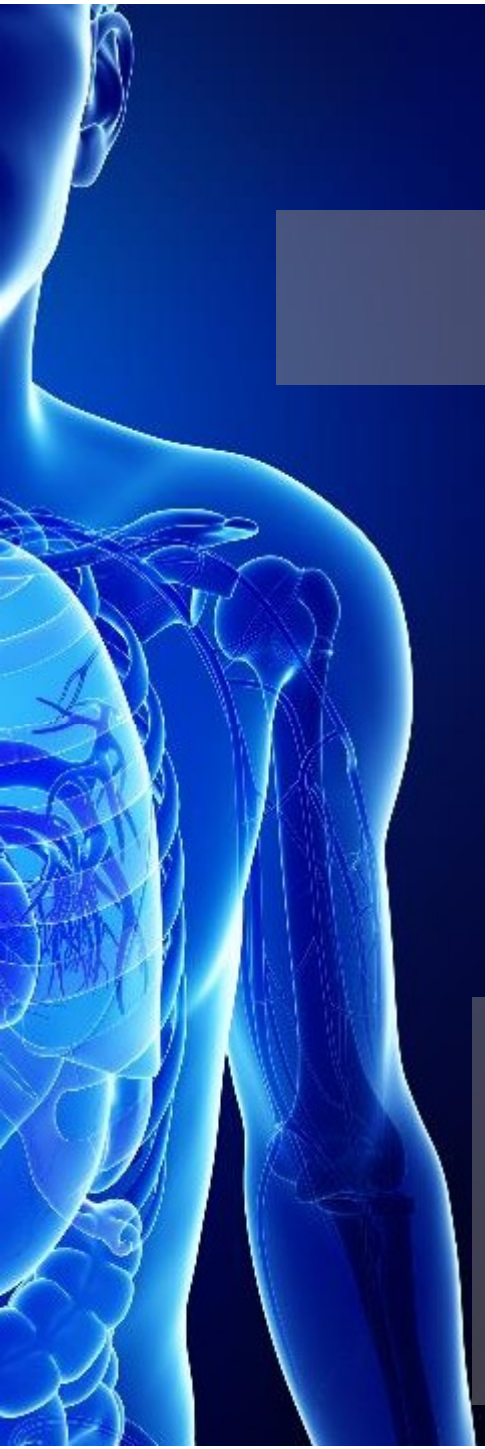


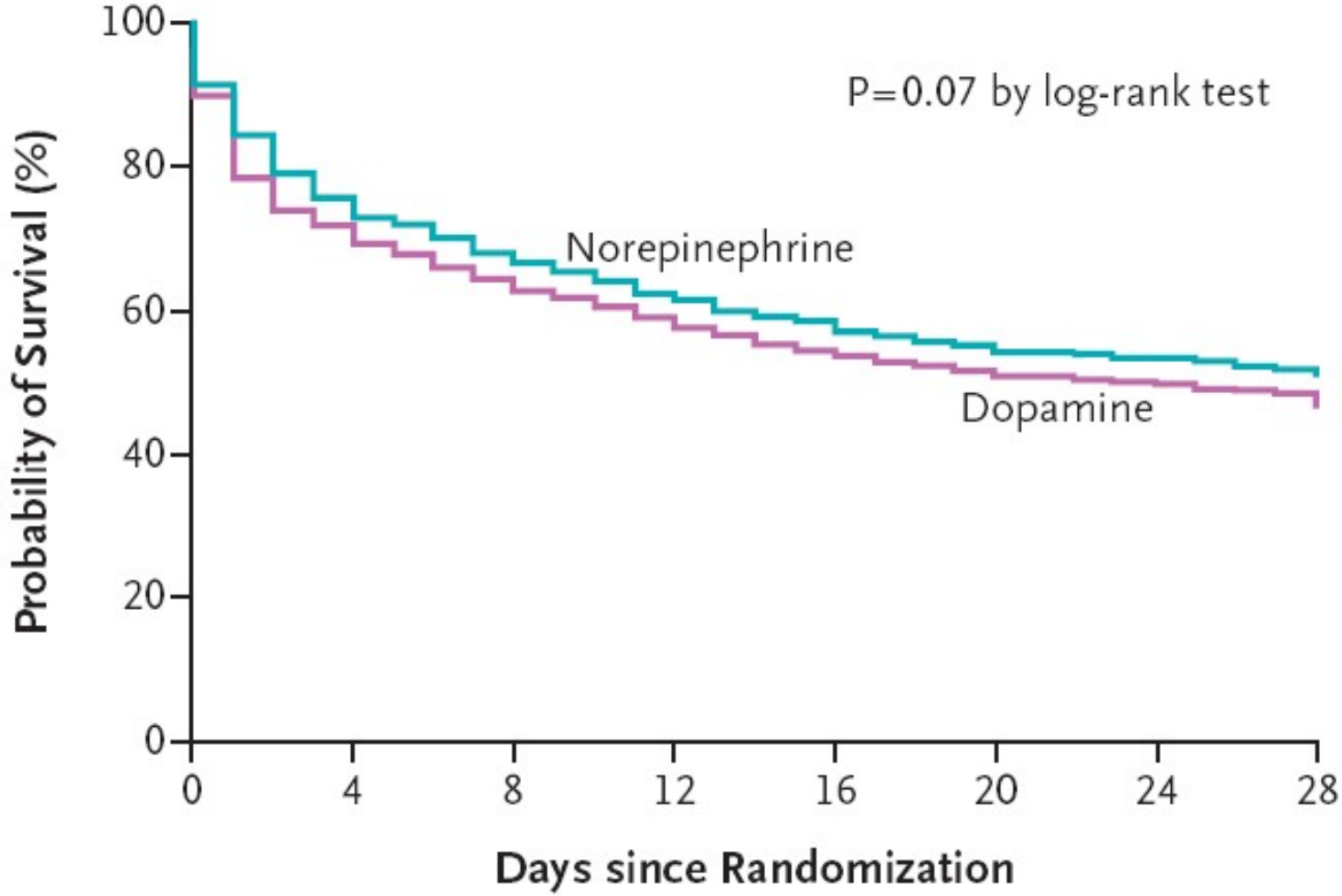
Place de la vasopressine

Daniel De Backer

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

Norepinephrine vs Dopamine in shock (SOAP investigators)

De Backer et a
NEJM 362: 779



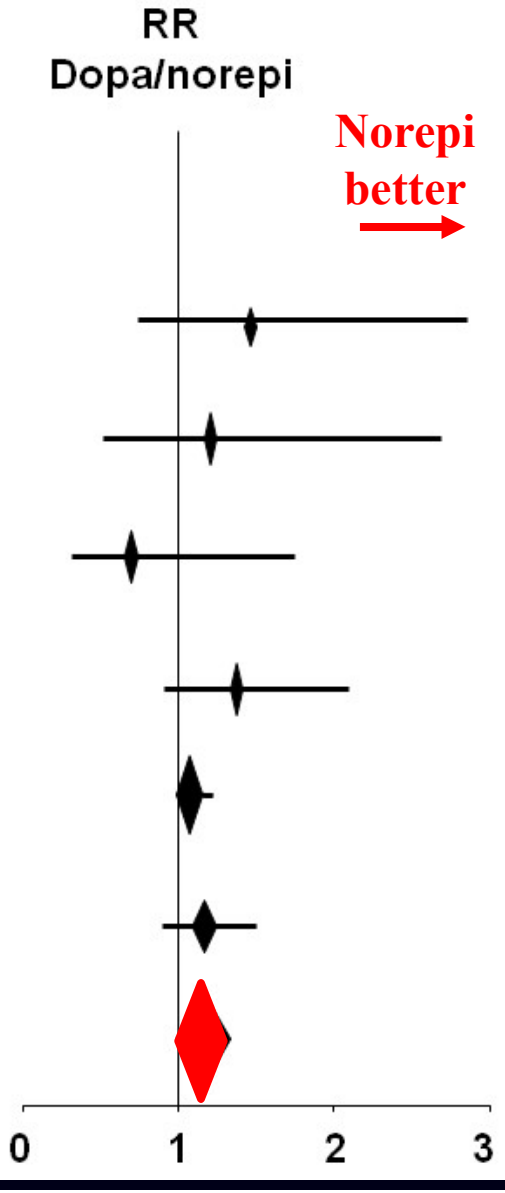
No. at Risk

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

Dopamine vs norepinephrine in septic shock
A meta-analysis

De Backer e
CCM 40:725

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]**

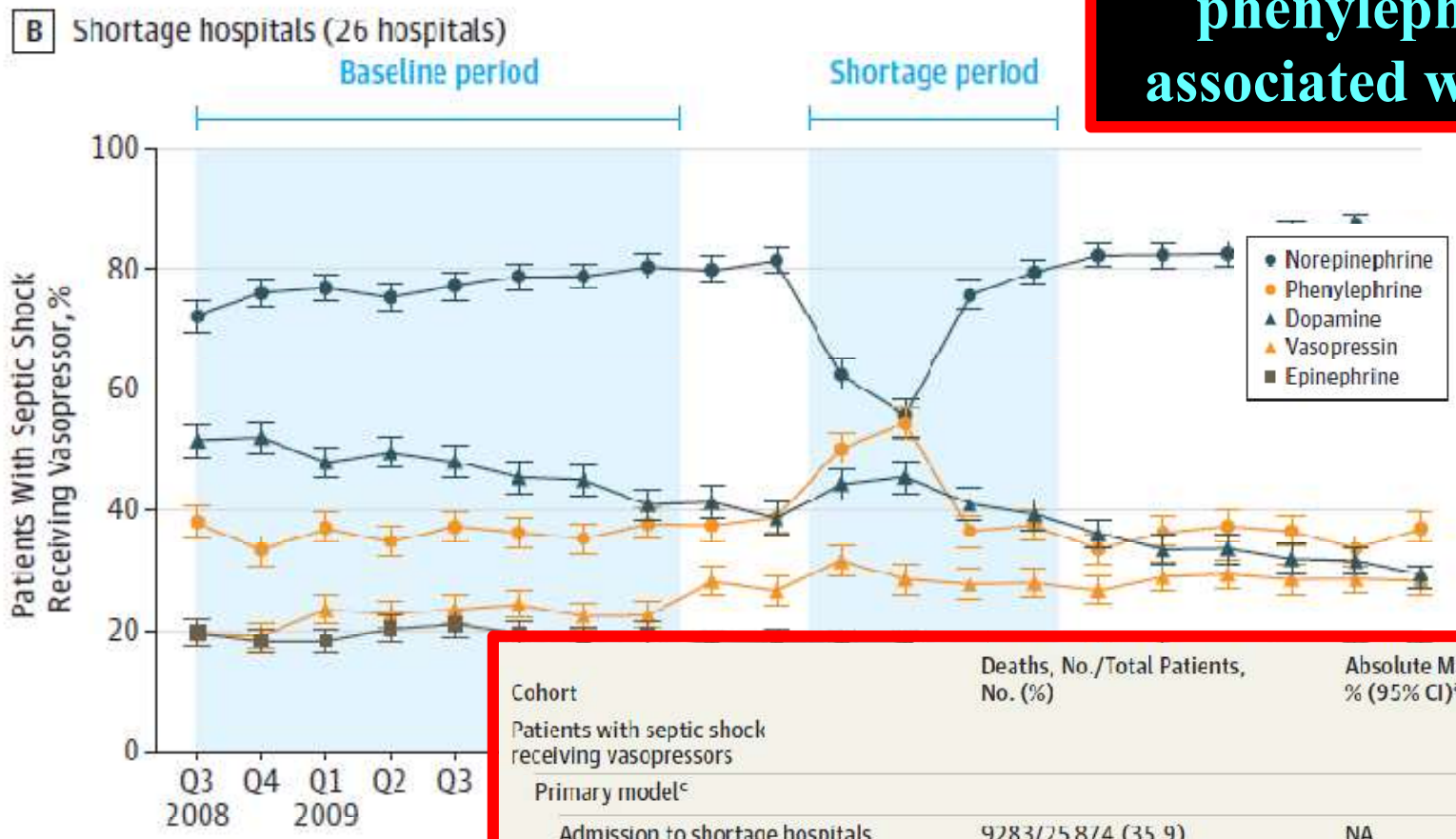


ociation Between US Norepinephrine Shortage Mortality Among Patients With Septic Shock

MD; Hayley B. Gershengorn, MD; May Hua, MD, MSc; Allan J. Walkey, MD, MSc; benfeld, MD, MSc; Hannah Wunsch, MD, MSc

Vail E e
JAMA

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

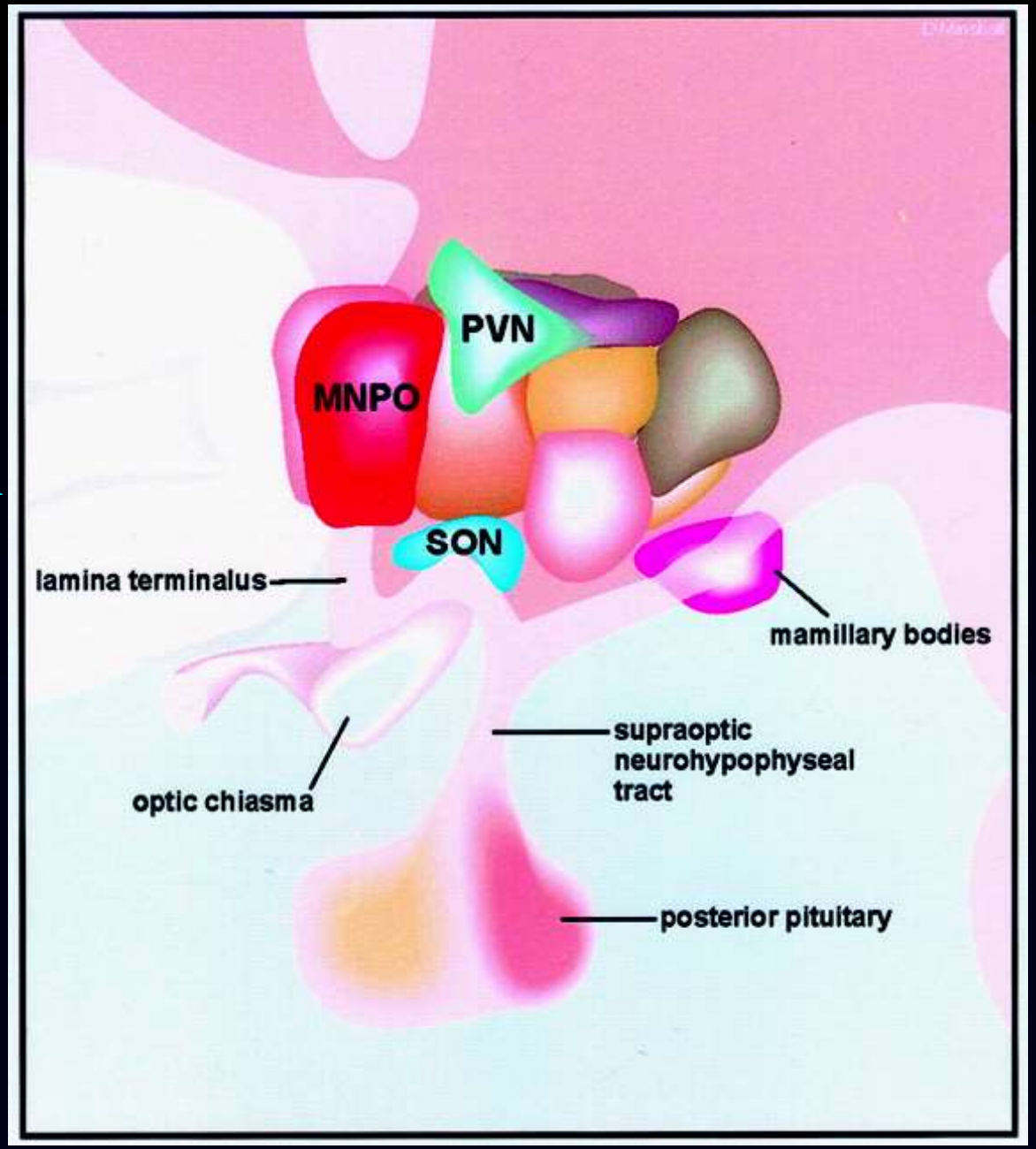

Vasopressin as an alternative?

VASOPRESSIN

Holmes et al
Chest 120:989;2

Nonapeptide hormone
ynthetized in supraoptic
nd paraventricular nuclei
f the hypothalamus

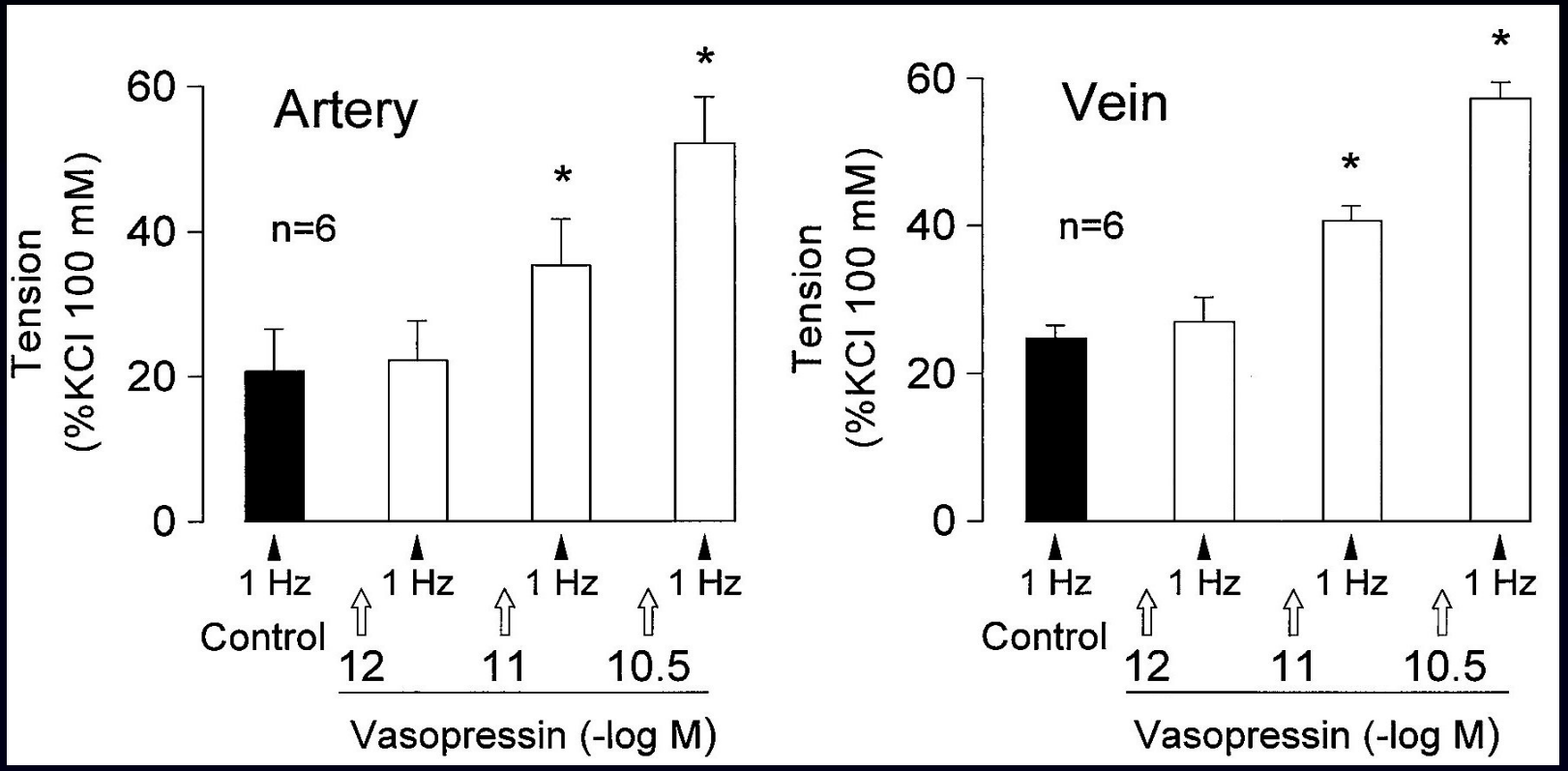
Transported and stored
n the posterior pituitary



Physiologic effects of vasopressin:

Segarra et al
J Pharm Exp T
286: 1315; 199

Pressure regulation



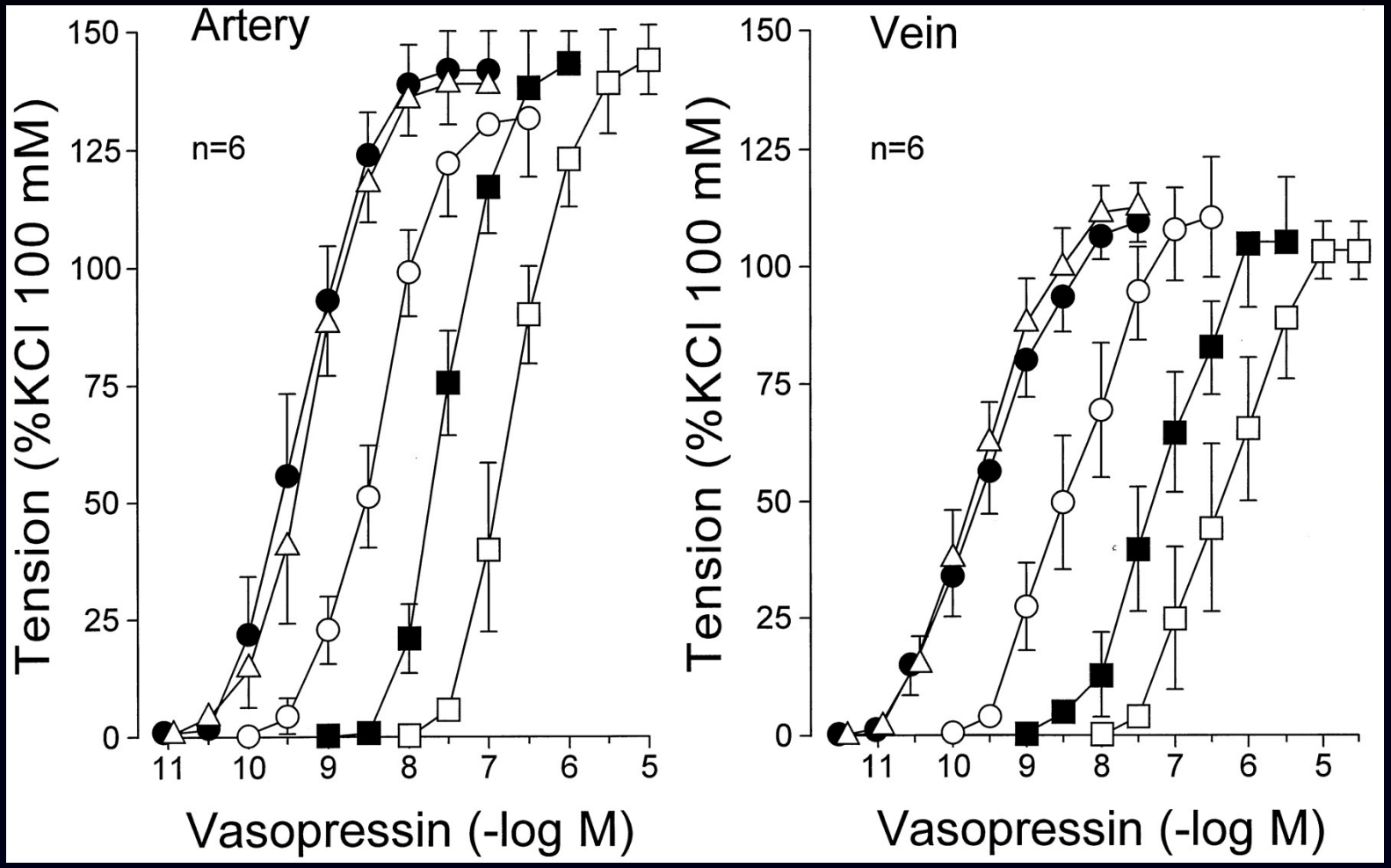
Vasopressin induces arterial and venous constriction

DDB U

Physiologic effects of vasopressin:

Segarra et al
J Pharm Exp
286: 1315; 199

1 receptor receptors are implicated in vasopressin induced vasoconstriction

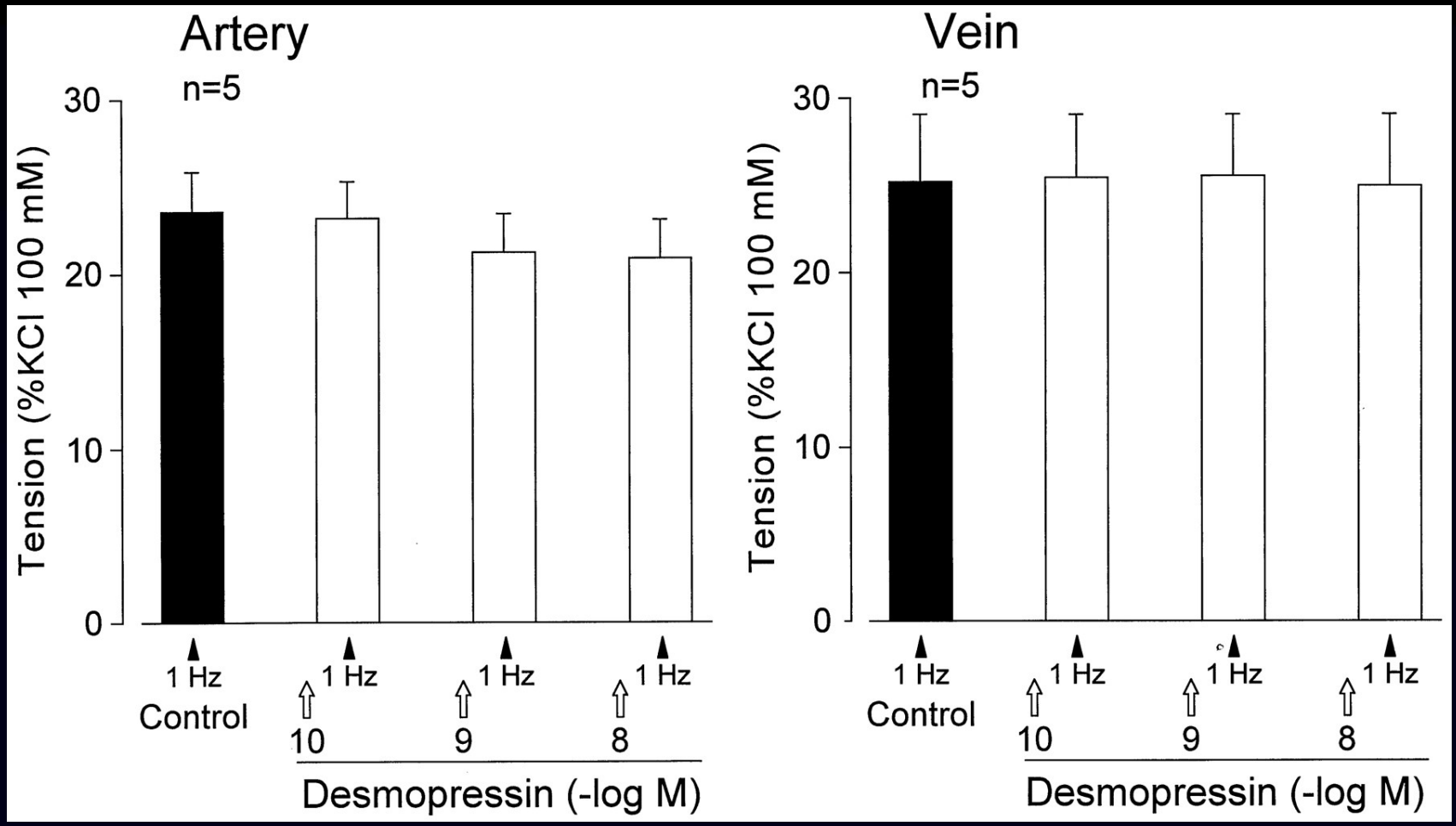


ctrl ==> increasing dose of V1 antagonist

DDB

Physiologic effects of vasopressin:

Segarra et al
J Pharm Exp T
286: 1315; 199



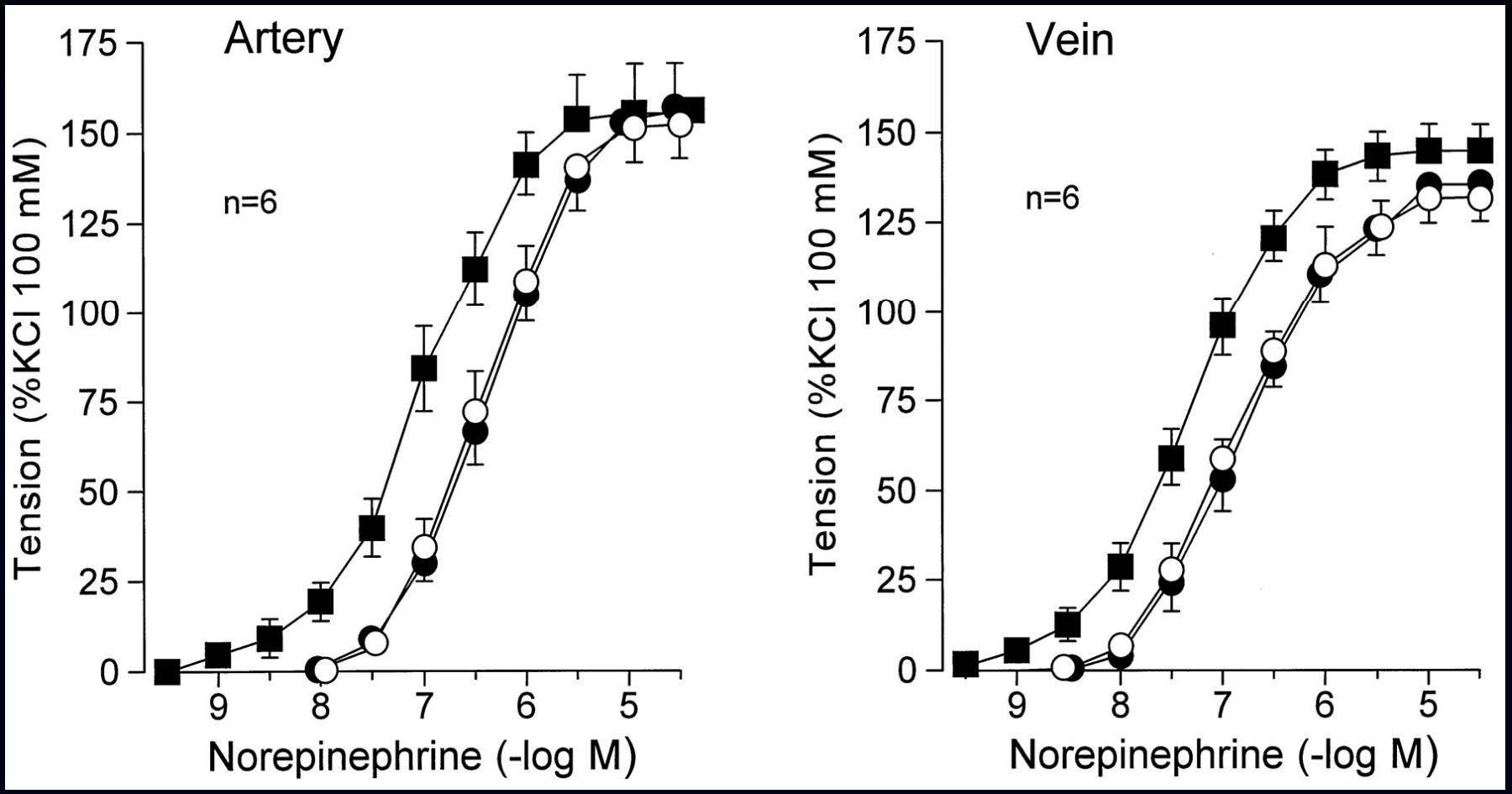
V1 but not V2 receptor stimulation induces arterial and venous constriction

DDB

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

VASOPRESSIN

Physiologic effects of vasopressin:

- V1 receptor => vasoconstriction
  phospholipase C and increased intracellular [CA]

- V2 receptor => antidiuretic action
  via adenylate cyclase stimilation and generation of cAMP

DDB

hysiologic 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)

DDB

VASOPRESSIN

sopressin 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)

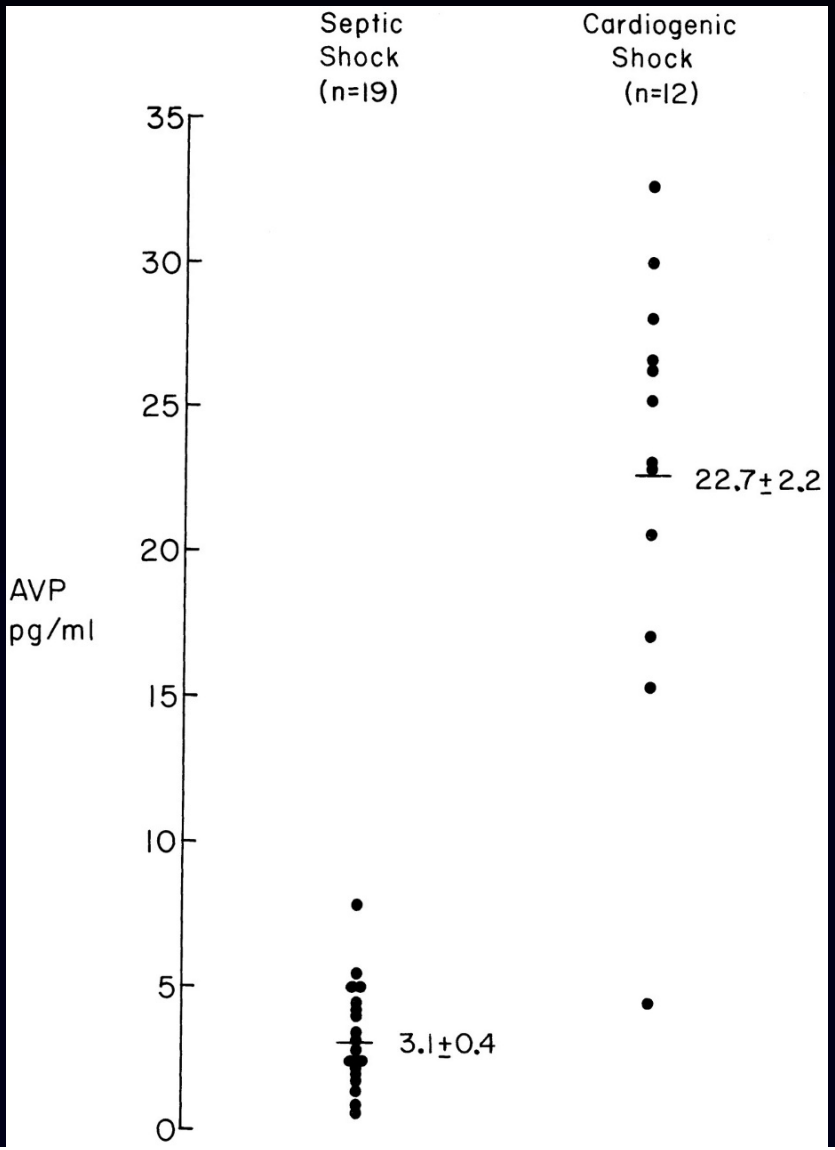
- **Inhibition of VP release**

  high NO and norepinephrine levels inhibit VP release

VASOPRESSIN

sopressin deficiency in septic shock

Landry et al
Circ 95:1122;1997

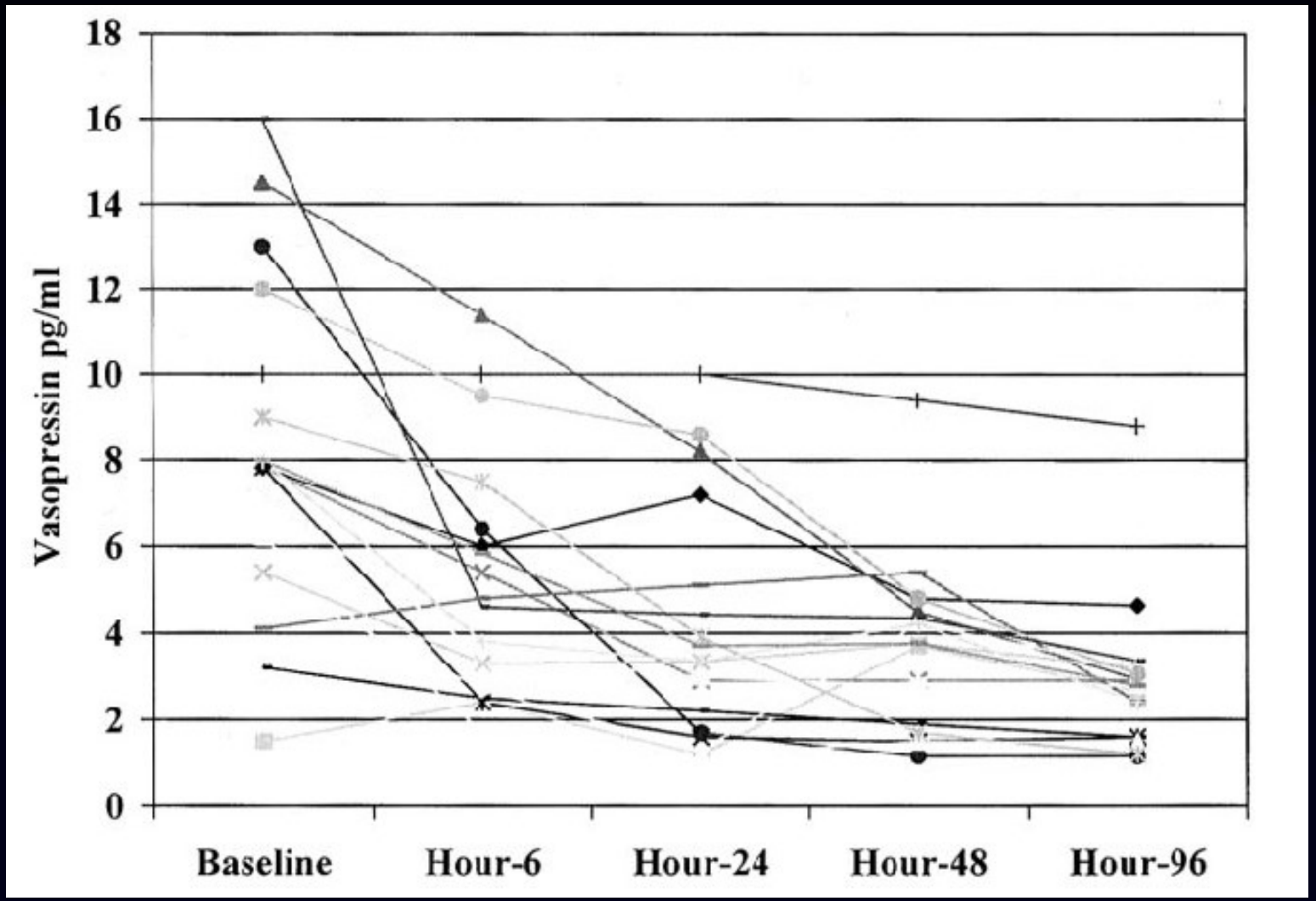


DDB

Vasopressin levels in septic shock

Sharshar et al
CCM 31:1752;

levels decrease with time



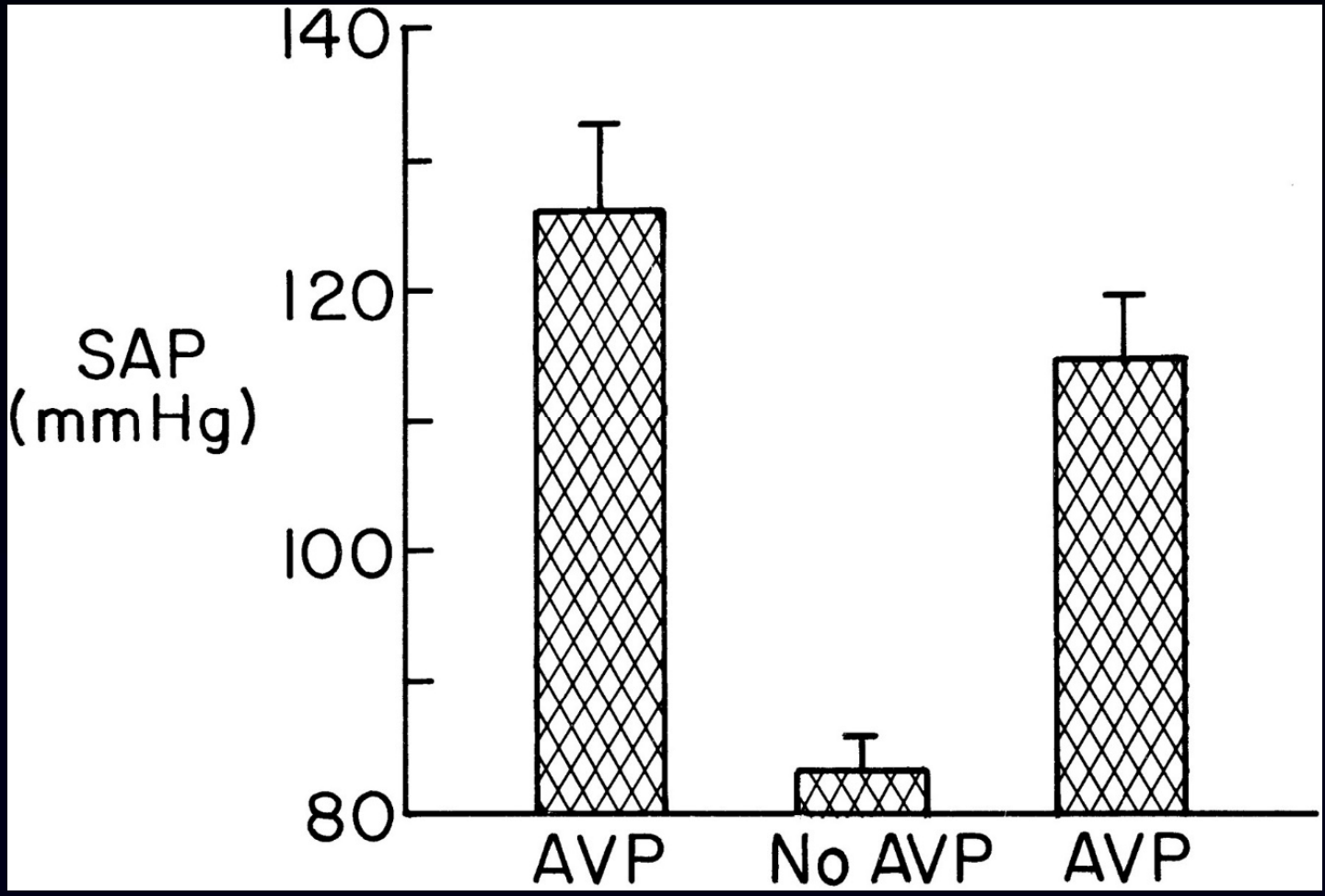
tic shock n=18

DDB

VASOPRESSIN

opressin deficiency in septic shock

Landry et al
Circ 95:1122;19

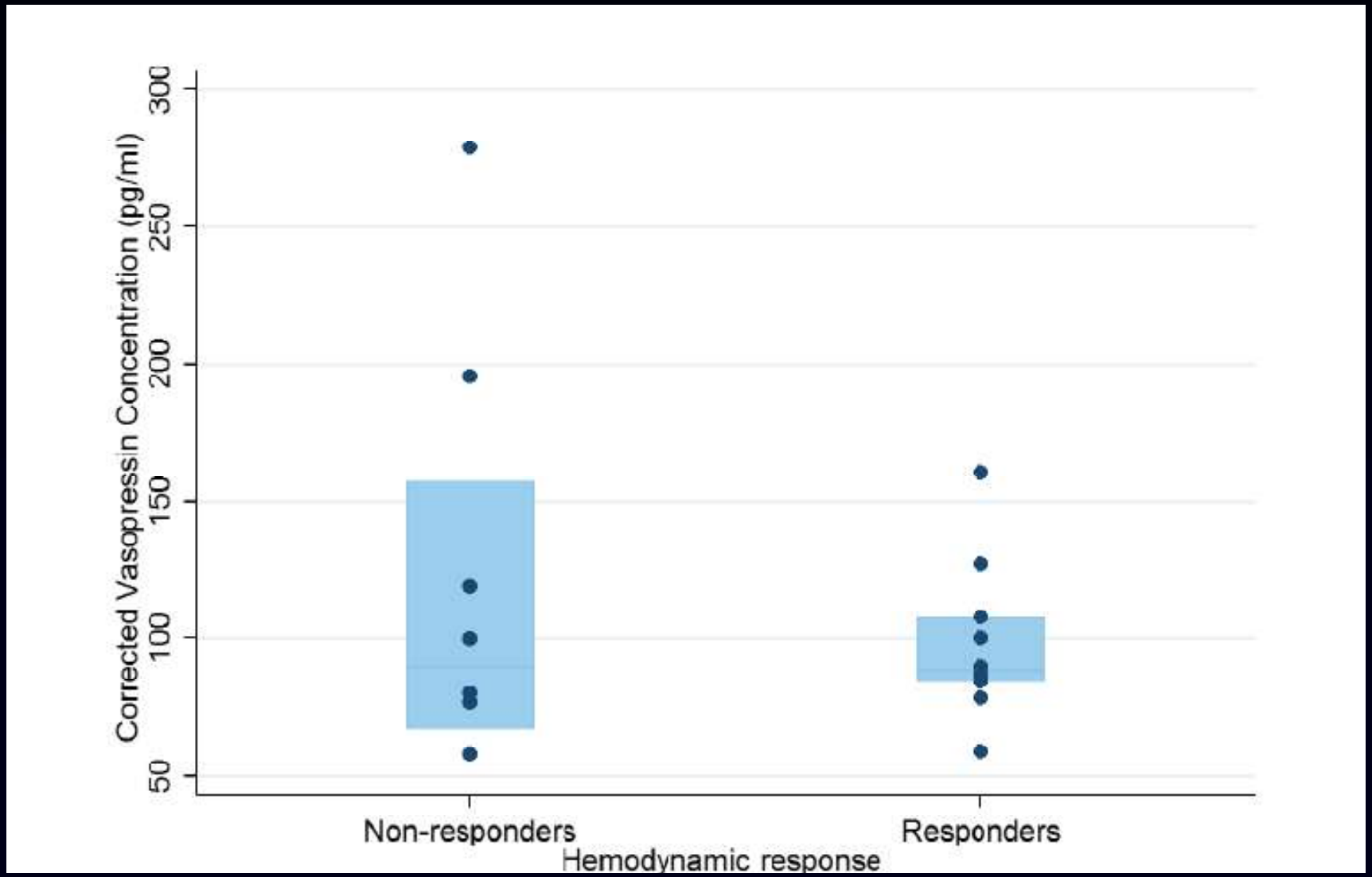


=> restoration of blood pressor by the administration of a small dose of vasopressin (0.04 u/min) normalizing VP levels

DDB

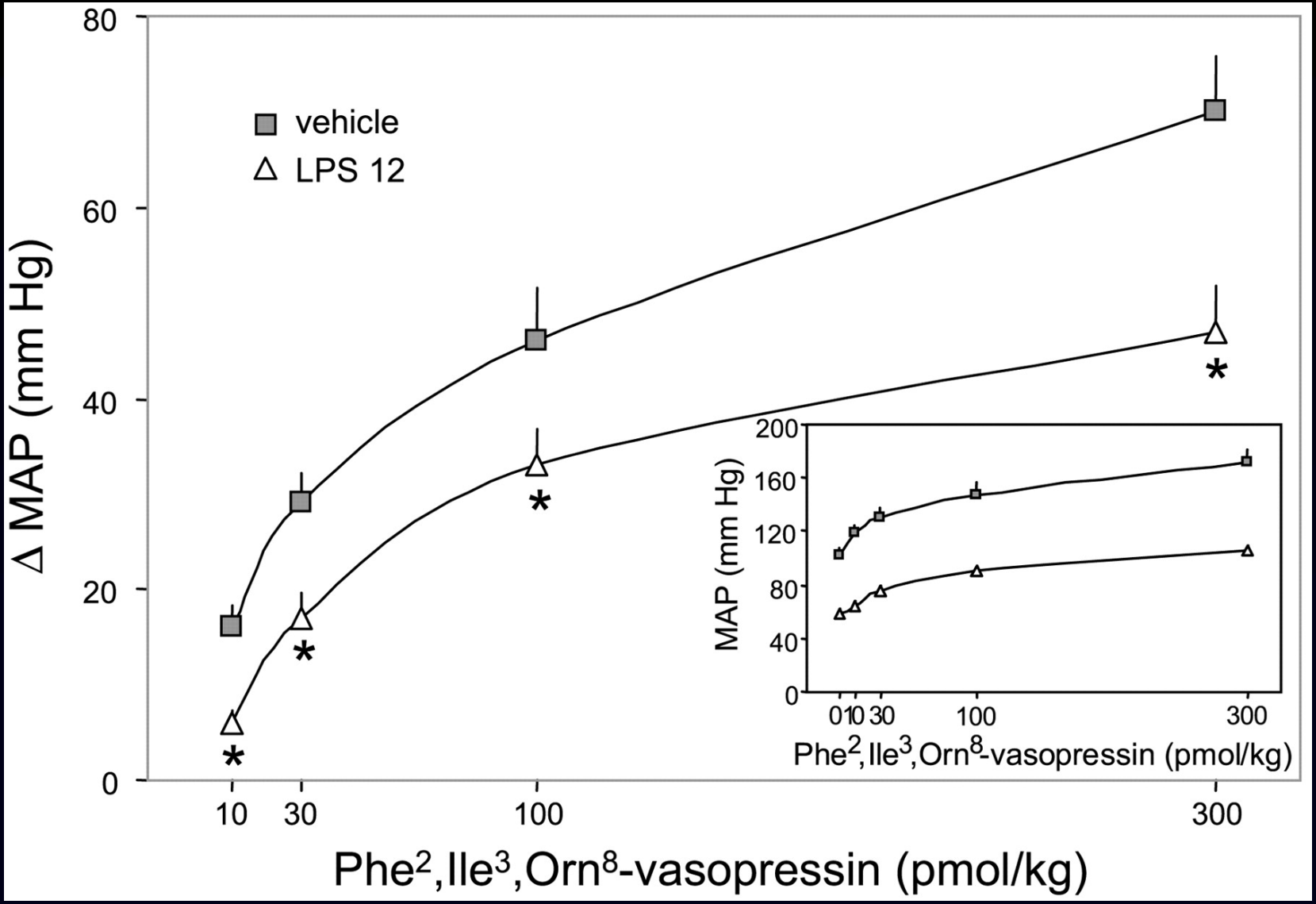
opressin Plasma Concentrations Are Not Associated
Hemodynamic Response to Exogenous Vasopressin
for Septic Shock

Yerke J et a
Pharmacother
2020



OWN REGULATION OF VASOPRESSIN RECEPTORS

Bucher et al
AJP 282:R979

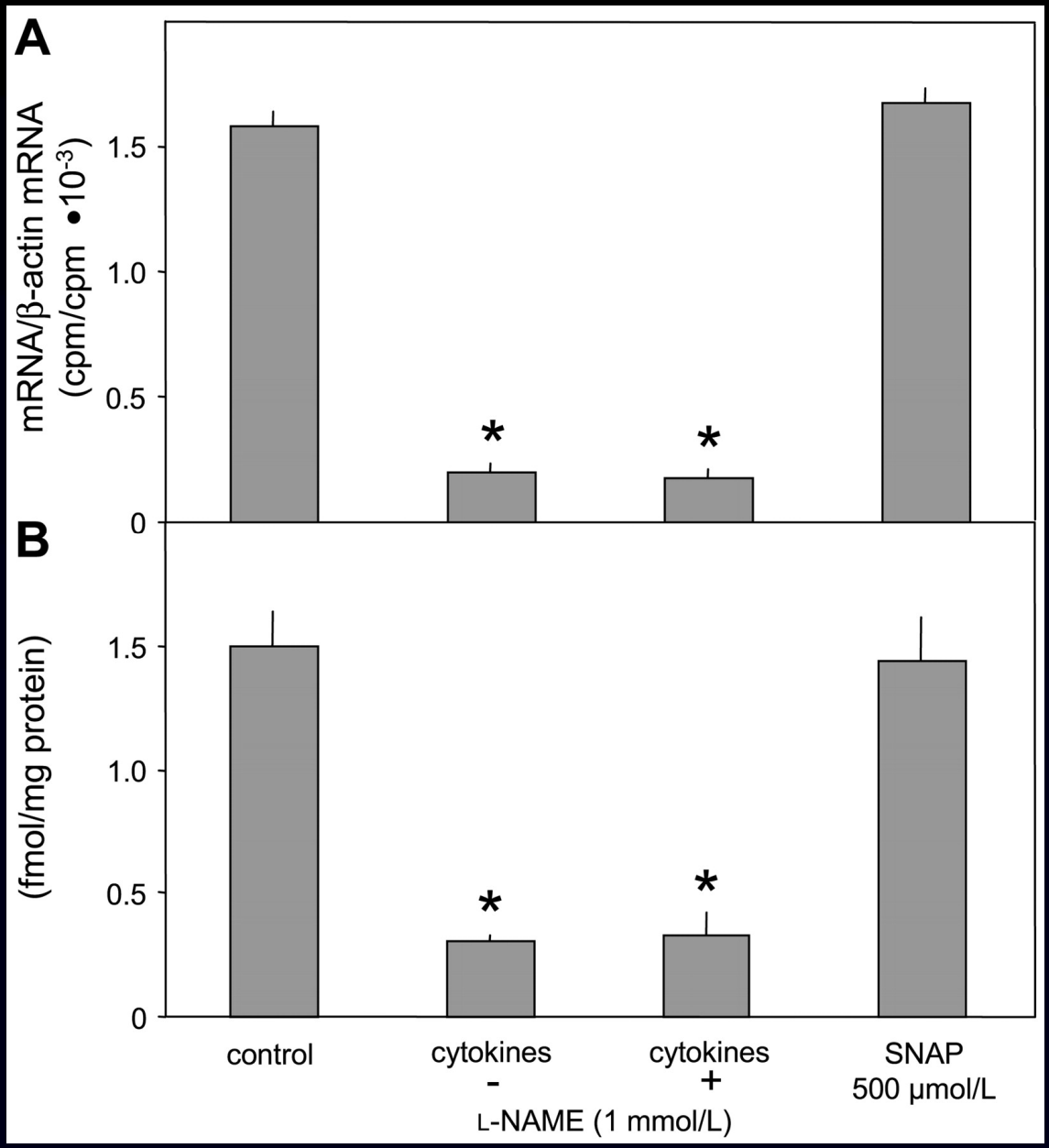


=> decreased sensibility to vasopressin in sepsis

DDB

WN REGULATION OF VASOPRESSIN RECEPTORS

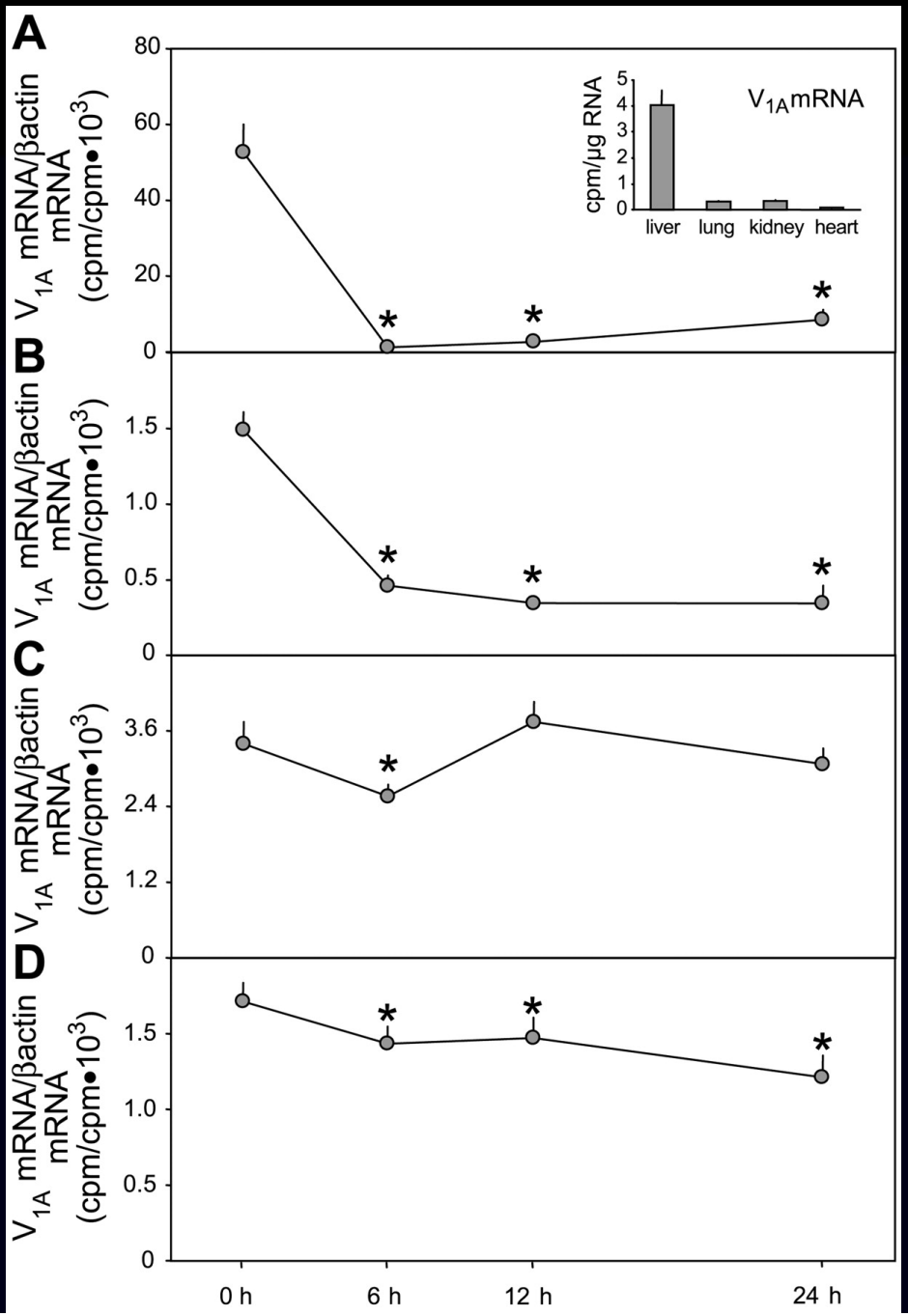
Bucher et al
AJP 282:R979;20



Related to cytokines, independently of NO

DDB

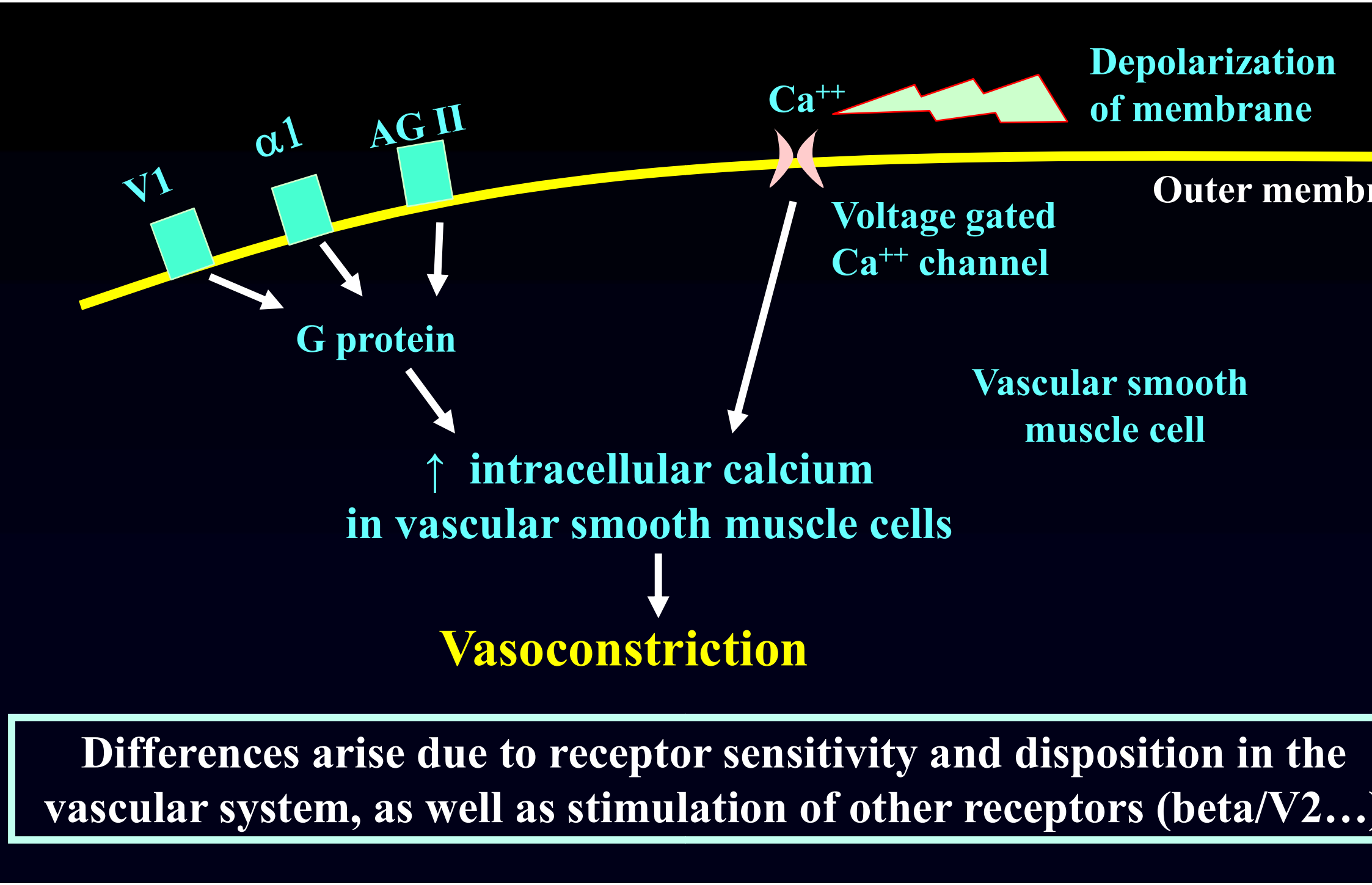
WN REGULATION OF VASOPRESSIN RECEPTORS



Bucher et al
AJP 282:R979;2002

Rapid decrease in V1 receptor mRNA transcription in various organs

DDB



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

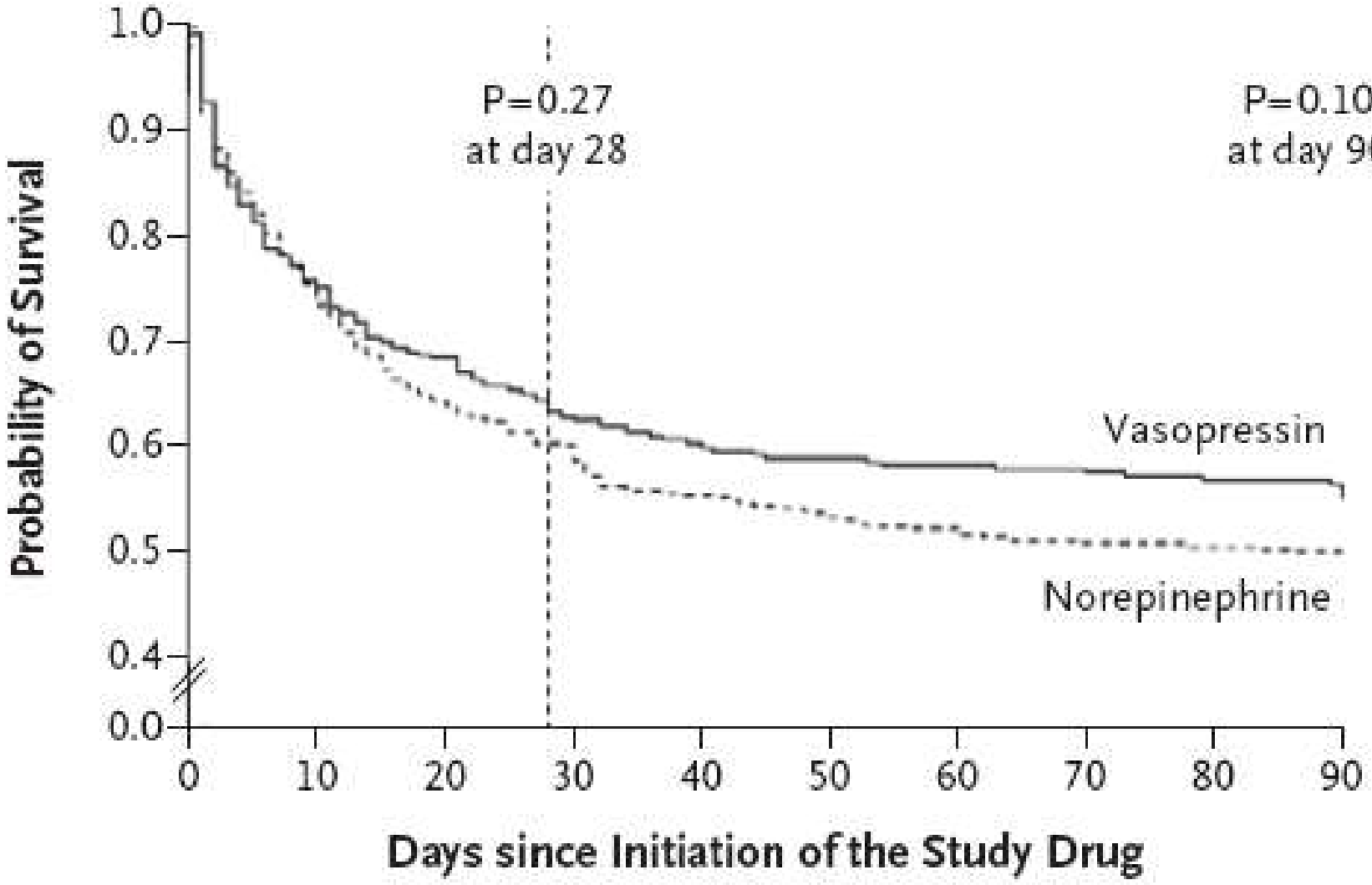
Evans
ICM 2
CCM 2

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.

ASST

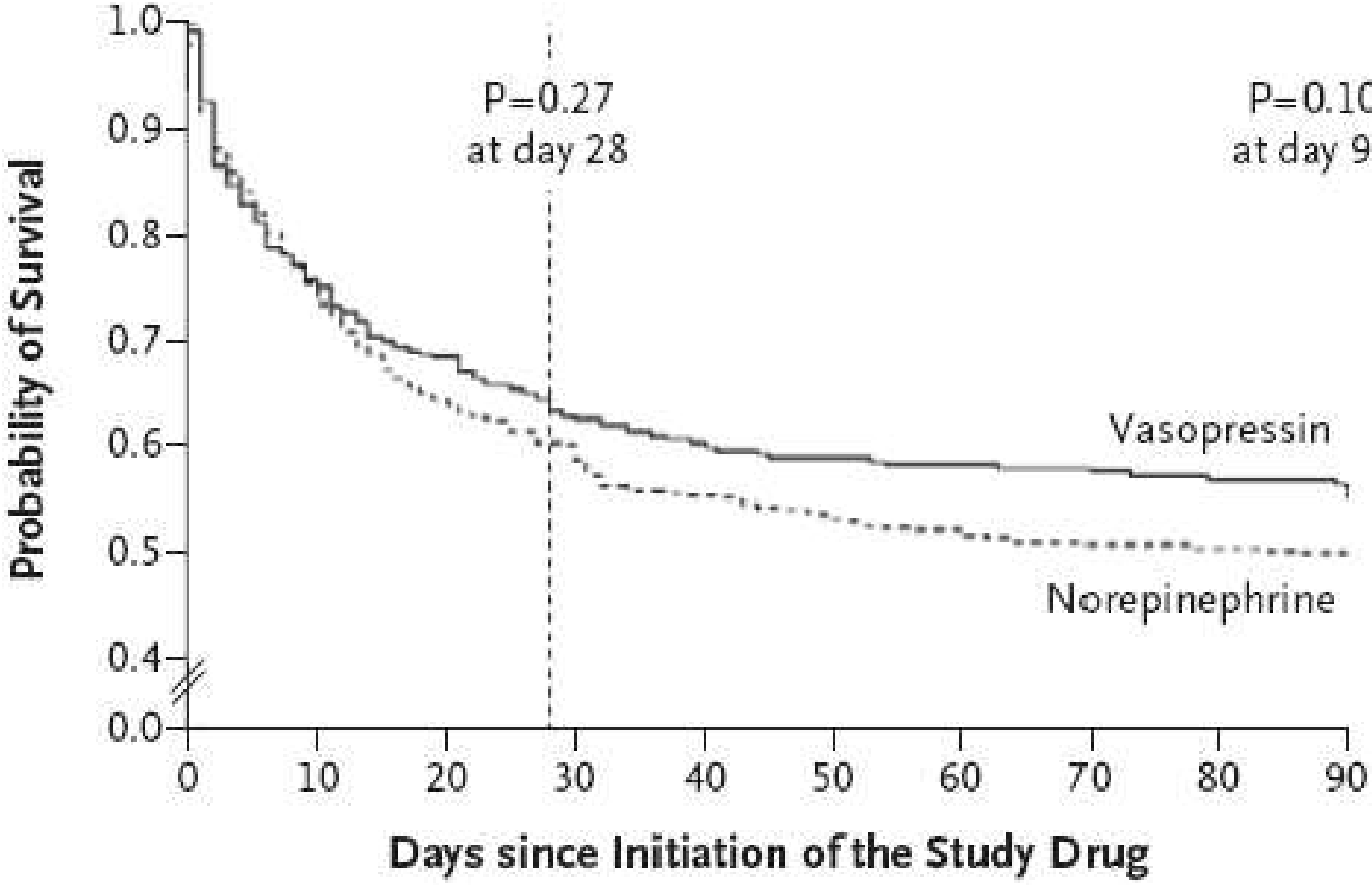
Russell et al
NEJM 358:877;



802 septic shock pts

VASST

Russell et al
NEJM 358:877;2



septic shock pts

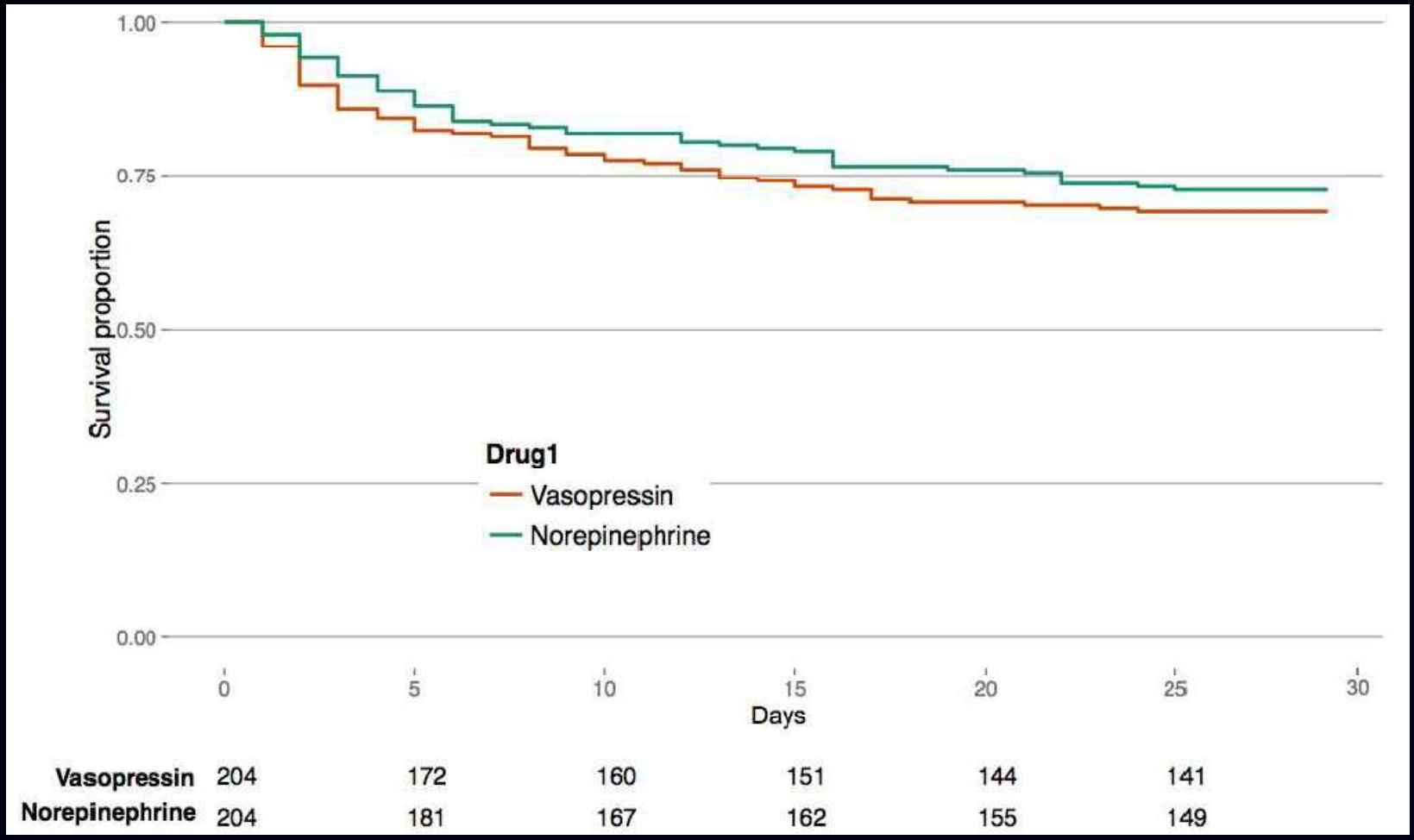
ginal Investigation

# of Early Vasopressin vs Norepinephrine on Kidney
e in Patients With Septic Shock
ANISH Randomized Clinical Trial

rdon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD;
a, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc;
umaran, 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
JAMA 2

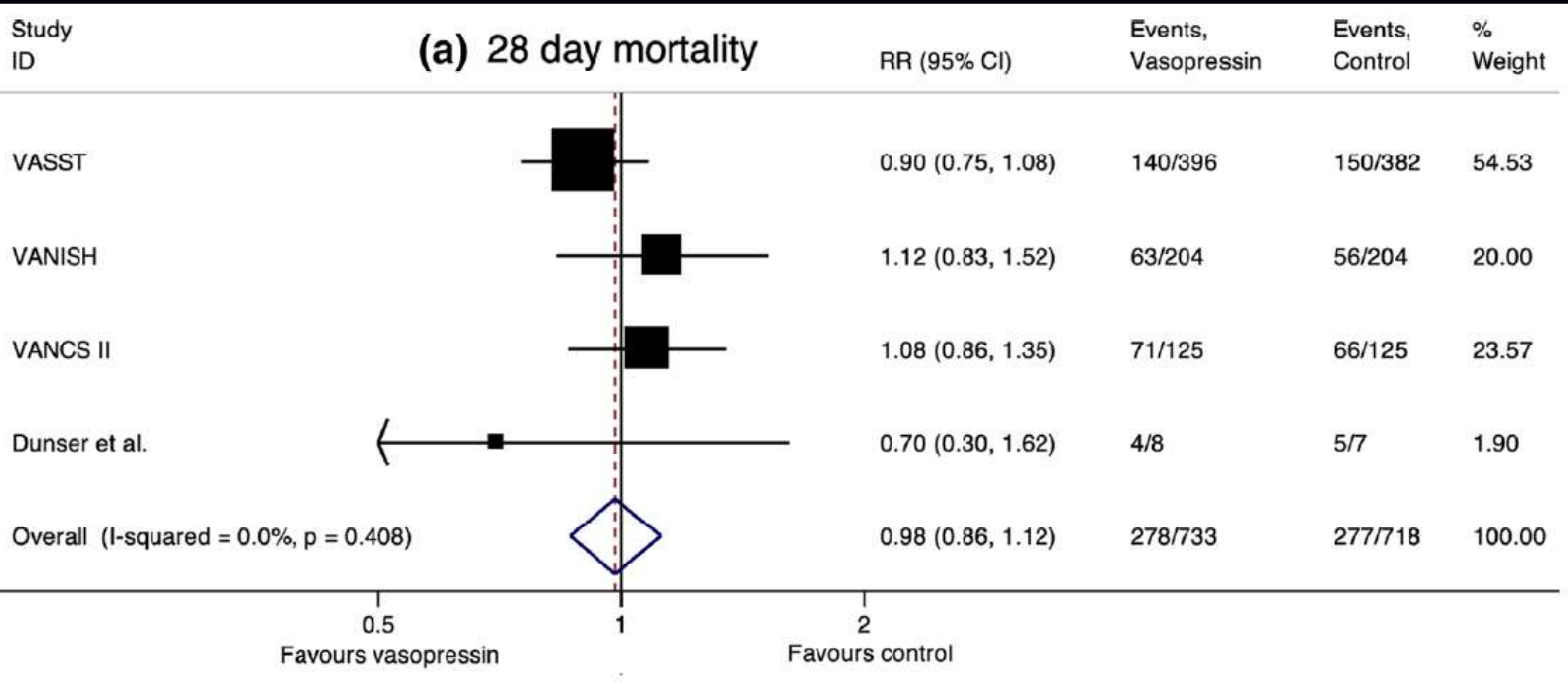


epi dose at randomization: 0.16 [0.10-0.31] mcg/kg.min

STEMATIC REVIEW

asopressin in septic shock: an individual atient data meta-analysis of randomised ontrolled trials

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



STEMATIC REVIEW

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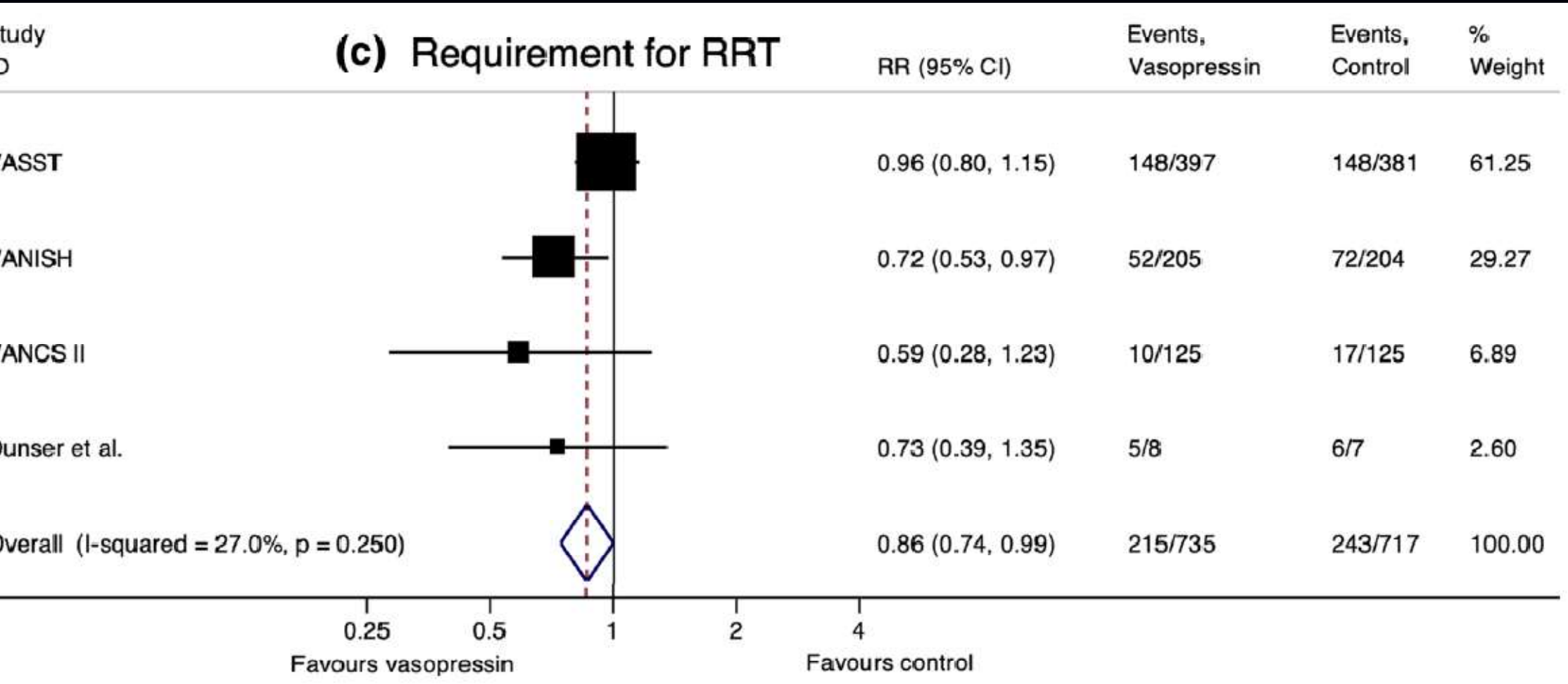
ICM 20



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

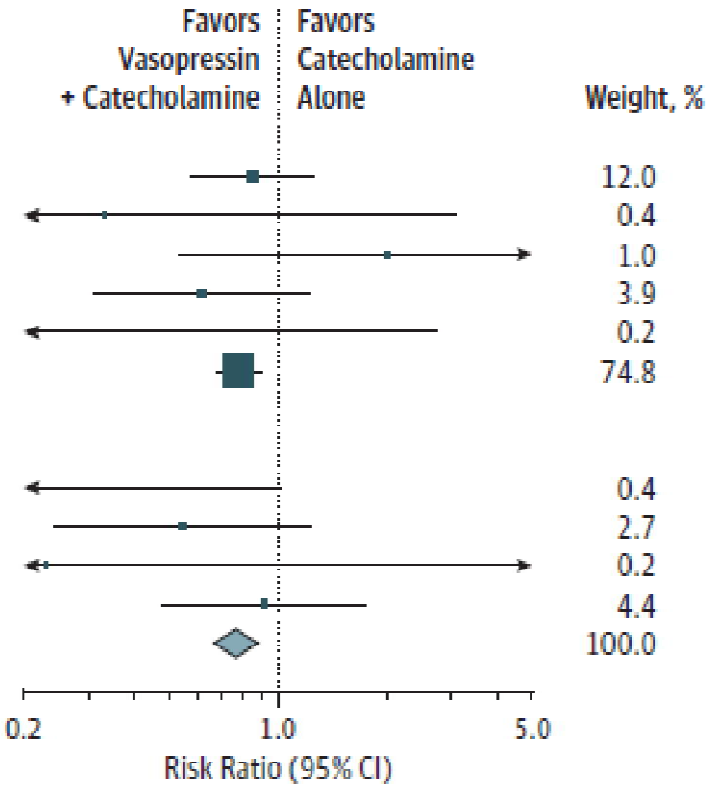
23 studi

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

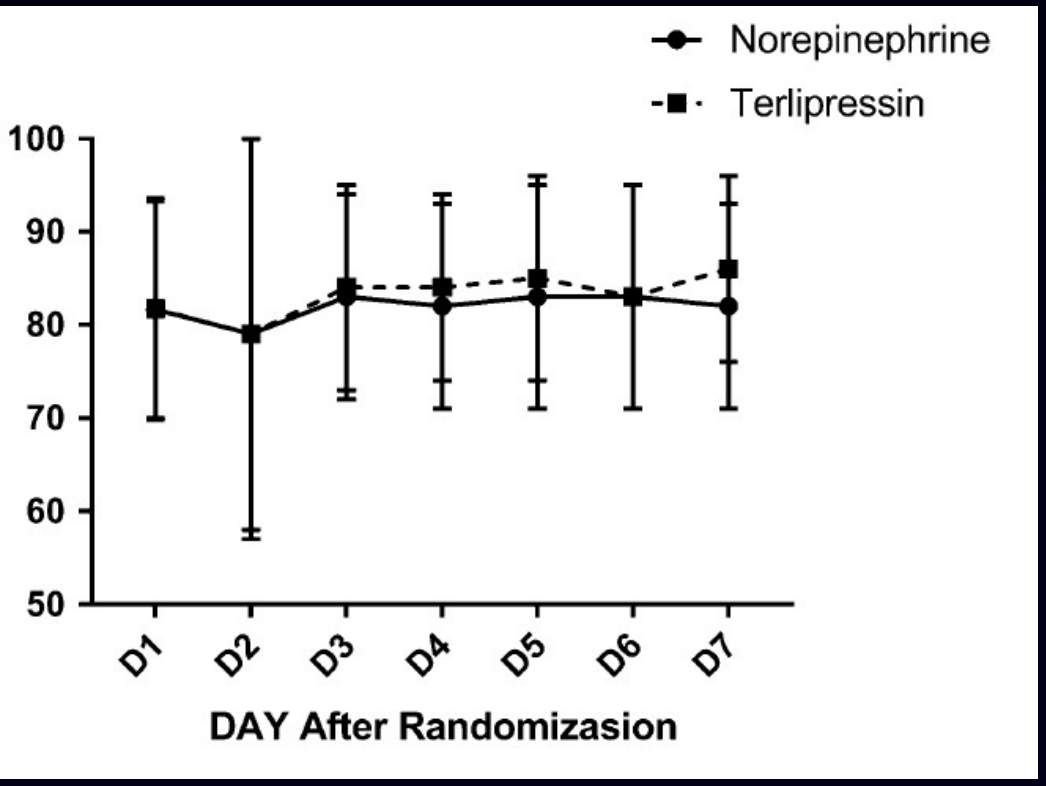
Morelli A Crit Care 2009
Liu Z et al ICM 2018

IGINAL

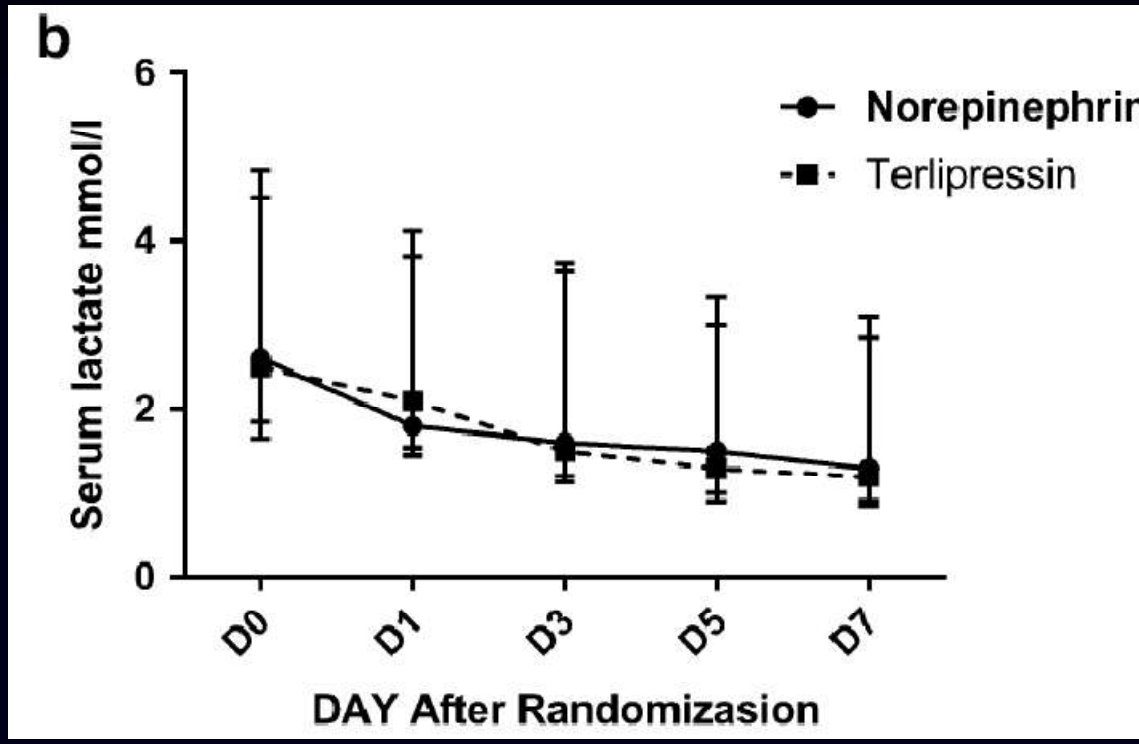
rlipressin versus norepinephrine infusion in patients with septic shock: a ulticentre, randomised, double-blinded trial

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

Liu Z
ICM 2



N=617



Evans
ICM 2
CCM 2

LOW

40 For adults with septic shock, we **suggest against** using terlipressin.

GINAL

lipressin versus norepinephrine nfusion in patients with septic shock: a lticentre, randomised, double-blinded trial

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

Liu Z et
ICM 20

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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Diarrhoea	1 (0.35%)	8 (2.72%)	0.037
Overall	31 (11.65%)	78 (30%)	< 0.01

Liu Z et
ICM 20

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
epinel
the ur
terlipr
use in

Any difference between vasopressin and terlipressin?

Evans L et al
ICM 2021
CCM 2021

Vasopressin in septic shock: an ind
patient data meta-analysis of rand
controlled trials **ICM 2**

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

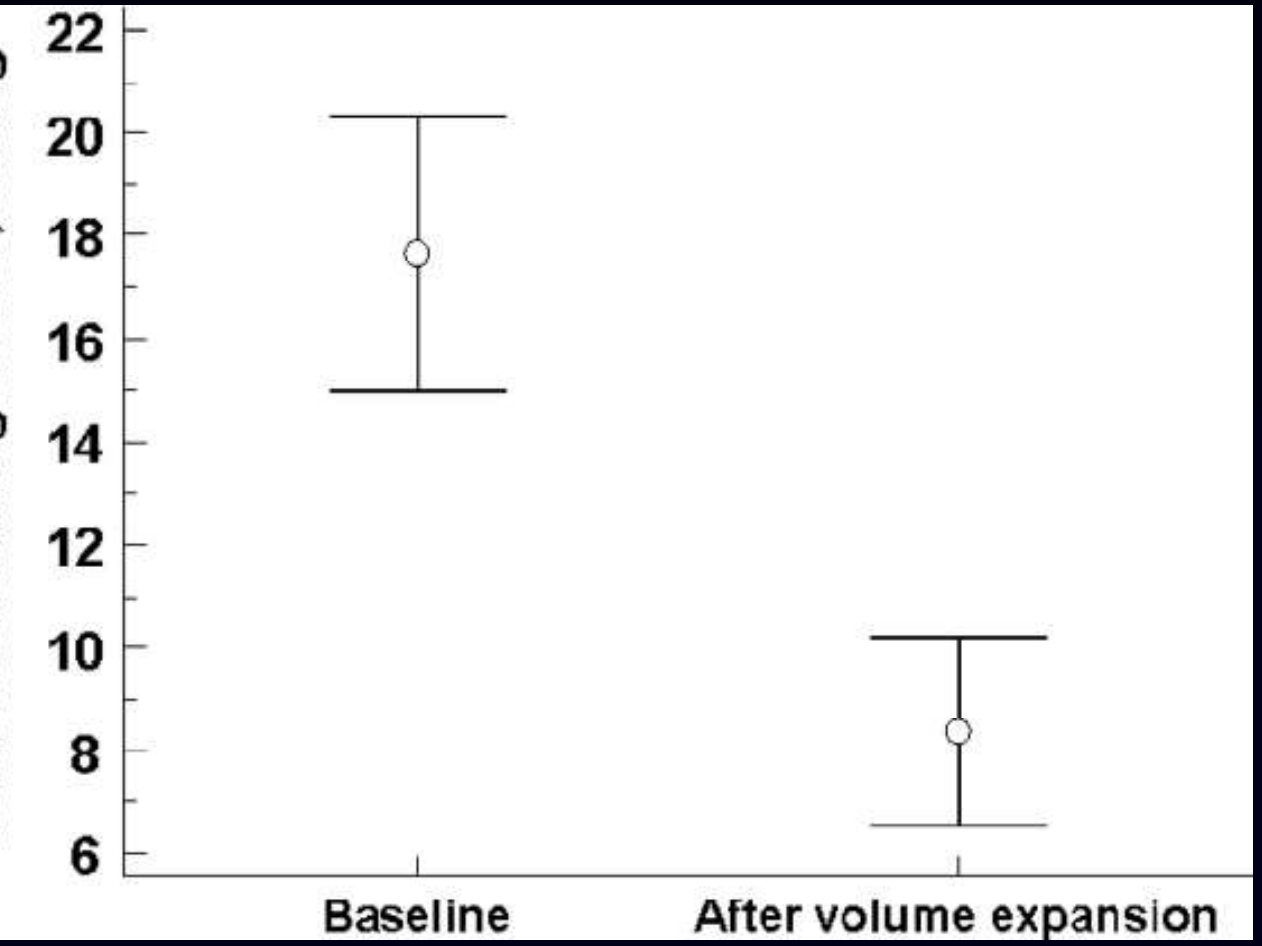
Outcome	Vasopressin	Norepinephrine	ARD[a] (95% CI)
Serious adverse events, no./total (%)	124/735 (16.9)	120/718 (16.7)	0.2 (– 3.7 to 4.0)
Digital ischaemia	21/735 (2.9)	8/718 (1.1)	1.7 (0.3–3.2)
Mesenteric ischaemia[b]	14/727 (1.9)	18/711 (2.5)	– 0.6 (– 2.1 to 0.9)
Acute coronary syndrome	18/735 (2.5)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

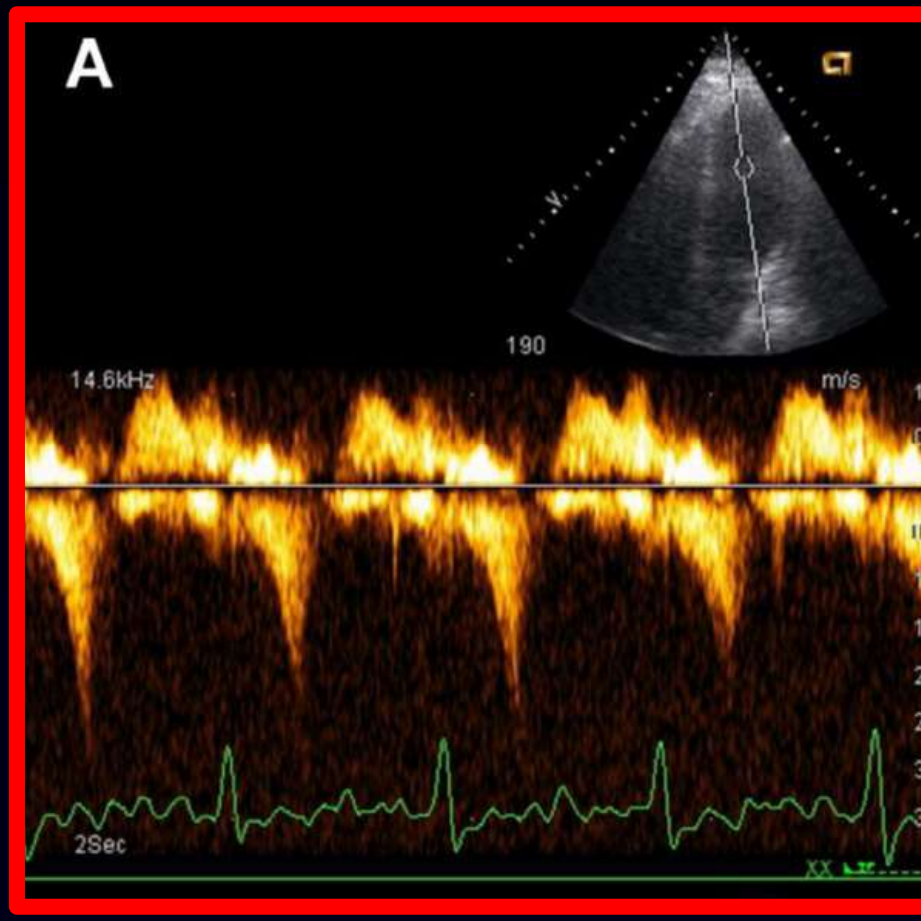
Vasopressin in specific situations ?

ok carefully for LVOT obstruction !

Chauvet JL et a
Crit Care 2015

218 pts septic shock
=> 47 pts with LVOT





sopressin in Patients with Septic Shock and Dynamic Left ntricular Outflow Tract Obstruction

Balik M et al Cardiovasc Drug T 2020

eter	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 [mmHg]
P	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–
VP	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-

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

Vasopressin and
lanchnic ischemia ?

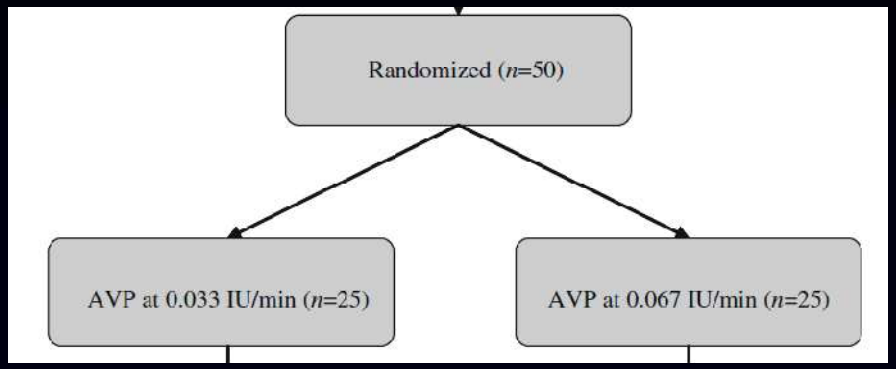
asopressors and Risk of Acute esenteric Ischemia: A Worldwide harmacovigilance Analysis and omprehensive Literature Review

Jozwiak M
Front Med

of interest	Overall	Norepinephrine	Epinephrine	Phenylephrine	Dopamine	Vasopressin	Terlipressin	Angioter
f cases	104	47	30	10	19	14	17	2
	59 (60.8%) [97]	28 (59.6%) [47]	15 (53.6%) [28]	3 (30.0%) [10]	10 (62.5%) [16]	9 (69.2%) [13]	9 (64.3%) [14]	2 (100.0
> 65 years-old	44 (47.8%) [92]	24 (53.3%) [45]	15 (53.6%) [28]	3 (37.5%) [8]	7 (43.8%) [16]	3 (25.0%) [12]	5 (35.7%) [14]	1 (50.0%
us adverse event	96 (100.0%) [96]	46 (100.0%) [46]	30 (100.0%)	7 (100.0%) [7]	17 (100.0%) [17]	14 (100.0%)	14 (100.0%) [14]	2 (100.
ns	47 (49.0%) [96]	22 (47.8%) [46]	15 (50.0%)	6 (85.7%) [7]	8 (47.1%) [17]	9 (64.3%)	8 (57.1%) [14]	0 (0.0

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

Torgersen C et al
ICM 36:57;2010



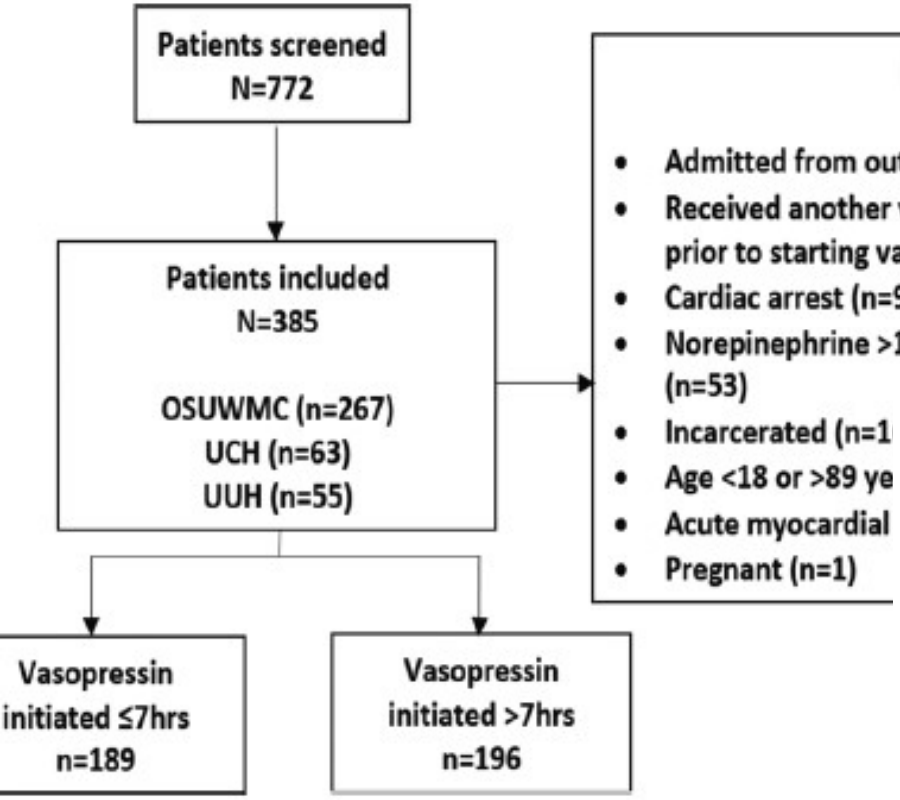
	0.033 IU/min	0.067 IU/min	*P*-value
Decrease in cardiac index, *n* (%)	4 (25)	7 (50)	0.26
Increase in serum transaminases, *n* (%)	10 (47.6)	15 (65.2)	0.36
Increase in total bilirubin, *n* (%)	4 (19)	6 (26.1)	0.72
Decrease in platelet count, *n* (%)	15 (71.4)	17 (73.9)	1

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

Shock 2022

EARLY INITIATION OF VASOPRESSIN REDUCES ORGAN FAILURE AND MORTALITY IN SEPTIC SHOCK

Alexandria C. Rydz,*,† Jessica L. Elefritz,* Megan Conroy,‡ Kathryn A. Disney,§ Christopher J. Miller,‖,¶ Kyle Porter,# and Bruce A. Doepker*



Excluded (n=387)

- Admitted from outside hospital on a vasopressor (n=121)
- Received another vasopressor besides norepinephrine prior to starting vasopressin (n=98)
- Cardiac arrest (n=91)
- Norepinephrine >1.5mcg/kg/min prior to vasopressin (n=53)
- Incarcerated (n=1
- Age <18 or >89 ye
- Acute myocardial
- Pregnant (n=1)

TABLE 2. **Outcomes**

New-onset arrhythmia (n = 335), n (%)	42 (
Mechanical ventilation, n (%)	313 (
AKI within 7 d, n (%)	215 (
Initiation of renal replacement therapy, n (%)	186 (
Change in SOFA score at 72 h*	1.7 :
ICU LOS, d†	6 (
Composite primary outcome, n (%)	238 (
Increase in SOFA >3 at 72 h (n = 292)	56 (
In-hospital all-cause mortality	231 (

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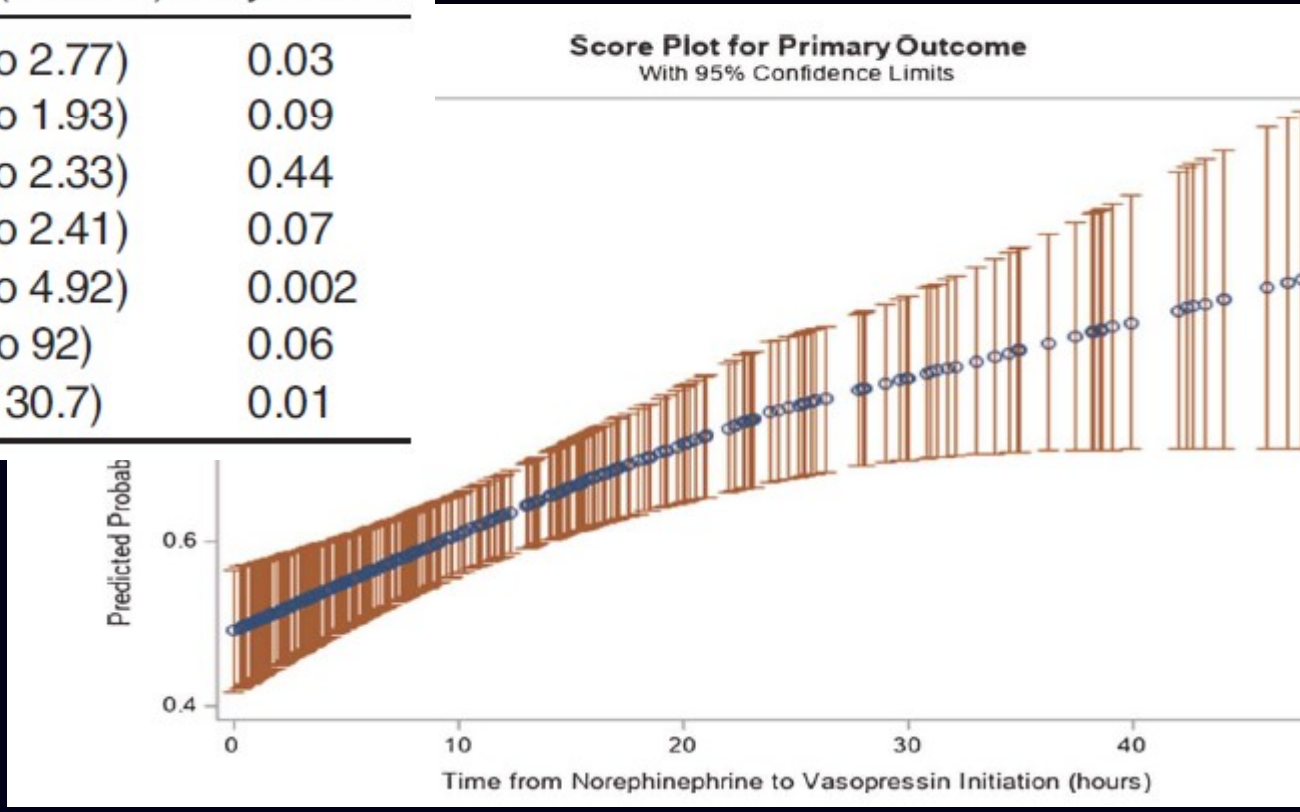
LE 5. **Multivariable logistic regression analysis for time to initiation of vasopressin based on 7-hour spilt**

able	Adjusted OR (95% CI)	Adjusted *P*
within 7 d	1.72 (1.07 to 2.77)	0.03
ation of renal replacement therapy	1.20 (0.75 to 1.93)	0.09
ospital all-cause mortality	1.48 (0.94 to 2.33)	0.44
nposite primary outcome	1.53 (0.97 to 2.41)	0.07
LOS, d	3.00 (1.07 to 4.92)	0.002
ation of mechanical ventilation, h	45.3 (–1.4 to 92)	0.06
ation of NE, h	17.8 (4.8 to 30.7)	0.01

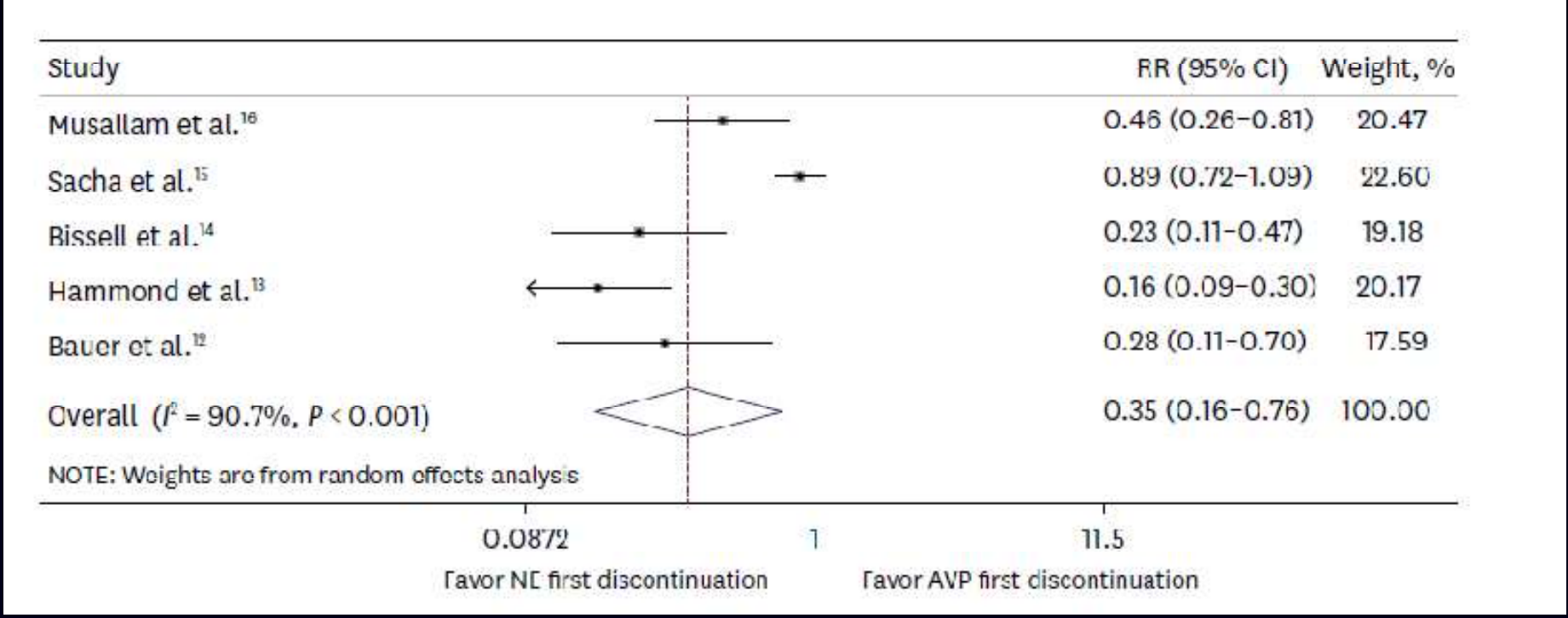


Weaning vasopressor agents:

Norepinephrine first or vasopressin first?

Incidence of Hypotension after Discontinuation of Norepinephrine or Arginine Vasopressin in Patients with Septic Shock: a Systematic Review and Meta-Analysis

Song JU et al
JKMS 2020



5 studies / 930 patients

Putting all together

asopressin in septic shock

- Early introduction of vasopressors in severe hypotension or low diastolic pressure in addition to fluid resuscitation.

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

- Vasopressin derivatives are excellent adjunctiv and in some cases alternative to norepinephrin

- Caution in hepatosplanchnic ischemia
- Benefits in AKI and AF


Thank you