Cardiorenal Biomarkers and Heart Failure

Nicholas Wettersten, MD

April 7th, 2017
Disclosures

- Still none, but looking for some

Chance

Pay poor tax of $15
Acute Kidney Injury Biomarkers

547 in 2015

4112 as of March 2017
Case 1

• 60 yo man presented with an NSTEMI at an OSH found to have CTO of LAD and 90% lesions in RCA and circumflex transferred for high risk revascularization. His MAP is 60 upon arrival and has an Impella percutaneous LVAD placed and gets revascularization of RCA and circumflex.
Case 2

• 45 yo woman with NICM admitted for decompensated heart failure. On exam she is warm and wet. Receives diuretics for 5 days and on day 6 creatinine goes from 0.8 to 1.2.
Who has or will develop AKI?
Do we need novel biomarkers?

• Both may or may not
• We need biomarkers to help guide us
Kidney Dysfunction is Common in Heart Failure

30%-67% of AHF patients have chronic kidney disease

>100,000 patients with acute heart failure

Worse Kidney Function = Worse Outcomes

Worsening Renal Function is Common in Acute Heart Failure

20%-40% of AHF patients develop worsening renal function

# Worsening Renal Function Increases Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CKD Events</th>
<th>CKD Total</th>
<th>no CKD Events</th>
<th>no CKD Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Heart Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Madsen</td>
<td>22</td>
<td>44</td>
<td>38</td>
<td>146</td>
<td>0.7%</td>
<td>2.84 [1.42, 5.71] 1994</td>
</tr>
<tr>
<td>Akhter (VMAC)</td>
<td>80</td>
<td>215</td>
<td>33</td>
<td>266</td>
<td>1.2%</td>
<td>4.16 [2.65, 6.61] 2004</td>
</tr>
<tr>
<td>Aronson</td>
<td>112</td>
<td>284</td>
<td>65</td>
<td>257</td>
<td>1.6%</td>
<td>1.92 [1.33, 2.78] 2004</td>
</tr>
<tr>
<td>Smith (NHCP)</td>
<td>8948</td>
<td>17207</td>
<td>11869</td>
<td>36433</td>
<td>3.4%</td>
<td>2.24 [2.16, 2.33] 2005</td>
</tr>
<tr>
<td>Anwaruddin (PRIDE)</td>
<td>17</td>
<td>207</td>
<td>13</td>
<td>392</td>
<td>0.6%</td>
<td>2.61 [1.24, 5.48] 2006</td>
</tr>
<tr>
<td>Pimenta</td>
<td>13</td>
<td>44</td>
<td>35</td>
<td>239</td>
<td>0.6%</td>
<td>2.44 [1.17, 5.12] 2007</td>
</tr>
<tr>
<td>Petretta</td>
<td>15</td>
<td>51</td>
<td>27</td>
<td>102</td>
<td>0.6%</td>
<td>1.16 [0.55, 2.44] 2007</td>
</tr>
<tr>
<td>Filippatos</td>
<td>17</td>
<td>145</td>
<td>3</td>
<td>157</td>
<td>0.2%</td>
<td>6.82 [1.95, 23.79] 2007</td>
</tr>
<tr>
<td>Heywood (ADHERE)</td>
<td>3731</td>
<td>75382</td>
<td>949</td>
<td>43083</td>
<td>3.3%</td>
<td>2.31 [2.15, 2.49] 2007</td>
</tr>
<tr>
<td>Patel (GWTG-HF)</td>
<td>384</td>
<td>10074</td>
<td>111</td>
<td>5486</td>
<td>2.5%</td>
<td>1.92 [1.55, 2.38] 2008</td>
</tr>
<tr>
<td>Klein (OPTIME-CHF)</td>
<td>69</td>
<td>468</td>
<td>19</td>
<td>469</td>
<td>1.0%</td>
<td>4.10 [2.42, 6.93] 2008</td>
</tr>
<tr>
<td>Arnsalem</td>
<td>759</td>
<td>2145</td>
<td>331</td>
<td>1648</td>
<td>2.9%</td>
<td>2.18 [1.88, 2.53] 2008</td>
</tr>
<tr>
<td>Takagi</td>
<td>14</td>
<td>75</td>
<td>8</td>
<td>119</td>
<td>0.4%</td>
<td>3.18 [1.27, 8.02] 2009</td>
</tr>
<tr>
<td>Campbell</td>
<td>32</td>
<td>119</td>
<td>21</td>
<td>121</td>
<td>0.8%</td>
<td>1.75 [0.94, 3.26] 2009</td>
</tr>
<tr>
<td>Hamaguchi (JCAF)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kimura</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Manzano-Fernando</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin-Pfizemey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Velavan (Euro HF)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Harjola</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaz Perez</td>
<td>28</td>
<td>54</td>
<td>22</td>
<td>74</td>
<td>0.6%</td>
<td>2.55 [1.23, 5.28] 2010</td>
</tr>
<tr>
<td>Carrasco</td>
<td>53</td>
<td>99</td>
<td>17</td>
<td>99</td>
<td>0.7%</td>
<td>5.56 [2.89, 10.70] 2011</td>
</tr>
<tr>
<td>Manzano - Fernandez</td>
<td>31</td>
<td>74</td>
<td>31</td>
<td>146</td>
<td>0.8%</td>
<td>2.67 [1.45, 4.92] 2011</td>
</tr>
<tr>
<td>Blair (EVEREST)</td>
<td>353</td>
<td>1055</td>
<td>184</td>
<td>966</td>
<td>2.5%</td>
<td>2.14 [1.74, 2.62] 2011</td>
</tr>
<tr>
<td>Tarantini (IS-AHF)</td>
<td>104</td>
<td>592</td>
<td>34</td>
<td>416</td>
<td>1.4%</td>
<td>2.39 [1.59, 3.61] 2011</td>
</tr>
<tr>
<td>Kao</td>
<td>11847</td>
<td>163402</td>
<td>13383</td>
<td>433054</td>
<td>3.4%</td>
<td>2.45 [2.39, 2.51] 2011</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>277499</td>
<td>534640</td>
<td>39.5%</td>
<td></td>
<td></td>
<td>2.39 [2.25, 2.54]</td>
</tr>
</tbody>
</table>

Damman K et al, Eur Heart J. 2014 Feb;35(7):455-69
**Cardiorenal Syndrome (CRS) General Definition:**
A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ.

<table>
<thead>
<tr>
<th>CRS Type I (Acute Cardiorenal Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRS Type II (Chronic Cardiorenal Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRS Type III (Acute Renocardiac Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt worsening of renal function (e.g. acute kidney ischaemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRS Type IV (Chronic Renocardiac Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CRS Type V (Secondary Cardiorenal Syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction</td>
</tr>
</tbody>
</table>

Complex Pathophysiology

Hemodynamic Effects
- Decreased output
- Venous Congestion

Neurohormonal Activation
- RAAS activation
- SNS

Exogenous Factors
- Diuretics
- ACE inhibitors
- Contrast

Inflammation
- Immune mediated
How to Define Kidney Injury?

<table>
<thead>
<tr>
<th>Stage</th>
<th>Based on sCr or eGFR</th>
<th>Based on Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1) $\uparrow$ sCr = 1.5-1.9 x baseline (within prior 7 days) OR 2) $\uparrow$ ≥0.3 mg/dL in sCr (prior 48h)$^\wedge$</td>
<td>Complicated in heart failure by diuretics</td>
</tr>
<tr>
<td>2</td>
<td>$\uparrow$ sCr = 2.0-2.9 x baseline</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1) sCr = 3 x baseline OR 2) sCr ≥4 mg/dL OR 3) LOF requiring renal replacement therapy OR 4) If &lt; 18 years old$\Downarrow$ eGFR to &lt;35 mL/min/1.73m²</td>
<td></td>
</tr>
</tbody>
</table>

sCr = serum creatinine; eGFR = estimated glomerular filtration rate; *change over 7 days; **with short term rise of ≥ 0.5 mg/dL; $^\wedge$short term rise (≤48h); conversion to SI units is 1 mg/dL = 88.4 µmol/L
New Paradigm for Kidney Injury

- No Damage/Injury OR Loss of Function
- No Damage/Injury BUT No Functional Change
- Damage/Injury AND Loss of Function
Time for Novel Biomarkers

Glomerular filtration:
- Cystatin C
- NGAL
- RBP

Proximal tubule:
- Cystatin C
- NAG
- α-GST
- γ-GT
- NGAL
- KIM–1
- IL–18
- RBP
- L-FABP
- α1/β2 microglobulin

Distal tubule:
- π-GST
- NAG
- NGAL

Collecting duct:
- NGAL

Ostermann, Crit Care. 2012 Sep 21;16(5):233
Neutrophil Gelatinase-Associated Lipocalin (NGAL)

- Small molecule of lipocalin found in neutrophils and renal tubular cells
- Physiology complex, but released during acute phase of toxic or ischemic kidney injury, mainly in loop of Henle and distal tubule
- Measurable in plasma and urine
- Evaluated in heart failure in the **Acute Kidney Injury N-gal Evaluation of Symptomatic heart failure Study (AKINESIS)**
AKINESIS

• 927 patients with AHF
• Primary outcome of acute kidney injury defined as increase in creatinine $\geq 0.5$ mg/dL or $\geq 50\%$ OR initiation of dialysis
• Secondary outcome in-hospital adverse events
• Evaluated initial and peak NGAL values
NGAL no Better than Creatinine for Primary Outcome

Maisel A et al, J Am Coll Cardiol. 2016 Sep 27;68(13):1420-31
Nor Any Better for Secondary Outcome

Maisel A et al, J Am Coll Cardiol. 2016 Sep 27;68(13):1420-31

- Peak NGAL: AUC 0.653, 95% CI 0.601-0.704
- First NGAL: AUC 0.691, 95% CI 0.643-0.740
- First Creatinine: AUC 0.686, 95% CI 0.634-0.738
NGAL May Identify a Low Risk Population

Adverse Events by eGFR and NGAL 150

<table>
<thead>
<tr>
<th>Any Adverse Outcome</th>
<th>eGFR &gt;60 NGAL &lt;150</th>
<th>eGFR &lt;60 NGAL &lt;150</th>
<th>eGFR &gt;60 NGAL &gt;150</th>
<th>eGFR &lt;60 NGAL &gt;150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events</td>
<td>7.4%</td>
<td>9.0%</td>
<td>11.7%</td>
<td>27.7%</td>
</tr>
</tbody>
</table>

P<0.001

Maisel A et al, J Am Coll Cardiol. 2016 Sep 27;68(13):1420-31
Urine NGAL Not Looking Much Better

ROC curves for different measurements:
- uNGAL admit ROC: 0.5935
- uNGAL peak ROC: 0.567
- Creat admit ROC: 0.6228

Reference line for comparison.
Kidney Injury Molecule 1 (KIM-1)

- Trans-membrane glycoprotein in proximal tubule
- Usually not detectable, but upregulated in acute tubular necrosis and ischemia
- Proposed to be involved in renal repair following injury
- Detectable in both urine and plasma
Urine KIM-1 Predicts Worsening Renal Function in Chronic Heart Failure

Hazard ratio of 1.23 for worsening renal function

Damman K et al, JACC Heart Fail. 2013 Oct;1(5):417-24
Urine KIM-1 May Track with Renal Congestion

Figure 4

Effect of Diuretic Reinitiation on Urinary KIM-1 and NAG and Urinary and Plasma NGAL

(A) Urinary KIM-1 and NAG. Median and interquartile ranges are presented. *p < 0.05 versus day 4, 0 h.

(B) Urinary and plasma NGAL. Median and interquartile ranges are presented. i.v. /H11005 intravenous; other abbreviations as in Figure 3.

Figure 3

Effect of Diuretic Withdrawal on Urinary KIM-1 and NAG and Serum and Urinary NGAL

(A) Urinary kidney injury molecule (KIM)-1 and N-acetyl-beta-D-glucosaminidase (NAG). Median and interquartile ranges are presented. *p < 0.01; †p < 0.075 versus day 1, baseline.

(B) Serum and urinary neutrophil gelatinase associated lipocalin (NGAL). Median and interquartile ranges are presented.

Damman K et al, J Am Coll Cardiol. 2011 May 31;57(22):2233-41
Plasma KIM-1 Not as Predictive of Outcomes

- 874 AHF patients from ASCEND trial
  - Higher baseline plasma KIM-1 levels associated with WRF and decreased diuresis
  - KIM-1 measured at 30 days (not baseline or 48-72 hours after) associated with 180 mortality

- 1588 AHF patients from PROTECT trial
  - Baseline KIM-1 only associated with 60 day HF rehospitalization, but not mortality

Grodin K et al, JACC Heart Fail. 2015 Oct;3(10):777-85
Proenkephalin (PENK)

- An endogenous opioid (enkephalins, endorphins, and dynorphins)
- Associated with cardiodepressive effects (negative inotropy, lower BP, lower HR)
- More stable than other forms
- Reflects glomerular filtration earlier than creatinine
- Associated with renal dysfunction and poor outcomes in ACS, cardiac surgery, and sepsis
1714 Patients with AHF, PENK Strong Association with WRF

Age  NS
Male  NS
PH Heart Failure  NS
PH IHD  NS
PH Hypertension  NS
PH Renal Failure  NS
PH Diabetes  NS
Systolic BP  .009
Heart Rate  NS
Plasma Urea  NS
Plasma Creatinine  NS
Plasma Sodium  .041
ACE/ARB  NS
Diuretic  NS
Natriuretic Peptide  NS
PENK  <0.0005

Ng et al, J Am Coll Cardiol. 2017 Jan 3;69(1):56-69
Higher PENK, Higher Mortality

Ng et al, J Am Coll Cardiol. 2017 Jan 3;69(1):56-69
[TIMP-2] [IGFBP7]

- Insulin-like growth factor-binding protein 7 (IGFBP7)
- Tissue inhibitor of metalloproteinases-2 (TIMP-2)
- Discovered from 340 candidate proteins
- Both involved in cell cycle arrest during early phase of injury
- Measured in urine
- Very high negative predictive value, good prognostic value overall (AUC 0.8)
- Value <0.3 highly unlikely to develop AKI
Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial

Melanie Meersch¹, Christoph Schmidt¹, Andreas Hoffmeier², Hugo Van Aken¹, Carola Wempe¹, Joachim Gerss³ and Alexander Zarbock¹*

• Identified high risk patients for AKI after cardiac surgery by \([\text{TIMP-2}] \times [\text{IGFBP7}] > 0.3\) measured 4 hours after cardiopulmonary bypass

• Instituted a KDIGO care bundle (hemodynamic optimization, avoiding hyperglycemia, avoiding nephrotoxins)
Biomarkers Used to Guide Therapy Reduced AKI

- Patients with AKI [%]
  - Control: 44.9% (all AKI), 71.7% (moderate and severe AKI)
  - Intervention: 29.7% (all AKI), 55.1% (moderate and severe AKI)

- Statistical significance:
  - P=0.004
  - P=0.009
And now for something completely different...
Follow-Up

The median (IQR) duration of the initial hospitalization was 9 (6 –15) days. Five patients died on or before the day of discharge from the initial hospitalization. The remaining 594 patients were discharged alive from hospital, 1 of whom was lost to follow-up. Data regarding deaths and hospitalizations were complete for all the other patients. The mean follow-up of these patients was 797 days (median [25th, 75th percentiles], 671 [261, 1275] days) from discharge. Within 1 year after discharge, 78 of these patients died (13.1%), 15 (2.5%) received a transplant, and 219 (36.9%) were rehospitalized for AHF.

Determinants of Outcomes

Estimated survival rates in the 4 groups are shown in the Figure (left). The unadjusted risk of death within 1 year of discharge in patients with WRF alone was not higher than in patients with neither WRF nor congestion. However, patients with both WRF and congestion were at significantly higher risk than patients with neither factor. Variables associated with an increased risk of death within 1 year after discharge at multivariable analysis were chronic obstructive pulmonary disease, chronic kidney disease, worse NYHA class, higher heart rate, lower blood pressure, lower body weight, and lower serum sodium (Table 2). After adjustment for these variables, the mortality risks for patients with either WRF alone or residual congestion at discharge alone were not significantly greater than that of patients with neither factor. The increased risk appeared to be driven primarily by the presence of congestion (Figure), and the interaction of congestion with WRF was not statistically significant (P = 0.3074). Patients with both
Urinary levels of novel kidney biomarkers and risk of true worsening renal function and mortality in patients with acute heart failure

Mateusz Sokolski¹,²*, Robert Zymliński², Jan Biegus¹,², Paweł Siwołowski², Sylwia Nawrocka-Millward², John Todd³, Malli Rama Yerramilli³, Joel Estis³, Ewa Anita Jankowska²,⁴, Waldemar Banasiak², and Piotr Ponikowski¹,²

- 132 patients with AHF
- Serial urine NGAL, KIM-1, and cystatin C
- WRF defined as ≥0.3 mg/dL increase creatinine or ≥25% decrease GFR
- ‘True WRF’ – deterioration or no improvement
- ‘Pseudo WRF’ – uneventful clinical course
AUC 0.74-0.83 for uNGAL and uKIM-1 for true WRF
Relationship Status: 

Interested in: Single
In a Relationship
Engaged
Married

Looking for: It's Complicated
In an Open Relationship
Widowed
More to the relationship

Physiology / Subclinical Disease

Phenotype

Intrinsic Kidney Disease
Diabetic Nephropathy
Hypertensive Nephropathy

Important Pathophysiologic Changes

Renal
- Nephron Loss
- GFR ↓
- Renal Blood Flow ↓
- Tubulo-interstitial Damage
- Albuminuria
- Renal Fibrosis
- Renal Congestion
- Na+/Water Retention

Acute Cardiovascular Events

Hospitalization
- Excessive Fluid Overload
- Refractory Symptoms
- Diuretic Resistance
- (Pseudo) WRF / AKI
- Severe Renal Dysfunction
- Progressive Organ Failure

Inhospital Mortality

Stabilization / Recovery

End Stage Cardiovascular Disease

Renal
- Peritoneal Dialysis
- Hemo Dialysis
- Kidney Transplantation
- Palliative Care

Heart
- Chronic HF management
- LVAD
- Heart Transplantation
- Palliative Care

End stage renal disease
- ↓↓↓ eGFR
- ↑↑↑ Albuminuria, tubular markers, (NTpro)BNP and Troponine

Biomarkers

Preserved eGFR
Absence albuminuria
↓ (NTpro)BNP
↓ Troponine

↓ eGFR
- ↑ Albuminuria
- ↑ NGAL/NAG/KIM-1/IL-18/L-FABP
- ↑ (NTpro)BNP
- ↑ Troponine

Heart Disease

HFREF: DCM

HFREF: Ischemic

Common Risk Factors

- Age / Race / Gender
- Hypertension
- Diabetes
- Smoking
- Genetic predisposition
- Ischemic Events
- Drugs

Modulating Factors

- RAAS activation
- SNS activation
- Endothelial Dysfunction
- Inflammation
- Anemia

Heart

- Reduced CO
- Increased wall stress
- Increased CVP
- Myocardial injury
- Myocardial Fibrosis

Servier Medical Art (adapted from) Servier Medical Art (http://www.servier.com/Powerpoint-image-bank), under the Creative Commons Attribution 3.0 Unported License (http://creativecommons.org/licenses/by/3.0/).
Future Directions

• Defining significant kidney injury (‘true’ AKI) complicated in HF
• Identifying non-significant WRF may be why prior biomarkers studies were negative
• A panel of biomarkers reflecting pathophysiology likely needed
• For our cases, need to identify injury early and if significant injury occurring to institute measures to reduce progression of AKI
Thank You