TRIALS TO BUILD AN EVIDENCE BASE FOR PHOSPHATE MANAGEMENT IN ESKD

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DISCLOSURES

- Consultant: Bayer, Enyo, Launch, Jnana, Pharmacosmos, Reata
- Scientific Advisory Board: Unicycive, Walden
- Board of Directors: Akebia
Phosphate & mortality: ESRD, CKD, non-CKD

Phosphate and arterial calcification

Giachelli CM. Kidney Int 2009
Hemodialysis: serum phosphate & mortality

Based on preclinical & observational data, opinion-based guidelines: Maintain P <5.5 mg/dl using binders, diet

But…there is no proof that lowering high phosphate in individual patients helps improve their outcomes!
HD: Ideal Setting for Pragmatic Trials

• Highly accessible study population
• Frequent & regular clinical encounters
• Highly granular & uniform data collection as part of routine clinical care
• Infrastructure of dialysis provider organizations allows for:
  – Centralized implementation
  – Inclusion of large number of facilities with broad geographic distribution
• Many unanswered questions about fundamental aspects of dialysis care
HiLo: Pragmatic trial of higher vs lower P in HD

What is the best blood level of phosphate for people with kidney failure on dialysis?

What is HILO?
HiLo is a clinical research study on how best to manage blood phosphate levels in patients on dialysis. Researchers will compare how participants feel, how often they are hospitalized, and how long they live based on the level of phosphate in their blood.

Why HILO?
Pragmatic randomized trial of High Or Standard PPhosphAte Targets in End-stage kidney disease
High-level comparison of trial designs

**HiLo**
- Pragmatic
- Targets: <5.5 vs >6.5 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Hierarchical win ratio
  - Death, all cause
  - Hospitalizations, all cause
- No outcome adjudication

**Phosphate**
- Pragmatic
- Targets: <4.65 vs 6.2–7.75 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Time to first event
  - CV death, non-fatal MI, coronary revasc, stroke, PAD event
- Outcomes are adjudicated
Primary outcome: All-cause mortality & hospitalization

• All-cause mortality is a gold standard outcome in clinical trials.
• Hospitalization is also extremely important to all stakeholders: patients, families, clinicians, dialysis providers, payers/Medicare.
• HyperP contributes to multiple complications that result in hospitalization.
• Hospitalization is an accepted endpoint in other therapeutic areas.
• Will be collecting real-time outcomes using EHR data.
Wins, losses and ties:

1. Red wins for later death
2. Red wins for later death despite more hospitalizations
3. Tie on death, hospitalizations despite subsequent death
4. Red wins for fewer hospitalizations after tie on death
5. Tie on death, hospitalizations
6. Blue wins for fewer hospitalizations after tie on death
7. Tie on death, hospitalizations despite more later hospitalizations
8. Red wins for fewer hospitalizations after tie on death
9. Blue wins for fewer hospitalizations after tie on death

Longitudinal follow-up time
Win ratio in use: HEART-FID Trial

Mentz RJ et al. NEJM 2023
Informed Consent

Informed Consent needed: the “research involves more than minimal risk”

• We use “eConsent:”
  • A relatively new pragmatic approach to clinical trial design
  • Informed consent obtained electronically by smart phone, tablet or computer
  • HiLo offers both written and video-based consent materials
  • Dialysis facility staff are asked to refer patients to the HiLo website

45 CFR Part 46 (“The Common Rule”)
At 10% enrollment…

- Imbalance in baseline characteristics between Hi and Lo arms

<table>
<thead>
<tr>
<th></th>
<th>Hi N=255</th>
<th>Lo N=179</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>57.5 ± 13.8</td>
<td>61.6 ± 13.9</td>
</tr>
<tr>
<td>Mean phosphate, mg/dl</td>
<td>6.6 ± 2.2</td>
<td>5.8 ± 1.7</td>
</tr>
</tbody>
</table>

- Imbalance in enrollment rates between arms

<table>
<thead>
<tr>
<th>Arm</th>
<th>% Ineligible</th>
<th>Approached</th>
<th>Consented</th>
<th>Consent Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hi</td>
<td>31.2%</td>
<td>625</td>
<td>237</td>
<td>37.9%</td>
</tr>
<tr>
<td>Lo</td>
<td>21.2%</td>
<td>502</td>
<td>318</td>
<td>63.3%</td>
</tr>
</tbody>
</table>

- Pivot to individual level randomization
High-level comparison of trial designs

**HiLo**
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- Data collected: clinical only
- Outcome: Hierarchical win ratio
  - Death, all cause
  - Hospitalizations, all cause
- No outcome adjudication
- Progress: n=550 (cluster)
  - 200 of 3800 (individual)

**Phosphate**
- Pragmatic
- Targets: <4.65 vs 6.2–7.75 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Time to first event
  - CV death, non-fatal MI, coronary revasc, stroke, PAD event
- Outcomes are adjudicated
- Progress: n=1400 of 4000

**Potential threat:** Calcium vs non-calcium
**LANDMARK Trial**

**QUESTION** Does lanthanum carbonate-based treatment without calcium-based phosphate binders reduce cardiovascular events compared with calcium carbonate-based treatment in patients with hyperphosphatemia undergoing hemodialysis?

**CONCLUSION** Among patients with chronic kidney disease (CKD) undergoing hemodialysis, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in cardiovascular events.

**POPULATION**
- 1271 Men
- 864 Women
- Adults with CKD, hyperphosphatemia, and ≥3 vascular calcification risk factor
- Median age: 69 years

**INTERVENTION**
- 2309 Patients randomized
- 2135 Patients analyzed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Lanthanum carbonate</td>
<td>750 mg/d oral lanthanum carbonate (3 doses, 250 mg each, after meals) or previously prescribed dose</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>3000 mg/d oral calcium carbonate (3 doses, 1000 mg each, after meals) or previously prescribed dose</td>
</tr>
</tbody>
</table>

**FINDINGS**
- Incident rate of composite cardiovascular events
  - Lanthanum carbonate: 4.8 events per 100 person-years (147 of 1063 patients)
  - Calcium carbonate: 4.3 events per 100 person-years (134 of 1072 patients)

The findings were not significant:
- Difference: 0.5 events per 100 person-years (95% CI: -0.57 to 1.56)
- Hazard ratio: 1.11 (95% CI: 0.88 to 1.41) \( P = .37 \)

**LOCATIONS**
- 273 Hemodialysis facilities in Japan

**PRIMARY OUTCOME**
- Composite of cardiovascular events: cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, TIA, or hospitalization for heart failure or ventricular arrhythmia

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If there is time...
FGF23 reduction & outcomes: EVOLVE Study

Etelcalcetide versus placebo in E:

2 separate trials, total:
IV etelcalcetide: n = 503
versus placebo: n = 513
3x weekly for 26 weeks

Block GA, et al. JAMA 2017
FGF23 reduction stabilizes LVH in ESRD

- Pilot RCT in Austria
- 1:1 randomize to etelcalcetide vs alfacalcidol
- N=62
- 1-year follow-up
- LVMI by cardiac MRI
A different approach?

**A  PTH-Centric Approach**

- **ESKD Population**
- **Randomization**
  - Etelcalcetide
  - Activated Vitamin D Analogs
- **Follow-Up**
  - Titrate PTH Into Target Range
- **Outcome**
  - Hierarchical Composite:
    1. CV Mortality
    2. HF Hospitalization
    3. Atrial Fibrillation

**B  FGF23-Centric Approach**

- **ESKD Population**
- **Randomization**
  - Etelcalcetide
  - Placebo
- **Follow-Up**
  - Fixed Dose or FGF23 Titration & PTH Rescue Therapy
- **Outcome**
  - Hierarchical Composite:
    1. CV Mortality
    2. HF Hospitalization
    3. Atrial Fibrillation
DISCUSSION