HOW CAN WE BETTER DEFINE OUTCOMES IN PROGRESSION OF CKD?

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Disclosure of Interests

- Pharmalink, research funding Tufts Medical Center
- Ardea, Consultant to Tufts Medical Center
- Otsuka, research funding Tufts Medical Center
- Metabolon, collaboration agreement for development of accuGFR
Current state of CKD Progression Endpoints

- Kidney failure is a hard clinical outcome of interest, but is late and earlier stages of disease are also associated with substantial morbidity.
- GFR decline is on the path to kidney failure; a sufficiently large change in GFR, defined as halving of GFR (2XSCr), is accepted as a clinical endpoint for the progression to kidney failure, but is also a late event in CKD and takes a long time to develop.
- Consequently, trials are restricted to patients with late stage or rapidly progressive disease.
- Treatments for earlier stages of disease may not be effective at later stages, thus use of currently used endpoints may miss the opportunity to identify effective treatments at earlier stages.
Outline

• Challenges in determining rate of progression of chronic kidney disease
• Markers of kidney damage as alternative endpoints
  – Total kidney volume for PKD
  – Proteinuric
• Change in GFR as alternative endpoints
  – Lesser declines in GFR
  – GFR slope
• Summary
Challenges in determining rate of progression of chronic kidney disease
Determinants of Physiological GFR

\[ GFR = N \times SNGFR \]
\[ SNGFR = K_f \times P_{UF} \]
\[ SNGFR = S \times k \times (\Delta P - \Delta \Pi) \]
# GFR Measurement and Estimation

<table>
<thead>
<tr>
<th>Description</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>True GFR (tGFR)</strong></td>
<td>Average value over 1-2 days</td>
</tr>
<tr>
<td><strong>Measured GFR (mGFR)</strong></td>
<td>Urinary or plasma clearance of exogenous filtration marker</td>
</tr>
<tr>
<td><strong>Estimated GFR (eGFR)</strong></td>
<td>Equations based on serum levels of endogenous filtration markers</td>
</tr>
</tbody>
</table>
Determinants of Creatinine as Filtration Marker

\[ U \times V = GFR \times S + TS \]
\[ G - E = GFR \times S + TS \]
\[ GFR = \frac{G - E - TS}{S} \]

Age, sex, race, weight
Interventions without vs. with an Acute Effect on GFR

Control Group
Declining N (number of nephrons)
Stable SNGFR (single-nephron GFR)

Intervention Group
No change in SNGFR
Slower decline in N

Control Group
Declining N (number of nephrons)
Stable SNGFR (single-nephron GFR)

Intervention Group
Acute effect – ↓ SNGFR, no change in N
Chronic effect – stable SNGFR, slower decline in N

Levey et al AJKD 2015, FDA-NKF Dec 2012 Workshop report
Control Group
Symmetrical distribution of GFR declines. Mean GFR decline <0.

Intervention Group
Uniform treatment effect: Same treatment effect in patients with fast vs. slow GFR declines.

Control Group
Symmetrical distribution of GFR declines. Mean GFR decline <0.

Intervention Group
Proportional treatment effect: Larger treatment effect in patients with fast vs. slow declines.

Levey et al AJKD 2015 FDA-NKF Dec 2012 Workshop report
Markers of Kidney Damage as Alternative Endpoints: TKV and Proteinuria
Conceptual Framework of Kidney Damage as Alternative Endpoint

ADPKD Progression

Kidney function (%)

Concentrating defect, Hypertension, Proteinuria

Pain, Hematuria, Stones, Infections

Age (years)
Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (TEMPO)

Total Kidney Volume

Change in 1/Scr

Torres et al NEJM 2012
On October 22, 2015 the EMA released a final Qualification Opinion in support of Total Kidney Volume for use as a prognostic biomarker in clinical trials for patients with Polycystic Kidney Disease.
Association between Change in Proteinuria and Clinical Endpoints

- Included large and small studies
- Change in proteinuria between 3-12 months
- Meta-analysis incorporated correlation of errors between surrogate and clinical outcome

- Restricted to larger studies
- Change in albuminuria short and long term
- Meta-analysis did not incorporate correlated errors

Renin-angiotensin system blockade versus placebo
Renin-angiotensin system blockade versus calcium channel blocker
Intensive blood pressure
Immunosuppressive therapies
GFR Change as Alternative Endpoints: Lesser decline in GFR and GFR slope
GFR Decline as an Endpoint for Clinical Trials in CKD: A Scientific Workshop Sponsored by the National Kidney Foundation and the US Food and Drug Administration

Andrew S Levey (Chair), Josef Coresh, Norman Stockbridge, Aliza Thompson, Edmund Lewis, Kerry Willis, Dick de Zeeuw, Alfred Cheung, John Lawrence, Kunihiro Matsushita, Lesley Inker, Tom Greene

Levey et al AJKD 2015 FDA-NKF Dec 2012 Workshop report
Observational Studies: Adjusted HR for ESRD Subsequent to % Change in eGFR during a 2-year baseline period

- **eGFR<60**
  - Ref. at 0%
  - -20%
  - -30%
  - -40%
  - -57%

- **eGFR≥60**
  - Ref. at 0%
  - -20%
  - -30%
  - -40%

*N = 1,530,648 participants in 22 cohorts, Coresh JAMA 2014*
Trials: Association between Treatment Effects on GFR decline and on clinical endpoint

Horizontal and vertical lines around each circle indicate the Bayesian CI for the treatment effect on the established and alternative end points.

Hazard ratio for Alternative Endpoint

Inker et al AJKD 2015
Simulations: Summary of performance of alternative end points for trials with 2- to 3-year durations of follow-up

<table>
<thead>
<tr>
<th>Acute effects</th>
<th>GFR high (Stage 2)</th>
<th>GFR medium (Stage 3)</th>
<th>GFR low (Stage 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40% decline</td>
<td>40% decline</td>
<td>40% decline</td>
</tr>
<tr>
<td>Large negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large positive</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key**</th>
<th>Type 1 error not acceptable (false positive for benefit)</th>
<th>Type 1 error not acceptable (false positive for harm)</th>
<th>Type 1 error acceptable but power not improved</th>
<th>Type 1 error acceptable and power improved</th>
</tr>
</thead>
</table>

*Assumptions: treatment effect is mixed proportional/uniform; acute effect attenuates to 0 at ESRD; trial duration 3 years for high GFR and 2 years for medium and low GFR. **Key: acceptable type 1 error ≈ 10% or less; improved power = smaller samples size for alternative vs. 57% decline in same trial duration

Greene et al AJKD 2015
Summary (Proposal) from the Conference

• A GFR decline of 30% could be a valid and useful surrogate end point for progression to kidney failure in clinical trials of CKD, with stronger support for decline of 40%
• Confirmatory measurement of Scr at baseline and after reaching the end point to confirm the eGFR decline
• Follow-up during the trial of at least 2 to 3 years to allow a thorough evaluation of benefits and harms.
## SPRINT: Kidney Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline eGFR &lt;60</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>14</td>
<td>15</td>
<td>0.89 (0.42, 1.87)</td>
<td>0.76</td>
</tr>
<tr>
<td>≥50% GFR decline</td>
<td>10</td>
<td>11</td>
<td>0.87 (0.36, 2.07)</td>
<td>0.75</td>
</tr>
<tr>
<td>Dialysis</td>
<td>6</td>
<td>10</td>
<td>0.57 (0.19, 1.54)</td>
<td>0.27</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Baseline eGFR &gt;60</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% eGFR decline</td>
<td>127</td>
<td>37</td>
<td>3.48 (2.44, 5.10)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

SPRINT Research group, NEJM 2015
Slope as an Outcome in Randomized Clinical Trials in CKD

Under the assumptions of 1) a linear mean rate of decline and 2) uniform treatment effects:

- Analyses comparing mean slopes provide greater statistical power than alternative strategies including time-to-event analyses.

- The potential advantages of slope-based analyses over time-to-event analyses can be very large in settings where event rates from the time-to-event analyses are expected to be low
  - Studies with high baseline eGFR
  - Studies with relatively slow progression
Challenges for Slope as Endpoint in CKD RCT

- Nonlinear long-term mean trajectories
- Non-uniform distribution
- Informative censoring due to ESRD
- Greater variability in eGFR at higher eGFR levels
- Modelled slope shows difficulty achieving convergence
Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD:
A Scientific Workshop Sponsored by the National Kidney Foundation, US Food and Drug Administration and European Medicines Agencies

Planning underway for March 2018
Brief Overview of Workshop Aims

• Examine evidence for use of change in albuminuria as endpoint, with a focus on higher baseline GFR
  – Review of past RCT’s
  – Restriction to specific diseases and interventions

• Examine evidence for using eGFR slope as an outcome, with a focus at higher baseline GFR
  – Review of past RCT’s and perform simulations
  – Include consideration of acute effects, use of chronic slope, nonlinearity
  – Goal is to characterize the situations in which slope-based analyses provide substantially greater statistical power than time-to-event analyses while retaining validity

• Develop methods to combine change in ACR and GFR for combined endpoint (individual vs group)
Summary

• There are several challenges to determining progression of GFR, and therefore to establishing endpoints for trials of CKD progression
• Markers of kidney damage may be appropriate alternative endpoints in selected circumstances, and also may be used as prognostic enrichment biomarker
• Lesser decline of GFR (40%, 30%) may be appropriate in some circumstances, but can lead to false conclusions in settings of strong acute effects, particularly at higher levels of GFR
• GFR slope has some promise, but also challenges and is currently under investigation
• Combination of changes in markers of kidney damage and GFR might ameliorate limitations with either
• **Co-investigators**
  – Andrew S Levey
  – Josef Coresh
  – Tom Greene

• **Tufts/CKD-EPI analytical team**
  – Chris Schmid
  – Kruti Pandya
  – Hocine Tighiouart
  – Hasi Mondal MS

• **JHU/ CKD-PC Analytical team**

• **Hiddo Lambers-Heerspink**

• **FDA**
  – Norman Stockbridge
  – Aliza Thompson
  – John Lawrence

• **Collaborators**
  – CKD-EPI
  – CKD-PC