Controversies in Septic Shock

Jerry Altshuler, PharmD, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
PGY-2 Critical Care Residency Program Director
The Mount Sinai Hospital

Drayton A. Hammond, PharmD, MBA, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
PGY-2 Critical Care Residency Program Director
Rush University Medical Center


@hockeypharmd and @drdraymba

Disclosure

No disclosures to provide.

Objectives

At the completion of this activity, pharmacists will be able to:

1. Determine the role of vasopressin in septic shock
2. Explain strengths and limitations regarding current angiotensin II data

At the completion of this activity, pharmacy technicians will be able to:

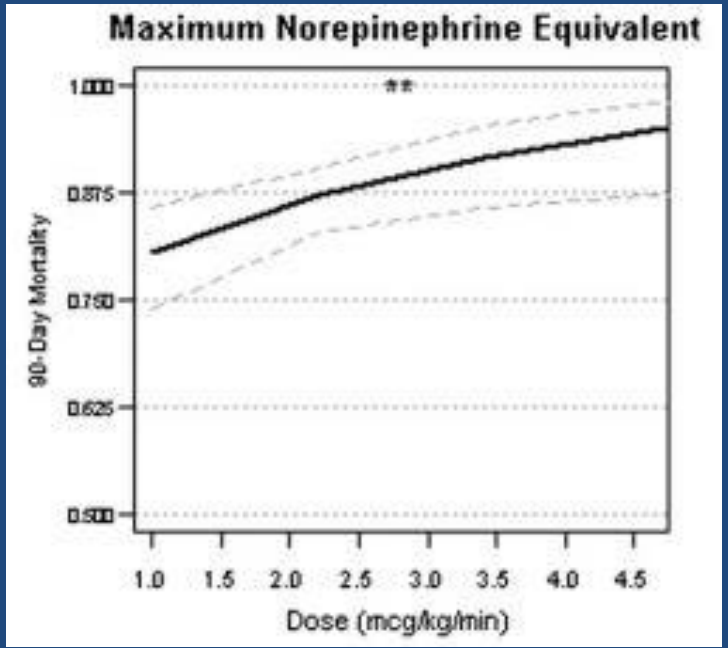
1. Identify advantages of vasopressin over catecholamine vasopressor
2. Describe adverse events associated with angiotensin II

Vasopressin: PRO (catecholamine-sparing & vasopressin-deficiency)

Catecholamine-sparing Strategy

- Catecholamine derivatives (e.g., NE, Epi) associated with adverse events and tachyphylaxis

- Increased catecholamine exposure associated with cardiotoxicity and greater mortality



Chest. 2013;143(3):664-71.

Sepsis-induced Myocardial Dysfunction

- Occurs in 25-50% of septic shock
  - Left and right ventricular dysfunction
- Potential sequelae of substantially elevated catecholamine levels (adrenergic storm)
- Resultant downregulation of β-adrenoceptors
- Exogenous catecholamines (e.g., NE) ensure available β-adrenoceptors stimulation but other receptors may be better target

Crit Care Med. 2009;13(5):230.

Vasopressin (AVP)

- Effects: vasoconstriction, ACTH release, water retention
- Endogenous AVP production rises rapidly then sharply declines in septic shock
- Exogenous AVP (0.03-0.06 units/min) may resolve this relative AVP-deficient state

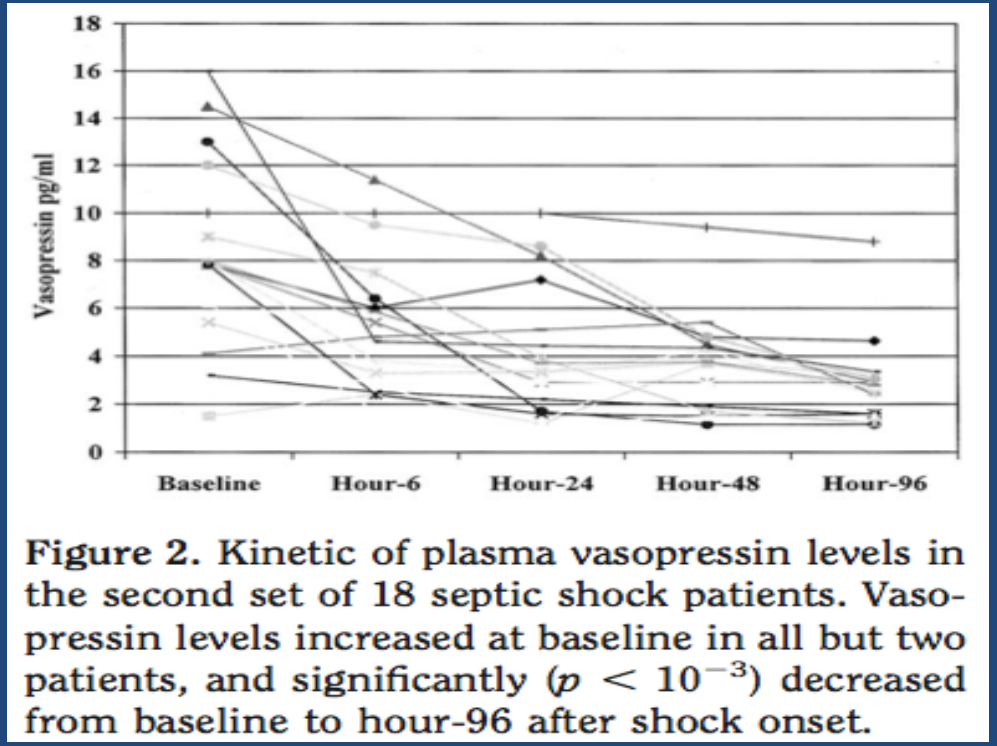
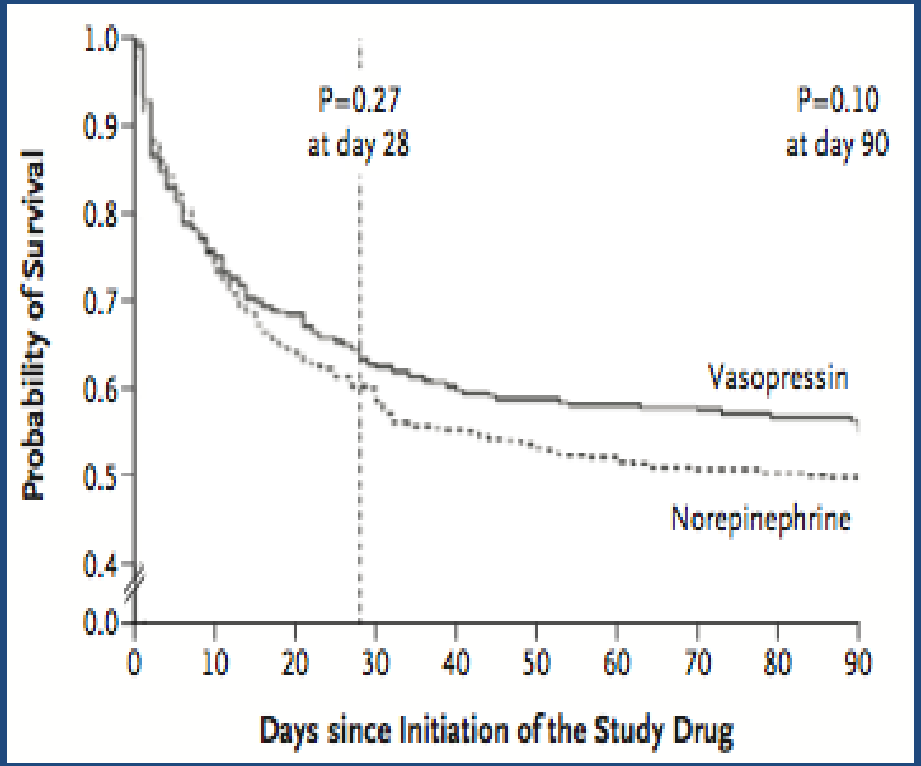


Figure 2. Kinetic of plasma vasopressin levels in the second set of 18 septic shock patients. Vasopressin levels increased at baseline in all but two patients, and significantly ($p < 10^{-3}$) decreased from baseline to hour-96 after shock onset.

Crit Care Med. 2003;31(6):1752-8.

Vasopressin and Septic Shock Trial (VASST)

- Similar mortality with AVP (mean initiation 12 hours) added to NE versus NE alone (*as good as*)
- Subgroup of “less severe” (NE≤14): non-significant reduction in 28-day mortality in NE+AVP group (26.5% vs. 35.7%, RR 0.74, 95% CI 0.55-1.01)

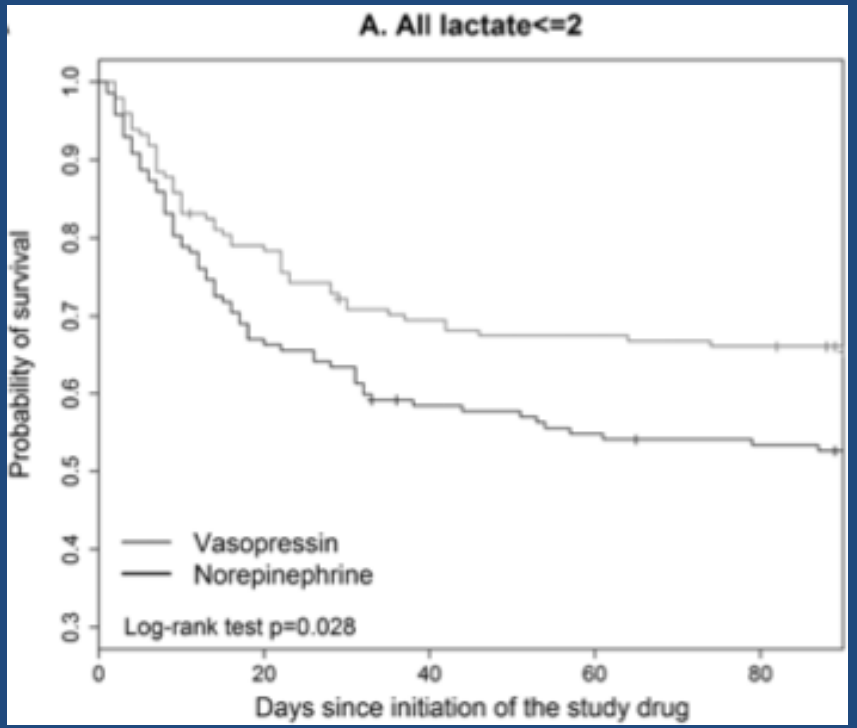


N Engl J Med. 2008;358:877-87.

Vasopressin (VASST re-analysis)

VASST re-analysis with Sepsis-3 def:

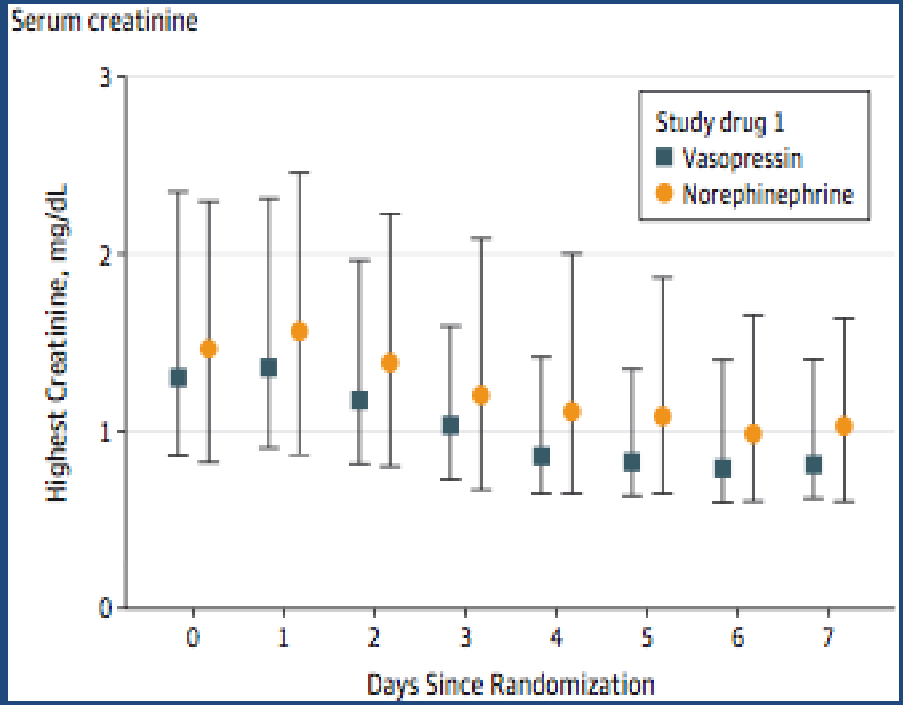
- Similar mortality with AVP added to NE versus NE alone in all patients (*as good as*)
- Reduction in mortality with AVP added to NE when lactate ≤ 2 mmol/L
- May have a role in less critically ill; **how do we know that up front?**



Crit Care Med. 2017;45(6):940-8.

Vasopressin versus Norepinephrine (VANISH)

- AVP (n=205) vs. NE (n=204)
- Survival without kidney failure similar (57.0% vs. 59.2%, ARR -2.3%, 95% CI -13.0 to 8.5%)
- Similar mortality at 28 days (30.9% vs. 27.5%, ARI 3.4, 95% CI -5.4 to 12.3)
- Similar outcomes to NE (*as good as*)



JAMA. 2016;316:509-18.

Sacha *et al. Ann. Intensive Care (2018) 8:35*
https://doi.org/10.1186/s13613-018-0379-5

Annals of Intensive Care

RESEARCH Open Access

Predictors of response to fixed-dose vasopressin in adult patients with septic shock

Outcome	Total (*N* = 938)	Non-responders (*N* = 512)	Responders (*N* = 426)	*P* value
In-hospital mortality, *n* (%)	608 (64.8)	367 (71.7)	241 (56.6)	< 0.001
ICU mortality, *n* (%)	561 (59.8)	347 (67.8)	214 (50.2)	< 0.001
ICU-free days at day 14	1.9 ± 3.6	1.6 ± 3.3	2.3 ± 3.8	< 0.001
Hospital-free days at day 28	3.4 ± 6.6	2.8 ± 6.0	4.2 ± 7.2	< 0.001
MV-free days at day 14	2.8 ± 4.9	2.2 ± 4.5	3.6 ± 5.3	< 0.001
SOFA score change[a]	0.6 ± 2.9	0.8 ± 2.9	0.3 ± 2.9	0.02
Respiration score change	2.3 ± 1.5	2.0 ± 1.5	2.5 ± 1.4	< 0.001
Coagulation score change	0.46 ± 1.0	0.5 ± 0.9	0.4 ± 1.0	0.19
Liver score change	0.1 ± 0.7	0.1 ± 0.8	0.7 ± 0.6	0.90
Neurological score change	− 0.1 ± 1.1	0.1 ± 1.1	− 0.2 ± 1.0	< 0.001
Cardiovascular score change	− 1.9 ± 1.7	− 1.6 ± 1.7	− 2.1 ± 1.7	< 0.001
CRRT initiation between AVP start and 72 h, *n* (%)[b]	190 (25.0)	112 (30.0)	78 (20.2)	0.002
CA dose change[c], mcg/min	+1.7 ± 40.6	+13.8 ± 51.2	− 12.8 ± 9.6	< 0.001
CA-free days at day 14	5.0 ± 5.8	3.9 ± 5.5	6.3 ± 6.0	< 0.001

CA catecholamine, *CRRT* continuous renal replacement therapy, *MV* mechanical ventilation, *SOFA* sequential organ failure assessment

[a] Evaluated at hour 48 after vasopressin initiation

[b] Evaluated only in patients who survived at least 24 h after vasopressin initiation

[c] Evaluated at hour 6 after vasopressin initiation

Early vasopressin (<4 h) to NE

Table 3. Patient Outcomes between Groups

Outcome	NE+AVP (n=41)	NE (n=41)	p value
Time to achieve and maintain MAP 65 mm Hg, hrs, median (IQR)	5.7 (1.7–10.3)	7.6 (3.6–16.7)	0.058
Time to initiation of second vasopressor, median (IQR)[a]	10.6 (3.8–30.9)	7.2 (4.1–18.5)	0.54
NE duration, hrs, median (IQR)	41.2 (26.9–78.3)	46.8 (36.1–91.3)	0.43
AVP duration, hrs, median (IQR)	28.3 (13.0–73.8)	35.6 (11.2–97.5)	0.68
NE amount in first 24 hrs, mg, median (IQR)	12.7 (7.2–26.7)	12.4 (6.2–24.8)	0.92
NE dosage at MAP 65 mm Hg, µg/min, median (IQR)	15 (5–26)	13 (5–22)	0.68
NE ≥ 15 µg/min at MAP 65 mm Hg, n (%)	24 (59)	20 (49)	0.51
Maximum NE dose, µg/min, median (IQR)	22 (10–30)	20 (10–30)	0.85
Mortality during hospitalization, n (%)	19 (46)	21 (51)	0.66
Mortality at 28 days, n (%)	19 (46)	18 (44)	0.82
ICU duration, days, median (IQR)	4.1 (2.4–8.9)	3.8 (2.1–7.4)	0.54
Hospital duration, days, median (IQR)	14.5 (5.1–21.8)	15.4 (8.2–33.8)	0.19
New-onset arrhythmia, n (%)	6 (15)	3 (7)	0.29

Pharmacotherapy. 2018;38:531-8.

Considerations for Vasopressin Usage

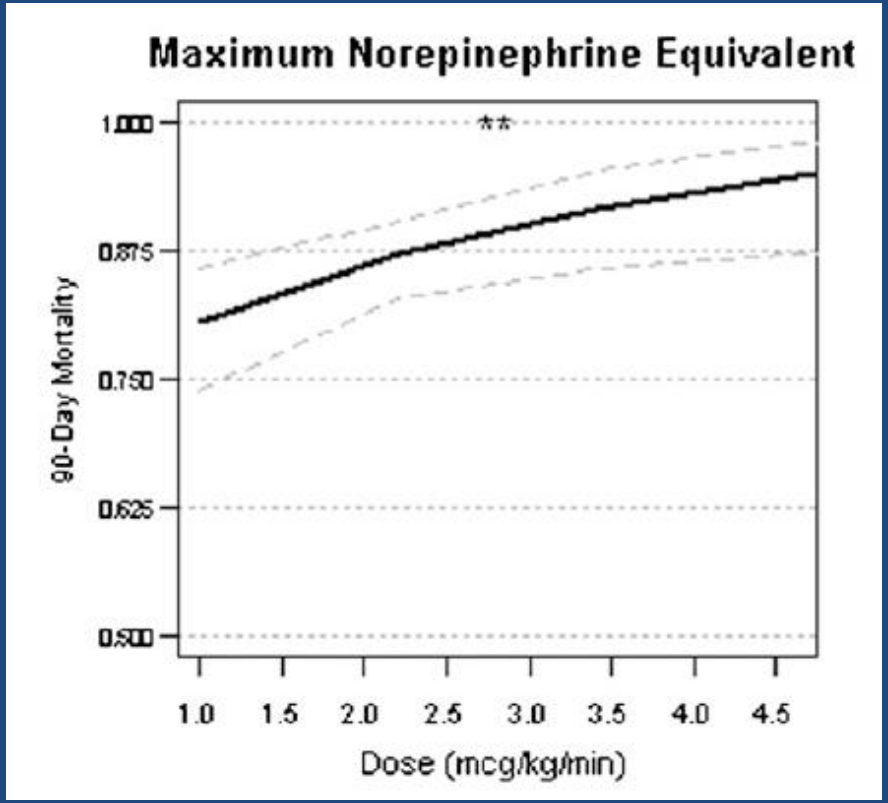
- Use earlier in septic shock may provide better outcomes
- Identifying responders (and non-responders) is critical
- Dysrhythmias, right-sided cardiac dysfunction
- Cost control measures
  - Infusion rate, IVPB size and concentration, RPh verification, MUE

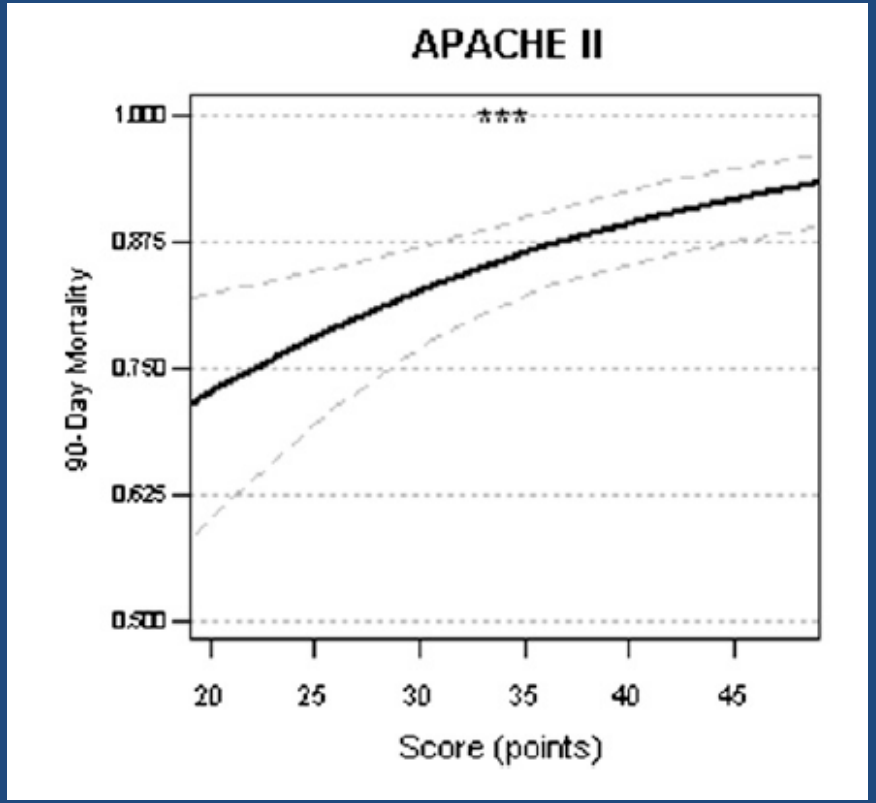
TAKEAWAY:

Norepinephrine ± Vasopressin ≥ Norepinephrine

Vasopressin: CON (unproven & costly)

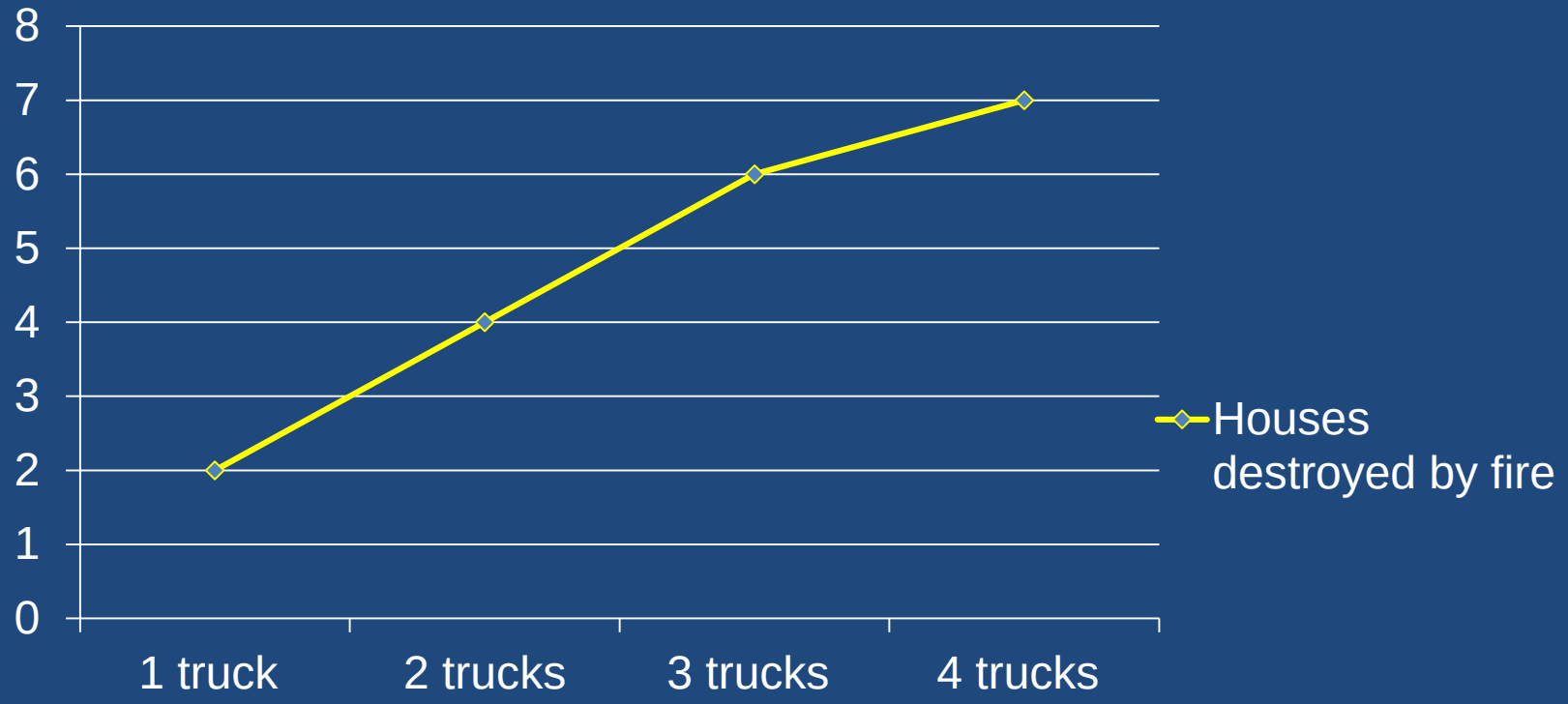
Norepinephrine and Mortality Trap





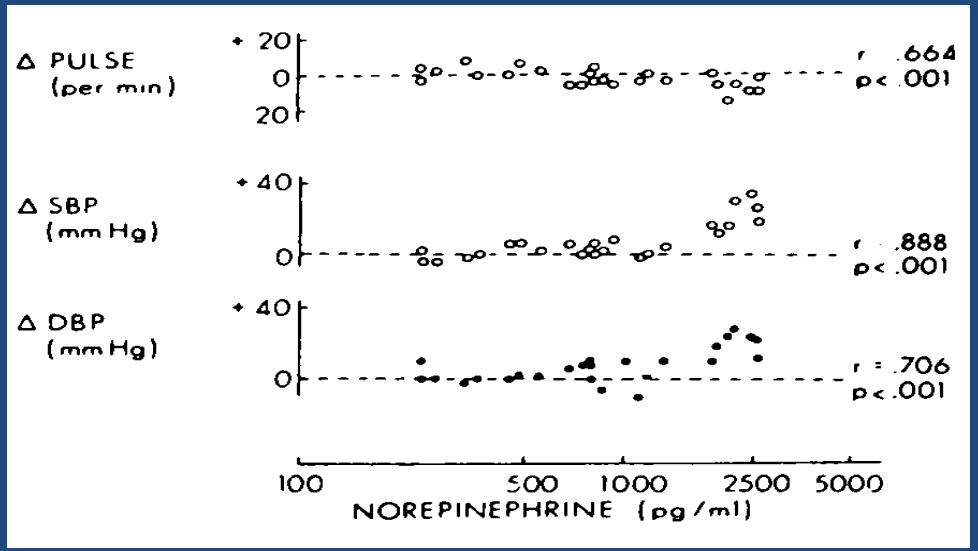
Chest. 2013;143:664-71.

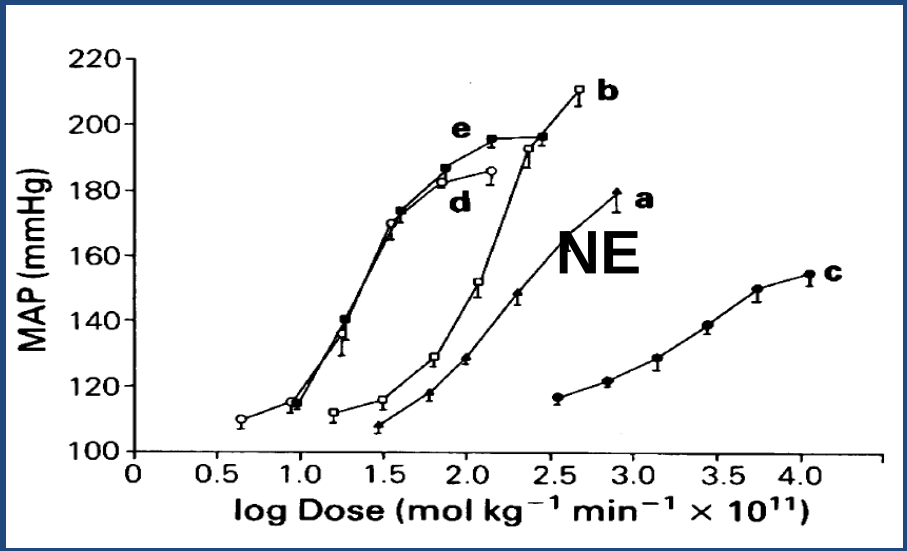
Houses Destroyed by Fire per Fire Truck Sent



Graph made up by Jerry Altshuler

Norepinephrine Dose Response

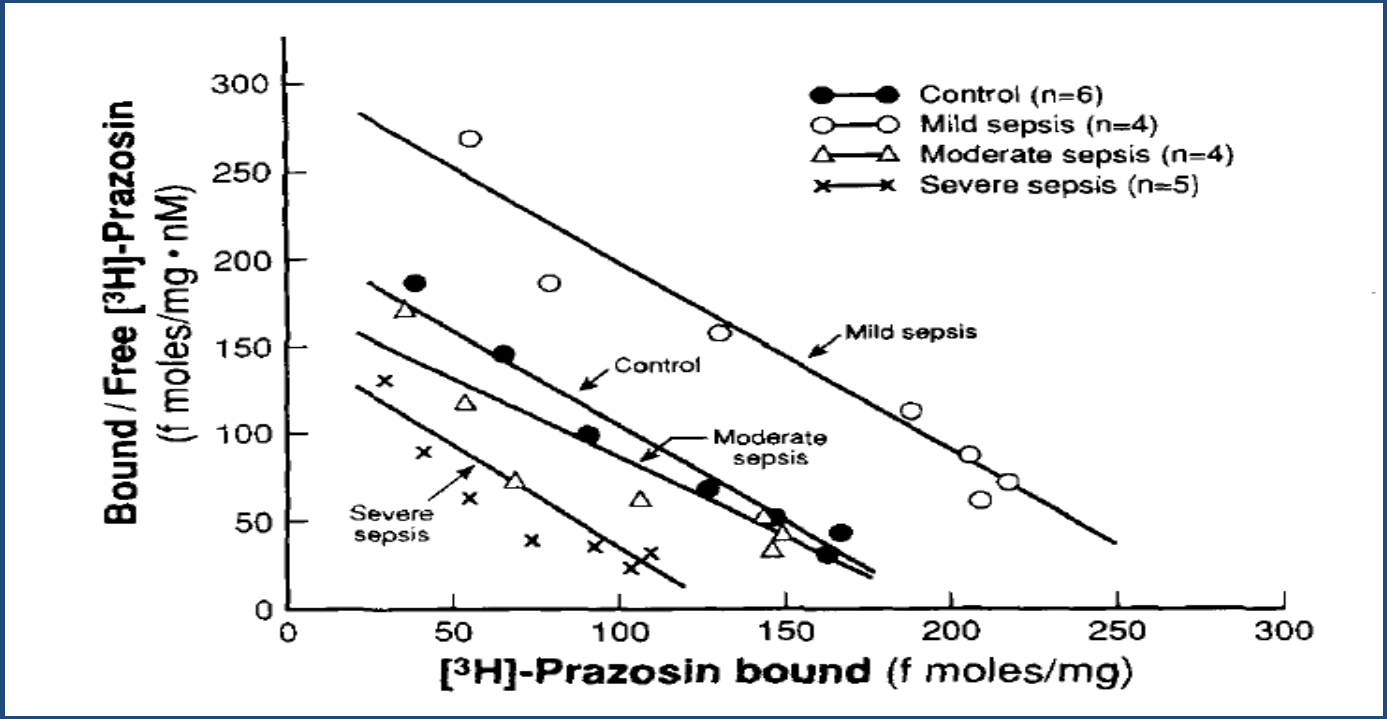




Crit Care Med. 1991 ;19:1566-79

Br J Pharmacol. 1986;89:389-94.

Alpha Receptor Regulation in Sepsis



Hepatology 1994;20:638-642

Society of Critical Care Medicine
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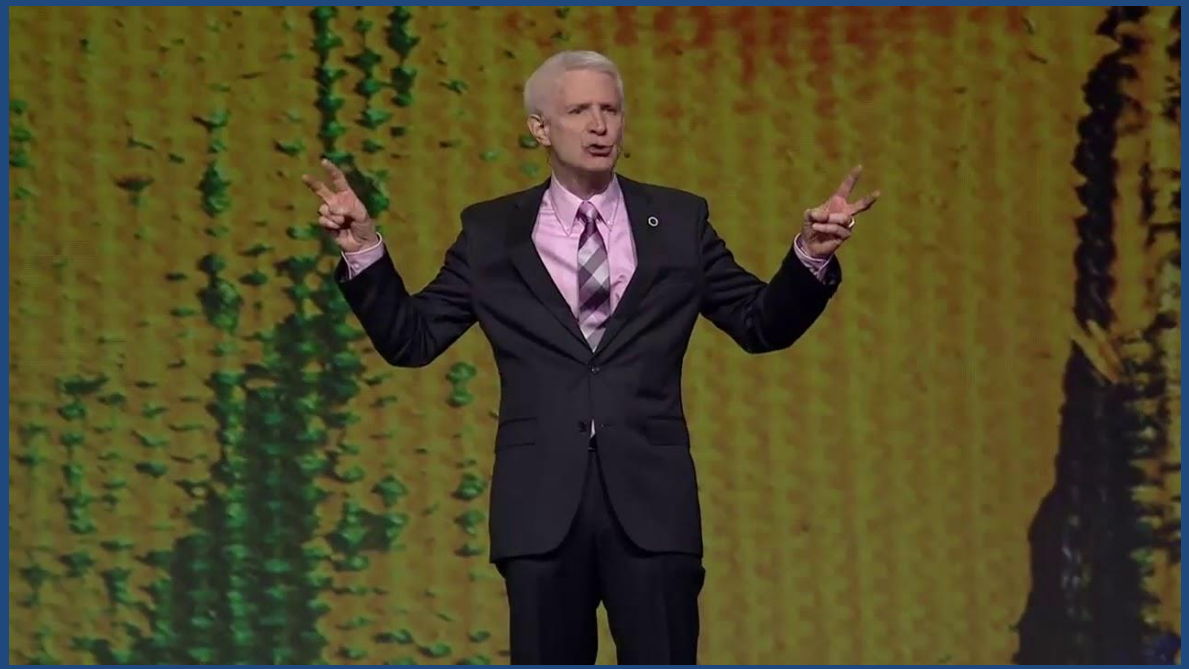
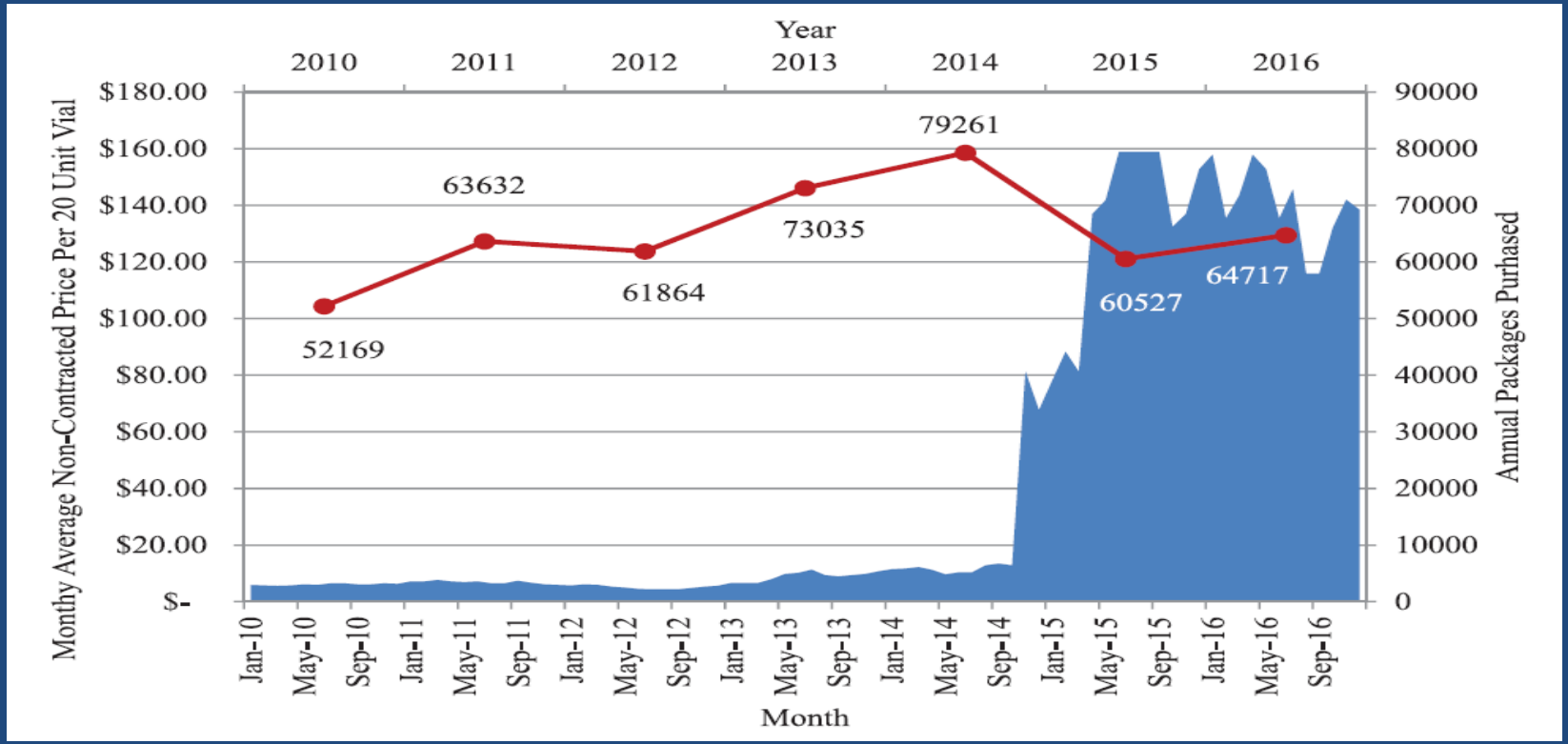


“Providing high-value care, specifically high-quality care at the most reasonable cost, should be a primary tenet for every critical care practitioner”

Vasopressin Price Explosion



Anesth Analg. 2018;127:1414-1420.

Vasopressin Avoidance

	Preintervention (n = 74)	Postintervention (n = 74)	*P* Value	Adjusted OR	95% CI	*P* Value
Time to reach goal MAP (hours)[a]	2 (1.0-3.6)	1.3 (1.0-2.2)	0.030	1.412	0.97-2.05	0.07
Hospital length of stay[a]	9 (5-16)	11 (7-19)	0.167			
Pre-Post group				10	0.30-341.38	0.20
APACHE II score				0.97	0.79-1.1	0.78
NE dose initiation				1.87	1.42-2.48	<0.0001
ICU length of stay[a]	6 (4-9)	7 (4-11)	0.474			
Pre-Post group				10.45	0.11-1026.59	0.31
APACHE II score				0.93	0.72-1.21	0.60
NE dose initiation				1.99	1.38-2.86	<0.0001
28-Day mortality	38 (51.4%)	21 (28.4%)	0.004			
Pre-Post group				0.34	0.16-0.71	0.004
APACHE II score				1.03	0.98-1.07	0.22
NE dose initiation				0.95	0.89-1.01	0.10

Ann Pharmacother. 2017 ;51:13-20.

VASST

Variable	Norepinephrine Group (N = 382)	Vasopressin Group (N = 396)	P Value†	Absolute Risk Reduction (95% CI)‡	Relative Risk (95% CI)§	Adjusted Odds Ratio¶
	no./total no. (%)			%		
Patients who underwent randomization and infusion						
28-day mortality	150/382 (39.3)	140/396 (35.4)	0.26	3.9 (–2.9 to 10.7)	0.90 (0.75 to 1.08)	0.88 (0.62 to 1.26)
90-day mortality	188/379 (49.6)	172/392 (43.9)	0.11	5.7 (–1.3 to 12.8)	0.88 (0.76 to 1.03)	0.81 (0.57 to 1.16)
Patients who underwent						

Stratum	Norepinephrine Group	Vasopressin Group	P Value†	Absolute Risk Reduction (95% CI)	Relative Risk (95% CI)
	no./total no. (%)			%	
More severe septic shock					
28-day mortality	85/200 (42.5)	88/200 (44.0)	0.76	–1.5 (–11.2 to 8.2)	1.04 (0.83 to 1.3)
90-day mortality	105/199 (52.8)	103/199 (51.8)	0.84	1.0 (–8.8 to 10.8)	0.98 (0.81 to 1.18)
Less severe septic shock					
28-day mortality	65/182 (35.7)	52/196 (26.5)	0.05	9.2 (–0.1 to 18.5)	0.74 (0.55 to 1.01)
90-day mortality	83/180 (46.1)	69/193 (35.8)	0.04	10.4 (0.4 to 20.3)	0.78 (0.61 to 0.99)

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

The Septic Shock 3.0 Definition and Trials: A Vasopressin and Septic Shock Trial Experience*

James A. Russell, MD[1,2]; Terry Lee, PhD[3]; Joel Singer, PhD[3]; John H. Boyd, MD[1,2]; Keith R. Walley, MD[1,2]; on behalf of the Vasopressin and Septic Shock Trial (VASST) Group

Trial	Original Definition	Original Definition	p	New Sepsis 3 Definition	New Sepsis 3 Definition	p
	28-d mortality, *n*/total *n* (%)	28-d mortality, *n*/total *n* (%)		28-d mortality, *n*/total *n* (%)	28-d mortality, *n*/total *n* (%)	
	Vasopressin	Norepinephrine		Vasopressin	Norepinephrine	
VASST	140/396 (35.4)	150/382 (39.3)	0.26	92/193 (47.7)	87/182 (47.8)	0.979
ARR (%)		3.9			0.1	
RRR (%)		9.9			0.2	
VASST—less severe shock stratum	52/196 (26.5)	65/182 (35.7)	0.05	19/57 (33.3)	29/66 (43.9)	0.229
ARR (%)		9.2			10.6	
RRR (%)		25.8			24.1	

Crit Care Med. 2017 ;45:940-948

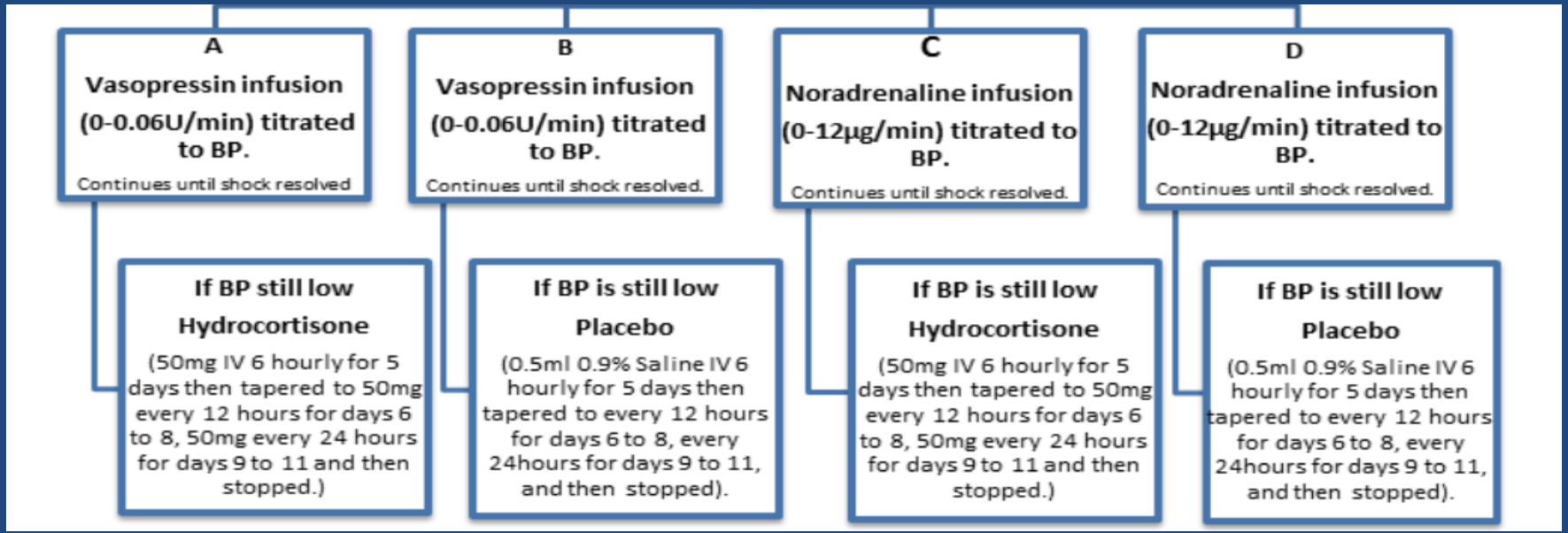
Population and Outcome	Original Definition			Baseline Lactate ≤ 2			Sepsis 3.0 Definition (Baseline Lactate > 2)			p for Homogeneity[a]
	Vasopressin	Norepinephrine	p	Vasopressin	Norepinephrine	p	Vasopressin	Norepinephrine	p	
VASST										
28-day mortality										
Event rate	140/396 (35.4)	150/382 (39.3)	0.259	40/147 (27.2)	52/142 (36.6)	0.086	92/193 (47.7)	87/182 (47.8)	0.979	0.189
ARR (%)	3.9			9.4			0.1			
RRR (%)	9.9			25.7			0.2			
90-day mortality										
Event rate	172/392 (43.9)	188/379 (49.6)	0.111	52/146 (35.6)	67/140 (47.9)	0.036	106/191 (55.5)	104/181 (57.5)	0.703	0.182
ARR (%)	5.7			12.3			2.0			
RRR (%)	11.5			25.7			3.5			
Time to death										
Hazard ratio (95% CI)	0.84 (0.68–1.04)		0.103	0.67 (0.46–0.96)		0.030	0.97 (0.74–1.27)		0.827	0.116
VASST—less severe shock stratum										
28-day mortality										
Event rate	52/196 (26.5)	65/182 (35.7)	0.054	26/100 (26.0)	32/82 (39.0)	0.061	19/57 (33.3)	29/66 (43.9)	0.229	0.761
ARR (%)	9.2			13.0			10.6			
RRR (%)	25.8			33.3			24.1			
90-day mortality										
Event rate	69/193 (35.8)	83/180 (46.1)	0.042	35/100 (35.0)	38/80 (47.5)	0.090	23/55 (41.8)	36/66 (54.5)	0.163	0.989
ARR (%)	10.4			12.5			12.7			
RRR (%)	22.3			26.3			23.3			
Time to death										
Hazard ratio (95% CI)	0.70 (0.50–0.96)		0.027	0.67 (0.42–1.06)		0.089	0.68 (0.40–1.15)		0.150	0.999

Crit Care Med. 2017 ;45:940-948

JAMA | Original Investigation

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

The VANISH Randomized Clinical Trial



VANISH

Table 1. Baseline Characteristics for Patients With Septic Shock

	Vasopressin + Hydrocortisone (n = 101)	Vasopressin + Placebo (n = 104)	Norepinephrine + Hydrocortisone (n = 101)	Norepinephrine + Placebo (n = 103)	Total Trial Population (n = 409)
Renal replacement therapy, No. (%)	2 (2)	4 (4)	2 (2)	3 (3)	11 (3)
Volume of IV fluid in previous 4 h, median (IQR), mL	1200 (757-2021)	1092 (725-2010)	1168 (606-2000)	1100 (613-2132)	1134 (662-2039)
Patients receiving open-label vasopressor at randomization, No. (%)	91 (90)	89 (86)	86 (85)	82 (80)	348 (85)
Time from onset of shock to receiving first study drug, median (IQR), h	3.2 (1.8-5)	3.5 (2-5.4)	3.7 (1.7-5)	3.5 (1.4-5.4)	3.5 (1.8-5.2)
Norepinephrine dose at randomization, median (IQR), μg/kg/min	0.16 (0.1-0.3) (n = 76)	0.15 (0.1-0.28) (n = 79)	0.2 (0.12-0.42) (n = 81)	0.16 (0.1-0.27) (n = 73)	0.16 (0.1-0.31) (n = 309)

JAMA. 2016;316:509-518

VANISH

	Vasopressin			Norepinephrine			Vasopressin vs Norepinephrine, Absolute Difference (95% CI)[b]
	Hydrocortisone[a]	Placebo	Total[a]	Hydrocortisone	Placebo	Total	
28-d Survivors who never developed kidney failure, No./total (%)[c]	46/81 (56.8)	48/84 (57.1)	94/165 (57.0)	46/77 (59.7)	47/80 (58.8)	93/157 (59.2)	−2.3 (−13.0 to 8.5)[d]
Kidney failure–free days in other patients, median (IQR), d[e]	5 (0-23)	12 (1-25)	9 (1-24)	13 (0-25)	14 (1-24)	13 (1-25)	−4 (−11 to 5)[d]
28-d Mortality, No./total (%)	33/100 (33.0)	30/104 (28.8)	63/204 (30.9)	29/101 (28.7)	27/103 (26.2)	56/204 (27.5)	3.4 (−5.4 to 12.3)
ICU mortality, No./total (%)	32/100 (32.0)	26/104 (25.0)	58/204 (28.4)	24/101 (23.8)	27/103 (26.2)	51/204 (25.0)	3.4 (−5.2 to 12.0)
Hospital mortality, No./total (%)	35/100 (35.0)	33/104 (31.7)	68/204 (33.3)	31/101 (30.7)	29/103 (28.2)	60/204 (29.4)	3.9 (−5.1 to 12.9)
Kidney failure, No./total (%)	41/101 (40.6)	46/104 (44.2)	87/205 (42.4)	46/101 (45.5)	51/103 (49.5)	97/204 (47.5)	−5.1 (−15.2 to 5.0)
Survivors	21/67 (31.3)	26/74 (35.1)	47/141 (33.3)	26/72 (36.1)	29/76 (38.2)	55/148 (37.2)	−3.8 (−15.5 to 7.9)
Nonsurvivors	20/33 (60.6)	20/30 (66.7)	40/63 (63.5)	20/29 (69)	22/27 (81.5)	42/56 (75)	−11.5 (−29.6 to 6.6)
Duration of kidney failure, median (IQR), d	4 (1 to 7)	2 (1 to 6)	3 (1 to 7)	3 (2 to 6)	4 (2 to 8)	4 (2 to 8)	−1 (2 to 0)
Survivors	4 (2 to 7)	3 (2 to 8)	4 (2 to 8)	4 (2 to 8)	4 (3 to 8)	4 (2 to 8)	0 (−3 to 2)
Nonsurvivors	2 (1 to 7)	2 (1 to 3)	2 (1 to 7)	3 (2 to 5)	2 (1 to 8)	3 (2 to 7)	−1 (−3 to 0)
Use of RRT, No./total (%)	29/101 (28.7)	23/104 (22.1)	52/205 (25.4)	32/101 (31.7)	40/103 (38.8)	72/204 (35.3)	−9.9 (−19.3 to −0.6)
Survivors	15/67 (22.4)	13/74 (17.6)	28/141 (19.9)	15/72 (20.8)	18/76 (23.7)	33/148 (22.3)	−2.4 (−12.5 to 7.7)
Nonsurvivors	14/33 (42.4)	10/30 (33.3)	24/63 (38.1)	17/29 (58.6)	22/27 (81.5)	39/56 (69.6)	−31.5 (−50.2 to −12.9
Duration of RRT, median (IQR), d	4 (2 to 7)	3 (2 to 5)	3 (2 to 7)	3 (2 to 8)	4 (2 to 8)	3 (2 to 8)	0 (−2 to 2)
Survivors	4 (2 to 8)	3 (3 to 14)	4 (2 to 10)	4 (2 to 10)	6 (2 to 12)	5 (2 to 11)	−1 (−4 to 2)
Nonsurvivors	4 (1 to 7)	2 (1 to 4)	2 (1 to 6)	3 (2 to 4)	3 (2 to 6)	3 (2 to 6)	−1 (−2 to 2)

JAMA. 2016;316:509-518

ORIGINAL

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

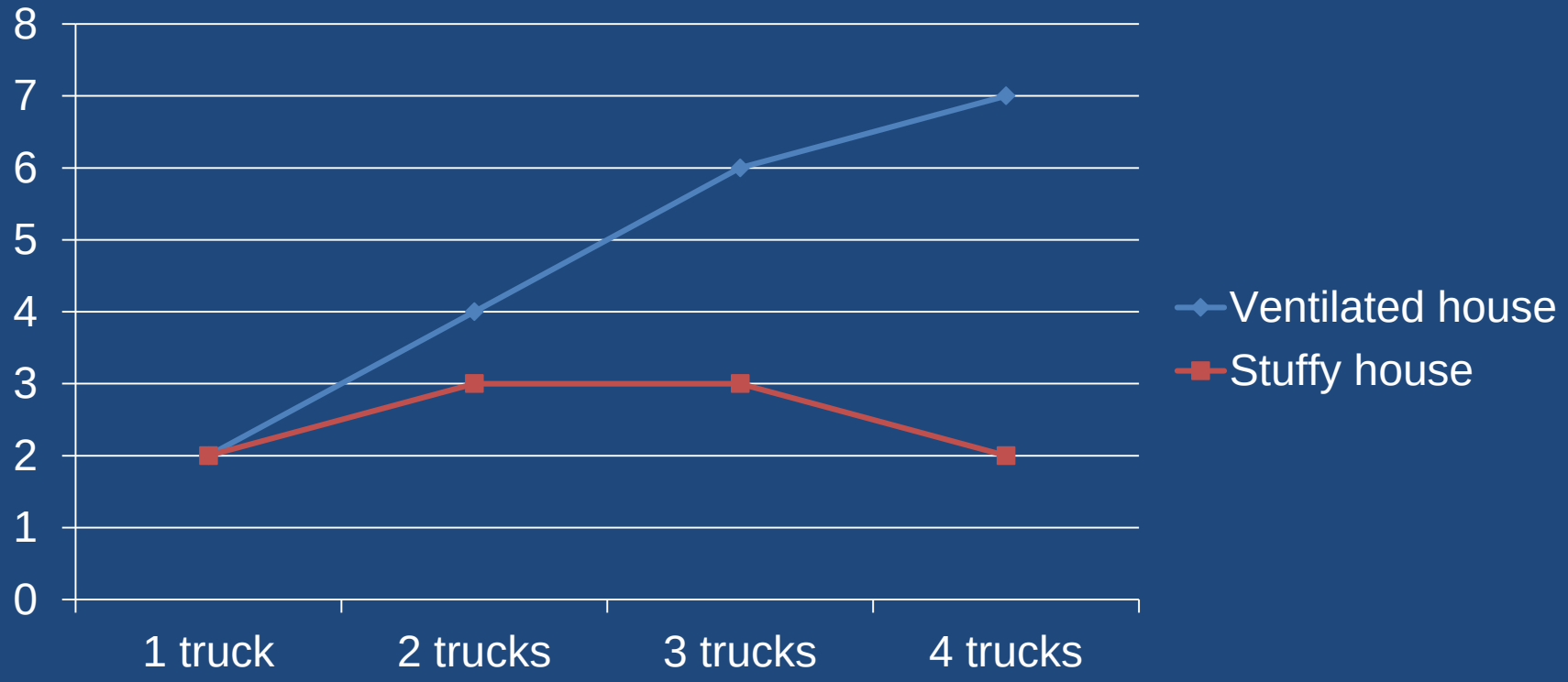
Variable	Norepinephrine group ($N = 266$)	Terlipressin group ($N = 260$)	p
28-day mortality *N* (%)	101/266 (38%)	104/260 (40%)	0.633
Days alive and free of vasopressor	14.66 ± 11.13	15.50 ± 11.14	0.424
Change of SOFA score from D0 to D7[a]	− 6 (− 10 to 5)[b]	− 7 (− 11 to 3)[b]	0.123

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

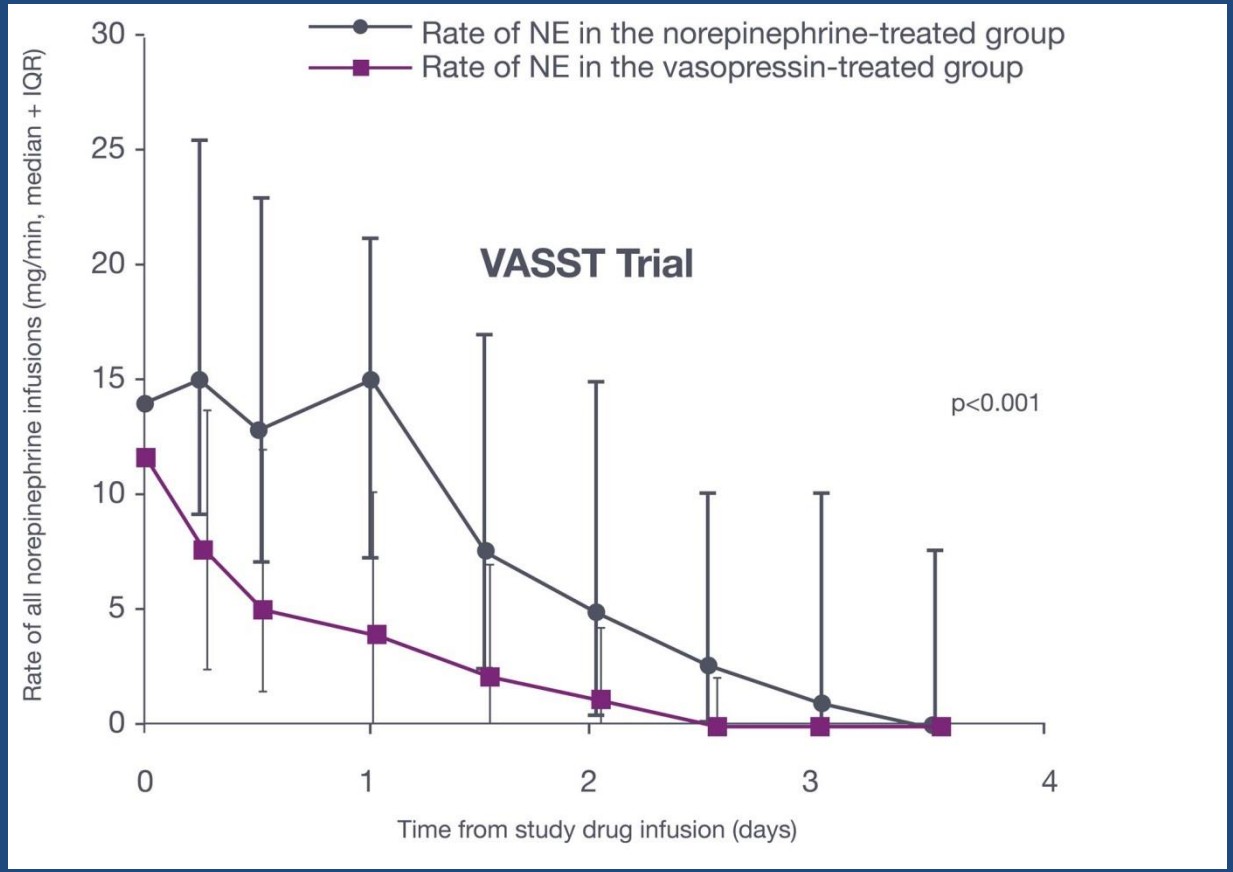
Intensive Care Med. 2018;44:1816-1825.

REBUTTAL Vasopressin: PRO (safety & cost-effectiveness)

Lives Lost from Fire per Fire Truck Sent

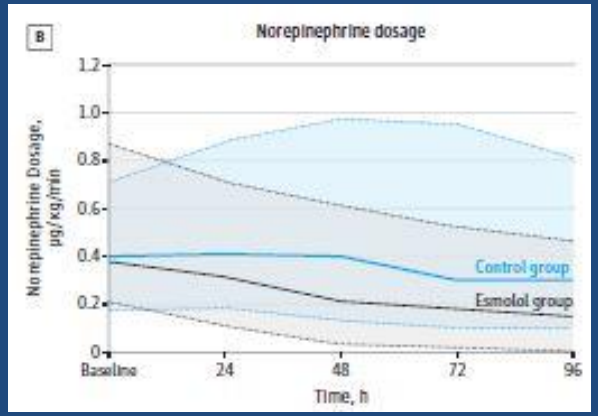


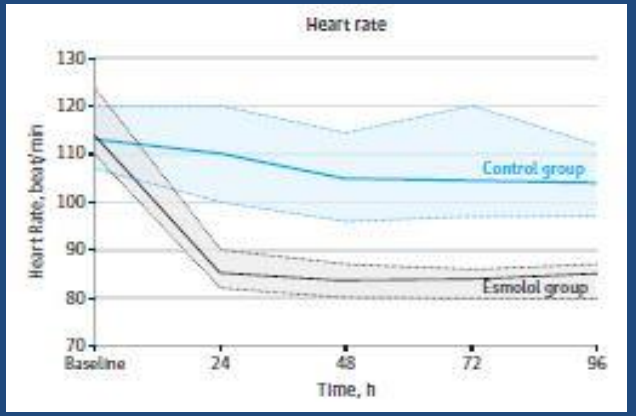
Graph adapted by Drayton Hammond

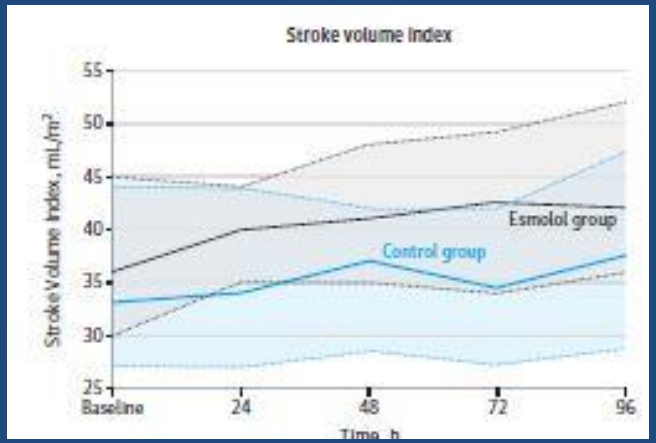


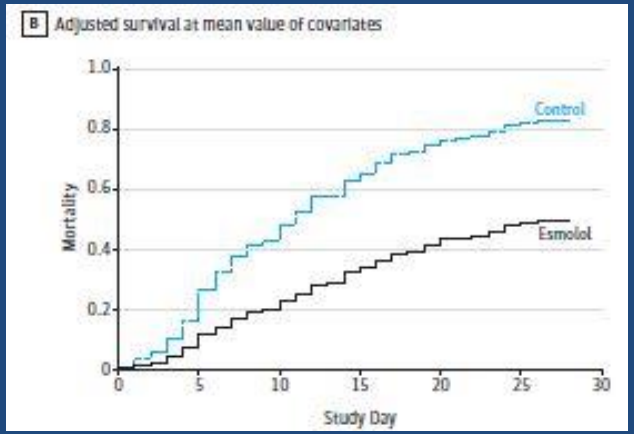
N Engl J Med 2008;358:877-87.

Make B1 Receptors Great Again (…by not overstimulating them)









JAMA 2013;310:1683-91.

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

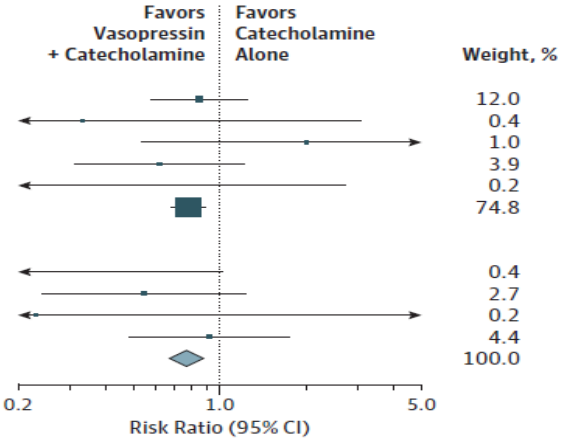
William F. McIntyre, MD; Kevin J. Um, BA; Waleed Alhazzani, MD, MSc; Alexandra P. Lengyel; Ludhmila Hajjar, MD; Anthony C. Gordon, MD; François Lamontagne, MD, MSc; Jeff S. Healey, MD, MSc; Richard P. Whitlock, MD, PhD; Emilie P. Belley-Côté, MD, MSc

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)
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)
Choudhury et al,[29] 2016	1	42	3	42	0.33 (0.04-3.08)
Clem et al,[30] 2016	6	41	3	41	2.00 (0.54-7.46)
Dünser et al,[39] 2003	8	24	13	24	0.62 (0.31-1.21)
Gordon et al,[20] 2016	0	205	3	204	0.14 (0.01-2.73)
Hajjar et al,[18] 2017	95	149	124	151	0.78 (0.67-0.89)
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)
Russell et al,[22] 2008	7	44	14	48	0.55 (0.24-1.23)
Russell et al,[23] 2017	0	31	1	21	0.23 (0.01-5.37)
Svoboda et al,[37] 2012	7	13	10	17	0.92 (0.48-1.74)
Total events (95% CI)	159	739	215	723	0.77 (0.67-0.88)

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

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



Cost-Effectiveness Considerations

- Cost control measures
  - Infusion rate, IVPB size and concentration, RPh verification, MUE

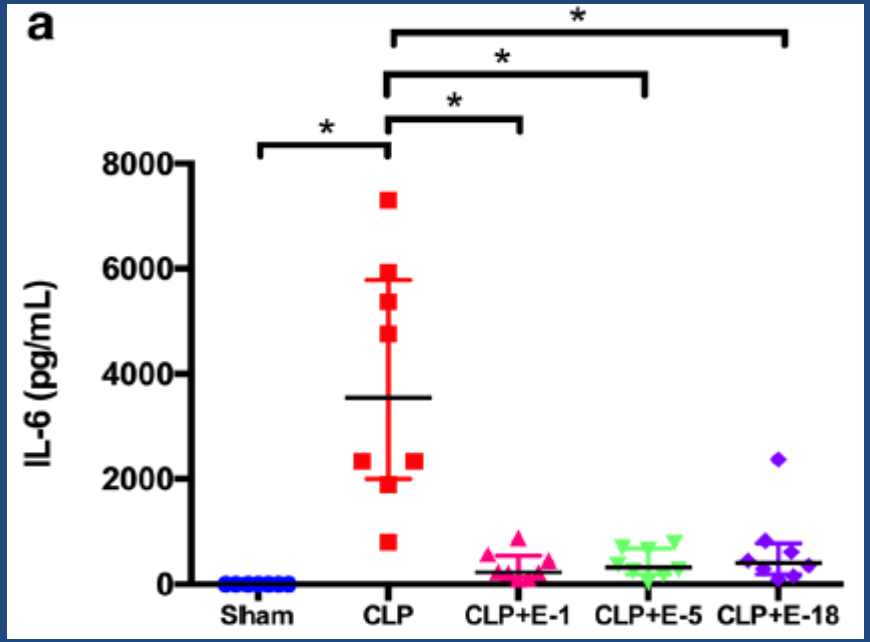
- Cost of vasopressors small vs costs of complications
  - NE ~$80 vs AVP ~$280 (per day)
  - RRT ~$40,000 vs AKI without RRT ~$14,000
  - NOAF ~$12,000 vs. no NOAF ~no cost

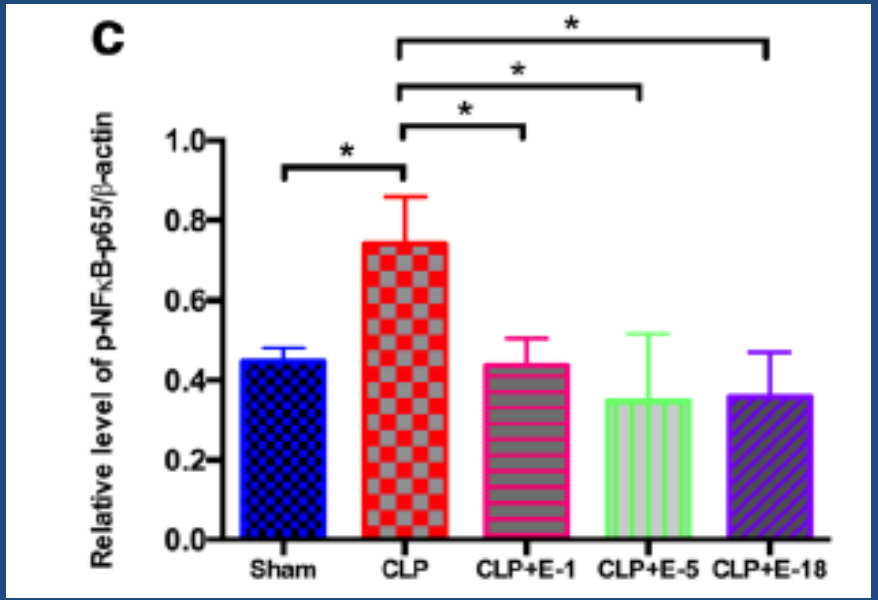
TAKEAWAY:

Vasopressin improves safety and its cost-effectiveness should be evaluated

REBUTTAL Vasopressin: CON (data inconsistent & contradictory)

Let's Talk about β





Crit Care. 2016 ;20:407.

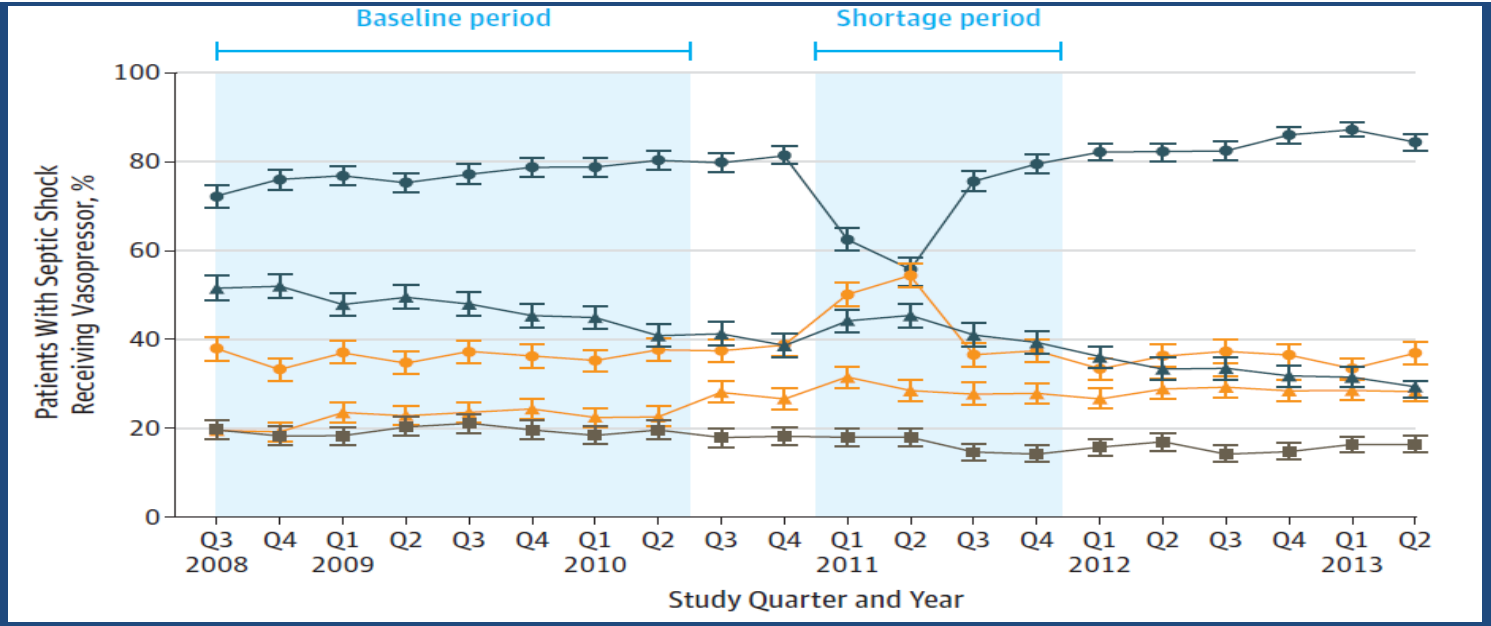
Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

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
Difference-in-differences model[d]				
Difference-in-differences estimator for shortage and consistent-use hospitals	NA	NA	1.17 (1.06-1.31)	.003

JAMA. 2017;3171433-1442.



Characteristic	Patients With Septic Shock in 26 Shortage Hospitals[a] Shortage Quarters (n = 1961)	Nonshortage Quarters (n = 25 874)	*P* Value	Patients With Septic Shock in 102 Consistent-Use Hospitals[b] (n = 120 759)
Vasopressor use, No. (%)[f]				
Norepinephrine	997 (50.8)	20 681 (79.9)	<.001	98 549 (81.6)
Phenylephrine	1081 (55.1)	9468 (36.6)	<.001	47 946 (39.7)
Dopamine	953 (48.6)	10 490 (40.5)	<.001	43 445 (36.0)
Vasopressin	622 (31.7)	6620 (25.6)	<.001	30 367 (25.2)
Epinephrine	348 (17.8)	4536 (17.5)	.81	25 118 (20.8)

JAMA. 2017;3171433-1442.

JAMA | Original Investigation

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

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A Atrial fibrillation

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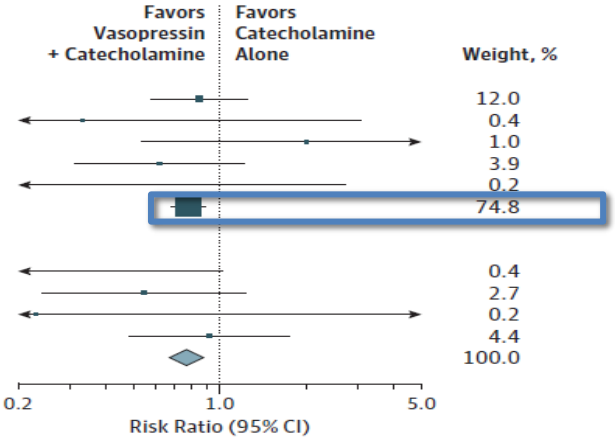
Overall effect: $z = 3.79$ ($P < .001$)



Meta Analysis

Group	No. With Events/Total No. of Patients: Vasopressin + Catecholamines	No. With Events/Total No. of Patients: Catecholamines Alone	Risk Difference % (95% CI)[a]	Relative Risk[a]: Risk Ratio (95% CI)	*P* Value	I^2 %	Quality of Evidence (Reason for Judgment)
28-d or 30-d Mortality							
All studies[18,21-27,29-32,36,38-41]	532/1453	591/1451	−4 (−7 to 0)	0.89 (0.82 to 0.97)	.009	0	Low (risk of bias)
Low risk of bias[24,39]	215/529	222/520	−2 (−8 to 4)	0.96 (0.84 to 1.11)	.6	0	
High risk of bias[18,21-23,25-27,29-32,36,38,40,41]	317/924	369/931	−4 (−8 to 0)	0.86 (0.77 to 0.95)	.004	0	
28-d or 30-d or ICU mortality[18,21-36,38-41,b,c]	567/1525	623/1505	−4 (−7 to −1)	0.89 (0.83 to 0.97)	.006	0	
Full text only[18,22,23,25,26,29-32,39-41,d]	334/993	356/984	−2 (−6 to 2)	0.91 (0.82 to 1.01)	.09	0	
Vasopressin[23,24,27,29,30,36,39,41,b]	404/1156	431/1160	−2 (−6 to 2)	0.94 (0.85 to 1.04)	.21	0	
Vasopressin analogues[21,22,25,26,31,32,38,40,41,b]	128/297	160/291	−10 (−18 to −3)	0.81 (0.70 to 0.94)	.005	0	
Sepsis[21-27,29-32,36,38-41]	509/1304	567/1300	−4 (−8 to −1)	0.89 (0.82 to 0.97)	.008	0	
Cardiac surgery[18]	23/149	24/151	−0 (−9 to 8)	0.97 (0.57 to 1.64)	.91	NA	
Requirement for Renal Replacement Therapy							
All studies[23,24,28,30,33,35,b,e]	97/412	125/393	−7 (−12 to −1)	0.74 (0.51 to 1.08)	.12	70	Moderate (imprecision)
Low risk of bias[24,30]	62/330	89/329	−7 (−13 to −2)	0.70 (0.53 to 0.92)	.01	0	
High risk of bias[23,28,33,35,b,c]	35/82	36/64	−5 (−16 to 7)	0.77 (0.42 to 1.43)	.41	67	
AKI as outcome[18,21,24,28,30,b]	154/515	204/516	−8 (−21 to 6)	0.73 (0.46 to 1.17)	.19	91	
Vasopressin[23,24,28,30,33,35,b,e]	93/397	125/393	−6 (−11 to −1)	0.76 (0.53 to 1.10)	.15	68	
Vasopressin analogues[35,b,e]	4/15	8/15	−27 (−60 to 7)	0.50 (0.19 to 1.31)	.16	NA	
Digital Ischemia							
All studies[18,23,24,26,29,30,39-41]	41/990	17/973	2 (−1 to 4)	2.38 (1.37 to 4.12)	.002	0	Moderate (post hoc outcome)
Low risk of bias[18,24,30,39,40]	23/906	9/883	1 (−1 to 3)	2.45 (1.10 to 5.43)	.03	0	
High risk of bias[23,26,29,41]	18/84	8/90	10 (0 to 19)	2.31 (1.08 to 4.94)	.03	0	
Defined as digital ischemia[18,23,29,30,33,39,40,f]	25/810	8/789	2 (0 to 3)	2.73 (1.27 to 5.87)	.01	0	
Vasopressin[18,23,24,29,30,33,39,b]	24/904	10/893	1 (−1 to 3)	2.35 (1.10 to 5.05)	.03	0	
Vasopressin analogues[26,40,41,b]	17/86	7/80	10 (−4 to 25)	2.40 (1.09 to 5.31)	.03	0	

JAMA. 2018 8;319:1889-1900.

Renal Outcomes of Vasopressin and Its Analogs in Distributive Shock: A Systematic Review and Meta-Analysis of Randomized Trials

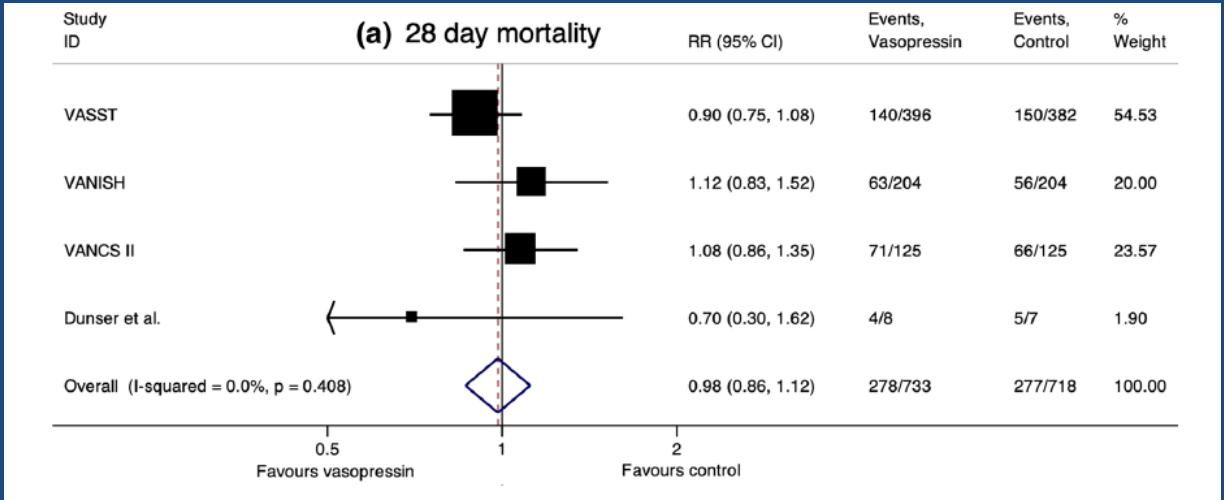
Wagner L. Nedel, MD, MSc[1–3]; Tatiana H. Rech, MD, PhD[1,4]; Rodrigo A. Ribeiro, MD, PhD[5,6]; José Augusto S. Pellegrini, MD, PhD[1]; Rafael B. Moraes, MD, PhD[1,3]

Subgroup of Studies	No. of Studies	Vasopressin or Analogs (*n*–Events)	Control (*n*–Events)	OR (95% CI)	I^2
Outcome: renal replacement therapy					
Blinded	3	751–204	737–241	0.57 (0.30–1.10)	80%; $p = 0.09$; random
Open	4	109–37	96–40	0.51 (0.23–1.12)	0%; $p = 0.09$; random
Vasopressin	7	845–237	833–281	0.60 (0.39–0.94)	46%; $p = 0.02$; random
Terlipressin	1	15–4	15–8	0.32 (0.07–1.47)	Not applicable
Outcome: acute kidney injury					
Blinded	4	797–378	782–419	0.67 (0.35–1.28)	86%; $p = 0.22$; random
Open	6	136–44	95–54	0.36 (0.19–0.71)	0%; $p = 0.003$; random
Vasopressin	8	891–411	878–459	0.64 (0.39–1.04)	68%; $p = 0.07$; random
Terlipressin	3	42–11	44–22	0.32 (0.12–0.83)	0%; $p = 0.02$; random

Crit Care Med. 2019;47:e44-e51.

SYSTEMATIC REVIEW

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



Intensive Care Med. 2019 May 6. doi: 10.1007/s00134-019-05620-2.

Breaking News

Characteristic	Entire Cohort			Matched Cohort		
	Epinephrine (n = 82)	Vasopressin (n = 84)	*P*	Epinephrine (n = 48)	Vasopressin (n = 48)	*P*
Shock-free survival duration (hours)	0 [0-120.9]	39.2 [0-115.3]	0.20	13.2 [0.0-121.0]	41.3 [0.0-125.9]	0.51
Vasopressor duration (hours)	33.1 [13.3-61.3]	53.5 [24.7-85.1]	0.008	36.9 [10.9-65.4]	41.9 [18.1-71.8]	0.43
7-Day mortality	43 (52.4)	29 (34.5)	0.02	23 (47.9)	19 (39.6)	0.35
28-Day mortality	50 (60.9)	46 (54.8)	0.42	27 (56.3)	28 (58.3)	0.84
Incident arrhythmia	18 (21.9)	21 (25.0)	0.64	13 (27.1)	11 (22.9)	0.64

[a]Data are presented as median [interquartile range] or n (%).

Ann Pharmacother. 2019 Apr 8:1060028019843664.. [Epub ahead of print]

Closing Thoughts

- Vasopressin never conclusively validated as a necessary therapy
- Potential benefits are inconclusive and contradictory
- Significantly increased price makes cost-effectiveness an important question
- Best use would be early in septic shock management as a trial and discontinue if no benefits seen

Angiotensin II: PRO (catecholamine-sparing & angiotensin II-deficiency)

Vasoplegia and Angiotensin II (AT2) Deficiency

- Uncontrolled vasodilation in vasodilatory shock that is hyporesponsive to catecholamine vasopressors
  - Non-catecholamine options must be utilized (e.g., AVP, steroids, AT2)

- AT2 levels reduced in sepsis
  - After 3 hours
  - Endotoxin production from Gram negatives
  - Pulmonary disease (i.e., ARDS, PNA) reduce endothelial conversion of AT1 to AT2

Ann Pharmacother. 2018;52:920-7.

RAAS Pathway

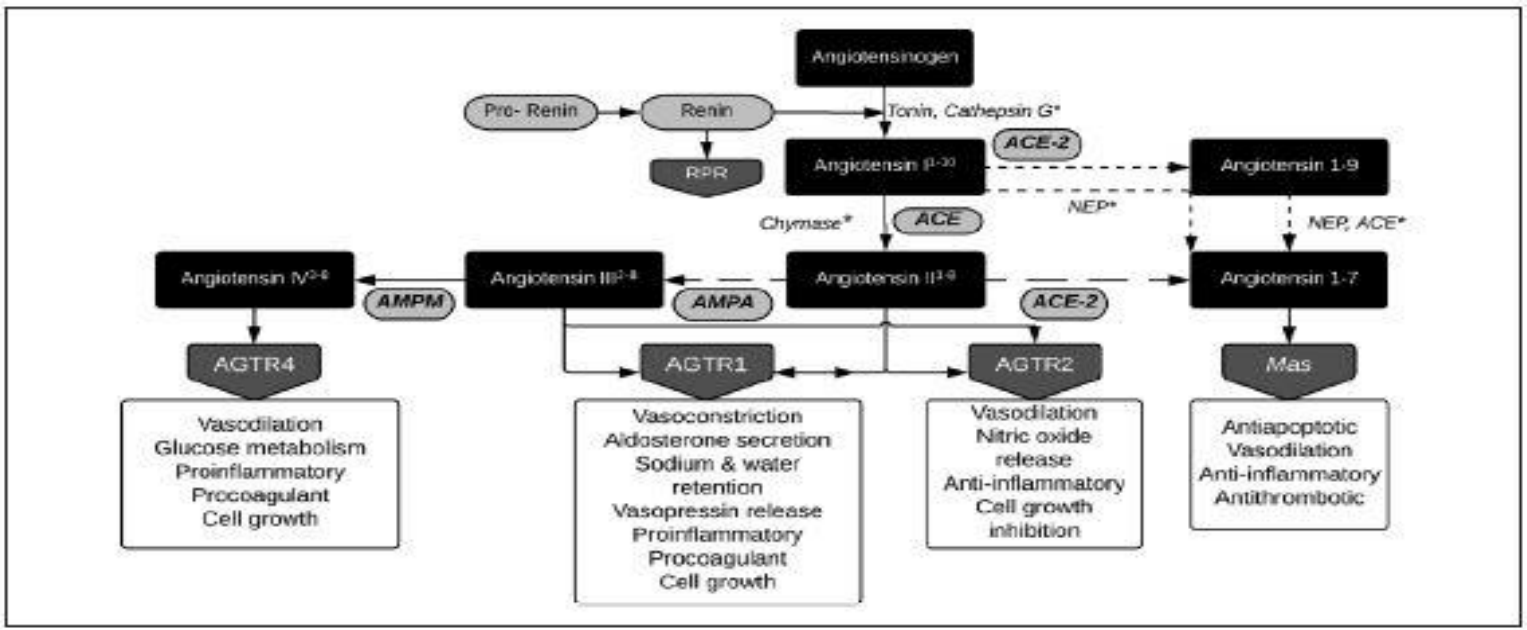


Figure 1. Renin angiotensin-aldosterone system network and pathways.
Abbreviations: ACE, angiotensin-converting enzyme; AGTR1, angiotensin II receptor type 1; AMPA, aminopeptidase A; AMPM, aminopeptidase M; NEP, neutral endopeptidase; RPR, renin/prorenin receptor; *secondary enzymatic pathways

Ann Pharmacother. 2018;52:920-7.

ATHOS-3

- FDA approved in Dec 2017 to increase BP in adults with septic or other distributive shock based on ATHOS-3

- ATHOS-3 purpose: to determine if adding AT2 to background vasopressors will improve BP in patients with catecholamine-resistant vasodilatory shock
  - 75 ICUs in 9 countries
  - Dosing based on pilot studies
  - 80% sepsis, 10% potentially sepsis

N Eng J Med. 2017;377:419-30.

End Points

Primary	• MAP response at hour 3
Secondary	• SOFA and SOFA-CV score changes • All-cause mortality at days 7 and 28
Safety	• Serious and all adverse events • Adverse event-related drug discontinuation

N Eng J Med. 2017;377:419-30.

ATHOS-3

- Double-blind, placebo-controlled RCT
- Inclusion
  - Cardiac index >2.3 L/min/m^2 OR $ScvO_2$ >70% with CVP >8 mm Hg
  - MAP 55-70 mm Hg
- Intervention
  - AT2 (n=163)
    - 20 ng/kg/min starting rate, up to 80 ng/kg/min for goal MAP >75 mm Hg during the first three hours
    - 1.25-40 ng/kg/min after three hours for MAP goal 65-75 mm Hg
    - Weaned off at 48 hours unless hemodynamic instability
  - Placebo (n=158)

N Eng J Med. 2017;377:419-30.

Baseline Vasopressor Use

	AT2 (n=163)	Placebo (n=158)	All Patients (n=321)
Vasopressin use during 6 h before randomization, n (%)	113 (69)	111 (70)	224 (70)
NE equivalents (mcg/kg/min), median (IQR)	0.33 (0.23-0.56)	0.34 (0.23-0.56)	0.34 (0.23-0.56)
NE equivalent dosage (mcg/kg/min), n (%)			
<0.35	83 (51)	83 (53)	166 (52)
≥0.35 to <0.5	34 (21)	27 (17)	61 (19)
≥0.5	46 (28)	48 (30)	94 (29)

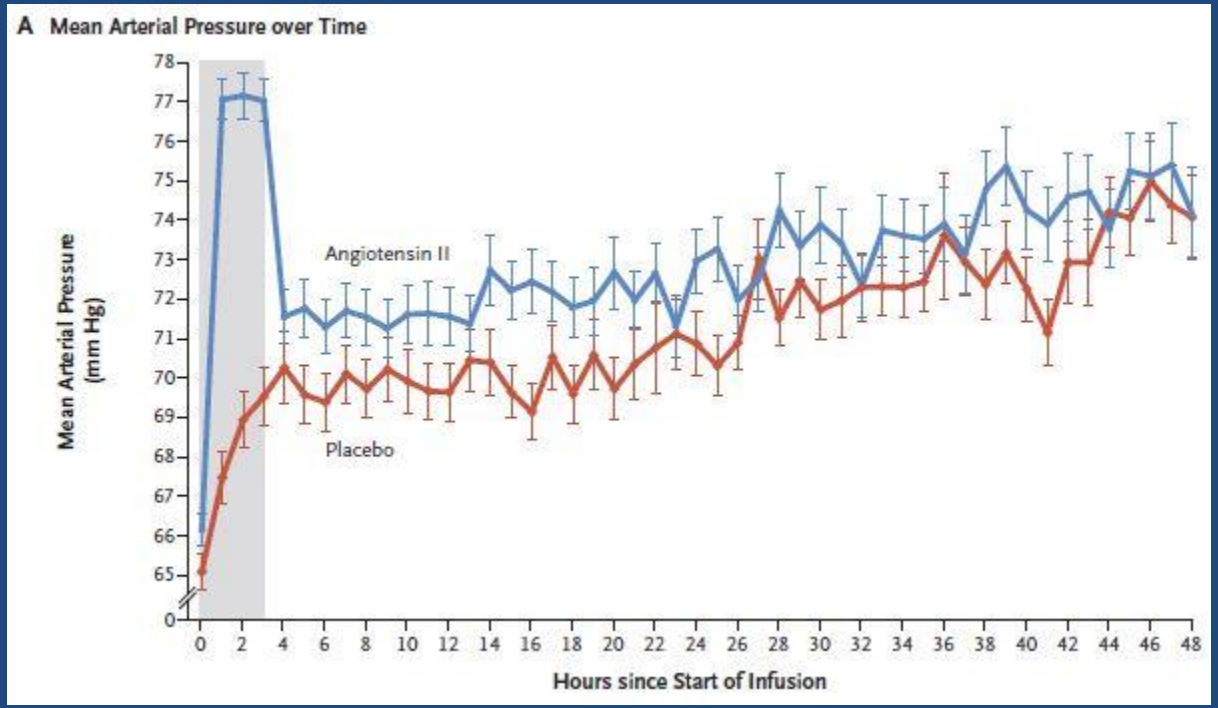
N Eng J Med. 2017;377:419-30.

Primary and Secondary Outcomes

	AT2	Placebo	OR/HR (95% CI)	p
Primary Endpoint				
MAP response at 3 h, n (%)	114 (70)	37 (23)	7.95 (4.47-13.3)	**<0.001**
Secondary Endpoints				
Mean delta SOFA-CV at 48 h	-1.75 ± 1.77	-1.28 ± 1.65	---	**0.01**
Mean delta SOFA at 48 h	1.05 ± 5.5	1.04 ± 5.34	---	0.49
Mean delta in NE-equivalent dosage from baseline to 3 h	-0.03 ± 0.1	0.03 ± 0.23	---	**<0.001**
7-day mortality, n (%)	47 (29)	55 (35)	0.78 (0.53-1.16)	0.22
28-day mortality, n (%)	75 (46)	85 (54)	0.78 (0.57-1.07)	0.12

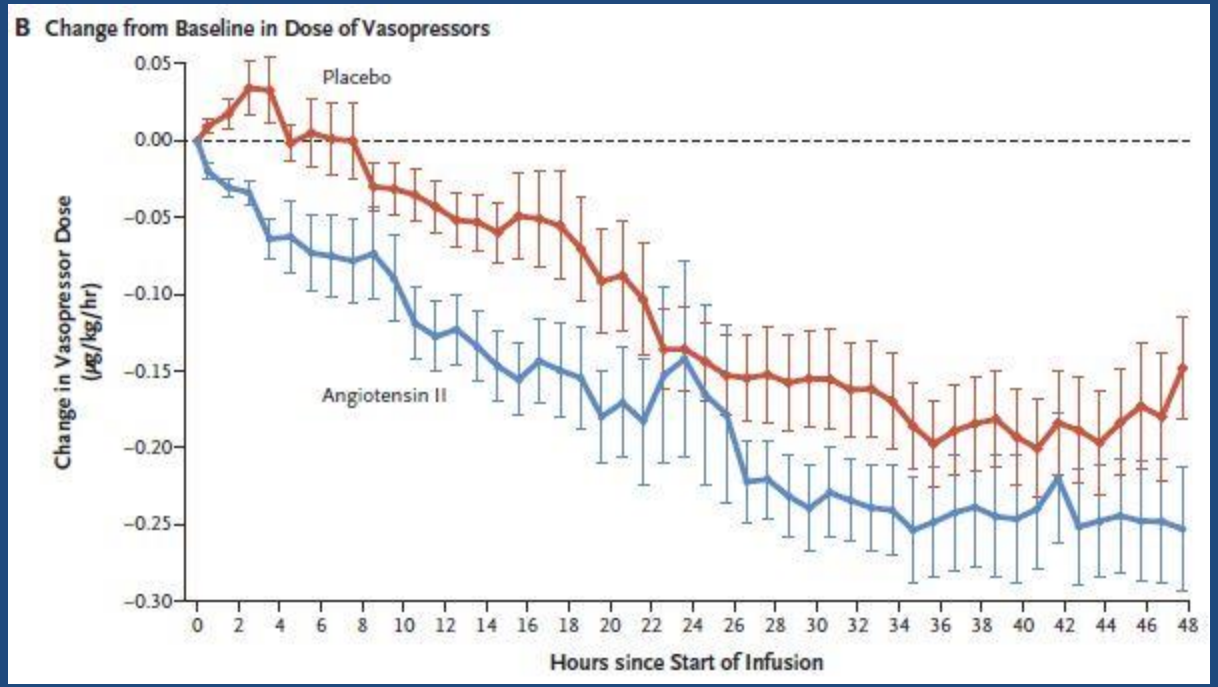
N Eng J Med. 2017;377:419-30.

MAP



N Eng J Med. 2017;377:419-30.

Norepinephrine Equivalent Dosage



N Eng J Med. 2017;377:419-30.

Conclusions

- AT2 generated higher MAP at hour 3 and lower catecholamine requirements
- AT2 was effective in patients unresponsive to low-to-medium-dose conventional vasopressors (e.g., NE and AVP)
- Potential differences in adverse effects favoring control group

N Eng J Med. 2017;377:419-30.

Patients with AKI and RRT at Study Drug Initiation

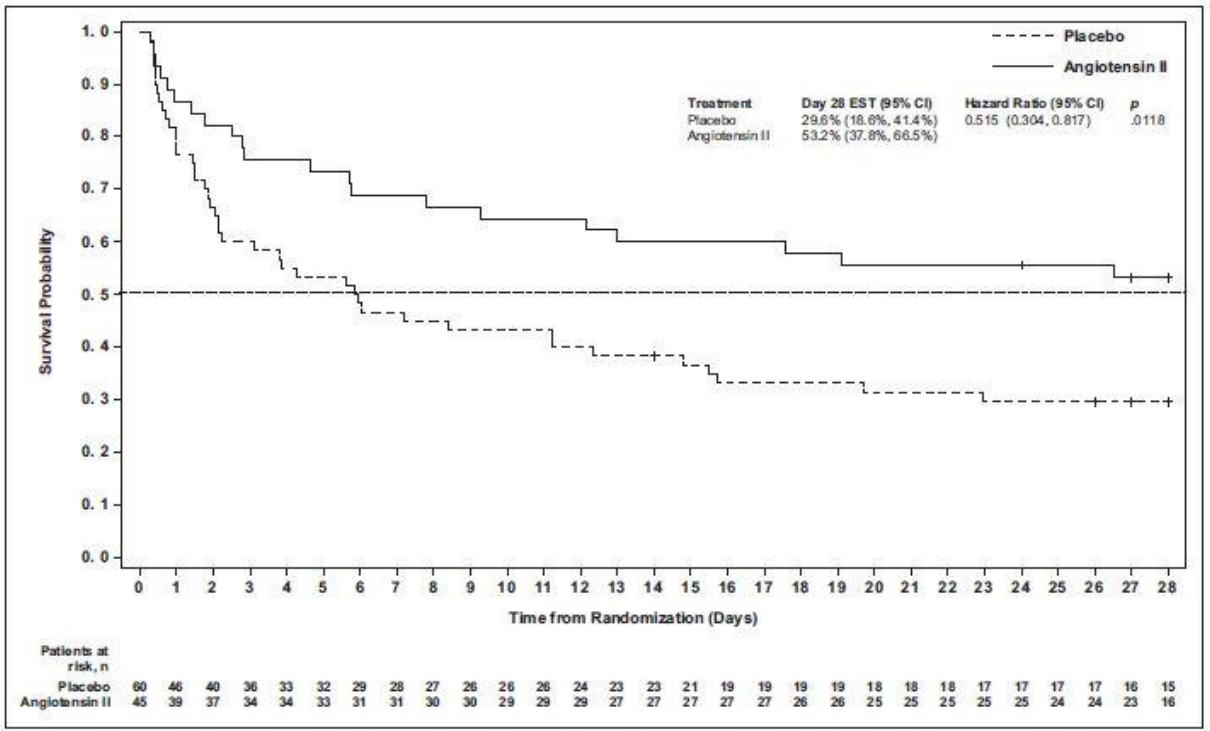


Figure 1. Survival probability through day 28. Patients in the angiotensin II group were more likely to survive to day 28 than those in the placebo group ($p = 0.012$).

Crit Care Med. 2018;46:949-57.

Patients with AKI and RRT at Study Drug Initiation

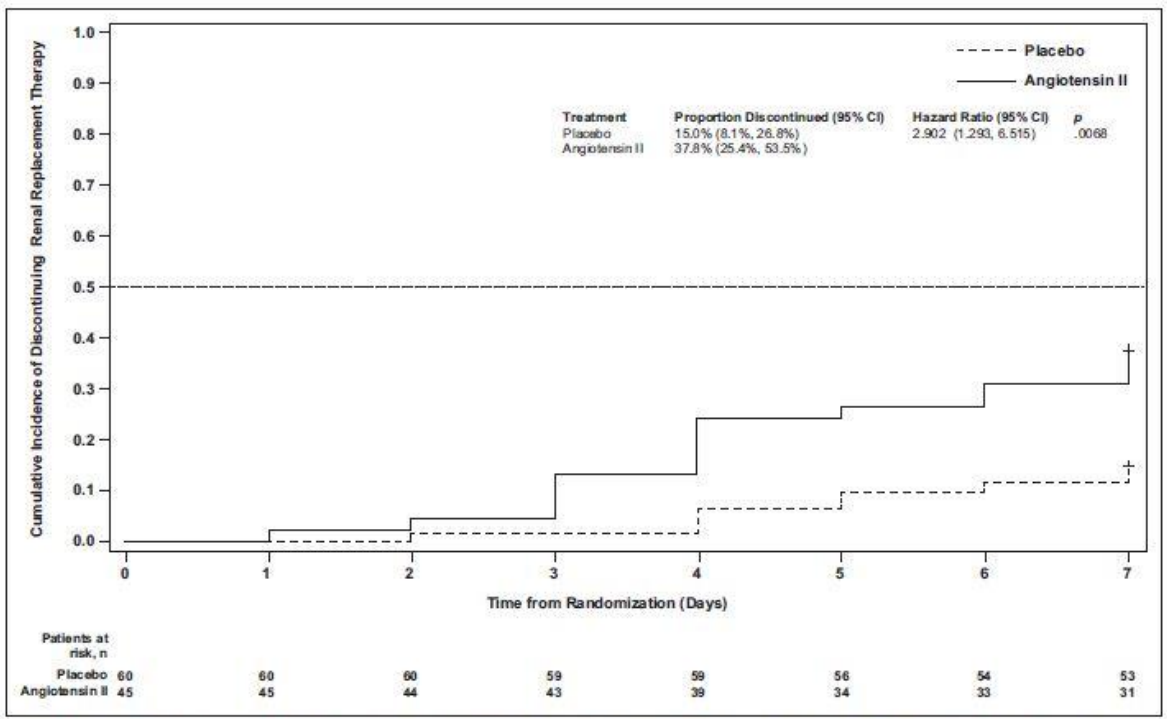


Figure 2. Cumulative incidence of time to discontinuation of renal replacement therapy through day 7. Subjects with death prior to day 7 are censored at day 7. Patients in the angiotensin II group were more likely to discontinue renal replacement therapy within 7 days than those in the placebo group ($p = 0.0068$).

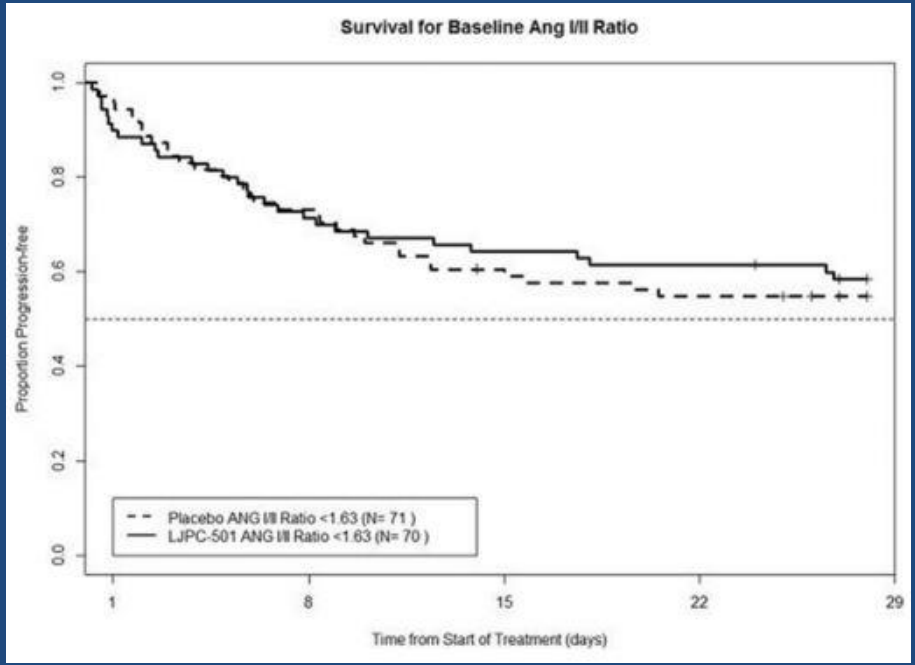
Crit Care Med. 2018;46:949-57.

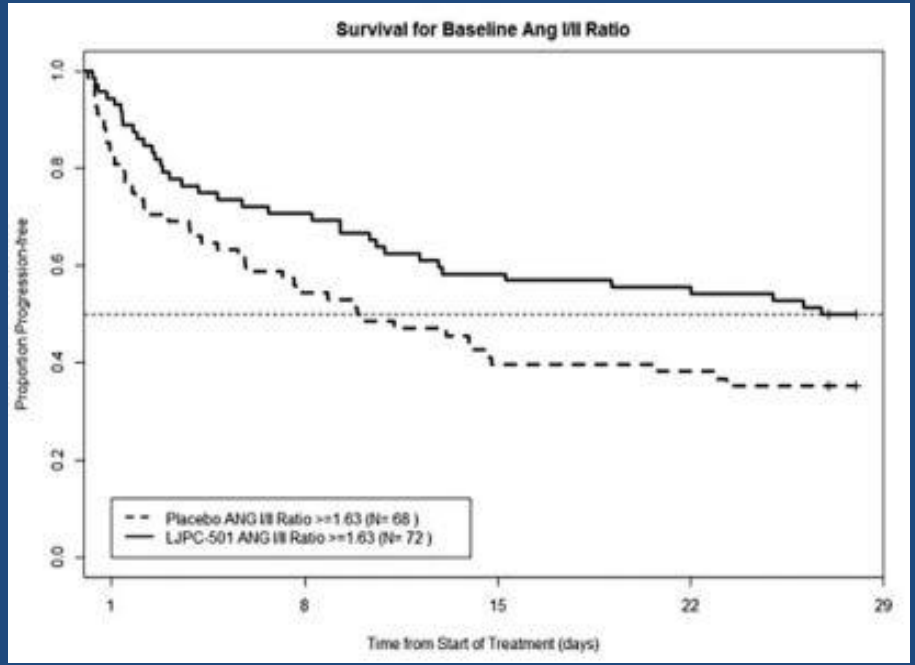
Patients with High Severity of Illness

- Severity of illness metrics (APACHE II > 30 [n = 123] and MAP < 65 mm Hg [n = 102]) were pre-specified and analyzed for 28-day all-cause mortality
- MAP achieved: 69.9% vs. 23.4%, p<0.001
- 28-day all-cause mortality
  - APACHE II >30: 51.8% vs. 70.8%, HR 0.62, 95% CI 0.39-0.98
  - Baseline MAP <65: 54.2% vs. 70.4%, HR 0.66, 95% CI 0.40-1.09

Crit Care Med. 2018;46:949-57.

Patients with High AT1:AT2





Intens Care Med Exper. 2017;5(Suppl 2):44.

ARDS

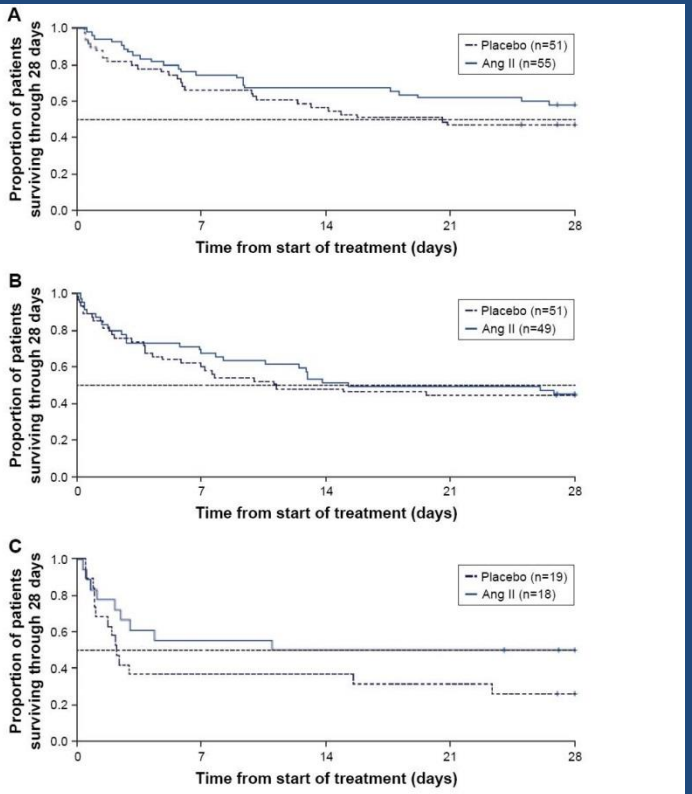


Figure 2 Progressive Kaplan–Meier analysis of the mortality effect of Ang II in patients with ARDS.
Notes: Kaplan–Meier estimate of survival of patients enrolled in the ATHOS-3 study through day 28 by severity of ARDS. In ATHOS-3, patients were randomized to standard of care therapy plus either placebo or Ang II. A post hoc subgroup analysis of patients in ATHOS-3 with ARDS at enrollment showed that the observed mortality benefit of patients receiving Ang II was more pronounced with higher severity of ARDS. (**A**) Patients with mild ARDS at baseline. (**B**) Patients with moderate ARDS at baseline. (**C**) Patients with severe ARDS at baseline. Reproduced from Busse LA, Gong T, Thompson M. Outcomes in patients with acute respiratory distress syndrome receiving angiotensin II for vasodilatory shock. *Critical Care*. 2018;22(Suppl 1):82.[131]
Abbreviations: Ang II, angiotensin II; ARDS, acute respiratory distress syndrome.

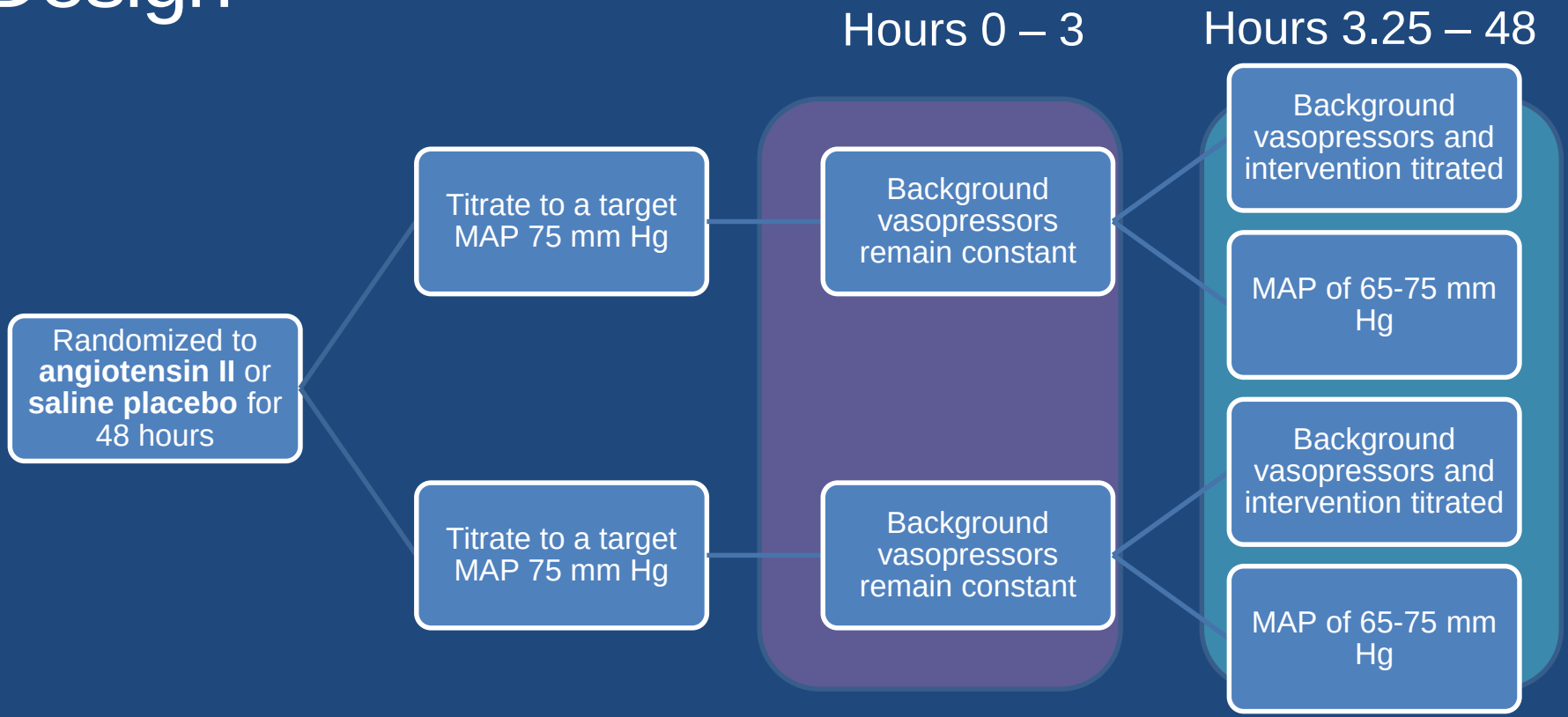
Crit Care. 2018;22(Suppl 1):82.

TAKEAWAY:

Angiotensin II has a role in catecholamine- and vasopressin-resistant septic shock, especially those with AKI (±RRT), high severity of illness, high angiotensin I to angiotensin II ratio, and/or severe ARDS

Angiotensin II: CON (Unclear benefit/clear harm)

Design


Hours 0 – 3
Hours 3.25 – 48
Randomized to **angiotensin II** or **saline placebo** for 48 hours
Titrate to a target MAP 75 mm Hg
Titrate to a target MAP 75 mm Hg
Background vasopressors remain constant
Background vasopressors remain constant
Background vasopressors and intervention titrated
MAP of 65-75 mm Hg
Background vasopressors and intervention titrated
MAP of 65-75 mm Hg

This Feels Familiar…

Administration of the nitric oxide synthase inhibitor N^G-methyl-L-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: Results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002)*

Jan Bakker, MD, PhD; Robert Grover, MBBS, FRCA; Angela McLuckie, MBBS, FRCA; Laurent Holzapfel, MD; Jan Andersson, MD, PhD; Robert Lodato, MD; David Watson, MBBS, FRCA; Steven Grossman, MD; Jill Donaldson, PhD; Jukka Takala, MD, PhD; on behalf of the Glaxo Wellcome International Septic Shock Study Group

N = 312
Improvement of MAP and sepsis

Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: Effect on survival in patients with septic shock*

Angel López; Jose Angel Lorente; Jay Steingrub; Jan Bakker; Angela McLuckie; Sheila Willatts; Michael Brockway; Antonio Anzueto; Laurent Holzapfel; Desmond Breen; Michael S. Silverman; Jukka Takala; Jill Donaldson; Carl Arneson; Geraldine Grove; Steven Grossman; Robert Grover

N = 797
Increased MAP
Increased mortality

Crit Care Med. 2004;32:1-12.
Crit Care Med. 2004;32:21-30.

AT-II Toxicities

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GIAPREZA™ safely and effectively. See full prescribing information for GIAPREZA.

GIAPREZA (angiotensin II) Injection for Intravenous Infusion
Initial U.S. Approval: 2017

INDICATIONS AND USAGE

GIAPREZA is a vasoconstrictor to increase blood pressure in adults with septic or other distributive shock. (1)

DOSAGE AND ADMINISTRATION

Dilute GIAPREZA in 0.9% sodium chloride prior to use. See Full Prescribing Information for instructions on preparation and administration of injection. Diluted solution may be stored at room temperature or under refrigeration and should be discarded after 24 hours. GIAPREZA must be administered as an intravenous infusion. (2.1)

- Start GIAPREZA intravenously at 20 nanograms (ng)/kg/min. Titrate as frequently as every 5 minutes by increments of up to 15 ng/kg/min as needed. During the first 3 hours, the maximum dose should not exceed 80 ng/kg/min. Maintenance dose should not exceed 40 ng/kg/min. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 2.5 mg/mL and 5 mg/2 mL (2.5 mg/mL) in a vial.

CONTRAINDICATIONS

None (4.1)

WARNINGS AND PRECAUTIONS

- There is a potential for venous and arterial thrombotic and thromboembolic events in patients who receive GIAPREZA. Use concurrent venous thromboembolism (VTE) prophylaxis. (5.1, 6.1)

ADVERSE REACTIONS

The most common adverse reactions reported in greater than 10% in GIAPREZA treated patients were thromboembolic events. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact La Jolla Pharmaceutical Company at 1-800-651-3861 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Angiotensin converting enzyme (ACE) inhibitors
  ACE inhibitors may increase response to GIAPREZA. (7.1)
- Angiotensin II Receptor Blockers (ARB)
  ARBs may reduce response to GIAPREZA. (7.2)

Vascular disorder	17 (10.4)	15 (9.5)
Hypotension	5 (3.1)	3 (1.9)
Peripheral ischemia	5 (3.1)	3 (1.9)
Shock	3 (1.8)	3 (1.9)
Deep-vein thrombosis	3 (1.8)	0
Distributive shock	1 (0.6)	4 (2.5)

AT II Toxicities

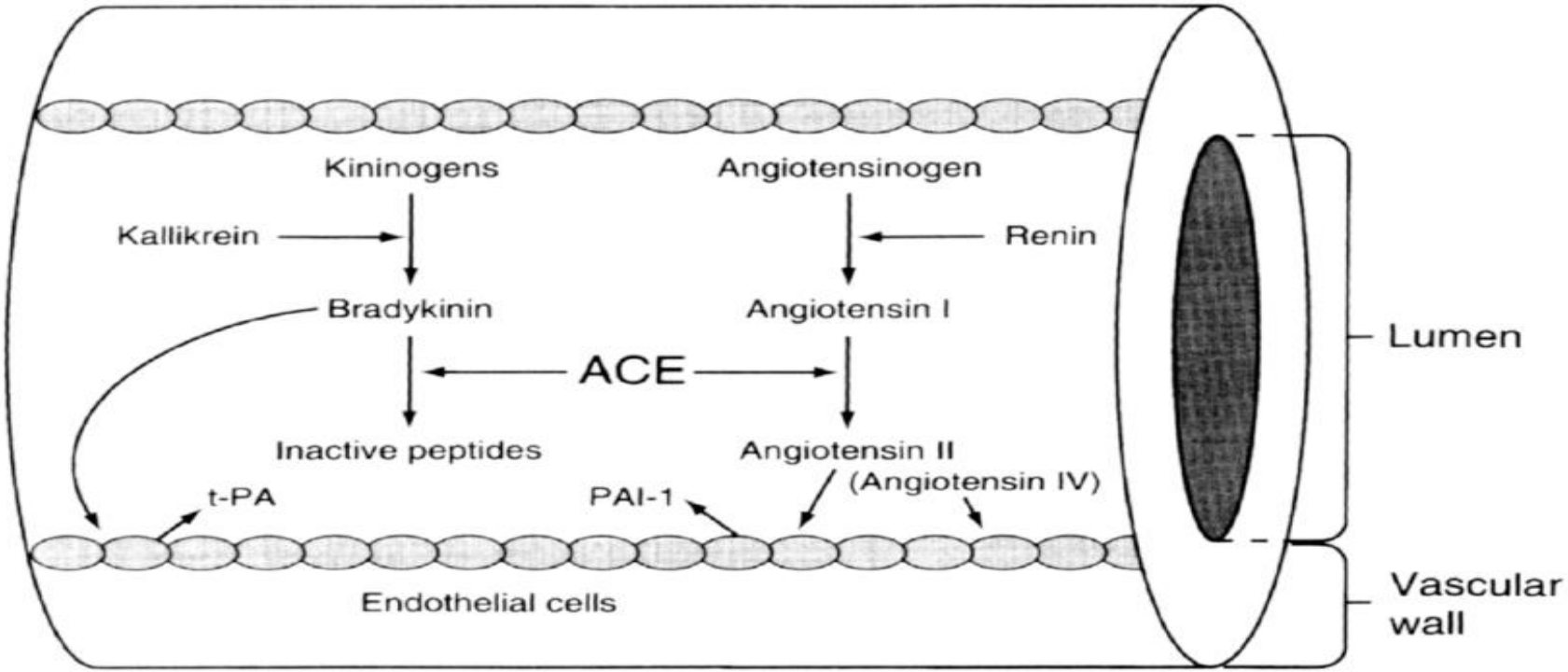
Adverse Event	GIAPREZA N=163	Placebo N=158
Thromboembolic events[a]	21 (12.9%)	8 (5.1%)
Deep vein thrombosis	7 (4.3%)	0 (0.0%)
Thrombocytopenia	16 (9.8%)	11 (7.0%)
Tachycardia	14 (8.6%)	9 (5.7%)
Fungal infection	10 (6.1%)	2 (1.3%)
Delirium	9 (5.5%)	1 (0.6%)
Acidosis	9 (5.5%)	1 (0.6%)
Hyperglycemia	7 (4.3%)	4 (2.5%)
Peripheral ischemia	7 (4.3%)	4 (2.5%)

[a] Including arterial and venous thrombotic events

Angiotensin II Regulates the Expression of Plasminogen Activator Inhibitor-1 in Cultured Endothelial Cells

A Potential Link between the Renin–Angiotensin System and Thrombosis

Douglas E. Vaughan, Stergios A. Lazos, and Kirk Tong
The Cardiovascular Divisions, Vanderbilt University Medical Center, and Nashville Veterans Affairs Medical Center, Nashville, Tennessee 37232

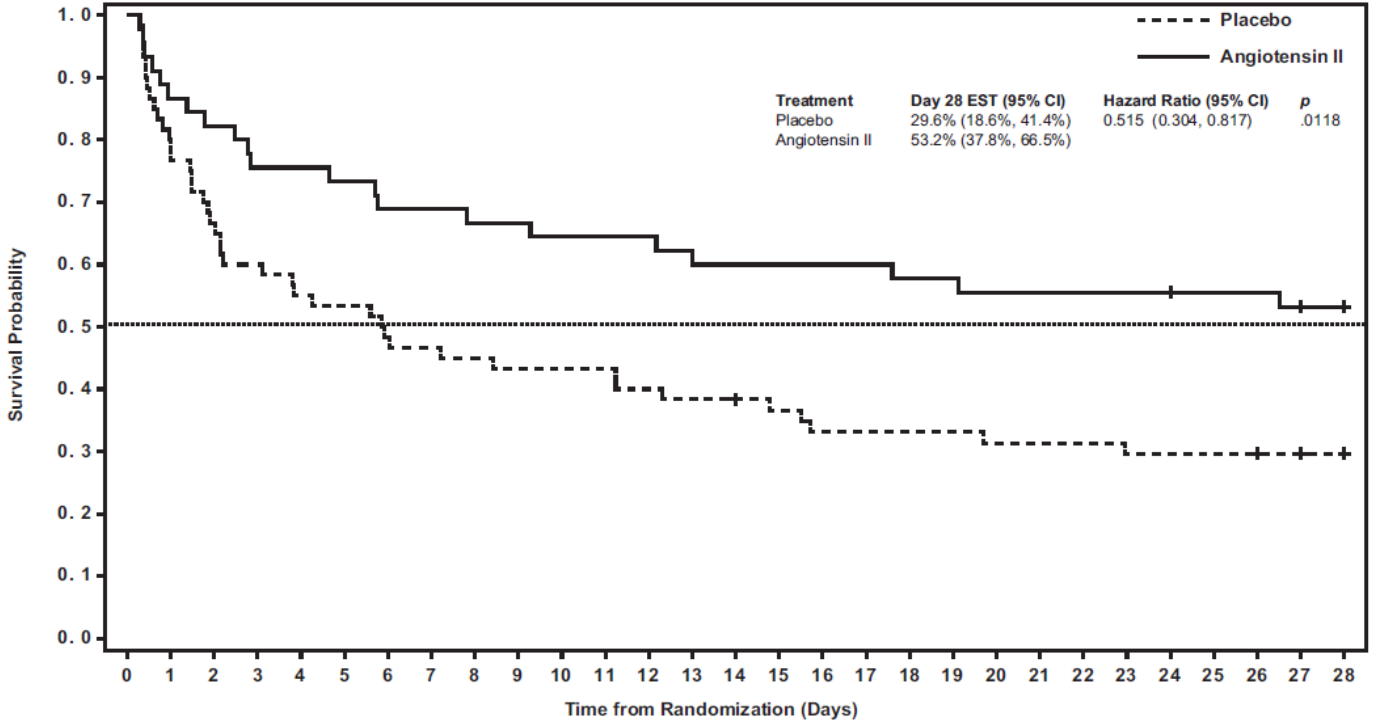


J Clin Invest. 1995;95:995-1001.
Am J Cardiol. 1997 6;79:12-6.

Variables Associated with Response

Parameter	Odds Ratio (95% CI)	P value
Treatment with angiotensin II vs placebo	12.4 (6.72-22.8)	< 0.001
Age ≥ 65 vs < 65 years	0.99 (0.56-1.74)	0.98
Male vs female	1.32 (0.74-2.34)	0.34
MAP at baseline < 65 vs ≥ 65 mm Hg	0.67 (0.36-1.23)	0.20
APACHE II score at baseline > 30 vs ≤ 30	1.04 (0.58-1.85)	0.90
Albumin at baseline < 2.5 vs ≥ 2.5 g/dL	0.40 (0.22-0.72)	0.002
Prior exposure to ARBs vs no exposure	0.24 (0.07-0.79)	0.02
Chest x-ray finding of ARDS vs no finding	2.03 (1.07-3.86)	0.03
Baseline NE equivalent dose ≥ 0.5 vs < 0.5 µg/kg/min	0.40 (0.21-0.77)	0.006

Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II

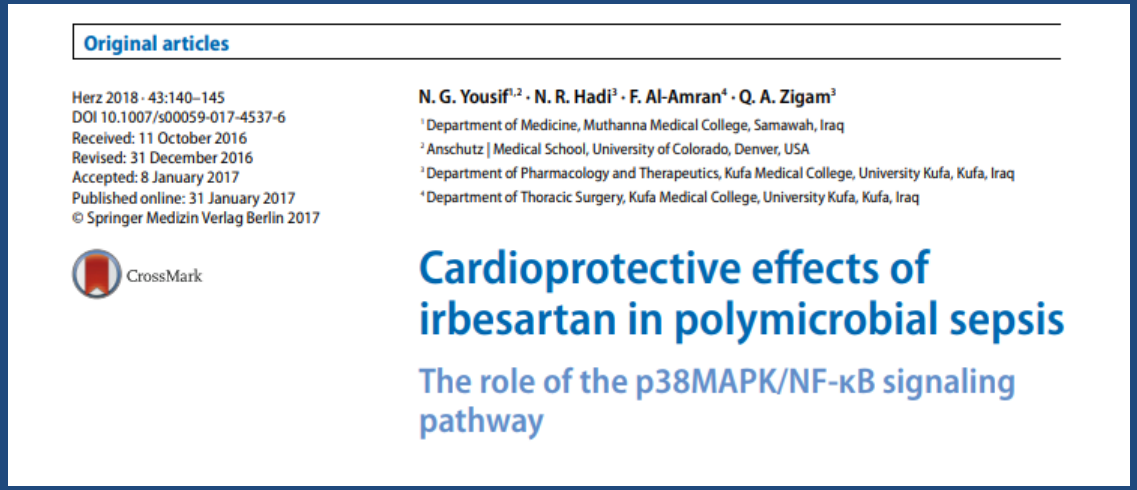


Crit Care Med. 2018;46:949-957.

Characteristic	Acute Kidney Injury + Renal Replacement Therapy at Study Drug Initiation			
	Placebo ($n = 60$)	Angiotensin II ($n = 45$)	All Patients (N = 105)	*p*
Age, yr	$n = 60$	$n = 45$	N = 105	
Median (IQR)	62.0 (51.0–73.5)	62.0 (50.0–72.0)	62.0 (51.0–73.0)	0.9613
Baseline mean arterial pressure (mm Hg)	$n = 60$	$n = 45$	N = 105	
Median (IQR)	65.7 (61.1–67.8)	65.7 (63.0–69.0)	65.7 (62.3–68.0)	0.1706
Baseline Acute Physiology and Chronic Health Evaluation II score	$n = 60$	$n = 45$	N = 105	
Median (IQR)	31.5 (27.0–38.0)	32.0 (24.0–37.0)	32.0 (26.0–38.0)	0.6176
Baseline albumin (g/dL)	$n = 60$	$n = 41$	N = 101	
Median (IQR)	2.3 (1.8–2.8)	2.3 (2.0–2.7)	2.3 (1.9–2.8)	0.6523
Baseline angiotensin I/II ratio	$n = 50$	$n = 41$	N = 91	
Median (IQR)	3.6 (1.1–10.2)	1.6 (0.8–4.2)	2.2 (1.0–7.4)	0.0253
Baseline Model for End-stage Liver Disease score	$n = 60$	$n = 45$	N = 105	
Median (IQR)	25.5 (23.0–30.0)	23.0 (19.0–28.0)	25.0 (22.0–29.0)	0.0095
Chest radiograph finding of acute respiratory distress syndrome, *n* (%)	$n = 60$	$n = 44$	N = 104	
Yes	27 (45.0%)	16 (36.4%)	43 (41.3%)	0.4242
Baseline norepinephrine equivalent dose (μg/kg/min)	$n = 60$	$n = 45$	N = 105	
Median (IQR)	0.46 (0.32–0.78)	0.36 (0.23–0.49)	0.42 (0.28–0.69)	0.0194

Crit Care Med. 2018;46:949-957.

Benefit with Blocking RAAS?



Original articles

Herz 2018 · 43:140–145
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CrossMark

N. G. Yousif[1,2] · N. R. Hadi[3] · F. Al-Amran[4] · Q. A. Zigam[3]

[1] Department of Medicine, Muthanna Medical College, Samawah, Iraq
[2] Anschutz | Medical School, University of Colorado, Denver, USA
[3] Department of Pharmacology and Therapeutics, Kufa Medical College, University Kufa, Kufa, Iraq
[4] Department of Thoracic Surgery, Kufa Medical College, University Kufa, Kufa, Iraq

Cardioprotective effects of irbesartan in polymicrobial sepsis

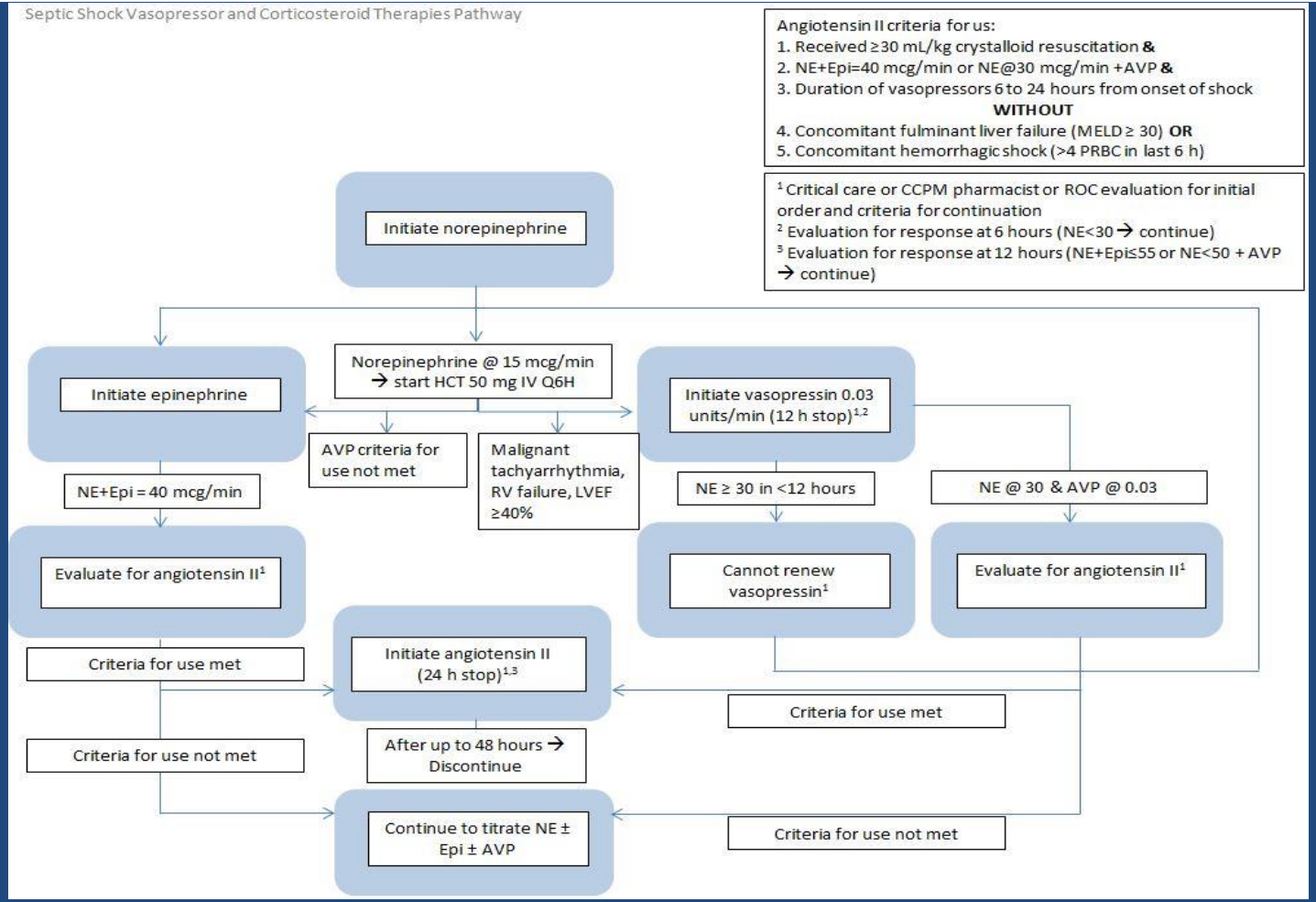
The role of the p38MAPK/NF-κB signaling pathway

Herz. 2018;43:140-145.

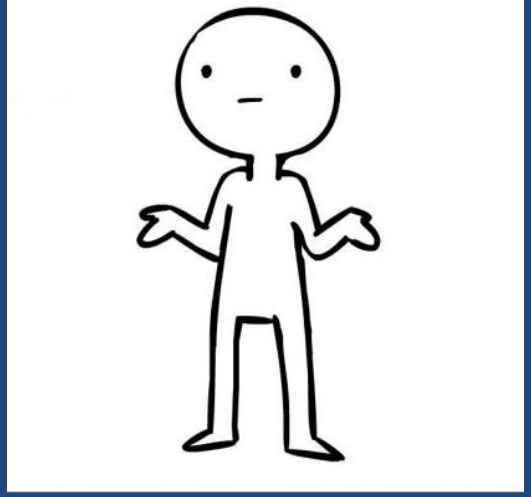
Closing Thoughts

- Raises BP well; uncertain if this leads to better outcomes though
- Adverse effects are legitimate concern
- Stewardship will be important given safety and financial concerns
- Ideal patients/compelling indications remain to be determined

Proposed Algorithm for Managing Hemodynamics in Septic Shock


Septic Shock Vasopressor and Corticosteroid Therapies Pathway
Angiotensin II criteria for us:
1. Received ≥30 mL/kg crystalloid resuscitation &
2. NE+Epi=40 mcg/min or NE@30 mcg/min +AVP &
3. Duration of vasopressors 6 to 24 hours from onset of shock
WITHOUT
4. Concomitant fulminant liver failure (MELD ≥ 30) OR
5. Concomitant hemorrhagic shock (>4 PRBC in last 6 h)
[1] Critical care or CCPM pharmacist or ROC evaluation for initial order and criteria for continuation
[2] Evaluation for response at 6 hours (NE<30 → continue)
[3] Evaluation for response at 12 hours (NE+Epi≤55 or NE<50 + AVP → continue)
Initiate norepinephrine
Initiate epinephrine
Norepinephrine @ 15 mcg/min → start HCT 50 mg IV Q6H
Initiate vasopressin 0.03 units/min (12 h stop)[1,2]
AVP criteria for use not met
Malignant tachyarrhythmia, RV failure, LVEF ≥40%
NE+Epi = 40 mcg/min
NE ≥ 30 in <12 hours
NE @ 30 & AVP @ 0.03
Evaluate for angiotensin II[1]
Cannot renew vasopressin[1]
Evaluate for angiotensin II[1]
Criteria for use met
Initiate angiotensin II (24 h stop)[1,3]
Criteria for use met
Criteria for use not met
After up to 48 hours → Discontinue
Continue to titrate NE ± Epi ± AVP
Criteria for use not met

Initiate norepinephrine & hydrocortisone 50 mg IV Q6H



Controversies in Septic Shock

Jerry Altshuler, PharmD, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
PGY-2 Critical Care Residency Program Director
The Mount Sinai Hospital

Drayton A. Hammond, PharmD, MBA, BCPS, BCCCP
MICU Clinical Pharmacy Specialist
PGY-2 Critical Care Residency Program Director
Rush University Medical Center


@hockeypharmd and @drdraymba