Use of Acute Kidney Injury Biomarkers in Clinical Trials
Design Considerations

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There are no financial or personal conflict of interests to declare related to the current presentation.

Learning Objectives
In randomized clinical trials, explain how AKI biomarkers may be used:

1. in eligibility criteria
2. as an intervention
3. as a surrogate outcome

To describe the advantages and disadvantages of using AKI biomarkers in these settings.
Case of post- CABG AKI

In this setting when can biomarkers be measured to identify patients for enrollment in a RCT?
70 year old diabetic engineer
elective coronary artery bypass surgery

Serum creatinine (umol/L)

<table>
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<th>before surgery</th>
<th>surgery</th>
<th>0-6 hrs</th>
<th>2 days</th>
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<td>1.5</td>
<td>low BP</td>
<td>1.6</td>
<td>2.8</td>
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Enroll patients at higher risk of post-op AKI:
- older age, poor LV, CHF
- valve + CABG, on pump, pre-op CKD
- Biomarker (BNP)

B

70 year old diabetic engineer
elective coronary artery bypass surgery

Serum creatinine (umol/L)

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Enroll patients at high risk of manifesting severe AKI in coming days

Biomarkers
Increase in serum creatinine (filtration marker)
NGAL, IL-18 * will present some real examples
70 year old diabetic engineer
elective coronary artery bypass surgery

Serum creatinine (umol/L)

before surgery: 1.5

surgery

0-6 hrs: 1.6

2 days: 2.8

Enroll patients at time obvious they have AKI, follow who will progress (dialysis need)
- No urine output, acidotic

Biomarkers
- serum creatinine (nature of rise)
- Injury biomarker (or low “repair” marker)

Examples in the Literature

Jupiter Trial
Ridker et al. NEJM 2008
CRP used in inclusion criteria.
Trial stopped early.
- reduced risk of composite CV outcome
- reduce CRP levels by 37%
CRP measurement not recommended in many clinical practice guidelines
**EARLYARF trial**  Endre et al. Kidney Int 2010

ICU or cardiac surgery (New Zealand)

- Started enrollment in 2006
- Urine GGT (γ-glutamyl transpeptidase)
- Urine AP (alkaline phosphatase)
- 2 enzymes in proximal tubule, increased in urine with ischemic injury to tubules.
- Randomized to 2 doses of EPO or placebo (done with 3.5 hours of biomarker elevation)
- Outcome: relative average plasma creatinine increase from baseline over 4 to 7 days (no effect of EPO)
- Use of the biomarker increased the event rate.
  - EA1 = 8% receipt of acute dialysis
  - EA2 = 11% receipt of acute dialysis

**ANTI-CIN Study**  (Austria)  Protocol: BMC Nephrology 2011

Schilcher et al.

- Intra-arterial contrast. Coronary angiogram. Endovascular intervention
- Measured 4 to 6 hours
- Outcome: 25% increase in the serum creatinine value from baseline
- Goal to screen 1200 patients and randomize 240 patients.

**Entry Criteria**

- Patients at risk of AKI
- Measure biomarkers
  - Low biomarkers: No enrollment
  - High biomarkers: Placebo, Randomize
- Intervention

**Inclusion Criteria**
1. Age ≥ 18 years in an ICU
2. Serum creatinine > upper threshold of normal
3. Evidence of severe AKI based on ≥ 2 of these 3 criteria:
   i. 2-fold increase in serum creatinine during hospitalization
   ii. Oliguria x 12 hours
   iii. whole-blood NGAL ≥400 ng/mL (point of care system)

**Intervention:** Early vs. Routine Initiation of Acute Dialysis

**Pilot:** Randomized 100 patients across 12 sites in Canada

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**C RONARY**

**Inclusion/Exclusion Criteria**

- **Inclusion Criteria**
  - Isolated CABG with median sternotomy
  - One of the following:
    1. Peripheral vascular disease
    2. Cerebrovascular disease
    3. Creatinine > upper limit of laboratory reference range
    4. Age ≥ 70 years
    5. Age 60 - 69 with at least **one risk factor** (diabetes, urgent revascularization, smoker, LVEF ≤ 35%)
    6. Age 55 - 59 with at least **two of the above risk factors**

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**AKI biomarker as eligibility criteria for RCT**

**Advantages**

- Enrolling group of patients with:
  - a higher event rate of severe AKI
  - a type of AKI that may be more responsive to intervention
  - reduce # of patients exposed to potential toxicity from the intervention

- If used as one of many criteria that identify patients at high risk for trial inclusion, may increase number of available patients for trial inclusion.

- If a biomarker ‘enthusiast’ may increase uptake of biomarker use in practice if intervention demonstrates benefit.
AKI Biomarker as Eligibility Criteria for RCT

Disadvantages

• An additional level of complexity
  – could delay randomization
  – may need fresh urine samples

• If biomarker inaccurate then not enriching the trial population as intended

• If used as a sole inclusion criteria:
  – Will have screen failures
  – Biomarker misclassification may exclude some patients who go on to develop AKI
  – May impact trial generalizability

AKI Biomarker as Sole Inclusion Criteria
(scenarios with TRIBE cohort, post-op early AKI detection)

<table>
<thead>
<tr>
<th>Sole Enrollment Criteria</th>
<th>Screen Failure Rate (%)</th>
<th>% of total AKI events identified</th>
<th>AKI event rate (2x Cr or dialysis)</th>
<th>Sample size require to detect a ≥ 30 % RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma NGAL &gt; 200 pg/mL</td>
<td>56</td>
<td>67</td>
<td>6%</td>
<td>~ 4700</td>
</tr>
<tr>
<td>CPB time &gt;120 minutes</td>
<td>63</td>
<td>60</td>
<td>7%</td>
<td>~ 4000</td>
</tr>
<tr>
<td>Plasma NGAL &gt; 200 &amp; CPB &gt; 120 minutes</td>
<td>78</td>
<td>53</td>
<td>9%</td>
<td>~ 3000</td>
</tr>
<tr>
<td>Urine IL-18 &gt; 60 pg/mL</td>
<td>80</td>
<td>51</td>
<td>10%</td>
<td>~ 2700</td>
</tr>
<tr>
<td>Urine IL-18 &gt; 60 pg/mL &amp; CPB &gt; 120 minutes</td>
<td>88</td>
<td>46</td>
<td>12%</td>
<td>~ 2200</td>
</tr>
</tbody>
</table>

2. AKI Biomarker Measurement as an Intervention (Screening)
1. Patients
   (in some setting)

2. No biomarker measurement
   Randomize
   Biomarker measurement

If biomarker elevated, provides ‘lead time’ to apply an efficacious intervention that would not be applied otherwise

Seen in chronic disease screening (cancer)

3. Biomarkers as Outcome

Clinically important outcomes
How a patient feels, functions or survives
Surrogate Outcomes

• Mild / moderate acute change in serum creatinine
• AKI biomarkers (i.e. NGAL, IL-18, KIM-1)

Help to pick an intervention worth of further testing
(to determine if intervention impacts clinically important outcomes)

US FDA position

BIC-MC Trial


Open heart surgery with cardiopulmonary bypass

4 hospitals, planned for 500 patients, stopped early at 350 patients

Randomized (n=668)

IV sodium bicarbonate

47.7% p = 0.03

24.3 ng/mL p = 0.01

Median increase in urine NGAL in first 24 hours after CABG

Biomarker here helped corroborate a safety concern.
It had more statistical power with given sample size to detect signal.

Other Examples of New AKI Biomarkers as Outcome in Literature

• Statin (short-term) in cardiac surgery
  – Prowle et al. Nephrology 2012
• Erythropoietin in cardiac surgery
  – de Seigneur et al. BMC Nephrology 2012
• Fenoldopam in pediatric cardiac surgery
• IV Alkaline Phosphatase ICU Sepsis
Use of Biomarkers as a Surrogate Outcome

Advantages

• Early trials are simply to detect an intervention worthy of further testing.
• In this regard, biomarker may reduce sample size requirement to detect an AKI signal than change in serum creatinine
  – if biomarker rises early, less influenced by ‘noise’ from other factors after surgery
  – may better detect ‘true’ injury
  – may have more favorable statistical properties (less variability)

Disadvantages

• Not established as a reliable surrogate
  – circular argument – need large trial
  – what cut-point; continuous vs. dichotomous

AKI Biomarker as Outcome
(hypothetical scenario with TRIBE cohort)

1. 2 intervention groups:
   – Treatment: CPB Time < 80 min
   – Control: CPB Time > 120 min
2. Used propensity based matching to successfully create 2 groups which were similar on all pre-operative characteristics. 153 patients in each group.
3. Compare outcomes between 2 groups
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<th>TREATMENT n=153</th>
<th>CONTROL n=153</th>
<th>P value</th>
<th>Total sample size</th>
</tr>
</thead>
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<tr>
<td>Urine IL-18</td>
<td>7.4 (2.9 to 19.9)</td>
<td>17.1 (7.2 to 68.5)</td>
<td>&lt;.0001</td>
<td>96</td>
</tr>
<tr>
<td>Urine NGAL</td>
<td>6.8 (2.9 to 17.2)</td>
<td>20.0 (5.1 to 214.5)</td>
<td>&lt;.0001</td>
<td>64</td>
</tr>
<tr>
<td>Urine KIM-1</td>
<td>0.3 (0.1 to 0.7)</td>
<td>0.4 (0.2 to 1.1)</td>
<td>0.009</td>
<td>360</td>
</tr>
<tr>
<td>Urine LFABP</td>
<td>9 (2.5 to 15.0)</td>
<td>44.4 (5.3 to 278.4)</td>
<td>&lt;.0001</td>
<td>89</td>
</tr>
<tr>
<td>Plasma NGAL</td>
<td>173 (107 to 250)</td>
<td>243 (170 to 320)</td>
<td>&lt;.0001</td>
<td>71</td>
</tr>
<tr>
<td>Delta Peak Serum Creatinine</td>
<td>0.08 (-0.04 to 0.22)</td>
<td>0.2 (0.05 to 0.4)</td>
<td>&lt;.0001</td>
<td>164</td>
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Measured ~ 6 hours after surgery. Median (25th to 75th percentile).

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