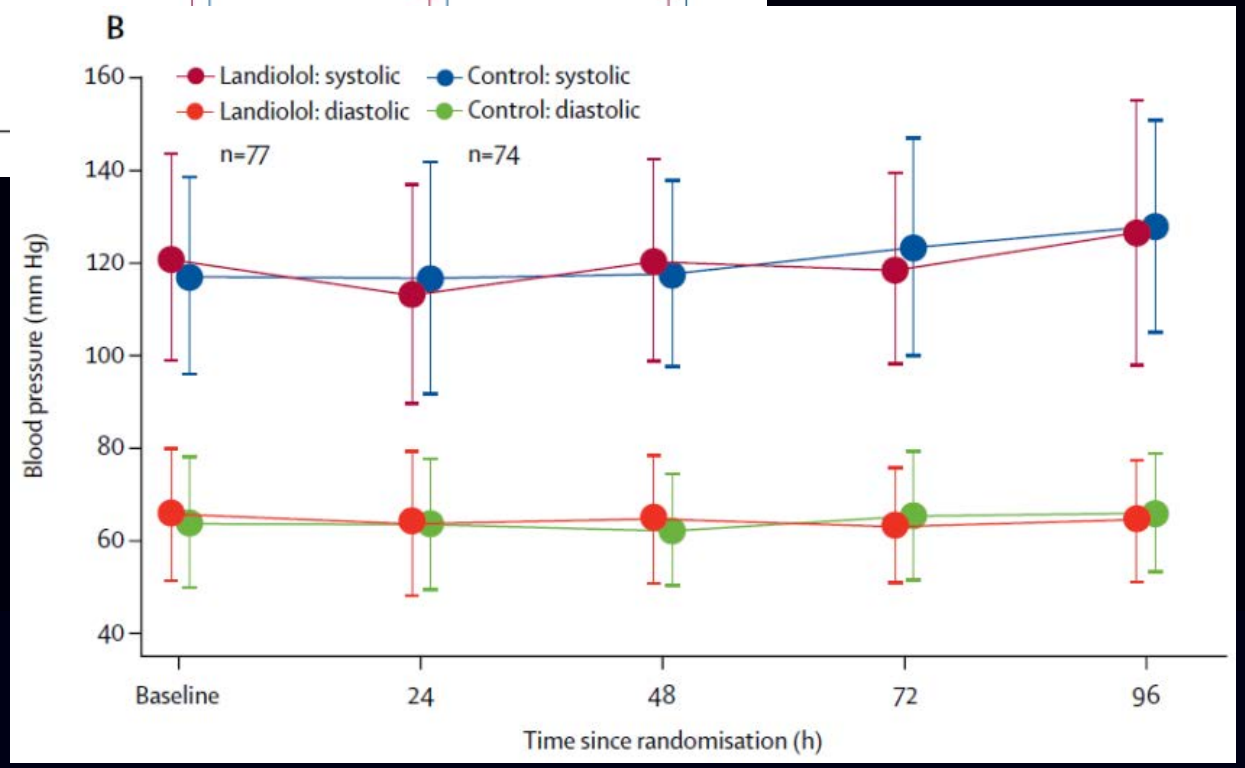
RCT 154 patients septic shock

Kakihana et al
Lancet 2020

Efficacy and safety of landiolol, an ultra-short-acting β1-selective antagonist, for treatment of sepsis-related tachyarrhythmia (J-Land 3S): a multicentre, open-label, randomised controlled trial

Yasuyuki Kakihana, Osamu Nishida, Takumi Taniguchi, Masaki Okajima, Hiroshi Morimatsu, Hiroshi Ogura, Yoshitsugu Yamada, Tetsuji Nagaoka, Eiichiro Morishima, Naoyuki Matsuda, on behalf of the J-Land 3S Study Group*





RCT 151 patients sepsis and septic shock

Some adverse signals were reported…..

Kakihana et al
Lancet 2020

	Landiolol (N=77)*	Control (N=74)
Patients with an adverse event	49 (64%)	44 (59%)
Patients with any serious adverse event	9 (12%)	8 (11%)
Adverse events leading to study drug discontinuation	9 (12%)	..
Hypotension†	9 (12%)	0
Delirium	7 (9%)	3 (4%)
Constipation	5 (6%)	3 (4%)
Diarrhoea	5 (6%)	2 (3%)
Hypokalaemia	5 (6%)	1 (1%)
Contact dermatitis	4 (5%)	4 (5%)
Atrial fibrillation	3 (4%)	4 (5%)
Insomnia	2 (3%)	5 (7%)
Hypophosphataemia	2 (3%)	3 (4%)
Erythema	0	3 (4%)

Data are n (%). Analyses were done on an as-assigned basis (safety analysis set).
*Includes one patient who was assigned to the control group but received landiolol. †Including blood pressure decrease.

and eight (11%) in the control group. Serious adverse events related to landiolol occurred in five (6%) of 77 patients, with blood pressure decreases in three (4%) patients and cardiac arrest, heart rate decreased, and ejection fraction decreased in one (1%) patient each. These events resolved or improved with dose reduction of landiolol, withdrawal, or other action. There were no

RCT 151 patients sepsis and septic shock

Some signals for undesired effects….

Morelli et al
JAMA 2013

Variable	Group	Baseline	24 h	48 h	72 h	96 h
Lactate [mmol·L^{-1}]	Esmolol	1.5 [1.1; 2.7]	1.5 [1.1; 2.0]	1.5 [1.0; 2.0]	1.5 [1.1; 2.3]	1.5 [1.1; 2.3]
	Control	1.9 [1.1; 3.1]	2.1 [1.3; 2.9]	1.9 [1.1; 3.2]	1.7 [1.2; 3.1]	1.5 [1.0; 2.6]

DO_2I [ml·min^{-1}·M^{-2}]	Esmolol	560 [440; 684]	426 [364; 519]	419 [330; 539]	447 [355; 530]	439 [364; 530]	-100 [-211; -38]	**<0.001**
	Control	479 [395; 658]	486 [388; 620]	461 [371; 568]	418 [358; 561]	452 [377; 579]	-32; [-108; 21]	

Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study

A. Morelli[1*], M. Singer[2], V. M. Ranieri[1], A. D'Egidio[1], L. Mascia[4], A. Orecchioni[1], F. Piscioneri[1], F. G
E. Greco[1], M. Peruzzi[4], G. Biondi-Zoccai[4,5], G. Frati[4,5] and S. M. Romano[6]

Morelli et al
ICM 2016

↓Ea 23%
↓ MAP 6%
↑ SV 25%

=EF
↓ dP/dt 18%

↑ EDV ~25%??

Variable	Baseline	4 h	*p* value
CO^{th} (L min^{-1})	5.4 ± 1.3	5.1 ± 1.4	0.11
SV^{th} (mL)	48 ± 14	59 ± 18	**<0.001**
CO^{p} (L min^{-1})	5.1 ± 1.3	5.0 ± 1.3	0.77
SV^{p} (mL)	47 ± 12	59 ± 16	**<0.001**
HR (min^{-1})	115 ± 11	88 ± 9[a]	**<0.001**
SVR (Dyn s^{-1} cm^{-5})	1234 ± 293	1102 ± 260	**0.001**
MAP (mmHg)	80 ± 12	75 ± 10	**0.005**
MPAP (mmHg)	30 ± 7	28 ± 6	**0.001**
PAOP (mmHg)	16 ± 3	16 ± 4	0.74
CVP (mmHg)	12 ± 3	12 ± 3	0.86
Ea^{p} (mmHg l^{-1})	2.2 ± 0.7	1.7 ± 0.5	**<0.001**
Ea^{th} (mmHg l^{-1})	2.0 ± 0.6	1.55 ± 0.5	**<0.001**
LVEF (%)	52 ± 11	53 ± 11	0.17
Art. dP/dt_{max} (mmHg ms^{-1})	1.08 ± 0.32	0.89 ± 0.29	**0.0009**
CCE (units)	−0.15 ± 0.5	−0.01 ± 0.4	**0.002**
CPwO (W)	0.53 ± 0.14	0.63 ± 0.24	**0.007**
NE dosage (μg kg^{-1} min^{-1})	0.7 ± 0.7	0.58 ± 0.55	**0.01**

Hemodynamic and anti-inflammatory effects of early esmolol use in hyperkinetic septic shock: a pilot study

Levy B et al
Crit Care 2021

	H0	H6	Δ H0–H6 (H6–H0)	*p* value
LVEF (%)	53 (50; 55)	45 (30; 57)	−8 (−18; 2)	0.074
LVEDV	89 (56; 114)	100 (44; 119)	9 (−21; 43)	0.38
VTI (cm)	17 (15; 17)	14 (12; 16)	−2 (−3; −1)	0.008
TDSa (cm/s)	11.0 (8.0; 13.0)	9.0 (7.0; 12.0)	−1.0 (−2.1; 0.0)	0.031
Peak E wave velocity (m/s)	0.90 (0.70; 1.00)	0.84 (0.80; 1.00)	0.00 (−0.10; 0.12)	0.95
Peak E' wave velocity (m/s)	0.11 (0.09; 0.12)	0.09 (0.08; 0.10)	−0.01 (−0.03; −0.01)	0.023
Peak A wave velocity (m/s)	0.77 (0.68; 1.03)	0.57 (0.47; 0.75)	−0.21 (−0.27; −0.06)	0.016
E/A	0.91 (0.80; 1.33)	1.52 (0.97; 1.88)	0.47 (0.20; 0.62)	0.031
E/E'	7.6 (6.5; 9.0)	9.5 (8.4; 12.3)	2.6 (1.0; 3.3)	0.023
DTI S' (cm/s)	9.0 (7.2; 14.0)	9.0 (8.0; 11.0)	−1.0 (−3.0; 0.0)	0.16
TAPSE (mm)	17.5 (16.0; 21.5)	15.5 (14.0; 16.5)	−1.0 (−4.0; −0.5)	0.031

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

Morelli et al
JAMA 2013

Exclusion criteria were age younger than 18 years, β-blocker therapy prior to randomization, pronounced cardiac dysfunction (ie, cardiac index ≤2.2 L/min/m² in the presence of a pulmonary arterial occlusion pressure >18 mm Hg), significant valvular heart disease, and pregnancy.

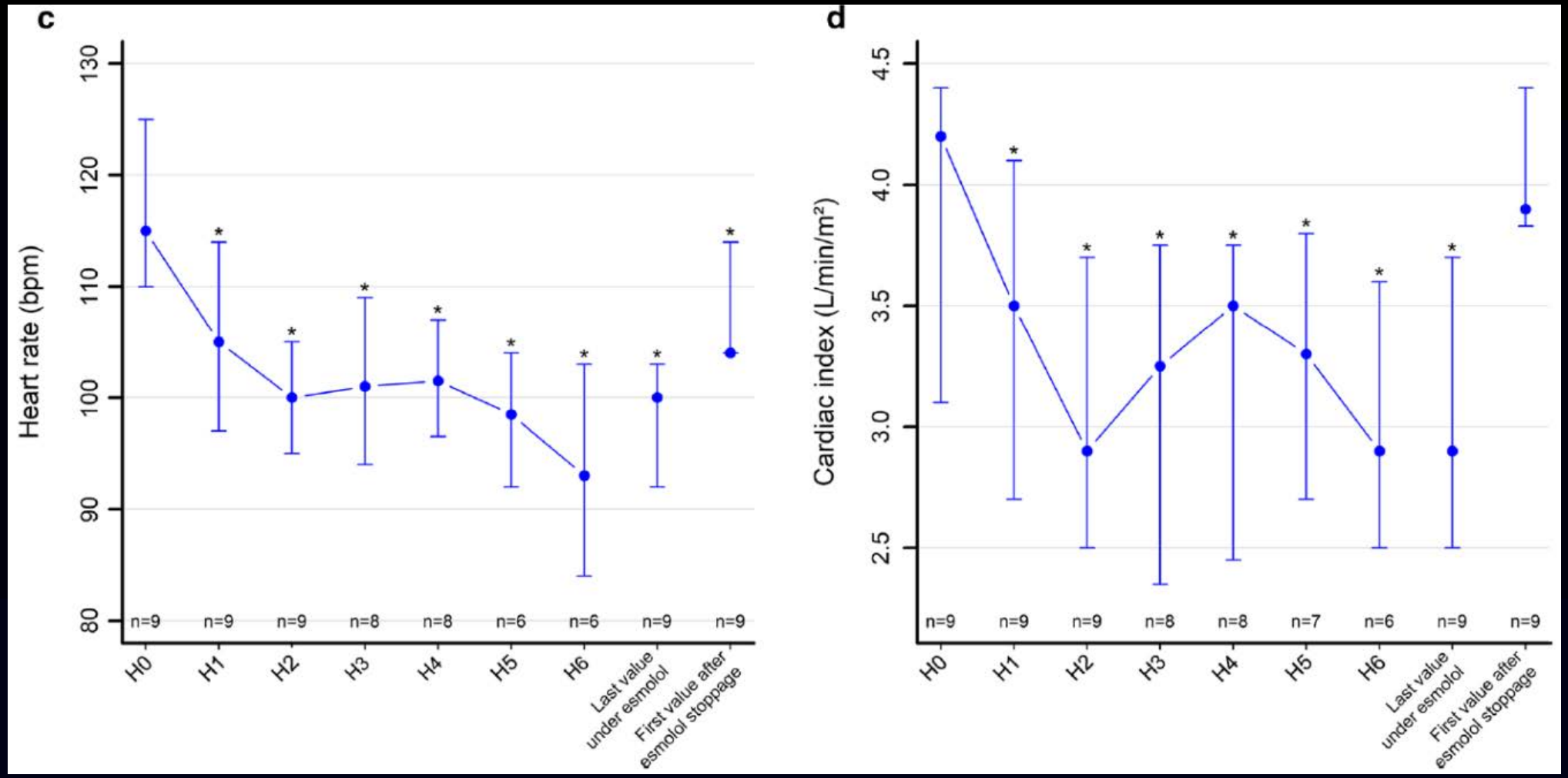
Morelli A et al
BJA 2020

Variable mean (SD)		High $_{art}dp/dt_{max}$ after esmolol (n=23)	Low $_{art}dp/dt_{max}$ after esmolol (n=22)	P-value
CO (L min^{-1})	Baseline	5.3 (1.3)	5.0 (1.3)	0.59
	4 h	5.7 (1.1)	4.4 (1.0)*	<0.001
SV (ml)	Baseline	48 (12)	46 (13)	0.59
	4 h	67 (14)*	50 (12)	<0.001
HR (beats min^{-1})	Baseline	113 (10)	116 (11)	0.33
	4 h	87 (10)*	90 (6)*	0.19
MAP (mm Hg)	Baseline	80 (12)	82 (13)	0.72
	4 h	76 (11)	74 (8)*	0.40

- **Despite exclusion of patients with low cardiac index, 22/45 (50%) patients did not tolerate introduction of beta-blockers.**

Hemodynamic and anti-inflammatory effects of early esmolol use in hyperkinetic septic shock: a pilot study

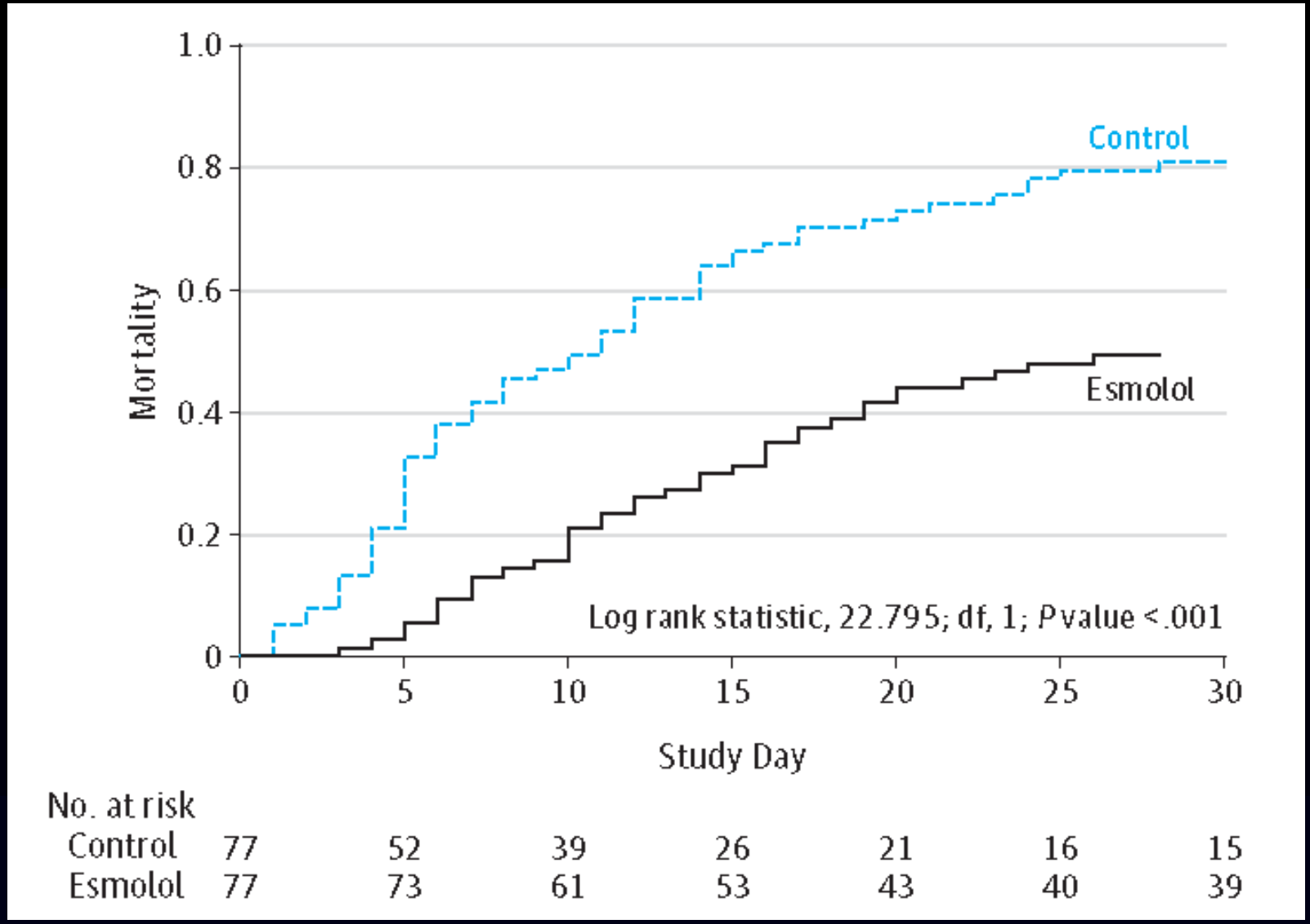
Levy B et al
Crit Care 2021



Despite some adverse signals,
survival benefit might be observed !

Beta-blockers

Morelli et al
JAMA 2013



RCT 154 patients septic shock

Survival benefit might be observed ??

Whitehouse T et al
JAMA 2023

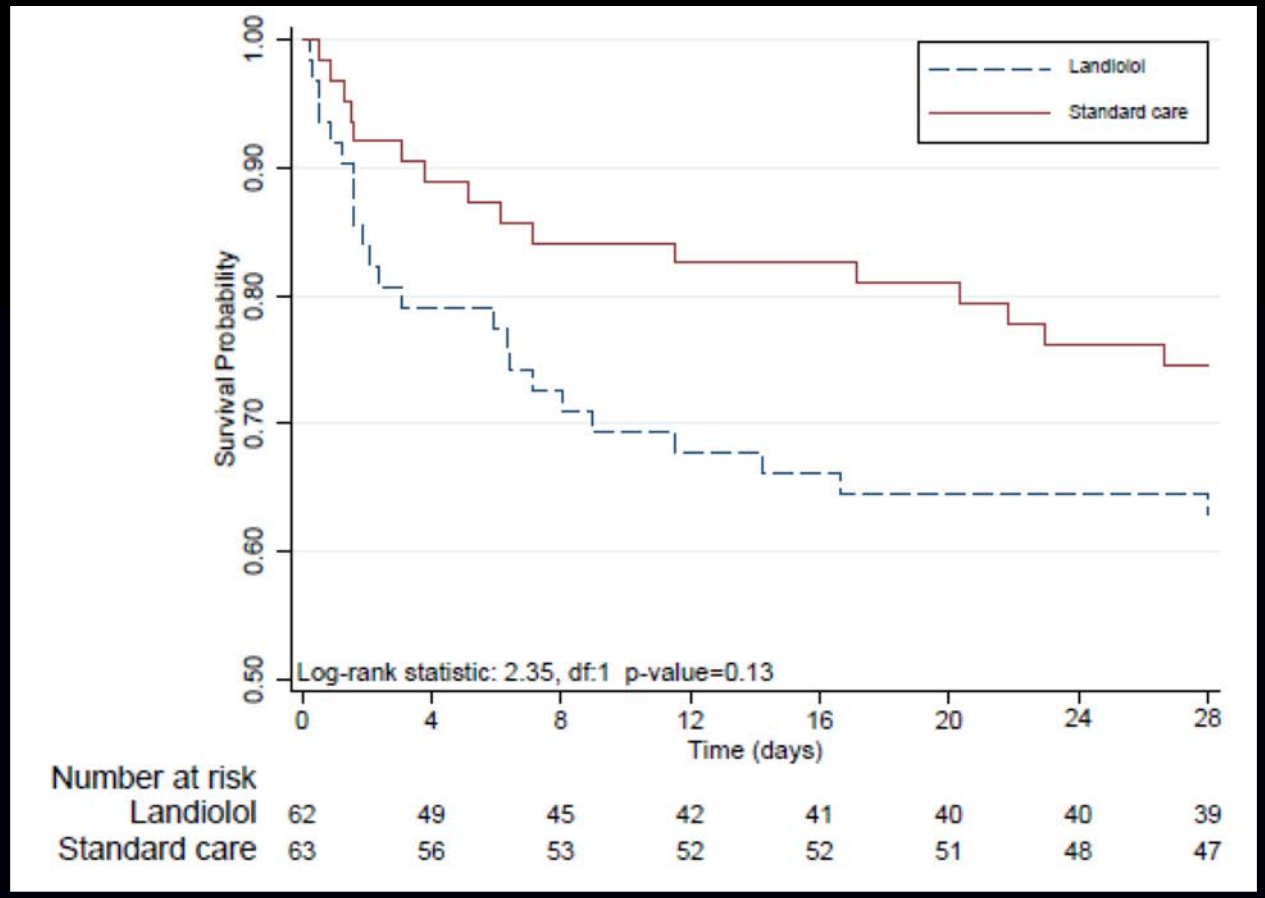
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

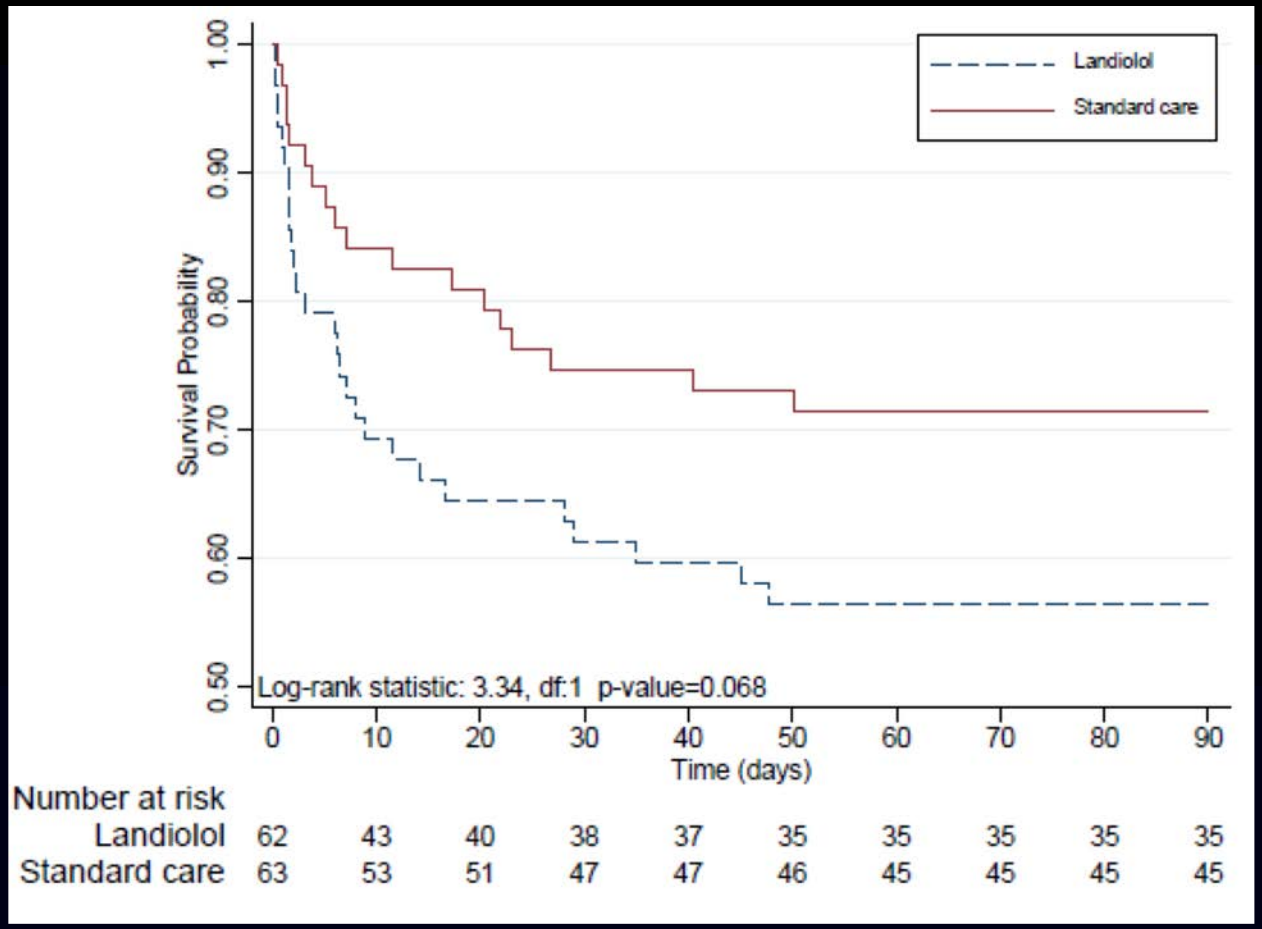
Landiolol and Organ Failure in Patients With Septic Shock
The STRESS-L Randomized Clinical Trial

Tony Whitehouse, MD; Anower Hossain, PhD; Gavin D. Perkins, MD; Anthony C. Gordon, MD; Julian Bion, MD; Duncan Young, MD; Danny McAuley, MD; Mervyn Singer, MD; Janet Lord, PhD; Simon Gates, PhD; Tonny Veenith, MD; Niall S. MacCallum, PhD; Joyce Yeung, MD; Richard Innes, MD; Ingeborg Welters, MD; Nafisa Boota, MSc; Emma Skilton, BSc; Belinder Ghuman, BSc; Maddy Hill, MPH; Scott E. Regan, BA; Dipesh Mistry, PhD; Ranjit Lall, PhD; for the STRESS-L Collaborators

Landiolol and Organ Failure in Patients With Septic Shock
The STRESS-L Randomized Clinical Trial

Whitehouse T et al
JAMA 2023





RCT 126 patients septic shock

But patients were not evaluated for cardiac output or cardiac function prior to inclusion in the trial…

Whitehouse T et al
JAMA 2023

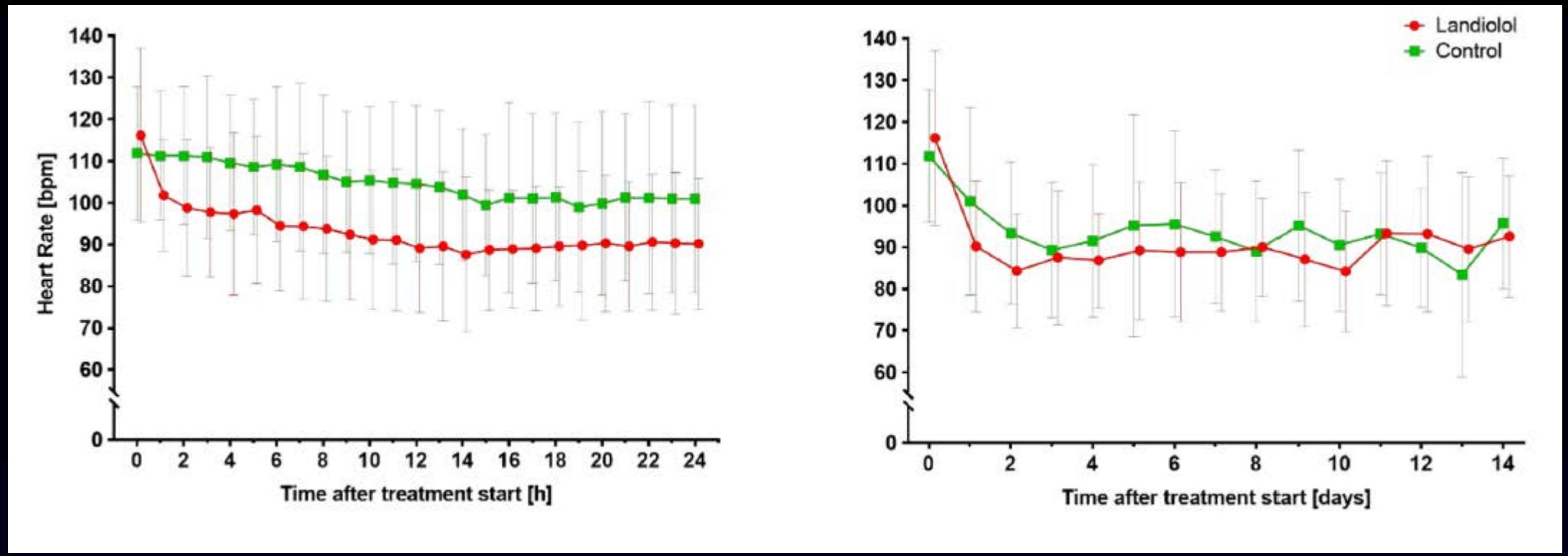
Trial Participants

The study recruited adult patients (≥18 years) in an ICU diagnosed with septic shock, defined by consensus criteria (Sepsis-3),[14] who having received adequate fluid resuscitation, were being treated with 0.1 µg/kg/min or more of norepinephrine (for >24 hours but <72 hours) at the time of randomization and were tachycardiac with a heart rate of 95/min or more. Sepsis-3 criteria were met if the patient had known or suspected infection, a Sequential Organ Failure Assessment (SOFA) score change of 2 or more from baseline, a blood lactate of 18 mg/dL (>2 mmol/L) at any point during shock resuscitation, and vasopressor therapy to maintain a mean arterial pressure either predefined by the clinician or at 65 mm Hg or higher. Patients were excluded if they had tachycardia because of pain or discomfort or had any noninfective form of vasodilatory shock (see trial protocol for extended inclusion and exclusion criteria Supplement 1).

Landiolol for heart rate control in patients with septic shock and persistent tachycardia. A multicenter randomized clinical trial (Landi-SEP)

Sebastian Rehberg[1*], Sandra Frank[2], Vladimír Černý[3,4,12,23,24], Radek Cihlář[5], Rainer Borgstedt[1], Gianni Biancofiore[6], Fabio Guarracino[7], Andreas Schober[8], Helmut Trimmel[9], Thomas Pernerstorfer[10],

Rehberg-S
ICM 2024



RCT 186 pts in septic shock

Landiolol for heart rate control in patients with septic shock and persistent tachycardia. A multicenter randomized clinical trial (Landi-SEP)

Rehberg-S
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Primary outcome:

1. **Achieving target HR 80-94 bpm each hour for 3 hours**
2. **Maintening this target for 3 more hours**
3. **No increase in vasopressor requirements within 24h**

Response	Landiolol group ($n=98$)	Control group ($n=98$)	Overall ($n=196$)	Effect estimate (95% CI)	*P* value
Primary response (multi-component)[a], n (%)	39 (39.8)	23 (23.5)	62 (31.6)	MD, 16.5% (3.4–28.8%)	0.01
Components of primary endpoint					
HR response (target HR reached and maintained)[b], n (%)	57 (58.2)	29 (29.6)	86 (43.9)	MD, 29% (15.1–41.3%)	< 0.001
HR response (target HR reached, not necessarily maintained)[c], n (%)	74 (75.5)	42 (42.9)	116 (59.2)	MD, 33% (19.4–44.9%)	< 0.001
Vasopressors response[d], n (%)	56 (57.1)	65 (66.3)	121 (61.7)	MD, − 9.2% (− 22 to 4.4%)	0.19

N = 186

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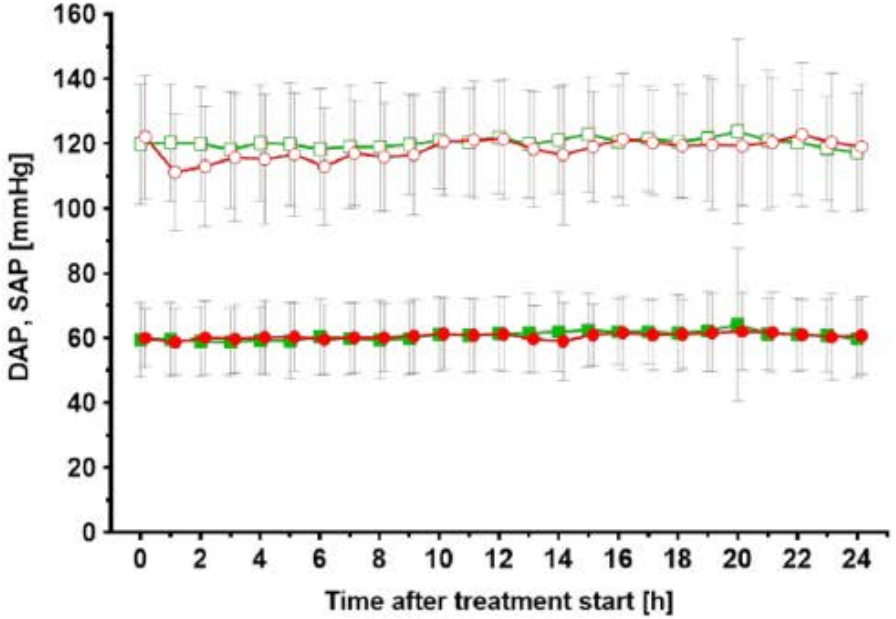
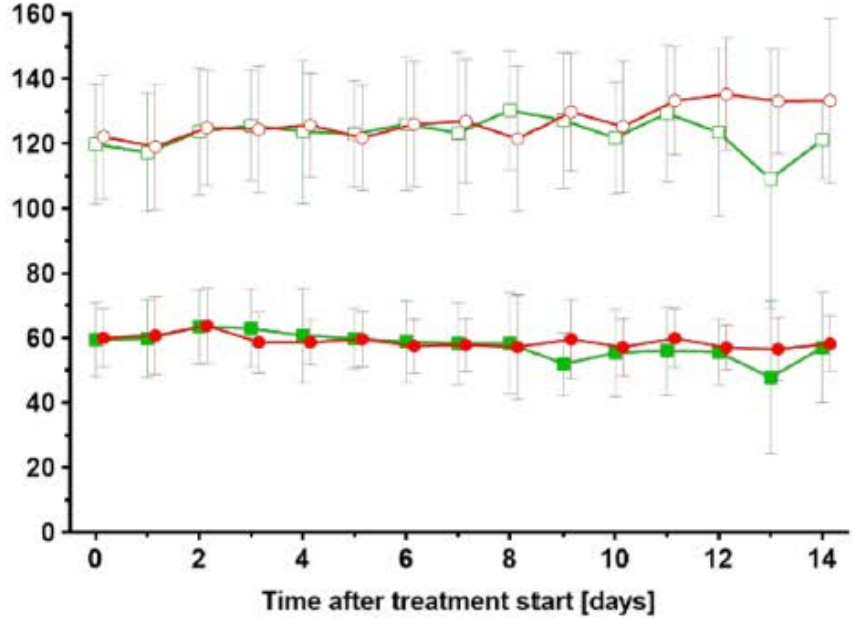
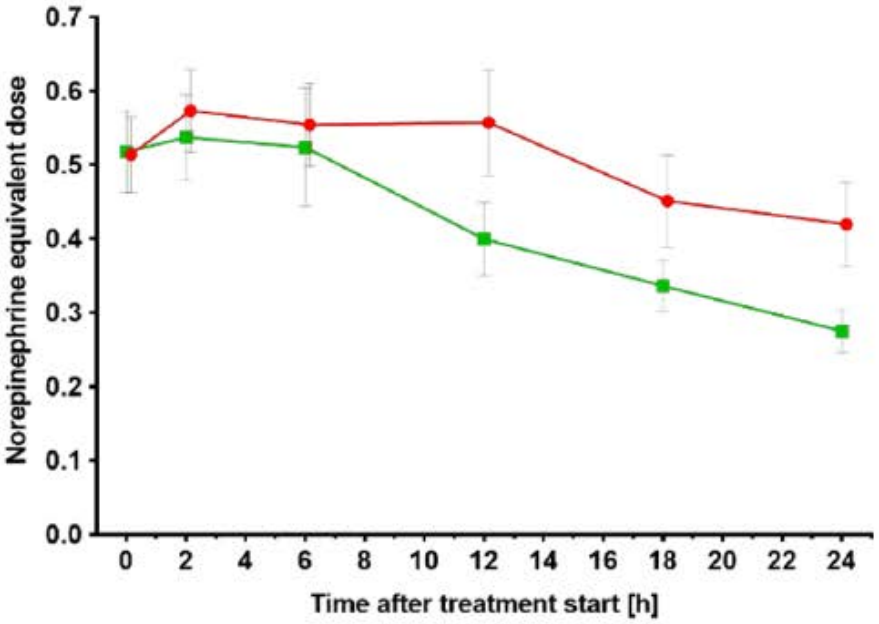
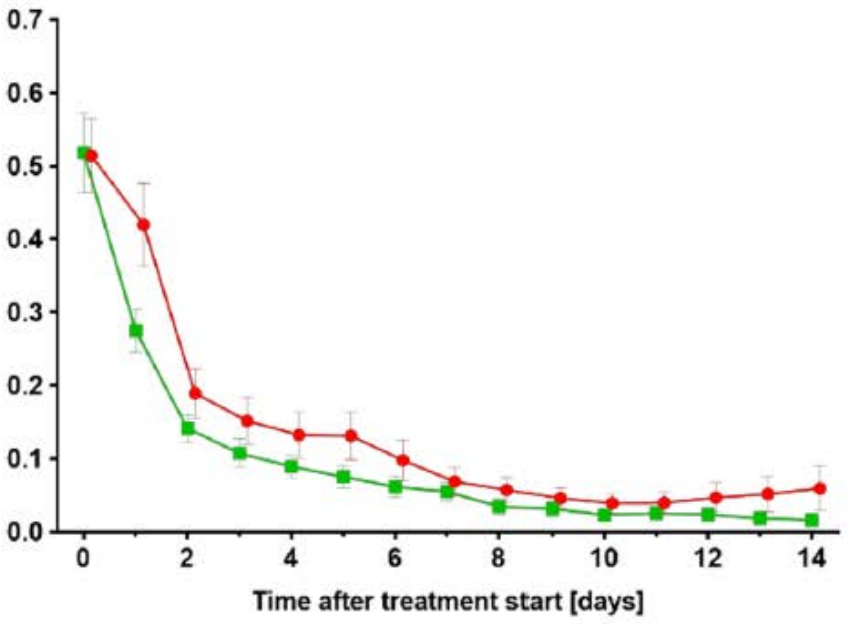




No difference in blood pressure but slower decrease in vasopressors





Landiolol for heart rate control in patients with septic shock and persistent tachycardia. A multicenter randomized clinical trial (Landi-SEP)

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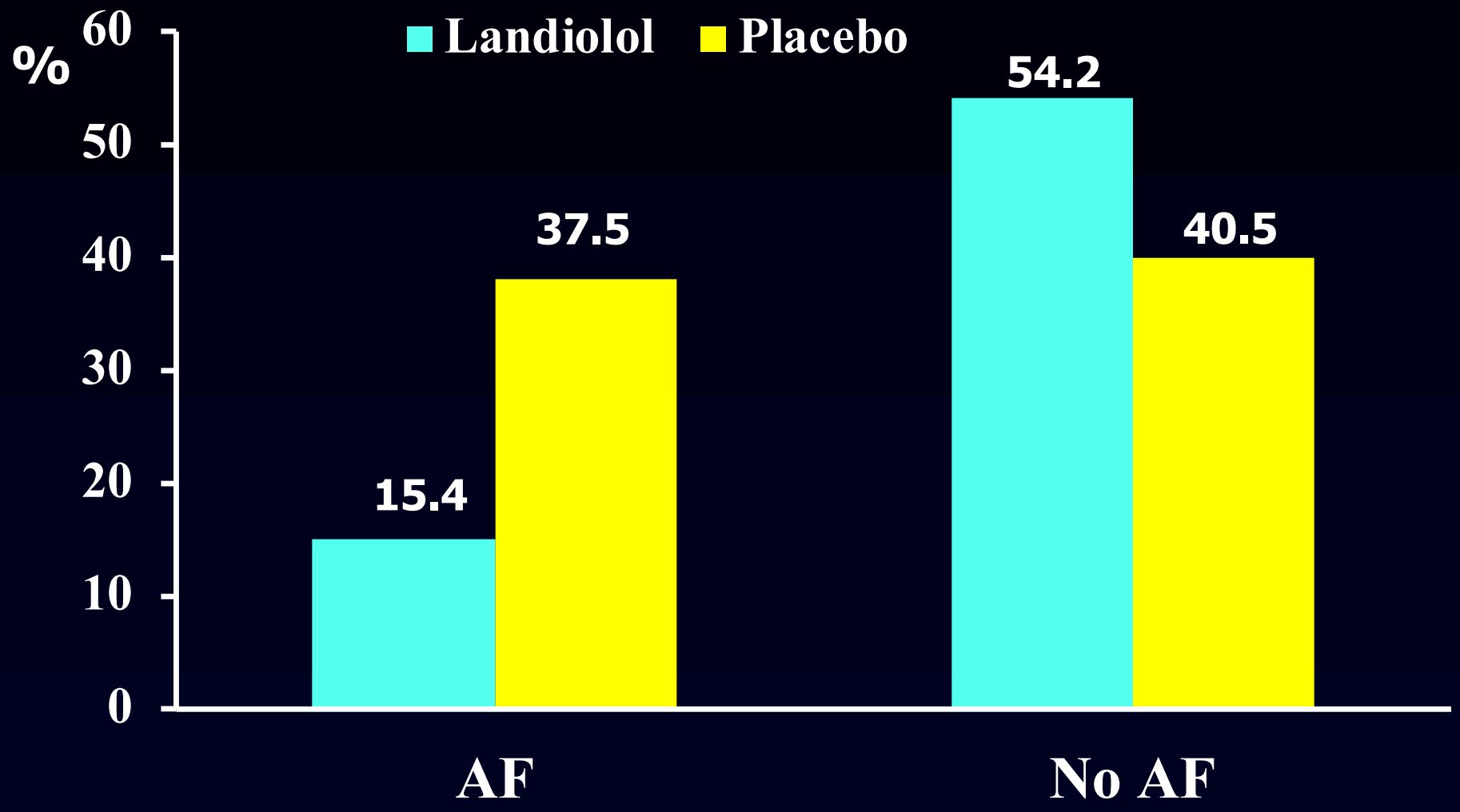
Secondary outcomes

Response	Landiolol group ($n = 98$)	Control group ($n = 98$)	Overall	Effect estimate (95% CI)	*P* value
28-day mortality, n (%)[a]	43 (43.9)	39 (40.2)	82 (42.1)	MD, 3.8% (– 9.9 to 17.3%)	0.60
ICU mortality, n (%)[b]	43 (43.9)	33 (34)	76 (39)	MD, 9.9% (– 3.8 to 23%)	0.16
Duration of ICU stay for patients alive on day 28, median (95% CI), days	14 (10.2–15.3)	13.9 (10.2–20.4)	–	HR, 1.17 (0.70–1.94)	0.55
Duration of hospital stay for patients alive on day 28	–	–	–	HR, 0.80 (0.41–1.54)	0.50

N = 186

Secondary analyses of LANDI-SEP: Atrial fibrillation

28-day mortality



N =				
186	n=26	n=24	n=72	n=74

(Un)Expected side effects of beta blockers in sepsis:

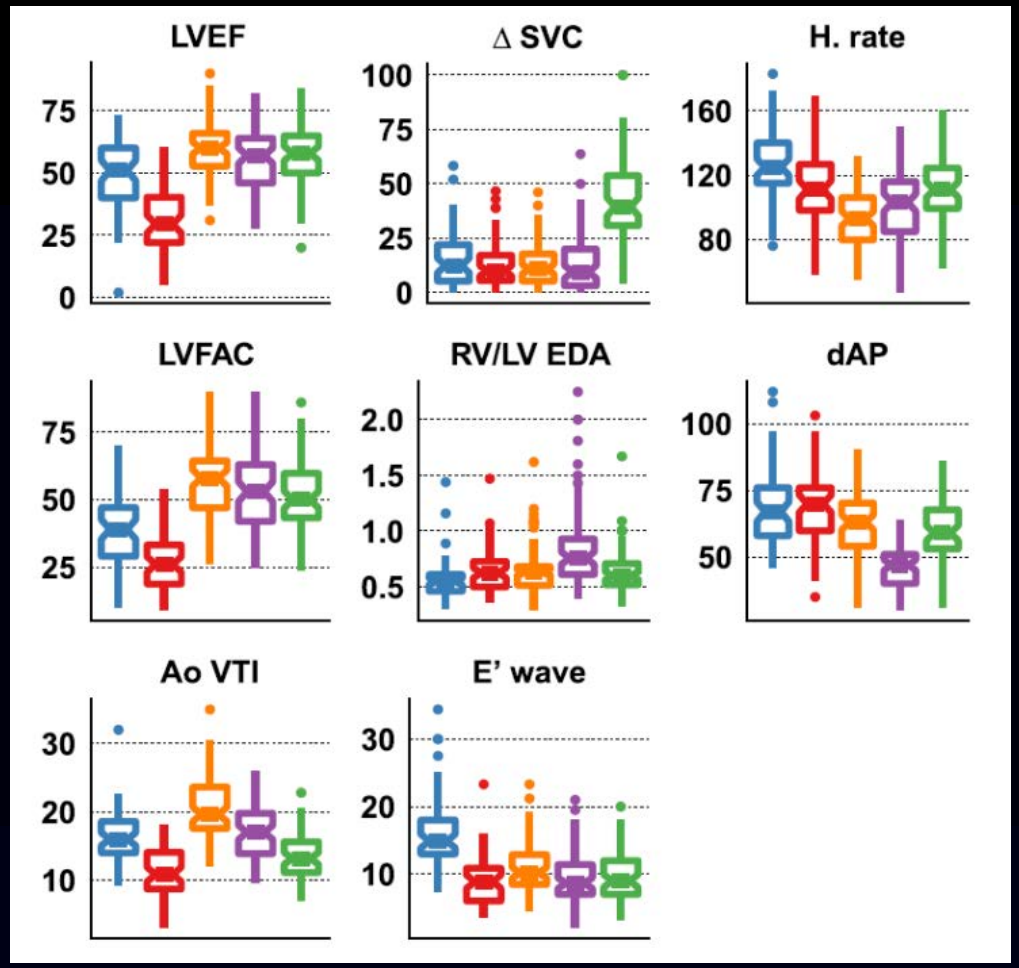
how to manage them?

Identification of the right patient

Ideally <u>before</u> administration of beta-blockers

Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis

Geri G et al
ICM 2019



- **LV systolic dysfunction 64(18%)**

  LVEF <40% & Ao VTI <14cm & LVFAC <33%

- **RV failure 81(23%)**

  RV/LV EDA >0.8 & sABP <100mmHg & dABP <51mmHg

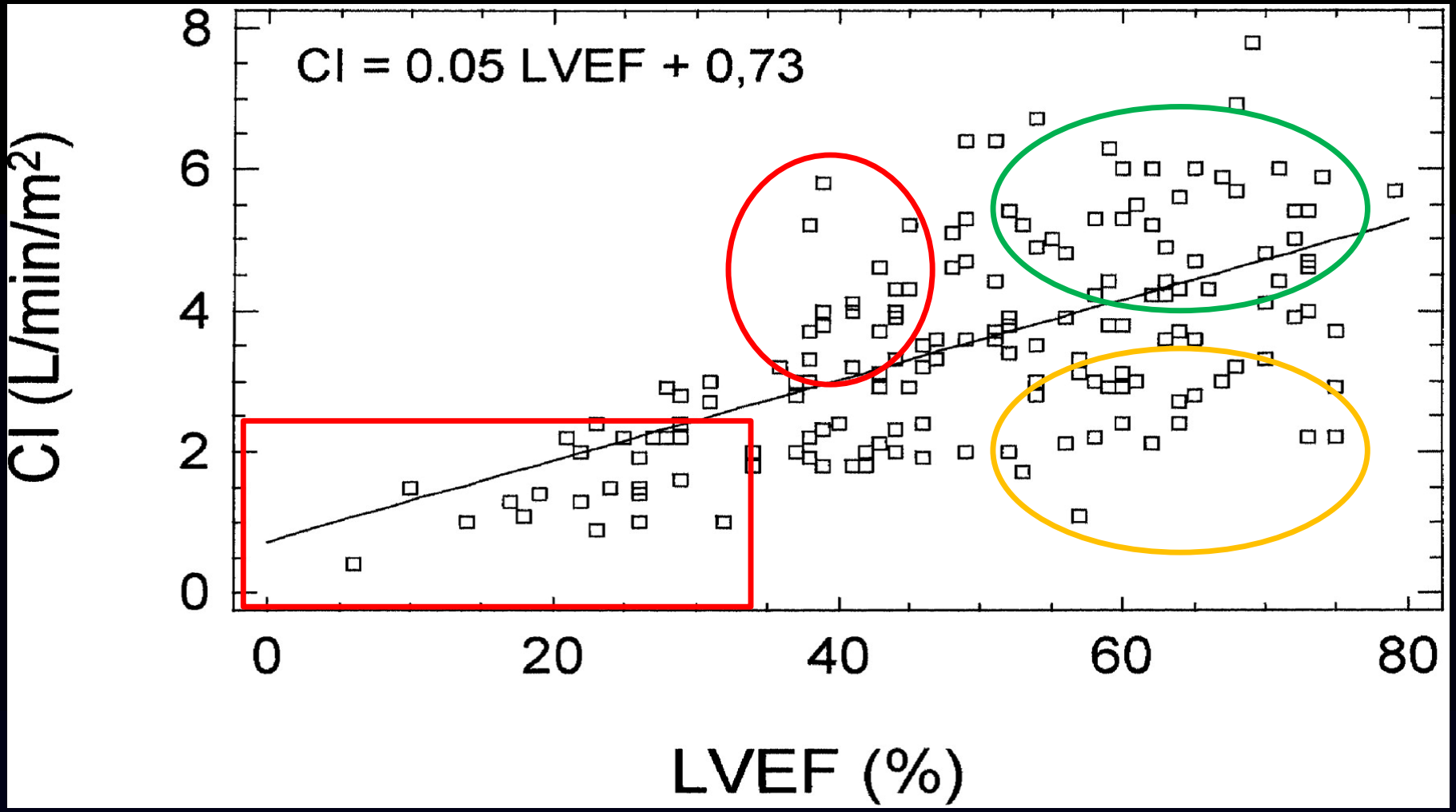
- **Still hypovolemic 70(19%)**

  Ao VTI < 16 cm & E wave < 67 cm/s & SVC > 39 %

N= 360

Which patients for beta-blockers?

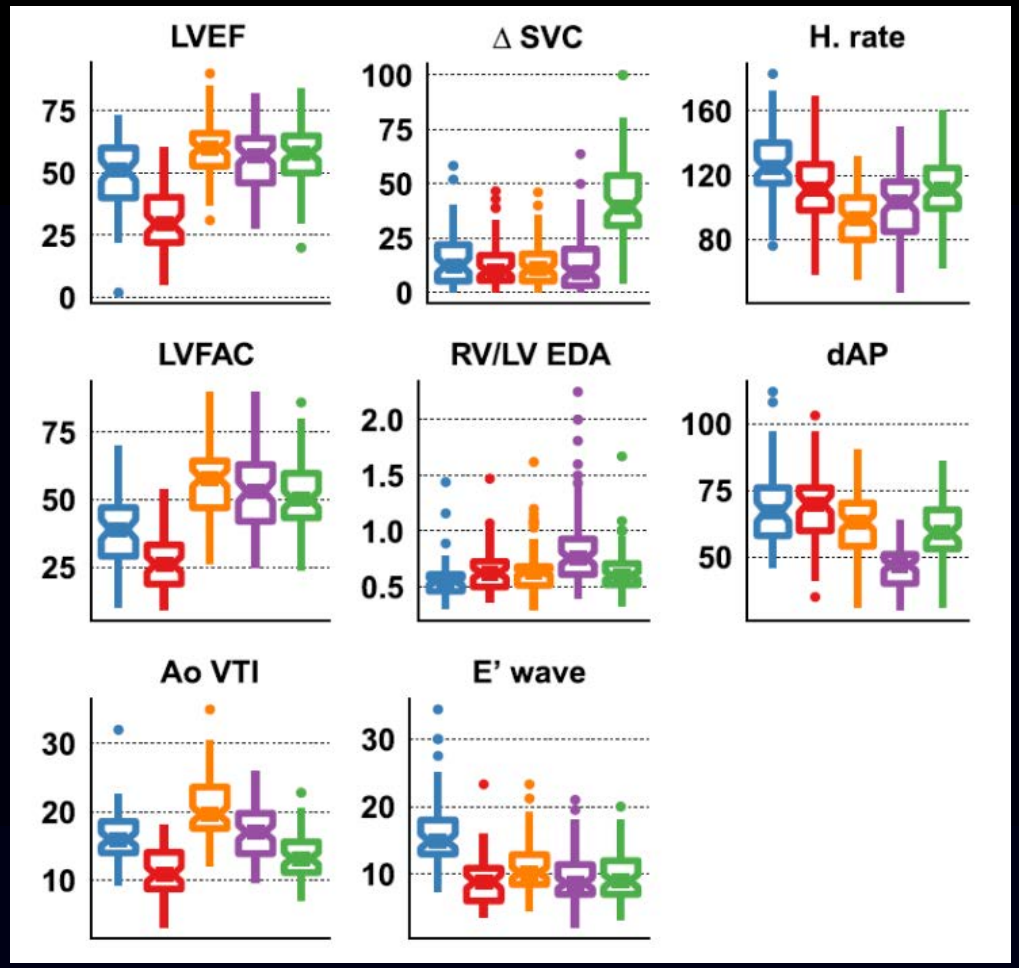
Vieillard-Baron et al
AJRCCM 168:1270;2003



Patients with septic shock

Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a post hoc analysis

Geri G et al
ICM 2019

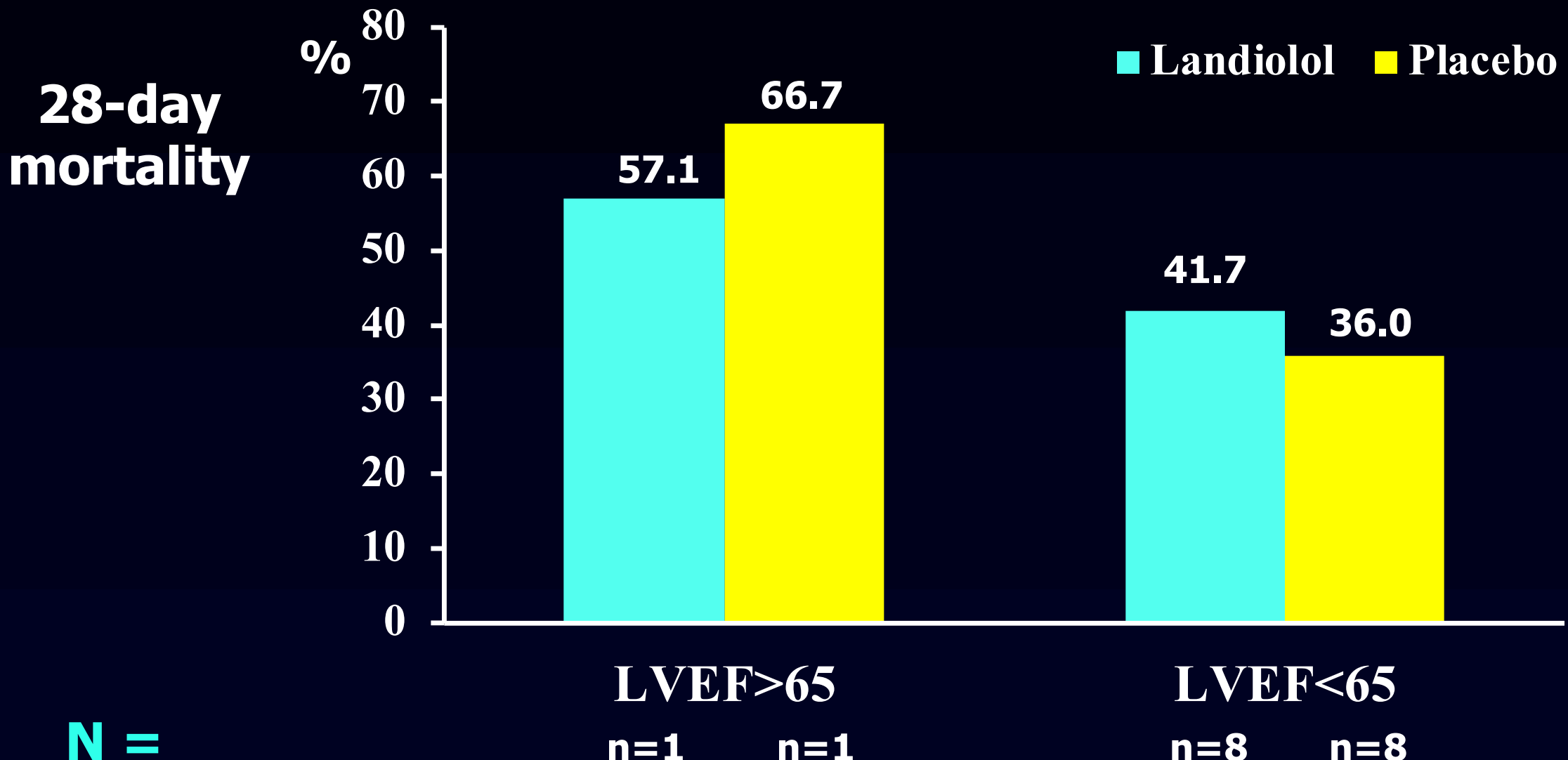


- **Well resuscitated** 61(17%)
- **LV systolic dysfunction** 64(18%)
  - LVEF <40% & Ao VTI <14cm & LVFAC <33%
- **Hyperkinetic** 84(23%)
  - Ao VTI >20cm & Heart rate <106bpm & LVFAC >58%
- **RV failure** 81(23%)
  - RV/LV EDA >0.8 & sABP <100mmHg & dABP <51mmHg
- **Still hypovolemic** 70(19%)
  - Ao VTI < 16 cm & E wave < 67 cm/s & SVC > 39 %

N= 360

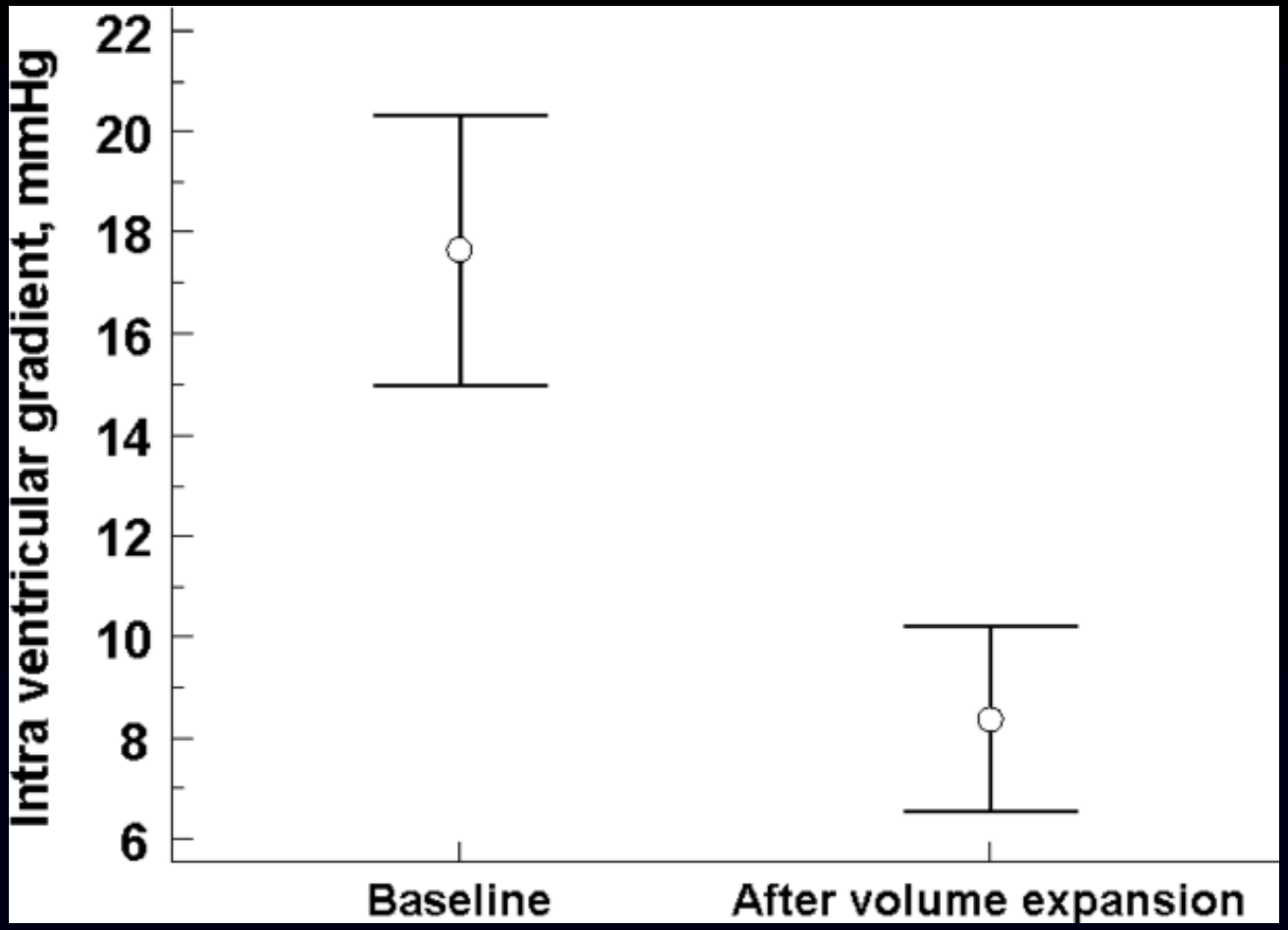
Secondary analyses of LANDI-SEP: Hyperkinetic (high EF)

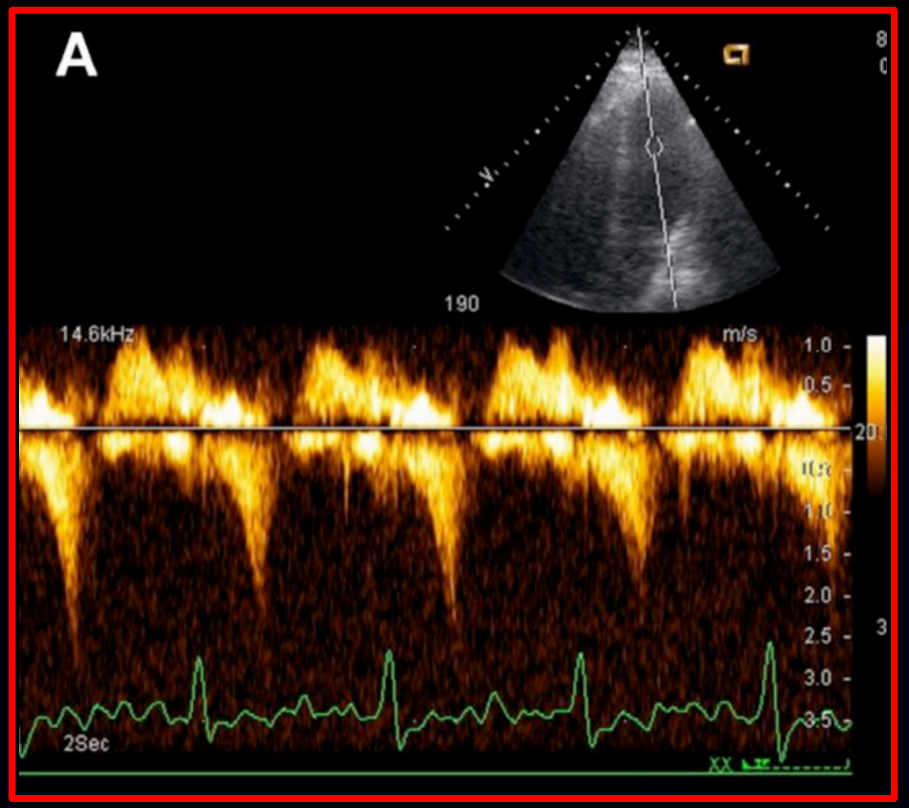
Rehberg-S
ICM 2024



Patients with LVOT obstruction may be excellent candidates !

218 pts septic shock
=> 47 pts with LVOT





Chauvet JL et al
Crit Care 2015

How to evaluate cardiac function with echo ?

LV systolic

- Ejection fraction
- S wave Mitral annulus
- dP/dT
- Strain rate

LV diastolic

- Mitral annulus E and A
- Strain rate

RV

- Dimension
- Shape (D shape)
- IV septum
- Tricuspid annulus
  - TAPSE
  - S wave
- Strain rate

Original Article

Efficacy and Safety of Esmolol in Treatment of Patients with Septic Shock

Wei Du, Xiao-Ting Wang, Yun Long, Da-Wei Liu

Department of Critical Care Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

Du W et al
Chin Med J
129:1658; 2016

Variables	With SV increase (n = 42)	Without SV increase (n = 21)	t	P
Age (years)	49.4 ± 17.0	52.4 ± 13.0	−0.2	0.474
Sex (male, %)	47.6	47.6	−0.1	0.924
APACHE II	16.1 ± 5.5	14.3 ± 4.2	0.3	0.542
Mechanical ventilation (%)	73.5	66.9	0.1	0.679
Baseline cardiac function (%)			−0.1	0.982
NYHA I	54.8	52.4		
NYHA II	35.7	38.1		
NYHA III	9.5	9.5		
NE dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.45 ± 0.18	0.48 ± 0.19	−0.1	0.487
Maximum dose of esmolol (mg/h)	110.6 ± 76.8	116.4 ± 89.9	−0.2	0.237
Total dose of esmolol (mg)	197.6 ± 108.7	184.5 ± 113.9	0.2	0.458
Time to achieve target heart rate (h)	1.7 ± 0.3	1.7 ± 0.5	0.1	0.786

SV: Stroke volume; APACHE: Acute Physiology and Chronic Health Evaluation; NYHA: New York Heart Association; NE: Norepinephrine.

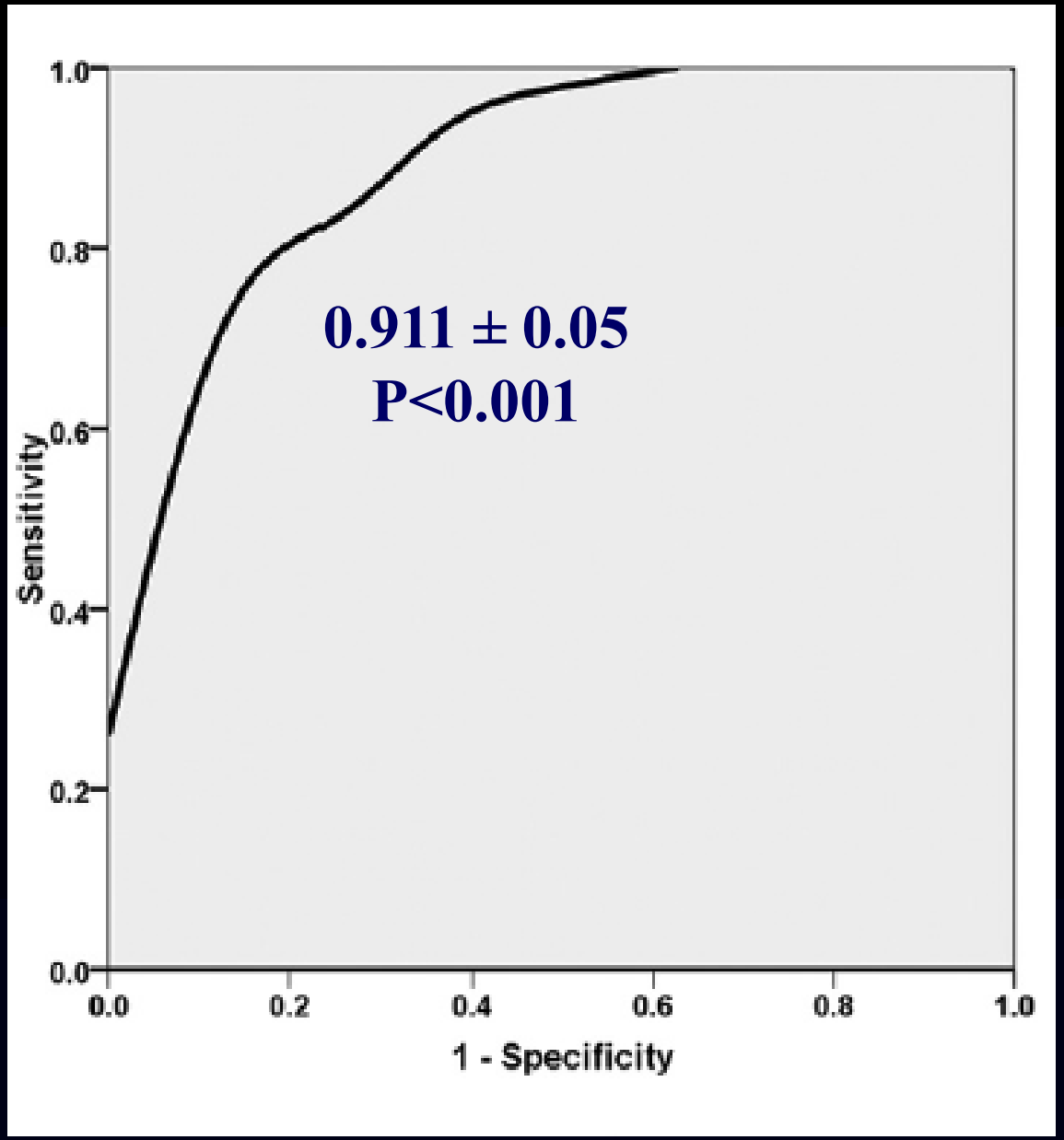
No obvious difference in clinical patterns between responders and non responders

MAPSE lat predicts the response of SV to esmolol

Du W et al
Chin Med J
129:1658; 2016

MAPSE lat 1.32

N=84



Do not forget other basic interventions before institution of Beta-blockers in sepsis

- Optimize fluid status
- Vasopressin derivatives instead of norepinephrine (and avoid epinephrine!)
- Temperature control
- Pain management

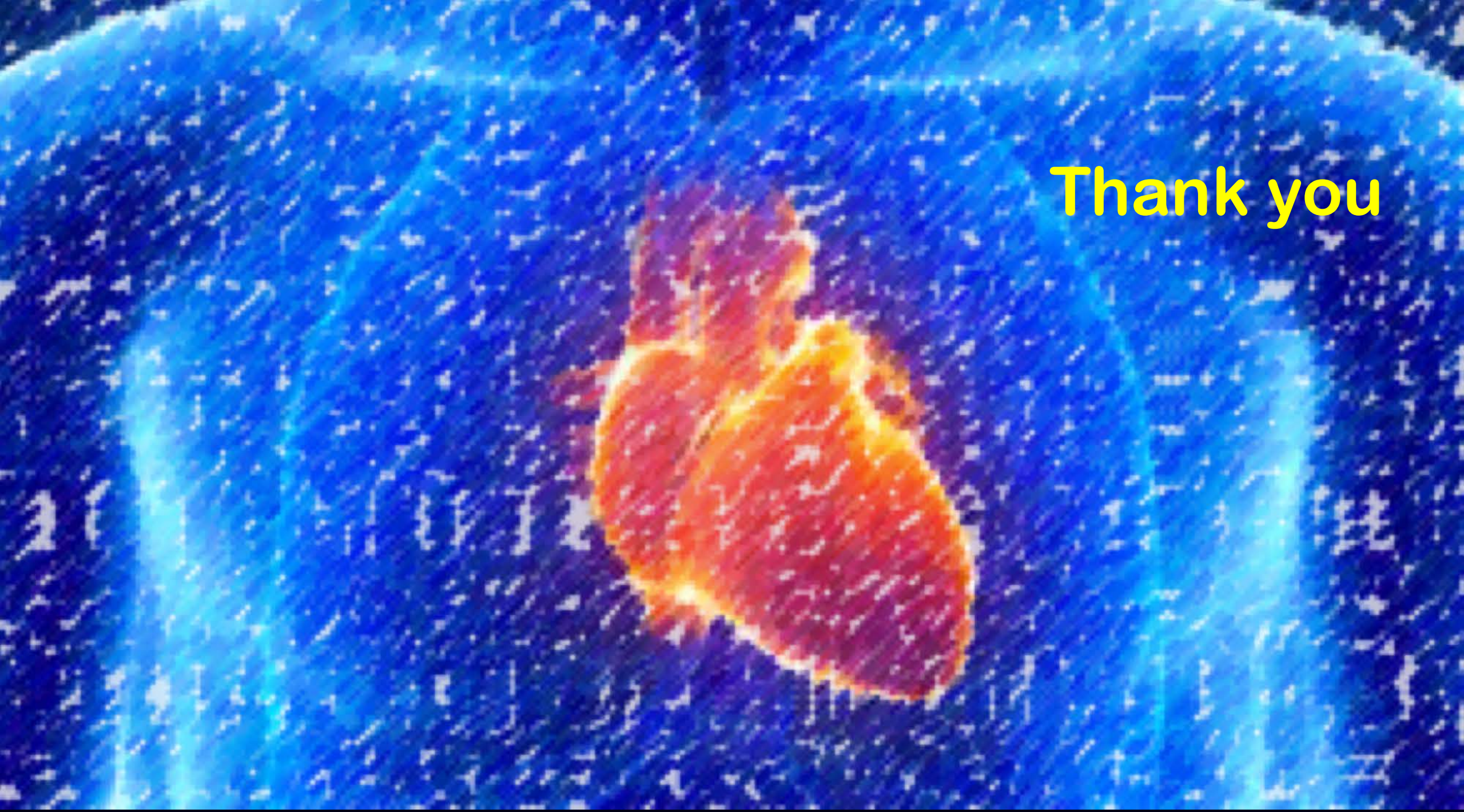
Beta-blockers in sepsis:

- The initial potentially beneficial effects of beta-blockers in sepsis are far from confirmed.

- Even after excluding patients with low cardiac output, up to 50% of the patients may fail to tolerate introduction of beta-blockers.

- Echocardiography may be particularly useful to identify patients who may / may not tolerate beta-blockers.

- If administered, the effects of Beta-blockers should be carefully evaluated, if possible in well conducted clinical trials.


Thank you