MANAGING ACUTE AND CHRONIC HYPERKALEMIA: SOLVING THE PUZZLE

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Disclosure Slide

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Outline

• **Recognition:** Review prevalence and risk factors for hyperkalemia
• **Management:** Review current management strategies
• **Treatment:**
  • Describe current approaches for the treatment of hyperkalemia both acutely and chronically
  • Highlight new option to treat hyperkalemia in patients on renoprotective therapies
Overview: Epidemiology of Hyperkalemia

• Prevalence in hospitalized patients ranges from 1%-10% depending on the definition of hyperkalemia\(^1\)

• Prevalence in patients with CKD ranges from 5%-50%, increasing as kidney function declines\(^2\)

• Hyperkalemia is more common in patients with\(^3\)
  • Reduced kidney function
  • Multiple medications (especially RAAS inhibitors)
  • Older age
  • Diabetes mellitus

Hyperkalemia Varies Widely in Studies and Guidelines

- The upper limit of normal (ULN) for serum K⁺ levels varies across guidelines and publications¹⁻⁶
  - Serum K⁺ levels of 5.0, 5.5, or 6.0 mEq/L are commonly used cutoffs for ULN
  - Some studies differentiate hyperkalemia by severity¹
    - Serum K⁺ levels ≥5.5-<6.0 mEq/L defined as moderate
    - Serum K⁺ levels ≥6.0 mEq/L defined as severe

K⁺: potassium

Overview: Epidemiology of Hyperkalemia

• Prevalence in hospitalized patients ranges from 1%-10% depending on the definition of hyperkalemia\(^1\)

• Prevalence in patients with CKD ranges from 5%-50%, increasing as kidney function declines\(^2\)

• Hyperkalemia is more common in patients with\(^3\)
  • Reduced kidney function
  • Multiple medications (especially RAAS inhibitors)
  • Older age
  • Diabetes mellitus

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Prevalence of Hyperkalemia Defined as Serum Potassium >5 mEq/l and/or Sodium Polystyrene Use in Diabetic and Non-diabetic Patients with CKD Stages 2, 3 and 4

## Hyperkalemia Rates in RAASi-Treated Patients in Randomized Trials

<table>
<thead>
<tr>
<th>Patient Population</th>
<th># of Patients</th>
<th>Definition</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AASK(^1): non-diabetic CKD</td>
<td>417</td>
<td>≥5.5</td>
<td>7.2%</td>
</tr>
<tr>
<td>J-LIGHT(^2): HTN-CKD</td>
<td>58</td>
<td>&gt;5.1 ≤6.9</td>
<td>5.2%</td>
</tr>
<tr>
<td>RENAAL(^3): diabetic nephropathy</td>
<td>751</td>
<td>≥5.5</td>
<td>10.8%</td>
</tr>
<tr>
<td>IDNT(^4): diabetic nephropathy</td>
<td>579</td>
<td>&gt;6</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

Predictors of Hyperkalemia Before Starting Therapy

• eGFR <45 ml/min/1.73m²

• serum potassium of >4.5 mEq/L

• eGFR <45 ml/min/1.73m² + serum [K+] >4.5 mEq/L (HIGHEST PREDICTOR) in the absence of RAAS blockers

Hyperkalemia: A Significant Risk Marker for Mortality
Spline Analysis Adjusted for Covariates, Showing Serum Potassium as a Continuous Variable with All-Cause Mortality

Serum K⁺ Concentrations and Survival in Hemodialysis Patients

Predialysis serum K⁺ categories in 74,219 MHD patients observed for up to 3 years

MHD: maintenance hemodialysis; MICS: malnutrition inflammation complex syndrome.
Admission Serum K+ Levels and In-Hospital Mortality among CKD Patients With and Without CVD

Analysis of 73,983 patients admitted to Mayo Clinic Rochester. A U-shaped curve showed higher in-hospital mortality associated with both hypo- and hyperkalemia

<table>
<thead>
<tr>
<th>Serum Potassium at Hospital Admission (mEq/L)</th>
<th>In-hospital Mortality (%)</th>
<th>Odds Ratio for in-hospital mortality after adjusting for potential cofounders*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td>10.2</td>
<td>3.26 (95%CI 2.03-4.98)</td>
</tr>
<tr>
<td>3.0-&lt;3.5</td>
<td>6.3</td>
<td>2.40 (95%CI 1.89-3.04)</td>
</tr>
<tr>
<td>3.5-&lt;4.0</td>
<td>2.8</td>
<td>1.38 (95%CI 1.15-1.66)</td>
</tr>
<tr>
<td>4.0-&lt;4.5</td>
<td>3.1</td>
<td>1.0 (REFERENCE)</td>
</tr>
<tr>
<td>4.5-&lt;5.0</td>
<td>2.8</td>
<td>1.0 (REFERENCE)</td>
</tr>
<tr>
<td>5.0-&lt;5.5</td>
<td>4.1</td>
<td>1.13 (95%CI 0.94-1.37)</td>
</tr>
<tr>
<td>≥5.5</td>
<td>3.3</td>
<td>1.89 (95%CI 1.49-2.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.62 (95%CI 2.73-4.76)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, race, GFR, principal diagnosis, Charlson comorbidity score, CAD, CHF, PVD, stroke, DM, COPD, cirrhosis, use of ACEI/ARB, diuretics and potassium supplements

CVD = cardiovascular disease
Traditional Treatment Options for Hyperkalemia
Traditional Treatment Options for Hyperkalemia

- Insulin
- Calcium gluconate salt
- β-andrenoreceptor agonists
- Diuretics
- Sodium bicarbonate
- Dialysis
- Sodium polystyrene sulfonate (SPS)
- RAASi reduction
- Dialysis
- Low K+ diet
- Membrane stabilization
- K+ redistribution
- K+ elimination
- Removal/reduction of drugs that ↑ serum K+

Thera

Emergent
Intermediate
Maintenance

Acute management

RAASi: renin-angiotensin-aldosterone system inhibitor, SPS: sodium polystyrene sulfonate

Standard Care of CHRONIC Hyperkalemia

- Review medication history
- Titrate or discontinue RAAS inhibitors
- Diuretic therapy
- Potassium binder therapy

Modifiable Risk Factors for Hyperkalemia in Patients on RAAS

• Reduce potassium intake:
  – Low potassium diet
  – Avoid potassium supplements, including salt substitutes and certain herbs

• Avoid Drugs That Concomitantly Interfere With Renal K+ Excretion:
  – Nonsteroidal antiinflammatory drugs
  – Beta-blockers
  – Calcineurin inhibitors: cyclosporine, tacrolimus
  – Heparin
  – Ketoconazole
  – Potassium-sparing diuretics: spironolactone, eplerenone, amiloride, triamterene
  – Trimethoprim
  – Pentamidine

## Medications Associated With Hyperkalemia

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>Inhibit conversion of angiotensin I to angiotensin II</td>
<td>Captopril, lisinopril, etc.</td>
</tr>
<tr>
<td>ARB</td>
<td>Inhibit activation of angiotensin I receptor by angiotensin II</td>
<td>Losartan, irbesartan, etc.</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>Block aldosterone receptor activation</td>
<td>Spironolactone, eplerenone</td>
</tr>
<tr>
<td>β-Adrenergic receptor blocker</td>
<td>Inhibit renin release</td>
<td>Propranolol, metoprolol, atenolol</td>
</tr>
<tr>
<td>Digitalis glycoside</td>
<td>Inhibit Na⁺-K⁺-ATPase; necessary for K⁺ secretion</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Heparin</td>
<td>Reduces production of aldosterone</td>
<td>Heparin sodium</td>
</tr>
<tr>
<td>K⁺-sparing diuretic</td>
<td>Block collecting duct apical Na⁺ channel, decreasing gradient for K⁺ secretion</td>
<td>Amiloride, triamterene</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Inhibit synthesis of prostaglandin E and prostacyclin, inhibiting renin release</td>
<td>Ibuprofen</td>
</tr>
<tr>
<td>Other</td>
<td>Block collecting duct apical Na⁺ channel, decreasing gradient for K⁺ secretion</td>
<td>Trimethoprim, pentamidine</td>
</tr>
</tbody>
</table>
Limitations of Diuretic Therapy

• Diuretic therapy is commonly used to treat hyperkalemia but has limited effectiveness in patients with advanced CKD

• Diuretic-induced kaliuresis is dependent on kidney function, adequate extracellular volume, and delivery of sodium to the cortical collecting tubule, all of which may be impaired in patients with advanced renal insufficiency and/or heart failure

• Syncope, orthostatic hypotension, gout, ototoxicity, and increasing azotemia secondary to volume depletion can limit the use of diuretics, especially in high doses or as combination strategies

• Please consult the reference list in the source article, Weir et al, for background information in the literature.
Do not use fludrocortisone!

• Volume overload
• Toxin for myocardium, kidney and vascular beds
Low Potassium Diet
K⁺ Quiz
Dairy Products

Ice cream  Yoghurt  Cheddar
Advising Your Patient About K⁺ Intake

1. None of these are high in potassium
2. Yoghurt > Ice cream > Cheddar
3. Ice cream > Yoghurt > Cheddar
4. Cheddar > Ice cream > Yoghurt
5. Ice cream > Cheddar > Yoghurt
# Dairy Products

<table>
<thead>
<tr>
<th>Food</th>
<th>Per Serving</th>
<th>mEqs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheddar cheese</td>
<td>1.5 oz.</td>
<td>1.1</td>
</tr>
<tr>
<td>Cottage cheese</td>
<td>1/2 cup</td>
<td>2.4</td>
</tr>
<tr>
<td>Ice cream, hard</td>
<td>1/2 cup</td>
<td>3.2</td>
</tr>
<tr>
<td>Milk, low fat 2%</td>
<td>1 cup</td>
<td>10.6</td>
</tr>
<tr>
<td>Yoghurt, plain, low fat</td>
<td>1 cup</td>
<td>13.6</td>
</tr>
</tbody>
</table>
Advising Your Patient About K⁺ Intake

1. None of these are high in potassium
2. Yoghurt > Ice cream > Cheddar
3. Ice cream > Yoghurt > Cheddar
4. Cheddar > Ice cream > Yoghurt
5. Ice cream > Cheddar > Yoghurt
Fresh Fruits

Blueberry
Watermelon
Cantaloupe
Advising Your Patient About K⁺ Intake

1. All of these are high in potassium
2. Blueberries > Cantaloupe > Watermelon
3. Cantaloupe > Watermelon > Blueberries
4. Watermelon > Cantaloupe > Blueberries
5. Cantaloupe > Blueberries > Watermelon
## Fresh Fruits

<table>
<thead>
<tr>
<th>FRUIT</th>
<th>Serving</th>
<th>K(mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blueberries, raw</td>
<td>1/2 cup</td>
<td>1.7</td>
</tr>
<tr>
<td>Grapes</td>
<td>10</td>
<td>2.4</td>
</tr>
<tr>
<td>Pineapple, raw</td>
<td>1/2 cup</td>
<td>2.9</td>
</tr>
<tr>
<td>Plum</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Strawberries</td>
<td>1/2 cup</td>
<td>3.2</td>
</tr>
<tr>
<td>Cherries, sweet, raw</td>
<td>10</td>
<td>3.9</td>
</tr>
<tr>
<td>Apple</td>
<td>1 medium</td>
<td>4.1</td>
</tr>
<tr>
<td>Peach</td>
<td>1</td>
<td>4.4</td>
</tr>
<tr>
<td>Peaches, canned</td>
<td>1/2 cup</td>
<td>4.1</td>
</tr>
<tr>
<td>Pear</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Orange</td>
<td>1</td>
<td>6.1</td>
</tr>
<tr>
<td>Banana</td>
<td>1 medium</td>
<td>11.6</td>
</tr>
<tr>
<td>Raisins</td>
<td>1/4 cup</td>
<td>14.2</td>
</tr>
<tr>
<td>Watermelon</td>
<td>1/8</td>
<td>14.4</td>
</tr>
<tr>
<td>Avocado</td>
<td>1/2</td>
<td>15.4</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>1/2</td>
<td>21.2</td>
</tr>
<tr>
<td>Cantaloupe</td>
<td>1/2</td>
<td>21.2</td>
</tr>
</tbody>
</table>
Advising Your Patient About K\(^+\) Intake

1. All of these are high in potassium
2. Blueberries > Cantaloupe > Watermelon
3. Cantaloupe > Watermelon > Blueberries
4. Watermelon > Cantaloupe > Blueberries
5. Cantaloupe > Blueberries > Watermelon
Vegetables

- Butternut squash
- Brussels sprouts
- Spinach
- Ice cream
- Yoghurt
Advising Your Patient About K+ Intake

1. All of these are unacceptably high in potassium
2. Butternut squash > Brussels sprouts > Spinach
3. Brussels sprouts > Butternut squash > Spinach
4. Spinach > Brussels sprouts > Butternut squash
5. They all taste dreadful
<table>
<thead>
<tr>
<th>Vegetable</th>
<th>Serving</th>
<th>K(mEq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lettuce, iceberg</td>
<td>1 cup</td>
<td>2.5</td>
</tr>
<tr>
<td>Celery, raw</td>
<td>1 stalk</td>
<td>3.5</td>
</tr>
<tr>
<td>Lettuce, romaine</td>
<td>1 cup</td>
<td>3.7</td>
</tr>
<tr>
<td>Corn, cooked</td>
<td>1 ear</td>
<td>3.9</td>
</tr>
<tr>
<td>Radishes</td>
<td>1/2 cup</td>
<td>4.7</td>
</tr>
<tr>
<td>Green beans, cooked</td>
<td>1 cup</td>
<td>4.9</td>
</tr>
<tr>
<td>Coleslaw</td>
<td>1 cup</td>
<td>6.1</td>
</tr>
<tr>
<td>Cabbage, red, raw,</td>
<td>1 cup</td>
<td>6.2</td>
</tr>
<tr>
<td>Cauliflower, cooked</td>
<td>1 cup</td>
<td>6.2</td>
</tr>
<tr>
<td>Carrot, raw</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>Spinach, raw</td>
<td>1 cup</td>
<td>6.6</td>
</tr>
<tr>
<td>Okra, cooked</td>
<td>1 cup</td>
<td>6.9</td>
</tr>
<tr>
<td>Tomato</td>
<td>1 medium</td>
<td>7.7</td>
</tr>
<tr>
<td>Eggplant, cooked, diced</td>
<td>1 cup</td>
<td>7.7</td>
</tr>
<tr>
<td>Peas, cooked</td>
<td>1 cup</td>
<td>8.1</td>
</tr>
<tr>
<td>Sweet potatoes, baked</td>
<td>1</td>
<td>8.8</td>
</tr>
<tr>
<td>Green pepper</td>
<td>1</td>
<td>8.9</td>
</tr>
<tr>
<td>Lima beans, cooked</td>
<td>1 cup</td>
<td>9.6</td>
</tr>
<tr>
<td>Mushrooms, sliced, raw</td>
<td>1 cup</td>
<td>10.0</td>
</tr>
<tr>
<td>Broccoli, cooked</td>
<td>1 cup</td>
<td>10.6</td>
</tr>
<tr>
<td>Turnips, boiled, mashed</td>
<td>1 cup</td>
<td>11.1</td>
</tr>
<tr>
<td>Beet greens, cooked</td>
<td>1 cup</td>
<td>12.3</td>
</tr>
<tr>
<td>Collards</td>
<td>1 cup</td>
<td>12.8</td>
</tr>
<tr>
<td>Zucchini, cooked, sliced</td>
<td>1 cup</td>
<td>13.0</td>
</tr>
<tr>
<td>Potato, baked</td>
<td>1 long</td>
<td>20.1</td>
</tr>
<tr>
<td>Brussels sprouts, cooked</td>
<td>1 cup</td>
<td>21.7</td>
</tr>
<tr>
<td>Squash, acorn, baked</td>
<td>1 cup</td>
<td>25.2</td>
</tr>
<tr>
<td>Spinach, cooked</td>
<td>1 cup</td>
<td>29.9</td>
</tr>
<tr>
<td>Squash, butternut, baked</td>
<td>1 cup</td>
<td>32.0</td>
</tr>
</tbody>
</table>
Advising Your Patient About K⁺ Intake

1. All of these are unacceptably high in potassium.
2. Butternut squash > Brussels sprouts > Spinach.
4. Spinach > Brussels sprouts > Butternut squash.
5. They all taste dreadful.
Adherence to a low potassium diet is suboptimal

Many patients are already on low carb and low salt diets
What’s left to eat?

Track fluid intake  Avoid alcohol  Limit caffeine  protein in severe

Down Titration of RAASi: Consequences
RAASi Use Falls From 43%–47% 8 Quarters Before ESRD to 33%–37% in the Quarter Following Initiation of ESRD

ACEI/ARB/renin inhibitor use in Part D enrollees in the transition to ESRD, 2011

ICD-9-CM codes

585.1 Chronic kidney disease, Stage 1
585.2 Chronic kidney disease, Stage 2 (mild)
585.3 Chronic kidney disease, Stage 3 (moderate)
585.4 Chronic kidney disease, Stage 4 (severe)
585.5 Chronic kidney disease, Stage 5 (excludes 585.6: Stage 5, requiring chronic dialysis.)*

Chronic kidney disease, unknown/unspecified

*In USRDS analyses, patients with ICD-9-CM code 585.6 & with no ESRD 2728 form or other indication of ESRD are considered to have code 585.5; see Appendix A for details.

CKD stage estimates are from a single measurement. For clinical case definition, abnormalities should be present ≥ 3 months.
Hyperkalemia Is a Leading Reason for Not Starting RAAS and the Major Reason for Discontinuation of RAAS in CKD Patients

• 279 CKD patients
• Baseline mean GFR was 33.3 mL/min/1.73 m² and the serum K⁺ was 4.73 mEq/L

Hyperkalemia Is a Leading Reason for Not Starting RAAS and the Major Reason for Discontinuation of RAAS in CKD Patients

Patients (%)

HD panel

Hyperkalemia
Acute renal injury
Renal artery stenosis
Hypotension
Very low GFR
Unknown/other

Reason for Not Starting RAAS
Discontinuation of RAAS at Any Time

(80 patients)
(51 patients)

13.8
66.6

CKD: chronic kidney disease; GFR: glomerular filtration rate; RAAS: renin-angiotensin-aldosterone system inhibitor.
Lower Doses of ACEi/ARB Have Not Been Shown to Be Effective in Slowing CKD Progression

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>N</th>
<th>OUTCOME (vs placebo)</th>
</tr>
</thead>
</table>
| RENAAL¹ | 1,513 | **Losartan 100 mg (71% of patients)**  
25% ↓RR doubling of serum creatinine  
28% ↓RR in progression to ESRD  |
|         |    | T2DM with hypertension  
+ macroalbuminuria  
+ mean eGFR: 41mL/min/1.73 m² |
| IDNT²   | 1,715 | **Irbesartan 300 mg**  
33% ↓RR doubling of SC  
23% ↓RR in progression to ESRD  |
|         |    | T2DM with hypertension  
+ macroalbuminuria  
+ mean eGFR: 50mL/min/1.73 m² |
| IRMA 2³ | 590  | **Irbesartan 300 mg**  
70 % ↓RR of progression to macroalbuminuria  
**Irbesartan 150 mg**  
No statistically significant effect in ↓RR of progression to macroalbuminuria (p=0.08)  |
|         |    | T2DM with hypertension  
+ microalbuminuria (20-200 µg/min UAE rate)  
+ <1.5 mg/dL serum creatinine |

ACEi: angiotensin-converting enzyme inhibitor(s); ARB: angiotensin II receptor blocker(s); CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; RR: relative risk; T2DM: type 2 diabetes mellitus; UAE: urinary albumin excretion.

Percent Mortality by Prior RAASi Dose

Potassium Binders: Therapeutic Facilitators?
Increased Potassium Secretion by the Colon During Decreased Renal Function

- The capacity of the colon for $K^+$ secretion adapts in ESRD
  - Enhanced active $K^+$ secretion
  - Increased apical membrane $K^+$ permeability
  - Most likely due to greater levels of BK channel protein expression

Apical BK channel expression with immunostaining in ESRD vs normal kidney function ($P<0.001$)

Visual Analogue Score

# Kayexalate: Highlights of USPI

<table>
<thead>
<tr>
<th>Indication / Approval</th>
<th>Kayexalate is indicated for the treatment of hyperkalemia / 1958</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limitation of Use:</td>
<td>KAYEXALATE should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>The effective lowering of serum potassium with KAYEXALATE may take hours to days.</td>
</tr>
<tr>
<td>Warning</td>
<td><strong>Binding to Other Orally Administered Medications:</strong> KAYEXALATE may bind orally administered medications, which could decrease their gastrointestinal absorption and lead to reduced efficacy. Administer other oral medications at least 3 hours before or 3 hours after KAYEXALATE. Patients with gastroparesis may require a 6 hour separation.</td>
</tr>
<tr>
<td>Dosing and Administration</td>
<td><strong>General Information:</strong> Administer KAYEXALATE at least 3 hours before or 3 hours after other oral medications. Patients with gastroparesis may require a 6 hour separation</td>
</tr>
</tbody>
</table>

SPS: sodium polystyrene sulfonate.
Randomized Study of Sodium Polystyrene Sulfonate: Safety Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>SPS (n=16)</th>
<th>Placebo (n=16)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (%)</td>
<td>25.0%</td>
<td>12.5%</td>
<td>0.65</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>12.5%</td>
<td>6.3%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>37.5%</td>
<td>25.0%</td>
<td>0.70</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>25.0%</td>
<td>50.0%</td>
<td>0.27</td>
</tr>
<tr>
<td>Electrolyte Disturbances:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia (&lt;3.5 mEq/L)</td>
<td>18.8%</td>
<td>0%</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypocalcemia (&lt;8.48 mg/dL)</td>
<td>18.8%</td>
<td>0%</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypomagnesemia (&lt;1.4 mEq/L)</td>
<td>31.2%</td>
<td>6.3%</td>
<td>0.17</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>75%</td>
<td>58.8%</td>
<td>0.47</td>
</tr>
</tbody>
</table>

“Use >7 days was not evaluated; therefore, interpretation of these results in the context of chronic use over several weeks should be done with caution.”

Patiromer Is a Novel, Nonabsorbed $K^+$ Binder

- Patiromer is a novel, spherical, nonabsorbed polymer
  - High-capacity $K^+$ binder
  - Average bead size (100 μM) is too large for patiromer to be absorbed from the GI tract, enabling patiromer to be passed through the entire GI tract and absorb more $K^+$
  - Uniform sphere shape, size, and low-swelling beads ratio

GI: gastrointestinal; $K^+$: potassium.
Part A: Treatment Phase (Single-Blind)

- Mild HK
  - Baseline Serum K⁺ 5.1-<5.5 mEq/L;
  - 4.2g BID starting dose (N=92)

- Moderate to Severe HK
  - Baseline Serum K⁺ 5.5-<6.5 mEq/L;
  - 8.4g BID starting dose (N=151)

Baseline Part A Week 4 Part B Sec. Endpoints

Part B: Randomized Withdrawal Phase (Single-Blind)

Subjects with part A baseline K⁺ 5.5 to < 6.5 and who completed part A and:
- Serum K⁺ 3.8-<5.1 mEq/L Part A week 4
  - Still on Patiromer
  - Still on RAAS therapy (n=107)

- Patiromer, continued RAAS (n=55)
- Placebo, continued RAAS (n=52)

Baseline Part B Week 4 Part B Primary Endpoint

* eGFR 15-60 ml/min/m²;

Sec.: secondary

Estimated Mean (95% CI) of Central Serum Potassium (mEq/L) Over Time

- Baseline Serum K+ 5.1 to <5.5 mEq/L
- Baseline Serum K+ 5.5 to <6.5 mEq/L
- Total

Study Visit:
- Baseline Day 3
- Week 1
- Week 2
- Week 3
- Week 4

OPAL-HK: Part B

Randomized, Placebo-Controlled Withdrawal Phase (Part B): Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=52)</th>
<th>Veltassa (n=55)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Median Change</td>
<td>0.72</td>
<td>0.00</td>
<td>0.72 (0.46, 0.99)</td>
</tr>
<tr>
<td>in Serum Potassium from</td>
<td></td>
<td></td>
<td>p-value &lt;0.001</td>
</tr>
<tr>
<td>Baseline (mEq/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- More placebo patients (91%; 95% CI: 83%, 99%) developed a serum potassium ≥5.1 mEq/L at any time during Part B than Veltassa patients (43%; 95% CI: 30%, 56%), $p<0.001$. More placebo patients (60%; 95% CI: 47%, 74%) developed a serum potassium ≥5.5 mEq/L at any time during Part B than Veltassa patients (15%; 95% CI: 6%, 24%), $p<0.001$. 

OPAL-HK Part B: Exploratory Endpoints

It is possible to transit to death from all states.
### Base case results (discounted), CKD stage 3-4 with HK on RAASi

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>QALYs</th>
<th>LYGs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patiromer</td>
<td>£84,281</td>
<td>5.80</td>
<td>7.60</td>
</tr>
<tr>
<td>No Patiromer</td>
<td>£80,160</td>
<td>5.58</td>
<td>7.34</td>
</tr>
<tr>
<td>Incremental</td>
<td>£4,121</td>
<td>0.22</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>ICER</strong></td>
<td></td>
<td><strong>£18,807 per QALY gained</strong></td>
<td><strong>£15,486 per LYG gained</strong></td>
</tr>
</tbody>
</table>

Tornado Diagram

Incremental cost-effectiveness ratio (ICER)

£0 £20,000 £40,000 £60,000

RR CKD to CKD progression - RAASI
Cost of CKD progression (ESRD)
Discount rate - costs
RR CKD to death (non-CV) - RAASI (all cause...)
Discount rate - utilities
HR for mortality with CKD 4 vs CKD 3
RR CKD progression to death - RAASI
Costs ESRD - Haemodialysis (HD) per patient month
Costs ESRD - ongoing post kidney transplant per...
% ESRD - haemodialysis (HD)
RR CKD to CV event (MI/stroke) - RAASI
prob CKD to CKD progression - no RAASI
% CV event - MI
Cost of CKD management

Lower range
Upper range

Sutherland, C. S. et al.
2017. A490. Abstract
AMETHYST-DN (Phase 2 One-Year Study):
Mean (95% CI) Serum Potassium over Time

The effect of treatment with patiromer for up to 52 weeks was evaluated in an open-label study of 304 hyperkalemic patients with CKD and type 2 diabetes mellitus on RAAS inhibitor therapy.
ADVERSE REACTIONS

Clinical Trials Experience (cont’d)

• Table 1 provides a summary of the most common adverse reactions (occurring in ≥2% of patients) in patients treated with patiromer in these clinical trials. Most adverse reactions were mild to moderate. Constipation generally resolved during the course of treatment.

### Adverse Reactions Reported in ≥2% of Patients

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Patients treated with Veltassa (N=666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>7.2%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>5.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2.0%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

Figure 1. ZS-9: A Novel Selective Potassium Trap

ZS-9 Crystal Structure

ZS-9 PROPERTIES

- Unique microporous zirconium silicate compound
- Designed to be selective for K⁺
- Builds on long history of Zr use in dialysis and other biomedical applications
- Insoluble and highly stable
- Non-systemically absorbed
- ZS-9 has 9.3 times more K⁺ binding capacity than Kayexalate® (SPS)
- ZS-9 is >125 times more selective for K⁺ than Kayexalate
- Kayexalate is more selective for Ca²⁺ than K⁺

Average Width of Micropore Opening 3Å
HARMONIZE TRIAL

- Multicenter, randomized, double-blind, placebo-controlled trial evaluating zirconium cyclosilicate (ZS-9) 3 times daily in an initial 48 hour open label phase (n=258)
- Patients (n=237) achieving normokalemia (3.5-5.0 meq/l) were randomized to once daily ZS-9, 5g (n=45), 10g (n=51) or 15g (n=56), or placebo (n=85) daily for 28 days.

Study Design

48-Hour Open Label Phase
- OPEN-LABEL
  - ZS DOSE
    - ZS 10g TID

Patients who achieve normokalemia (K+ = 3.5 to 5.0 mEq/L) proceed to Randomized Phase

28 Day Randomized Phase
- DOUBLE-BLIND, RANDOMIZED
  - STUDY DRUG DOSES
    - Placebo QD
    - ZS 5g QD
    - ZS 10g QD
    - ZS 15g QD

Kosiborod M et.al. JAMA 2014;312 (21):2223-2233.
Study 2 - Mean Serum Potassium Levels in the Acute and Randomized Withdrawal Phases

- Average sK+ levels decreased from 5.6 to 4.5 mEq/L during treatment in acute phase.
- Following the acute phase of the study, there was a DB randomized withdrawal phase where patients who achieved K+ levels between 3.5 and 5 mEq/L were randomized to 1 of 3 doses of LOKELMA administered QD for 28 days, or placebo just before breakfast.
Sodium Zirconium Cyclosilicate among Individuals with Hyperkalemia
A 12-Month Phase 3 Study

• Of 751 participants, 746 (99%) achieved normokalemia during the correction phase (mean serum potassium (4.8 mmol/L) and entered the maintenance phase; 466 (63%) participants completed the 12-month trial. Participants were predominantly white, men, and age ≥65 years old; 74% had an eGFR<60 ml/min per 1.73 m2

• 65% used renin-angiotensin-aldosterone system inhibitors.

• Mean daily sodium zirconium cyclosilicate dose was 7.2 g

• Mean serum potassium was 4.7 mmol/L (95% confidence interval, 4.6 to 4.7); mean serum potassium values ≤5.1 and ≤5.5 mmol/L were achieved by 88% and 99% of participants, respectively.

• Among 263 renin-angiotensin-aldosterone system inhibitor–naïve participants, 14% initiated renin-angiotensin-aldosterone system inhibitor therapy.

Spinowitz, BS, et al. CJASN June 2019, 14 (6) 798-809.
Proportion of participants who achieved a potassium (K+) value of (A) 3.5–5.0, (B) 3.5–5.5, or (C) >5.0 mmol/L by i-STAT and serum K+ during the correction phase (CP)

Bruce S. Spinowitz et al. CJASN 2019;14:798-809
Mean Serum Potassium Over Time in ITT Population

Correction Phase

Maintenance Phase

Mean (95% CI) Serum K+ (mmol/L)

Time (days)

24–72 hours

Bruce S. Spinowitz et al. CJASN 2019;14:798-809
Adverse events and deaths in the maintenance-phase safety population

<table>
<thead>
<tr>
<th>MedDRA Preferred Term, n (%)</th>
<th>Maintenance Phase, n=746</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events (≥5% of participants)</td>
<td>489 (66)</td>
</tr>
<tr>
<td>Anemia</td>
<td>44 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>48 (6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>56 (8)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>72 (10)</td>
</tr>
<tr>
<td>SMQ edema</td>
<td>113 (15)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>37 (5)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>59 (8)</td>
</tr>
</tbody>
</table>

- Spinowitz BS et al. CJASN June 2019, 14 (6) 798-809.
Summary

• Recognition:
  • Hyperkalemia rates are high in real-world CKD populations
  • Elevated serum potassium is associated with increased mortality in non-dialysis and dialysis CKD populations

• Management:
  • Long-term strategies to minimize the risk of hyperkalemia, including dietary restrictions or reduction of RAAS therapy, have significant limitations
  • Down-titration or discontinuation of RAAS therapy is a common consequence of hyperkalemia

• Treatment:
  • Sodium polystyrene sulfonate has been approved by FDA since 1958
  • Patiromer and SZC are newer agents with well described safety and tolerability profiles