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

Steven D. Weisbord MD, MSc
What is CI-AKI?

• Acute decline in kidney fxn 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$^a$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartholomew et al.</td>
<td>20,479</td>
<td>22</td>
<td>16 - 31</td>
</tr>
<tr>
<td>From et al.</td>
<td>3,236</td>
<td>3.4</td>
<td>2.6 - 4.4</td>
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<tr>
<td>Gruberg et al.</td>
<td>439</td>
<td>3.9</td>
<td>2.0 - 7.6</td>
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<td>Levy et al.</td>
<td>357</td>
<td>5.5</td>
<td>2.9 - 13.2</td>
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<tr>
<td>McCullough et al.</td>
<td>1,826</td>
<td>6.6</td>
<td>3.3 - 12.9</td>
</tr>
<tr>
<td>Rihal et al.</td>
<td>7,586</td>
<td>10.8</td>
<td>6.9 - 17.0</td>
</tr>
<tr>
<td>Shema et al.</td>
<td>1,111</td>
<td>3.9</td>
<td>1.2 - 12.0</td>
</tr>
<tr>
<td>Weisbord et al</td>
<td>27,608</td>
<td>1.8</td>
<td>1.4 - 2.5</td>
</tr>
</tbody>
</table>

a – denotes OR of death

<table>
<thead>
<tr>
<th>Study authors</th>
<th># patients</th>
<th>Follow-up (months)</th>
<th>Adjusted HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al.</td>
<td>7,856</td>
<td>90</td>
<td>3.1</td>
<td>2.4 - 4.0</td>
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<tr>
<td>Goldenberg et al.</td>
<td>78</td>
<td>60</td>
<td>2.7</td>
<td>1.7 - 4.5</td>
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<tr>
<td>Harjai et al.</td>
<td>985</td>
<td>24</td>
<td>2.6</td>
<td>1.5 - 4.4</td>
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<tr>
<td>Rihal et al.</td>
<td>7,075</td>
<td>6</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Solomon et al.</td>
<td>294</td>
<td>12</td>
<td>3.2†</td>
<td>1.1 - 8.7</td>
</tr>
</tbody>
</table>

* 6-month mortality 9.8% with CIAKI v. 2.3% without CIAKI (p<0.001)
† reflects incident rate ratio of death, CVA, AMI, ESRD requiring RRT
Association of CIAKI with acceleration in CKD

<table>
<thead>
<tr>
<th>Investigator</th>
<th># pts</th>
<th>Follow up</th>
<th>Risk of progressive CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenberg</td>
<td>78</td>
<td>2 yrs</td>
<td>$\Delta$ eGFR -20 v. -6</td>
</tr>
<tr>
<td>Ribichini</td>
<td>216</td>
<td>1 month</td>
<td>$\Delta$ eGFR -21 v. -1</td>
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<tr>
<td>Maoli</td>
<td>502</td>
<td>1 month</td>
<td>$\uparrow$ SCr 1.6 v. 1.4</td>
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<tr>
<td>James</td>
<td>11,249</td>
<td>3 months</td>
<td>OR 4.7 mild CKD*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR 17 severe CKD*</td>
</tr>
<tr>
<td>Weisbord</td>
<td>~25,000</td>
<td>3 months</td>
<td>OR 2.4 $\dagger$</td>
</tr>
</tbody>
</table>

*adjusted odds of $\uparrow$ SCr >50% or ≥ 0.3 mg/dL

$\dagger$ odds of $\uparrow$ 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 CIAKI and timing of events

- Contrast administration
  - Mismatch of oxygen delivery/demand
  - Generation of reactive oxygen species

  Direct tubular cell toxicity
  - Medullary hypoxia
  - Tubular cell injury

  Reduction in glomerular filtration
  - Elevation in SCr

- Occurs within minutes
- Occurs within minutes/hours
- Occurs within many hours to days
Challenge in current clinical practice

**EARLY DIAGNOSIS**

- Currently unable to diagnose CI-AKI @ 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/implemention 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?
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
Challenge in current clinical practice

FORECASTING LONGER-TERM PROGNOSIS

<10% of pts with AKI and residual renal impairment referred to nephrology w/i 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>
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<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>Briguori</td>
<td>410</td>
<td>410</td>
<td>s CyC</td>
<td>8</td>
</tr>
<tr>
<td>Briguori</td>
<td>294</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>
<td>12</td>
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<tr>
<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>
</tr>
</tbody>
</table>

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

Published studies of biomarkers in CIAKI to date
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
PRESERVE trial design

Baseline pre-angiography SCr measurement, assessment of baseline demographic/clinical characteristics and pre-angiography urine albumin/creatinine

Randomization 1:1:1:1

| IV isotonic bicarbonate oral NAC | IV isotonic saline oral NAC |
| IV isotonic bicarbonate oral Placebo | IV isotonic saline oral Placebo |

Index angiogram

96 hour post-angiography SCr measurement to assess for development of CIAKI ($2^0$ trial outcome)

90 day $1^0$ outcome assessment (death, dialysis, persistent renal injury)

Link to USRDS and death files to assess 1 year ESRD and mortality
Study outcomes

• **1⁰ 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 2⁰ 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°C & 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) CIAKI and; b) serious, adverse, longer-term outcomes
## Biomarkers of interest

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

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<thead>
<tr>
<th>Tier 3 – Lowest priority biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine KIM-1</td>
</tr>
</tbody>
</table>

* For data normalization
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
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

6,900 pts consent for biomarkers

585 cases with 90-day outcome

Stratified random sample of 585 controls without 90-day outcome

Analyses of biomarkers between cases and controls
Summary

- CI-AKI 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 CI-AKI 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