Biomarkers in AKI Clinical Trials - Are they ready?  YES

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Competing Interests

Consulting:
- Fresenius
- Gambro
- Baxter
- Astute Medical
- Alere
- Opsona
- Abbott
- AM Pharma
- BioAegis
- Roche
- Spectral Diagnostics
- CytoSorbents

Grant support:
- Baxter
- Gambro
- Astute Medical
- Alere

IP/Licensing:
- Astute Medical
- CytoSorbents
- Spectral Diagnostics
Clinical uses for (AKI) Biomarkers

- Risk assessment
- Diagnosis
  - Syndrome detection
  - Etiology
- Disease monitoring/Prognostication
- Response to therapy
- Recovery

Stage-Based Management

<table>
<thead>
<tr>
<th>AKI Stage</th>
<th>High Risk</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue all nephrotoxic agents and procedures</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Ensure volume status and perfusion status</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Consider functional hemodynamic re-evaluation</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Monitor urine output and renal function</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Avoid hyperkalemia</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Consider alternatives to radiostereotactic procedures</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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</tr>
<tr>
<td>Monitor inotrope and vasoactive drug use</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Consider dialysis in drug poisoning</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Consider RRT and nonrenal therapy</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Consider ICU admission</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Stage-based management of AKI: Shading of boxes indicates priority of action—solid shading indicates actions that are equally appropriate at all stages whereas graded shading indicates increasing priority as intensity increases.

Kidney Disease: Improving Global Outcomes
WWW.KDIGO.ORG

**Biomarkers in AKI research**

**Entry criteria (Inclusion or Exclusion)**
- Enrichment: Exclude low risk patients
- Narrow for effect: Exclude cases where drug can’t help
  - Wrong etiology
  - Injury already occurred

**Adjudication of Endpoints**
- Increase endpoint detection
- Improve adjudication accuracy

**Improve risk:benefit ratio**
- Avoid exposing low risk patients to adverse effects

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**uNGAL AUC 0.68 for RIFLE24**

- 7:48 (1:7)
- 22:177 (1:8)
- 5:177 (1:35)
New Intervention 20% RRR

- Expected event rates
  - 50% placebo
  - 40% treated
- RRR 20%
- ARR 10%
- Sample size required: 776
- Cost @12k per subject: $9,312,000

Scenario 1: restrict to high (>50%) risk

- Expected event rates
  - 50% placebo
  - 40% treated
- RRR 20%
- ARR 10%
- Sample size required: 776
- Cost @12k per subject: $9,312,000

Scenario 1: Restrict to >50% risk

- Expected event rates
  - 66% placebo
  - 53% treated
- RRR 20%
- ARR 13.25%
- Sample size required: 430
- Cost @12k per subject: $5,160,000
**Scenario 2: 50% enrolled have 0 risk**

- **Expected event rates**
  - 50% placebo
  - 40% treated
- **RRR 20%**
- **ARR 10%**
- **Sample size required:** 776
- **Cost @12k per subject:** $9,312,000

**Scenario 3: 50% can’t be helped**

- **Expected event rates**
  - 50% placebo
  - 40% treated
- **RRR 20%**
- **ARR 10%**
- **Sample size required:** 776
- **Cost @12k per subject:** $9,312,000

**Scenario 3: 50% can’t be helped**

- **Expected event rates**
  - 50% placebo
  - 45% treated
- **RRR 10%**
- **ARR 5%**
- **Sample size required:** 3044
- **Cost @12k per subject:** $36,528,000
**Scenario 4: 10% Already have endpoint**

- Expected event rates
  - 50% placebo
  - 40% treated

- RRR 20%
- ARR 10%

- Sample size required: 776
- Cost @12k per subject: $9,312,000

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**Scenario 4b: 10% Already have endpoint Biomarker excludes 100%**

- Expected event rates
  - 54% placebo
  - 45% treated

- RRR 16%
- ARR 8.8%

- Sample size required: 1022
- Cost @12k per subject: $12,264,000

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**Scenario 4c: 10% Already have endpoint Biomarker excludes 66%**

- Expected event rates
  - 54% placebo
  - 45% treated

- RRR 16%
- ARR 8.8%

- Sample size required: 1022
- Sample size required: 882
- Cost @12k per subject: $12,264,000
- Cost @12k per subject: $10,584,000
### Scenario 4d: 10% Already have endpoint Biomarker excludes 33%

+ **Expected event rates**
  - 54% placebo
  - 45% treated

+ **RRR 16%**

+ **ARR 8.8%**

+ **Sample size required:** 1022

+ **Cost @12k per subject:** $12,264,000

### Scenario 5: 10% or 20% events are missed

+ **Expected event rates**
  - 50% placebo
  - 40% treated

+ **RRR 20%**

+ **ARR 10%**

+ **Sample size required:** 776

+ **Cost @12k per subject:** $9,312,000

### Scenario 6: Biomarker increased events by 30% but with 0%, 10%, 30% FP rate

+ **Expected event rates**
  - 50% placebo
  - 40% treated

+ **RRR 20%**

+ **ARR 10%**

+ **Sample size required:** 776

+ **Cost @12k per subject:** $9,312,000
Adjudicated AKI (Expert Panel)

Scenario 7: 20% RRR, but Harms 8%

1000 pts
400 get AKI anyway but 32 also have harm
100 avoid AKI 8 also have harm
500 get no benefit 40 also have harm
92 helped
72 harmed
4 both helped and harmed
Conclusions

- Existing biomarkers for AKI are Ready for AKI trials.
- Even marginally effect biomarkers can have a dramatic positive impact on therapeutic trials
  - Enrichment for events
  - Narrowing in on cases where intervention will work
  - Avoid enrolling patients past chance to save or too low risk to benefit
  - Improve Risk:Benefit ratio for drugs
- Biomarkers will reduce RCT costs by millions of dollars!

Biomarkers of AKI Trials?
YOU Can’t Afford Not Too

The end...