Novel biomarker panel approach to renal assessment

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Disclosures

• Consulting/Grant Support:
  • Astute Medical
  • Alere
  • Abbott
Other Disclosures

• Patent filing for use of [TIMP-2]•[IGFBP7] together with RIPC and other therapies to prevent AKI.
  • University of Pittsburgh
  • University of Munster
  • Astute Medical

• Off label use: Blood pressure cuff
Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury


See related commentary by Ronco et al., http://ccforum.com/content/17/1/117
TIMP-2 and IGFBP7 Outperform Existing Biomarkers

AUC for [TIMP-2]•[IGFBP7] was significantly greater than any existing biomarkers.
[TIMP-2] • [IGFBP7] = 0.3

AUC = 0.82 (0.76-0.88)

Bihorac, et al. AJRCCM 2014
Risk Stratification

AKI Stage 2-3 < 12 Hours

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Low Risk &lt; 0.3</th>
<th>High Risk 0.3 – 2.0</th>
<th>Highest Risk &gt;2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk = 2.7%</td>
<td>1.0</td>
<td>4.2</td>
<td>17.4</td>
</tr>
</tbody>
</table>
Urinary [TIMP-2]•[IGFBP7] Performs Well In Patients With History Of Heart Failure

AUC = 0.89 (0.83-0.94)

Manuscript Under Review by Sapphire and Topaz investigators
Cell Cycle Arrest In Response To Cell Stress

- An Alarm Signal Of Impending Cell Damage
## KDIGO Management Options

### Why Risk Assessment Is Needed and What To Do For a Positive Test

**KDIGO Consensus Guideline for AKI**

<table>
<thead>
<tr>
<th>AKI Stage</th>
<th>High Risk</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue all nephrotoxic agents when possible</td>
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<tr>
<td>Ensure volume status and perfusion pressure</td>
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<tr>
<td>Consider functional hemodynamic monitoring</td>
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<tr>
<td>Monitor serum creatinine and urine output</td>
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<tr>
<td>Avoid hyperglycemia</td>
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<tr>
<td>Consider alternatives to radiocontrast procedures</td>
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<tr>
<td>Non-invasive diagnostic workup</td>
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<tr>
<td>Consider invasive diagnostic workup</td>
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<tr>
<td>Check for changes in drug dosing</td>
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<tr>
<td>Consider renal replacement therapy</td>
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<tr>
<td>Consider ICU admission</td>
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<tr>
<td>Avoid subclavian catheters if possible</td>
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</tbody>
</table>

*Start when patients are at high risk...*

**KDIGO:** Kidney Disease Improving Global Outcomes; *Kidney International Supplements.* 2012;2,1. doi: 0.1038/kisup.2012
Cardiac surgery-associated AKI

• ...the most common preventable form of AKI in developed countries
• Over a million procedures performed annually in the US
• AKI complicates 7-19% of cases; leading to doubling of costs
  Dasta et al. NDT 2008;23:1970–4
• Nationally, AKI may account for as much as 25% of total health care costs associated with cardiac surgery or $2.1 billion per year.

• Major on safety concern for patients

• RIPC benefit may be limited to specific patient subgroups
  • Strongest evidence in very high risk patients (CCF score > 6)
  • Non-responders by biomarkers incurred no benefit
  • Opportunity to improve on prior success
Performance in CT surgery

- 105 and 55 CT surgery patients in Sapphire and Topaz trials.

- Overall, 14 patients (9%) were positive for the endpoint (stage 2-3 AKI within 12h).

- The area under the ROC curve (AUC) was 0.86 (95% CI 0.76-0.97, p<0.0001).

- Relative risk for AKI above the 0.3 cutoff was 7.0 (95% CI 1.6-30.2, p=0.003).
Urinary TIMP-2 and IGFBP7 as Early Biomarkers of Acute Kidney Injury and Renal Recovery following Cardiac Surgery

Melanie Meersch, Christoph Schmidt, Hugo Van Aken, Sven Martens, Jan Rossaint, Kai Singbartl, Dennis Görlich, John A. Kellum, Alexander Zarbock

A

- Pre-CPB
- 4 h
- 12 h
- 24 h

Urine TIMP2*IGFBP7 (ng/ml^2/1000)
## Determining Risk

<table>
<thead>
<tr>
<th>Clinical Evidence of AKI</th>
<th>Clinical Suspicion</th>
<th>Urinary [TIMP-2]•[IGFBP7]</th>
<th>Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Low</td>
<td>≤ 0.3</td>
<td>LOW</td>
</tr>
<tr>
<td>Negative</td>
<td>Low</td>
<td>&gt;0.3 &lt;2.0</td>
<td>Moderate</td>
</tr>
<tr>
<td>Positive</td>
<td>Any</td>
<td>Any</td>
<td>High</td>
</tr>
<tr>
<td>Any</td>
<td>High</td>
<td>Any</td>
<td>High</td>
</tr>
<tr>
<td>Negative</td>
<td>Low</td>
<td>≥ 2.0</td>
<td>High</td>
</tr>
</tbody>
</table>

# Biomarker-Guided Decision Tree

<table>
<thead>
<tr>
<th>Action</th>
<th>Low Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitor sCr</td>
<td>Standard Care (daily)</td>
<td>Every 12 hrs until decrease</td>
<td>Every 12 hrs until decrease</td>
</tr>
<tr>
<td></td>
<td>(I/0s reviewed every 12 hours)</td>
<td>Strict I/0s keep Foley</td>
<td>Strict I/0s keep Foley</td>
</tr>
<tr>
<td>Monitor Urine Output</td>
<td>Standard Care</td>
<td>For Oliguria, may use balanced fluid IF CVP &lt; 8; Hold Lasix unless pulmonary edema</td>
<td>May use balanced fluid IF CVP &lt; 8 AND evidence of hypovolemia (not just oliguria); hold Lasix</td>
</tr>
<tr>
<td>Ensure volume status</td>
<td>Lasix as needed</td>
<td>No NSAIDS or ACE/ARBs</td>
<td>No NSAIDS or ACE/ARBs</td>
</tr>
<tr>
<td>Avoid Nephrotoxic meds</td>
<td></td>
<td>Standard care</td>
<td>Adjust doses (narcotics)*</td>
</tr>
<tr>
<td>Cardiac management</td>
<td>Usual care</td>
<td>Monitor SCVO2 if h/o abnormal LV Fx</td>
<td>Monitor SVO2, Echo or PA catheter if &lt; 55% – Inotropes to keep CI &gt;2.2</td>
</tr>
<tr>
<td>Recheck markers</td>
<td>NA</td>
<td>24 hrs</td>
<td>12 hrs</td>
</tr>
</tbody>
</table>

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**Cardiac management**

- Usual care
- Monitor SCVO2 if h/o abnormal LV Fx
- Inotropes to keep CI >2.2

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**Recheck markers**

- NA
- 24 hrs
- 12 hrs
Cell Cycle Arrest In Response To Cell Stress

- An Alarm Signal Of Impending Cell Damage
- A protective mechanism?
Effect of Remote Ischemic Preconditioning on Kidney Injury Among High-Risk Patients Undergoing Cardiac Surgery: A Randomized Clinical Trial

Alexander Zarbock, MD; Christoph Schmidt, MD; Hugo Van Aken, MD; Carola Wempe, PhD; Sven Martens, MD; Peter K. Zahn, MD; Britta Wolf, MD; Ulrich Goebel, MD; Christian I. Schwer, MD; Peter Rosenberger, MD; Helene Haeberle, MD; Dennis Görlich, PhD; John A. Kellum, MD; Melanie Meersch, MD; for the RenalRIPC Investigators

**Importance**
No interventions have yet been identified to reduce the risk of acute kidney injury in the setting of cardiac surgery.

**Objective**
To determine whether remote ischemic preconditioning reduces the rate and severity of acute kidney injury in patients undergoing cardiac surgery.

**Design, Setting, and Participants**
In this multicenter trial, we enrolled 240 patients at high risk for acute kidney injury, as identified by a Cleveland Clinic Foundation score of 6 or higher, between August 2013 and June 2014 at 4 hospitals in Germany. We randomized them to receive remote ischemic preconditioning or sham remote ischemic preconditioning.

Published on line May 29, 2015
Acute kidney injury biomarkers

Zarbock et al. JAMA 2015
1. DAMPs are released from muscle

2. Alarm markers released from Renal Epithelium

3. Preconditioned kidney is protected

Skeletal Muscle

RIPC

Sham

No DAMPs released

Renal Tubular Epithelium is preconditioned

Resistant to AKI

Renal Tubular Epithelium is naïve

AKI

Naïve kidney is injured

Zarbock A et al. JAMA 2015
A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery


1385 Patients
AKI (2-3): 5.1% vs 6.1%
Euroscore 4.2
(1% mortality risk)
No Effect on any primary or secondary endpoints

Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery

D.J. Hausenloy, L. Candilio, R. Evans, C. Ariti, D.P. Jenkins, S. Kolvekar, R. Knight, G. Kunst, C. Laing, J. Nicholas, J. Pepper, S. Robertson, M. Xenou, T. Clayton, and D.M. Yellon, for the ERICCA Trial Investigators*

1612 Patients
AKI (2-3): 8.7% vs 7.6%
Euroscore 5
(<2% mortality risk)
No Effect on any primary or secondary endpoints
Elevated $[\text{TIMP-2}] \cdot [\text{IGFBP7}]$ Is Associated With Worse Long-Term Outcomes

(log rank $p < 0.002$)

Koyner et al, JASN 2014
Conclusions

• Markers of cell-cycle arrest (TIMP-2 and IGFBP7) appear to be robust measures of risk for AKI (manifesting in the next 12-24h)

• Underlying biology suggestive of an “alarm-phase” marker before actual damage has occurred.

• TIMP-2 and IGFBP7 work well in heart failure and cardiac surgery

• Interventions will be patient specific but numerous interventions exist (cardiac, fluid management, nephrotoxic drugs, etc.)

• Potential to exploit this mechanism as a therapy –RIPC causes increases in TIMP-2 and IGFBP7 and protection from subsequent injury (though much more study is required)