Lights, Camera, (Vaso)Action! Vasoactive Agents for Catecholamine Refractory Septic Shock

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October 28, 2017

MEDICINE *of* THE HIGHEST ORDER

UR MEDICINE

Conflicts of Interest

I have no conflicts of interest to disclose

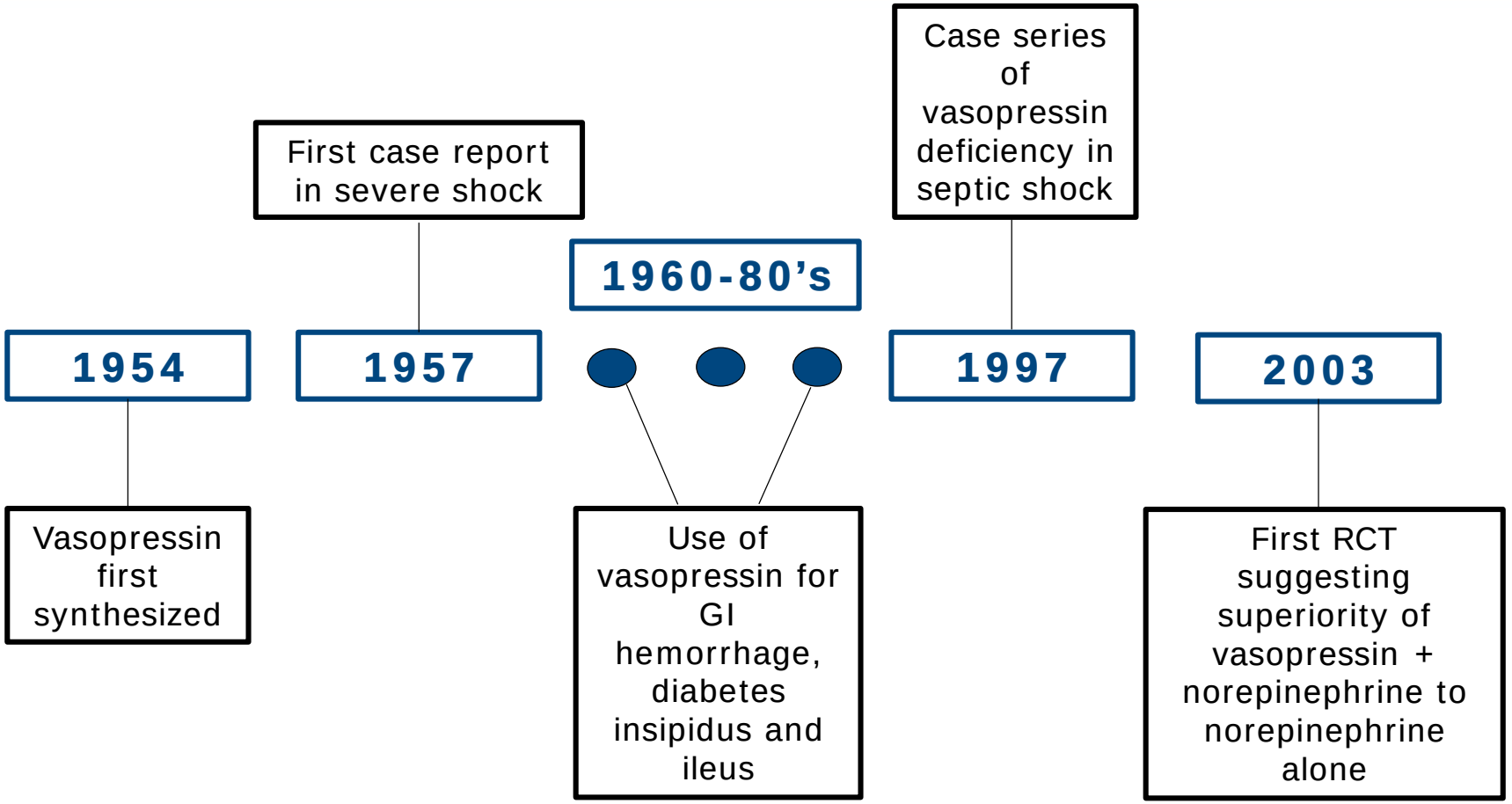
Presentation Objectives

1. Discuss the currently available literature evaluating angiotensin II as a treatment modality for septic shock.

2. Interpret the results of the ATHOS-3 trial and its applicability to the management of patients with septic shock.

Vasopressin

Vasopressin: A History



Matis-Gradwohl I, et al. Crit Care. 2013;17:1002.

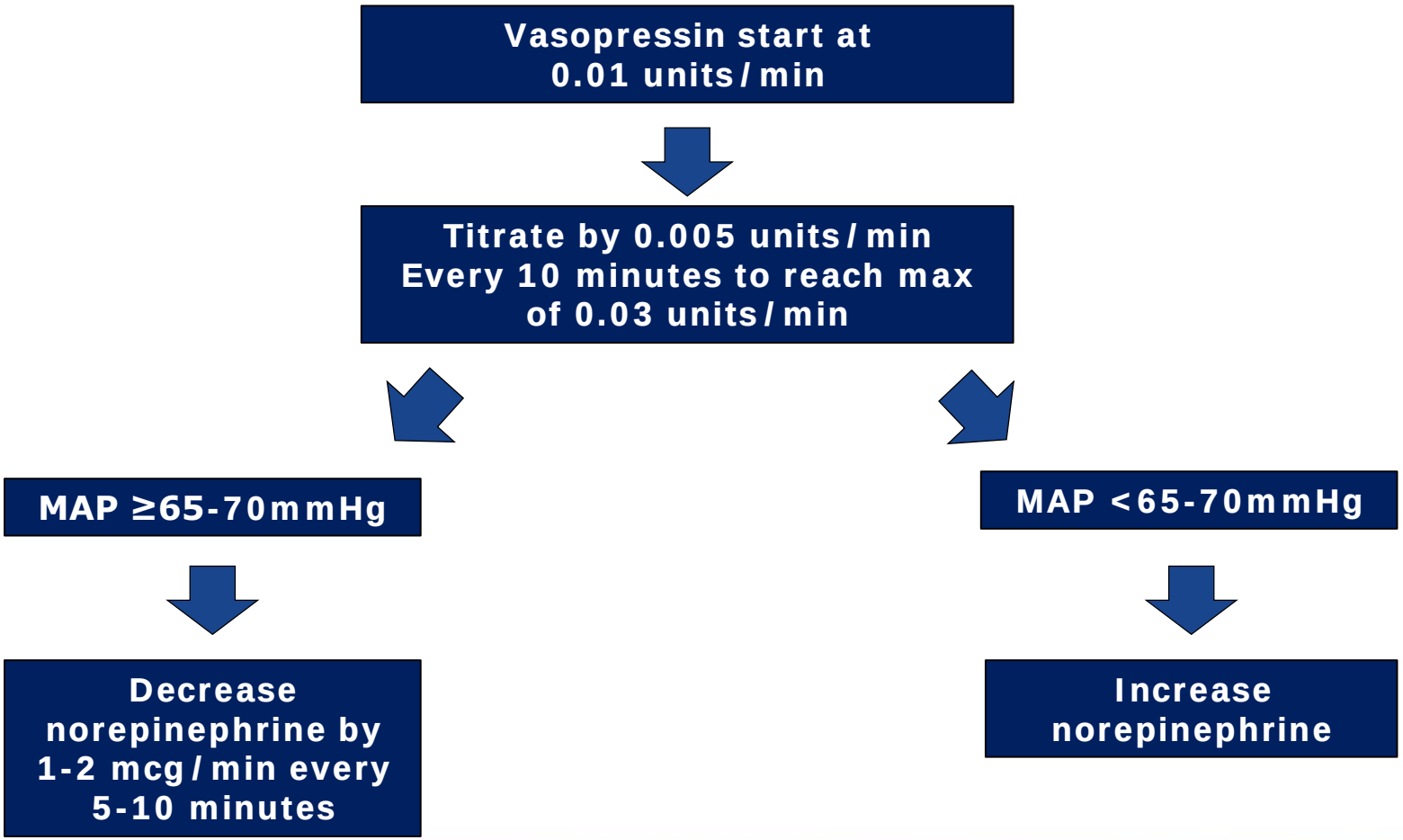
Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

VASST Trial

Design	Mutlicenter, international, randomized, double-blind trial
Population	• n = 778 • Refractory septic shock
Intervention	Vasopressin 0.01-0.03 units/min vs. Norepinephrine alone

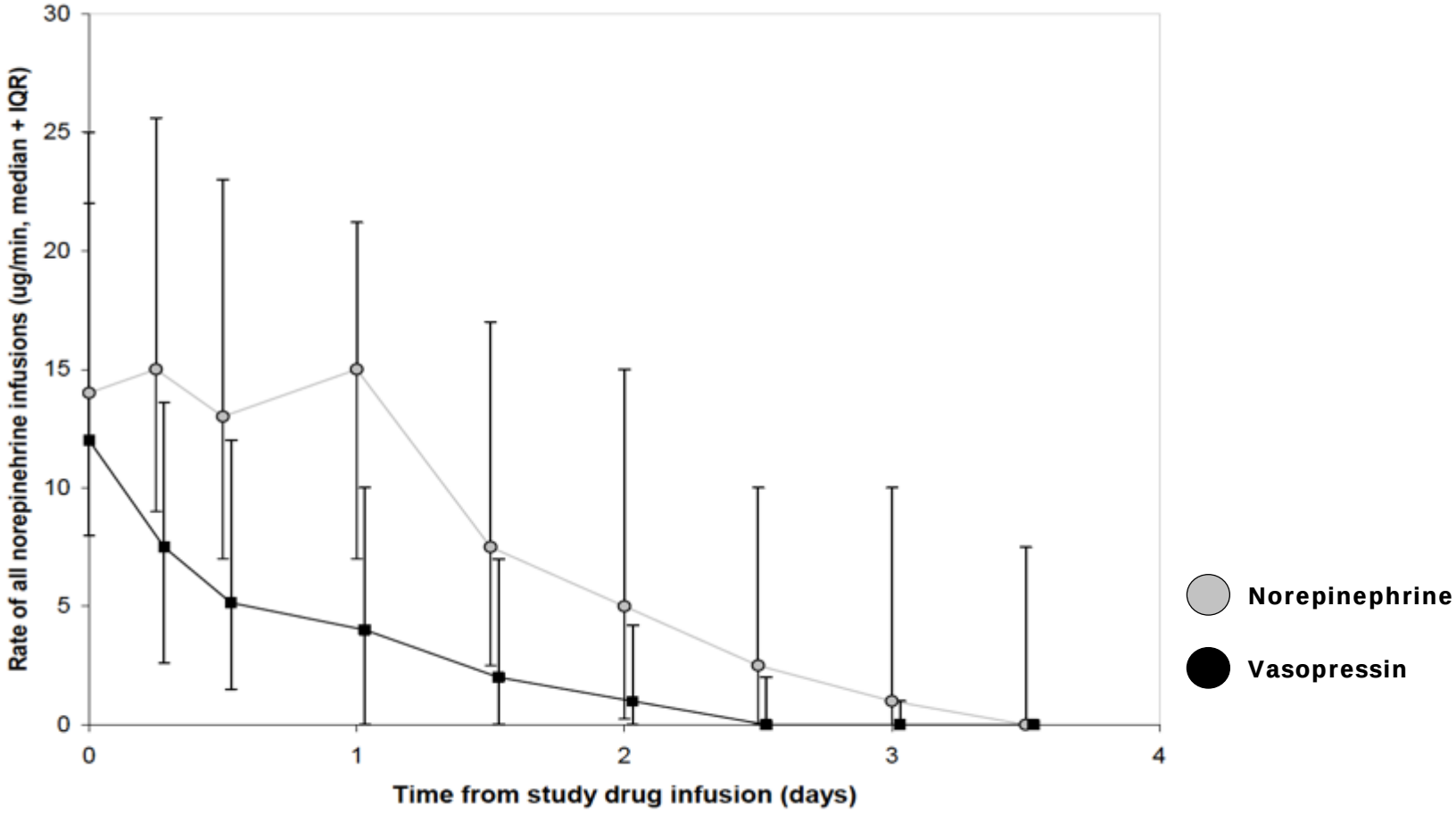
Russell JA, et al. New Engl J Med. 2008;358:877-87.

Drug Titration



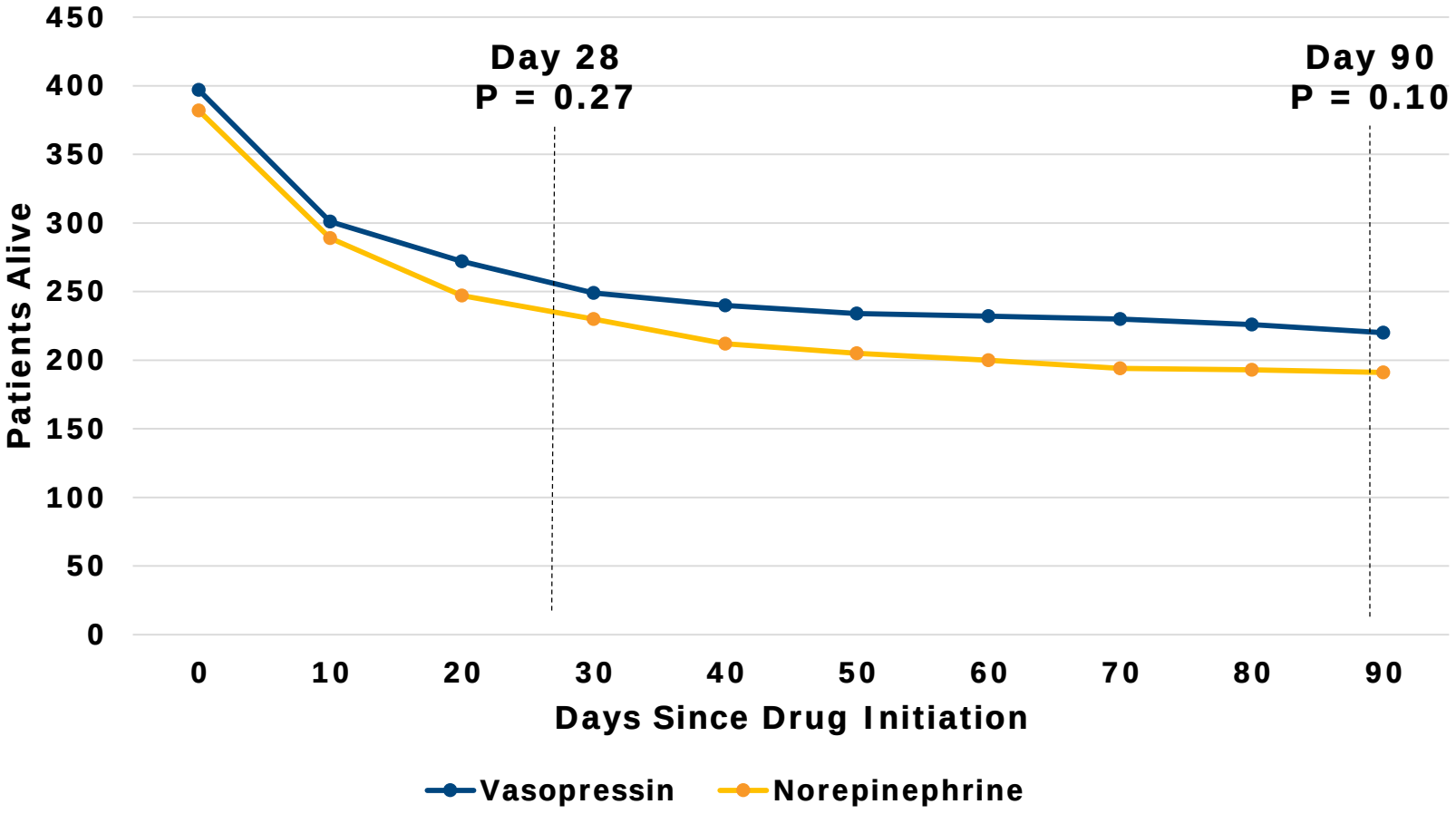
Russell JA, et al. New Engl J Med. 2008;358:877-87.

Norepinephrine Requirements



Russell JA, et al. New Engl J Med. 2008;358:877-87.

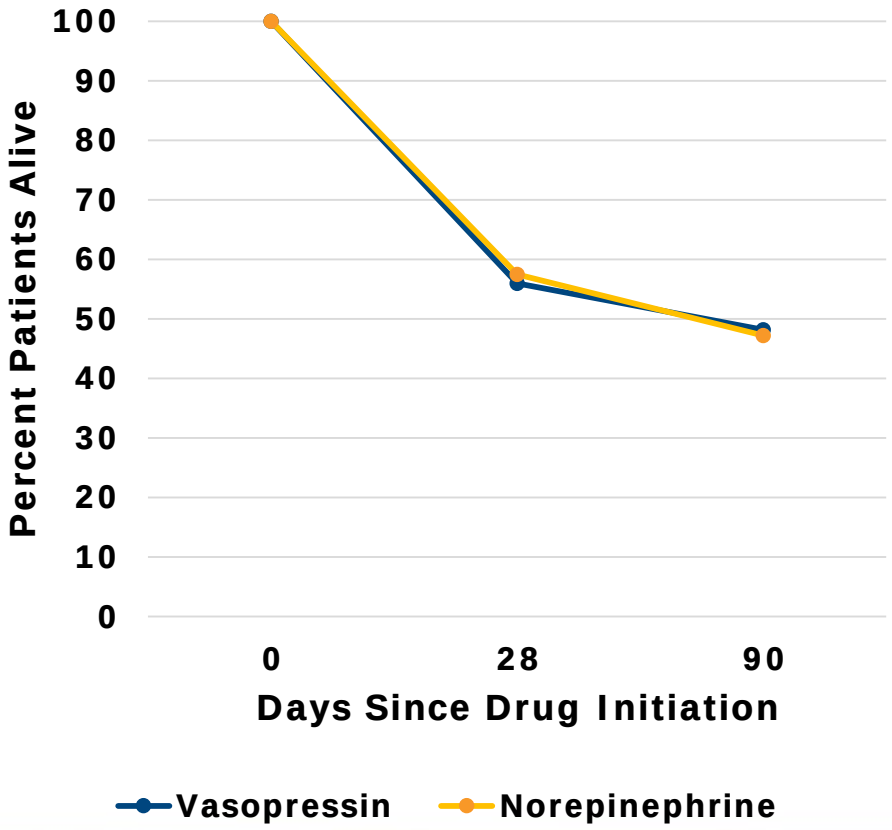
Mortality



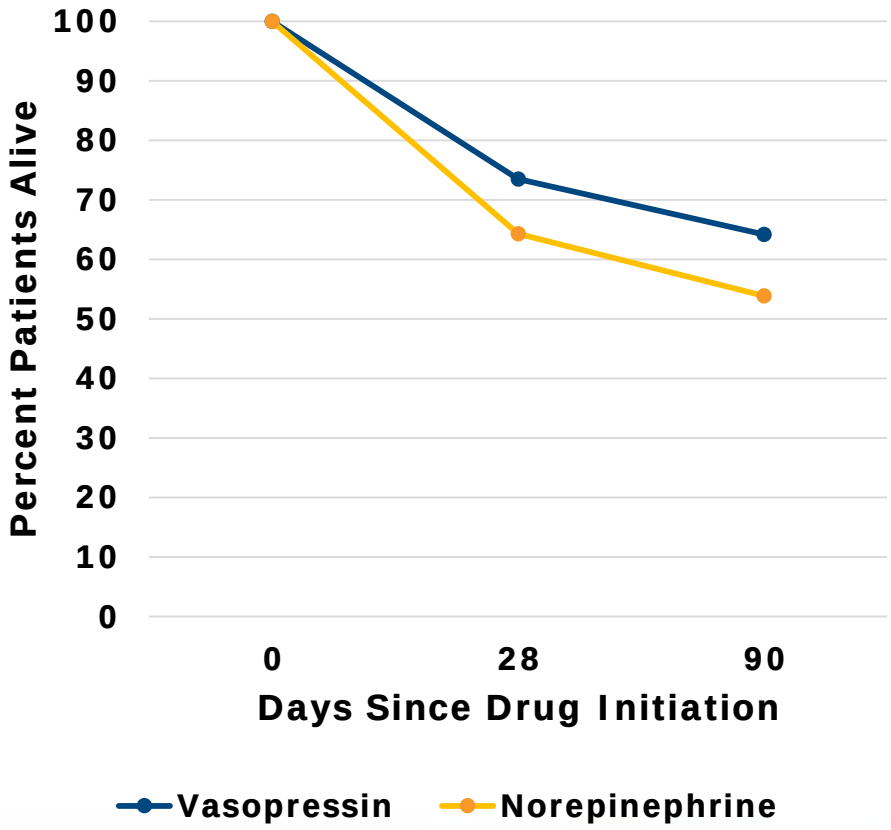
Russell JA, et al. New Engl J Med. 2008;358:877-87.

Subgroup Analyses

More Severe Septic Shock



Less Severe Septic Shock



Russell JA, et al. New Engl J Med. 2008;358:877-87.

Secondary Outcomes

Organ Dysfunction

Vasopressor free days Ventilator free days Renal replacement free days Organ failure free days SIRS free days	No significant differences

Adverse Effects

Acute myocardial infarction Cardiac arrest Life-threatening arrhythmia Digital ischemia Cerebrovascular accident	No significant differences

Russell JA, et al. New Engl J Med. 2008;358:877-87.

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

The VANISH Randomized Clinical Trial

Design

2x2 factorial, multicenter, double-blind, randomized controlled trial

Population

- n = 409
- Refractory septic shock

Intervention

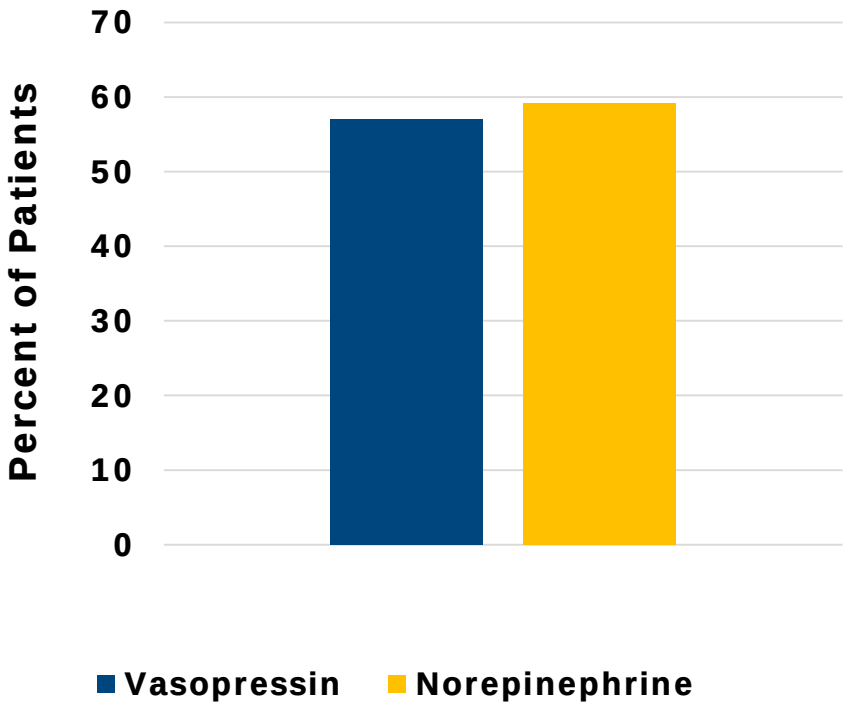
Vasopressin titrated up to 0.06 units/min
- With placebo
- With hydrocortisone

Norepinephrine
- With placebo
- With hydrocortisone

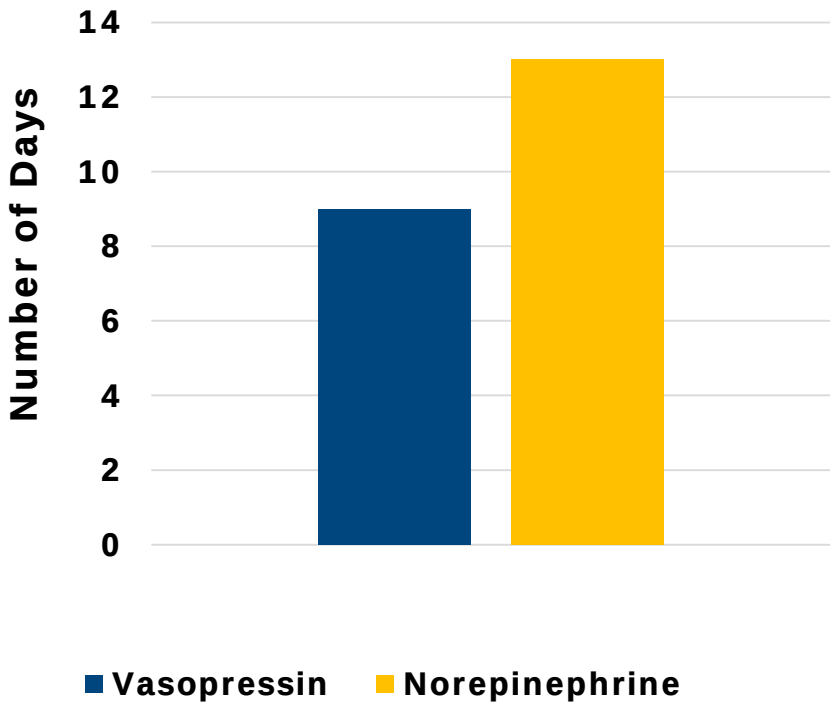
Gordon AC, et al. JAMA. 2016;316:509-518.

Primary Outcome

Renal Failure-Free Patients

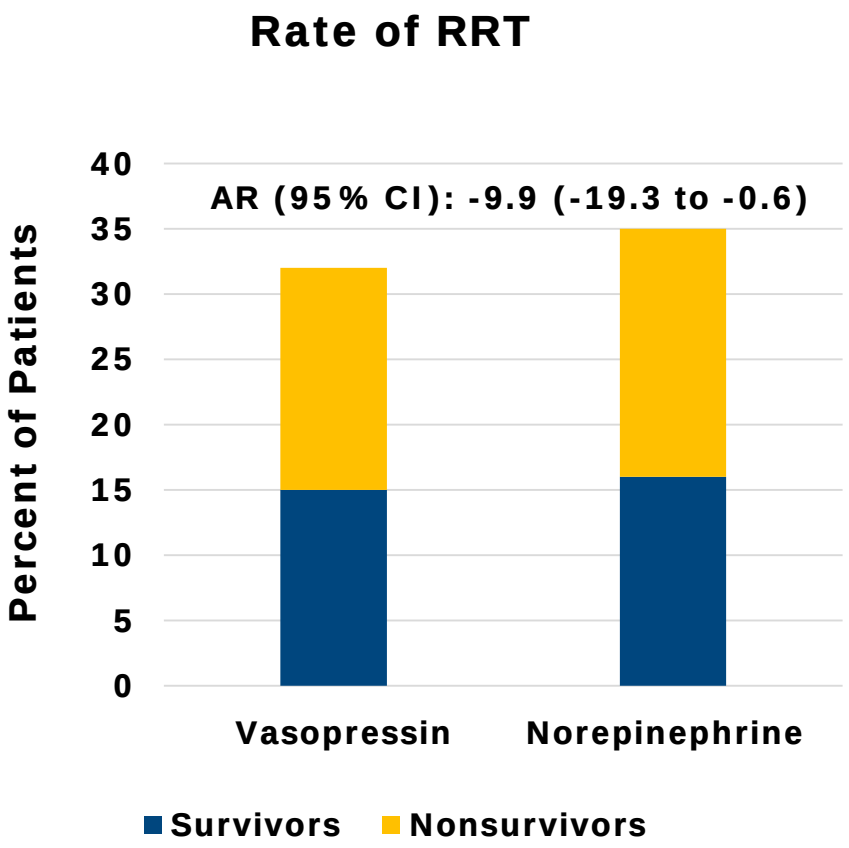


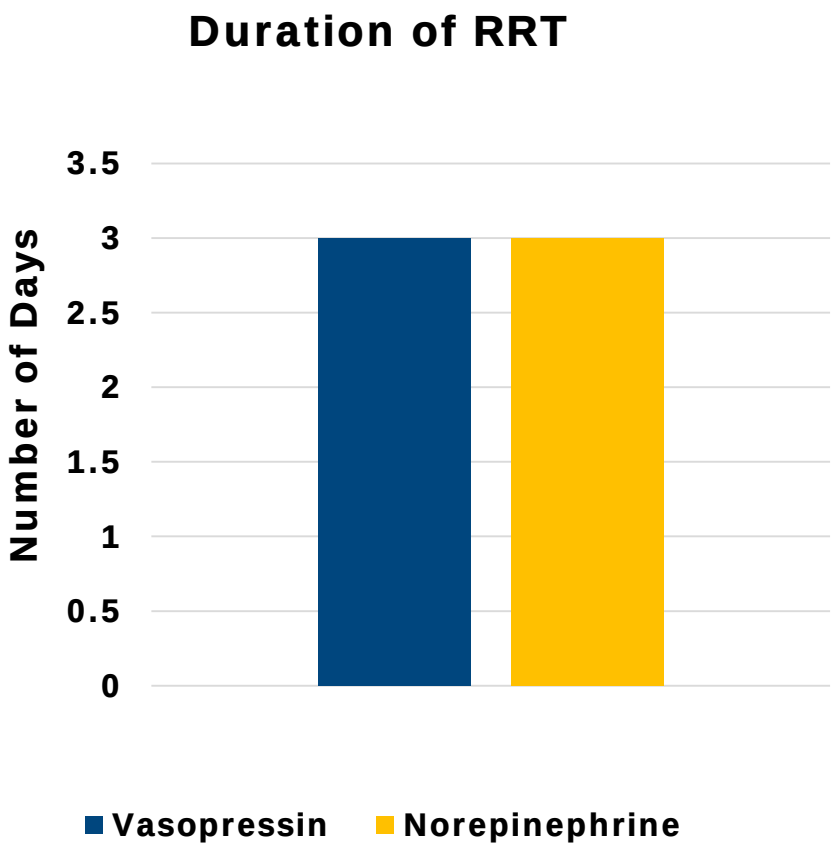
Renal Failure-Free Days



Gordon AC, et al. JAMA. 2016;316:509-518.

Renal Replacement Therapy (RRT)





Gordon AC, et al. JAMA. 2016;316:509-518.

Cost Considerations

Pre-April 2014

0.04 unit/min IV infusion
Average wholesale price (AWP): **$8.67/day**

April 2014
Vasopressin rebranded with indication for catecholamine refractory vasodilatory shock

April 2014-present

0.04 unit/min IV infusion
Average wholesale price (AWP): **$415.80/day**

Curtis N, et al. Am J Health-Syst Pharm. 2017;74:105-6.

Take Home Points

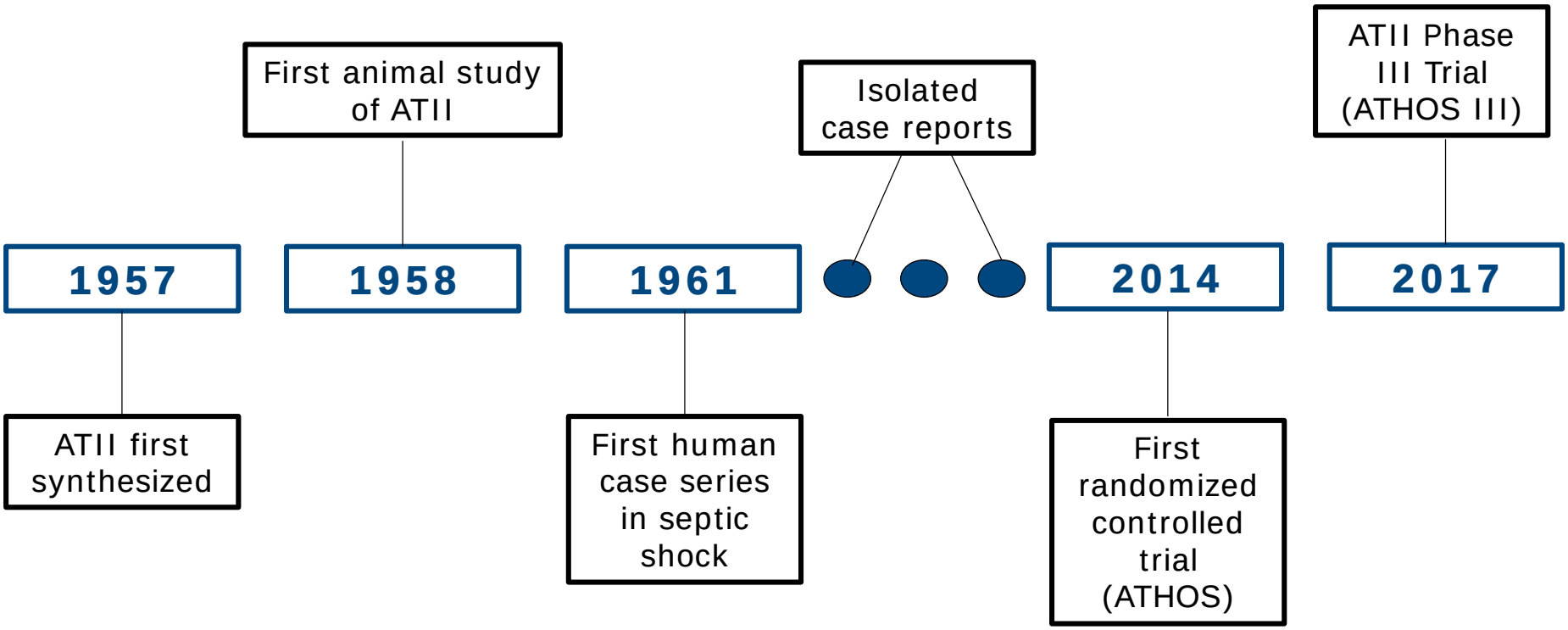
- **Early Scientific Data**
  - Observed decreased secretion of vasopressin in patients with septic shock
  - Suggested potential for vasopressin to reduce catecholamine dose requirements and improve outcomes in patients with septic shock

- **VASST & VANISH Trials**
  - No improvement in mortality with addition of vasopressin to catecholamine therapy
  - No reduction in adverse effects or outcomes with addition of vasopressin to catecholamine therapy

- **Bottom Line**
  - No strong evidence to support benefit of adding vasopressin to catecholamine therapy

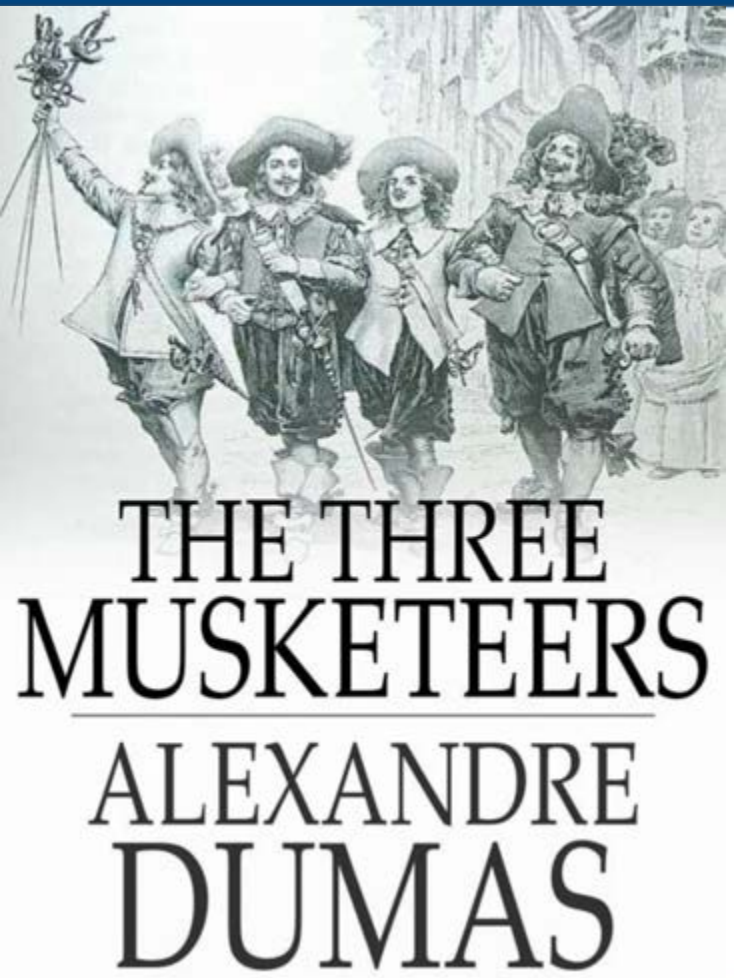
Angiotensin II

Angiotensin II: A History



Khanna A, et al. New Engl J Med. 2017;377:419-30.

The Three Musketeers



D'artagnan: Impetuous, hotheaded	Epinephrine
Porthos: Muscular, boisterous, vain	Norepinephrine
Aramis: Sophisticated, pensive	Vasopressin
Athos: Leader of the musketeers, mysterious, secretive	Angiotensin II

Bellomo R, et al. Crit Care Resusc. 2017;19:3-4.

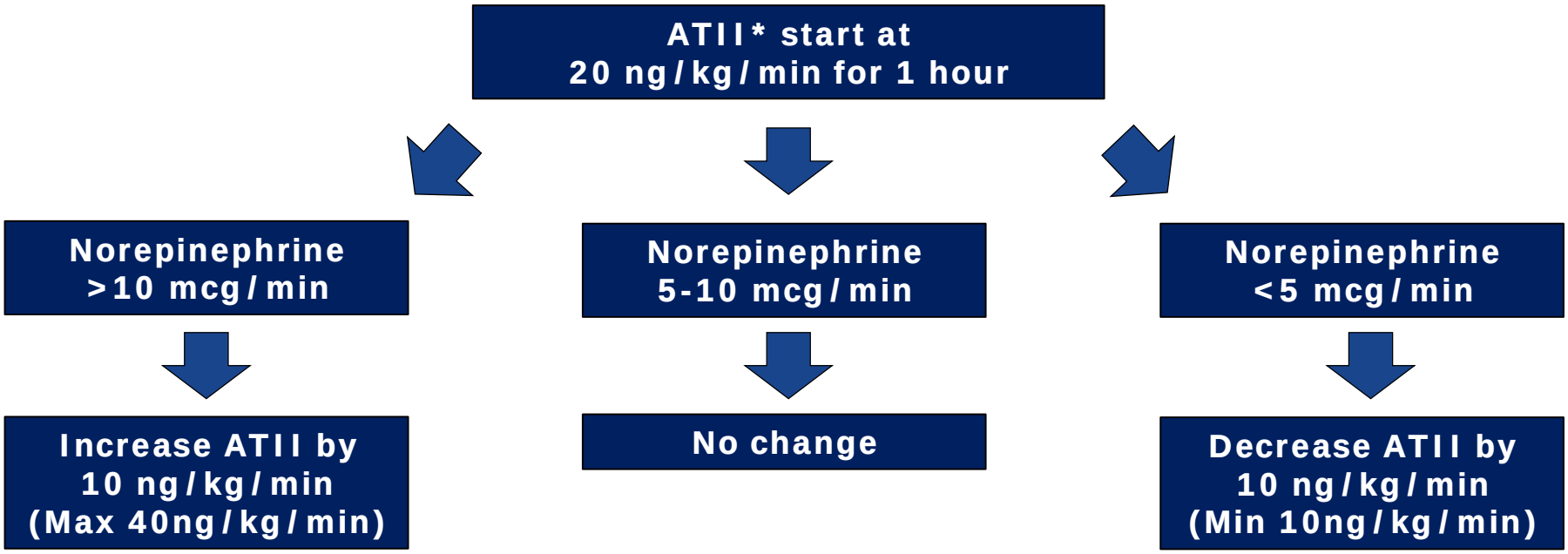
Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study

Design	Randomized controlled trial
Population	• n = 20 • Refractory septic shock
Intervention	ATII vs. Norepinephrine alone

ATII: Angiotensin II

Chawla LS, et al. Crit Care. 2014;18:534.

Drug Titration



Infusions co-titrated to maintain mean arterial pressure (MAP) of 65

Assessments repeated every hour for 6 hours

Chawla LS, et al. Crit Care. 2014;18:534.

Primary Outcome

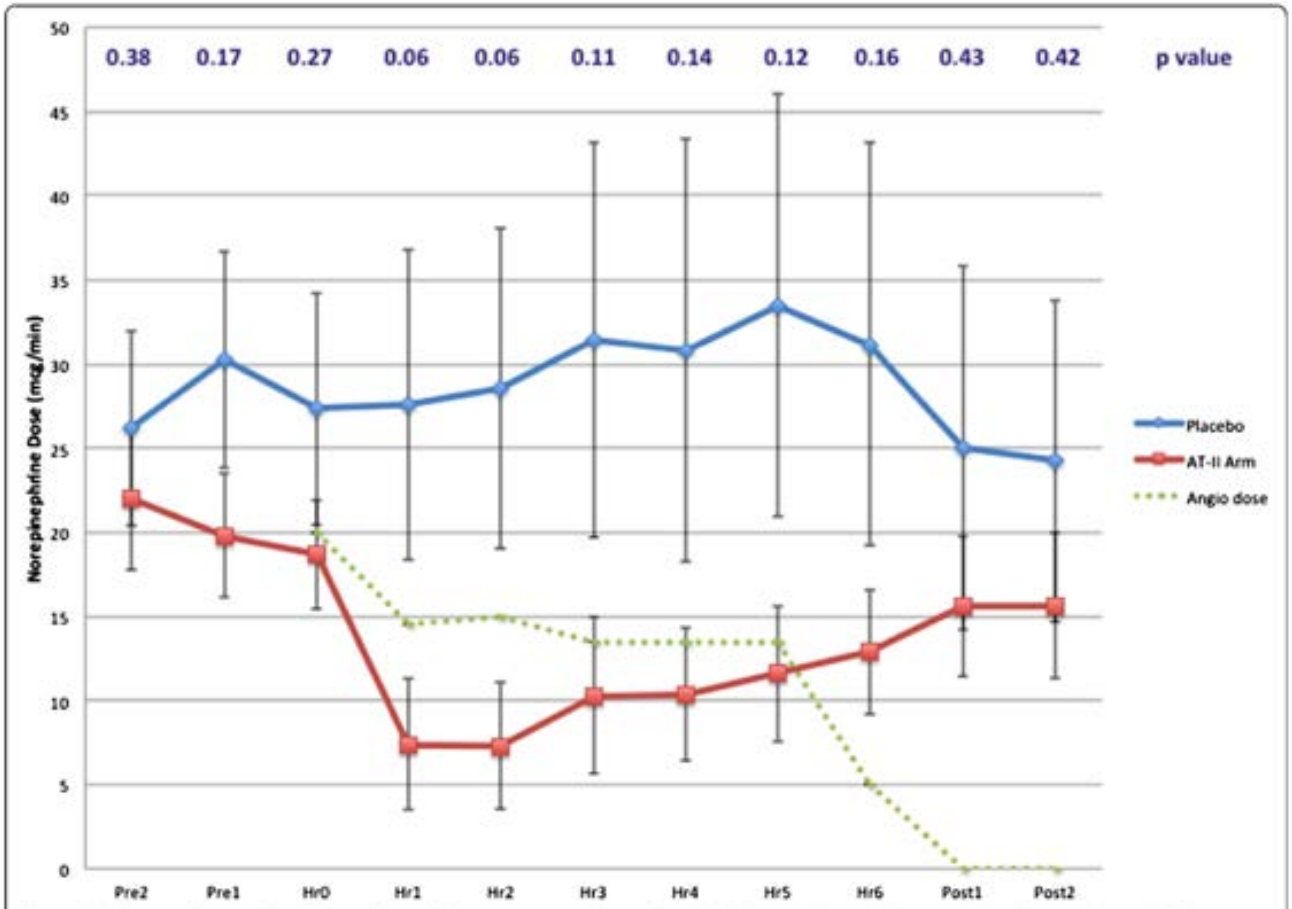
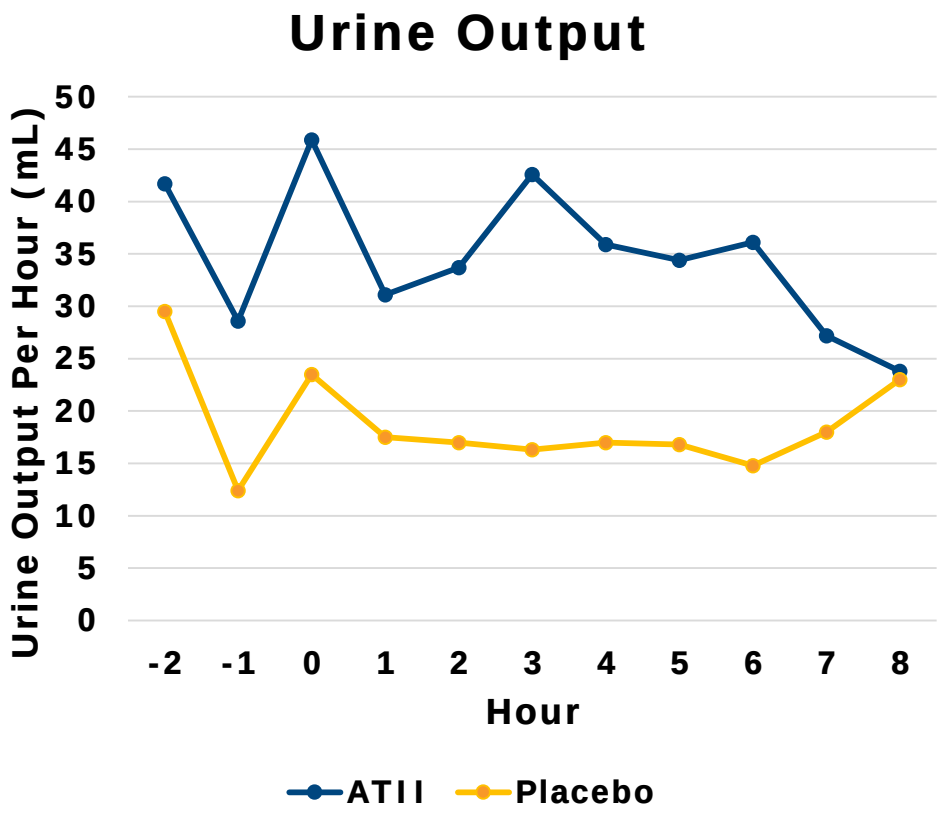
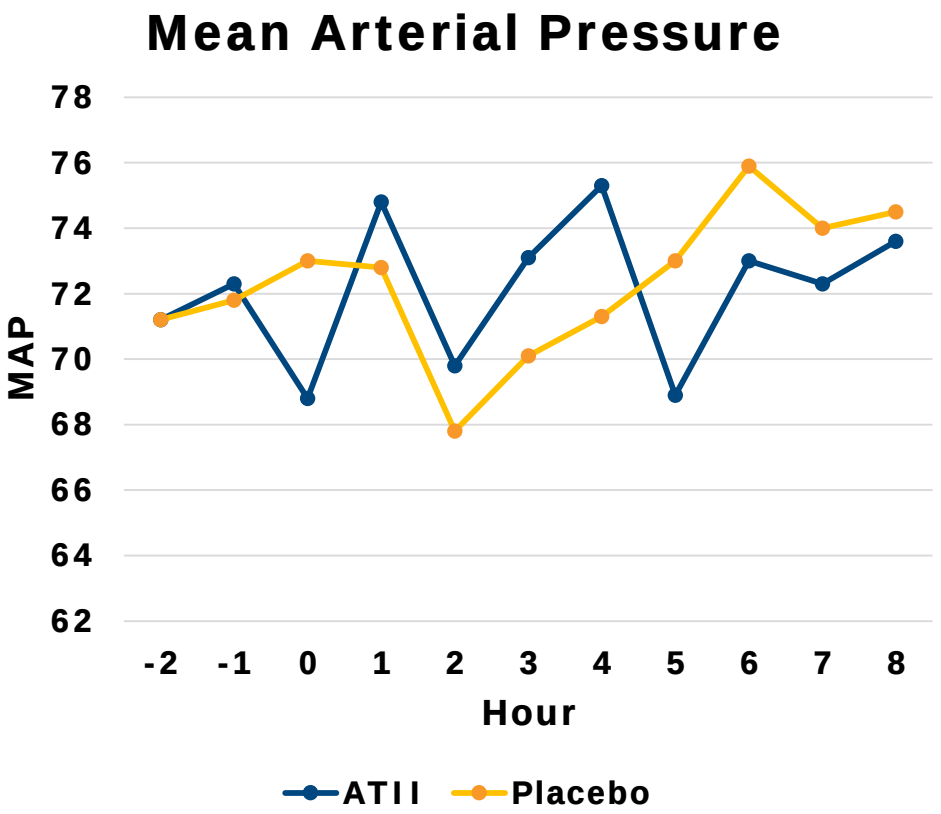


Figure 3 Changes in norepinephrine dose with concurrent angiotensin II. AT-II arm, angiotensin-II arm; Angio dose, angiotensin-II dose.

Chawla LS, et al. Crit Care. 2014;18:534.

Secondary Outcomes





Chawla LS, et al. Crit Care. 2014;18:534.

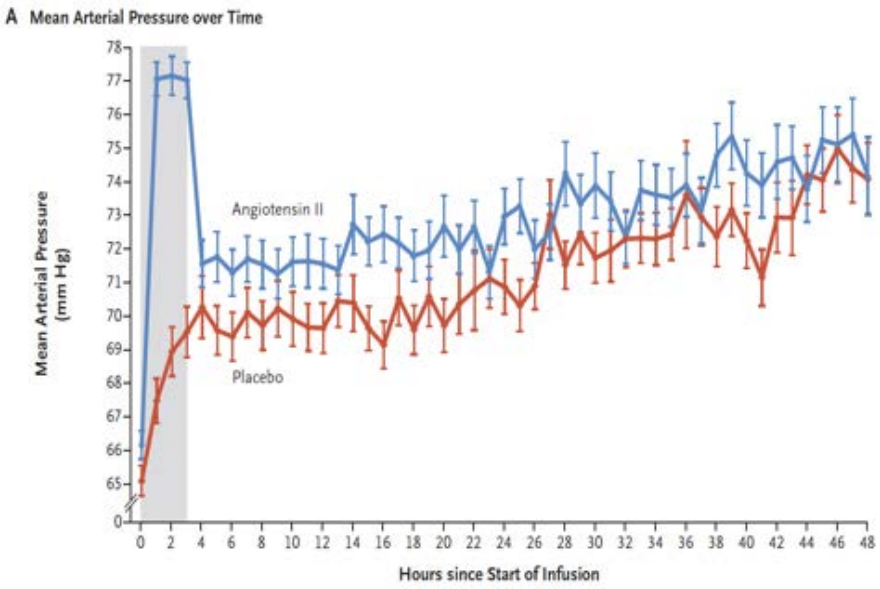
Angiotensin II for the Treatment of Vasodilatory Shock

ATHOS-3 Trial

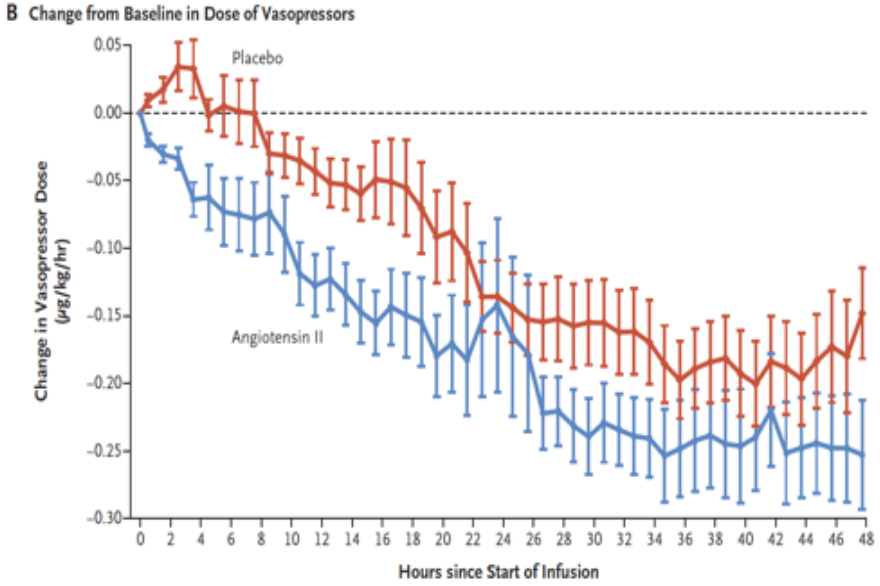
Design	Phase III, international, multicenter, randomized, placebo-controlled trial
Population	• n = 321 • Refractory septic shock
Intervention	ATII vs. Norepinephrine alone

Khanna A, et al. New Engl J Med. 2017;377:419-30.

Primary Outcome



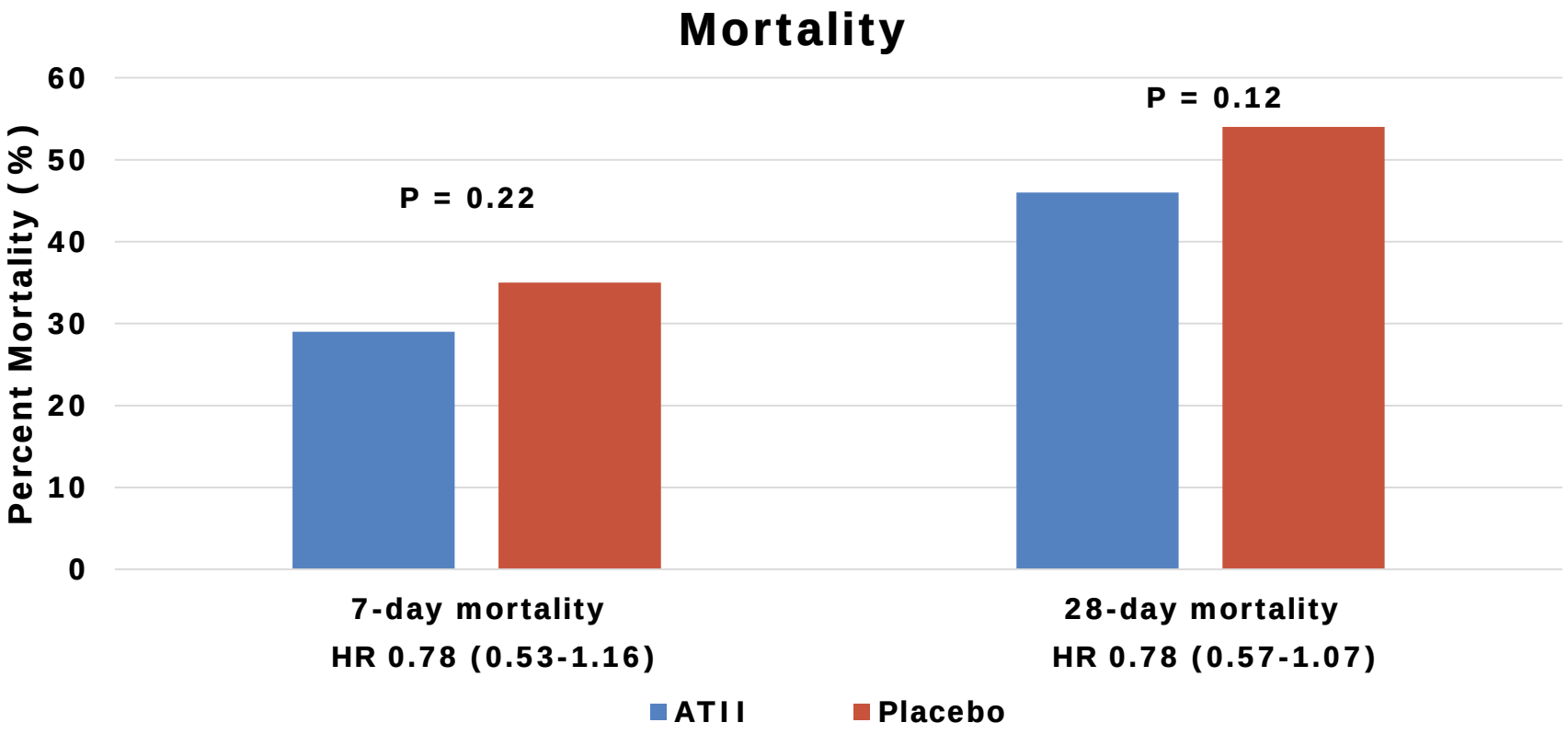
MAP response at 3 hours:
OR 7.95 (95% CI 4.76-13.3), **p <0.001**



Mean change in norepinephrine dose at 3 hours:
-0.03 vs. 0.03, **p <0.001**

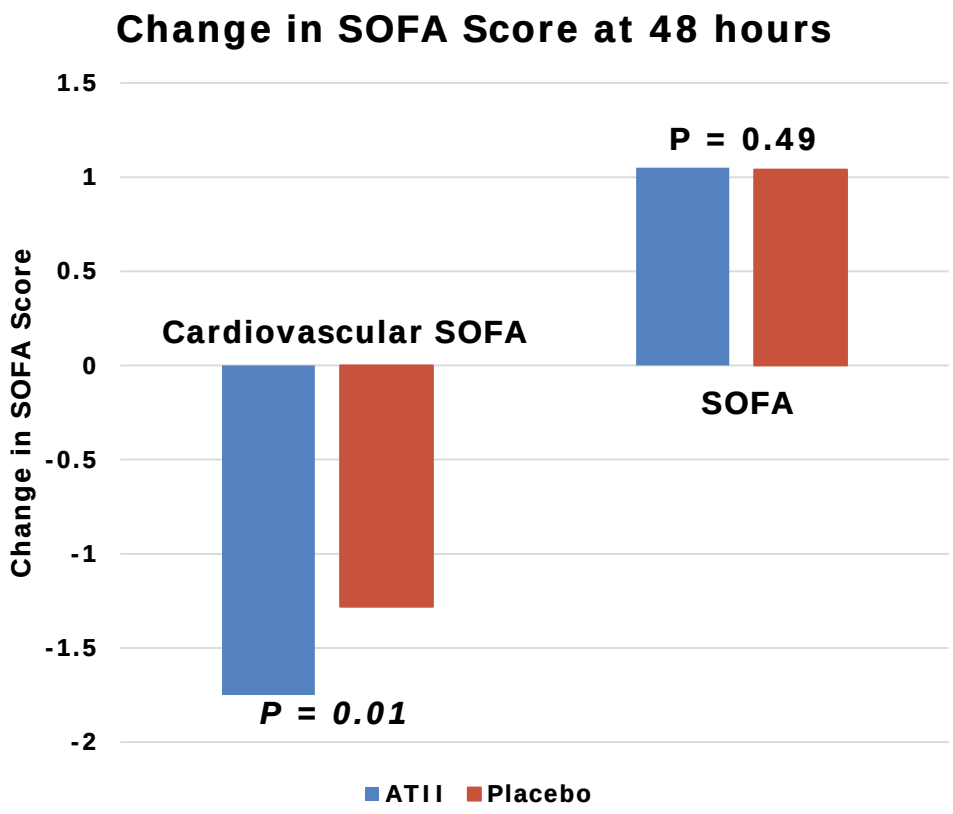
Khanna A, et al. New Engl J Med. 2017;377:419-30.

ATHOS 3: Secondary Outcomes



Khanna A, et al. New Engl J Med. 2017;377:419-30.

SOFA Scores

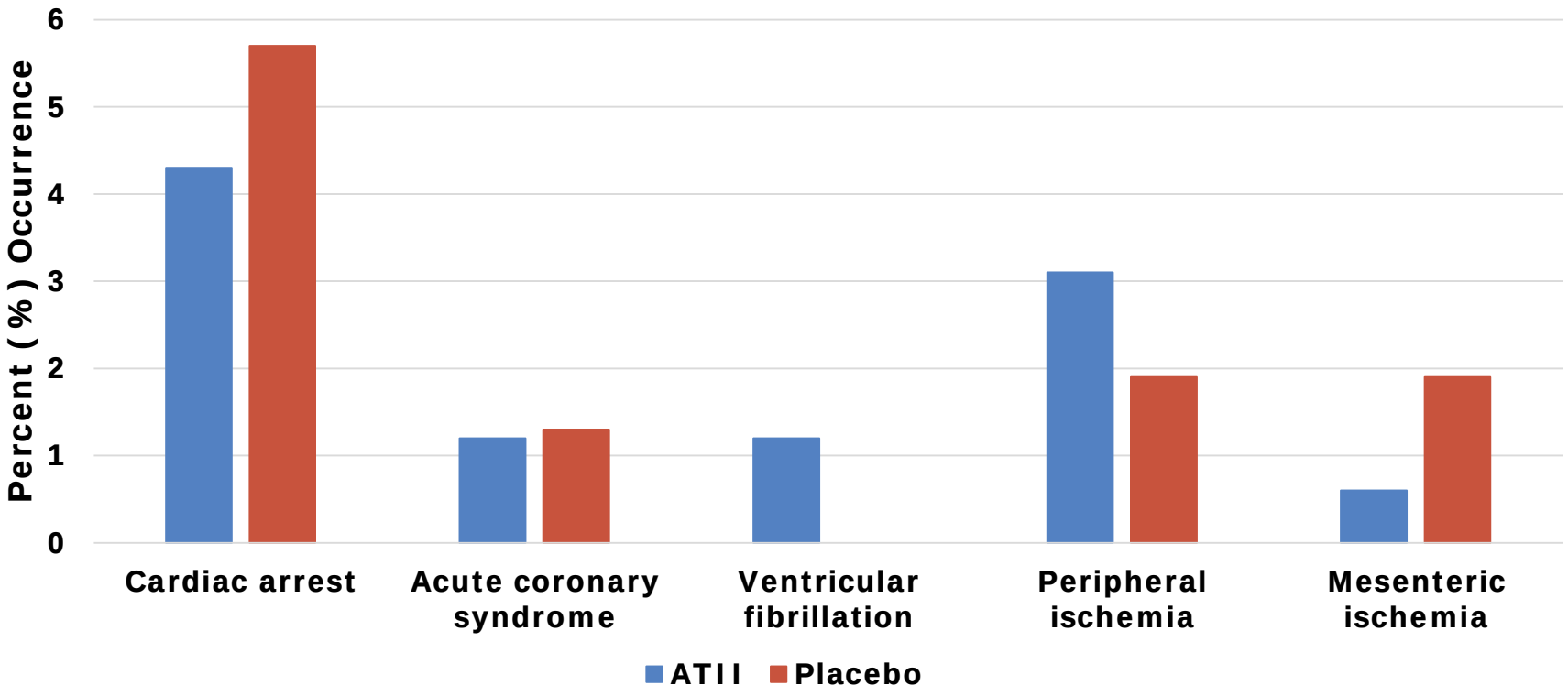


Cardiovascular SOFA Scoring	
Characteristic	Score
MAP ≥ 70mmHg	0
MAP < 70mmHg	1
Dopamine ≤ 5 mcg/kg/min	2
Norepinephrine ≤ 0.1 mcg/kg/min	3
Norepinephrine > 0.1 mcg/kg/min	4

SOFA: Sequential Organ Failure Assessment Score

Khanna A, et al. New Engl J Med. 2017;377:419-30.

Adverse Events



Khanna A, et al. New Engl J Med. 2017;377:419-30.

Conflicts of Interest

Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study

Lakhmir S Chawla[1,3*], Laurence Busse[2], Ermira Brasha-Mitchell[3], Danielle Davison[3], Jacqueline Honiq[3], Ziyad Alotaibi[4] and Michael G Seneff[3]

Angiotensin II for the Treatment of Vasodilatory Shock

Ashish Khanna, M.D., Shane W. English, M.D., Xueyuan S. Wang, M.D., Kealy Ham, M.D., James Tumlin, M.D., Harold Szerlip, M.D., Laurence W. Busse, M.D., Laith Altaweel, M.D., Timothy E. Albertson, M.D., M.P.H., Ph.D., Caleb Mackey, M.D., Michael T. McCurdy, M.D., David W. Boldt, M.D., Stefan Chock, M.D., Paul J. Young, M.B., Ch.B., Ph.D., Kenneth Krell, M.D., Richard G. Wunderink, M.D., Marlies Ostermann, M.D., Ph.D., Raghavan Murugan, M.D., Michelle N. Gong, M.D., Rakshit Panwar, M.D., Johanna Hästbacka, M.D., Ph.D., Raphael Favory, M.D., Ph.D., Balasubramanian Venkatesh, M.D., B. Taylor Thompson, M.D., Rinaldo Bellomo, M.D., Jeffrey Jensen, B.S., Stew Kroll, M.A., Lakhmir S. Chawla, M.D., George F. Tidmarsh, M.D., Ph.D., and Adam M. Deane, M.D., for the ATHOS-3 Investigators*

Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3): protocol for a phase III, double-blind, randomised controlled trial

Lakhmir S Chawla, James A Russell, Sean M Bagshaw, Andrew D Shaw, Stuart L Goldstein, Mitchell P Fink and George F Tidmarsh

Lakhmir Chawla and George Tidmarsh are employees of and own stock in La Jolla Pharmaceutical Company, are medical monitors for the study, and have assigned patents relating to the use of angiotensin II for hypotension.

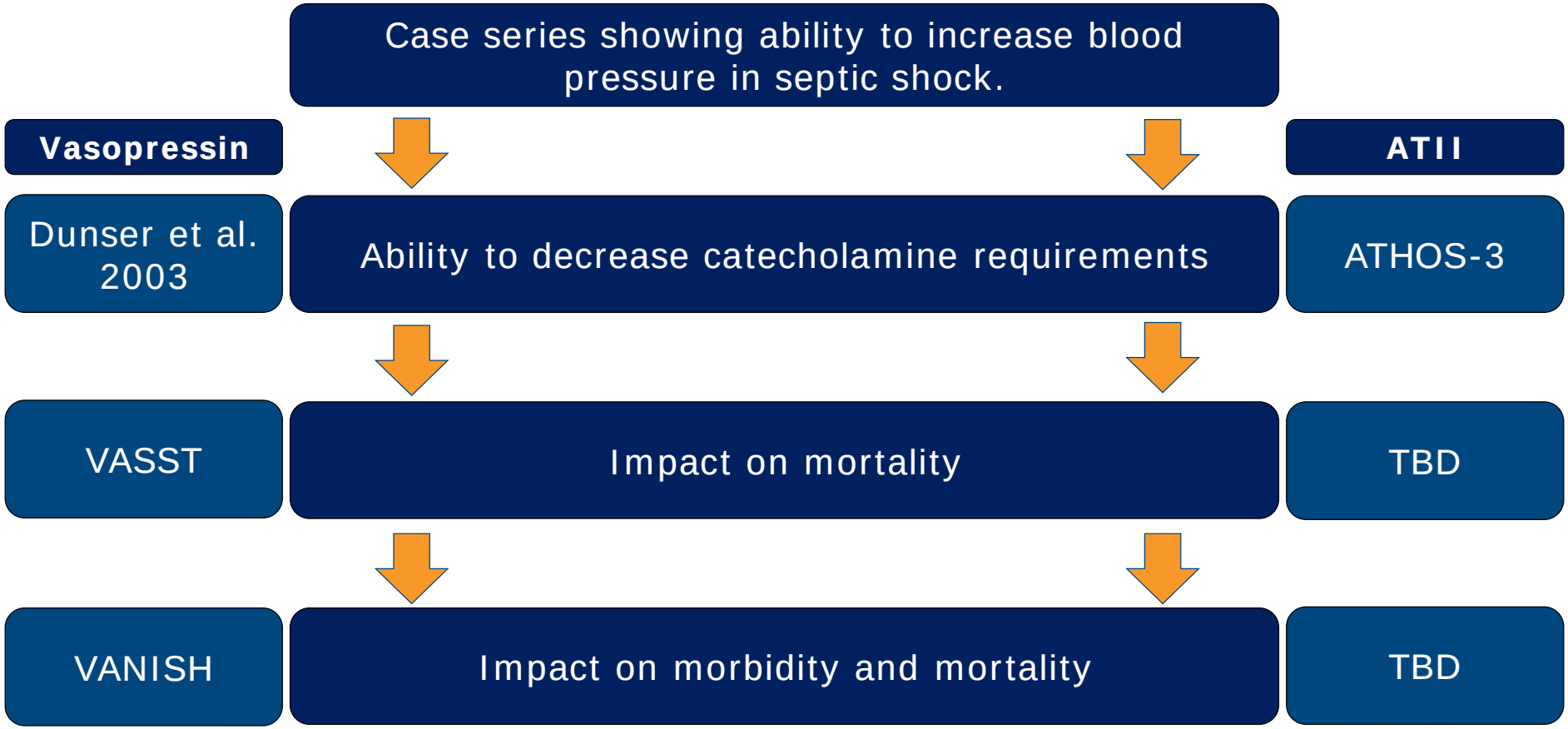
Take Home Points

- **ATHOS & ATHOS 3 trials**
  - ATII increases MAP and decreases norepinephrine dose requirements
  - No significant differences in clinically significant outcomes

- **Clinical Application**
  - ATII represents an option to increase MAP in catecholamine refractory patients with vasodilatory shock
  - Evidence to support clinical benefits of using ATII at this time are lacking

- **Areas for Future Research**
  - Larger studies powered to investigate clinically significant outcomes
  - Subgroup analyses to determine patient populations in which ATII may be preferable to standard of care

Vasopressin versus Angiotensin II



Conclusions

Morbidity and mortality in septic shock remain high despite current standard of care

Vasopressin and angiotensin II represent options to assist in hemodynamic maintenance in catecholamine refractory septic shock.

Current evidence does not support the use of vasopressin to reduce morbidity or mortality in catecholamine refractory septic shock.

Angiotensin II has not yet been demonstrated to improve morbidity or mortality, however further evidence is needed to determine a potential role in therapy.

Questions?

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September 27, 2017

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The New England Journal of Medicine

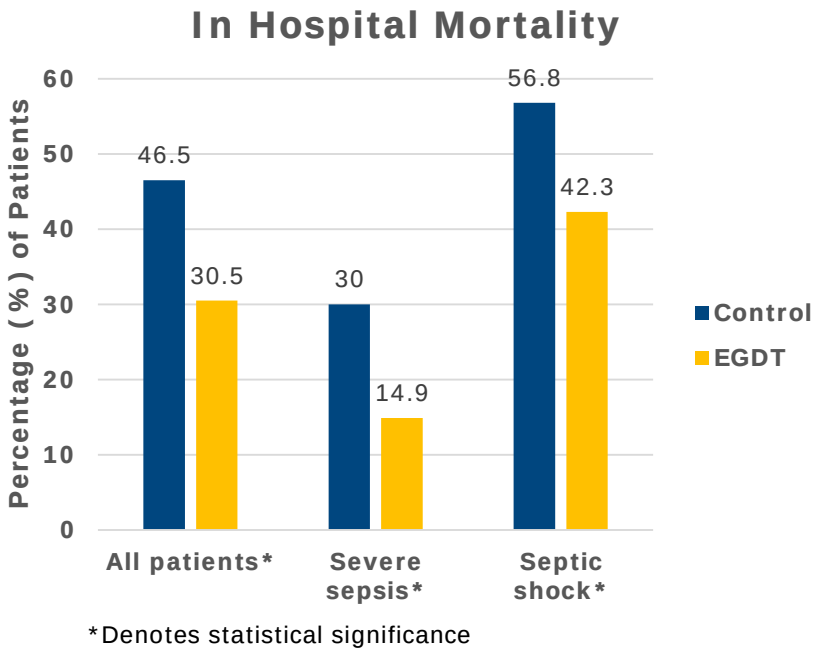
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S.,

Design	Randomized controlled trial

Population	• n = 263
	• Patients presenting to ED with severe sepsis or septic shock
	  • 2 of 4 SIRS criteria
	  • SBP <90 mmHg (after fluid resuscitation*)
	  • Lactate >4 mmol/L

Intervention	Early goal-directed therapy or standard care
Outcomes	Primary: In-hospital mortality

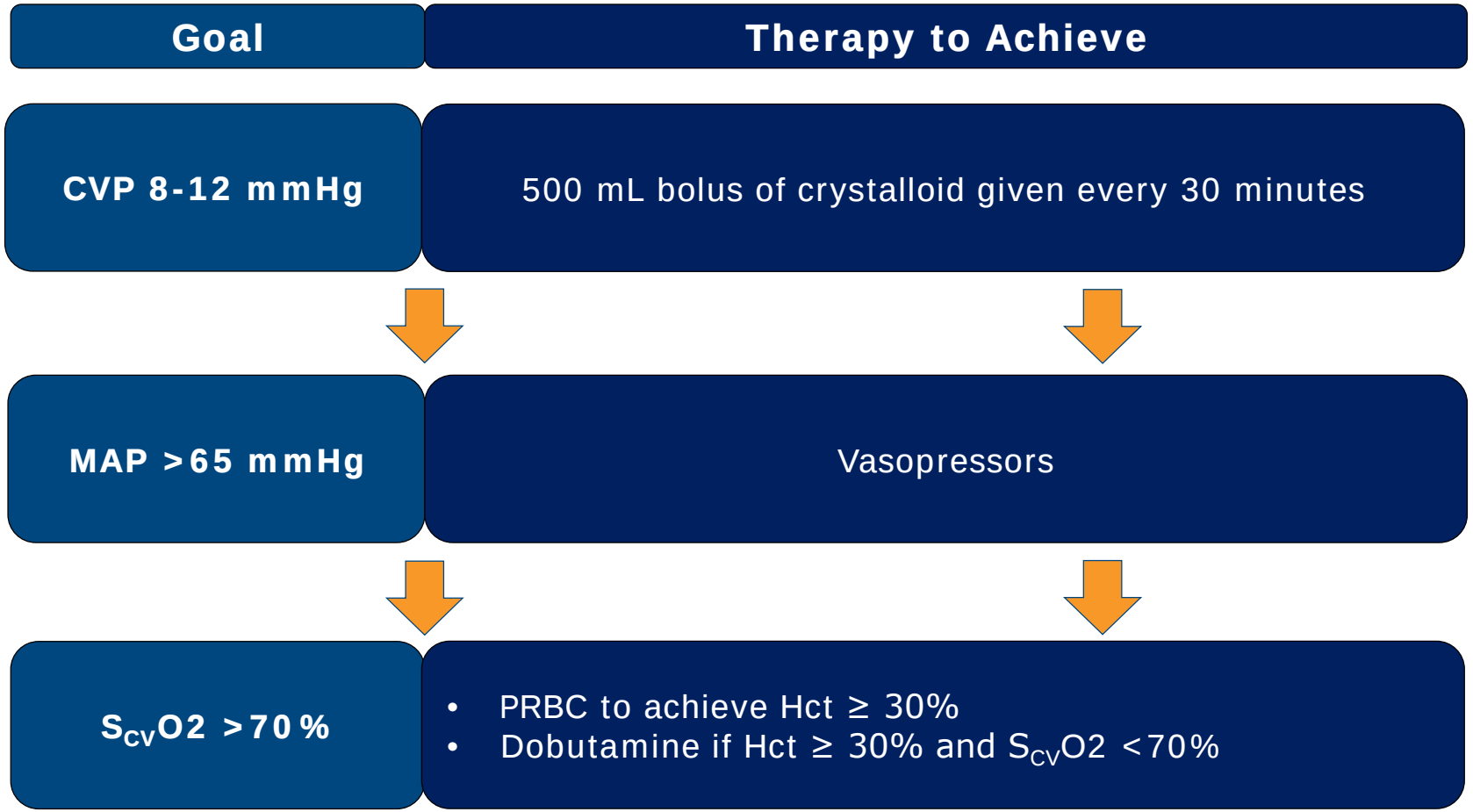


*Denotes statistical significance

ED: Emergency department; EGDT: Early goal-directed therapy; SIRS: Systemic inflammatory response syndrome; SBP: Systolic blood pressure

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New Engl J Med 2001;345(19)1368-77.

Early Goal Directed Therapy



CVP: Central venous pressure; Hct: Hematocrit MAP: Mean arterial pressure; PRBC: Packed red blood cells; SCVO2: Central venous oxygen saturation

Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New Engl J Med 2001;345(19)1368-77.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

Surviving Sepsis Campaign Bundle

Within 3 Hours

Measure lactate

Obtain blood cultures prior to administration of antibiotics

Administer broad spectrum antibiotics

Administer 30 mL/kg crystalloid for hypotension or lactate >4 mmol/L

Within 6 Hours

Administer vasopressors for hypotension refractory to fluid resuscitation to maintain MAP >65 mmHg

Re-measure lactate if initial lactate elevated

Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017; 43(3):304-377

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

Surviving Sepsis Bundle in Practice

Trial	Study Population	Intervention	Conclusion
ProCESS (2014)	n = 1343 31 United States academic center	EGDT vs. Protocolized standard care vs. Standard care	No difference in all-cause in-hospital mortality at 60 days
ARISE (2014)	n = 1591 51 centers in Australasia	EGDT vs. Standard care	No difference in all-cause mortality at 90 days
PROMISE (2015)	n = 1260 56 sites in United Kingdom	EGDT vs. Standard care	No difference in mortality or clinically important outcomes at 90 days

Angus DC, et al. "A randomized trial of protocol-based care for early septic shock". *The New England Journal of Medicine*. 2014. 370(10):1683-1693.

ARISE and ANZICS writers. "Goal-directed resuscitation for patients with early septic shock". *The New England Journal of Medicine*. 2014. 371(16):1496-1506.

Mouncey PR, et al. "Trial of early, goal-directed resuscitation for septic shock". *The New England Journal of Medicine*. 2015. 372(14):1301-1311.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

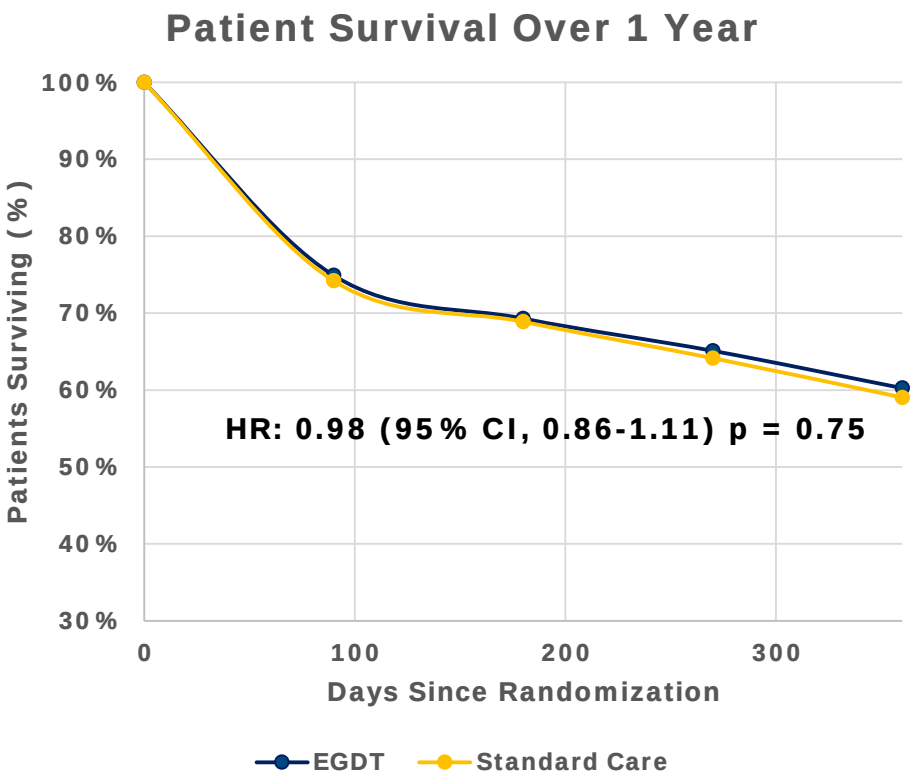
The PRISM Investigators*

Design	Meta-analysis of patient data from ProCESS, ARISE, and PROMISE trials
Population	• n = 3273 • 138 hospitals in 7 countries

Outcomes	• Primary: All-cause mortality at 90 days
	• Secondary:
	  • In-hospital mortality
	  • 28-day mortality
	  • Duration of survival to one year
	  • Duration of hospital stay
	  • Duration of mechanical ventilation, vasopressors, and renal replacement therapy
	  • Costs and cost-effectiveness at 90 days

The PRISM Investigators. Early, goal-directed therapy for septic shock- a patient level meta-analysis. New Engl J Med 2017;376:2223-34.

PRISM: Results



Need for Organ Support	
Type	**Hazard Ratio (% receiving)**
Mechanical Ventilation	1.05 (0.89 to 1.24) p = 0.57
Vasopressors or Inotropes	1.42 (1.23 to 1.64) p = <0.001
Renal Replacement Therapy	1.02 (0.81 to 1.28) p = 0.88

Conclusion: No significant difference with EGDT in patient survival.

The PRISM Investigators. Early, goal-directed therapy for septic shock- a patient level meta-analysis. New Engl J Med 2017;376:2223-34.

What Is the Harm?: Fluids

- **Positive Fluid Balances Associated with Mortality**
  - Sadaka et al. (2014)
    - Positive balance at 24 hours increased risk of mortality
      - HR 1.519 (1.353 to 1.685) for 12-L (+) vs. 6-L (+).
  - Sirvent et al. (2015)
    - Positive balance at 48, 72, and 96 hours increased risk of mortality
  - Boyd et al. (2011)
    - More positive fluid balances at 12 hours and 4 days correlated with mortality.
    - Survival was highest in patients 3-L (+) at 12 hours.
  - Micek et al. (2013)
    - Non-survivors of septic shock had higher positive fluid balance
      - 4374 mL vs. 2959 mL, p = 0.004
  - Marik et al. (2017)
    - Review of premier hospital database (n= 23,513)
    - **2.3% increased mortality with each liter above 5 L**

Sadaka F, et al. J Intensive Care Med. 2014;29(4):213-7.
Sirvent J, et al. Am J Emerg Med. 2015;33(2):186-9.
Boyd JH, et al. Crit Care Med. 2011;39(2): 259-265.
Micek ST, et al. Crit Care. 2013:17:R246.
Marik PE, et al. Intensive Care Med 2017; 43:625–632.
Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

What is the Harm?: Catecholamines

- Schmittinger (2012)
  - Surgical intensive care unit patients
  - Factors independently associated with adverse cardiac events:
    - Number catecholamine vasopressors: OR 1.73; 95% CI 1.08-2.77; p = 0.02
    - Duration of catecholamine vasopressor therapy: OR 1.01; 95% CI 1-1.01; p = 0.002
  - Patients with adverse cardiac events had higher mortality: 25.9% vs. 1.7%, p < 0.001

Catecholamine	Adverse Effects
Norepinephrine	Tachycardia Peripheral/GI ischemia
Epinephrine	Tachycardia Peripheral/GI ischemia
Dopamine	Tachycardia Arrhythmias
Phenylephrine	Reflex bradycardia

Schmittinger CA, Torgersen C, Luckner G, et al. Adverse cardiac events during catecholamine vasopressor therapy: a prospective observational study. Intensive Care Med. 2012;38(6):950-958.
Belletti A, Castro ML, Silvetti S, et al. The effect of inotropes and vasopressors on mortality: a meta-analysis of randomized clinical trials. Br J Anaesth. 2015; 115(5):656-75.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

Arginine Vasopressin in Advanced Vasodilatory Shock

A Prospective, Randomized, Controlled Study

Design	Prospective, randomized, controlled study

Population	• n = 48
	• Vasodilatory shock due to cardiovascular surgery or sepsis
	  • MAP <70 mmHg
	• Refractory to:
	  • Volume resuscitation (fluid administration based on stroke volume response)
	  • High-dose vasopressors (> 0.5 mcg/kg/min norepinephrine)

Intervention	• Vasopressin 4 units/h + standard of care Or • Standard of care

Outcomes	• Primary: "Differences in hemodynamics between groups during 48-h observation period"
	• Secondary: Changes in single-organ function
	  • GI mucosal: gut mucosal $PrCO_2$ to arterial $PrCO_2$ gradient
	  • Acid-base: arterial lactate, pH
	  • Renal: SCr
	  • Hepatic: AST, ALT, Tbili
	  • Heme: Platelets
	  • Cardiac: Troponin

Dunser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock. Circulation. 2003;107:2313-9.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

Arginine Vasopressin in Advanced Vasodilatory Shock

A Prospective, Randomized, Controlled Study

Organ System	Difference
GI mucosa	$PrCO_2$: 63±25 vs. 67±24, p = 0.03 Pr-aCO_2: 20±24 vs. 21±24, p = 0.014
Acid-Base	Not significant
Renal	Not significant
Hepatic	AST, ALT: No difference Bilirubin: 9.26±5.81 vs. 3.86±5.56, p = 0.001
Heme	Not significant
Cardiac	Not significant

ICU Mortality: 70.8% vs. 70.8%, p = 1

Conclusion: Vasopressin improved MAP and lowered Norepinephrine dose requirements, without observed impact on mortality

Dunser MW, Mayr AJ, Ulmer H, et al. Arginine vasopressin in advanced vasodilatory shock. Circulation. 2003;107:2313-9.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

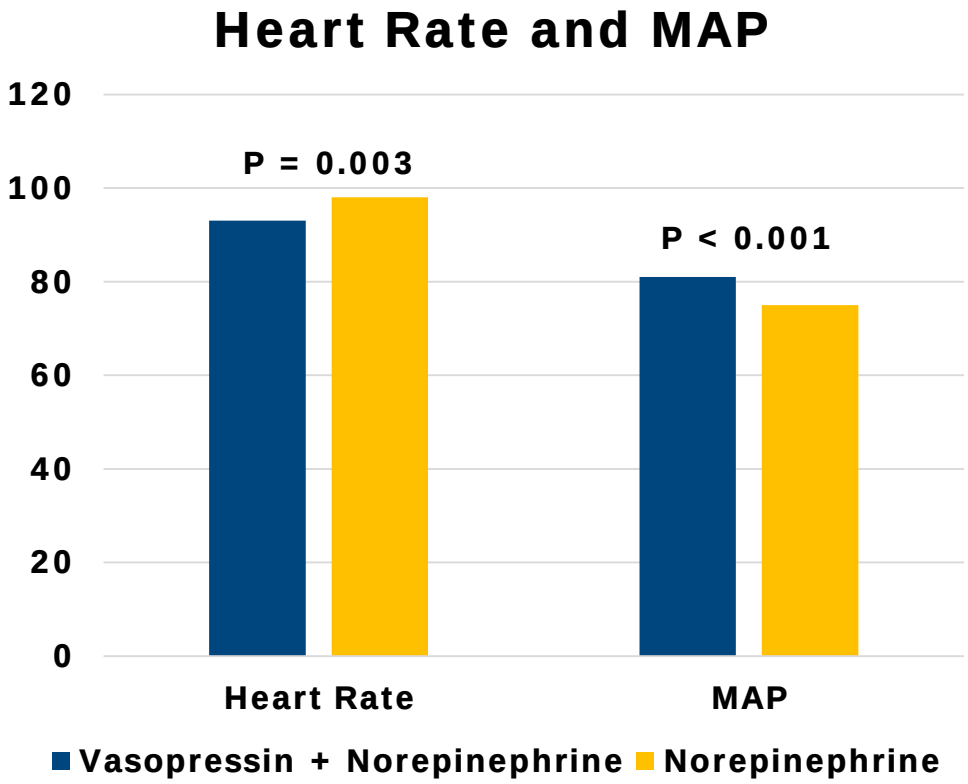
Arginine Vasopressin in Advanced Vasodilatory Shock

A Prospective, Randomized, Controlled Study

Design:
Prospective, randomized controlled trial

Population:
- n = 48
- Refractory vasodilatory shock

Intervention:
Vasopressin 0.06 units/min vs. Norepinephrine alone

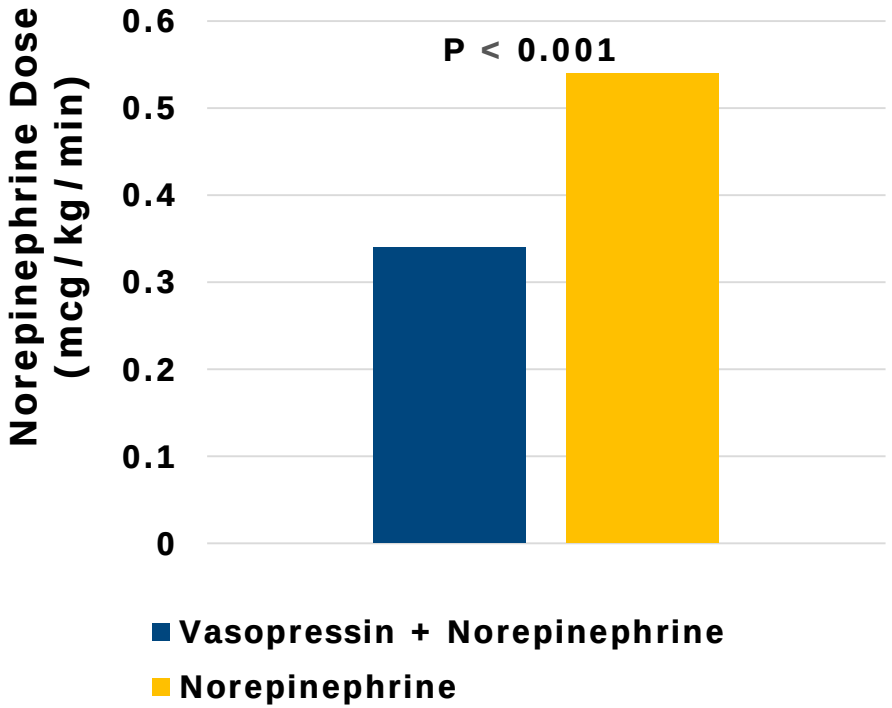


Dunser MW, et al. Circulation. 2003;107:2313-9.

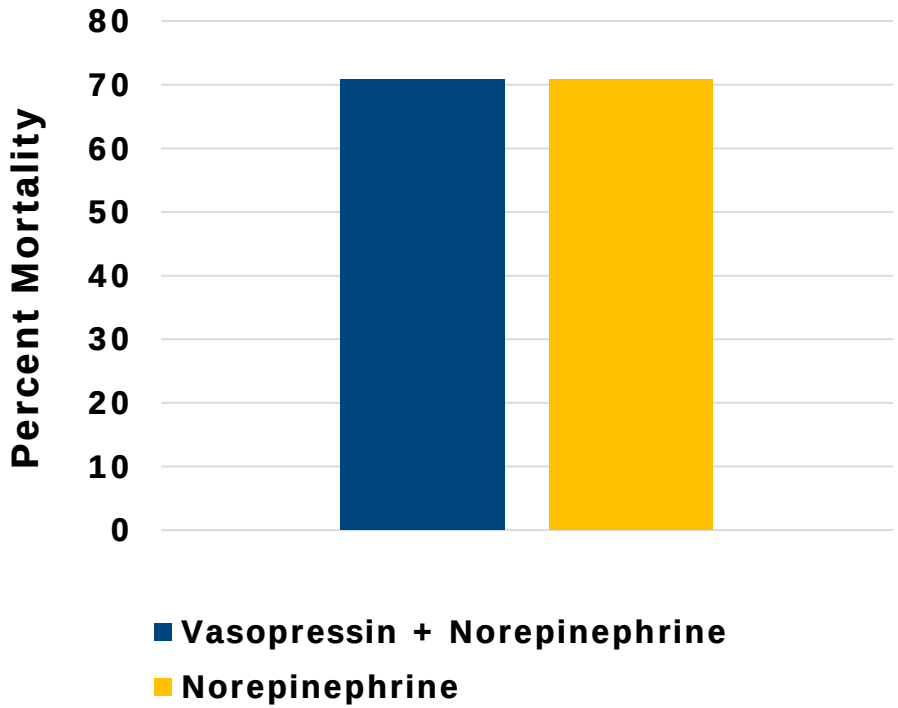
Arginine Vasopressin in Advanced Vasodilatory Shock

A Prospective, Randomized, Controlled Study

Norepinephrine Dose Requirements



ICU Mortality



Dunser MW, et al. Circulation. 2003;107:2313-9.

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

VASST Trial	
Design	Multicenter, international, randomized, double-blind trial

Population	• n = 778
	• Septic shock (Surviving Sepsis Campaign definition)
	  • SBP <90 mmHg
	• Refractory to:
	  • Volume resuscitation (After 500mL of normal saline)
	  OR
	  • High-dose vasopressors (> 5 mcg/min norepinephrine) for at least six hours

Intervention	• Vasopressin 0.6-1.8 units/h + standard of care Or • Norepinephrine 5-15 mcg/min + standard of care

Outcomes	• Primary: 28 day all-cause mortality
	• Secondary:
	  • 90-day mortality
	  • Days alive and free of (through day 28)
	  • Organ dysfunction, vasopressors , mechanical ventilation, renal replacement therapy, SIRS, corticosteroid use
	  • Hospital and ICU length of stay
	  • Rates of serious adverse events

Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. New Engl J Med. 2008;358:877-87.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

VASST Trial: Organ Dysfunction Outcomes

Variable	Norepinephrine	Vasopressin	P-value
Vasopressor free days	17 (0-24)	19 (0-24)	0.58
Ventilator free days	6 (0-20)	8.5 (0-20)	0.61
Renal replacement free days	23 (5-28)	25 (6-28)	0.64
Organ failure free days	0 (0-6)	0 (0-9)	0.14
SIRS free days	6 (0-15)	6 (0-18)	0.21

Russell JA, et al. New Engl J Med. 2008;358:877-87.

VASST Trial: Serious Adverse Events

Variable	Norepinephrine	Vasopressin	P-value
Acute myocardial infarction or ischemia	1.8%	2.0%	1.00
Cardiac arrest	2.1%	0.8%	0.14
Life-threatening arrhythmia	1.6%	2.0%	0.79
Acute mesenteric ischemia	3.4%	2.3%	0.39
Hyponatremia	0.3%	0.3%	1.00
Digital ischemia	0.5%	2.0%	0.11
Cerebrovascular Accident	0.3%	0.3%	1.00

Conclusion: Addition of vasopressin did not reduce occurrence of serious adverse events compared to norepinephrine.

Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. New Engl J Med. 2008;358:877-87.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

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

The VANISH Randomized Clinical Trial

Design	2x2 factorial, multicenter, double-blind, randomized controlled trial

Population	• n = 409
	• Septic shock (Surviving Sepsis Campaign definition)
	  • ”Hypotension requiring vasopressors”
	• Refractory to:
	  • “Adequate” volume resuscitation (assessed by clinical examination)

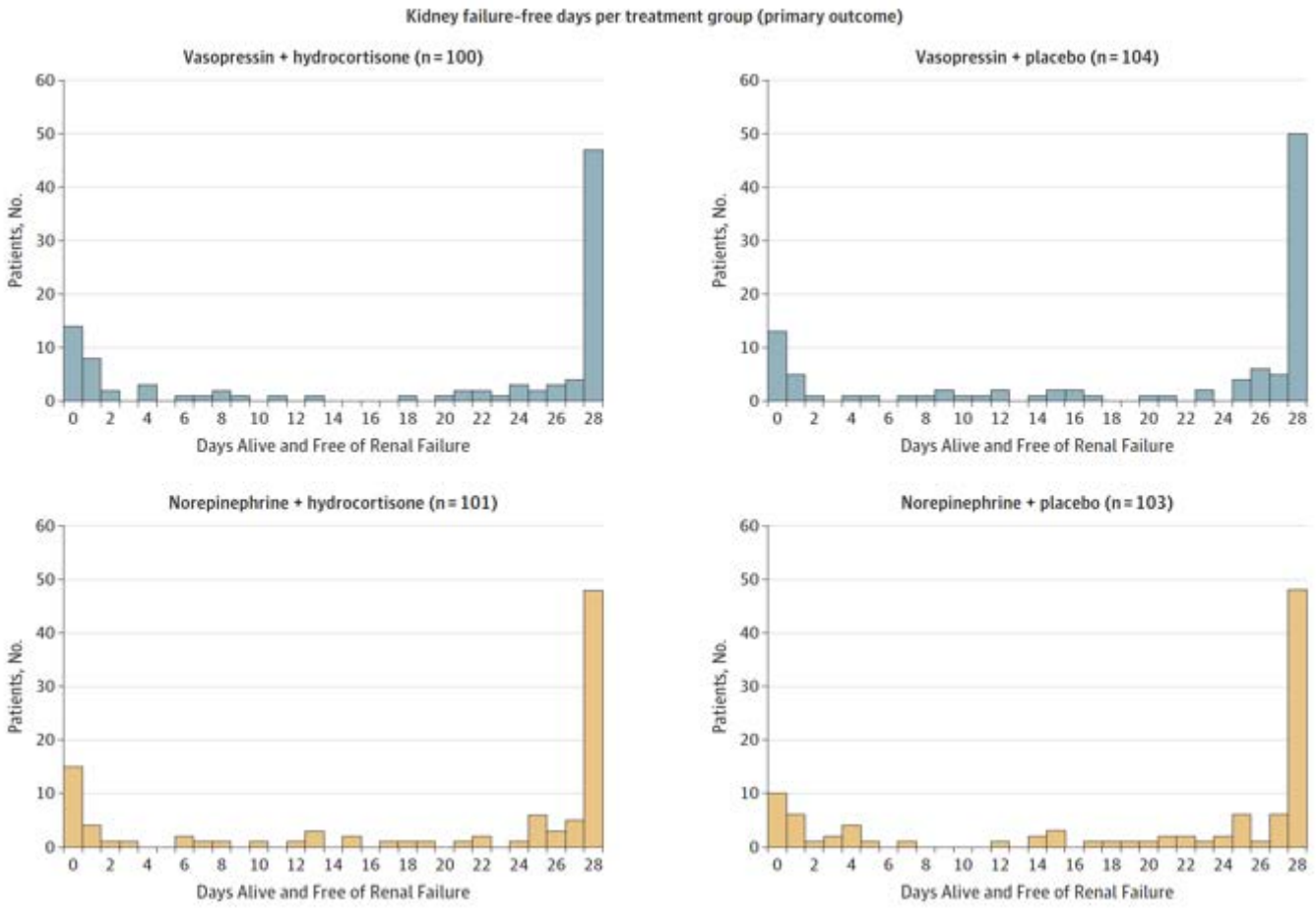
Intervention	• Vasopressin (titrated up to 0.06 units/min) + hydrocortisone OR • Vasopressin + placebo OR • Norepinephrine + hydrocortisone OR • Norepinephrine + placebo

Outcomes	• Primary: Renal failure free days through day 28
	• Secondary:
	  • Rate of renal replacement therapy
	  • Mortality
	  • Serious adverse events

Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock. JAMA. 2016;316(5):509-518.

Kumar A, et al. Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 21, 299-324.

VANISH Trial: Primary Outcome



Renal failure free days (Vasopressin vs. Norepinephrine):
-4 (95% CI: -11 to 5)

28-day survivors who never developed renal failure
-2.3 (95% CI: -13.0 to 8.5)

Conclusion: No reduction in renal failure with vasopressin compared to norepinephrine

Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock. JAMA. 2016;316(5):509-518.

Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study

Lakhmir S Chawla[1,3*], Laurence Busse[2], Ermira Brasha-Mitchell[3], Danielle Davison[3], Jacqueline Honiq[3], Ziyad Alotaibi[4] and Michael G Seneff[3]

Design	Randomized controlled trial

Population	• n = 20
	• High output shock
	  • Cardiovascular SOFA score of 4
	  • Cardiac index (CI) > 2.4 L/min/BSA 1.73 m^2
	• Adequately fluid resuscitated
	  • Such that fluid bolus would not increase CI by 15%

Intervention	• ATII infusion + standard of care Or • Placebo + standard of care
Outcomes	• Primary: Effect of ATII on norepinephrine dose requirements • Secondary: Effect of ATII on urine output, serum lactate, cardiac output, and 30-day mortality

Chawla LS, Busse L, Brasha-Mitchell E, et al. Intravenous angiotensin II for the treatment of high-output shock (ATHOS trial): a pilot study. Crit Care. 2014;18:534

Angiotensin II for the Treatment of Vasodilatory Shock

Design	Phase III, international, multicenter, randomized, placebo-controlled trial

Population	• n = 321
	• Vasodilatory shock
	  • CI > 2.3 L/min/m^2
	  • MAP 55-70 mmHg
	• Refractory to:
	  • Volume resuscitation (25 mL/kg in past 24 hours)
	  • High-dose vasopressors (> 2 mcg/min norepinephrine)

Intervention	• ATII infusion + standard of care Or • Placebo + standard of care

Outcomes	• Primary: MAP at 3 hours (response defined as increase ≥10 mmHg or increase to ≥75 without increases in background vasopressors)
	• Secondary:
	  • Change in cardiovascular SOFA score
	  • Change in SOFA score
	  • Adverse events
	  • All-cause mortality at 7 and 28 days

Khanna A, English SW, Wang XS, et al. Angiotensin II for the treatment of vasodilatory shock. New Engl J Med. 2017; 377:419-30