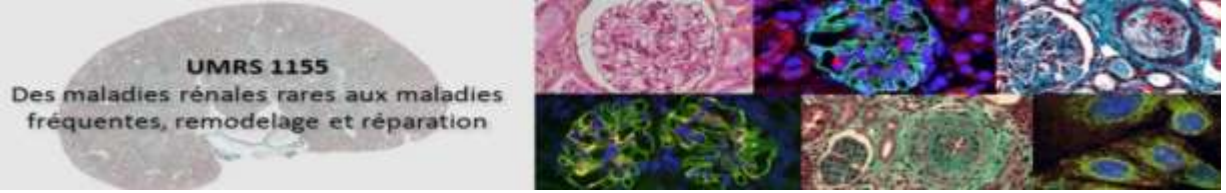


ACTUALITÉS NÉPHROLOGIQUES Jean Hamburger HÔPITAL NECKER

Actualités thérapeutiques dans l'IRA

Stéphane Gaudry
M.D., Ph.D.
MIR
Hôpital Avicenne, Bobigny/ Hôpital Jean Verdier, Bondy
CORAKID, UMRS 1155, Tenon, PARIS

INI CRCT CARDIOVASCULAR & RENAL CLINICAL TRIALISTS

Hôpitaux Universitaires Avicenne Jean-Verdier René-Muret Paris-Seine Saint-Denis

Université Sorbonne Paris Nord

Conflict of interest

Studies (AKIKI, AKIKI2, ICRAKI) funded by grants from French Ministry of Health and French Ministry of research

- Which vasopressor to improve renal outcomes?
- Vitamin B3 for renal protection ?
- How to personalize RRT initiation ?
- RRT modalities: what’s new ?

Which vasopressor to improve renal outcomes?

To answer the question, we need to understand the **pathophysiological mechanisms** involved in acute kidney injury and distributive shock

REVIEW ARTICLE

MECHANISMS OF DISEASE

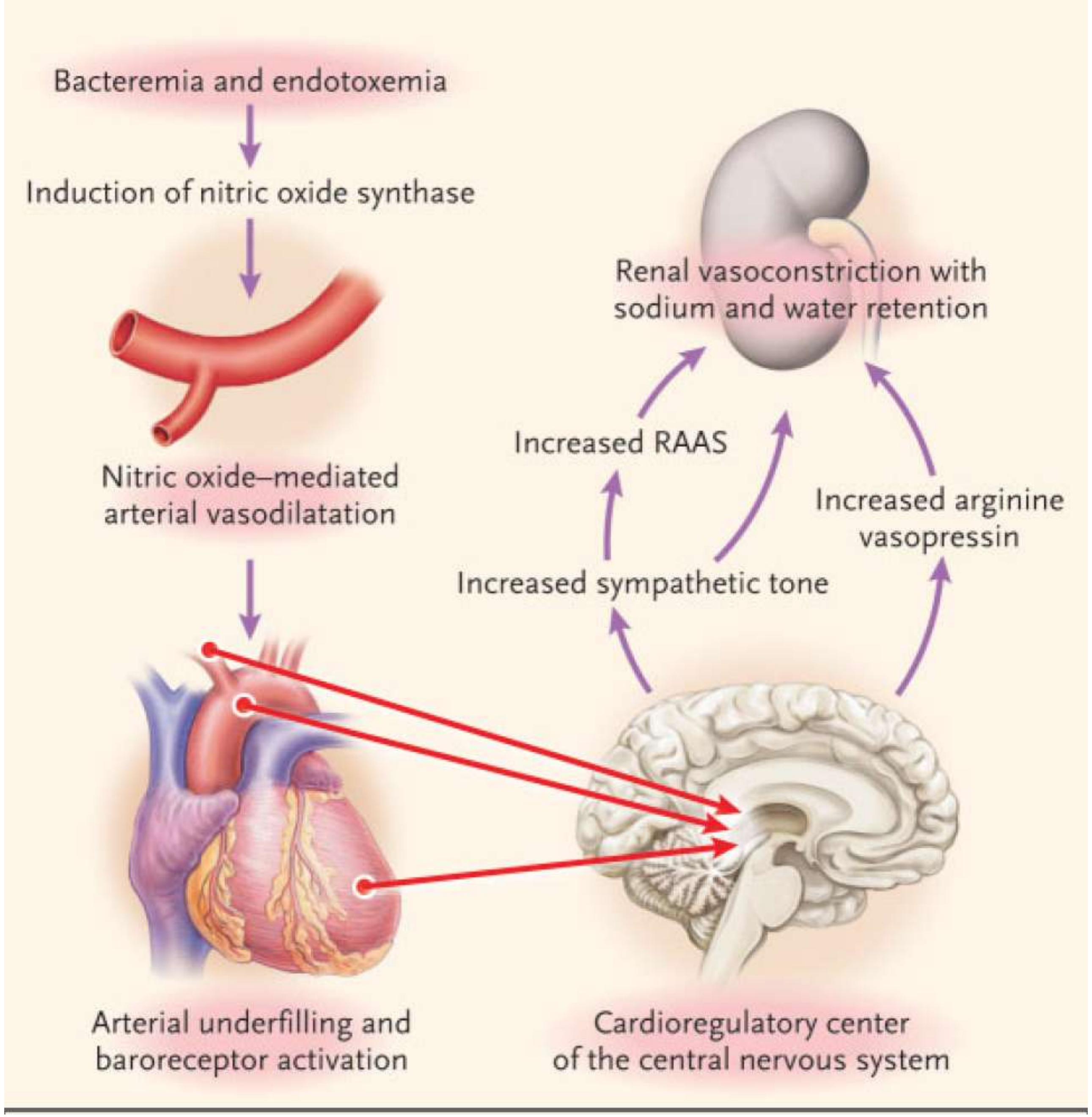
Acute Renal Failure and Sepsis

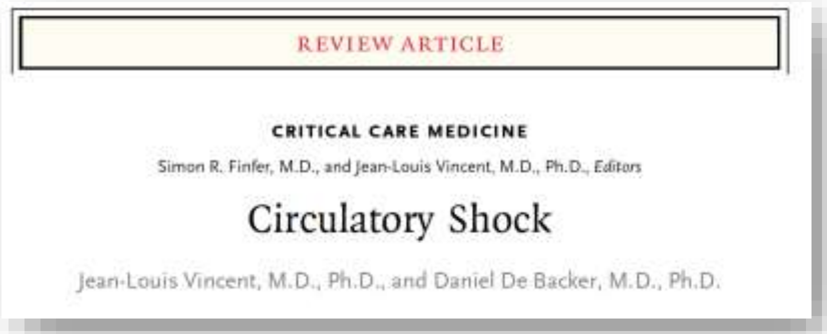
Robert W. Schrier, M.D., and Wei Wang, M.D.

20 years ago……

Endotoxin model
Hypodynamic systemic circulation
- Low cardiac output
- Renal vasoconstriction

Renal Blood Flow (RBF) decrease





REVIEW ARTICLE

CRITICAL CARE MEDICINE

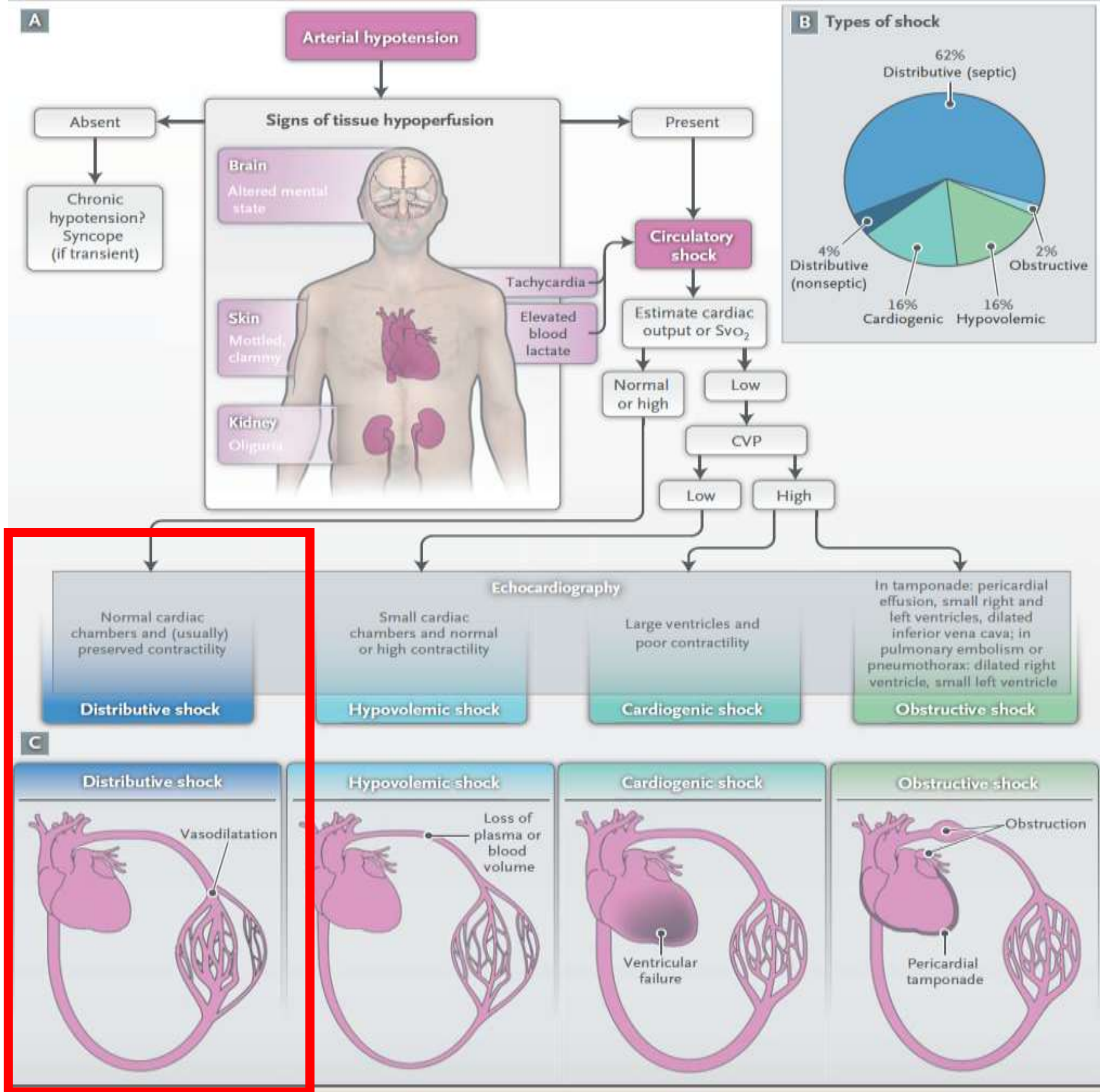
Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., Editors

Circulatory Shock

Jean-Louis Vincent, M.D., Ph.D., and Daniel De Backer, M.D., Ph.D.

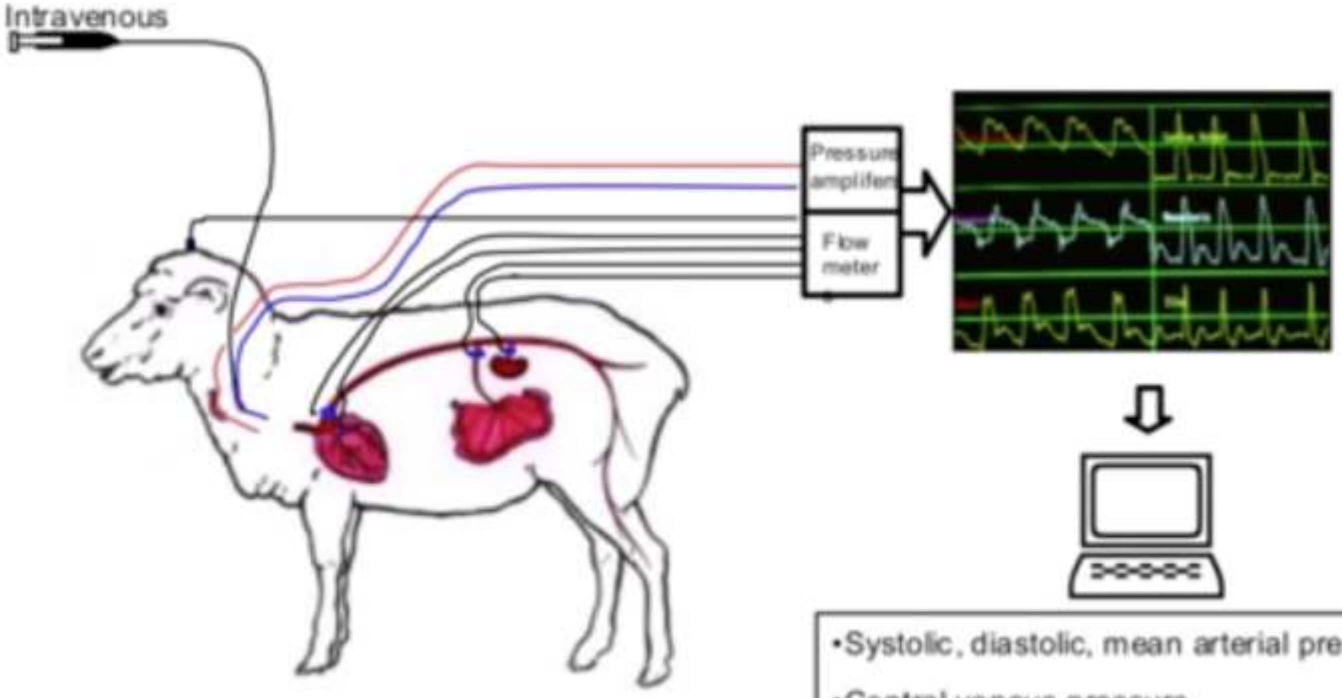
“In **distributive shock**, the main deficit lies in the periphery, with **decreased systemic vascular resistance** and **altered oxygen extraction**.

Typically, in such cases **cardiac output is high**, although it may be low as a result of associated myocardial depression”




Pr Rinaldo Bellomo

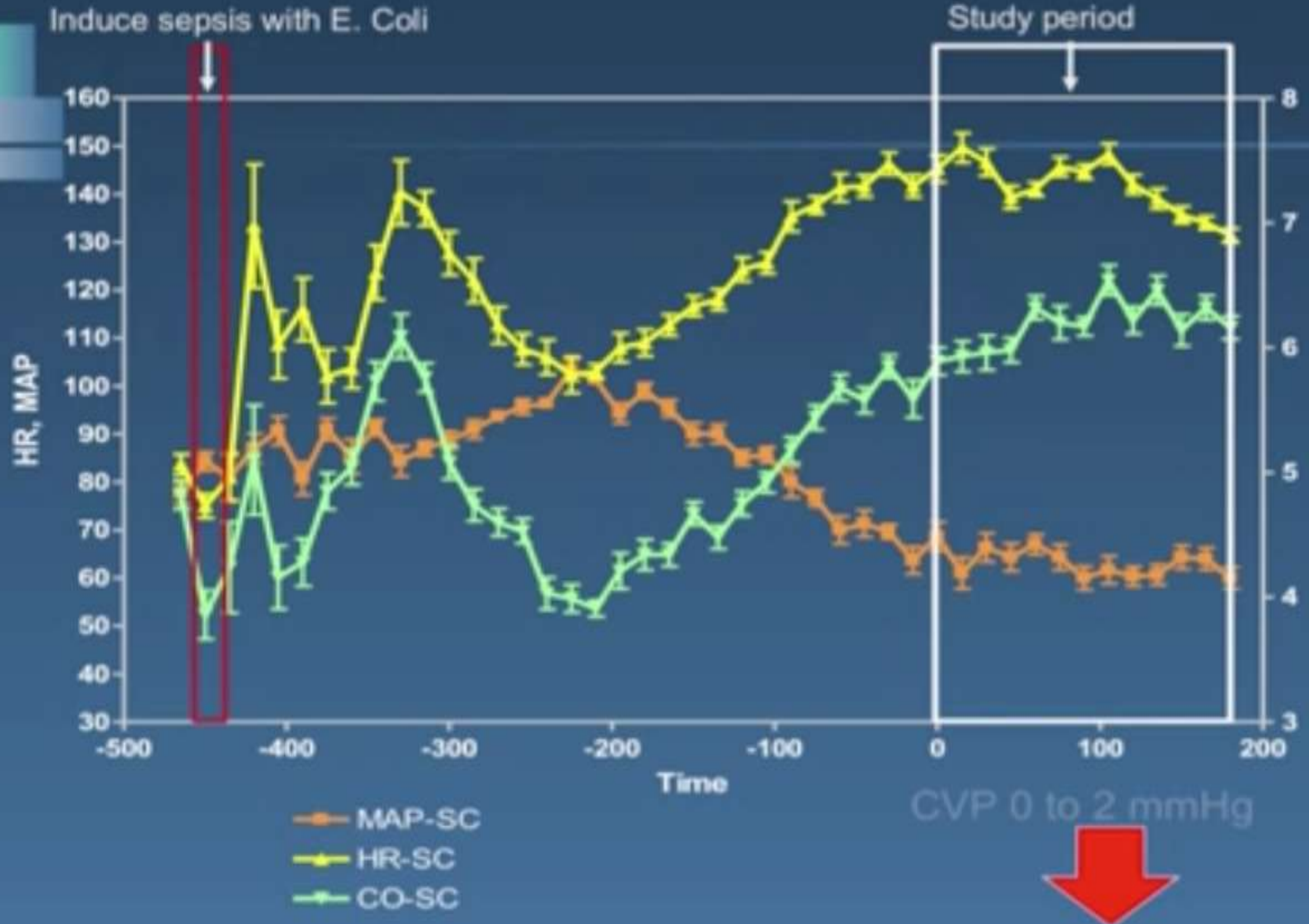
Haemodynamic measurements in conscious sheep



- Systolic, diastolic, mean arterial pressure
- Central venous pressure
- Cardiac output, heart rate, stroke volume, maximum aortic flow, dF/dt
- Regional flows and conductances
- urinary flow

Renal blood flow measurement

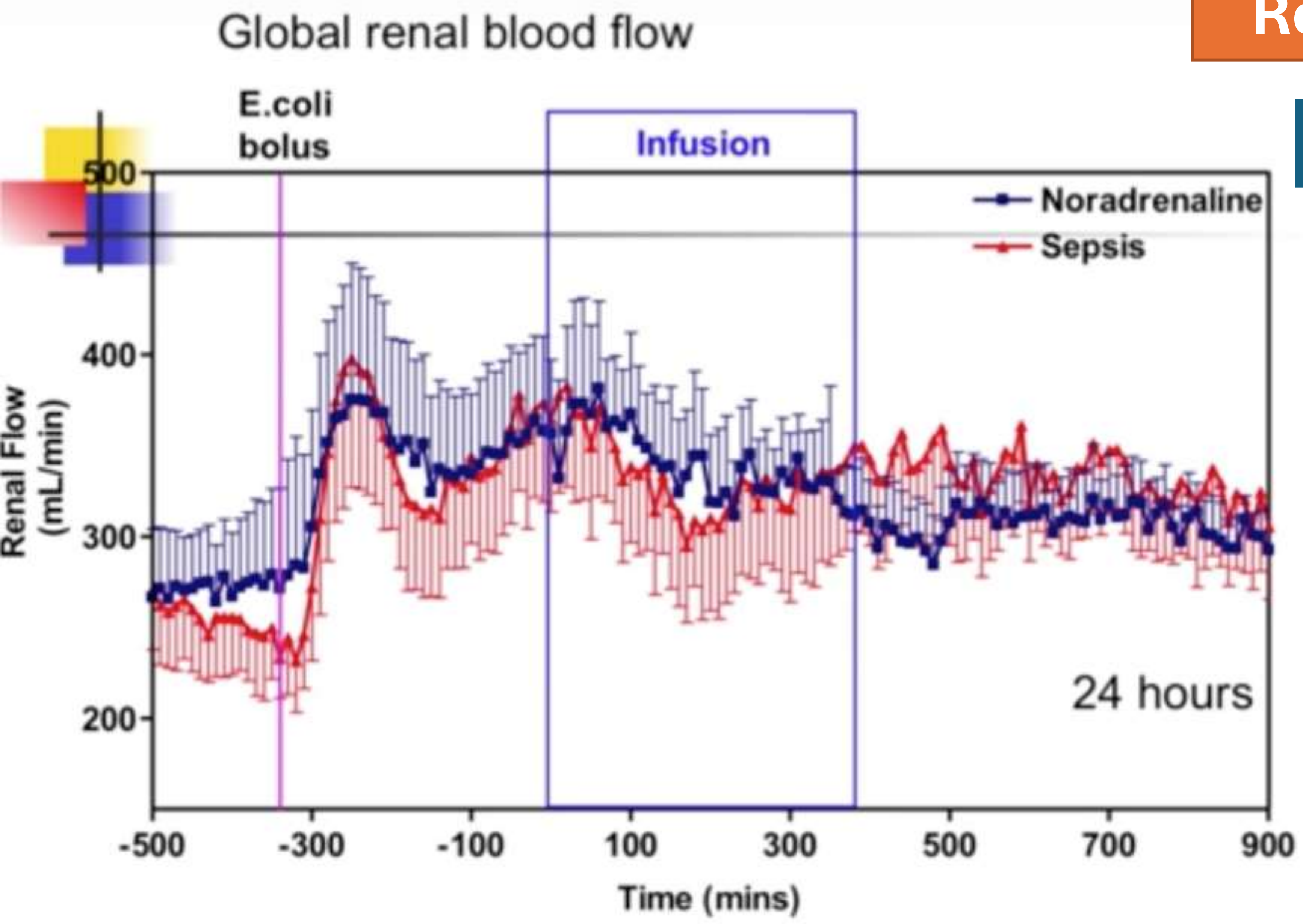
Example of induction of experimental Gram negative sepsis: hemodynamics



severe oliguria/anuria (AKI)

Renal vasodilation !!

≠ ischemic AKI

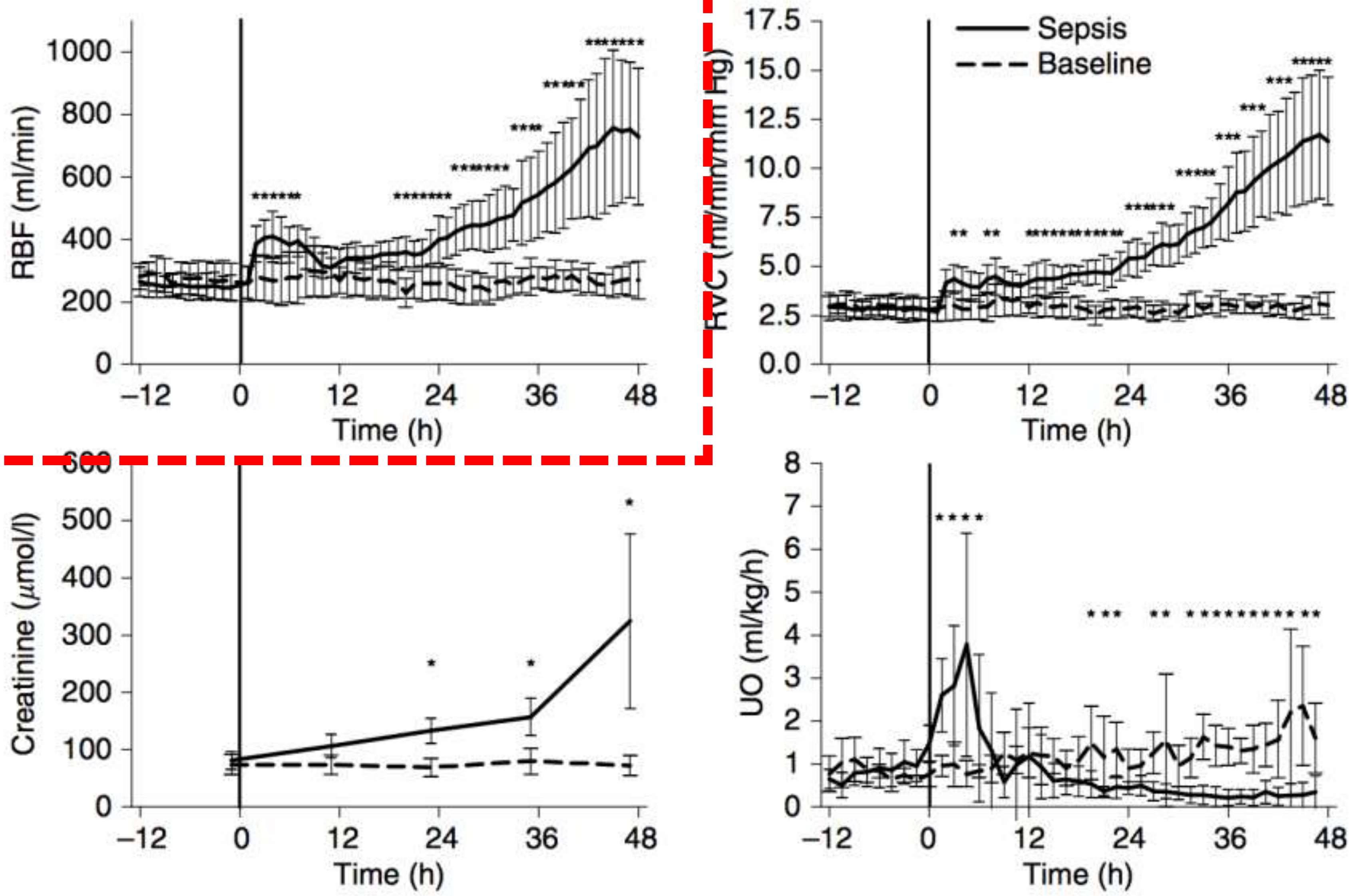


original article
http://www.kidney-international.org

Renal blood flow in experimental septic acute renal failure

C Langenberg[1], L Wan[2], M Egi[2], CN May[3] and R Bellomo[2]

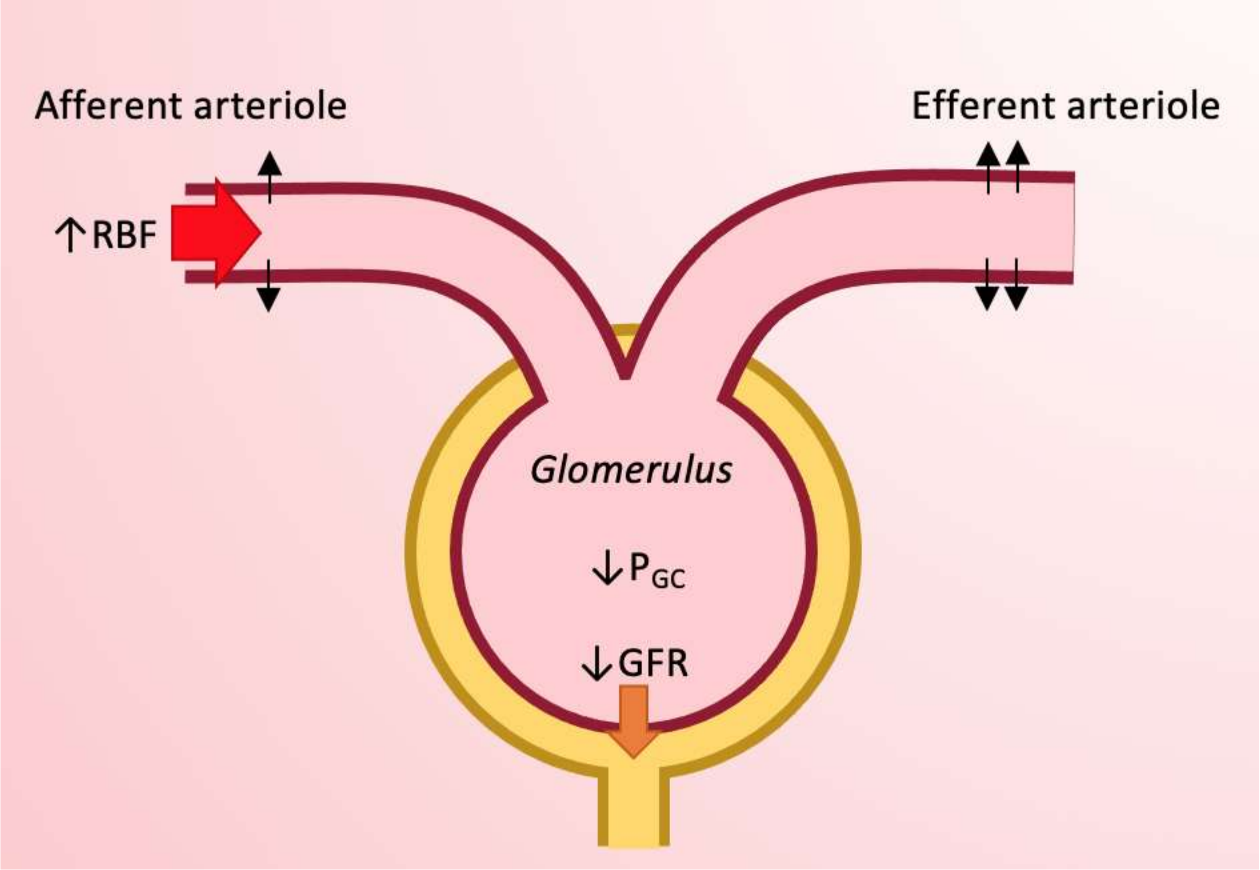
48 hours septic AKI model



How to explain that renal blood flow is **dissociated** from **glomerular filtration rate ?**

How to explain that renal blood flow is dissociated from glomerular filtration rate ?

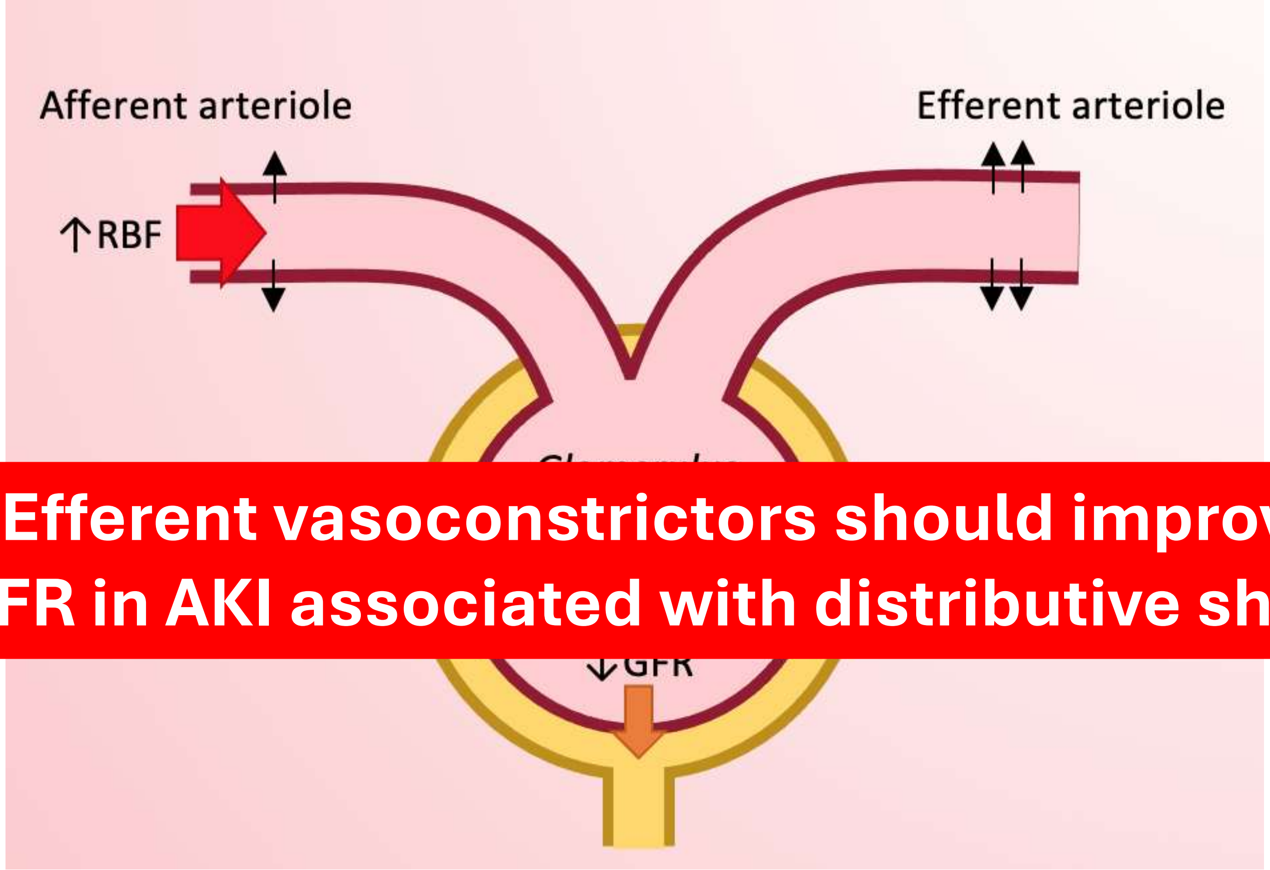
Afferent arteriola vasodilation (+) and efferent arteriola vasodilation (+++)



Picod *et al.*, Ann Intensive Care 2024

How to explain that renal blood flow is dissociated from glomerular filtration rate ?

Afferent arteriola vasodilation (+) and efferent arteriola vasodilation (+++)



Efferent vasoconstrictors should improve GFR in AKI associated with distributive shock

Picod *et al.*, Ann Intensive Care 2024

	Afferent vasoconstriction	Efferent vasoconstriction
Norepinephrine	+	+
Vasopressin	+	++
Angiotensin II	+	++

Edwards *et al.*, Am J Physiol 1983
Edwards *et al.*, Am J Physiol 1989
Denton *et al.*, Am J Physiol 2000

Vasopressors: the choice

Norepinephrine

Vasopressin

Angiotensin II

 www.kidney-international.org

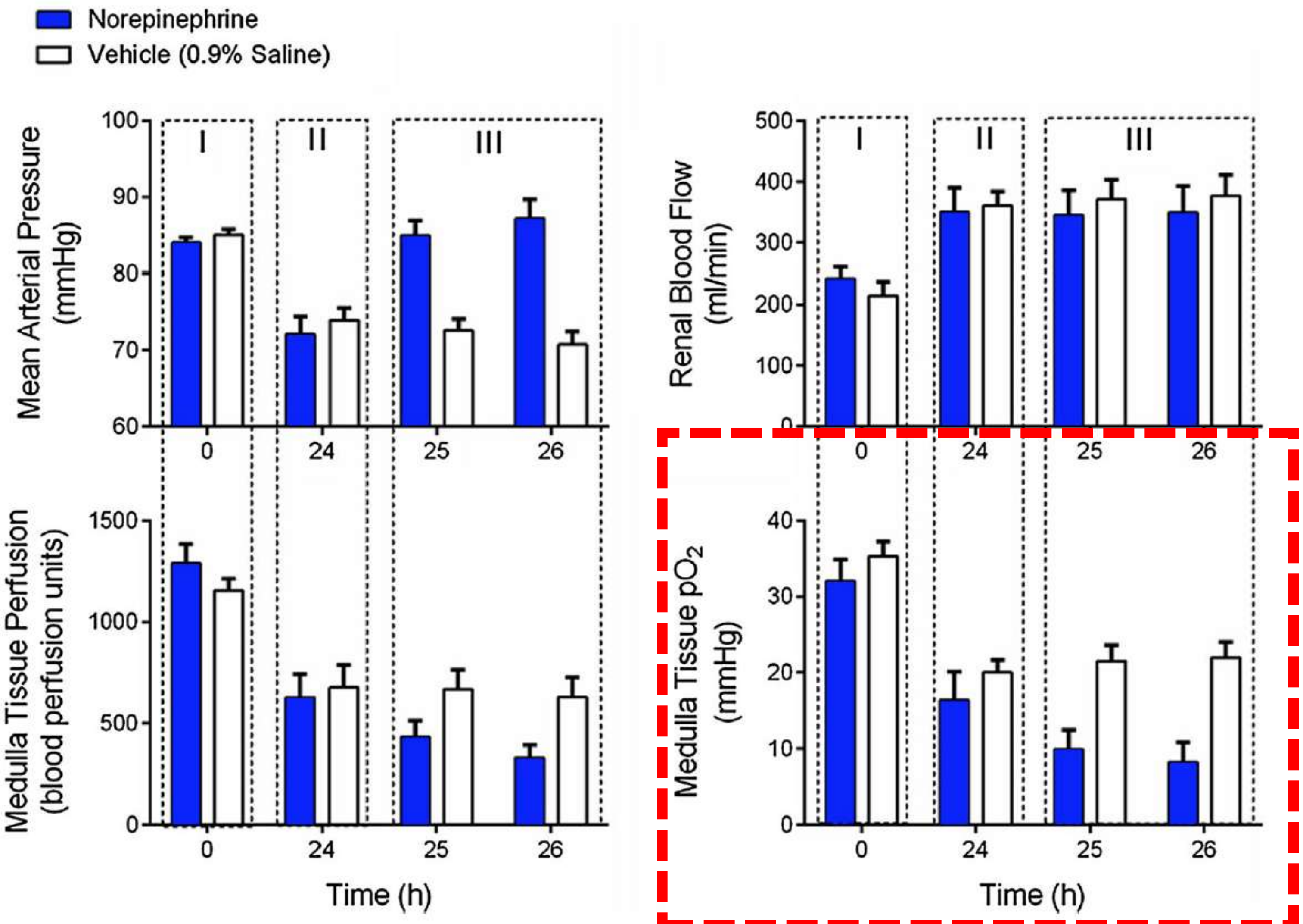
Norepinephrine

Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury

see commentary on page 22

Yugeesh R. Lankadeva[1], Junko Kosaka[1], Roger G. Evans[2], Simon R. Bailey[3], Rinaldo Bellomo[4] and Clive N. May[1]

Decrease in O_2 pressure in the renal medulla



Vasopressors: the choice

Norepinephrine

Vasopressin

Angiotensin II

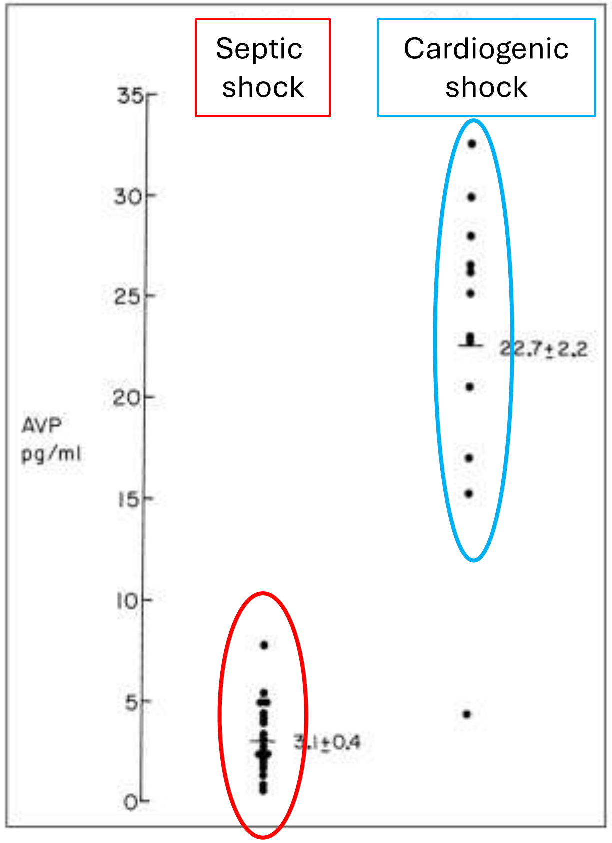
Vasopressin

Vasopressin deficiency in septic shock

ARTICLE

Vasopressin Deficiency Contributes to the Vasodilation of Septic Shock

Donald W. Landry, Howard R. Levin, Ellen M. Gallant, Robert C. Ashton, Susan Seo, David D'Alessandro, Mehmet C. Oz, and Juan A. Oliver



Landry *et al.*, Circulation 1997

Vasopressin deficiency in septic shock

ARTICLE

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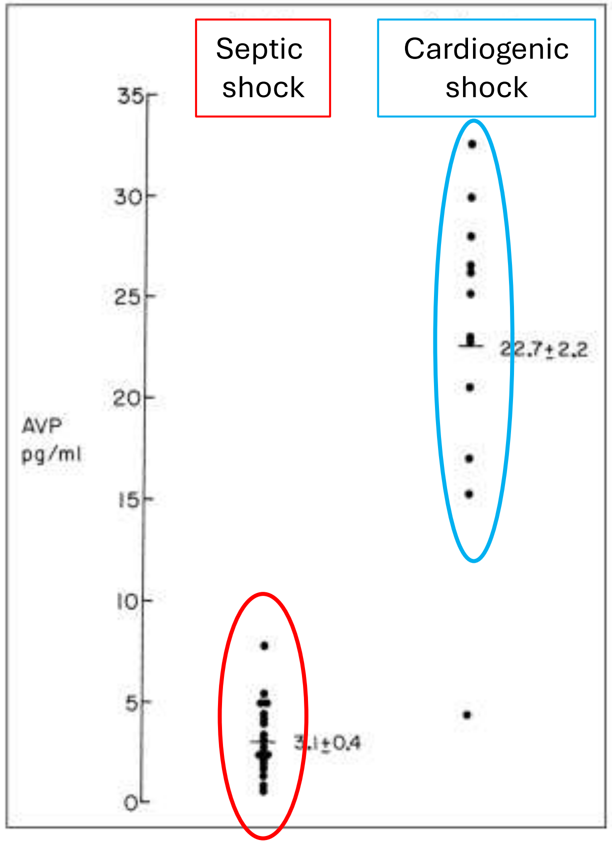
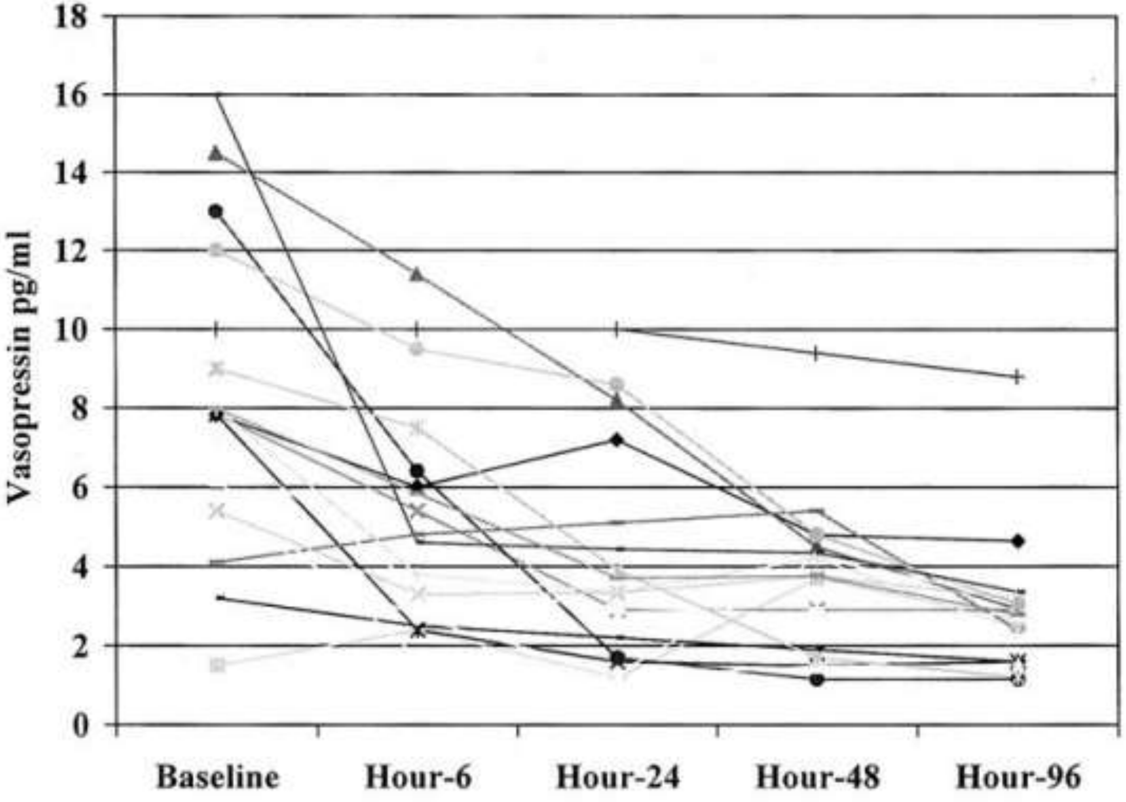


Landry *et al.*, Circulation 1997

Circulating vasopressin levels in septic shock

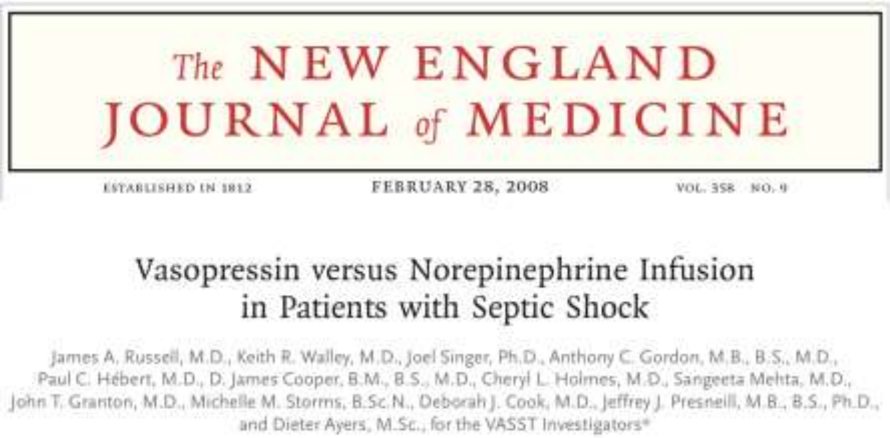
Tarek Sharshar, MD; Anne Blanchard, MD, PhD; Michel Paillard, MD; Jean Claude Raphael, MD; Philippe Gajdos, MD; Djillali Annane, MD, PhD



Sharshar *et al.*, Crit Care Med 2003

Vasopressin

VASST trial
NEJM 2008



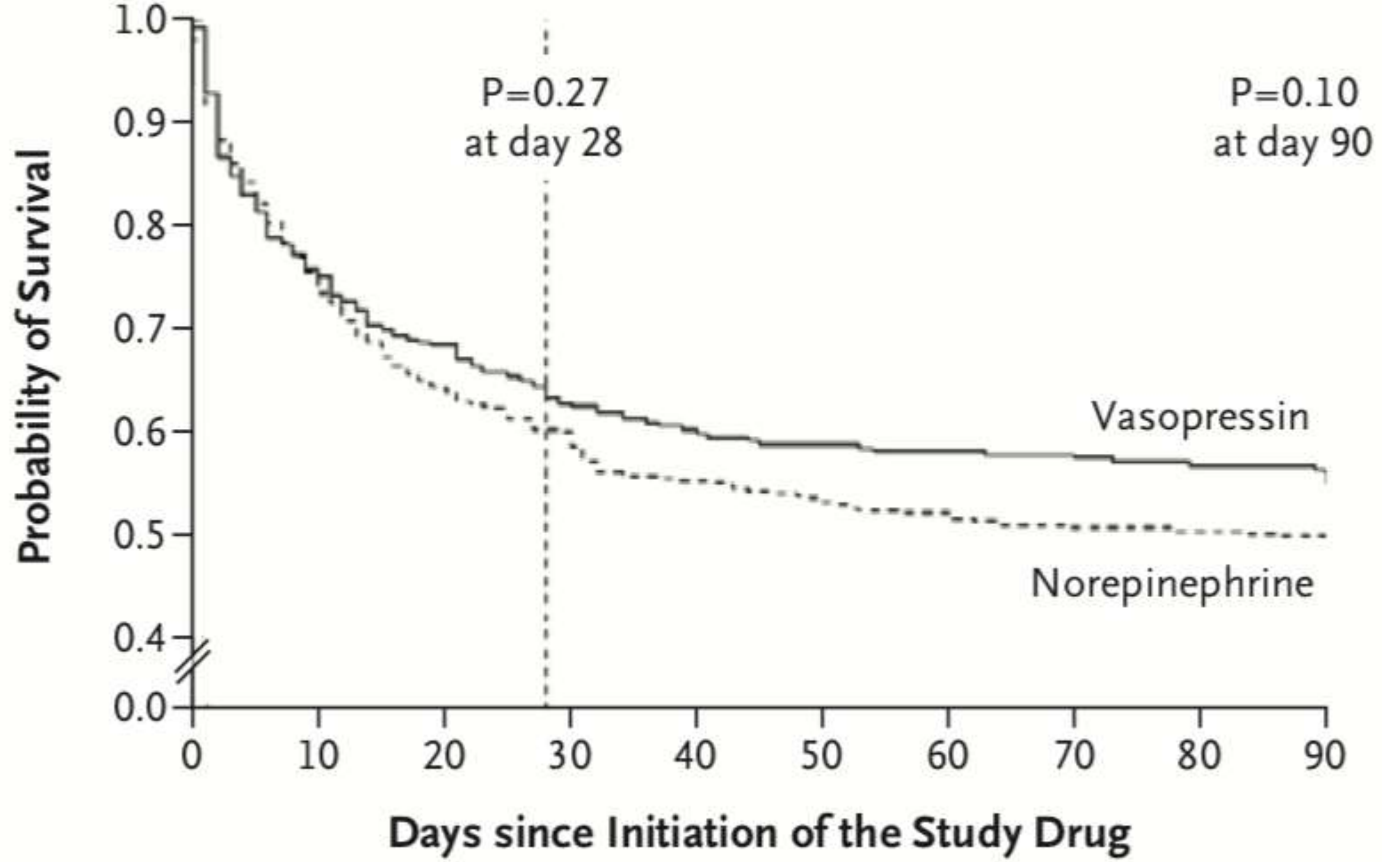
The NEW ENGLAND JOURNAL of MEDICINE

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*

- Septic shock with ≥ 5µg/min norepinephrine
- Randomization:
  - **Vasopressin (0.01 to 0.03 U/min**)
  - vs norepinephrine
- N=778



No. at Risk

Vasopressin	397	301	272	249	240	234	232	230	226	220
Norepinephrine	382	289	247	230	212	205	200	194	193	191

ORIGINAL ARTICLE

Identification of Acute Kidney Injury Subphenotypes with Differing Molecular Signatures and Responses to Vasopressin Therapy

Pavan K. Bhatraju[1,2], Leila R. Zelnick[2], Jerald Herting[3], Ronit Katz[2], Carmen Mikacenic[1], Susanna Kosamo[1], Eric D. Morrell[1], Cassianne Robinson-Cohen[2], Carolyn S. Calfee[4,5,6], Jason D. Christie[7,8*], Kathleen D. Liu[9,10], Michael A. Matthay[4,5,6], William O. Hahn[11], Victoria Dmyterko[1], Natalie S. J. Slivinski[12], Jim A. Russell[13,14], Keith R. Walley[13,14], David C. Christiani[15,16,17], W. Conrad Liles[18], Jonathan Himmelfarb[2], and Mark M. Wurfel[1,2]

AJRCCM

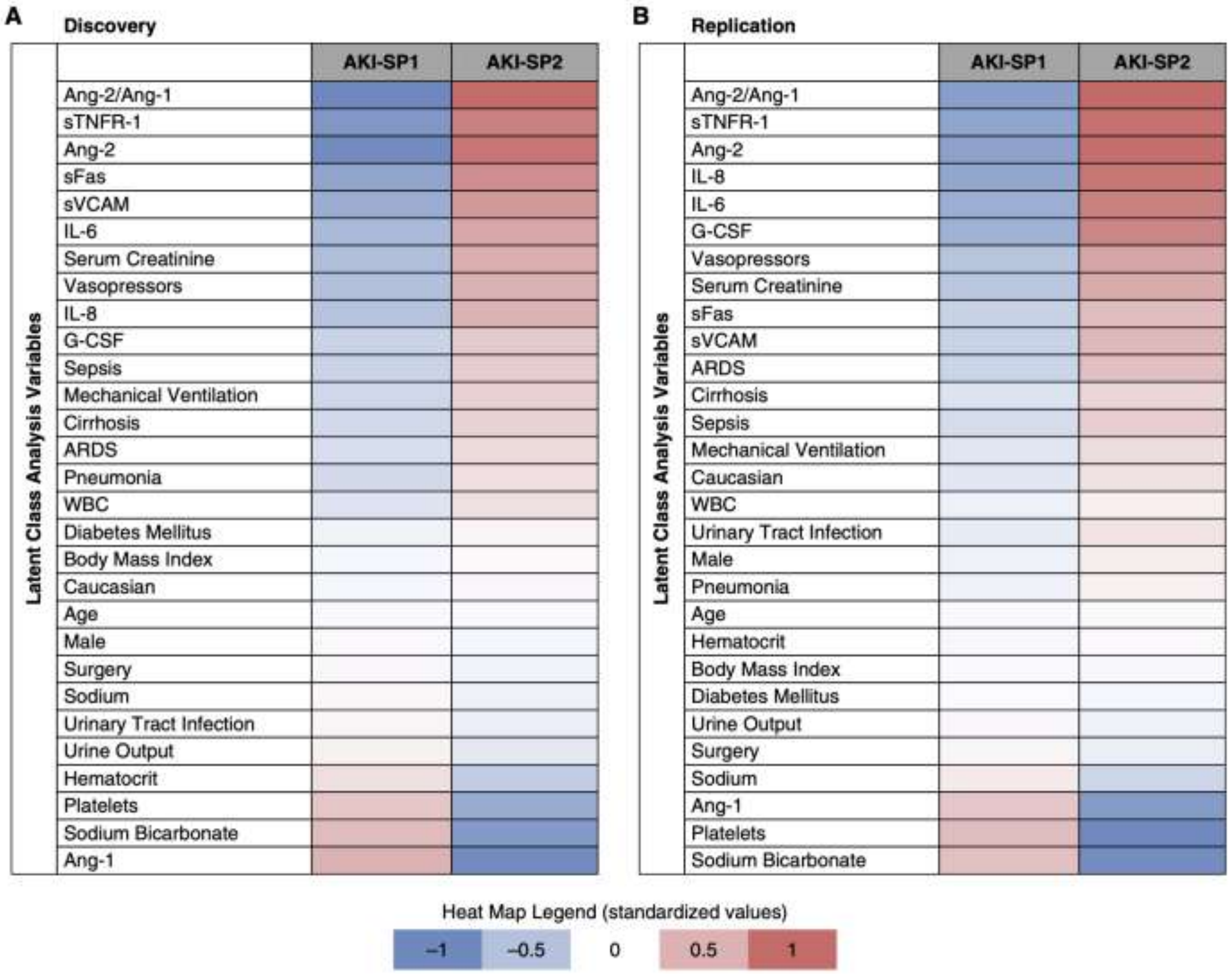
Vasopressin

Personnalization of vasopressor selection

Identification of AKI subphenotypes

↓

classification model was applied to patients with AKI in VASST



ORIGINAL ARTICLE

Vasopressin

Identification of Acute Kidney Injury Subphenotypes with Differing Molecular Signatures and Responses to Vasopressin Therapy

Pavan K. Bhatraju[1,2], Leila R. Zelnick[2], Jerald Herting[3], Ronit Katz[2], Carmen Mikacenic[1], Susanna Kosamo[1], Eric D. Morrell[1], Cassianne Robinson-Cohen[2], Carolyn S. Calfee[4,5,6], Jason D. Christie[7,8*], Kathleen D. Liu[9,10], Michael A. Matthay[4,5,6], William O. Hahn[11], Victoria Dmyterko[1], Natalie S. J. Slivinski[12], Jim A. Russell[13,14], Keith R. Walley[13,14], David C. Christiani[15,16,17], W. Conrad Liles[18], Jonathan Himmelfarb[2], and Mark M. Wurfel[1,2]

	AKI-SP1				AKI-SP2			
	Norepinephrine	Vasopressin	RR (95% CI)†	*P* Value	Norepinephrine	Vasopressin	RR (95% CI)†	*P* Value
Clinical outcomes								
7-d renal nonrecovery	24 (46)	23 (38)	0.80 (0.51–1.25)	0.32	44 (63)	44 (56)	0.99 (0.76–1.30)	0.96
28-d mortality	16 (31)	11 (18)	0.53 (0.30– 0.94)	0.03	30 (43)	31 (40)	1.03 (0.68–1.55)	0.88
90-d mortality	24 (46)	16 (27)	0.54 (0.32–0.92)	0.02	34 (49)	35 (45)	0.99 (0.70–1.42)	0.99

Identification of AKI subphenotypes could improve risk prognostication and may be useful for predictive enrichment in clinical trials.

Vasopressin

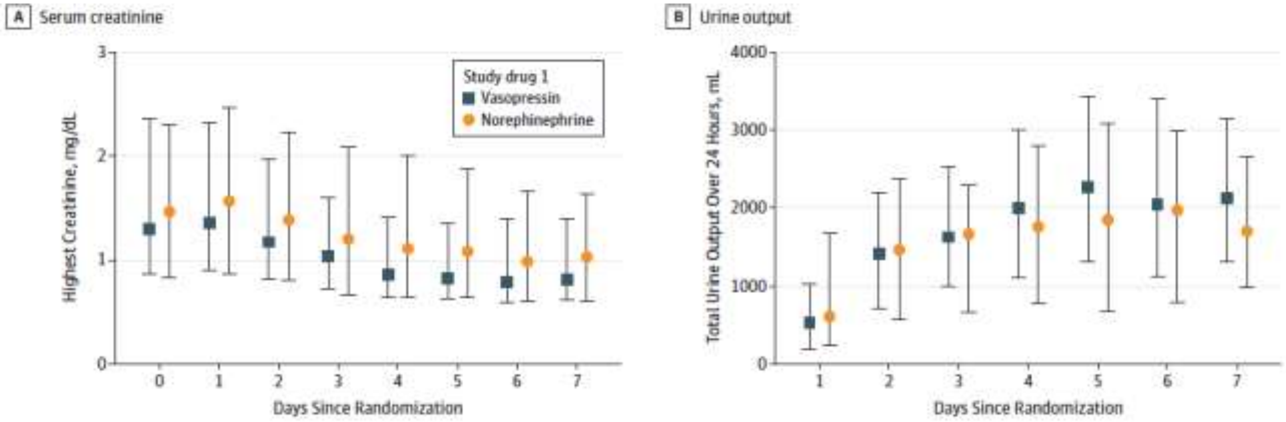
JAMA | Original Investigation

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock
The VANISH Randomized Clinical Trial

2016

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

- Septic shock requiring vasopressors
- Randomization:
  - ➢ **Vasopressin (0.01 to 0.06 U/min)**
  - ➢ vs norepinephrine
- N=409



Primary outcome: kidney failure–free days during the 28-day period after randomization
No difference between vasopressin and norepinephrine groups ($p = 0.88$)

Vasopressin

JAMA | Original Investigation

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock
The VANISH Randomized Clinical Trial

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There was **less use of RRT in the vasopressin group** than in the norepinephrine group (25.4% for vasopressin vs 35.3%for norepinephrine; difference, −9.9% [95%CI, −19.3%to −0.6%]).

Vasopressin

Vasopressin *versus* Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery

The VANCS Randomized Controlled Trial

primary endpoint
composite of mortality or severe complications

- Vasodilatory shock after cardiac surgery requiring vasopressors
- Randomization:
  - **Vasopressin (0.01 to 0.06 U/min**)
  - vs norepinephrine
- N=330

Table 2. Primary and Secondary Outcomes in the Two Groups

Variable	Norepinephrine (n = 151)	Vasopressin (n = 149)	Unadjusted Odds Ratio or Hazard Ratio or Between-group Difference (95% CI)	*P* Value	Adjusted* Odds Ratio or Hazard Ratio or Between-group Difference (95%CI)	*P* Value
Primary outcome, n (%)	74 (49.0)	48 (32.2)	0.55 (0.38 to 0.80)	0.0014	0.52 (0.36 to 0.75)	0.0005
30-d mortality	24 (15.9)	23 (15.4)	0.99 (0.56 to 1.76)	0.98	1.11 (0.62 to 1.96)	0.73
MV > 48 h	13 (8.6)	8 (5.4)	0.62 (0.26 to 1.49)	0.28	0.62 (0.26 to 1.51)	0.30
Sternal wound infection	15 (9.9)	7 (4.7)	0.46 (0.19 to 1.13)	0.09	0.48 (0.19 to 1.18)	0.11
Reoperation	10 (6.6)	10 (6.7)	0.8 (0.52 to 1.23)	0.31	0.79 (0.51 to 1.22)	0.28
Stroke	4 (2.6)	4 (2·7)	1.03 (0.26 to 4.11)	0.97	1.08 (0.27 to 4.39)	0.91
Acute renal failure	54 (35.8)	15 (10.3)	0.26 (0.15 to 0.46)	< 0.0001	0.26 (0.15 to 0.46)	< 0.0001
Secondary outcomes, n (%)						
Infection	23 (15.2)	16 (10.7)	0.67 (0.34 to 1.33)	0.25	0.71 (0.35 to 1.42)	0.33
Septic shock	13 (8.6)	9 (6.0)	0.68 (0.28 to 1.65)	0.40	0.73 (0.3 to 1.81)	0.50
Atrial fibrillation	124 (82.1)	95 (63.8)	0.38 (0.22 to 0.65)	0.0004	0.37 (0.22 to 0.64)	0.0004
Ventricular arrhythmias	32 (21.2)	27 (18.1)	0.82 (0.46 to 1.46)	0.50	0.8 (0.45 to 1.43)	0.45
Length of ICU stay (d), median (IQR)	6 (4 to 9)	5 (4 to 7)	−2.42 (−4.11 to −0.73)	0.0050	−2.28 (−3.94 to −0.62)	0.0071
Length of hospital stay (d), median (IQR)	13 (10 to 20)	10 (8 to 12)	−3.76 (−6.1 to −1.42)	0.0016	−3.66 (−6.01 to −1.32)	0.0022

Hajjar *et al.*, Anesthesiology 2017

Vasopressin

SYSTEMATIC REVIEW

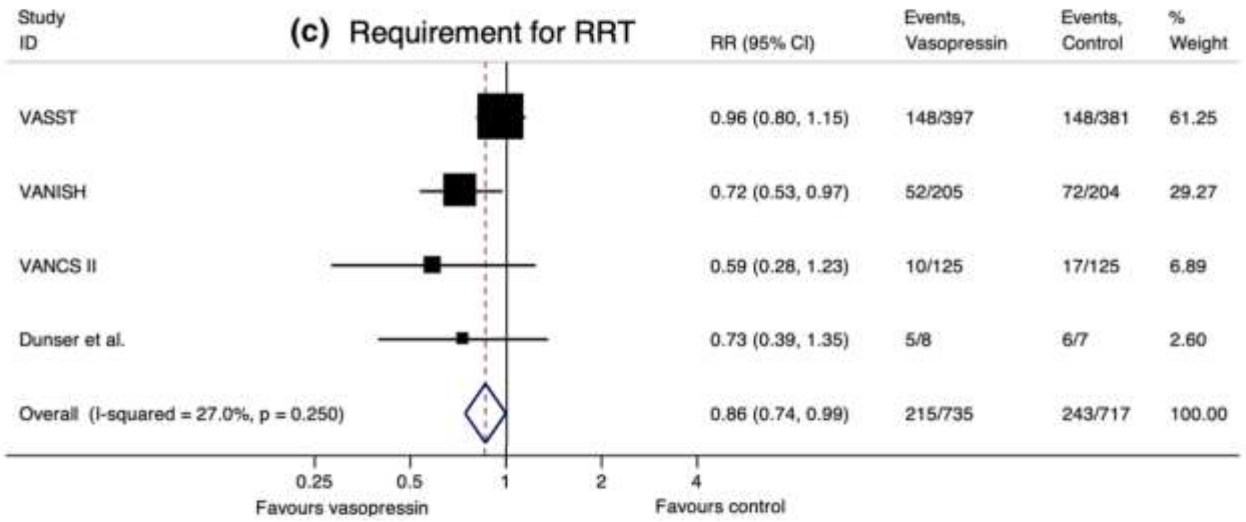
Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials

IPDMA

4 RCTs
1453 patients

- VASST
- VANISH
- VANCS II
- Dunser *et al.*

- No effect on 28-day mortality
  RR [0.86-1.12]
- Vasopressin **reduced the requirement for RRT**
  RR 0.86 [0.74-0.99]

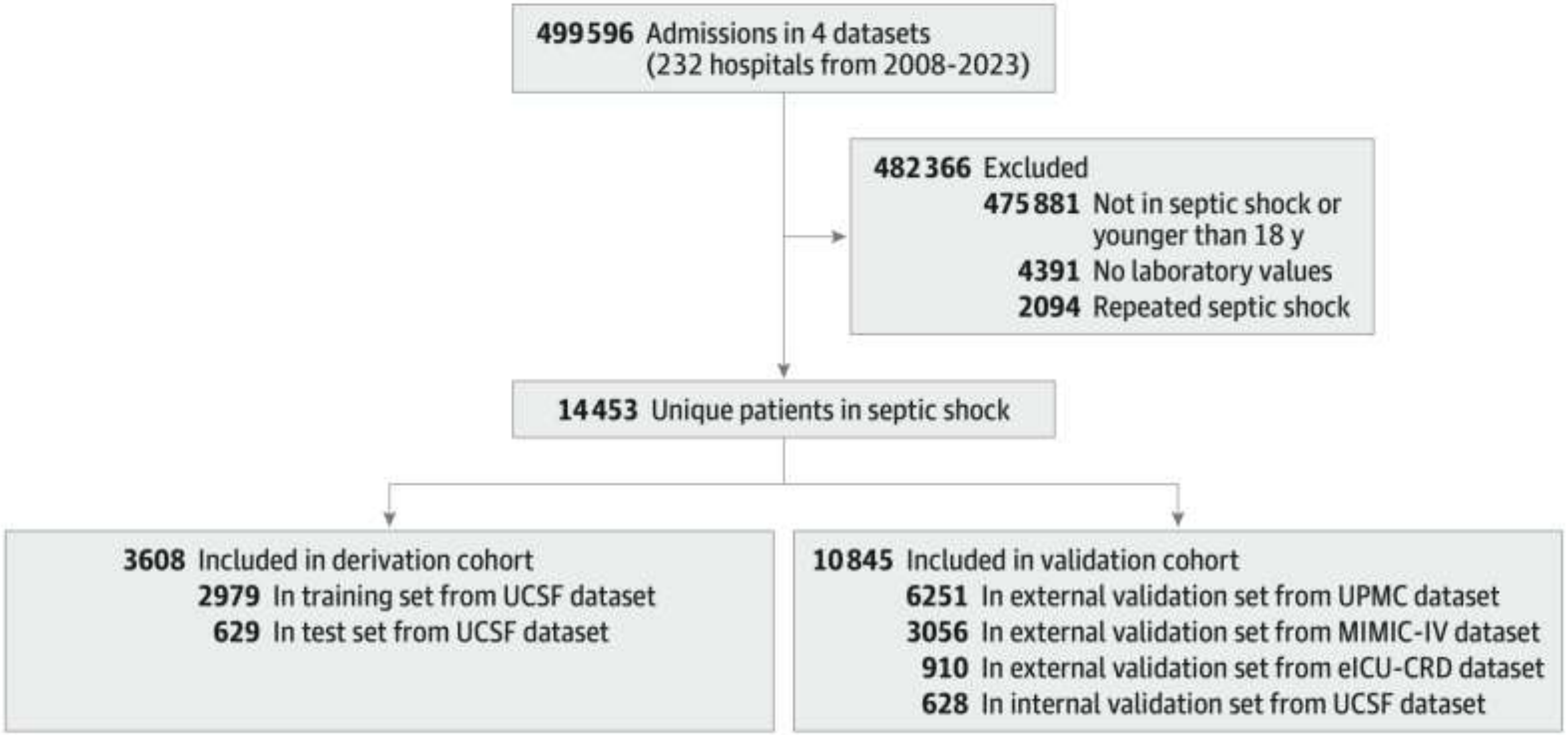


Nagendran *et al.*, Intensive Care Med 2019

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Optimal Vasopressin Initiation in Septic Shock
The OVISS Reinforcement Learning Study

Alexandre Kalimouttou, MD; Jason N. Kennedy, MS; Jean Feng, PhD; Harvineet Singh, PhD; Suchi Saria, PhD;
Derek C. Angus, MD, MPH; Christopher W. Seymour, MD, MSc; Romain Pirracchio, MD, MPH, PhD



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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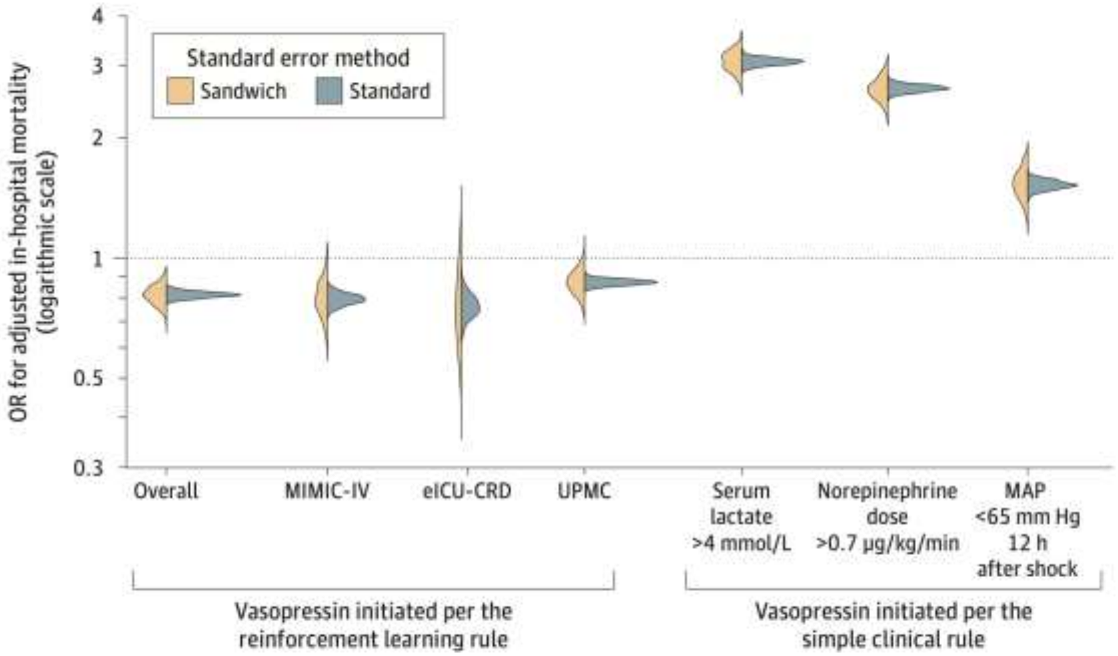
CONCLUSIONS AND RELEVANCE In adult patients with septic shock receiving norepinephrine, the use of vasopressin was variable. A reinforcement learning model developed and validated in several observational datasets recommended more frequent and earlier use of vasopressin than average care patterns and was associated with reduced mortality.



Vasopressin

There are **arguments to suggest that vasopressin improves renal outcomes** but there is **still no RCT** that demonstrates a positive effect

It is urgent to conduct such a trial

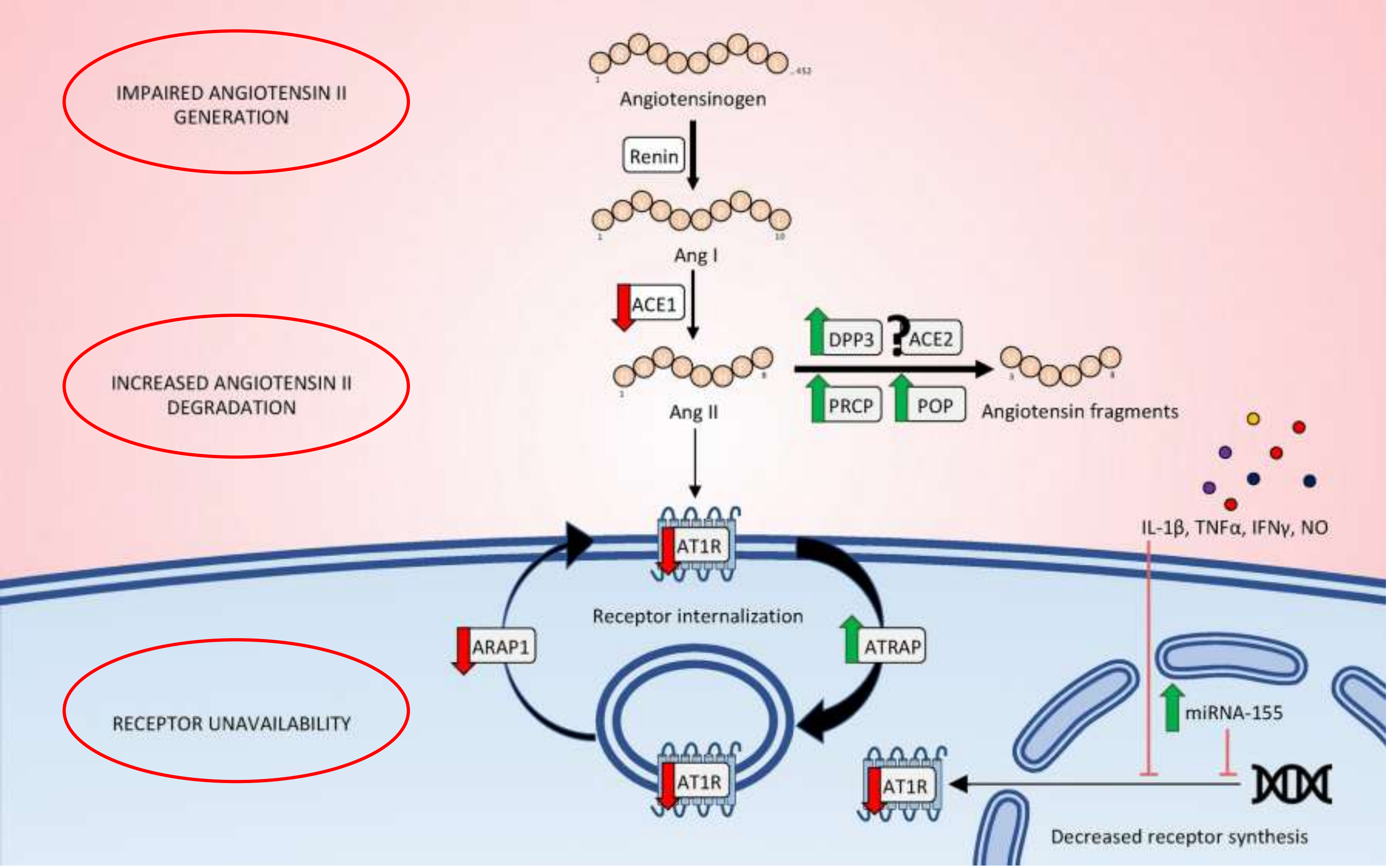
Vasopressors: the choice

Norepinephrine

Vasopressin

Angiotensin II

Angiotensin II deficiency in septic shock



Picod *et al.*, Ann Intensive Care 2024

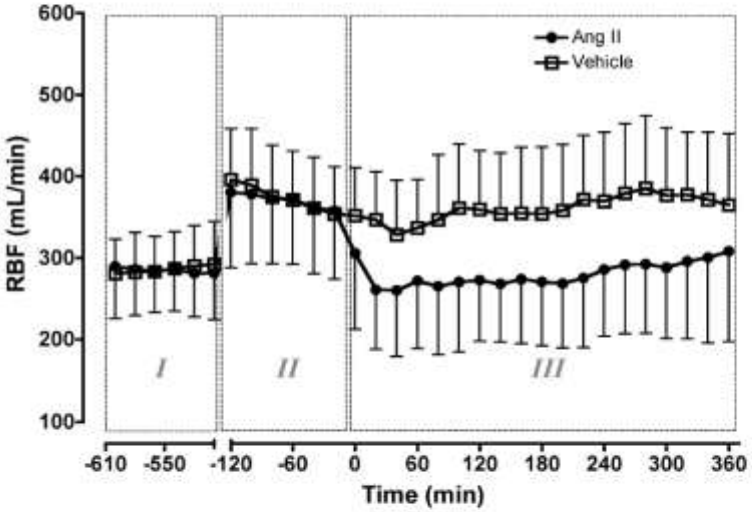
Research

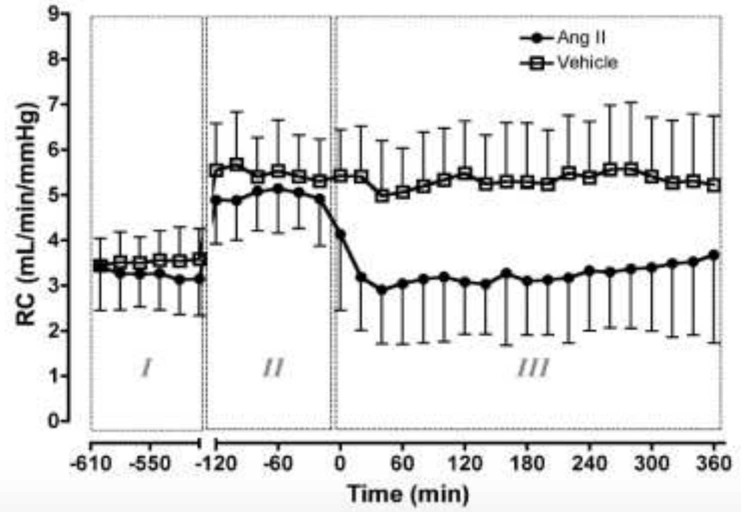
Angiotensin II in experimental hyperdynamic sepsis

Li Wan[1,2,3,4], Christoph Langenberg[1], Rinaldo Bellomo[2,3] and Clive N May[1]

Open Access

Angiotensin II





RBF goes down with Angiotensin II

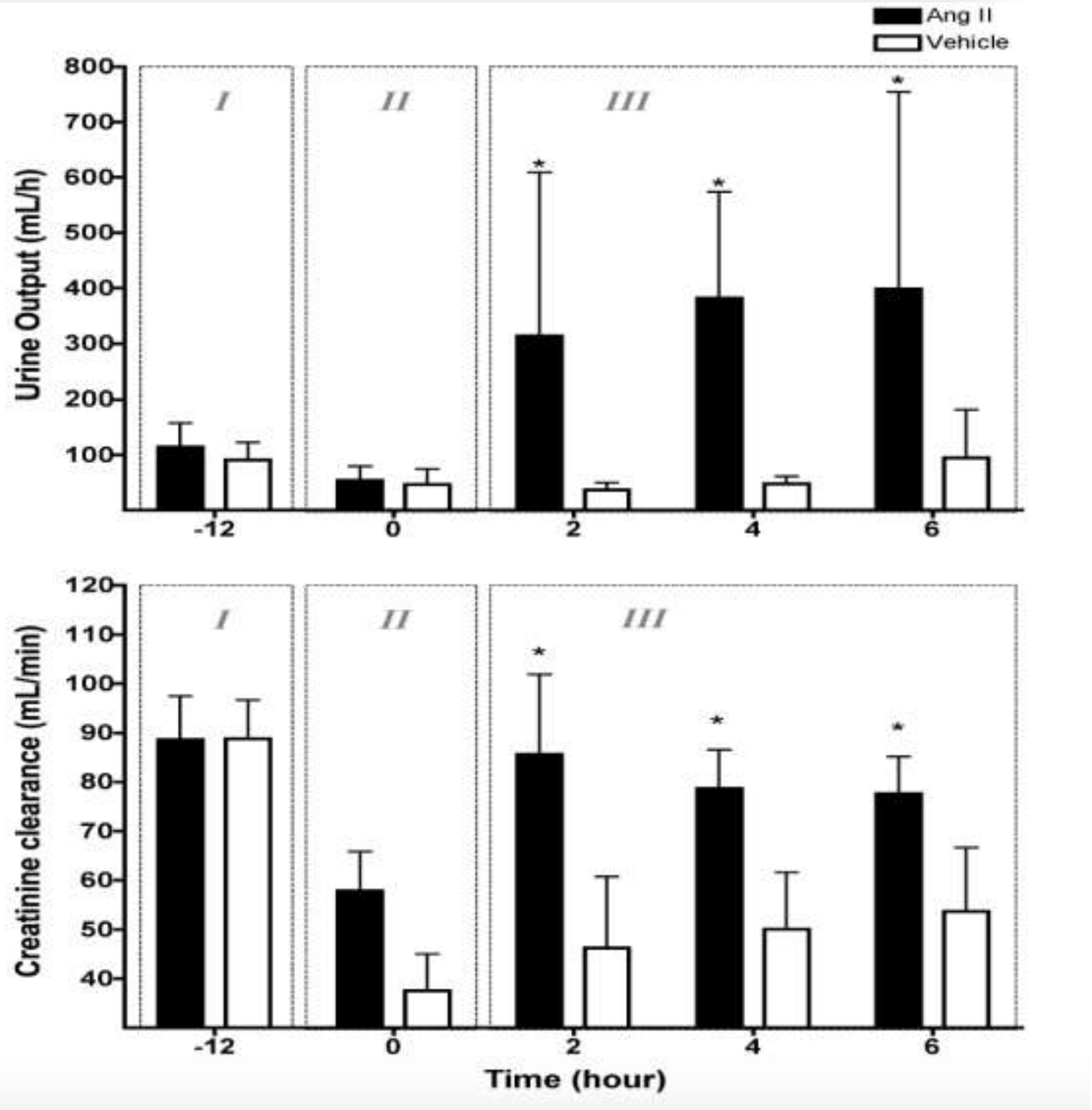
Angiotensin II

Research

Open Access

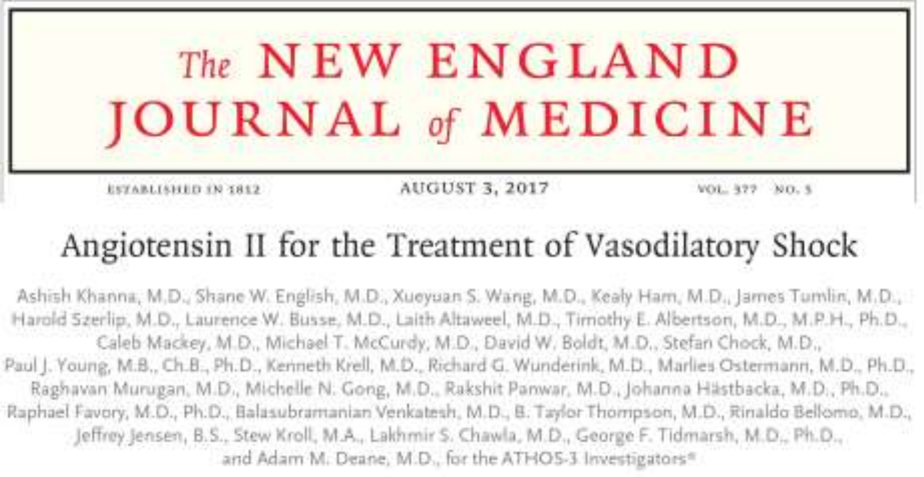
Angiotensin II in experimental hyperdynamic sepsis

Li Wan[1,2,3,4], Christoph Langenberg[1], Rinaldo Bellomo[2,3] and Clive N May[1]



Angiotensin II

ATHOS 3 Trial


The NEW ENGLAND JOURNAL of MEDICINE

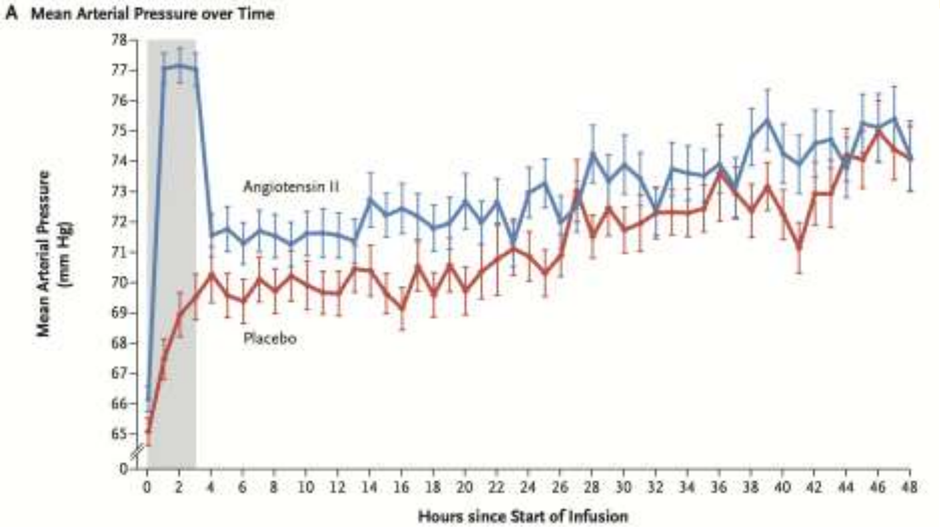
ESTABLISHED IN 1812 AUGUST 3, 2017 VOL. 377 NO. 5

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*

- Vasodilatory shock with ≥ 0.2µg/kg/min norepinephrine-equivalent
- Randomization: **Ang II (20 to 200 ng/kg/min**) vs placebo

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



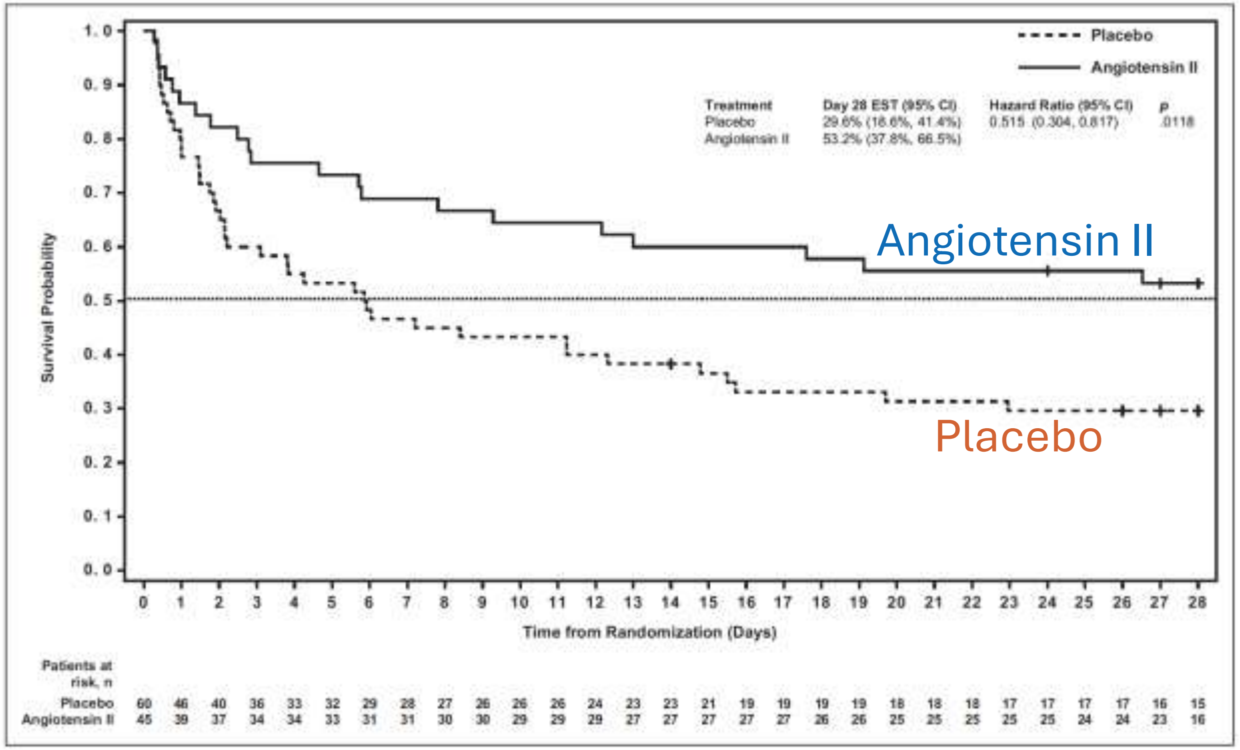
Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II

CCM, March 2018

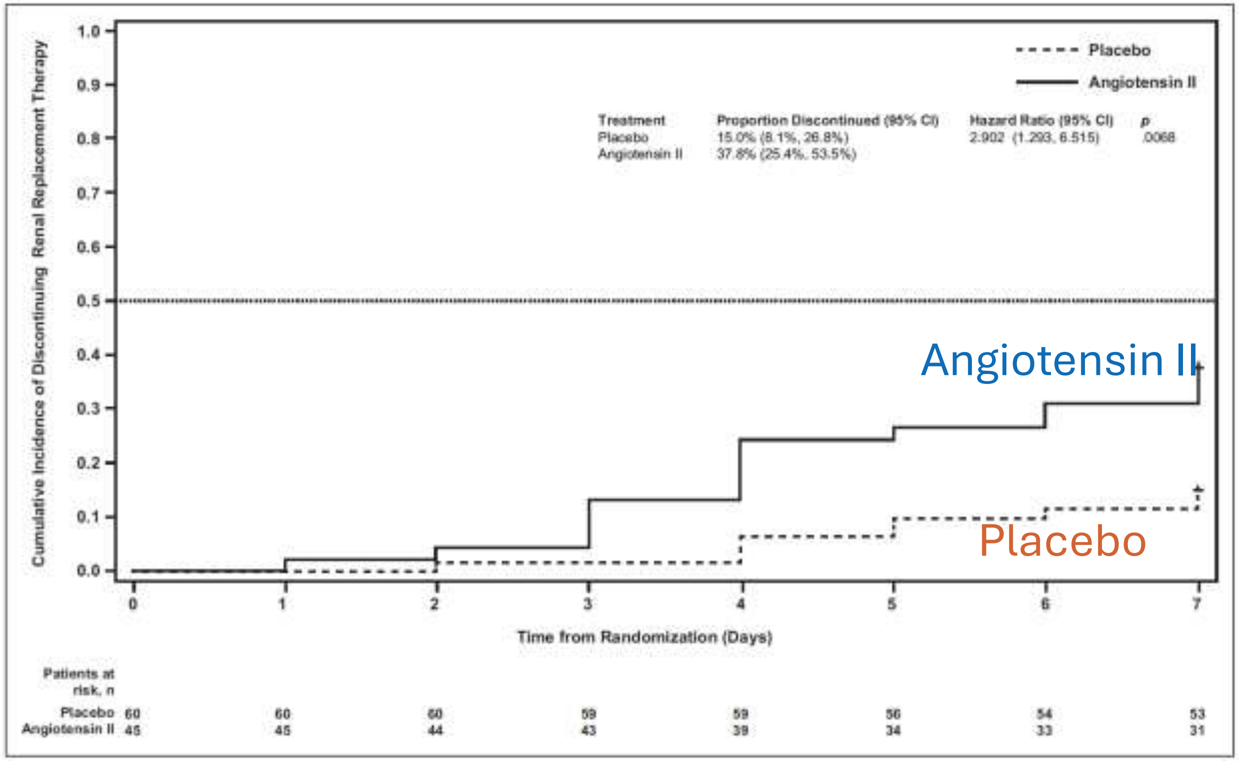
Angiotensin II

PATIENTS RECEIVING RRT AT RANDOMIZATION

Survival



Liberation from RRT



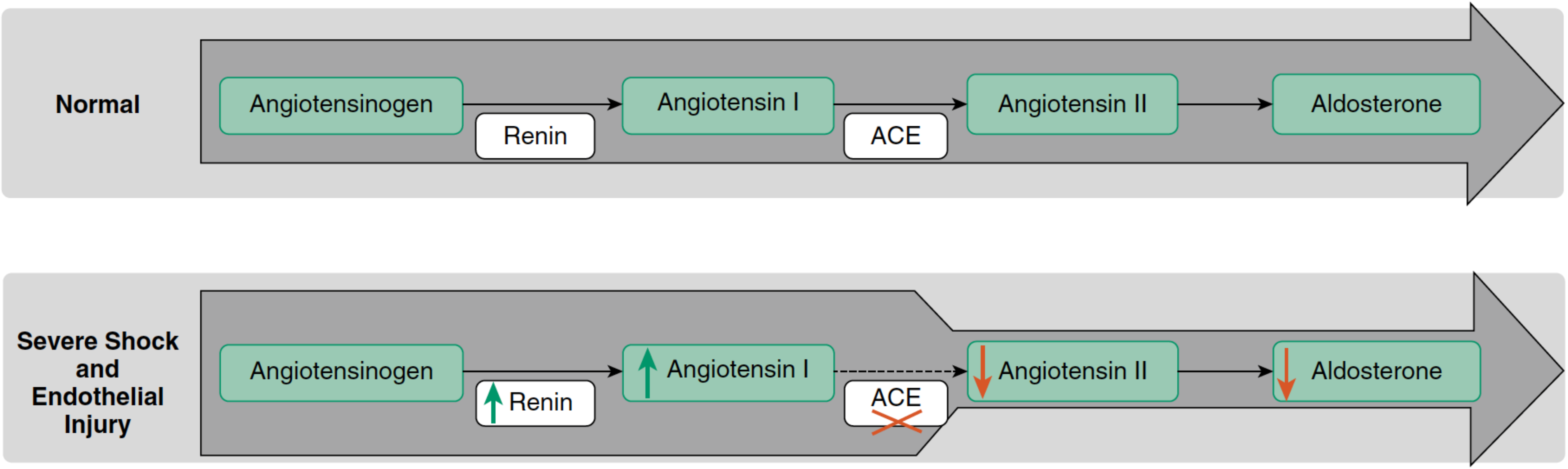
Angiotensin II

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



ORIGINAL ARTICLE

AJRCCM

Angiotensin II

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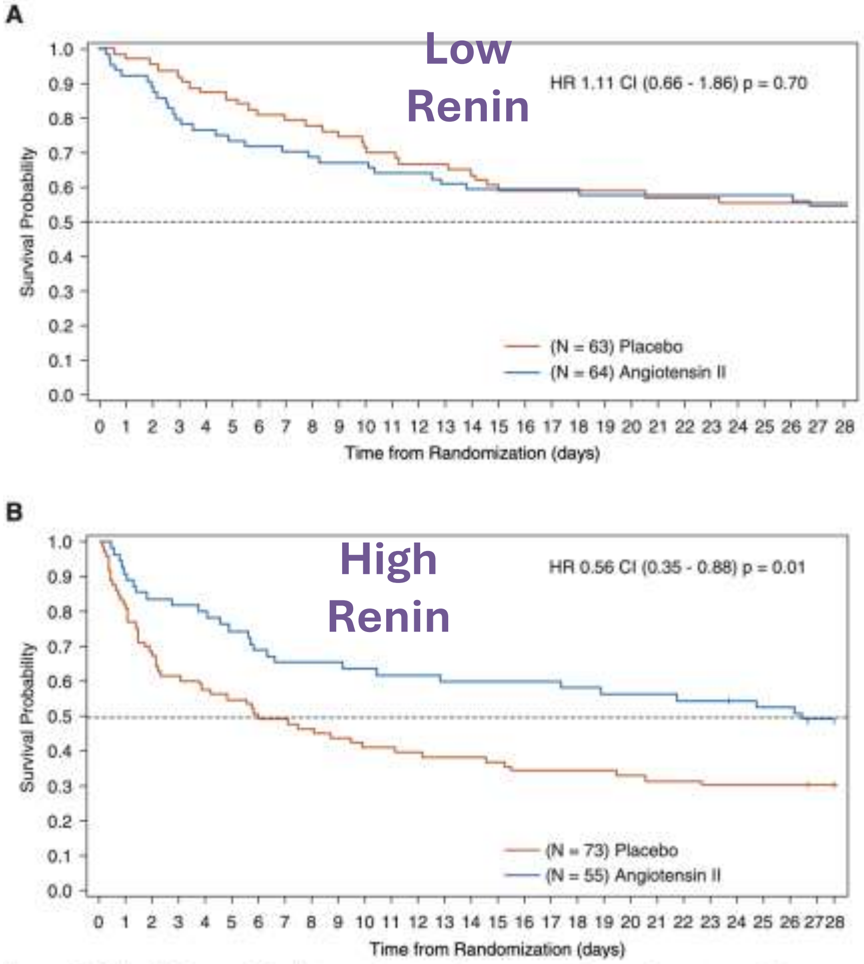
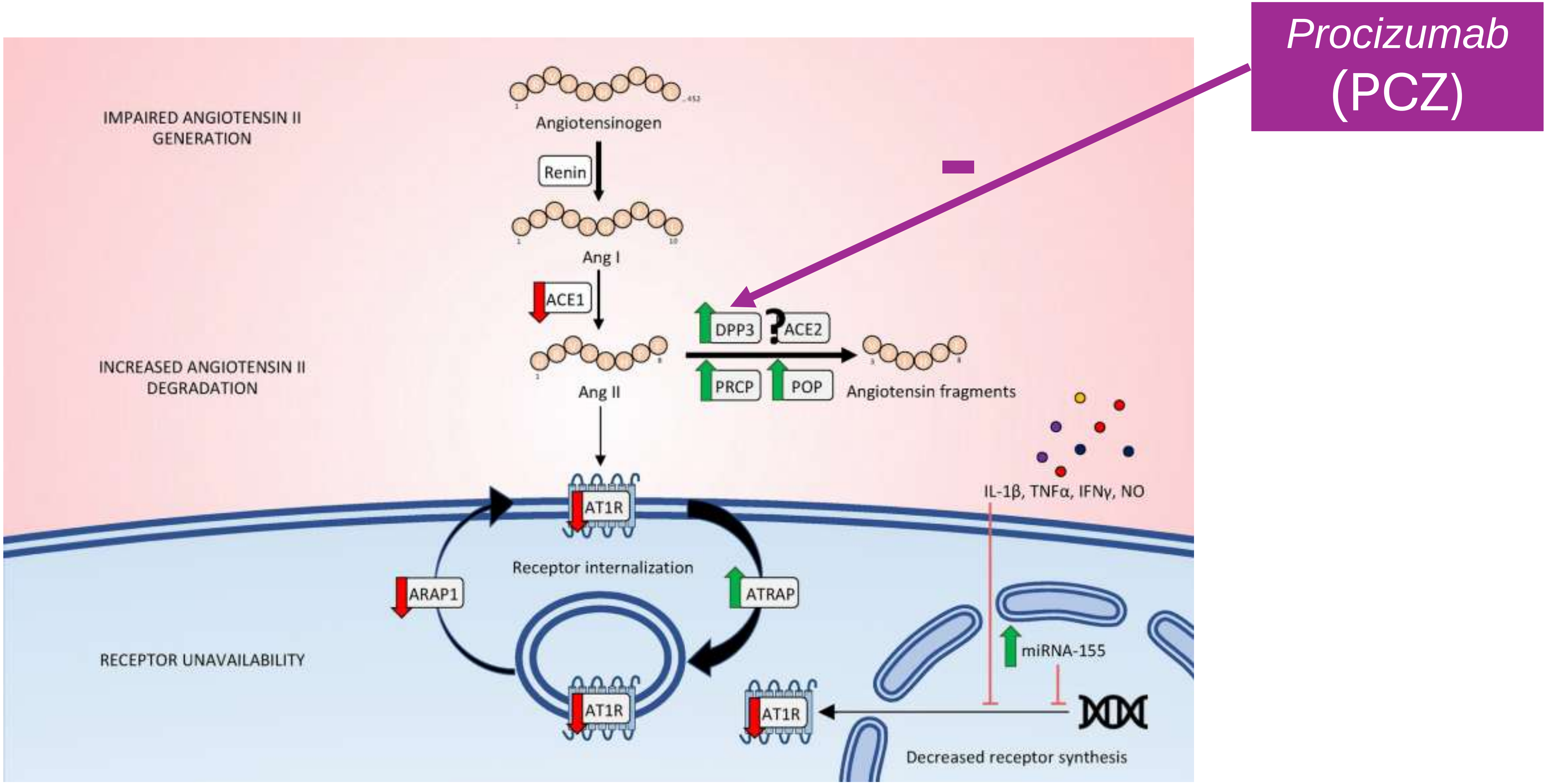


In patients with **renin concentrations above the study population median**, angiotensin II significantly **reduced 28-day mortality** to 28 of 55 (**50.9%)** patients compared with 51 of 73 patients (**69.9%)** treated with placebo (unstratified HR, 0.56; 95% CI, 0.35 to 0.88; p= 0.012)

Angiotensin II

There are **arguments to suggest that angiotensin II improves renal outcomes** but there is **still no RCT** that demonstrates a positive effect

It is urgent to conduct such a trial

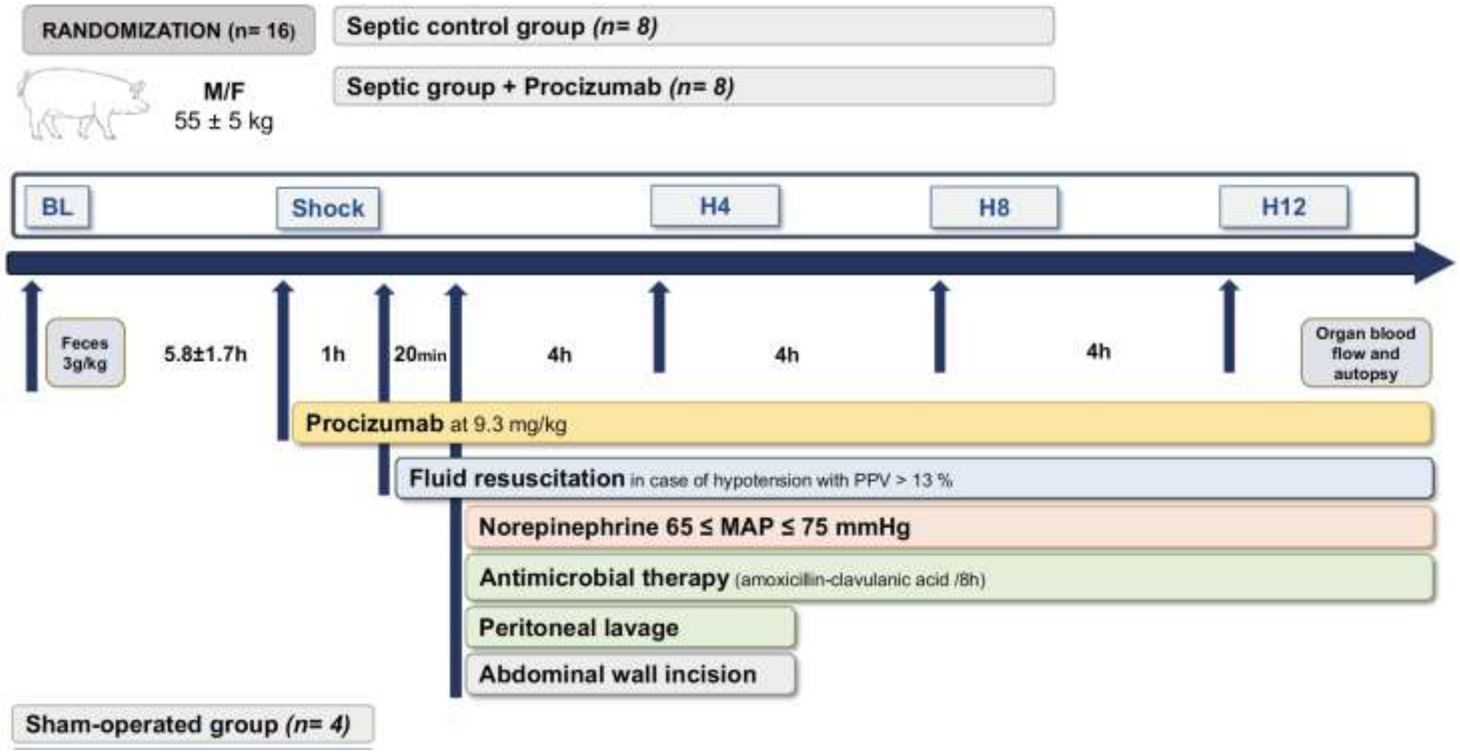

Procizumab
(PCZ)
-
IMPAIRED ANGIOTENSIN II GENERATION
Angiotensinogen
Renin
Ang I
ACE1
INCREASED ANGIOTENSIN II DEGRADATION
Ang II
DPP3
?
ACE2
PRCP
POP
Angiotensin fragments
IL-1β, TNFα, IFNγ, NO
AT1R
Receptor internalization
ARAP1
ATRAP
miRNA-155
RECEPTOR UNAVAILABILITY
AT1R
AT1R
Decreased receptor synthesis

RESEARCH ARTICLES Open Access

Inhibition of circulating dipeptidyl-peptidase 3 by procizumab in experimental septic shock reduces catecholamine exposure and myocardial injury

Bruno Garcia[1,2*], Benoit ter Schiphorst[1,2], Karine Santos[3], Fuhong Su[1], Laurence Dewachter[4], Francisco Vasques-Nóvoa[5], Estela Rocha-Oliveira[5], Roberto Roncon-Albuquerque Jr.[5], Theo Uba[3], Oliver Hartmann[3], Adrien Picod[6], Feriel Azibani[6], Jacques Callebert[6,7], Serge Goldman[8], Filippo Annoni[1,9], Raphaël Favory[2], Jean-Louis Vincent[1,9], Jacques Creteur[1,9], Fabio Silvio Taccone[1,9], Alexandre Mebazaa[6,10] and Antoine Herpain[1,11]

Procizumab (PCZ)



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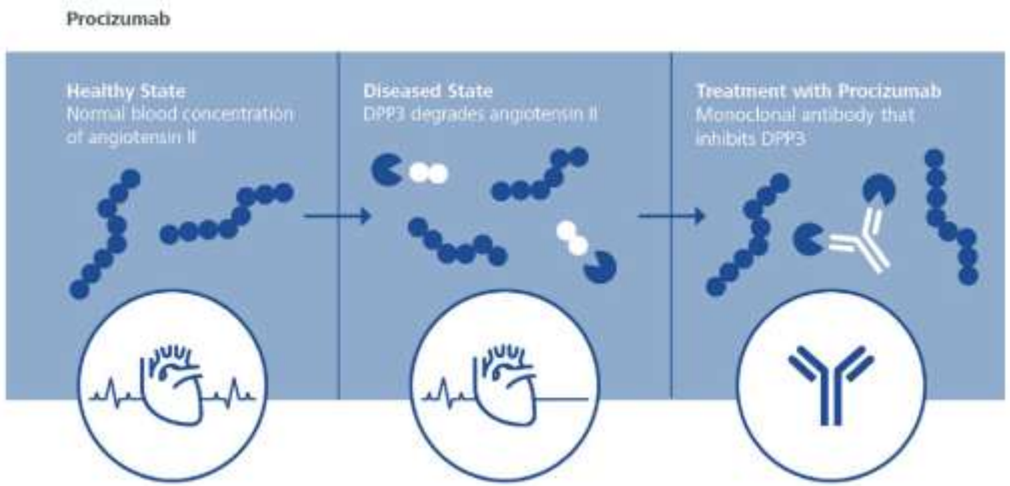


DPP3 Inhibition by Procizumab

▼
- Norepinephrine requirement
- Fluids
- Myocardial and vascular interleukin-6 expression

▲
- PaO_2 / FiO_2 ratio
- Angiotensin II (normalized angiotensin I / angiotensin II ratio)

✕
- Myocardial injury

Conclusion: Which vasopressor to improve renal outcomes?

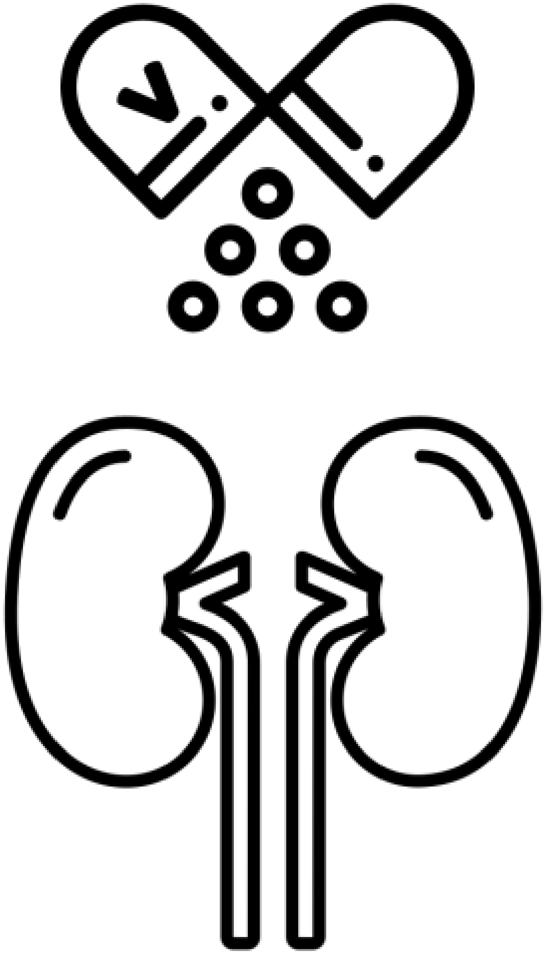
- At the early phase of vasodilatory shock-associated AKI, renal blood flow is increased due to a **preferential efferent arteriole vasodilation.**
- **Vasopressin** is associated with a (moderate) reduction of the need for RRT (in secondary analyses)
- **Angiotensin II** might be associated with improved outcomes in patients with severe AKI (in secondary analyses)

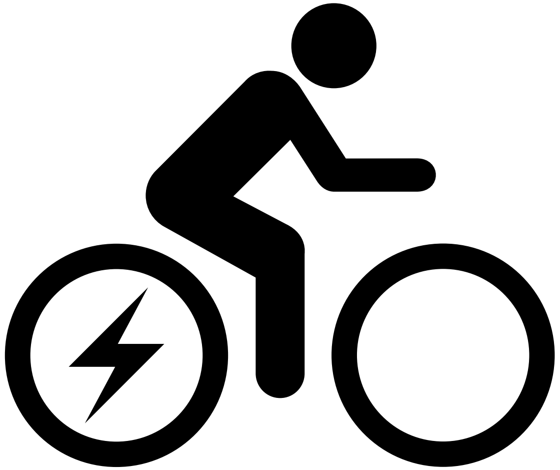
➢ **We still lack a precise strategy of vasopressor use in vasodilatory shock**
  - Timing of each vasopressor
  - Potential combinations: **Vasopressin** + **angiotensin II?**

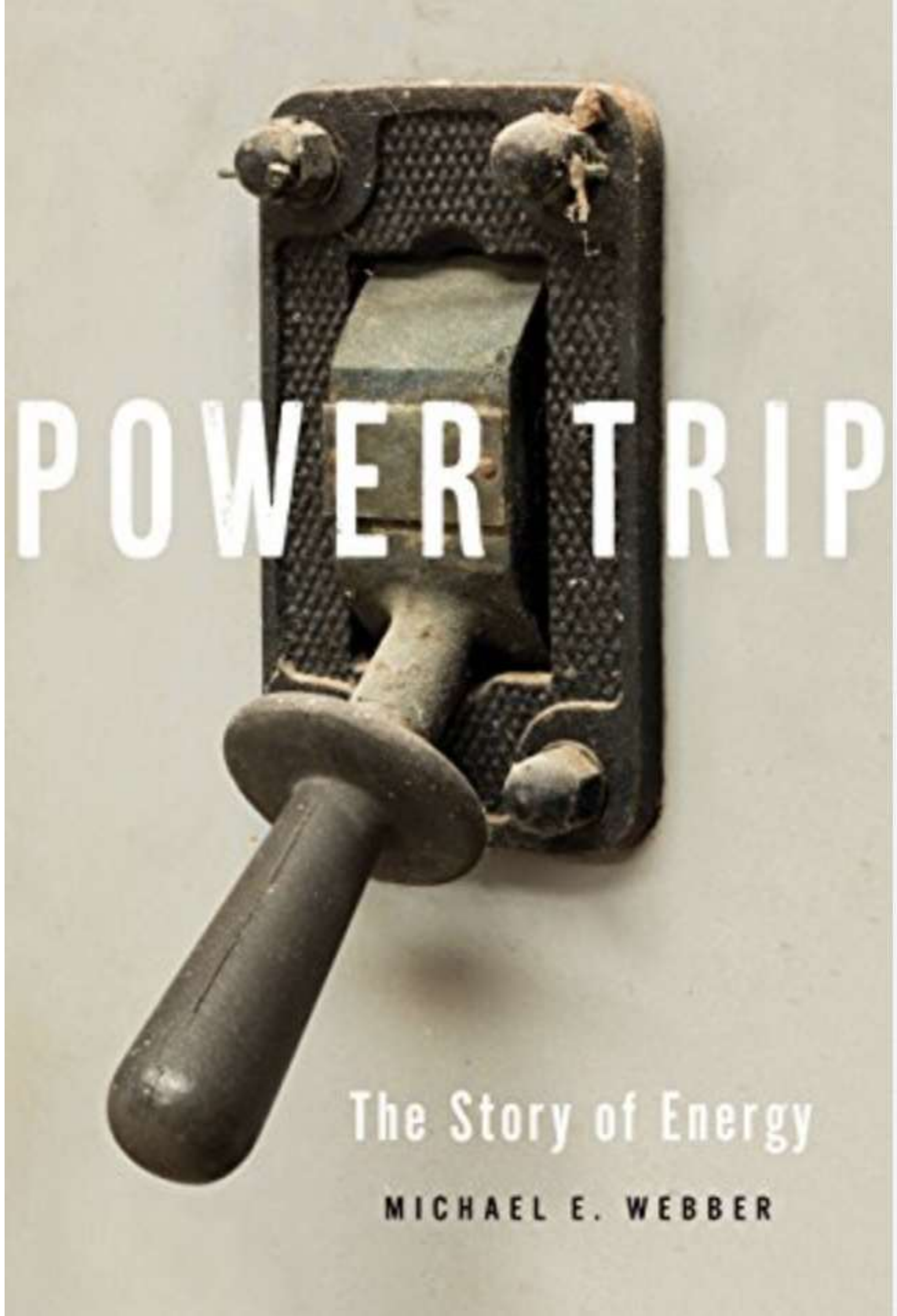
Long term (renal) outcomes?


Vitamin B3 for renal protection ?

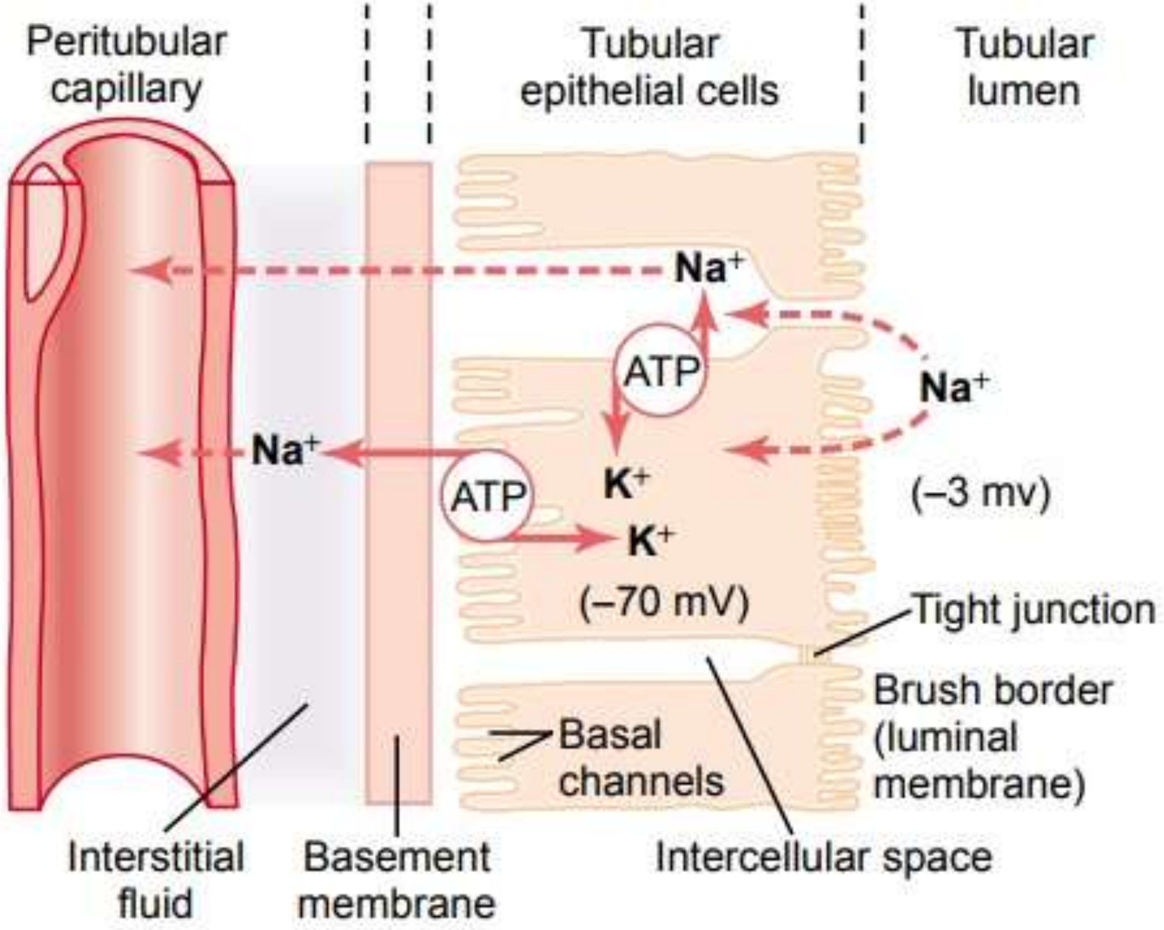
Vitamin B3 for renal protection?







The renal tubule returns **~140 l per day of filtered plasma water back to the circulation** by establishing **energy-intensive electrochemical gradients** between the filtrate and vasculature.



- The renal tubule is highly metabolically active and requires a constant supply of ATP to provide the energy required to pump solutes across unfavourable gradients.

The **kidney** is second to the heart in **mitochondrial abundance**

LETTER

doi:10.1038/nature17184

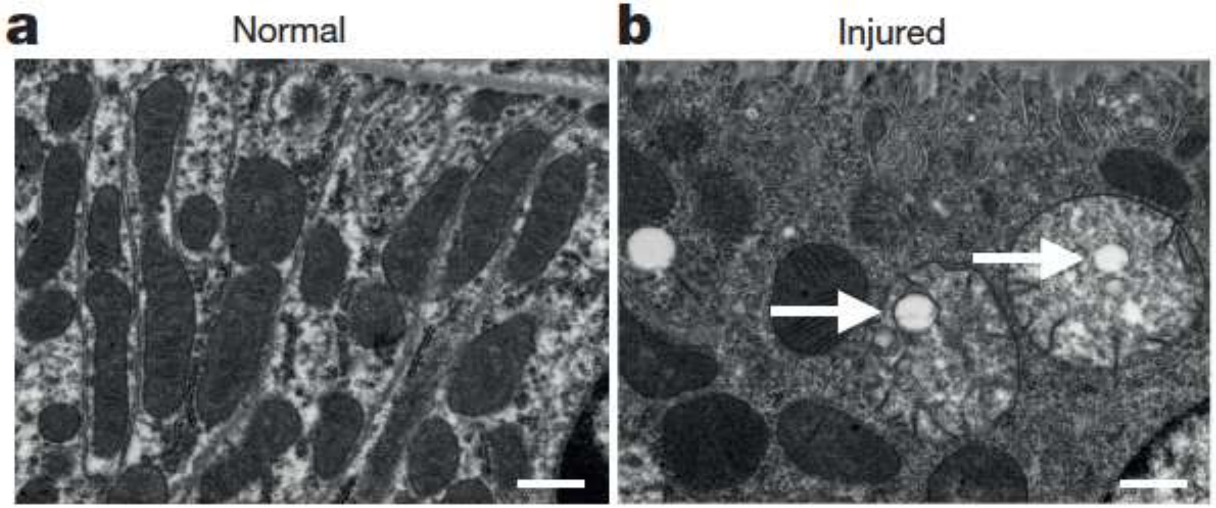
FAT accumulation

PGC1α drives NAD biosynthesis linking oxidative metabolism to renal protection

Mei T. Tran[1,2], Zsuzsanna K. Zsengeller[1,2,3], Anders H. Berg[3,4], Eliyahu V. Khankin[1,2], Manoj K. Bhasin[2,5], Wondong Kim[6], Clary B. Clish[7], Isaac E. Stillman[4], S. Ananth Karumanchi[1,2,8], Eugene P. Rhee[6,7] & Samir M. Parikh[1,2]

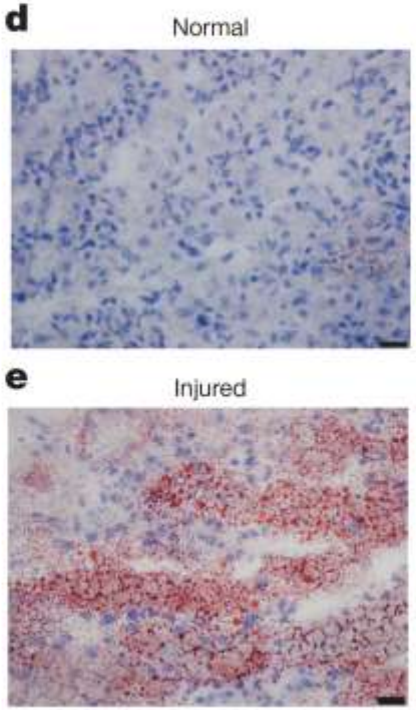
Following **transient local ischaemia:**

- Renal function worsened
- Tubular mitochondria swelled
- Pronounced accumulation of acylglycerols developed in tubules



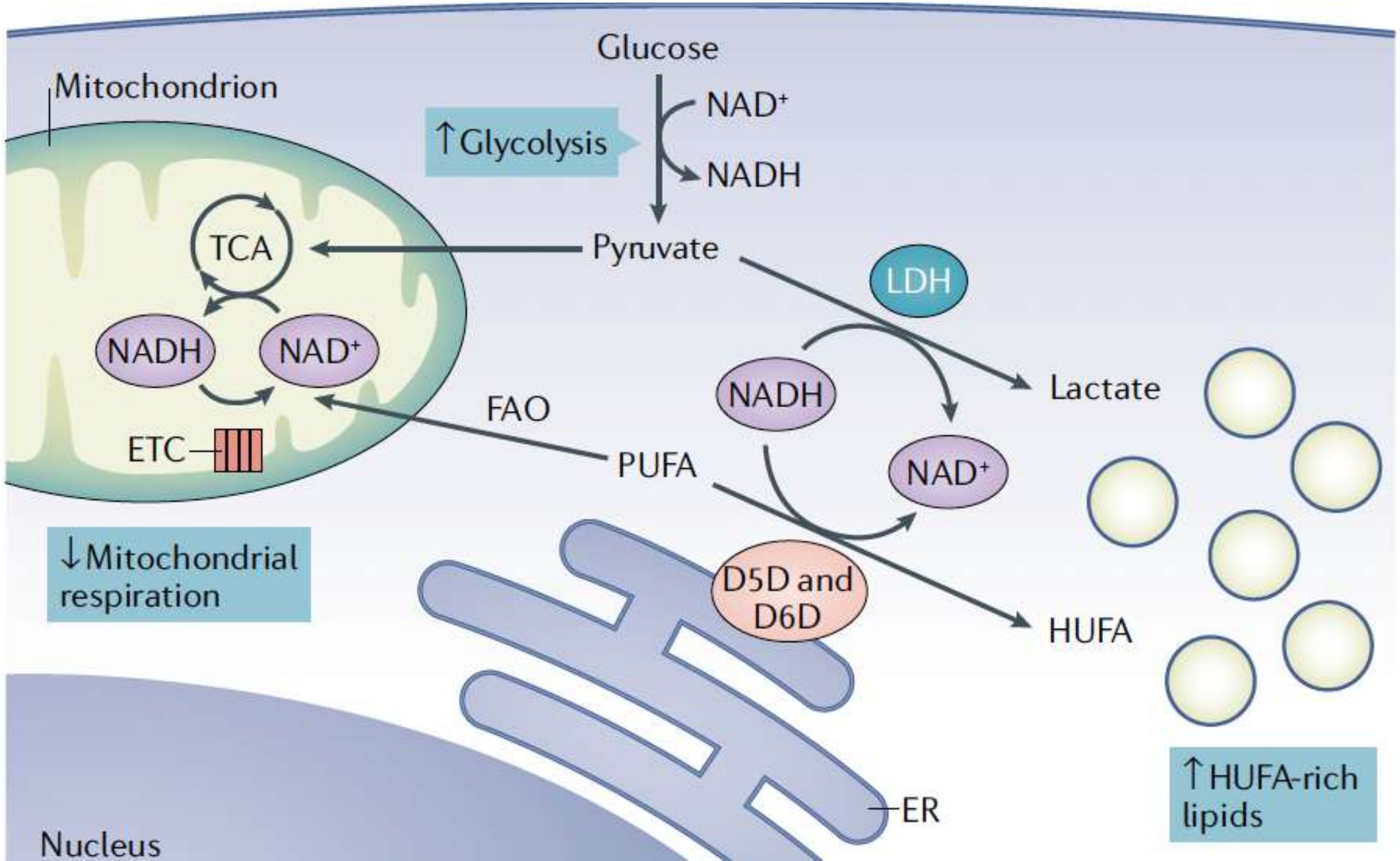
Pre-ischaemic normal morphology

swollen mitochondria

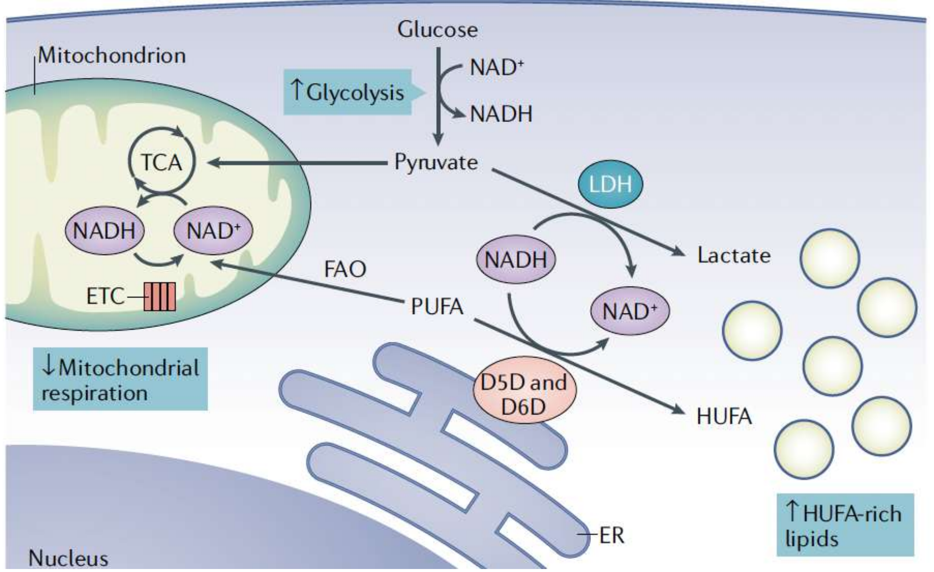


fat accumulation

Nicotine Adenine Dinucleotide (NAD+) has critical roles in the **generation of ATP** from fuel substrates and as a **substrate for important enzymes** that regulate cellular health and stress responses.



AKI and NAD+



AKI leads to decrease in NAD+ levels

combination of <u>reduced NAD+ biosynthesis</u> and <u>increase NAD+ consumption</u>

Vitamine B3
a water-soluble vitamin family

1. Nicotinic acid (Niacin)
2. Nicotinamide (NAM)
3. Nicotinamide riboside (NR)

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1. Nicotinic acid (Niacin)
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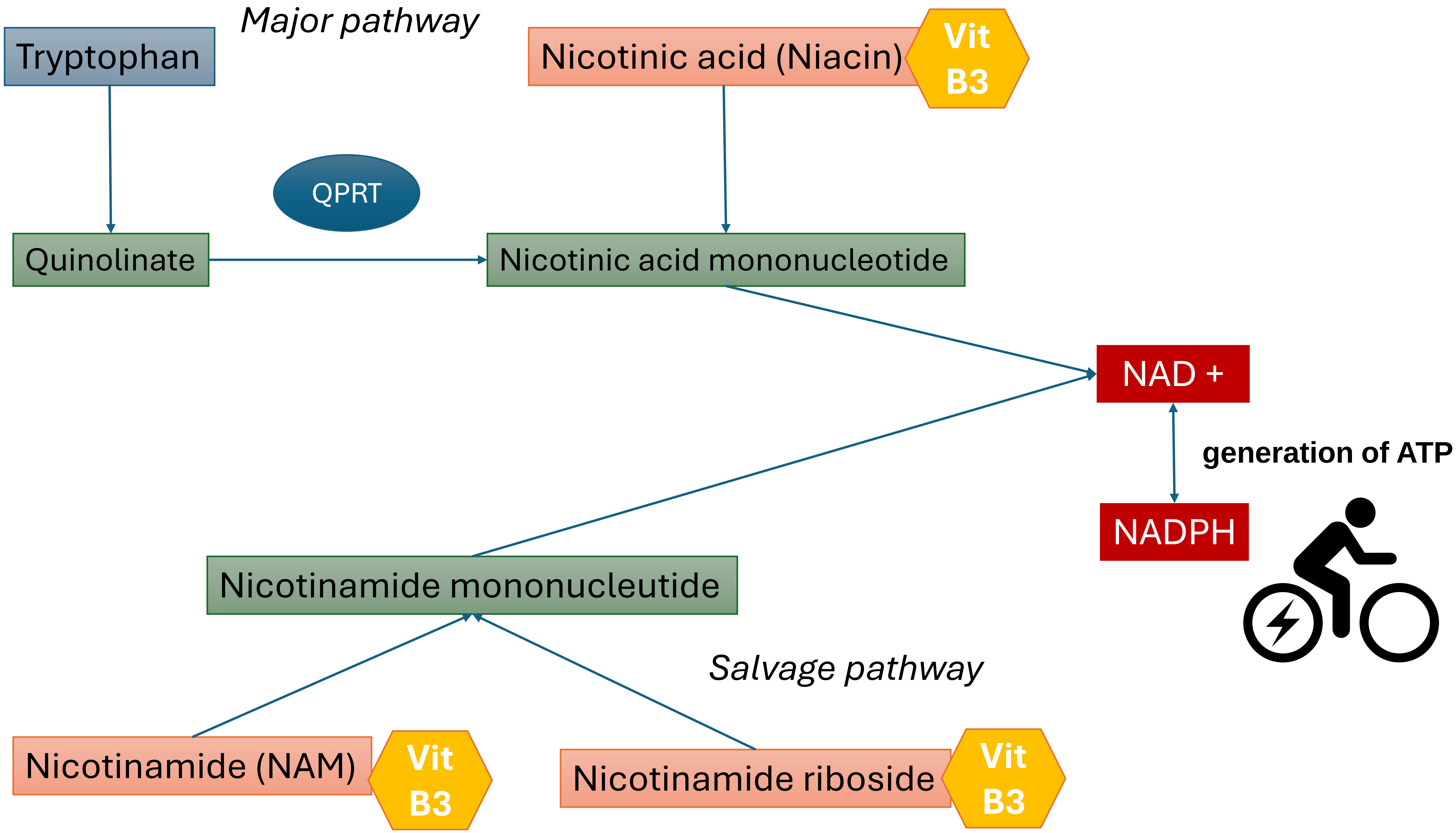
Vit B3

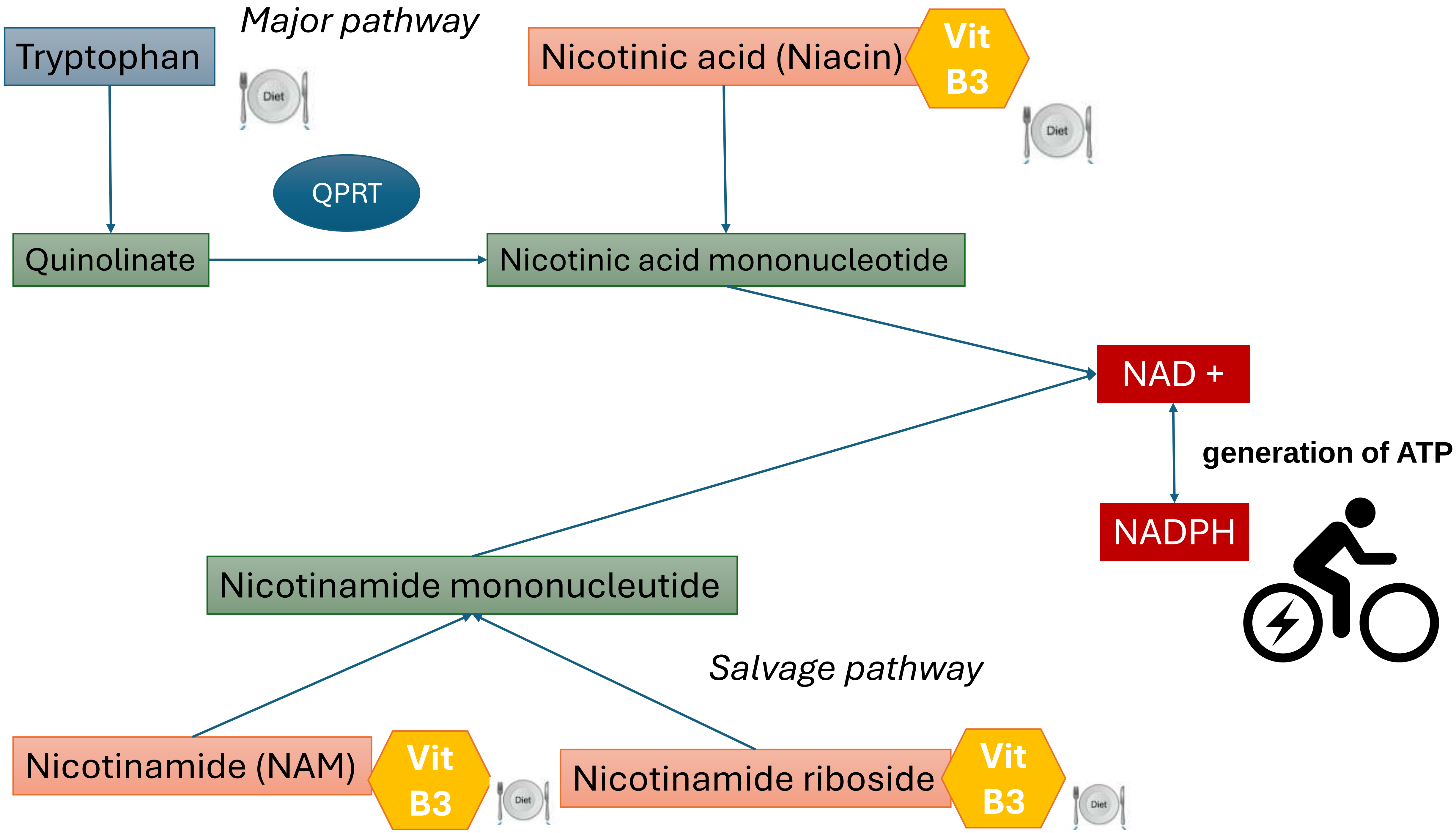
Vit B3

Vit B3

All precursors of **NAD +** and **NADP+**



Major pathway
Tryptophan
Nicotinic acid (Niacin)
Vit B3
QPRT
Quinolinate
Nicotinic acid mononucleotide
NAD +
generation of ATP
NADPH
Nicotinamide mononucleutide
Salvage pathway
Nicotinamide (NAM)
Vit B3
Nicotinamide riboside
Vit B3



Major pathway
Tryptophan
Diet
QPRT
Nicotinic acid (Niacin)
Vit B3
Diet
Quinolinate
Nicotinic acid mononucleotide
NAD +
generation of ATP
NADPH
Nicotinamide mononucleutide
Salvage pathway
Nicotinamide (NAM)
Vit B3
Diet
Nicotinamide riboside
Vit B3
Diet

Joseph Goldberger
1874 -1929

Niacin (Vit B3) deficiency results in pellagra

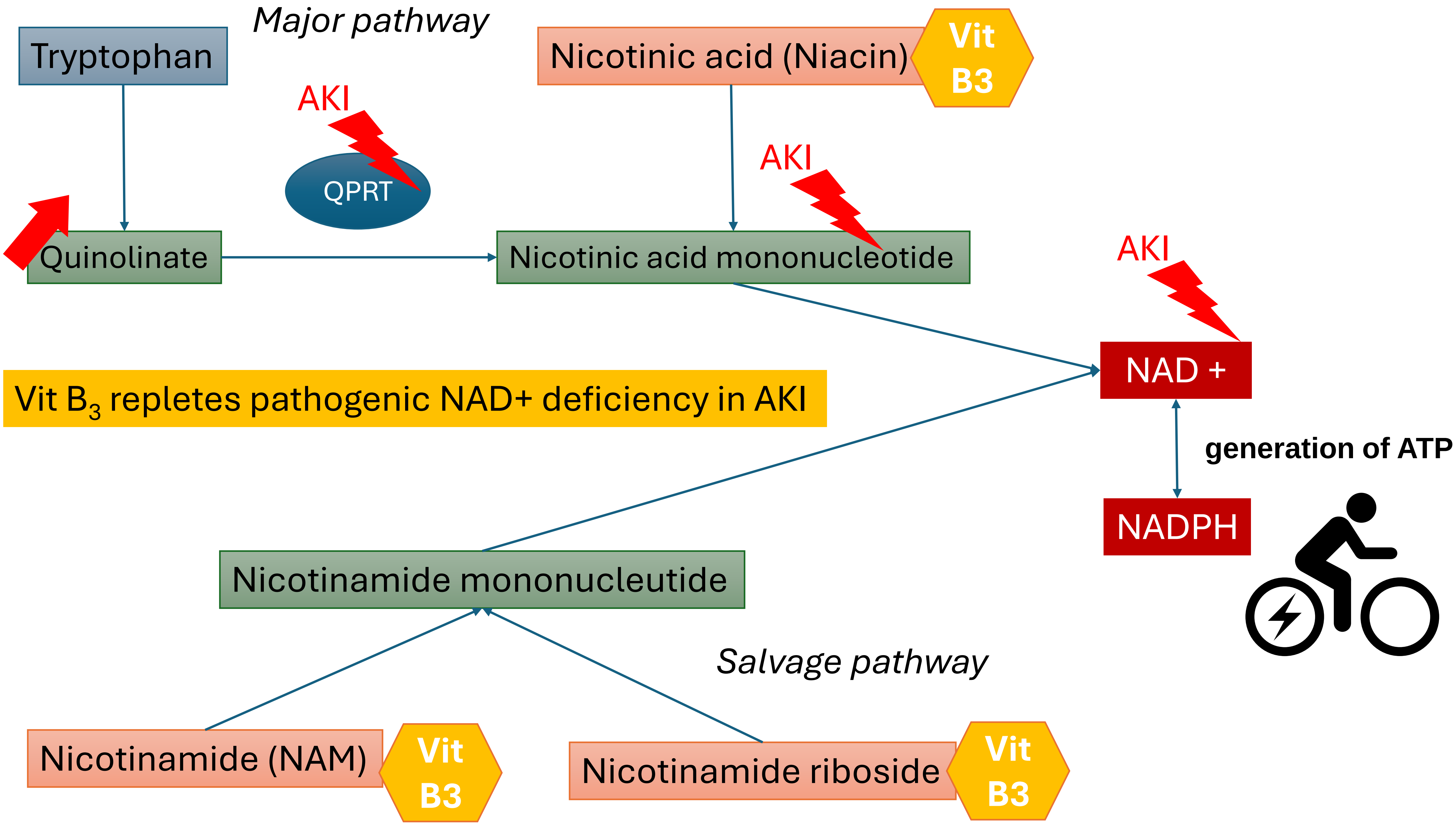
- Photosensitive pigmented dermatitis
- Diarrhea
- Dementia

Small Boy with Pellagra

Woman with Pellagra

Man with Pellagra

Vit B3 = Vit PP for *pellagra preventive*


Major pathway
Tryptophan
AKI
QPRT
Quinolinate
Nicotinic acid (Niacin)
Vit B3
AKI
Nicotinic acid mononucleotide
AKI
NAD +
Vit B_3 repletes pathogenic NAD+ deficiency in AKI
generation of ATP
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Vit B3

LETTER

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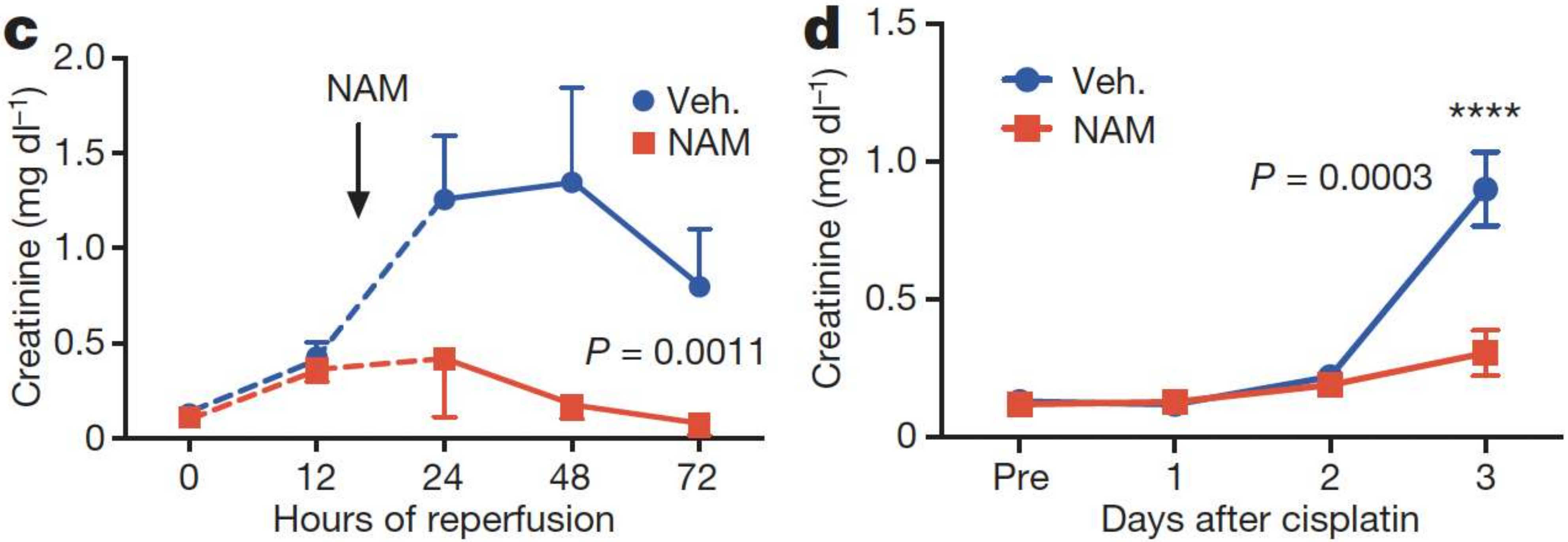
Nature 2016



Exogenous NAM improve renal function (creatinine)
in post-ischemic AKI mice or cisplatine-induced AKI

nature medicine ARTICLES
https://doi.org/10.1038/s41591-018-0138-z

Nature Med 2018

Human data

De novo NAD+ biosynthetic impairment in acute kidney injury in humans

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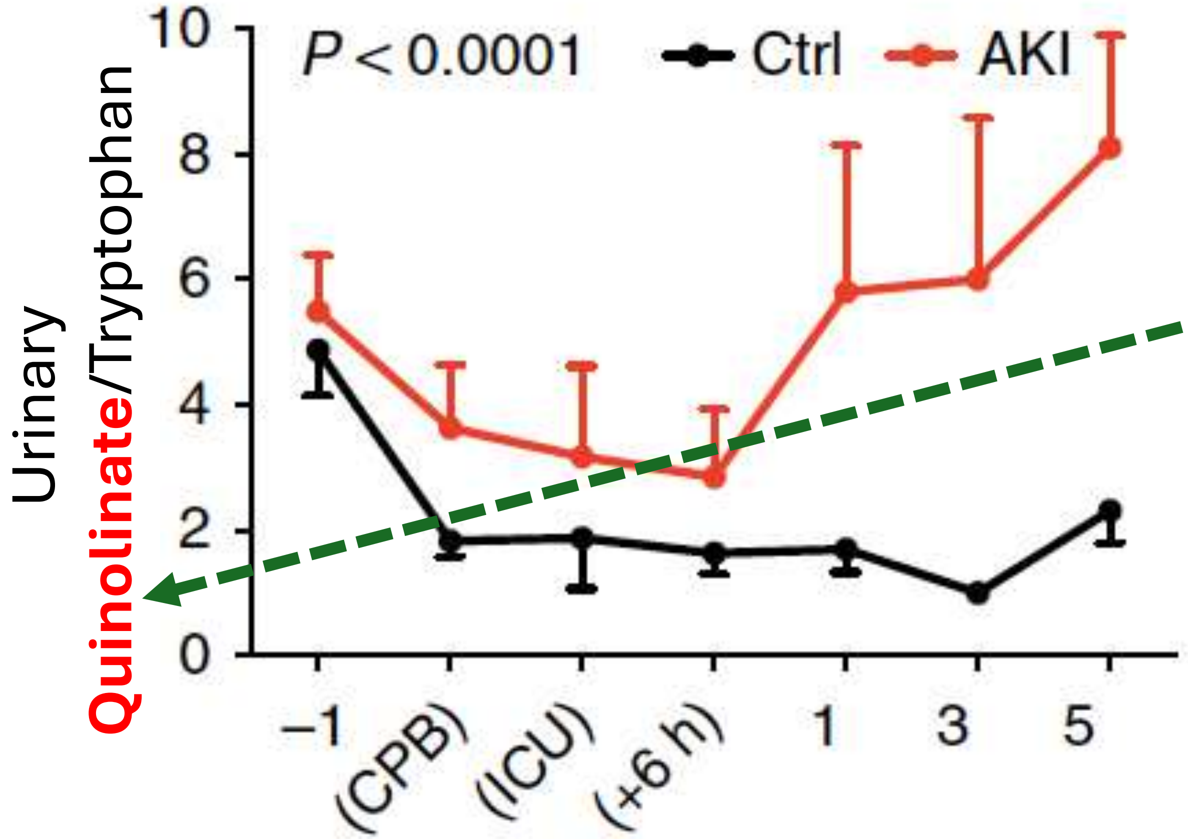
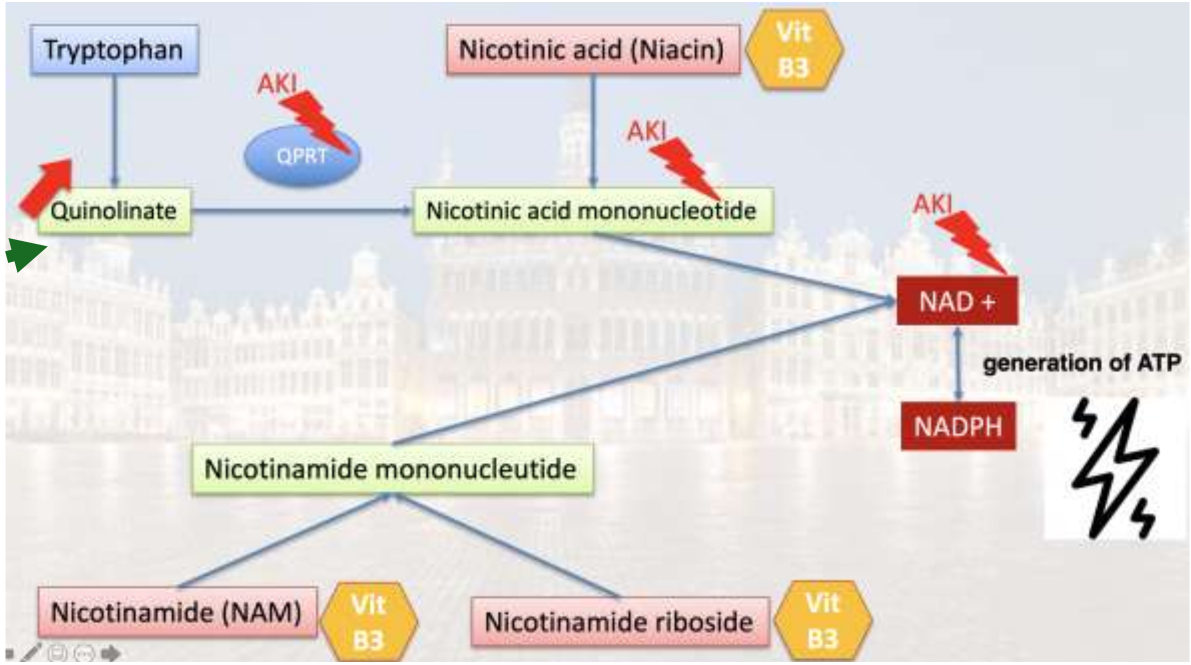
Prospective cohort of patients exposed to renal ischemia by **cardiac pump surgery**





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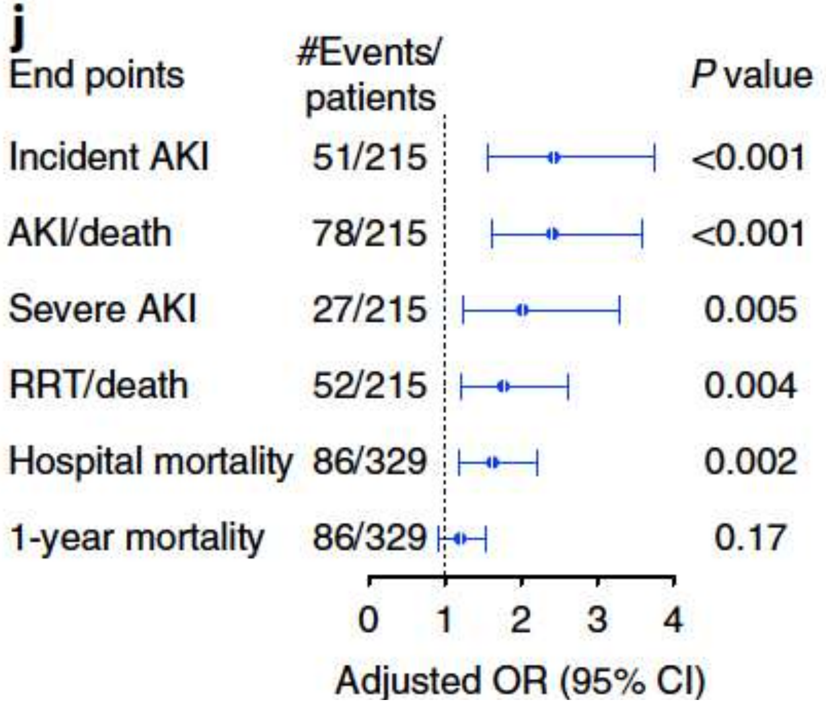
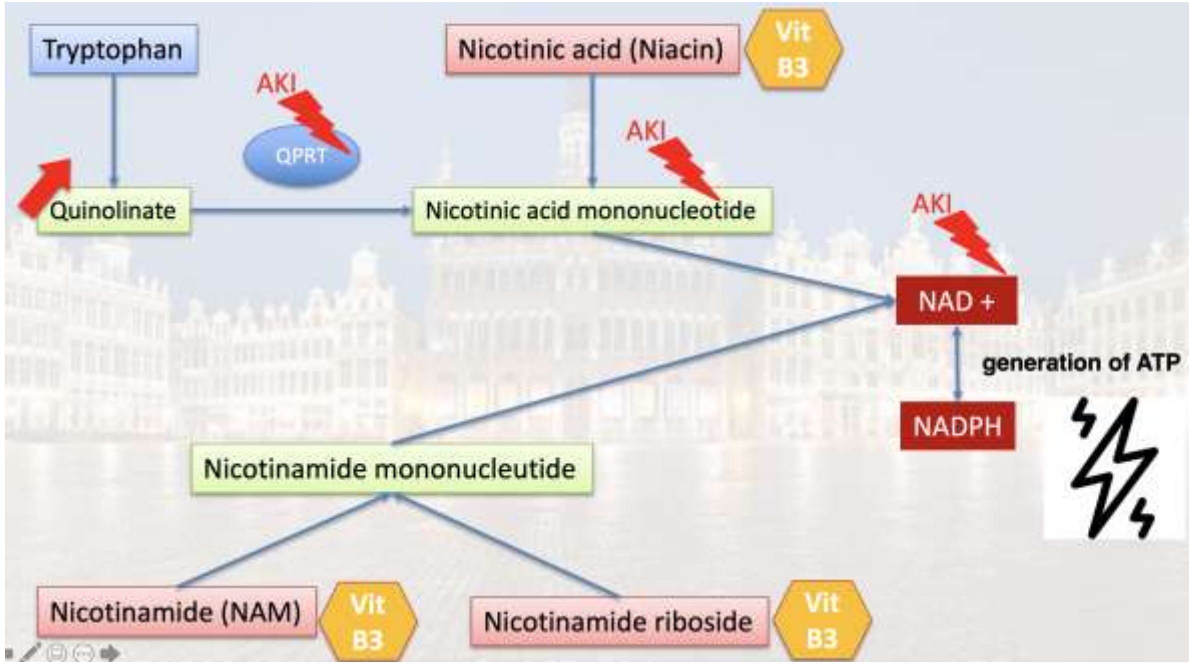


Urinary
Quinolinate/Tryptophan



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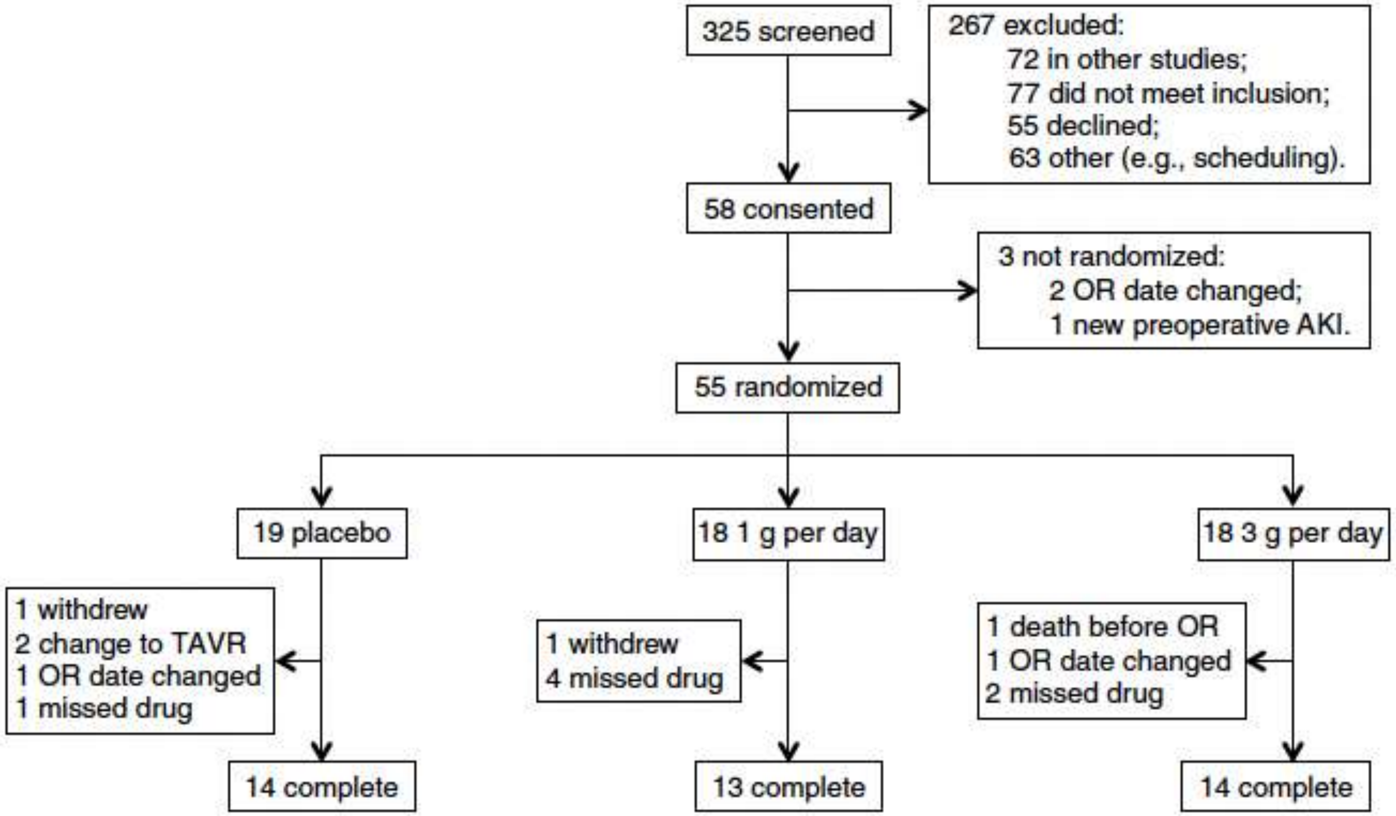
Pilot RCT of oral Vitamin B3 (NAM) administration

- Patients: **Cardiac surgery**
- Groups:
  - placebo
  - NAM 1g/day (d-1, d-0, d+1)
  - NAM 3g/day (d-1, d-0, d+1)



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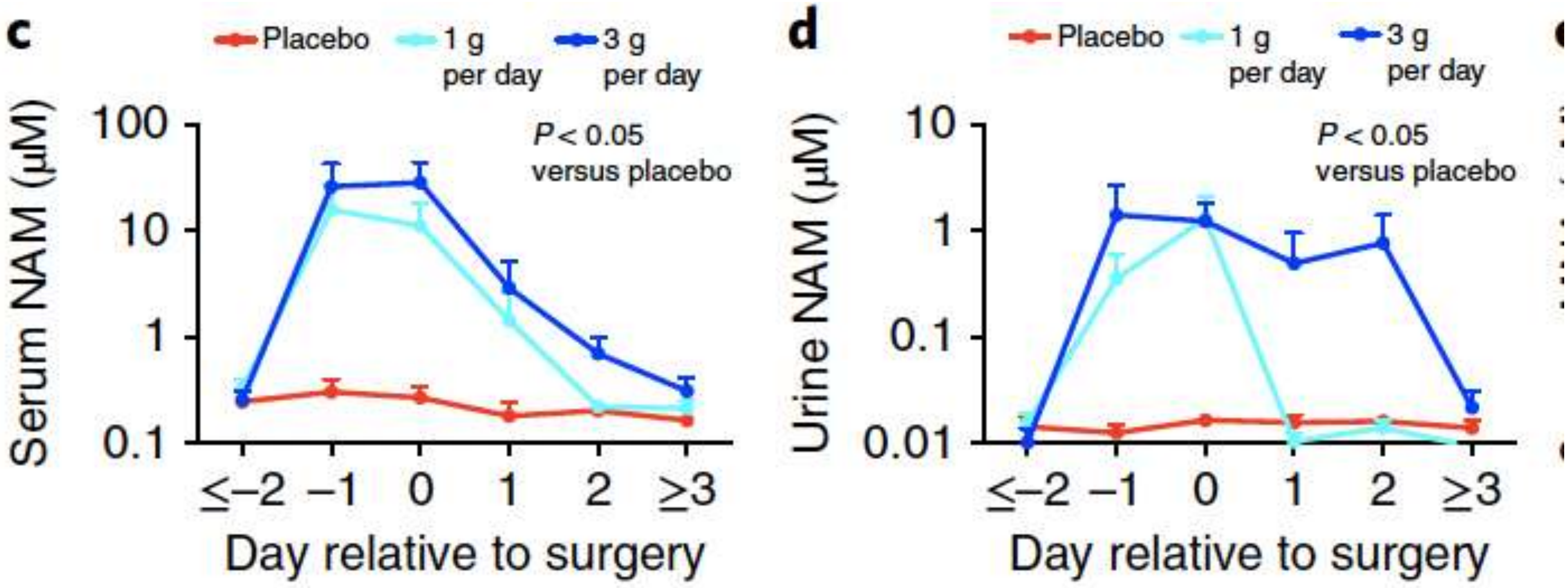
Pilot RCT of oral Vitamin B3 (NAM) administration

NAM administration increased blood and urine NAM



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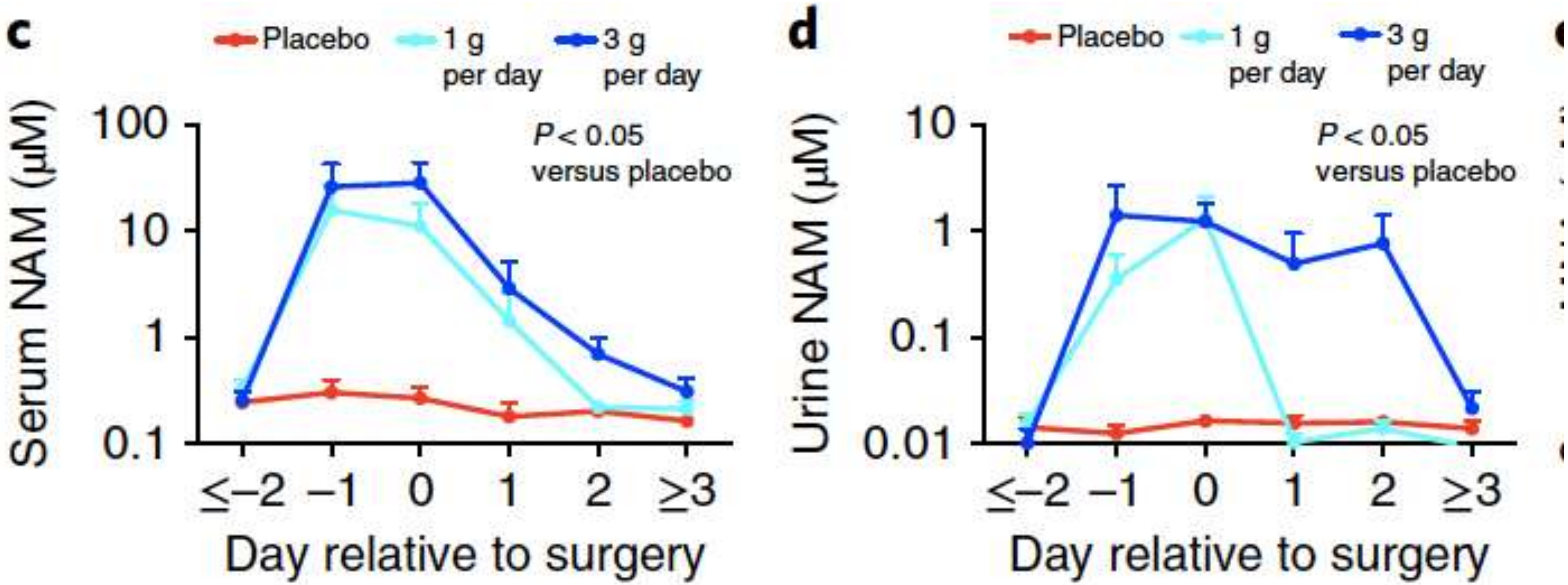

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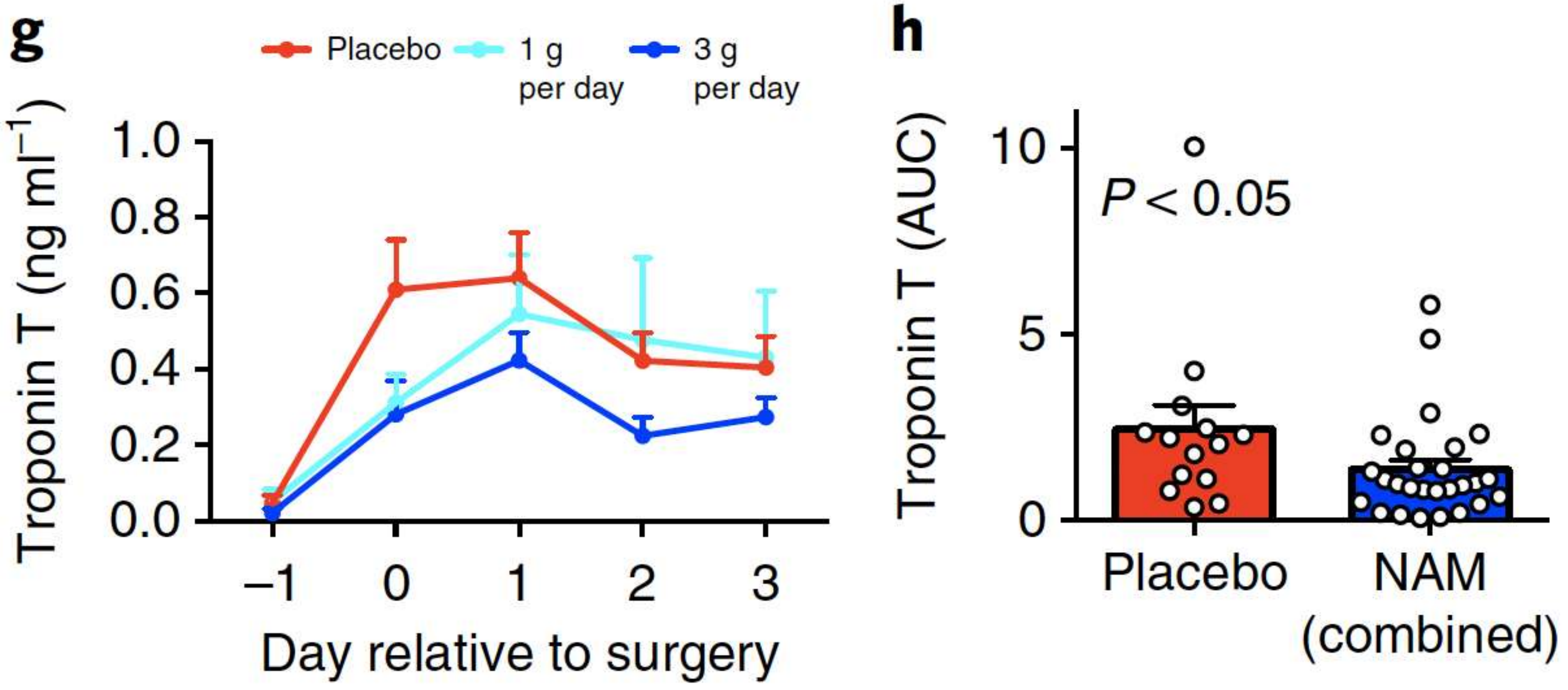
NAM administration associated with **lower level of cardiac injury markers** (Troponin T)



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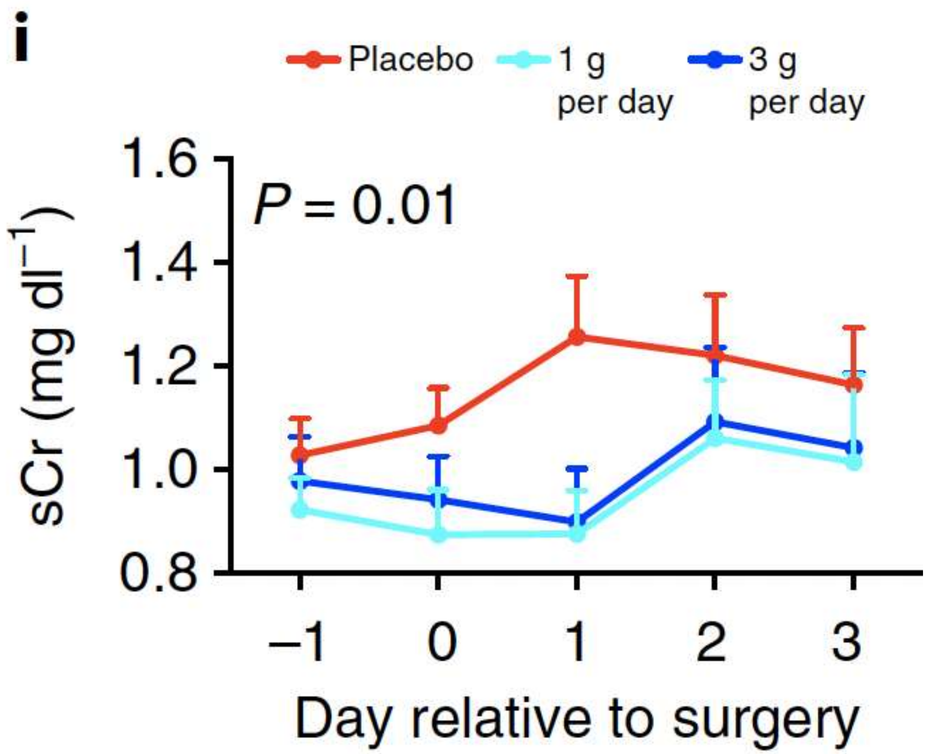
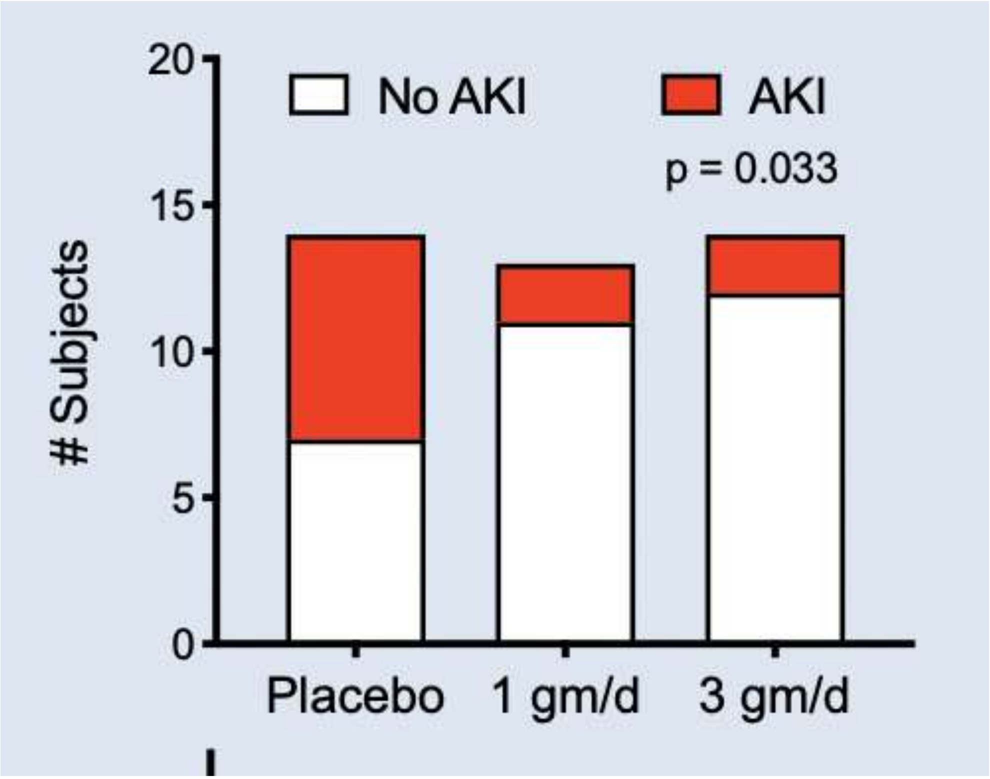
Pilot RCT of oral Vitamin B3 (NAM) administration

NAM administration associated with **better estimated renal function**





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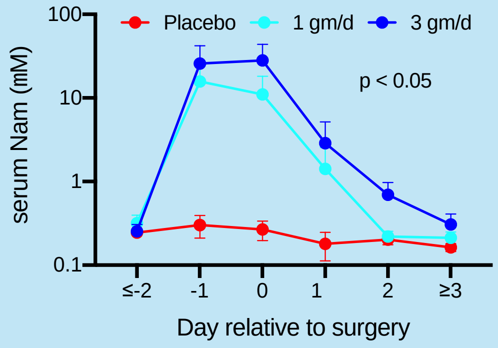
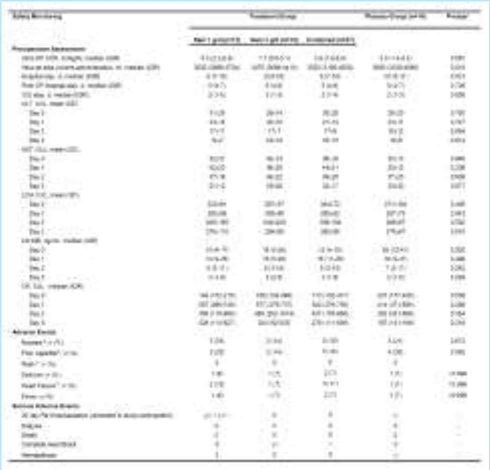
Human data

To summarize this first RCT

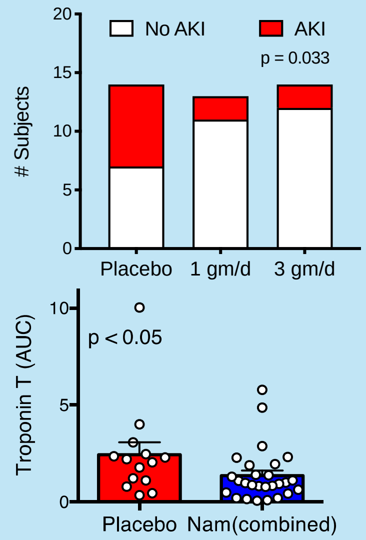
PK/PD

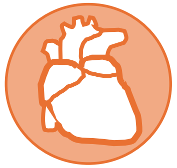


Safety



Efficacy





Poyan Mehr
Nat Med 2018

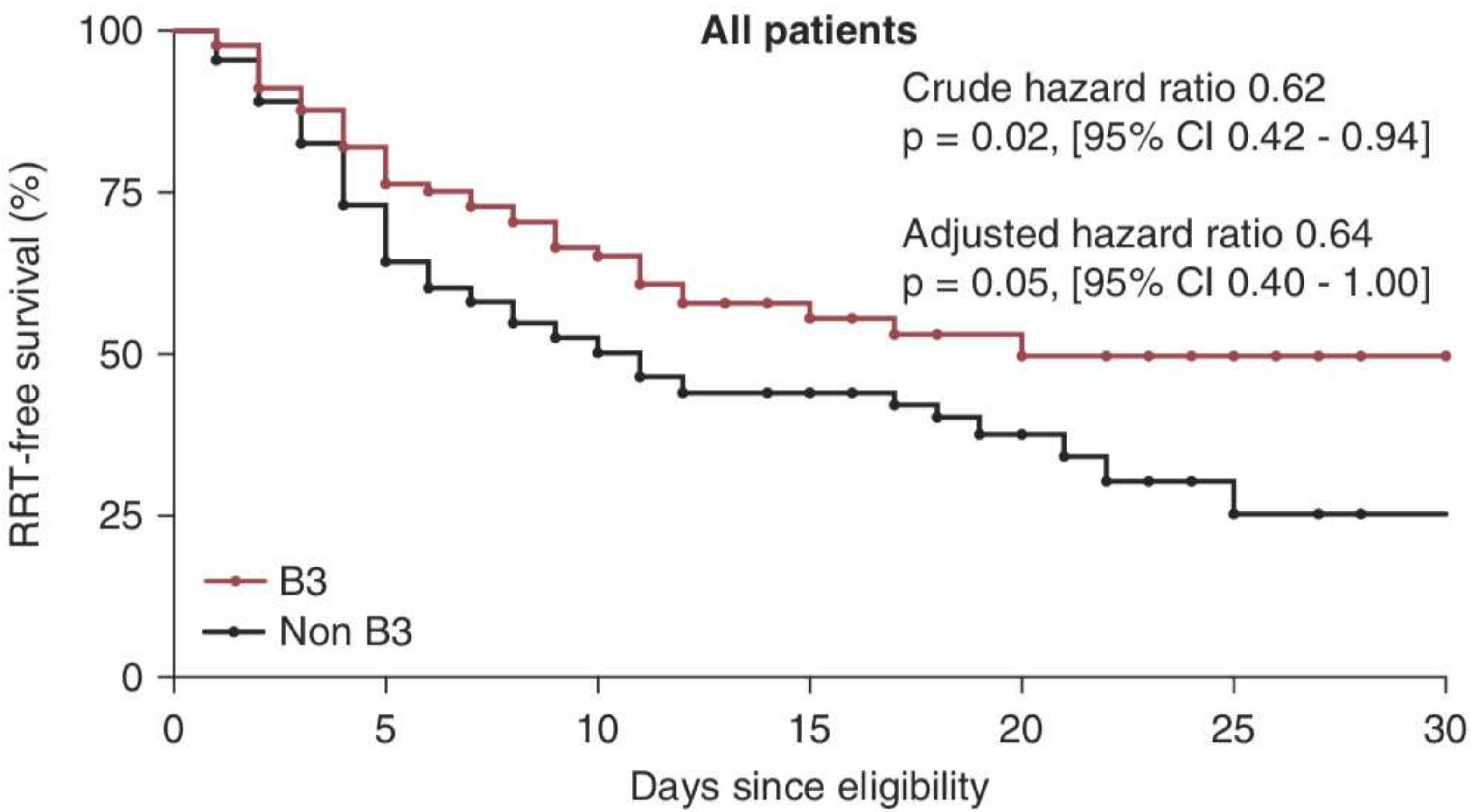
What's new since 2018?

Kidney360

Niacinamide May Be Associated with Improved Outcomes in COVID-19-Related Acute Kidney Injury: An Observational Study

Nathan H. Raines,[1] Sarju Ganatra,[2] Pitchaphon Nissaisorakarn,[1] Amar Pandit,[1] Alex Morales,[1] Aarti Asnani,[1] Mehrnaz Sadrolashrafi,[4] Rahul Maheshwari,[3] Rushin Patel,[2] Vigyan Bang,[2] Katherine Shreyder,[2] Simarjeet Brar,[2] Amitoj Singh,[2] Sourbha S. Dani,[2] Sarah Knapp,[6] Ali Poyan Mehr,[7] Robert S. Brown,[1] Mark L. Zeidel,[1] Rhea Bhargava,[1] Johannes Schlondorff,[1] Theodore I. Steinman,[1] Kenneth J. Mukamal,[5] and Samir M. Parikh[1]

niacinamide was associated with a **lower risk of RRT or death**



Is niacinamide useful in the treatment of COVID-associated AKI?

Kidney360

N=201

SARS-CoV-2 PCR positive patients with AKI (>96 hours) not on dialysis (eGFR>15).

	KRT or death	Total mortality	Change in sCr per day in KDIGO 2/3
Controls N=111 (91 from sister hospital without B3 protocol; 20 pre-B3 protocol)	55.9%	44.1%	0.2 mg/dl/d SE 0.08
HR All	0.64 [0.40-1.00]	0.59 [0.33-1.05]	P-value 0.03
HR KDIGO 2/3	0.29 [0.13-0.65]	0.17 [0.05-0.52]	
Niacinamide N=90 (B3, 1 gram daily x 7 days)	42.2%	24.4%	0.0 mg/dl/d SE 0.026

Conclusion: Niacinamide was associated with lower risk of KRT/death and improved creatinine trajectory among patients with severe COVID-19-related AKI.

Nathan H. Raines, Sarju Ganatra, Pitchaphon Nissaisorakarn, ***et al. Niacinamide may be Associated with Improved Outcomes in COVID-19-Related Acute Kidney Injury: An Observational Study*. *Kidney360.*** doi: 10.34067/KID.0006452020.

Visual Abstract by Joel Topf, MD

Niacinamide and Renal Recovery After AKI: A Randomized, Controlled Trial

SA-OR04

Kohli, Harbir S.; Garg, Sahil; Kaur, Jaskiran; Yadav, Ashok K.; Kumar, Vivek

Author Information

Journal of the American Society of Nephrology 34(11S):p 60, November 2023. | *DOI:* 10.1681/ASN.20233411S160b

SA-OR04

Niacinamide and Renal Recovery After AKI: A Randomized, Controlled Trial

Harbir S. Kohli, Sahil Garg, Jaskiran Kaur, Ashok K. Yadav, Vivek Kumar.
Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Background: Incomplete recovery following community acquired acute kidney injury CA-AKI may be seen in 15-20% of patients. Strategies to improve recovery rates and follow-up of such patients are required. The impaired NAD+ biosynthesis pathway has been recently implicated in AKI. Niacinamide, which bypasses the salvage denovo pathway and produces NAD, could be protective. Its role in recovery following AKI has been postulated. In this pilot phase of clinical trial, role of niacinamide supplementation in recovery after CA-AK was investigated.

Methods: The study was an open label, randomized, controlled trial. Patients of CA-AK aged 18-70 years were enrolled. Underlying CKD, urinary tract obstruction, malignancy, heart failure, pregnancy, lactating women or poor performance status were excluded. Participants were randomized to receive either niacinamide (500 mg BD for 14 days) or no intervention. Follow-up visits were at 1and 4 months after hospital discharge. The primary outcome was difference in renal recovery at 4 months after discharge. Renal recovery was defined as eGFR ≥60 ml/min/1.73m² at 4 months after hospital discharge. Secondary outcome measures were differences in eGFR between groups at 1 and 4 months after hospital discharge. Trial was prospectively registered (CTRI/2022/03/040892).

Results: Over a period of 6 months starting June 2022, 89 patients were screened. 50 patients were enrolled and randomized. Infections (70%), toxic envenomations (8%), rhabdomyolysis (8%) and drug induced AKI (6%) were leading causes. Majority (49 of 50) had stage 3 AKI with 32 (64%) requiring kidney replacement therapy. 6 patients expired and one patient did not report for follow up. Finally 43 patients were analyzed for outcome measures. The clinical characteristics: age, sex, DM, HT, AKI stage, were similar between groups at baseline. Renal recovery at 4 months was significantly higher in the niacinamide group (20/21, **95.2%**) as compared to the controls (15/22, **68.18%** p0.023). eGFR (ml/my/1.73m²) at 1 month (99.9±27.9 vs 71.9±33.3 p0.040) and 4 months (108.2±26.2 vs 77.7±31.3 p0.001) after hospital discharge were also significantly higher in the intervention group as compared to control group. No major drug-related adverse events were recorded.

Conclusions: Niacinamide supplementation improved renal recovery at 4 months after hospital discharge in patients with severe AKI.

Funding: Government Support - Non-U.S.

VITAKI
(NCT04589546)

CHU AMIENS PICARDIE

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- Multicenter RCT
- **Septic shock** patients
- Nicotinamide 1g/day (72 hours)
- Primary outcome: **MAKE-30**

(Mortality; RRT; renal dysfunction)

Completed

Graft Acute Kidney Injury: Vitamin B3 to Facilitate Renal Recovery In the Early Life of a Transplant (GABRIEL)

ClinicalTrials.gov ID NCT05513807

Sponsor Assistance Publique - Hôpitaux de Paris

Information provided by Assistance Publique - Hôpitaux de Paris (Responsible Party)

Last Update Posted 2024-07-10

How to personalize RRT initiation ?

KDIGO

2012

Absolute indications to start RRT
Life-threatening complications

- Refractory **severe hyperkalemia**
- Refractory **severe metabolic acidosis** ($pH<7.15$)
- **Pulmonary edema** resistant to diuretics

What is the question ?

In critically ill patients with **severe AKI** who have **no life-threatening complication**, should we delay RRT ?

2016
NEJM


THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

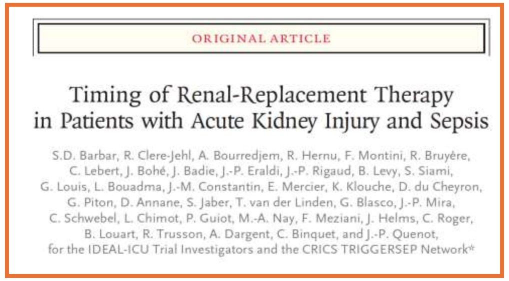
Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

Stéphane Gaudry, M.D., David Hajage, M.D., Frédérique Schortgen, M.D., Laurent Martin-Lefevre, M.D., Bertrand Pons, M.D., Eric Boulet, M.D., Alexandre Boyer, M.D., Guillaume Chevrel, M.D., Nicolas Lerolle, M.D., Ph.D., Dorothée Carpentier, M.D., Nicolas de Prost, M.D., Ph.D., Alexandre Lautrette, M.D., Anne Bretagnol, M.D., Julien Mayaux, M.D., Saad Nseir, M.D., Ph.D., Bruno Megarbane, M.D., Ph.D., Marina Thirion, M.D., Jean-Marie Forel, M.D., Julien Maizel, M.D., Ph.D., Hodane Yonis, M.D., Philippe Markowicz, M.D., Guillaume Thiery, M.D., Florence Tubach, M.D., Ph.D., Jean-Damien Ricard, M.D., Ph.D., and Didier Dreyfuss, M.D., for the AKIKI Study Group*

AKIKI

- **Multicenter** RCT
- n=**620**
- Mixed ICU patients

2018
NEJM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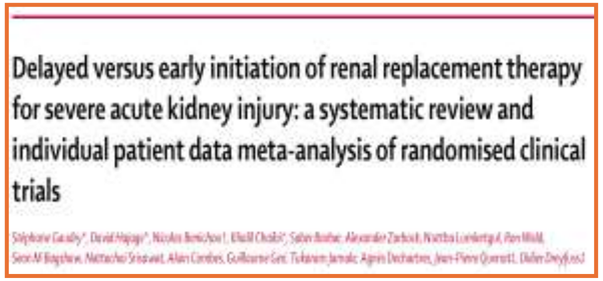
Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

S.D. Barbar, R. Clere-Jehl, A. Bourredjem, R. Hernu, F. Montini, R. Bruyère, C. Lebert, J. Bohé, J. Badie, J.-P. Eraldi, J.-P. Rigaud, B. Levy, S. Siami, G. Louis, L. Bouadma, J.-M. Constantin, E. Mercier, K. Klouche, D. du Cheyron, G. Piton, D. Annane, S. Jaber, T. van der Linden, G. Blasco, J.-P. Mira, C. Schwebel, L. Chimot, P. Guiot, M.-A. Nay, F. Meziani, J. Helms, C. Roger, B. Louart, R. Trusson, A. Dargent, C. Binquet, and J.-P. Quenot, for the IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network*

IDEAL-ICU

- **Multicenter** RCT
- n=**488**
- Septic ICU patients

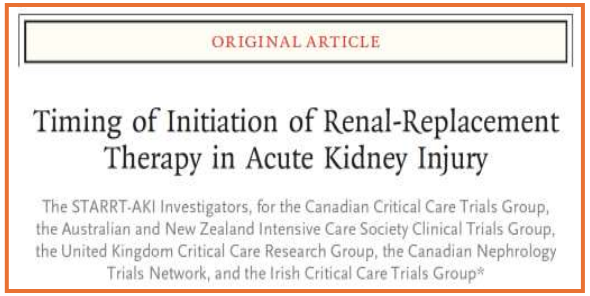
2020
Lancet


Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

IPDMA

- 10 RCTs
- n=1879

2020
NEJM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STARRT-AKI

- **Multicenter** RCT
- n=**2927**
- Mixed ICU patients

Study Interventions

Early Strategy Group

RRT as soon as possible

Within 6 hours after inclusion criteria

Delayed Strategy Group

RRT only if pre-specified criteria present

Delayed Strategy Group

Pre-specified criteria

- **Severe hyperkalemia**
  potassium > 6 mmol/l, or > 5.5 mmol/l *Despite medical treatment*

- **Severe acidosis** (pH <7.15)

- **Acute pulmonary edema** due to fluid overload
  Responsible for severe hypoxemia

- **Oliguria/Anuria >72 hours**

- **Serum urea concentration >** 40mmol/l

Gaudry et al NEJM 2016


The New England Journal of Medicine

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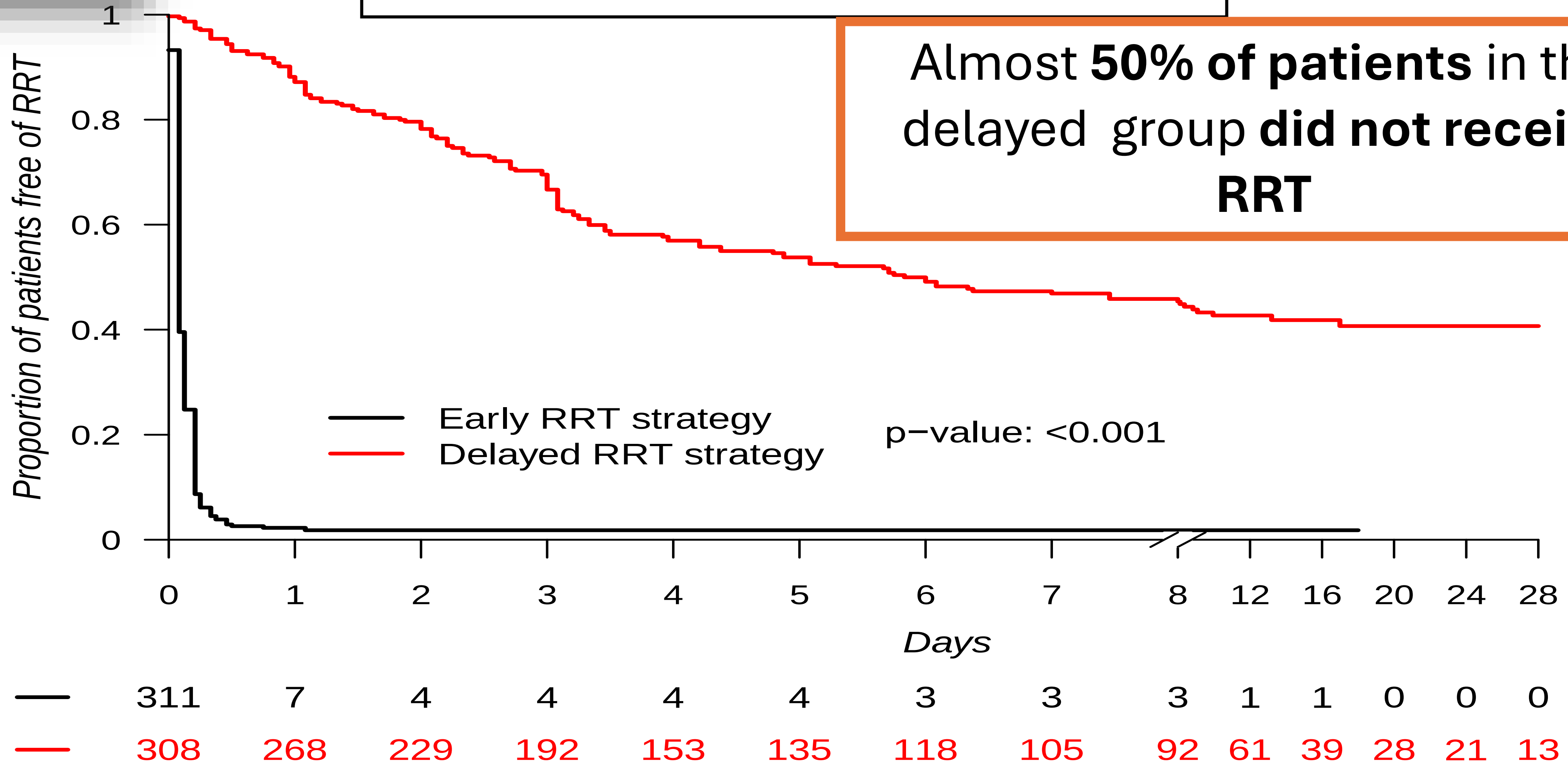
Patients free of RRT

AKIKI



Almost **50% of patients** in the delayed group **did not receive RRT**

THE NEW ENGLAND JOURNAL of MEDICINE

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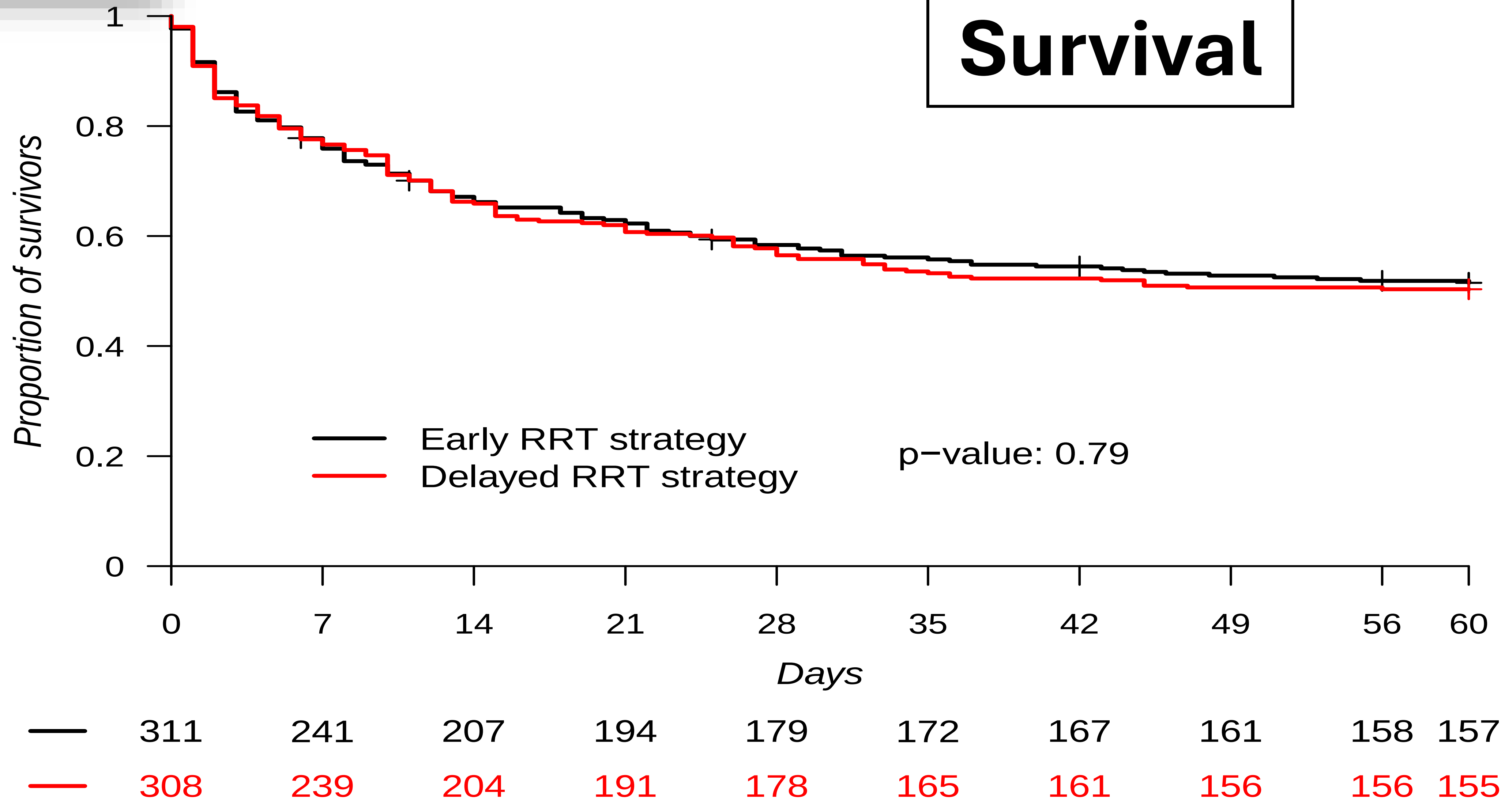
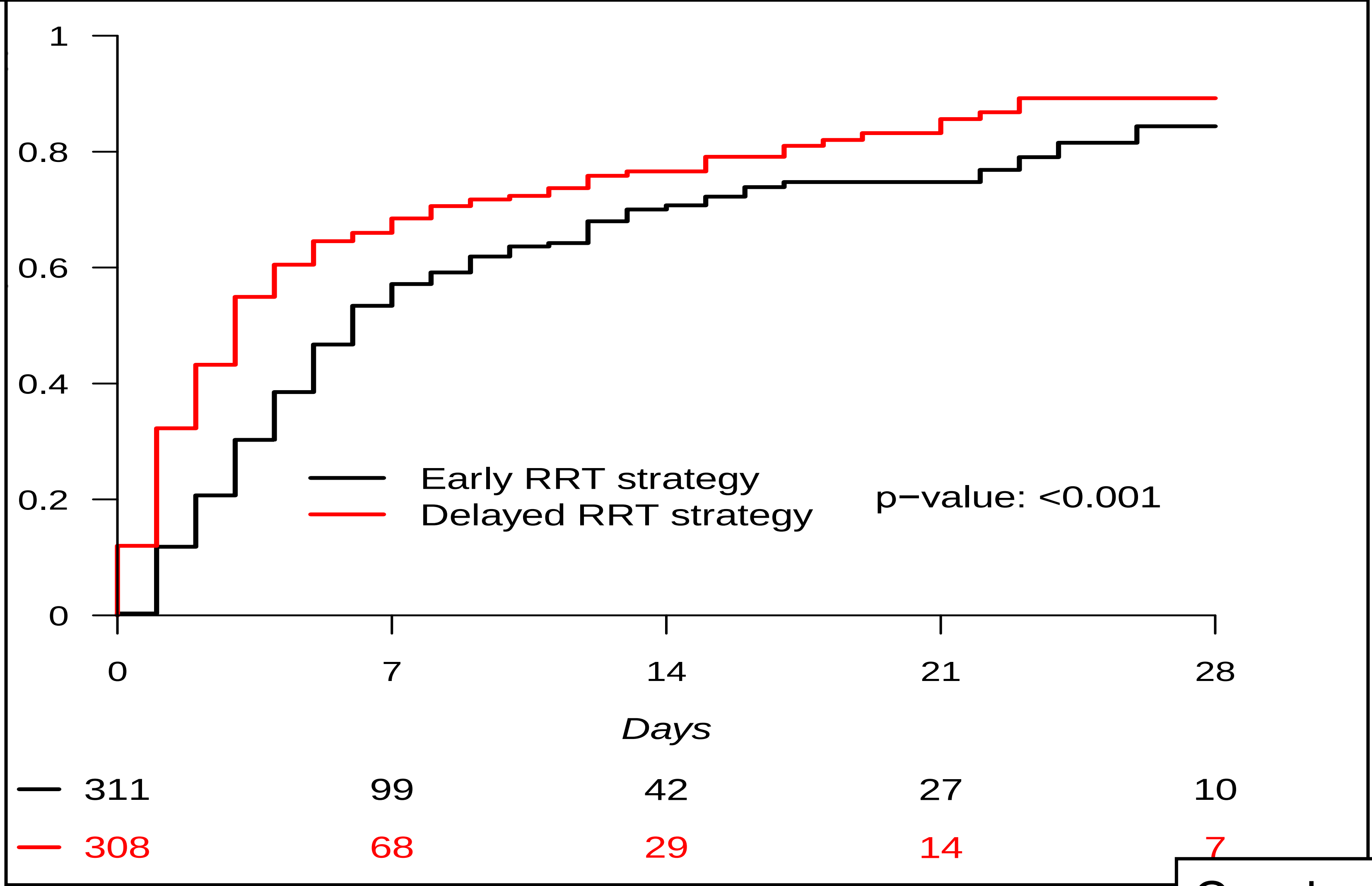
AKIKI

Survival

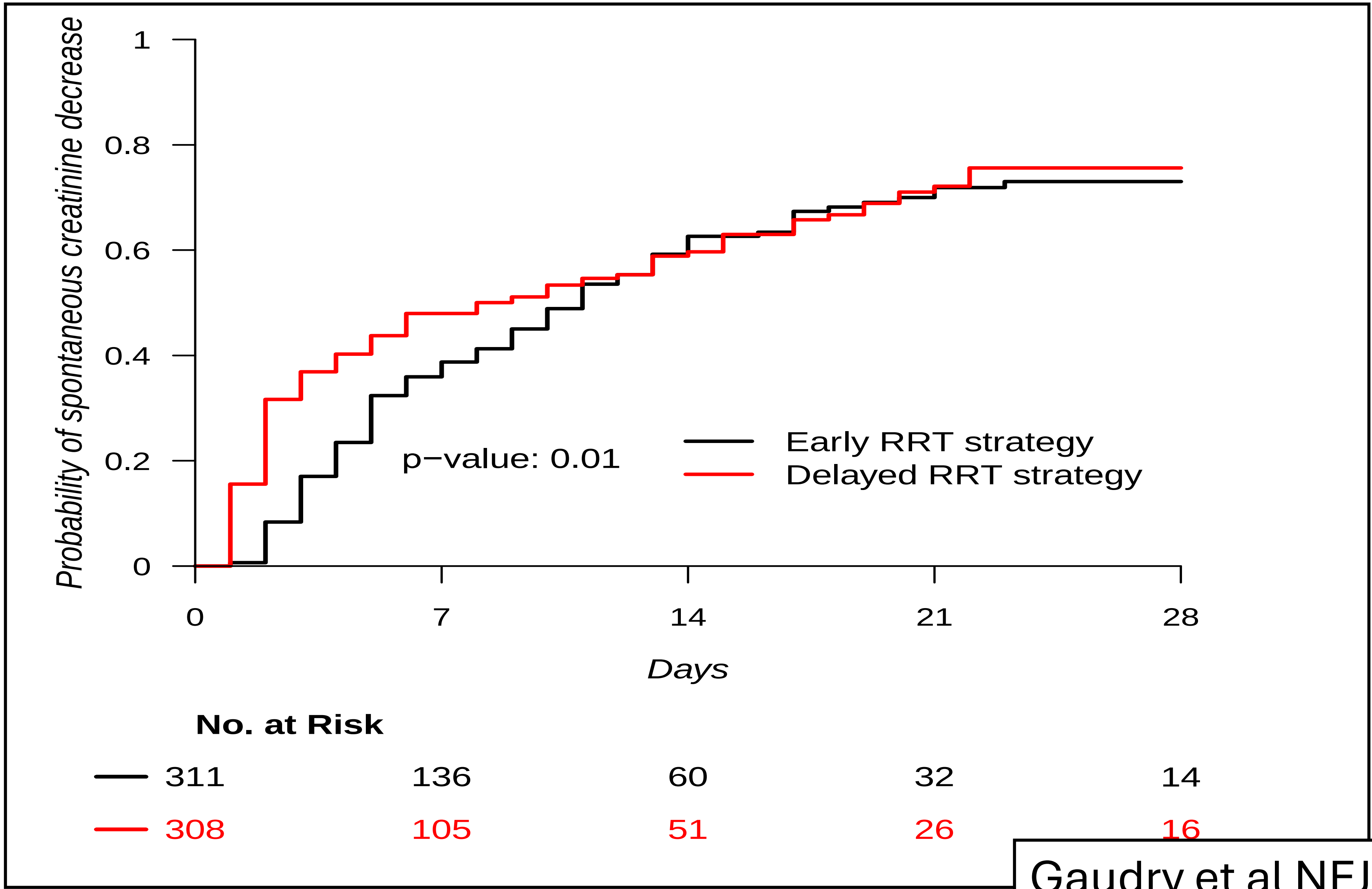


Adequate urine output with no need for RRT



Gaudry et al NEJM 2016

Spontaneous creatinine decrease



Gaudry et al NEJM 2016

Does Hemodialysis Delay Recovery from Acute Renal Failure?

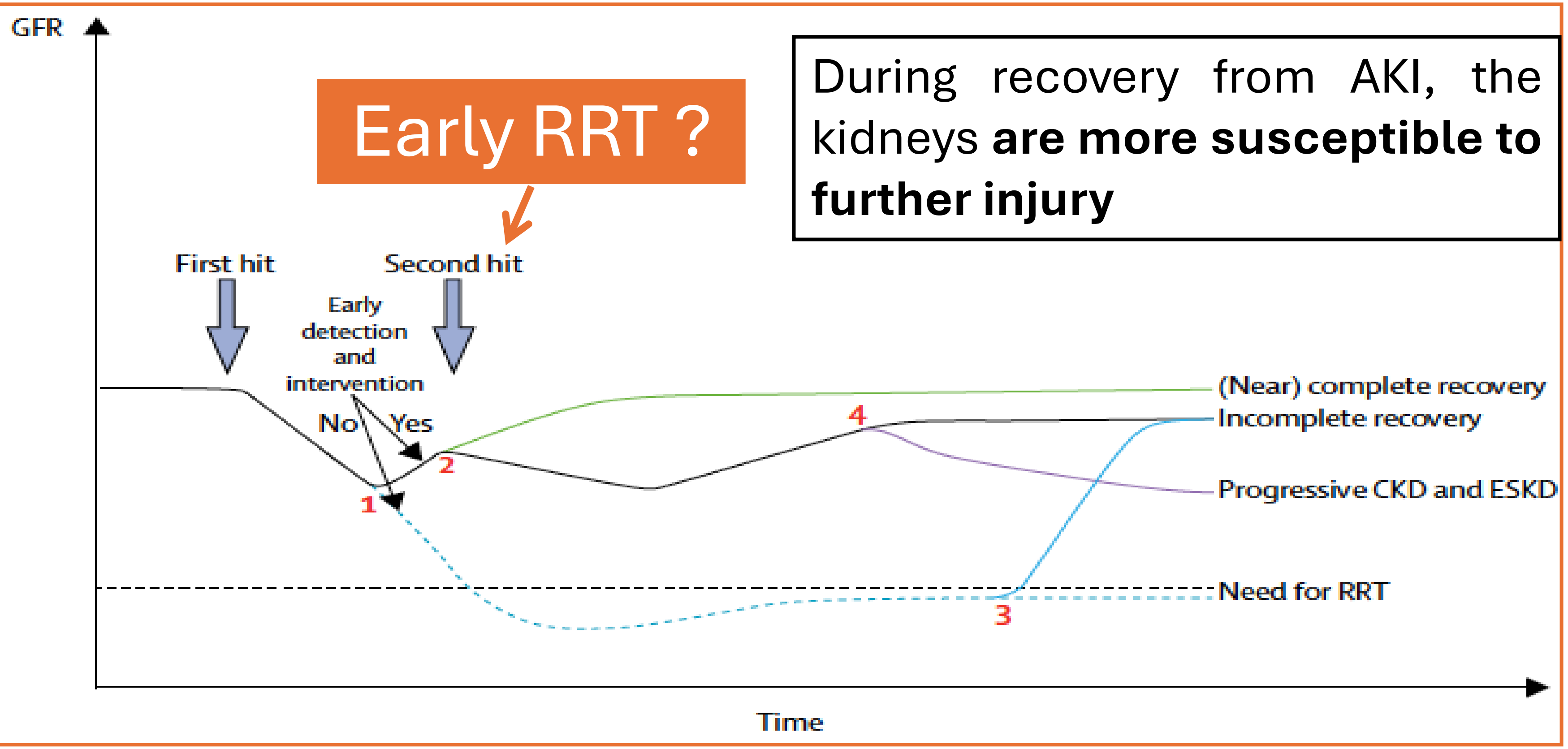
John D. Conger
University of Colorado School of Medicine and the VA Medical Center, Denver, Colorado

Seminars in Dialysis—Vol 3, No 3 (July–Sept) 1990 pp 146–148

Intensive care medicine and renal transplantation 1

Management of patients at risk of acute kidney injury

Jill Vanmassenhove, Jan Kielstein, Achim Jörres, Wim Van Biesen



During recovery from AKI, the kidneys **are more susceptible to further injury**

Does Hemodialysis Delay Recovery from Acute Renal Failure?

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University of Colorado School of Medicine and th... ...er, Colorado

Seminars in Dial... ...ept) 1990 pp 146–148

Intensive care medicine and renal transplantation 1

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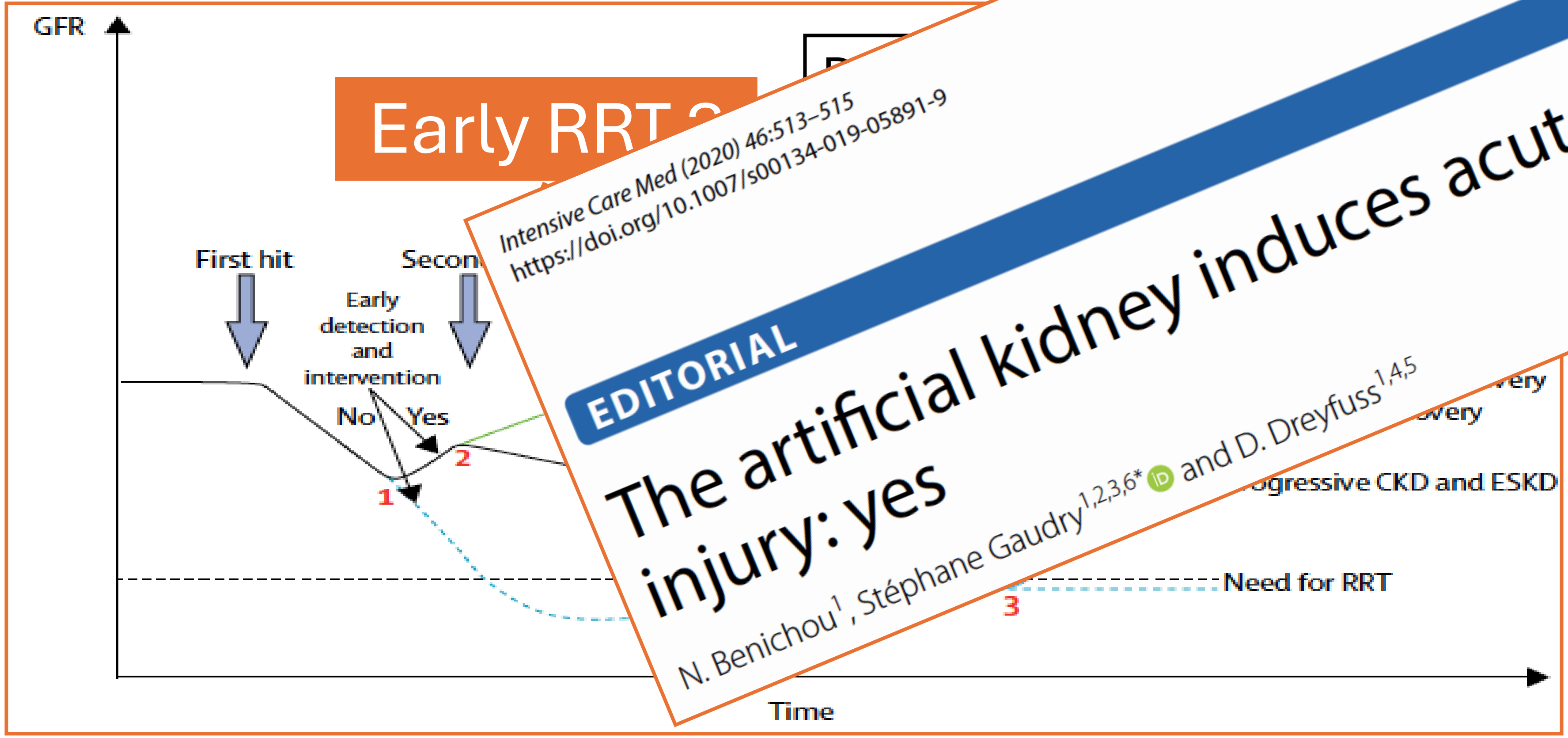


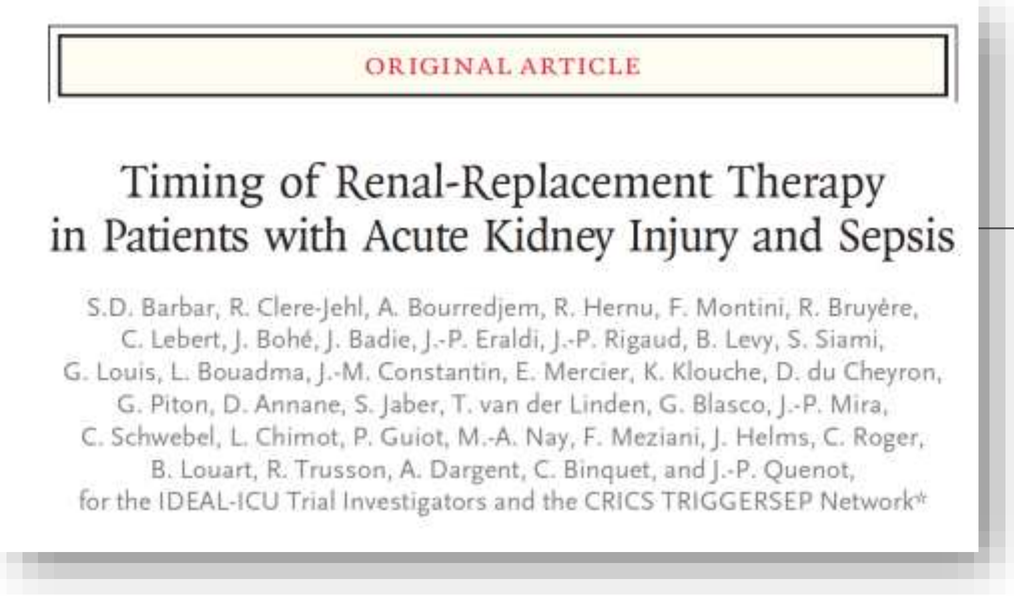
Intensive Care Med (2020) 46:513–515
https://doi.org/10.1007/s00134-019-05891-9

Check for updates

EDITORIAL

The artificial kidney induces acute kidney injury: yes

N. Benichou[1], Stéphane Gaudry[1,2,3,6*] and D. Dreyfuss[1,4,5]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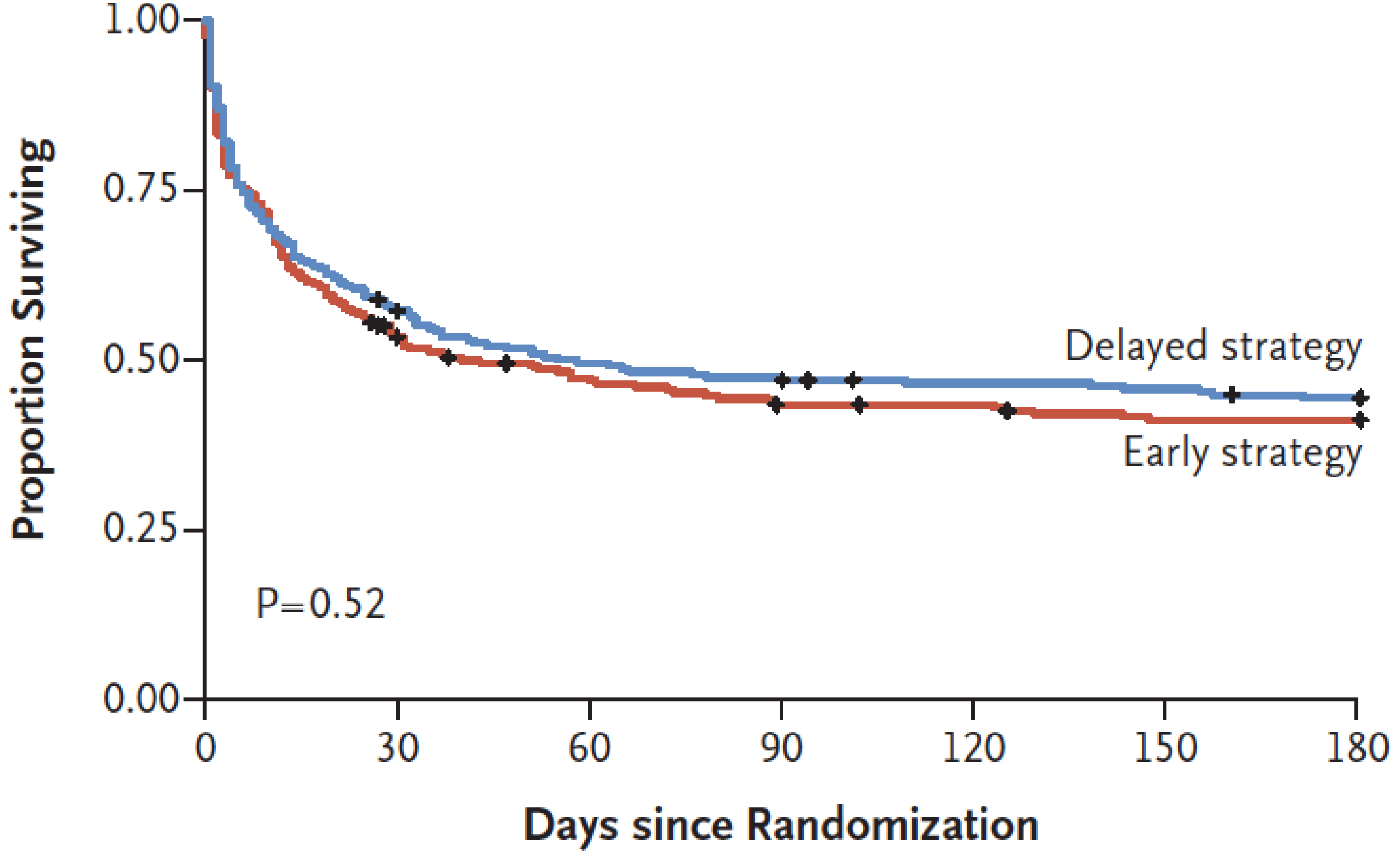
11 OCT 2018

488 patients

IDEAL-ICU

In the delayed-strategy group, **38%** (93 patients) did not receive RRT



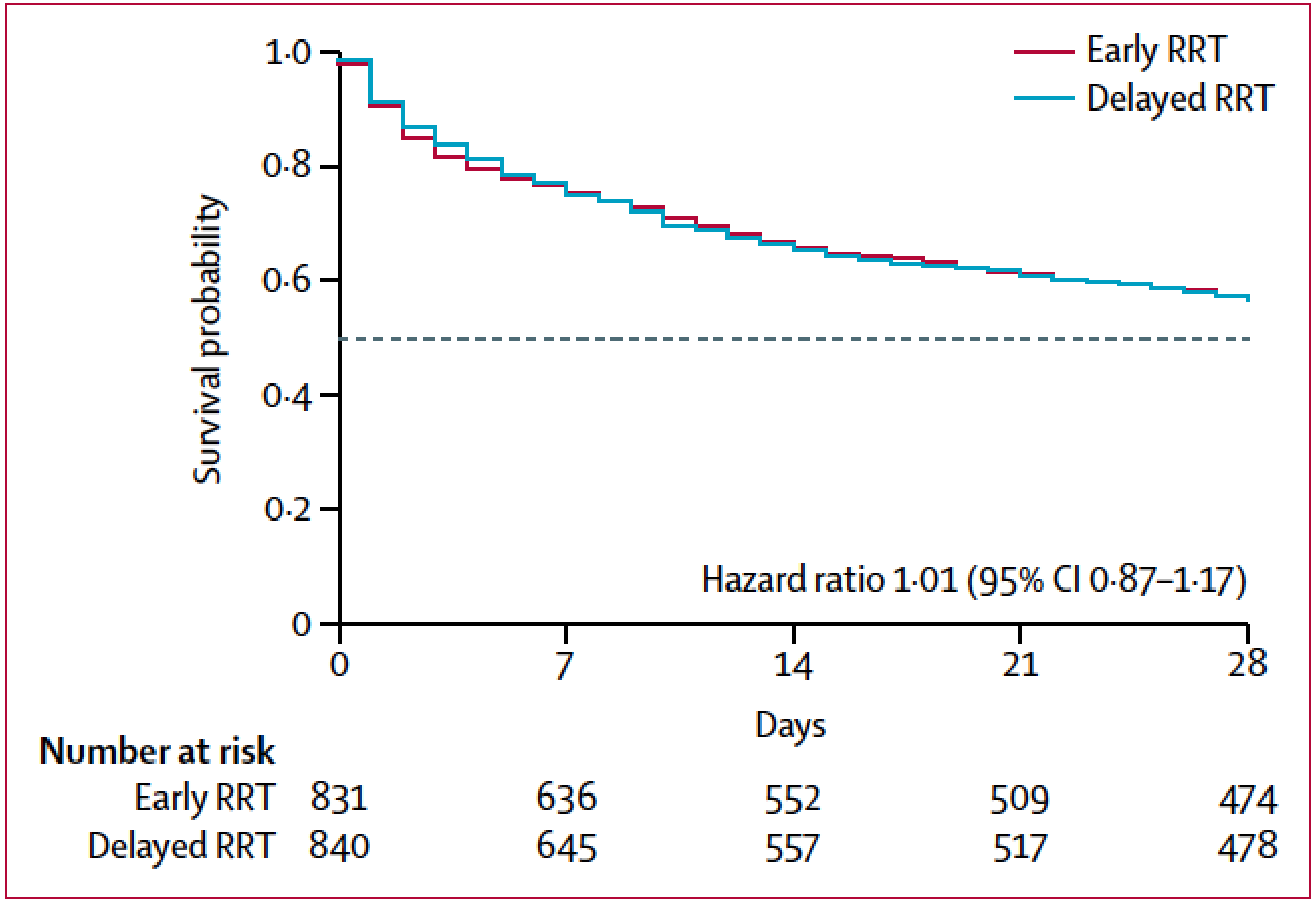
No. at Risk

	0	30	60	90	120	150	180
Delayed strategy	242	137	117	112	107	105	101
Early strategy	246	127	109	99	98	92	92

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

2020

Stéphane Gaudry*, David Hajage*, Nicolas Benichou†, Khalil Chaïbi†, Saber Barbar, Alexander Zarbock, Nuttha Lumlertgul, Ron Wald, Sean M Bagshaw, Nattachai Srisawat, Alain Combes, Guillaume Geri, Tukaram Jamale, Agnès Dechartres, Jean-Pierre Quenot‡, Didier Dreyfuss‡



42% never received RRT in the **delayed group**

ORIGINAL ARTICLE

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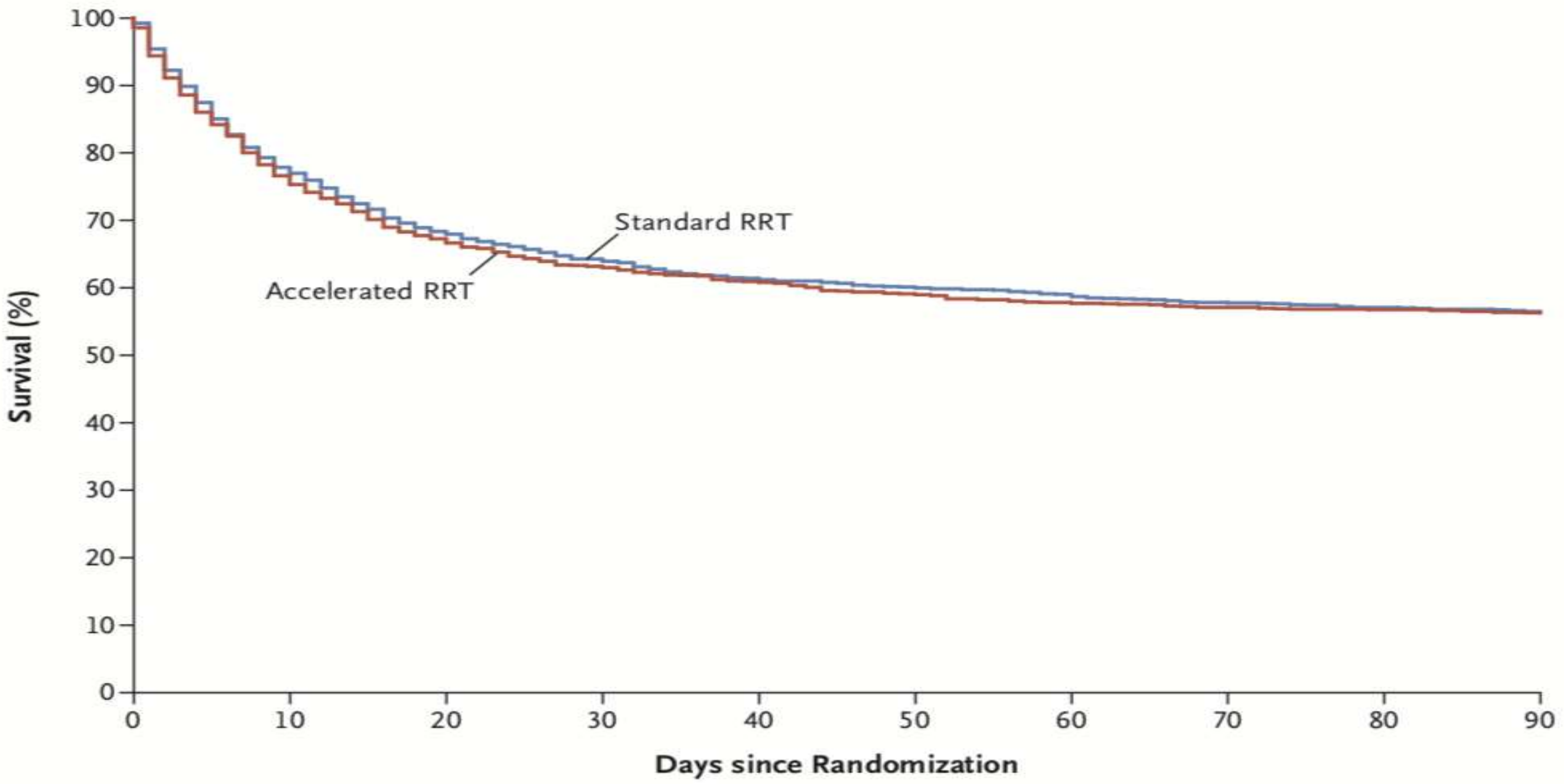
The STARRT-AKI Investigators, for the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, the United Kingdom Critical Care Research Group, the Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group*

STARRT-AKI 2020

STARRT-AKI confirmed the results of AKIKI and IDEAL-ICU

STARRT-AKI confirmed that the **"wait and see"** approach should be the **standard of care**

All-cause mortality Day 90



No. at Risk										
Standard RRT	1462	1138	999	939	897	878	862	844	833	823
Accelerated RRT	1465	1122	985	925	892	865	846	835	830	823

Artificial Kidney-Induced Kidney Injury

ORIGINAL ARTICLE

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The STARRT-AKI Investigators, for the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society Clinical Trials Group, the United Kingdom Critical Care Research Group, the Canadian Nephrology Trials Network, and the Irish Critical Care Trials Group*

Confirmation of this concept

STARRT-AKI

RRT dependence after 90 days

Early strategy: 10.4% vs **Delayed strategy: 6.0%**

RR:1.74 (95% CI: 1.24 to 2.43)

ORIGINAL ARTICLE STARRT-AKI

Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury

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Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

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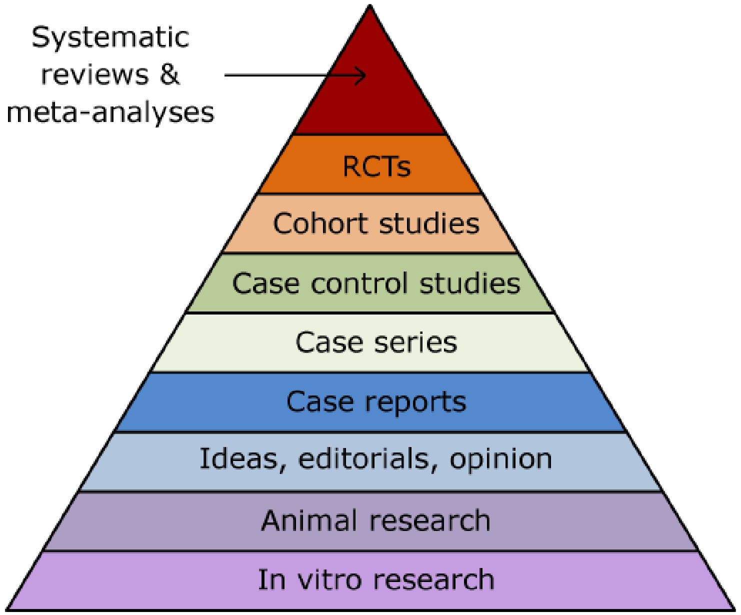
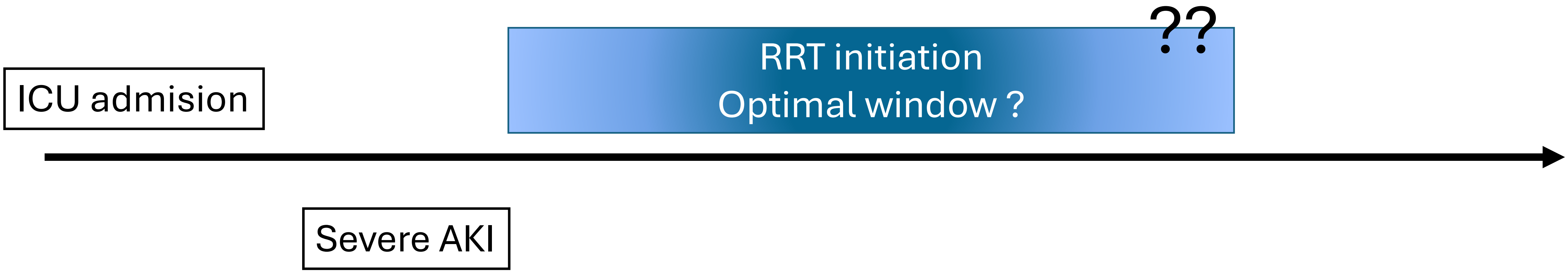
In the context of severe AKI, and in the absence of life-threatening complications (refractory severe hyperkalemia, refractory severe metabolic acidosis or pulmonary edema resistant to diuretics), delaying RRT initiation is recommended



High level of evidence

Major uncertainty remained concerning the duration for which RRT can be postponed without risk



Major uncertainty remained concerning the duration for which RRT can be postponed without risk

??

RRT initiation
Optimal window ?

ICU admision

Severe AKI

The Artificial Kidney Initiation in Kidney Injury 2 (AKIKI 2)
A Multi-Centre, Randomized, Controlled Trial


Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial

Stéphane Gaudry, David Hajage, Laurent Martin-Lefevre, Saïd Lebbah, Guillaume Louis, Sébastien Moschietto, Dimitri Titeca-Beauport, Béatrice La Combe, Bertrand Pons, Nicolas de Prost, Sébastien Besset, Alain Combes, Adrien Robine, Marion Beuzelin, Julio Badie, Guillaume Chevrel, Julien Bohé, Elisabeth Coupez, Nicolas Chudeau, Saber Barbar, Christophe Vinsonneau, Jean-Marie Forel, Didier Thevenin, Eric Boulet, Karim Lakhal, Nadia Aissaoui, Steven Grange, Marc Leone, Guillaume Lacave, Saad Nseir, Florent Poirson, Julien Mayaux, Karim Asehnoune, Guillaume Geri, Kada Klouche, Guillaume Thiery, Laurent Argaud, Bertrand Rozec, Cyril Cadoz, Pascal Andreu, Jean Reignier*, Jean-Damien Ricard*, Jean-Pierre Quenot†, Didier Dreyfuss†

Lancet 2021

AKIKI1

Delayed Strategy Group

Pre-specified criteria

- **Severe hyperkalemia**
  potassium > 6 mmol/l, or > 5.5 mmol/l *Despite medical treatment*
- **Severe acidosis** (pH <7.15)
- **Acute pulmonary edema** due to fluid overload
  Responsible for severe hypoxemia

- **Oliguria/Anuria >72 hours**
- **Serum urea concentration >** 40mmol/l

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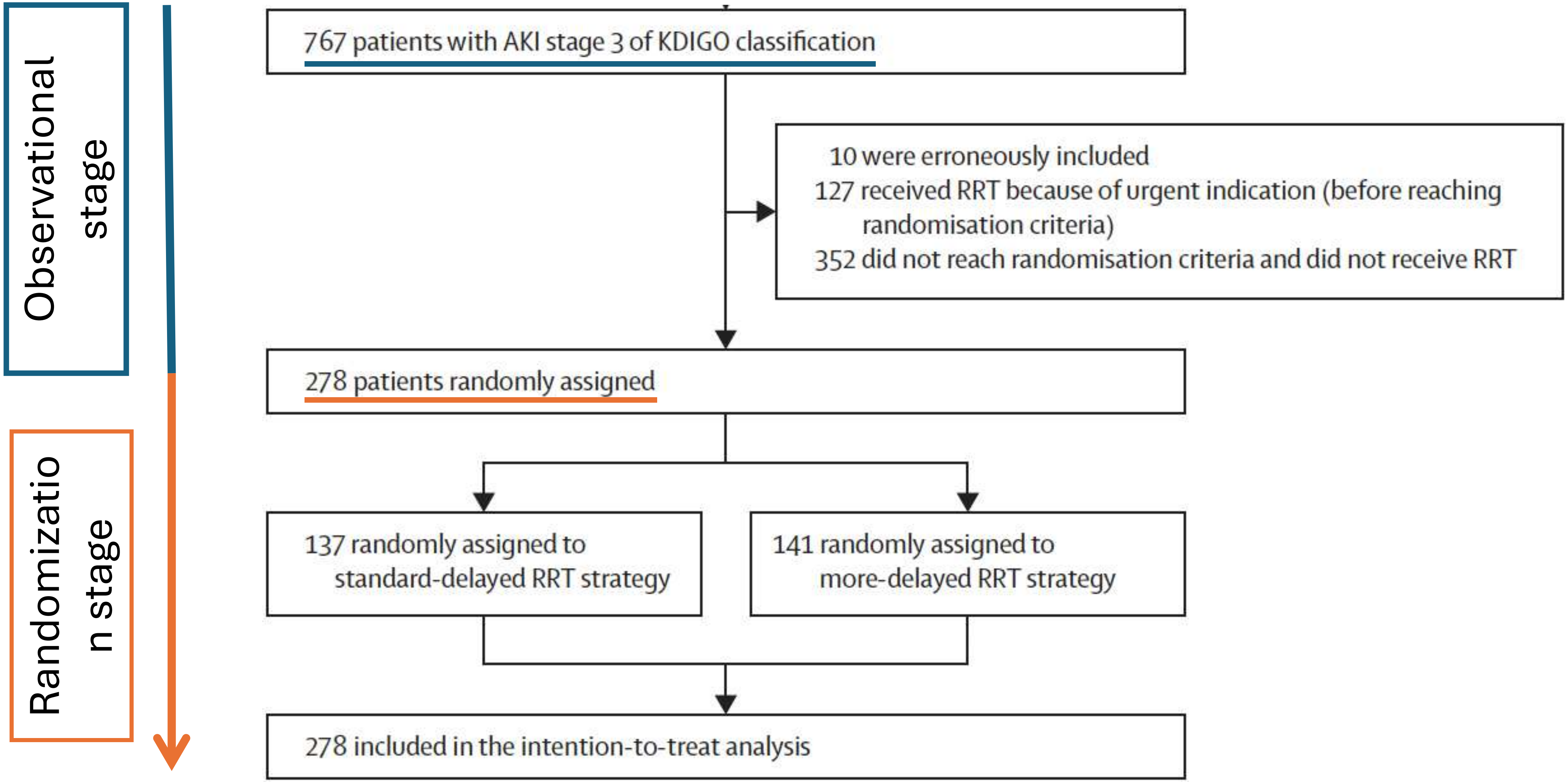

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Primary endpoint

The **median number of RRT-free days** was 12 days (IQR 0-25) in the delayed strategy and 10 days (IQR 0-24) in the more-delayed strategy (**p=0.93**)

Prespecified multivariate analysis

Odds ratio for **death at 60 days**
2.16 (95% CI, 1·17 – 4·01, **p=0·014**)
with **more-delayed** versus delayed strategy

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
More-delayed strategy	1·34 (0·96–1·89)	0·13	1·65 (1·09–2·50)	0·018
Simplified Acute Physiology Score III	1·03 (1·02–1·05)	<0·0001	1·03 (1·01–1·05)	0·0005
Mechanical ventilation	2·90 (1·47–5·70)	<0·0001	3·44 (1·52–7·81)	0·0020
Catecholamine infusion	1·69 (1·17–2·44)	0·0080	1·13 (0·69–1·84)	0·64
Sepsis status	..	0·064	..	0·19
Sepsis	0·78 (0·47–1·30)	..	0·56 (0·28–1·12)	..
Septic shock	1·44 (0·98–2·12)	..	0·91 (0·51–1·64)	..
Time between ICU admission and acute kidney injury	0·69 (0·36–1·31)	0·24	0·70 (0·31–1·59)	0·39

NEURAKI study
ICM; March, 2024

Volume 50, Issue 3

March 2024

Intensive Care Med
https://doi.org/10.1007/s00134-024-07339-1

ORIGINAL

Check for updates

Renal replacement therapy initiation strategies in comatose patients with severe acute kidney injury: a secondary analysis of a multicenter randomized controlled trial

Thomas Rambaud[1,2], David Hajage[3], Didier Dreyfuss[4], Saïd Lebbah[3], Laurent Martin-Lefevre[5], Guillaume Louis[6], Sébastien Moschietto[7], Dimitri Titeca-Beauport[8], Béatrice La Combe[9], Bertrand Pons[10], Nicolas De Prost[11], Sébastien Besset[12], Alain Combes[13], Adrien Robine[14], Marion Beuzelin[15], Julio Badie[16], Guillaume Chevrel[17], Julien Bohe[18], Elisabeth Coupez[19], Nicolas Chudeau[20], Saber Barbar[21], Christophe Vinsonneau[22], Jean-Marie Forel[23], Didier Thevenin[24], Eric Boulet[25], Karim Lakhal[26], Nadia Aissaoui[27], Steven Grange[28], Marc Leone[29], Guillaume Lacave[30], Saad Nseir[31], Florent Poirson[1], Julien Mayaux[32], Karim Ashenoune[33], Guillaume Geri[34], Kada Klouche[35], Guillaume Thiery[36], Laurent Argaud[37], Bertrand Rozec[38], Cyril Cadoz[39], Pascal Andreu[40], Jean Reignier[41], Jean-Damien Ricard[12,42], Jean-Pierre Quenot[39,43], Romain Sonneville[44,45] and Stéphane Gaudry[1,4,46,47*]

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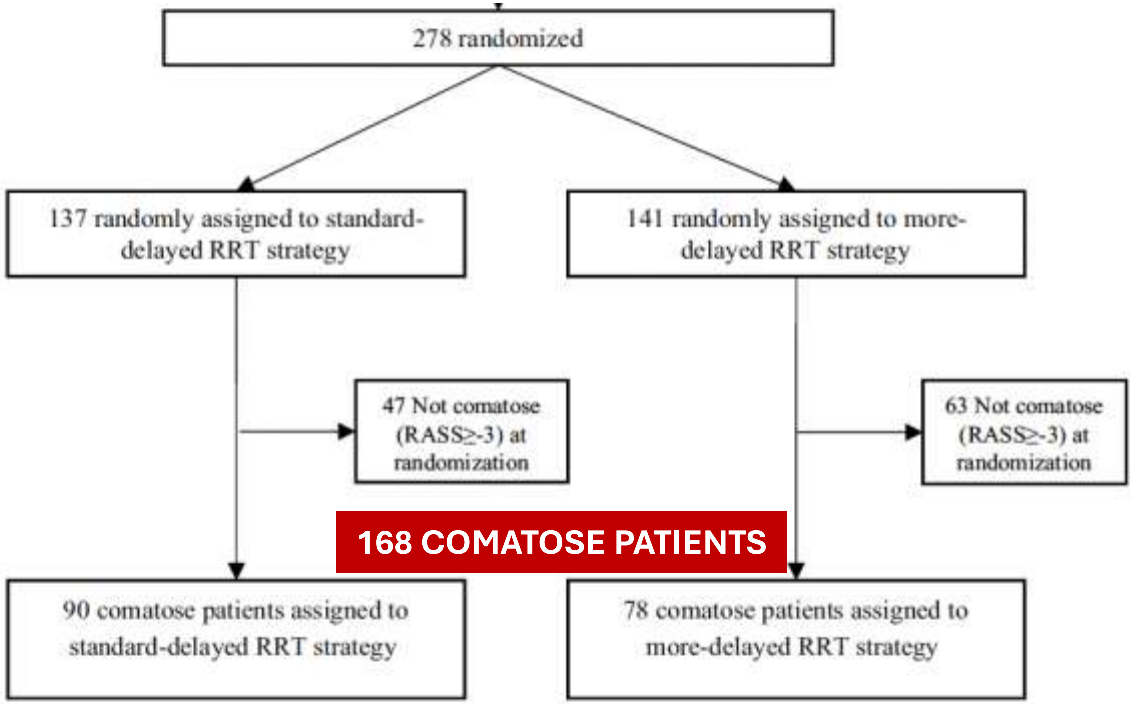
NEURAKI study

Post-hoc analysis of the AKIKI2 trial

- Adults
- Invasive MV and/or catecholamine infusion
- AKI Stage 3 of KDIGO classification
  - + oliguria or anuria for more than 72 h
  - or BUN > 112 mg/dL (serum urea concentration of 40 mmol/L)
- **Comatose at randomization (RASS<-3)**

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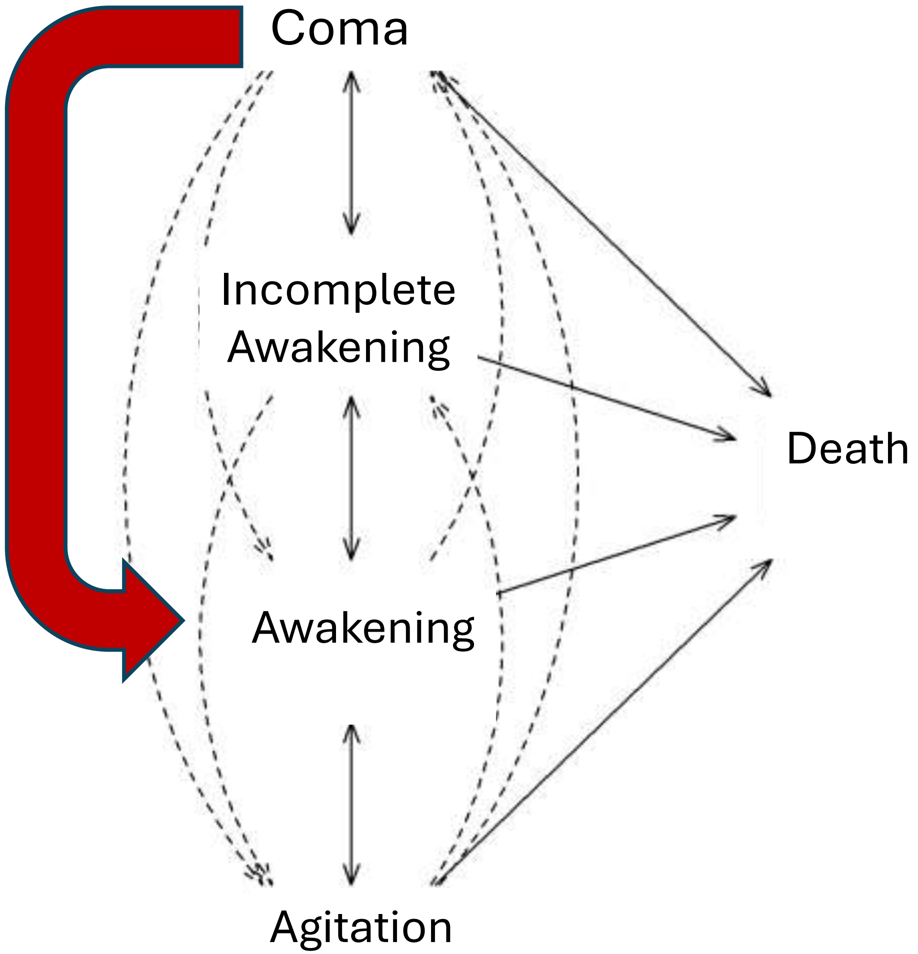
Outcomes



PRIMARY OUTCOME

transition intensity from coma to awakening during the first 28 days after randomization

Intensive Care Med
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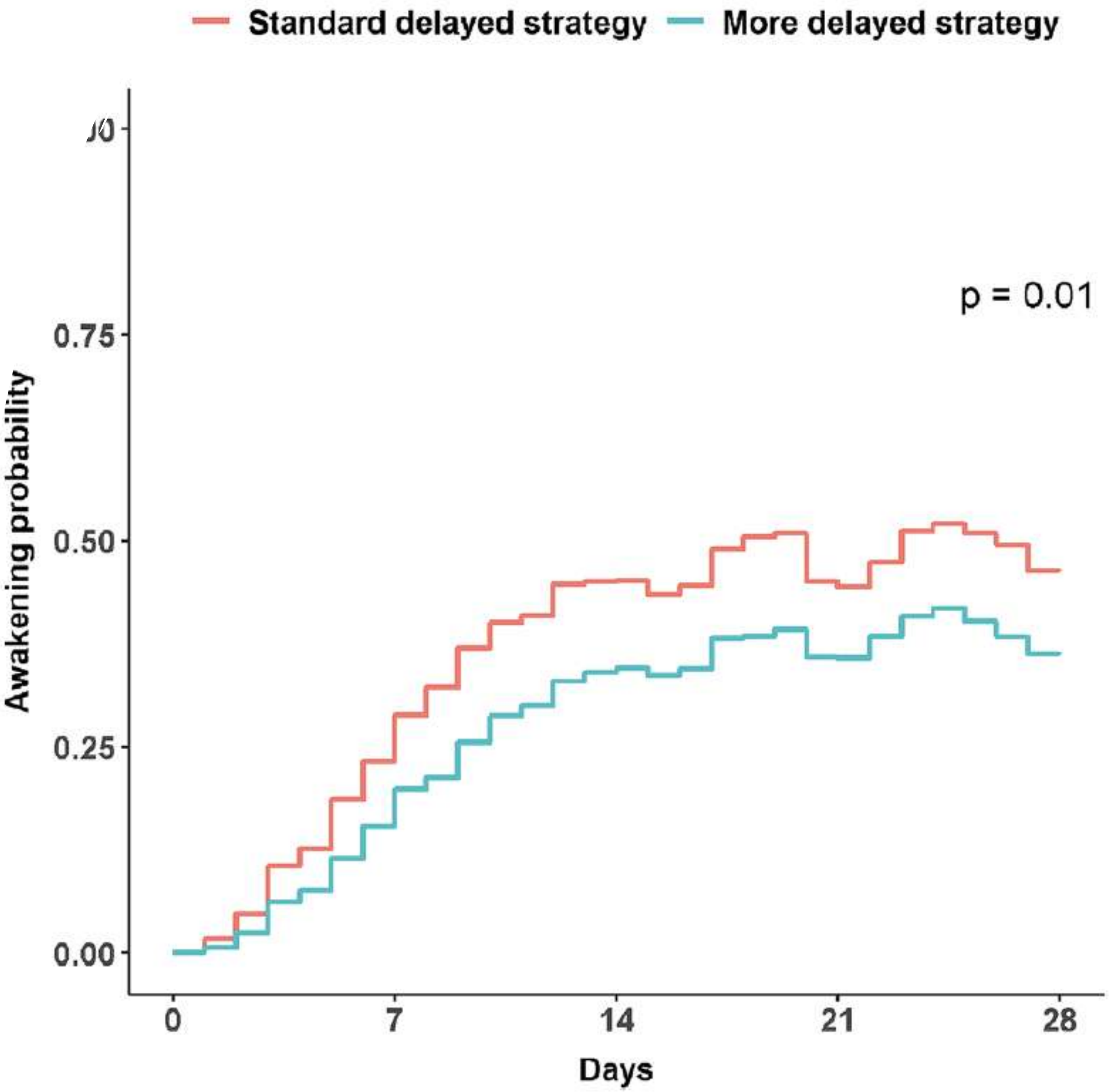
Primary outcome

The transition intensity from coma to awakening was **lower in the more-delayed strategy group**

(HR= 0.36 (0.17–0.78); p = 0.010)

The 2 sensitivity analyses yielding comparable results



Probability of being awake according to the randomization

Secondary outcomes

An **increase of the plasma urea level** on a given day was associated with a significantly lower probability of being awake the following day

Table 2 Impact of plasmatic urea level a given day on the neurological state the following day

References	Coma	Awakening	Incomplete awakening	Agitation	Death
Coma	1	0.983 (0.968–0.998), $p=0.018$	1.006 (0.995–1.015), $p=0.283$	1.012 (0.994–1.03), $p=0.170$	1.024 (1.002–1.048), $p=0.039$
Awakening	1.018 (1.002–1.033), $p=0.018$	1	1.024 (1.007–1.039), $p=0.005$	1.03 (1.012–1.049), $p=0.002$	1.042 (1.018–1.067), $p<0.001$
Incomplete awakening	0.994 (0.985–1.005), $p=0.282$	0.977 (0.963–0.993), $p=0.005$	1	1.006 (0.989–1.026), $p=0.494$	1.018 (0.995–1.044), $p=0.129$
Agitation	0.988 (0.971–1.006), $p=0.170$	0.971 (0.954–0.988), $p=0.002$	0.994 (0.975–1.012), $p=0.496$	1	1.012 (0.986–1.038), $p=0.389$
Death	0.977 (0.94 –0.998), $p=0.039$	0.96 (0.937–0.982), $p<0.001$	0.982 (0.958–1.005), $p=0.129$	0.989 (0.963–1.015), $p=0.390$	1

Mechanisms underlying the observed benefits of RRT?

- Accumulation of uremic toxins
- Blood–brain barrier dysfunction
- Neurotoxicity of drugs
- Electrolyte imbalance (calcium and sodium disorders)

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- Accumulation of uremic toxins
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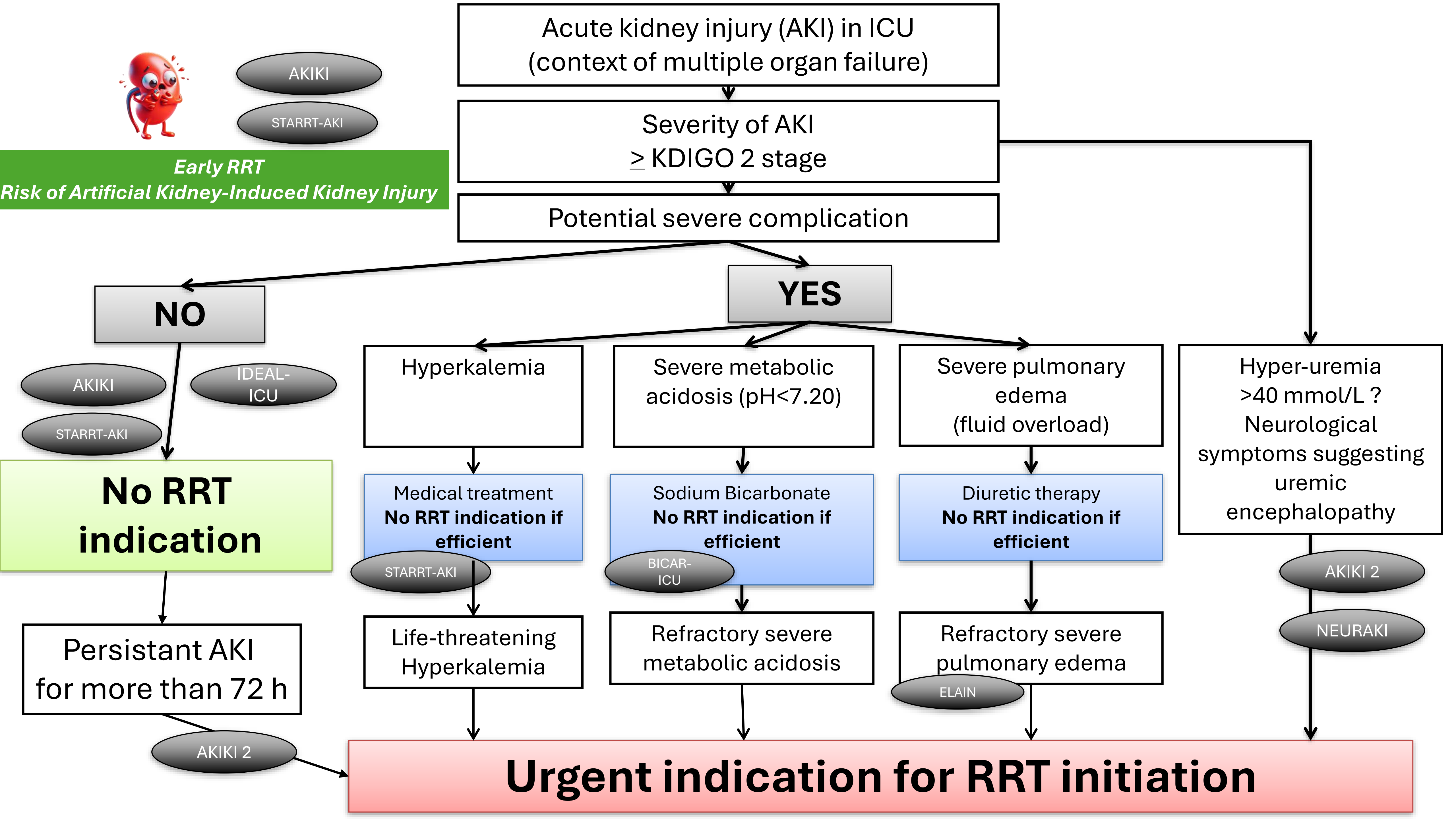
RRT

Vanholder, Toxins, 2022

Uremic toxins: *Good or bad ?*

Neurotoxicity



Acute kidney injury (AKI) in ICU
(context of multiple organ failure)
Severity of AKI
≥ KDIGO 2 stage
Potential severe complication
AKIKI
STARRT-AKI
Early RRT
Risk of Artificial Kidney-Induced Kidney Injury
NO
YES
AKIKI
IDEAL-ICU
STARRT-AKI
No RRT indication
Persistant AKI for more than 72 h
AKIKI 2
Hyperkalemia
Medical treatment
No RRT indication if efficient
STARRT-AKI
Life-threatening Hyperkalemia
Severe metabolic acidosis (pH<7.20)
Sodium Bicarbonate
No RRT indication if efficient
BICAR-ICU
Refractory severe metabolic acidosis
Severe pulmonary edema
(fluid overload)
Diuretic therapy
No RRT indication if efficient
Refractory severe pulmonary edema
ELAIN
Hyper-uremia
>40 mmol/L ?
Neurological symptoms suggesting uremic encephalopathy
AKIKI 2
NEURAKI
Urgent indication for RRT initiation

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

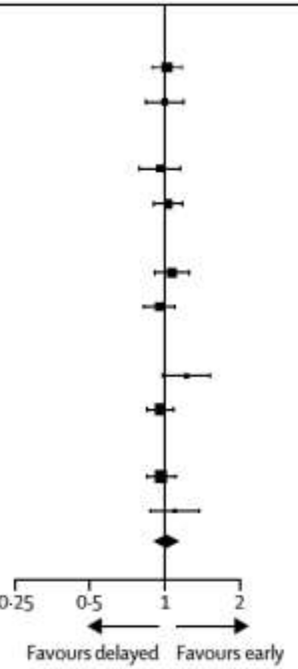
Stéphane Gaudry*, David Hajage*, Nicolas Benichou†, Khalil Chaibi†, Saber Barbar, Alexander Zarbock, Nuttha Lumlertgul, Ron Wald, Sean M Bagshaw, Nattachai Srisawat, Alain Combes, Guillaume Geri, Tukaram Jamale, Agnès Dechartres, Jean-Pierre Quenot‡, Didier Dreyfuss‡

Is there any subpopulation of patients in ICU which could benefit from early or delayed RRT strategy ?

2020

B

	28-day mortality, n/N (%) Delayed RRT	28-day mortality, n/N (%) Early RRT	Risk ratio (95% CI)	$P_{interaction}$
Sex				0·869
Male	228/528 (43%)	221/526 (42%)	1·02 (0·89–1·17)	
Female	138/309 (45%)	134/301 (45%)	1·00 (0·84–1·19)	
Age (years)				0·520
≤66	126/355 (35%)	143/388 (37%)	0·96 (0·79–1·16)	
>66	240/482 (50%)	212/439 (48%)	1·03 (0·91–1·17)	
SOFA score at randomisation				0·284
≤12	179/430 (42%)	165/425 (39%)	1·07 (0·91–1·26)	
>12	181/390 (46%)	185/383 (48%)	0·95 (0·82–1·09)	
Sepsis status at randomisation				0·062
No sepsis	98/209 (47%)	77/207 (37%)	1·22 (0·98–1·52)	
Sepsis	258/605 (43%)	267/600 (45%)	0·96 (0·85–1·09)	
Chronic kidney disease*				0·359
No	243/600 (41%)	271/655 (41%)	0·97 (0·85–1·11)	
Yes	92/180 (51%)	62/135 (46%)	1·09 (0·87–1·37)	
Overall			**1·01 (0·91–1·13)**	



But

The conventional subgroup analyses performed "one variable at a time" fail to convey meaningful results as they cannot fully capture all the relevant

Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials

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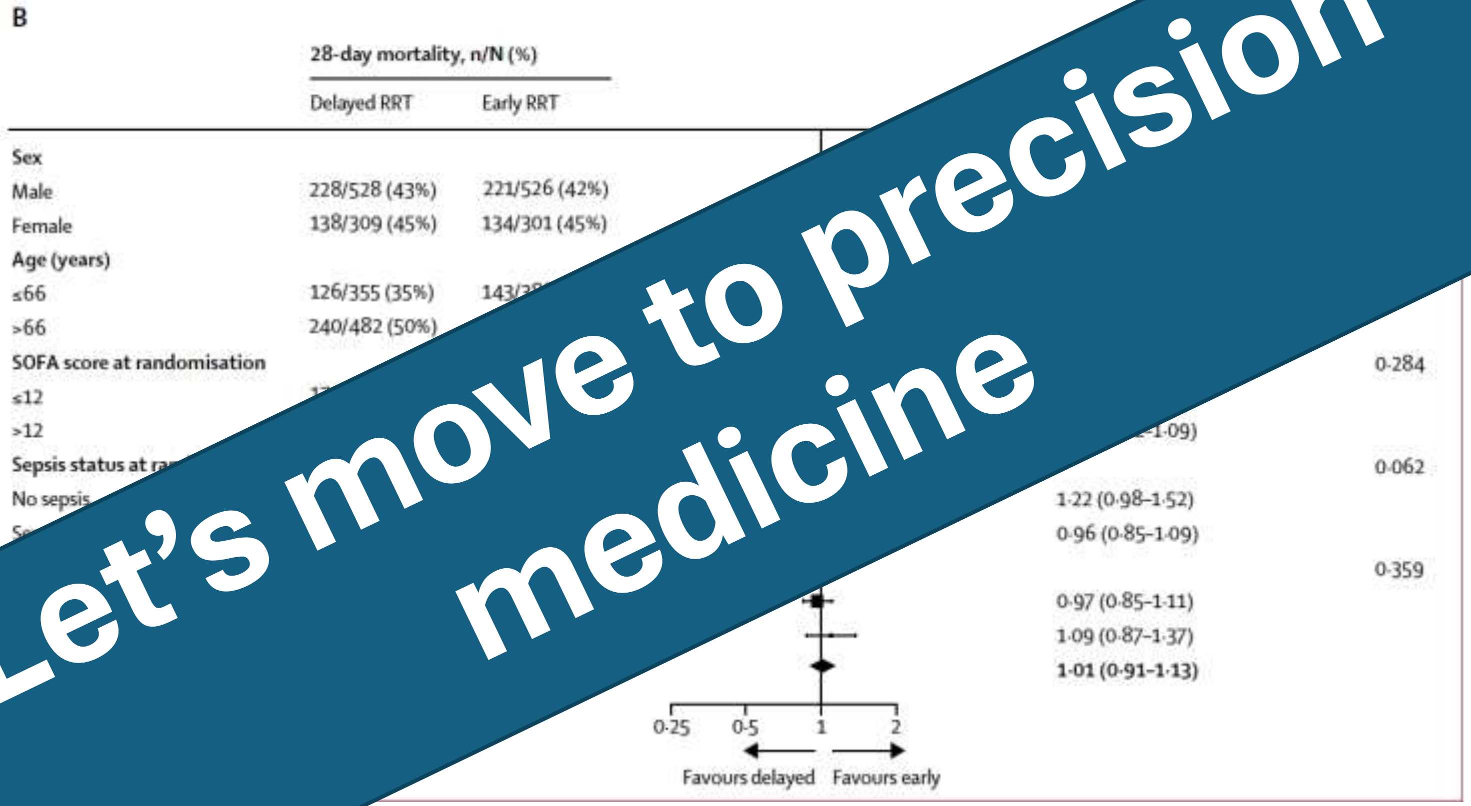
2020

Is there any subpopulation of patients in ICU which could benefit from early or delayed RRT strategy ?



Let’s move to precision medicine

But

The conventional subgroup analyses performed “one variable at a time” fail to convey meaningful results as they cannot fully capture all the relevant

An example:
Should treatment always be the same for **coronary artery disease**?

Sarah
59 yo
Diabetes mellitus
Insulin
LVEF 50%
Creatinine clearance 50ml/min
Left main coronary artery disease

Donald
69 yo
Diabetes mellitus
No insulin
LVEF 45%
Creatinine clearance 40ml/min
Three vessel artery disease

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2009 VOL. 360 NO. 10

the SYNTAX Investigators

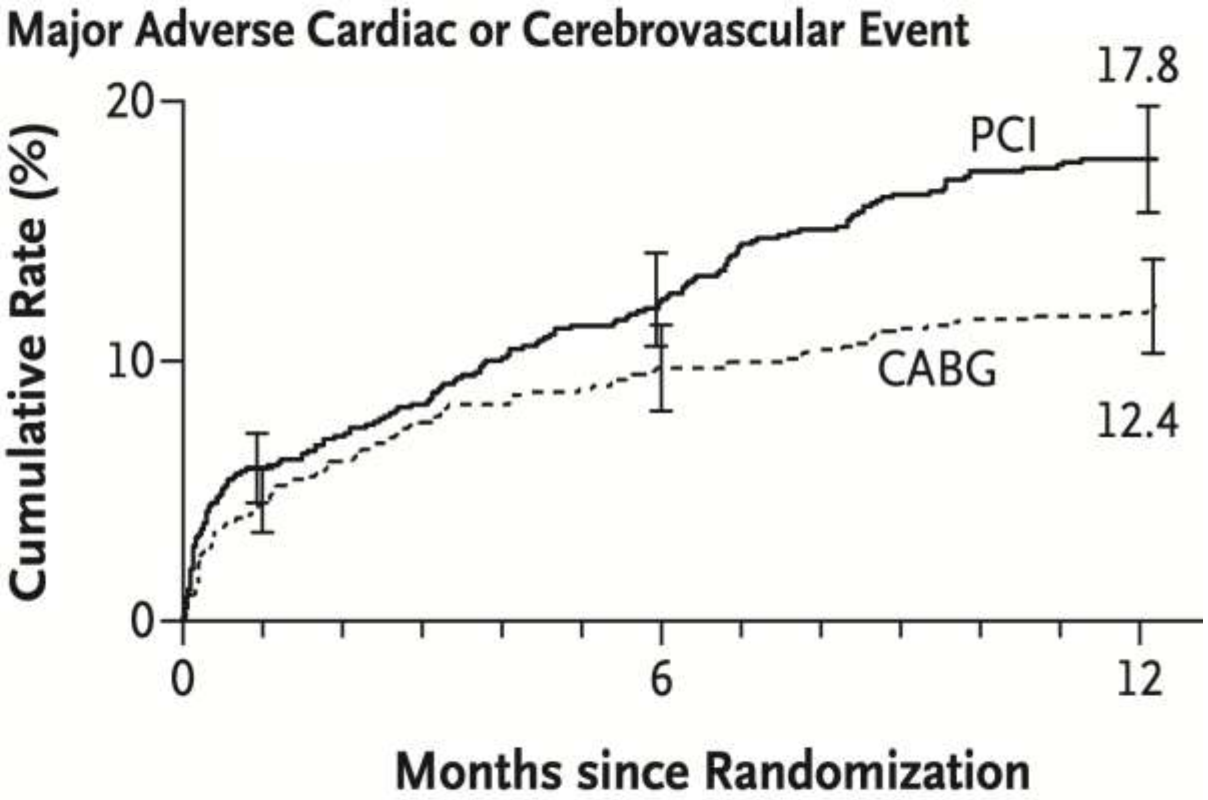
Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease

Patients “previously untreated three-vessel coronary disease and those with left main coronary artery disease”

Intervention “Percutaneous Coronary Intervention (PCI)”

Control “Coronary-Artery Bypass Grafting (CABG)”

Primary Outcome major adverse cardiac or cerebrovascular event (MACCE)



<u>Conclusion:</u> CABG remains the standard of care for patients with three-vessel or left main coronary artery disease, since the use of CABG, as compared with PCI, resulted in lower rates of the combined end point of major adverse cardiac or cerebrovascular events at 1 year

Redevelopment and validation of the SYNTAX score II to individualise decision making between percutaneous and surgical revascularisation in patients with complex coronary artery disease: secondary analysis of the multicentre randomised controlled SYNTAXES trial with external cohort validation

Kuniaki Takahashi, Patrick W Serruys, Valentin Fuster, Michael E Farkouh, John A Spertus, David J Cohen, Seung-Jung Park, Duk-Woo Park, Jung-Min Ahn, Arie Pieter Kappetein, Stuart J Head, Daniel J F M Thuijs, Yoshinobu Onuma, David M Kent, Ewout W Steyerberg, David van Klaveren, on behalf of the SYNTAXES, FREEDOM, BEST, and PRECOMBAT trial investigators

Heterogeneity of treatment effect

Treatment Effect Modeling: example

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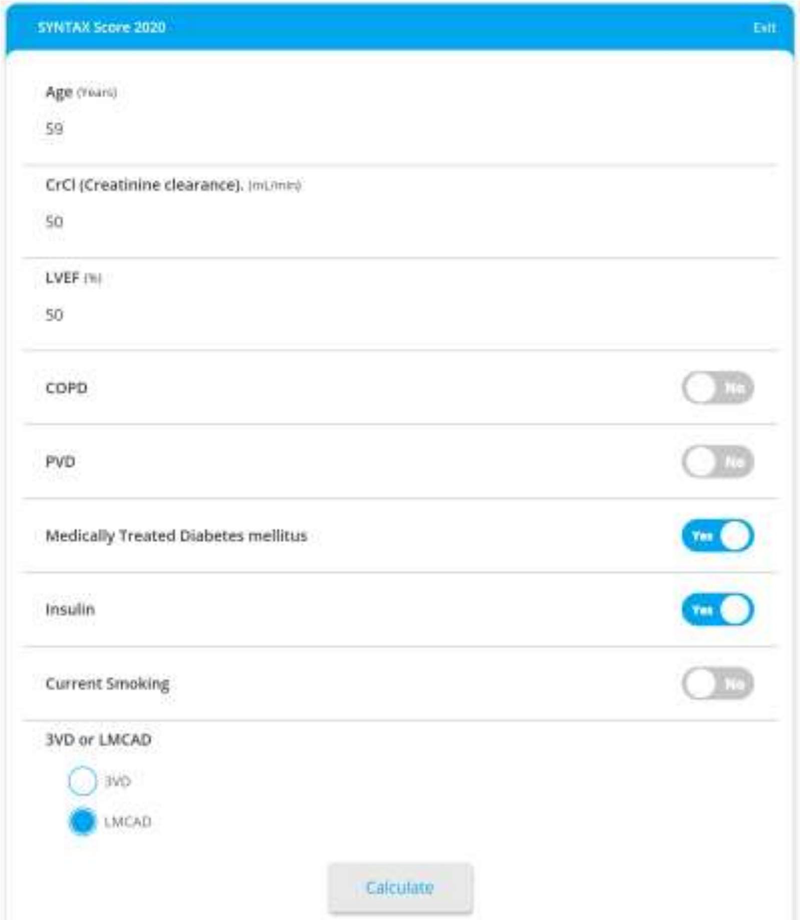
59 yo
Diabetes mellitus
Insulin
LVEF 50%
Creatinine clearance 50ml/min
Left main coronary artery disease



https://syntaxscore2020.com/
Takahashi et al. Lancet. 2020.

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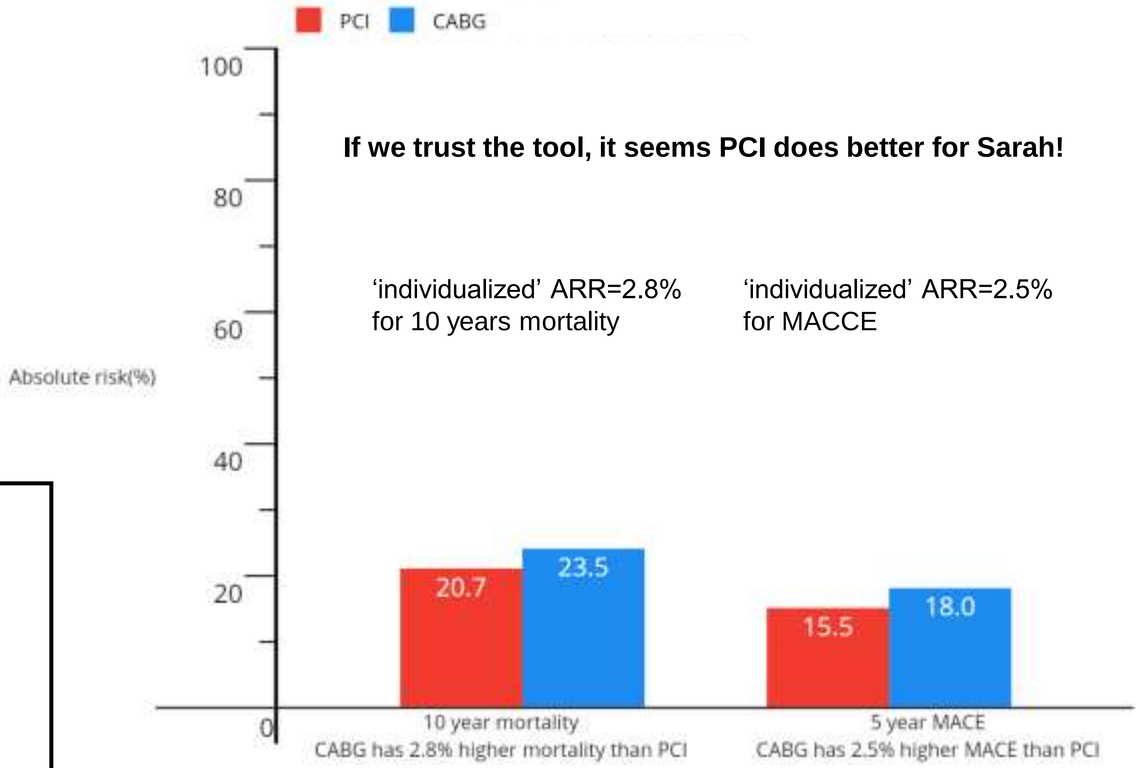

If we trust the tool, it seems PCI does better for Sarah!

'individualized' ARR=2.8% for 10 years mortality

'individualized' ARR=2.5% for MACCE

https://syntaxscore2020.com/
Takahashi et al. Lancet. 2020.

Treatment Effect Modeling: example

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Diabetes mellitus
No insulin
LVEF 45%
Creatinine clearance 40ml/min
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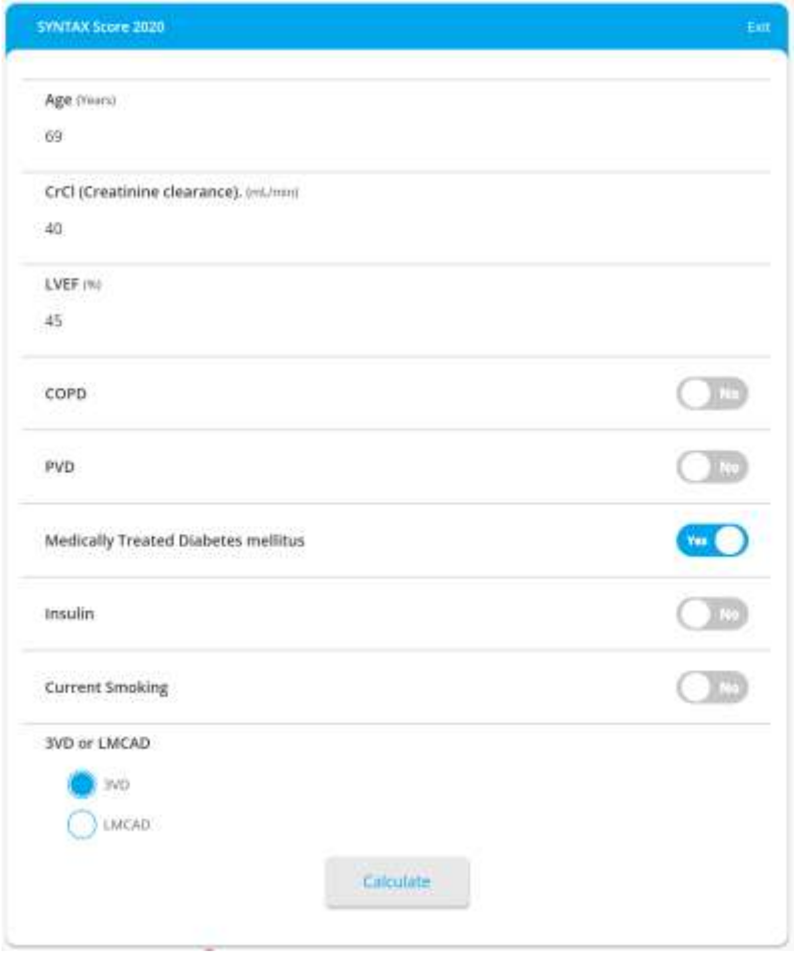

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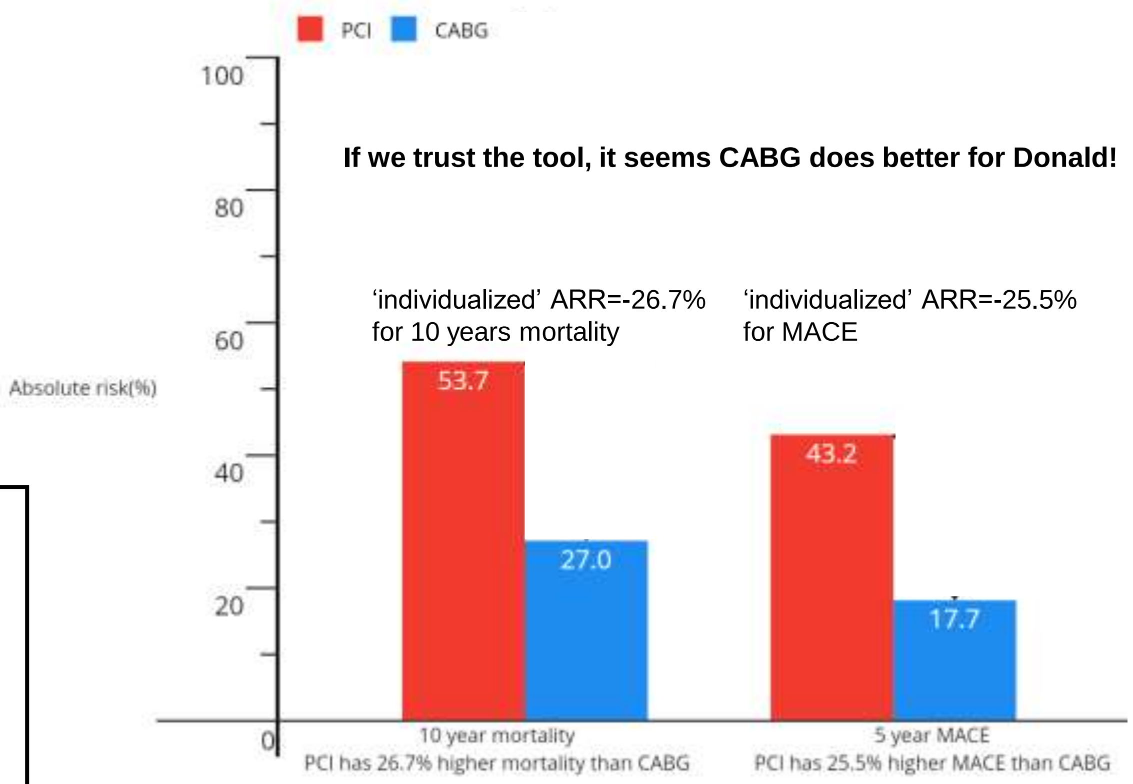

https://syntaxscore2020.com/
Takahashi et al. Lancet. 2020.

Could we do the same with the RRT initiation strategies ?

RESEARCH Open Access

Check for updates

Personalization of renal replacement therapy initiation: a secondary analysis of the AKIKI and IDEAL-ICU trials

François Grolleau[1*], Raphaël Porcher[1], Saber Barbar[2], David Hajage[3], Abderrahmane Bourredjem[4], Jean-Pierre Quenot[5†], Didier Dreyfuss[6†] and Stéphane Gaudry[7†]

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- Data from **AKIKI and IDEAL-ICU**
- **Risk prediction model for RRT initiation within 48 hours** (in delayed strategy)
- Estimate **treatments effects** within levels of predicted risks
- n=**1107 patients**

RESEARCH Open Access

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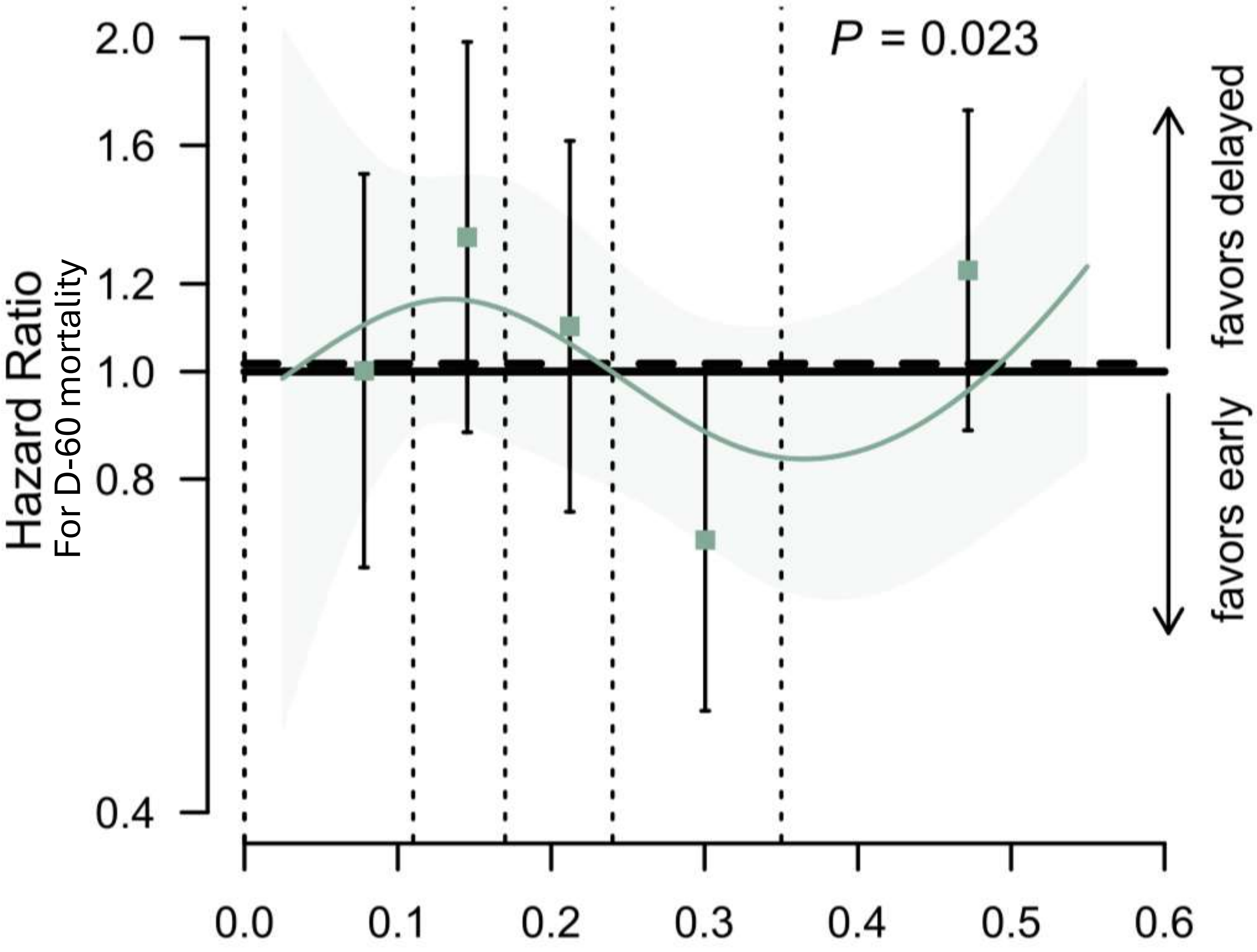
Patients at **intermediate-high risk** of RRT initiation within 48 h may have benefited from an early strategy (absolute risk difference, 14%; 95% CI, − 27% to − 1%)



Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit:

a Precision Medicine Approach

Plug values from the time point when severe acute kidney injury occurs* (KDIGO III or RIFLE failure stage).

SOFA
range in training data: 3 to 21

10

pH
range in training data: 6.88 to 7.54

7,3

Potassium (mmol/L)
range in training data: 2.4 to 7.4 mmol/L

4,5

Urea (mmol/L)
range in training data: 2 to 59 mmol/L

20

Weight (kg)
range in training data: 34 to 200 kg

80

Immunosuppressive Drug (non-corticosteroid)

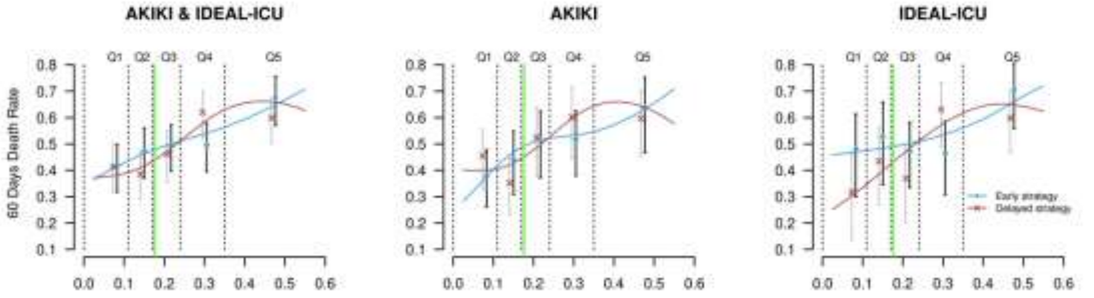
Yes

No

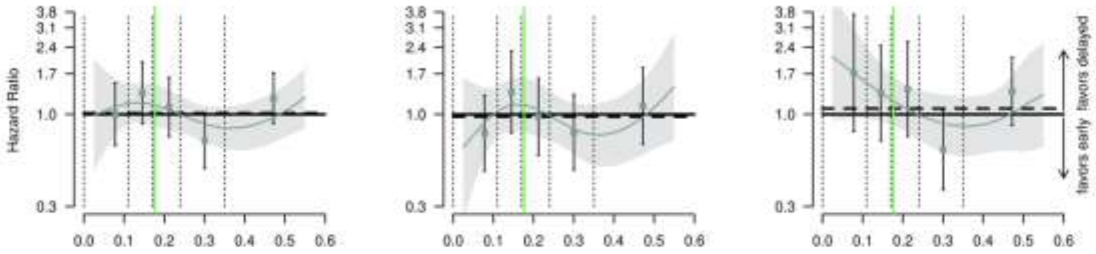
Predict

**Provided the patient meets inclusion/exclusion criterion for the AKIKI or IDEAL-ICU trials.*

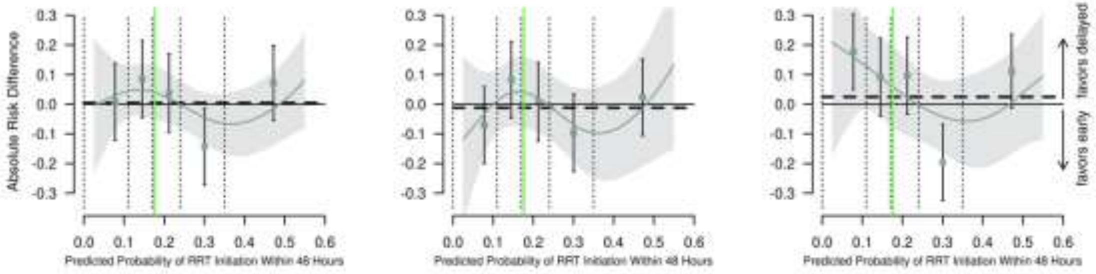
The predicted probablity of RRT initiation within 48 hours is 18% which corresponds to the 60-day mortality outcome below.



	AKIKI & IDEAL-ICU	AKIKI	IDEAL-ICU
Early	48% 95% CI [41%;54%]	49% 95% CI [40%;57%]	49% 95% CI [41%;56%]
Delayed	44% 95% CI [37%;50%]	45% 95% CI [36%;53%]	43% 95% CI [35%;51%]



	AKIKI & IDEAL-ICU	AKIKI	IDEAL-ICU
HR	1.13 95% CI [0.86;1.48]	1.10 95% CI [0.78;1.55]	1.19 95% CI [0.87;1.64]



	AKIKI & IDEAL-ICU	AKIKI	IDEAL-ICU
ARD	4.0% 95% CI [-5.1%;13.0%]	4.1% 95% CI [-8.0%;16.1%]	5.8% 95% CI [-7.8%;19.5%]

RRT = Renal-Replacement Therapy; CI = Confidence Interval; HR = Hazard Ratio; ARD = Absolute Risk Difference

RESEARCH Open Access

Personalization of renal replacement therapy initiation: a secondary analysis of the AKIKI and IDEAL-ICU trials

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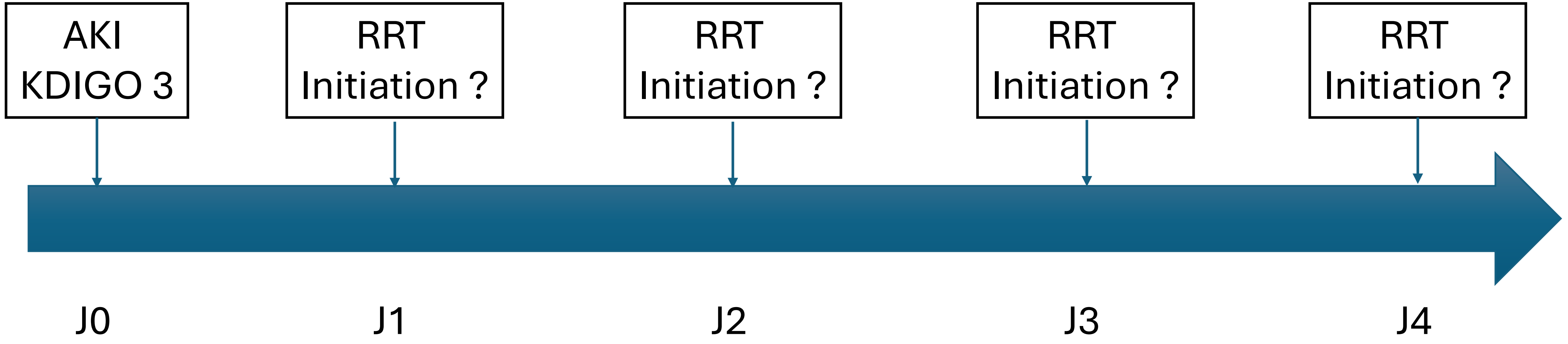
One major issue:

Static case where the decision to initiate RRT is only pondered at AKI onset …..despite the **dynamic nature of AKI**

Cost and Time ++++

To learn an optimal RRT initiation strategy, the ideal method would be to conduct a **Sequential Multiple Assignment Randomized Trial (SMART)** where AKI patients are sequentially randomized each day (RRT or not)



Journal of the American Medical Informatics Association, 2024, 31(5), 1074–1083
https://doi.org/10.1093/jamia/ocae004
Advance access publication 7 March 2024
Research and Applications

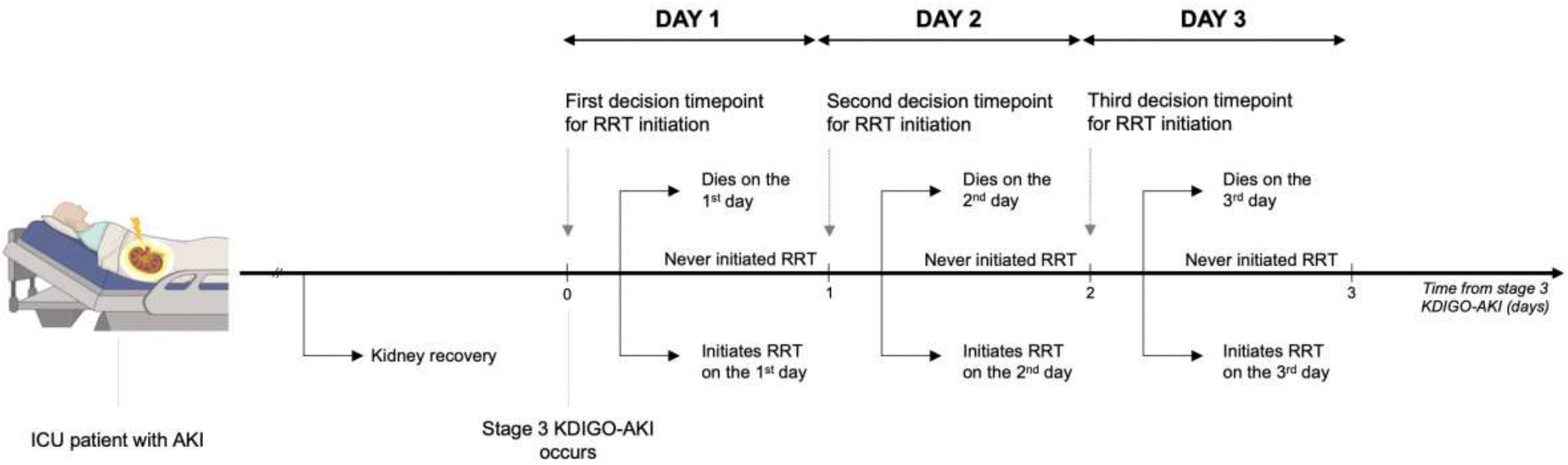
Research and Applications

Personalizing renal replacement therapy initiation in the intensive care unit: a reinforcement learning-based strategy with external validation on the AKIKI randomized controlled trials

François Grolleau, MD, PhD[1,2,*], François Petit, PhD[1,†], Stéphane Gaudry, MD, PhD[3,4,5,†], Élise Diard, MS[1,2], Jean-Pierre Quenot, MD, PhD[6,7,8], Didier Dreyfuss, MD[5,9], Viet-Thi Tran, MD, PhD[1,2], Raphaël Porcher, PhD[1,2]

Statistical reinforcement learning based strategy

optimal dynamic strategies for RRT initiation ?

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Research and Applications

Personalizing renal replacement therapy initiation in the intensive care unit: a reinforcement learning-based strategy with external validation on the AKIKI randomized controlled trials

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Reinforcement learnin

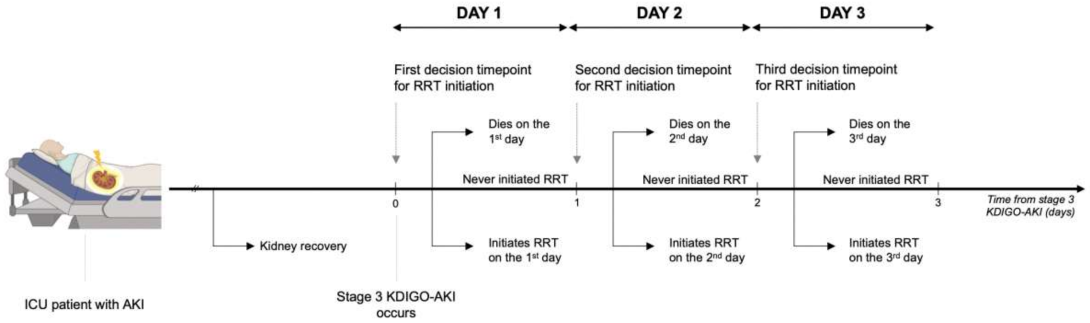
Participants: adult ICU patients with severe AKI, receiving invasive MV and/or,catecholamine infusion

Devellopment
3 748 patients

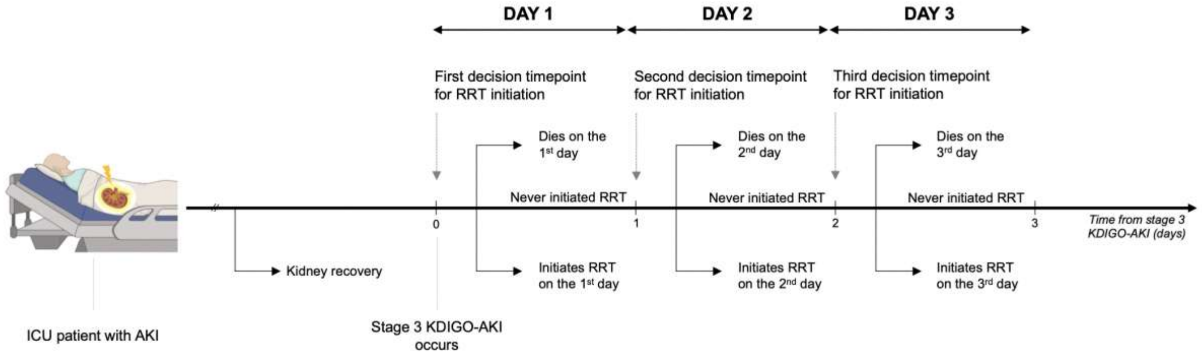
MIMIC-III database

Validation
1 068

AKIKI and AKIKI2



Primary outcome: **hospital-free days at day 60**



Devellopment
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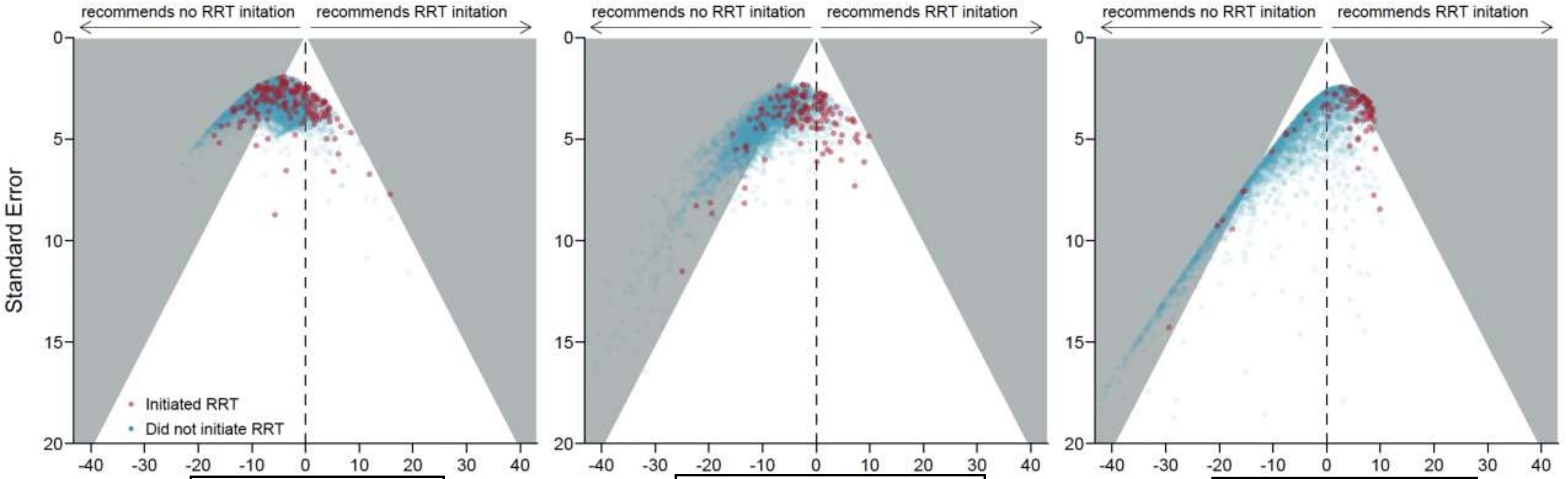
AKIKI and AKIKI2

Parameters that influence decision to start
At day 1, day 2 and day 3

Blip parameter estimates from learned strategies

multiple imputation analysis of one hundred data sets.

Tailoring covariate	$\hat{\psi}$	(95% CI)
First decision		
$Intercept_1$	-39.589	(-63.885 to -15.294)
Age $_{t=1}$ *(years)*	0.245	(0.035 to 0.454)
Creatinine $_{t=1}$ *(mg/dL)*	1.349	(-0.317 to 3.015)
Potassium $_{t=1}$ *(mmol/L)*	3.409	(-0.547 to 7.364)
Second decision		
$Intercept_2$	-7.747	(-23.343 to 7.849)
SOFA score $_{t=2}$	0.514	(-0.372 to 1.400)
Blood urea nitrogen $_{t=2}$ *(mg/dL)*	0.095	(-0.033 to 0.223)
$\lvert pH_{t=1} - pH_{t=2} \rvert$	-63.874	(-118.998 to -8.750)
Urine output $_{t=1}$ + Urine output $_{t=2}$ *(ml/kg/h)*	-7.734	(-15.303 to -0.165)
Third decision		
$Intercept_3$	5.397	(-14.443 to 25.237)
Urine output $_{t=3}$ *(ml/kg/h)*	-19.316	(-34.365 to -4.268)
Blood urea nitrogen $_{t=3}$/Blood urea nitrogen $_{t=1}$	1.922	(-10.974 to 14.818)

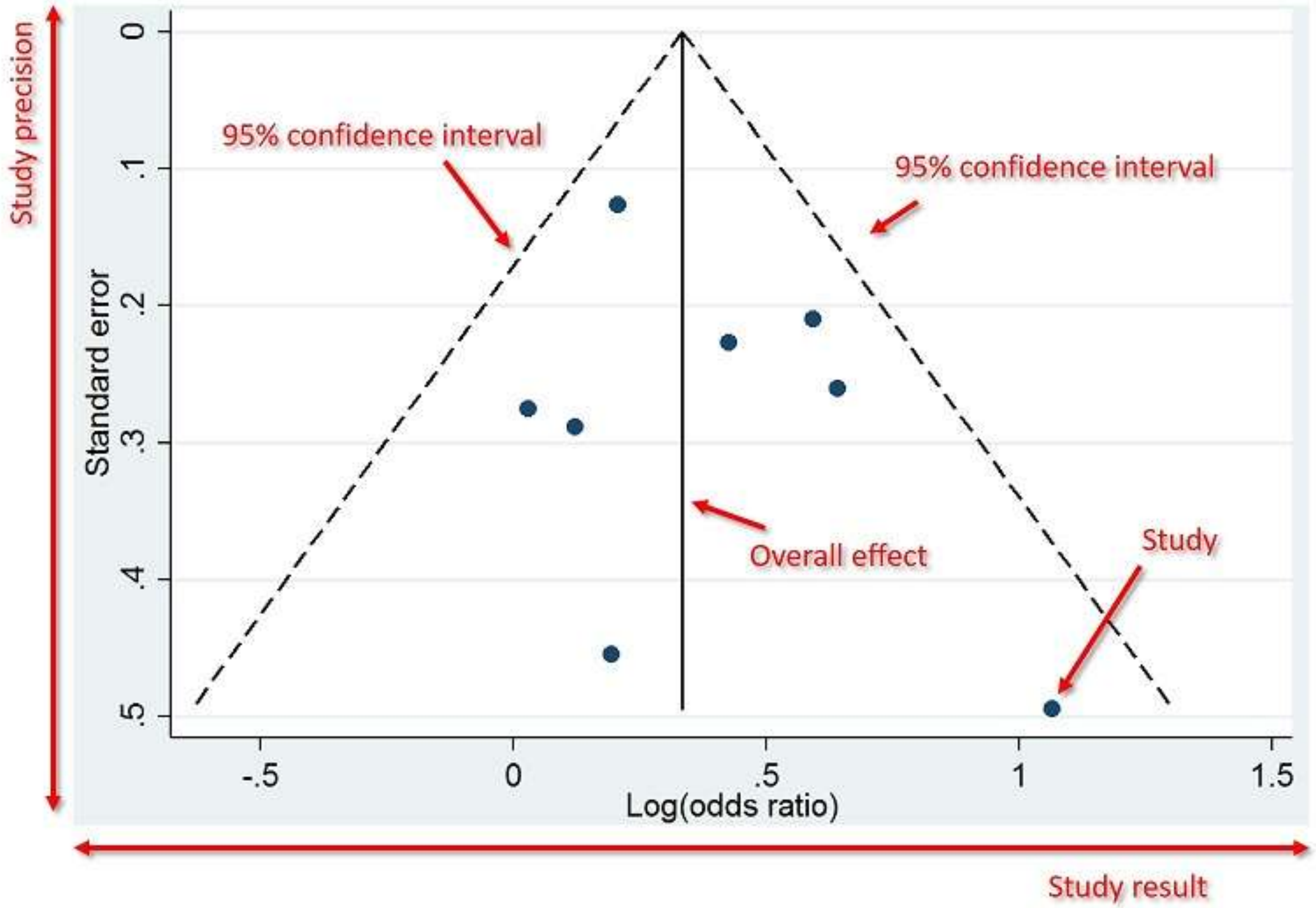


First decision

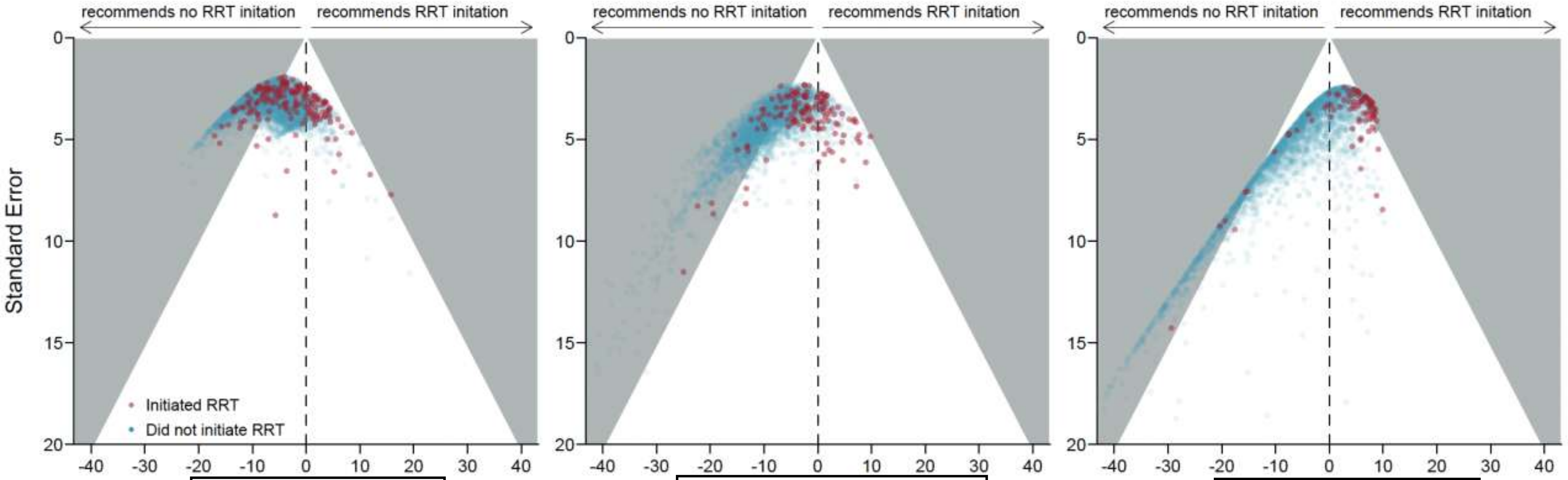
Second decision

Third decision

Figure 2



Inspired by funnel plots in meta-analysis

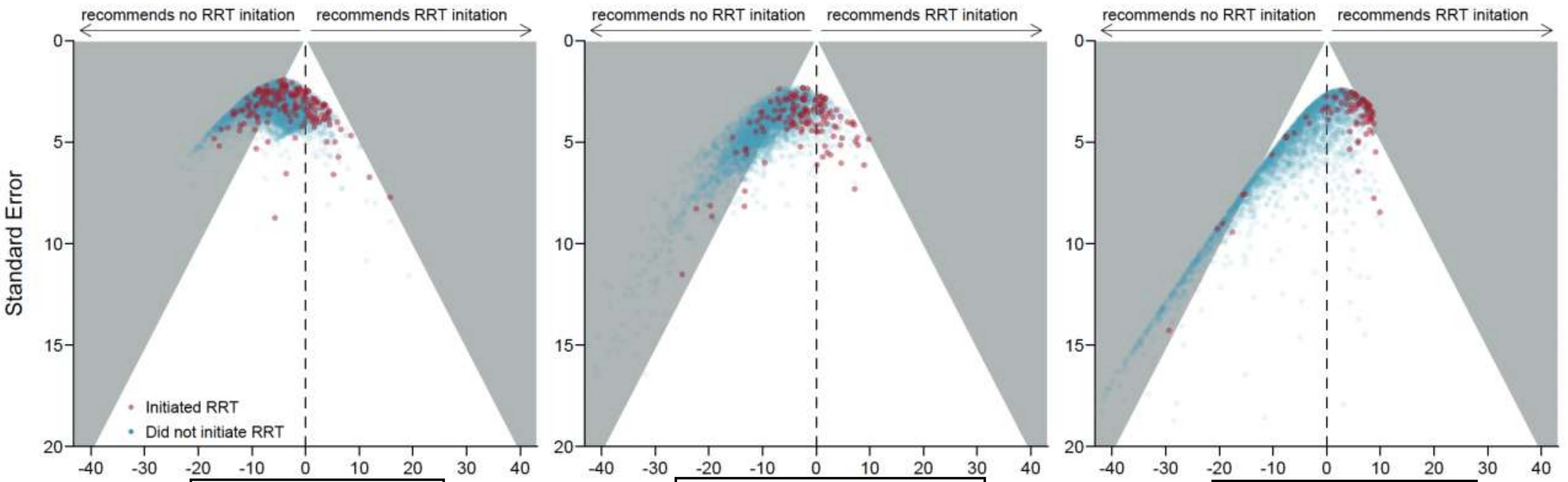


First decision

Second decision

Third decision

- **Each dot** = a **patient** for whom a decision whether to initiate RRT needed to be made
- Dot colors depict the RRT prescription
- **On the on *x*-axis**, predicted blips indicate on a **« Hospital free day D60 » scale** the magnitude of individual-patient harm (negative blips) or benefit (positive blips) from initiating RRT at a particular timepoint.
- **Uncertainty** in the individual-patient blips is represented on ***y*-axis**.

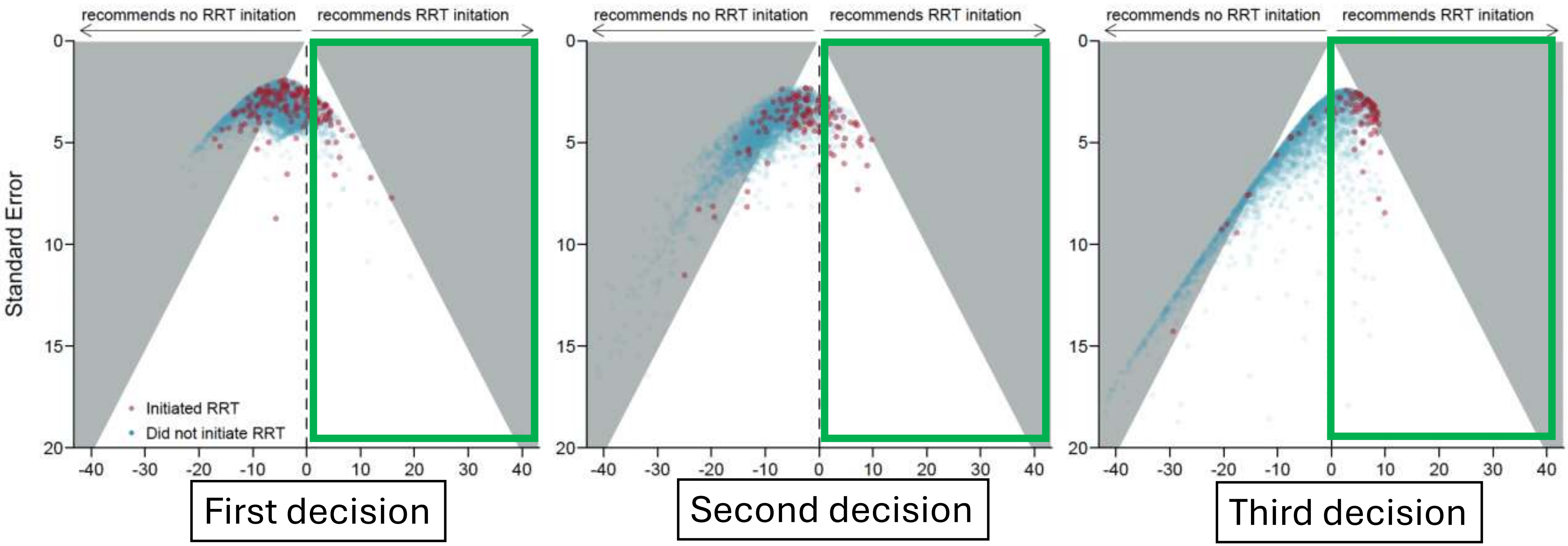


First decision

Second decision

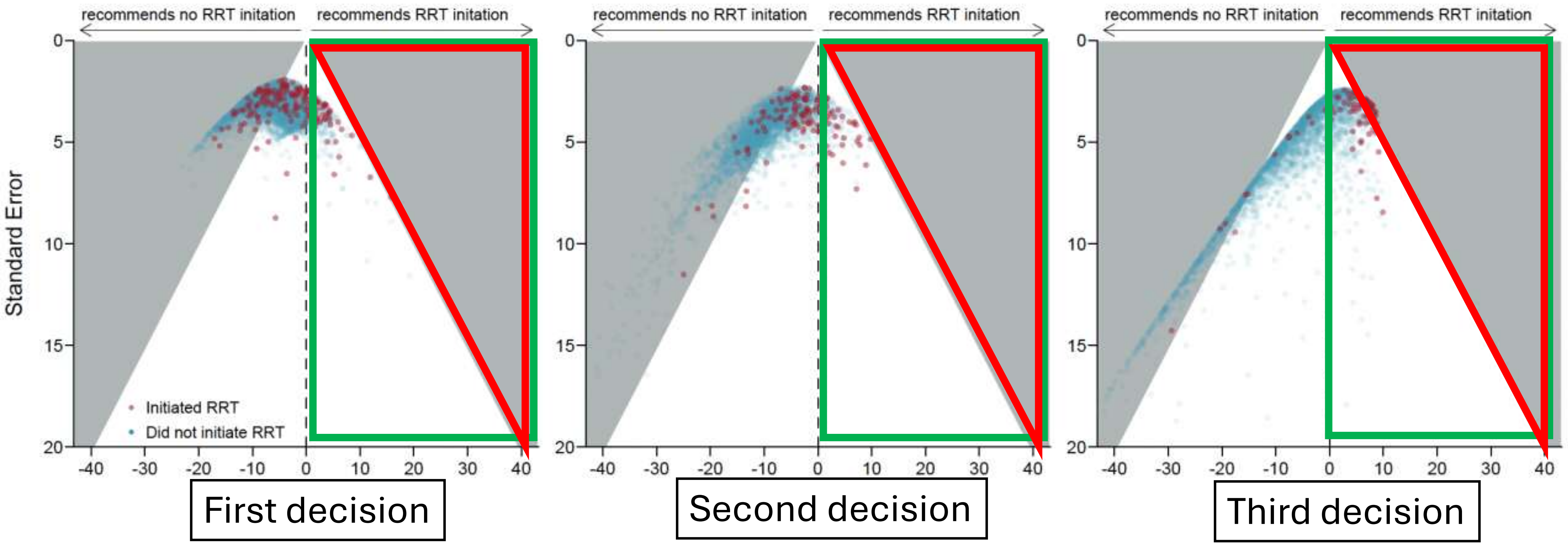
Third decision

Dots falling in **gray-shaded aeras** represent patients for whom there is evidence of either **harm** (left-hand aeras), or **benefit** (right-hand aeras) **from RRT initiation** at the 0.05 alpha level.



- **A crude strategy** would recommend initiating RRT if a patient's dot fell on the right-hand side of the dashed line

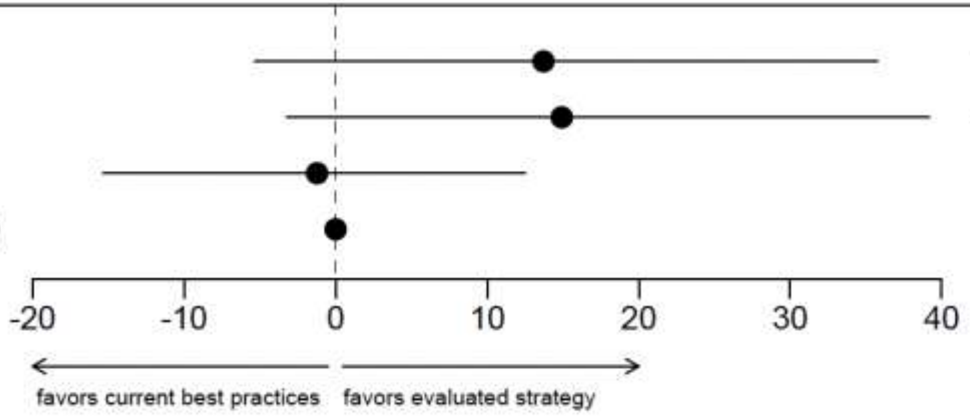
Learning an optimal strategy….



- **A crude strategy** would recommend initiating RRT if a patient's dot fell on the right-hand side of the dashed line
- **A stringent strategy** would recommend initiating RRT only if a patient's dot fell in the right-hand gray-shaded aera.

Learning an optimal strategy….

Evaluated strategy	Mean Difference in HFD60 (95% CI)	Patients initating RRT within three days	Hospital mortality
Crude strategy	13.7 (-5.3 to 35.7)	53%	41%
Stringent strategy	14.9 (-3.2 to 39.2)	14%	38%
Treat all within 24 hours	-1.2 (-15.3 to 12.5)	100%	43%
Standard-delayed (reference)	0 –	38%	45%



Compared to current best practices (i.e., the standard-delayed strategy), the **crude** and **stringent** strategies yielded a 13.7 days and 14.9 days improvement in mean **hospital-free days at day 60** respectively

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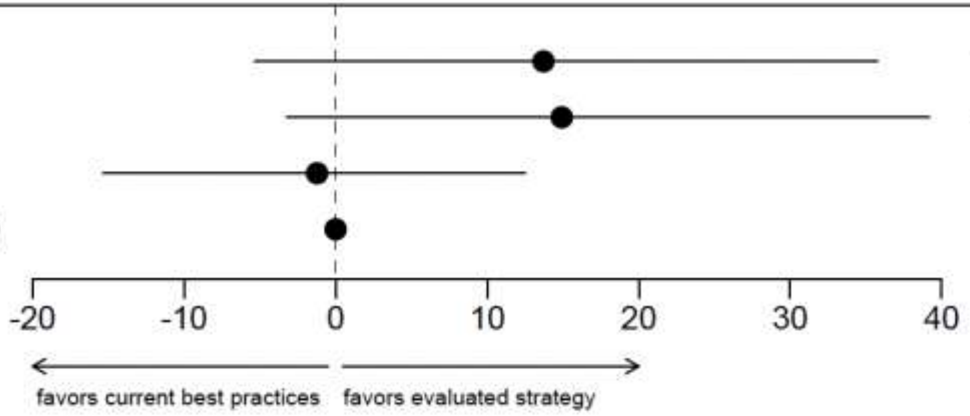


Compared to current best practices (i.e., the standard-delayed strategy), the **crude** and **stringent** strategies yielded a 13.7 days and 14.9 days improvement in mean **hospital-free days at day 60** respectively

Personalizing renal replacement therapy initiation in the ICU: a statistical reinforcement learning approach

First day

Plug values the variables below take at the time stage 3 KDIGO-AKI occurs.

Age (years)
range in validation set: 19 to 90

70

Creatinine (mg/dL)
range in validation set: 0.3 to 10.4

2,5

Blood urea nitrogen (mg/dL)
range in validation set: 5 to 140

55

Potassium (mmol/L)
range in validation set: 2.6 to 8.0

5

pH (mmol/L)
range in validation set: 6.88 to 7.63

7,3

Urine output (mL/kg/h)
range in validation set: 0.0 to 7.2

0,1

Second day

Plug values the variables below take just before stage 3 KDIGO-AKI occurrence + 24 hours.†

SOFA
range in validation set: 3 to 20

10

Blood urea nitrogen (mg/dL)
range in validation set: 5 to 215

65

pH (mmol/L)
range in validation set: 6.50 to 7.63

7,35

Urine output (mL/kg/h)
range in validation set: 0.0 to 4.8

0

Third day

Plug values the variables below take just before stage 3 KDIGO-AKI occurrence + 48 hours.‡

Blood urea nitrogen (mg/dL)
range in validation set: 5 to 151

68

Urine output (mL/kg/h)
range in validation set: 0.0 to 4.5

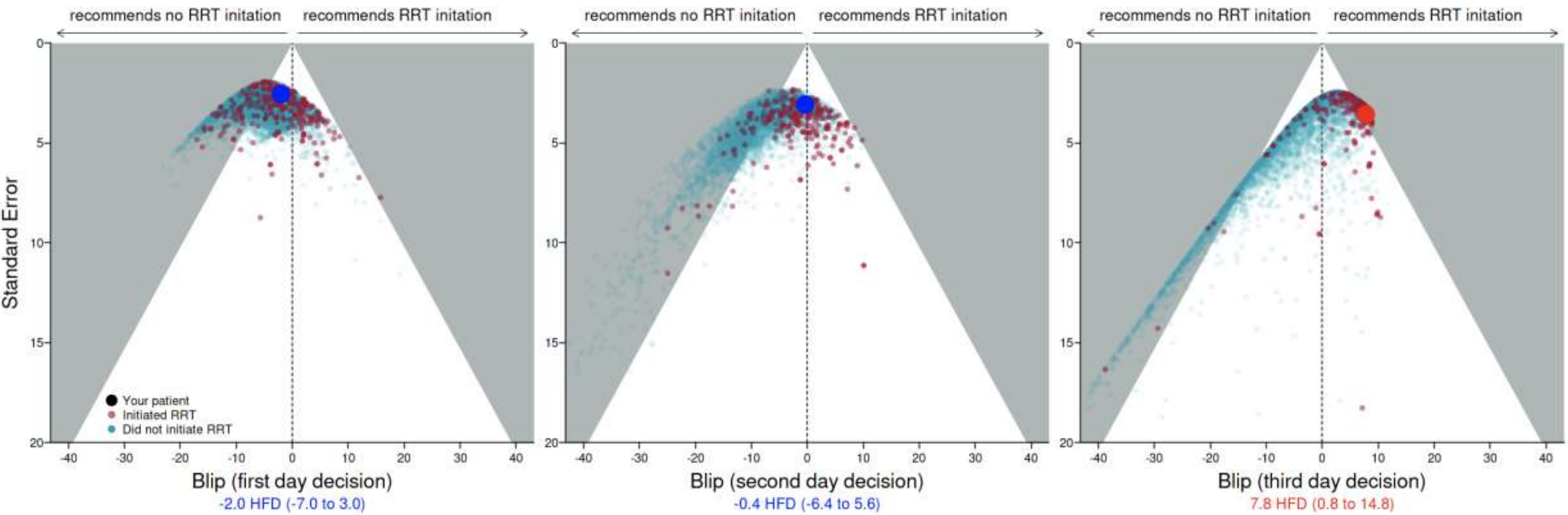
0

SEE INDIVIDUAL-PATIENT RECOMMENDATION

Personalizing renal replacement therapy initiation in the ICU:
a statistical reinforcement learning approach

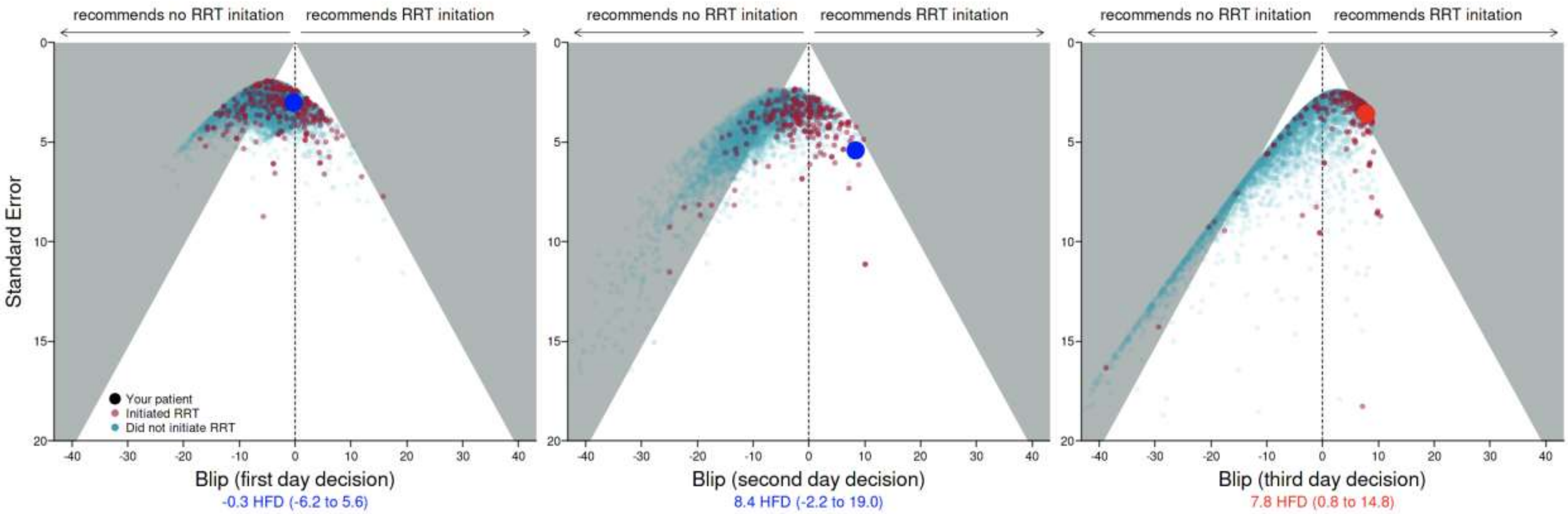
For a patient with stage 3 KDIGO-AKI and the evolving characteristics below, the stringent strategy recommends:

RRT initiation on the third day (i.e., between 48 and 72 hours after stage 3 KDIGO-AKI occurence).



Example 1: the stringent strategy recommends RRT initiation on the third day

http://dynamic-rrt.eu/



- **Another example**
- The crude strategy recommends to initiate RRT the second day
- The stringent recommend to initiate RRT the third day

http://dynamic-rrt.eu/

What is the future for personalization of RRT initiation ?

1. Integrate the **recommendation system with the software of some ICU** for an automatic extraction at time 0 (KDIGO 3) and the data necessary to make recommendations
2. Make **decisions jointly by intensivist and the recommendation system**
3. After 5 years, **redevelop the recommendation system** to make it more robust

   (it can now be trained on more data that has been automatically extracted and specifically collected to answer this question)

4. **Repeat steps (1-3) every 5 years** until system performance reaches a plateau

RRT modalities: what’s new ?

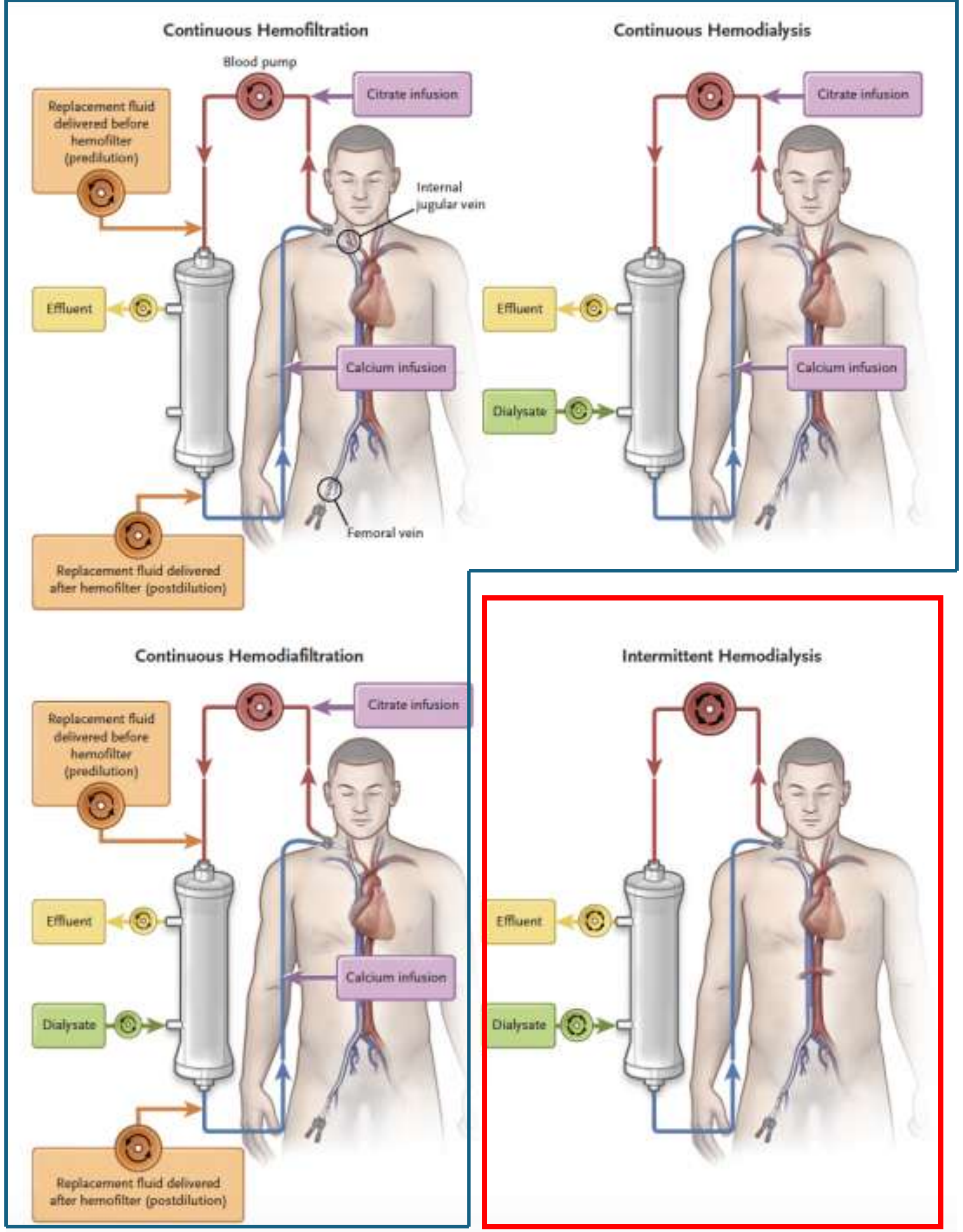
REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

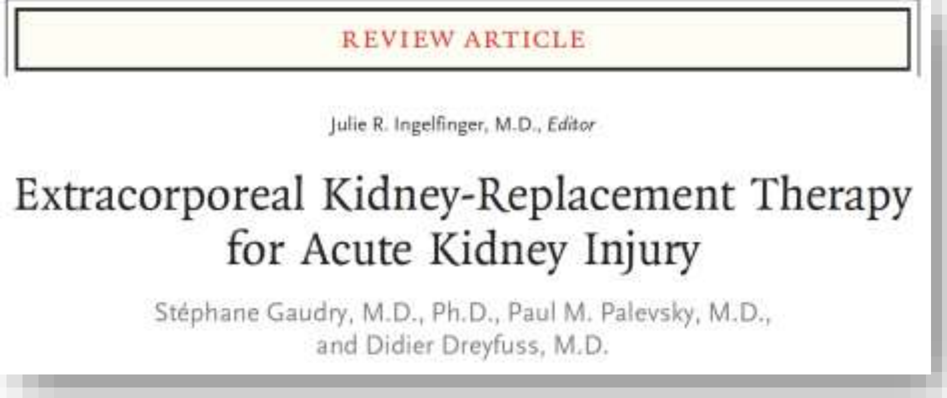
Extracorporeal Kidney-Replacement Therapy for Acute Kidney Injury

Stéphane Gaudry, M.D., Ph.D., Paul M. Palevsky, M.D., and Didier Dreyfuss, M.D.

CRRT



IHD



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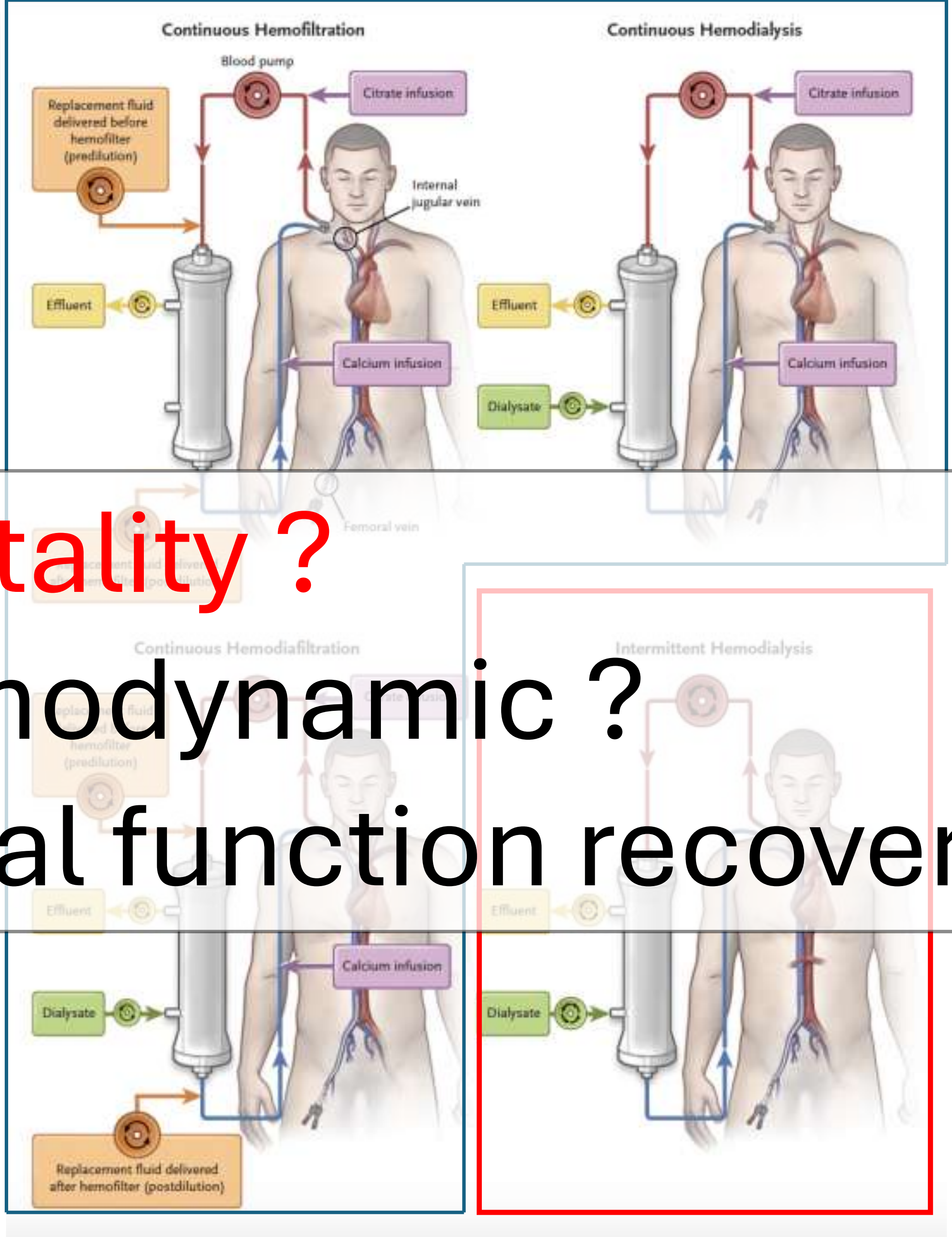


CRRT

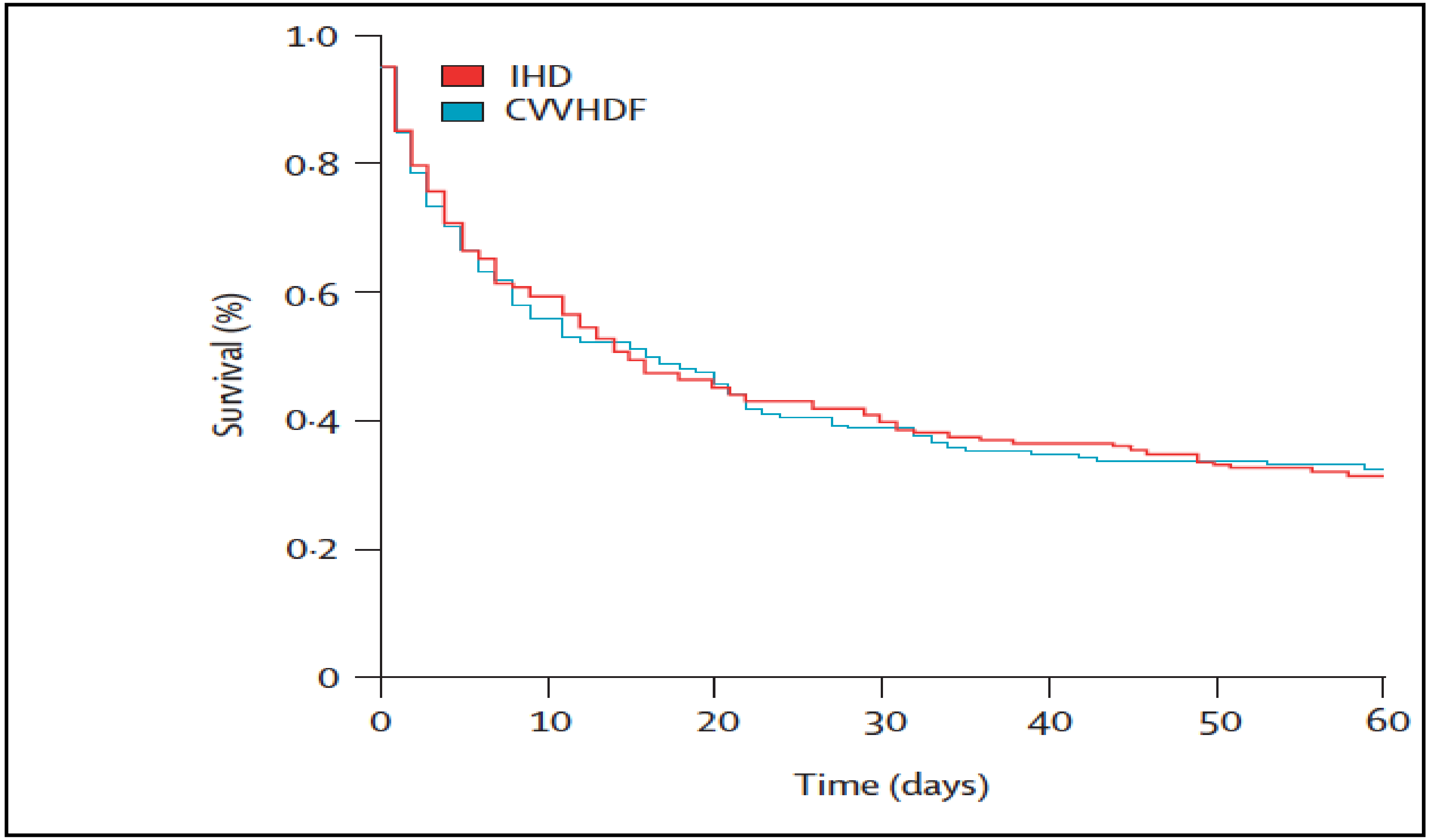
- Mortality ?
- Hemodynamic ?
- Renal function recovery ?

IHD

Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial

Christophe Vinsonneau, Christophe Camus, Alain Combes, Marie Alyette Costa de Beauregard, Kada Klouche, Thierry Boulain, Jean-Louis Pallot, Jean-Daniel Chiche, Pierre Taupin, Paul Landais, Jean-François Dhainaut, for the Hemodiafe Study Group*

Lancet 2006
HEMODIAFE



RESEARCH Open Access

Continuous renal replacement therapy *versus* intermittent hemodialysis as first modality for renal replacement therapy in severe acute kidney injury: a secondary analysis of AKIKI and IDEAL-ICU studies

Stéphane Gaudry[1,2,3,4*], François Grolleau[5], Saber Barbar[6], Laurent Martin-Lefevre[7], Bertrand Pons[8], Éric Boulet[9], Alexandre Boyer[10], Guillaume Chevrel[11], Florent Montini[12], Julien Bohe[13], Julio Badie[14], Jean-Philippe Rigaud[15], Christophe Vinsonneau[16], Raphaël Porcher[5], Jean-Pierre Quenot[17,18,19†] and Didier Dreyfuss[3,20†]

Critical Care 2022

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MATERIALS AND METHODS

- **Secondary analysis** of two multicentre RCTs (**AKIKI** and **IDEAL-ICU**)
- We **merged the two datasets**
- We included **patients allocated to the early strategy** in order to emulate a trial where patients would have been randomised to receive either IHD or CRRT within 12 hours after severe AKI

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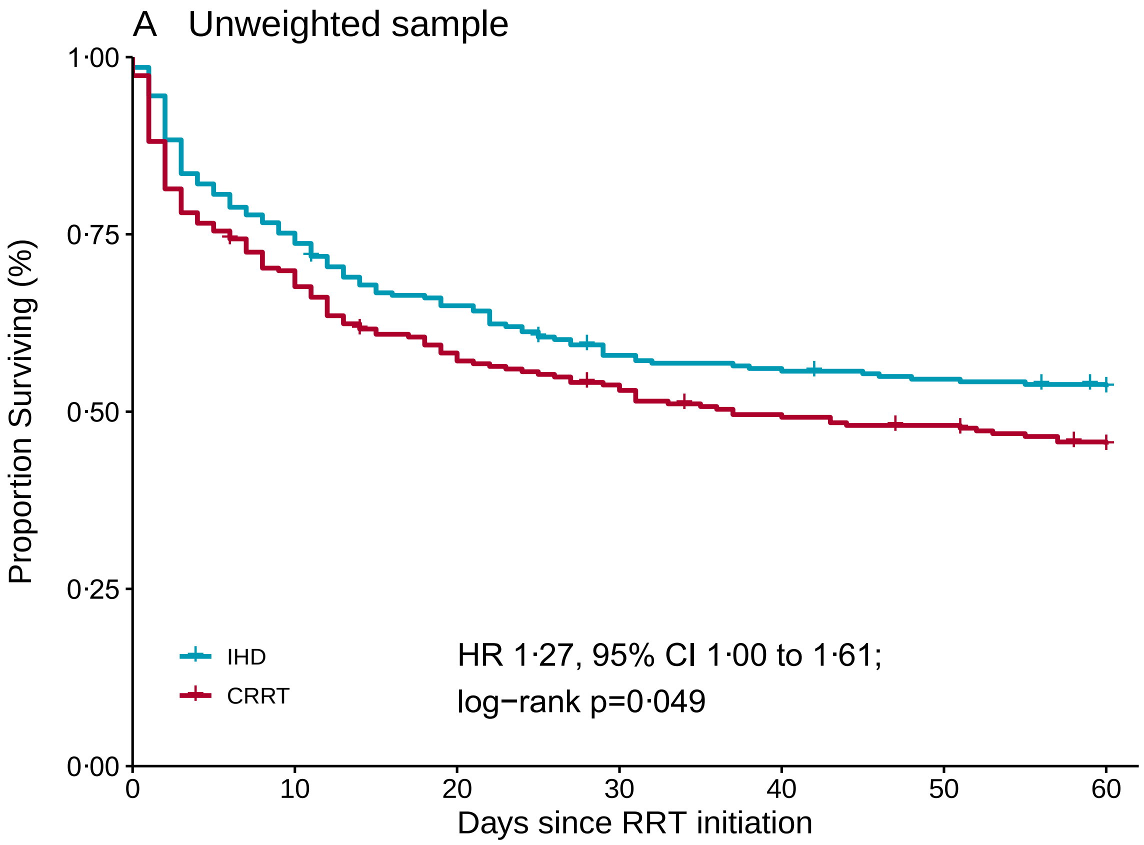
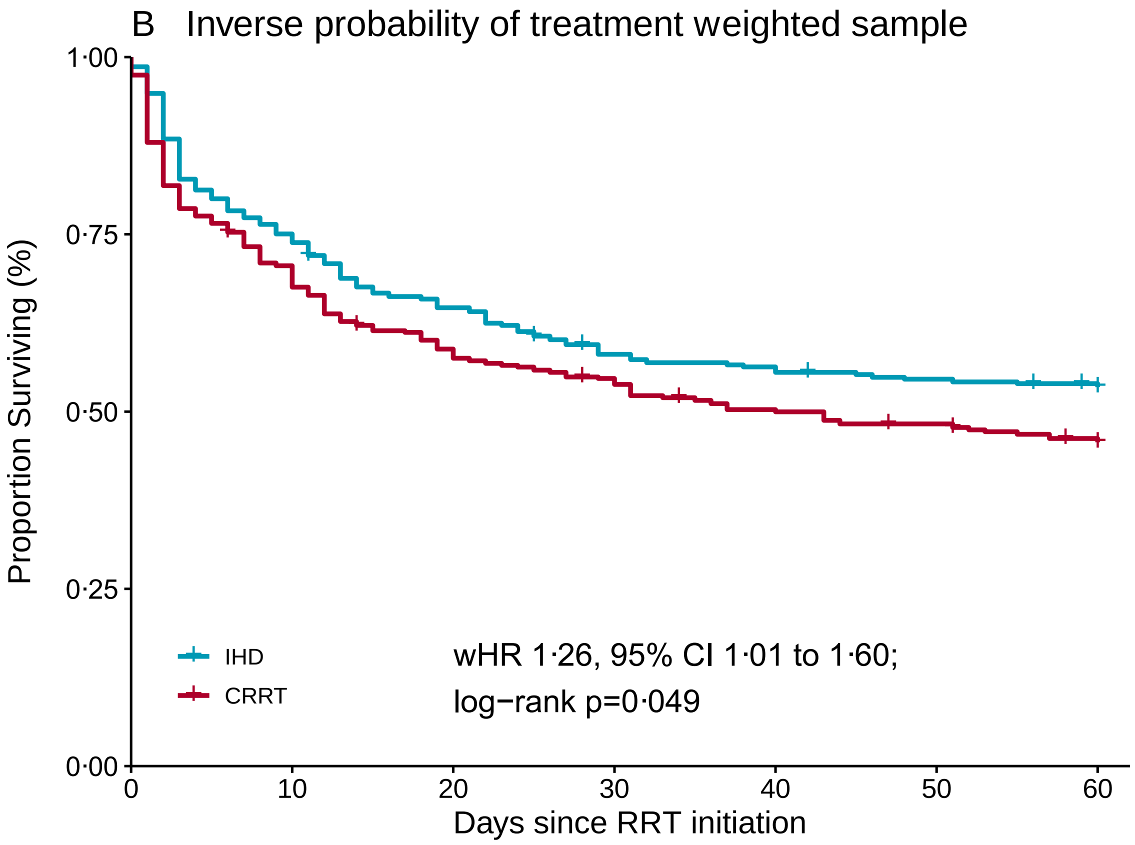
- Primary outcome: **60-day overall survival**
- **Propensity-score methods** to balance the differences in baseline characteristics between groups



Number at risk

IHD	274	206	177	156	151	146	142
CRRT	269	187	155	142	130	125	117



Number at risk

IHD	272	204	175	155	150	145	142
CRRT	268	188	156	144	132	126	119

The weighted Kaplan-Meier death rate at day 60 was 54·4% in the CRRT group and 46·5% in the IHD group (weighted HR 1·26, 95% CI 1·01 to 1·60)

Initiation of Continuous Renal Replacement Therapy Versus Intermittent Hemodialysis in Critically Ill Patients with Severe Acute Kidney Injury: A Secondary Analysis of STARRT-AKI trial

Ron Wald[1], Stephane Gaudry[2], Bruno R. da Costa[3], Neill K.J. Adhikari[4], Rinaldo Bellomo[5], Bin Du[6], Martin P. Gallagher[7], Eric A. Hoste[8], François Lamontagne[9], Michael Joannidis[10], Kathleen D. Liu[11], Daniel F. McAuley[12], Shay P. McGuinness[13], Alistair D. Nichol[14], Marlies Ostermann[15] Paul M. Palevsky[16], Haibo Qiu[17], Ville Pettilä[18], Antoine G. Schneider[19], Orla M. Smith[20], Suvi T. Vaara[21], Matthew Weir[22], Didier Dreyfuss[23], Sean M Bagshaw[24]

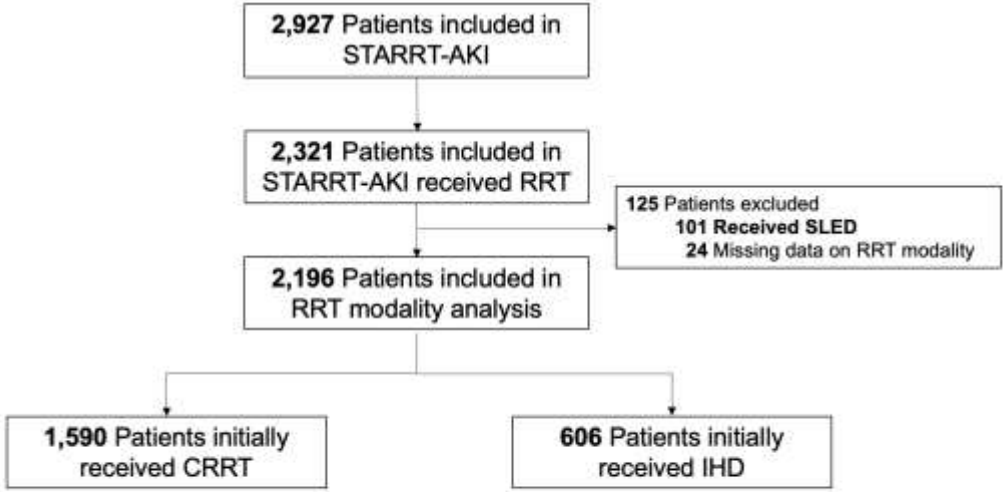
On behalf of the STARRT-AKI Investigators§

STARRT AKI

Ron Wald

Sean Bagshaw

- **All patients** (<u>early and delayed group</u>)
- **Propensity score methods**
- **Primary outcome:** composite of death or RRT dependence at 90-days



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On behalf of the STARRT-AKI Investigators§

STARRT AKI

Ron Wald

Sean Bagshaw

After balancing baseline characteristics, CRRT was associated with a lower risk of the death or RRT dependence at 90-days compared with IHD (**OR 0.81; 95% CI, 0.66-0.99**)

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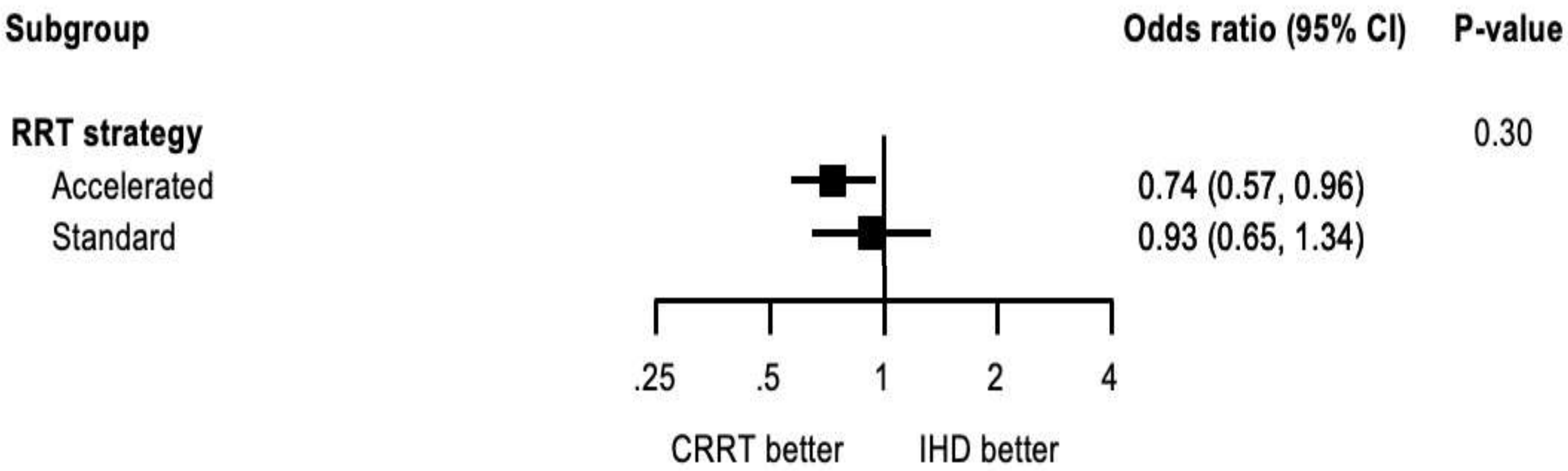

To summarize

- **No modality of RRT shows clear superiority** (mortality, hypotension)
- Previous studies provided **conflicting results on renal recovery**
  - A majority of **observational** studies
    - ✓ persistence of cofounding by indication
    - ✓ renal recovery define strictly as independence from RRT
- We need **additional trials with composite outcome** (mortality and renal recovery)

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ
Liberté
Égalité
Fraternité

ICRAKI trial

non-inferiority multicenter open-label randomized controlled trial

PHRC 2022

- Adults under invasive MV or receiving catecholamine infusion
- RRT indication(s)
  - severe hyperK+, severe metabolic acidosis, severe pulmonary edema
  - AKI stage 3 with serum urea concentration >40 mmol/L or oligo-anuria>3 days

RANDOMIZATION

CRRT group

IHD group

Primary endpoint
major adverse kidney event 90 days after randomization (MAKE90)
death *or* RRT *or* serum creatinine > 25% basal value

Number of participants: 1000
ICU centers: n=26

Critical Care and Resuscitation 27 (2025) 100107

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Original Article

Study protocol and statistical plan for the ICRAKI trial: Intermittent haemodialysis versus continuous renal replacement therapy for severe acute kidney injury in critically ill patients☆

ICRAKI trial

Inclusion rate: **501**/1000

In my clinical practice

Within 24/48 hours after ICU admission

- Avoid RRT
- Avoid UF

Before weaning off vasopressors

UF? Probably not…

After weaning off vasopressors

- UF +
- Adapt to goals and tolerance
- **IHD** for patients who need **rehabilitation**
- **CRRT** for **very fragile patients** with persistent capilary leak

If IHD: use **long sessions**!!
Other option: hybrid therapies

MERCI !

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CORAKID, UMRS 1155, Tenon, PARIS