Mass General Brigham

Vasopressors: how to choose and deliver

Jeremy R. DeGrado, PharmD, BCCCP
Clinical Pharmacy Manager
PGY2 Critical Care Pharmacy Residency Program Director
Brigham and Women's Hospital

Statement of Disclosures

- Consultant (Marinus Pharmaceuticals)

Learning Objectives

Describe the potential advantages and disadvantages of medications for hemodynamic support in patients with shock

Describe the role of various adjunctive therapies in patients with shock

Goals of resuscitation and hemodynamic support

Early achievement of patient-specific goals

Improve organ perfusion

Address underlying cause of shock

Goals and strategies are dependent on underlying pathophysiology

- Volume expansion vs. removal
- Cardiac function
- Peripheral vasodilation vs. vasoconstriction

Multimodal approach

Vasopressors – lowest possible dose for shortest possible duration

Rhodes A, et al. *Crit Care Med.* 2017; (43)3:304-377
Evans L, et al. *Crit Care Med* 2021;49(11):e1063-e1143
McIntyre WF, et al. *JAMA* 2018;319:1889-1900
Laghlam et al. Ann Intensive Care 2024

Differential Diagnosis of Shock Based on Hemodynamic Parameters

	Pump Function	Preload	Afterload	Tissue Perfusion
	Cardiac Index (CI) (2.5-4.7 L/min/m^2)	PCWP (8-12 mm Hg)	SVR (800-1400 dynes.sec/cm^5)	Mixed S_vO2 (≥ 65%)
Distributive Shock	**High**	**Low**	**Low**	**Low**
Hypovolemic Shock	**Normal**	**Low**	**Normal**	**Low**
Cardiogenic Shock	**Low**	**High**	**High**	**Low**

PCWP = pulmonary capillary wedge pressure
SVR = systemic vascular resistance

Massaro AF. Approach to the Patient with Shock. Chapter 296. Pp 2039-2043. In: Jameson JL et al, eds. *Harrison's Principles of Internal Medicine,* 20th ed. New York, NY: McGraw-Hill; 2018.
Vincent JL et al. *N Engl J Med*. 2013;369:1726-1734.

Target Receptor Effects

Catecholamine

Alpha-1 (agonists)
- Vascular smooth muscle
  - Vasoconstriction

Beta-1 (agonists)
- Positive inotropy

Beta-2 (agonists)
- Vasodilation

Dopamine (DA) (agonists)
- Renal, mesenteric, coronary beds
  - Vasodilation of renal vasculature

Non-catecholamine

Vasopressin I (agonists)
- Vascular smooth muscle
  - Vasoconstriction

Phosphodiesterase III inhibitor (antagonists)
- Positive inotropy
- Vasodilation

Angiotensin II, type 1 (agonists)
- Vascular smooth muscle
  - Vasoconstriction

Hollenberg SM. *Crit Care Clin*. 2009;25:781-802.
Russell JA. *Intensive Care Med*. 2019;45(11):1503-1517.

Agent	Receptors	Preload	HR	SV	CO	Afterload
Phenylephrine	α_1	↔ or ↑	↔ or ↓	↔	↔ or ↓	↑
Norepinephrine	$\alpha_1 > \beta_1$	↔ or ↑	↔ or ↑	↔ or ↑	↔ or ↑	↑
Dopamine	$\beta_1 > \alpha_1$	↔ or ↑	↑	↑	↑	↑
Epinephrine	$\alpha_1 = \beta_1$	↔ or ↑	↑	↑	↑	↑
Vasopressin	V_1R, V_2R	↔ or ↑	↓	↔	↔	↑
Angiotensin II	AT-R1, AT-R2	↔ or ↑	↑	↔	↔	↑
Dobutamine	$\beta_1 > \beta_2$	↔ or ↓	↑	↑	↑	↔ or ↓
Milrinone	PDE III Inhib	↔ or ↓	↔ or ↑	↑	↑	↓

Resuscitation goals and vasopressor selection / dosing

2019 European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma

Recommendations to manage blood pressure:

- Restricted volume replacement strategy to achieve target blood pressure until bleeding can be controlled (Grade 1B)
- **Initial phase, no brain injury: Permissive hypotension is recommended with a target systolic blood pressure of 80-90mmHg (mean arterial pressure 50-60 mm Hg) until initial major bleeding has been stopped (Grade 1C)**
- **Severe traumatic brain injury (Glasgow Coma Scale score ≤ 8): Maintain MAP ≥ 80 mm Hg (Grade 1C)**
- **Life-threatening hypotension: Administer vasopressors in addition to fluids to maintain target arterial pressure (Grade 1C)**
- Myocardial dysfunction: Inotropic infusion is recommended (Grade 1C)

Spahn DR et al. *Crit Care.* 2019;23(1):98.

2021 Update to European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

- IV loop diuretics (I, LOE C)
- **Inotropic agents may be considered for those w/ an SBP <90mmHg and evidence of hypoperfusion (IIb, LOE C)**
- **A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock to increase blood pressure and organ perfusion (IIB, LOE B)**
- Short-term MCS should be considered with cardiogenic shock as BTR, BTD, BTB. (IIa, LOE C)
- IABP is not routinely recommended in post-MI cardiogenic shock (III, LOE B)

McDonagh TA et al. *Eur Heart J*. 2021;42:3599-3726.
Seferovic PM et al. *Eur J Heart Fail*. 2019 Oct; 21(10):1169-1186.

2022 Clinical Expert Consensus Statement on the Classification of Cardiogenic Shock

Description	Physical exam/bedside findings	Biochemical markers	Hemodynamics
Stage A: At risk			
Not currently experiencing signs or symptoms of CS, but at risk (e.g. large acute MI, acute on chronic heart failure)	Normal JVP, clear lungs, warm and well perfused	Normal labs (e.g. renal function and normal lactic acid)	Normotensive • CI ≥2.5 • CVP <10 • PA sat ≥65%
Stage B: Beginning			
Clinical evidence of relative hypotension or tachycardia without hypoperfusion	-Elevated JVP -Rales in lungs -Warm and well perfused	-Normal lactate -Minimal renal function impairment -Elevated BNP	• SBP <90 or MAP <60 or >30 mmHg drop from baseline • Pulse ≥ 100 bpm • CI ≥ 2.2 • PA sat ≥ 65%
Stage C: Classic			
Hypoperfusion requiring intervention (inotrope, pressor, mechanical support) beyond volume resuscitation to restore perfusion Typically present with relative hypotension	-Looks unwell -Ashen, mottled, dusky -Volume overload -Extensive rales -Killip class 3 or 4 -BiPap or MV -Cold, clammy -Acute alterations in metal status -Urine output < 30 mL/hr	May include any: -Lactate ≥ 2 -Creatinine doubling or -Increasing LFTs -Elevated BNP#	Any of: • SBP <90 mmHg OR MAP <60 mmHg OR >30 mmHg drop from baseline AND drugs/device used to maintain BP Hemodynamics • CI <2.2, PCWP >15, RAP/PCWP ≥0.8, PAPI <1.85, cardiac power output ≤0.6

CS = Cardiogenic shock, MI = Myocardial infraction, JVP = Jugular venous pressure, LFT = Liver function tests, MV = Mechanical ventilation, BNP = Brain natriuretic peptide, CPR = Cardiopulmonary resuscitation, ECMO = Extracorporeal membrane oxygenation

Naidu SS et al. *JACC* 2022;79;9:933-946.

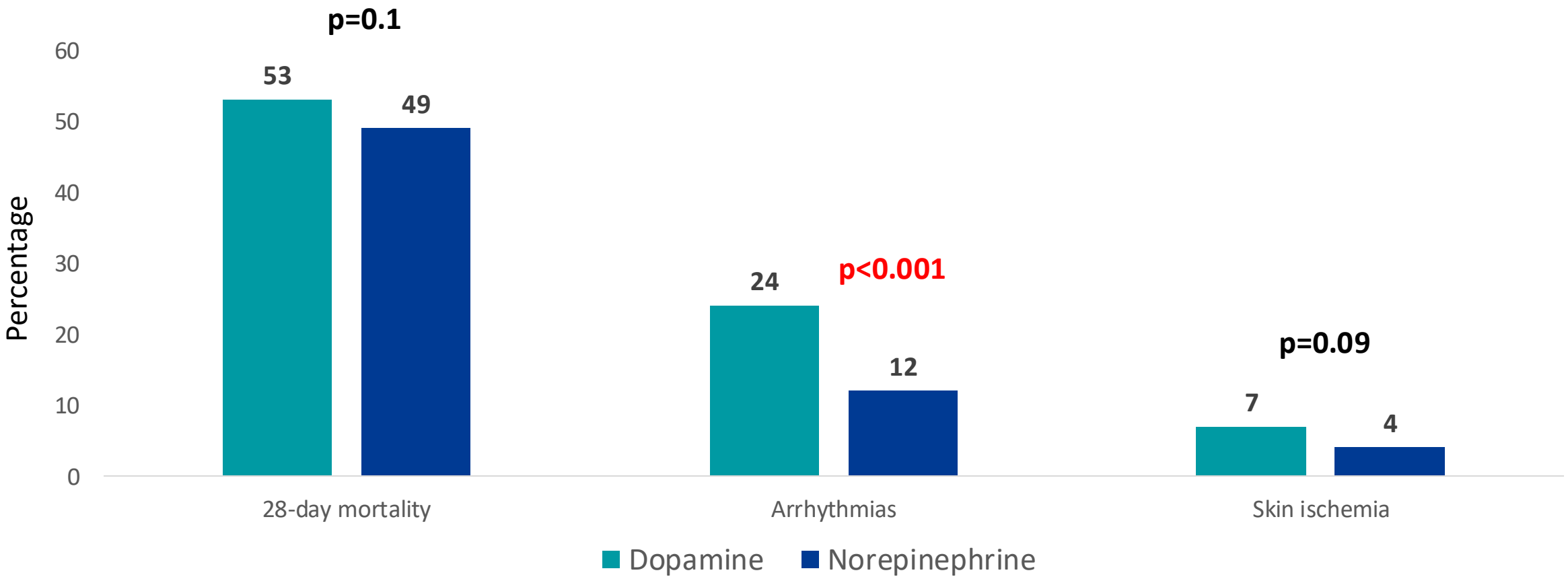
2022 Clinical Expert Consensus Statement on the Classification of Cardiogenic Shock

Description	Physical exam/bedside findings	Biochemical markers	Hemodynamics
Stage D: Deteriorating			
Similar to category "C" but are getting worse	Any stage "C"	Any Stage "C" and deteriorating	Any Stage C and requiring multiple pressors or additional mechanical circulatory support
Stage E: Extremis			
Cardiac arrest with ongoing CPR and/or ECMO, being supported by multiple interventions	Near Pulselessness Cardiac collapse MV Defibrillator used	-CPR -pH ≤ 7.2 -Lactate ≥ 8	• No SBP without resuscitation • PEA or refractory VT/VF • Hypotension despite maximal support

CS = Cardiogenic shock, MI = Myocardial infraction, JVP = Jugular venous pressure, LFT = Liver function tests, MV = Mechanical ventilation, BNP = Brain natriuretic peptide, CPR = Cardiopulmonary resuscitation, ECMO = Extracorporeal membrane oxygenation

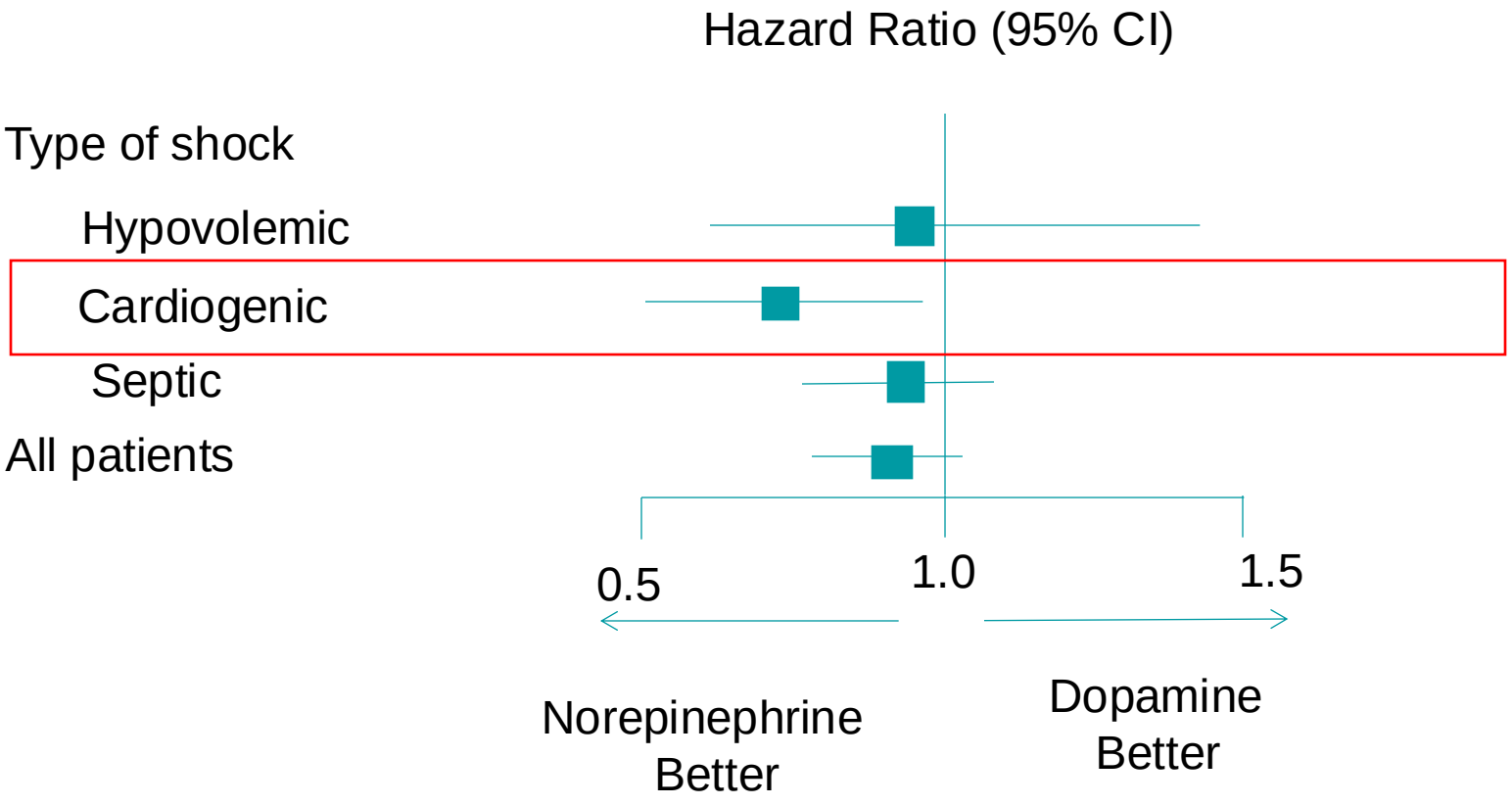
Naidu SS et al. *JACC* 2022;79;9:933

Norepinephrine vs. Dopamine in shock



De Backer D, et al. *N Engl J Med.* 2010;362:779-789.

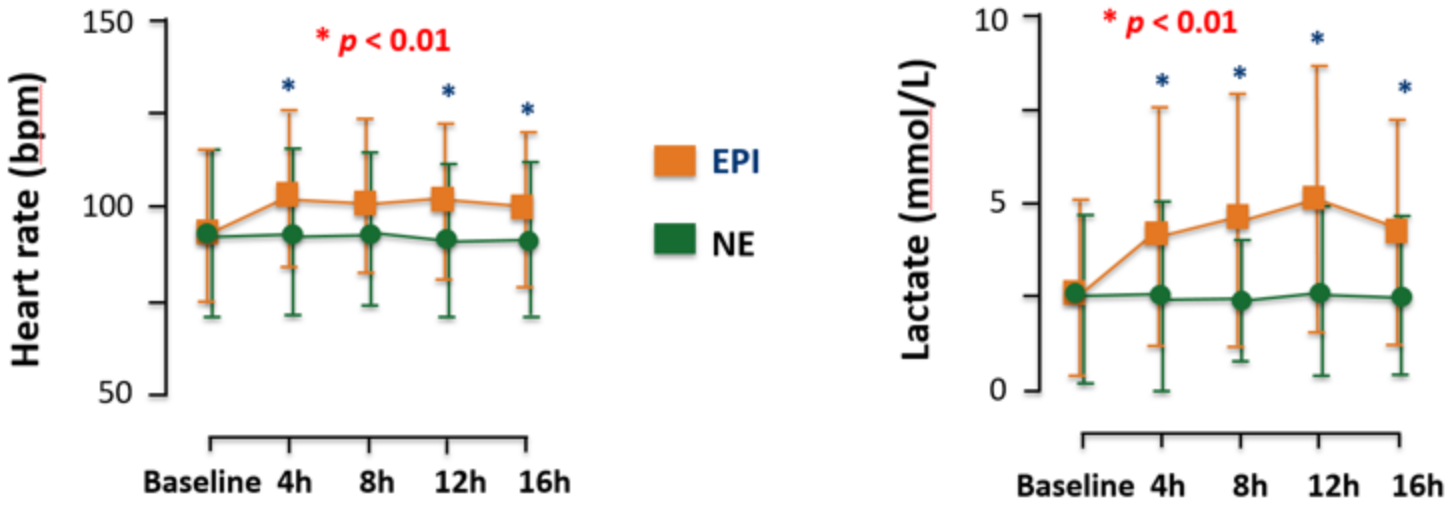
28-day mortality of Dopamine vs. Norepinephrine based on type of shock



De Backer D et al. *N Engl J Med*. 2010; 362:779-89.

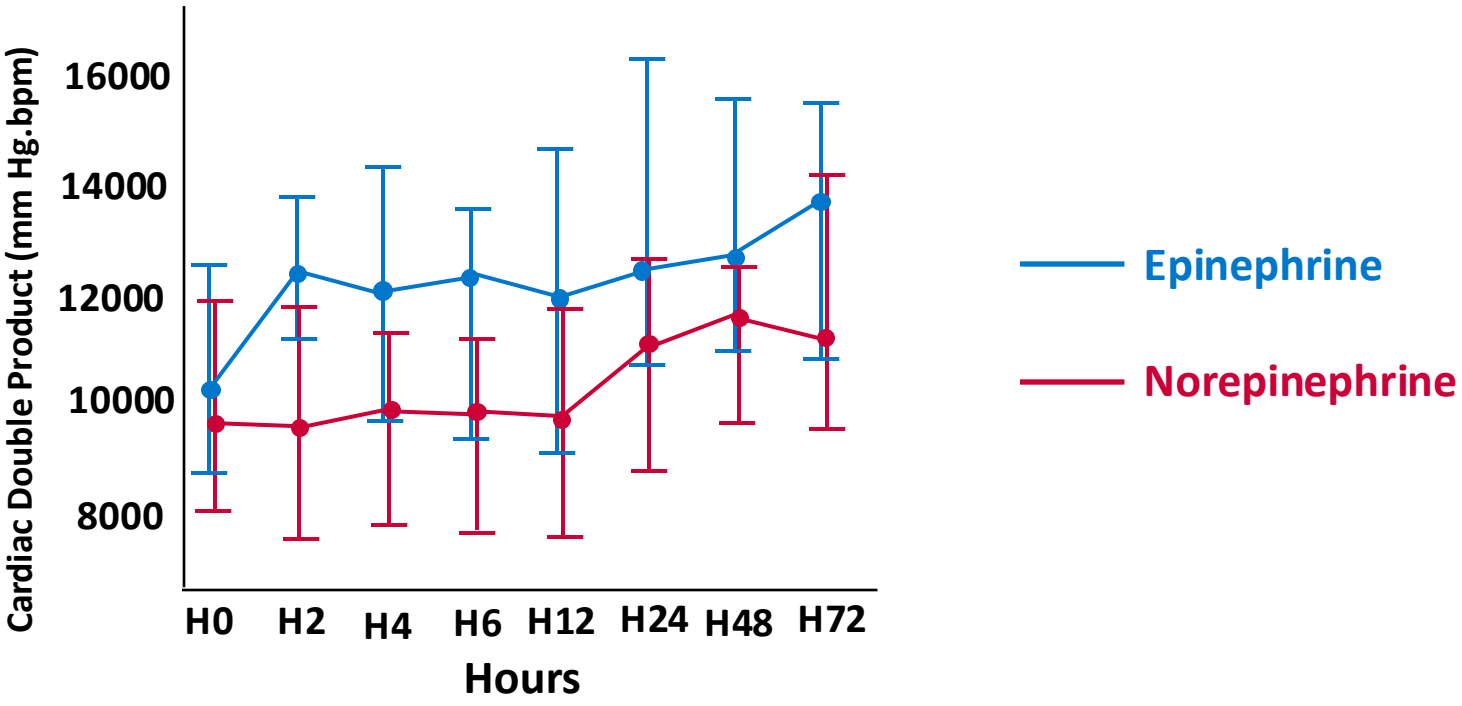
Norepinephrine vs. Epinephrine – CAT Study

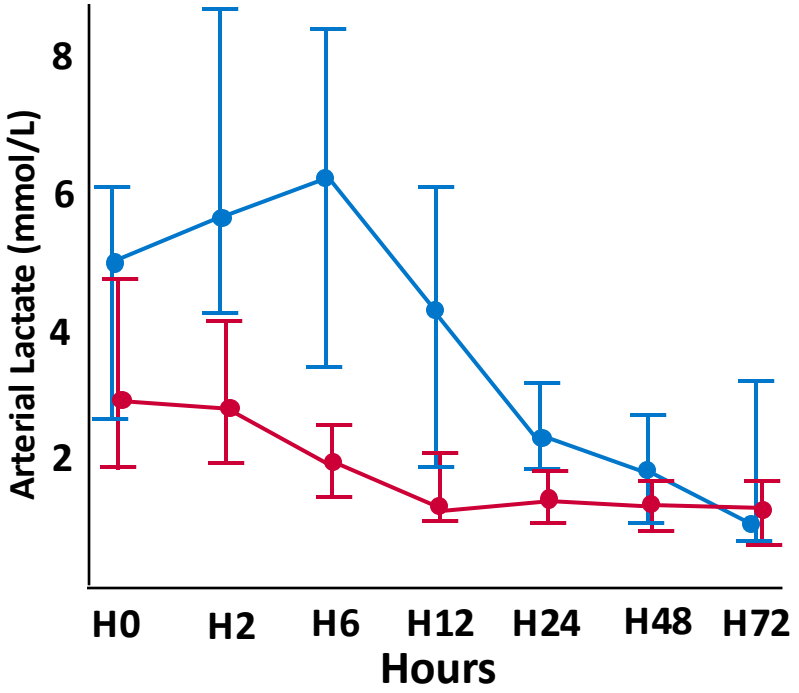
Variable	Epinephrine (n=139)	Norepinephrine (n=138)	p value
Time to MAP goal, min (median)	35.1	40	0.26
Vasopressor-free days	26	25.4	0.31
Study drug discontinued, n (%)	18 (12.9)	4 (2.8)	0.002
Day 28 mortality	31 (22.5)	36 (26.1)	0.48
Day 28 mortality, sepsis	17 (22.4)	24 (29.3)	0.32
Day 28 mortality, acute circulatory failure	15 (23.4)	17 (27)	0.65



Myburgh JA, et al. *Intensive Care Med*. 2008; 34:2226-2234

Epinephrine vs. Norepinephrine in Cardiogenic Shock

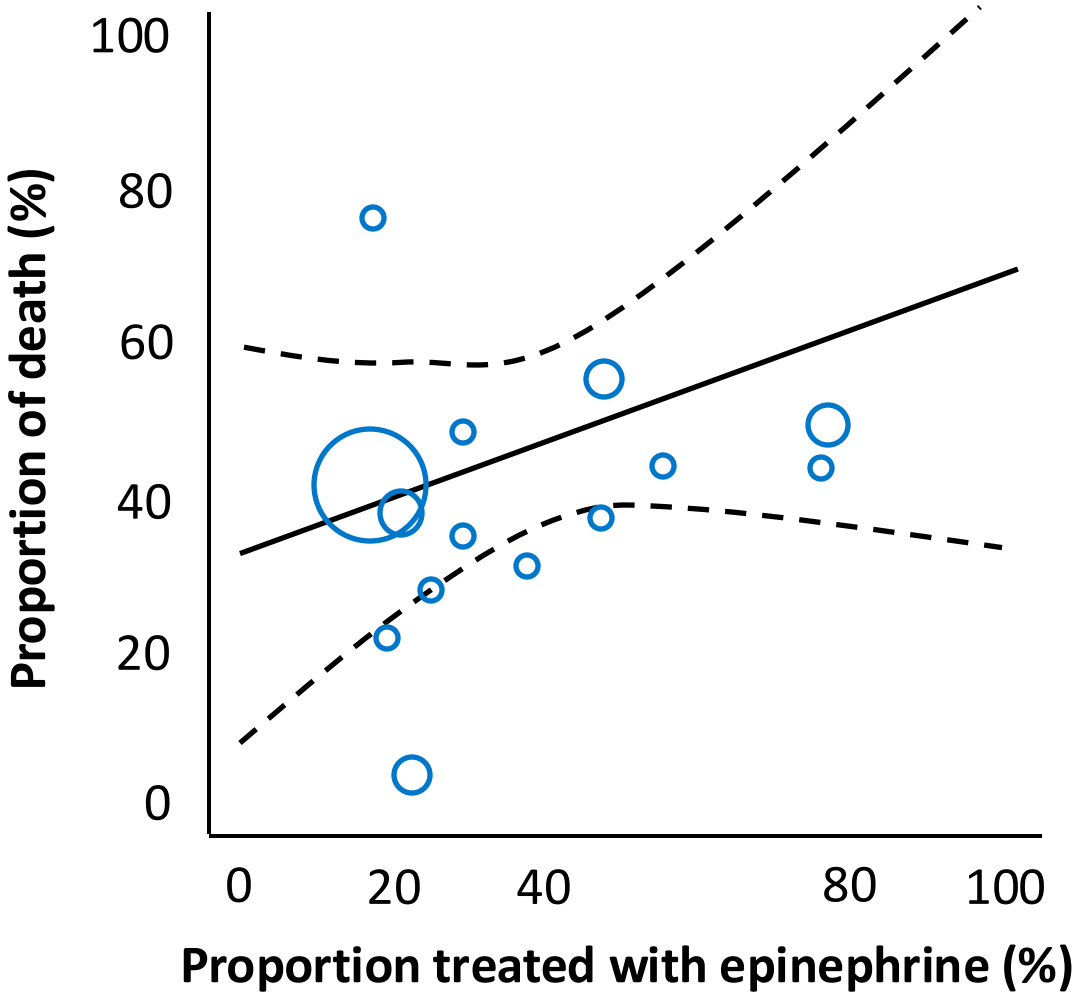




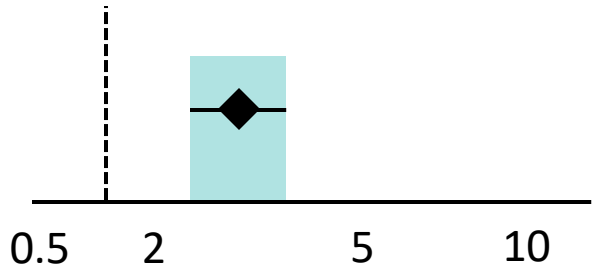
Variable	Epinephrine (n=27)	Norepinephrine (n=30)	p value
Refractory shock	10 (37)	2 (7)	0.008
Arrhythmia	11 (41)	10 (33)	0.59
Death w/in 7 days	8 (30)	3 (10)	0.093
Death w/in 28 days	13 (48)	8 (27)	0.11

Levy B et al. J Am Coll Card 2018;7(2):173-182

Epinephrine in Cardiogenic Shock – Meta-analysis



	No. of patients	No. of patients (EPI)	OR for short-term mortality [95% CI]
All studies	2583	947	3.33 [2.81 – 3.94]



Leopold V, et al. Intensive Care Med 2018;44(6):847-56

DOREMI

Randomized, double-blind, single center trial comparing dobutamine to milrinone in cardiogenic shock (n=192)

Primary endpoint: in-hospital death from any cause, resuscitated cardiac arrest, receipt of cardiac transplant or mechanical circulatory support non-fatal MI, TIA/stroke, RRT

- No difference in either treatment, p=0.47

Secondary endpoint: duration on inotropes, LOS, AKI and normalization of lactate

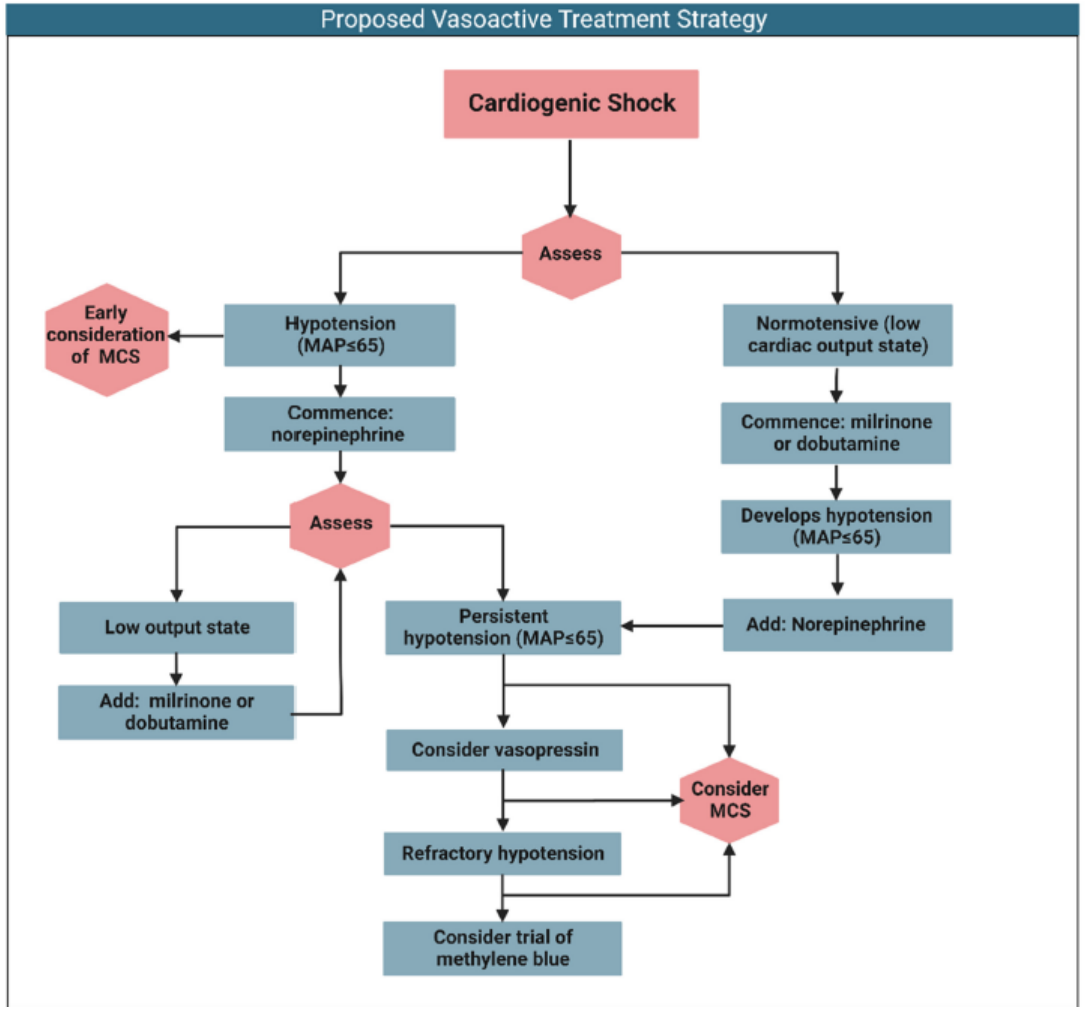
- No differences in either treatment

Safety: Sustained hypotension, ventricular or atrial arrhythmias, or need for antiarrhythmics, additional cardiac support

- No differences in either treatment

Mathew R et al. *N Engl J Med*. 2021;385: 516-525

Approach to vasoactive therapy in cardiogenic shock



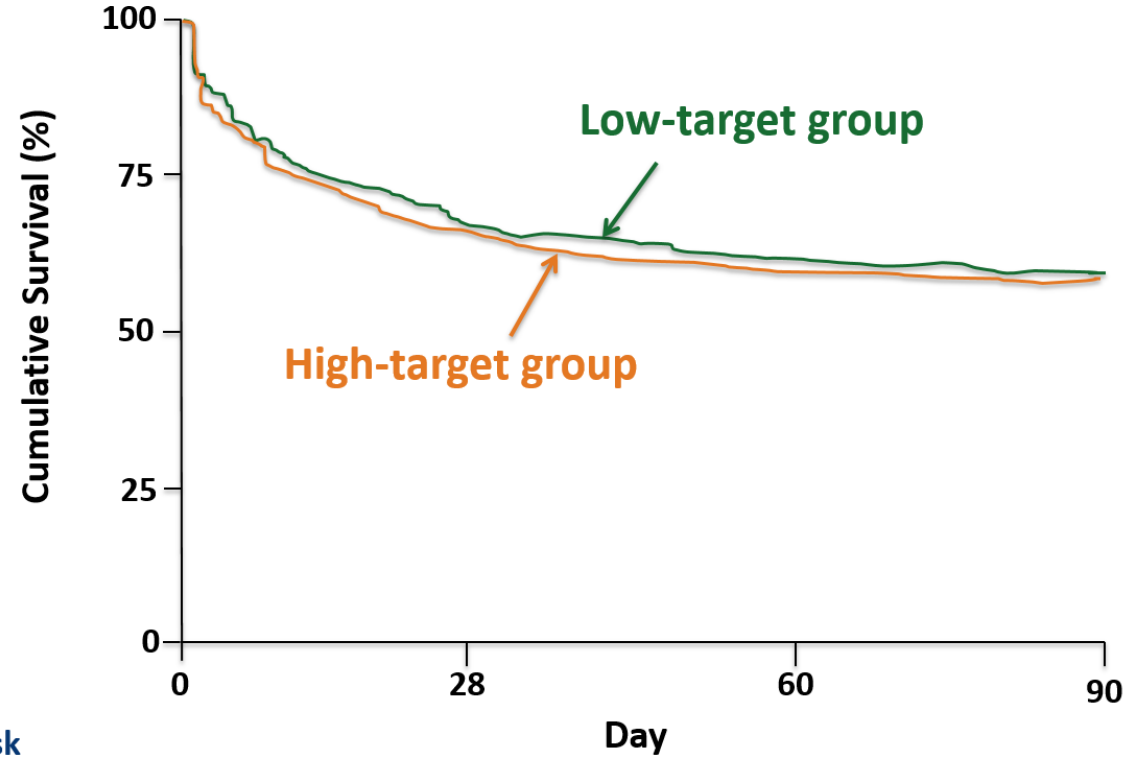
Bloom JE, et al. J Am Heart Assoc 2023;12:e029787

Surviving Sepsis Campaign: Initial Resuscitation

- Sepsis and septic shock are medical emergencies, and treatment should begin immediately - best practice statement (BPS)
- Fluid recommendations:
  - 30 mL/kg of IV crystalloid fluid be given within first 3 hours of sepsis-induced hypoperfusion - weak recommendation, low quality of evidence (QOE)
  - Dynamic variables be used in lieu of static variables to predict fluid responsiveness where available – weak recommendation, low QOE
- Initial target MAP of 65 mm Hg in septic shock requiring vasopressors – strong recommendation, moderate QOE
- Guiding resuscitation to normalize lactate when lactate is elevated – weak recommendation, low QOE

Evans L et al. *Crit Care Med*. 2021;49:e1063-1143.
Rhodes A et al. *Crit Care Med*. 2017;45(3):486-552.

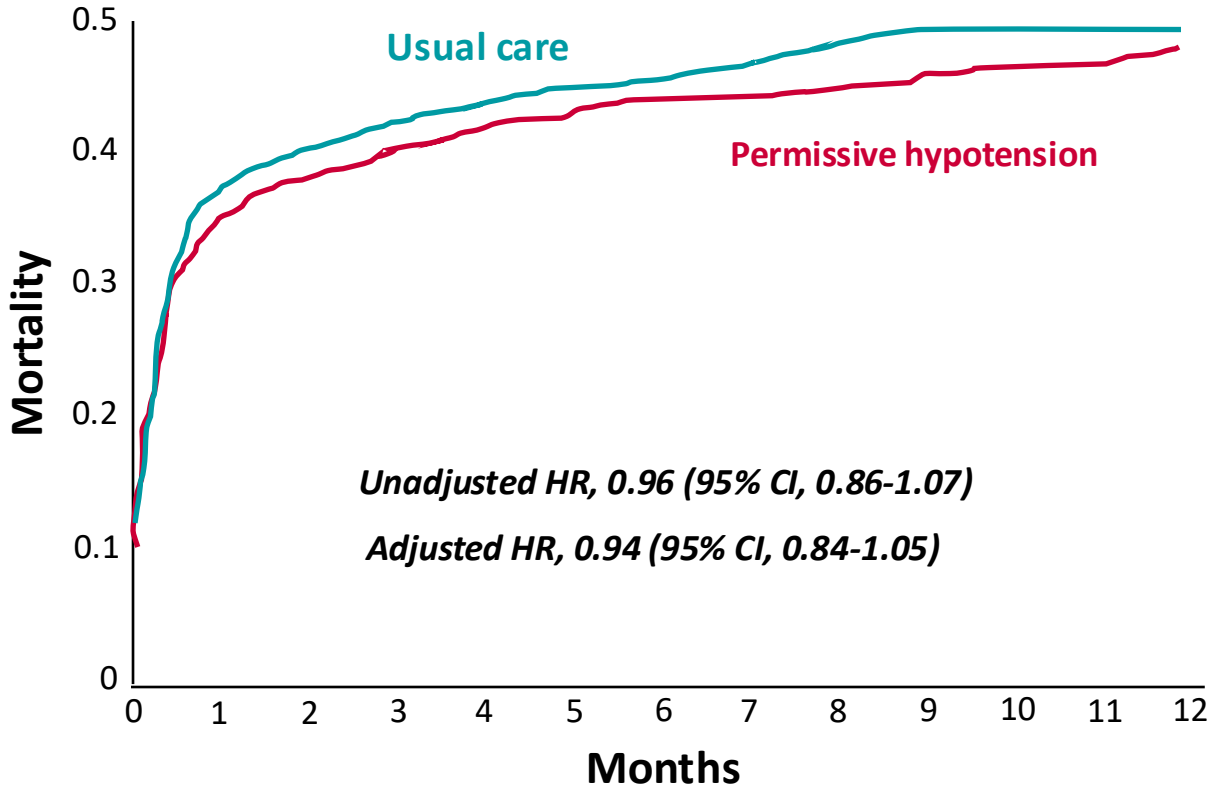
SEPSISPAM



No. at risk				
Low target	379	256	233	225
High target	375	249	227	219

Asfar P, et al. *N Engl J Med.* 2014; 370:1583-1593
Demiselle J, et al. Crit Care Med 2021;49:e412-422

65 Trial

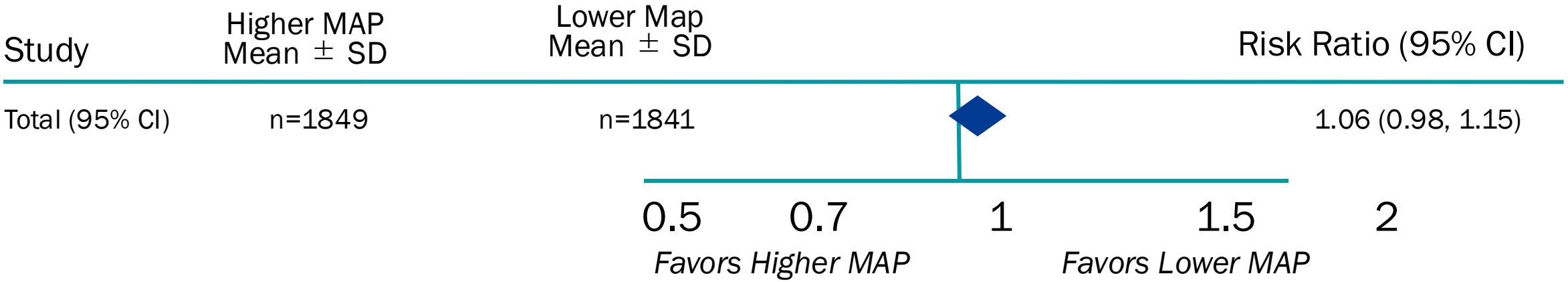


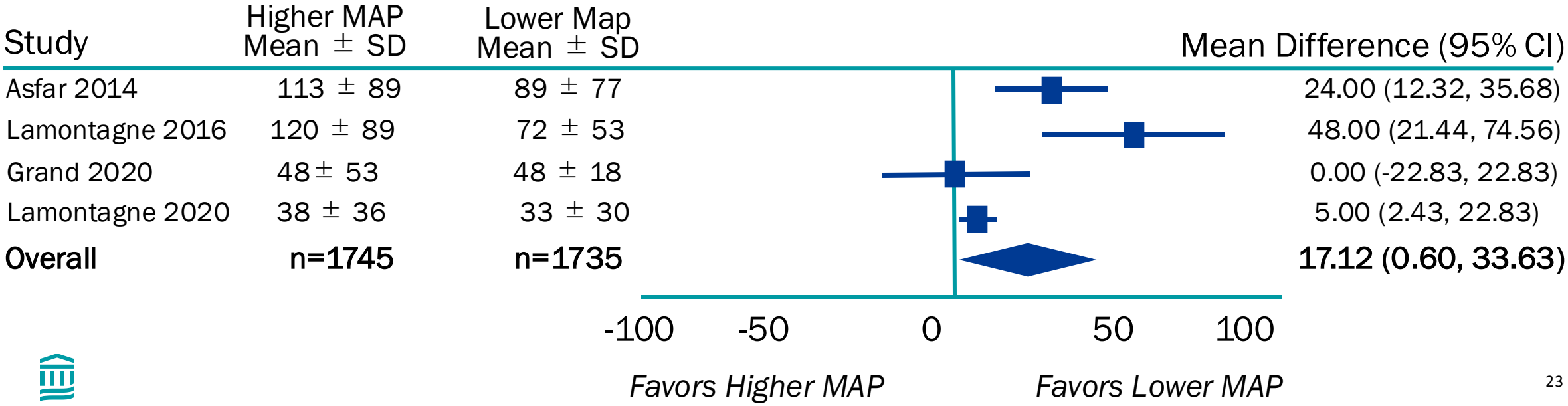
No. at risk

Permissive hypotension	1283	794	743	721	699	667	631	596	545	509	480	442	409
Usual Care	1300	772	727	697	677	642	604	569	525	489	459	435	395

Lamontagne F et al. *JAMA* 2020;323(10):938-949.

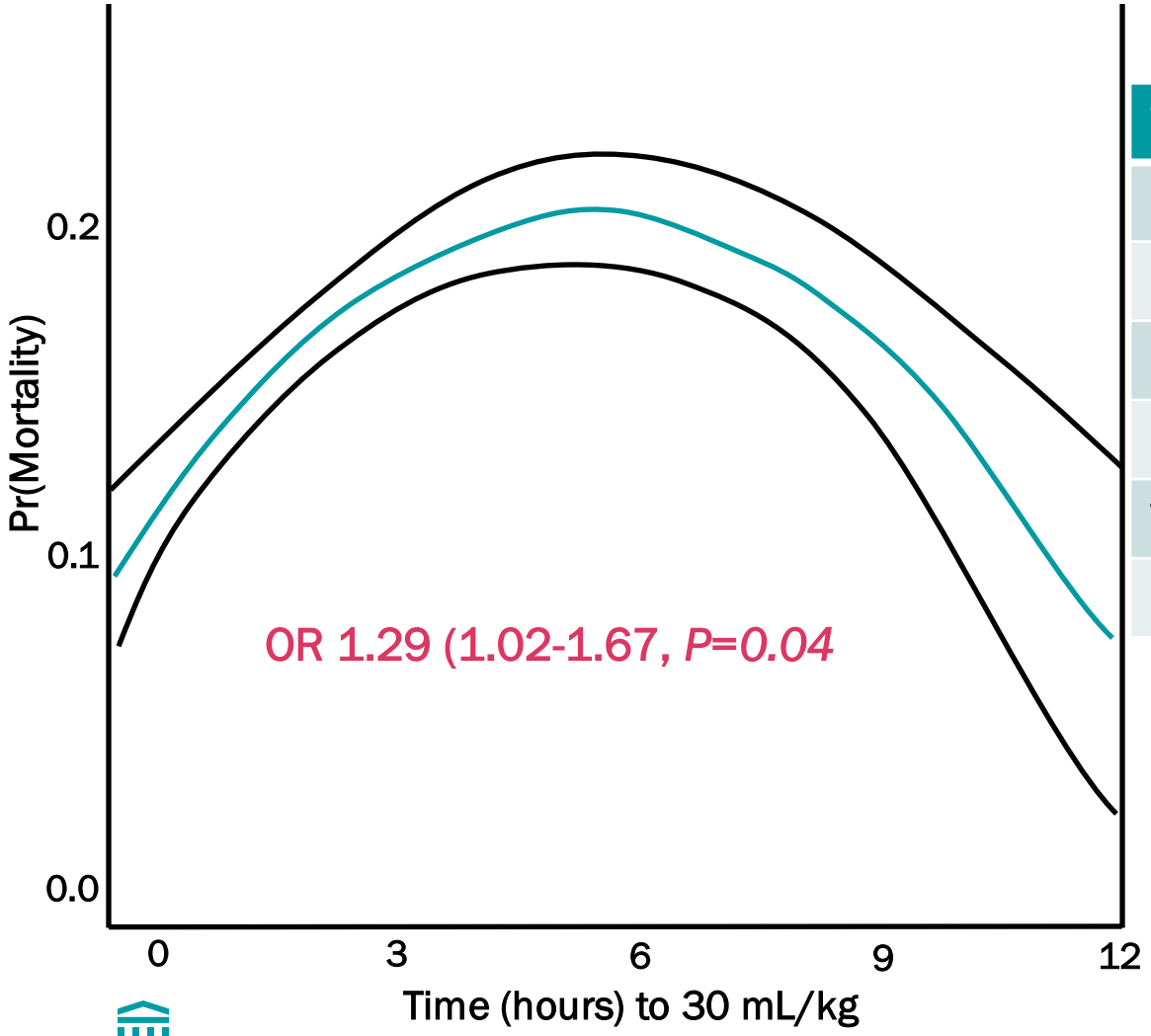
“High” vs. “Low” Targets





Carayannopolous KL, et al. *Crit Care Med* 2023;51(2):241-253

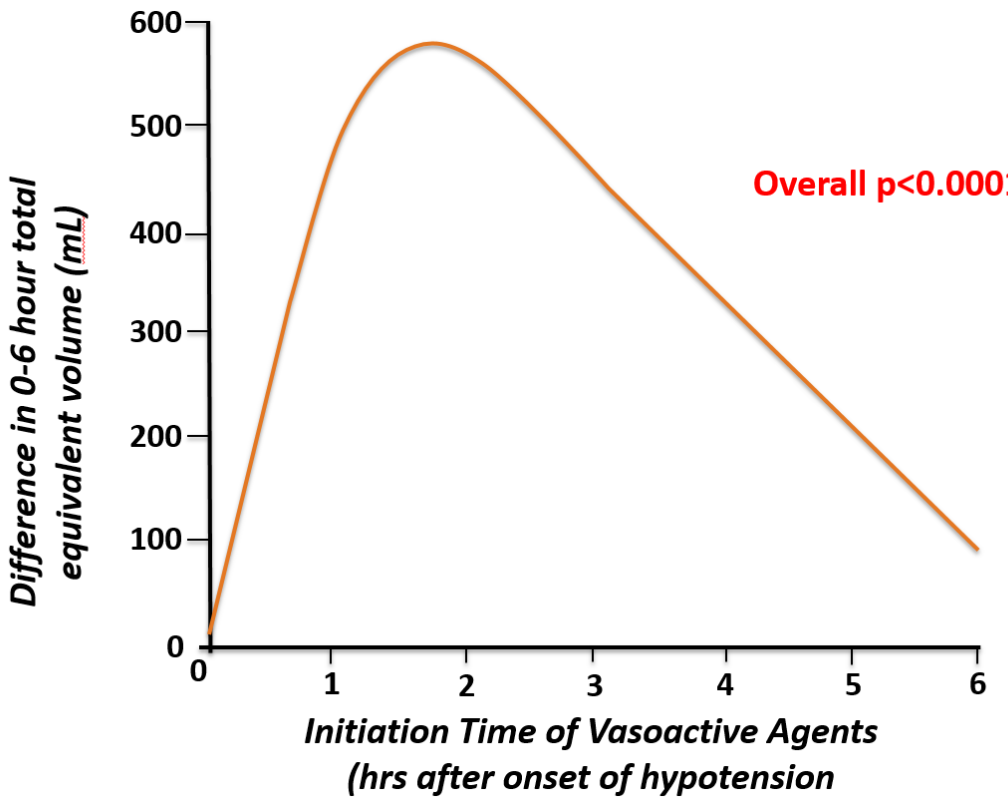
Early fluid resuscitation

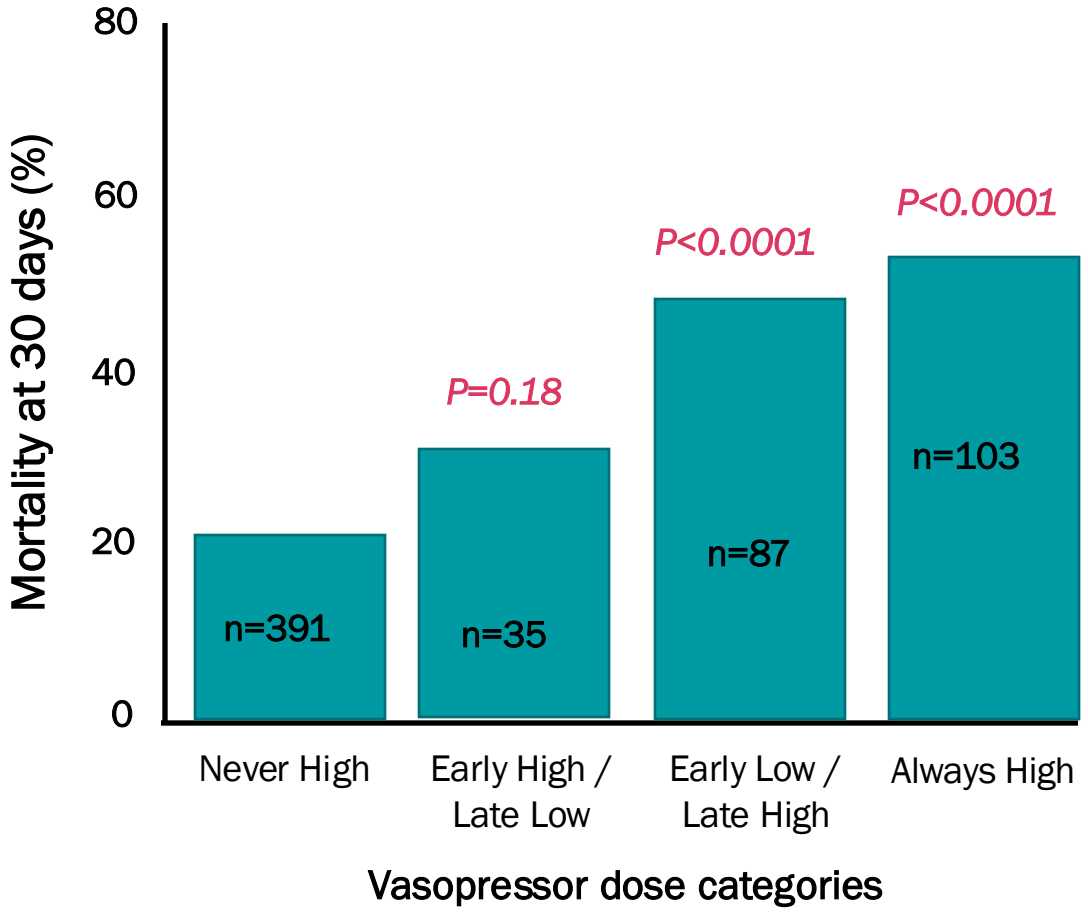


Variable	OR	95% CI	P value
30 mL/kg by 1-3 h	1.11	0.62-2.01	0.74
30 mL/kg by 3-6 h	1.83	0.97-3.52	0.06
30 mL/kg by 6-24 h	1.51	0.75-3.06	0.25
30mL/kg not by 24h	2.69	1.37-5.37	0.004
Time to antibiotics, h	1.02	0.97-1.07	0.34
Lactic acid, mmol/L	1.17	1.11-1.24	<0.001

Kuttab HI, et al. *J Intensive Care Med* 2023;38(11):1051-1059

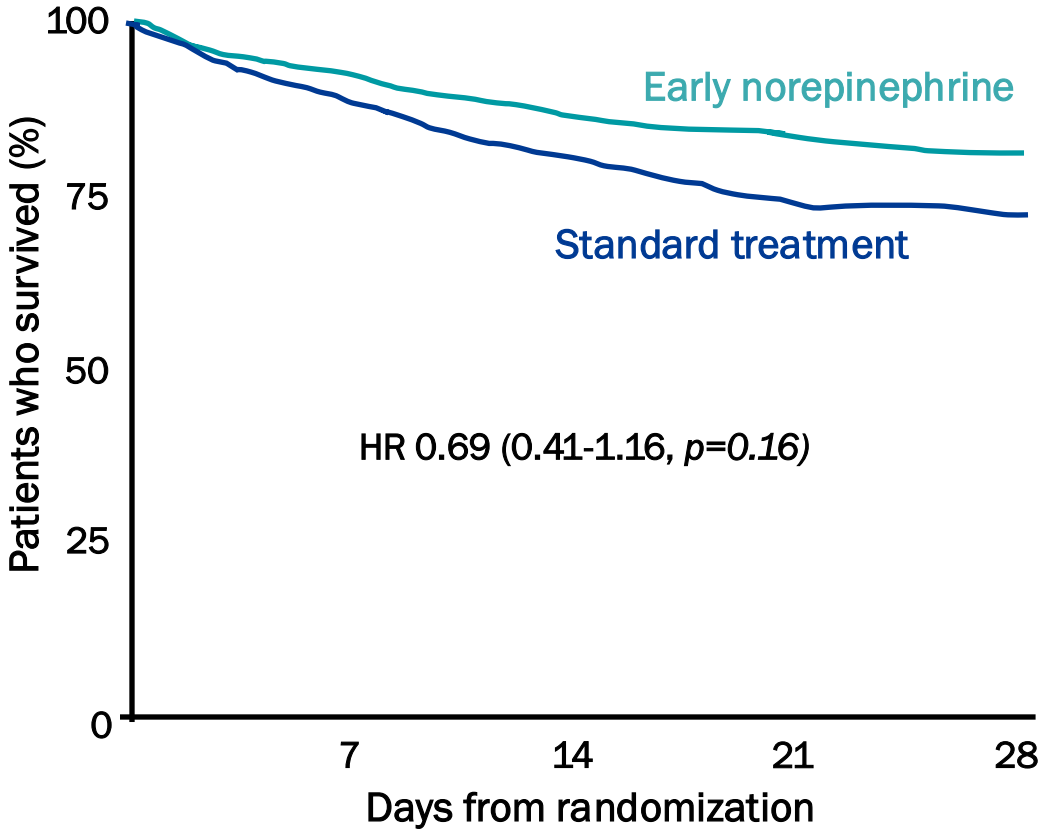
Fluid Administration and Vasopressor Initiation





Waechter J, et al. *Crit Care Med*. 2014; 42:2158-2168
Roberts RJ, et al. *Crit Care Med* 2020; 48(10):1445-1453

Early Norepinephrine in septic shock (CENSER)



	Early NE (n=155)	Standard (n=155)	OR (95% CI)	p value
Age, y*	65	68		
APACHE II*	21	20		
ICU LOS, d*	2	1		0.57
Hospital LOS, d*	10	10		0.37
Target MAP + perfusion at 6h$^{\alpha}$	118 (76.1)	75 (48.4)	3.4 (2.1-5.6)	<0.001
28-day mortality	24 (15.5)	34 (21.9)	0.79 (0.53-1.11)	0.15
Hospital mortality	35 (22.6)	38 (24.5)	0.95 (0.72-1.24)	0.69

* Median; $^{\alpha}$ n (%)

Permpikul C, et al. *Am J Respir Crit Care Med* 2019;199(9):1097-1105

SSC Guidelines – Vasopressors and Adjunctive Therapies

2021

Strong Recommendations

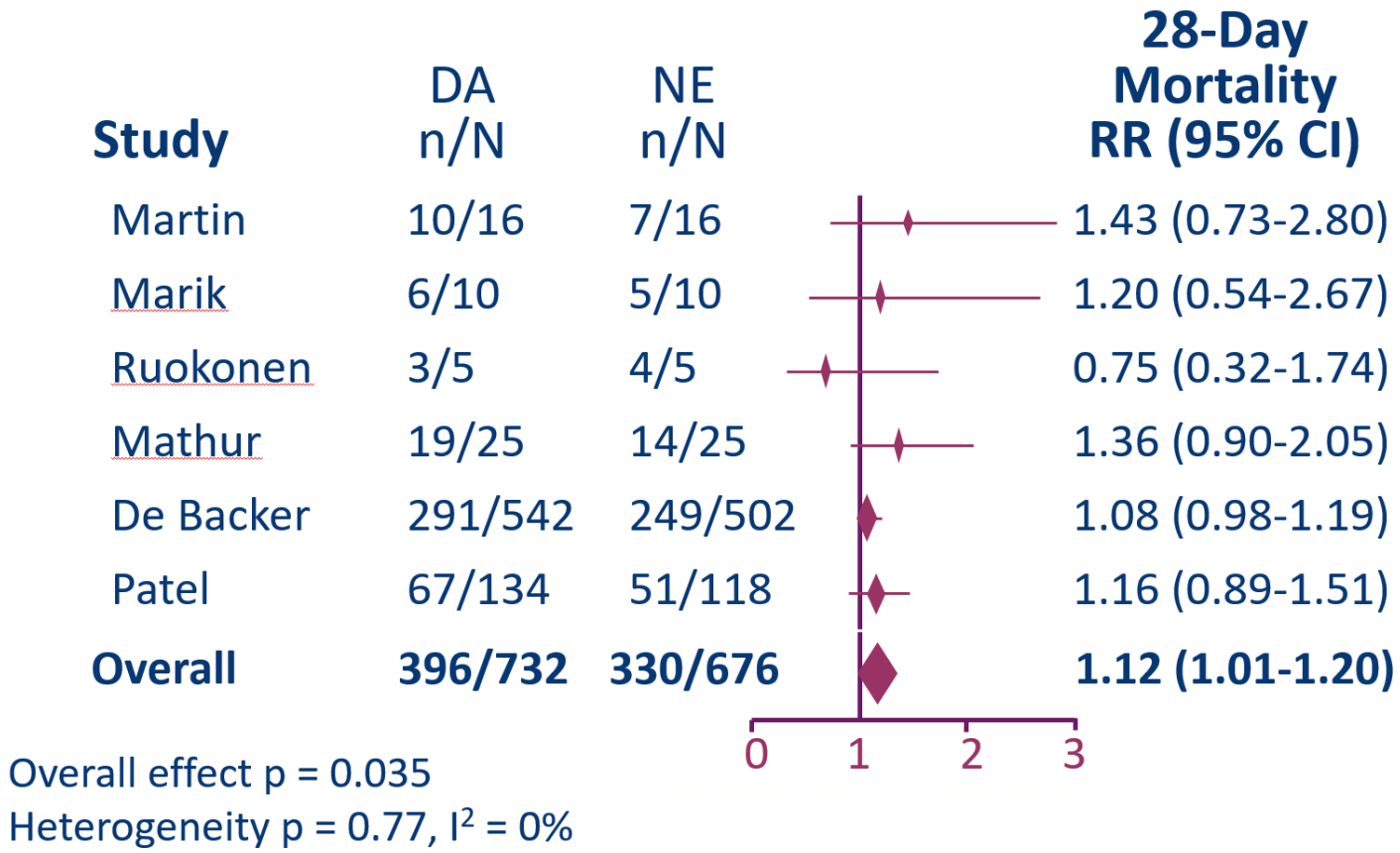
- Norepinephrine as first-line over other vasopressors
  - Dopamine, vasopressin, epinephrine, selepressin, angiotensin II

Weak Recommendations

- Adding vasopressin if inadequate MAP on NE
- Adding epinephrine if inadequate MAP on NE and VP
- Adding corticosteroids if ongoing vasopressor requirement in septic shock (suggestion if NE or Epi ≥ 0.25 mcg/kg/min)
- Adding insulin therapy at glucose level ≥ 180 mg/dL
- Against use of IV vitamin C
- Against use of sodium bicarbonate unless severe acidemia (pH ≤ 7.2) and AKI

Norepinephrine vs. Dopamine in Septic Shock

NE vs. DA in Septic Shock Meta-Analysis



Overall effect p = 0.035
Heterogeneity p = 0.77, I^2 = 0%

De Backer D, et al. *Crit Care Med*. 2012;40:725-730.

Phenylephrine in patients with septic shock

Efficacy?

- Morelli, et al. 2008 (n = 32 pts w/septic shock)
  - Randomized, double-blind controlled trial
  - ↑ MAP with NE vs. PE
  - No difference in % pts achieving goal MAP, CO, SVR

Safety?

- Morelli, et al. 2008 (n = 15 pts w/septic shock)
  - Open-labeled crossover study
  - ↓ HR with PE vs. NE
  - ↓ splanchnic perfusion, ↓ creatinine clearance, ↑ arterial lactate

Morelli A, et al. Crit Care 2008;12:R143
Morelli A, et al. Shock 2008;29:446-451

Vasoactive medication “normal” dosing

Vasopressors (“normal” dose range):

- Angiotensin II *(0-40 ng/kg/min)*
- Dopamine *(0-20 mcg/kg/min)*
- Epinephrine *(0-10 mcg/min)*
- Norepinephrine *(0-30 mcg/min)*
- Phenylephrine *(0-300 mcg/min)*
- Vasopressin *(0-0.04 units/min)*

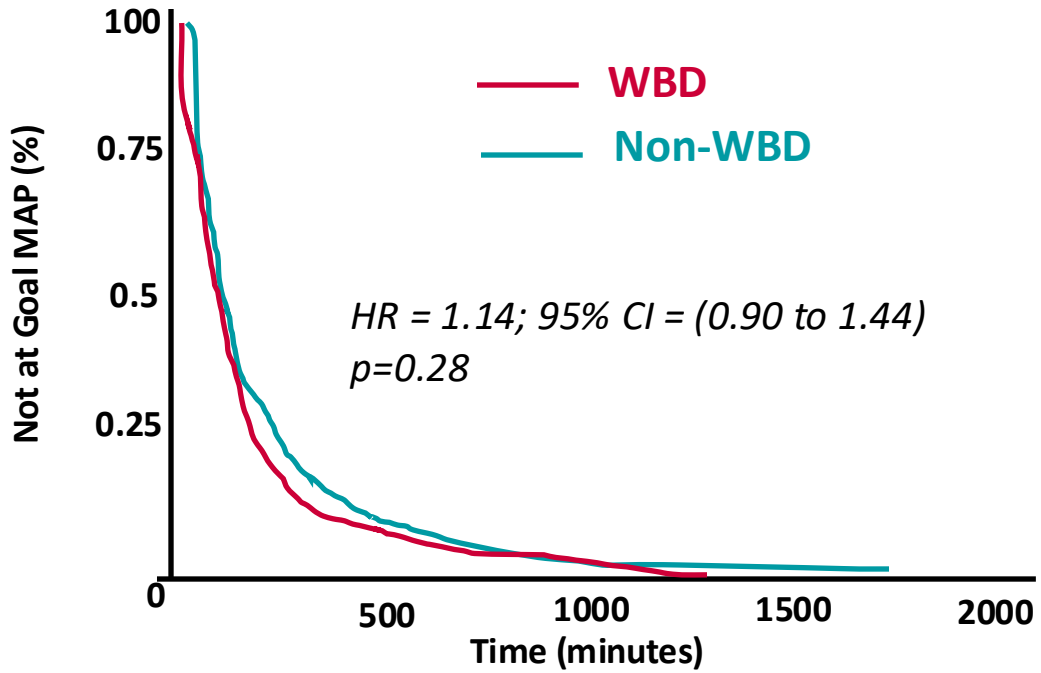
Inotropes (normal dose range):

- Dobutamine *(0-20 mcg/kg/min)*
- Milrinone *(0-0.75 mcg/kg/min)*

Variable	Non-WBD (n=232)	WBD (n=252)	P value
NE Standardized Titration Protocol	69%	61%	0.165
Maximum dose in protocol	92%	78%	0.668
Override max dose allowable	85%	68%	0.011
Max dose, mcg/min	30 (30 to 50) [Range 20 to 400]	---	
Max dose, mcg/kg/min	----	1.0 (0.5 to 3) [Range 0.2 to 10]	
Max dose, equivalent, mcg/min (70kg patient)	30 (30 to 50) [Range 20 to 400]	70 (35 to 210) [Range 14 to 700]	<0.001

Russell JA. *Intensive Care Med*. 2019;45(11):1503-1517.
Smith SE, et al. J Pharm Pract 2024 [online ahead of print]

Weight-based dosing



Variable	Non-WBD (n=143)	WBD (n=144)	P value
MAP (baseline), mm Hg	57 (51-64)	58 (52-63)	0.15
MAP (1hr), mm Hg	69 (62-80)	69 (61-77)	0.49
MAP (6hr), mm Hg	70 (65-75)	68 (64-75)	0.24
Time until goal MAP, minutes	60 (17.5-193.5)	58 (16.8-118.5)	0.28
Cumulative NE dose, mg	10.5 (3.9-25.6)	12.6 (4.9-45.9)	0.04
Time until NE d/c, hours	27 (12-51)	33 (15-69)	0.03
All variables presented as median (IQR)			

Vadiei N, et al. Ann Pharmacother 2017;51(3):194-202

Peripheral administration of vasopressors

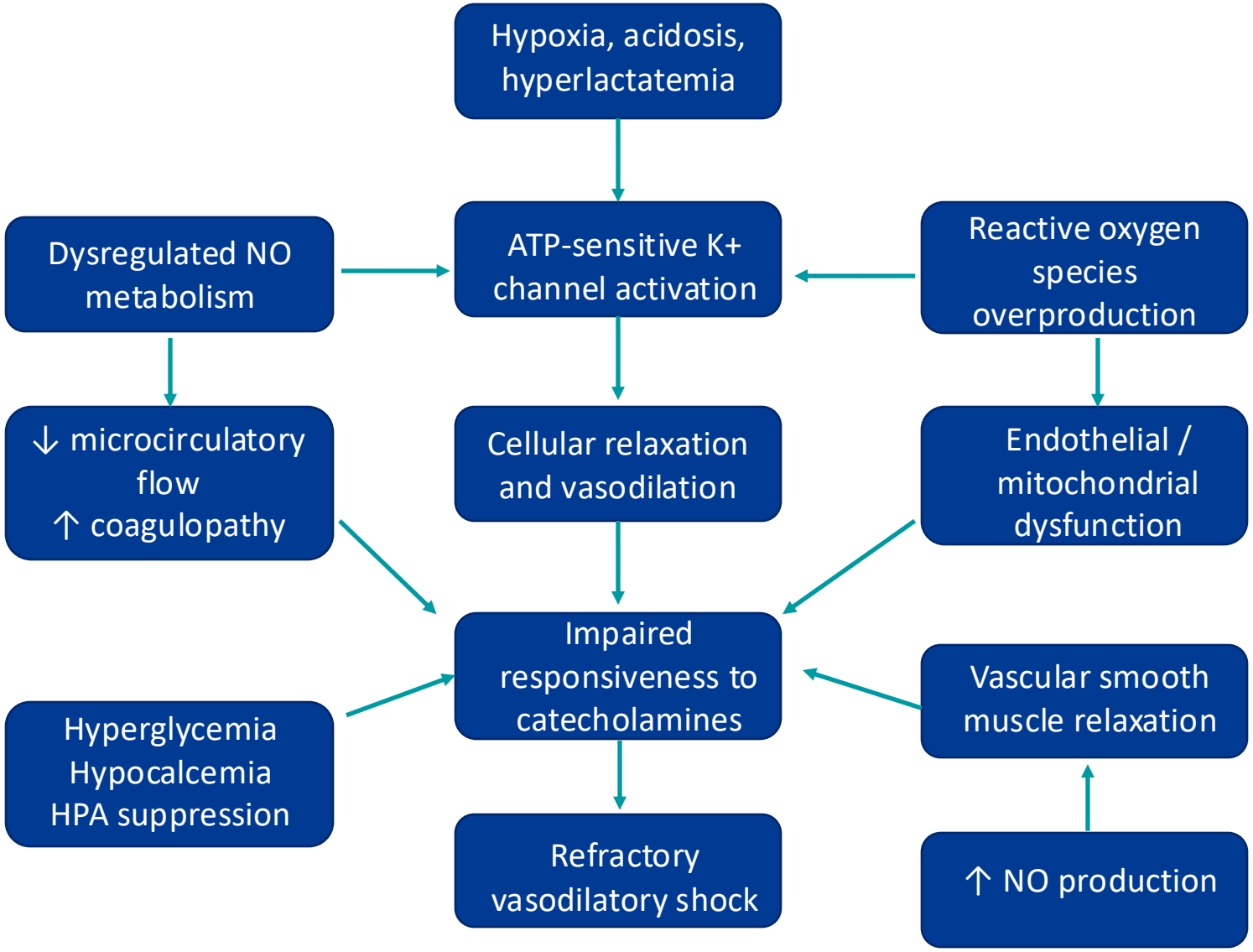
Variable	Adjusted OR for peripheral initiation (95% CI)	p value
Age, per y	1.01 (0.99-1.03)	0.63
Admission from post-acute care facility	0.69 (0.37-1.31)	0.23
Hospitalized prior 90d	0.93 (0.55-1.57)	0.77
Congestive heart failure	1.05 (0.63-1.73)	0.85
BMI, per kg/m2	0.98 (0.97-1.00)	0.015
Initial lactate, per mM	1.02 (0.95-1.08)	0.66
Initial creatinine, per mg/dL	1.03 (0.94-1.13)	0.50
Hospital effect, median OR (95% CI)	2.19 (1.31-3.07)	n/a

Variable	Peripheral (n=400)	Central (n=154)	p value or Adjusted OR (95% CI)
Line initiation, hr (median)	2.5	2.7	p=0.002
Norepinephrine initial vasopressor (%)	84.3	96.8	p=0.001
In-hospital mortality	129 (32.3)	65 (42.2)	0.66 (0.39-1.12)
30-d mortality	162 (40.5)	75 (48.7)	0.76 (0.45-1.27)
90-d mortality	187 (46.8)	84 (54.5)	0.77 (0.46-1.28
New dialysis	29 (7.3)	14 (9.1)	0.79 (0.34-1.77)
Central line removed for complication	2 (0.5)	2 (1.3)	n/a

Munroe ES, et al. Chest 2023

Non-catecholamine vasoactive agents

Pathophysiology of vasodilatory shock



Jentzer JC et al. *Chest* 2018;154(2):416-426

Lower vs. Higher exposure to vasopressors

Outcome	Events / Patients	Measure of Effect	Effect Estimate (95% CI)
90-day mortality	1421 / 3357	RR	0.94 (0.87-1.02)
90-day mortality, adjusted	1421 / 3357	OR	0.93 (0.85-1.01)
ICU mortality	1036 / 3343	RR	0.96 (0.87-1.06)
Hospital mortality	1373 / 3376	RR	0.95 (0.88-1.03)
New-onset supraventricular arrhythmia	90 / 3476	OR	0.55 (0.36-0.86)
New-onset ventricular arrhythmia	61 / 3476	OR	0.97 (0.58-1.61)
Acute kidney injury	385 / 3358	RR	1.10 (0.93-1.29)
Ventilator-free days	3351 / 3351	MD	0.71 (-0.13 to 1.54)

Richards-Belle A, et al. *Crit Care Med* 2023;51(2):254-266

Complications of vasopressor therapy

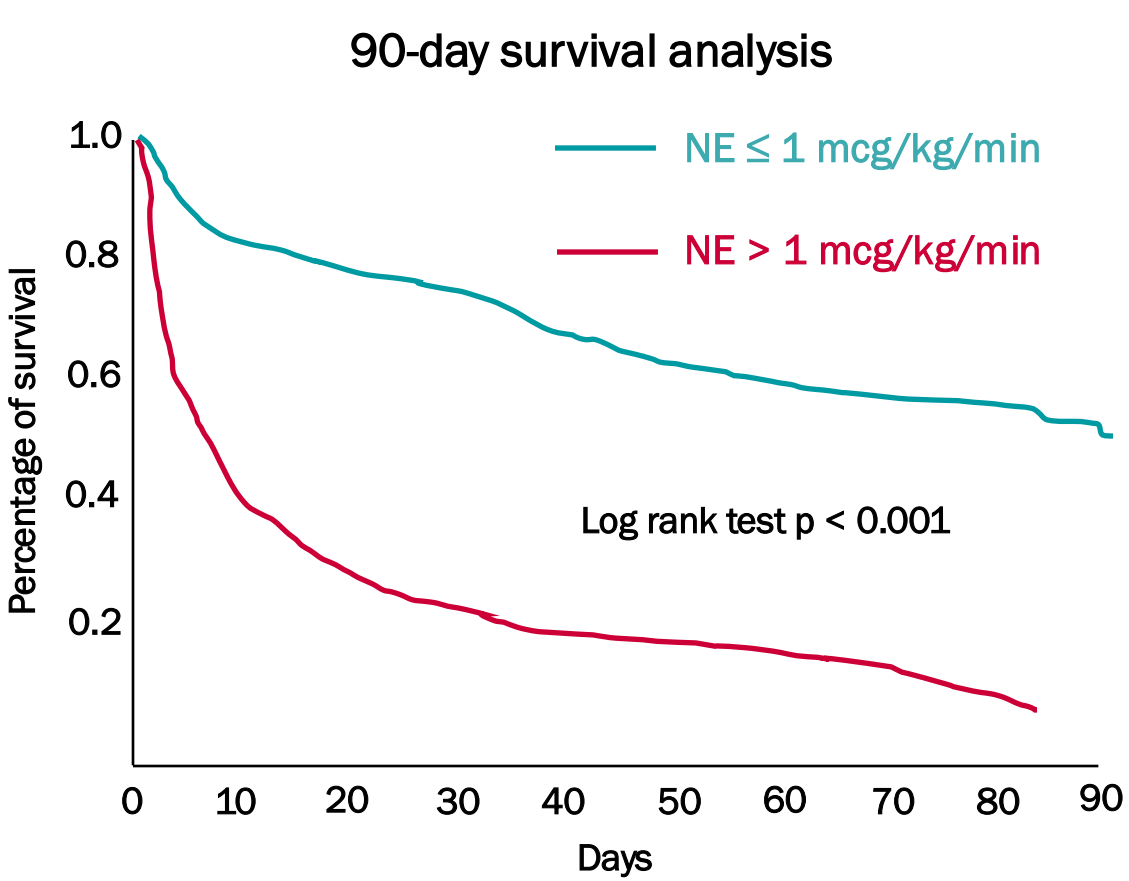
Tachycardia/tachyarrhythmias
Tachyphylaxis
Reflex bradycardia (phenylephrine)
↓ myocardial oxygen supply
↑ myocardial oxygen consumption
↓ Cardiac output / Index

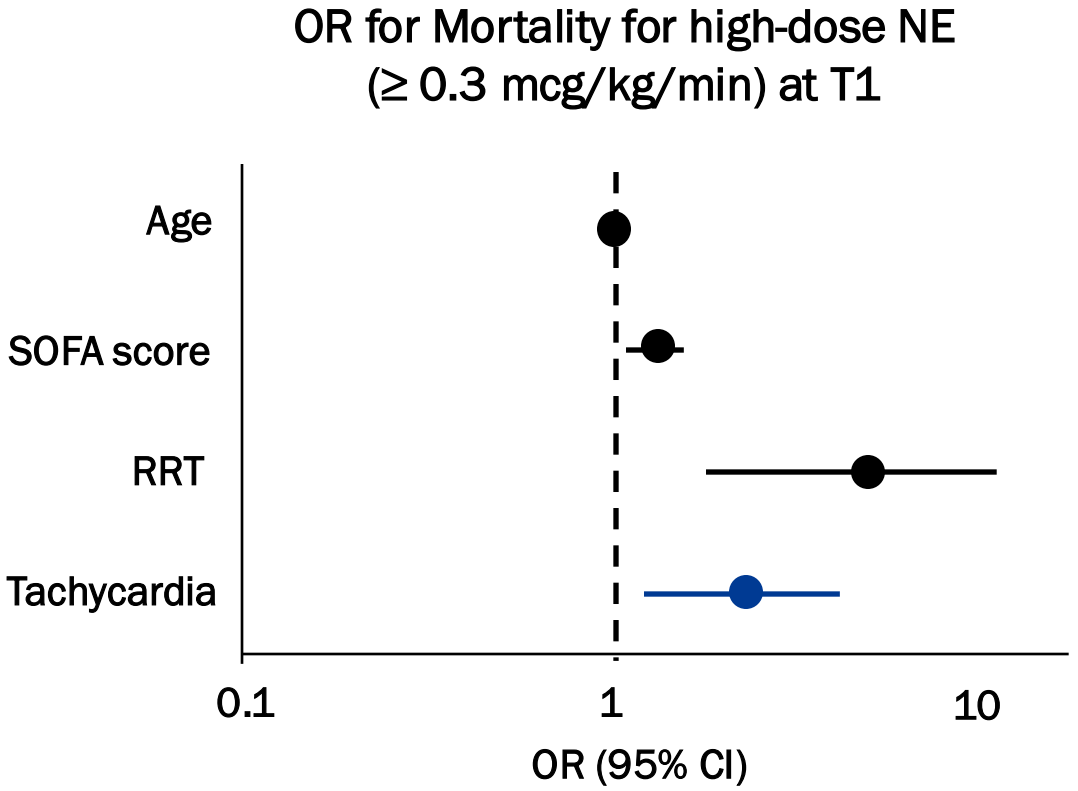
Thrombosis
Digital ischemia
Limb ischemia
↓ splanchnic blood flow
Dopamine

- Prolactin suppression
- ↑ glucose
- ↓ thyroid stimulating hormone
- ↑ risk of acute renal failure with low dose

Hollenberg SM. *Crit Care Clin*. 2009;25:781-802.
Russell JA. *Intensive Care Med*. 2019;45(11):1503-1517.

Norepinephrine (NE) dose, tachycardia, and outcomes

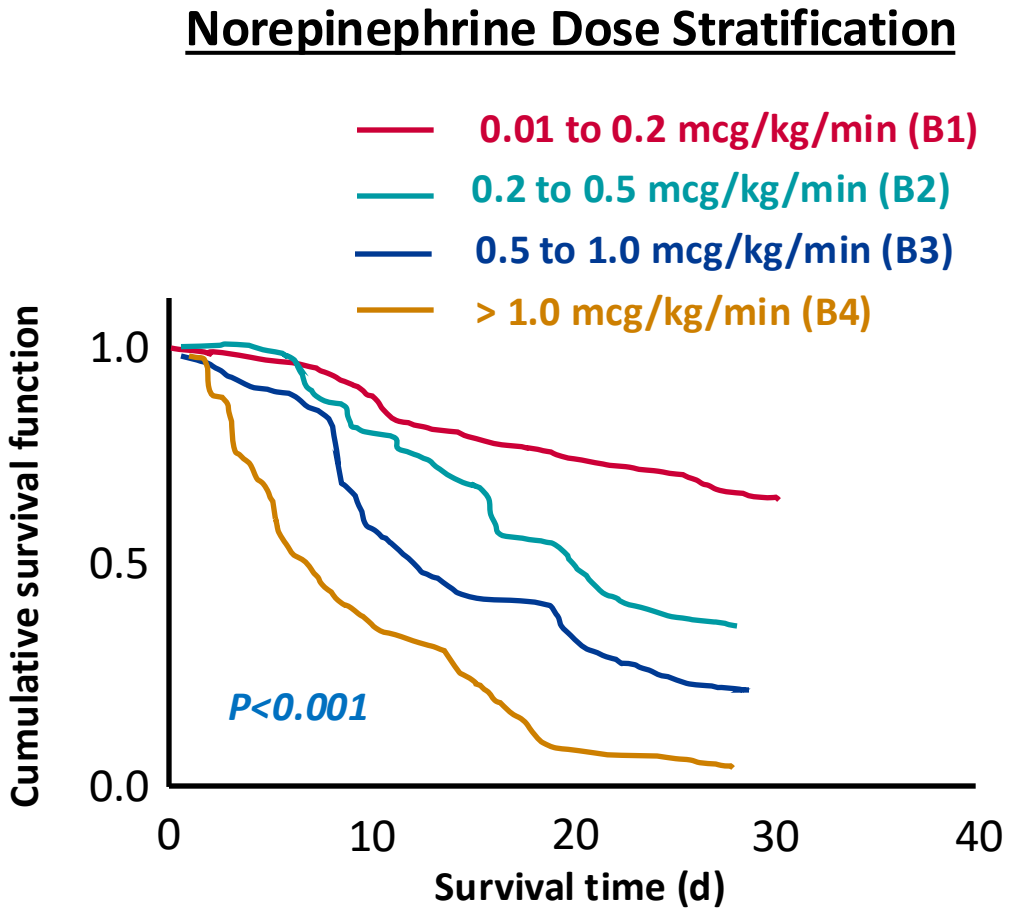




RRT = renal replacement therapy

Domizi R, et al. *J Crit Care* 2020; 57:185-190
Martin C, et al. *Shock* 2015; 44(4):305-309

Norepinephrine dose effects



Variable	B1 (n=63)	B2 (n=31)	B3 (N=38)	B4 (n=28)	P value
Age, y	66.5	65.2	67.2	64.7	0.115
APACHE II	22.6	24.7	27.4	31.0	<0.001
SOFA	8.8	9.4	9.8	11.6	<0.001
Δ IL-1β	0.08	0.05	0.01	-0.26	0.026
Δ IL-6	-12.7	-1.6	-18.8	-91.8	0.023
Δ IL-10	0.16	0.52	0.54	3.28	0.001
T lymphocyte	-27.0	-12	-43	-80.5	0.002
TNF-α	0.1	1.2	0.7	0.01	0.18

Wang Q, et al. Shock 2024;62(1):32-43

Patient case

- KB is a 67-year-old man with a history of T2DM, ESRD (iHD), and left BKA 2 weeks ago for non-healing foot ulcer who presents from a rehabilitation facility with altered mental status.
- Exam – T 39˚C, HR 117 beats/min, BP 85/50 mm Hg (MAP 62), Foul odor and green discharge from incision site on left leg.
- Labs – Hgb 7.3 g/dL, Hct 23.1%, Na 144 mEq/L, K 4.8 mEq/L, Cl 112 mEq/L, lactate 4.1 mmol/L, ScVO2 81%.
- He continues to receive additional IV fluids as he appears fluid responsive. However, given his low MAP, the decision is made to initiate vasopressor therapy (norepinephrine).

Patient case (continued)

After 4 hours in the ED, KB (80 kg) remains in shock (MAP < 65 mm Hg, lactate 3.4 mmol/L) and is currently receiving norepinephrine at 11 mcg/min. **According to the 2021 Surviving Sepsis Campaign Guidelines, when should vasopressin be considered?**

- A) Now given that the norepinephrine dose ~ 10-15 mcg/min
- B) After initiating norepinephrine + epinephrine
- C) Instead of further increasing norepinephrine (when norepinephrine 0.25 to 0.5 mcg/kg/min)
- D) Instead of further increasing norepinephrine (ideally within first 12 hours of septic shock onset)

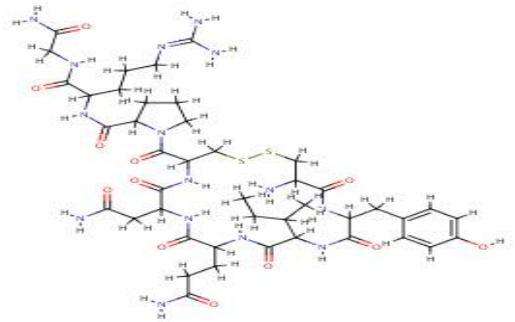
Vasopressin insufficiency in Septic Shock

Circulating levels of vasopressin in shock

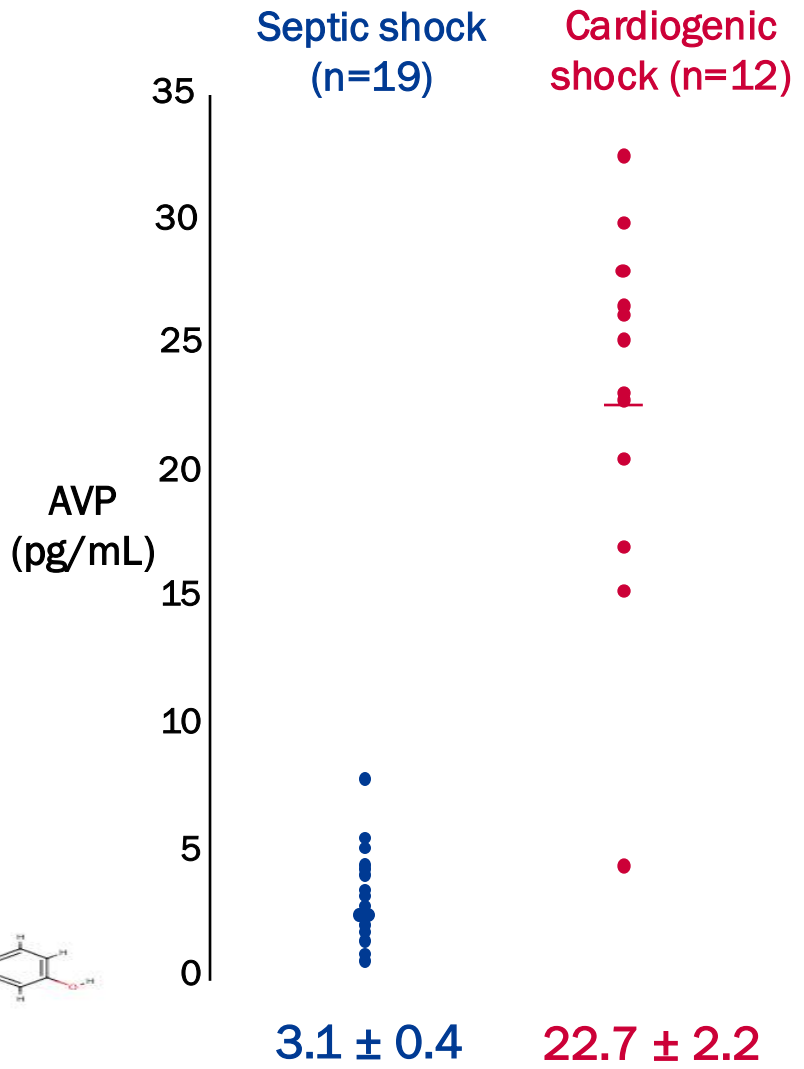
- Initially elevated but quickly decrease (6 to 24 hours after onset)
- Significantly lower in septic shock ("relative vasopressin insufficiency")

Low fixed-dose vasopressin infusion (0.01-0.04 units/min) in septic shock:

- Restores depleted physiologic levels
  - 0.04 units/min ~150-290 pg/L
- Spares high dose catecholamine
- ↑ MAP and SVR (V_{1a} receptor activation)
- Antidiuretic hormone (V_2 receptor activation)
- Dose-dependent tissue ischemia



Vasopressin

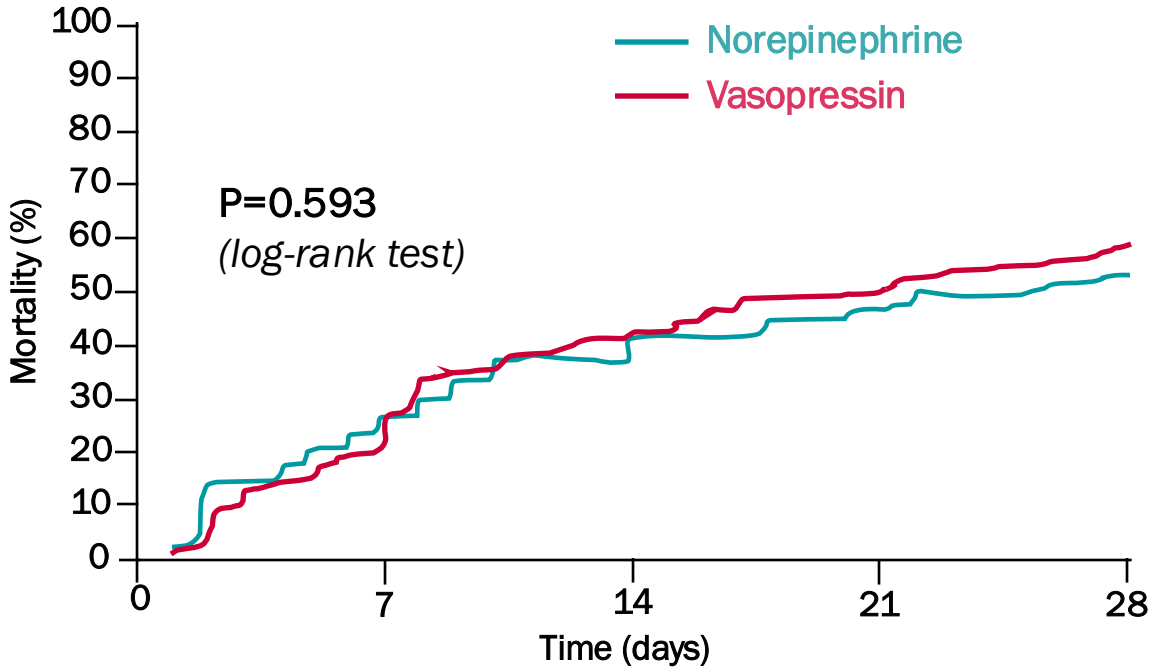


Landry DW, et al. *Circ* 1997;95(5):1122-1125 (adapted)
Hollenberg SM. *Crit Care Clin.* 2009; 25:781–802.
Szumita PM, et al. *Am J Health Syst Pharm*. 2005; 62(18):1931-1936
Sharshar T, et al. *Crit Care Med* 2003;31:1752-1758
Hollenberg SM. *Crit Care Clin.* 2009;25:781-802.
Schurr JW et al. *Shock*. 2017;48(3):284-293.

Vasopressin vs. Norepinephrine – VANCS II

Variable	VP (n=125)	NE (n=125)	P value
28-day mortality [α]	71 (56.8)	66 (52.8)	0.53
90-day mortality [α]	90 (72)	94 (75.2)	0.57
Days alive without vasopressors [β]	10 [1-23]	12 [1-24]	0.70
SOFA 24 hr [β]	8 [5-11]	7 [5-10]	0.43
NE use "open label" [α]	67 (53.6)	51 (40.8)	0.04
Renal replacement therapy [α]	10 (8.0)	17 (13.6)	0.15

[α] n (%); [β] median [IQR]



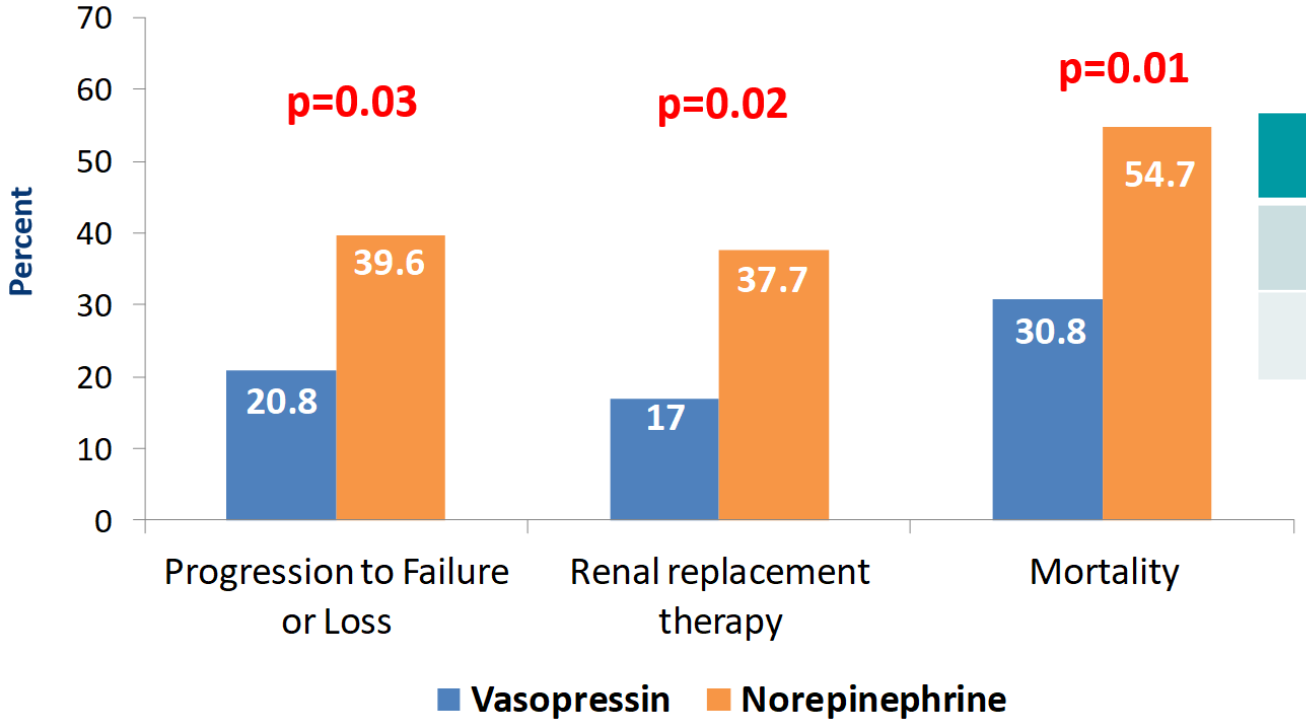
Patients at risk

VP	125	99	72	61	54
NE	125	95	77	66	58

Hajjar LA, et al. *Crit Care Med* 2019;47(12):1743-1750

VASST

Patients	• Adult ICU patients with septic shock receiving norepinephrine
Methods	• Norepinephrine 5-15 mcg/min vs. Norepinephrine + vasopressin 0.01-0.03 units/min
Results	• 28-day mortality: vasopressin 35.4% vs. norepinephrine 39.3% p=0.26 • Vasopressin group had a lower heart rate (p<0.001) • Vasopressin group had reduced norepinephrine use (p<0.001) • Patients with less severe shock had lower mortality with vasopressin use

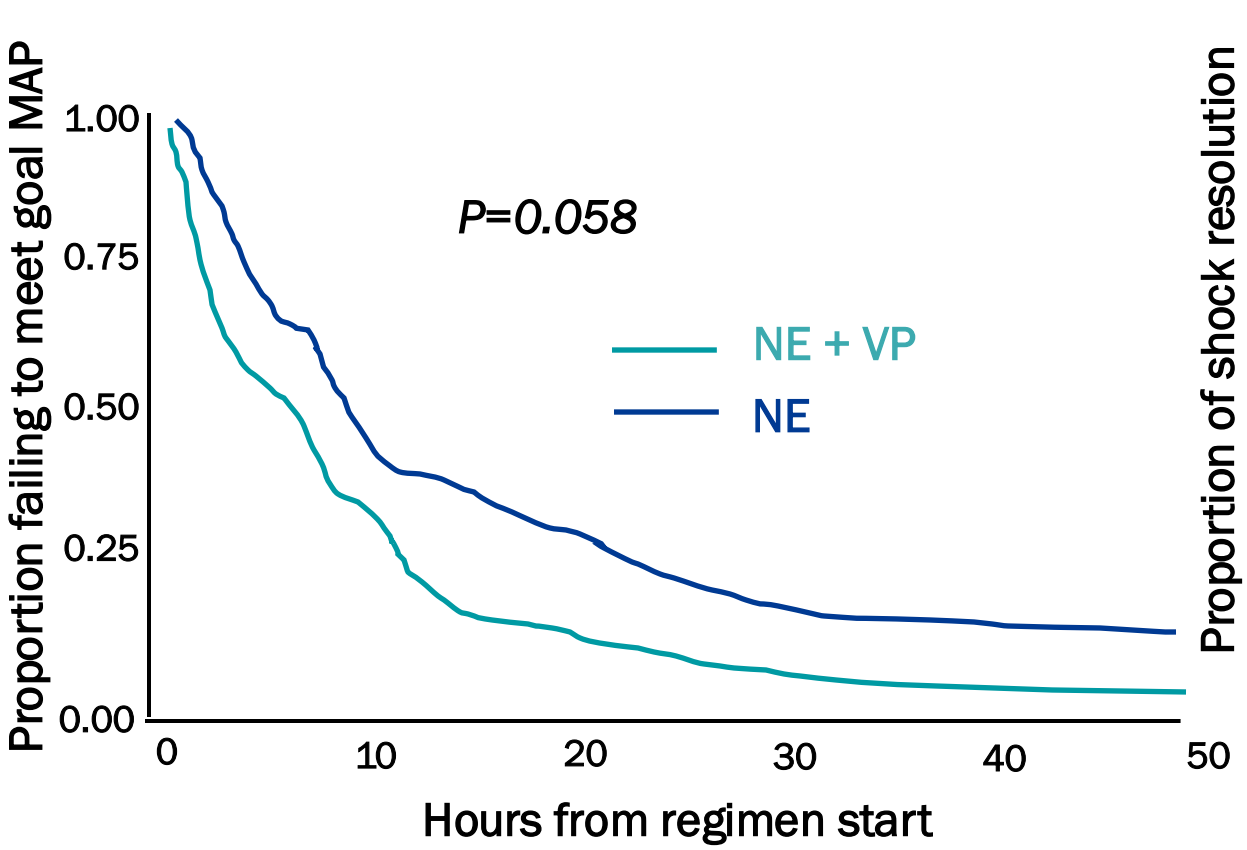


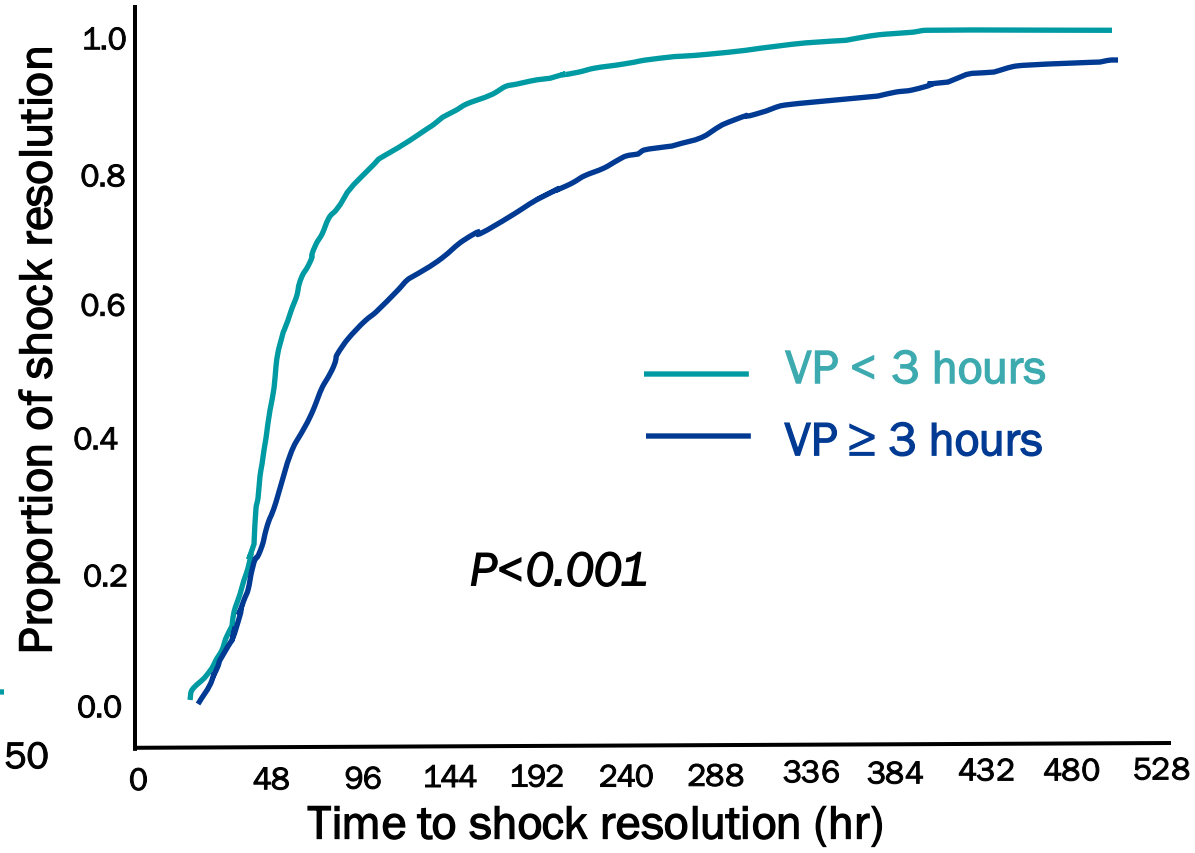
Time to VP	NE mortality	VP mortality
< 12 hours	40.5%	33.2%
> 12 hours	37.5%	37.7%

VP = vasopressin; NE = norepinephrine

Russell JA, et al. *N Engl J Med*. 2008; 358:877-887.
Russell JA. *Crit Care*. 2011; 15:226-245.
Gordon AC, et al. *Intensive Care Med*. 2010; 36:83-91.

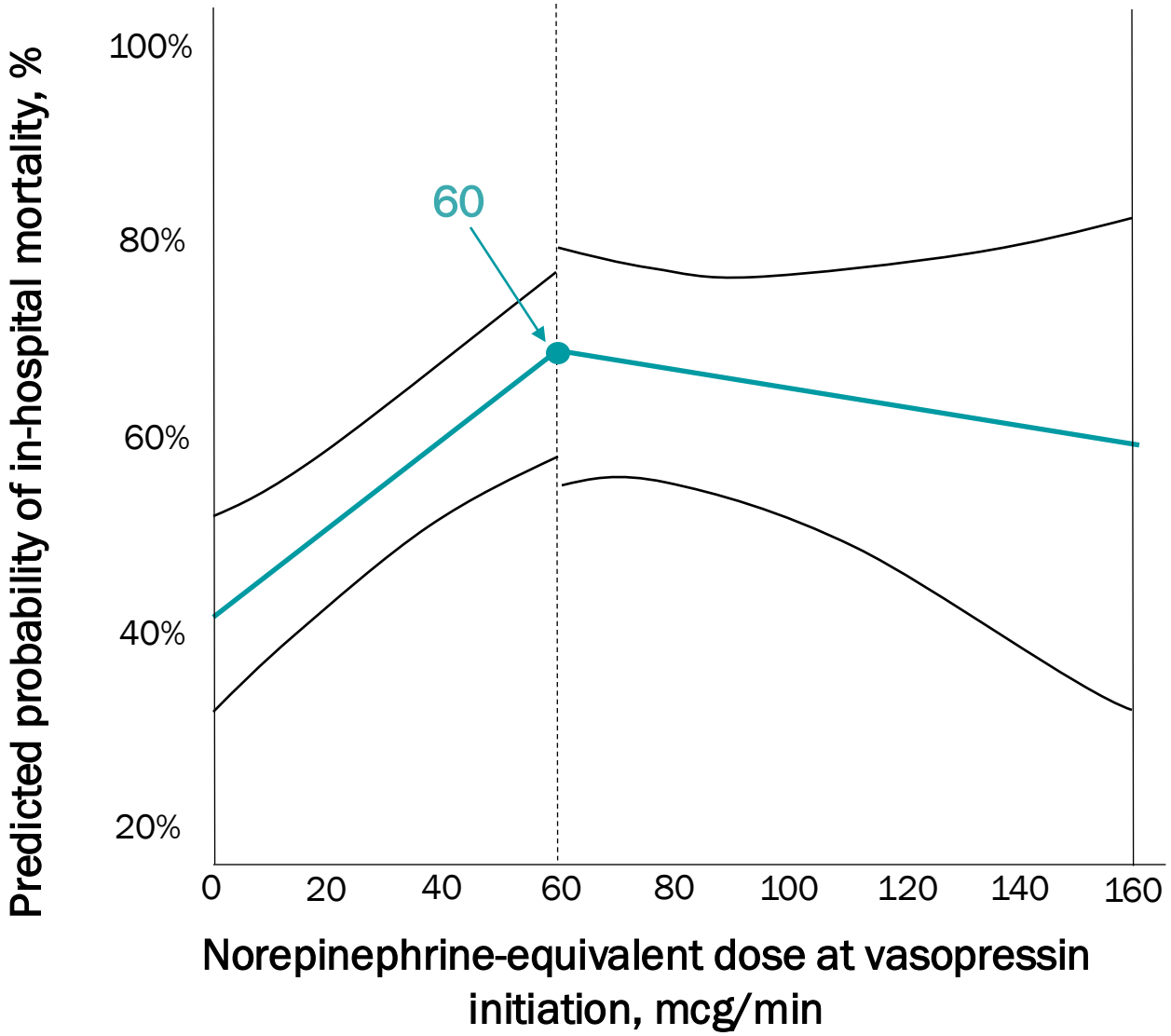
Early vasopressin added to norepinephrine





Hammond DA, et al. *Pharmacother* 2018;38(5):531-538
Brask AL, et al. *Ann Pharmacother* 2023;57(5):521-526

Vasopressin initiation



Variable	Survivors (n=660)	Non-survivors (n=950)	p value
Age, mean	62	64	<0.01
Medical ICU, %	51.4	72.6	<0.01
APACHE III, mean	95.9	118.0	<0.01
SOFA score, mean	12.6	15.0	<0.01
Lactate, mmol/L, median	3.0	4.8	<0.01
VP dose 0.03 u/min, %	38.5	54.7	<0.01
VP dose 0.04 u/min, %	48.8	34.8	<0.01
Time from shock to VP, hr, median	5.0	5.7	0.02
NEE dose at VP initiation, mcg/min, median	20.0	30.0	<0.01

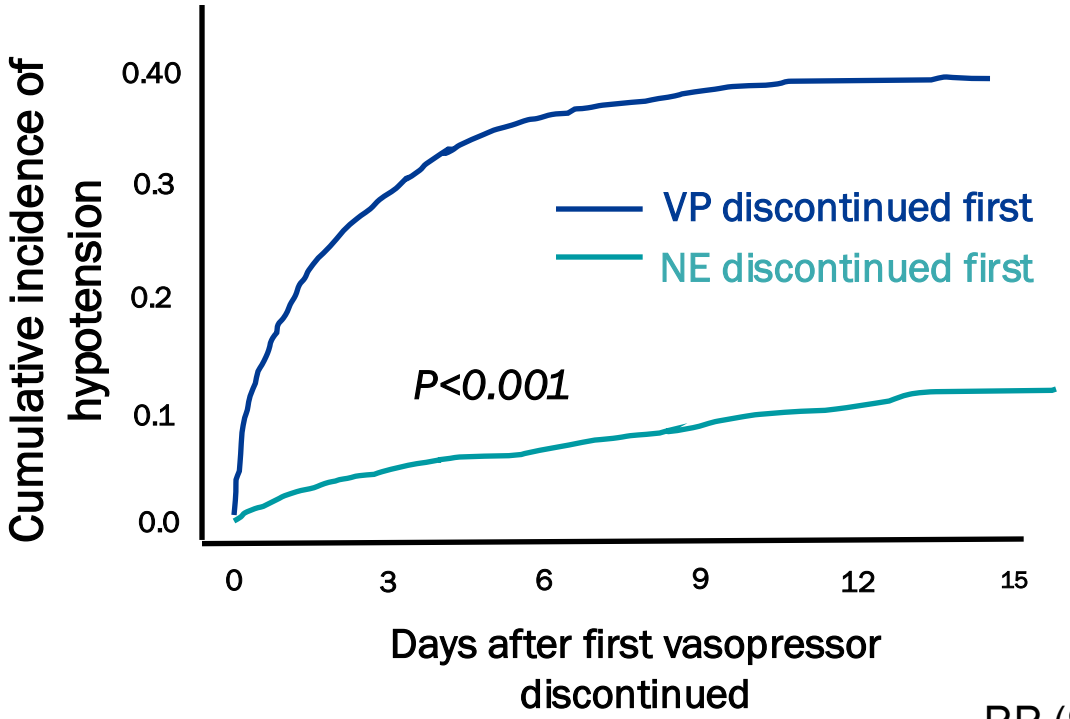
Sacha GL, et al. *Crit Care Med* 2022;50(4):614-623

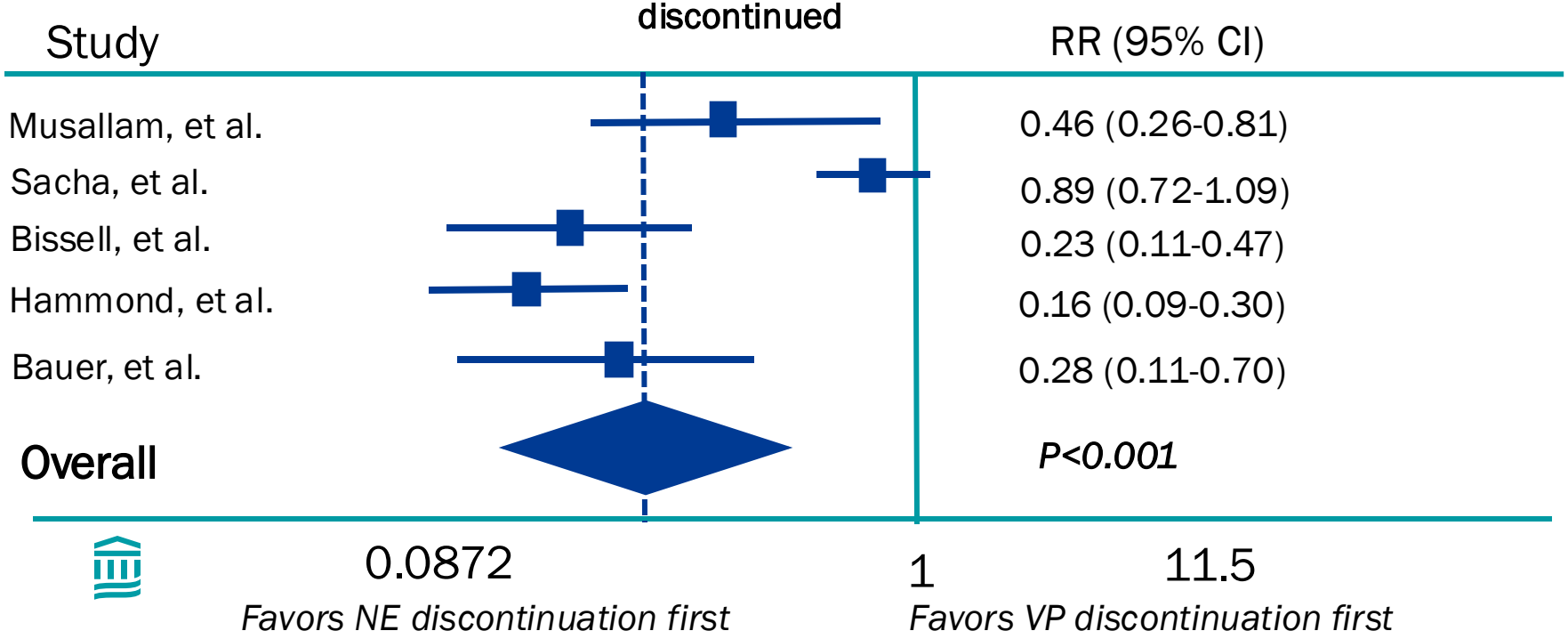
Vasoactive Discontinuation Order

Outcomes	Abrupt discontinuation (n=958)	Tapered discontinuation (n=360)	p value
Median time to ICU discharge, days (95% CI)	7.9 (7.2-8.7)	7.3 (6.3-9.3)	0.6
Total AVP duration, days	1.4 (0.6-2.6)	1.7 (1.1-3.2)	<0.001
Total vasoactive duration, days	3.1 (1.7-5.0)	3.2 (2.0-5.3)	0.15
ICU mortality, n (%)	209 (21.8)	65 (18.0)	0.13
Hospital mortality, n (%)	277 (28.9)	112 (31.1)	0.44
Hypotension w/in 24hr, n (%)	381 (39.7)	150 (41.7)	0.53
Restart/Increase AVP	55 (5.7)	42 (11.7)	<0.001

Lam SW, et al. Shock 2021;55(2):210-214

Vasopressor Discontinuation





Song X, et al. *Sci Rep* 2021
Song JU, et al. *J Korean Med Sci* 2020;35(1)

Audience poll – when would you consider initiation of angiotensin II in patients with septic shock?

A) NE or EPI (moderate dose) + VP

B) NE or EPI (≥ 0.25 mcg/kg/min) + VP

C) NE + EPI + VP

D) 3+ vasopressors + methylene blue and/or hydroxocobalamin

E) Never

Angiotensin II in Septic Shock

Renin-angiotensin-aldosterone system (RAAS)

- Low angiotensin II and angiotensin converting enzyme levels associated with increased mortality
- Renin concentrations correlated with urine output, MAP, and ICU mortality

Angiotensin II

- Major component of RAAS
- Release activated by hypotension and intravascular volume depletion
- Increase in SVR through contraction of vascular smooth muscle (AT_1 receptor)
- Caution
  - Thrombosis, infection, bronchospasm, delirium

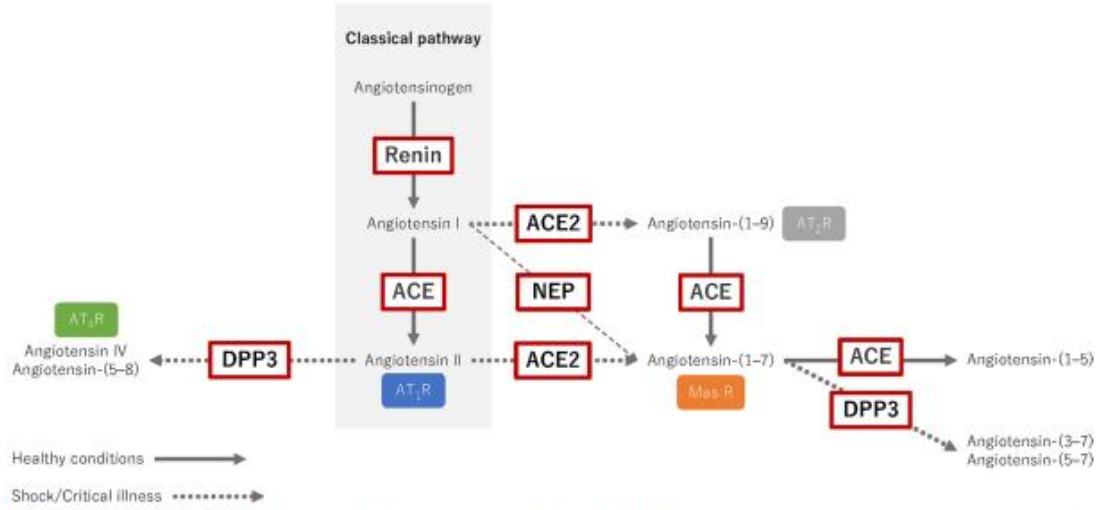


Fig. 1 Classical and alternative pathways of the renin-angiotensin system. *ACE* angiotensin-converting enzyme, *AT_1R* angiotensin II type I receptor, *AT_2R* angiotensin II type II receptor, *AT_4R* angiotensin II type IV receptor, *DPP3* dipeptidyl peptidase 3, *NEP* neprilysin

Zhang W, et al. Exp Ther Med. 2014;7:1342-1348

Gleeson PJ, et al. Crit Care Med. 2019;47(2):152-158

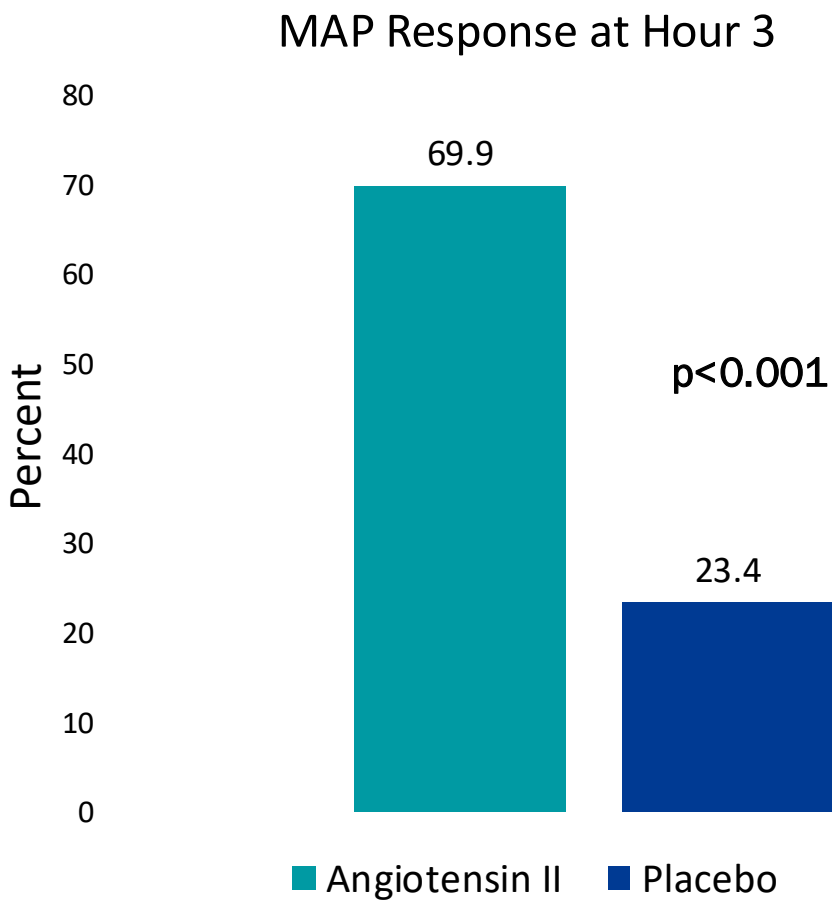
Bauer SR, et al. *Pharmacotherapy*. 2018 Aug;38(8):851-861

Rodriguez R, Fernandez EM. *Am J Health Syst Pharm*. 2019 Jan 16;76(2):101-107

Giapreza (angiotensin II) package insert. San Diego, CA: La Jolla Pharmaceutical; 2018.

Kotani Y, et al. *Ann Intensive Care* 2024;14:79

Angiotensin II – ATHOS 3



Endpoint	AT II	Placebo	P value
Δ CV SOFA at 48h$^{\alpha}$	-1.75 ± 1.77	-1.28 ± 1.65	0.01
Δ total SOFA at 48h$^{\alpha}$	1.05 ± 5.50	1.04 ± 5.34	0.49
Δ NE-equiv dose at 3h$^{\alpha}$	-0.03 ± 0.10	0.03 ± 0.23	<0.001
All cause mortality day 7$^{\beta}$	47 (29)	55 (35)	0.22
All cause mortality day 28$^{\beta}$	75 (46)	85 (54)	0.12

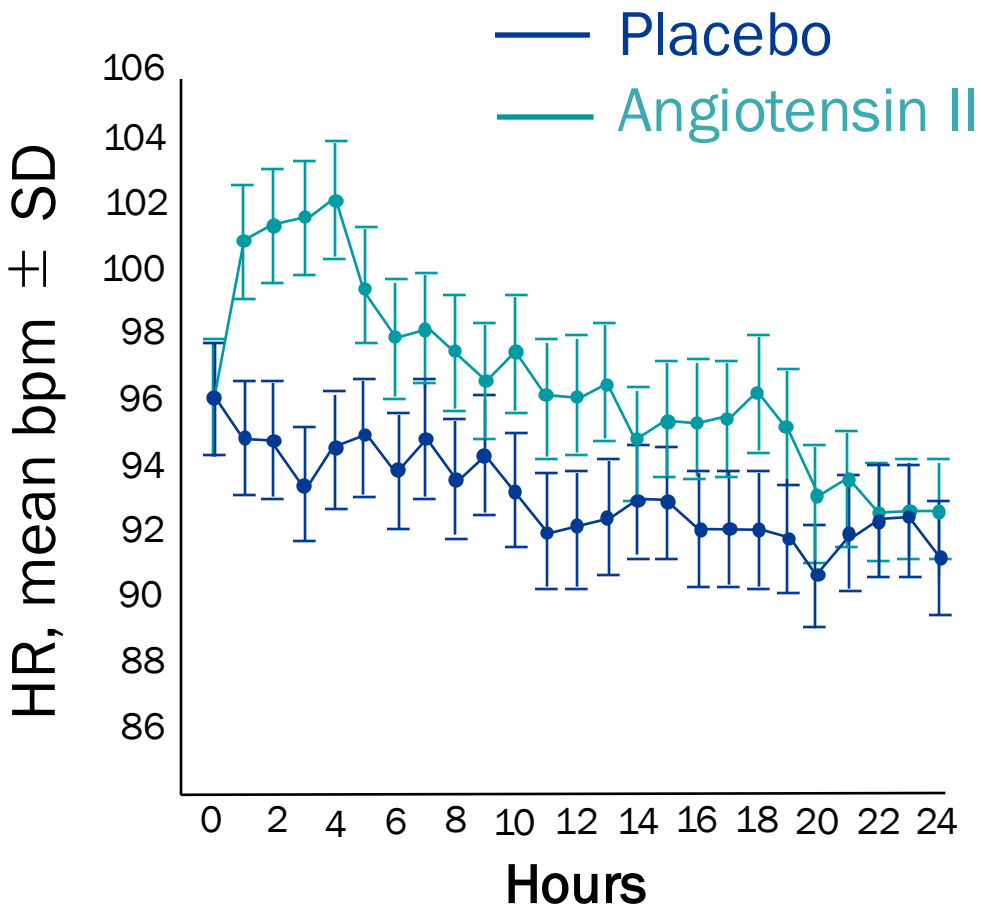
α mean ± SD
β No. (%)

AT II = angiotensin II

Khanna A, et al. *N Engl J Med*. 2017; 377:419-430

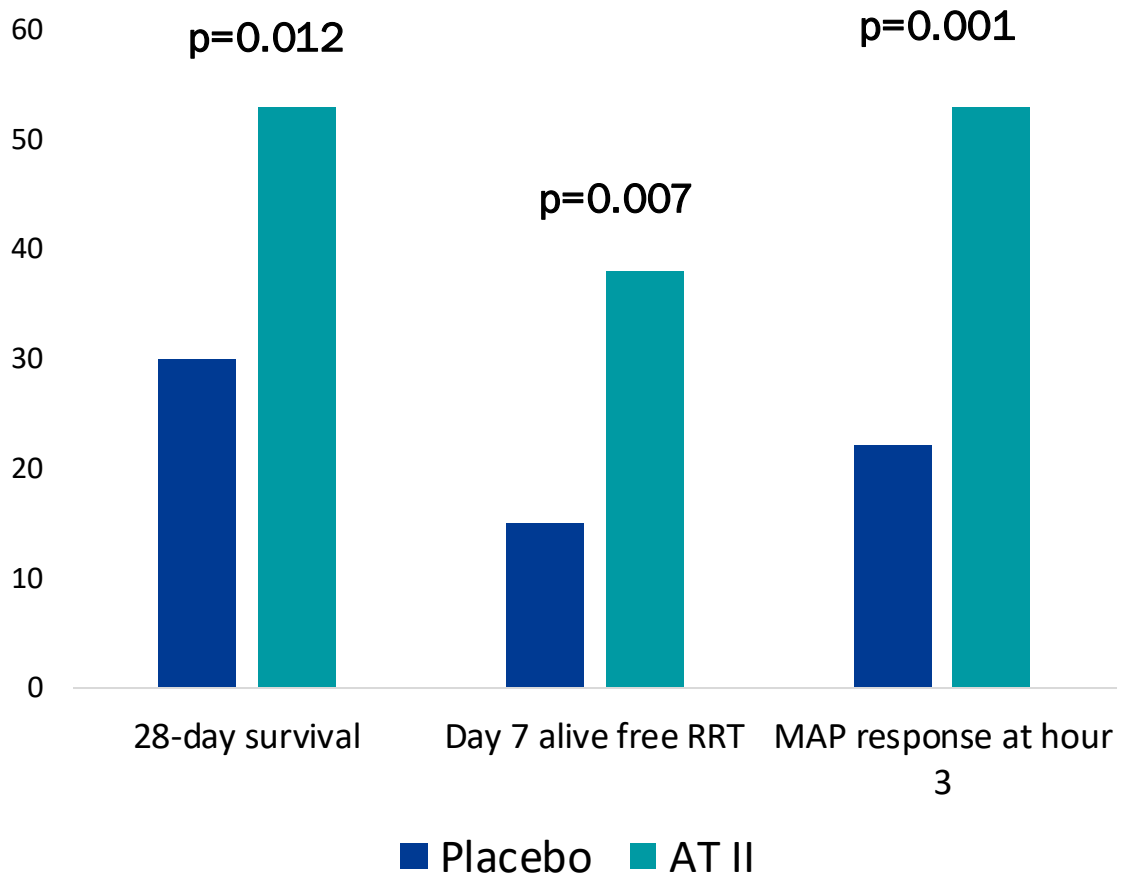
Angiotensin II - safety

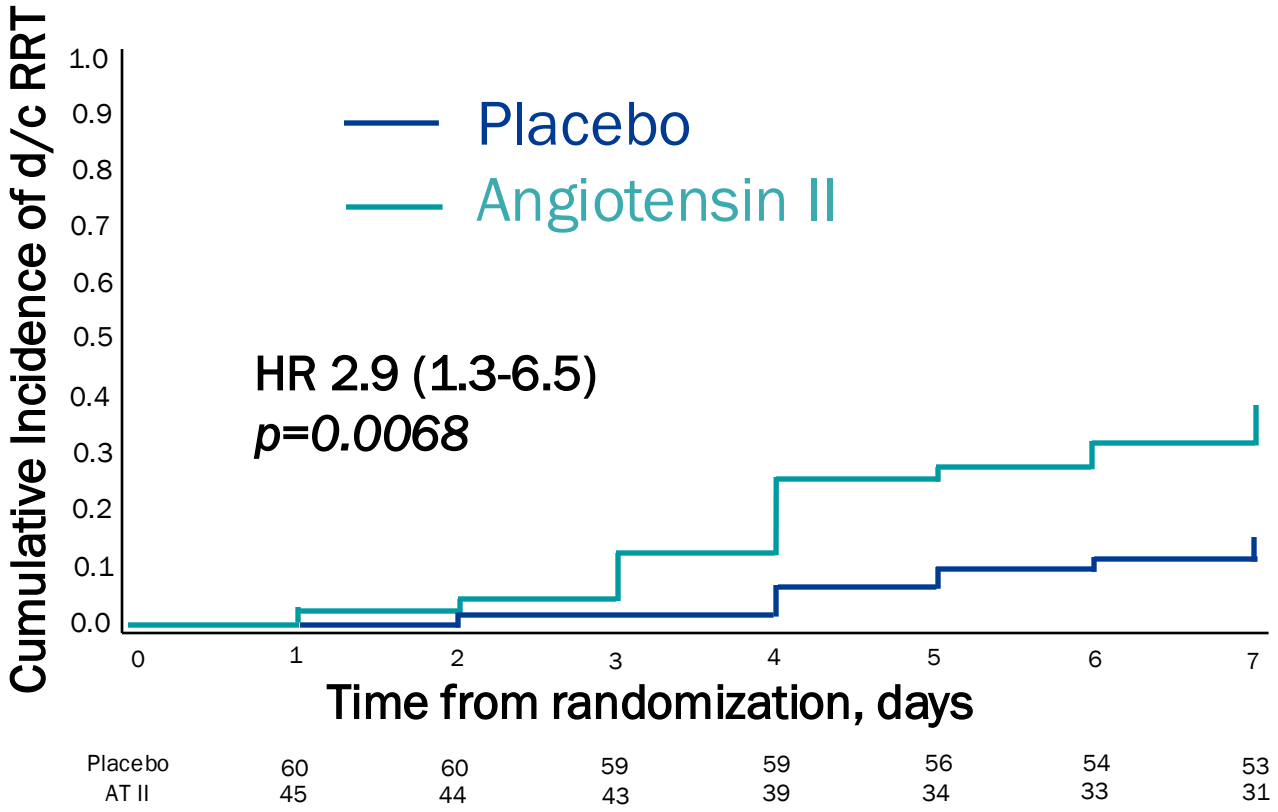
Outcome, n (%)	AT II (n=163)	Placebo (n=158)	P value
Deep vein thrombosis	7 (4.3)	0	0.01
Thrombotic events	21 (12.9)	8 (5.1)	0.02
Fungal infection	10 (6.1)	2 (1.3)	0.04
Delirium	9 (5.5)	1 (0.6)	0.02
Tachycardia	14 (8.6)	9 (5.7)	0.39



Khanna A, et al. *N Engl J Med*. 2017; 377:419-430
Bauer SR, et al. *Pharmacother* 2018;38:851-861

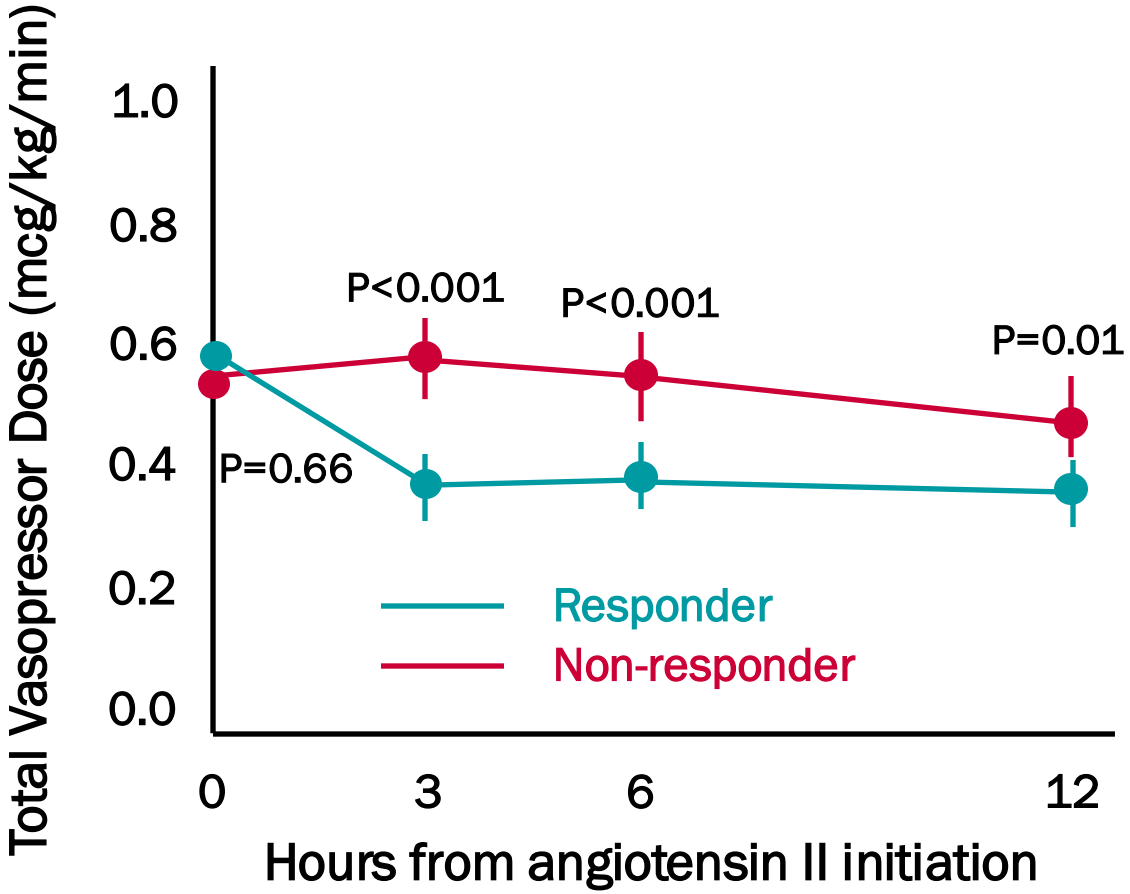
Angiotensin II – Severe AKI and RRT

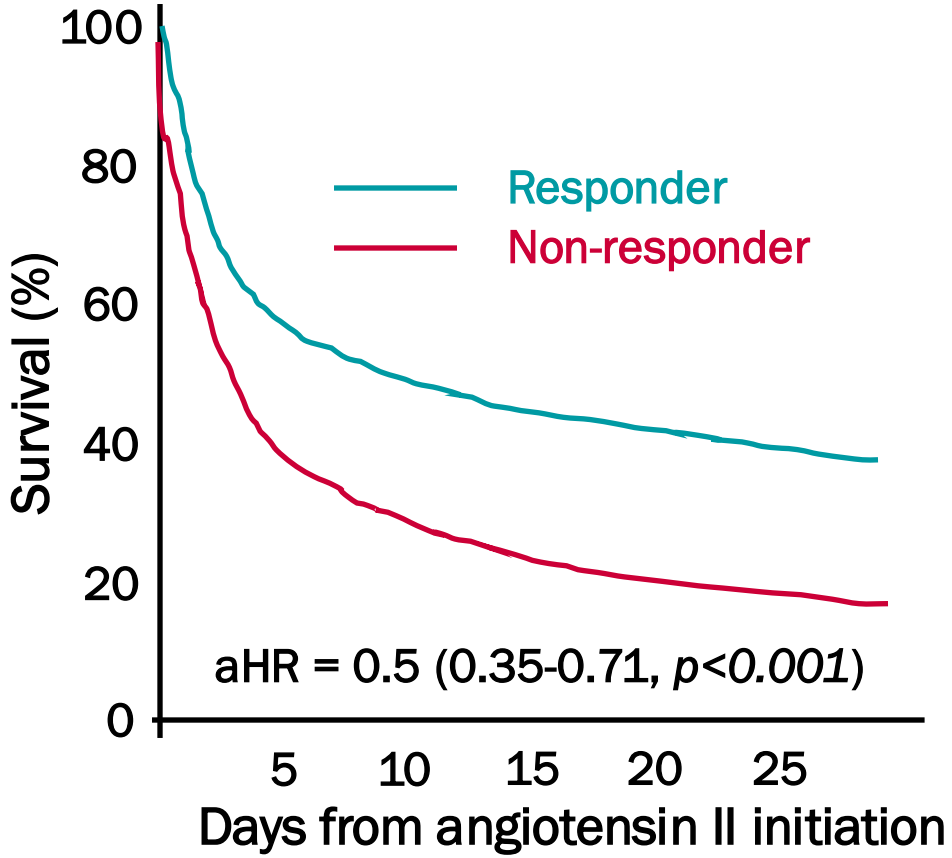




Tumlin JA, et al. *Crit Care Med* 2018;46(6):949-957

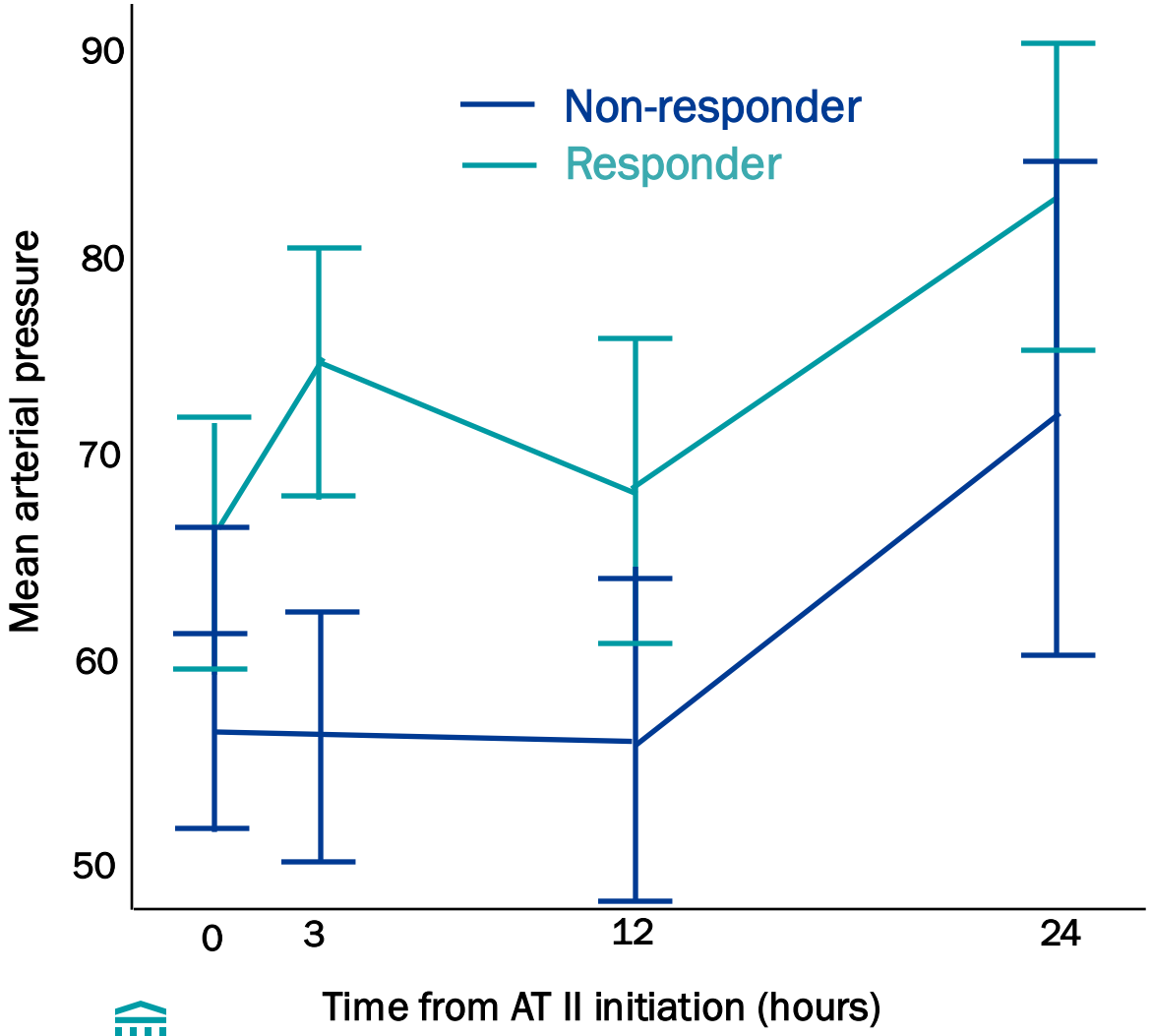
ATII – Multicenter post-marketing





Wieruszewski PM, et al. *CHEST* 2021;159:596-605

AT II – Propensity-weighted real-world

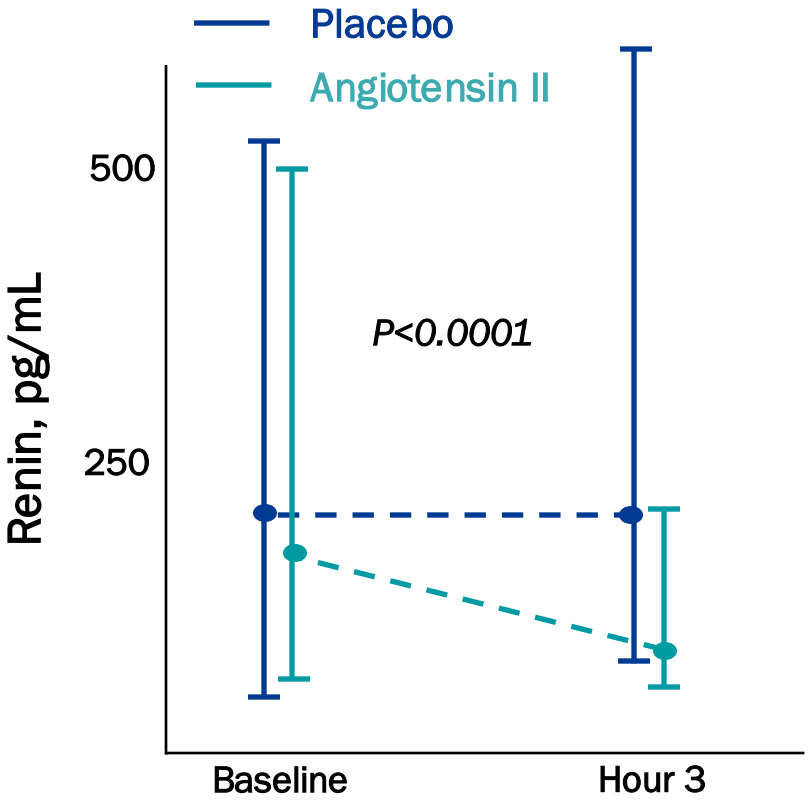


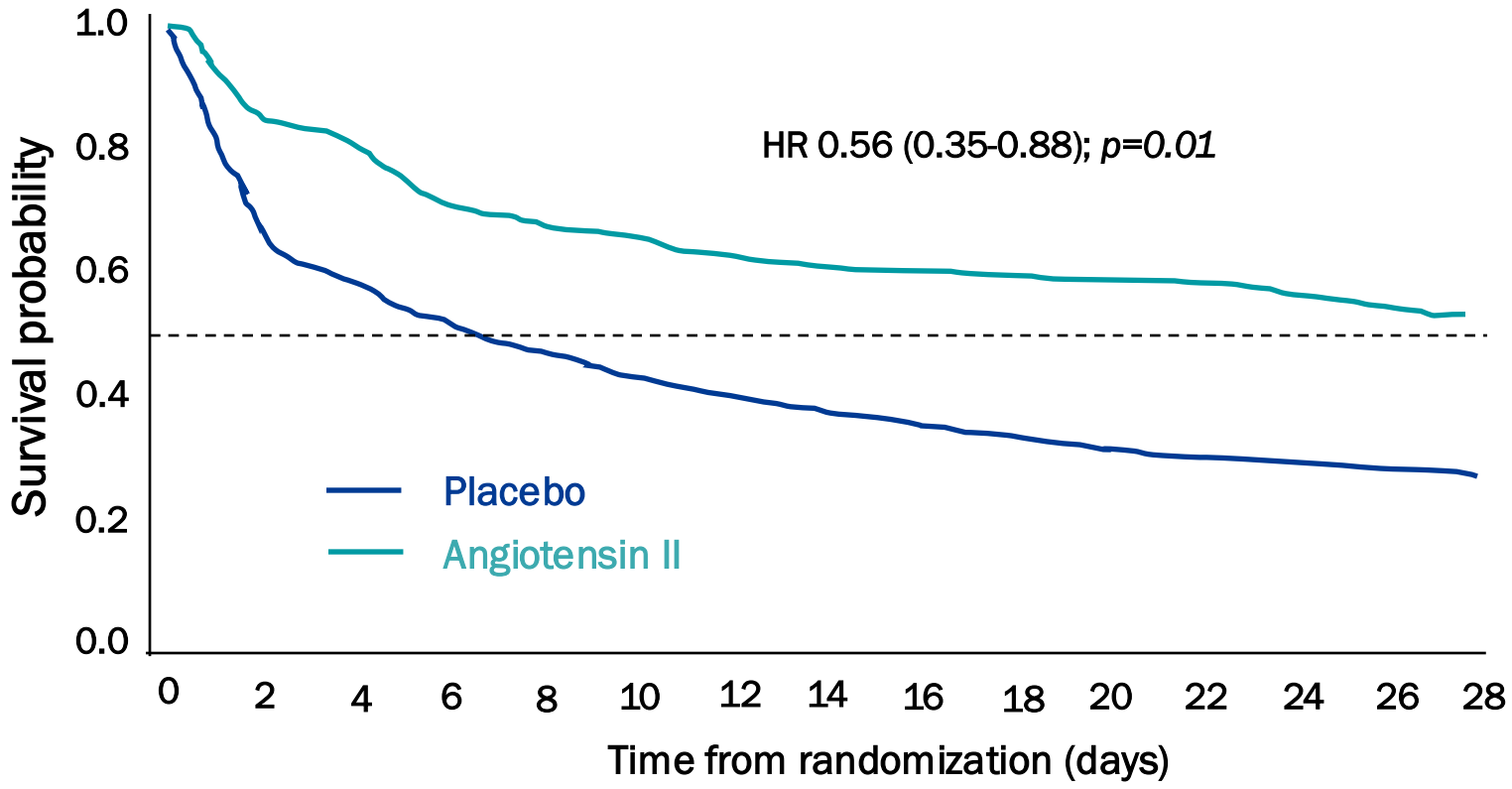
Predictor variable	OR (CI)	p value
Age	1.04 (1.00-1.08)	0.06
Recent ARB / ACEI	1.45 (0.42-5.03)	0.56
Lactate	1.12 (1.00-1.25)	0.06
Corticosteroids	0.86 (0.29-2.55)	0.79
Duration of MV	1.00 (0.99-1.00)	0.20
Number of vasopressors	1.73 (0.77-3.87)	0.18
Duration of vasopressors	1.00 (1.00-1.01)	0.13
SOFA score	1.25 (1.05-1.49)	0.01
Angiotensin II	3.10 (0.82-11.77)	0.10

ARB = angiotensin receptor blocker; ACEI = angiotensin-converting enzyme inhibitor; SOFA = sequential organ failure assessment

Quan M, et al. *Crit Care Explor* 2022

ATII – Renin as predictor of response

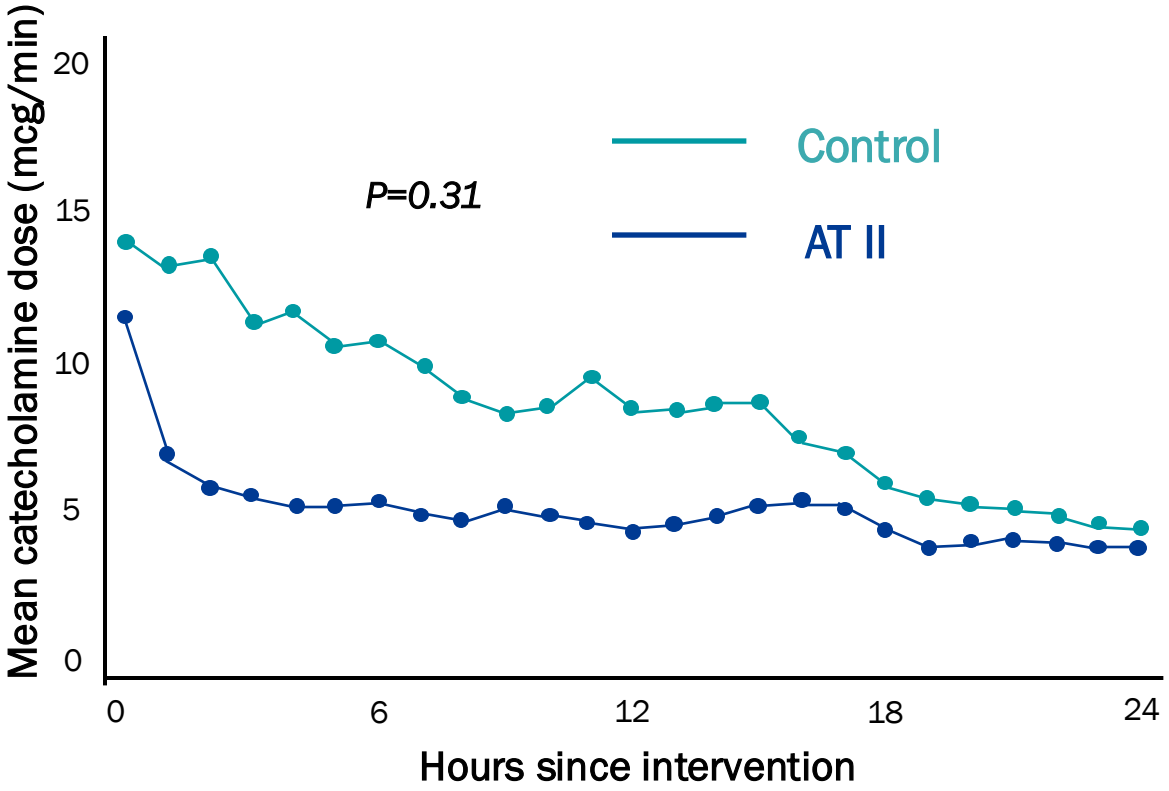


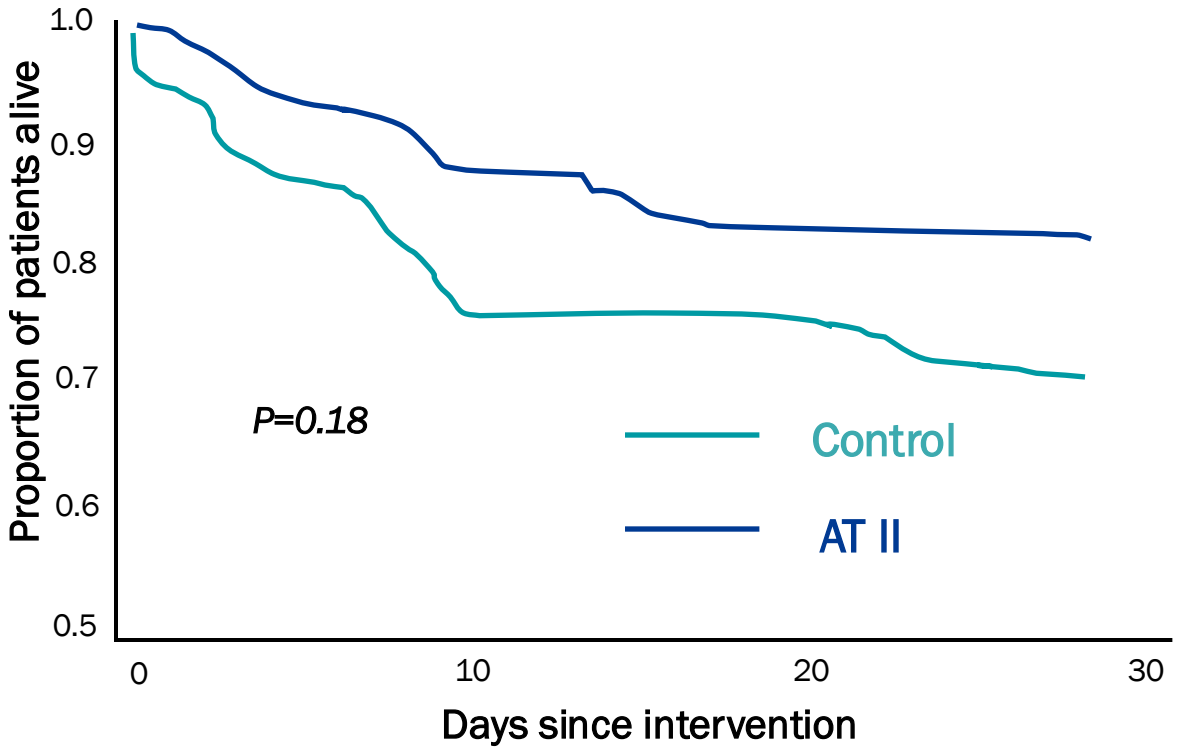


Renin, pg/mL	Placebo	Angiotensin II	p value
Hour 0	193.7 (58.1-489.9)	146.1 (62.4-412.2)	0.43
Hour 3	187.9 (62.3-562.2)	85.0 (52.3-189.1)	0.002

Bellomo R, et al. *Am J Respir Crit Care Med* 2020;9:1253-1261

ATII – First-line vasopressor (ARAMIS)





See EJ, et al. *Shock* 2023;59(5):691-696

Other adjunctive therapies

Catecholamine-sparing therapies in vasodilatory shock

Fluids
Vasopressin
Corticosteroids
Angiotensin II
Ascorbic acid, thiamine, hydrocortisone
Methylene blue
Hydroxocobalamin
Midodrine
Sodium bicarbonate / Tromethamine

Audience poll – when would you consider initiation of IV corticosteroids?

A) NE or EPI + VP

B) NE or EPI (≥ 0.25 mcg/kg/min) + VP

C) NE + EPI + VP

D) Only if suspicion for critical illness-related corticosteroid insufficiency

E) When Pharmacy says hydrocortisone is no longer on the shortage list

Corticosteroid controversy

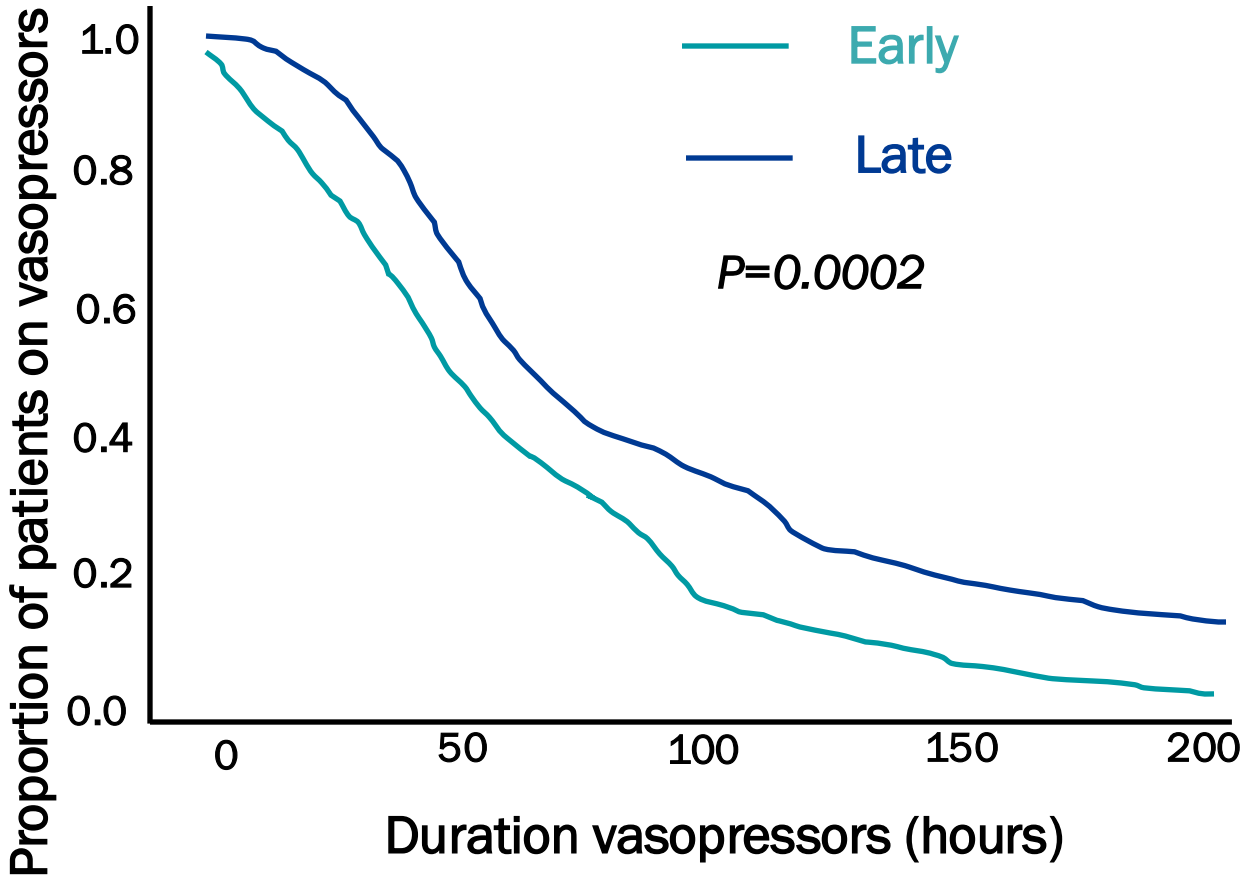
Why the discrepancy in mortality
- Patient factors
  - Severity of illness
  - Patient population
- Intervention differences
  - Time to study drug
  - Dosing and method of drug administration
  - Fludrocortisone?
- 28 vs. 90-day mortality

Importance of secondary endpoints
- Weaning off vasopressors consistent throughout literature
- Weaning off ventilator

Ongoing discussions
- Which steroid(s)?
- What dose/method of administration
- Duration? Weaning?
- Patient population? Timing relative to septic shock onset?
- Other outcomes (quality of life, etc.)

Lamontagne F, et al. *BMJ* 2018;362:k3284

Impact of early administration of hydrocortisone

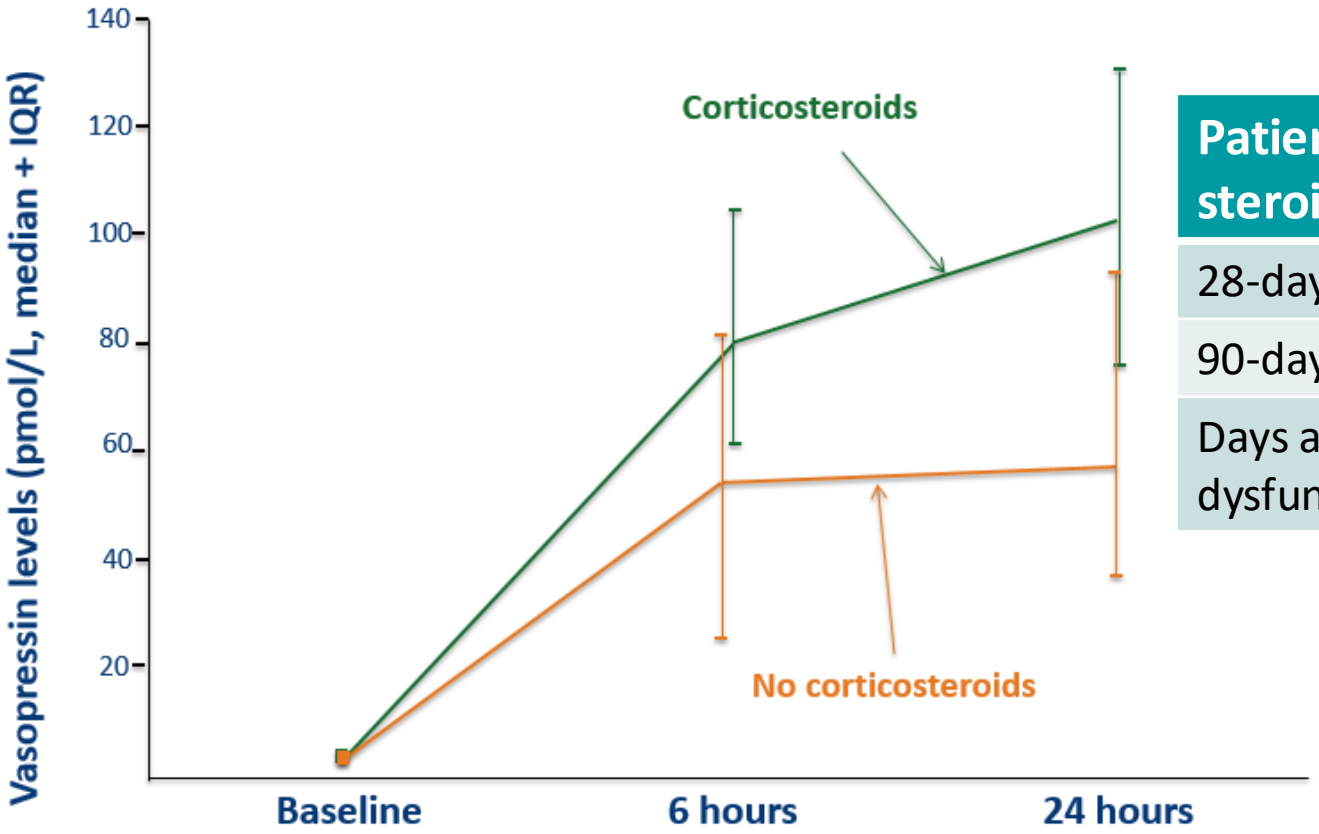


Variable	Early (n=99)	Late (n=99)	p value
Age, years	69.7	68.4	0.41
SOFA score	12	12	0.78
Lactate, mg/dL	5.1	3.4	0.015
NE-equivalent dose at HC, mcg/min	20	12	0.026
ICU LOS, d	3.6	5.1	0.015
Hospital LOS, d	8.9	10.9	0.022
In-hospital mortality, %	42.4	48.5	0.39

All values expressed as median unless specified

Ragoonanan D, et al. *Ann Pharmacother* 2022;56(3):264-270

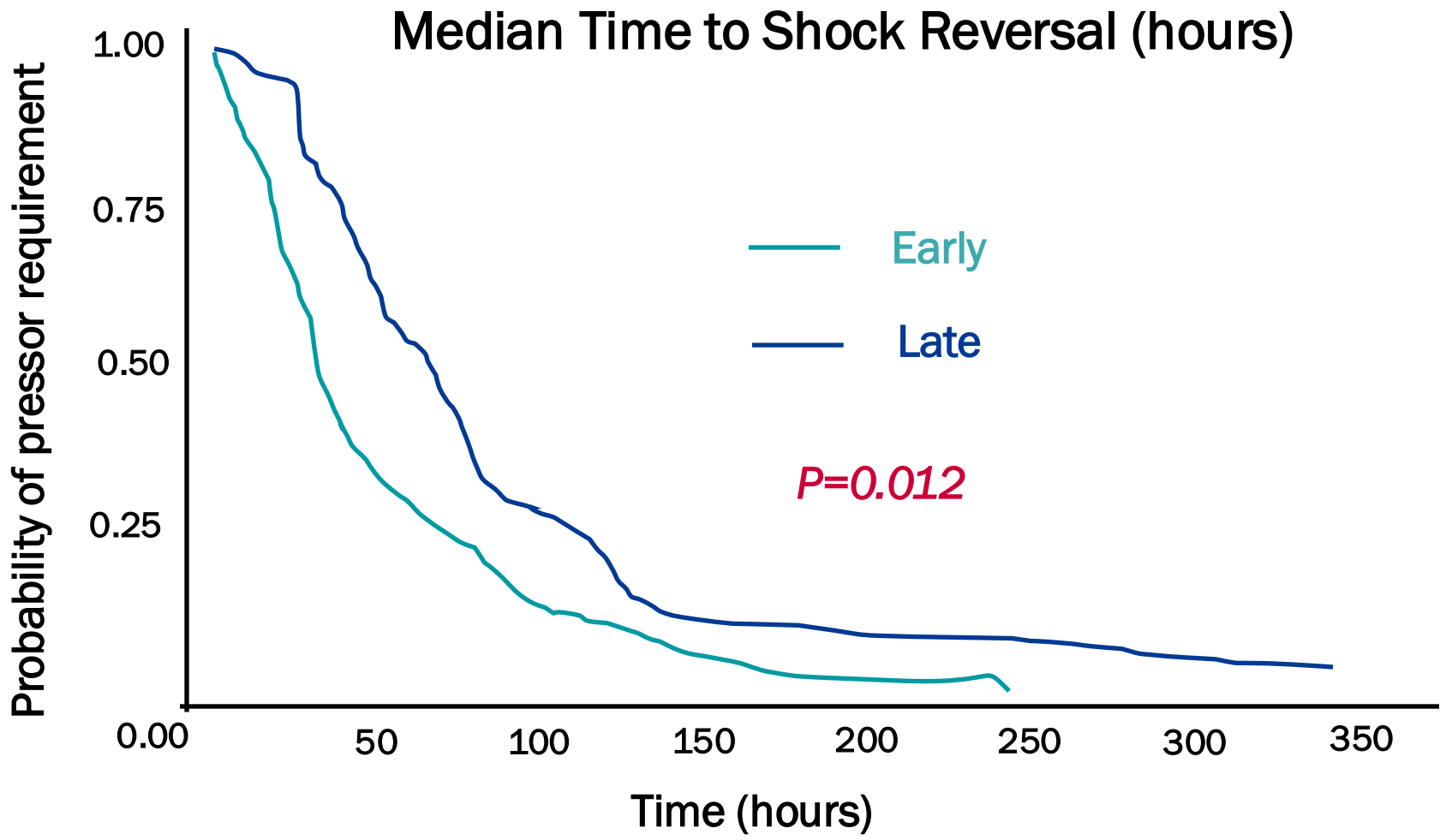
VASST – Vasopressin + Corticosteroids



Patients who received steroids (n=589)	NE group (%)	VP group (%)	P value
28-day mortality	44.7	35.9	0.03
90-day mortality	55.5	45.2	0.01
Days alive without organ dysfunction (survivors)	1	4	0.08

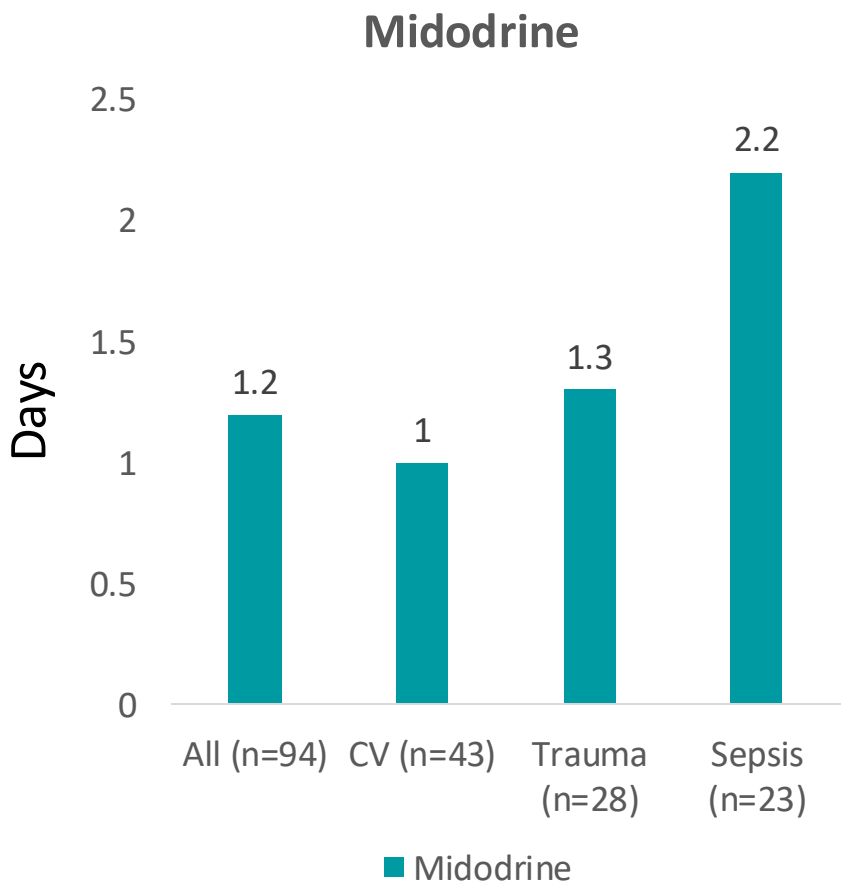
Russell JA et al. *Crit Care Med* 2009;37:811-818

Impact of early administration of both vasopressin and hydrocortisone



Alshehri AM, et al. *Ann Pharmacother* 2024;58(5):461-468

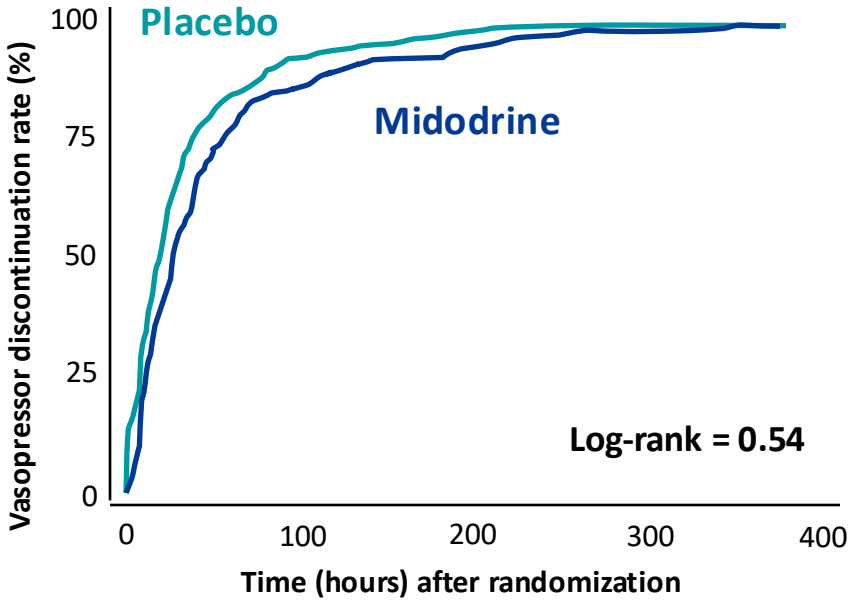
Midodrine early returns



Variable	Control (n=140)	Midodrine (n=135)	*P* value
Age, y*	65 ± 19	69.3 ± 16	0.14
APACHE 4*	84.3 ± 26.8	82.5 ± 26.4	0.55
Steroids$^{\alpha}$	40 (28.6)	35 (26)	0.72
Vasopressor duration, d$^{\beta}$	3.8	2.9	<0.001
Vasopressor reinitiated$^{\alpha}$	21 (15)	7 (5.2)	0.007
Change in creatinine, mg/dL*	0.8 ± 1.6	0.5 ± 1.3	0.048
ICU LOS*	9.4 ± 6.7	7.5 ± 5.9	0.017
ICU mortality$^{\alpha}$	26 (18.6)	15 (11.1)	0.08
* mean ± SD; $^{\alpha}$n (%); $^{\beta}$mean			

Whitson MR, et al. *Chest* 2016;149(6):1380-1383
Poveromo LM, et al. *J Clin Ther* 2016;41:260-265

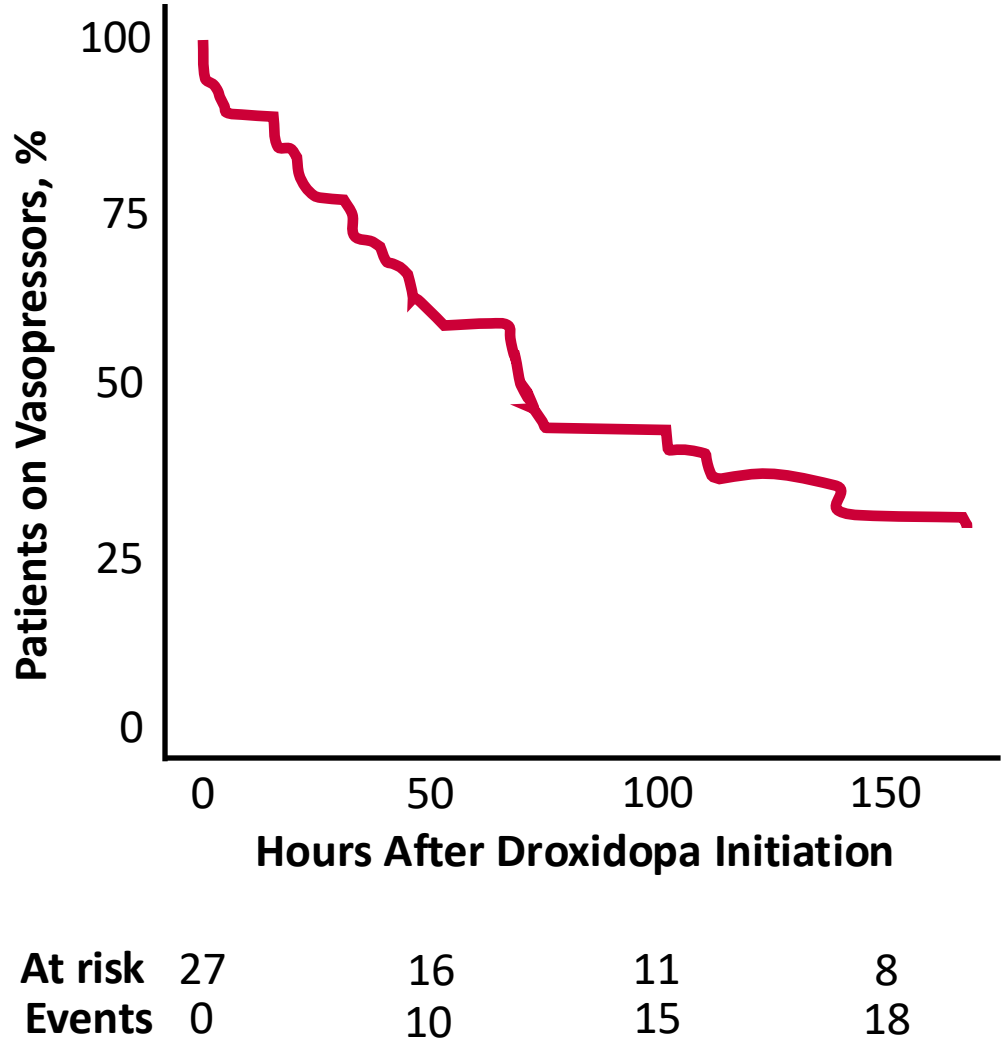
MIDAS



Endpoint	Midodrine (n=66)	Placebo (n=66)	P value
APACHE II$^{\beta}$	14.7 ± 5.2	14.8 ± 5.9	NS
Duration vasopressor admin prior, h	35.5 (28-55)	35.4 (24.7-43.8)	NS
Time to vasopressor d/c, h	23.5 (10-54)	22.5 (10.4-40)	0.62
Time to ready for ICU discharge, d	5 (4-7)	5 (4-6.5)	0.64
ICU LOS, d	6 (5-8)	6 (4-8)	0.46
Hospital LOS, d	11 (9-21)	14 (9-22)	0.45
ICU readmission rate, n (%)	1 (1.5)	3 (4.5)	0.62
Bradycardia*	5 (7.6)	0 (0)	0.02
α median (IQR); β mean ± SD; * n (%)			

Santer P, et al. *Intensive Care Med* 2020;46:1884-1893

Droxidopa for vasopressor weaning in patients with persistent hypotension



Characteristic	All patients (n=30)
Age, years *	62 (54, 68)
Weight, kg *	73 (60, 88)
Hypertension at baseline α	14 (47)
SOFA score at droxidopa initiation *	7.0 (6.0, 9.75)
Duration vasopressors prior to droxidopa, days *	16 (10, 27)
Midodrine 24hr prior to droxidopa initiation α	27 (90)
Vasopressors discontinued within 7 days α	19 (70.3)
Time to vasopressor discontinuation, hours *	70 (34, 192)
Mean NEE in 24hr before initiation, mcg/kg/min	0.08
Mean NEE in 24hr after initiation, mcg/kg/min	0.02
ICU LOS, days *	44 (24, 85)
Hospital LOS, days *	63 (43, 118)

** Median (IQR); α n (%)*

Webb AJ, et al. J Intensive Care Med 2024 [online ahead of print]

Wrap-up

Take home points

Vasopressors are often essential for restoration and maintenance of blood pressure and organ perfusion

Vasopressors, particularly catecholamines when administered at higher doses, are associated with poor outcomes and side effects

A multimodal, patient-specific, shock-dependent vasopressor regimen should be strongly considered in most patients

Questions?


Mass General Brigham