FUTURE THERAPIES FOR AKI- WHAT'S LIKELY TO MAKE IT TO THE CLINIC?

Patrick Murray, MD, FASN, FRCPI, FJFICMI,
University College Dublin School of Medicine,
KDIGO AKI Controversies Conference Plenary 3
Rome, April 26th, 2019

Disclosures: Patrick Murray

- Scientific Advisory Boards:
  - FAST Biomedical
  - AM-Pharma
  - Sphingotec
- Research Funding:
  - Abbott
  - Genomic Medicine Ireland

Conceptual framework for AKI risk

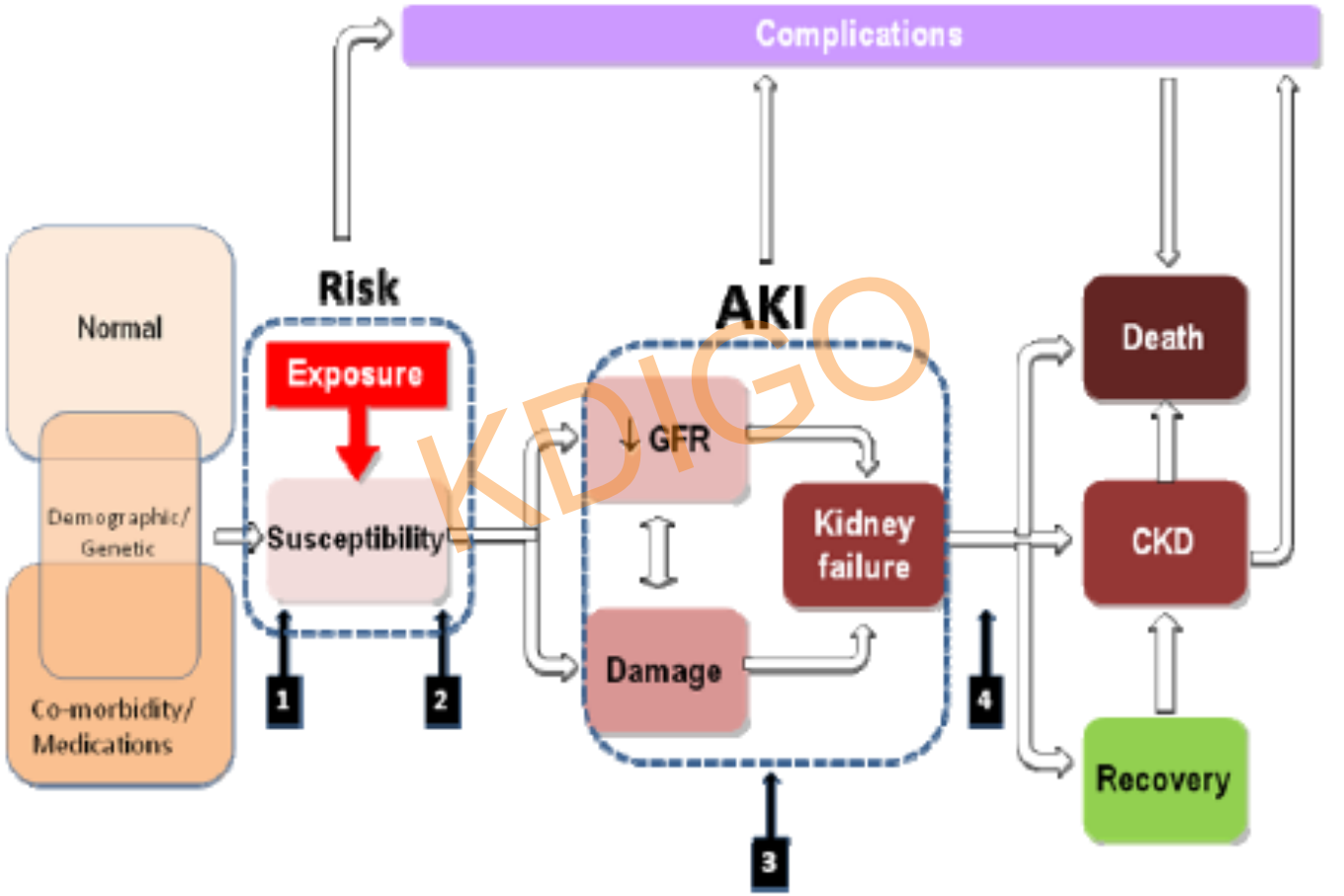


Figure 1: Suggested levels of risk assessment with relevance to AKI

Primary Prevention

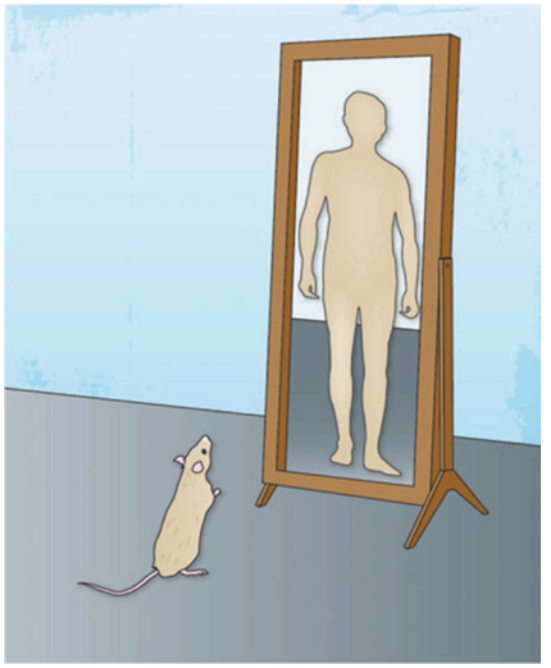
Secondary Prevention

AKI Therapy: State of the Art

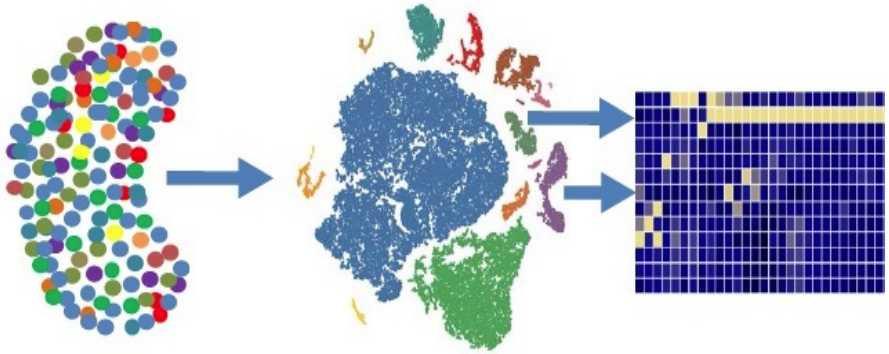
No drug has been developed and approved for the prevention or therapy of AKI

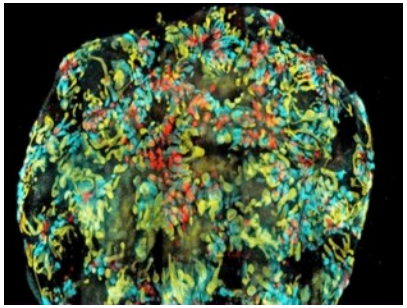
- Experimental models may be unrepresentative of clinical AKI
  - Patient comorbidities (chronic diseases; multiple acute insults)
    - Solution: greater model complexity (co-morbidities, co-interventions, delayed administration timepoints)
  - Delayed, mis-directed therapy in clinical trials
    - Solution: biomarker-guided early intervention trials; BM-enriched case definitions

Tools for the future….

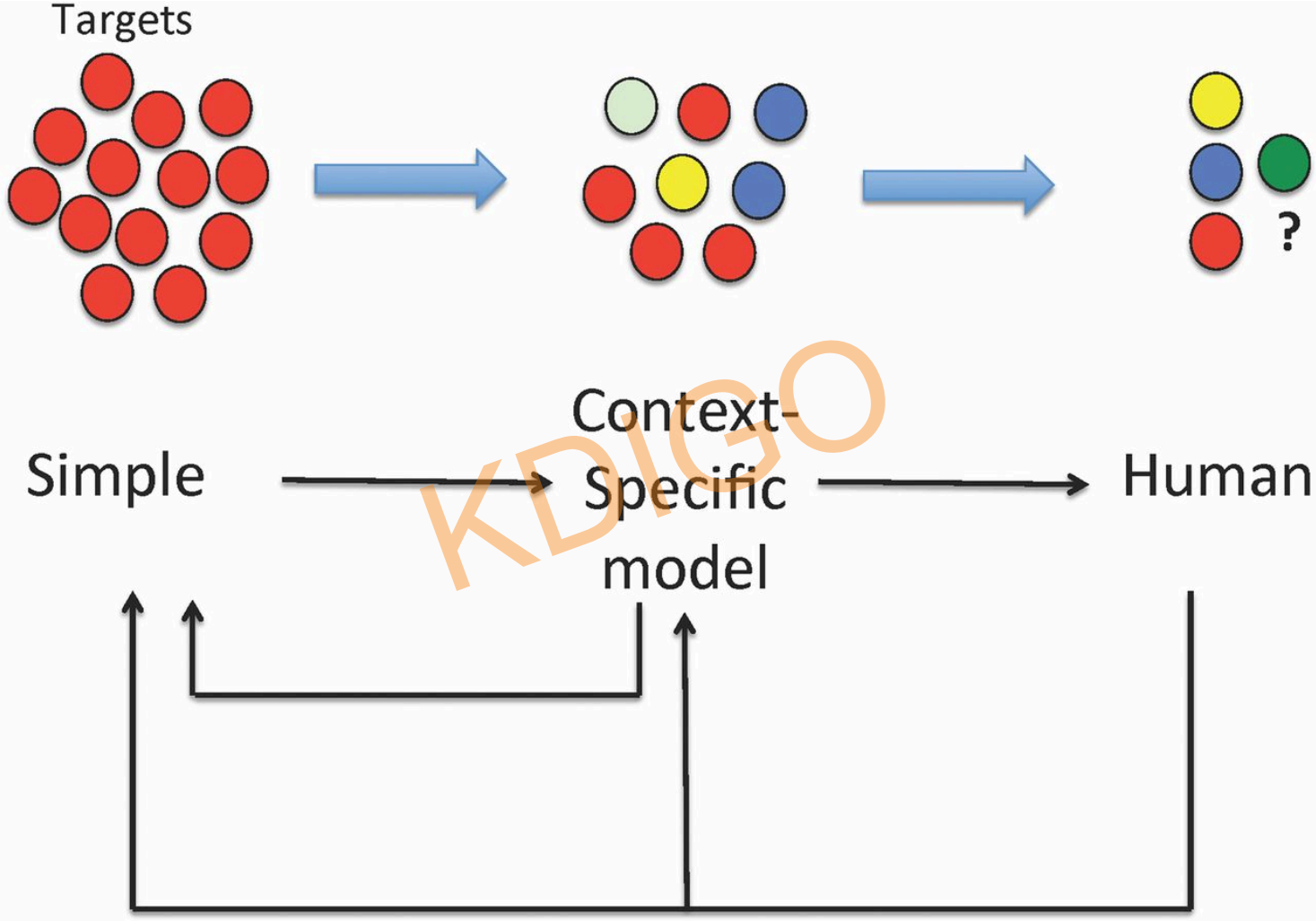


Justice M., Disease Models & Mechanisms 2016 9: 101-103



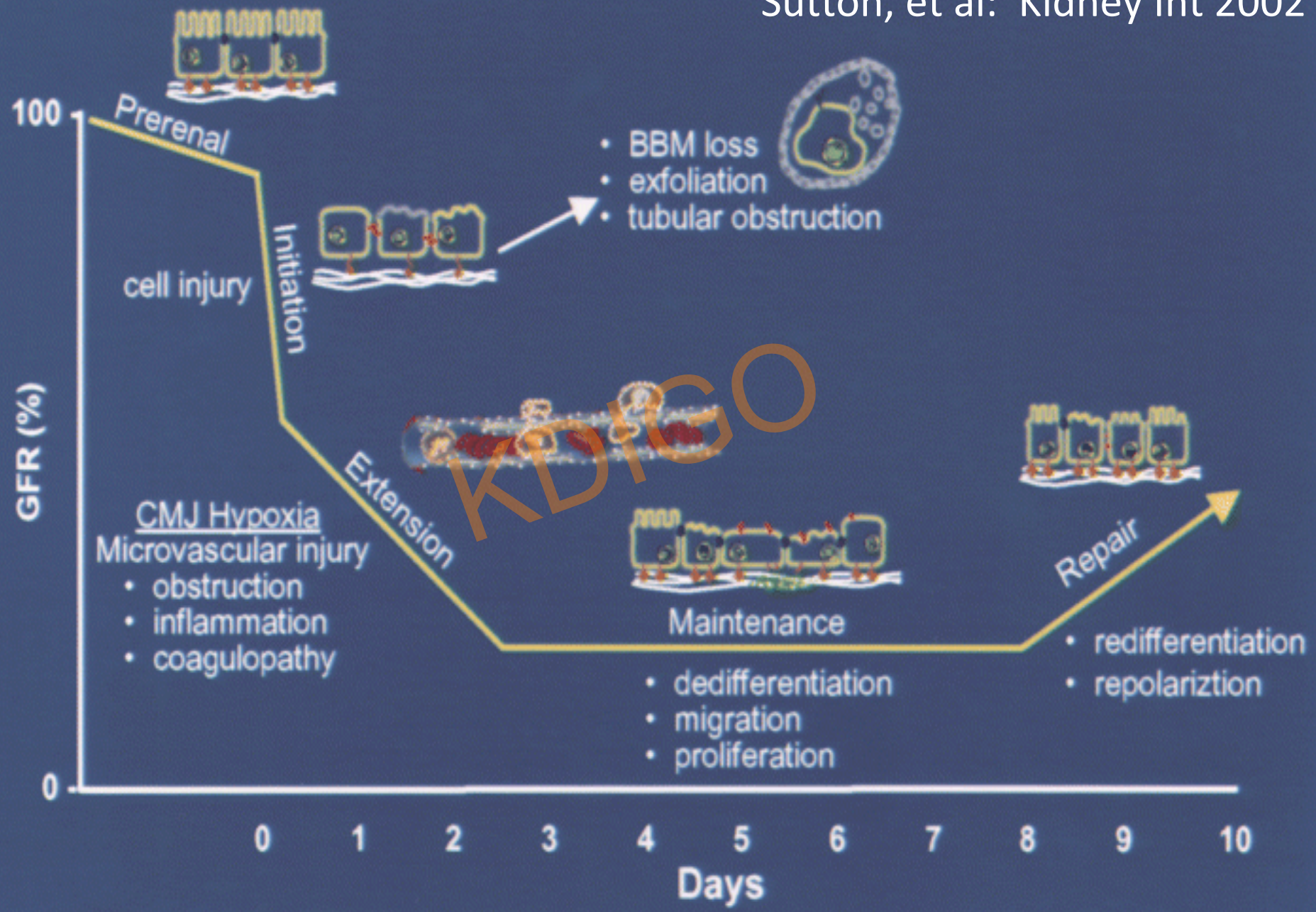


Development & Translation of Experimental Models of AKI

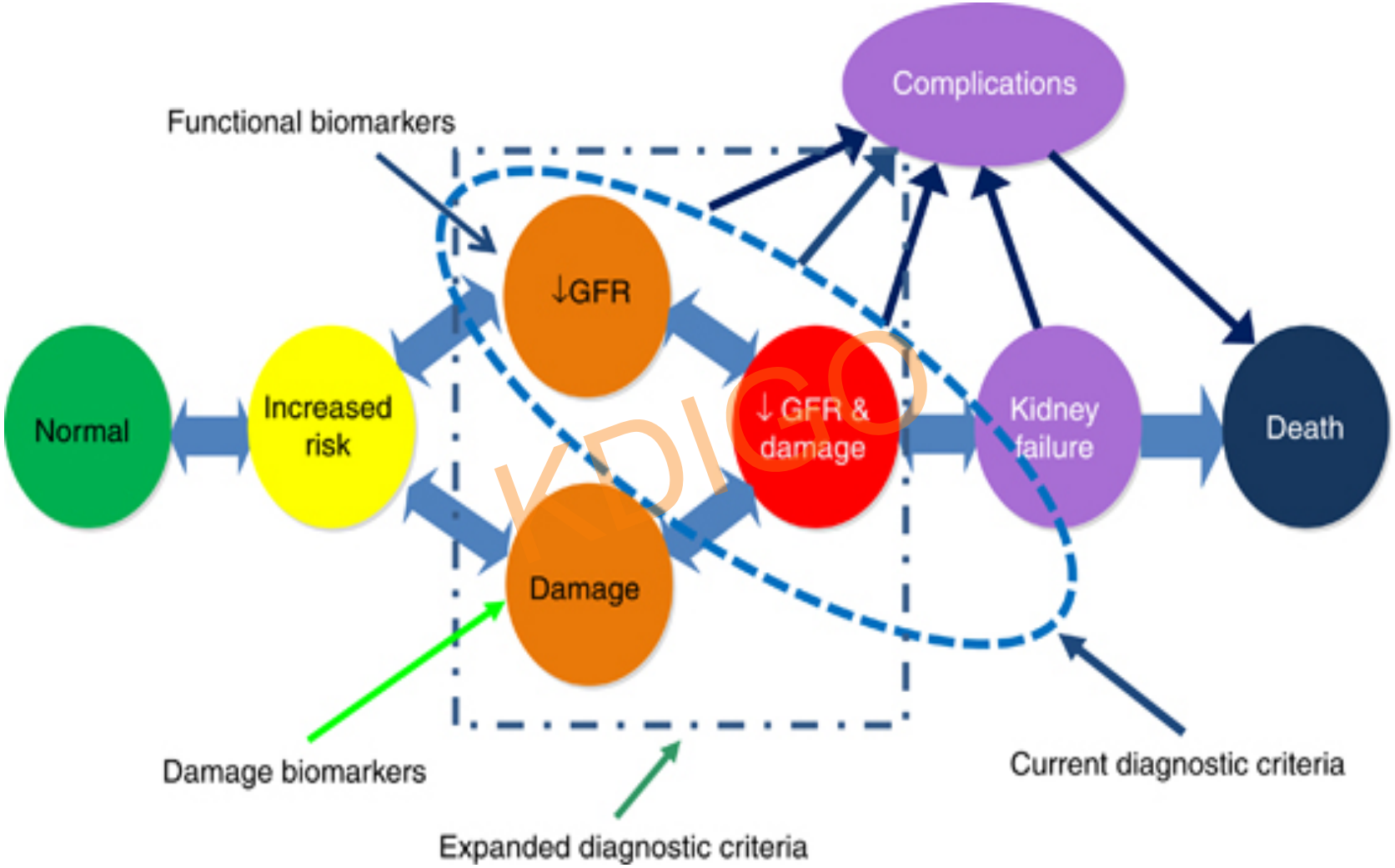


Anupam Agarwal et al. JASN 2016;27:1288-1299

Sutton, et al: Kidney Int 2002



Evolution of AKI Conceptual Framework



www.ADQI.org

ADQI

Murray PT, et al, for the ADQI Workgroup: 2014;85:513-521

Pharmacologic Approach to Optimization of Renal Perfusion

- **1) MAP: fluids, inotropes, pressors targeting MAP 60-80mmHg**
- **2) CO: fluids, inotropes, vasodilators to achieve "adequate" cardiac output**
- 3) Renovascular resistance: renal vasodilators
- 4) Corticomedullary blood flow distribution: renal vasodilators
- 5) Renal tubular oxygen consumption: diuretics (±other effects: loop diuretics, mannitol)

AKI in Sepsis: Effects of EGDT

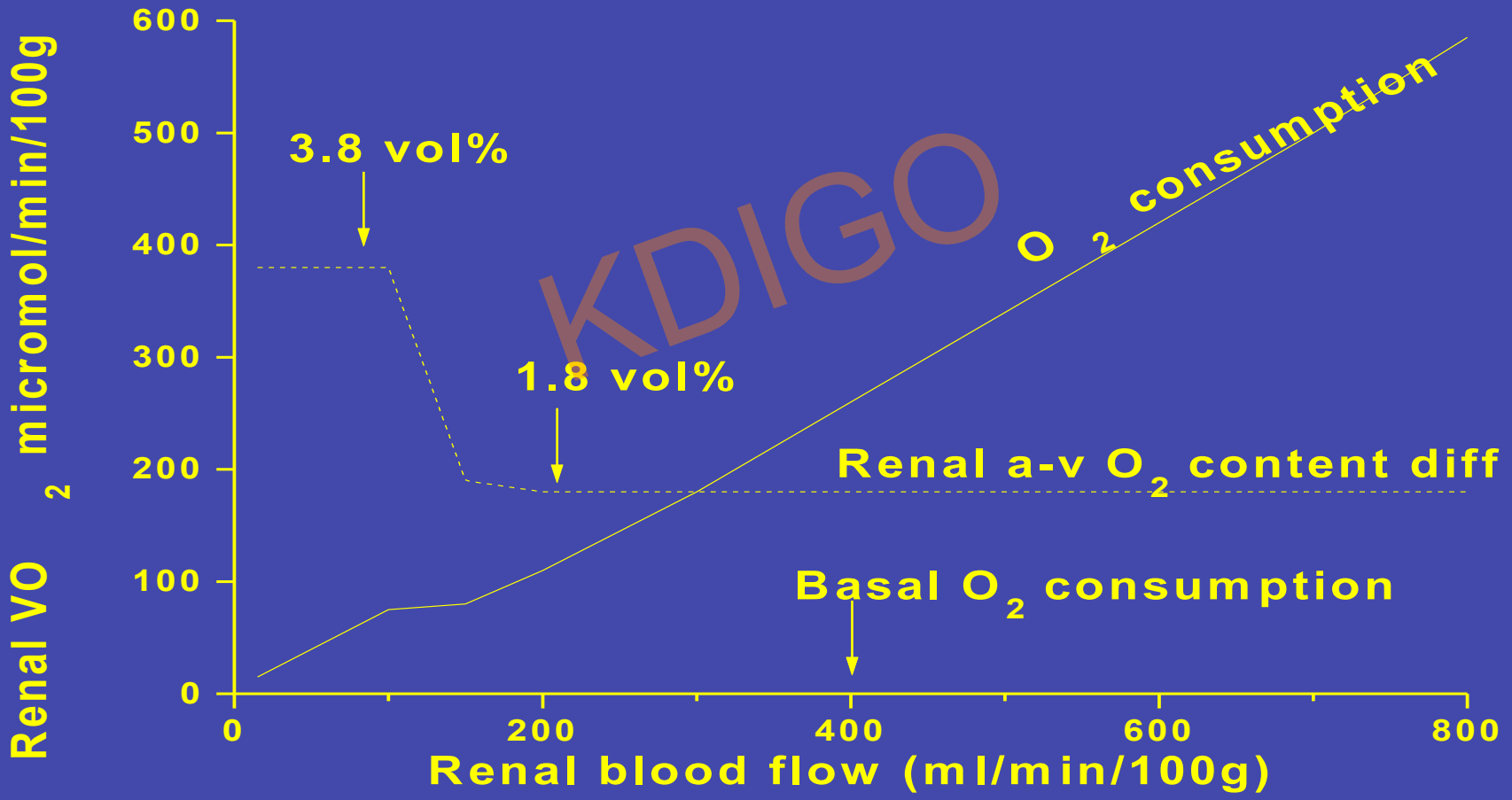
	Mortality 90d n/N (%)		RRT Incidence n/N (%)		RRT Duration (Days)	Median (IQR)
	Usual	**EGDT**	**Usual**	**EGDT**	**Usual**	**EGDT**
ProCESS	139/412 (33.7%)	129/405 (31.9%)	11/397 (2.8%)	12/382 (3.1%)	8.3±13.7	7.1±10.8
		P=0.66		P=NS	(Mean±SD)	P=0.92
ARISE	150/796 (18.8%)	147/792 (18.6%)	108/798 (13.5%)	106/793 (13.4%)	85.9 (29.3-182.9) (hr)	57.8 (25.3-175) (hr)
		P=0.9		P=0.94		P=0.4
ProMISE	181/620 (29.2%)	184/623 (29.5%)	81/614 (13.2%)	88/620 (14.2%)	N/A	N/A
		P=0.9		P=0.62		
PL Meta-analysis	475/1871 (25.4%)	462/1852 (24.9%)	198/1874 (10.6%)	204/1852 (11%)	4 (2-7) * RRT grp	3 (2-7) *RRT grp
		P=0.68		P=0.91		P=0.68

Rowan KM, et al, for PRISM Investigators. NEJM 2017;376(23):2223-33

Pharmacologic Approach to Optimization of Renal Perfusion

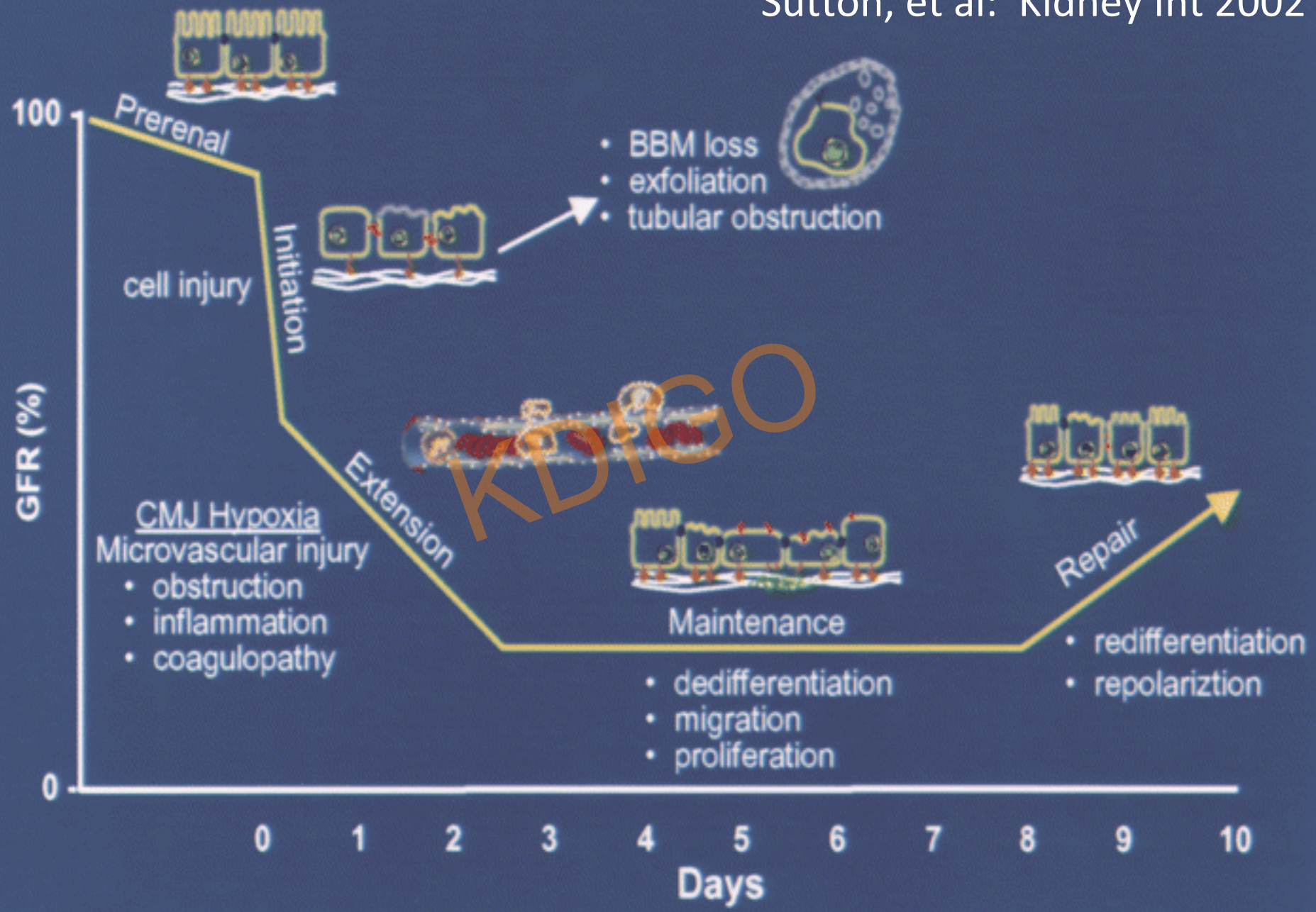
- 1) MAP: fluids, inotropes, pressors targeting MAP 60-80mmHg
- 2) CO: fluids, inotropes, vasodilators to achieve "adequate" cardiac output
- **3) Renovascular resistance: renal vasodilators**
- **4) Corticomedullary blood flow distribution: renal vasodilators**
- **5) Renal tubular oxygen consumption: diuretics (±other effects: loop diuretics, mannitol)**

Renal Oxygen Consumption



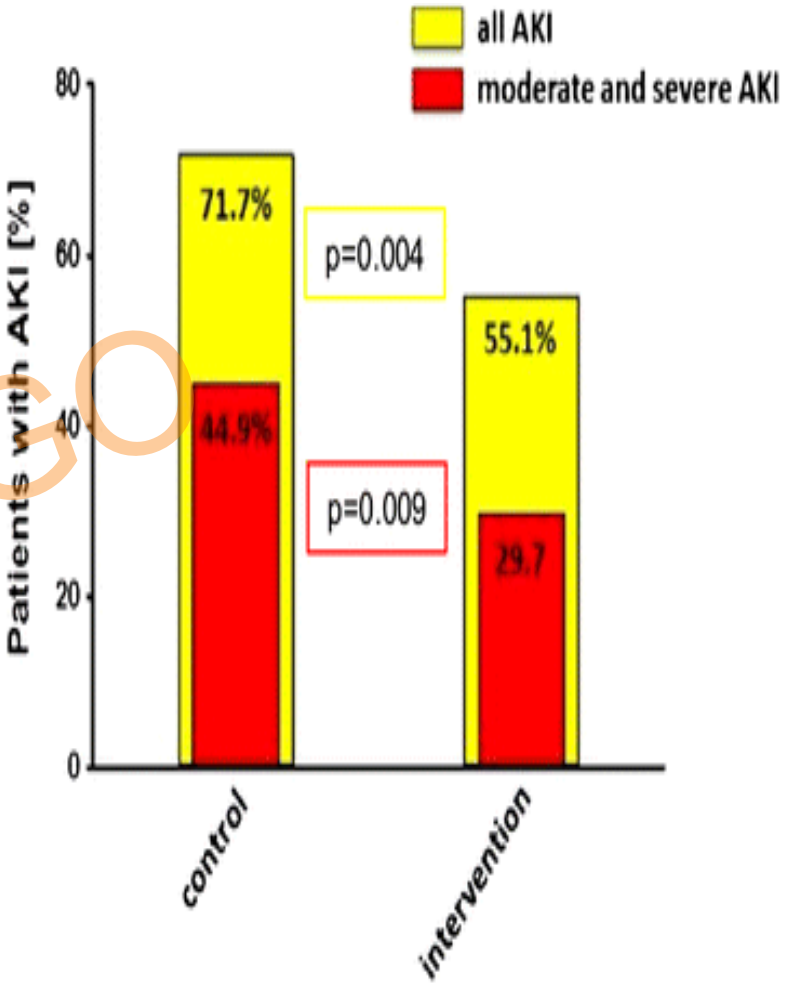
Valtin & Schaefer, 1995

Sutton, et al: Kidney Int 2002



PrevAKI Trial: Biomarker-Guided Prevention of Cardiac Surgery-Associated AKI

- Single-centre, RCT in **high risk** CPB patients
  - [TIMP2].[IGFBP7] ≥0.3 @ 4h post-CPB
- Randomized: standard care vs KDIGO CT Surgery Bundle
- Primary Endpoint: AKI ≤ 72h postop:
- Control (99/138, 71.7%) vs. Intervention (76/138, 55.1%); p=0.004
- Stage 2/3 AKI: Control (44.9%) vs. Intervention (29.7%); p=0.009
- No difference in RRT, MAKE 30, 60, 90



Meersch M, et al: Intensive Care Med 2017;43:1551-61

Conceptual framework for AKI risk

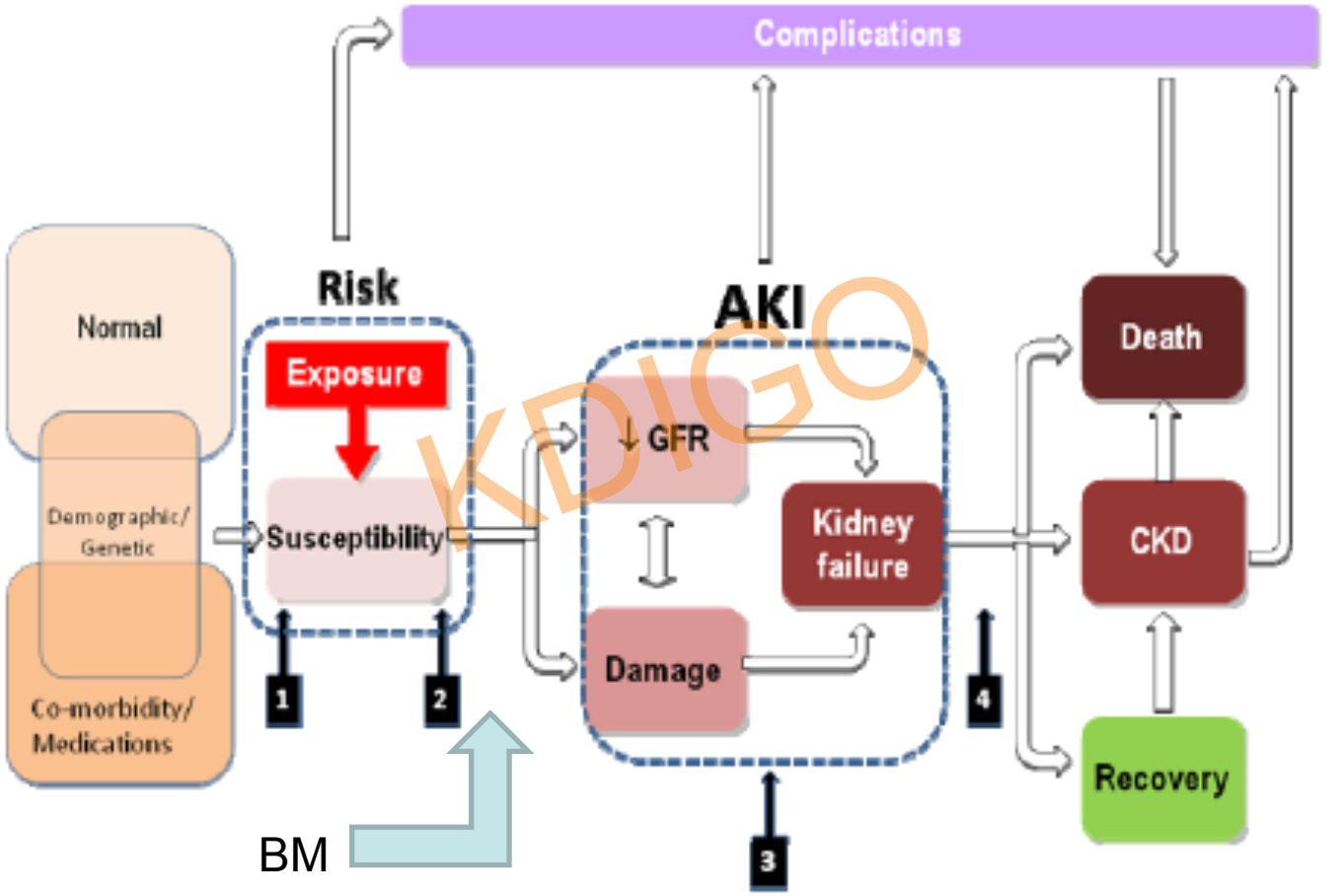
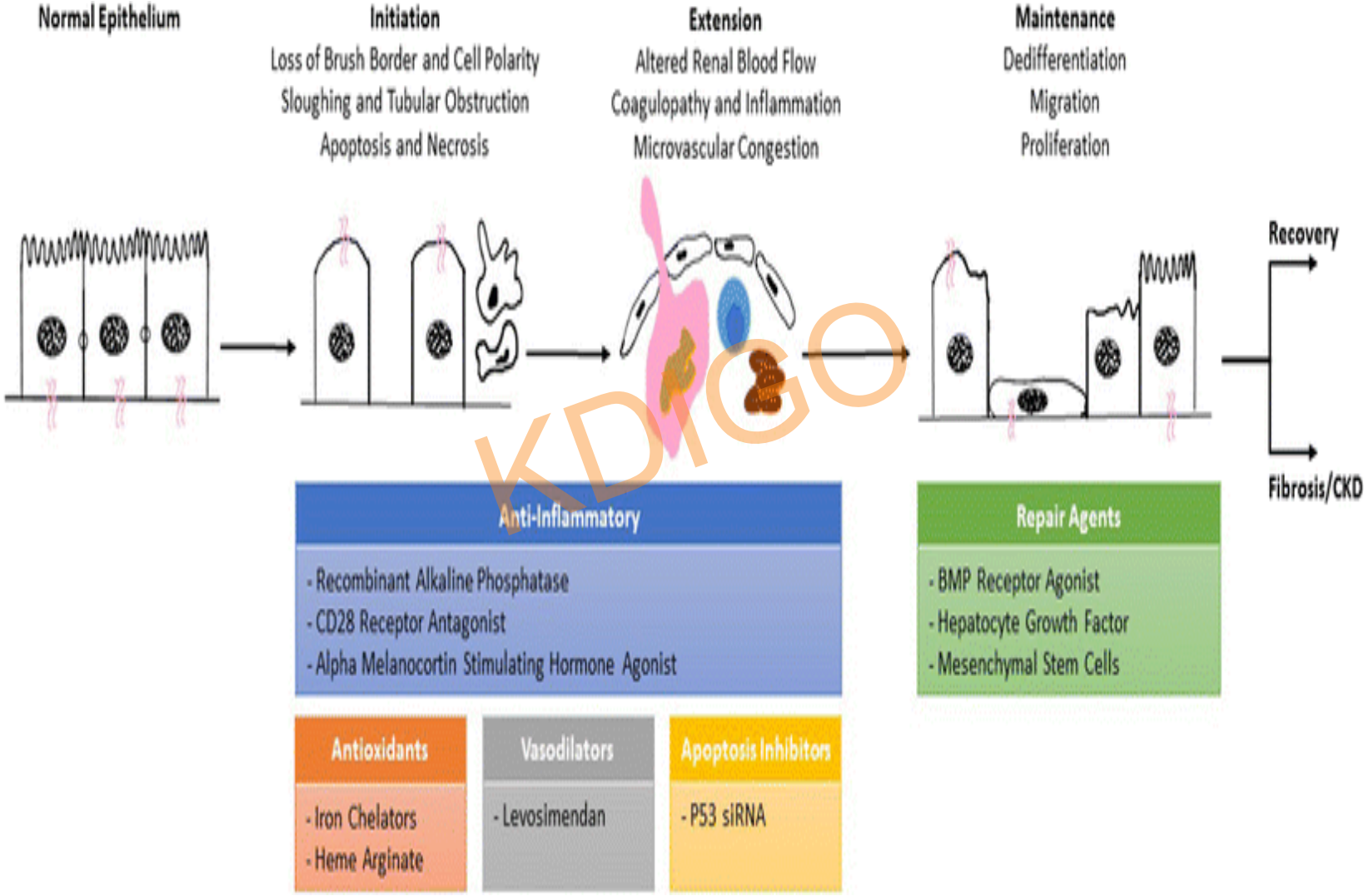


Figure 1: Suggested levels of risk assessment with relevance to AKI

Primary Prevention

Secondary Prevention

NOVEL AKI THERAPEUTICS

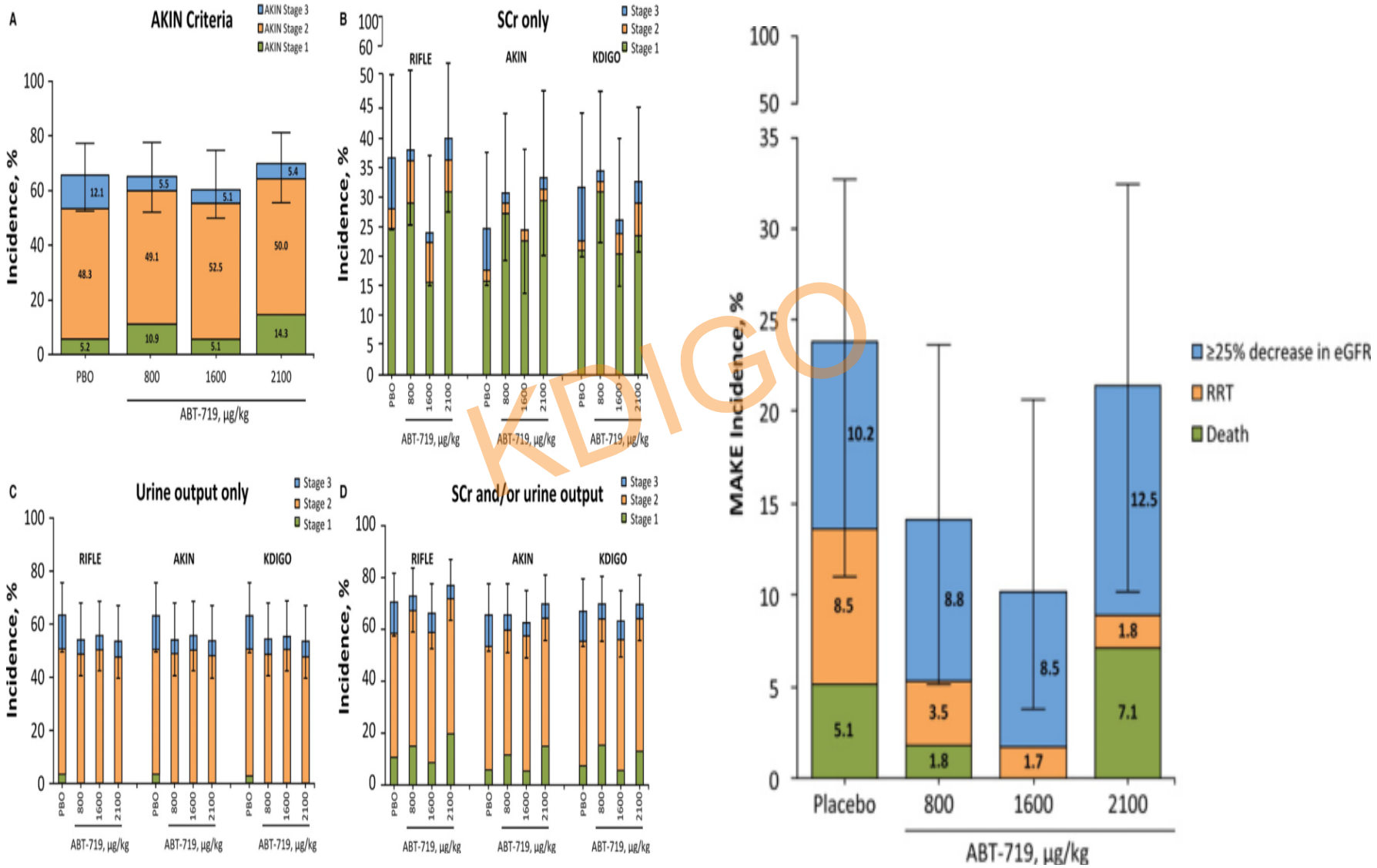


Benoit & Devarajan, Pediatr Nephrol 2018;33:779-987

Selected Novel AKI Therapies in Human Development

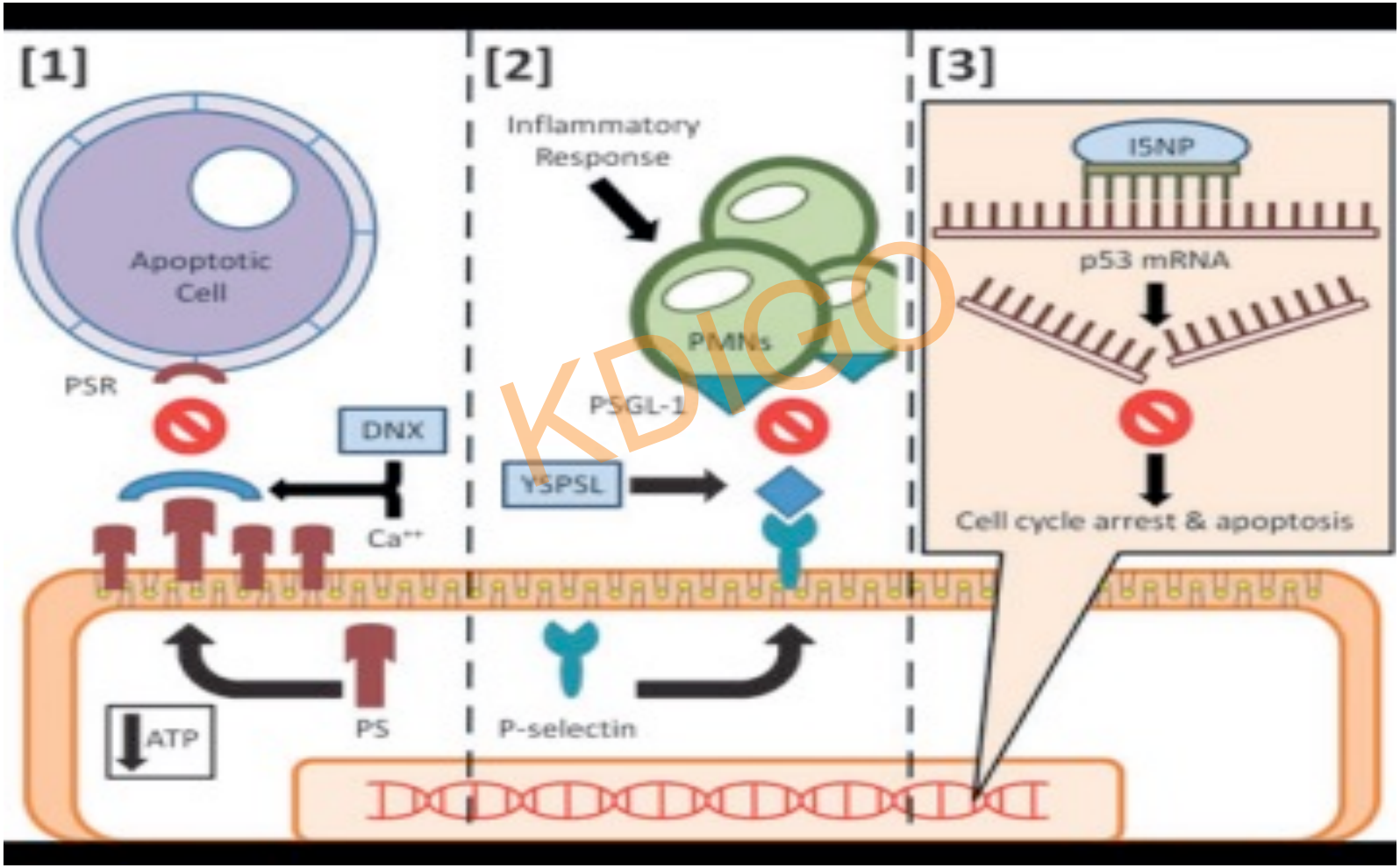
AGENT	Site of Action	Mechanism of Action	Drug Development Stage / NCT #	Role in AKI
QPI-1002/ Teprasiran	Gene silencing	Temporary suppression of p53 expression	Phase 3/ NCT03510897 (CS) NCT02601283 (DGF)	Prevention
Alkaline Phosphatase	Anti-sepsis	Anti-inflammatory effect through generation of adenosine (from ATP) & De-phosphorylation of endotoxin	Phase 2	Treatment
Deferiprone	Iron Chelator	Antioxidant	Phase 2/ NCT01146925	Prevention & Treatment

ABT-719 (α-MSH) for CS-AKI



McCullough PA, et al: J Am Heart Assoc. 2016;5: e003549 doi: 10.1161/JAHA.116.003549

Delayed Graft Function: Targets



Powell JT, et al: Clin Transplant 2013;27: 484–491

I5NP/QPI Rx for CS-AKI Prevention

Phase 2 double-blind study (N=341: QPI=165, Placebo (PL)=176) undergoing CS at 41 sites (NCT#02610283).

Subjects undergoing non-emergent CS at risk for AKI were enrolled (risk factors included: Age ≥ 70 years; eGFR ≤ 60 mL/min/1.73m^2, diabetes, proteinuria, congestive heart failure)

Subjects were stratified by eGFR: ≥ vs < 60mL/min/1.73m^2

Demographics and AE profiles were similar between treatment groups

Corteville D, et al: ASN Renal Week 2017: abstract SA-OR124

I5NP/QPI Rx for CS-AKI Prevention

QPI treatment resulted in a 26% relative risk reduction (RRR) of AKI (AKIN): (37% QPI vs. 50% PL; p=0.020). Risk reductions were consistently observed across predefined populations (age, diabetes, CS type, gender, baseline eGFR).

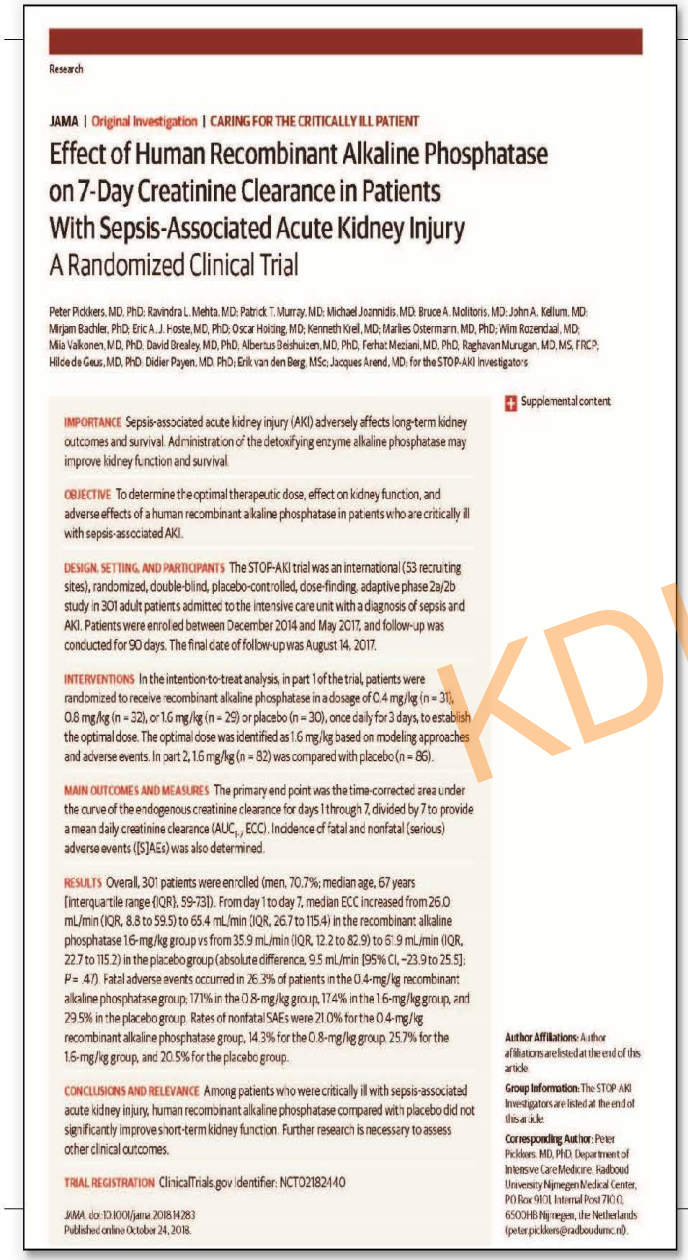
QPI improved AKI across all AKIN grades (by 18%–61%; p=0.012)

Duration of AKIN AKI from Days 0-5 was shorter with QPI (p=0.013)

QPI significantly impacted AKI incidence, grade and duration by RIFLE and KDIGO criteria

Composite of Death, RRT and Reduction of eGFR by 25% at Day 90 favored QPI in a subpopulation (N=241) with either proteinuria, and/or low base line eGFR, and/or diabetes, (37% QPI vs 51% PL; RRR=29%; p=0.024

Corteville D, et al: ASN Renal Week 2017: abstract SA-OR124



Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury
A Randomized Clinical Trial

Peter Pickkers, MD, PhD; Ravindra L. Mehta, MD; Patrick T. Murray, MD; Michael Joannidis, MD; Bruce A. Molitoris, MD; John A. Kellum, MD; Mirjam Bachler, PhD; Eric A. J. Hoste, MD, PhD; Oscar Holiing, MD; Kenneth Kiel, MD; Marilies Ostermann, MD, PhD; Wim Rozendaal, MD; Mia Valkonen, MD, PhD; David Brealey, MD, PhD; Albertus Beishuizen, MD, PhD; Ferhat Meziani, MD, PhD; Raghavan Murugan, MD, MS, FRCP; Hilde de Geus, MD, PhD; Didier Payen, MD, PhD; Erik van den Berg, MSc; Jacques Arend, MD; for the STOP-AKI Investigators

Supplemental content

IMPORTANCE Sepsis-associated acute kidney injury (AKI) adversely effects long-term kidney outcomes and survival. Administration of the detoxifying enzyme alkaline phosphatase may improve kidney function and survival.

OBJECTIVE To determine the optimal therapeutic dose, effect on kidney function, and adverse effects of a human recombinant alkaline phosphatase in patients who are critically ill with sepsis-associated AKI.

DESIGN, SETTING, AND PARTICIPANTS The STOP-AKI trial was an international (53 recruiting sites), randomized, double-blind, placebo-controlled, dose-finding, adaptive phase 2a/2b study in 301 adult patients admitted to the intensive care unit with a diagnosis of sepsis and AKI. Patients were enrolled between December 2014 and May 2017, and follow-up was conducted for 90 days. The final date of follow-up was August 14, 2017.

INTERVENTIONS In the intention-to-treat analysis, in part 1 of the trial, patients were randomized to receive recombinant alkaline phosphatase in a dosage of 0.4 mg/kg (n = 31), 0.8 mg/kg (n = 32), or 1.6 mg/kg (n = 29) or placebo (n = 30), once daily for 3 days, to establish the optimal dose. The optimal dose was identified as 1.6 mg/kg based on modeling approaches and adverse events. In part 2, 1.6 mg/kg (n = 82) was compared with placebo (n = 86).

MAIN OUTCOMES AND MEASURES The primary end point was the time-corrected area under the curve of the endogenous creatinine clearance for days 1 through 7, divided by 7 to provide a mean daily creatinine clearance (AUC_{1-7}, ECC). Incidence of fatal and nonfatal (serious) adverse events ([S]AEs) was also determined.

RESULTS Overall, 301 patients were enrolled (men, 70.7%; median age, 67 years [interquartile range {IQR}, 59-73]). From day 1 to day 7, median ECC increased from 26.0 mL/min (IQR, 8.8 to 59.5) to 65.4 mL/min (IQR, 26.7 to 115.4) in the recombinant alkaline phosphatase 1.6-mg/kg group vs from 35.9 mL/min (IQR, 12.2 to 82.9) to 51.9 mL/min (IQR, 22.7 to 115.2) in the placebo group (absolute difference, 9.5 mL/min [95% CI, −23.9 to 25.5]; $P = .47$). Fatal adverse events occurred in 26.3% of patients in the 0.4-mg/kg recombinant alkaline phosphatase group; 17.1% in the 0.8-mg/kg group, 17.4% in the 1.6-mg/kg group, and 29.5% in the placebo group. Rates of nonfatal SAEs were 21.0% for the 0.4-mg/kg recombinant alkaline phosphatase group, 14.3% for the 0.8-mg/kg group, 25.7% for the 1.6-mg/kg group, and 20.5% for the placebo group.

CONCLUSIONS AND RELEVANCE Among patients who were critically ill with sepsis-associated acute kidney injury, human recombinant alkaline phosphatase compared with placebo did not significantly improve short-term kidney function. Further research is necessary to assess other clinical outcomes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02182440

JAMA. doi:10.1001/jama.2018.14283
Published online October 24, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The STOP-AKI Investigators are listed at the end of this article.

Corresponding Author: Peter Pickkers, MD, PhD, Department of Intensive Care Medicine, Radboud University Nijmegen Medical Center, PO Box 9101, Internal Post 710.0, 6500HB Nijmegen, the Netherlands (peter.pickkers@radboudumc.nl).

JAMA Journal of the American Medical Association

P Pickkers and coauthors

Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury: A Randomized Clinical Trial

Published online October 24, 2018

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com

2 small Phase-II Studies – bovine AP

Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients*

Critical Care Medicine

Suzanne Heemskerk, PhD; Rosalinde Masereeuw, PhD; Olof Moesker; Martijn P. W. J. M. Bouw; Johannes G. van der Hoeven, MD, PhD; Wilbert H. M. Peters, PhD; Frans G. M. Russel, PhD; Peter Pickkers, MD, PhD; on behalf of the APSEP Study Group

NATURE REVIEWS | RESEARCH HIGHLIGHTS

ACUTE KIDNEY INJURY

Alkaline phosphatase in sepsis-induced AKI

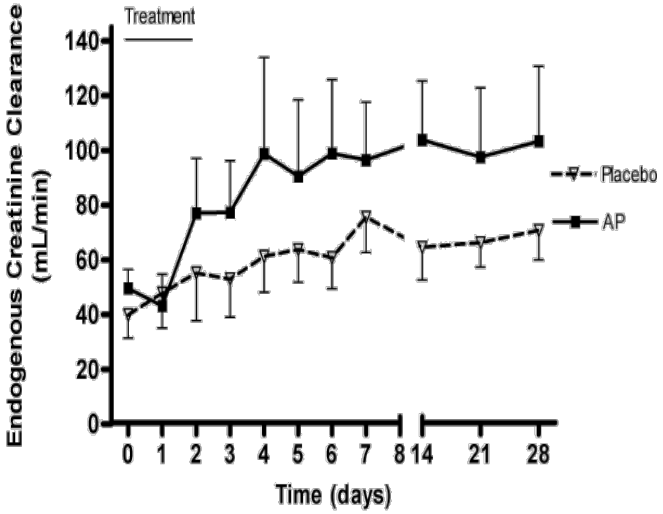
Pickkers et al. Critical Care 2012, 16:R14
http://ccforum.com/content/16/1/R14

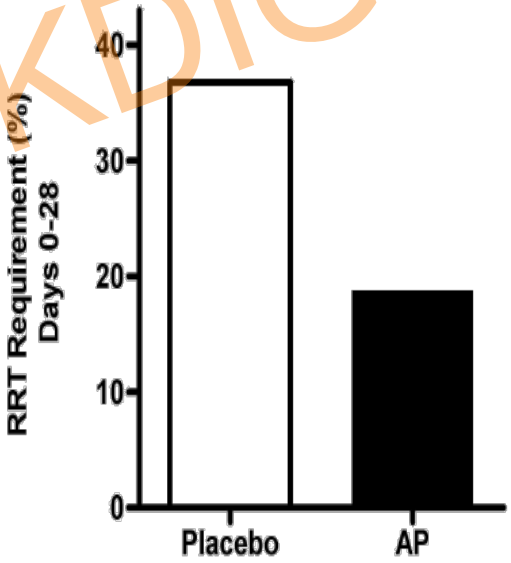
CRITICAL CARE

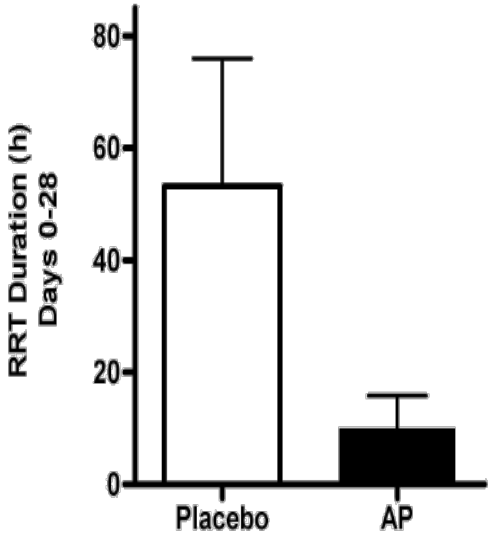
RESEARCH Open Access

Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial

Peter Pickkers[1*], Suzanne Heemskerk[1,2], Jeroen Schouten[3], Pierre-François Laterre[4], Jean-Louis Vincent[5], Albertus Beishuizen[6], Philippe G Jorens[7], Herbert Spapen[8], Michael Bulitta[9], Wilbert HM Peters[10] and Johannes G van der Hoeven[1]

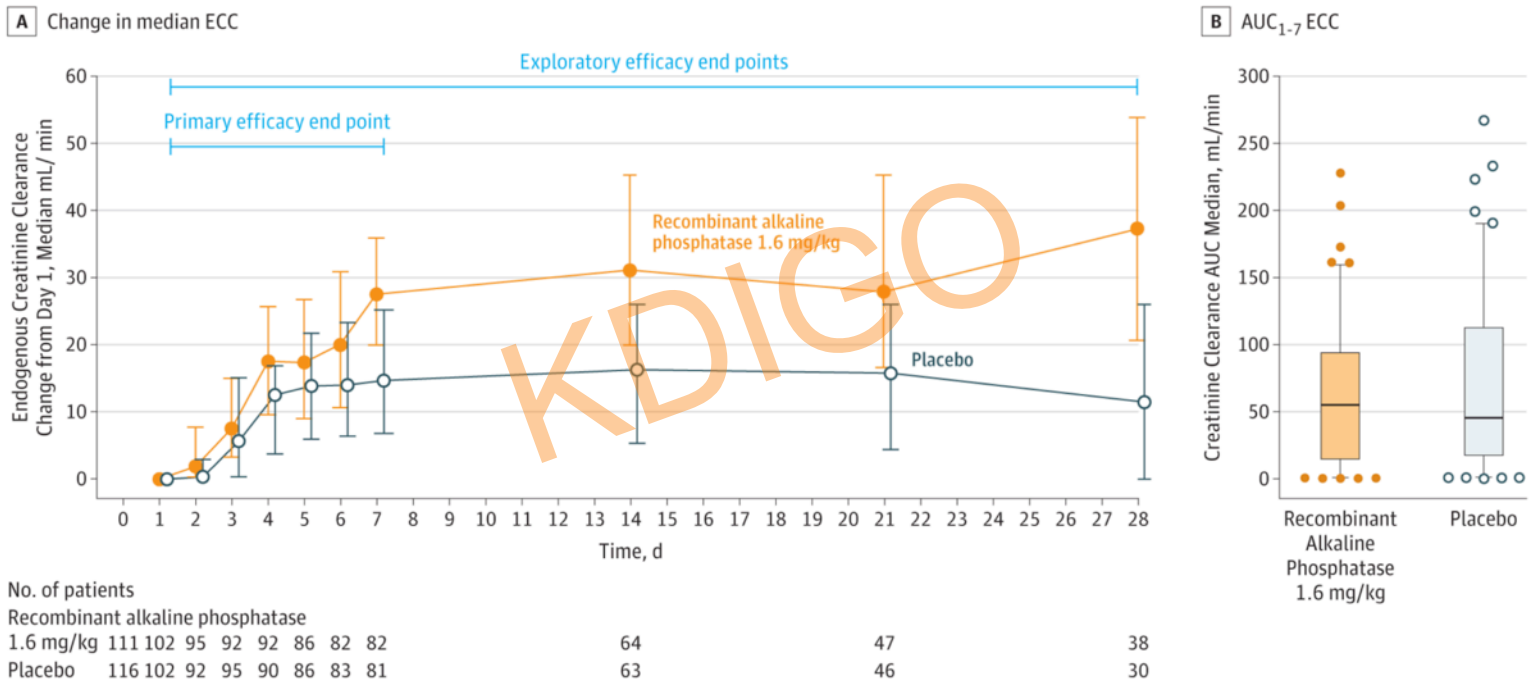




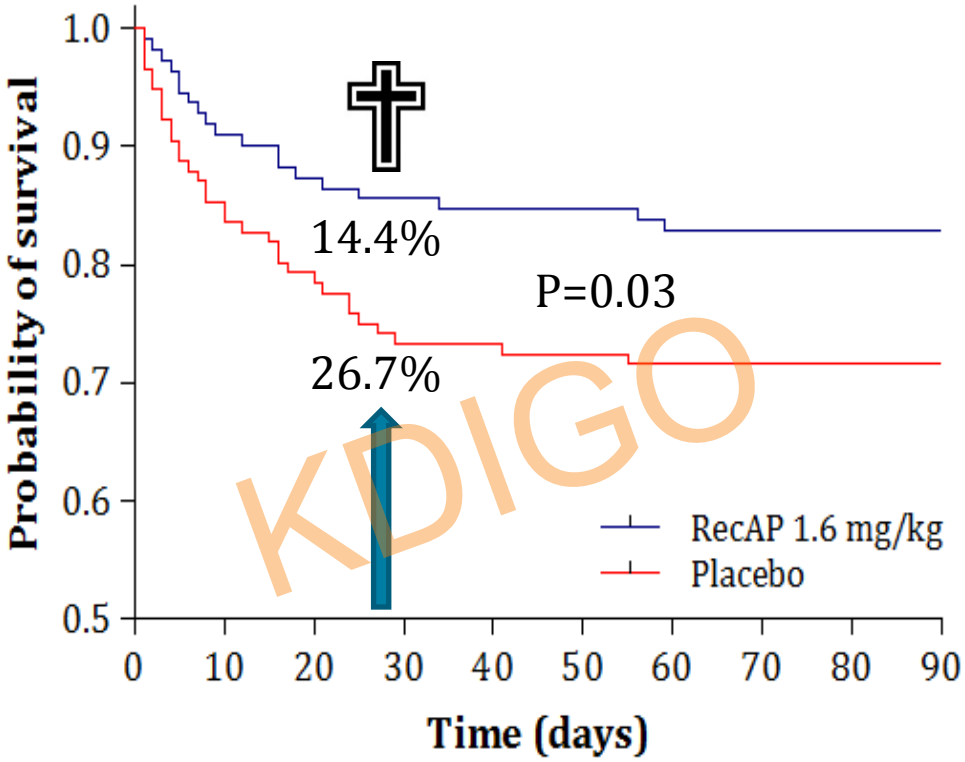


From: **Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney InjuryA Randomized Clinical Trial**

JAMA. Published online October 24, 2018. doi:10.1001/jama.2018.14283



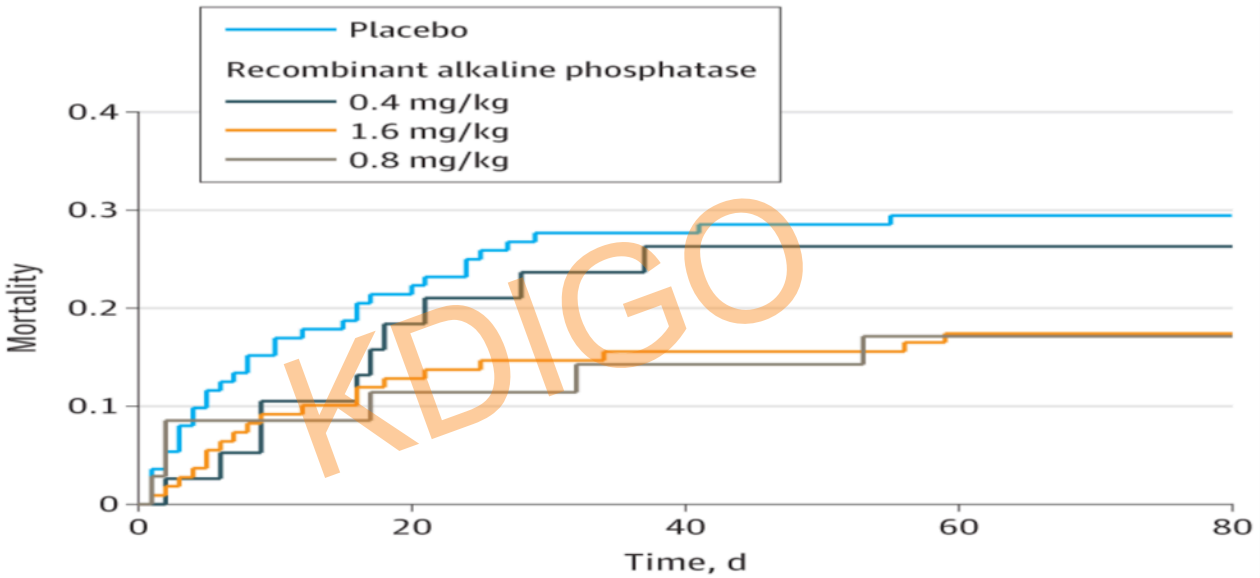
28-day Survival



No. at Risk					
RecAP 1.6 mg/kg	111	98	95	93	92
Placebo	116	92	86	84	83

From: **Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney InjuryA Randomized Clinical Trial**

JAMA. Published online October 24, 2018. doi:10.1001/jama.2018.14283

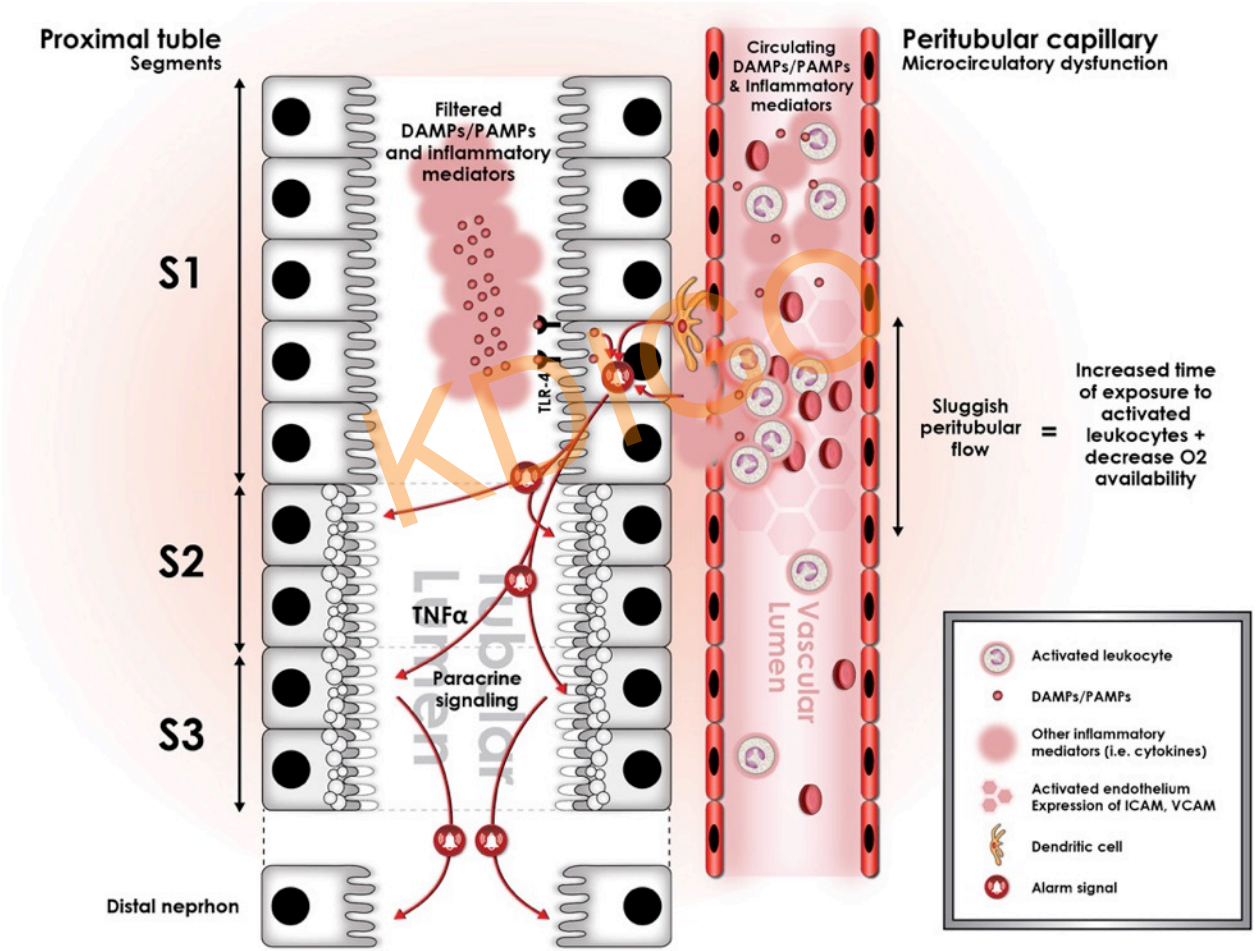


No. at risk

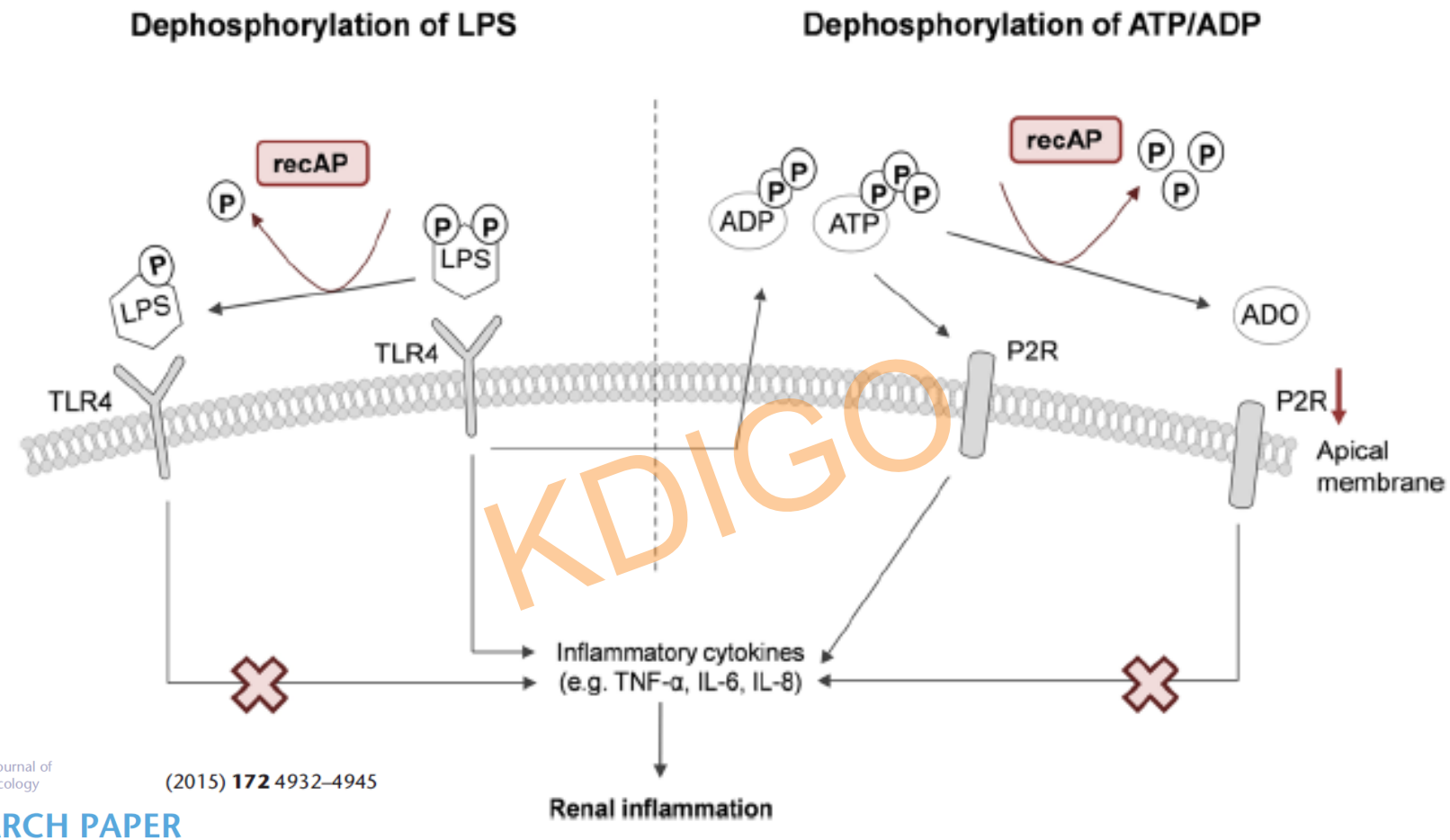
Recombinant alkaline phosphatase					
Placebo	112	88	81	79	79
0.4 mg/kg	38	31	28	28	28
0.8 mg/kg	35	31	30	29	29
1.6 mg/kg	109	95	92	90	90

:

Pathogenesis of Septic AKI



Powell JT, et al: Clin Transplant 2013;27: 484–491



British Journal of Pharmacology (2015) **172** 4932–4945

RESEARCH PAPER

Alkaline phosphatase protects against renal inflammation through dephosphorylation of lipopolysaccharide and adenosine triphosphate

E Peters[1,2], S Geraci[3], S Heemskerk[1,2], M J Wilmer[2], A Bilos[2], B Kraenzlin[3], N Gretz[3], P Pickkers[1]* and R Masereeuw[2,4,*]

Radboudumc Intensive Care

Catalytic (Labile) Iron and AKI

Iron-catalyzed generation of reactive oxygen species

In the first step, ferric ion is reduced to ferrous:

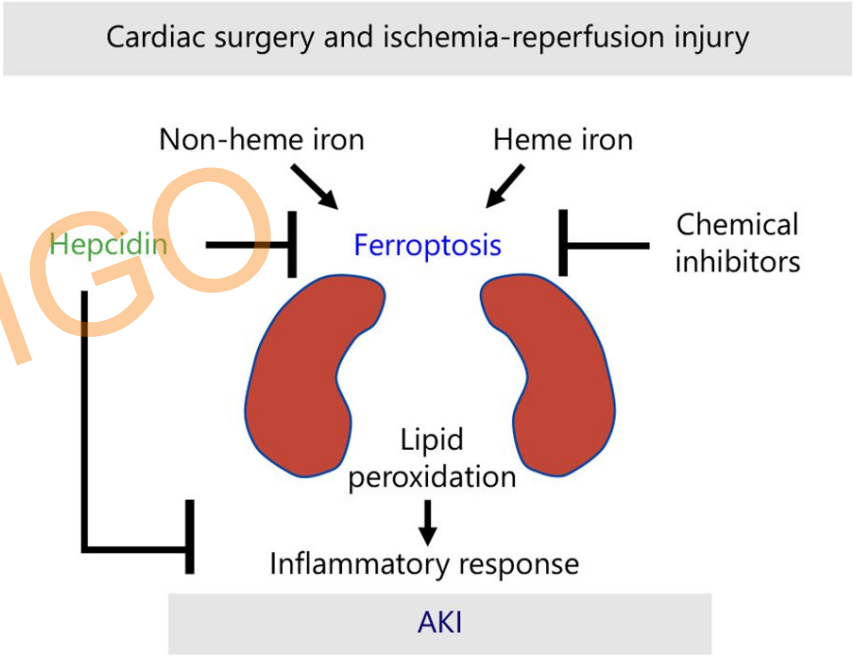
$Fe^{3+} + \bullet O_2^- \rightarrow Fe^{2+} + O_2$

The second step, involves generation of the highly reactive hydroxyl radical

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$ (fenton reaction)

Net reaction:

$\bullet O_2^- + H_2O_2 \rightarrow \bullet OH + OH^- + O_2$



Swamimathan S, et al: Nephron 2018;140:156-59

Iron, Hepcidin, and Death in Human Acute Kidney Injury

METHODS

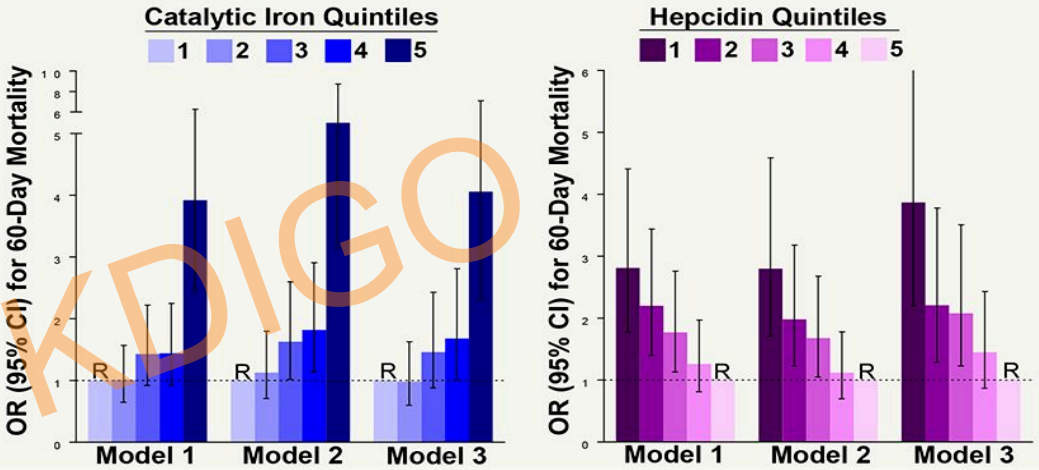
807 Critically ill patients with AKI requiring RRT

Measurement of the following in stored plasma samples:

- Catalytic Iron
- Total Iron
- Transferrin
- Ferritin
- Free Hemoglobin
- Hepcidin

Primary Endpoint: **60d Mortality**

MAIN FINDINGS



CONCLUSION Higher concentrations of catalytic iron and lower concentrations of hepcidin are each independently associated with mortality in critically ill patients with AKI-RRT

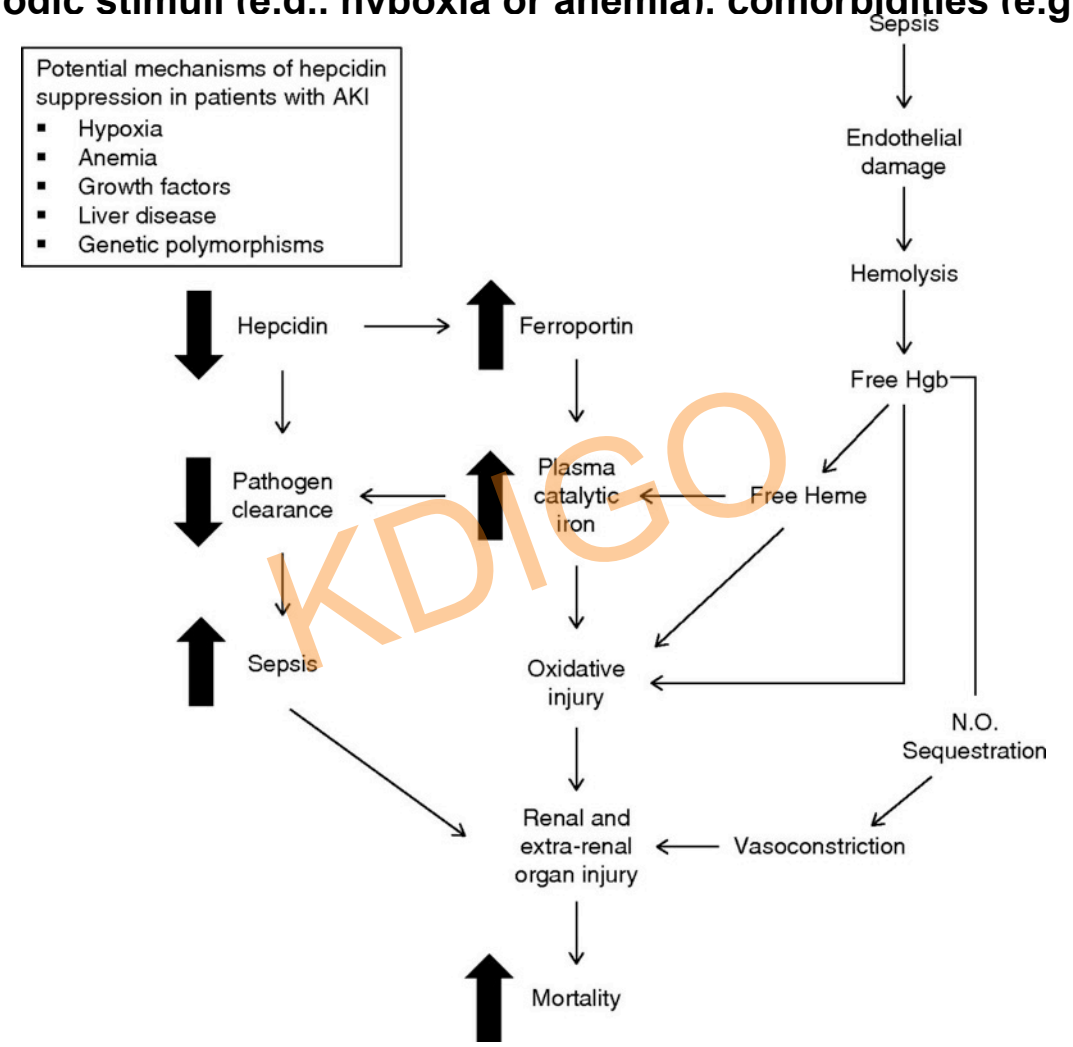
doi: 10.1681/ASN.2018100979

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

David E. Leaf et al. JASN 2019;30:493-504

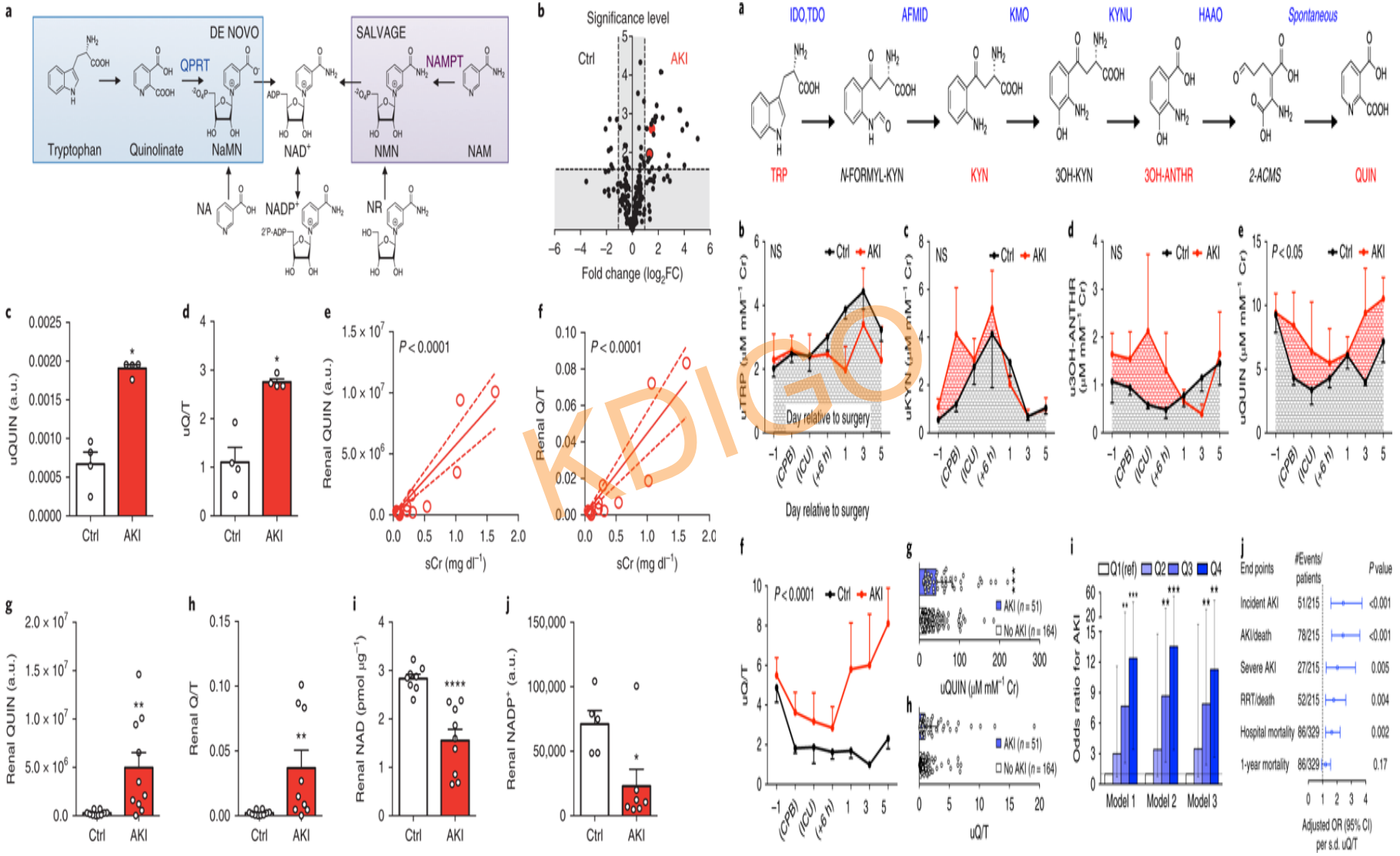
JASN

Potential pathways linking hepcidin and catalytic iron with death in AKI. Critically ill patients with AKI may have decreased circulating concentrations of hepcidin due to a variety of physiologic stimuli (e.g., hypoxia or anemia), comorbidities (e.g., live...



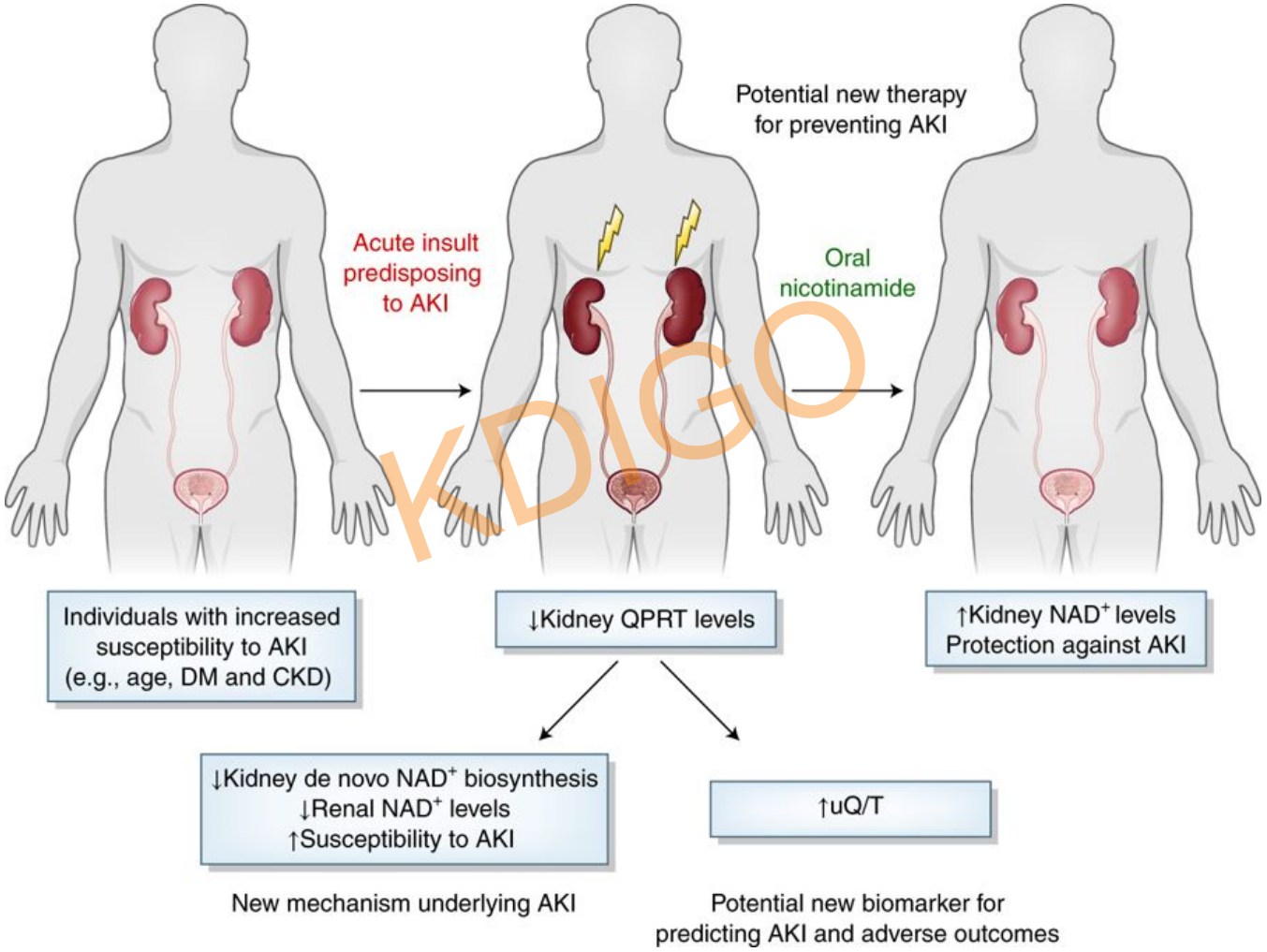
David E. Leaf et al. JASN 2019;30:493-504

De novo NAD+ biosynthetic impairment in Human AKI



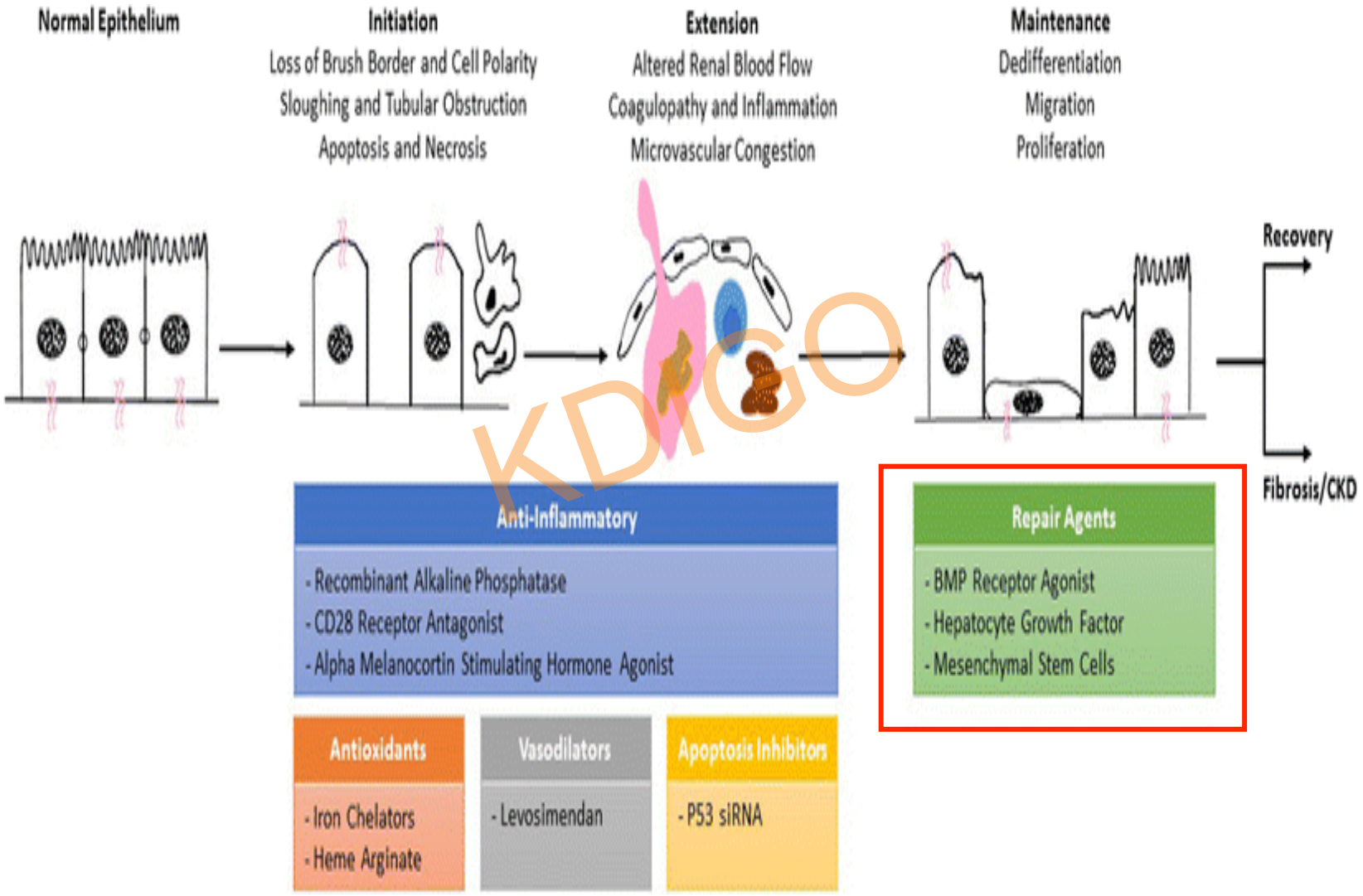
Mehr AP, et al: Nature Medicine 2018;24(9):1351-59

AKI Bioenergetics



Bulluck H, Hausenloy DJ: Nature Medicine 2018;24:1304-12

NOVEL AKI THERAPEUTICS

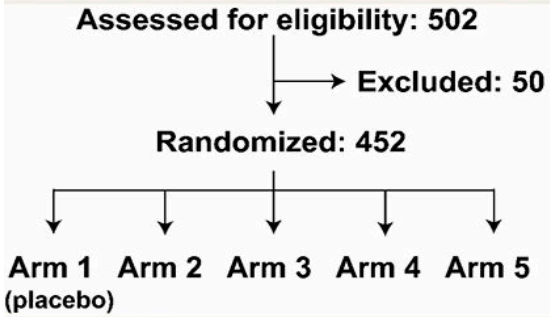


Benoit & Devarajan, Pediatr Nephrol 2018;33:779-987

Perioperative THR-184 and Acute Kidney Injury after Cardiac Surgery

METHODS

Randomized clinical trial to assess the effects of THR-184, a bone morphogenetic protein-7 agonist, on AKI after cardiac surgery.



OUTCOME

The proportion of patients who developed acute kidney injury within 7 days of surgery was similar in THR-184 treatment groups relative to placebo

	Arm 1 (N=113)	Arm 2 (N=34)	Arm 3 (N=34)	Arm 4 (N=116)	Arm 5 (N=104)
Development of AKI using the full KDIGO definition					
Incidence (%)	77.9	79.4	76.5	75.9	74.0
95% CI	69.1-85.1	62.1-91.3	58.8-89.3	67.0-83.3	64.5-82.1
Odds ratio*		1.16	0.97	0.91	0.84
95% CI		0.45-3.01	0.39-2.44	0.49-1.69	0.45-1.58
p-value†		0.76	0.95	0.76	0.59

CONCLUSION

Administration of perioperative THR-184 in a range of doses failed to reduce the incidence, severity or duration of AKI in high risk cardiac surgery patients.

doi: 10.1681/ASN.2017020217

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

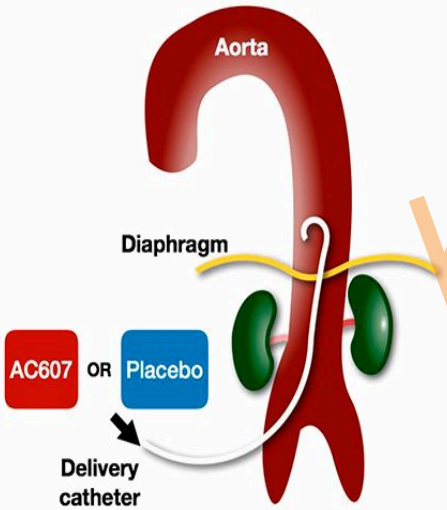
Jonathan Himmelfarb et al. JASN 2018;29:670-679

JASN

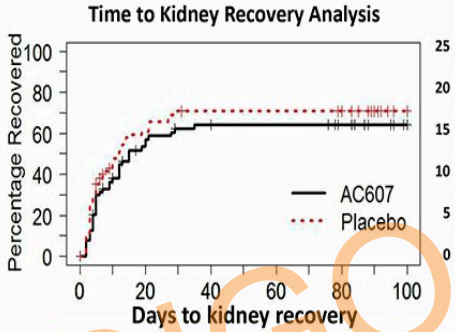
Allogeneic Mesenchymal Stem Cells for Treatment of Acute Kidney Injury after Cardiac Surgery

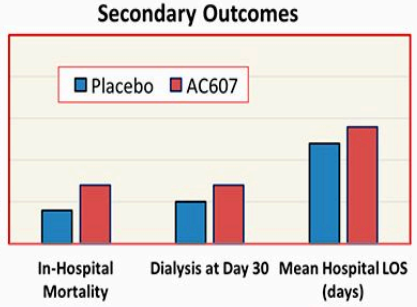
METHODS

156 cardiac surgery patients with early postop AKI randomized to receive mesenchymal stem cells (AC607) or placebo



RESULTS





	AC607	Placebo
Median Days to recovery (IQR)	15 (10-29)	12 (6-21)
Hazard Ratio	0.81 (0.53-1.24)	

CONCLUSION

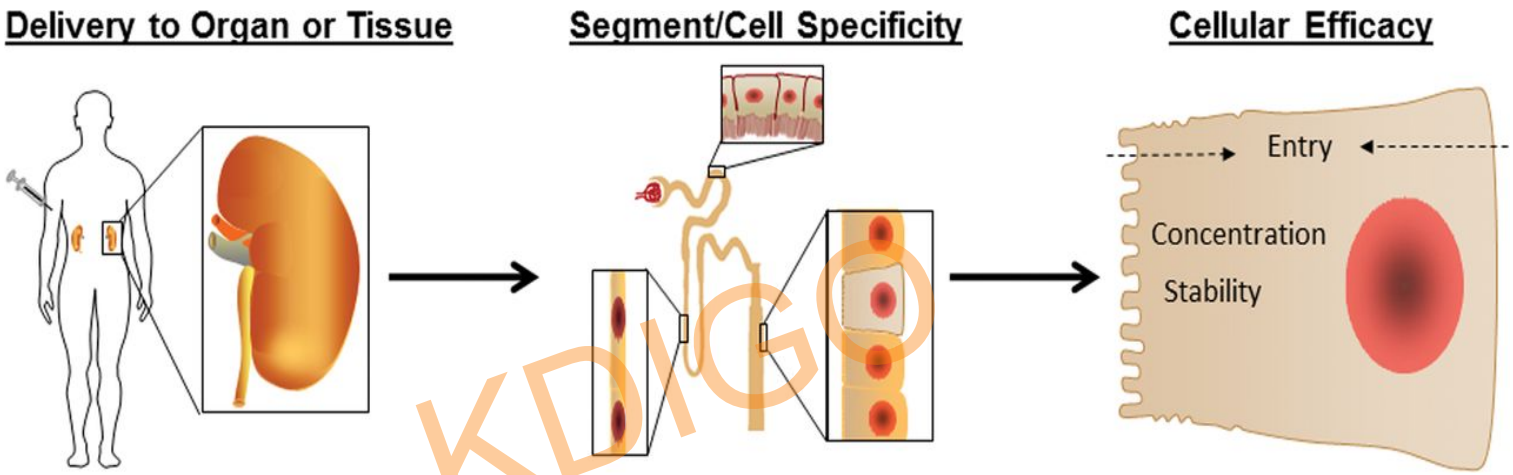
After cardiac surgery, administration of allogeneic mesenchymal stem cells within 48 hours of AKI onset did not decrease the time to recovery of kidney function, provision of dialysis or mortality.

Article citation goes here.

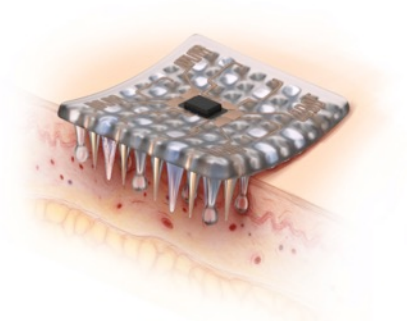
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

Madhav Swaminathan et al. JASN 2018;29:260-267

Challenge of miRNA therapeutics…



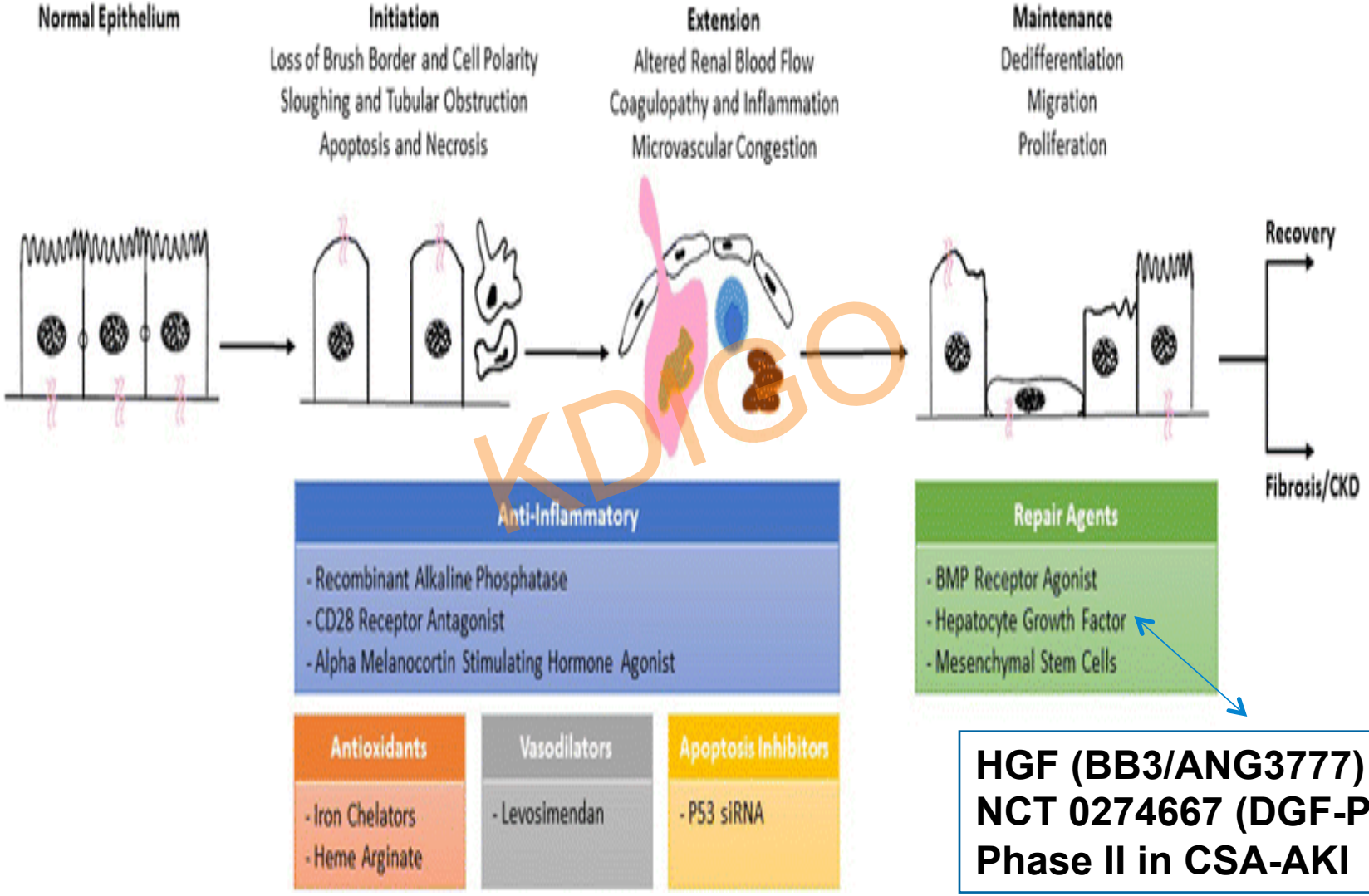
Kriegel A, Clinical Science (2012): 122, 439-447



Can we load these miRNA into nanoparticles/devices for targeted drug delivery

http://mdd.ucd.ie/research/

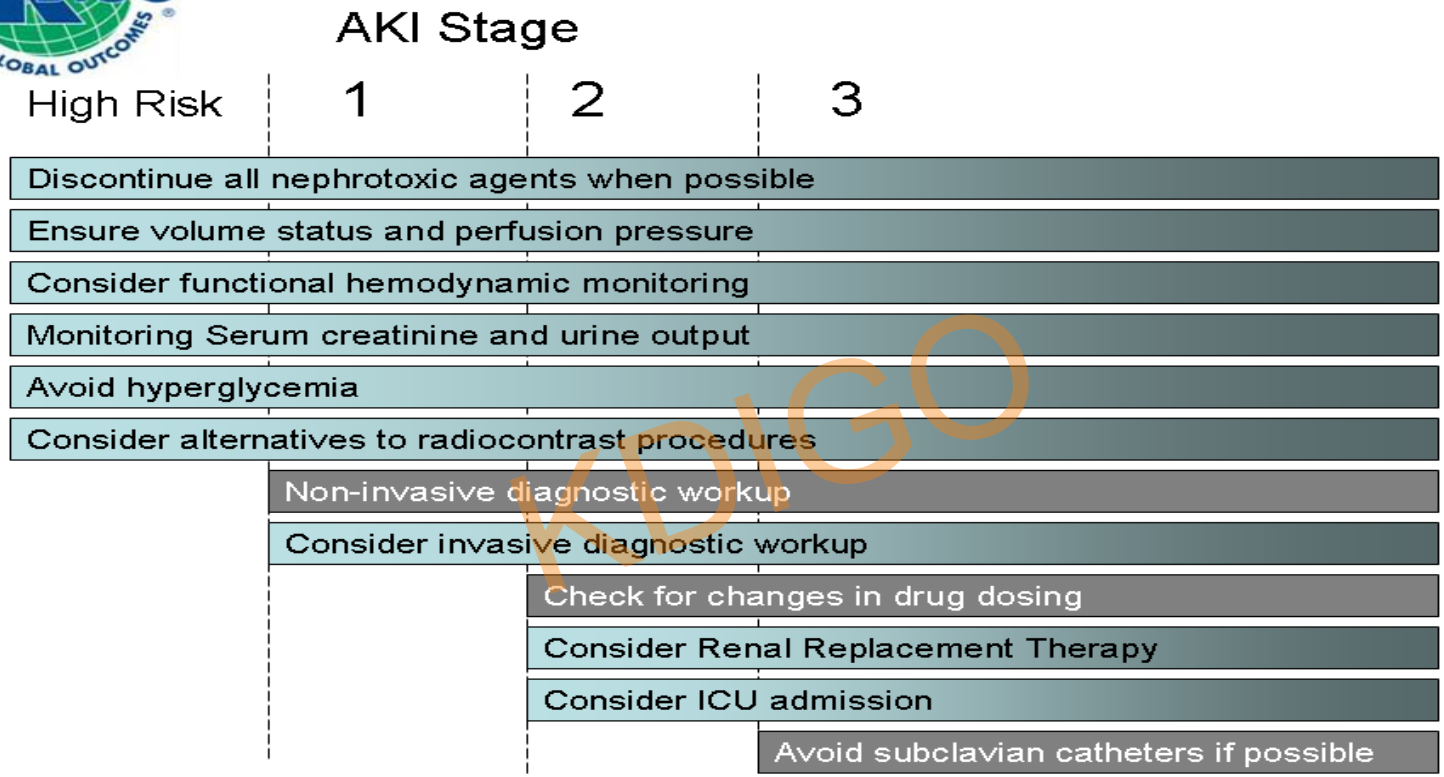
NOVEL AKI THERAPEUTICS



HGF (BB3/ANG3777)
NCT 0274667 (DGF-Ph3)
Phase II in CSA-AKI

Benoit & Devarajan, Pediatr Nephrol 2018;33:779-987

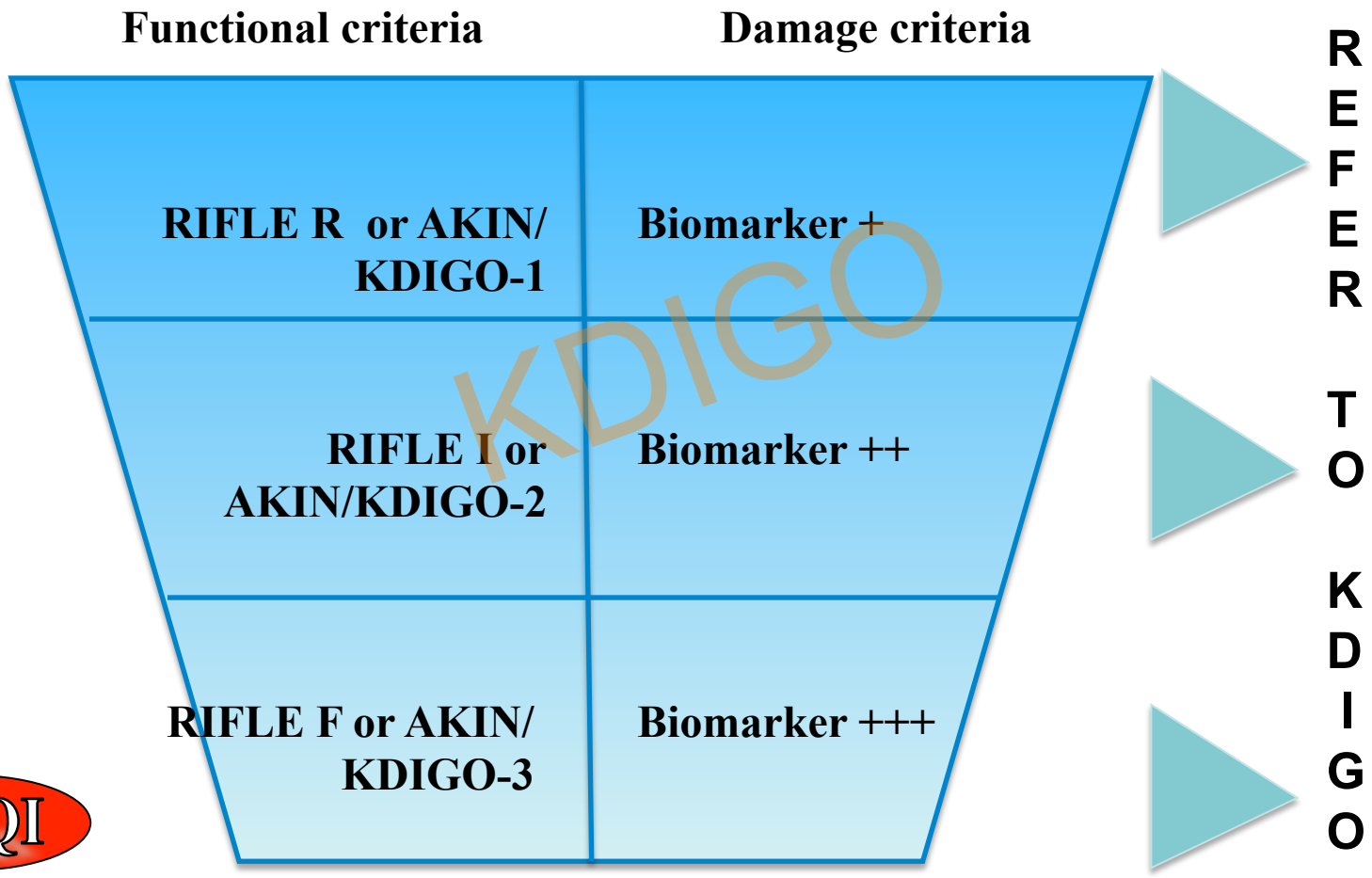
Stage-Based AKI Management



Stage-based management of AKI: Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.

KDIGO AKI Work Group: KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int, Suppl,* 2012;2(1):1-138

The New Spectrum of AKI Diagnostics



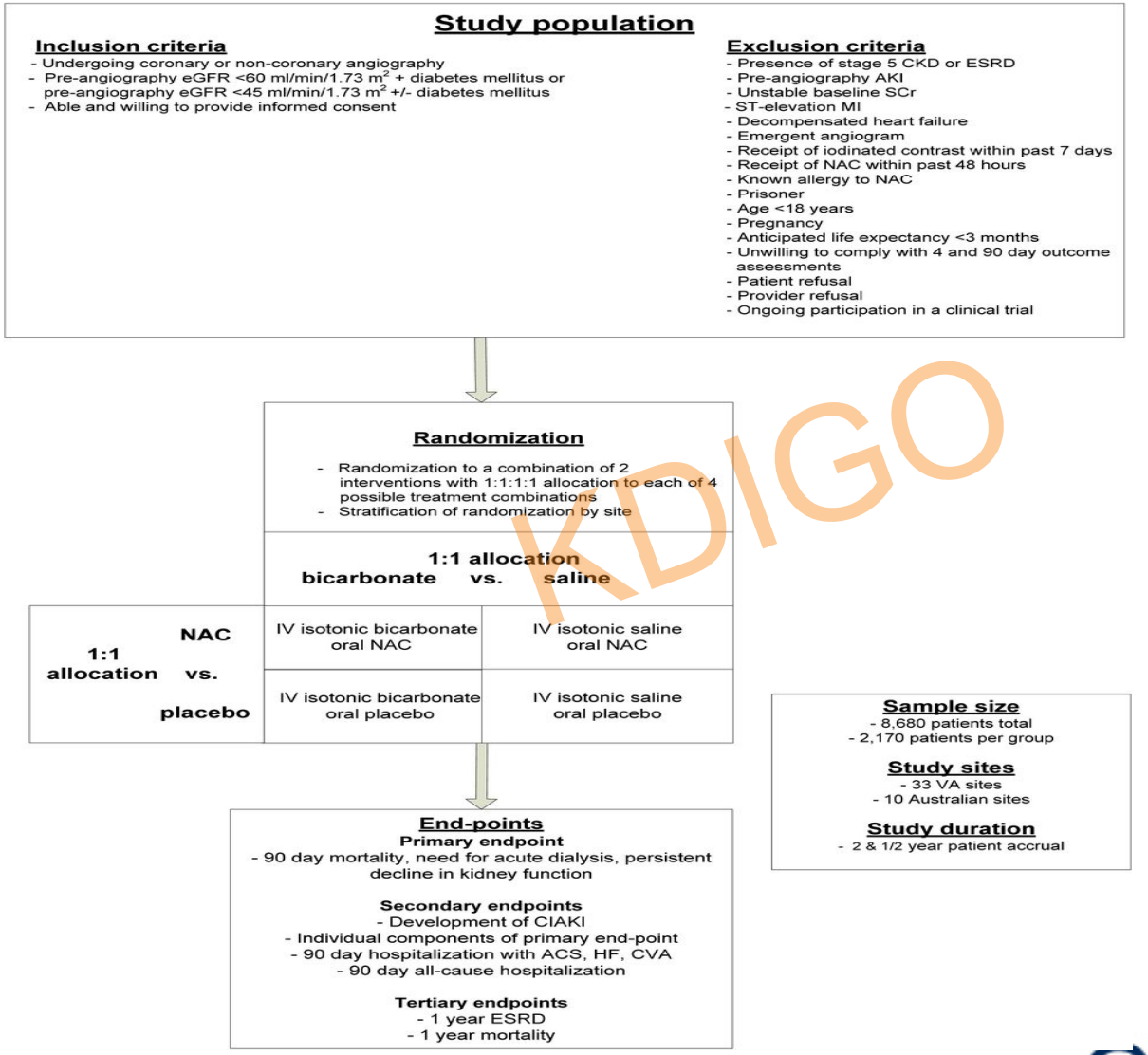
ADQI

Murray PT, et al for the ADQI Workgroup: Kidney Int 2014;85:513-521

INSERT HEADER HERE (WITH BACKGROUND)

- Hepatorenal

Overview of the Prevention of Serious Adverse Events following Angiography (PRESERVE) study design



ClinicalTrials.gov: NCT01467466

Steven D. Weisbord et al. CJASN 2013;8:1618-1631

CJASN

PRESERVE TRIAL: OUTCOMES

Table 3. Primary and Secondary End Points.

Outcome	Sodium Bicarbonate (N=2511)	Sodium Chloride (N=2482)	Odds Ratio (95% CI)	P Value	Acetylcysteine (N=2495)	Placebo (N=2498)	Odds Ratio (95% CI)	P Value
	no. of patients (%)				*no. of patients (%)*			
Primary end point*	110 (4.4)	116 (4.7)	0.93 (0.72–1.22)	0.62	114 (4.6)	112 (4.5)	1.02 (0.78–1.33)	0.88
Secondary end points								
Contrast-associated acute kidney injury†	239 (9.5)	206 (8.3)	1.16 (0.96–1.41)	0.13	228 (9.1)	217 (8.7)	1.06 (0.87–1.28)	0.58
Death by 90 days	60 (2.4)	68 (2.7)	0.87 (0.61–1.24)	0.43	67 (2.7)	61 (2.4)	1.10 (0.78–1.57)	0.59
Need for dialysis by 90 days	32 (1.3)	29 (1.2)	1.09 (0.65–1.81)	0.73	30 (1.2)	31 (1.2)	0.97 (0.58–1.60)	0.90
Persistent kidney impairment by 90 days	28 (1.1)	25 (1.0)	1.10 (0.64–1.91)	0.71	26 (1.0)	27 (1.1)	0.96 (0.56–1.66)	0.89
Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days	272 (10.8)	251 (10.1)	1.08 (0.90–1.29)	0.40	244 (9.8)	279 (11.2)	0.86 (0.71–1.04)	0.11
All-cause hospitalization by 90 days	1071 (42.7)	1052 (42.4)	1.01 (0.90–1.13)	0.85	1069 (42.8)	1054 (42.2)	1.03 (0.91–1.15)	0.64

* The primary end point was a composite of death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 days. Data regarding 90-day creatinine levels were missing in 119 patients (4.7%) in the sodium bicarbonate group, 103 (4.1%) in the sodium chloride group, 105 (4.2%) in the acetylcysteine group, and 117 (4.7%) in the placebo group.

† Contrast-associated acute kidney injury was defined as an increase in serum creatinine of at least 25% or at least 0.5 mg per deciliter (44 μmol per liter) from baseline at 3 to 5 days after angiography. Data regarding serum creatinine levels on days 3 to 5 were missing in 212 patients (8.4%) in the sodium bicarbonate group, 229 (9.2%) in the sodium chloride group, 210 (8.4%) in the acetylcysteine group, and 231 (9.2%) in the placebo group.

Weisbord SD et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1710933

Remote Ischemic Pre-conditioning

Short-Term Outcomes

	Control (n=120)	RIPC (n=120)	P value
AKI (72h) %	52.5	37.5	0.02
Stage 1	26.7	25	
Stage 2	11.7	6.7	
Stage 3	14.2	5.8	
RRT	15.8	5.8	

Medium-Term Outcomes

	Control (N=120)	RIPC (n=120)	P value
MAKE (90d) %	20	14.2	0.034
AKI non-recovery (90d) %	23.2	5.3	0.02

Zarbock A, et al: JAMA 2015;313(21):2133-41

Zarbock A, et al: Anesthesiology 2017;126:787-798

RIPC for Cardiac Surgery: Negative Trials & Meta-analysis

	Control (n=772)	RIPC (n=749)	P value
AKI (72h) %	38	38.3	0.98
Stage 1	29.3	30.7	
Stage 2	5.7	5.1	
Stage 3	3	2.5	
RRT	?	?	

Hausenloy DJ, et al: NEJM 2015;373:1408-1417

	Control (N=693)	RIPC (n=692)	P value
Stage 2/3 AKI (14d) %	5.1	6.1	0.45
RRT (14d) %	?	?	?

Meybohm, et al: NEJM 2015;373:1397-1407

Meta-analysis: RIPC for renoprotection (RR; 95% CI)

AKI (AKIN): 0.76; 0.57-1.00
AKI (RIFLE): 0.91; 0.75-1.12
RRT: 0.85; 0.37-1.94

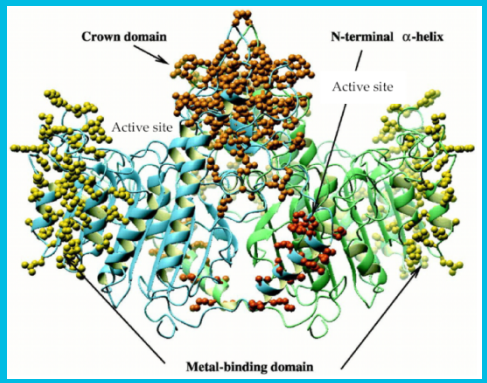
Menting TP, et al: Cochrane Database;2017:1-119

Alkaline Phosphatase for Septic AKI

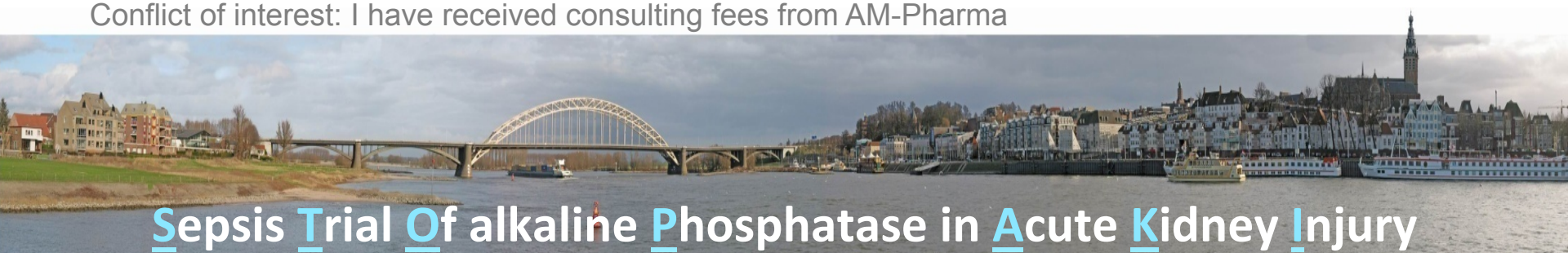
Phase IIb Trial Results

CRRT, San Diego 2018

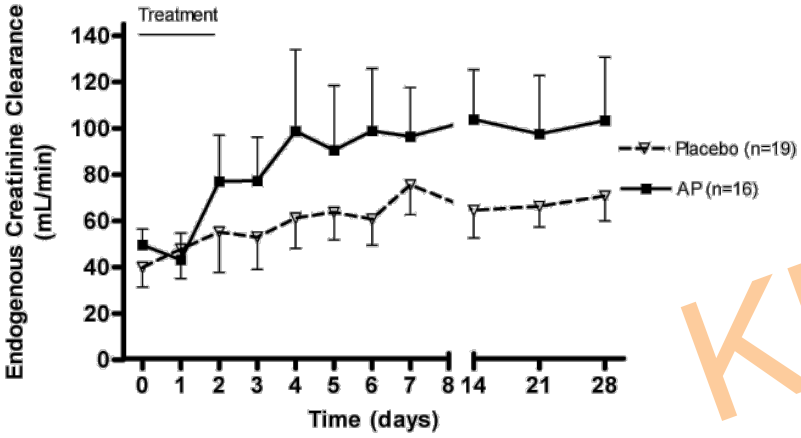
Peter Pickkers
Department of Intensive Care Medicine

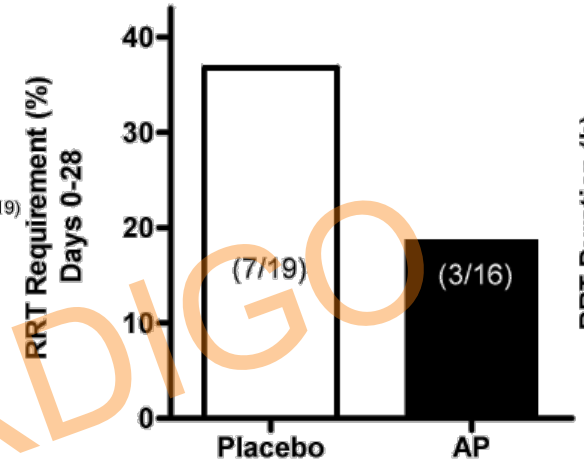


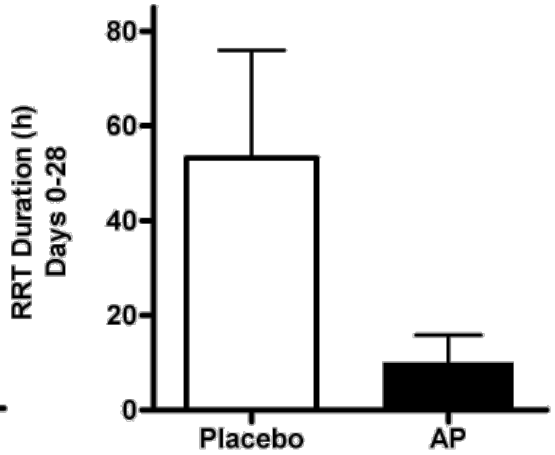
Conflict of interest: I have received consulting fees from AM-Pharma



Two small Phase-II Studies with bovine AP







Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients*

Suzanne Heemskerk, PhD; Rosalinde Masereeuw, PhD; Olof Moesker; Martijn P. W. J. M. Bouw; Johannes G. van der Hoeven, MD, PhD; Wilbert H. M. Peters, PhD; Frans G. M. Russel, PhD; Peter Pickkers, MD, PhD; on behalf of the APSEP Study Group

Pickkers *et al. Critical Care* 2012, **16**:R14
http://ccforum.com/content/16/1/R14

CRITICAL CARE

RESEARCH Open Access

Alkaline phosphatase for treatment of sepsis-induced acute kidney injury: a prospective randomized double-blind placebo-controlled trial

Peter Pickkers[1*], Suzanne Heemskerk[1,2], Jeroen Schouten[3], Pierre-François Laterre[4], Jean-Louis Vincent[5], Albertus Beishuizen[6], Philippe G Jorens[7], Herbert Spapen[8], Michael Bulitta[9], Wilbert HM Peters[10] and Johannes G van der Hoeven[1]

NATURE REVIEWS | RESEARCH HIGHLIGHTS

ACUTE KIDNEY INJURY

Alkaline phosphatase in sepsis-induced AKI

Inclusion criteria

- Informed consent
- 18-85 yrs
- Sepsis <96 hr
  - (Sepsis2 criteria*)
- AKI <24 hrs
  - (AKIN criteria#)

Exclusion criteria

- Pregnant women/HIV/drug abuse/ hematological malignancy
- Weight >115 kg
- Life-support limitations
- Rapidly fatal outcome
- Urosepsis
- Already on/<24 hrs in need of RRT
- Immunosuppressive treatment
- Liver: Child-Pugh class C
- Pancreatitis
- Participant in another trial
- CKD (eGFR<60 ml/min)
- AKI caused by other reason
- Improvement in renal function prior to study drug administration

*Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250-6

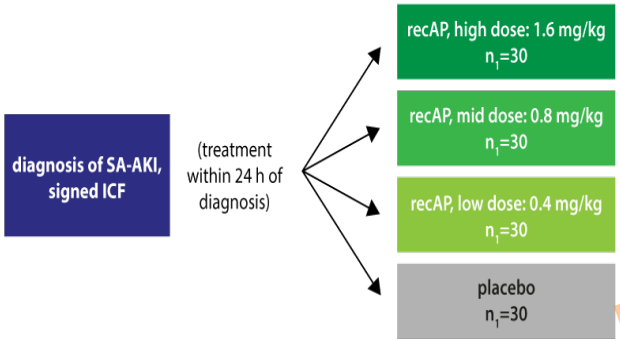
#Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

Table 1. Demographic and Baseline Disease Characteristics

Characteristic	Placebo (N=116)	recAP 0.4 mg/kg (N=31)	recAP 0.8 mg/kg (N=32)	recAP 1.6 mg/kg (N=111)	Total (N=290)
Age, median [IQR] — years	68.0 [61.0 - 75.0]	67.0 [61.0 - 72.0]	66.5 [62.5 -72.0]	65.0 [57.0 – 73.0]	67.0 [59.0 – 73.0]
Male — no. (%)	84 (72.4)	23 (74.2)	16 (50.0)	82 (73.9)	205 (70.7)
Caucasian — no. (%)	95 (81.9)	25 (80.6)	27 (84.4)	95 (85.6)	242 (83.4)
Weight, median [IQR] — kg	79.2 [70.0 – 86.5]	78.0 [70.0 – 86.0]	79.0 [72.0 – 90.0]	80.0 [71.8 – 90.0]	80.0 [70.0 – 89.1]
Height, median [IQR] — cm	174.0 [165.0 – 178.0]	172.5 [165.0 – 184.0]	167.0 [160.0 – 174.0]	173.0 [168.0 – 179.0]	173.0 [165.0 – 178.5]
BMI, median [IQR] — kg/m^2	26.3 [23.9 – 29.4]	25.8 [22.4 – 28.4]	27.4 [25.2 -30.7]	26.8 [23.9 -30.2]	26.6 [23.9 – 29.4]
Disease severity					
APACHE II score, median [IQR]	26.0 [20.0 – 33.5]	30.0 [25.0 – 35.0]	26.0 [20.0 – 34.5]	25.0 [19.0 – 31.0]	26.0 [21.0 – 33.0]
SAPS, median [IQR]	47.0 [39.0 – 60.0]	52.0 [42.0 – 70.0]	50.5 [38.0 – 60.5]	50.0 [42.0 – 61.0]	49.5 [40.0 – 63.0]
SOFA score, median [IQR]	10.0 [8.0 – 12.0]	10.0 [8.0 – 13.0]	9.0 [8.0 – 11.0]	10.0 [8.0 – 12.0]	10 [8.0 – 12.0]
Mechanical ventilation — no. (%)	68 (58.6)	23 (74.2)	20 (62.5)	70 (63.1)	181 (62.4)
Vasopressor/inotropic therapy use — no. (%)	103 (88.8)	28 (90.3)	30 (93.8)	102 (91.9)	263 (90.7)
Vital signs					
Heart rate, median [IQR] — beats/min	98.0 [85.0 – 111.0]	93.0 [77.0 – 115.0]	90.0 [75.5 – 107.5]	95.0 [83.0 – 110.0]	95.5 [81.0 – 110.0]
Systolic blood pressure, median [IQR] — mm Hg	112.0 [101.5 – 131.5]	108.0 [100.0 – 119.0]	118.5 [96.0 – 131.0]	107.0 [95.0 – 119.0]	110.0 [98.0 – 123.0]
Diastolic blood pressure, median [IQR] — mm Hg	56.5 [51.0 – 63.5]	54.0 [49.0 – 62.0]	58.0 [54.0 – 62.0]	55.0 [49.0 – 62.0]	56.0 [50.0 – 62.0]
Body temperature — no. (%)					
<36°C	11 (9.5)	4 (12.9)	5 (15.6)	11 (9.9)	31 (10.7)
≥36°C to ≤38°C	76 (65.5)	20 (64.5)	22 (68.8)	79 (71.2)	197 (67.9)
>38°C	27 (23.3)	7 (22.6)	5 (15.6)	18 (16.2)	57 (19.7)
Renal function					
eGFR, median [IQR] — ml/min	37.5 [23.9 -50.8]	27.2 [20.0 – 42.4]	25.6 [20.4 – 40.7]	29.7 [20.5 – 46.5]	31.8 [21.0 – 47.8]
ECC, median [IQR; no.] — ml/min					
Day 0	31.8 [14.7 -62.5; 49]	14.4 [8.8 – 58.0; 10]	26.0 [5.4 – 30.6; 12]	24.1 [10.5 – 54.9; 46]	27.9 [9.3 – 58.0; 117]
Day 1	35.9 [12.2 – 82.9; 103]	28.3 [4.3 – 64.4; 30]	25.2 [9.4 -61.0; 31]	26.0 [8.8 – 59.5; 102]	29.4 [10.0 – 67.9, 266]
AKI stage — no. (%)					
Stage 1	91 (78.4)	22 (71.0)	23 (71.9)	81 (73.0)	217 (74.8)
Stage 2	16 (13.8)	5 (16.1)	5 (15.6)	17 (15.3)	43 (14.8)
Stage 3	5 (4.3)	4 (12.9)	4 (12.5)	11 (9.9)	24 (8.3)
Urine output, median [IQR] — ml/h	60.0 [21.8 – 99.3]	50.0 [21.7 – 101.7]	27.4 [16.4 – 50.0]	39.1 [10.9 – 85.7]	46.3 [16.7 – 91.7]
Serum creatinine, median [IQR] — mg/dl	1.8 [1.3 – 2.4]	2.3 [1.5 – 2.8]	1.9 [1.5 – 2.8]	2.0 [1.4 – 2.8]	1.9 [1.4 – 2.6]

Results

Design Part 1



	recAP			Placebo
	1.6 mg/kg	0.8 mg/kg	0.4 mg/kg	
$AUC_{1\text{-}7}$ ECC – ml/min [IQR]				46.2 [21.5 – 114.6]

DSMB: Part 2: recAP 1.6 mg/kg vs placebo

Blinded to study personnel

Safety

TREATMENT-EMERGENT (SERIOUS) ADVERSE EVENTS

	Treatment emergent AEs				Treatment emergent SAEs			
		recAP				recAP		
Adverse event	Placebo (N=112)	0.4 mg (N=38)	0.8 mg (N=35)	1.6 mg (N=109)	Placebo (N=112)	0.4 mg	0.8 m	1.6 mg =109)
Total number of events	806	277	252	898				76
Number of patients with at least one treatment-emergent event	111 (99.1)	35 (92.1)						3.1)
Gastrointestinal disorders	49 (43.8)							0.1)
Infections and infestations								.5)
Metabolism and nutrition disorders								
General disorders and administration site conditions								5 (4.6)
Cardiac disorders							3 (8.6)	9 (8.3)
Psychiatric disorders						0	0	1 (0.9)
Respiratory, thor					14 (12.5)	6 (15.8)	3 (8.6)	9 (8.3)
Vascul				(33.0)	7 (6.3)	1 (2.6)	0	5 (4.6)
In			(28.6)	30 (27.5)	1 (0.9)	0	0	1 (0.9)
Blo			8 (22.9)	24 (22.0)	2 (1.8)	2 (5.3)	0	2 (1.8)
Ski		7 (18.4)	5 (14.3)	22 (20.2)	0	0	0	1 (0.9)
Nerv	15 (13.4)	6 (15.8)	10 (28.6)	19 (17.4)	1 (0.9)	4 (10.5)	1 (2.9)	4 (3.7)
Renal	12 (10.7)	6 (15.8)	2 (5.7)	16 (14.7)	2 (1.8)	1 (2.6)	0	1 (0.9)
Injury, ions	15 (13.4)	13 (34.2)	7 (20.0)	14 (12.8)	3 (2.7)	3 (7.9)	2 (5.7)	0
Muscul issue disorders	14 (12.5)	3 (7.9)	1 (2.9)	13 (11.9)	1 (0.9)	0	0	0
Hepatob ders	9 (8.0)	1 (2.6)	1 (2.9)	9 (8.3)	4 (3.6)	1 (2.6)	0	0
Endocrine disorders	4 (3.6)	1 (2.6)	1 (2.9)	3 (2.8)	0	0	0	0
Eye disorders	2 (1.8)	3 (7.9)	1 (2.9)	3 (2.8)	0	0	0	0
Ear and labyrinth disorders	1 (0.9)	0	0	2 (1.8)	0	0	0	1 (0.9)
Neoplasm benign, malignant and unspecified (incl cyst and polyps)	1 (0.9)	0	0	1 (0.9)	0	0	0	0
Congenital, familial and genetic disorders	0	0	0	1 (0.9)	0	0	0	0
Reproductive system and breast disorder	0	0	0	1 (0.9)	0	0	0	0

Number of adverse effects: similar in all groups
No dose-dependency signal
No immunogenicity

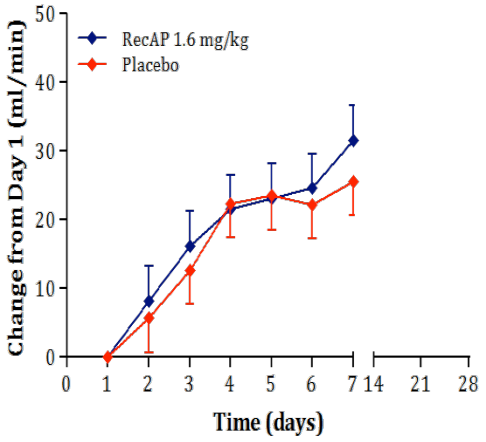
KDIGO

Primary endpoint

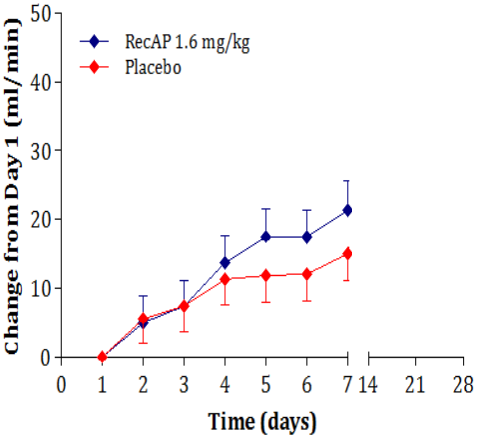
RecAP 1.6 mg/kg vs placebo

Endpoint	recAP 1.6 mg/kg	Placebo	Mean difference (95% CI)	P-value
Area under the time-corrected ECC curve (AUC1-7), median [IQR] — ml/min	55.1 [15.0–93.9]	45.6 [17.7–112.4]	7.8 (-7.4; 23.0)	0.312
RRT incidence (day 1–28), —%	36.0	29.3	1.4 (0.8; 2.4)	0.281
RRT-free days (day 1–28), median [IQR] —days	28 [16-28]	28 [16-28]	0.7 (1.8; 3.2)	0.601

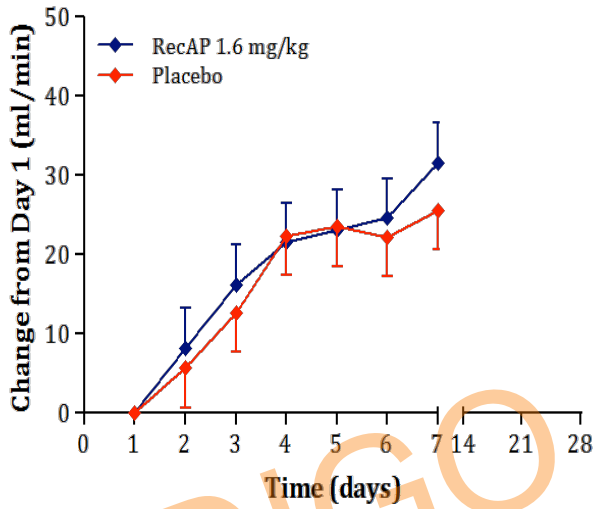
A Endogenous Creatinine Clearance



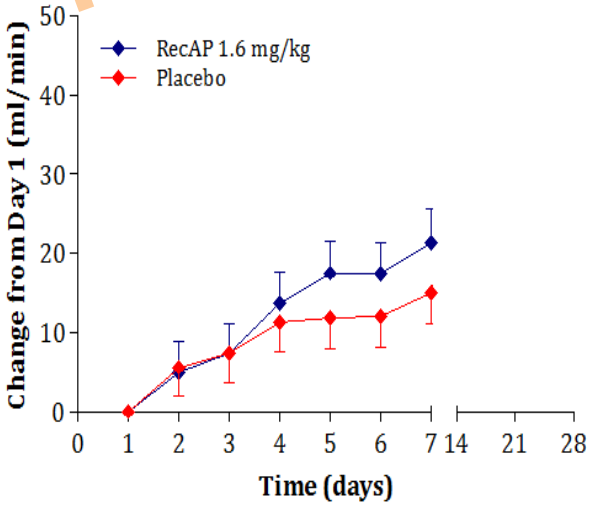
B BUN Clearance



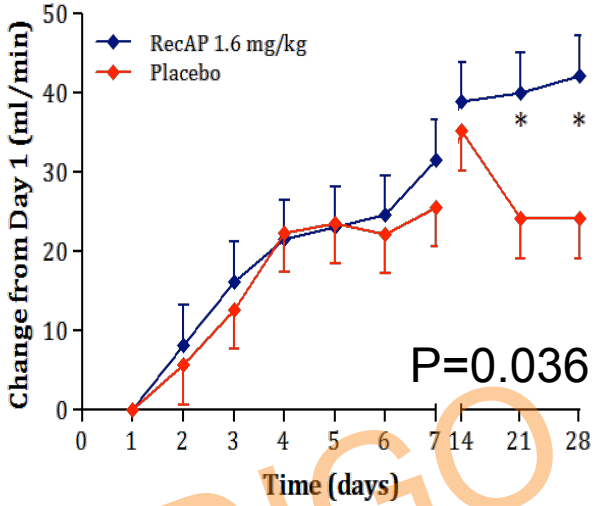
A Endogenous Creatinine Clearance



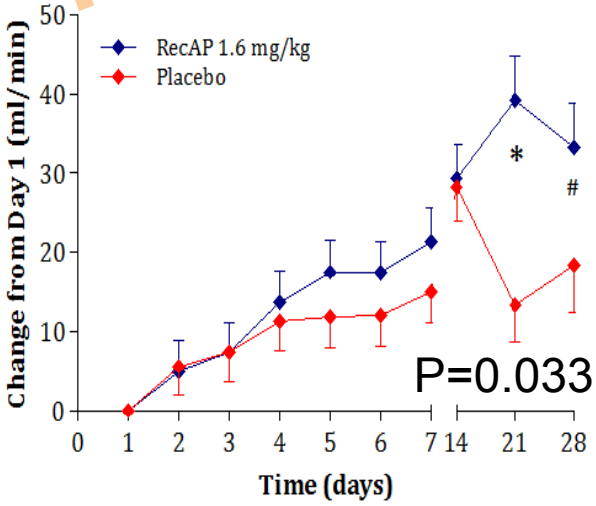
B BUN Clearance

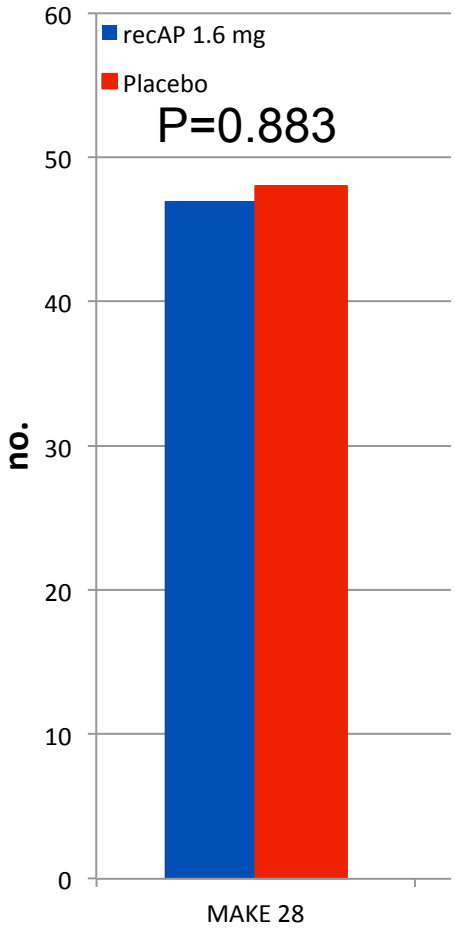


A Endogenous Creatinine Clearance

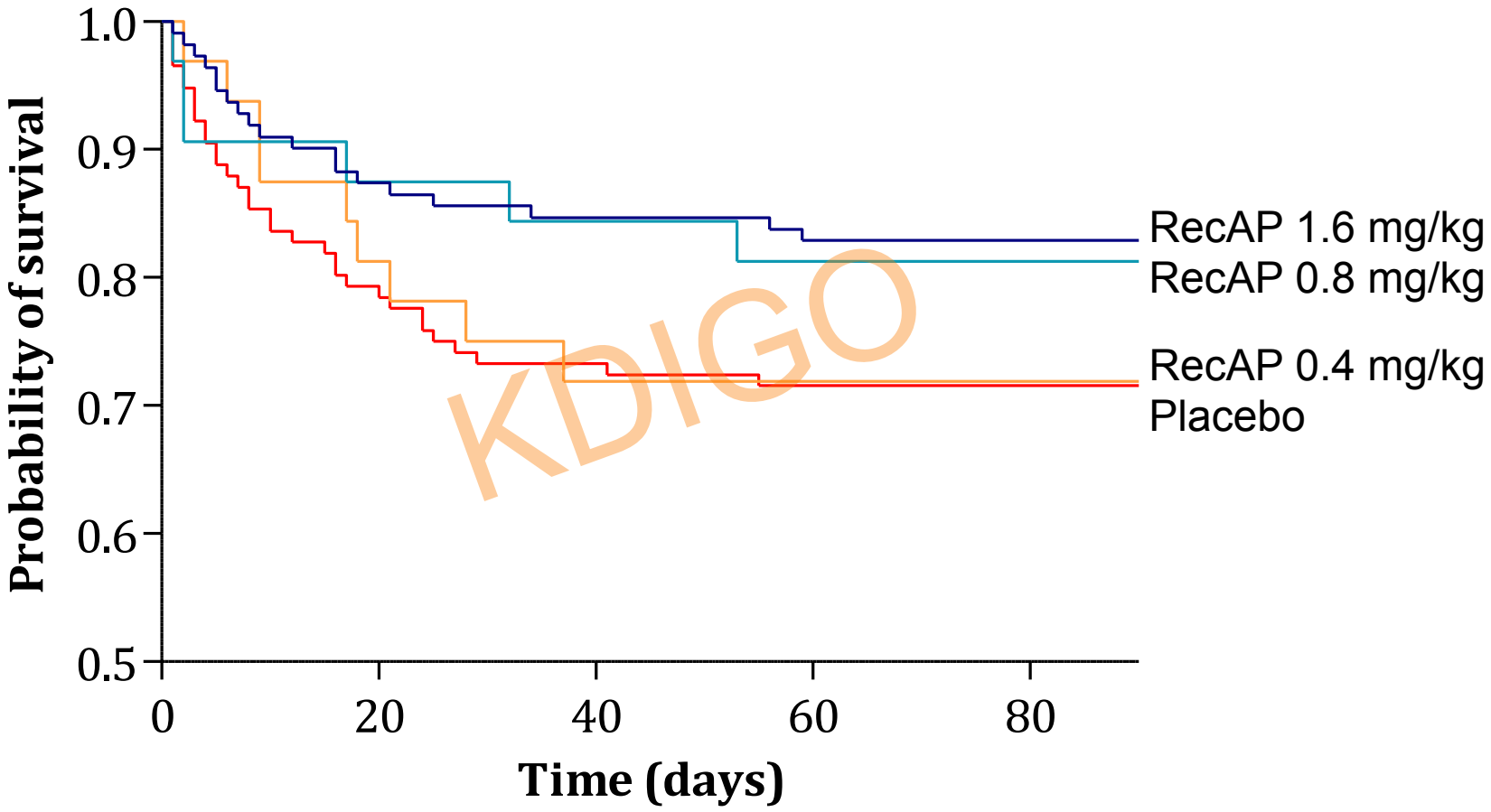


B BUN Clearance





MAKE composite 1 (Day 28)
Dialysis dependent before or on D28
Died before or on D28


Probability of survival
1.0
0.9
0.8
0.7
0.6
0.5
0
20
40
60
80
Time (days)
RecAP 1.6 mg/kg
RecAP 0.8 mg/kg
RecAP 0.4 mg/kg
Placebo
KDIGO