Contemporary concepts in acute kidney injury and the journey to personalized care

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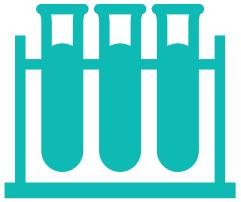
Definition

Heterogeneous syndrome describing an acute reduction in GFR

Defined by the KDIGO criteria



50% in 7 days or 26.5 µmol/L in 48 hours

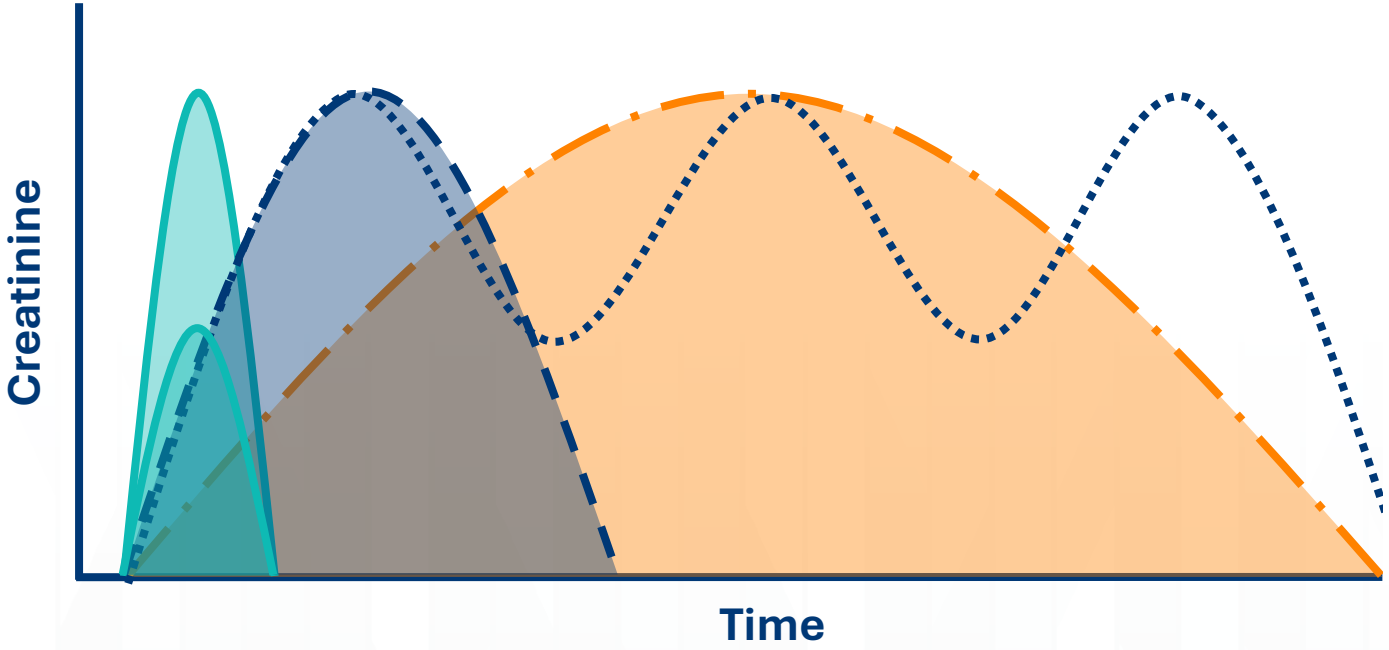
<0.5mL/kg/h for 6 hours

Acute KRT initiation

***Biomarkers may play a future role**

KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012; 2: 1–138

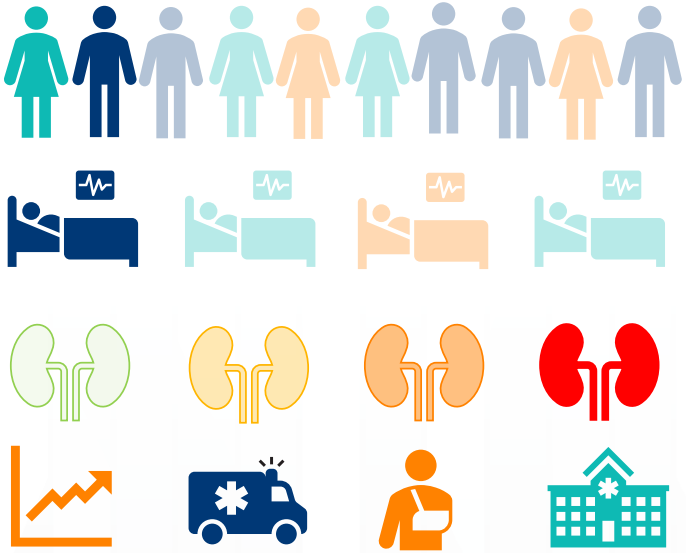
Phenotypes



1. Severity
2. Duration
3. Frequency

KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012; 2: 1–138

Epidemiology



20% hospitalised patients

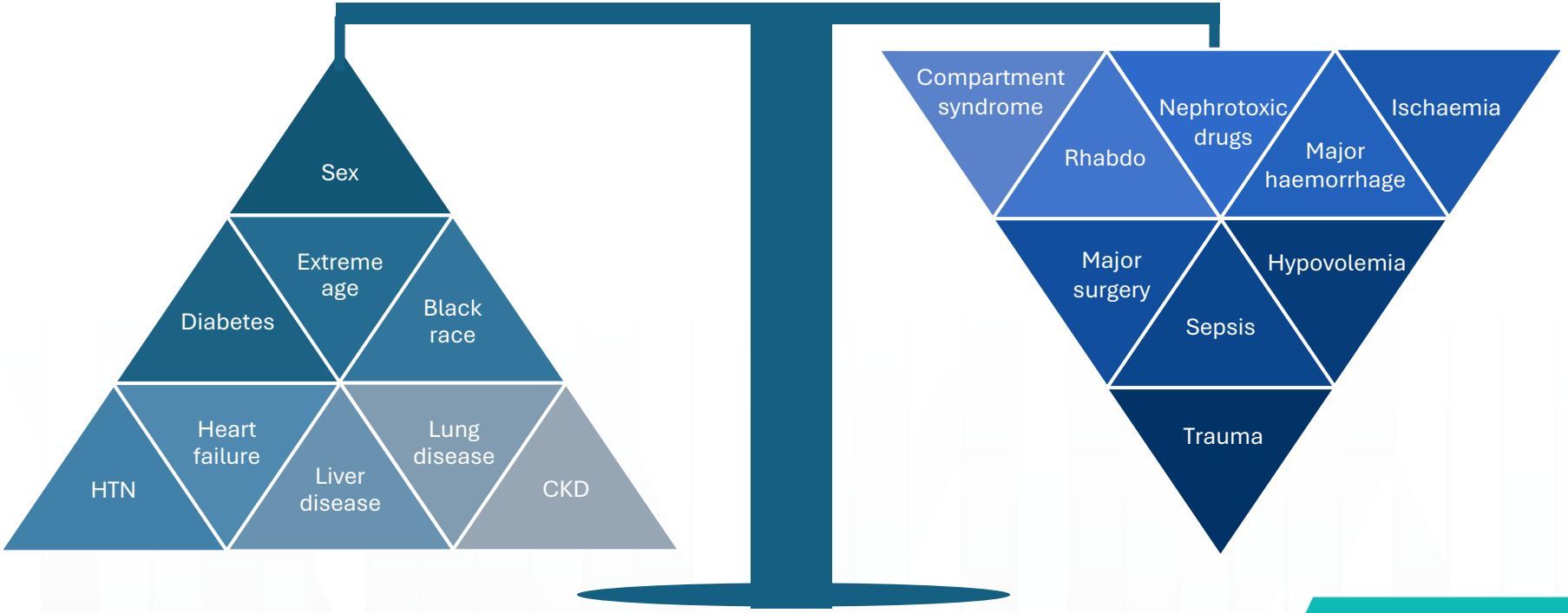
25-50% in critically ill patients

10% kidney replacement therapy

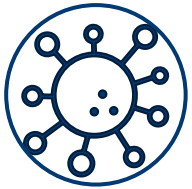
Expected to double over next decade

Prowle et al. 2017. Acute Kidney Injury in Burns and Trauma. 10.1016/B978-0-323-44942-7.00038-8.

Risk factors vs precipitants

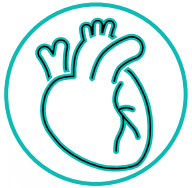


Key mechanisms



Inflammation

- Activation of innate/adaptive immune system → pro-inflammatory milieu
- Cytokine release, complement activation, coagulation



Alterations in macro- and microcirculation

- Hypovolemia → medullary hypoperfusion; hypervolemia → congestion
- Altered renal blood flow, dysfunction of angiotensin II signalling

Metabolic dysregulation

- Reprioritised energy expenditure (survival at expense of function)
- Oxidative stress, reprogrammed substrate utilisation

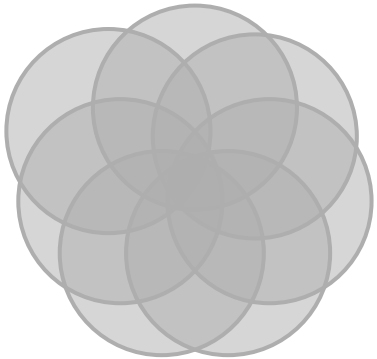
Peerapornratana S et al. Kidney Int. 2019 Nov;96(5):1083-1099.

Subphenotypes

Major surgery

Nephrotoxic drugs

Sepsis



Haemorrhage

Hypovolaemia

Abdominal compartment syndrome

Rhabdomyolysis

Innate/adaptive immune activation

Microcirculation dysfunction

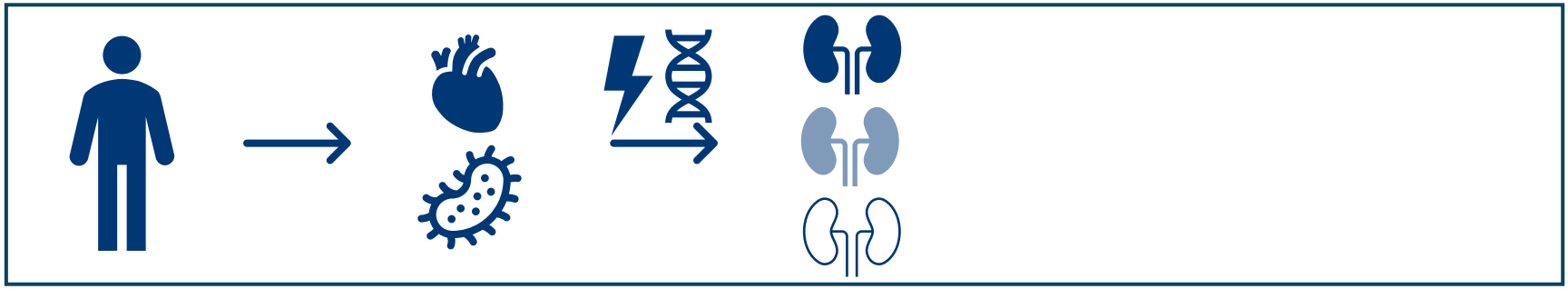
Complement activation

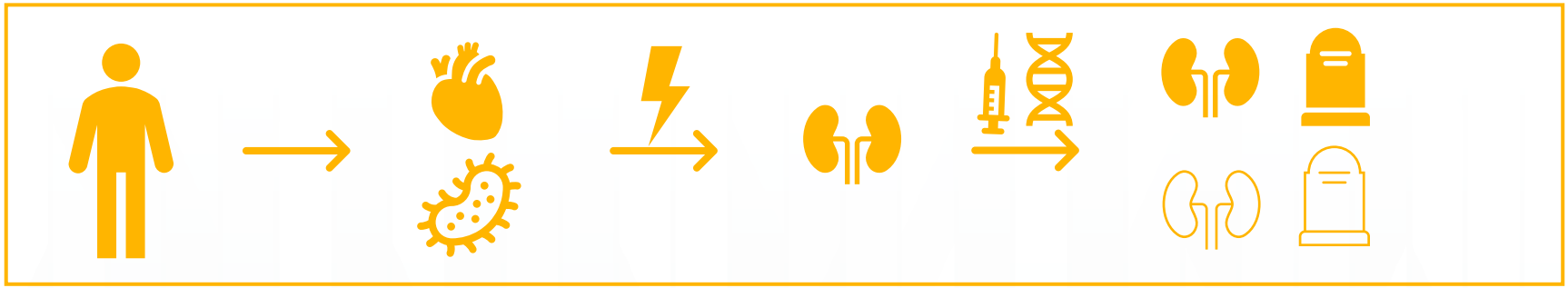
Macrocirculation dysfunction

Coagulation

Oxidative stress

Mitochondrial dysfunction





Searching for Genes That Matter in Acute Kidney Injury: A Systematic Review

Clin J Am Soc Nephrol 4: 1020-1031, 2009

Jonathan C. T. Lu,* Steven G. Coca,*† Uptal D. Patel,‡ Lloyd Cantley,*
and Chirag R. Parikh,*† for the Translational Research Investigating Biomarkers
and Endpoints for Acute Kidney Injury (TRIBE-AKI) Consortium

Determinantes genéticos del riesgo y pronóstico del daño renal agudo: una revisión sistemática☆

Med Intensiva. 2012;36(9):626–633

P. Cardinal-Fernández[a,b,*], A. Ferruelo[a,b], A. Martín-Pellicer[a,b], N. Nin[a,b],
A. Esteban[a,b] y J.A. Lore

Genetic predisposition to acute kidney injury – a systematic review

BMC Nephrology 16:197, 2015

Laura M. Vilander[1*], Mari A. Kaunisto[2,3] and Ville Pettilä[1]

AKI management

AKI management

Remove further insults

- Discontinue nephrotoxic agents, check drug levels and doses
- Relieve renal tract obstruction or compartment syndrome

Optimise renal perfusion

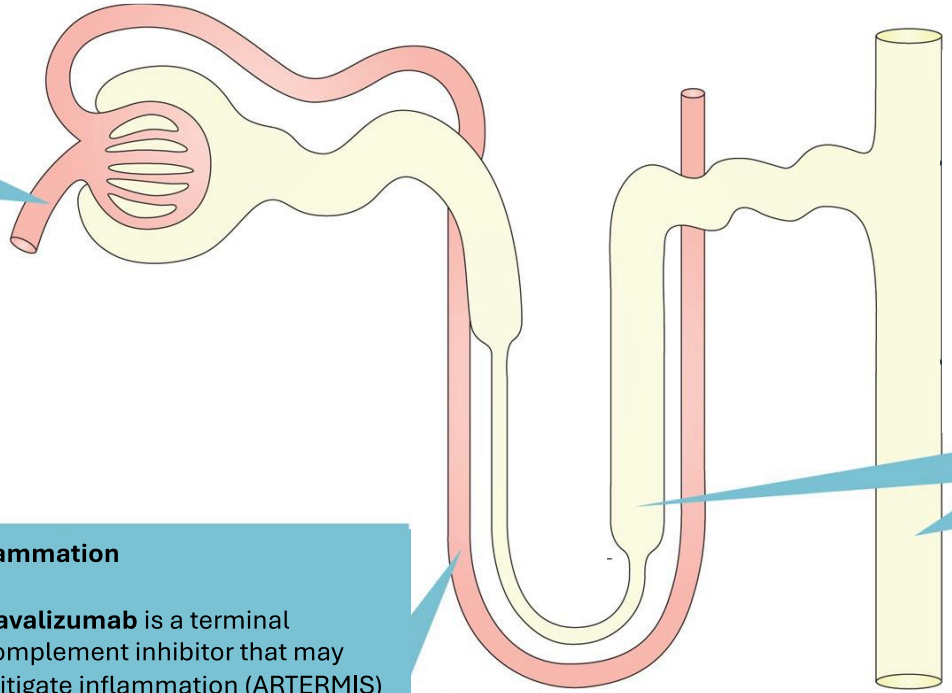
- Control any sources of bleeding
- Normalise the circulation with fluids and/or vasopressors

Reverse biochemical derangements

- Treat hyperkalemia and acidaemia, and hypocalcaemia in rhabdomyolysis
- Renal replacement therapy

Renal macrocirculation and microcirculation

- **Angiotensin II infusion** increases trans-glomerular pressure (ARAMIS)
- **Amino acid infusion** increases glomerular filtration rate (PROTECTION)



Oxidative stress

- **Bicarbonate infusion** restores acid-base balance (SODABIC)
- **Vitamin C infusion** reduces oxidative stress (MEGA-SCORES)

Inflammation

- **Ravalizumab** is a terminal complement inhibitor that may mitigate inflammation (ARTERMIS)

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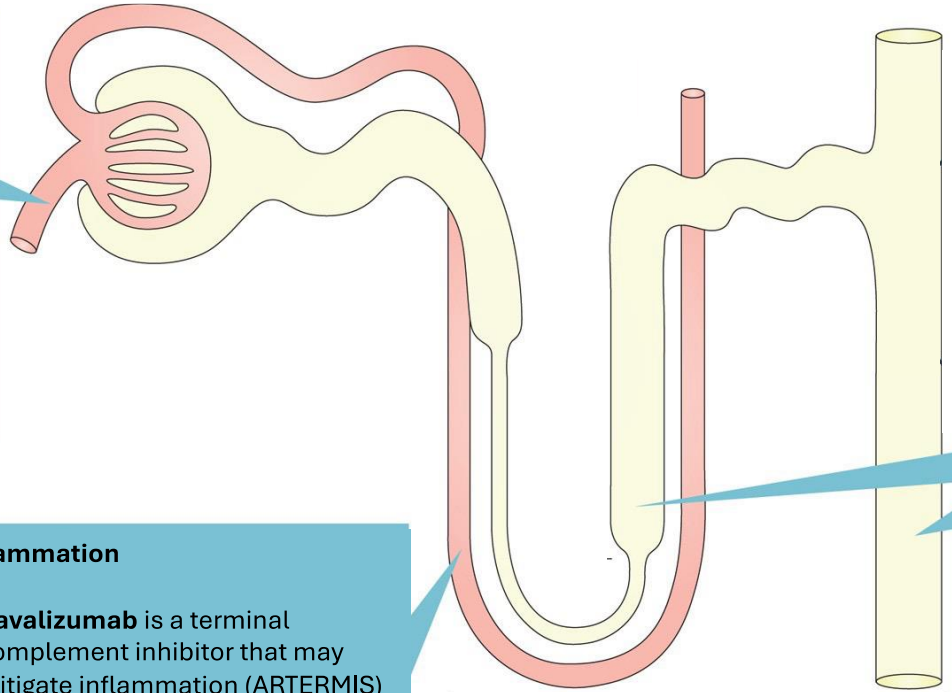

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Angiotensin II for the Treatment of Vasodilatory Shock

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*

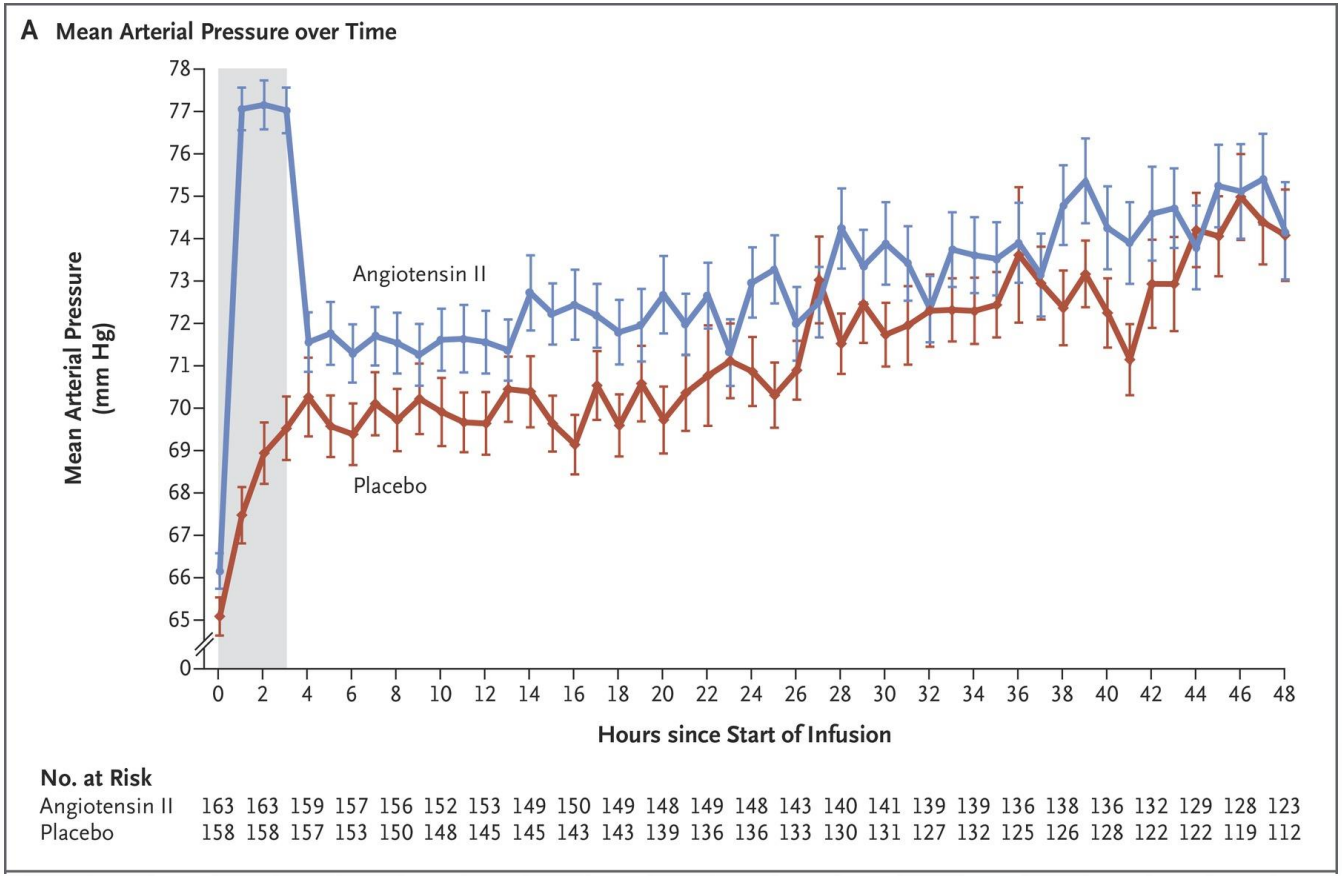
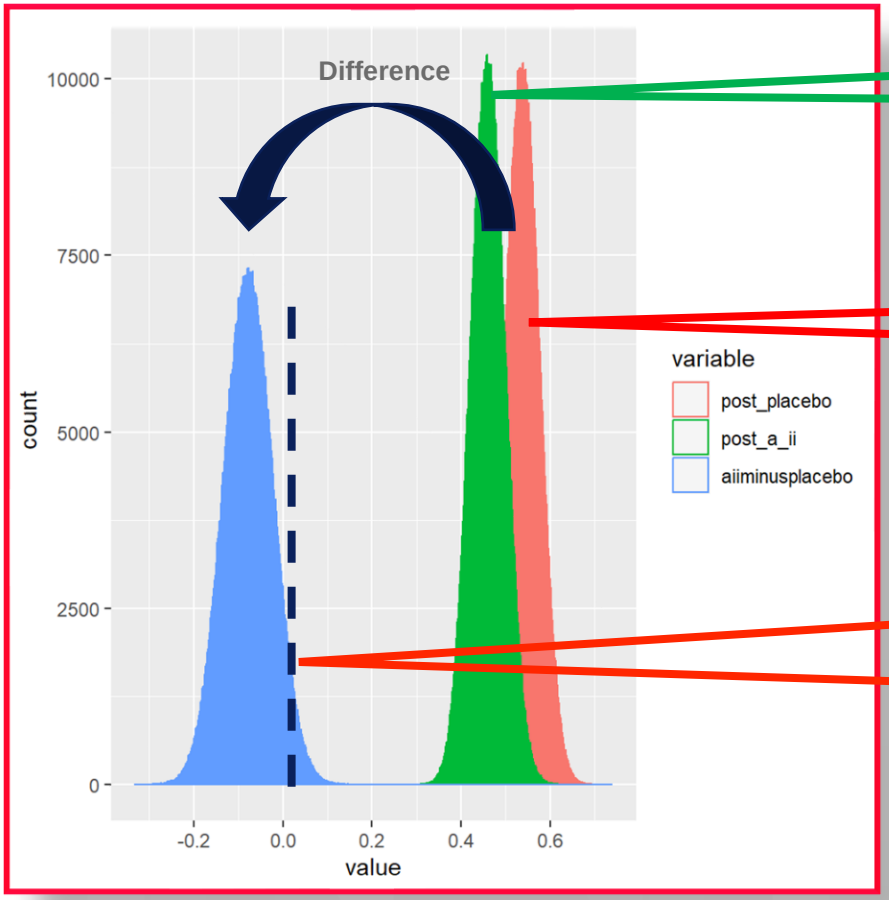

A Mean Arterial Pressure over Time
Mean Arterial Pressure (mm Hg)
78
77
76
75
74
73
72
71
70
69
68
67
66
65
0
Angiotensin II
Placebo
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
Hours since Start of Infusion
No. at Risk
Angiotensin II 163 163 159 157 156 152 153 149 150 149 148 149 148 143 140 141 139 139 136 138 136 132 129 128 123
Placebo 158 158 157 153 150 148 145 145 143 143 139 136 136 133 130 131 127 132 125 126 128 122 122 119 112

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



Ang2
75/163 = 46%

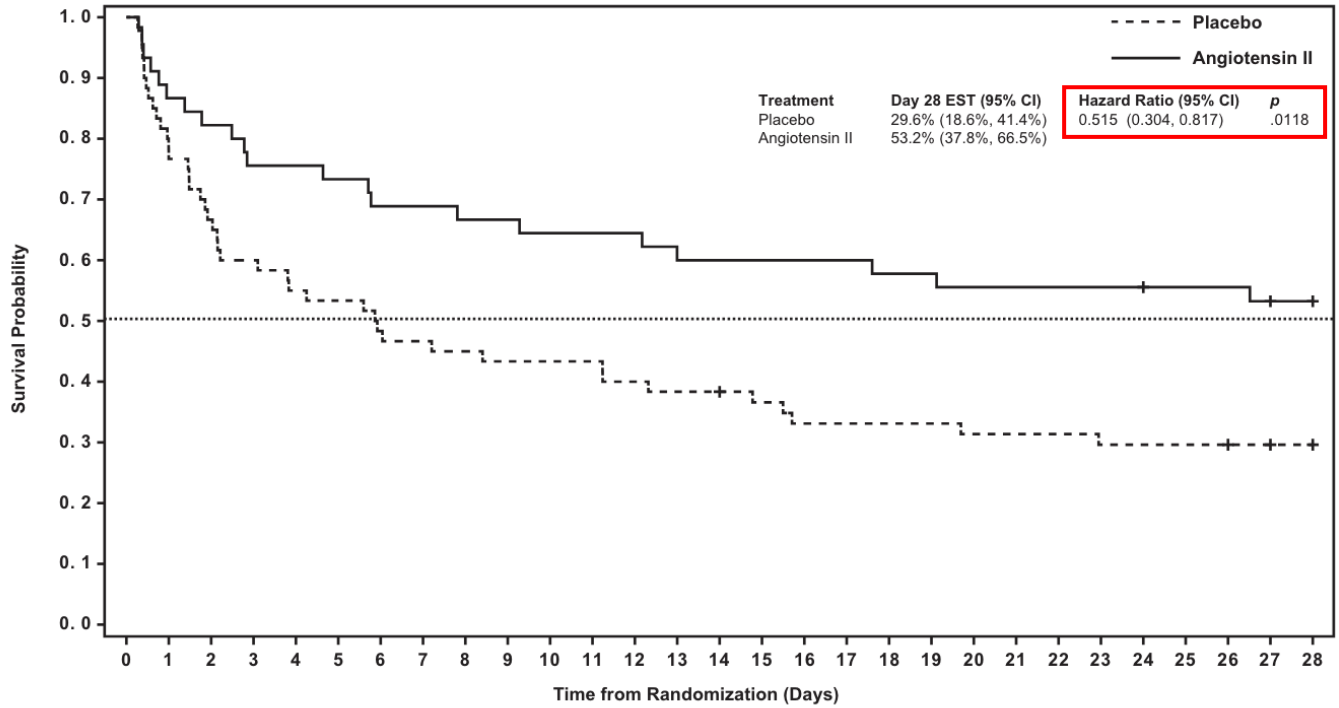
Placebo
85/158 = 54%

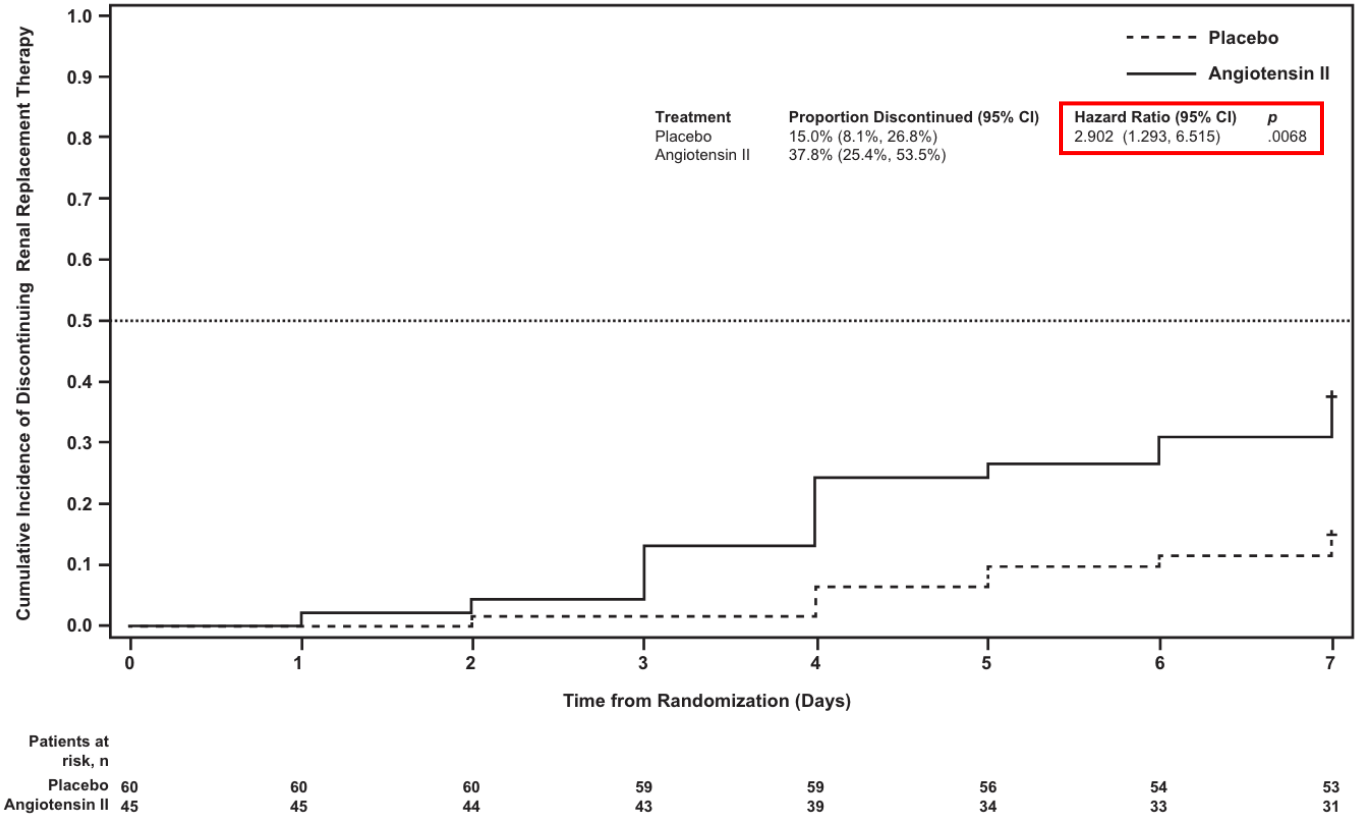
Ang2 minus Placebo

- **Median advantage 7.7%**
- **Posterior probability 91.7% that mortality difference favours Ang2**

Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II

James A. Tumlin, MD[1]; Raghavan Murugan, MD, MS, FRCP, FCCM[2]; Adam M. Deane, MD, PhD[3]; Marlies Ostermann, MD, PhD[4]; Laurence W. Busse, MD[5]; Kealy R. Ham, MD[6]; Kianoush Kashani, MD, MSc[7]; Harold M. Szerlip, MD[8]; John R. Prowle, MD, MA, MB, BChir, MSc, FFICM, FRCP[9]; Azra Bihorac, MD, MS, FCCM, FASN[10]; Kevin W. Finkel, MD, FACP, FASN, FCCM[11]; Alexander Zarbock, MD[12]; Lui G. Forni MD, MB, PhD[13]; Shannan J. Lynch, PhD[14]; Jeff Jensen, BS[14]; Stew Kroll, MA[14]; Lakhmir S. Chawla, MD[14]; George F. Tidmarsh, MD, PhD[14]; Rinaldo Bellomo, MD, MBBS, FRACP, FCICM, FAAHMS[15]; on behalf of the Angiotensin II for the Treatment of High-Output Shock 3 (ATHOS-3) Investigators


Placebo
Angiotensin II
Treatment
Day 28 EST (95% CI)
Hazard Ratio (95% CI)
p
Placebo
29.6% (18.6%, 41.4%)
0.515 (0.304, 0.817)
.0118
Angiotensin II
53.2% (37.8%, 66.5%)
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Time from Randomization (Days)
Patients at risk, n
Placebo 60 46 40 36 33 32 29 28 27 26 26 26 24 23 23 21 19 19 19 19 18 18 18 17 17 17 17 16 15
Angiotensin II 45 39 37 34 34 33 31 31 30 30 29 29 29 27 27 27 27 27 26 26 25 25 25 25 25 24 24 23 16


Placebo
Angiotensin II
Treatment
Proportion Discontinued (95% CI)
Hazard Ratio (95% CI)
p
Placebo
15.0% (8.1%, 26.8%)
2.902 (1.293, 6.515)
.0068
Angiotensin II
37.8% (25.4%, 53.5%)
Cumulative Incidence of Discontinuing Renal Replacement Therapy
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
Time from Randomization (Days)
Patients at risk, n
Placebo 60 60 60 59 59 56 54 53
Angiotensin II 45 45 44 43 39 34 33 31

ORIGINAL ARTICLE

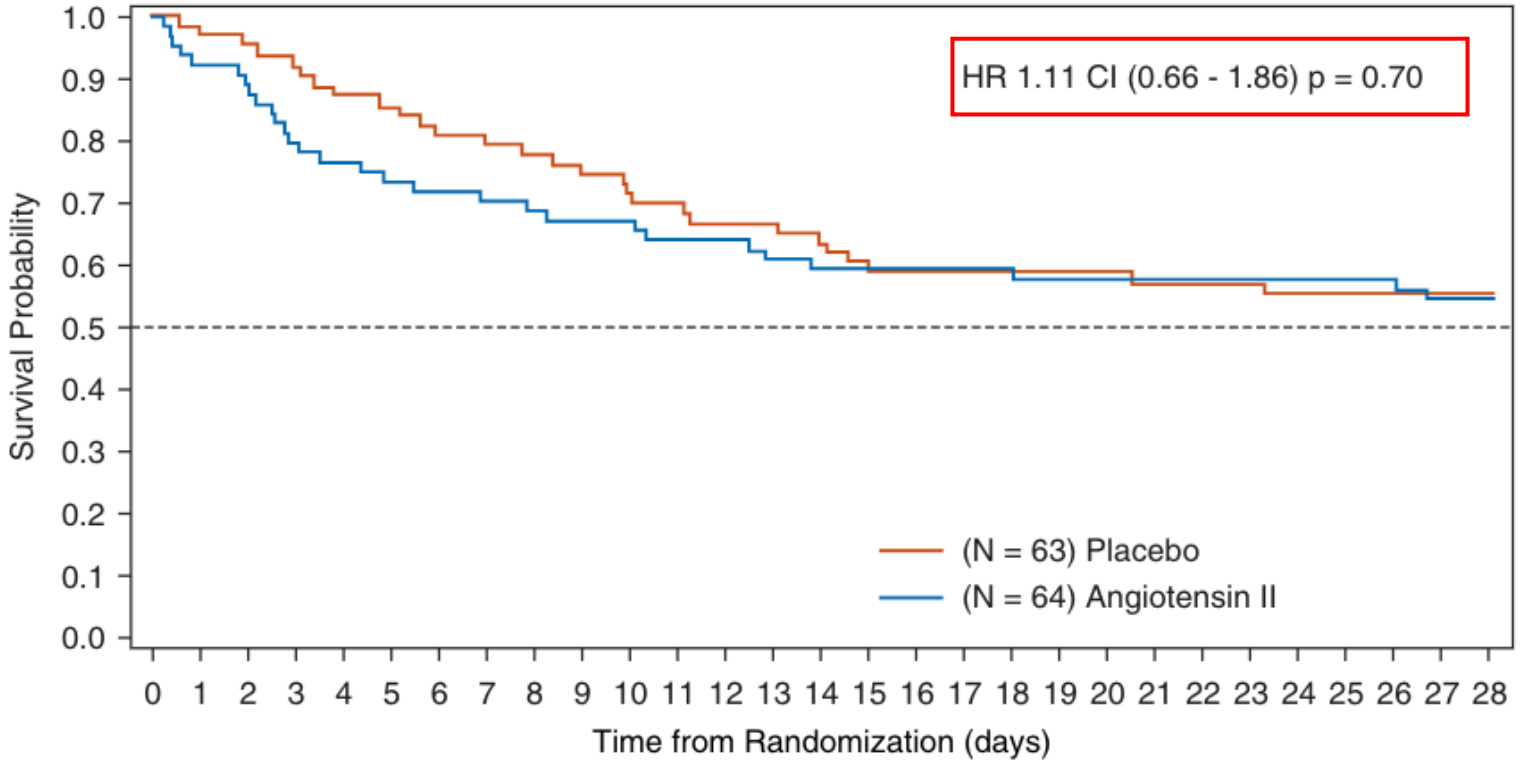
Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock

A Clinical Trial

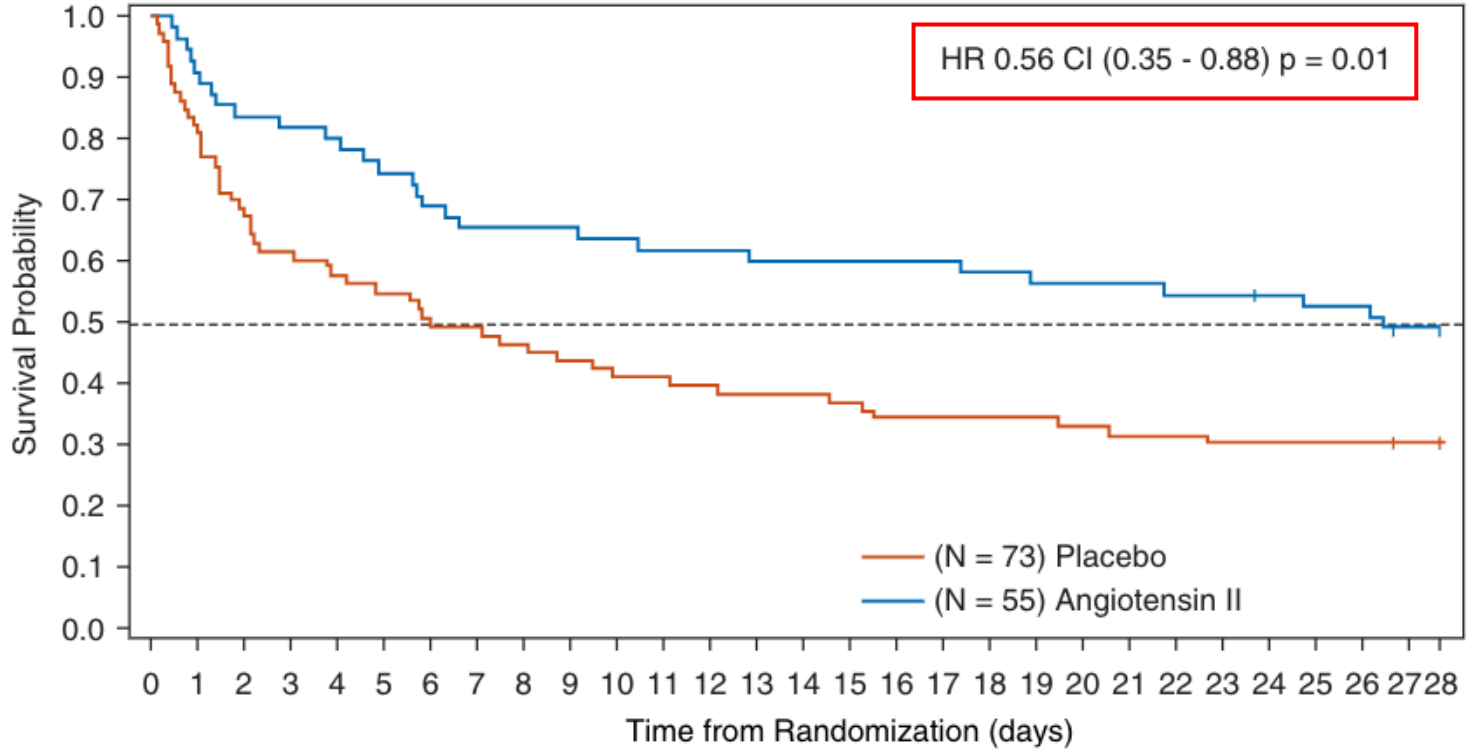
Rinaldo Bellomo[1,2], Lui G. Forni[3,4], Laurence W. Busse[5], Michael T. McCurdy[6], Kealy R. Ham[7], David W. Boldt[8], Johanna Hästbacka[9], Ashish K. Khanna[10,11], Timothy E. Albertson[12], James Tumlin[13], Kristine Storey[14], Damian Handisides[14], George F. Tidmarsh[14,15], Lakhmir S. Chawla[14,16], and Marlies Ostermann[17]; on behalf of the ATHOS-3 Investigators

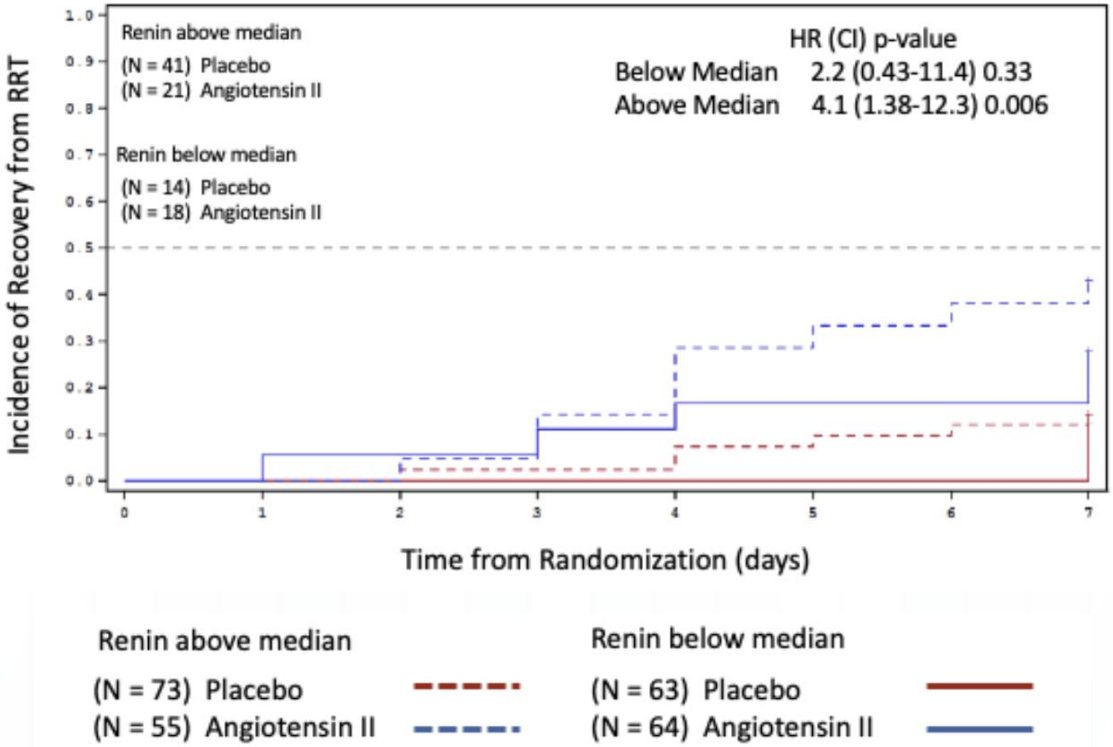
[1]Centre for Integrated Critical Care, Department of Medicine & Radiology, The University of Melbourne, Melbourne, Victoria, Australia; [2]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; [3]Intensive Care Unit, Royal Surrey Hospital Foundation Trust, Guildford, United Kingdom; [4]Department of Clinical & Experimental Medicine, School of Biosciences & Medicine, University of Surrey, Guildford, United Kingdom; [5]Division of Pulmonary, Allergy, Critical Care and Sleep Medicine, Department of Medicine, and [13]Renal Division, Department of Medicine, Emory University Medical Center, Emory University, Atlanta, Georgia; [6]Division of Pulmonary & Critical Care Medicine, School of Medicine, University of Maryland, Baltimore, Maryland; [7]Department of Critical Care, Regions Hospital, University of Minnesota, St. Paul, Minnesota; [8]Division of Critical Care, Department of Anesthesiology and Perioperative Medicine, University of California, Los Angeles, Los Angeles, California; [9]Division of Intensive Care Medicine, Department of Perioperative, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [10]Department of Anesthesiology, Section on Critical Care Medicine, School of Medicine, Wake Forest University, Winston-Salem, North Carolina; [11]Outcomes Research Consortium, Cleveland, Ohio; [12]Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, School of Medicine, University of California-Davis, Northern California Health System, Mather, California; [14]La Jolla Pharmaceutical Company, San Diego, California; [15]Stanford University, Palo Alto, California; [16]Department of Medicine, Veterans Affairs Medical Center, San Diego, California; and [17]Department of Critical Care, Guy's & St. Thomas' Hospital, King's College London, London, United Kingdom

A


HR 1.11 CI (0.66 - 1.86) p = 0.70
(N = 63) Placebo
(N = 64) Angiotensin II
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Time from Randomization (days)

B


HR 0.56 CI (0.35 - 0.88) p = 0.01
Survival Probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
(N = 73) Placebo
(N = 55) Angiotensin II
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Time from Randomization (days)



Severe AKI patients with **high renin** were **more likely to liberate from RRT** if they received angiotensin II versus placebo (RR 4.11, 95% CI 1.38 to 12.29, p=0.006)

Severe AKI patients with **low renin** were **not more likely to liberate from RRT** with angiotensin II versus placebo (RR 2.22, 95% CI 0.43 to 11.42, p=0.33)

The Acute Renal effects of Angiotensin II Management in Shock – the ARAMIS study

ARAMIS pilot

It is **safe** and **feasible** to administer angiotensin II as primary vasopressor for vasodilatory hypotension

There is an association between angiotensin II and **decreased risks of ICU death** and **troponin elevation, and lower peak serum creatinine**

The noradrenaline to angiotensin II conversion ratio is **10:1 (7:1 in ARB)**

There is an interaction between **prior RAS exposure**, **renin level**, and **angiotensin II responsiveness**

ARAMIS-2

Multicentre **phase 2b** open-label **RCT** comparing angiotensin II to conventional agents as first line vasopressors (77 randomised)

Renal outcomes: peak creatinine, AKI stage, CRRT initiation and duration

Pre-specified **sub-groups**
-baseline renin, ACE2, DPP4
-RAS inhibitor exposure

Pre-specified **sub-studies**
-RNA expression
-CD39 level

(ARAMIS-3)

Multicentre **seamless phase 2/3** open-label **adaptive RCT** comparing angiotensin II to conventional agents with randomisation stratified by renin. **POC renin** testing performed in eligible patients on vasopressor therapy for <24 hours

Other work

DARK-sepsis
SPiDeR
DRAgONFly

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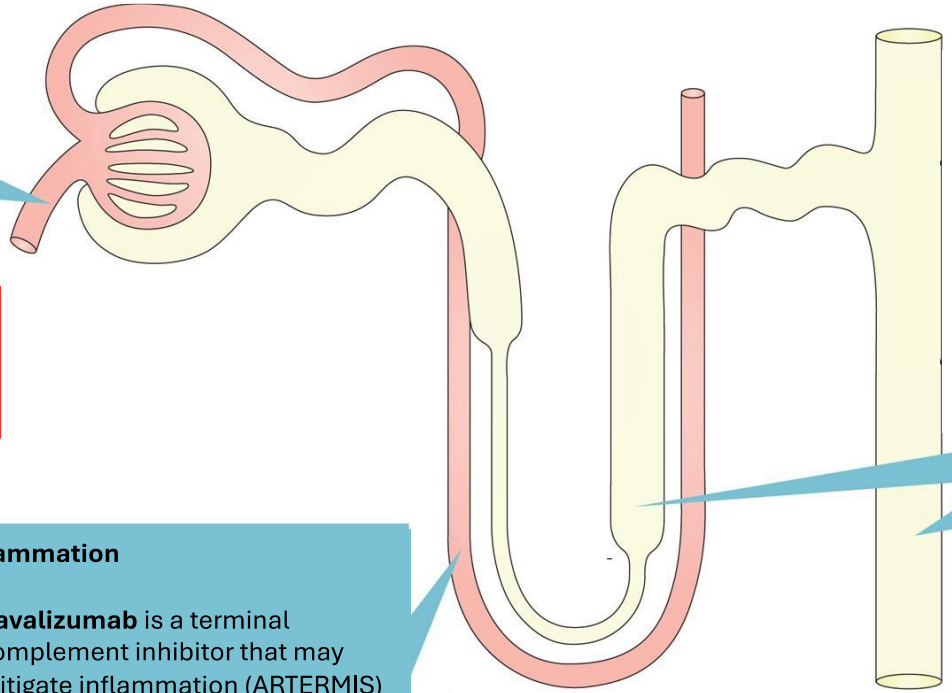

Oxidative stress

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Inflammation

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ORIGINAL ARTICLE

A Randomized Trial of Intravenous Amino Acids for Kidney Protection

G. Landoni, F. Monaco, L.K. Ti, M. Baiardo Redaelli, N. Bradic, M. Comis, Y. Kotani, C. Brambillasca, E. Garofalo, A.M. Scandroglio, C. Viscido, G. Paternoster, A. Franco, S. Porta, F. Ferrod, M.G. Calabrò, A. Pisano, I. Vendramin, G. Barucco, F. Federici, L. Severi, A. Belletti, A. Cortegiani, A. Bruni, C. Galbiati, A. Covino, E. Baryshnikova, G. Giardina, M. Venditto, D. Kroeller, C. Nakhnoukh, L. Mantovani, S. Silvetti, M. Licheri, F. Guarracino, R. Lobreglio, A.L. Di Prima, S. Fresilli, R. Labanca, M. Mucchetti, R. Lembo, R. Losiggio, T. Bove, M. Ranucci, E. Fominskiy, F. Longhini, A. Zangrillo, and R. Bellomo, for the PROTECTION Study Group*

METHODS

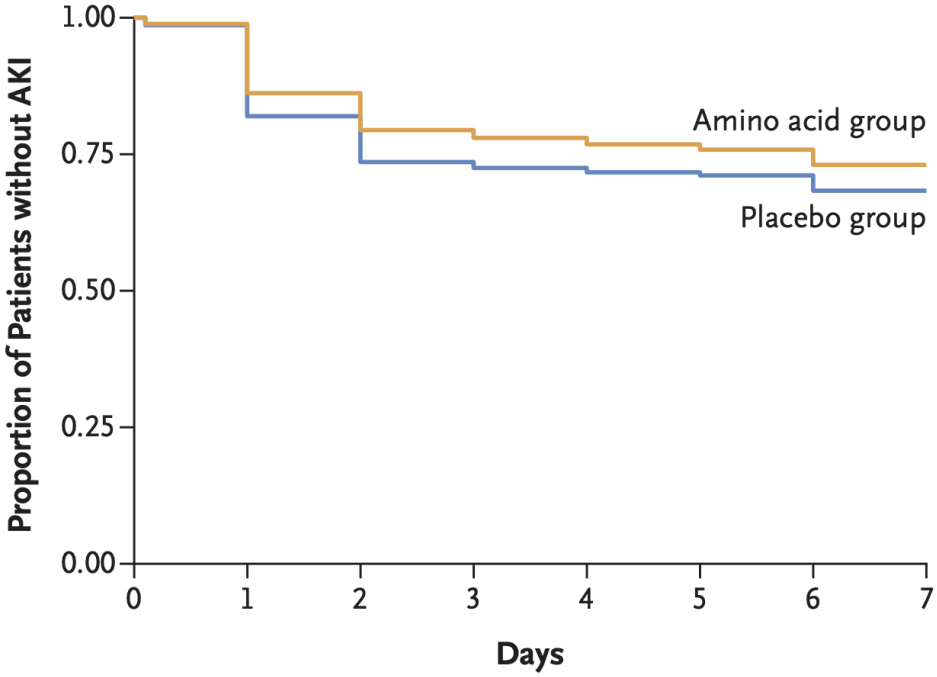
In a multinational, double-blind trial, we randomly assigned adult patients who were scheduled to undergo cardiac surgery with cardiopulmonary bypass to receive an intravenous infusion of either a balanced mixture of amino acids, at a dose of 2 g per kilogram of ideal body weight per day, or placebo (Ringer's solution) for up to 3 days. The primary outcome was the occurrence of AKI, defined according to the Kidney Disease: Improving Global Outcomes creatinine criteria. Secondary outcomes included the severity of AKI, the use and duration of kidney-replacement therapy, and all-cause 30-day mortality.

Table 2. Trial Interventions.*

Variable	Amino Acid Group (N=1759)		Placebo Group (N=1752)	
	Value	No. with Missing Data	Value	No. with Missing Data
Median infusion rate (IQR) — ml/hr	40 (40–42)	17	40 (40–42)	23
Median dose (IQR)				
In milliliters	1260 (1000–2592)	26	1272 (1000–2790)	25
In grams	126 (100–259)	26	127 (100–279)	25
Median duration of infusion (IQR) — hr	30 (25–56)	14	31 (25–68)	16
Reason for cessation of regimen — no. (%)		6		4
Discharge from intensive care unit	1284 (73.0)		1246 (71.1)	
Completion of 72-hr infusion	392 (22.3)		403 (23.0)	
Initiation of kidney-replacement therapy	6 (0.3)		14 (0.8)	
Death	9 (0.5)		5 (0.3)	
Withdrawal of consent	1 (0.1)		0 (0.0)	
Adverse reactions	0 (0.0)		0 (0.0)	
Error	31 (1.8)		25 (1.4)	
Physician decision	13 (0.7)		32 (1.8)	
Logistic reasons	2 (0.1)		5 (0.3)	

Table 3. Clinical Outcomes.*

Outcome	Amino Acid Group (N=1759)		Placebo Group (N=1752)		Relative Risk (95% CI)	P Value
	Value	No. with Missing Data	Value	No. with Missing Data		
Primary outcome						
In-hospital AKI — no. (%)†	474 (26.9)	2	555 (31.7)	0	0.85 (0.77 to 0.94)	0.002
Stage 1	430 (24.4)		492 (28.1)		0.87 (0.78 to 0.97)	
Stage 2	15 (0.9)		11 (0.6)		1.36 (0.63 to 2.95)	
Stage 3	29 (1.6)		52 (3.0)		0.56 (0.35 to 0.87)	
Secondary outcomes						
Use of kidney-replacement therapy — no. (%)	24 (1.4)	5	33 (1.9)	3	0.73 (0.43 to 1.22)	
Median duration of kidney-replacement therapy (IQR) — hr	64 (17–100)	1	64 (21–81)	2	9.79 (–62.13 to 81.70)‡	
Median duration of mechanical ventilation (IQR) — hr	11 (6–17)	48	11 (6–17)	47	–0.60 (–3.70 to 2.49)‡	
Median duration of stay in intensive care unit (IQR) — hr	30 (21–66)	24	34 (21–68)	21	1.39 (–4.78 to 7.57)‡	
Median duration of stay in hospital (IQR) — no. of nights	7 (5–9)	4	7 (6–9)	2	0.28 (–0.36 to 0.92)‡	
Mortality — no. (%)						
Before discharge from intensive care unit	34 (1.9)	1	38 (2.2)	1	0.89 (0.56 to 1.41)	
30-day	50 (2.8)	1	49 (2.8)	1	1.02 (0.69 to 1.50)	
90-day	56 (3.2)	19	53 (3.0)	23	1.05 (0.73 to 1.52)	
180-day	68 (3.9)	34	68 (3.9)	35	1.00 (0.72 to 1.38)	

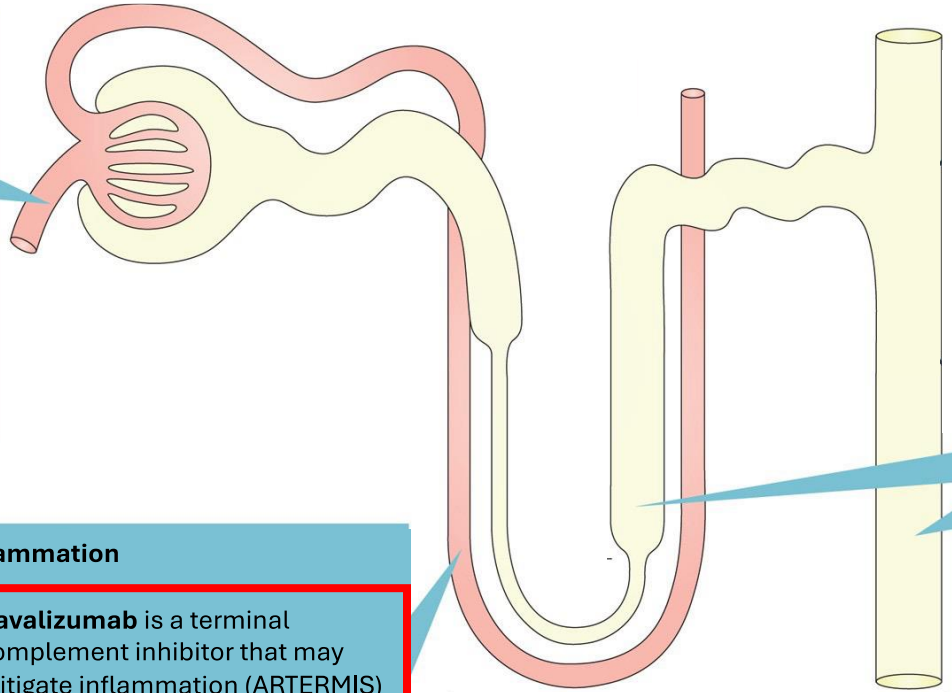


No. at Risk

Amino acid group	1759	1739	1516	1397	1372	1351	1334	1285
Placebo group	1752	1728	1436	1289	1270	1256	1246	1197

Renal macrocirculation and microcirculation

- **Angiotensin II infusion** increases trans-glomerular pressure (ARAMIS)
- **Amino acid infusion** increases glomerular filtration rate (PROTECTION)



Oxidative stress

- **Bicarbonate infusion** restores acid-base balance (SODABIC)
- **Vitamin C infusion** reduces oxidative stress (MEGA-SCORES)

Inflammation

- **Ravalizumab** is a terminal complement inhibitor that may mitigate inflammation (ARTERMIS)

ARTEMIS STUDY

Key Inclusion Criteria

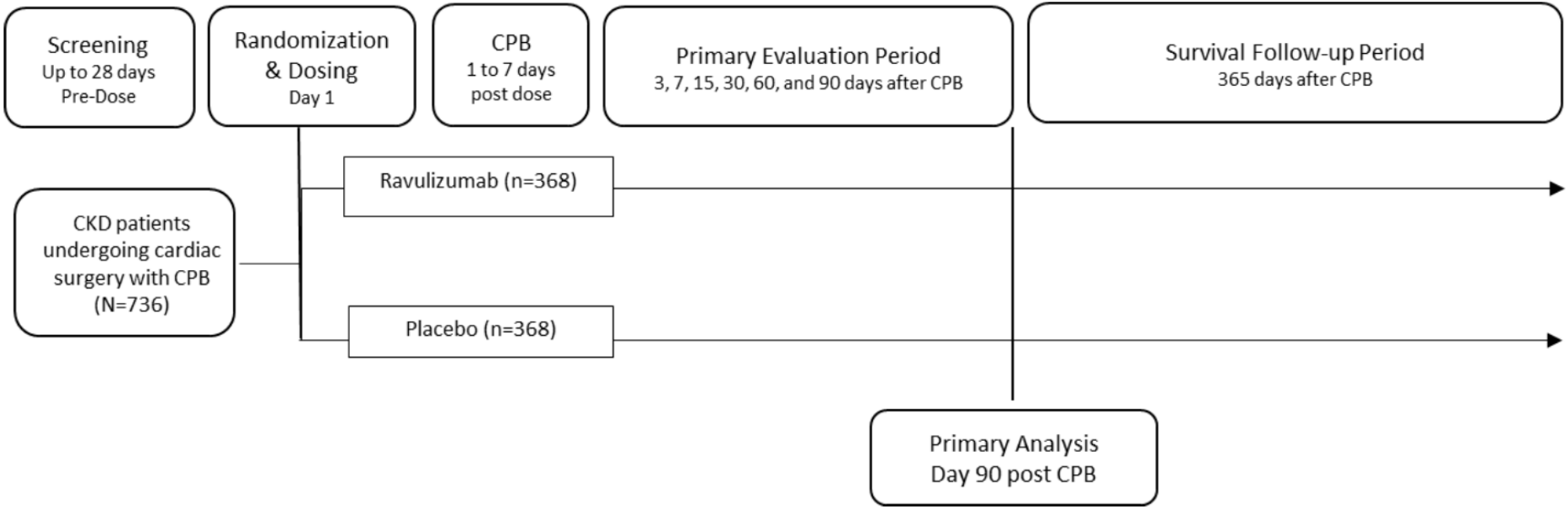
- ≥ 18 to ≤ 90 years of age at the time of consent
- Planned non-emergent sternotomy with CPB procedure for the following surgeries:
  - Multi-vessel coronary artery bypass graft (CABG)
  - Valve replacement or repair; ascending aorta surgery permitted if combined with aortic valve replacement or repair
  - Combined CABG and valve surgery; inclusion of single-vessel CABG when combined with valve replacement or repair is permitted

  Note: Surgery should be scheduled to occur within 35 days of screening (up to 28-day screening period with randomization and dosing within 1 to 7 days prior to CPB).
- Known CKD for at least 90 days with eGFR ≥ 20 to < 60 mL/min/1.73m2, (CKD Stage 3A, 3B, or 4) at screening

Key Exclusion Criteria

- Emergency or salvage cardiac surgery is expected at screening or randomization, as assessed by the Investigator
- Single-vessel CABG without valve surgery is planned
- Off-pump surgery is planned (e.g., surgery without CPB)
- Any use of KRT or presence of AKI within 30 days of randomization (AKI defined as 1.5× increase in sCr over baseline), except transient (≤ 5 days) Stage 1 AKI after iodinated contrast exposure
- Recipient of a solid organ or bone marrow transplantation
- Cardiogenic shock, hemodynamic instability, use of intra-aortic balloon pump, extracorporeal membrane oxygenation, or left ventricular assist device within 72 hours of randomization

N=736


Screening
Up to 28 days
Pre-Dose
Randomization
& Dosing
Day 1
CPB
1 to 7 days
post dose
Primary Evaluation Period
3, 7, 15, 30, 60, and 90 days after CPB
Survival Follow-up Period
365 days after CPB
CKD patients undergoing cardiac surgery with CPB (N=736)
Ravulizumab (n=368)
Placebo (n=368)
Primary Analysis
Day 90 post CPB

Renal macrocirculation and microcirculation

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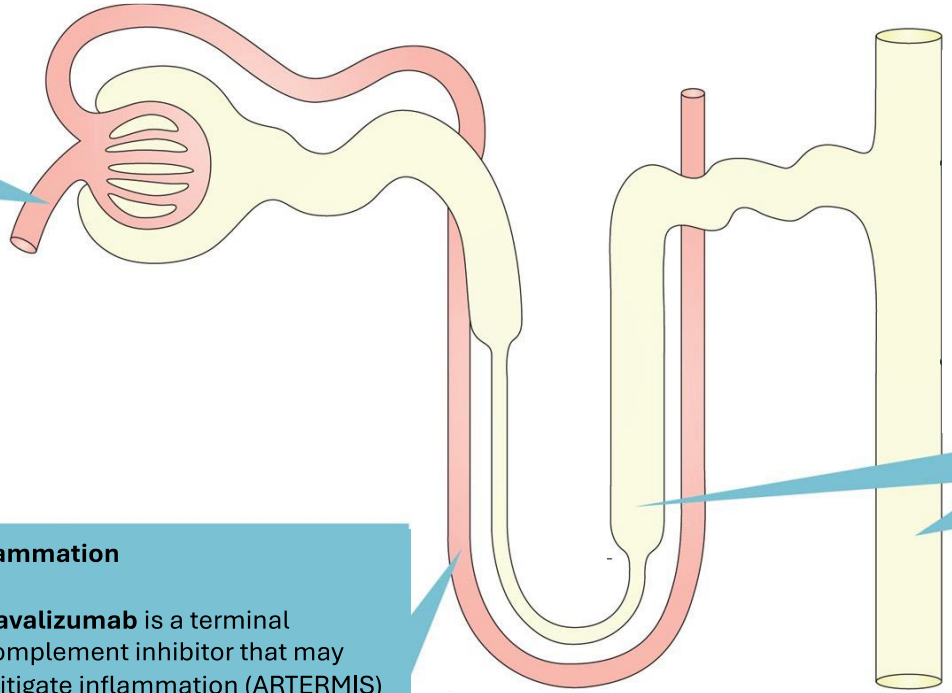
- **Amino acid infusion** increases glomerular filtration rate (PROTECTION)



Oxidative stress

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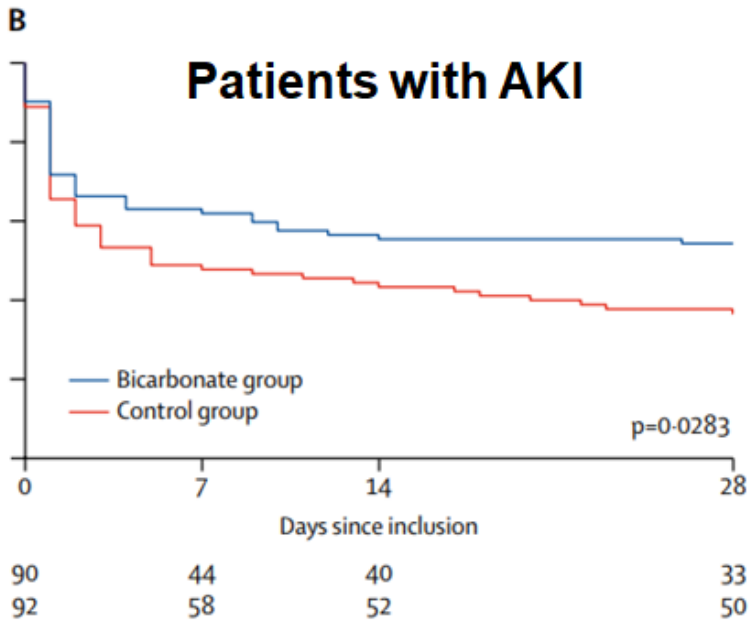
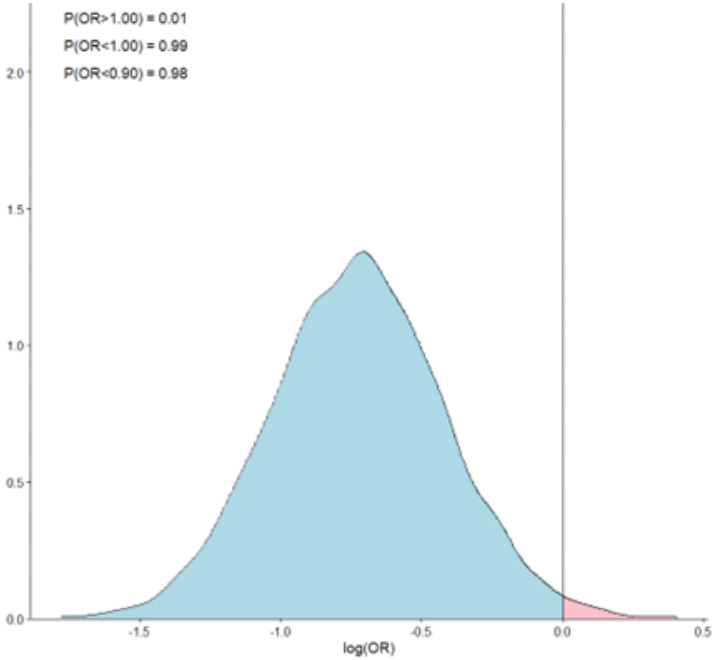
Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

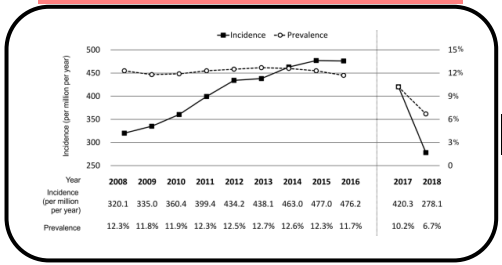




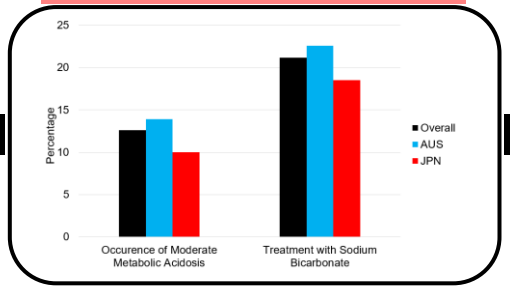
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

71. For adults with septic shock and hypoperfusion-induced lactic acidemia, we suggest against using sodium bicarbonate therapy to improve hemodynamics or to reduce vasopressor requirements.	***Weak,*** *low quality of evidence*
72. For adults with septic shock and severe metabolic acidemia (pH ≤ 7.2) and acute kidney injury (AKIN score 2 or 3), we suggest using sodium bicarbonate therapy	***Weak,*** *low quality of evidence*

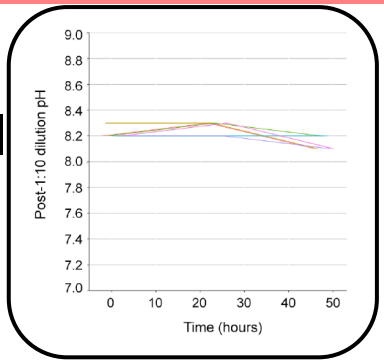
Retrospective study
Prevalence and outcomes of moderate metabolic acidosis



Retrospective study
To assess current clinical practice

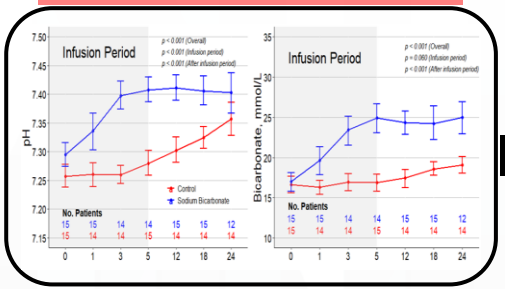


Feasibility study
To test the stability of the solution

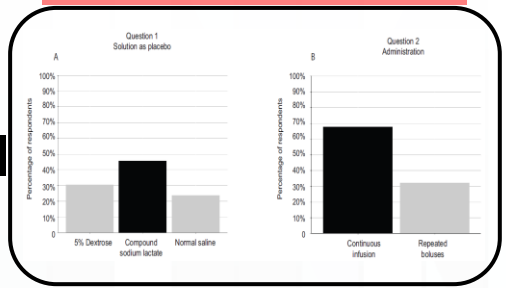


SODa BIC Phase III international trial

Pilot trial
To examine possible effects and feasibility



Survey study
Shape of the intervention and control arm



Feasibility study
To test the feasibility of double-blinding

	Incorrect	Correct	P
Number of answers	24	36	
SB solution	10 (41.7%)	16 (44.4%)	> 0.99
Participants			0.63
Doctor	9 (37.5%)	11 (30.6%)	
Nurse	15 (62.5%)	24 (66.7%)	
Pharmacist	0 (0)	1 (2.8%)	
Years worked in ICU, mean (SD)	10.2 ± 9.7	10.0 ± 8.5	0.96
Clue	13 (54.2%)	15 (41.7%)	0.49
Bubble	5 (38.5%)	3 (20.0%)	
Volume	3 (23.1%)	5 (33.3%)	
Colour	3 (23.1%)	3 (20.0%)	
Puncture	1 (7.7%)	1 (6.7%)	
Other	1 (7.7%)	3 (20.0%)	

Renal macrocirculation and microcirculation

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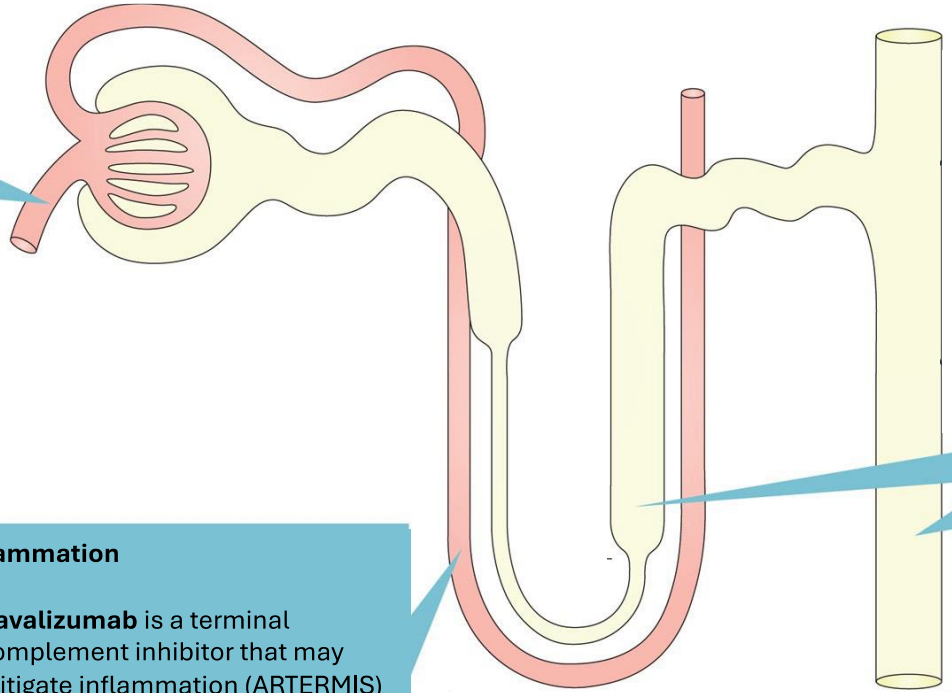

Oxidative stress

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Inflammation

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Vitamin C levels fall in critical illness (especially in sepsis) due to reduced intake and increased oxidative consumption.

Oxidative stress is a major contributor to the pathophysiology of acute kidney injury. Humans cannot synthesise vitamin C.

Administration of vitamin C may reverse the pathophysiological response to severe physiological stress.

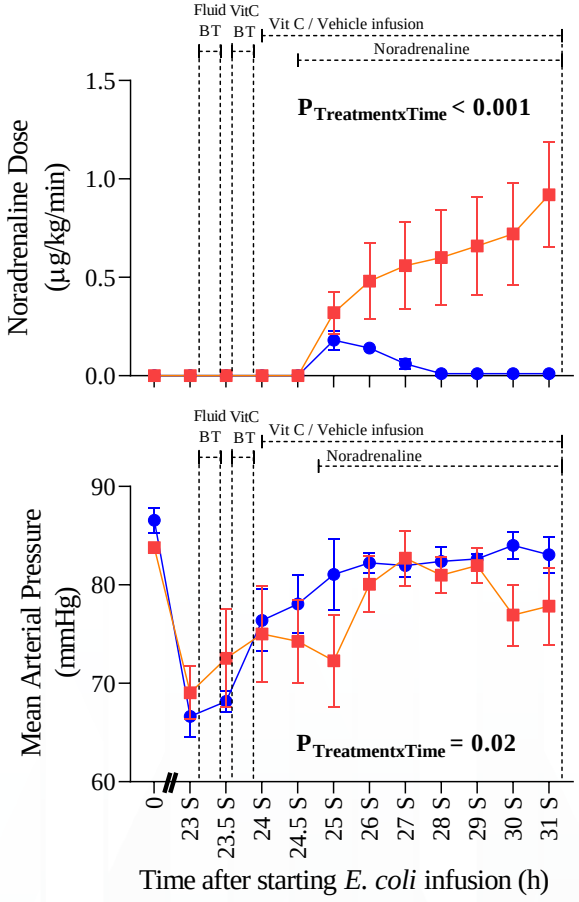
ONLINE LABORATORY INVESTIGATION

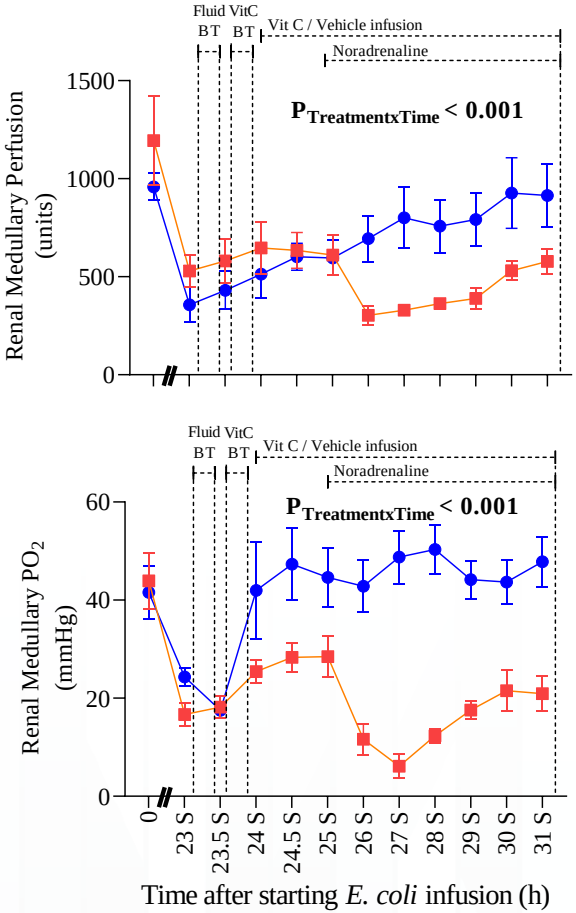
OPEN

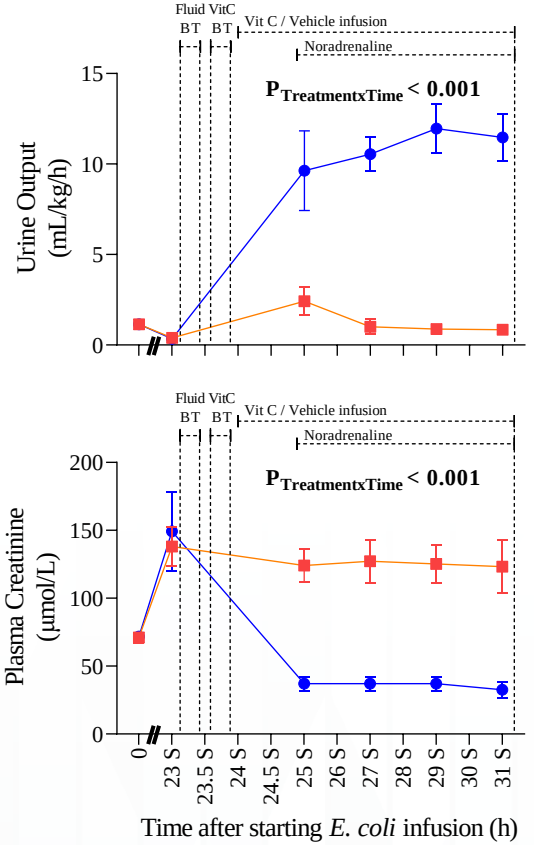
Reversal of the Pathophysiological Responses to Gram-Negative Sepsis by Megadose Vitamin C

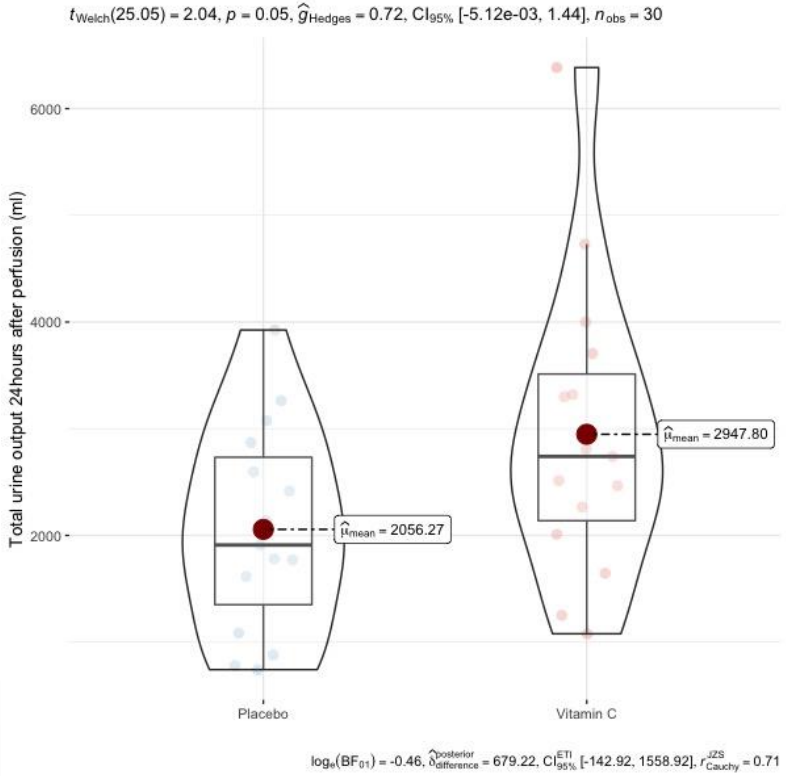
OBJECTIVES: Oxidative stress appears to initiate organ failure in sepsis, justifying treatment with antioxidants such as vitamin C at megadoses. We have therefore investigated the safety and efficacy of megadose sodium ascorbate in sepsis.

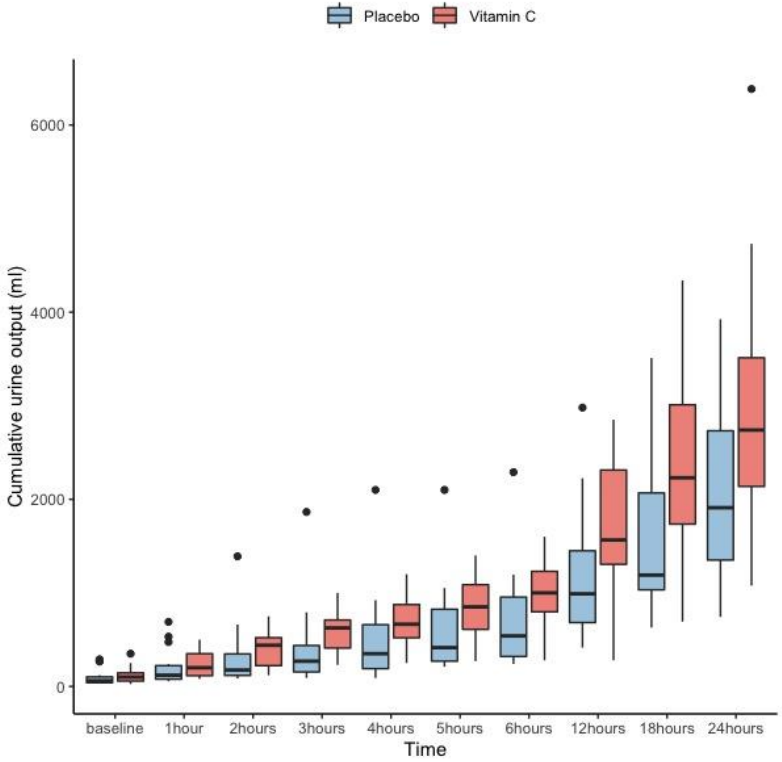
Yugeesh R. Lankadeva, PhD[1,2]
Rachel M. Peiris, BSc (Hons)[1]
Nobuki Okazaki, MD[1,3]
Ian E. Birchall, PhD[4]

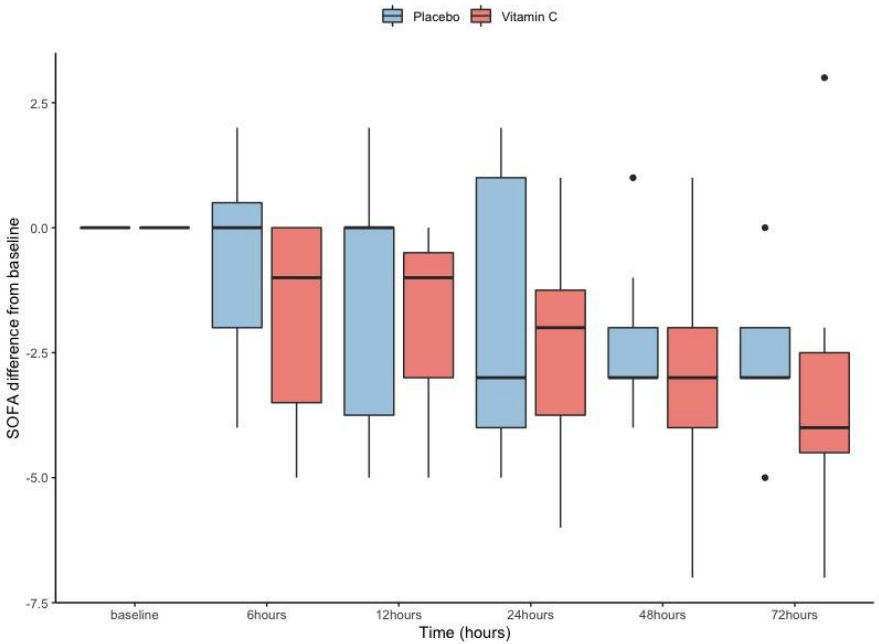

Fluid VitC
BT
BT
Vit C / Vehicle infusion
Noradrenaline
Noradrenaline Dose (µg/kg/min)
$P_{TreatmentxTime} < 0.001$
Mean Arterial Pressure (mmHg)
$P_{TreatmentxTime} = 0.02$
Time after starting *E. coli* infusion (h)

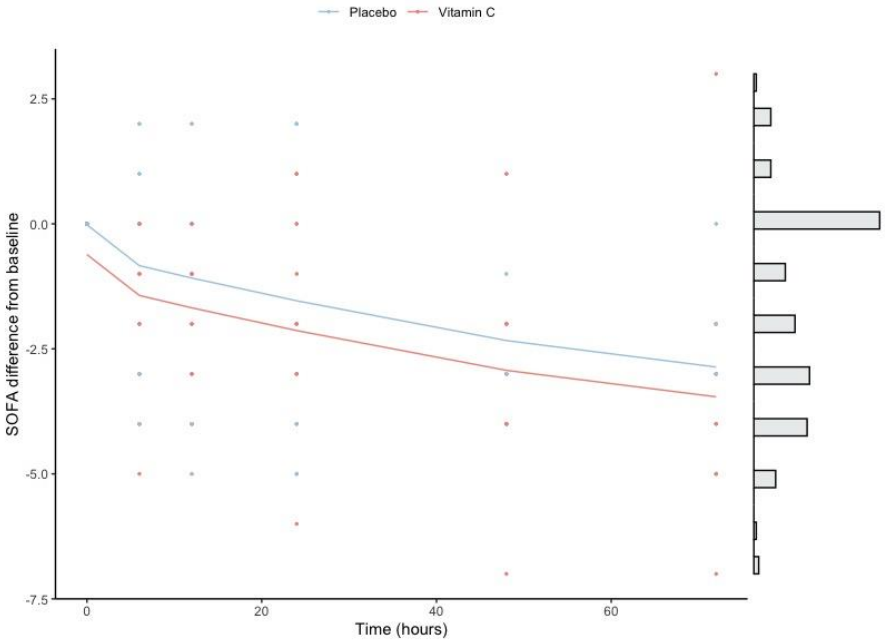

Fluid VitC
BT
BT
Vit C / Vehicle infusion
Noradrenaline
Renal Medullary Perfusion (units)
$P_{TreatmentxTime} < 0.001$
Renal Medullary PO_2 (mmHg)
$P_{TreatmentxTime} < 0.001$
Time after starting *E. coli* infusion (h)


Fluid VitC
BT
BT
Vit C / Vehicle infusion
Noradrenaline
Urine Output (mL/kg/h)
$P_{TreatmentxTime} < 0.001$
Plasma Creatinine (µmol/L)
$P_{TreatmentxTime} < 0.001$
Time after starting *E. coli* infusion (h)


$t_{Welch}(25.05) = 2.04$, $p = 0.05$, $\hat{g}_{Hedges} = 0.72$, $CI_{95\%}$ [-5.12e-03, 1.44], $n_{obs} = 30$
Total urine output 24hours after perfusion (ml)
6000
4000
2000
$\hat{\mu}_{mean} = 2056.27$
$\hat{\mu}_{mean} = 2947.80$
Placebo
Vitamin C
$\log_e(BF_{01}) = -0.46$, $\hat{\delta}^{posterior}_{difference} = 679.22$, $CI^{ETI}_{95\%}$ [-142.92, 1558.92], $r^{JZS}_{Cauchy} = 0.71$


Placebo
Vitamin C
Cumulative urine output (ml)
6000
4000
2000
0
baseline
1hour
2hours
3hours
4hours
5hours
6hours
12hours
18hours
24hours
Time





Linear mixed model with time as random effect

	Value	Std.Error	DF	t.value	p.value
(Intercept)	-0.46345251	0.345913517	147	-1.339793	0.1823801
Time	-0.03608248	0.008962237	4	-4.026057	0.0157850
Vitamin C	-0.61460371	0.299735737	147	-2.050485	**0.0420935**

$4.9m MRFF grant awarded to the MEGA-SCORES group for a large sepsis trial

Researchers from the Florey Institute and the Department of Critical Care will lead clinical trials across Australia to test a transformative therapy for patients with sepsis in intensive care units.

What's new and emerging in AKI?

AKI phenotypes

Micro- and macrovascular dysfunction: angiotensin II, amino acids

Inflammation: complement inhibition

Oxidative stress: sodium bicarbonate, mega dose sodium ascorbate

Personalised care