

Controversies in Septic Shock

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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. Recommend appropriate clinical settings for corticosteroids in septic shock
3. Explain strengths and limitations regarding current angiotensin II data

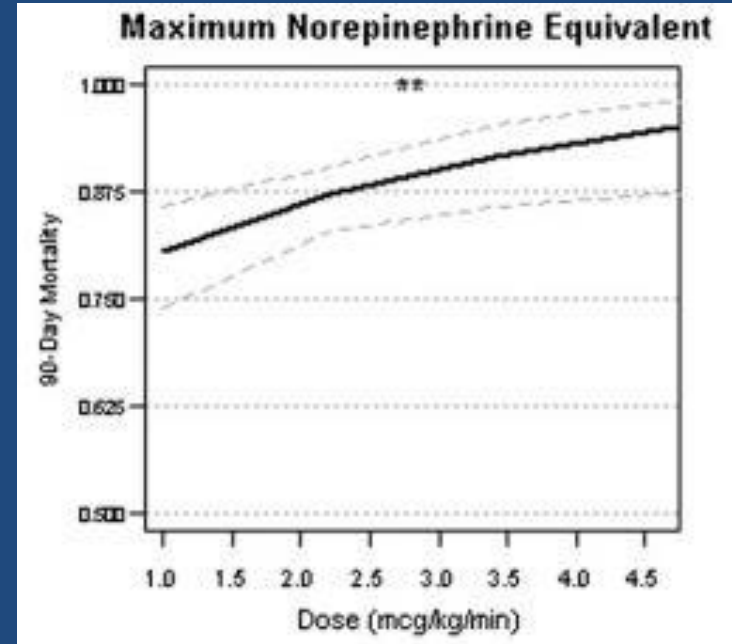
At the completion of this activity, pharmacy technicians will be able to:

1. Identify advantages of vasopressin over catecholamine vasopressor
2. List endpoints that may be improved by corticosteroids in septic shock
3. 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



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

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

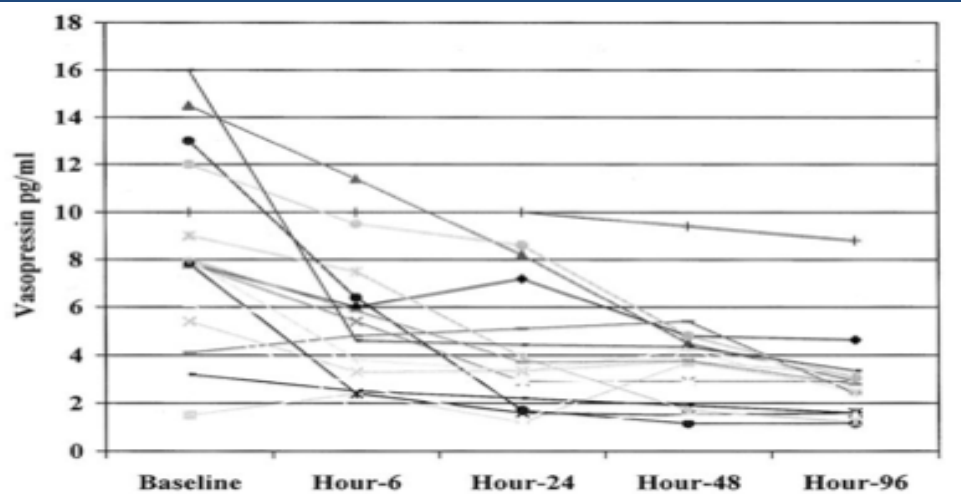
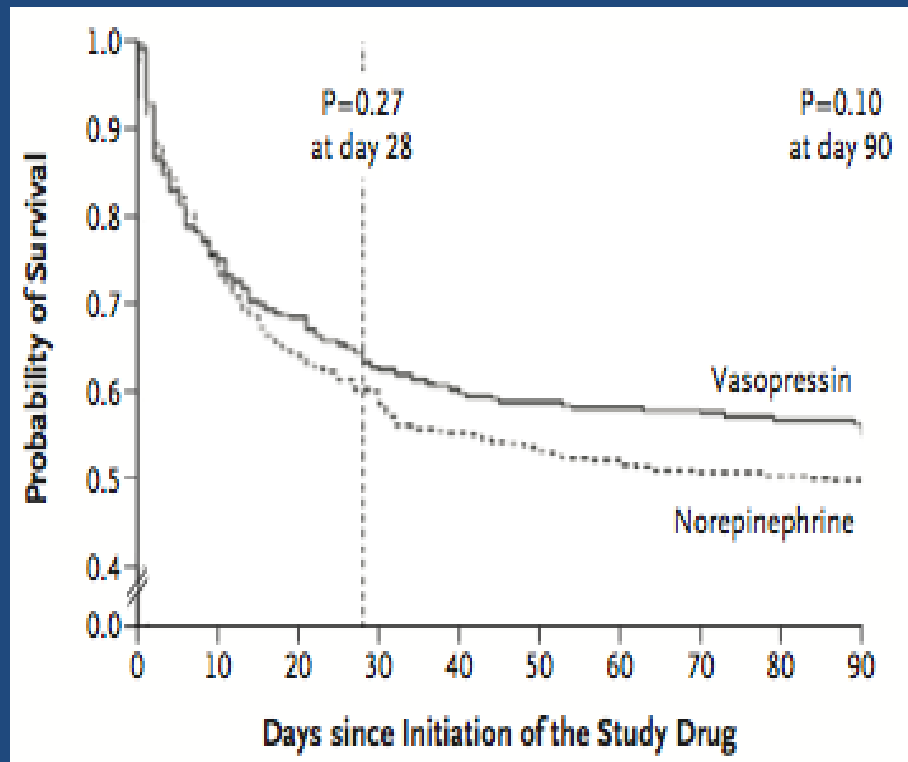


Figure 2. Kinetic of plasma vasopressin levels in the second set of 18 septic shock patients. Vasopressin levels increased at baseline in all but two patients, and significantly ($p < 10^{-3}$) decreased from baseline to hour-96 after shock onset.

Vasopressin and Septic Shock Trial (VASST)

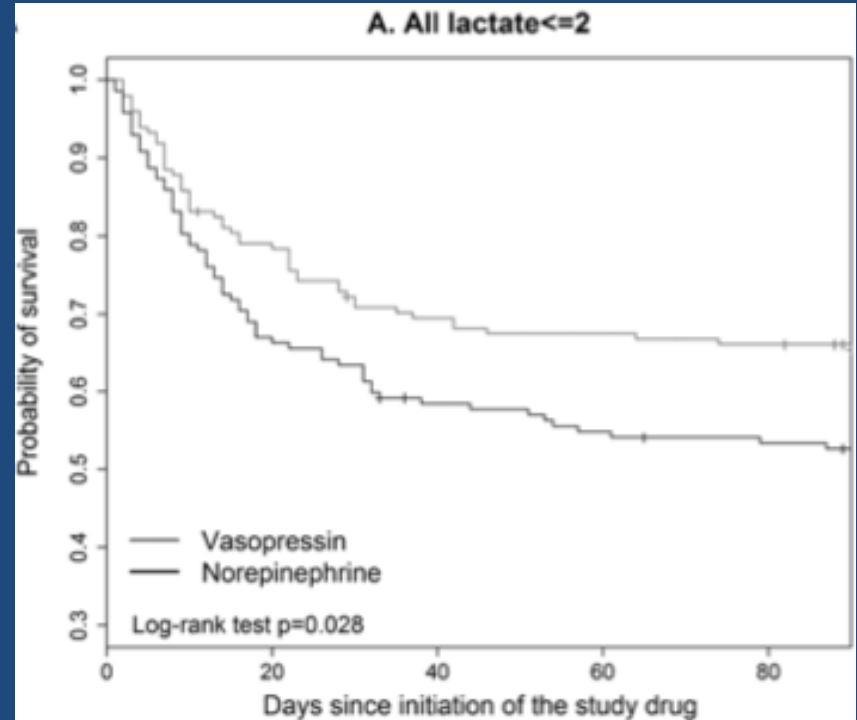
- Similar mortality with AVP (mean initiation 12 hours) added to NE versus NE alone (*as good as*)
- Subgroup of “less severe” ($NE \leq 14$): non-significant reduction in 28-day mortality in NE+AVP group (26.5% vs. 35.7%, RR 0.74, 95% CI 0.55-1.01)



Vasopressin (VASST re-analysis)

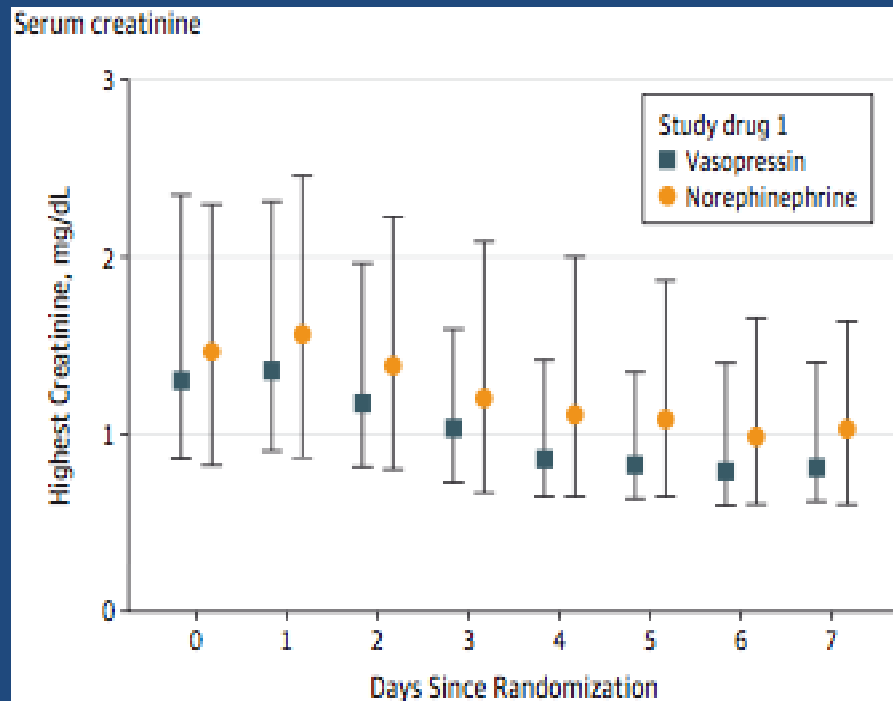
VASST re-analysis with Sepsis-3 def:

- 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?



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*)



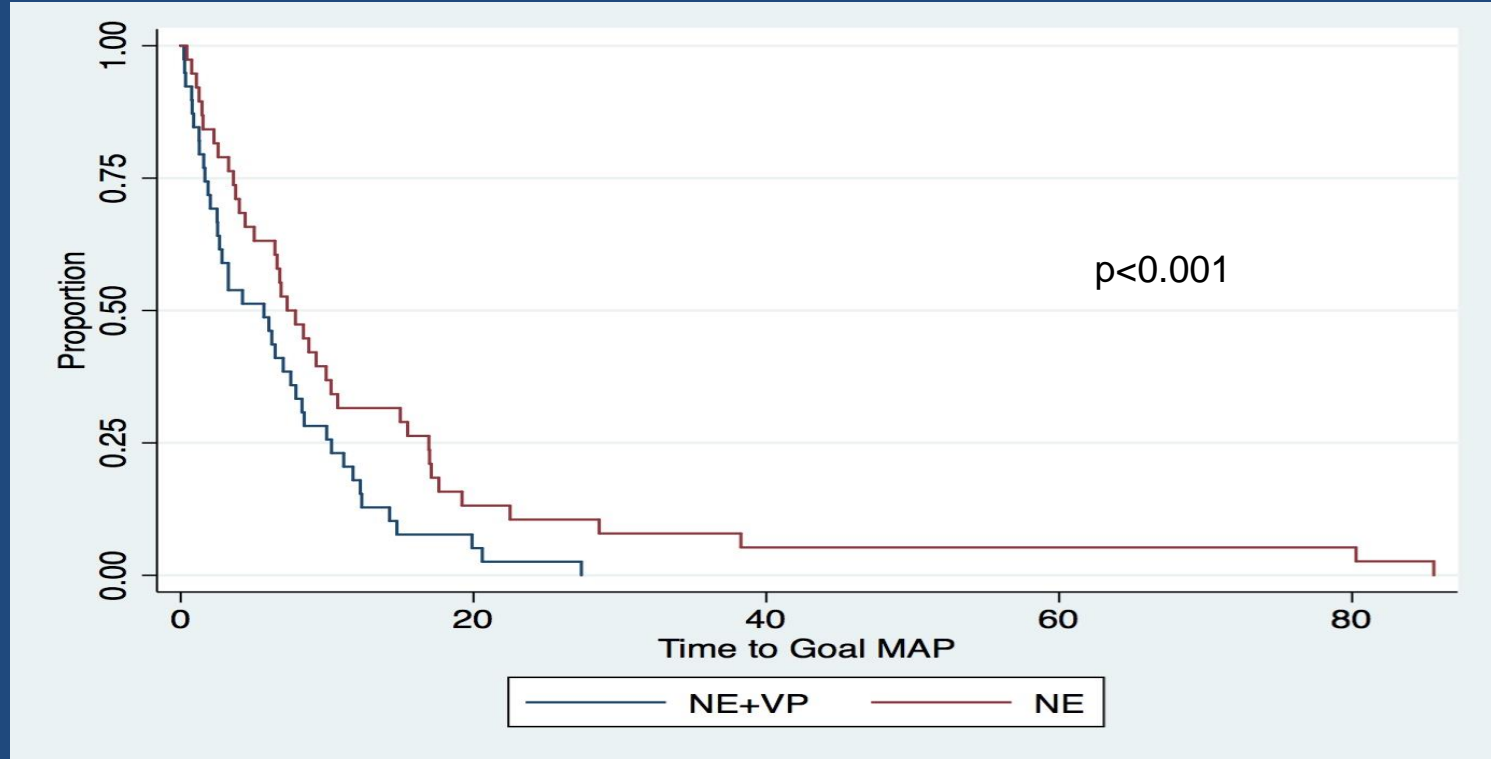
Early Vasopressin added to Norepinephrine

- Longer durations of hypotension associated with increased mortality in septic shock
- Randomized trial (NCT02454348)
- Formal protocol for vasopressor initiation for patients with septic shock in the institution during the study period (November 2015 to June 2016)
 - November 2015 to February 2016: NE monotherapy
 - March 2016 to June 2016: NE and AVP (within 4 hours)

Primary and Secondary Outcomes

Characteristic	NE+AVP (n=48)	NE alone (n=48)	p-value
Time to MAP target (h)	6.7 (6.4)	13.4 (18.6)	0.038
Mortality during hospitalization, n (%)	19 (46)	21 (51)	0.659
Mortality at 28 days, n (%)	19 (46)	18 (44)	0.824
ICU duration, d (mean \pm SD)	7.07 (6.70)	6.52 (7.07)	0.717
Hospital duration, d (mean \pm SD)	15.41 (11.79)	23.26 (22.96)	0.057
New-onset arrhythmia, n (%)	6 (15)	3 (7)	0.289
NE duration (h)	72.3 (80.2)	80.6 (84.6)	0.647
AVP duration (h)	50.9 (56.3)	59.7 (59.2)	0.581

Time to Goal Mean Arterial Pressure



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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

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

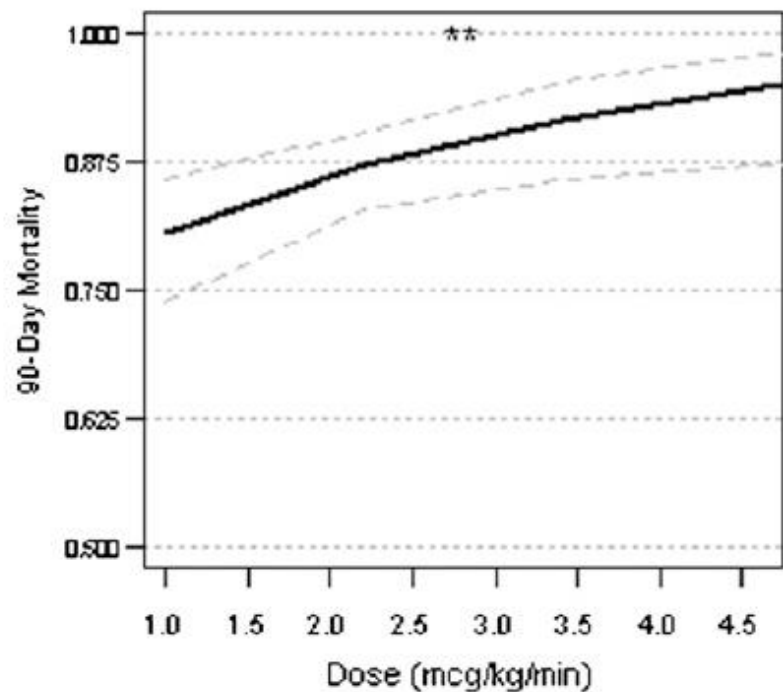
TAKEAWAY:

Norepinephrine \pm Vasopressin \geq Norepinephrine

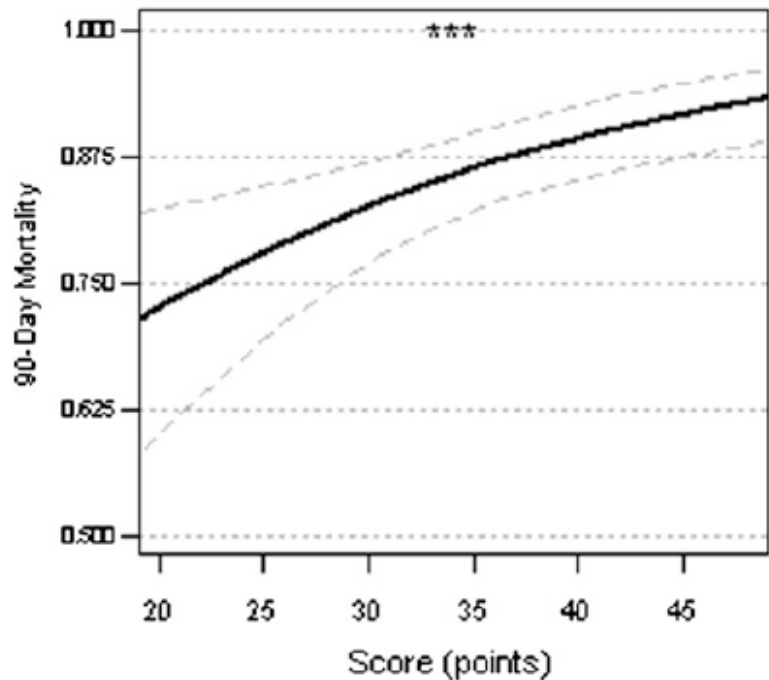
Vasopressin: CON
(unproven & costly)

Norepinephrine and Mortality Trap

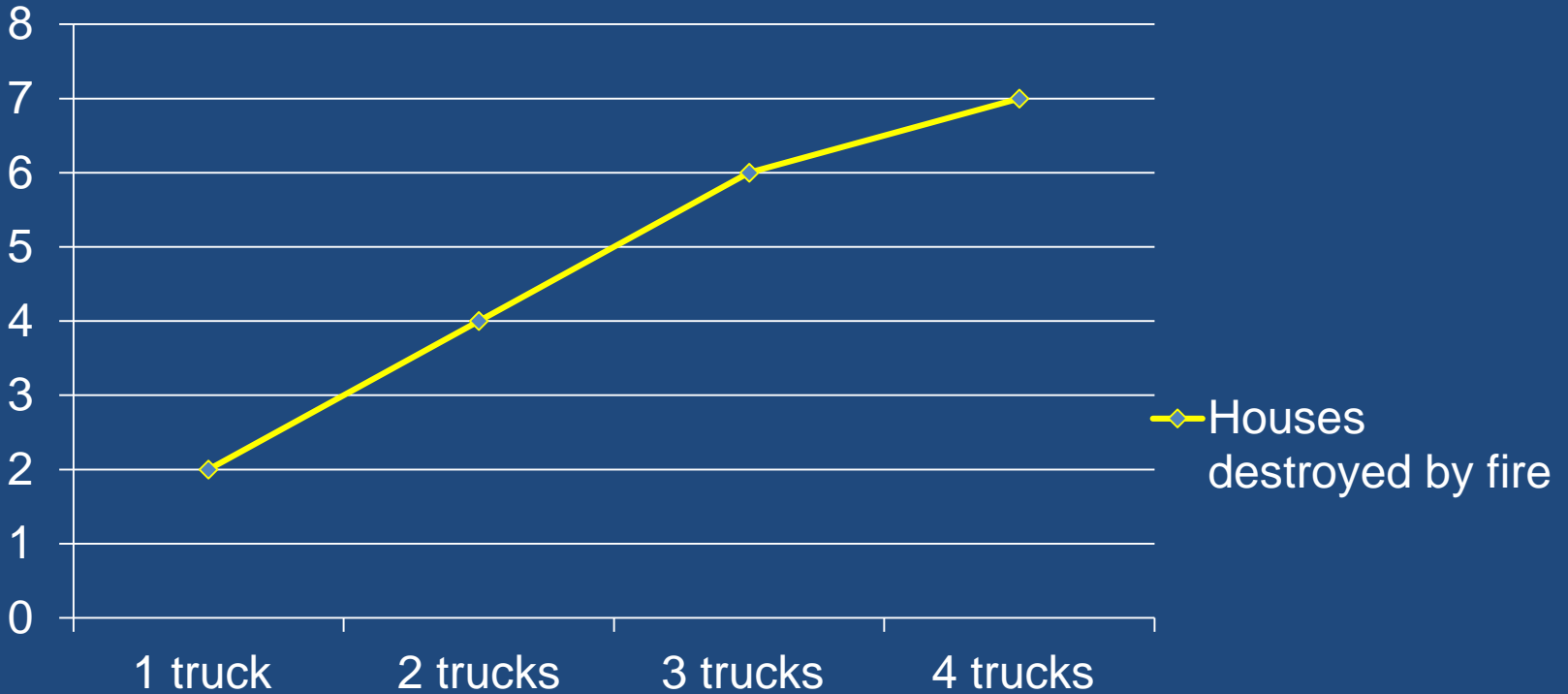
Maximum Norepinephrine Equivalent



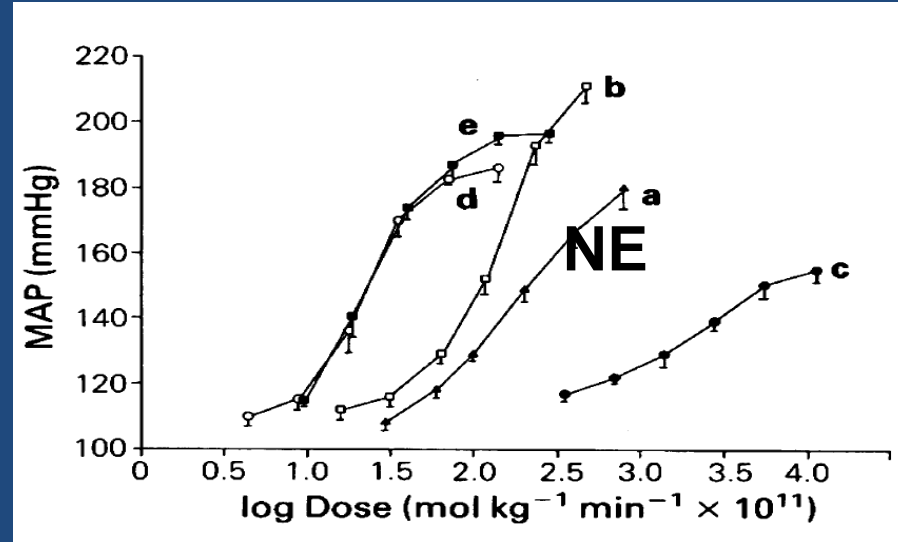
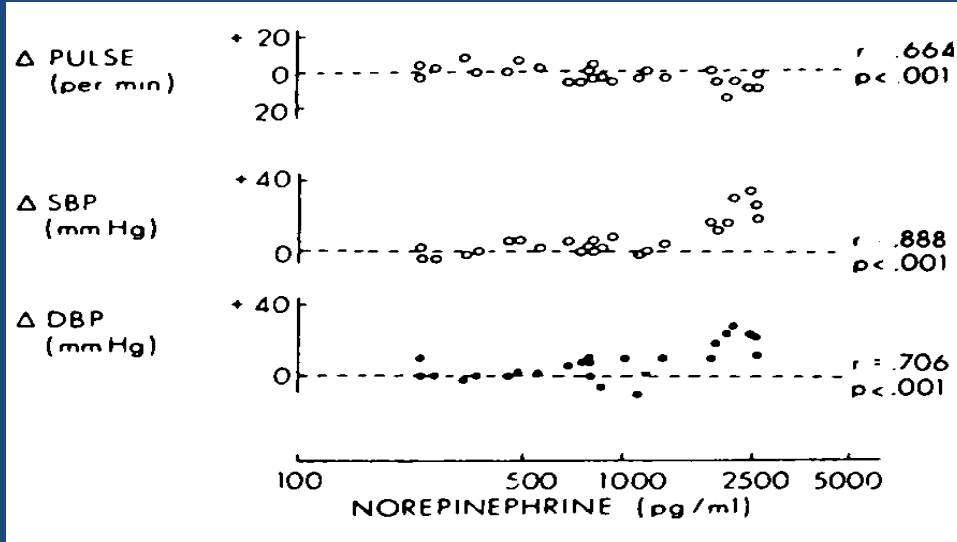
APACHE II



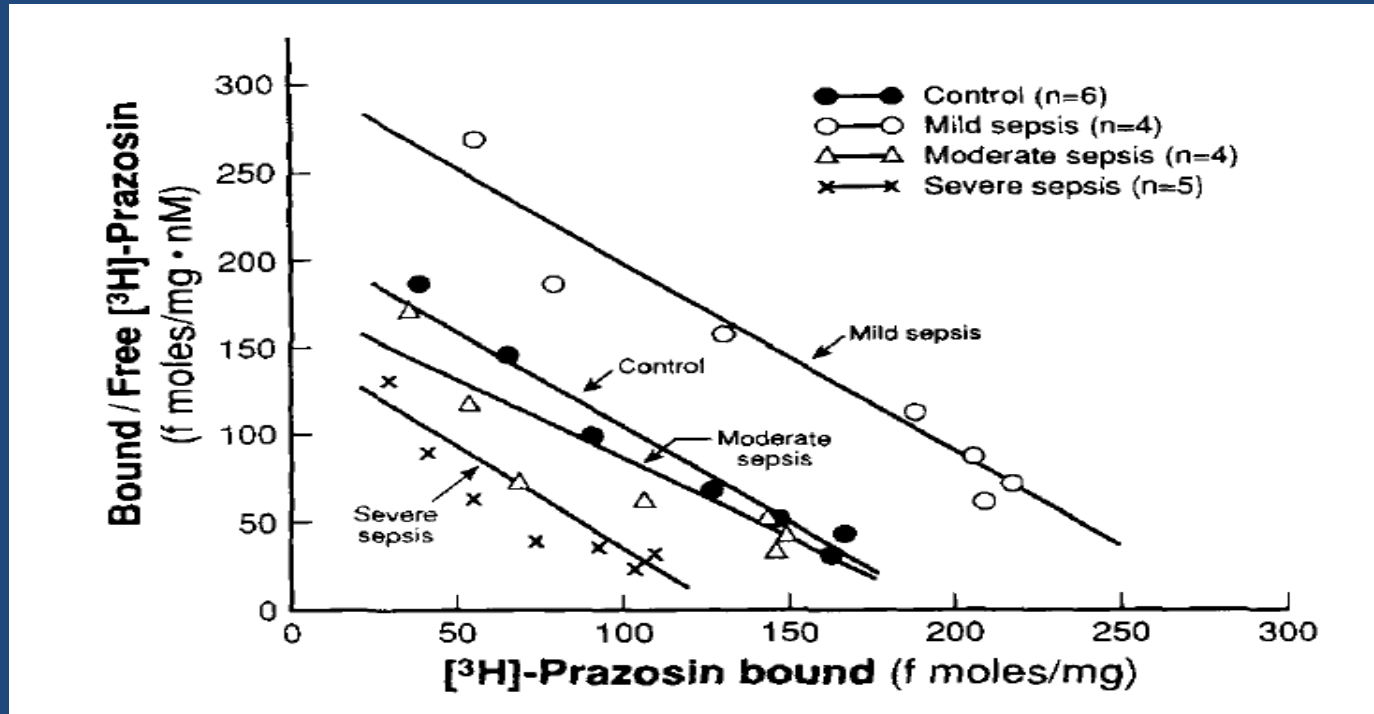
Houses Destroyed by Fire per Fire Truck Sent

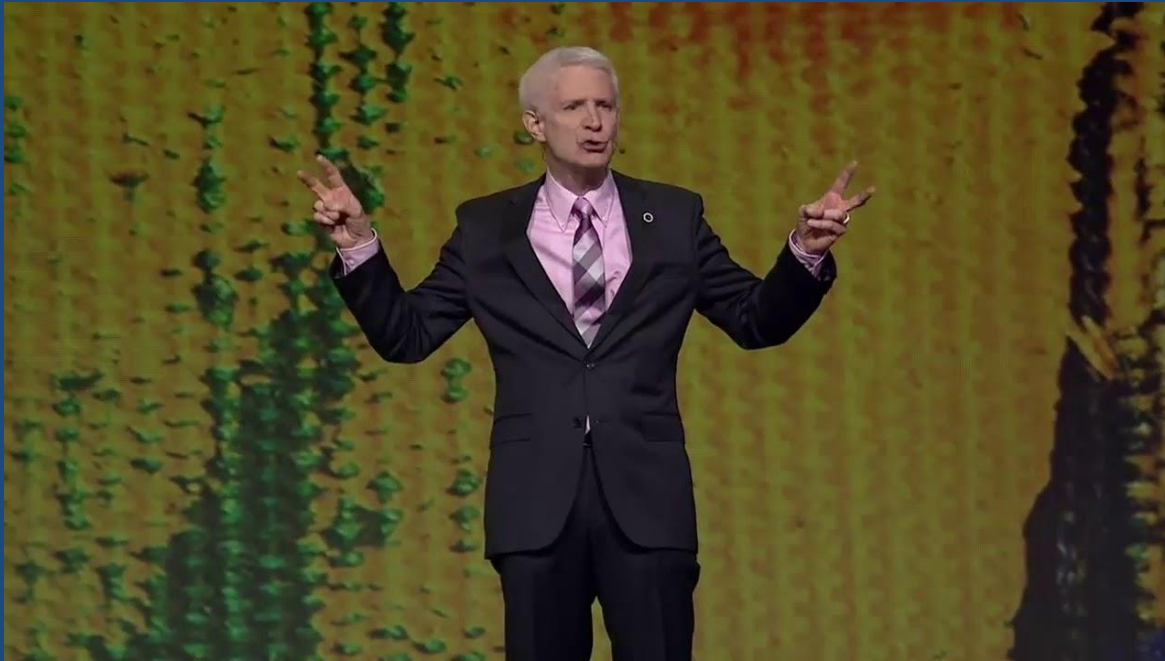


Norepinephrine Dose Response



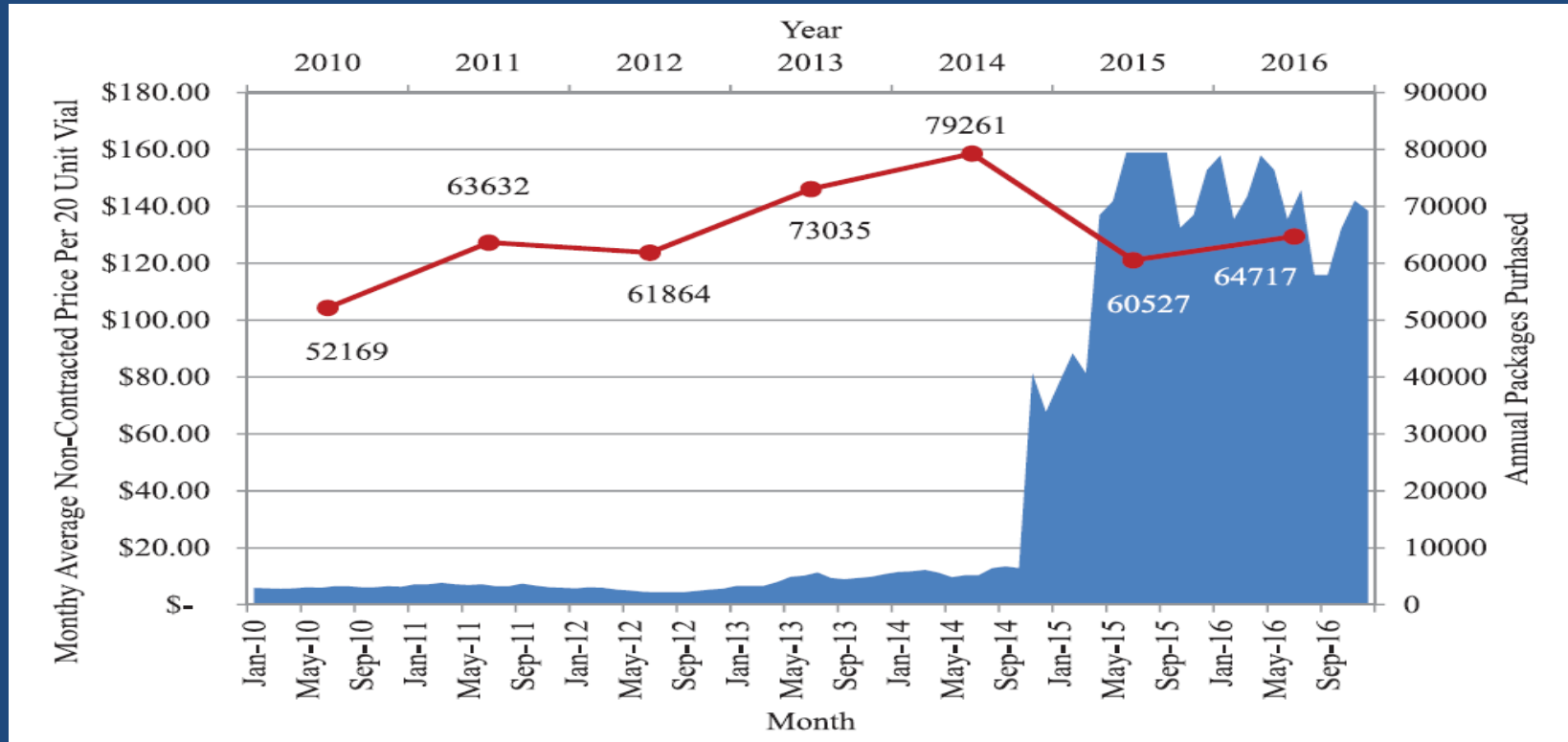
Alpha Receptor Regulation in Sepsis





“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



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

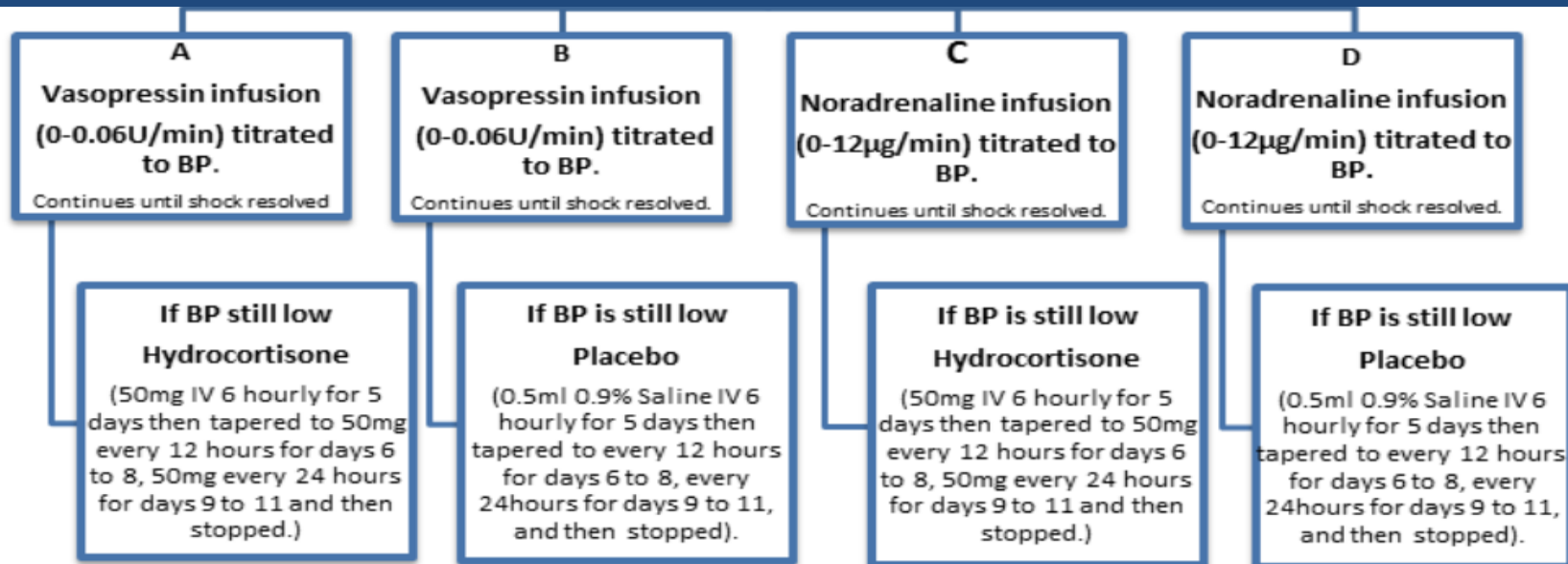
VASST

Variable	Norepinephrine Group (N = 382) <i>no./total no. (%)</i>	Vasopressin Group (N = 396) <i>no./total no. (%)</i>	P Value†	Absolute Risk Reduction (95% CI)‡ %	Relative Risk (95% CI)§	Adjusted Odds Ratio¶
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 <i>no./total no. (%)</i>	Vasopressin Group <i>no./total no. (%)</i>	P Value†	Absolute Risk Reduction (95% CI) %	Relative Risk (95% CI)
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)

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)

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)

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

James A. Russell, MD^{1,2}; Terry Lee, PhD³; Joel Singer, PhD³; 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	

Population and Outcome	Original Definition			Baseline Lactate ≤ 2			Sepsis 3.0 Definition (Baseline Lactate > 2)			p for Homogeneity*
	Vasopressin	Norepi- nephrine	p	Vasopressin	Norepi- nephrine	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

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

Table 3 Results of multivariable analyses

Outcome	OR (95% CI)	P value
Multivariable analysis and association with response to vasopressin ^a		
Non-medical ICU	1.70 (1.18–2.46)	0.005
Lactate at AVP initiation, mmol/L	0.93 (0.89–0.97)	< 0.001

Table 4 Predefined cohorts of interest

Cohort of interest	Responders <i>N</i> (%)	Non-responders <i>N</i> (%)	<i>P</i> value	OR (95% CI) hemodynamic response	OR (95% CI) ICU mortality
<i>Lactate concentration</i>					
> 1.4 mmol/L ^a	211 (78.4)	321 (88.7)	< 0.001	2.15 (1.39–3.32) [^]	0.39 (0.25–0.60) [^]
≤ 1.4 mmol/L	58 (21.6)	41 (11.3)			
<i>CA equivalent dose</i>					
≥ 15 mcg/min ^a	370 (86.9)	424 (82.8)	0.087	0.57 (0.36–0.92) [^]	0.62 (0.44–0.89) [^]
< 15 mcg/min	56 (13.1)	88 (17.2)			

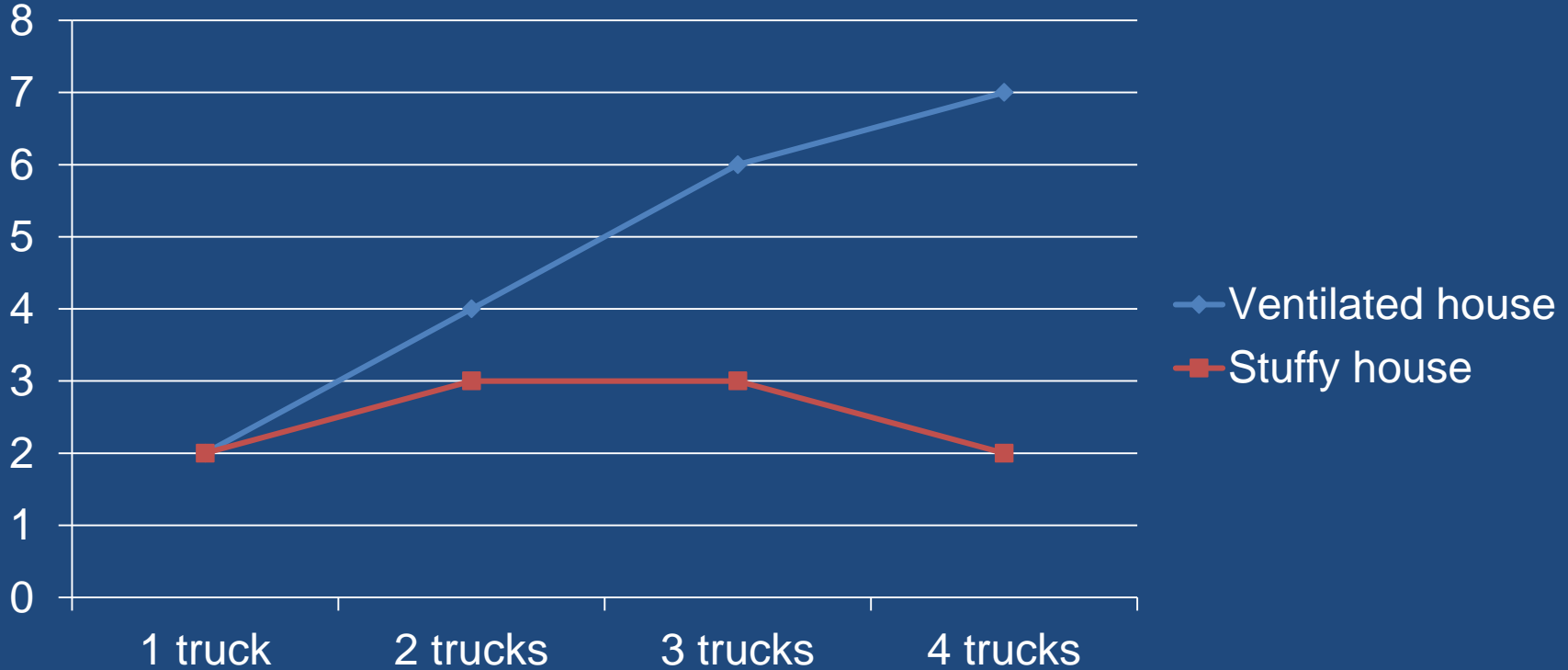
Terlipressin versus norepinephrine as infusion in patients with septic shock: a multicentre, randomised, double-blinded trial

Variable	Norepinephrine group (<i>N</i> = 266)	Terlipressin group (<i>N</i> = 260)	<i>p</i>
28-day mortality <i>N</i> (%)	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

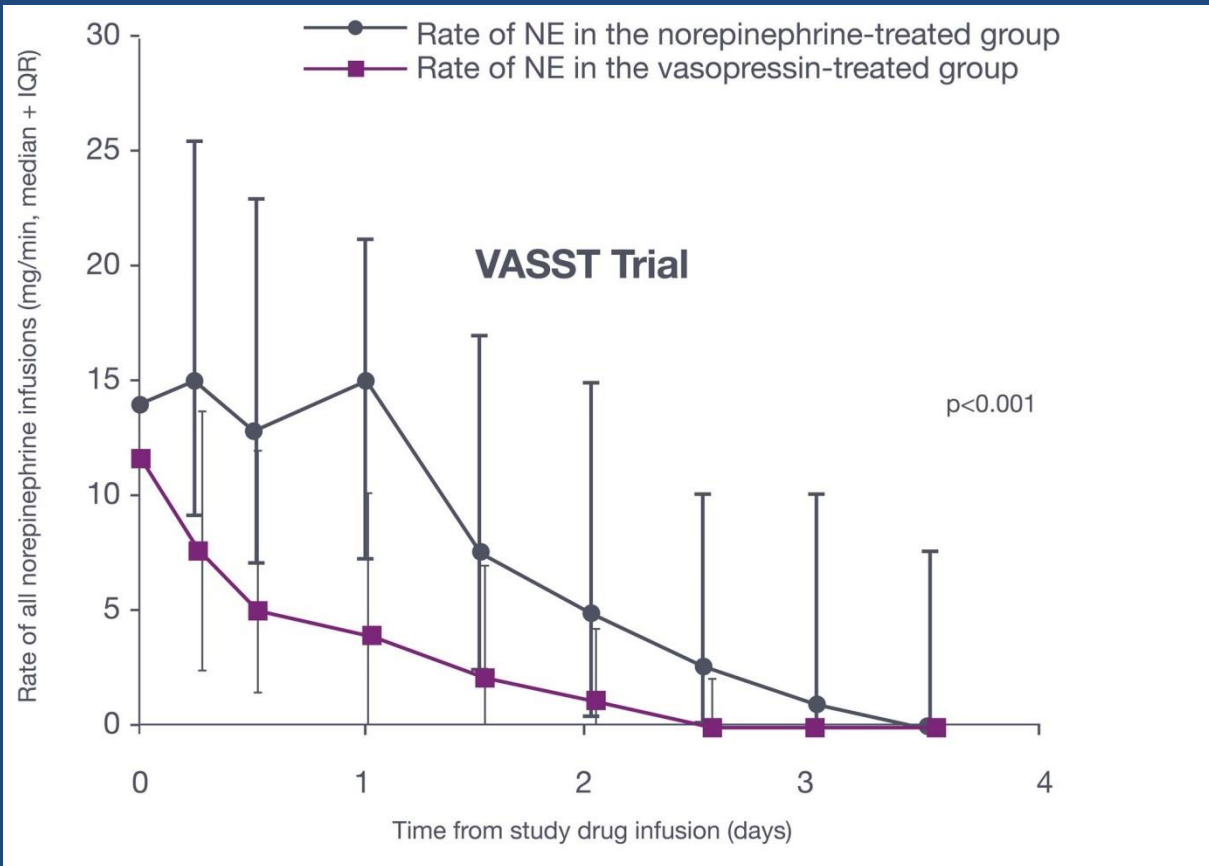
Variable <i>N</i> (%)	Norepinephrine group (<i>n</i> = 266)	Terlipressin group (<i>n</i> = 260)	<i>p</i>
Acute myocardial infarction or ischaemia	4 (1.39%)	2 (0.68%)	0.45
Life-threatening arrhythmia	6 (2.08%)	7 (2.38%)	1.00
Acute mesenteric ischaemia	1 (0.35%)	3 (1.02%)	0.62
Hyponatraemia	18 (6.25%)	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

REBUTTAL Vasopressin: PRO (safety & cost-effectiveness)

Lives Lost from Fire per Fire Truck Sent



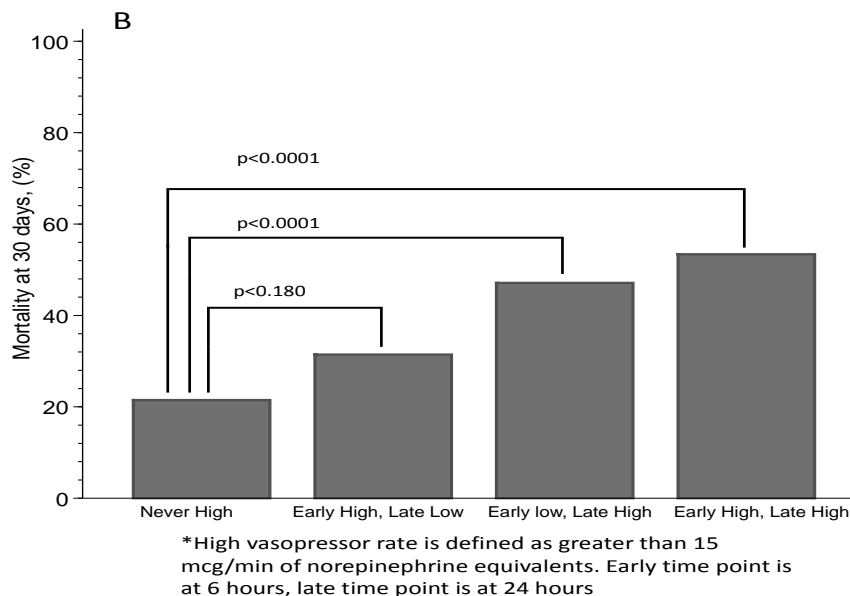
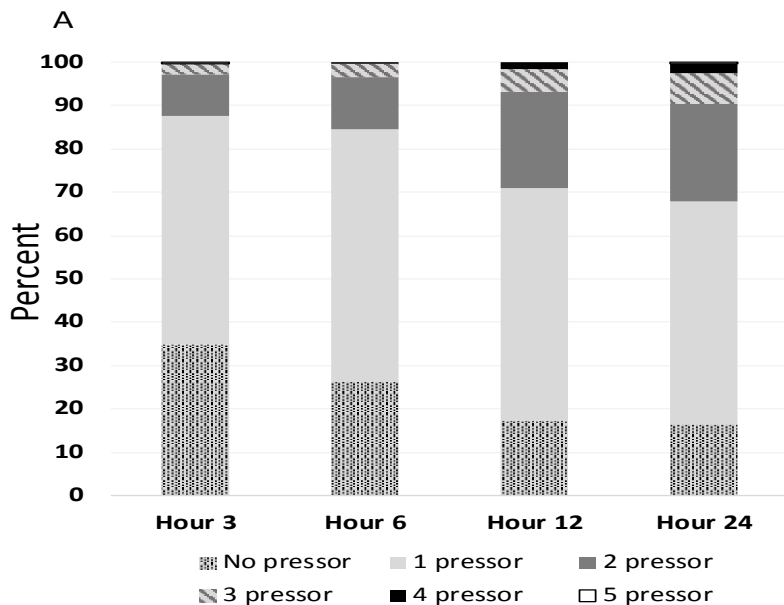
Graph adapted by Drayton Hammond



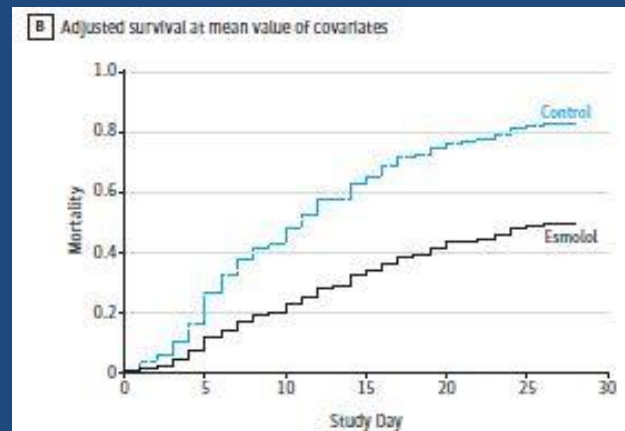
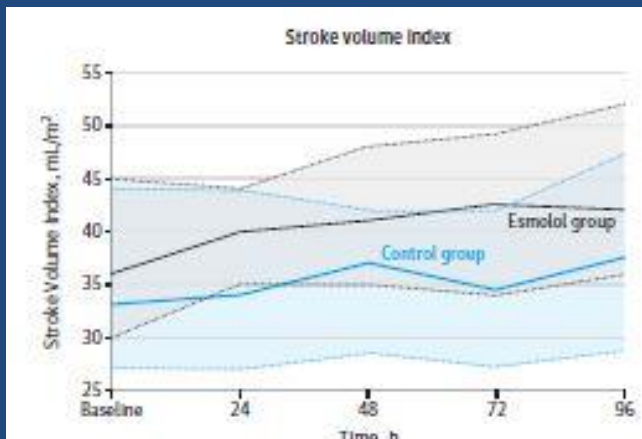
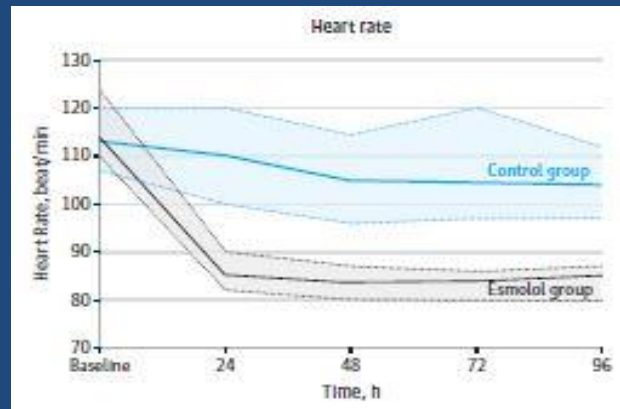
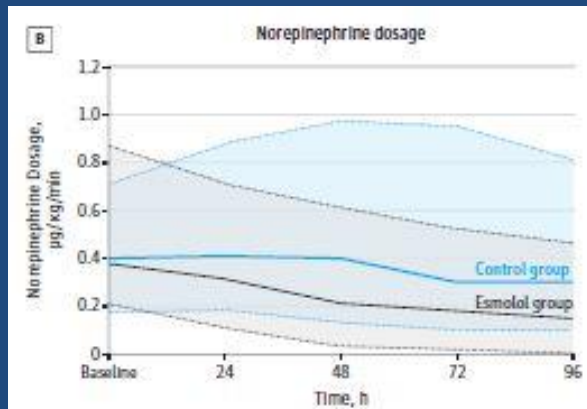
VOLUME-CHASER: Vasopressor Dosage

Prospective, observational cohort from 35 sites with 616 patients with septic shock

Figure 1: A- Vasopressor count over time; B- Mortality stratified by vasopressor dose categories at 6 and 24 hours*



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



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

A Systematic Review and Meta-analysis

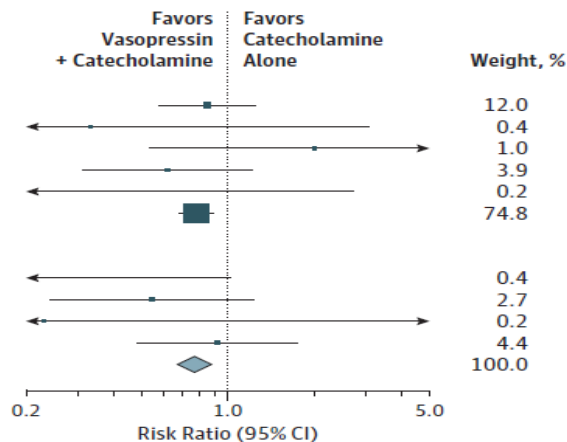
William F. McIntyre, MD; Kevin J. Um, BA; Waleed Alhazzani, MD, MSc; Alexandra P. Lengyel; Ludhmila Hajjar, MD; Anthony C. Gordon, MD; François Lamontagne, MD, MSc; Jeff S. Healey, MD, MSc; Richard P. Whitlock, MD, PhD; Emilie P. Belley-Côté, MD, MSc

A Atrial fibrillation

Source	Vasopressin + Catecholamine ^a		Catecholamine Alone		Risk Ratio (95% CI)
	No. With Events	Total No. of Patients	No. With Events	Total No. of Patients	
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: $\tau^2 = 0.00$; $\chi^2_9 = 9.10$ ($P = .43$); $I^2 = 1\%$

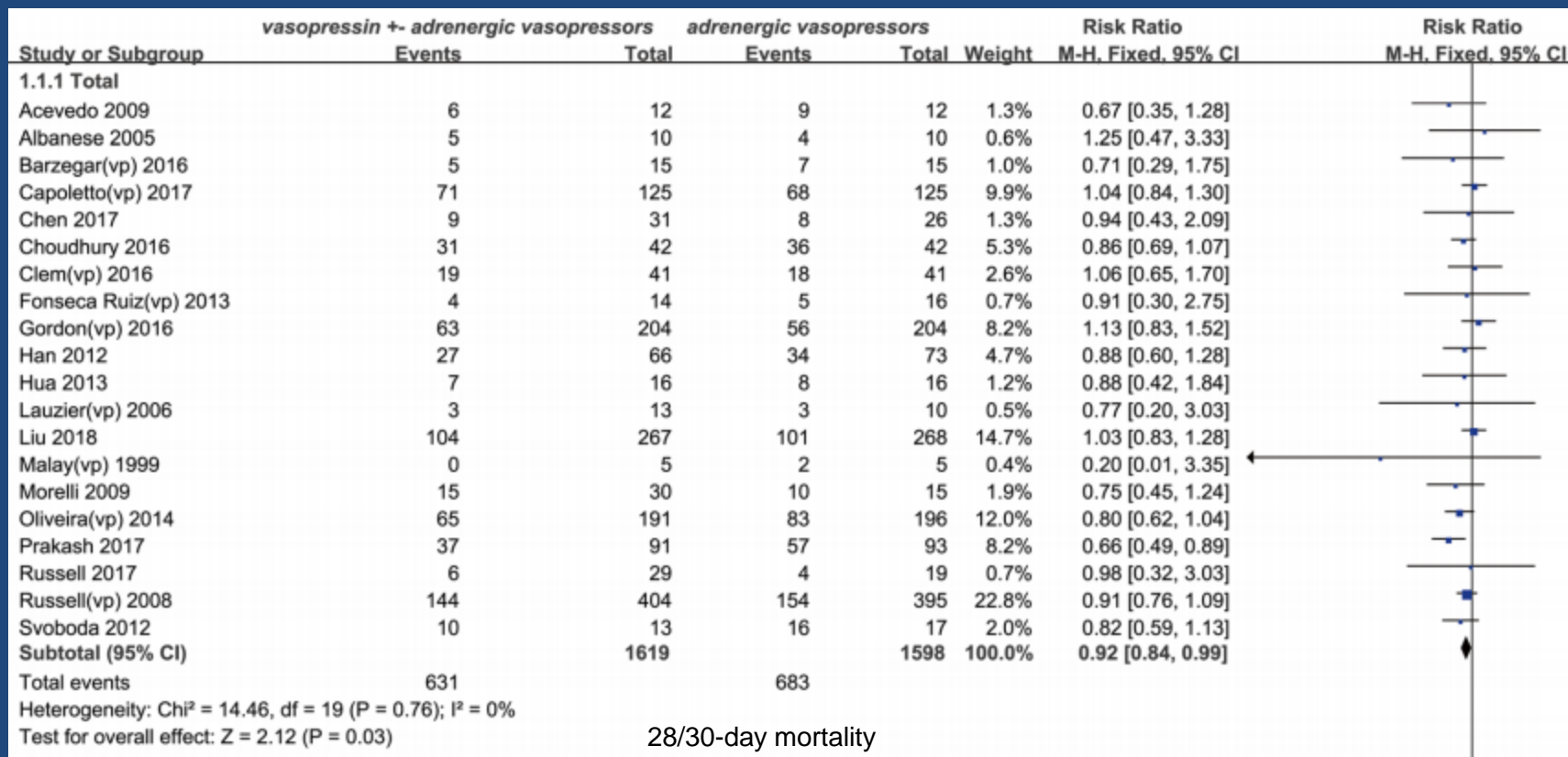
Overall effect: $z = 3.79$ ($P < .001$)



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

Breaking News

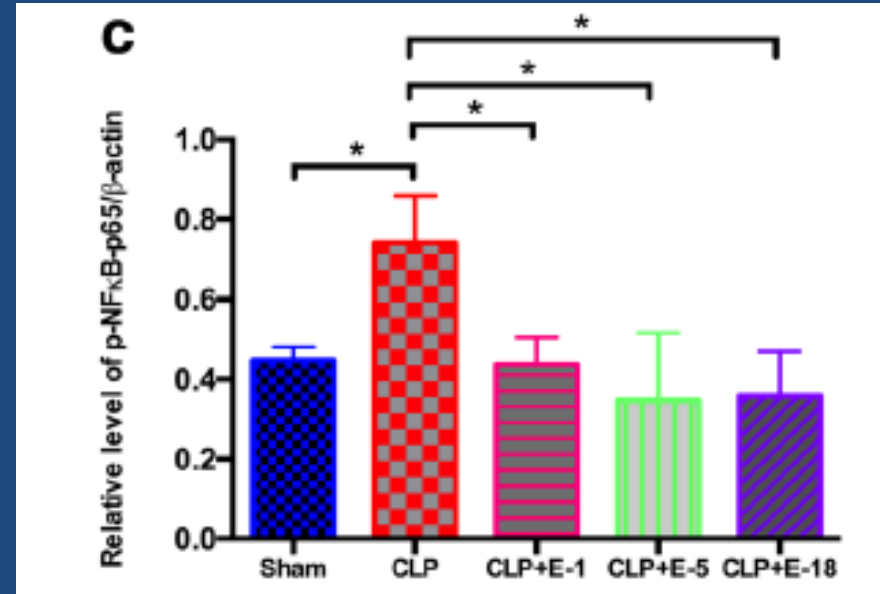
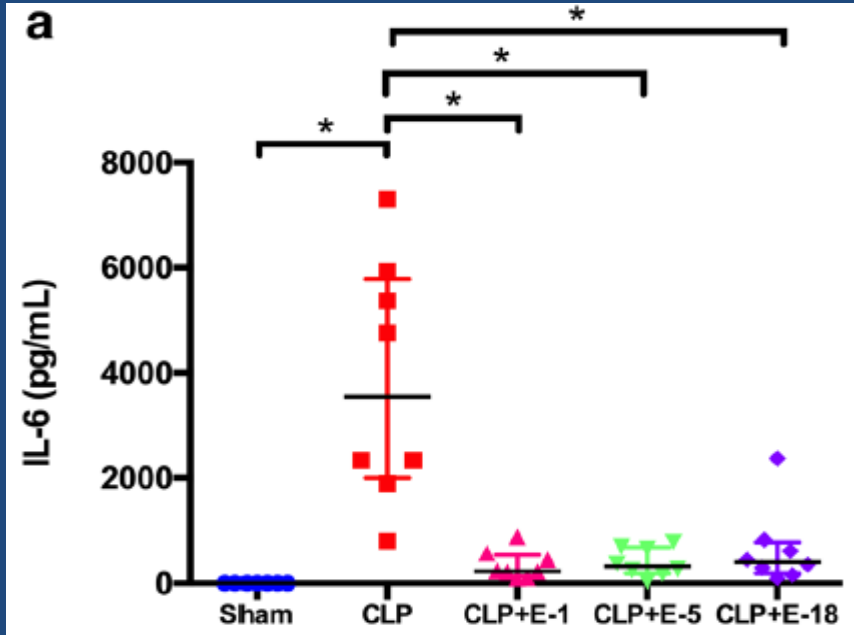


TAKEAWAY:

Vasopressin improves safety and its cost-effectiveness should be evaluated

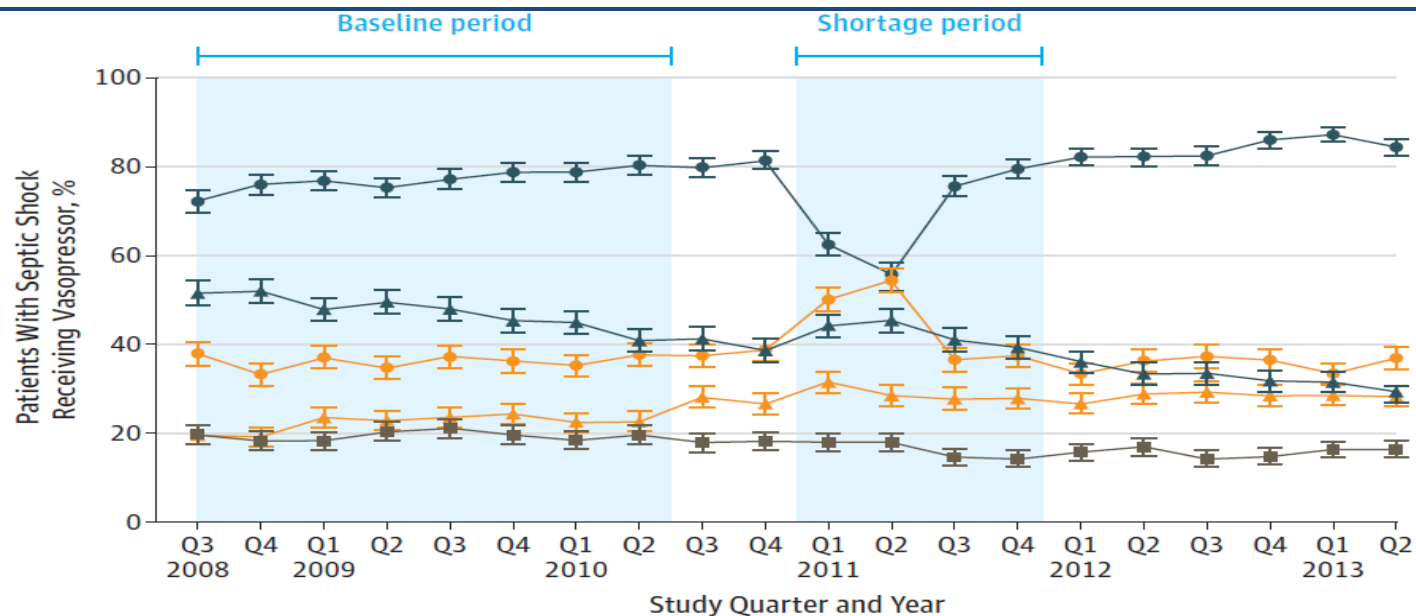
REBUTTAL Vasopressin: CON
(data inconsistent &
contradictory)

Let's Talk about β



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



Characteristic	Patients With Septic Shock in 26 Shortage Hospitals ^a			Patients With Septic Shock in 102 Consistent-Use Hospitals ^b (n = 120 759)
	Shortage Quarters (n = 1961)	Nonshortage Quarters (n = 25 874)	P Value	
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)

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

A Systematic Review and Meta-analysis

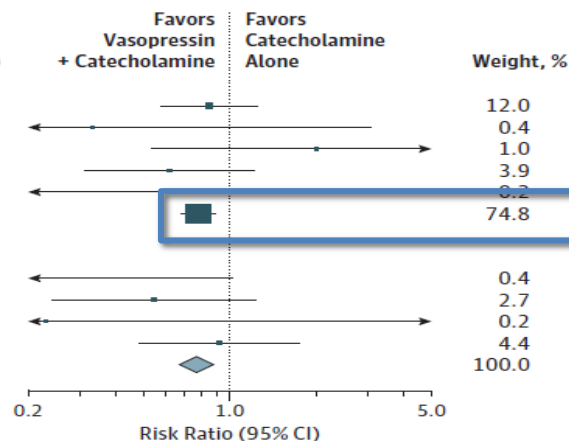
William F. McIntyre, MD; Kevin J. Um, BA; Waleed Alhazzani, MD, MSc; Alexandra P. Lengyel; Ludhmila Hajjar, MD; Anthony C. Gordon, MD; François Lamontagne, MD, MSc; Jeff S. Healey, MD, MSc; Richard P. Whitlock, MD, PhD; Emilie P. Belley-Côté, MD, MSc

A Atrial fibrillation

Source	Vasopressin + Catecholamine ^a		Catecholamine Alone		Risk Ratio (95% CI)
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Abdullah et al, ²⁵ 2012	0	17	0	17	Not estimable
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Total events (95% CI)	159	739	215	723	0.77 (0.67-0.88)

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 9.10$ ($P = .43$); $I^2 = 1\%$

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



Meta Analysis

Group	No. With Events/Total No. of Patients		Risk Difference % (95% CI) ^a	Relative Risk ^a			Quality of Evidence (Reason for Judgment)
	Vasopressin + Catecholamines	Catecholamines Alone		Risk Ratio (95% CI)	P Value	I ² %	
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	

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

Wagner L. Nedel, MD, MSc¹⁻³; Tatiana H. Rech, MD, PhD^{1,4}; Rodrigo A. Ribeiro, MD, PhD^{5,6}; José Augusto S. Pellegrini, MD, PhD¹; 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

DOVSS Trial

Table 2 Outcomes by treatment group

	AVP group (n = 40)	NE group (n = 38)	P value
Development of hypotension within one hour after tapering of vasopressor			
Hypotension on tapering the first vasopressor	9 (22.5)	26 (68.4)	< 0.001
Hypotension on tapering sequential second vasopressor (n = 43)	20 (64.5)	3 (25.0)	0.020
Hypotension on tapering the first or second vasopressor	29 (72.5)	29 (76.3)	0.700
Time to hypotension after tapering vasopressor, hours (n = 58)	4.3 (2.5 – 5.1)	2.0 (1.2 – 2.5)	< 0.001
MAP at the time of hypotension developed on tapering of vasopressor, mmHg (n = 58)	61 (58 – 62)	62 (59 – 63)	0.111
CVP at the time of hypotension developed on tapering of vasopressor, mmHg (n = 58)	10 (7–14)	9 (6–13)	0.810
Total vasopressor duration, hours	58.4 (33.9 – 100.0)	43.8 (28.9 – 81.9)	0.169
Clinical outcomes			
ICU mortality	15 (37.5)	11 (28.9)	0.423
ICU length of stay, days	9 (6 – 13)	7 (2 – 12)	0.107
28-day mortality	17 (42.5)	12 (32.4)	0.362
Hospital mortality	23 (57.5)	13 (34.2)	0.039
Hospital length of stay, days	25 (15 – 38)	21 (13 – 37)	0.542

AVP, vasopressin; NE, norepinephrine; MAP, mean arterial pressure; CVP, central venous pressure; ICU, intensive care unit

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) ^a	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) ^a	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

Closing Thoughts

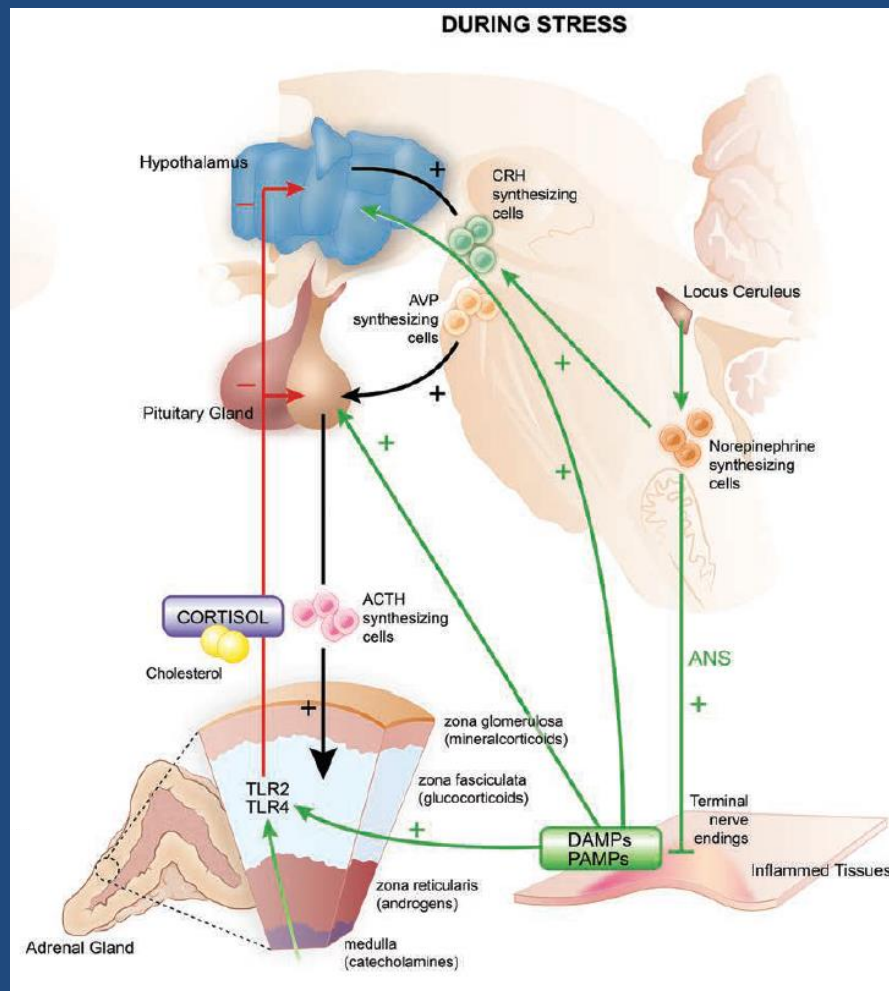
- Vasopressin never conclusively validated as a necessary therapy
- Potential benefits are inconclusive and contradictory
- Significantly increased price makes cost-effectiveness an important question
- Best use would be early in septic shock management as a trial and discontinue if no benefits seen

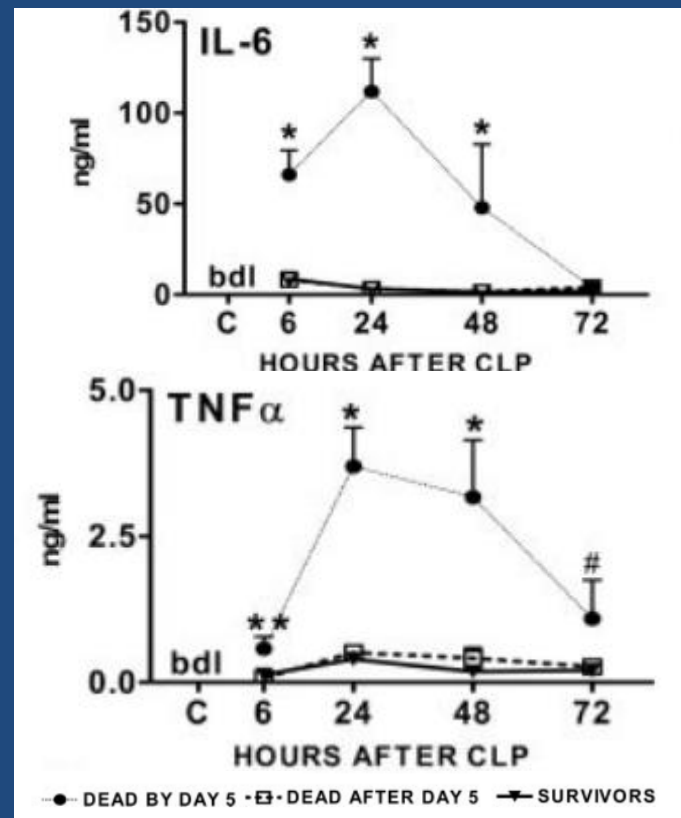
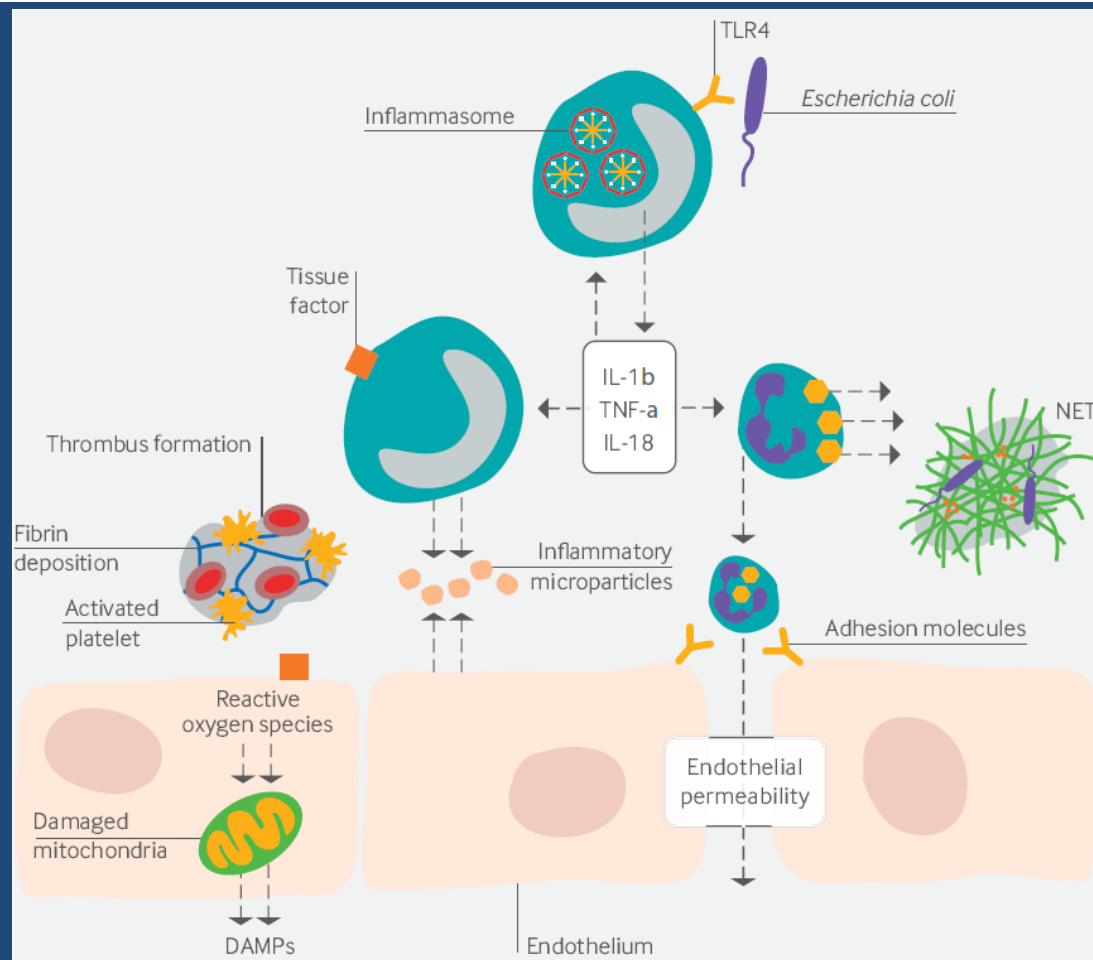
Corticosteroids: PRO
(low risk, high reward)

Who wants con steroids?

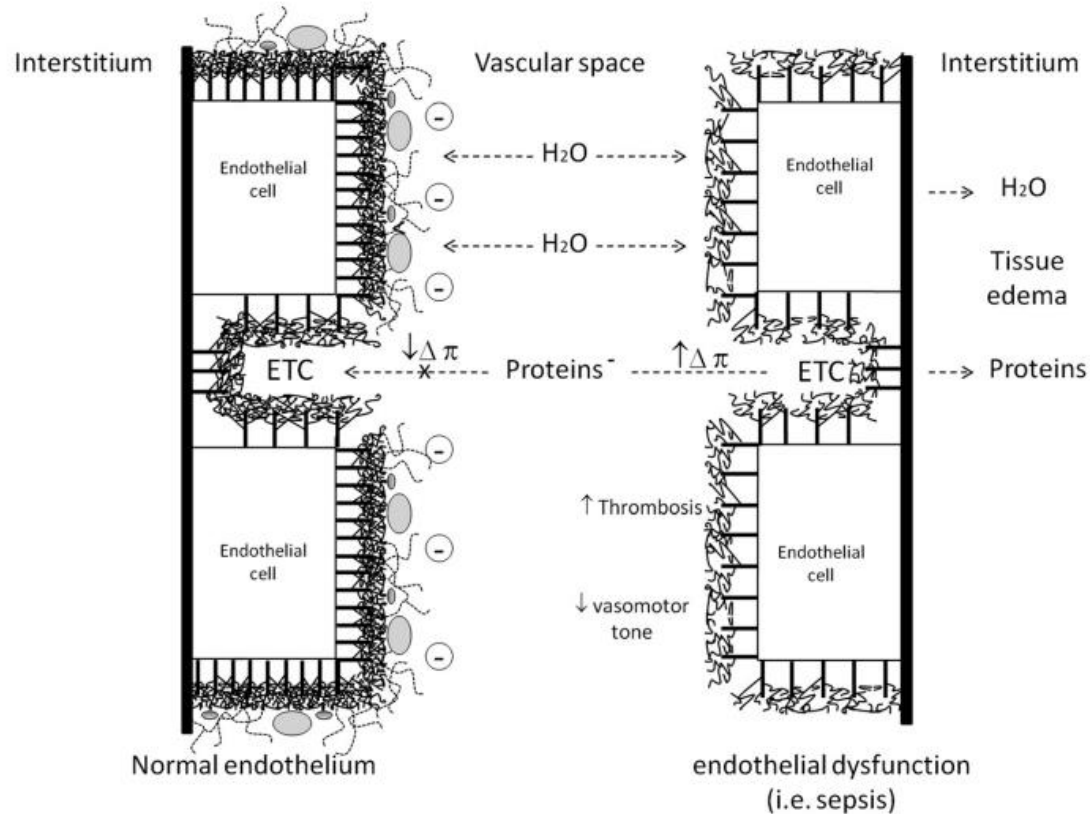


HPA Axis in Critical Illness

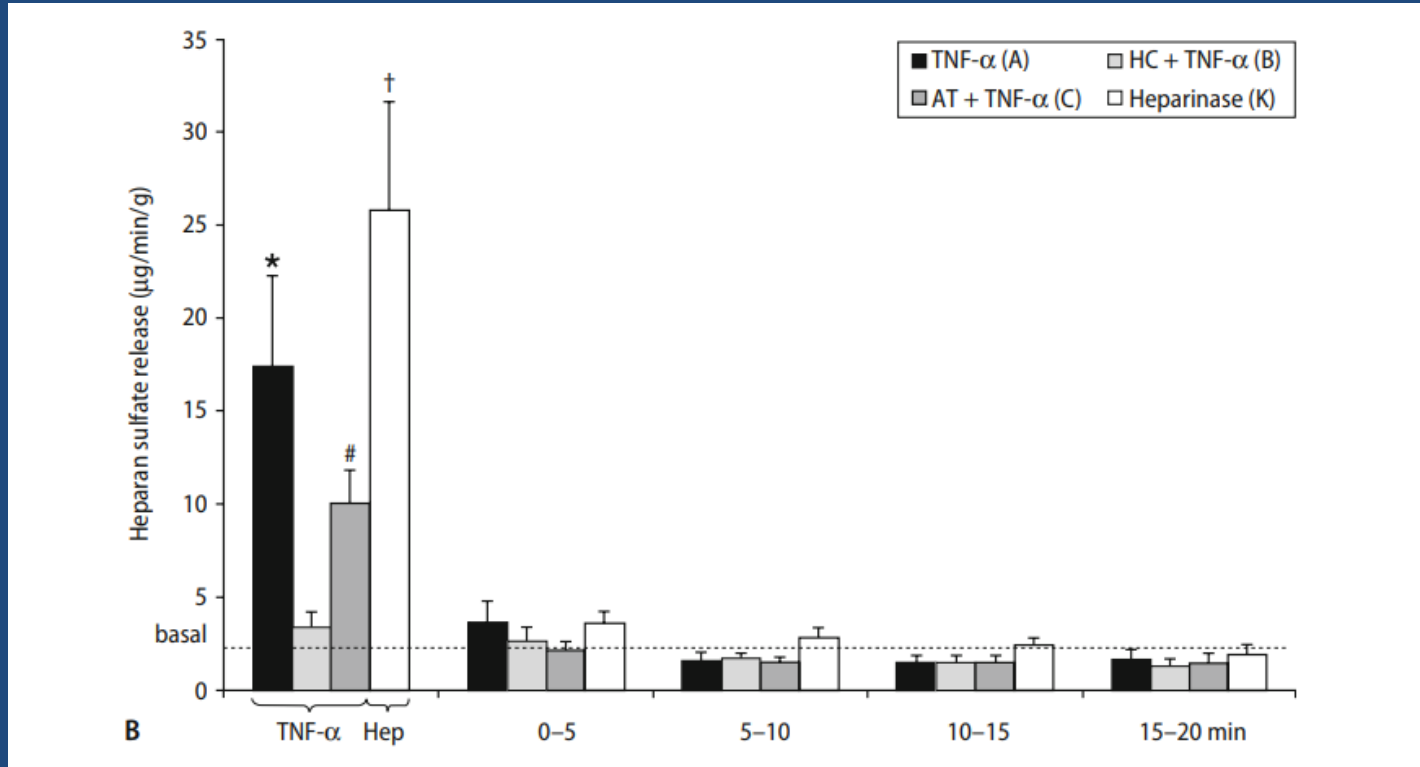




Glycocalyx

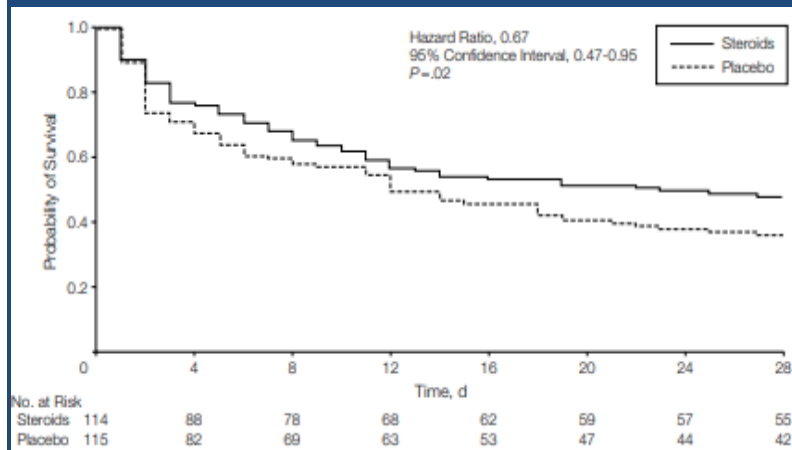


Glucocorticoids and the Glycocalyx

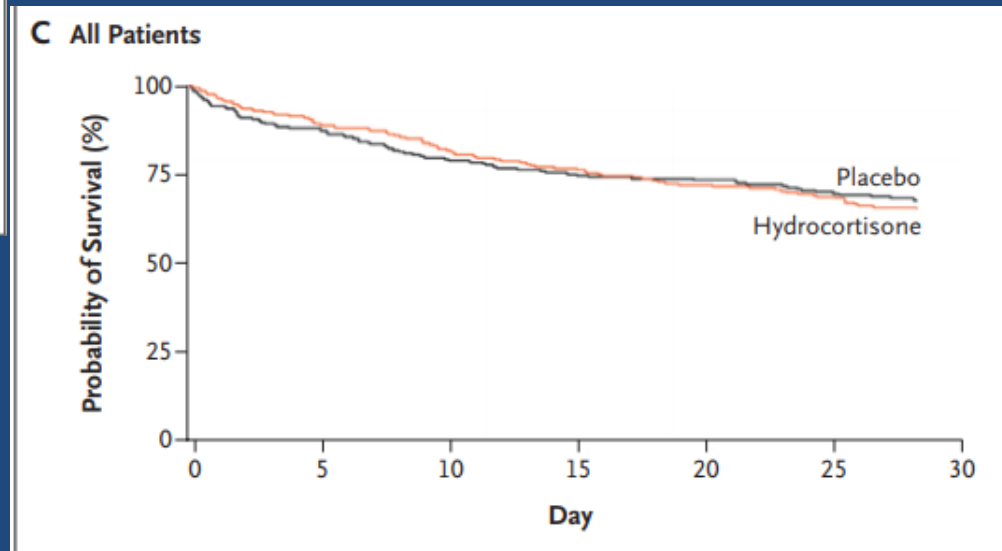
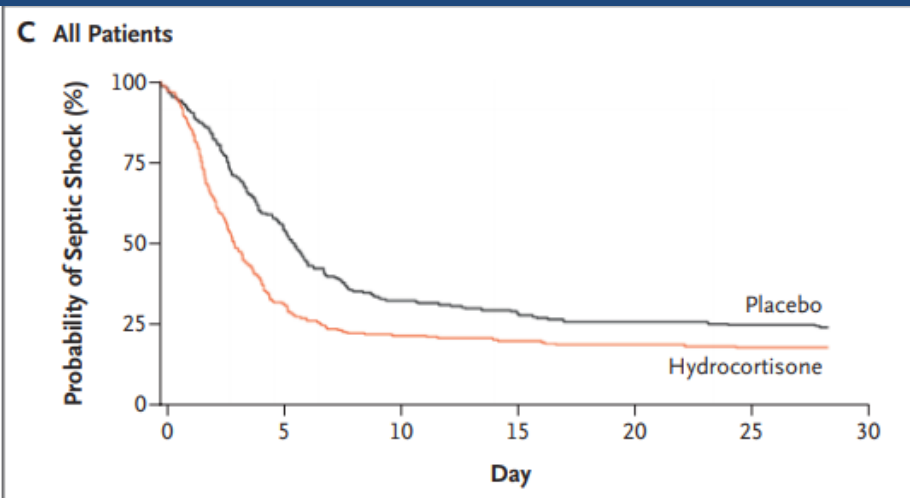


Annane 2002

Variable	No. (%)		Adjusted OR (95% CI)	P Value
	Placebo	Steroids		
Nonresponders				
No. of patients	115	114		
28-day mortality	73 (63)	60 (53)	0.54 (0.31-0.97)	.04
ICU mortality	81 (70)	66 (58)	0.50 (0.28-0.89)	.02
Hospital mortality	83 (72)	70 (61)	0.53 (0.29-0.96)	.04
1-Year mortality	88 (77)	77 (68)	0.57 (0.31-1.04)	.07
Responders				
No. of patients	34	36		
28-Day mortality	18 (53)	22 (61)	0.97 (0.32-2.99)	.96
ICU mortality	20 (59)	24 (67)	0.99 (0.31-3.16)	.99
Hospital mortality	20 (59)	25 (69)	1.20 (0.38-3.76)	.75
1-Year mortality	24 (71)	25 (69)	0.70 (0.20-2.40)	.57
All Patients				
No. of patients	149	150		
28-Day mortality	91 (61)	82 (55)	0.65 (0.39-1.07)	.09
ICU mortality	101 (68)	90 (60)	0.61 (0.37-1.02)	.06
Hospital mortality	103 (69)	95 (63)	0.67 (0.40-1.12)	.12
1-Year mortality	112 (75)	102 (68)	0.62 (0.36-1.05)	.08



CORTICUS



...and this is where we put the non-significant results.



som^{ee}cards
user card

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

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VOL. 378 NO. 9

Adjunctive Glucocorticoid Therapy in Patients
with Septic Shock

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone
for Adults with Septic Shock



ADRENAL Results

Outcome	Hydrocortisone (N=1853)	Placebo (N=1860)	Odds Ratio, Hazard Ratio, or Absolute Difference (95% CI)	P Value
Primary outcome				
90-day mortality — no./total no. (%)	511/1832 (27.9)	526/1826 (28.8)	0.95 (0.82 to 1.10) [†]	0.50
Secondary outcomes				
28-day mortality — no./total no. (%)	410/1841 (22.3)	448/1840 (24.3)	0.89 (0.76 to 1.03) [†]	0.13
Median time to resolution of shock (IQR) — days	3 (2 to 5)	4 (2 to 9)	1.32 (1.23 to 1.41) [‡]	<0.001
Recurrence of shock — no. (%)	365 (19.7)	343 (18.4)	1.07 (0.94 to 1.22) [†]	0.32
Median time to discharge from the ICU (IQR) — days	10 (5 to 30)	12 (6 to 42)	1.14 (1.06 to 1.23) [‡]	<0.001
No. of days alive and out of the ICU	58.2±34.8	56.0±35.4	2.26 (0.04 to 4.49) [§]	0.047 [¶]
Median time to discharge from the hospital (IQR) — days	39 (19 to NA)	43 (19 to NA)	1.06 (0.98 to 1.15) [‡]	0.13
No. of days alive and out of the hospital	40.0±32.0	38.6±32.4	1.45 (−0.59 to 3.49) [§]	0.16
Median time to cessation of initial mechanical ventilation (IQR) — days	6 (3 to 18)	7 (3 to 24)	1.13 (1.05 to 1.22) [‡]	<0.001
No. of days alive and free from mechanical ventilation	61.2±35.6	59.1±36.1	2.18 (−0.11 to 4.46) [§]	0.06
Recurrence of mechanical ventilation — no./total no. (%)	180/1842 (9.8)	154/1850 (8.3)	1.18 (0.96 to 1.45) [†]	0.11
No. of days alive and free from renal-replacement therapy	42.6±39.1	40.4±38.5	2.37 (−2.00 to 6.75) [§]	0.29
Use of renal-replacement therapy — no. (%)	567 (30.6)	609 (32.7)	0.94 (0.86 to 1.03) [†]	0.18
New-onset bacteremia or fungemia — no. (%)	262 (14.1)	262 (14.1)	1.00 (0.86 to 1.16) [†]	0.96
Blood transfusion — no./total no. (%)	683/1848 (37.0)	773/1855 (41.7)	0.82 (0.72 to 0.94) [†]	0.004

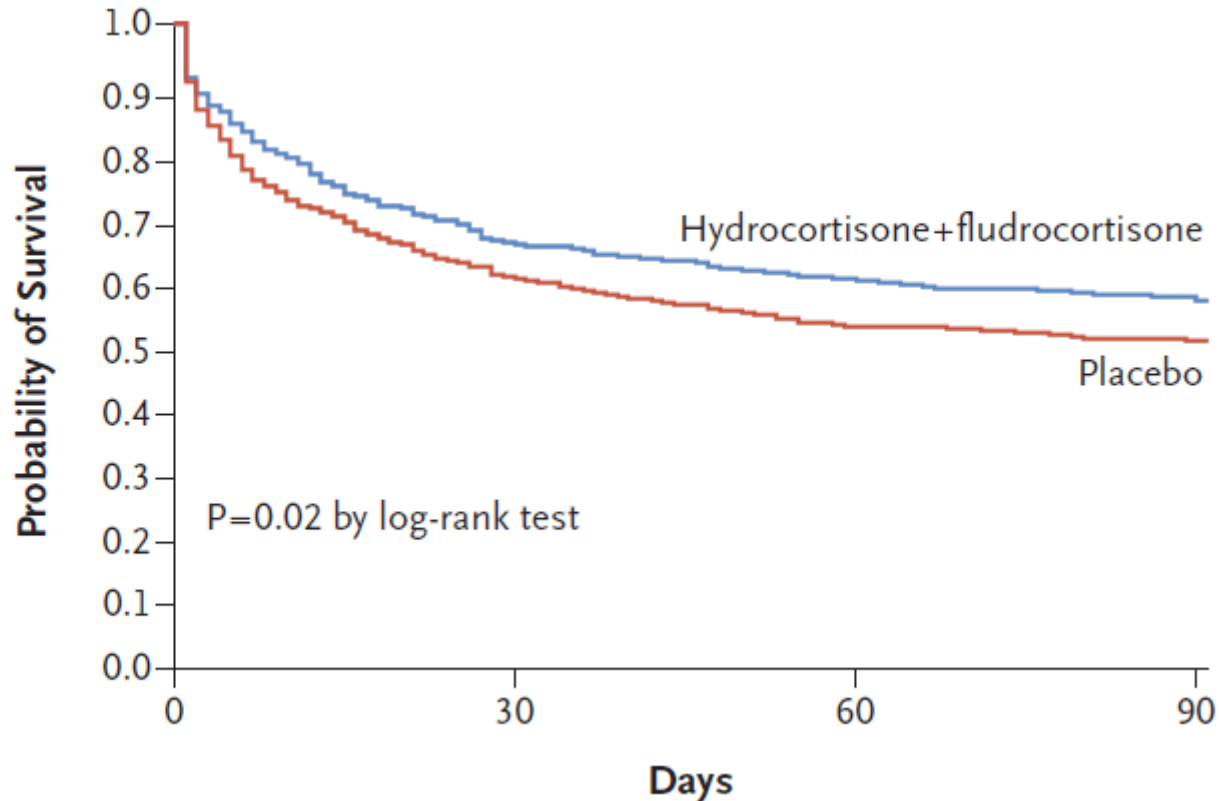
ADRENAL Safety

LIST OF SHORT COURSE HYDROCORTISONE



Adverse Event	Hydrocortisone (N=1835)	Placebo (N=1829)
No. of patients with event	21	6
No. of events		
Total adverse events	27	6
Hyperglycemia	6	3
Hypernatremia	3	0
Hyperchloremia	1	0
Hypertension	3	0
Bleeding	2	1†
Encephalopathy	3	0
Leukocytosis	2	0
Myopathy‡	3†	0
Septic arthritis	1	0
Ischemic bowel	1†	0
Abdominal-wound dehiscence	0	1†
Circulatory shock	1†	0
Thrombocytopenia	1	0
Miscellaneous	0	1

APROCCHSS Results



APROCCHSS Results

Outcome	Placebo (N = 627)	Hydrocortisone plus Fludrocortisone (N = 614)	All Patients (N = 1241)	Relative Risk (95% CI) [†]	P Value
Primary outcome: death from any cause at day 90 — no. (%)	308 (49.1)	264 (43.0)	572 (46.1)	0.88 (0.78–0.99)	0.03
Secondary outcomes					
Death from any cause					
At day 28 — no. (%)	244 (38.9)	207 (33.7)	451 (36.3)	0.87 (0.75–1.01)	0.06
At ICU discharge — no./total no. (%)	257/627 (41.0)	217/613 (35.4)	474/1240 (38.2)	0.86 (0.75–0.99)	0.04
At hospital discharge — no./total no. (%)	284/627 (45.3)	239/613 (39.0)	523/1240 (42.2)	0.86 (0.76–0.98)	0.02
At day 180 — no./total no. (%)	328/625 (52.5)	285/611 (46.6)	613/1236 (49.6)	0.89 (0.79–0.99)	0.04
Decision to withhold or withdraw active treatment by day 90 — no./total no. (%)	61/626 (9.7)	64/614 (10.4)	125/1240 (10.1)	1.07 (0.77–1.49)	0.69
Vasopressor-free days to day 28 [‡]					
Mean	15±11	17±11	16±11	—	<0.001
Median (IQR)	19 (1–26)	23 (5–26)	21 (2–26)		
Ventilator-free days to day 28 [‡]					
Mean	10±11	11±11	11±11	—	0.07
Median (IQR)	4 (0–21)	10 (0–22)	8 (0–21)		
Organ-failure-free days to day 28 [‡]					
Mean	12±11	14±11	13±11	—	0.003
Median (IQR)	12 (0–24)	19 (0–25)	15 (0–24)		

APROCCHSS Safety

Event	Placebo (N = 627)	Hydrocortisone plus Fludrocortisone (N = 614)	Relative Risk (95% CI) [†]	P Value
≥1 Serious event by day 180 — no./total no. (%)	363/626 (58.0)	326/614 (53.1)	0.92 (0.83–1.01)	0.08
≥1 Serious bleeding event by day 28 — no./total no. (%)	119/626 (19.0)	127/614 (20.7)	1.09 (0.87–1.36)	0.46
Gastroduodenal bleeding — no./total no. (%)	45/626 (7.2)	39/614 (6.4)	0.88 (0.58–1.34)	0.56
≥1 Episode of superinfection by day 180 — no./total no. (%)	178/626 (28.4)	191/614 (31.1)	1.09 (0.92–1.30)	0.30
Site of superinfection — no./total no. (%)				
Lung	116/626 (18.5)	127/614 (20.7)	1.12 (0.89–1.40)	0.34
Blood	48/626 (7.7)	49/614 (8.0)	1.04 (0.71–1.53)	0.84
Catheter-related	37/626 (5.9)	40/614 (6.5)	1.10 (0.71–1.70)	0.66
Urinary tract	33/626 (5.3)	40/614 (6.5)	1.24 (0.79–1.93)	0.35
Other	57/626 (9.1)	70/614 (11.4)	1.25 (0.90–1.74)	0.18
New sepsis — no./total no. (%)	122/626 (19.5)	134/614 (21.8)	1.12 (0.90–1.39)	0.31
New septic shock — no./total no. (%)	103/626 (16.5)	109/614 (17.8)	1.08 (0.84–1.38)	0.54
Hyperglycemia				
≥1 Episode of blood glucose levels ≥150 mg/dl by day 7 — no./total no. (%)	520/626 (83.1)	547/614 (89.1)	1.07 (1.03–1.12)	0.002
No. of days with ≥1 episode of blood glucose levels ≥150 mg/dl by day 7				
Mean	3.4±2.5	4.3±2.5	—	<0.001
Median (IQR)	3 (1–6)	5 (2–6)		

Corticosteroids: CON
(no mortality benefit)

Surviving Sepsis Campaign 2016

H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Decision Points

- Early in care (<12 or <24 h)
 - Is this just sepsis without shock?
 - If this is septic shock, is it predominately an SVR or CO problem?
 - Will synergistic medications (e.g., vasopressin) be used too?
- Late in care (<24 h)
 - If refractory septic shock, has the window of benefit passed?
 - Do (non-mortality) benefits outweigh risks?

“Time” Points

- Sepsis
- Early septic shock
- Late(r) septic shock

Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis

The HYPRESS Randomized Clinical Trial

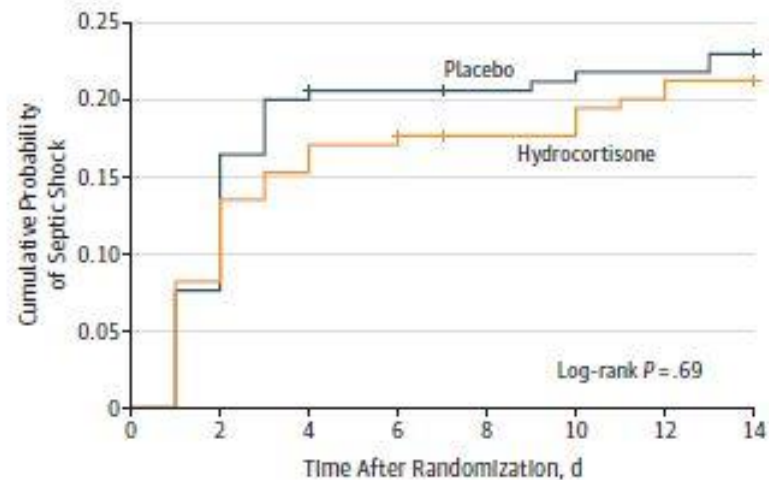
Table 1. Baseline Characteristics^a

Characteristic	Placebo (n = 176)	Hydrocortisone (n = 177)	Total (N = 353)
Male, No./total No. (%)	111/176 (63.1)	118/177 (66.7)	229/353 (64.9)
Age, mean (SD), y	64.6 (14.6)	65.5 (14.2)	65.0 (14.4)
Type of admission, No./total No. (%)			
Surgery, elective	42/176 (23.9)	27/176 (15.3)	69/352 (19.6)
Surgery, emergency	32/176 (18.2)	44/176 (25.0)	76/352 (21.6)
Nonsurgery, elective	4/176 (2.3)	5/176 (2.8)	9/352 (2.6)
Nonsurgery, emergency	98/176 (55.7)	100/176 (56.8)	198/352 (56.3)
SOFA score, mean (SD) ^{b,c}	6.2 (2.4)	6.4 (2.6)	6.3 (2.5)
APACHE II score, mean (SD) ^{b,d}	18.5 (6.0)	19.5 (6.9)	19.0 (6.5)

Table 2. Primary and Secondary End Points^a

End Point	Placebo (n = 176)	Hydrocortisone (n = 177)	Total (N = 353)	P Value
Primary				
Septic shock, No./total No. (%) [95% CI]				
ITT population	39/170 (22.9) [17.2-30.0]	36/170 (21.2) [15.6-28.1]	75/340 (22.1) [17.9-26.9]	.70
PP population	33/156 (21.2) [15.4-28.4]	29/155 (18.7) [13.3-25.7]	62/311 (19.9) [15.8-24.8]	.59
Secondary				
Mortality, No./total No. (%) [95% CI]				
28 d	14/170 (8.2) [5.0-13.4]	15/171 (8.8) [5.4-14.0]	29/341 (8.5) [6.0-12.0]	.86
90 d	28/168 (16.7) [11.8-23.0]	34/171 (19.9) [14.6-26.5]	62/339 (18.3) [14.5-22.8]	.44
180 d	37/167 (22.2) [16.5-29.0]	45/168 (26.8) [20.7-34.0]	82/335 (24.5) [20.2-29.4]	.32
ICU	14/172 (8.1) [4.9-13.2]	13/171 (7.6) [4.5-12.6]	27/343 (7.9) [5.5-11.2]	.85
Hospital	22/172 (12.8) [8.6-18.6]	23/171 (13.5) [9.1-19.4]	45/343 (13.1) [10.0-17.1]	.86
LOS, median (IQR), d				
ICU	9 (6-17)	8 (5-15)	8 (5-16)	.23
Hospital	25 (16-40)	26 (16-46)	26 (16-43)	.36
Mechanical ventilation, No./total No. (%) [95% CI]	103/172 (59.9) [52.4-66.9]	91/171 (53.2) [45.8-60.5]	194/343 (56.6) [51.3-61.7]	.21
MV-free time, median (IQR), d	5 (2-7)	4 (2-7)	4 (2-7)	.34
RRT, No./total No. (%) [95%CI]	21/172 (12.2) [8.1-17.9]	21/171 (12.3) [8.2-18.0]	42/343 (12.2) [9.2-16.1]	.98
RRT-free time, median (IQR), d	7 (4-14)	6 (4-12)	7 (4-13)	.35

Figure 2. Time to Septic Shock



“Time” Points

- Sepsis
 - **Steroids are not beneficial**
- Early septic shock
- Late(r) septic shock

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Hydrocortisone Therapy for Patients with Septic Shock

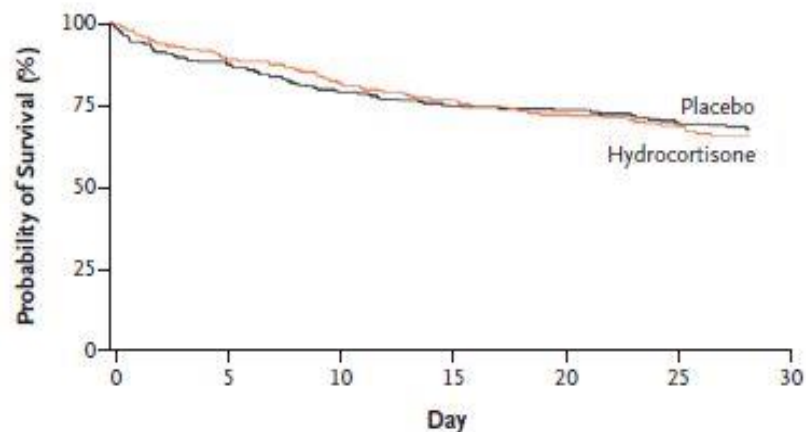
Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

Table 2. Clinical Characteristics of the Patients at Baseline, According to Subgroup.*

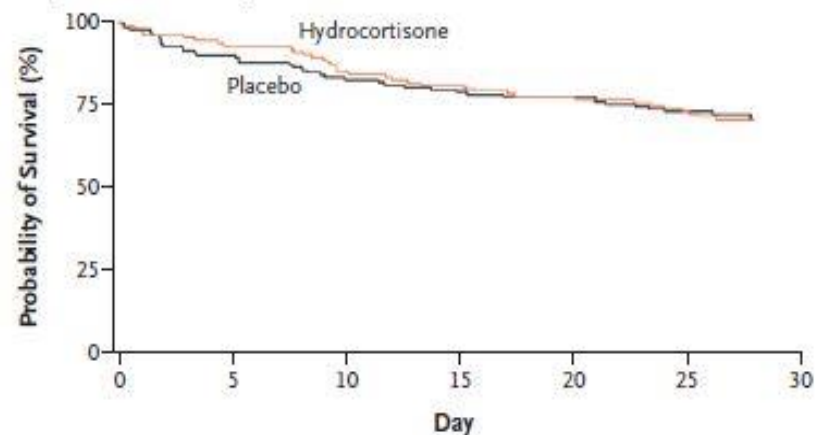
Variable	No Response to Corticotropin				Response to Corticotropin				All Patients			
	No. of Patients	Hydrocortisone (N=125)	No. of Patients	Placebo (N=108)	No. of Patients	Hydrocortisone (N=118)	No. of Patients	Placebo (N=136)	No. of Patients	Hydrocortisone (N=251)	No. of Patients	Placebo (N=248)
Cortisol — $\mu\text{g/dl}$	125		108		118		136		243		244	
Before corticotropin		30 \pm 20		29 \pm 19		27 \pm 19		29 \pm 21		28 \pm 20		29 \pm 20
60 min after corticotropin		33 \pm 19		32 \pm 18		46 \pm 22		46 \pm 23		39 \pm 22		39 \pm 22
Response to corticotropin test		3 \pm 4		3 \pm 4		18 \pm 11		16 \pm 6		11 \pm 11		10 \pm 8
Receiving vasopressor or inotrope at baseline — no. (%)		125 (100)		108 (100)		117 (99)		131 (96)		249 (99)		243 (98)
Type of vasopressor†												
Norepinephrine — no. (%)		116 (93)		104 (96)		103 (87)		124 (91)		224 (89)		231 (93)
Maximum dose — $\mu\text{g/kg/min}$		0.5 \pm 0.5		0.5 \pm 0.5		0.4 \pm 0.7		0.4 \pm 0.5		0.5 \pm 0.6		0.4 \pm 0.5
Epinephrine — no. (%)		19 (15)		9 (8)		14 (12)		13 (10)		35 (14)		22 (9)
Maximum dose — $\mu\text{g/kg/min}$		0.8 \pm 1.6		0.2 \pm 0.1		0.3 \pm 0.4		1.4 \pm 3.3		0.6 \pm 1.2		0.9 \pm 2.6
Dopamine — no. (%)		10 (8)		9 (8)		16 (14)		19 (14)		27 (11)		29 (12)
Maximum dose — $\mu\text{g/kg/min}$		12.9 \pm 9.6		7.1 \pm 6.3		9.8 \pm 6.1		8.3 \pm 7.1		10.4 \pm 7.5		7.9 \pm 6.6

Variable	No Response to Corticotropin		P Value	Response to Corticotropin		P Value	All Patients		P Value
	Hydrocortisone (N= 125)	Placebo (N= 108)		Hydrocortisone (N= 118)	Placebo (N= 136)		Hydrocortisone (N= 251)	Placebo (N= 248)	
Death within 28 days — no. (%)	49 (39.2)	39 (36.1)	0.69	34 (28.8)	39 (28.7)	1.00	86 (34.3)	78 (31.5)	0.51
Relative risk (95% CI)	1.09 (0.77 to 1.52)			1.00 (0.68 to 1.49)			1.09 (0.84 to 1.41)		
Absolute difference — % (95% CI)	3.1 (−9.5 to 15.7)			0.1 (−11.2 to 11.4)			2.8 (−5.5 to 11.2)		
Death in ICU — no./total no. (%)	58/125 (46.4)	44/108 (40.7)	0.43	41/118 (34.7)	45/135 (33.3)	0.89	102/251 (40.6)	89/247 (36.0)	0.31
Relative risk (95% CI)	1.14 (0.85 to 1.53)			1.04 (0.74 to 1.47)			1.13 (0.90 to 1.41)		
Absolute difference — % (95% CI)	5.7 (−7.1 to 18.4)			1.4 (−10.3 to 13.1)			4.6 (−3.9 to 13.1)		

C All Patients



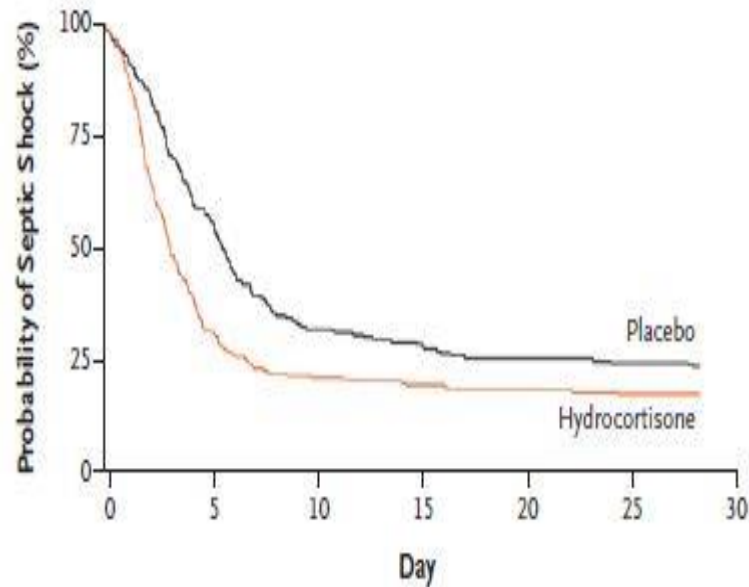
B Response to Corticotropin



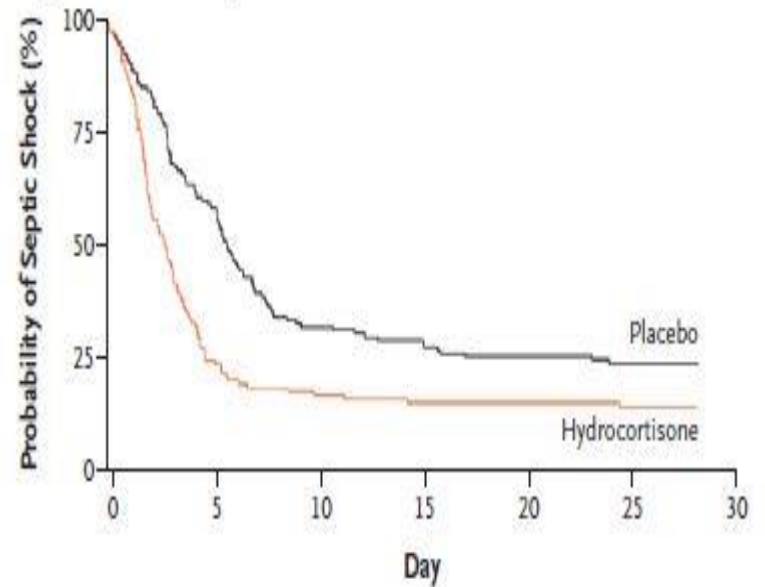
Treatment group			
	Steroid	Placebo	Total
	N (%)	N (%)	N(%)
Treatment start within 12 h			
Alive	125 (63.1)	128 (68.8)	253 (65.9)
Died	73 (36.9)	58 (31.2)	131 (34.1)
Total	198 (100.0)	186 (100.0)	384 (100.0)
Treatment start between 12 to 24 h			
Alive	20 (80.0)	19 (79.2)	39 (79.6)
Died	5 (20.0)	5 (20.8)	10 (20.4)
Total	25 (100.0)	24 (100.0)	49 (100.0)
Treatment start between 24 and 48 h			
Alive	11 (57.9)	18 (58.1)	29 (58.0)
Died	8 (42.1)	13 (41.9)	21 (42.0)
Total	19 (100.0)	31 (100.0)	50 (100.0)
Treatment start between 48 and 72 h			
Alive	8 (100.0)	5 (83.3)	13 (92.9)
Died	0 (0)	1 (16.7)	1 (7.1)
Total	8 (100.0)	6 (100.0)	14 (100.0)
Treatment start after more than 72 h			
Alive	1 (100.0)	-	1 (100.0)
Total	1 (100.0)	-	1 (100.0)
Total ITT population			
Alive	165 (65.7)	170 (68.8)	335 (67.3)
Died	86 (34.3)	77 (31.2)	163 (32.7)
Total	251 (100.0)	247 (100.0)	498 (100.0)

Reversal of Shock

C All Patients



B Response to Corticotropin



“Time” Points

- Sepsis
- Early septic shock
 - **If moderately ill, no mortality benefit but faster shock reversal**
- Late(r) septic shock

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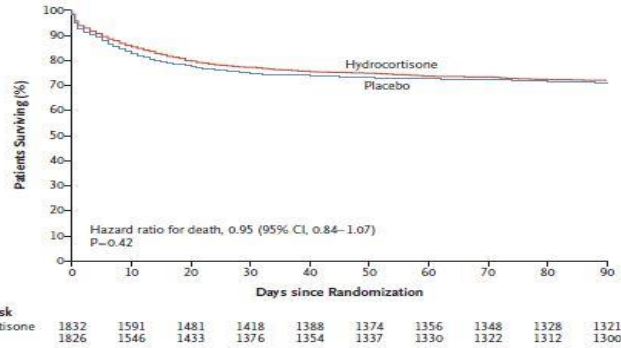
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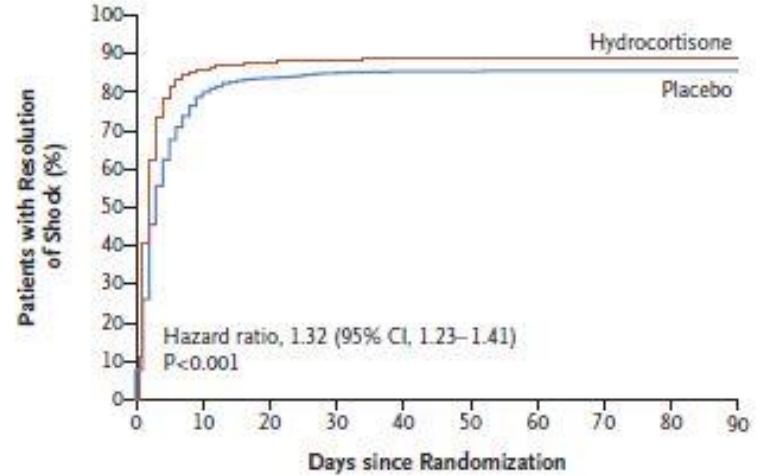
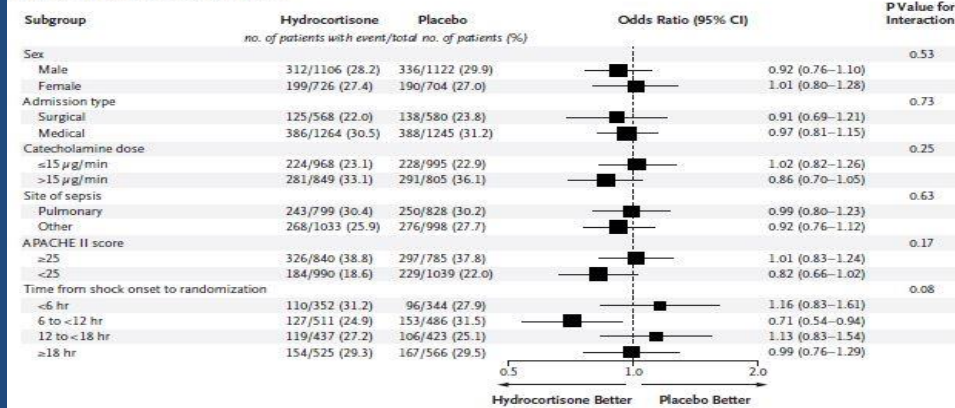
Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

Characteristic	Hydrocortisone (N=1853)	Placebo (N=1860)
Age — yr	62.3±14.9	62.7±15.2
Male sex — no./total no. (%)	1119/1853 (60.4)	1140/1860 (61.3)
Weight — kg	85.8±26.6	85.6±26.3
Admission type — no./total no. (%)†		
Medical	1273/1849 (68.8)	1266/1857 (68.2)
Surgical	576/1849 (31.2)	591/1857 (31.8)
APACHE II score‡		
Median	24.0	23.0
Interquartile range	19.0–29.0	18.0–29.0
Therapy at baseline — no./total no. (%)§		
Mechanical ventilation	1845/1849 (99.8)	1855/1857 (99.9)
Inotropes or vasopressors	1843/1853 (99.5)	1854/1860 (99.7)
Norepinephrine	1823/1853 (98.4)	1821/1860 (97.9)
Vasopressin	280/1853 (15.1)	321/1860 (17.3)
Epinephrine	134/1853 (7.2)	113/1860 (6.1)
Other	157/1853 (8.5)	173/1860 (9.3)
Antimicrobial agent	1817/1848 (98.3)	1821/1857 (98.1)
Renal-replacement therapy	228/1849 (12.3)	242/1857 (13.0)

A Survival



B Subgroup Analysis of Death at 90 Days

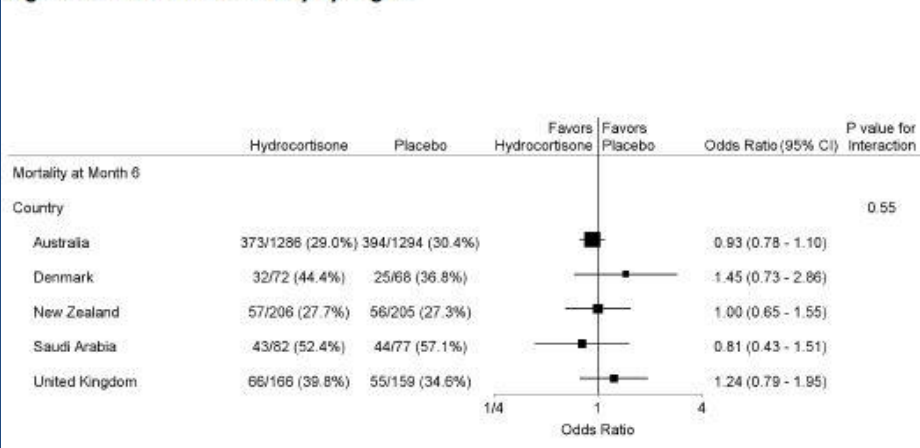


ADRENAL 6-month Mortality

Table S1: Analysis of mortality at 6 months

	Hydrocortisone (N=1853)	Placebo (N=1860)	Odds Ratio	95% CI	P-value
6 month mortality					
Unadjusted	571/1812 (31.5%)	574/1803 (31.8%)	0.99	0.86-1.13	0.83
Adjusted for stratification variables ¹			0.98	0.85-1.13	0.77
Adjusted for additional covariates ²			0.99	0.85-1.15	0.90

Figure S1: Six Month Mortality by Region



“Time” Points

- Sepsis
- Early septic shock
 - **If moderately ill, no mortality benefit but faster shock reversal**
 - **If severely ill, possible mortality benefit**
- Late(r) septic shock
 - **No mortality benefit but faster shock reversal**

TAKEAWAY:

Corticosteroids may provide a mortality benefit in a small subset of critically ill patients with septic shock

REBUTTAL Corticosteroids: PRO (How and When)

Trial Comparison

	Annane 2002	CORTICUS 2008	ADRENAL 2018	Annane 2018
N	299	499	3,800	1,241
Mortality benefit?	Yes	No	No	Yes
Control group mortality	63%	31.5	24.3%	49.1%
Time from shock onset	≤ 8 hours	≤ 72 hours	20.9 ± 90 hours	≤ 24 hours
Dosing	Bolus	Bolus	Continuous	Bolus
Taper?	No	Yes	No	No
Fludrocortisone?	Yes	No	Yes	No

Bolus vs CI

	HC continuous infusion group	HC bolus group	p
Shock reversal at day 7, n (%)			
Intent-to-treat group	13/37 (35)	22/33 (66)	0.008
Per protocol	13/29 (44)	22/29 (75)	0.01
Time from shock to HC initiation, hours, median (IQR),	3 (1-12)	3 (2-5)	0.88
Time from ICU admission to randomization, days, median (IQR)	1 (0-5.5)	0 (0-1)	0.20
Mean \pm SD	6.3 \pm 14.6	5.3 \pm 14.4	0.78
Vasopressors-free days, median (IQR)	7 (1,5-12,5)	10 (1,5-18)	0.59
ICU LOS, d, median (IQR)	11 (7,5-30)	16 (10-26)	0.78
Hospital LOS, d, median (IQR)	13 (8-30)	17 (10-32)	0.35
Duration of MV, d, median (IQR)	10 (5,5-25,5)	12 (9-22,5)	0.58
28-day mortality, n (%)			
Intent-to-treat group	24/37 (64)	16/33 (48)	0.25
Per protocol	16/29 (55)	12/29 (41)	0.43

Abrupt versus gradual cessation of steroids in patients with septic shock



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Study endpoints.

Endpoints	Abrupt withdrawal (n = 46)	Tapered steroid (n = 41)	p-Value
Primary endpoint			
Patients re-initiated on vasopressor therapy- no. (%)	1 (2.2)	7 (17.1)	0.024
Secondary endpoints			
Avg. glucose prior to withdrawal or taper - mg/dl	152.8 ± 9.6	155.6 ± 10.9	0.698
Avg. glucose during analysis- mg/dl	125.1 ± 9.9	150.8 ± 12.3	< 0.001
Avg. glucose during analysis pts excluding those with DM- mg/dl	114.8 ± 7.1	141.1 ± 12.6	<0.001
Hyperglycemia requiring treatment - no. (%)	13 (28.3)	25 (70)	< 0.002
ICU Length of stay- days	8.28	10.73	0.14

REBUTTAL Corticosteroids: CON (high risk data & adverse effects)

Best Practices in Sepsis Continuously Evolve

- Sepsis definitions (i.e., SIRS vs. SOFA)
- Standards of care (e.g., fluid choice, fluid amount, ScvO₂)
- Vasopressors (dopamine saga)
- Steroids...

Data Informing Meta-Analyses

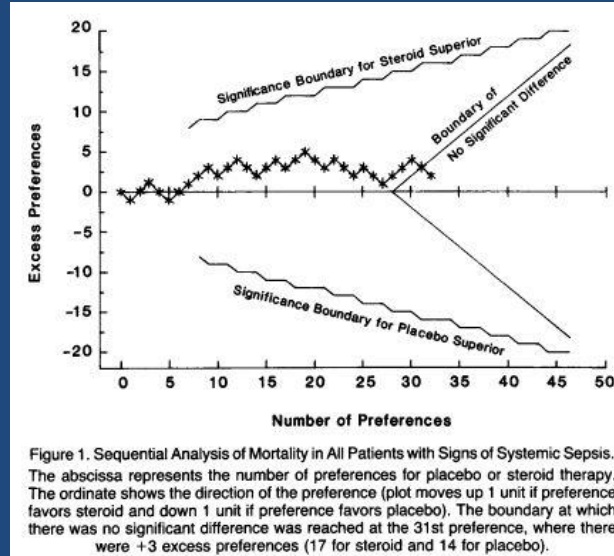
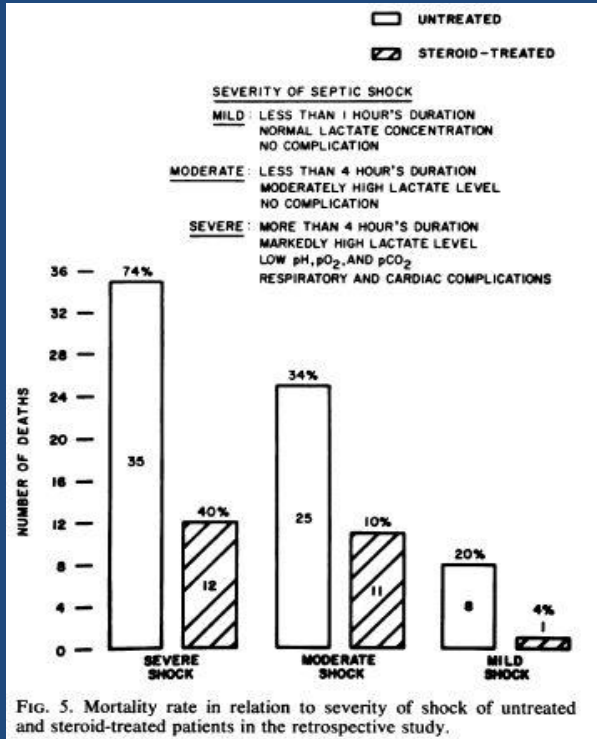


TABLE 6. Mortality

	Sepsis Syndrome Alone (%)		Shock Present on Admission (%)		Development of Shock After Admission (%)	
Total ^a	10/77	(13)	19/69	(28) ^c	19/44	(43) ^c
Nonbacteremic	8/50	(16)	7/34	(21)	9/20	(45) ^c
Bacteremic	2/26	(8)	11/34 ^b	(32)	10/24	(42) ^c
Gram (-)	1/16	(6)	8/23	(35)	7/16	(43) ^c
Gram (+)	1/10	(10)	3/11	(27)	3/8	(38)

Comparisons are with sepsis syndrome alone group.

^a Follow-up data were available for 190 of 191 patients (mortality data not available for one patient with sepsis syndrome alone).

^b One patient with shock present on admission died from a primary fungemia.

^c $p < .05$; ^d $p < .01$; ^e $p < .001$.



Obi-Wan Kenobi quote adapted by Drayton

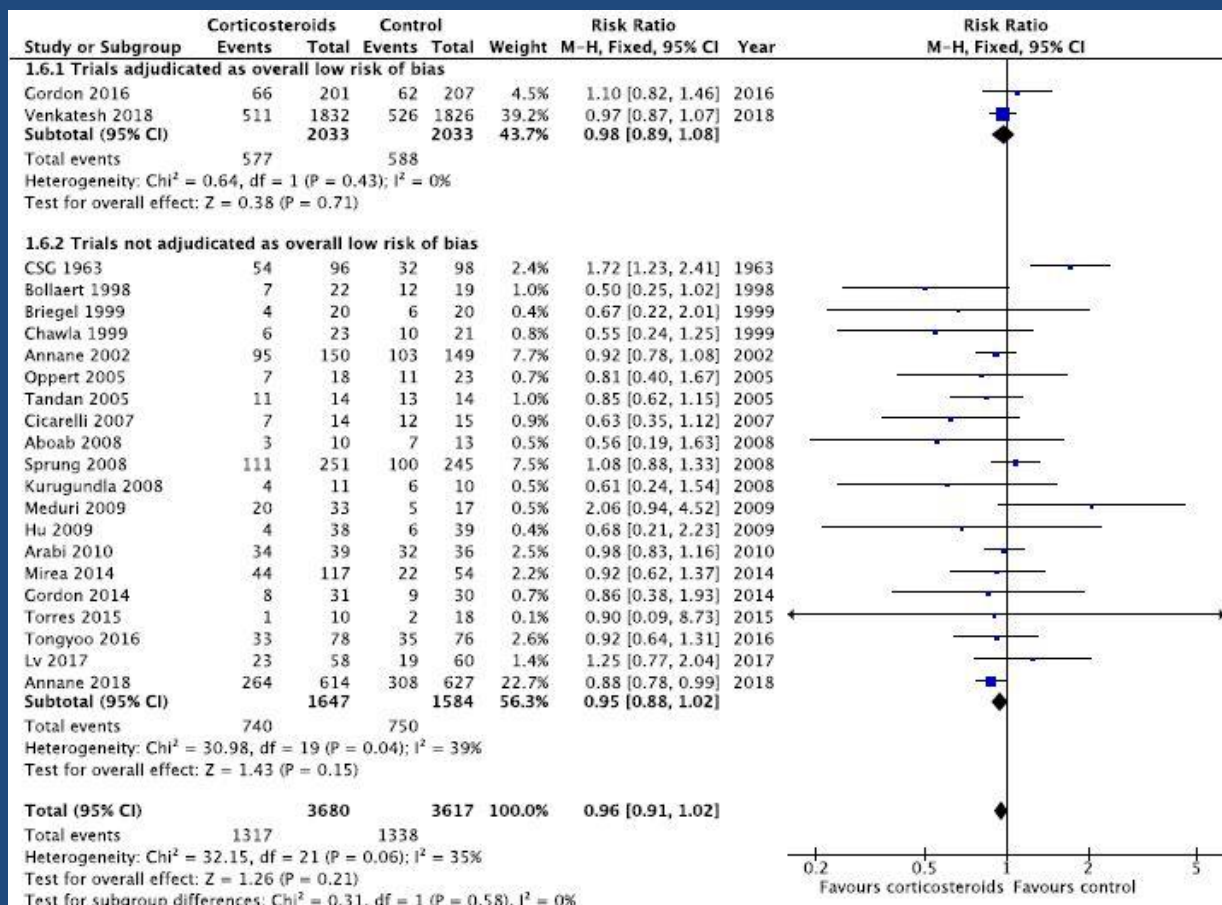


Fig. 3 Forrest plot showing the effect of corticosteroids compared to placebo or control on short-term mortality for patients with septic shock

APROCCHSS Trial

- Large (though potentially still inadequate n) trial (n=1241) power to detect 10% mortality difference favoring steroids
 - Steroids provided as IV bolus (50 mg Q6H) within 24 hours of shock
 - Patients typically quite sick (NE ~70 mcg/min)
 - Trial enrolled 8 years (stopped twice (2 years in total): drotrecogin alfa and DSMB for quality of trial agents & serious adverse events)
- Mortality benefit at 90 days: 43% vs. 49.1% (RR 0.88 95% CI 0.78-0.99, p=0.03)
 - Fragility index = 3
 - Similar mortality at 28 days (33.7% vs. 38.9%, p=0.06)

Fludrocortisone?

- Steroid group received fludrocortisone 50 mcg PO daily
 - Is this even absorbed on norepinephrine 70 mcg/min?
 - ~One-third of septic patients with unmeasurable serum fludrocortisone
- Is this even necessary or beneficial?
 - Hydrocortisone has glucocorticoid and mineralocorticoid activity
 - Data from COITSS trial found no benefit with fludrocortisone + hydrocortisone vs. hydrocortisone alone (secondary outcome)

Corticosteroid Adverse Effects

Outcome Timeframe	Study Results and Measurements	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)	Plain Text Summary
		No Corticosteroids	Corticosteroids		
Neuromuscular weakness	Relative risk: 1.21 (95% CI, 1.01–1.45) Based on data from 6,178 patients in seven studies	250/1,000 Difference: 53 more per 1,000 (95% CI, 3 more to 130 more)	303/1,000	Low Due to serious imprecision and indirectness and borderline inconsistency ^c	Corticosteroids may result in a small increase in neuromuscular weakness.
Gastrointestinal bleeding	Relative risk: 1.09 (95% CI, 0.86–1.38) Based on data from 4,243 patients in 17 studies	35/1,000 Difference: 3 more per 1,000 (95% CI, 5 fewer to 13 more)	38/1,000	Low Due to serious indirectness and imprecision ^d	Corticosteroids may have little or no difference on gastrointestinal bleeding
Neuropsychiatric events	Relative risk: 0.58 (95% CI, 0.33–1.03) Based on data from 1,004 patients in five studies	59/1,000 Difference: 25 fewer per 1,000 (95% CI, 40 fewer to 2 more)	34/1,000	Low Due to serious imprecision and serious indirectness ^e	Corticosteroids may achieve a small reduction in neuropsychiatric events.
Hypernatremia	Relative risk: 1.64 (95% CI, 1.32–2.03) Based on data from 5,015 patients in six studies	36/1,000 Difference: 23 more per 1,000 (95% CI, 12 more to 37 more)	59/1,000	Moderate Due to serious indirectness ^f	Corticosteroids probably increase the risk of hypernatremia.

Corticosteroid Adverse Effects

Outcome Timeframe	Study Results and Measurements	Absolute Effect Estimates		Certainty in Effect Estimates (Quality of Evidence)	Plain Text Summary
		No Corticosteroids	Corticosteroids		
Superinfection	Relative risk: 1.02 (95% CI, 0.89–1.18) Based on data from 4,519 patients in 21 studies	161/1,000 Difference: 3 more per 1,000 (95% CI, 18 fewer to 29 more)	164/1,000	Low Due to serious imprecision and serious indirectness ^c	Corticosteroids may have little or no impact on superinfection.
Stroke	Relative risk: 2.07 (95% CI, 0.45–9.61) Based on data from 1,105 patients in three studies	5/1,000 Difference: 5 more per 1,000 (95% CI, 3 fewer to 43 more)	10/1,000	Very low Due to serious indirectness and very serious imprecision ^g	Whether or not corticosteroids impact the risk of stroke is uncertain.
Myocardial infarction	Relative risk: 0.91 (95% CI, 0.45–1.82) Based on data from 1,080 patients in three studies	30/1,000 Difference: 3 fewer per 1,000 (95% CI, 16 fewer to 25 more)	27/1,000	Very low Due to serious indirectness and very serious imprecision ^g	Whether or not corticosteroids impact the risk of myocardial infarction is uncertain.
Hyperglycemia	Relative risk: 1.16 (95% CI, 1.08–1.24) Based on data from 7,563 patients in 15 studies	181/1,000 Difference: 29 more per 1,000 (95% CI, 14 more to 43 more)	210/1,000	Moderate Due to serious indirectness ^h	Corticosteroids probably increase the incidence of hyperglycemia.

TAKEAWAY:

Adverse effects are common with corticosteroids

Closing Thoughts

- Faster shock reversal is likely (and meaningful)
- Mortality reduction is possible (earlier initiation & sicker)
- Adverse effects are overstated
- Best use would be early in septic shock management

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

RAAS Pathway

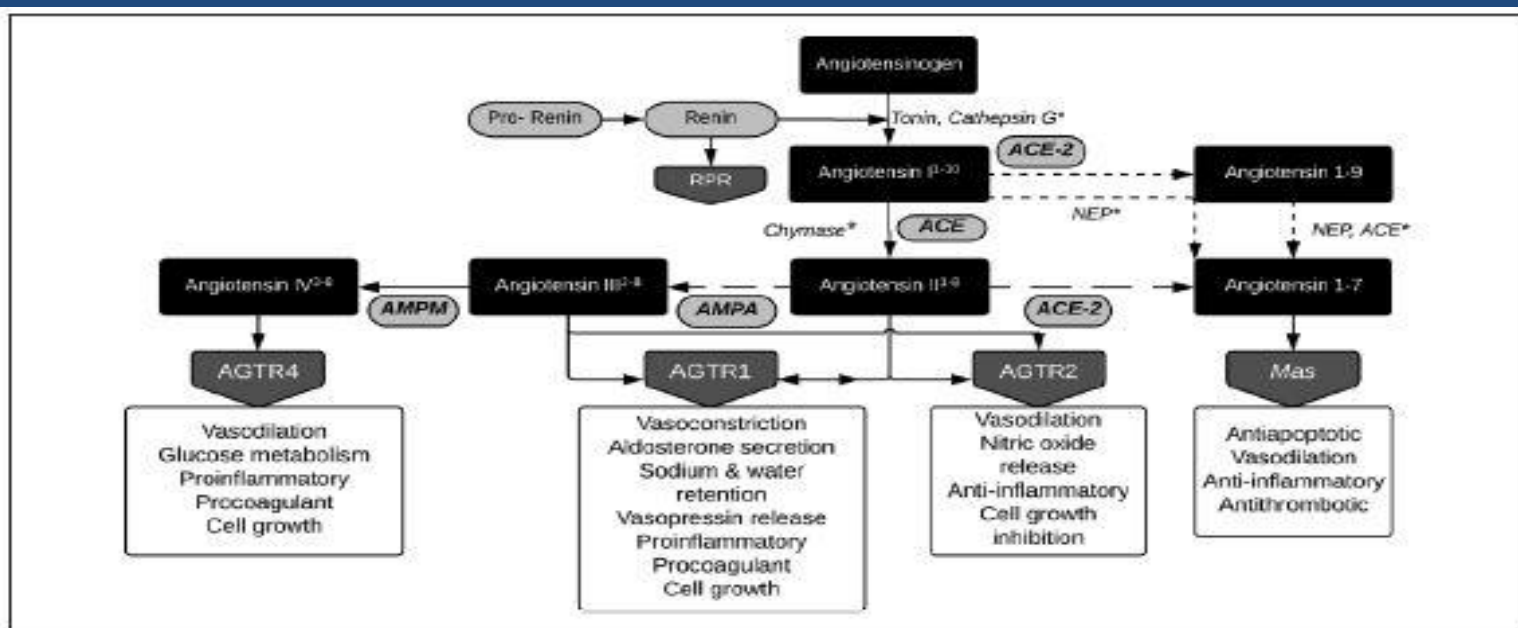


Figure 1. Renin-angiotensin-aldosterone system network and pathways.

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

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

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

ATHOS-3

- Double-blind, placebo-controlled RCT
- Inclusion
 - Cardiac index >2.3 L/min/m² OR ScvO₂ $>70\%$ 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)

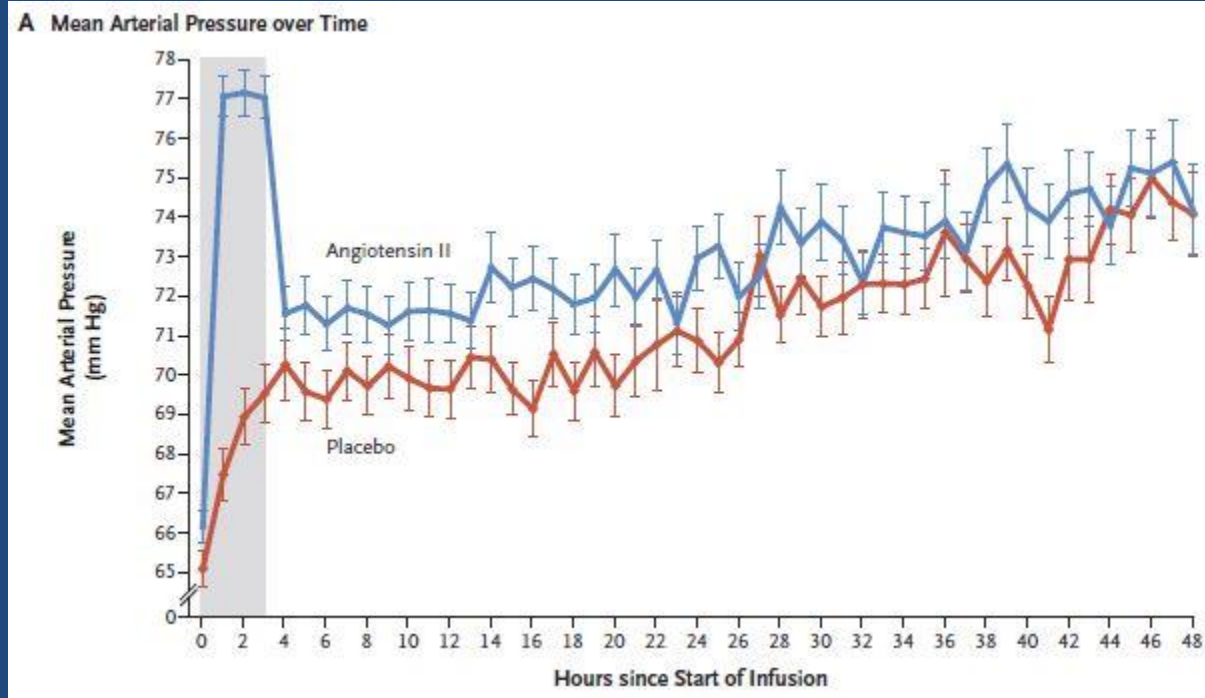
Baseline Vasopressor Use

	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)

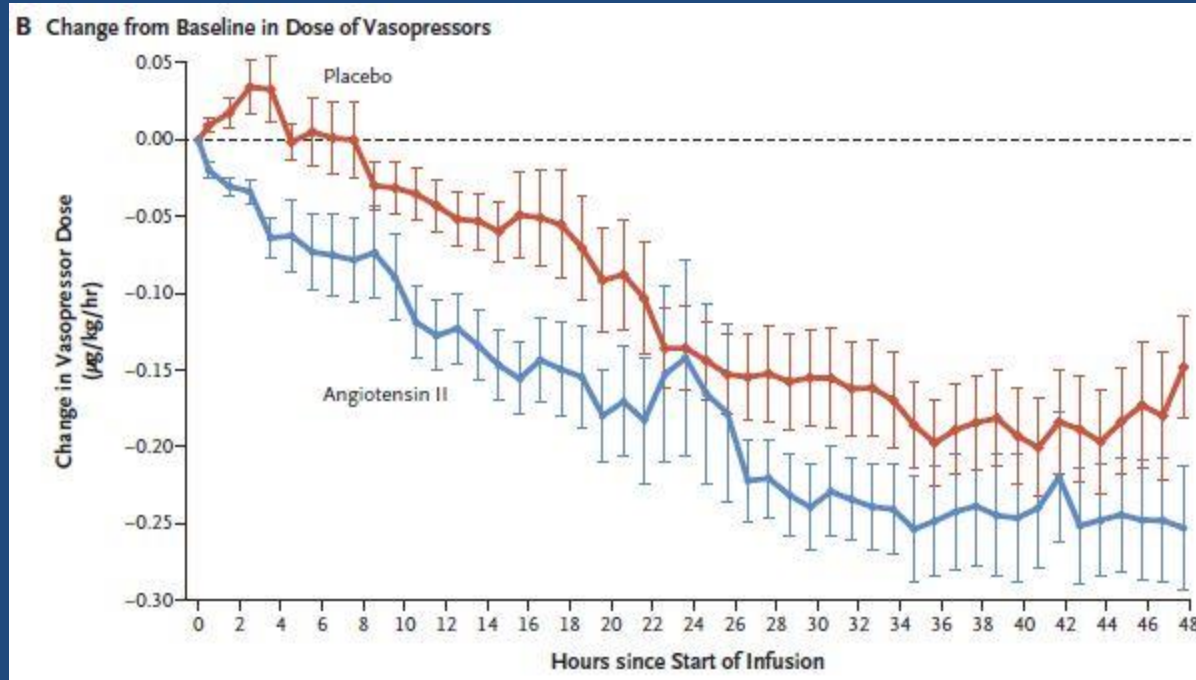
Primary and Secondary Outcomes

	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

MAP



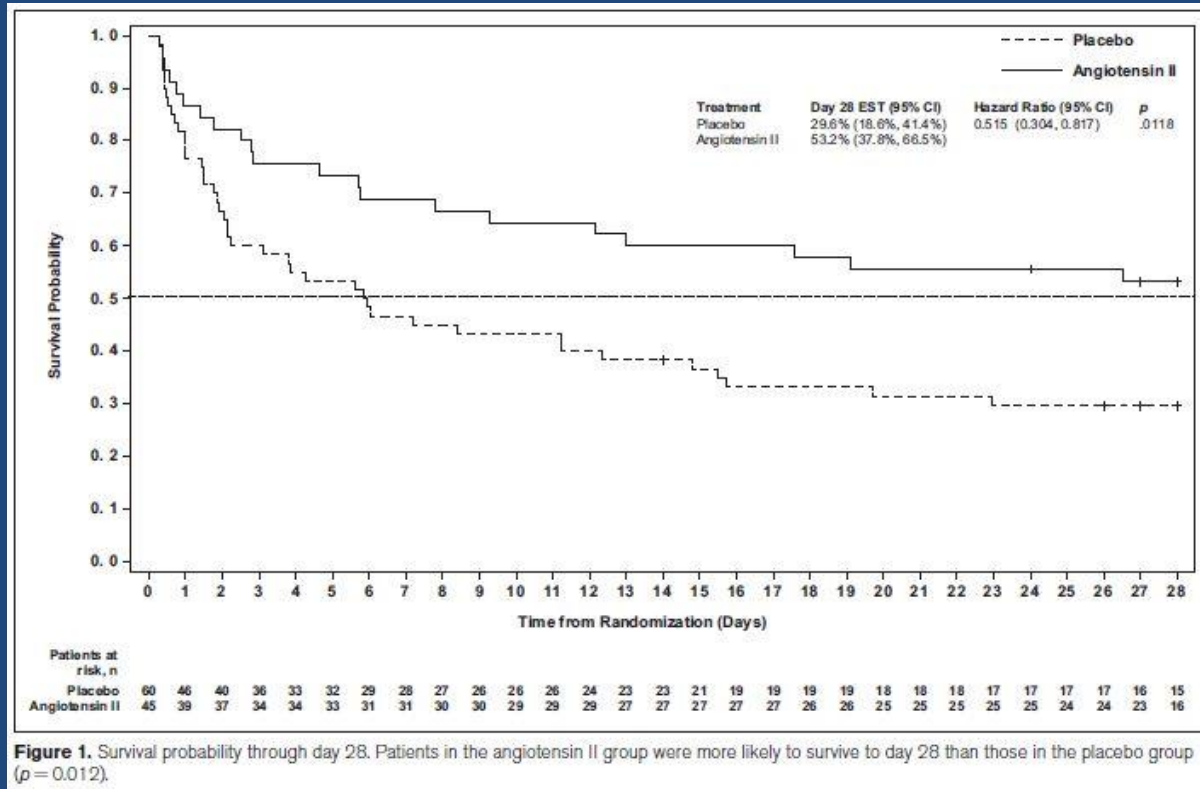
Norepinephrine Equivalent Dosage



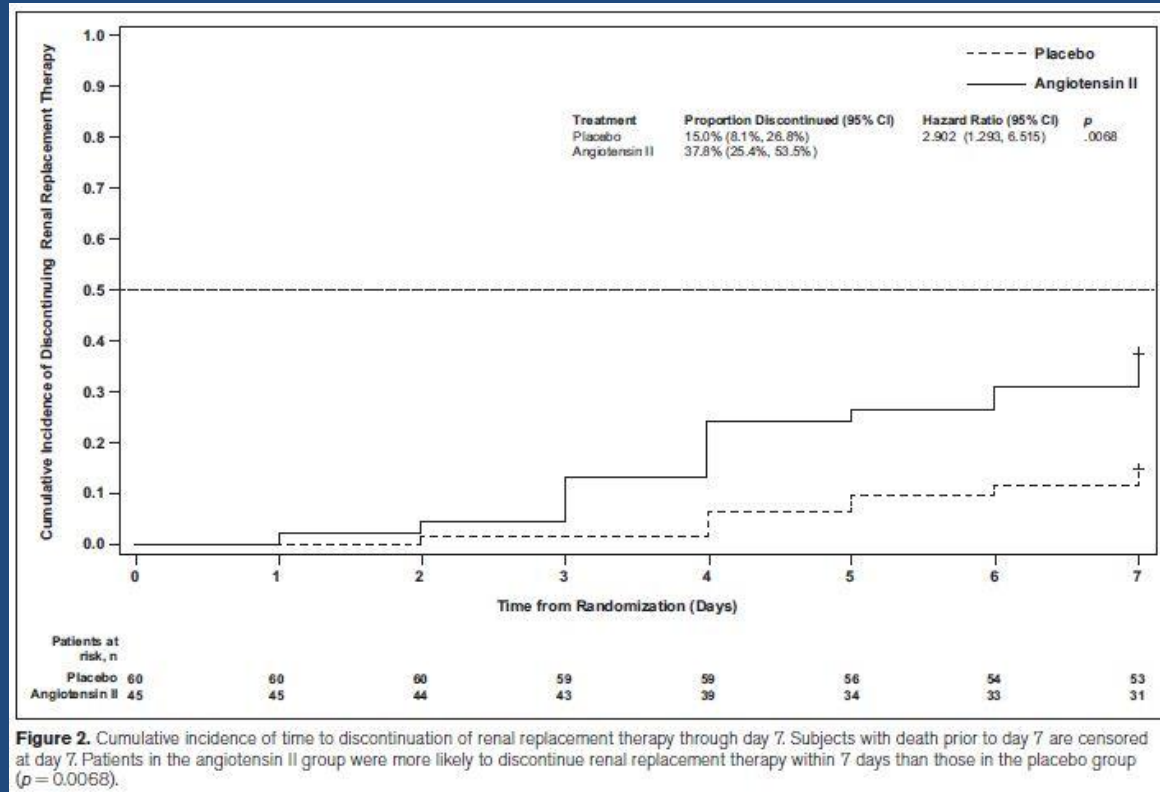
Conclusions

- 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

Patients with AKI and RRT at Study Drug Initiation



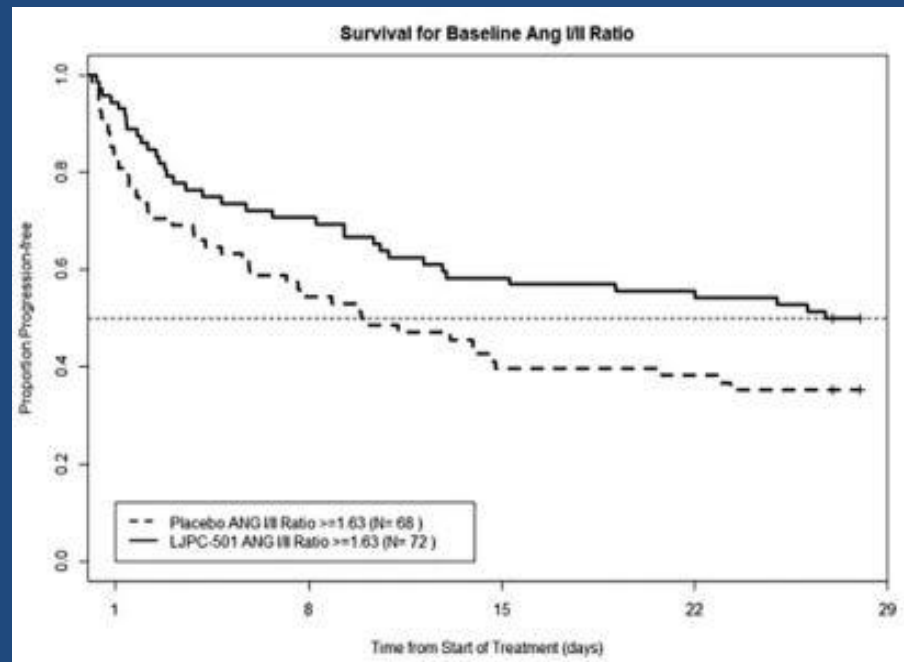
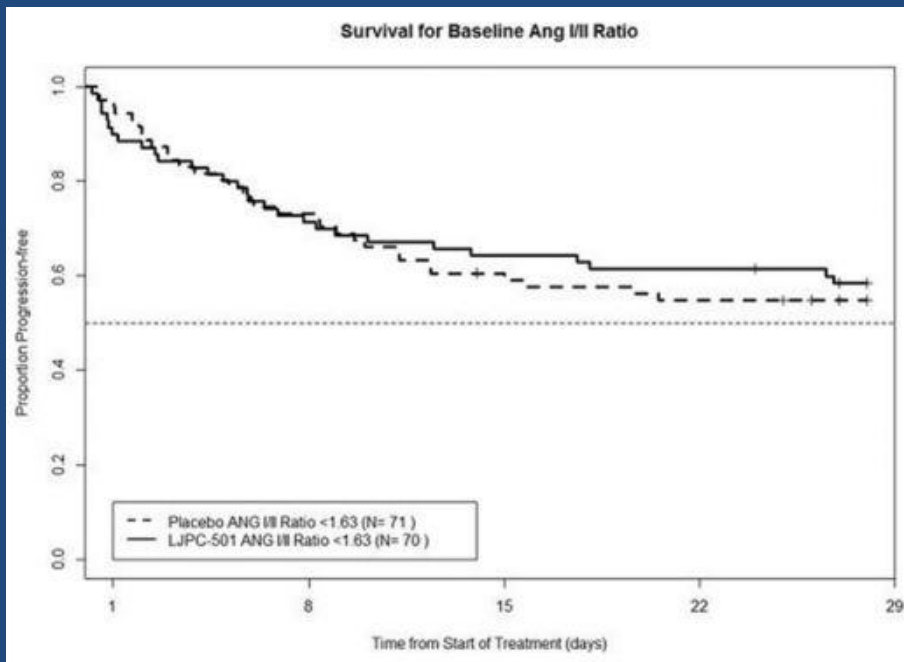
Patients with AKI and RRT at Study Drug Initiation



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

Patients with High AT1:AT2



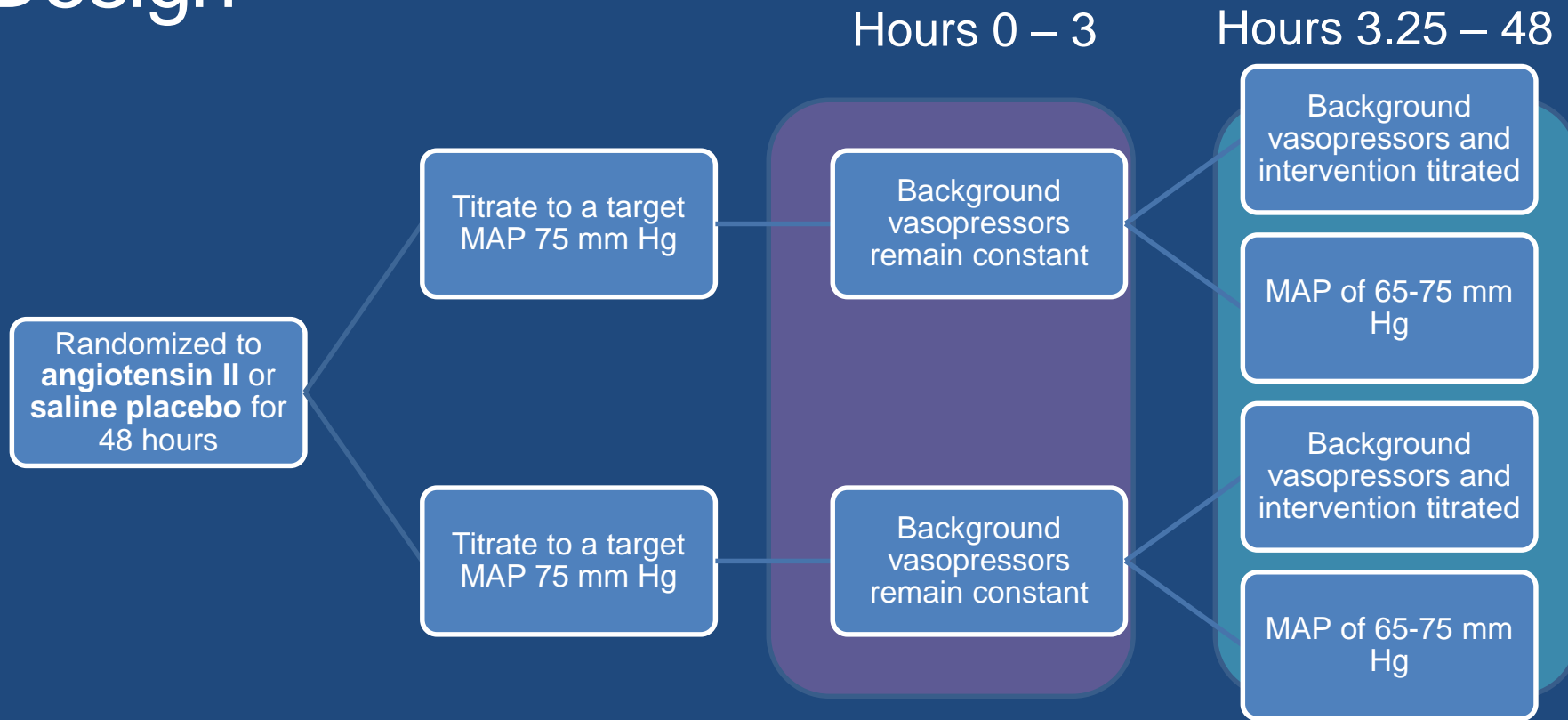
TAKEAWAY:

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

Angiotensin II: CON

(Unclear benefit/clear harm)

Design



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

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%)

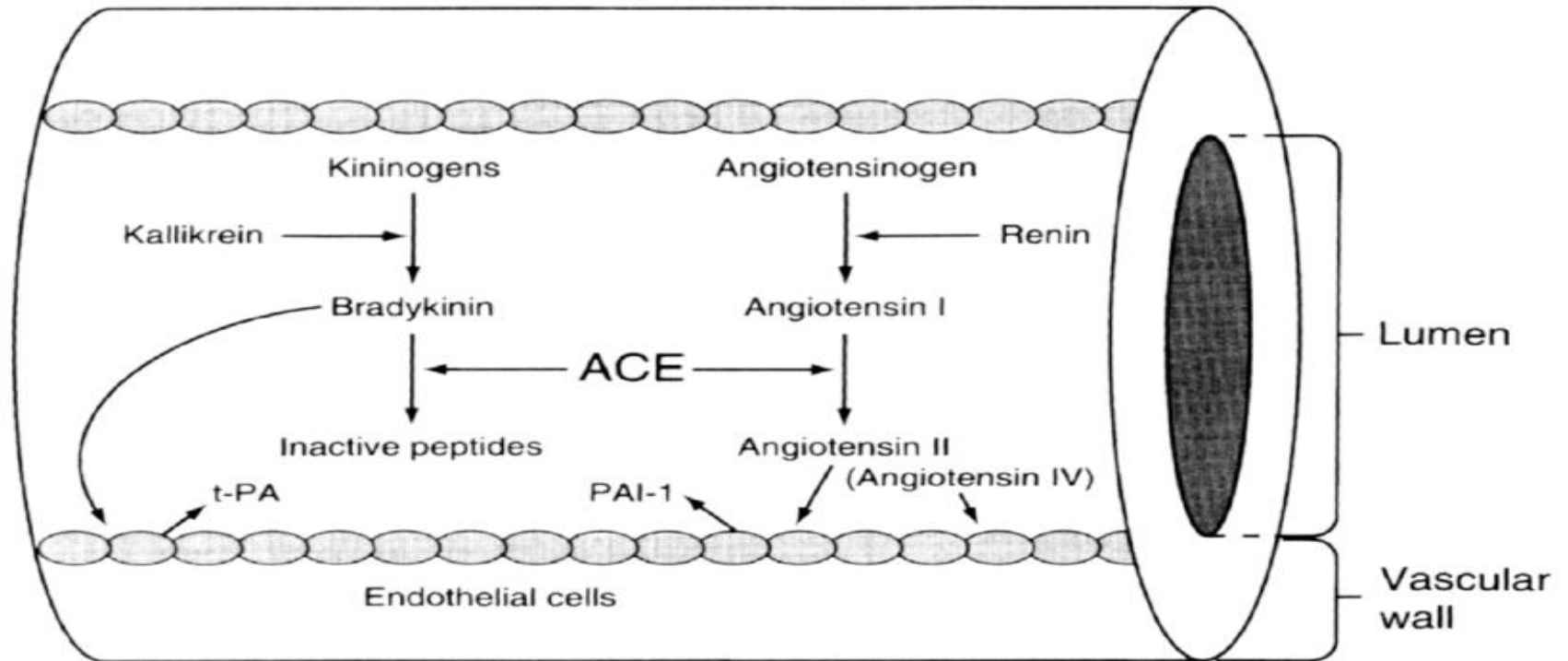
^a Including arterial and venous thrombotic events

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

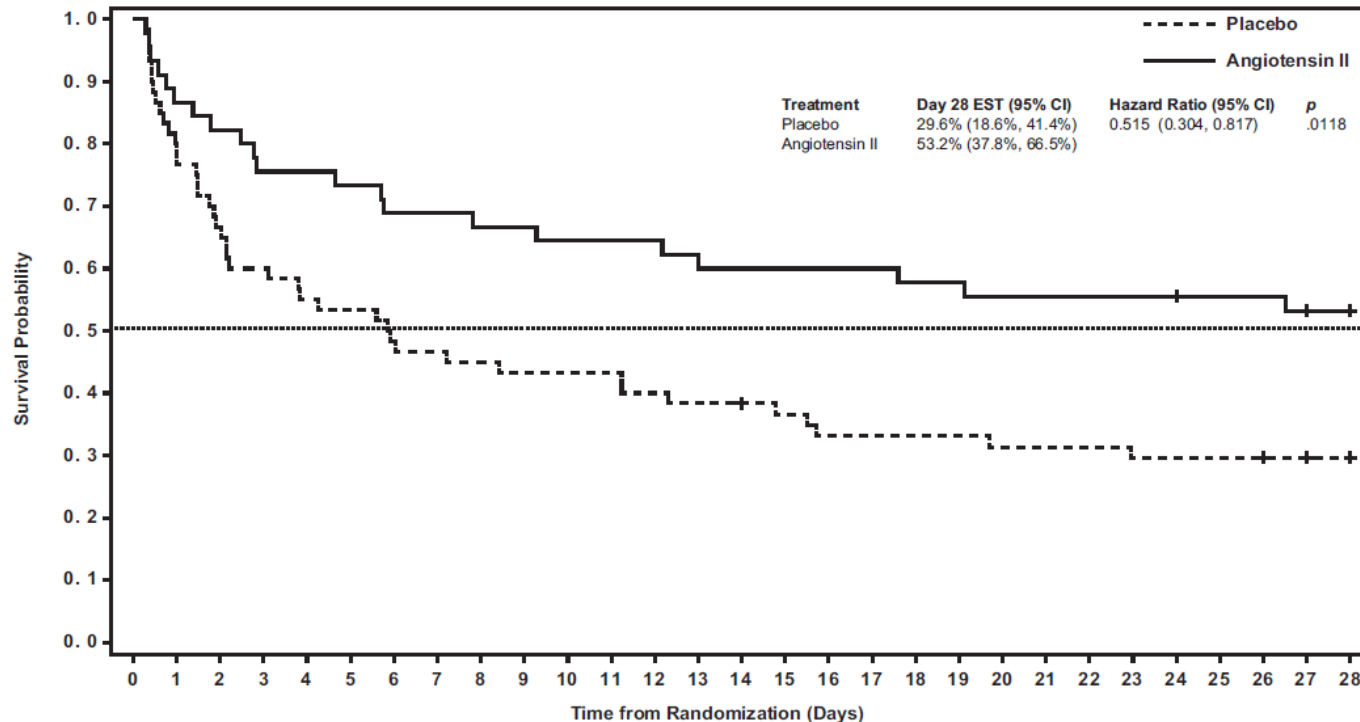
The Cardiovascular Divisions, Vanderbilt University Medical Center, and Nashville Veterans Affairs Medical Center, Nashville, Tennessee 37232



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



Characteristic	Acute Kidney Injury + Renal Replacement Therapy at Study Drug Initiation			p
	Placebo (n = 60)	Angiotensin II (n = 45)	All Patients (N = 105)	
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

Benefit with Blocking RAAS?

Original articles

Herz 2018 · 43:140–145
DOI 10.1007/s00059-017-4537-6
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Cardioprotective effects of irbesartan in polymicrobial sepsis

The role of the p38MAPK/NF-κB signaling
pathway

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

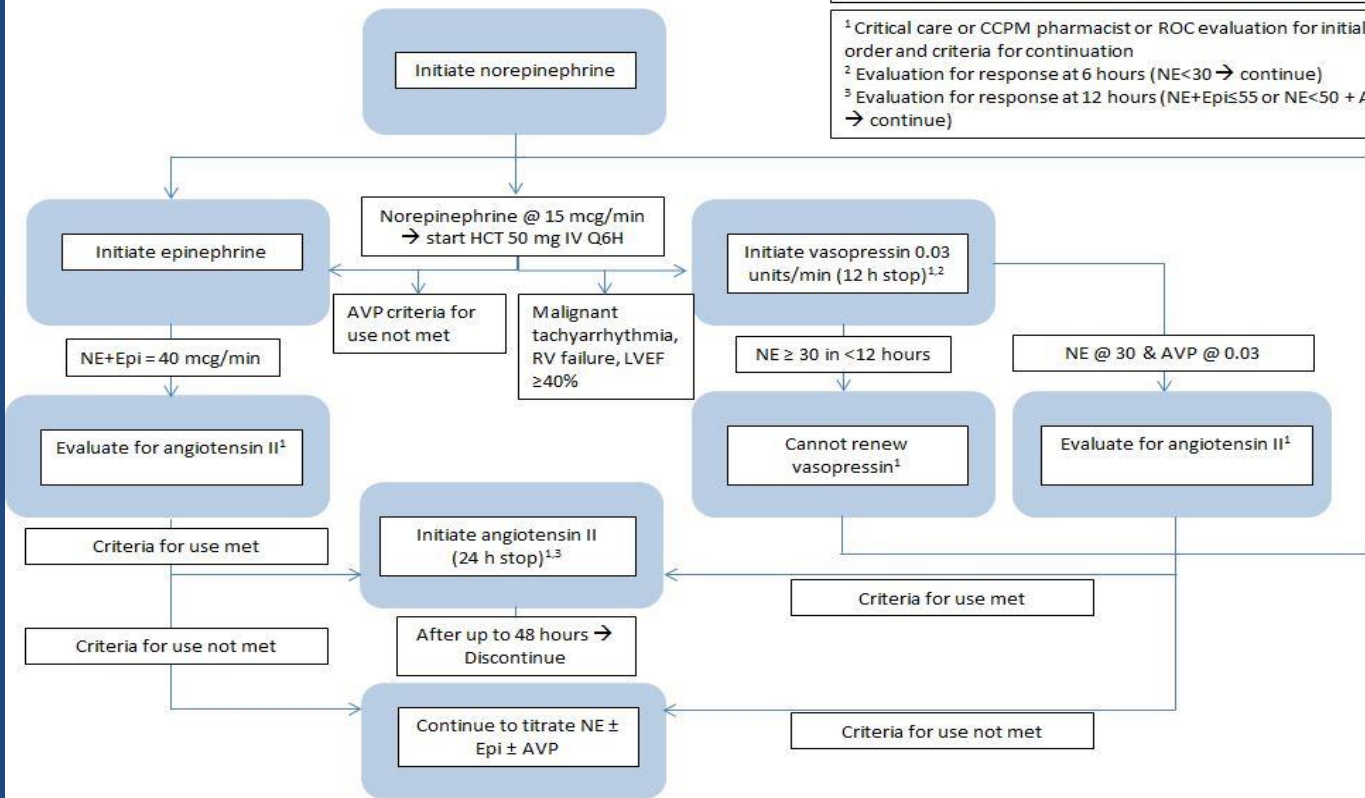
Angiotensin II criteria for us:

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)

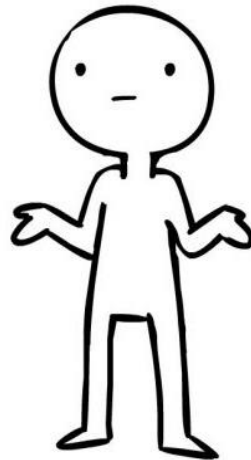
¹ Critical care or CCPM pharmacist or ROC evaluation for initial order and criteria for continuation

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
& hydrocortisone 50 mg
IV Q6H



Controversies in Septic Shock

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