Disclosures

Consultant for CVS Caremark, Harvard Clinical Research Institute

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Expert defense witness for litigation related to GE product Omniscan; data monitoring committee for Takeda trial on febuxostat
Biomarkers in AKI Clinical Trials: Are They Ready or Not?

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My Un-enviable Task

"I found the old format much more exciting."
My Un-enviable Task

• In an international meeting jointly sponsored by ASN and AACC on AKI biomarkers...

• On a topic upon which my professional efforts are focused...

• To argue that AKI biomarkers are not ready for use
Premise

• Current novel biomarkers of AKI are not ready for use in clinical trials

• For the purposes of this debate, I will use a narrow definition of “biomarker”
  • Examples: NGAL, KIM-1, L-FABP, others
  • Not serum creatinine, urine output, other conventional labs
Roles of AKI biomarkers

• Using biomarkers for clinical trial “enrichment”
  • Aid trial design by enrolling or treating patients according to biomarker

• Surrogate endpoints
  • Rather than “hard endpoint” (death; dialysis; doubling of serum creatinine), utilize novel biomarkers of tubular injury

• Pre-clinical or early phase toxicology screening
  • Identify safe versus dangerous compounds in early phase studies
Roles of AKI biomarkers

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• Pre-clinical or early phase toxicology screening
  • Identify safe versus dangerous compounds in early phase studies
  (albuminuria is not even acceptable yet)

Studies under way
  (F-NIH Kidney Safety Project; IMI-SAFE T)
Roles of AKI biomarkers

- Using biomarkers for clinical trial “enrichment”
  - Aid trial design by enrolling or treating patients according to biomarker
Case study

Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYYARF trial)  
Kidney International (2010) 77, 1020–1030; doi:10.1038/ki.2010.25; published online 17 February 2010

Zoltán H. Endre¹, Robert J. Walker², John W. Pickering¹, Geoffrey M. Shaw¹,³, Christopher M. Frampton¹, Seton J. Henderson¹,³, Robyn Hutchison², Jan E. Mehrtens¹,³, Jillian M. Robinson¹, John B.W. Schollum²,⁶, Justin Westhuyzen¹, Leo A. Celi², Robert J. McGinley⁴, Isaac J. Campbell¹ and Peter M. George⁵

- Double-blind, placebo-controlled trial on early treatment with erythropoietin 500 U/kg IV for prevention of AKI
- Consecutive ICU patients or high risk cardiac surgery patients
- Intervention and triage trial
  - Urine obtained for GGT, AP, and creatinine
  - If biomarker > 46.3 → enroll in RCT [N = 162]
  - If biomarker < 46.3 → not a candidate for RCT, but observe
528 ICU admissions
528 ICU admissions
94 developed acute kidney injury

How can a biomarker make this trial more efficient?
528 ICU admissions
94 developed acute kidney injury

Apply biomarker test (urine GGT * alk phos < 43):
293 patients without AKI would not have to be enrolled
528 ICU admissions
94 developed acute kidney injury

With biomarker-driven inclusion strategy, EARLY ARF was able to enrich cohort from 17.8% AKI incidence to 23.0%. More efficient, less costly.

A “better” biomarker would have been even more efficient

Apply biomarker test (urine GGT * alk phos < 43):
  293 patients without AKI would not have to be enrolled
  Lose 52 patients who would have developed AKI
Biomarker enrichment designs

By applying biomarker cutoff for entry, interventional trials can target higher risk patients: gains in efficiency

Performance of the enrichment design depends on sensitivity, specificity, and prevalence of AKI

\[
\# \text{biomarker } + = \text{true positive } + \text{false positive}
\]

\[
\# \text{biomarker } - = \text{true negative } + \text{false negative}
\]
Biomarker enrichment designs

By applying biomarker cutoff for entry, interventional trials can target higher risk patients: gains in efficiency

Performance of the enrichment design depends on sensitivity, specificity, and prevalence of AKI

\[
\text{# biomarker } + = \text{sens} \times \text{prev} + (1-\text{spec}) \times (1-\text{prev})
\]

\[
\text{# biomarker } - = [\text{spec} \times (1-\text{prev})] + [\text{prev} \times (1-\text{sens})]
\]
Biomarker enrichment designs

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\# \text{ biomarker}^+ = \text{true positive} + \text{false positive}
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\[
\# \text{ biomarker}^- = \text{true negative} + \text{false negative}
\]
Biomarker enrichment designs

\[ \text{RANDOMIZE FEWER} \]

\[ \text{SCREEN ALL} \]

\# biomarker + = true positive + false positive

\# biomarker - = true negative + false negative
Example

- Prevention trial in cardiac surgery – AKI
- Sample size estimate of # AKI = 200
- Assume incidence = 20%, \( N = 1000 \)

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<tr>
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<tbody>
<tr>
<td>No need to screen</td>
<td>Screen <strong>more</strong> than 1000</td>
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<tr>
<td>Enroll <strong>1000</strong> patients, randomize all</td>
<td>Randomize <strong>fewer</strong> than 1000 patients</td>
</tr>
<tr>
<td>Have enrolled <strong>800</strong> who are not informative</td>
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<tr>
<td>Enroll 1000 patients, randomize all</td>
<td>Randomize 782</td>
</tr>
<tr>
<td>Have enrolled 800 who are not informative</td>
<td>45% sens 68% spec</td>
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Example

- Prevention trial in cardiac surgery – AKI
- Sample size estimate of # AKI = 200
- Assume incidence = 20%, N = 1000

**WITHOUT BIOMARKER**

No need to screen

Enroll 1000 patients, randomize all

Have enrolled 800 who are not informative

**WITH BIOMARKER**

Screen 1,250

Randomize 400

80% sens
80% spec
Example

- Prevention trial in cardiac surgery – AKI
- Sample size estimate of \( \# \text{ AKI} = 200 \)
- Assume incidence = 20%, \( N = 1000 \)

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<tr>
<td>Enroll 1000 patients, randomize all</td>
<td>Randomize 289</td>
</tr>
<tr>
<td>Have enrolled 800 who are not informative</td>
<td>90% sens 90% spec</td>
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Argument up until now...

- Biomarker enrichment strategy can optimize clinical trial design

- Based on sensitivity, specificity, and incidence, one can estimate gains in efficiency

- Potential downsides:
  - Cost
  - Turnaround time
  - Generalizability limited to biomarker +
However...

- Do currently available “novel” biomarkers outperform clinical risk prediction models?

- Are sensitivity and specificity of NGAL, KIM-1, L-FABP, or other biomarkers superior to carefully constructed clinical risk prediction models?
Clinical models

A Clinical Score to Predict Acute Renal Failure after Cardiac Surgery

J Am Soc Nephrol 2005

Area under the ROC

A Risk Prediction Score for Kidney Failure or Mortality in Rhabdomyolysis

JAMA Int Med 2013

Area under the ROC

Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children

Kidney Int 2013

Area under the ROC
Clinical models

Area under the ROC-- biomarkers

NGAL: 0.60 – 0.85

KIM-1: 0.60 – 0.85

IGFBP7*TIMP-2: 0.80

Kashani et al. Crit Care 2013
Vanmassenhov et al. NDT 2013
Clinical models vs. biomarker

- Carefully constructed clinical models are outstanding, difficult to “beat”
  - Particularly when incorporating routine variables (eGFR, diabetes) plus context-specific variables: bypass duration; cause of rhabdomyolysis; urine output; early change in SCr

- Enrichment designs can be performed equally well with clinical models
  - Faster, cheaper, no threat to generalizability as with biomarker-enrichment designs
“Conventional” biomarkers


“At 24h postop, the performance of fluid balance was comparable to that of preop conventional and postop 24h novel biomarkers”

NCT01602328, A Study to Evaluate AC607 for AKI in cardiac surgery (ACT-AKI). (Allocure, Inc. study of mesenchymal stem cells for AKI treatment/prevention)

“Inclusion criteria: 0.5 mg/dL rise in SCr within 48 of bypass”

DiSomma et al. Additive value of NGAL to clinical judgment in AKI diagnosis in the ED. Critical Care 2013.

AUC of NGAL for AKI diagnosis at time 0: 0.799
AUC of clinical judgment at time 0: 0.837


AUC of clinical model 0.69 Adding IL-18, increases to 0.76
(Note however that clinical model excludes postop SCr, urine output)
Biomarker + clinical model?

• Why not incorporate biomarker enrichment design on top of carefully constructed clinical prediction model?

  - High clinical risk score
    - + biomarker $\rightarrow$ randomize
    - - biomarker $\rightarrow$ exclude

• Change in C-statistic, integrated discrimination index, net risk reclassification

  • Metrics that capture improvement in risk prediction
Biomarker + clinical model?

• Improving upon good clinical risk prediction models with novel biomarkers is difficult

• Framingham risk score + 10 biomarkers of multiple biologic pathways (CRP; bNP; aldosterone; urine ACR; others)

• Change in C-statistic can be minimal: 0.80 to 0.82
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Conclusions

- AKI biomarkers studied to date are not superior to good clinical risk prediction models
- Any gain in C-statistic, net risk reclassification may be statistically significantly, but clinically trivial
- Downsides to biomarker-enrichment designs need to be carefully considered
  - Additional expense of screening, testing
  - Turnaround time for test result
  - Threat to generalizability
Thank You!