Vasopressin:
Vanished or Vitalized for Shock

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Disclosure

- I have no financial relationship with any pharmaceutical companies, biomedical device manufacturers or distributors, or others whose products or services may be considered related to the content of my presentation.

Abbreviations

- ACTH: Adrenocorticotropic hormone
- AKI: Acute kidney injury
- CPB: Cardiopulmonary bypass
- DA: Dopamine agonist
- ESRD: End-stage renal disease
- ESLD: End-stage liver disease
- HCT: Hydrocortisone
- MAP: mean arterial pressure
- NE: norepinephrine
- RIFLE: risk, injury, failure, loss, end-stage
- RRT: Renal replacement therapy
- UG: Ungraded

Objectives

01

Describe the pharmacology of vasopressin and its role in shock

02

Review the literature evaluating the use of vasopressin in septic shock and vasoplegia

03

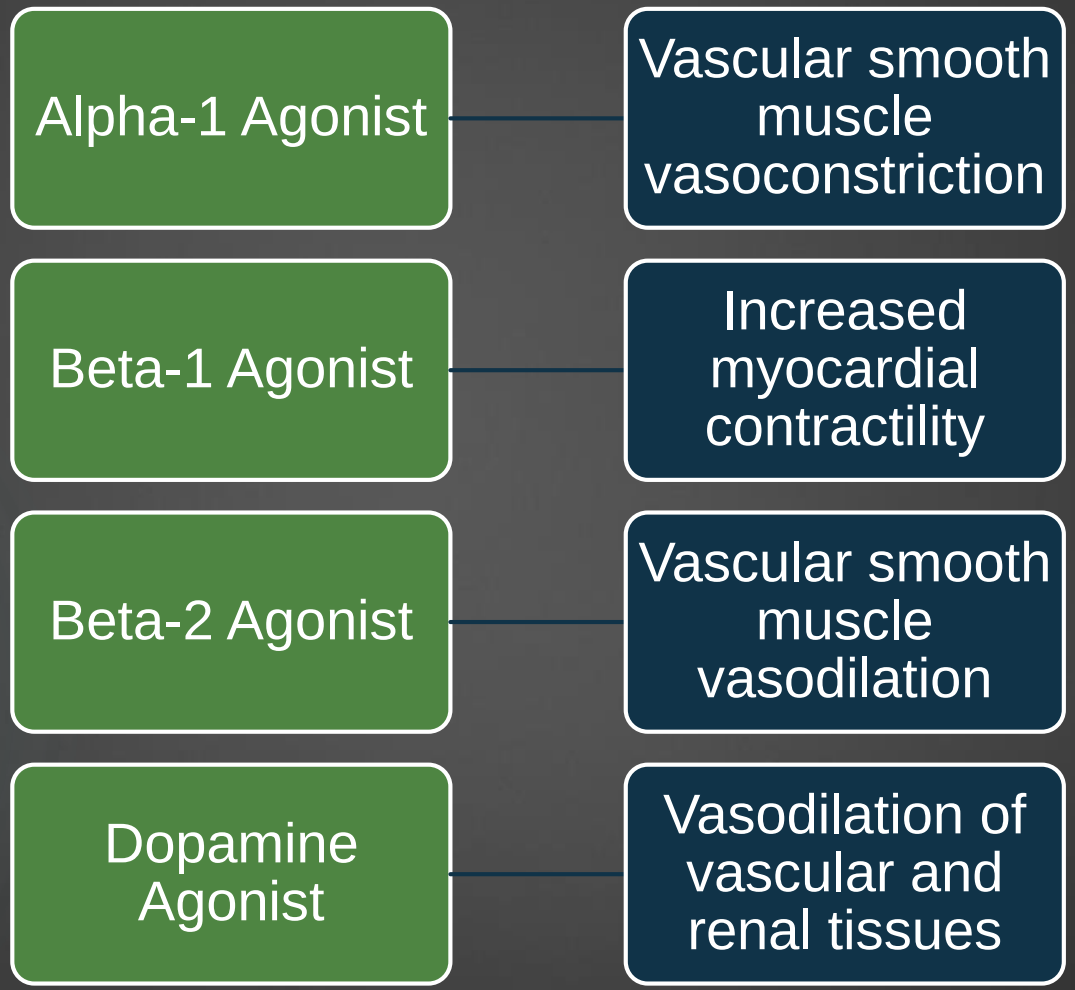
Discuss applications of vasopressin in the critically ill adult

Pharmacology of Vasopressors

01

Describe the pharmacology of vasopressin and its role in shock

Vasopressors and Receptors



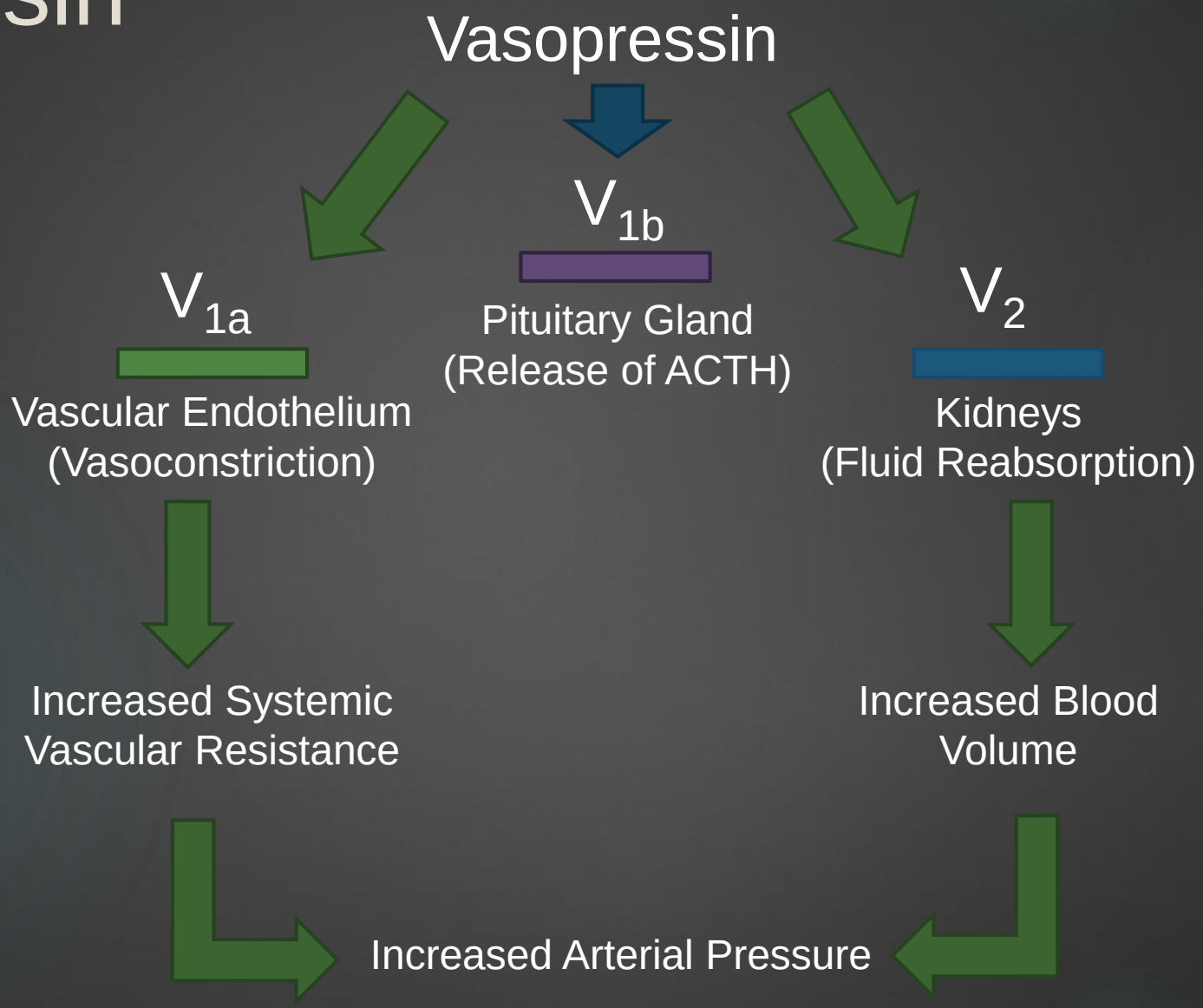
Overgaard CB, et al. *Circulation*. 2008.

Vasopressors and Receptors

Vasopressor	Alpha-1	Beta-1	Beta-2	DA
Phenylephrine	****	-	-	-
Norepinephrine	****	**	*	-
Epinephrine	****	***	**	-
Dopamine	**	***	*	****
Dobutamine	*	****	**	-
Isoproterenol	-	****	****	-

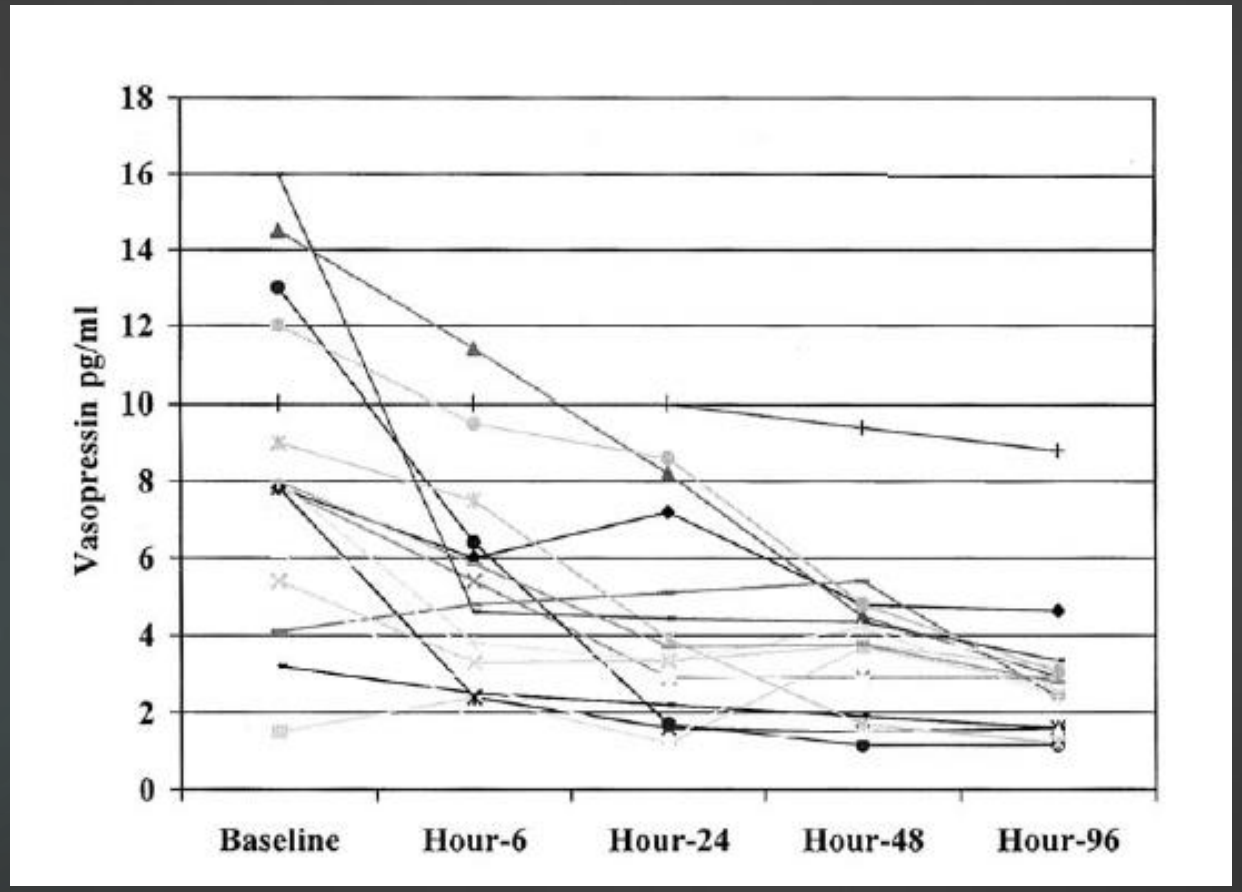
Overgaard CB, et al. *Circulation*. 2008.

Vasopressin



Gheorghita V, et al. *Germs*. 2015.

Circulating Vasopressin Levels in Septic Shock



Sharshar T, et al. *Crit Care Med*. 2003.

Surviving Sepsis Campaign

2008

- 1. NE or dopamine – *strong recommendation, low quality*
- 2. Epinephrine, vasopressin, and phenylephrine should **not** be used as first line – *weak recommendation, low quality*
- 3. Vasopressin 0.03U/min may be added to NE – *best practice statement*

2012

- 1. NE as the first choice – *strong recommendation, moderate quality*
- 2. Epinephrine if additional agent needed – *weak recommendation, moderate quality*
- 3. Vasopressin 0.03U/min added to NE – *best practice statement*

2016

- 1. NE as the first choice – *strong recommendation, moderate quality*
- 2. Vasopressin or epinephrine added to NE if additional agent needed to raise MAP – *weak recommendation, moderate quality*

Dellinger RP, et al. *Intensive Care Med.* 2008.
Dellinger RP, et al. *Intensive Care Med.* 2013.
Rhodes A, et al. *Intensive Care Med.* 2017.

Literature Review - Vasopressin

01

Describe the pharmacology of vasopressin and its role in shock

02

Review the literature evaluating the use of vasopressin in septic shock and vasoplegia

Mortality benefit in septic shock?

- VASST. Russell JA, et al. *N Engl J Med*. 2008.
- Russell JA, et al. *Crit Care Med*. 2017.

Prevention of acute kidney injury in shock?

- Gordon AC, et al. *Intensive Care Med*. 2010.
- VANISH. Gordon AC, et al. *JAMA*. 2016.
- VANCS. Hajjar LA, et al. *Anesthesiology*. 2017.

Discontinuation Strategies

Hammond

jjjjj

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2008 VOL. 358 NO. 9

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

VASST Background

Study Design

- Multicenter, randomized, stratified, double-blind trial July 2001-April 2006

Study Patients

- Septic shock resistant to fluids and receiving at least 5mcg/min of NE

Primary outcome

- Death from any cause assessed at 28 days after the start of the infusion

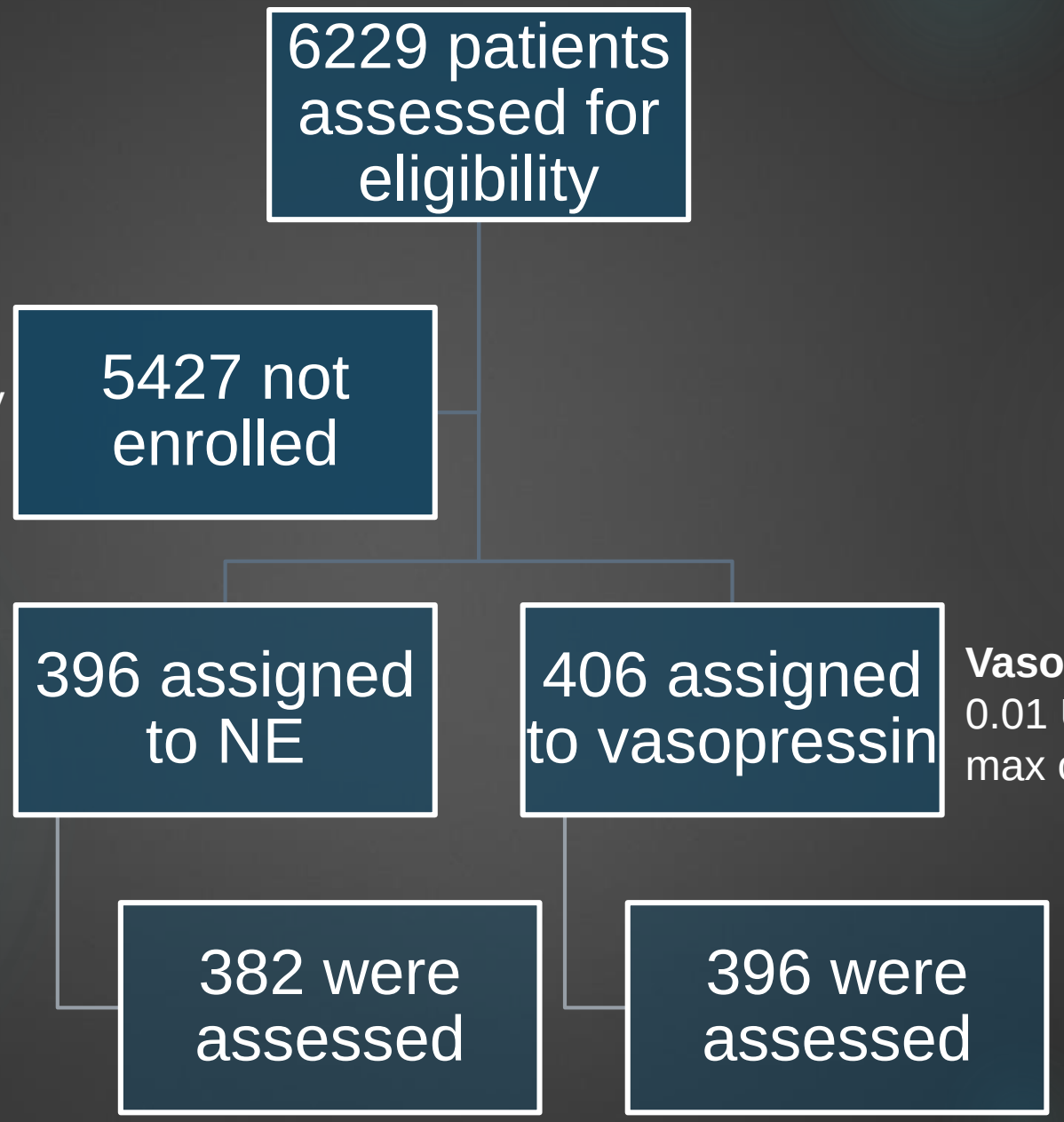
Secondary Outcomes

- Included 90-day mortality, rate of serious adverse events

Russell JA, et al. *N Engl J Med*. 2008.

VASST Methods

Exclusion:
- Unstable coronary syndrome
- >24 hours since meeting entry criteria
- NYHA class III or IV heart failure



NE:
5mcg/min titrated up to max of 15mcg/min

Vasopressin:
0.01 U/min titrated up to max of 0.03 U/min

Russell JA, et al. *N Engl J Med*. 2008.

VASST
Baseline Characteristics

Characteristic - no. (%)	NE Group (n=382)	Vasopressin Group (n=397)	P Value
Age – yr	61.8±16	59.3±16.4	0.03
APACHE II score	27.1±6.9	27±7.7	0.84
Chronic renal failure	48 (12.6)	40 (10.1)	0.34
New renal failure	258 (67.5)	264 (66.5)	0.68
Lung infection source	165 (43.2)	162 (40.8)	-
Abdomen infection source	100 (26.2)	111 (28)	-
Other infection source	117 (30.6)	124 (31.2)	-
Time to study-drug infusion – hr	11.5±9.4	11.9±8.9	0.57
At randomization: NE alone	222 (58.1)	296 (74.6)	0.63
No NE	53 (13.9)	53 (13.4)	0.83
Two or more vasopressors	111 (29.1)	124 (31.2)	0.51

Russell JA, et al. *N Engl J Med*. 2008.

VASST Results

- Primary Outcome: rate of death from any cause at day 28
  - Vasopressin group 35.4% vs NE group 39.3%; P=0.26

More Severe Septic Shock	NE Group	Vasopressin Group	P Value
28-day mortality	42.5%	44.0%	0.76
90-day mortality	52.8%	51.8%	0.84
Less Severe Septic Shock			
28-day mortality	35.7%	26.5%	0.05
90-day mortality	46.1%	35.8%	0.04

Russell JA, et al. *N Engl J Med*. 2008.

VASST
Results – Adverse Events

- Cardiac arrest
  - Vasopressin group 0.8% vs NE group 2.1%; P=0.14
- Digital Ischemia
  - Vasopressin group 2.0% vs NE group 0.5%; P=0.11

Russell JA, et al. *N Engl J Med*. 2008.

VASST
Author's Conclusions

1	No overall difference in 28- or 90-day mortality between NE and vasopressin use
2	Low dose vasopressin infusion allowed a rapid decrease in the total NE dose while maintaining MAP
3	Limitations: Observed mortality was lower than predicted, mean time to randomization and infusion was 12 hours

Russell JA, et al. *N Engl J Med*. 2008.

VASST Takeaway

- No difference in adverse events or aggregate outcomes
- Vasopressin may reduce total NE requirements while maintaining MAP
- May reduce mortality in less severe septic shock

Russell JA, et al. *N Engl J Med*. 2008.

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

Septic Shock 3.0 definition:

- Patients on vasopressors to maintain MAP >65mmHg and lactate >2mmol/L despite adequate fluid resuscitation

Outcomes analysis including VASST patients that met Septic Shock 3.0 definition

Compared 28-day mortality rates of vasopressin-to-NE groups in lactate ≤2 or >2mmol/L

Russell JA, et al. *Crit Care Med*. 2017.

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

Results

- No difference in mortality rates between vasopressin and NE when lactate >2
- Lower mortality with vasopressin vs NE when lactate ≤2

Russell JA, et al. *Crit Care Med*. 2017.

The Effects of Vasopressin on Acute Kidney Injury in Septic Shock

Acute Kidney Injury

- High prevalence in critical illness and septic shock
- Vasopressin targets V2 receptor in kidney

Methods

- Post-hoc analysis
- VASST patients were classified into one of the RIFLE categories

Outcomes

- 28-day mortality, rate of progression to renal failure or loss, use of RRT, serum creatinine over time up to day 28

Gordon AC, et al. *Intensive Care Med*. 2010.

The Effects of Vasopressin on Acute Kidney Injury in Septic Shock

- Results

	Norepinephrine	Vasopressin	P Value
Rate of progression from Risk to Failure or Loss over 28 days	21 (39.6%)	11 (20.8%)	0.03
Use of RRT in Risk Category	20 (37.7%)	9 (17%)	0.02
28-day mortality in Risk Category	29 (54.7%)	16 (30.8%)	0.01

- Developed hypothesis: is there a benefit of using vasopressin in septic shock to reduce risk of renal failure prior to development of significant organ failure

Gordon AC, et al. *Intensive Care Med*. 2010.

JAMA | Original Investigation

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

The VANISH Randomized Clinical Trial

Anthony C. Gordon, MD; Alexina J. Mason, PhD; Neeraja Thirunavukkarasu, MSc; Gavin D. Perkins, MD; Maurizio Cecconi, MD; Magda Cepkova, MD; David G. Pogson, MB BCh; Hollmann D. Aya, MD; Aisha Anjum, BSc; Gregory J. Frazier, MSc; Shalini Santhakumaran, MSc; Deborah Ashby, PhD; Stephen J. Brett, MD; for the VANISH Investigators

VANISH Background

Study Design

- Multicenter, factorial (2x2), double-blind, randomized controlled trial from February 2013 to May 2015

Study Patients

- Adults with sepsis and required vasopressors despite adequate fluid resuscitation

Primary Outcome

- Number of kidney failure-free days

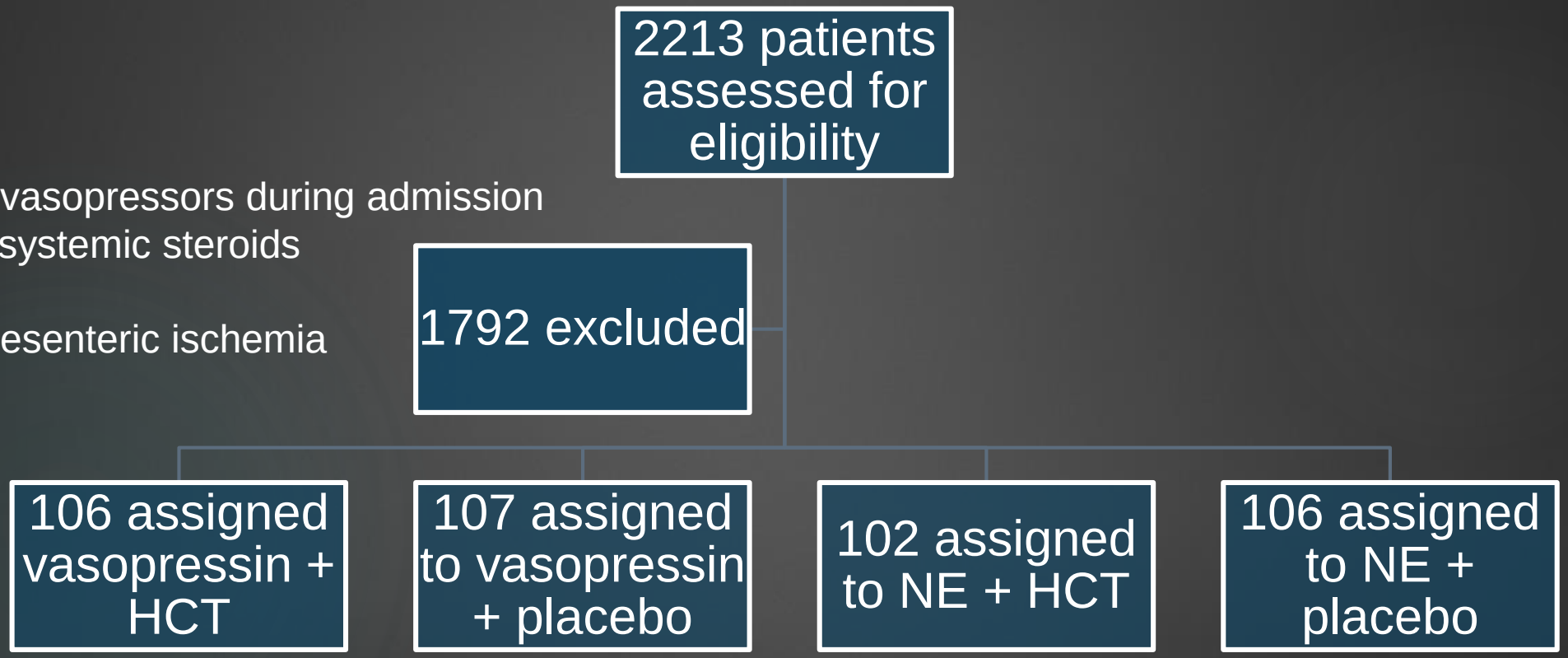
Secondary Outcomes

- Rate of RRT
- 28-day survivors who never developed kidney failure
- 28-day mortality

Gordon AC, et al. *JAMA*. 2016.

VANISH Methods

Exclusion:
- Previous vasopressors during admission
- Need for systemic steroids
- ESRD
- Known mesenteric ischemia



Gordon AC, et al. *JAMA*. 2016.

VANISH Methods

Study Drug 1

Vasopressin

- Titrated up to 0.06 U/min

Norepinephrine

- Titrated up to 12 mcg/min

Maximum rate achieved

Study Drug 2

Hydrocortisone or Placebo

- 50mg IV bolus every 6 hours x 5 days
- Followed by every 12 hours x 3 days
- Followed by every day x 3 days

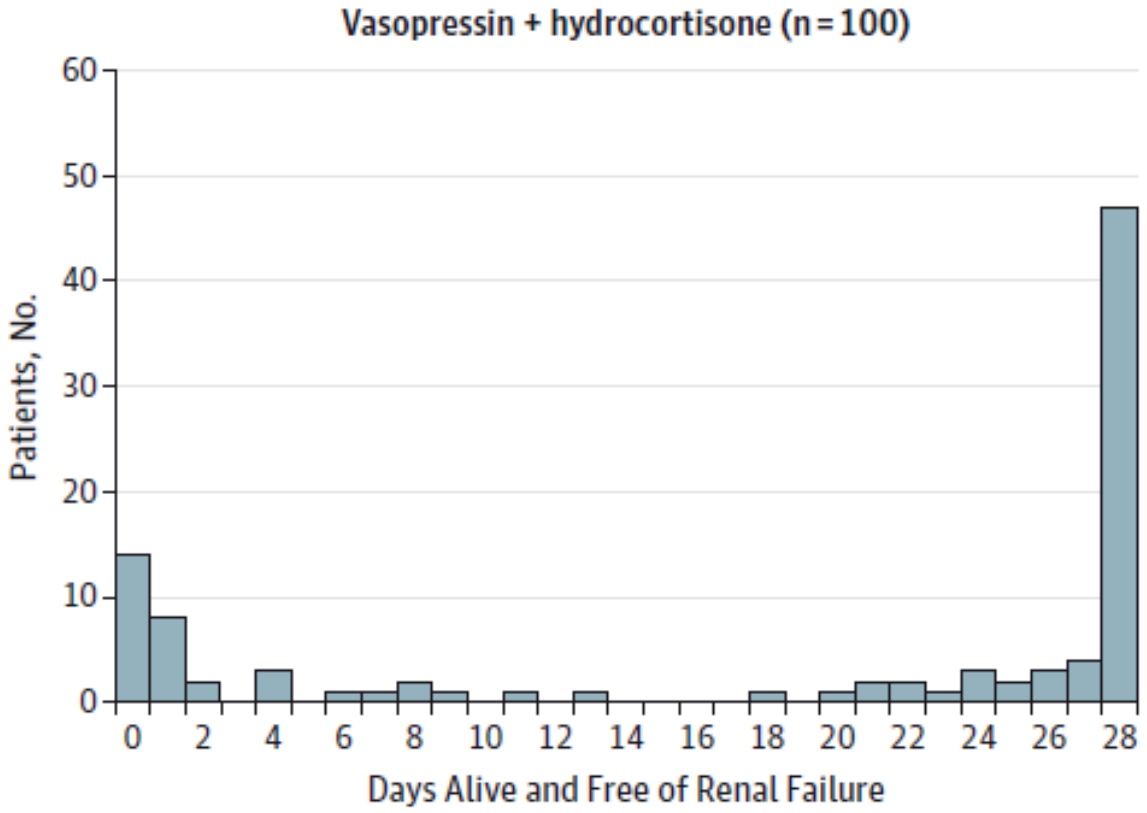
Gordon AC, et al. *JAMA*. 2016.

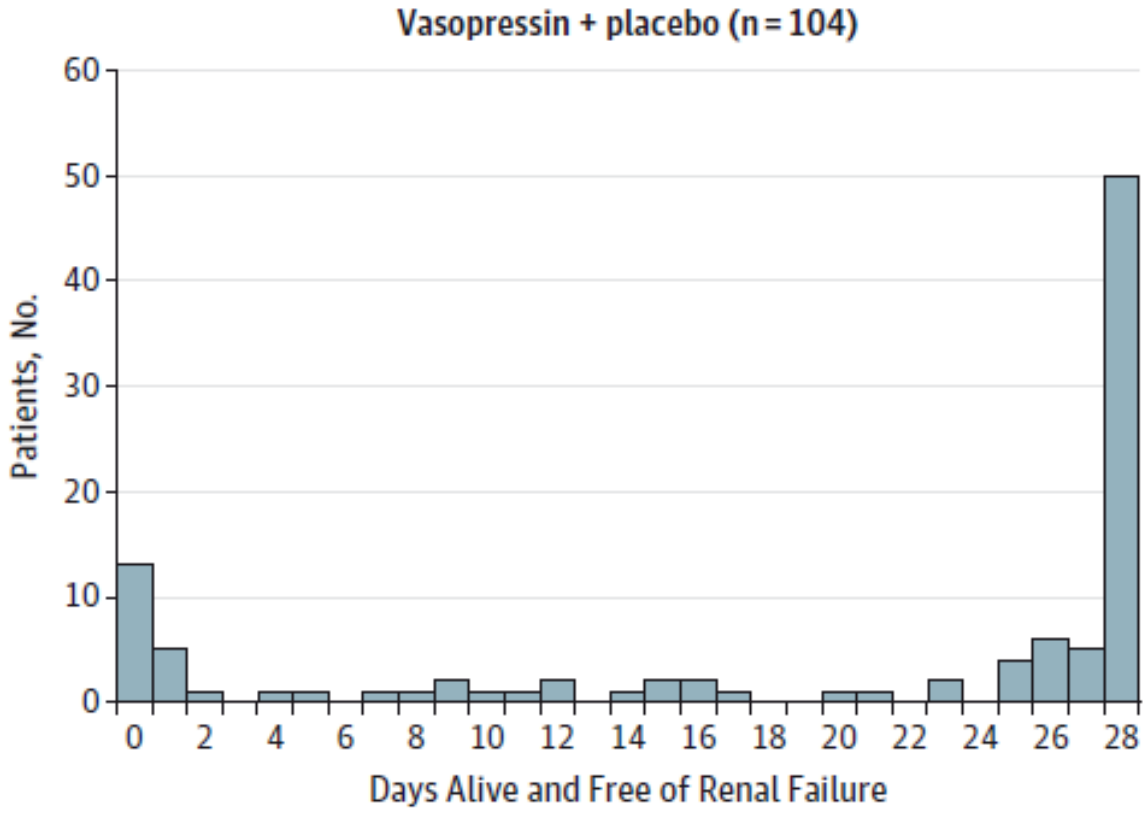
VANISH
Baseline Characteristics

Characteristic	Vasopressin + HCT (n=101)	Vasopressin (n=104)	NE + HCT (n=101)	NE (n=103)
Age, median (IQR)	66 (57-76)	67 (59-77)	63 (52-76)	66 (54-77)
APACHE II score, median (IQR)	24 (19-30)	24 (19-29)	24 (20-30)	24 (19-30)
New renal failure, no.	19	19	24	23
Time to study-drug infusion – median (IQR)	3.2 (1.8-5)	3.5 (2-5.4)	3.7 (1.7-5)	3.5 (1.4-5.4)
Open-label vasopressor at randomization, no.	91	89	86	82
NE dose at randomization, median (IQR), mcg/kg/min	0.16 (0.1-0.3)	0.15 (0.1-0.28)	0.2 (0.12-0.42)	0.16 (0.1-0.27)

Gordon AC, et al. *JAMA*. 2016.

VANISH
Results – Kidney failure-free days

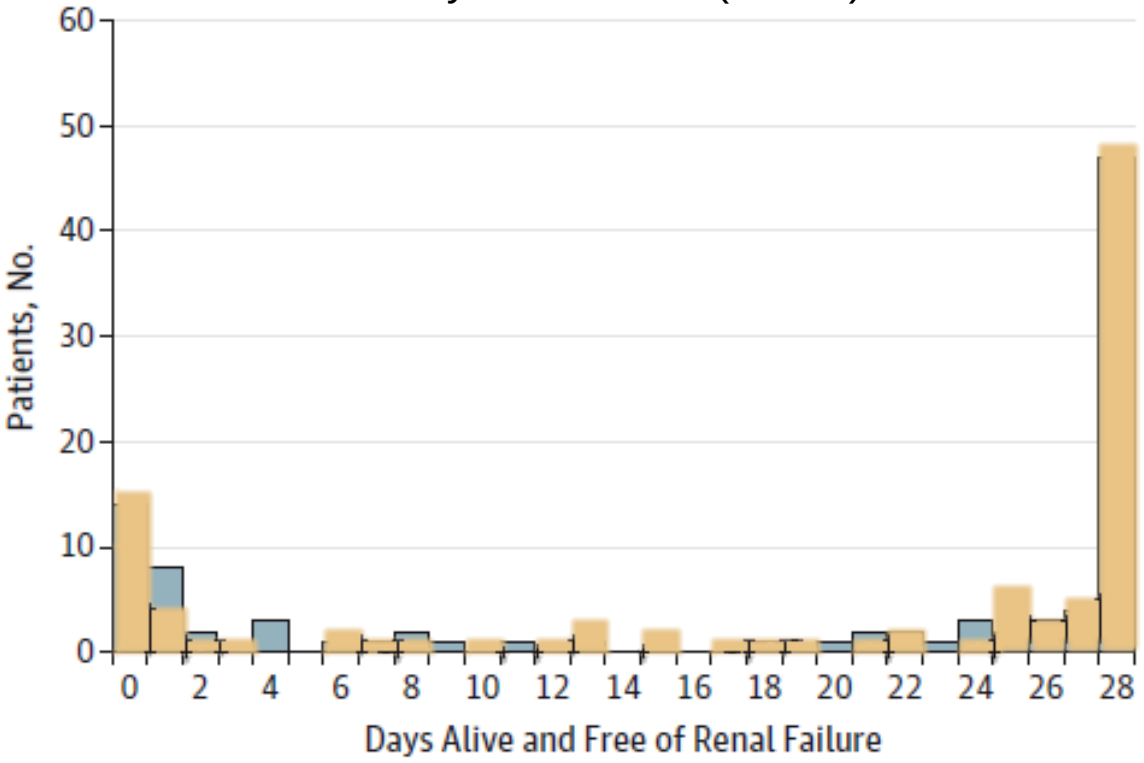




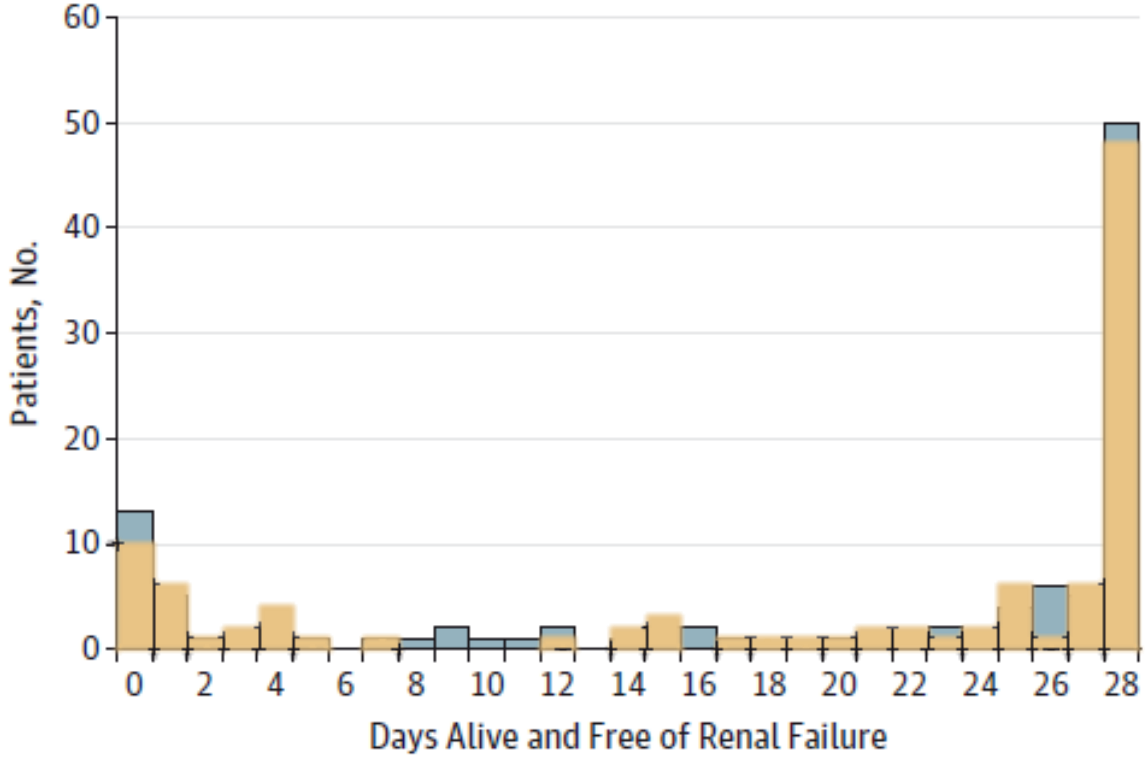
Gordon AC, et al. *JAMA*. 2016.

VANISH
Results – Kidney failure-free days

NE + hydrocortisone (n=101)



NE + placebo (n=103)



P=0.88

Gordon AC, et al. *JAMA*. 2016.

VANISH Results

Outcome, No./Total (%)	Vasopressin	Norepinephrine	Absolute Difference (95% CI)
28-d survivors who never developed kidney failure	94/165 (57)	93/157 (59.2)	-2.3 (-13 to 8.5)
Kidney failure-free days in other patients, median (IQR)	9 (1-24)	13 (1-25)	-4 (-11 to 5)
28-d mortality	63/204 (30.9)	56/204 (27.5)	3.4 (-5.4 to 12.3)
Use of RRT	52/205 (25.4)	72/204 (35.3)	-9.9 (-19.3 to -0.6)

Gordon AC, et al. *JAMA*. 2016.

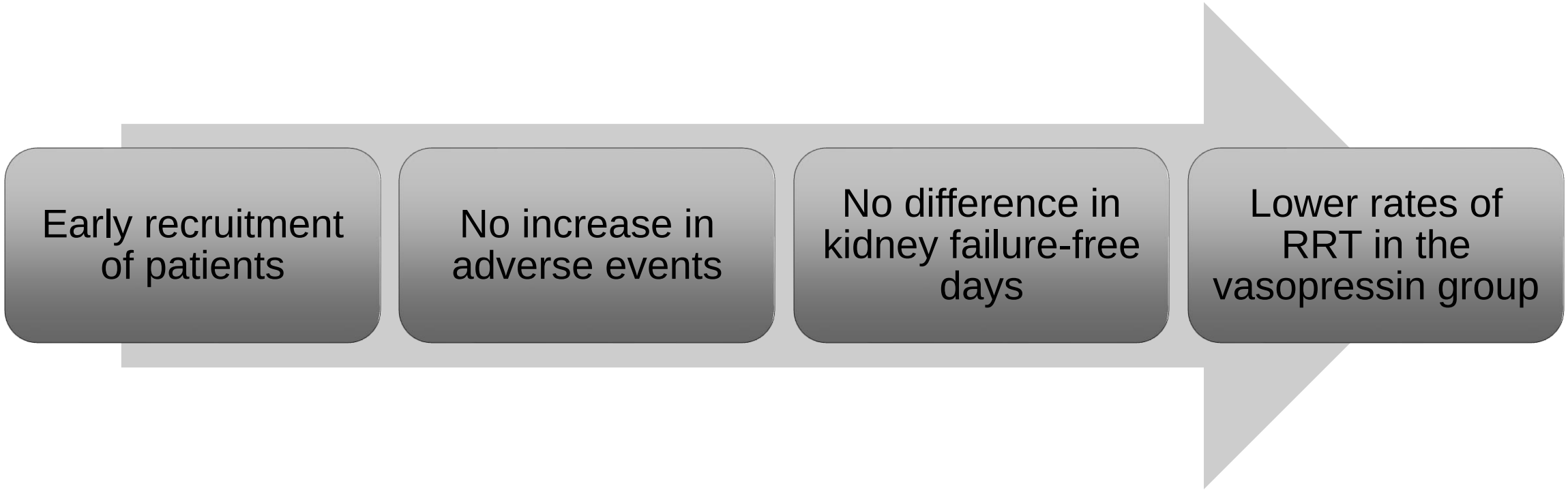
VANISH
Results – Adverse Events

Adverse Event, No./Total	Vasopressin	NE	Absolute Difference (95% CI)
Digital ischemia	11/205	3/204	3.9 (-0.1 to 7.9)
Life-threatening arrhythmia	2/205	5/204	-1.5 (-4.5 to 1.5)
Acute coronary syndrome	7/205	2/204	2.5 (-0.9 to 5.8)

- Mean dose when adverse events occurred:
  - Vasopressin – 0.06 U/min
  - Norepinephrine – 0.55 mcg/kg/min

Gordon AC, et al. *JAMA*. 2016.

VANISH Takeaway



Gordon AC, et al. *JAMA*. 2016.

Vasoplegia and Cardiac Surgery

- Common complication of CBP with an incidence of 5-25%
- Characterized by:
  - Hypotension
  - High or normal cardiac output
  - Low systemic vascular resistance

Critical Care Medicine | January 2017

Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery: The VANCS Randomized Controlled Trial

Ludhmila Abrahao Hajjar, M.D., Ph.D.; Jean Louis Vincent, M.D., Ph.D.; Filomena Regina Barbosa Gomes Galas, M.D., Ph.D.; Andrew Rhodes, M.D., Ph.D.; Giovanni Landoni, M.D.; et al

Anesthesiology 1 2017, Vol.126, 85-93. doi:10.1097/ALN.0000000000001434

VANCS Methods

Study Design

- Single center, prospective, randomized, double-blind, controlled trial enrolled patients from January 2012 to March 2014

Study Patients

- Patients undergoing cardiac surgery requiring CPB if they required vasopressors within 48 hours of CPB weaning

Primary Outcome

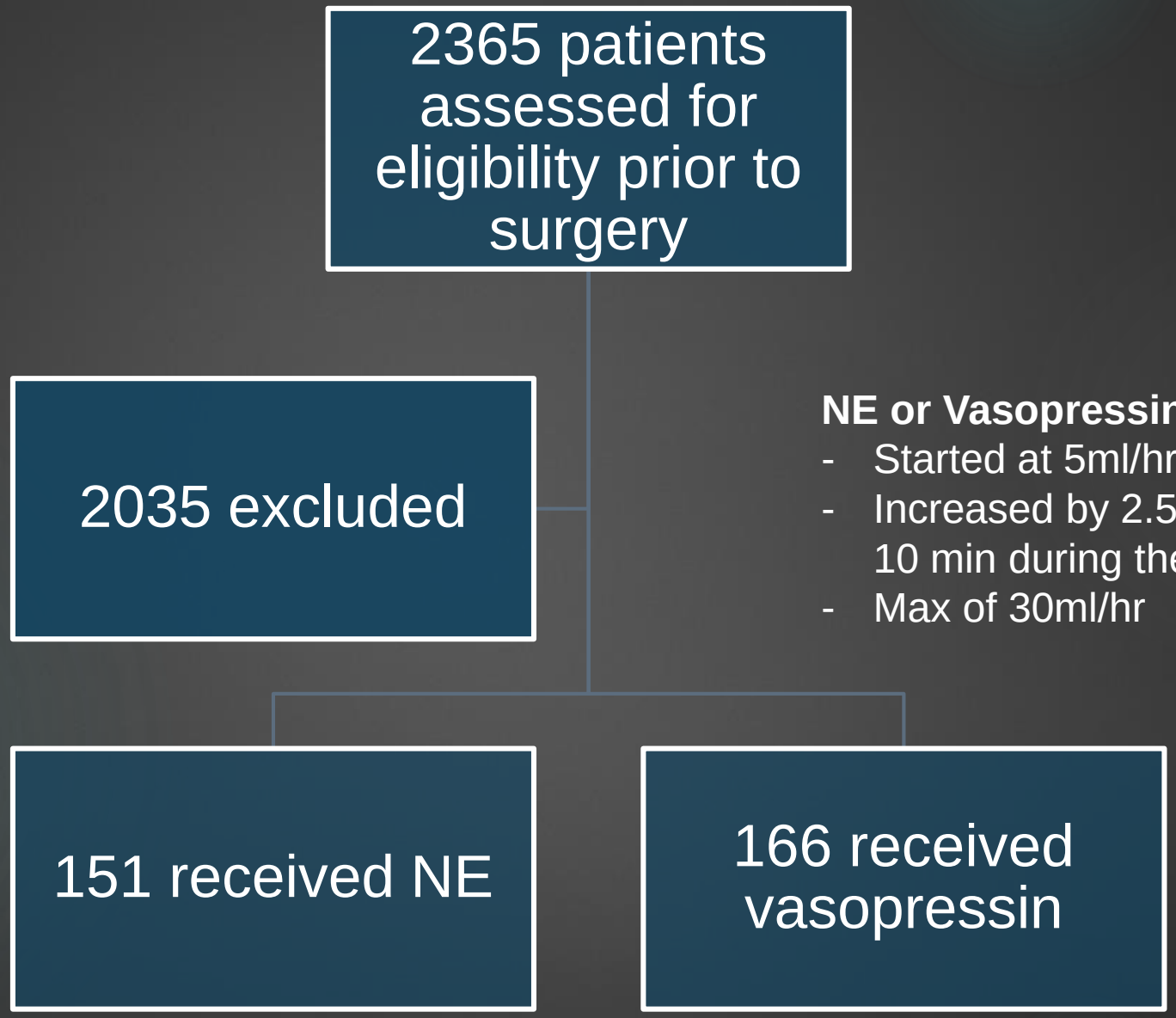
- Composite endpoint of mortality or severe postoperative complications within 30 days after randomization

Secondary Outcomes

- 30-day incidence of arrhythmias, ICU and hospital length of stay
- Post-hoc analysis of AKIN stages, need for RRT

Hajjar LA, et al. *Anesthesiology*. 2017.

VANCS Methods



Exclusion:
- Aortic surgery
- Heart transplantation
- Preop use of vasopressor
- Use of a ventricular assist device
- Sodium <130mEq/L
- Acute coronary syndrome

NE or Vasopressin Titration:
- Started at 5ml/hr
- Increased by 2.5ml/hr every 10 min during the first hour
- Max of 30ml/hr

Hajjar LA, et al. *Anesthesiology*. 2017.

VANCS
Baseline Characteristics

Variable	NE (n=151)	Vasopressin (n=149)
Age, mean and SD	55±13	54±14
CABG, no. (%)	73 (48.4)	64 (43)
Valve surgery, no. (%)	47 (31.1)	55 (36.9)
Combined cardiac surgery, no. (%)	31 (20.5)	30 (20.1)
Chronic renal failure, no. (%)	44 (29.1)	37 (24.8)

Hajjar LA, et al. *Anesthesiology*. 2017.

VANCS Results

Variable	Norepinephrine (n=151)	Vasopressin (n=149)	P Value
Composite Primary Outcome	74 (49%)	48 (32.2%)	0.0014
Acute Renal Failure	54 (35.8%)	15 (10.3%)	<0.0001
Length of ICU stay	6 (4-9)	5(4-7)	0.005
Length of hospital stay	13 (10-20)	10 (8-12)	0.0016
AKIN Stage 1	28 (18.5%)	29 (20%)	0.12
Stage 2	18 (11.9%)	9 (6.2%)	0.0057
Stage 3	49 (32.5%)	12 (8.3%)	<0.0001
Required RRT	21 (13.9%)	4 (2.7%)	0.0016
Additional open-label NE	29 (19.2%)	17 (11.4%)	0.06

Hajjar LA, et al. *Anesthesiology*. 2017.

VANCS
Results – Adverse Events

Variable	Norepinephrine (n=151)	Vasopressin (n=149)	P Value
Atrial fibrillation	(82.1%)	(63.8%)	0.0004
Digital ischemia	2 (1.3%)	3 (2%)	0.68
Mesenteric ischemia	2 (1.3%)	3 (2%)	0.68

Hajjar LA, et al. *Anesthesiology*. 2017.

VANCS
Author's Conclusions

1	Evaluated vasopressin as initial drug for management of vasoplegic shock after cardiac surgery
2	Vasopressin reduced composite endpoint of death or severe complications over 30 days compared to norepinephrine

Hajjar LA, et al. *Anesthesiology.* 2017.

VANCS Takeaway

Early administration of vasopressin

Vasopressin arm had a lower incidence of renal failure and need for RRT

Reduction in composite endpoint but no reduction in 30-day mortality

Hajjar LA, et al. *Anesthesiology*. 2017.

Vasopressor Discontinuation Strategies

Hammond DA, et al. *J Intensive Care Med.* 2017.	Musallam N, et al. *Ann Pharmacother.* 2018.	Bredhold, et al. *Crit Care Med.* 2018.
• Retrospectively enrolled 92 patients • Vasopressin discontinued first, more clinically significant hypotension developed, 67.8% vs 10.9%, $p < 0.001$	• Retrospective study enrolled 80 patients; NE vs vasopressin • Hypotension within 24 hours of first agent discontinued was higher when vasopressin was discontinued first (62.2% vs 28.6%; $P = 0.004$)	• Retrospective study evaluated 86 patients receiving NE and vasopressin • No difference in ICU LOS • NE first 17% vs vasopressin 31%; $p = 0.38$

Price Comparison

	Price, AWP	Concentration
Vasopressin	$200.70	20 units/100mL
Norepinephrine	$21.04-43.68	8000mcg/250ml
Epinephrine	$18.88	8000mcg/250ml
Phenylephrine	$22.00	200mcg/ml 250ml

Utility of Vasopressin

Vasopressin should be used early in the treatment of shock

Potential to lower AKI and need for RRT

Future Research

- Flat rate vs titration of vasopressin
- Optimal timing of vasopressin initiation
- Cost-effectiveness of vasopressin
- Ongoing clinical trials

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