Angiotensin II in Vasodilatory Shock

Past, Present, & Future

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Objectives

- **Define shock**
- **Describe impact of vasodilatory shock on individuals & society**
- **Discuss resuscitation principles & endpoints**
- **Highlight mechanism & significance of maintaining MAP**
- **Discuss angiotensin II history & role in vasodilatory shock**

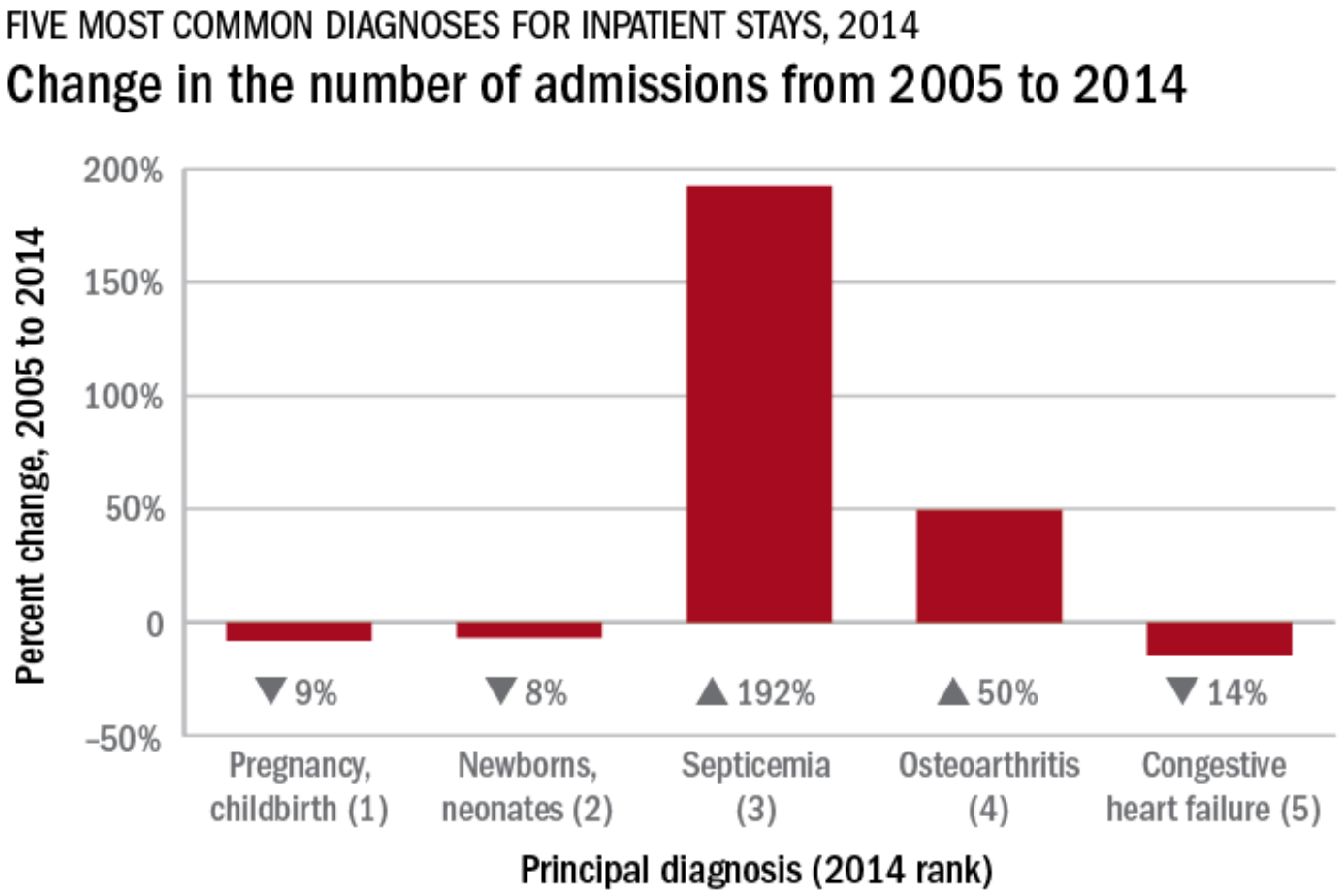
Disclosures

- Site investigator for ATHOS-3 trial
- Previously on Speakers' Bureau for La Jolla Pharmaceuticals

Types of Shock

Hypovolemic (16%)	• Internal/external fluid/blood loss
Cardiogenic (16%)	• Ischemia, heart failure, dysrhythmias, acute valvular dysfunction
Obstructive (2%)	• PE, tamponade, tension PTX, abdominal compartment syndrome
Distributive (Vasodilatory) (66%)	• **Septic shock** (94%) • Non-septic (6%) → anaphylaxis, SIRS, acute pancreatitis, post-pump vasoplegia, neurogenic

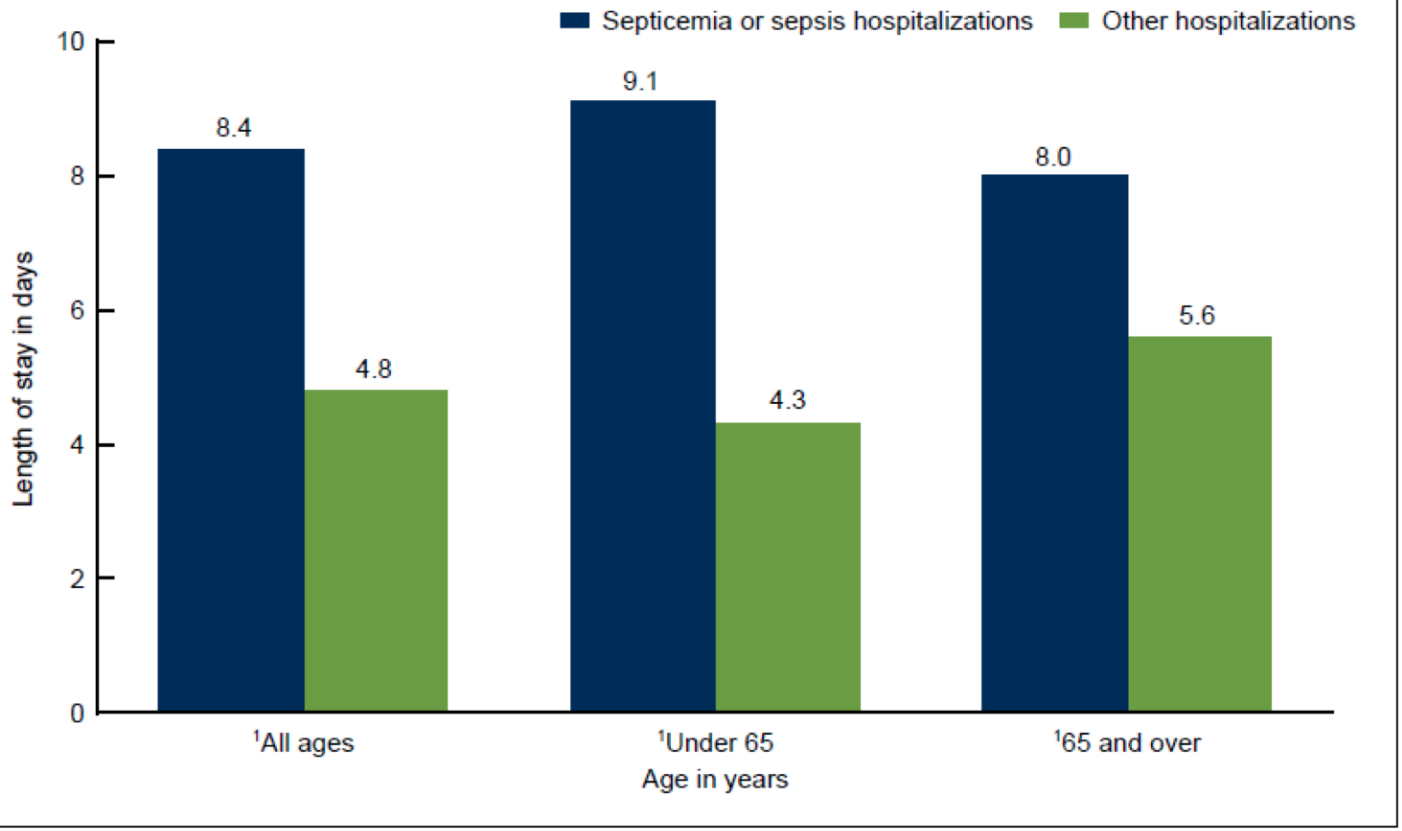
More Sepsis Admissions



AHRQ 2016

Sepsis & Hospital LOS

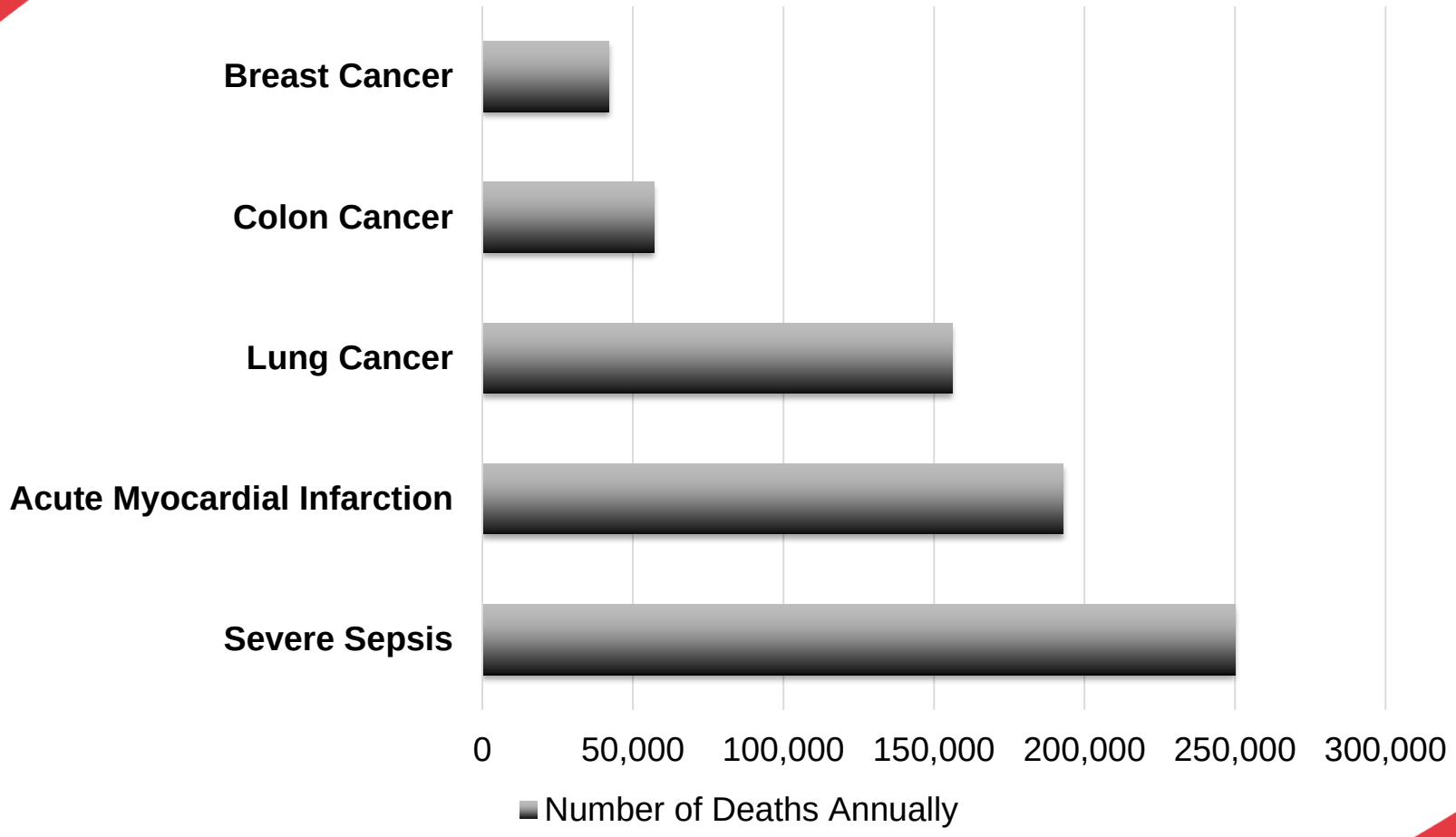
Figure 4. Average length of stay for those hospitalized for septicemia or sepsis compared with those hospitalized for other conditions, 2008



[1]Difference is statistically significant at the 0.05 level.

SOURCE: CDC/NCHS, National Hospital Discharge Survey, 2008.

Sepsis Mortality Comparison



CDC 2014

Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Theodore J. Iwashyna, MD, PhD
E. Wesley Ely, MD, MPH
Dylan M. Smith, PhD
Kenneth M. Langa, MD, PhD

COGNITIVE IMPAIRMENT AND physical disability are major health burdens and drivers of health care costs. The onset of disability is associated with worsened mortality[1] and substantial increases in medical costs over subsequent years,[2] including a disproportionate strain on Medicaid and Medicare. Both cognitive and physical disability impose yet further burdens on families and informal caregivers.[3] Irreversible cognitive and physical impairment following acute illnesses are particularly feared outcomes and weigh heavily on patient decision making.[4]

Hundreds of thousands of patients endure severe sepsis each year in the United States.[5] It has been suspected that many are discharged with a new—but poorly defined—constellation of cognitive and functional impairments,[6] which may explain their reduced quality of life.[7] Even hospitalizations for less severe illness often result in a period of functional dis-

Context Cognitive impairment and functional disability are major determinants of caregiving needs and societal health care costs. Although the incidence of severe sepsis is high and increasing, the magnitude of patients' long-term cognitive and functional limitations after sepsis is unknown.

Objective To determine the change in cognitive impairment and physical functioning among patients who survive severe sepsis, controlling for their presepsis functioning.

Design, Setting, and Patients A prospective cohort involving 1194 patients with 1520 hospitalizations for severe sepsis drawn from the Health and Retirement Study, a nationally representative survey of US residents (1998-2006). A total of 9223 respondents had a baseline cognitive and functional assessment and had linked Medicare claims; 516 survived severe sepsis and 4517 survived a nonsepsis hospitalization to at least 1 follow-up survey and are included in the analysis.

Main Outcome Measures Personal interviews were conducted with respondents or proxies using validated surveys to assess the presence of cognitive impairment and to determine the number of activities of daily living (ADLs) and instrumental ADLs (IADLs) for which patients needed assistance.

Results Survivors' mean age at hospitalization was 76.9 years. The prevalence of moderate to severe cognitive impairment increased 10.6 percentage points among patients who survived severe sepsis, an odds ratio (OR) of 3.34 (95% confidence interval [CI], 1.53-7.25) in multivariable regression. Likewise, a high rate of new functional limitations was seen following sepsis: in those with no limits before sepsis, a mean 1.57 new limitations (95% CI, 0.99-2.15); and for those with mild to moderate limitations before sepsis, a mean of 1.50 new limitations (95% CI, 0.87-2.12). In contrast, nonsepsis general hospitalizations were associated with no change in moderate to severe cognitive impairment (OR, 1.15; 95% CI, 0.80-1.67; *P* for difference vs sepsis=.01) and with the development of fewer new limitations (mean among those with no limits before hospitalization, 0.48; 95% CI, 0.39-0.57; *P* for difference vs sepsis <.001 and mean among those with mild to moderate limits, 0.43; 95% CI, 0.23-0.63; *P* for difference=.001). The declines in cognitive and physical function persisted for at least 8 years.

Conclusions Severe sepsis in this older population was independently associated with substantial and persistent new cognitive impairment and functional disability among survivors. The magnitude of these new deficits was large, likely resulting in a pivotal

Iwashyna TJ, et al. JAMA. 2010 Oct 27;304(16):1787-94.

What Is Shock?

At a cellular level, oxygen consumption exceeds delivery

$$VO_2 > DO_2$$

Preload

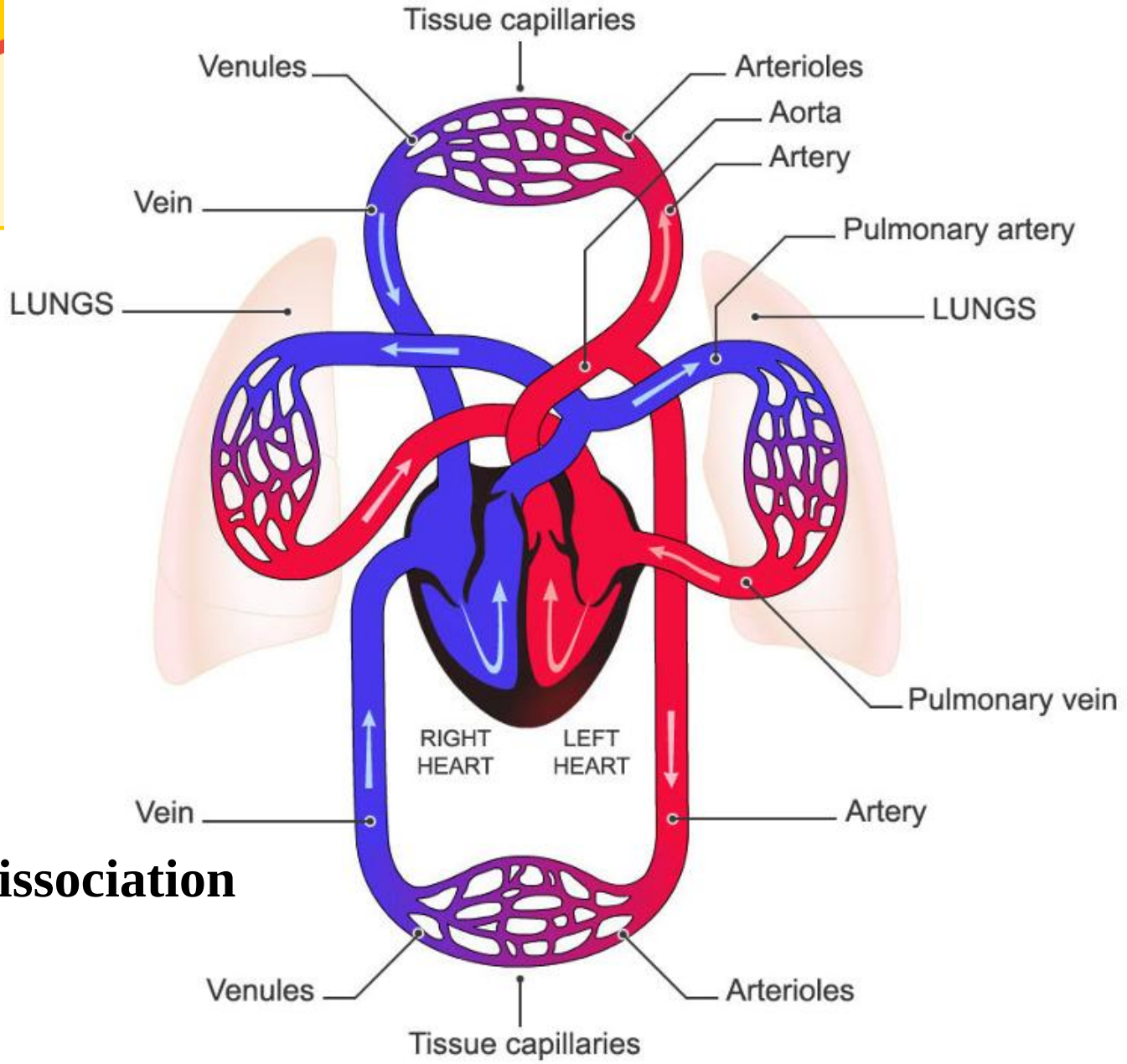
Stroke Volume

***Macro*-circulation**

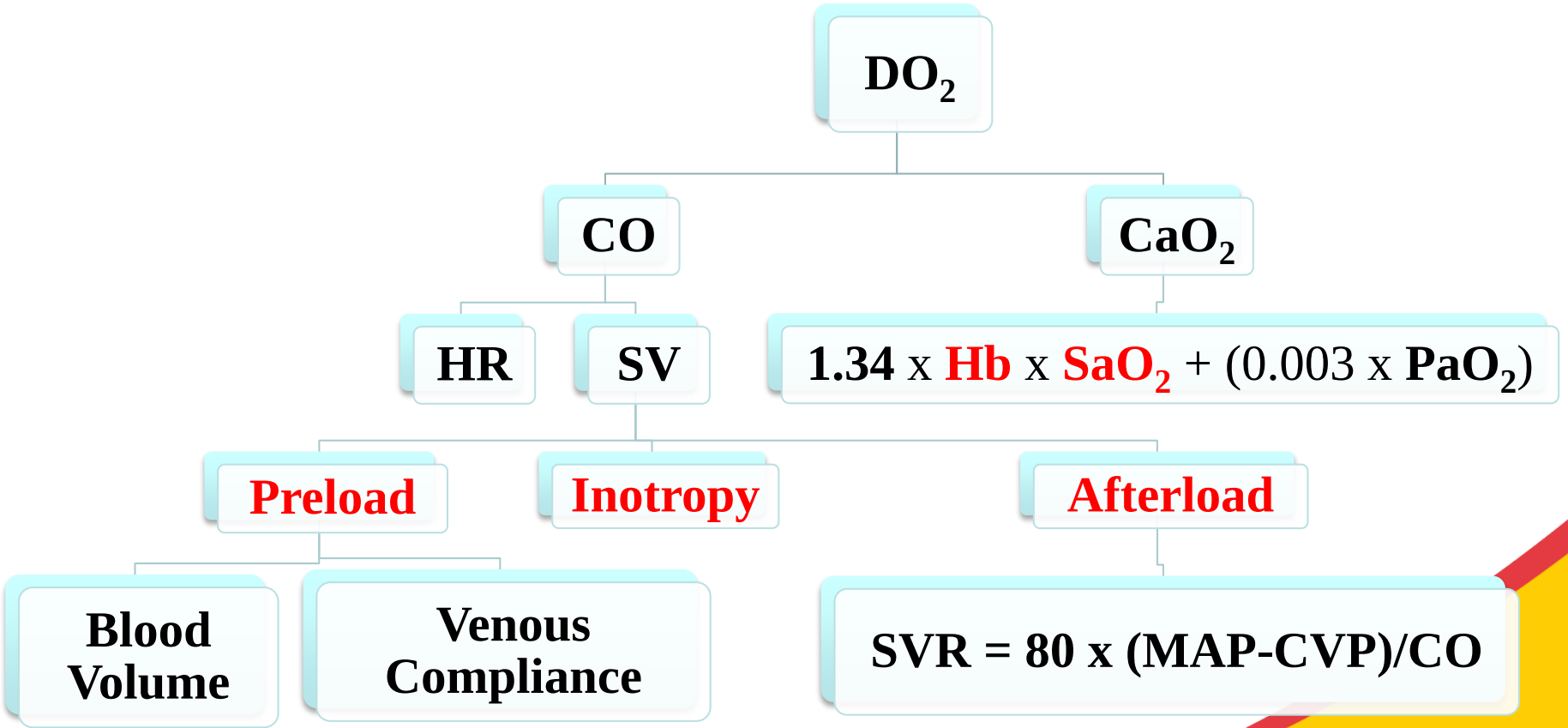
***Micro*-circulation**

Oxyhemoglobin Dissociation

Mitochondria

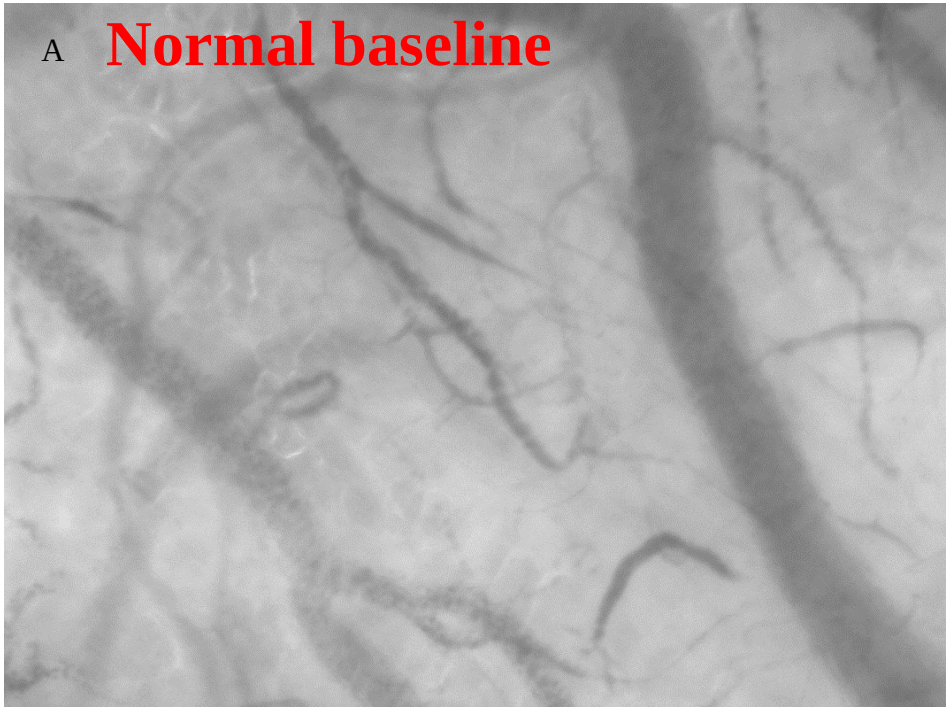


Macrocirculation



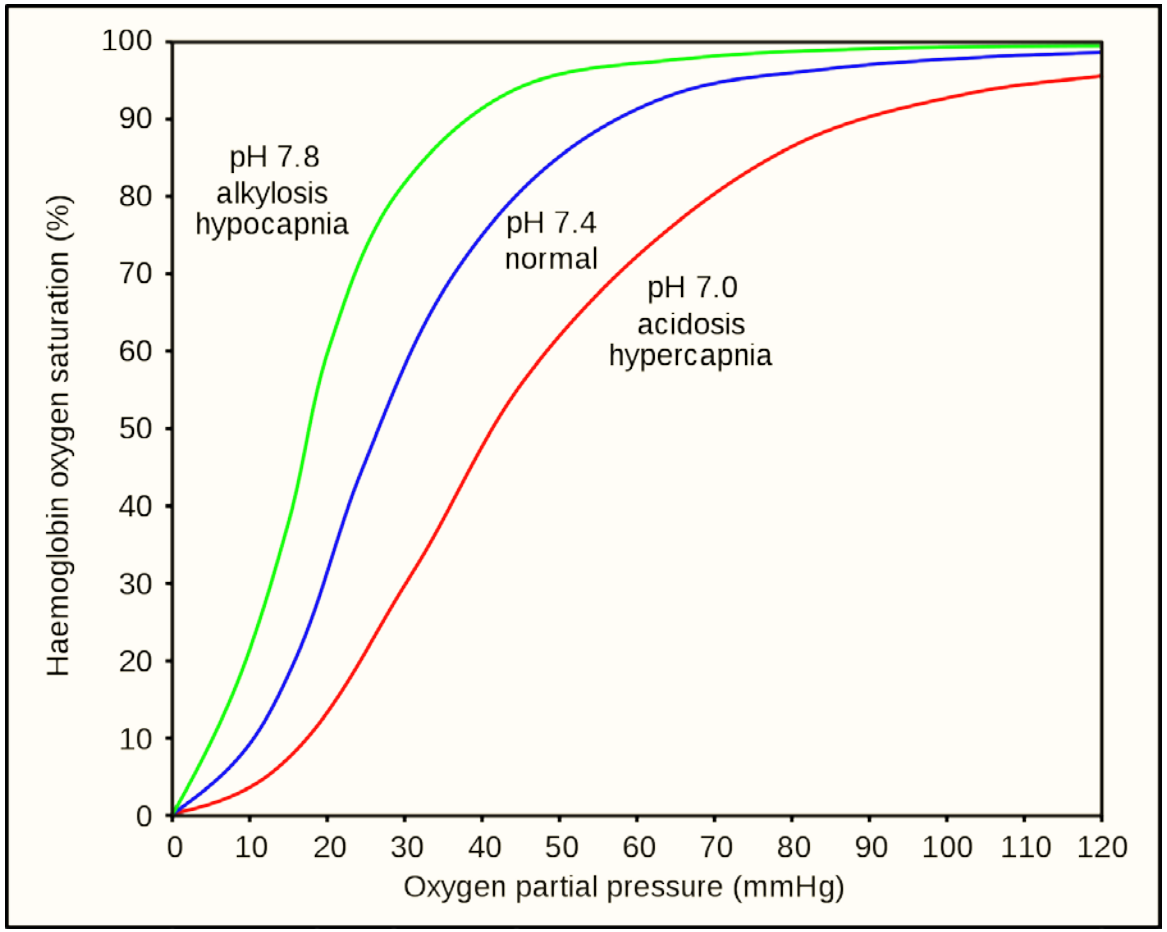
Microcirculation

Microcirculation, before and after CAR-T therapy



A. Baseline: near-normal microcirculation (MFI >2.6; POEM 4 [normal with mild heterogeneity])
B. Hour 66: dysfunctional microcirculation (MFI 2.0; POEM 2 [impaired]), 12h before hypotension & ICU transfer

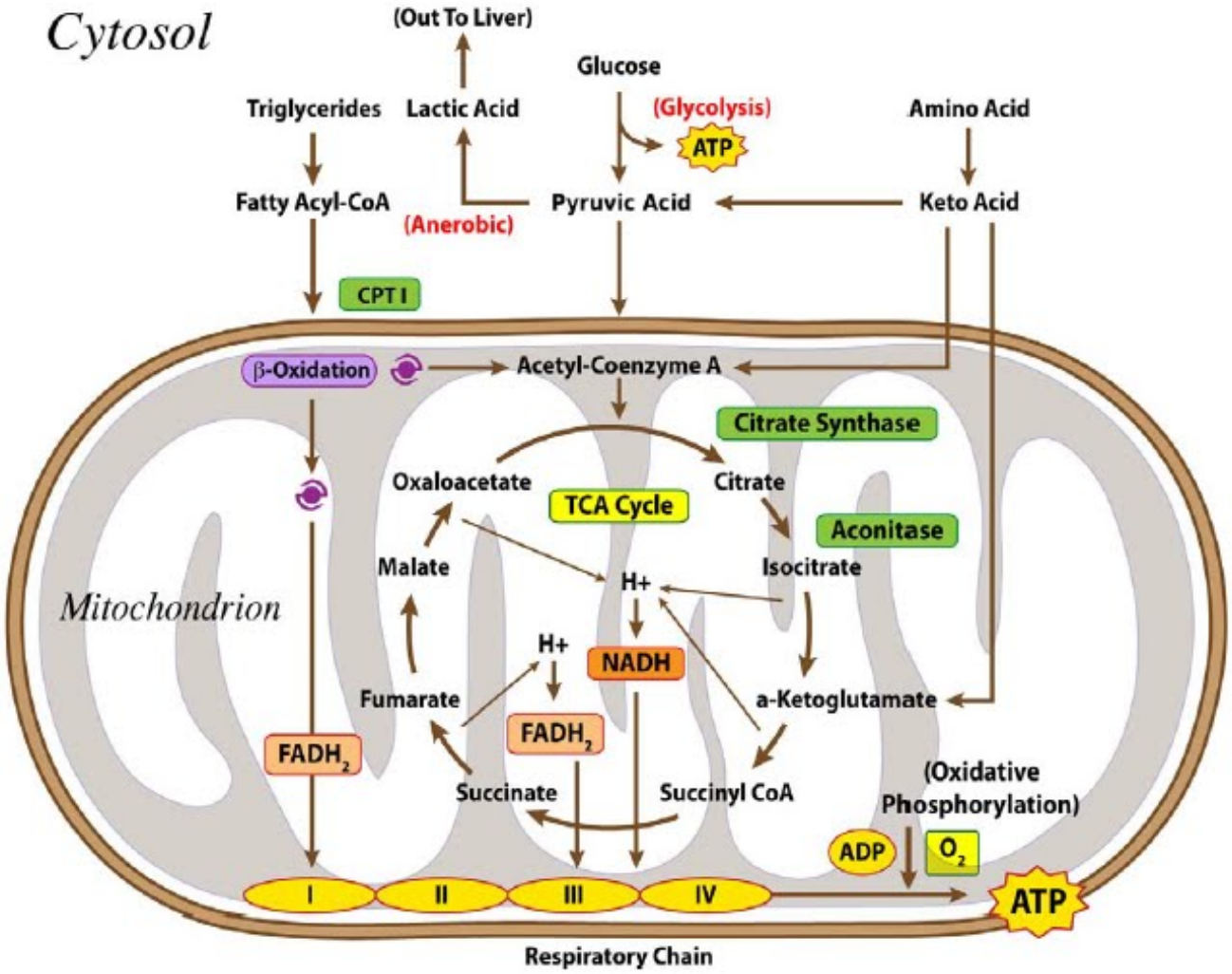
Cellular Oxygen Unloading



Spiegel RJ, Winters ME, McCurdy MT. Cerebral resuscitation: shifting away from the basics. *Resuscitation*. 2017 Dec; 121:e11.

Spiegel RJ, Kappler SB, McCurdy MT. What is the association with dissociation? *JAMA Neurology*. 2018; 75(12):1571-2.

Mitochondrial Function



Resuscitation Principles

Diagnosing & Anticipating Badness

What am I dealing with?

What originally caused it?

What can result from the underlying problem or my treatment of it?

Concomitant Management

Source control – ASAP!

- *Mechanical correction (e.g., percutaneous cholecystostomy, PICC removal)*
- *Antimicrobials*

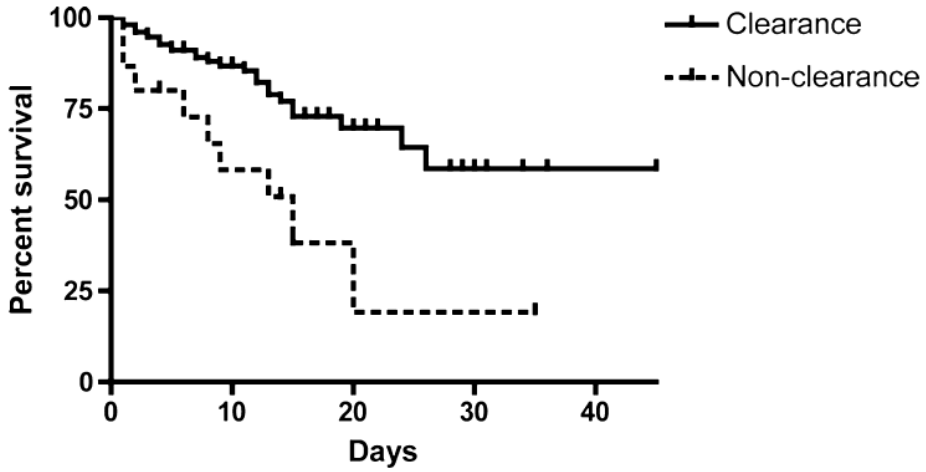
Supportive measures

- *Cardiovascular – MAP ≥65 mmHg*
- *Lung – low tidal volumes*
- *Kidneys – avoid nephrotoxins*
- *Brain – avoid deliriogenic meds (e.g., benzodiazepines)*

Endpoints of Resuscitation

Correction of metabolic acidosis

Lactate clearance >10% associated with improved survival



Optimization of end-organ function

Arnold RC, et al. *Shock* 2009 Jul; 32(1):35-9.
Hasanin A, et al. *J Intensive Care*. 2017; 5:24.

In Medicine (and life),

the sooner a problem is recognized and appropriately corrected,

the better the outcome.

Preload

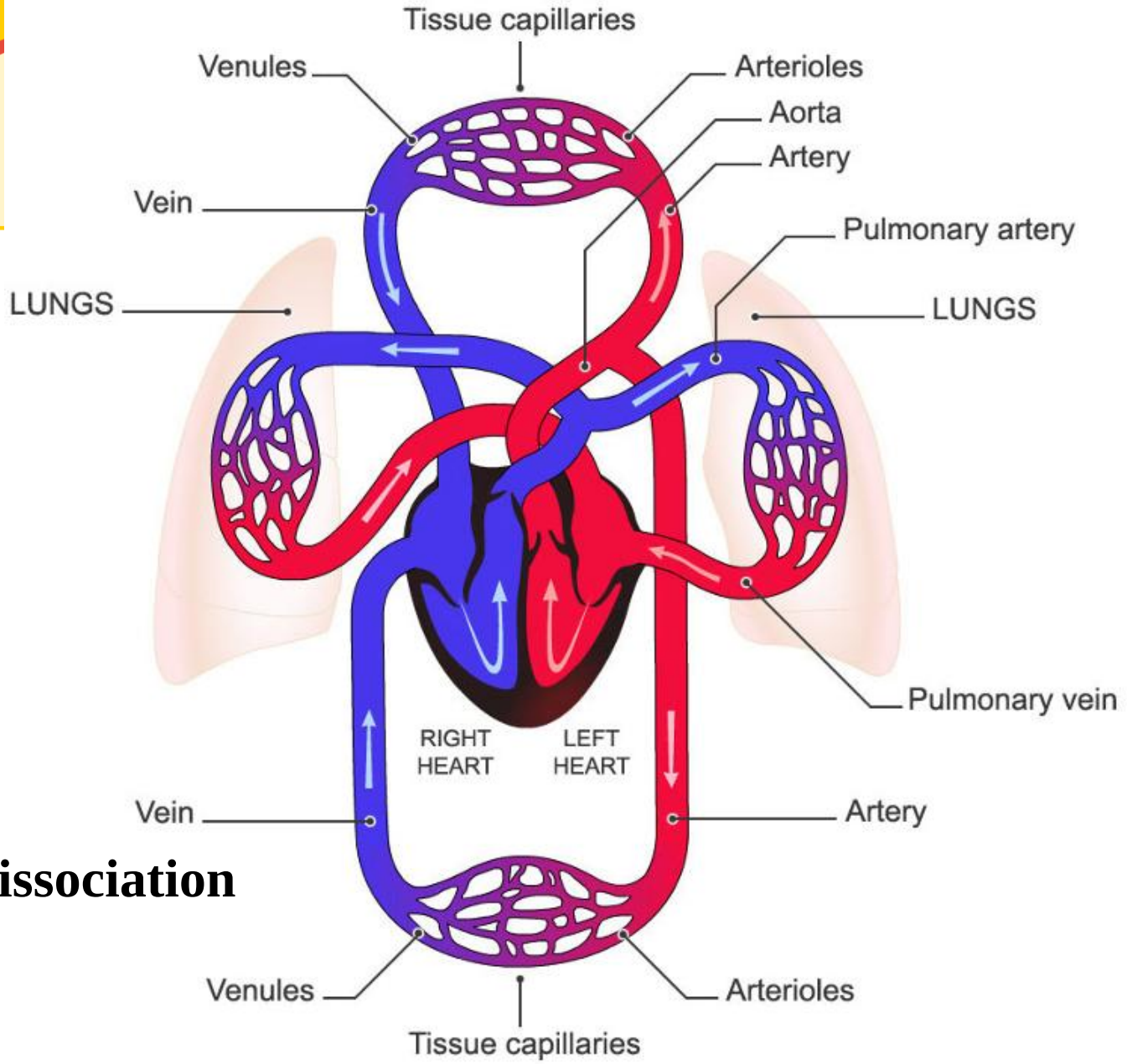
Stroke Volume

***Macro*-circulation**

***Micro*-circulation**

Oxyhemoglobin Dissociation

Mitochondria



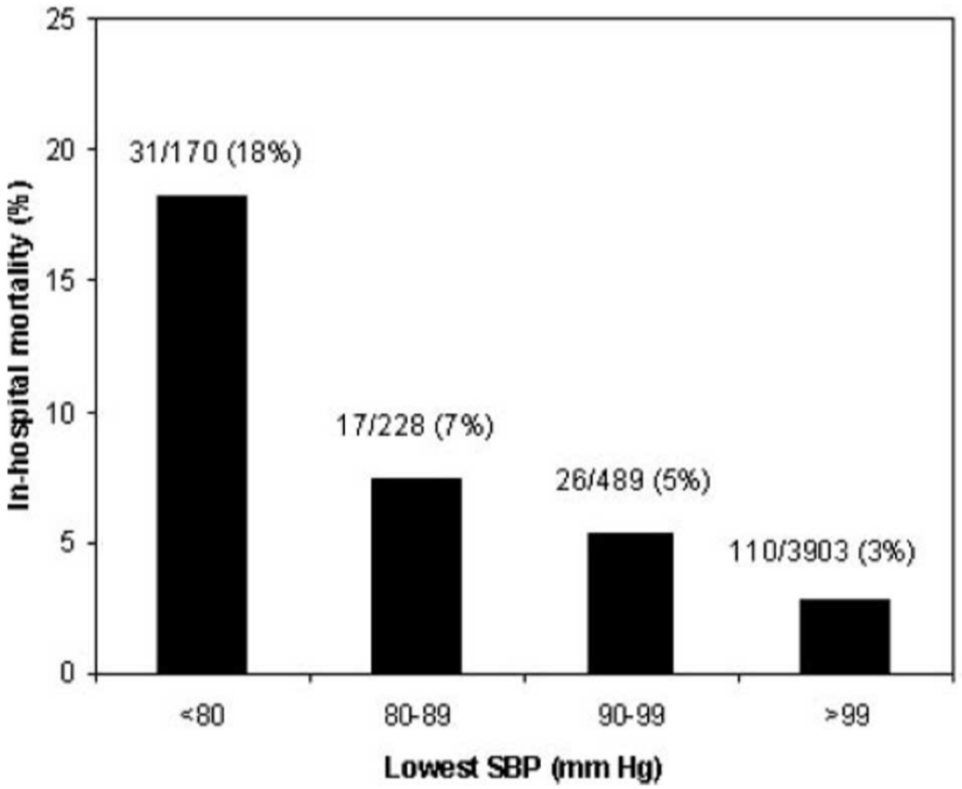
MAP Matters!

Low MAP in ED

ED hypotension common

19% (887 of 4790 patients) hypotensive

(SBP <100 mmHg)



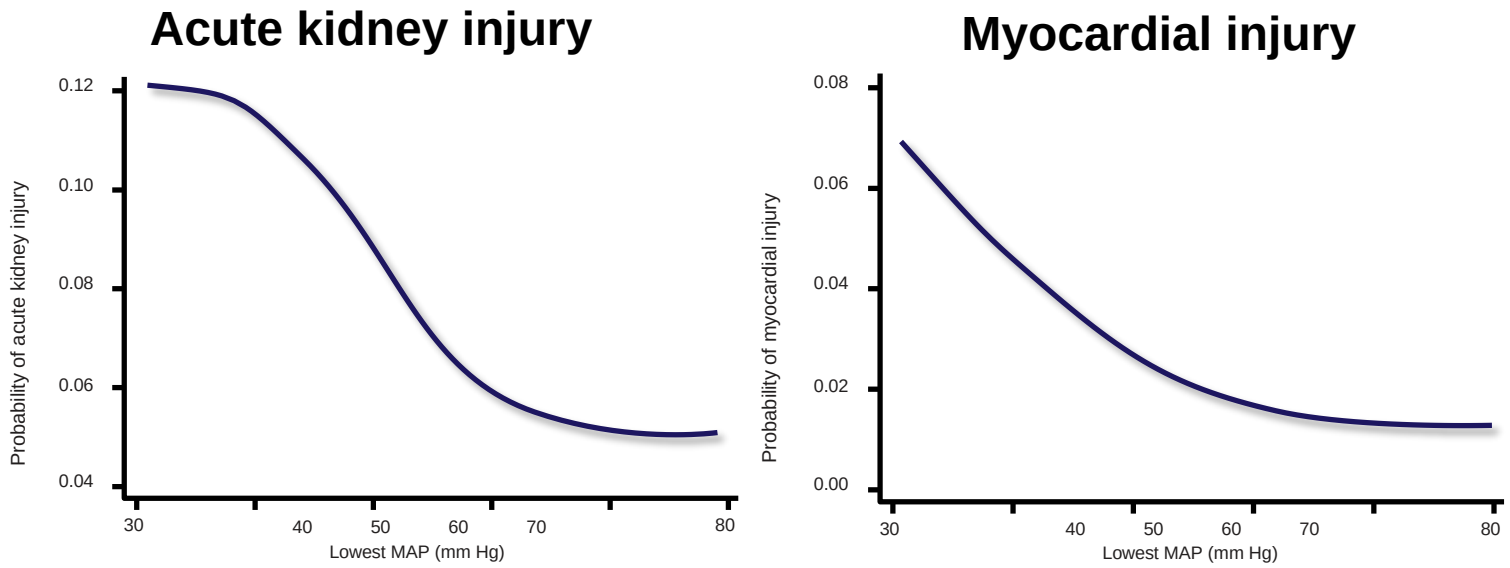
Inpatient mortality

8% of hypotensive patients *versus* **3%** normotensive patients

Hypotension independently predicts in-hospital mortality (OR 2.0)

Jones AE, et al. *Chest*. 2006; 130; 941-6.

Low MAP during Surgery



Risk of both kidney and cardiac injury increases with decreasing MAP

Walsh M, et al. *Anesthesiology*. 2013; 119:507-15.

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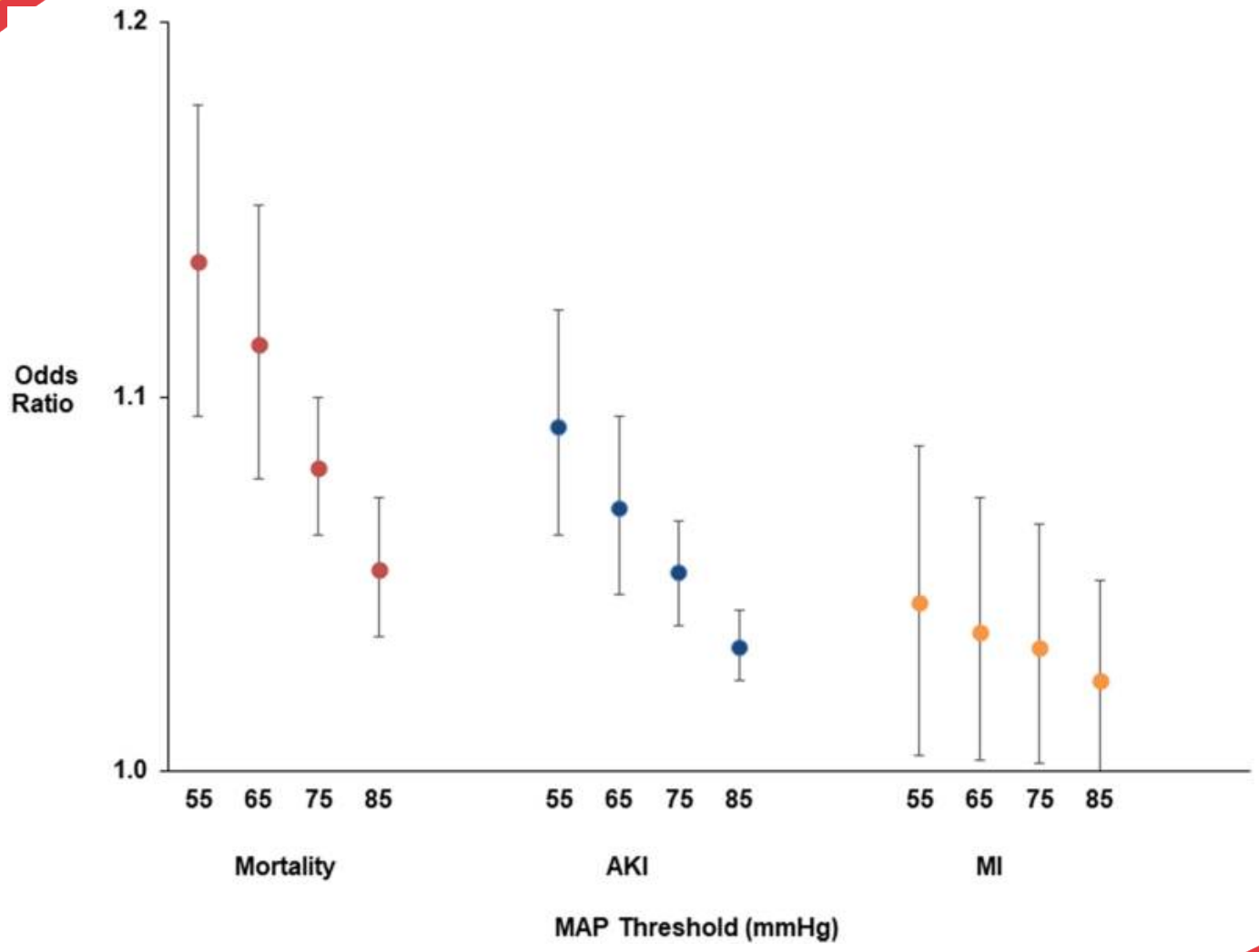
Low MAP in ICU: Cardiac Injury, AKI, and Death



Maheshwari K, et al. *Intensive Care Med*. 2018; 44:857-67.

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Do IV Fluids (Preload) Help?

Understanding the relationship among multiple hemodynamic variables is essential to target therapy to improve end-organ perfusion

“Preload” is often clinically synonymous with “volume load”

- Readily available at bedside
- Minimally invasive
- Does not require “higher level of care”
- Presumptively, diagnostic & therapeutic…

Hypovolemia is BAD

Death

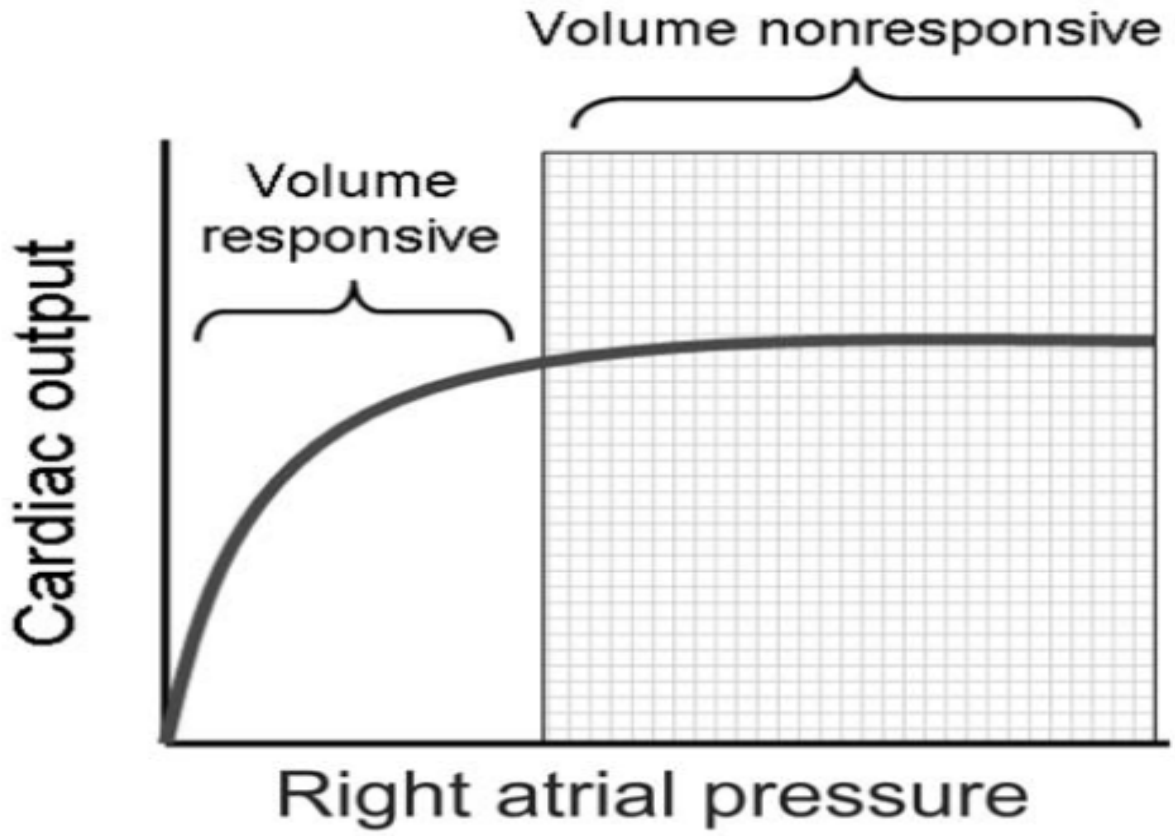
- *Massive hemorrhage*
- *Cholera*

Kidneys

- *In ~30k ICU pts, 26% AKI cases from hypovolemia*

Chino S, et al. *JAMA*. 2005; 294:813-8.

Frank-Starling Curve



Knowlton FP, Starling EH. *J Physiol*. 1912; 4(3):206-19.
Markwalder J, Starling EH. *J Physiol*. 1914; 48(4):348-56.
Patterson SW, Starling EH. *J Physiol*. 1914; 48(5):357-79.

Why Even Assess Volume Status?

Only 50% of patients respond to an IV fluid bolus!

Corollary: 50% do *not* respond to an IV fluid bolus!

Primum non nocere

The half that *doesn't* need IV fluid will have received a harmful therapy

Bentzer P, et al. *JAMA*. 2016; 316(12):1298-309.

Hypervolemia is BAD

Death

- Vera ST, et al. Crit Care. 2012; 16(5):R197.
- Bhaskar P, et al. Intensive Care Med. 2015; 41(8):1445-53.
- Marik PE. Ann Intensive Care. 2014; 4:21.
- Kelm DJ, et al. Shock. 2015; 43(1):68-73.
- Garzotto F, et al. Crit Care. 2016; 20:196.
- Payen D, et al. Crit Care. 2008; 12:R74.

Kidneys

- Prowl JR, et al. Nat Rev Nephron. 2010; 6:107-115.
- Bellomo R, et al. Crit Care Med. 2012; 40:1753-60.
- Bouchard J, et al. Kidney Int. 2009; 76:422-7.
- Raimundo M, et al. Shock. 2015; 44:431-7.

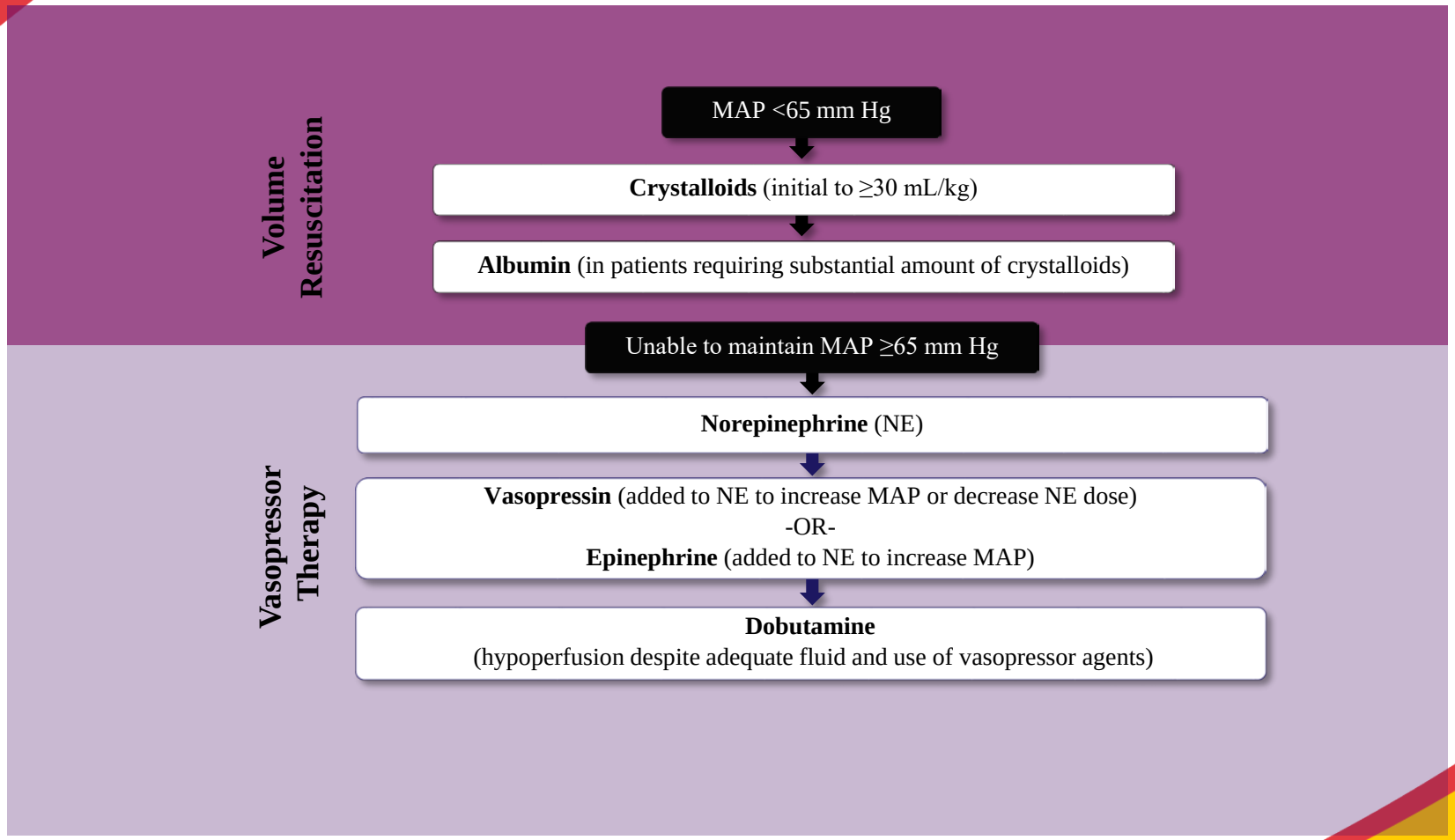
Lungs

- NIH-NHLBI ARDS Network. N Engl J Med. 2006; 354:2564-75.
- Rosenberg AL, et al. J Intensive Care. 2009; 24(1):35-46.
- Silversides JA, et al. Intensive Care Med. 2016 Oct 12. *Epub*

Don't "*fill* the tank."

"*Shrink* the tank."

Septic Shock Guidelines



Rhodes A, et al. *Intensive Care Med*. 2017; 43:304-77.

Are We Okay with Existing Mortality?...

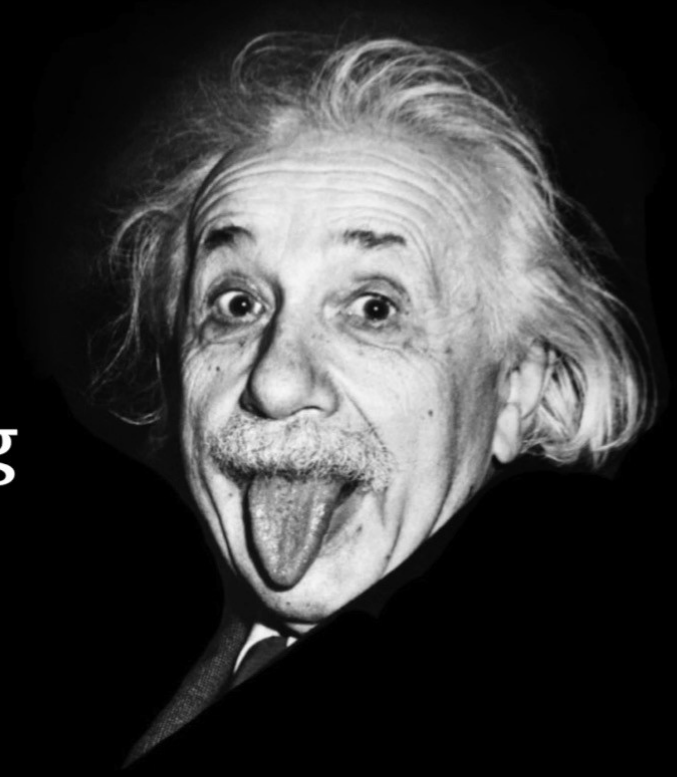
Severe vasodilatory shock has 30-day

>50% mortality

Bassi E, et al. *Crit Care Res Pract*. 2013; 2013:654708.
De Backer D, et al. *N Engl J Med*. 2010; 362:779-89.

"Insanity is doing the same thing over and over again and expecting different results"

Albert Einstein



A New Approach Is Needed

- **Lessons from antibiotics for septic shock…**
  - Broad-spectrum antibiotics, then deescalate per antibiogram
  - Earlier administration yields better outcomes

- **Broad-spectrum vasopressors, then personalized approach?**

  Chawla LS, et al. Crit Care. 2019; 23:124.

  Levine AR, et al. Crit Care Med. 2020. (In press)

- **Balanced approach to most pharmacological interventions generally yields synergistic benefits and mitigates side effects**

Physiologic Response to Vasodilatory Shock

Sympathetic System

Adrenal medulla

Catecholamines → α & ß receptors

Arginine Vasopressin Pathway

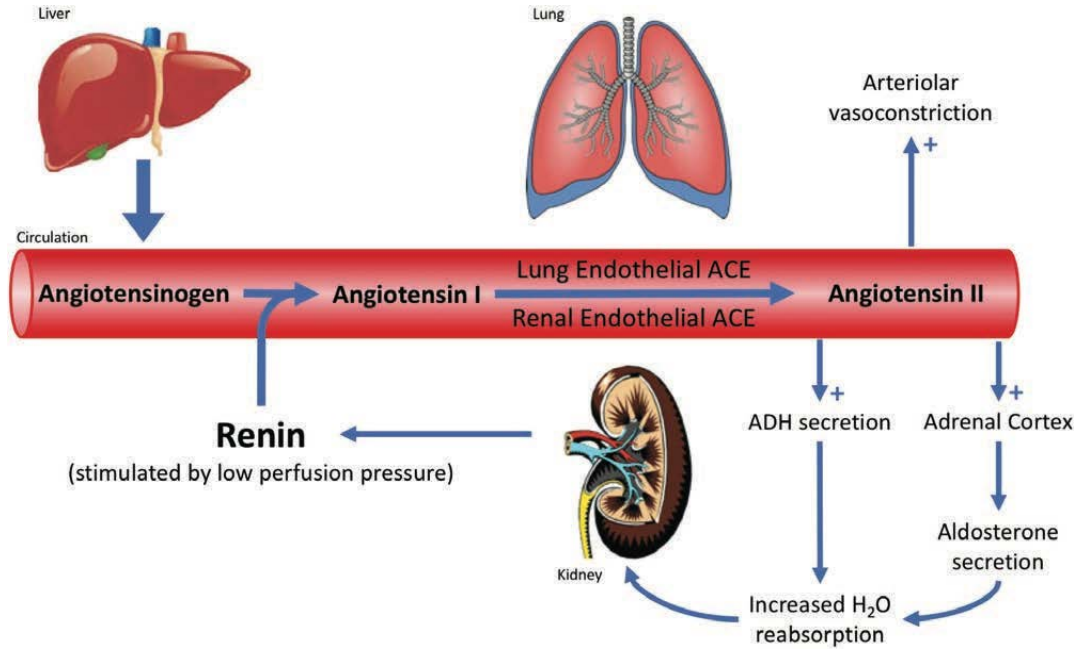
Posterior pituitary

ADH → V_1 & V_2 receptors

Renin-Angiotensin-Aldosterone System (RAAS)

Kidney (renin), liver (angiotensinogen), lung (ACE)

Angiotensin II → AT_1 & AT_2 receptors



Chow JH, et al. AA Pract. 2018 Apr 23.

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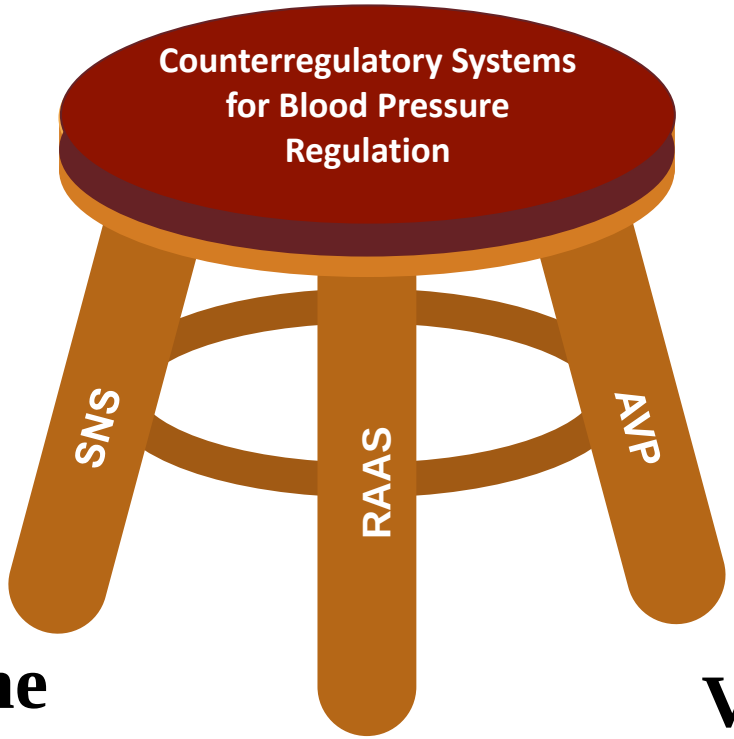
Physiologic Response to Vasodilatory Shock



Norepinephrine
Epinephrine

Angiotensin II

Vasopressin

Russell JA, et al. *New Engl J Med*. 2008; 358(9):877-87.
Khanna AK, et al. *New Engl J Med*. 2017; 377(9):419-30.
De Backer D, et al. *New Engl J Med*. 2010; 362:779-89.

Catecholamines in Blood Pressure Management

Anti-*hyper*tensives

- **Beta-blockers**
- **Alpha$_1$-blockers**
- **Alpha$_2$-agonists**

Anti-*hypo*tensives

- **Norepinephrine**
- **Epinephrine**
- **Dopamine**
- **Phenylephrine**

Vasopressin in Blood Pressure Management

Anti-*hyper*tensives

- **Direct renin inhibitors**
- **ACE-Inhibitors**
  - *Lisinopril most commonly prescribed antihypertensive in U.S.*
- **Angiotensin Receptor Blockers**
- **Angiotensin Receptor-Neprilysin Inhibitors**

Anti-*hypo*tensives

- **Angiotensin II**

RAAS in Blood Pressure Management

Anti-*hyper*tensives

- **Direct renin inhibitors**
- **ACE-Inhibitors**
  - *Lisinopril most commonly prescribed antihypertensive in U.S.*
- **Angiotensin Receptor Blockers**
- **Angiotensin Receptor-Neprilysin Inhibitors**

Anti-*hypo*tensives

- **Angiotensin II**

RECAP

1) **Shock is bad & may have many physiological causes**

2) **Maintaining an adequate blood pressure is important**

3) **How should we maintain BP?...**
   1) **Excess fluids are bad**
   2) **Pressors require escalation of care**

4) **3 physiologic systems exist to regulate BP – which one?**
   1) **Catecholamines → effective but dysrhythmias & ⇧ lactate**
      McIntyre WF, et al. JAMA. 2018 May 8; 319(18): 1889–1900.
   2) **Vasopressin → 50% effective and slow-acting**
      Sacha GL, et al. Ann Intensive Care. 2018; 8: 35.
   3) **RAAS → ?...**

Go back to where you started, or as far back as you can, examine all of it, travel your road again and tell the truth about it. Sing or shout or testify or keep it to yourself: but know whence you came.

James Baldwin

(1924-1987)

Go Tell It on the Mountain, 1953

Discovery & Isolation: 1930s

1898

Renin-angiotensin system discovered while reporting the pressor effect of rabbit kidney extracts → named ‘renin’

Tigerstedt R, Bergman PG. *Skand Arch Physiol*. 1898; 8:223-71.

1931

Relationship between pathologic renal alterations and development of systemic hypertension

Volhard F. *Handbuch der Inneren Medizin*, vol 6. Berlin: Springer Verlag; 1931:1-1023.

1934

Experimental hypertension induced in dogs by clamping renal artery

Goldblatt H, et al. *J Exp Med*. 1934; 59:347-79.

Discovery & Isolation: 1930s-1940s

1936

Argentinian group (Drs. Houssay, Fasciolo, Taquini, Braun-Menendez)

1) Induced HTN using Goldblatt technique → renal secretion of pressor similar to renin

Houssay BA, Fasciolo JC. *Bol Acad Nac Med*. 1937; 18:342-4.

2) Substance isolated → intense & fast-acting but brief pressor effect → named "**hypertensin**"

Fasciolo JC, et al. *J Physiol*. 1938;94:281-93.

3) Venous blood from ischemic kidney of hypertensive dog → immediate & profound vasoconstrictrion

Braun-Menendez E, et al. *Rev Soc Arg Biol*. 1939; 15:420-5.

4) Identified RAAS pathway → kidney secreted renin, converting "hypertensinogen" to "hypertensin"

Leloir LF, et al. *Rev Soc Arg Biol*. 1940; 16:75-80.

Indianapolis group (Dr. Irvine Page at Eli-Lilly Labs)

Identified octapeptide pressor formed through interaction of renin & its activator → "**angiotonin**"

Kohlstaedt KG, et al. *Proc Soc Exp Biol Med*. 1938; 39:214-5.

Page IH, Helmer OM. *Proc Center Soc Clin Invest*. 1939; 12:17.

Discovery & Synthesis: 1950s

1954

Skeggs discovers two types of angiotensin (angiotensin I & II), ACE, & renin substrates

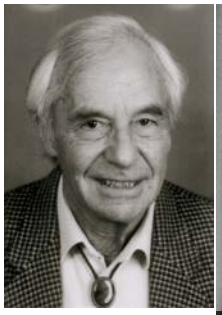
Skeggs LT, et al. *J Exp Med*. 1954;99:275.

1957

Angiotensin II synthesized (*bovine formulation*) → short shelf life

Dr. Irving Page at Cleveland Clinic

Schwarz H, et al. *J Am Chem Soc*. 1957; 5697-703.



Dr. Robert Schwyzer at CIBA Laboratories in Basel, Switzerland

- *Marketed pressor as "Hypertensin"*

Schwyzer R, et al. *Chimia*. 1957; 11:335-8.

1957

U Michigan Conference: Dr. Braun-Menéndez and Page agree on its name

"**hypertensin**" + "**angiotonin**" = "**angiotensin**"

Braun-Menendez E, Page IH. *Science*. 1958; 127:242.

Normal Serum Levels in Humans

Normal levels of ang II in arterial blood are **~0.02 µg/L**

Infusion dose

= (basal concentration) x (volume distribution) ÷ (weight) ÷ (half-life)

= (0.02 mcg/L) x (1000 ng/mcg) x (25 L) ÷ (100 kg) ÷ (1 minute)

= **5 ng/kg/min**

Wolf RL, et al. Circulation. 1961 May; 23:754-8.

Catt KJ, et al. Br Med J. 1969; 1(5647):819-21.

Angiotensin II in Clinical Use: 1960s-1990s

Clinical Experience with Angiotensin II in the Treatment of Shock

Francesco del Greco, M.D., and David C. Johnson, M.D., Chicago

SEVERAL VASOPRESSOR AGENTS have been employed in recent years for treating shock and severe hypotension. The most powerful of these agents, levarterenol bitartrate, is limited in its use because of undesirable side effects.

In 1957, Schwyzer et al.[1] and Bumpus, Schwartz, and Page[2] reported the successful synthesis of a new vasopressor agent, angiotensin II. Extensive physiological and pharmacological studies in animals and man have shown that angiotensin II is considerably more potent than levarterenol.[3, 4] To date, only a few, limited studies concerning the effectiveness of angiotensin II in the treatment of shock in man have appeared, mostly in European literature.[5-9] The present report deals with a clinical evaluation of angiotensin II (valine-5 angiotensin II amide [Hypertensin]) in the treatment of shock due to various etiologies.

The effects of using angiotensin in the treatment of shock from various causes were studied in 21 patients. The blood pressure returned to normal in every instance excepting 6 patients who were moribund when treatment was begun. Of 6 patients who were in advanced bacteremic shock and whose prognosis was considered hopeless, 4 survived as did one with severe shock associated with postoperative intracranial bleeding and two with severe barbiturate poisoning. Angiotensin was also used in treating 10 patients in whom hypotension appeared in the course of dialysis by an artificial kidney. Six survived. In this series of cases angiotensin produced no side effects of any sort.

del Greco F, Johnson DC. *JAMA*. 1961; 178:994-9.

Clinical Use: 1960s-1990s

Numerous case reports and experimental studies

Clinical use largely in Europe

>1,100 studies from 1941-1999 involving IV infusion of Ang II in humans

Ang II effects in humans with shock (SBP <90 mmHg or MAP <65 mmHg)?

24 studies (353 patients) published in English

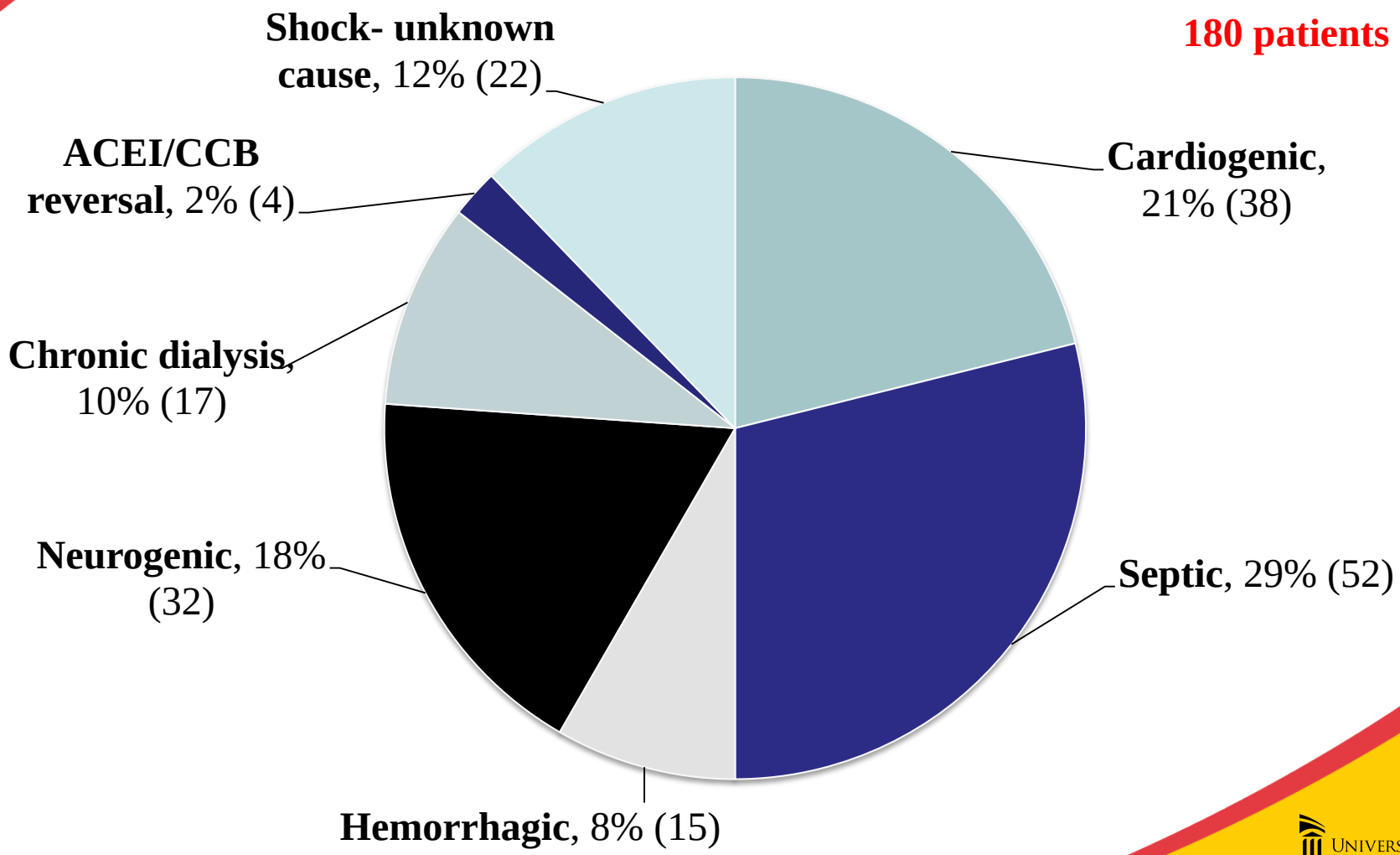
Excluding ATHOS & ATHOS-3: 180 patients

Clinical use: sepsis, cardiac arrest, heart failure, intraoperative, dialysis, ACE-I OD

Busse LW, et al. *Crit Care Med.* 2017 Aug; 45(8):1285-94.

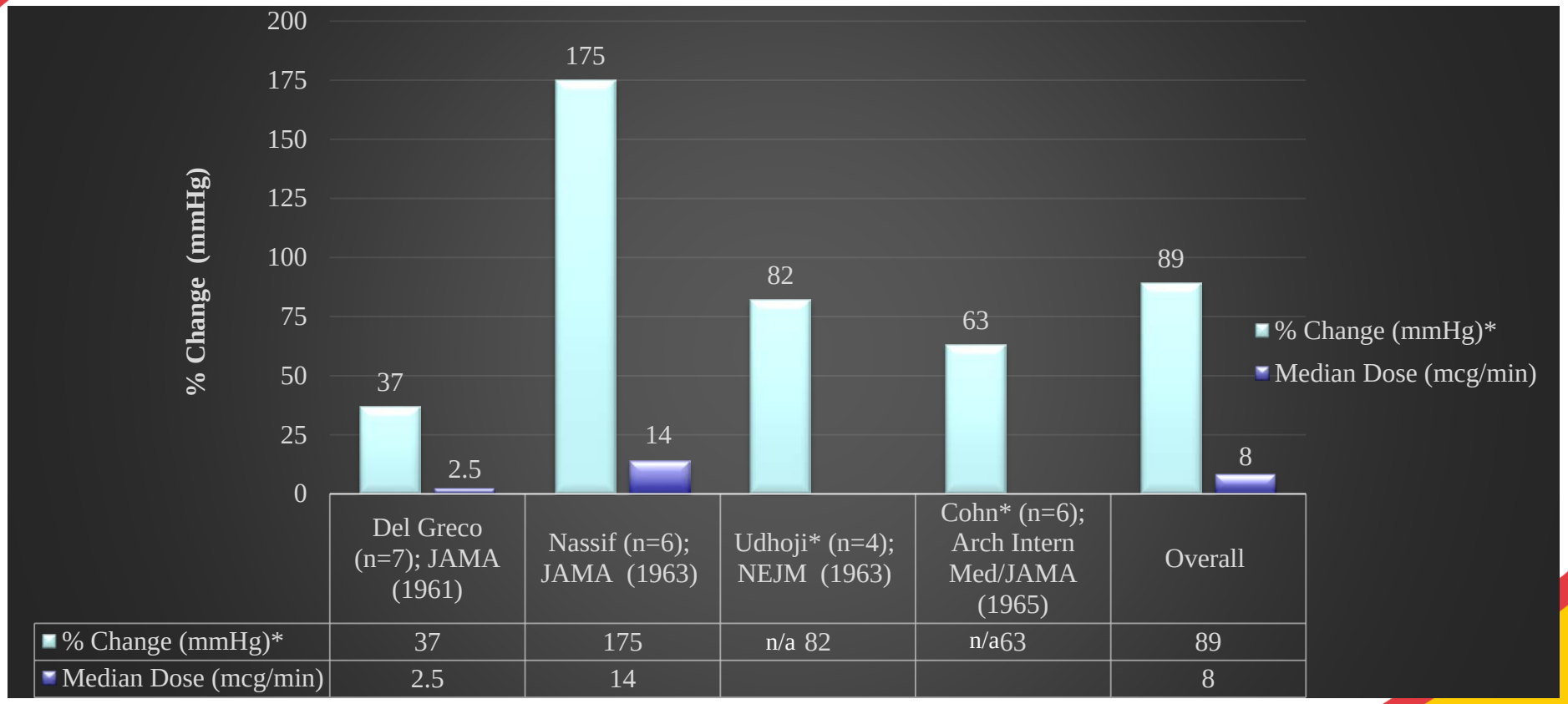
Busse LW, et al. *Crit Care*. 2017 Dec 28; 21(1):324.

Angiotensin II in Shock (1961-1998)



Busse LW, et al. *Crit Care*. 2017 Dec 28; 21(1):324.

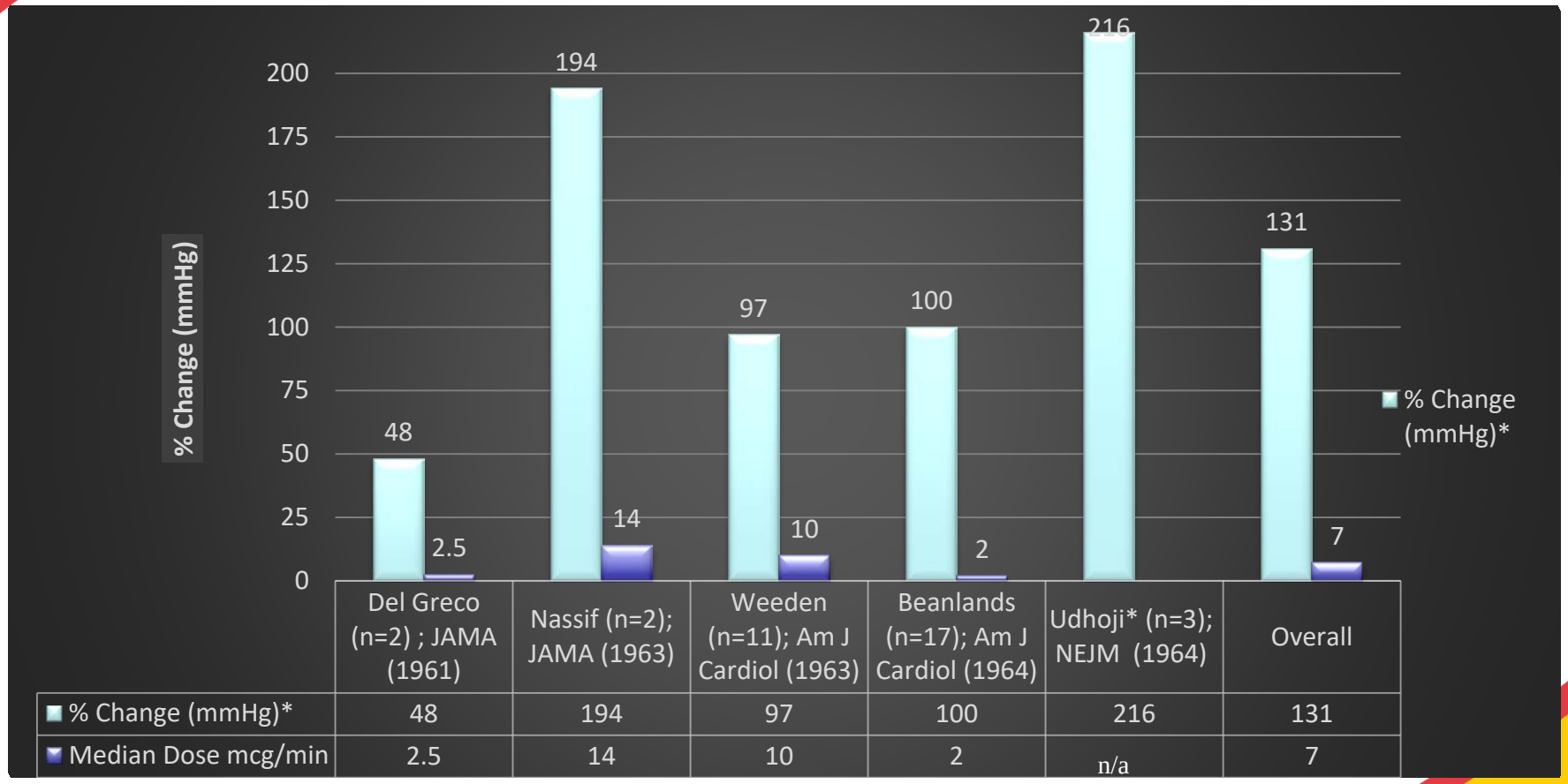
Angiotensin II: Septic Shock



	Del Greco (n=7); JAMA (1961)	Nassif (n=6); JAMA (1963)	Udhoji* (n=4); NEJM (1963)	Cohn* (n=6); Arch Intern Med/JAMA (1965)	Overall
% Change (mmHg)*	37	175	n/a 82	n/a63	89
Median Dose (mcg/min)	2.5	14			8

Busse LW, et al. *Crit Care*. 2017 Dec 28; 21(1):324.

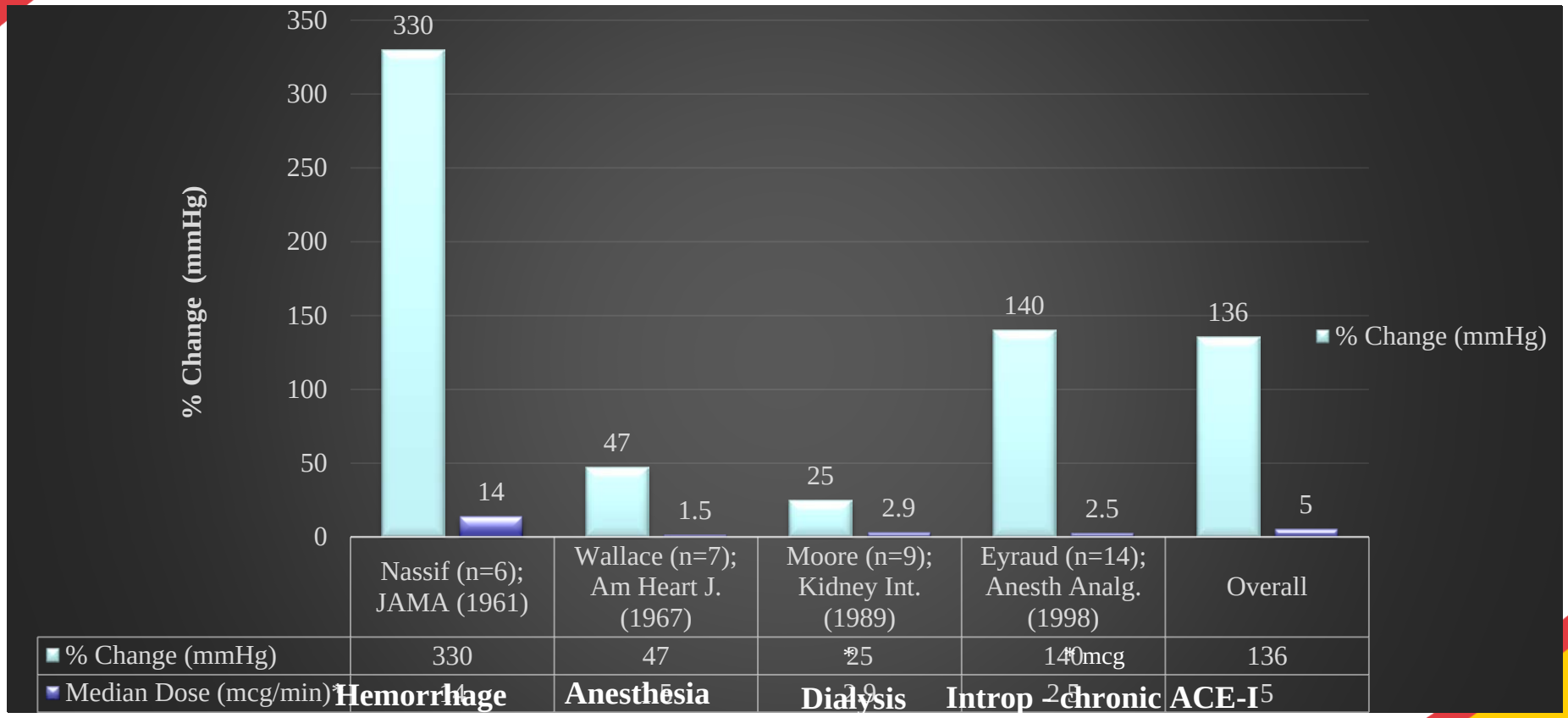
Angiotensin II: Cardiogenic Shock



	Del Greco (n=2) ; JAMA (1961)	Nassif (n=2); JAMA (1963)	Weeden (n=11); Am J Cardiol (1963)	Beanlands (n=17); Am J Cardiol (1964)	Udhoji* (n=3); NEJM (1964)	Overall
% Change (mmHg)*	48	194	97	100	216	131
Median Dose mcg/min	2.5	14	10	2	n/a	7

Busse LW, et al. *Crit Care*. 2017 Dec 28; 21(1):324.

Angiotensin II: Other Causes of Shock



Busse LW, et al. *Crit Care*. 2017 Dec 28; 21(1):324.

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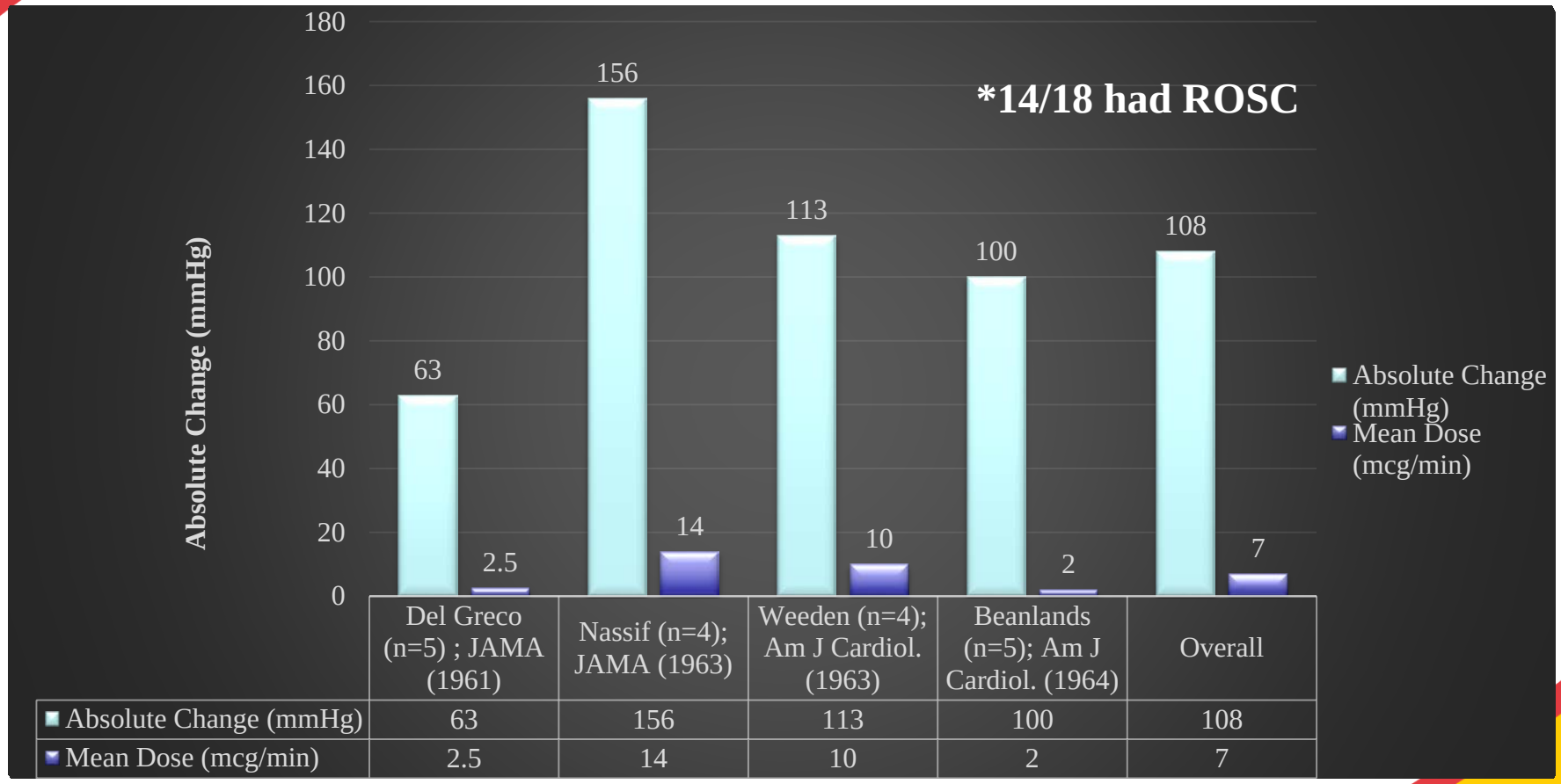
Angiotensin II: Cardiac Arrest



	Del Greco (n=5) ; JAMA (1961)	Nassif (n=4); JAMA (1963)	Weeden (n=4); Am J Cardiol. (1963)	Beanlands (n=5); Am J Cardiol. (1964)	Overall
Absolute Change (mmHg)	63	156	113	100	108
Mean Dose (mcg/min)	2.5	14	10	2	7

Busse LW, et al. *Crit Care*. 2017 Dec 28; 21(1):324.

McCurdy MT, et al. *Crit Care Med*. 2019 May; 247(5):e436.

End of an Era: 1990s

Continued but <u>limited</u> use in humans

Why?

- *Evolving understanding of sepsis as a clinical entity*
- *Focus on increasing DO_2?*
- *Desire for single-drug solutions to diseases?*
- *Focus on immunotherapy?*

Meanwhile…

- *Increased focus on RAAS-related **hyper**tension → >**20k** PubMed citations for "ang II & HTN"*

Bone RC, et al. *Chest*. 1992 Jun;101(6):1644-55.
Rackow, EC, et al. *JAMA*. 1988;259(13):1989-1993.
Villar J, et al. *Chest*. 1990; 98:3:687-92.
Bakker J, Vincent JL. *J Crit Care*. 1991;6(3):152-9.

<u>1996</u>

CIBA-Geigy & Sandoz merge to form Novartis

Angiotensin II production halted

Renewed Focus on Distributive Shock: 2000s

EGDT highlighted multimodal approach to sepsis

Mortality *could* improve→ Surviving Sepsis Campaign

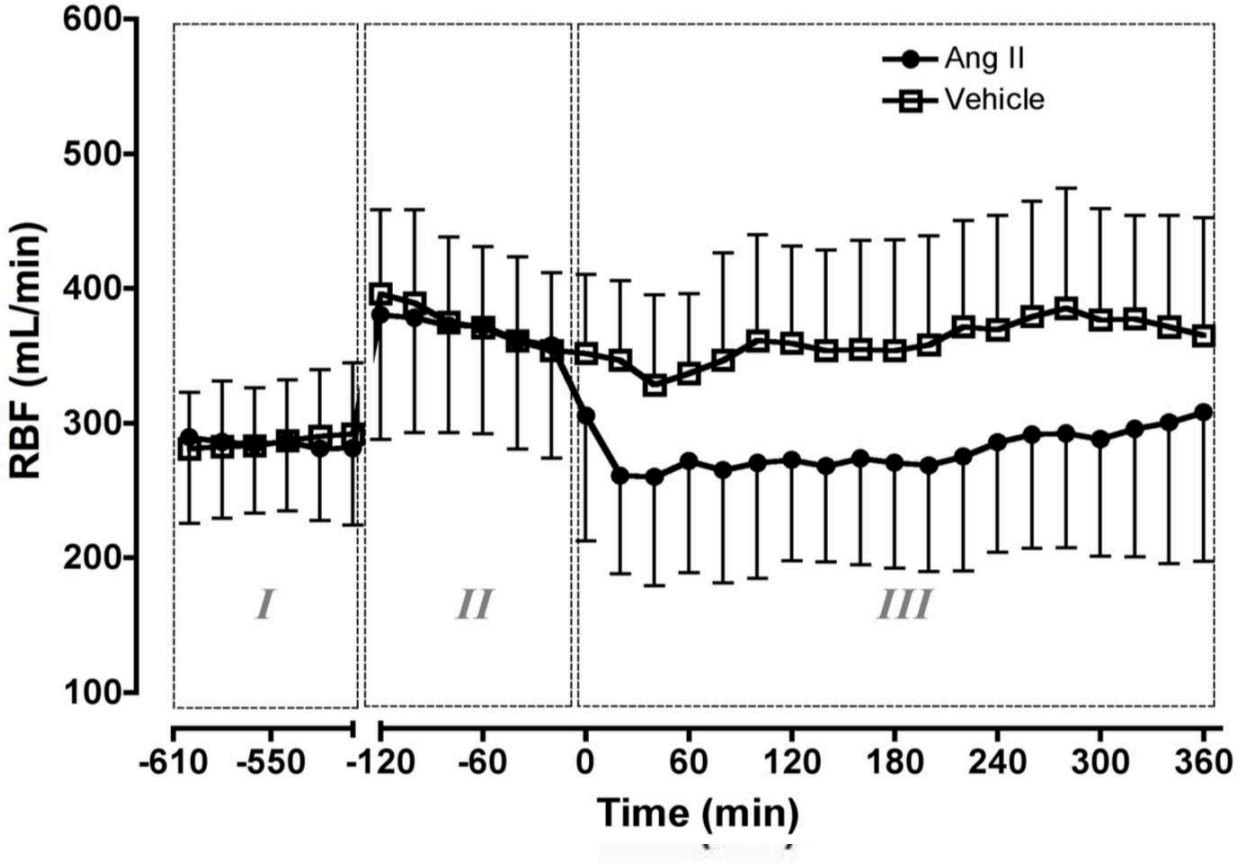
VASST explores use of other vasopressors

Explores if a more balanced vasoactive approach may improve outcomes

Rivers E, et al. *N Engl J Med*. 2001 Nov 8;345(19):1368-77.

Russell JA, et al. *N Engl J Med*. 2008 Feb 28;358(9):877-87.

Bellomo, 2009

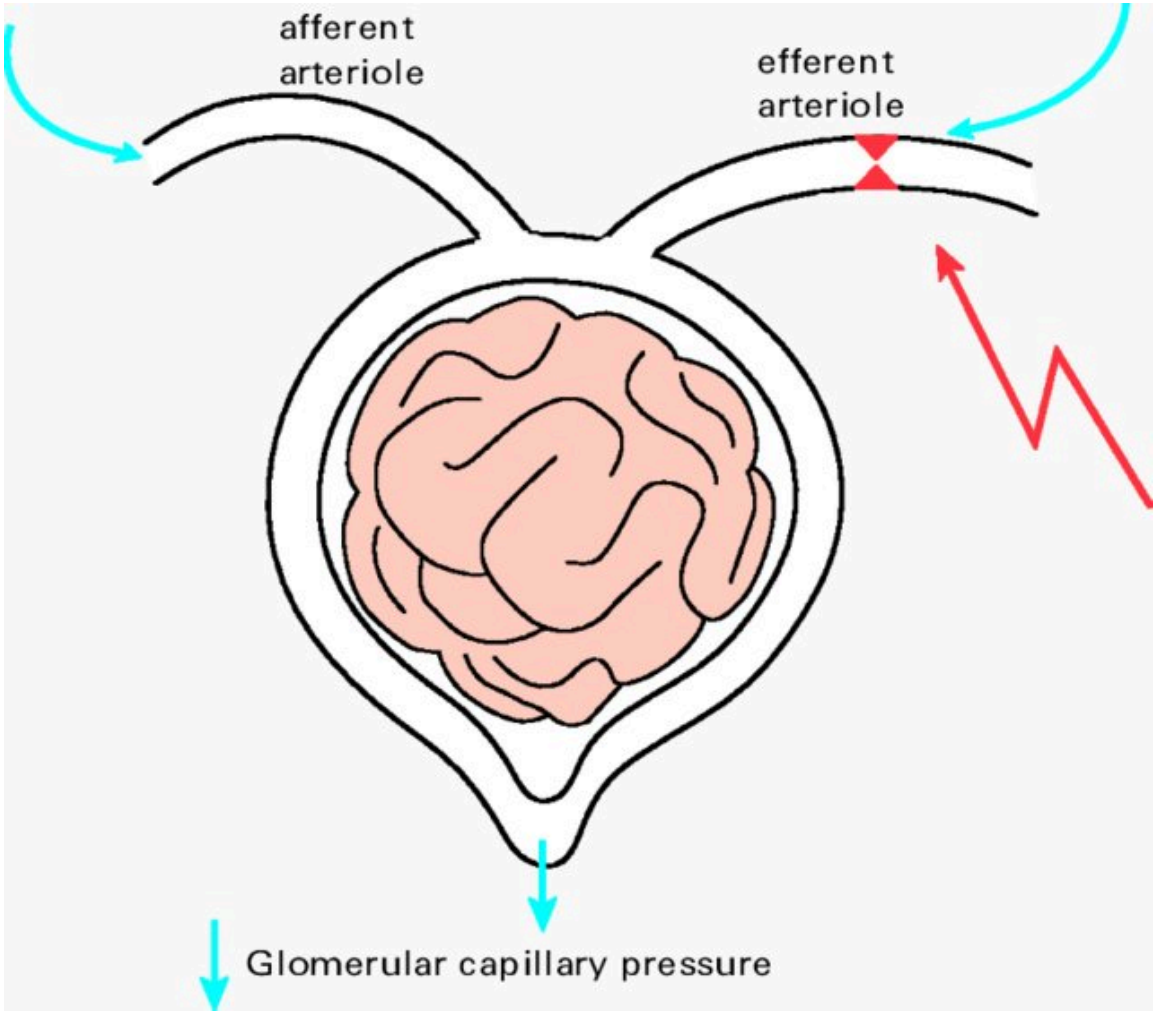


↑ **UOP >7x control**
(p <0.0001)

↑ **creat clearance**
(p <0.05)

Wan L, et al. *Crit Care*. 2009;13(6):R190.

Ang II & Renal Function



Pre-ATHOS

2009

Patent for synthetically-derived human molecule of ang II

2013

Larry Busse, working with Mink Chawla at George Washington University, obtains synthetically-derived human molecule of Ang II from a German company that produces designer peptides

2014

ATHOS trial published

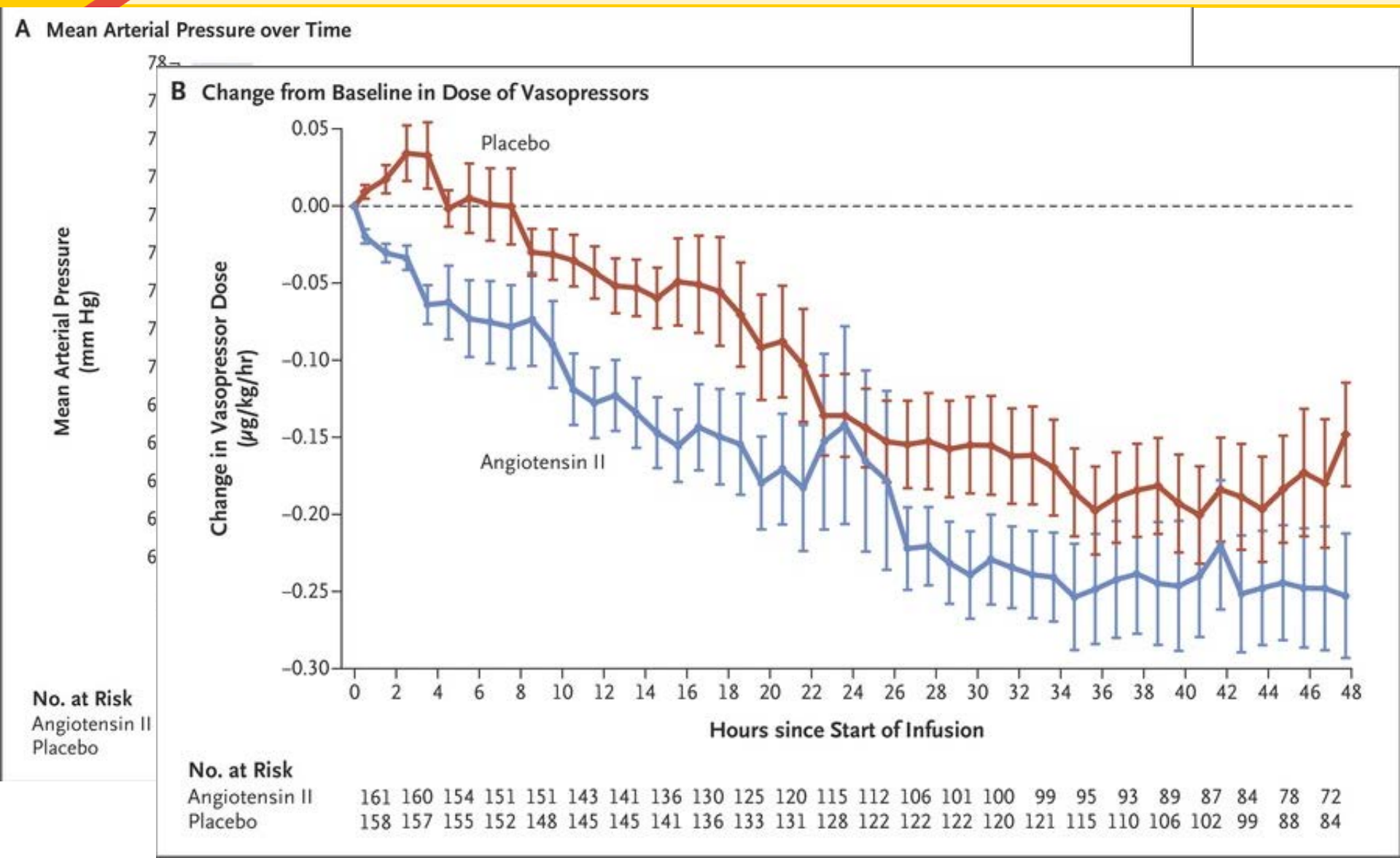
Chawla LS, et al. *Crit Care*. 2014 Oct 6;18(5):534.

ATHOS-3

- International, randomized, double-blind, placebo-controlled trial
- 9 countries, 75 ICUs
- 344 patients randomized in 1:1 fashion to standard of care **plus** *either* angiotensin II *or* saline
- **Primary outcome**: 3-hour MAP after start of infusion
  - Baseline increase of ≥10 mmHg or increase to ≥75 mmHg,
    - *without increase in dose of background vasopressors*

Khanna AK, et al. *N Engl J Med*. 2017 Aug 3; 377:419-30.

ATHOS-3


A Mean Arterial Pressure over Time
Mean Arterial Pressure (mm Hg)
No. at Risk
Angiotensin II
Placebo
B Change from Baseline in Dose of Vasopressors
Change in Vasopressor Dose (μg/kg/hr)
0.05
0.00
−0.05
−0.10
−0.15
−0.20
−0.25
−0.30
Placebo
Angiotensin II
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
Hours since Start of Infusion
No. at Risk
Angiotensin II 161 160 154 151 151 143 141 136 130 125 120 115 112 106 101 100 99 95 93 89 87 84 78 72
Placebo 158 157 155 152 148 145 145 141 136 133 131 128 122 122 122 120 121 115 110 106 102 99 88 84

ATHOS-3

Table 2. Primary and Secondary End Points.*

End Point	Angiotensin II (N=163)	Placebo (N=158)	Odds or Hazard Ratio (95% CI)	P Value
Primary efficacy end point: MAP response at hour 3 — no. (%)†	114 (69.9)	37 (23.4)	Odds ratio, 7.95 (4.76–13.3)	<0.001
Secondary efficacy end points				
Mean change in cardiovascular SOFA score at hour 48‡	−1.75±1.77	−1.28±1.65		0.01
Mean change in total SOFA score at hour 48§	1.05±5.50	1.04±5.34		0.49
Additional end points				
Mean change in norepinephrine-equivalent dose from baseline to hour 3¶	−0.03±0.10	0.03±0.23		<0.001
All-cause mortality at day 7 — no. (%)	47 (29)	55 (35)	Hazard ratio, 0.78 (0.53–1.16)	0.22
All-cause mortality at day 28 — no. (%)	75 (46)	85 (54)	Hazard ratio, 0.78 (0.57–1.07)	0.12

* Plus–minus values are means ±SD.
† Response with respect to mean arterial pressure (MAP) at hour 3 after the start of infusion was defined as an increase from baseline of at least 10 mm Hg or an increase to at least 75 mm Hg, without an increase in the dose of background vasopressors.
‡ Scores on the cardiovascular Sequential Organ Failure Assessment (SOFA) range from 0 to 4, with higher scores indicating more severe dysfunction.
§ The total SOFA score ranges from 0 to 20, with higher scores indicating more severe dysfunction.
¶ Data were missing for three patients in the angiotensin II group and for one patient in the placebo group.

Choosing A Study Endpoint?

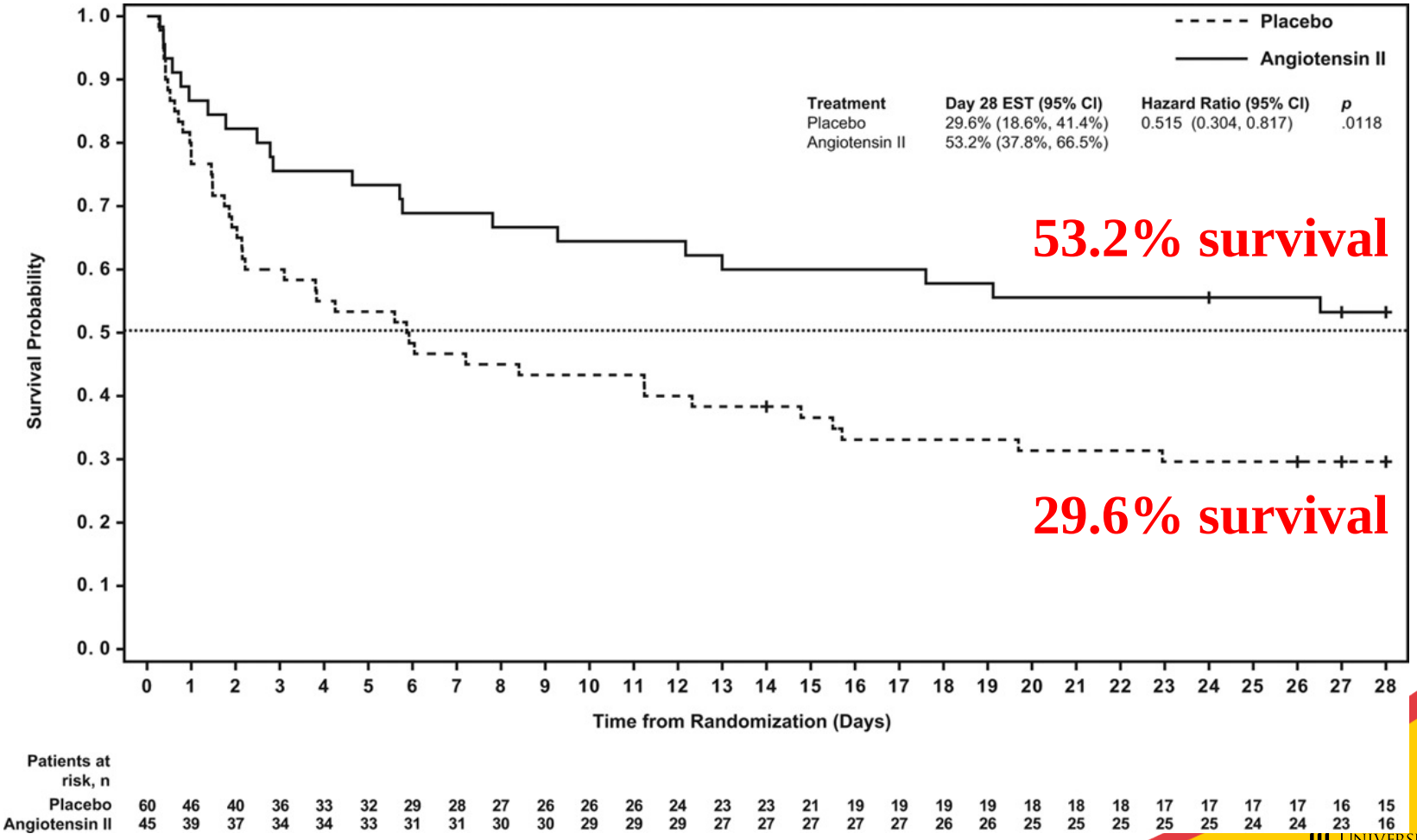
Mortality?

- As compared to other vasopressors, no single vasopressor has been shown to improve mortality
- Optimal clinical outcomes in patients with severe, life-threatening disease result from the cumulative effect of many minor interventions done properly
- There are outcomes much worse than death…

MAP increase

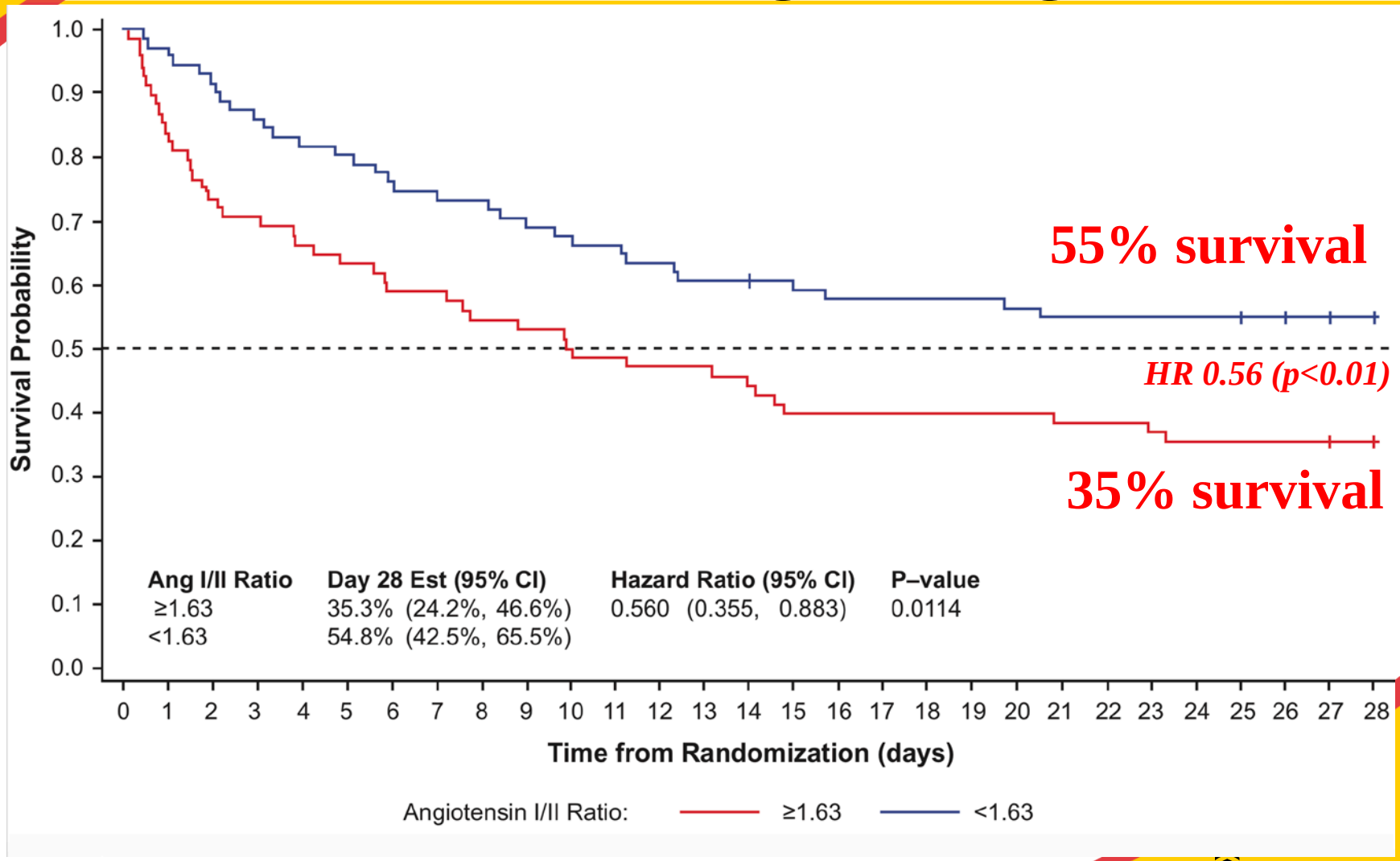
Renal Replacement Therapy

Primary outcome: 28-day survival



Tumlin JA, et al. *Crit Care Med*. 2018 Jun; 46(6):949-57.

Survival According To Ang 1:Ang 2 Ratio



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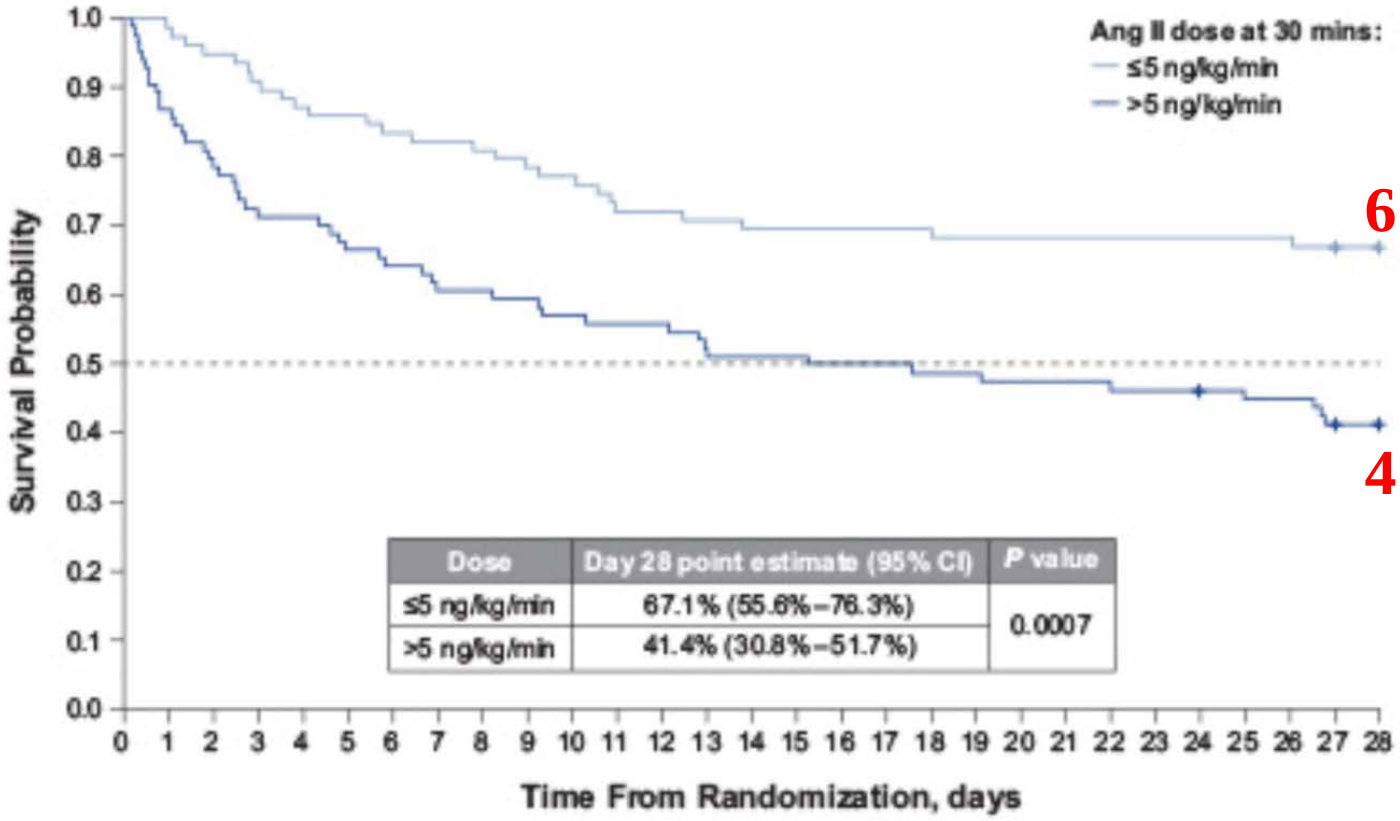
Bellomo R, et al. (*Unpublished*)

Physiologic Repletion

Primary outcome: 28-day survival by Ang II dose (≤5 *vs* >5 ng/kg/min at 30 min)



Dose	Day 28 point estimate (95% CI)	*P* value
≤5 ng/kg/min	67.1% (55.6%–76.3%)	0.0007
>5 ng/kg/min	41.4% (30.8%–51.7%)	

67% survival

41% survival

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Ham KR, Boldt DW, McCurdy MT, et al. *Ann Intensive Care*. 2019 Jun 3;9(1):63.

Who May Benefit?: Existing RAAS Deficits

- **Liver failure →** Decreased angiotensinogen production

  Coleman PJ, et al. *Semin Cardiothorac Vasc Anesth*. 2019 Sep 20:1089253219877876.

- **Premorbid ACE-I use →** Lisinopril #1 antihypertensive in U.S.

  Carpenter JE, et al. *J Emerg Med*. 2019 Sep; 57(3):339-44.

- **Intrinsic ACE defects →** Sepsis, ARDS, Extracorporeal therapies
  - **RRT** — Tumlin JA, et al. *Crit Care Med*. 2018 Jun;46(6):949-957.
  - **ECMO** — Evans A, et al. *Ann Thorac Surg*. 2019; 108:e5-7.
  - **Ang1/Ang2 ratio** — Bellomo R, et al. *Crit Care*. 2020. *(Accepted for publication)*
  - **High renin** — Gleeson PJ, et al. *Crit Care Med*. 2019 Feb; 47(2):152-8.
  - **APACHE >30** — Szerlip H, et al. *Crit Care Med*. 2018; 46(1):3.

- **Cardiac arrest →** ⇧ MAP, so ⇧ CPP; ⇩ epi

  McCurdy MT, et al. *Crit Care Med*. 2019 2019 May;47(5):e436.

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Men must be taught as if you taught them not,
And things unknown proposed as things forgot.

Alexander Pope

An Essay on Criticism, 1709, pt.iii, 1, 15

Questions?

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