Using biomarkers in the management and prognosis of contrast-induced acute kidney injury

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What is CI-AKI?

- Acute decline in kidney function after intravascular administration of iodinated contrast
- Commonly defined by ↑ Scr of ≥25% and/or 0.5mg/dl w/i 48-96 hrs
- Principal risk factor is CKD, particularly with DM
- Estimated incidence varies:
  - Our data indicate ~ 10% in pts with eGFR <60 ml/min/1.73m² undergoing angiography
  - Other studies ~ 44% of highest risk hospitalized pts

Is CI-AKI, defined by these small increases in Scr, a clinically significant condition?
### Association of CIAKI with short- and long-term mortality

<table>
<thead>
<tr>
<th>Study authors</th>
<th>Number of patients</th>
<th>Adjusted OR*</th>
<th>95% CI</th>
<th>Study authors</th>
<th>Number of patients</th>
<th>Adjusted OR*</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Tarnoff et al.</td>
<td>20,319</td>
<td>22</td>
<td>36-31</td>
<td>Brown et al.</td>
<td>7,596</td>
<td>95</td>
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<td>From et al.</td>
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<td>2.6-4.4</td>
<td>Goldenberg et al.</td>
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<td>60</td>
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<td>Enzinger et al.</td>
<td>499</td>
<td>3.9</td>
<td>2.9-7.9</td>
<td>Hulst et al.</td>
<td>985</td>
<td>24</td>
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<td>Luy et al.</td>
<td>357</td>
<td>5.5</td>
<td>2.9-11.2</td>
<td>Henkel et al.</td>
<td>787</td>
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<td>McCullough et al.</td>
<td>1,328</td>
<td>6.6</td>
<td>3.3-11.9</td>
<td>Rinaldi et al.</td>
<td>975</td>
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<td>Rinaldi et al.</td>
<td>2,616</td>
<td>10.8</td>
<td>6.9-17.0</td>
<td>Solomon et al.</td>
<td>294</td>
<td>12</td>
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<td>Shima et al.</td>
<td>1,111</td>
<td>3.9</td>
<td>1.2-12.0</td>
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<tr>
<td>Weissfeld et al.</td>
<td>1,808</td>
<td>1.8</td>
<td>1.4-2.3</td>
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</tbody>
</table>

a - denotes OR of death

### Association of CIAKI with acceleration in CKD

<table>
<thead>
<tr>
<th>Investigator</th>
<th># pts</th>
<th>Follow up</th>
<th>Δ eGFR</th>
<th>Risk of progressive CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenberg</td>
<td>78</td>
<td>2 yrs</td>
<td>Δ eGFR</td>
<td>v.-6</td>
</tr>
<tr>
<td>Ribichi</td>
<td>216</td>
<td>1 month</td>
<td>Δ eGFR</td>
<td>v.-1</td>
</tr>
<tr>
<td>Maoli</td>
<td>502</td>
<td>1 month</td>
<td>↑ SCR</td>
<td>1.6 v. 1.4</td>
</tr>
<tr>
<td>James</td>
<td>11,249</td>
<td>3 months</td>
<td>OR 4.7 mild CKD*</td>
<td></td>
</tr>
<tr>
<td>Weissfield</td>
<td>~25,000</td>
<td>3 months</td>
<td>OR 17 severe CKD*</td>
<td></td>
</tr>
</tbody>
</table>

* adjusted odds of ↑ SCR >50% or ≥ 0.3 mg/dL
† odds of ↑ SCR ≥50%

### Costs of single episode of CIAKI

- Economic assessment using decision analytic model:
  - In-hospital costs > $10,300
  - 1 yr costs > $11,800

Subramanian et al. J. Medical economics. 2007;10(2):119-34
Collectively, these studies associate CI-AKI with serious adverse outcomes and costs and suggest it is a clinically significant condition.

Are there aspects of CI-AKI management that could potentially benefit from the use of biomarkers?

**Challenge in current clinical practice**

**STRATIFYING RISK**

- Risk stratification based on baseline factors → CKD (+DM)
- Large # of ‘at-risk’ pts undergoing CE-procedures > 750K/yr
- Requires ‘resource intensive’ preventive care (i.e., IV fluids) in large # of pts, many of whom will not develop CI-AKI
- Precludes use of more expensive preventive interventions that may be effective (e.g. ANP), but have potential side fx
- Some pts who develop CI-AKI were low-risk prior to procedure based on current stratification variables
  - Few tools to identify such patients at present
  - Could biomarkers measured pre-contrast help stratify risk for CI-AKI?

**Challenge in current clinical practice**

**EARLY DIAGNOSIS**

Pathophysiology of CI-AKI and timing of events
Challenge in current clinical practice

**EARLY DIAGNOSIS**
- Currently unable to diagnose CI-AKI at time of tubular injury
- Most pts discharged same day w/o f/u SCR assessment
- CI-AKI → transient ↑ SCR w/o clinical sx; hence undiagnosed
- Inability to dx incipient tubular injury:
  - Prevents identification of pts who may benefit from close observation/continued inpt mgmt
  - Precludes development/implementation of interventions that, if given early, might mitigate further renal damage

Could biomarkers measured early post-contrast help diagnose incipient CI-AKI and improve post-contrast processes of care?

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Challenge in current clinical practice

**FORECASTING LONGER-TERM EFFECTS**
- Many episodes of CI-AKI:
  - Transient and asymptomatic
  - In outpatients
  - Undiagnosed
- Very few pts with CI-AKI die or require acute RRT
- However, persistent renal injury/progressive CKD may be an important sequela
- At present, little known on factors that predict risk for progressive CKD following CI-AKI

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Challenge in current clinical practice

**FORECASTING LONGER-TERM PROGNOSIS**

<10% of pts with AKI and residual renal impairment referred to nephrology w/1 yr*

We appear to do a very poor job of following pts after AKI

This may be true with CI-AKI

Could biomarkers at time of CE-procedures help forecast long-term outcomes and inform appropriate post-AKI renal f/u?

* Before dying, RRT, recovery
Studies of biomarkers of CIAKI to date

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts (N)</th>
<th>Pts with CKD (N)</th>
<th>Biomarker</th>
<th>CIAKI %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alharazy</td>
<td>100</td>
<td>100</td>
<td>s NGAL</td>
<td>11</td>
</tr>
<tr>
<td>Bachorzewska et al</td>
<td>35</td>
<td>0</td>
<td>u/s NGAL</td>
<td>0</td>
</tr>
<tr>
<td>Bachorzewska et al</td>
<td>100</td>
<td>0</td>
<td>u/s NGAL, s CyC</td>
<td>11</td>
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<tr>
<td>Bachorzewska et al</td>
<td>60</td>
<td>0</td>
<td>u/s NGAL, s CyC</td>
<td>10</td>
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<tr>
<td>Bachorzewska et al</td>
<td>25</td>
<td>0</td>
<td>u/s NGAL, u L-FABP</td>
<td>NR</td>
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<tr>
<td>Brigioni</td>
<td>410</td>
<td>410</td>
<td>s CyC</td>
<td>8</td>
</tr>
<tr>
<td>Brigioni</td>
<td>204</td>
<td>≥142</td>
<td>s CyC</td>
<td>16</td>
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<tr>
<td>Hirsch et al.</td>
<td>91</td>
<td>0</td>
<td>u/s NGAL</td>
<td>12</td>
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<tr>
<td>Ling et al.</td>
<td>150</td>
<td>NR</td>
<td>u NGAL, u IL-18</td>
<td>9</td>
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<tr>
<td>Malyszko et al.</td>
<td>140</td>
<td>0</td>
<td>†</td>
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<td>McCullough</td>
<td>63</td>
<td>63*</td>
<td>s NGAL</td>
<td>3</td>
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<tr>
<td>Nakamura et al.</td>
<td>96</td>
<td>69</td>
<td>u L-FABP</td>
<td>14</td>
</tr>
<tr>
<td>Shaker et al.</td>
<td>30</td>
<td>0</td>
<td>s NGAL, s CyC</td>
<td>7</td>
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</table>

† panel included. uNGAL/uNGAL, uKIM-1/uL-FABP, uIL-18
*eGFR <75ml/min/1.73m²

Collective findings of prior studies

- Early (2-4 hr) increases in u & s NGAL seen in pts with CI-AKI (moderate sens/spec 70-90%)
- s CyC and u IL18 increase later (~24 hrs) & are moderately predictive of CI-AKI
- u L-FABP increases early (2-4 hrs) and peaks later (e.g. 24 hrs) in pts with CI-AKI
- Pre-angiography u L-FABP higher in pts who develop CI-AKI

* Findings based on 1-2 studies

Caveats to studies to date

- Small # pts
  - Limited power to characterize diagnostic/prognostic capacity of biomarkers
- ~ 50% of pts had normal kidney function
  - Small absolute # pts (<200) with CI-AKI
  - Generalizability of findings to CKD pts unclear
    * Diabetes and GFR affect baseline levels of some biomarkers
- Few analyses of risk stratification of pre-angio biomarkers
- Limited analyses of panels of biomarkers
- Only 2 studies tracked long-term outcomes
Knowledge to date

- CI-AKI is common and associated with adverse outcomes
- Challenges to care include accurate risk stratification, early dx, prediction of long-term outcomes
- These challenges may adversely affect our ability to reduce adverse pt-centered outcomes
- Findings of preliminary biomarkers studies of CI-AKI promising, but limited by study design/size/population

Are there opportunities to address the gaps in knowledge on the potential role of biomarkers in CI-AKI?

PRESERVE trial

- Multi-center, double-blind, randomized, comparative effectiveness prevention trial funded by VA CSP
- 7,680 pts from 33 VA medical centers with CKD undergoing coronary or non-coronary angiography
  - eGFR 45-60 with DM or eGFR <45 with or without DM
- 2x2 factorial design to compare effectiveness of:
  - IV sodium bicarbonate v. IV sodium chloride
  - Oral NAC v. oral placebo
- Commencement of enrollment – fall 2013
Study outcomes

- 1st outcome:
  - Death and/or dialysis w/i 90 days and/or persistent renal injury (↑ SCR ≥50%) @ 90 days
  - Death and dialysis based on active f/u thru 90 days
  - Persistent renal injury – confirmed by 2 SCR assessments at 90 and 90-104 days
    • Mobile phlebotomy available to collect blood for 90 day outcome
- CI-AKI 2nd outcome
  - Based on SCR measured at 96 hrs
    • Mobile phlebotomy available to collect blood

PRESERVE as a resource for biomarker analyses

- Very large number of patients (up to 7,680)
- Comprehensive assessment of CI-AKI and 90-day outcomes
  - Minimizes misclassification
  - Confirm (or refute) association of CI-AKI with longer-term outcomes
- All patients will have CKD
  - High incidence of AKI (~15%)
  - High risk for adverse 90-day outcomes (~9%)
- Provides opportunity to investigate fx of preventive interventions on biomarkers
- All are VA pts → integrated electronic health record

NIH/NIDDK funding for biorepository

- Recent receipt of funding for collection & storage of blood and urine from PRESERVE pts
- Blood (20 ml) & urine (10 ml) collected at study sites pre- and 4 hrs post-angiography
- Spun/ aliquoted/labeled and stored locally at -80° & shipped in bulk to Boston VA
- Shipped ~ quarterly to NIDDK biorepository for long-term storage and future use
- Samples to be made available to qualified investigators in future
Limitations of PRESERVE biorepository

- Samples from just 2 time points (baseline & 4 hr)
- Almost all pts are male
- All pts will have CKD (no pts with nl GFR)
- Comprehensive f/u data only to 90 days
- Buffy coat will not be collected
  - No genetic analyses

Biomarker analysis - aims

**AIM 1:** To assess whether serum and/or urine biomarkers measured prior to angiography are able to stratify the risk of developing: a) CI-AKI and; b) 90-day death, need for dialysis, persistent renal injury

**AIM 2:** To assess whether serum and/or urine biomarkers measured 4 hours following angiography: a) permit the early diagnosis of CI-AKI and; b) are able to stratify the risk of developing 90-day death, need for dialysis, persistent renal injury

**AIM 3:** To examine the effect of IV sodium bicarbonate and oral NAC on serum and urine biomarkers 4 hours following angiography and their capacity to predict the development of: a) CI-AKI and; b) serious, adverse, longer-term outcomes

Biomarkers of interest

<table>
<thead>
<tr>
<th>Tier 1 – Highest priority biomarkers (+ urine creatinine)</th>
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</thead>
<tbody>
<tr>
<td>Biomarker</td>
</tr>
<tr>
<td>Urine NGAL</td>
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<tr>
<td>Serum NGAL</td>
</tr>
<tr>
<td>Urine L-FABP</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
</tr>
<tr>
<td>Urine Albumin</td>
</tr>
<tr>
<td>Urine Creatinine</td>
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<tr>
<td>Serum Creatinine *</td>
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<thead>
<tr>
<th>Tier 2 – Moderate priority biomarkers</th>
</tr>
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<tbody>
<tr>
<td>Urine IL-18</td>
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<tr>
<td>Urine Cystatin C</td>
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<thead>
<tr>
<th>Tier 3 – Lowest priority biomarkers</th>
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</thead>
<tbody>
<tr>
<td>Urine KIM-1</td>
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</tbody>
</table>

* For data normalisation
Analyses - capacity of pre-angio biomarkers to predict CIAKI, 4h post-angio biomarkers to dx CIAKI, and fx of interventions on biomarkers for dx CIAKI

Nested case control analysis of specific aims 1a, 2a, 3a

7,650 trial participants

0,000 pts consent for biomarkers

Random sample of 555 cases with CIAKI

Stratified random sample of 555 controls without CIAKI

Analyses of biomarkers between cases and controls

Analyses – Capacity for pre-angio and 4 hr biomarkers to predict development of 90-day outcome

Nested case control analysis of specific aims 1b, 2b, 3b

7,680 trial participants

0,000 pts consent for biomarkers

555 cases with 60-day outcome

Stratified random sample of 555 controls without 90-day outcome

Analyses of biomarkers between cases and controls

Summary

• CIAKI common & associated with adverse outcomes
• Current limitations in risk stratification, dx, and prognosis
• Prior studies suggest biomarkers might be useful; findings preliminary and limited
• PRESERVE is a clinical trial of CIAKI in high-risk pts that will provide a large biorepository of blood and urine samples
• We are seeking funding to analyze key biomarkers from this study
• Samples stored at NIDDK biorepository will be available to qualified investigators in the future