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

©2016 by American Society of Nephrology

www.ADQI.org
Evolution of AKI Conceptual Framework

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

www.ADQI.org
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

<table>
<thead>
<tr>
<th></th>
<th>Mortality 90d n/N (%)</th>
<th>RRT Incidence n/N (%)</th>
<th>RRT Duration (Days)</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual</td>
<td>EGDT</td>
<td>Usual</td>
<td>EGDT</td>
</tr>
<tr>
<td><strong>ProCESS</strong></td>
<td>139/412 (33.7%)</td>
<td>129/405 (31.9%)</td>
<td>11/397 (2.8%)</td>
<td>12/382 (3.1%)</td>
</tr>
<tr>
<td><strong>ARISE</strong></td>
<td>150/796 (18.8%)</td>
<td>147/792 (18.6%)</td>
<td>108/798 (13.5%)</td>
<td>106/793 (13.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ProMISE</strong></td>
<td>181/620 (29.2%)</td>
<td>184/623 (29.5%)</td>
<td>81/614 (13.2%)</td>
<td>88/620 (14.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>PL Meta-analysis</strong></td>
<td>475/1871 (25.4%)</td>
<td>462/1852 (24.9%)</td>
<td>198/1874 (10.6%)</td>
<td>204/1852 (11%)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

* RRT grp

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
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5) Renal tubular oxygen consumption: diuretics (±other effects: loop diuretics, mannitol)
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

Conceptual framework for AKI risk

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

Benoit & Devarajan, Pediatr Nephrol 2018;33:779-987
### Selected Novel AKI Therapies in Human Development

<table>
<thead>
<tr>
<th>AGENT</th>
<th>Site of Action</th>
<th>Mechanism of Action</th>
<th>Drug Development</th>
<th>Role in AKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>QPI-1002/ Teprasiran</td>
<td>Gene silencing</td>
<td>Temporary suppression of p53 expression</td>
<td>Phase 3/ NCT03510897 (CS) NCT02601283 (DGF)</td>
<td>Prevention</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>Anti-sepsis</td>
<td>Anti-inflammatory effect through generation of adenosine (from ATP) &amp; De-phosphorylation of endotoxin</td>
<td>Phase 2</td>
<td>Treatment</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Iron Chelator</td>
<td>Antioxidant</td>
<td>Phase 2/ NCT01146925</td>
<td>Prevention &amp; Treatment</td>
</tr>
</tbody>
</table>
ABT-719 (α-MSH) for CS-AKI

Delayed Graft Function: Targets
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/1.73m², diabetes, proteinuria, congestive heart failure)

Subjects were stratified by eGFR: ≥ vs < 60mL/min/1.73m²

Demographics and AE profiles were similar between treatment groups

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)

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

P Pickkers and coauthors

Published online October 24, 2018

Available at jama.com and on The JAMA Network Reader at mobile.jamanetwork.com
Alkaline phosphatase treatment improves renal function in severe sepsis or septic shock patients*

Suzanne Heemskerk, PhD; Rosealinde Masereeuw, PhD; Olof Moresk; Martijn P. W. J. M. Buxx; Johannes G. van der Heeven, MD, PhD; Wilbert H. M. Peters, PhD; Frans G. M. Russel, PhD; Peter Pickkers, MD, PhD; on behalf of the ARP Study Group

Alkaline phosphatase in sepsis-induced AKI

Nature Reviews | Research Highlights

Acute Kidney Injury

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

Peter Pickkers1,2, Suzanne Heemskerk1,2, Jeon Schouten1, Pierre-Francois Latem1,2, Jean-Louis Vreeen1, Albertus Beethuizen1, Philipp G. Jorres1, Herbert Sparen1, Michael Bull2, Wilbert HH Peters3, and Johannes G van der Heeven1

Endogenous Creatinine Clearance (ml/min)

Time (days)

Placebo

AP

RRT Requirement (%)

Days 0-28

0

10

20

30

40

Endogenous Creatinine Clearance (ml/min)

Time (days)

Placebo

AP

RRT Duration (h)

Days 0-28

0

60

70

80

RRT Duration (h)

Placebo

AP

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

JAMA. Published online October 24, 2018. doi:10.1001/jama.2018.14283
28-day Survival

No. at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>111</th>
<th>98</th>
<th>95</th>
<th>93</th>
<th>92</th>
</tr>
</thead>
<tbody>
<tr>
<td>RecAP 1.6 mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>116</td>
<td>92</td>
<td>86</td>
<td>84</td>
<td>83</td>
</tr>
</tbody>
</table>

P = 0.03
From: Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury A Randomized Clinical Trial

JAMA. Published online October 24, 2018. doi:10.1001/jama.2018.14283
Pathogenesis of Septic AKI

Dephosphorylation of LPS

Dephosphorylation of ATP/ADP

TLR4

recAP

P

P

P

LPS

P

P

P

ADP

ATP

recAP

P

P

P

ADO

Apical membrane

Inflammatory cytokines
(e.g. TNF-α, IL-6, IL-8)

Renal inflammation

British Journal of Pharmacology

RESEARCH PAPER

Alkaline phosphatase protects against renal inflammation through dephosphorylation of lipopolysaccharide and adenosine triphosphate
Catalytic (Labile) Iron and AKI

Iron-catalyzed generation of reactive oxygen species

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

\[ \text{Fe}^{3+} + \cdot\text{O}_2^- \rightarrow \text{Fe}^{2+} + \text{O}_2 \]

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

\[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \cdot\text{OH} \] (Fenton reaction)

Net reaction:

\[ \cdot\text{O}_2^- + \text{H}_2\text{O}_2 \rightarrow \cdot\text{OH} + \text{OH}^- + \text{O}_2 \]

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**

doi: 10.1681/ASN.2018100979

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

David E. Leaf et al. JASN 2019;30:493-504
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., liver disease, genetic polymorphisms) may further contribute to hepcidin suppression. Decreased hepcidin leads to increased iron release, which can exacerbate oxidative injury and organ dysfunction, ultimately leading to mortality.

David E. Leaf et al. JASN 2019;30:493-504
De novo NAD+ biosynthetic impairment in Human AKI

AKI Bioenergetics

Individuals with increased susceptibility to AKI (e.g., age, DM and CKD)

↓Kidney QPRT levels

↓Kidney de novo NAD⁺ biosynthesis
↓Renal NAD⁺ levels
↑Susceptibility to AKI

Potential new therapy for preventing AKI

Oral nicotinamide

↑Kidney NAD⁺ levels
Protection against AKI

↓uQ/T

New mechanism underlying AKI

Potential new biomarker for predicting AKI and adverse outcomes

Bulluck H, Hausenloy DJ: Nature Medicine 2018;24:1304-12
**Novel AKI Therapeutics**

- **Normal Epithelium**
  - Initiation
    - Loss of Brush Border and Cell Polarity
    - Sloughing and Tubular Obstruction
    - Apoptosis and Necrosis
  - Extension
    - Altered Renal Blood Flow
    - Coagulopathy and Inflammation
    - Microvascular Congestion
  - Maintenance
    - Dedifferentiation
    - Migration
    - Proliferation

- **Anti-Inflammatory**
  - Recombinant Alkaline Phosphatase
  - CD28 Receptor Antagonist
  - Alpha Melanocortin Stimulating Hormone Agonist

- **Repair Agents**
  - BMP Receptor Agonist
  - Hepatocyte Growth Factor
  - Mesenchymal Stem Cells

- **Antioxidants**
  - Iron Chelators
  - Heme Arginate

- **Vasodilators**
  - Levosimendan

- **Apoptosis Inhibitors**
  - P53 siRNA

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.

- Assessed for eligibility: 502
- Excluded: 50
- Randomized: 452

**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.

<table>
<thead>
<tr>
<th>Arm 1 (N=113)</th>
<th>Arm 2 (N=34)</th>
<th>Arm 3 (N=34)</th>
<th>Arm 4 (N=116)</th>
<th>Arm 5 (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>77.9</td>
<td>79.4</td>
<td>76.5</td>
<td>75.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>69.1-85.1</td>
<td>62.1-91.3</td>
<td>58.8-89.3</td>
<td>67.0-83.3</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.16</td>
<td>0.97</td>
<td>0.91</td>
<td>0.84</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.45-5.01</td>
<td>0.39-2.44</td>
<td>0.49-1.69</td>
<td>0.45-15.58</td>
</tr>
<tr>
<td>p-value</td>
<td>0.76</td>
<td>0.95</td>
<td>0.76</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**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

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

<table>
<thead>
<tr>
<th>Secondary Outcomes</th>
<th>AC607</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Hospital Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis at Day 30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Hospital LOS (days)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Median Days to recovery (IQR): 15 (10-29) vs. 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.

Madhav Swaminathan et al. JASN 2018;29:260-267
Challenge of miRNA therapeutics...

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


http://mdd.ucd.ie/research/
**NOVEL AKI THERAPEUTICS**

- **Normal Epithelium**
- **Initiation**
  - Loss of Brush Border and Cell Polarity
  - Sloughing and Tubular Obstruction
  - Apoptosis and Necrosis
- **Extension**
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  - Proliferation
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**Antioxidants**
- Iron Chelators
- Heme Arginate

**Vasodilators**
- Levosimendan

**Apoptosis Inhibitors**
- P53 siRNA

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

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

The New Spectrum of AKI Diagnostics

Functional criteria

- RIFLE R or AKIN/KDIGO-1
- RIFLE I or AKIN/KDIGO-2
- RIFLE F or AKIN/KDIGO-3

Damage criteria

- Biomarker +
- Biomarker ++
- Biomarker +++


www.ADQI.org
• Hepatorenal
Overview of the Prevention of Serious Adverse Events following Angiography (PRESERVE) study design

**Study population**

- Undergoing coronary or non-coronary angiography
- Pre-angiography eGFR <60 ml/min/1.73 m² or diabetes mellitus or pre-angiography eGFR <45 ml/min/1.73 m² +/- diabetes mellitus
- Able and willing to provide informed consent

**Exclusion criteria**

- Presence of stage 5 CKD or ESRD
- Pre-angiography AKI
- Unstable baseline Scr
- ST-elevation MI
- Decompensated heart failure
- Emergent angiogram
- Receipt of iodinated contrast within past 7 days
- Receipt of NAC within past 48 hours
- Known allergy to NAC
- Prisoner
- Age <18 years
- Pregnancy
- Anticipated life expectancy <3 months
- Unwilling to comply with 4 and 90 day outcome assessments
- Patient refusal
- Provider refusal
- Ongoing participation in a clinical trial

**Randomization**

- Randomization to a combination of interventions with 1:1:1 allocation to each of 4 possible treatment combinations
- Stratification of randomization by site

**1:1 allocation**

- Bicarbonate vs. saline

<table>
<thead>
<tr>
<th>1:1 allocation vs. placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC</td>
<td>IV isotonic bicarbonate oral NAC</td>
</tr>
<tr>
<td></td>
<td>IV isotonic saline oral NAC</td>
</tr>
<tr>
<td>Placebo</td>
<td>IV isotonic bicarbonate oral placebo</td>
</tr>
<tr>
<td></td>
<td>IV isotonic saline oral placebo</td>
</tr>
</tbody>
</table>

**End-points**

- **Primary endpoint**
  - 90 day mortality, need for acute dialysis, persistent decline in kidney function

- **Secondary endpoints**
  - Development of CIAKI
  - Individual components of primary end-point
  - 90 day hospitalization with ACS, HF, CVA
  - 90 day all-cause hospitalization

- **Tertiary endpoints**
  - 1 year ESRD
  - 1 year mortality

**Sample size**

- 8,680 patients total
- 2,170 patients per group

**Study sites**

- 33 VA sites
- 10 Australian sites

**Study duration**

- 2 & 1/2 year patient accrual

ClinicalTrials.gov: NCT01467466
### Table 3. Primary and Secondary End Points.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sodium Bicarbonate (N = 2511)</th>
<th>Sodium Chloride (N = 2482)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Sodium Bicarbonate (N = 2495)</th>
<th>Sodium Chloride (N = 2498)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point</strong></td>
<td>110 (4.4)</td>
<td>116 (4.7)</td>
<td>0.93 (0.72–1.22)</td>
<td>0.62</td>
<td>114 (4.6)</td>
<td>112 (4.5)</td>
<td>1.02 (0.78–1.33)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contrast-associated acute kidney injury†</td>
<td>239 (9.5)</td>
<td>206 (8.3)</td>
<td>1.16 (0.96–1.41)</td>
<td>0.13</td>
<td>228 (9.1)</td>
<td>217 (8.7)</td>
<td>1.06 (0.87–1.28)</td>
<td>0.58</td>
</tr>
<tr>
<td>Death by 90 days</td>
<td>60 (2.4)</td>
<td>68 (2.7)</td>
<td>0.87 (0.61–1.24)</td>
<td>0.43</td>
<td>67 (2.7)</td>
<td>61 (2.4)</td>
<td>1.10 (0.78–1.57)</td>
<td>0.59</td>
</tr>
<tr>
<td>Need for dialysis by 90 days</td>
<td>32 (1.3)</td>
<td>29 (1.2)</td>
<td>1.09 (0.65–1.81)</td>
<td>0.73</td>
<td>30 (1.2)</td>
<td>31 (1.2)</td>
<td>0.97 (0.58–1.60)</td>
<td>0.90</td>
</tr>
<tr>
<td>Persistent kidney impairment by 90 days</td>
<td>28 (1.1)</td>
<td>25 (1.0)</td>
<td>1.10 (0.64–1.91)</td>
<td>0.71</td>
<td>26 (1.0)</td>
<td>27 (1.1)</td>
<td>0.96 (0.56–1.66)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days</td>
<td>272 (10.8)</td>
<td>251 (10.1)</td>
<td>1.08 (0.90–1.29)</td>
<td>0.40</td>
<td>244 (9.8)</td>
<td>279 (11.2)</td>
<td>0.86 (0.71–1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>All-cause hospitalization by 90 days</td>
<td>1071 (42.7)</td>
<td>1052 (42.4)</td>
<td>1.01 (0.90–1.13)</td>
<td>0.85</td>
<td>1069 (42.8)</td>
<td>1054 (42.2)</td>
<td>1.03 (0.91–1.15)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

* 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.

## Remote Ischemic Pre-conditioning

### Short-Term Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control (n=120)</th>
<th>RIPC (n=120)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI (72h) %</td>
<td>52.5</td>
<td>37.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage 1</td>
<td>26.7</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>11.7</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>14.2</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>RRT</td>
<td>15.8</td>
<td>5.8</td>
<td></td>
</tr>
</tbody>
</table>

### Medium-Term Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control (N=120)</th>
<th>RIPC (n=120)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAKE (90d) %</td>
<td>20</td>
<td>14.2</td>
<td>0.034</td>
</tr>
<tr>
<td>AKI non-recovery (90d) %</td>
<td>23.2</td>
<td>5.3</td>
<td>0.02</td>
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</table>

### RIPC for Cardiac Surgery: Negative Trials & Meta-analysis

<table>
<thead>
<tr>
<th></th>
<th>Control (n=772)</th>
<th>RIPC (n=749)</th>
<th>P value</th>
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<tbody>
<tr>
<td>AKI (72h) %</td>
<td>38</td>
<td>38.3</td>
<td>0.98</td>
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<tr>
<td>Stage 1</td>
<td>29.3</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>5.7</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Stage 3</td>
<td>3</td>
<td>2.5</td>
<td></td>
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<tr>
<td>RRT</td>
<td>?</td>
<td>?</td>
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<table>
<thead>
<tr>
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<th>Control (N=693)</th>
<th>RIPC (n=692)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Stage 2/3 AKI (14d) %</td>
<td>5.1</td>
<td>6.1</td>
<td>0.45</td>
</tr>
<tr>
<td>RRT (14d) %</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>


**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

Sepsis Trial Of alkaline Phosphatase in Acute Kidney Injury
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; Max W. I. M. Boon; 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 A8SEP Study Group.

Plekken et al. Critical Care 2012; 16:R14
http://ccforum.com/content/16/1/R14

RESEARCH

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

Peter Pickkers1, Suzanne Heemskerk1,2, Jeroen Schouten1, Pierre-François Laterr1, Jean-Louis Vincent1, Albertus Bethuizen3, Philippe G. Jorens3, Herbert Sassen4, Michael Bults3, Wilbert HM Peters5 and Johannes G van der Hoeven1

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
• AKI caused by other reason
• Improvement in renal function prior to study drug administration

---


### Table 1. Demographic and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=116)</th>
<th>0.4 mg/kg (N=31)</th>
<th>0.8 mg/kg (N=32)</th>
<th>1.6 mg/kg (N=111)</th>
<th>Total (N=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [IQR] — years</td>
<td>68.0 [61.0 - 75.0]</td>
<td>67.0 [61.0 - 72.0]</td>
<td>66.5 [62.5 - 72.0]</td>
<td>65.0 [57.0 - 73.0]</td>
<td>67.0 [59.0 - 73.0]</td>
</tr>
<tr>
<td>Male — no. (%)</td>
<td>84 (72.4)</td>
<td>23 (74.2)</td>
<td>16 (50.0)</td>
<td>82 (73.9)</td>
<td>205 (70.7)</td>
</tr>
<tr>
<td>Caucasian — no. (%)</td>
<td>95 (81.9)</td>
<td>25 (80.6)</td>
<td>27 (84.4)</td>
<td>95 (85.6)</td>
<td>242 (83.4)</td>
</tr>
<tr>
<td>Weight, median [IQR] — kg</td>
<td>79.2 [70.0 - 86.5]</td>
<td>78.0 [70.0 - 86.0]</td>
<td>79.0 [72.0 - 90.0]</td>
<td>80.0 [71.8 - 90.0]</td>
<td>80.0 [70.0 - 89.1]</td>
</tr>
<tr>
<td>Height, median [IQR] — cm</td>
<td>174.0 [165.0 - 178.0]</td>
<td>172.5 [165.0 - 184.0]</td>
<td>167.0 [160.0 - 174.0]</td>
<td>173.0 [168.0 - 179.0]</td>
<td>173.0 [165.0 - 178.5]</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APACHE II score, median [IQR]</td>
<td>26.0 [20.0 - 33.5]</td>
<td>30.0 [25.0 - 35.0]</td>
<td>26.0 [20.0 - 34.5]</td>
<td>25.0 [19.0 - 31.0]</td>
<td>26.0 [21.0 - 33.0]</td>
</tr>
<tr>
<td>SAPS, median [IQR]</td>
<td>47.0 [39.0 - 60.0]</td>
<td>52.0 [42.0 - 70.0]</td>
<td>50.5 [38.0 - 60.5]</td>
<td>50.0 [42.0 - 61.0]</td>
<td>49.5 [40.0 - 63.0]</td>
</tr>
<tr>
<td>SOFA score, median [IQR]</td>
<td>10.0 [8.0 - 12.0]</td>
<td>10.0 [8.0 - 12.0]</td>
<td>9.0 [8.0 - 11.0]</td>
<td>10.0 [8.0 - 12.0]</td>
<td>10.0 [8.0 - 12.0]</td>
</tr>
<tr>
<td>Mechanical ventilation — no. (%)</td>
<td>68 (58.6)</td>
<td>23 (74.2)</td>
<td>20 (62.5)</td>
<td>70 (63.1)</td>
<td>181 (62.4)</td>
</tr>
<tr>
<td>Vasopressor/inotropic therapy use — no. (%)</td>
<td>103 (88.8)</td>
<td>28 (90.3)</td>
<td>30 (93.8)</td>
<td>102 (91.9)</td>
<td>263 (90.7)</td>
</tr>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, median [IQR] — beats/min</td>
<td>98.0 [85.0 - 111.0]</td>
<td>93.0 [77.0 - 115.0]</td>
<td>90.0 [75.5 - 107.5]</td>
<td>95.0 [83.0 - 110.0]</td>
<td>95.5 [81.0 - 110.0]</td>
</tr>
<tr>
<td>Systolic blood pressure, median [IQR] — mm Hg</td>
<td>112.0 [101.5 - 131.5]</td>
<td>108.0 [100.0 - 119.0]</td>
<td>118.5 [96.0 - 131.0]</td>
<td>107.0 [95.0 - 119.0]</td>
<td>110.0 [98.0 - 123.0]</td>
</tr>
<tr>
<td>Diastolic blood pressure, median [IQR] — mm Hg</td>
<td>56.5 [51.0 - 63.5]</td>
<td>54.0 [49.0 - 62.0]</td>
<td>58.0 [54.0 - 62.0]</td>
<td>55.0 [49.0 - 62.0]</td>
<td>56.0 [50.0 - 62.0]</td>
</tr>
<tr>
<td>Body temperature — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;36°C</td>
<td>11 (9.5)</td>
<td>4 (12.9)</td>
<td>5 (15.6)</td>
<td>11 (9.9)</td>
<td>31 (10.7)</td>
</tr>
<tr>
<td>≥36°C to ≤38°C</td>
<td>76 (65.5)</td>
<td>20 (64.5)</td>
<td>22 (68.8)</td>
<td>79 (71.2)</td>
<td>197 (67.9)</td>
</tr>
<tr>
<td>&gt;38°C</td>
<td>27 (23.3)</td>
<td>7 (22.6)</td>
<td>5 (15.6)</td>
<td>18 (16.2)</td>
<td>57 (19.7)</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, median [IQR] — ml/min</td>
<td>37.5 [23.9 - 50.8]</td>
<td>27.2 [20.0 - 42.4]</td>
<td>25.6 [20.4 - 40.7]</td>
<td>29.7 [20.5 - 46.5]</td>
<td>31.8 [21.0 - 47.8]</td>
</tr>
<tr>
<td>ECC, median [IQR; no.] — ml/min</td>
<td>51.8 [14.7 - 62.5; 49]</td>
<td>14.4 [8.8 - 58.0; 10]</td>
<td>26.0 [5.4 - 30.6; 12]</td>
<td>24.1 [10.5 - 54.9; 46]</td>
<td>27.9 [9.3 - 58.0; 117]</td>
</tr>
<tr>
<td>Day 0</td>
<td>35.9 [12.2 - 82.9; 103]</td>
<td>28.3 [4.3 - 64.4; 30]</td>
<td>25.2 [9.4 - 61.0; 31]</td>
<td>26.0 [8.8 - 59.5; 102]</td>
<td>29.4 [10.0 - 67.9; 266]</td>
</tr>
<tr>
<td>Day 1</td>
<td>51.8 [14.7 - 62.5; 49]</td>
<td>14.4 [8.8 - 58.0; 10]</td>
<td>26.0 [5.4 - 30.6; 12]</td>
<td>24.1 [10.5 - 54.9; 46]</td>
<td>27.9 [9.3 - 58.0; 117]</td>
</tr>
<tr>
<td>AKI stage — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>91 (78.4)</td>
<td>22 (71.0)</td>
<td>23 (71.9)</td>
<td>81 (73.0)</td>
<td>217 (74.8)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>16 (13.8)</td>
<td>5 (16.1)</td>
<td>5 (15.6)</td>
<td>17 (15.3)</td>
<td>43 (14.8)</td>
</tr>
<tr>
<td>Stage 3</td>
<td>5 (4.3)</td>
<td>4 (12.9)</td>
<td>4 (12.5)</td>
<td>11 (9.9)</td>
<td>24 (8.3)</td>
</tr>
<tr>
<td>Serum creatinine, median [IQR] — mg/dl</td>
<td>1.8 [1.3 - 2.4]</td>
<td>2.3 [1.5 - 2.8]</td>
<td>1.9 [1.5 - 2.8]</td>
<td>2.0 [1.4 - 2.8]</td>
<td>1.9 [1.4 - 2.6]</td>
</tr>
</tbody>
</table>
**Results**

**Design Part 1**

- **Placebo**
  - 1.6 mg/kg
  - 0.8 mg/kg
  - 0.4 mg/kg

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>ECC (ml/min [IQR])</th>
</tr>
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<tbody>
<tr>
<td>1.6 mg/kg</td>
<td>60.7 [3.7–92.4]</td>
</tr>
<tr>
<td>0.8 mg/kg</td>
<td>63.5 [8.1–96.8]</td>
</tr>
<tr>
<td>0.4 mg/kg</td>
<td>47.0 [6.6–88.4]</td>
</tr>
</tbody>
</table>

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

- Blinded to study personnel

---

**KDIGO**
Safety

TREATMENT-EMERGENT (SERIOUS) ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Treatment emergent AEs</th>
<th></th>
<th>Treatment emergent SAEs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=112)</td>
<td>0.4 mg (N=38)</td>
<td>0.8 mg (N=35)</td>
<td>1.6 mg (N=109)</td>
</tr>
<tr>
<td>Total number of events</td>
<td>806</td>
<td>277</td>
<td>252</td>
<td>899</td>
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<tr>
<td>Number of patients with at least one treatment-emergent event</td>
<td>111 (99.1)</td>
<td>35 (92.1)</td>
<td>23 (65.7)</td>
<td>13 (55.6)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>49 (43.8)</td>
<td>17 (45.9)</td>
<td>14 (40.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>47 (42.5)</td>
<td>6 (16.2)</td>
<td>5 (14.3)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>1 (0.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>14 (12.5)</td>
<td>14 (12.5)</td>
<td>7 (20.0)</td>
<td>3 (12.5)</td>
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<tr>
<td>Psychiatric disorders</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vascular disorders</td>
<td>5 (4.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Injury</td>
<td>14 (12.5)</td>
<td>14 (12.5)</td>
<td>7 (20.0)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Blood</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>Skin</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>Nervous system and sense organs</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Renal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injury</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (6.3)</td>
<td>1 (2.6)</td>
<td>1 (2.6)</td>
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<td>Dermatological disorders</td>
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<td>Endocrine disorders</td>
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<td>Eye disorders</td>
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<td>Ear and labyrinth disorders</td>
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<td>Neoplasm benign, malignant and unspecified (incl cyst and polyps)</td>
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<tr>
<td>Congenital, familial and genetic disorders</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>Reproductive system and breast disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

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

### RecAP 1.6 mg/kg vs placebo

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

![Graph A: Endogenous Creatinine Clearance](image1)

- **A** Endogenous Creatinine Clearance

![Graph B: BUN Clearance](image2)

- **B** BUN Clearance
A  Endogenous Creatinine Clearance

B  BUN Clearance
A  Endogenous Creatinine Clearance

B  BUN Clearance

P=0.036

P=0.033
### Intensive Care

- **P = 0.883**
- **P = 0.045**
- **P = 0.031**

#### MAKE composite 3 (Day 90)
- eGFR < 60 mL/min at D60
- Dialysis dependent before or on D90
- Died before or on D90

### Placebo

<table>
<thead>
<tr>
<th>no.</th>
<th>recAP 1.6 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>49</td>
<td>51</td>
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<tr>
<td>40</td>
<td>39</td>
<td>41</td>
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<td>30</td>
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<td>20</td>
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<td>10</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

### KDIGO

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