Managing Chronic Hyperkalemia in Renal Disease: New Tools

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Disclosure

Speaker name: Prof. Bernard Canaud

☐ I have the following potential conflicts of interest to report:

☐ Consulting

☒ Employment in industry (FMC)

☐ Shareholder in a healthcare company

☐ Owner of a healthcare company

☐ Other(s)

☐ I do not have any potential conflict of interest
Outline of the Presentation

1. Chronic hyperkalemia: a common and serious problem in CKD patients
   - Patients at risk
   - Risks and complications

2. Chronic hyperkalemia: indirect consequences – clinical concerns
   - Limit usage of medications protecting kidney and cardiovascular system

3. Monitoring of chronic hyperkalemia: pitfalls and errors

4. Managing chronic hyperkalemia in CKD patients
   - Traditional ways
   - New tools

5. Take home message
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5. Take home message
Distribution of Serum K in Diabetic and Non-Diabetic Patients

Nested case–control study in outpatient renal clinic
360 CKD patients: 180 T2 diabetics/180 non-diabetics

Prevalence of Hyperkalemia in Diabetic and Non-Diabetic Patients

Nested case–control study in outpatient renal clinic
360 CKD patients: 180 T2 diabetics/180 non-diabetics

Prevalence of Hyperkalemia in Diabetic and Non-Diabetic Patients According to CKD Stage

Nested case–control study in outpatient renal clinic
360 CKD patients: 180 T2 diabetics/180 non-diabetics

Patients at Risk of Hyperkalemia

- Chronic kidney disease (GFR<30ml/min)
- Distal Tubular Acidosis (type IV) with hyperkalemia
- Acute kidney injury
- Cardiac failure (Cardio-Renal syndrome)
- Diabetics (Diabetic nephropathy, Degenerative)
- Elderly
- Combined pathologies
- Patients receiving drugs that modulate renal elimination of potassium
  - Reducing production of angiotensin II (angiotensin-converting enzyme inhibitors, direct renin inhibitors, β-adrenergic receptor antagonists)
  - Blocking angiotensin II receptors (angiotensin receptor blocker blockers)
  - Antagonizing action of aldosterone on mineralocorticoid receptors (mineralocorticoid receptor blocker blockers)
K is a Serial Killer in Chronic Kidney Disease Patients
Hyperkalemia

**Acute Hyperkalemia**
- Imminent risk of death
- Emergency action required

**Chronic Hyperkalemia**
- Delayed risk of death
- Long-term action required
Typical Case of Severe Hyperkalemia
Almost lethal...

A 62-year old man with chronic renal insufficiency reported having reduced exercise tolerance for the previous week...

Serum Potassium was 9.1mmol/l
Serum Potassium was 3.1mmol/l

IV Calcium Chloride
IV Sodium Bicarbonate
Glucose + Insulin therapy and Hemodialysis
Cardiotoxicity of Hyperkalemia

Action potential of myocardial contractile cell

Depolarization: sodium influx
Rapid depolarization: potassium efflux
Plateau: calcium influx
Repolarization: potassium efflux
Hyperkalemia*

Potassium Gauge Meter

Hyperkalemia

* Normal pH, Normal AB status
Long Interdialytic Interval Increases Mortality Risk in HD Patients

Annualized Mortality Rate

Annualized CVD Admission Rate

Relative risk of mortality (all-cause) by day

US
Europe
Japan

22,163 HD patients DOPPS US, Europe, Japan

32,065 HD Patients - USA
End-Stage Renal Disease Clinical Performance Measures Project


Cause of Death in Prevalent Dialysis Patients in the United States, 2005 to 2007

Saravanan P et al, Circ Arrhythm Electrophysiol. 2010;3:553-559
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5. Take home message
Potassium Balance in Normal Subject
Potassium Homeostasis – Zero Balance

<table>
<thead>
<tr>
<th>Dietary Intake</th>
<th>100 mM/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary Output</td>
<td>92 mM/day</td>
</tr>
<tr>
<td>Stool Output</td>
<td>8 mM/day</td>
</tr>
<tr>
<td>Normal Plasma [K+]</td>
<td>3.5 - 4.5 mM/L</td>
</tr>
<tr>
<td>ECF K+</td>
<td>65mM (1-2%)</td>
</tr>
<tr>
<td>ICF K+</td>
<td>3500 mmol (98-99%)</td>
</tr>
</tbody>
</table>
Potassium Balance in CKD5D Patient
No More Potassium Homeostasis – Positive Balance

Dietary Intake
100 mM/day

Plasma [K+]
3.5 – 6.0 mM/L

Stool Output
8 mM/day

Urinary + Dialysis Output
80 mM/48hr

ICF K+
3500 mmol (98-99%)

ECF K+
65 mM (1-2%)

Potassium Gauge Meter
Transcellular Shifts of Potassium

Acidosis

\[ \text{ECF} \rightarrow \text{ICF} \rightarrow \text{ECF} \]

\[ H^+ \rightarrow K^+ \rightarrow \text{Mg}^{++} \rightarrow \text{Ca}^{++} \]

Alkalosis

\[ \text{ECF} \rightarrow \text{ICF} \rightarrow \text{ECF} \]

\[ H^+ \rightarrow K^+ \rightarrow \text{Mg}^{++} \rightarrow \text{Ca}^{++} \]
Conditions Reducing Potassium Excretion Increase Risk of Hyperkalemia

Potassium in diet

RAAS Inhibition
Aldosterone Antagonist

K absorption from small intestine

↓ GFR

AKI-CKD

CRS

↓ GFR

Diabetes

Reduced K excretion

HD

DM
Indirect Consequences of Hyperkalemia

Limit usage of protective medications

Renin Angiotensin Aldosterone System (RAAS)
Aldosterone Blockade (AB)

Antihypertensive
Nephroprotection
Cardioprotection
Vasculoprotection
Neuroprotection
Antiproteinuric
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   - Traditional ways
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5. Take home message
Phlebotomy and Blood Collection May Affect Hyperkalemia
# Hyperkalemia and ECG

<table>
<thead>
<tr>
<th>Approximate Serum $[K^+]$ (mEq/L)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–5</td>
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<tr>
<td>6–7</td>
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<td>8</td>
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<td>9</td>
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<td>10</td>
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</tr>
</tbody>
</table>

T wave tenting
CRISIS (Chronic Renal Insufficiency Standards Implementation Study)

Prospective epidemiological study of outcomes in chronic kidney disease (CKD).

376 CKD patients were eligible for the study

163 had ECG + serum potassium measurement

19 patients were excluded
(complete left or right bundle branch block or a ventricular paced ECG rhythm)

145 included in the final study cohort

Variation in the Relationship Between Serum K and the Amplitude of the Tallest T:R Wave

T:R Ratio of the amplitude of the tallest precordial T-wave and R-wave

T Wave Tenting Common but Not Predictive
T:R Less Sensitive but More Specific

• **Tenting** was as common in normal range serum potassium as hyperkalemia (33 versus 31%) and less common than in left ventricular hypertrophy (44%)

• **T:R** was less sensitive (24 versus 33%) but more specific (85 versus 67%) than tenting at correctly identifying hyperkalemia ≥6.0 mmol/L.
Cardiovascular and Sudden Death Risk As Estimated from T-Wave to R-Wave Ratio

Cardiovascular event-free survival

Cumulative event-free survival for sudden death

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Managing Chronic Hyperkalemia

Traditional Tools

You can lower the amount of Potassium in potatoes and sweet potatoes by 1/3 by double boiling them.

1. Wash and peel the potato
2. Cut into thin slices
3. Place in a large pot with water (at least double the amount)
4. Bring water to a boil
5. Drain water.
6. Add water (at least double the amount)
7. Bring water to a boil again and cook until soft.
Increase Urine Excretion with Loop Diuretics

- *Bumetanide*
- Ethacrynic acid (Edecrin)
- Furosemide (Lasix)
- Torsemide (Demadex)

Loop Diuretics*
Thick Ascending Loop of Henle

* Bumetanide
Ethacrynic acid (Edecrin)
Furosemide (Lasix)
Torsemide (Demadex)
Correct Acidosis & Facilitate K Transfer
Sodium Bicarbonate Supplementation
Increase K Excretion in Feces
Resin Binding Potassium in Colon

Potassium in diet

RAAS Inhibition
Aldosterone Antagonist

↓ GFR

Diabetes

K absorption from small intestine

Cation resin exchange binds K in colon

Increased K excretion

Reduced K excretion
Restore K Mass Balance in CKD5 HD Patient
Hemodialysis
## Resin Binding Potassium in the Intestine: Old

<table>
<thead>
<tr>
<th>Sodium Polystyrene Sulfonate</th>
<th>Calcium Polystyrene Sulphonate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kayexalate</strong></td>
<td><strong>Sorbisterit</strong></td>
</tr>
<tr>
<td>• Organic enteral <em>potassium-sodium</em> exchange resin</td>
<td>Available in Europe</td>
</tr>
<tr>
<td>• Non-selectively binds potassium and other cations (calcium &amp; magnesium)</td>
<td>• Organic enteral <em>potassium-calcium</em> exchange resin</td>
</tr>
<tr>
<td>• Approved by the US FDA in 1958</td>
<td>• Non-selectively binds potassium and other cations (calcium &amp; magnesium)</td>
</tr>
<tr>
<td>• Commonly given with Sorbitol</td>
<td>• Commonly given with Sorbitol</td>
</tr>
<tr>
<td>• Diarrhea upregulates luminal losses of potassium</td>
<td>• Diarrhea upregulates luminal losses of potassium</td>
</tr>
<tr>
<td>• Uncomfortable</td>
<td>• Uncomfortable</td>
</tr>
<tr>
<td>• Side effects</td>
<td>• Side effects</td>
</tr>
<tr>
<td>• Sodium load</td>
<td>• ECF volume depletion</td>
</tr>
<tr>
<td>• ECF volume depletion</td>
<td>• Pain, Electrolyte imbalance</td>
</tr>
<tr>
<td>• Pain, Electrolyte imbalance</td>
<td>• Diarrhea...</td>
</tr>
<tr>
<td>• Occlusion...</td>
<td></td>
</tr>
</tbody>
</table>
Potassium Exchange Resin

K⁺ being exchanged for Ca²⁺

Sodium Polystyrene Sulfonate

K⁺ being exchanged for Na⁺

Calcium Polystyrene Sulphonate
## Clinical Studies Using Sodium Polystyrene Sulfate (Kayexalate) to Reduce Serum K Levels

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Trial</th>
<th>Study Design</th>
<th>Participants</th>
<th>Endpoints</th>
<th>Baseline</th>
<th>SPS Therapy vs Placebo and Reduction of K (&lt; 96 h)</th>
<th>SPS Therapy vs Placebo and Reduction of K (&gt; 96 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kessler C et al(^1)</td>
<td>Retrospective cohort study</td>
<td>Single dose (low, mid, and high) of SPS</td>
<td>HTN, DM, CKD, HF, ARF patients with hyperkalemia (K &gt; 5.1 mEq/L) (n = 122)</td>
<td>Mean change in K after SPS treatment</td>
<td>K 5.4 mEq/L (15 g) K 5.5 mEq/L (30 g) K 5.8 mEq/L (45 g) K 5.9 mEq/L (60 g)</td>
<td>Not placebo controlled</td>
<td>NR</td>
</tr>
<tr>
<td>Thompson K et al(^2)</td>
<td>Retrospective cohort study</td>
<td>Pretreated formula or expressed breast milk with SPS before patient use</td>
<td>CKD, AKI patients (&lt; 2 y) with hyperkalemia (K &gt; 5.5 mEq/L) (n = 13)</td>
<td>Mean change in K after SPS treatment in 48 h</td>
<td>K 6.34 mEq/L</td>
<td>Not placebo controlled</td>
<td>NR</td>
</tr>
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New and Emerging Potassium Binders

- 2 new potassium binders
  - Patiromer
    - Approved by the US FDA for treatment of hyperkalemia on 10/21/2015\(^a\)
    - Mechanism of action: nonabsorbed cation exchange polymer that binds potassium in exchange for calcium predominantly in the distal colon and increases fecal potassium excretion\(^b\)
  - ZS-9*
    - Emerging agent
    - Mechanism of action: inorganic cation exchanger with a crystalline structure that entraps potassium along the entire length of the GI tract\(^c\)

*The US FDA has not yet approved this agent for use.

### Patiromer Sorbitex Calcium

**patiromer; RLY5016; Relypsa Inc., Redwood City, CA**

- A novel potassium exchange polymer
- Powder, dry, odorless for suspension in water
- Consists of spherical beads with an average diameter of 100 μm
- Lower viscosity than polymeric drugs and powder (eg, sodium polystyrene sulfonate)
- Contains sorbitol (29% of weight) and calcium accounts (11%)
  - 2 g of sorbitol + 0.8 g of calcium for every 4.2 g of patiromer
- Patiromer passes through gastrointestinal tract without degradation
- Principal site of action is colon
- Acts approximately 7 hours after ingestion
- Chronic therapy to treat hyperkalemia.
## Sodium Zirconium Cyclosilicate (SZ-9)

<table>
<thead>
<tr>
<th>Sodium Zirconium Cyclosilicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZS-9; ZS Pharma, Inc., Coppell, TX</td>
</tr>
</tbody>
</table>

- A novel potassium exchange crystalline lattice
- ZS-9 is a potassium ion trap that was 3-dimensional structure engineered
  - High affinity to potassium and balanced ratio of exchange ions
- ZS-9 is a highly selective crystalline lattice that preferentially entraps potassium cations over other cations over divalent cations (eg, calcium and magnesium)
- ZS-9 appears to bind ammonium, resulting in net acid loss, systemic reduction in blood urea nitrogen, and elevation in plasma bicarbonate.
- ZS-9 will be available as a tasteless, odorless, insoluble, and non absorbed powder (given with 40-120 mL of water per dose), and potentially a tablet
- It requires no special handling or special preparation and does not have to be given in solution or with cathartics such as sorbitol.
- Several clinical trials have tested ZS-9
Crystal Structure of SZ-9.

Blue spheres = oxygen atoms, red spheres = zirconium atoms, green spheres = silicon atoms.
# Clinical Studies Using Patiromer Sorbitex Calcium to Reduce Serum K Levels

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical Trial</th>
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<th>Patiromer Therapy vs Placebo Reduction of K (&lt; 96 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Securities and Exchange Commission</td>
<td>RY5S016-101</td>
<td>Phase 1, randomized double-blind, placebo-controlled trial</td>
<td>Healthy volunteers, n = 33 (25/8)</td>
<td>Safety and tolerability, urinal and fecal patiromer excretion</td>
<td>No change</td>
<td>Significant dose-dependent increase in fecal potassium excretion and decrease in urinary potassium excretion at doses of 15-60 g/d compared with placebo.</td>
</tr>
<tr>
<td>US Securities and Exchange Commission</td>
<td>RY5S016-102</td>
<td>Phase 1, open-label trial</td>
<td>n = 12 (12/0)</td>
<td>Pharmacological activity, safety</td>
<td>Not placebo controlled</td>
<td>Significant increase in fecal potassium excretion and a concomitant decrease in urinary potassium excretion across the QD/BID/TID dosing regimen.</td>
</tr>
<tr>
<td>US Securities and Exchange Commission</td>
<td>RY5S016-103</td>
<td>Phase 1, single-blind trial</td>
<td>Patients with CKD and hyperkalemia, n = 15 (56/49)</td>
<td>Time to onset of potassium-lowering action</td>
<td>Not placebo controlled</td>
<td>First statistically significant change at 7 h. Mean K did not normalize by 48 h.</td>
</tr>
<tr>
<td>US Securities and Exchange Commission</td>
<td>RY5S016-201</td>
<td>Phase 2, proof-of-concept trial</td>
<td>Patients with hyperkalemia receiving hemodialysis, n = 6 (6/0)</td>
<td>Efficacy/safety of a fixed dose of patiromer</td>
<td>Not placebo controlled</td>
<td>Pharmacological action in reducing serum potassium levels and well-tolerated.</td>
</tr>
<tr>
<td>Pitt B et al.</td>
<td>RY5S016-202</td>
<td>Phase 2, prevention trial</td>
<td>Patients with HF receiving a RAAS inhibitor, ACE inhibitor, or ARB, n = 103 (56/49)</td>
<td>Efficacy/safety in preventing hyperkalemia</td>
<td>K 4.7 mEq/L (n = 55) or placebo (n = 49), BID for 4 wk, patiromer → reduction in K at 24 and 72 h, placebo → increase in K at 24 and 72 h.</td>
<td></td>
</tr>
<tr>
<td>Tamargo J et al.</td>
<td>RY5S016-204</td>
<td>Phase 2, prevention trial</td>
<td>Patients with CKD treated with a RAAS inhibitor, ACE inhibitors, ARB, n = 63 (36/30)</td>
<td>Efficacy/safety of a titration regimen in preventing hyperkalemia</td>
<td>AU</td>
<td>At the end of 8 wk, 91% of patients → 3.5.5 mEq/L; 84% of patients → 4.0.5.1 mEq/L.</td>
</tr>
<tr>
<td>Tamargo J et al.</td>
<td>RY5S016-205</td>
<td>Phase 2b, preventive trial</td>
<td>Hypertension patients with diabetic nephropathy treated with ACE inhibitors and/or ARB, n = 306 (306/0)</td>
<td>Efficacy/safety in treating hyperkalemia, determination of starting dose, and long-term safety in chronic treatment</td>
<td>AU</td>
<td>The primary outcomes were the changes in K from baseline to the end of the study, but results were not published.</td>
</tr>
<tr>
<td>Weir MR et al.</td>
<td>OPAL-HC</td>
<td>A 2-part phase 3 trial</td>
<td>Patients with hyperkalemia, CKD, HF receiving RAAS inhibitor therapy</td>
<td>Patiromer safety of patiromer, Part B: effect of withdrawing patiromer on control of serum potassium levels; mild hyperkalemia, K &lt; 6.5 mEq/L, for moderate-severe hyperkalemia.</td>
<td>AU</td>
<td></td>
</tr>
</tbody>
</table>

Patiromer Effects in CKD Patients Receiving RAAS Inhibitors and Hyperkalemia

Time to First Occurrence of Hyperkalemia after Randomization


![Graph showing time to first occurrence of hyperkalemia after randomization.](image-url)
### Clinical Studies Using Sodium Zirconium Cyclosilicate (ZS-9) to Reduce Serum K Levels

<table>
<thead>
<tr>
<th>Study</th>
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<th>ZS-9 Therapy vs Placebo and Reduction of K (&lt; 96 h)</th>
<th>ZS-9 Therapy vs Placebo and Reduction of K (&gt; 96 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ash SR et al.</td>
<td>ZS002</td>
<td>Phase II trial</td>
<td>Patients with hyperkalemia (K ≥ 6 mEq/L, eGFR (30-60 mL/min/1.73 m²), CKD, on RAAS inhibitor therapy (n = 90)</td>
<td>Rate of change in serum potassium from baseline over 48 h</td>
<td>K 5.6 mEq/L</td>
<td>ZS-9: 0.3, 3, or 10 g, TID for ≥ 2 d; at 3 and 10 g, ZS-9 produced a rapid decrease in K over the first 48 h; at 10 g, mean rate of decline in K was −0.68 mEq/L, and the maximum K was −0.92 mEq/L</td>
<td>None</td>
</tr>
<tr>
<td>Singh B et al.</td>
<td>ZS003</td>
<td>First phase III trial</td>
<td>Patients with hyperkalemia, regardless of etiology (CKD, DM, HF) on RAAS inhibitor therapy (n = 753)</td>
<td>Primary: rate of change in serum potassium from baseline to day 14</td>
<td>Acute phase: K 5.3 mEq/L</td>
<td>48-h induction phase: K*: 3.5-5.0 mEq/L</td>
<td>ZS-9: 5 g (n = 64) → K 4.7 mEq/L</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Secondary: rate of change in serum potassium from 48 h to day 14</td>
<td>Extended phase: ZS-9 10 g (n = 30), K 4.5 mEq/L placebo (n = 30), K 4.5 mEq/L</td>
<td>ZS-9: 10 g (n = 63) → K 4.5 mEq/L Placebo (n = 129) → K 5.0 mEq/L</td>
<td>12-d maintenance phase</td>
</tr>
<tr>
<td>Packham DK et al.</td>
<td>ZS004</td>
<td>The HARMONIZE trial</td>
<td>Patients with hyperkalemia, regardless of etiology (CKD, DM, CHF) on RAAS inhibitor therapy (n = 258)</td>
<td>Primary: comparison of mean potassium from day 8 to day 28</td>
<td>K 5.6 mEq/L</td>
<td>Open-label induction phase: ZS-9 10 g (n = 237) → K 4.5 mEq/L (normal K 3.5-5.0 mEq/L) TID for 48 h</td>
<td>Double-blind randomized withdrawal phase (mean K &lt; 5.18 mEq/L) QD for 28 d</td>
</tr>
<tr>
<td>Kosiborod M et al.</td>
<td>ZS005</td>
<td>Planned phase III trial</td>
<td>Patients with hyperkalemia (&gt; 5.0 mEq/L) regardless of etiology (n = 600)</td>
<td>Primary: long-term safety and tolerability</td>
<td>&gt; 5.0 mEq/L</td>
<td>48- to 72-h open-label acute phase: ZS-9: 10 g, TID for 48-72 h</td>
<td>ZS-9: 10 g, QD during 1 y (5-g dose titration if needed)</td>
</tr>
<tr>
<td>El-Shahawy M et al.</td>
<td></td>
<td></td>
<td></td>
<td>Secondary: proportion of patients normokalemia during induction phase and during 28-d maintenance period</td>
<td></td>
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</tr>
</tbody>
</table>

Acute Dose-Effects of SZ-9 on Serum Potassium

Extended Dose-Effect of SZ-9 on Serum Potassium

Design of the HARMONIZE trial in CKD Ambulatory Patients with a Serum K level ≥ 5.1 mEq/L

Time Behavior of Serum Potassium Concentrations According to SZ-9 Dosage

Comparative Effectiveness of SPS, Patiromer Sorbitex Calcium and Sodium Zirconium Cyclosilicate According to Baseline eGFR

<table>
<thead>
<tr>
<th>Study</th>
<th>Lowering Serum Potassium Agents</th>
<th>Estimated Glomerular Filtration Rate (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Lin Y-C et al³⁰</td>
<td>SPS</td>
<td>Control subjects (n = 72) Baseline eGFR 59 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Weir MR et al²⁷</td>
<td>Patiromer calcium (RLY5016)³⁹</td>
<td>Placebo (n = 52) Baseline eGFR 39 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Kosiborod M et al¹³</td>
<td>Sodium zirconium cyclosilicate (ZS-9)³⁹</td>
<td>Open-label phase (n = 258) Baseline eGFR 46 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

Comparison of Sodium Zirconium Cyclosilicate and Patiromer Sorbitex Calcium

<table>
<thead>
<tr>
<th>Mechanism and Administration</th>
<th>Sodium Zirconium Cyclosilicate</th>
<th>Patiromer Sorbitex Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Inorganic crystal → selective potassium trap</td>
<td>Organic polymer → nonspecific binding of cations</td>
</tr>
<tr>
<td>Site potassium binding</td>
<td>Entire GI tract</td>
<td>Colon</td>
</tr>
<tr>
<td>Administration</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Daily drug total (g)</td>
<td>5-10</td>
<td>21-35</td>
</tr>
<tr>
<td>Volume expansion</td>
<td>None</td>
<td>Swelling (H₂O absorbed)</td>
</tr>
<tr>
<td>Storage</td>
<td>Room temperature</td>
<td>2-8°C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Onset (h) @ 4 h [baseline potassium &gt; 5.5 (mEq/L)]</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Median time to normalization (h)</td>
<td>2.2</td>
<td>&gt; 48 (estimated 1 wk)</td>
</tr>
<tr>
<td>Response rate</td>
<td>98% at 24 h</td>
<td>76% at 1 mo</td>
</tr>
<tr>
<td>Potassium level maintained (mEq/L)</td>
<td>4.5 (5-10 g QD)</td>
<td>4.6 (17.5 g BID)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal adverse event rate</td>
<td>3.5%</td>
<td>19%</td>
</tr>
<tr>
<td>Open-label phase</td>
<td>6% vs 14% for placebo</td>
<td>13% vs 6% for placebo</td>
</tr>
<tr>
<td>Randomized phase</td>
<td>None</td>
<td>10 g for every 21 g of polymer</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>None</td>
<td>~ 4 g calcium load but small amounts absorbed, may bind PO₄</td>
</tr>
<tr>
<td>Calcium</td>
<td>None</td>
<td>No significant changes</td>
</tr>
<tr>
<td>Magnesium</td>
<td>No hypomagnesia</td>
<td>24% with Mg²⁺ &lt; 1.8 mg/dL</td>
</tr>
<tr>
<td>Fluoride</td>
<td>No impact</td>
<td>Increased serum fluoride</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>↑ 2.3 mEq/L in 15 d</td>
<td>No significant changes</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>↓ Potentially due to binding of ammonium</td>
<td>No significant changes</td>
</tr>
<tr>
<td>Drug-drug interaction</td>
<td>None</td>
<td>Valsartan and rosiglitazone</td>
</tr>
<tr>
<td>Sodium absorption</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

# Safety Results for Sodium Polystyrene Sulfonate, Patiromer Sorbitex Calcium, and Sodium Zirconium Cyclosilicate


<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Sodium Polystyrene Sulfonate (n = 58)</th>
<th>Patiromer, Dose Group 1 (4.2 g, BID for Mild Hyperkalemia) (n = 92)</th>
<th>Patiromer, Dose Group 2 (8.4 g, BID for Moderate to Severe Hyperkalemia) (n = 151)</th>
<th>Sodium Zirconium Cyclosilicate, (n = 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Open-label Treatment Phase†</td>
<td>Open-label Treatment Phase†</td>
<td>Open-label Treatment Phase†</td>
<td>Open-label Treatment Phase†</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>19 (33)</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Necrosis, n (%)</td>
<td>35 (62)†</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Ulceration, n (%)</td>
<td>23 (48)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Perforation, n (%)</td>
<td>5 (9)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Abdominal pain/tenderness, n (%)</td>
<td>33 (57)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>6 (11)</td>
<td>4 (4)</td>
<td>4 (3)</td>
<td>NR</td>
</tr>
<tr>
<td>GI bleed, n (%)</td>
<td>9 (22)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>3 (7)</td>
<td>2 (2)</td>
<td>6 (4)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Constipation, n (%)</td>
<td>NR</td>
<td>9 (10)</td>
<td>17 (11)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Cardiac failure, congestive</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Remote left ventricular infarct and cardiomegaly in a case report†</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>NR</td>
<td>0 (0)</td>
<td>6 (4)</td>
<td>NR</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>NR</td>
<td>0 (0)</td>
<td>4 (3)</td>
<td>NR</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>NR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Hypertension</td>
<td>NR</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>NR</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>NR</td>
<td>2 (2)</td>
<td>5 (3)</td>
<td>NR</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>NR</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>NR</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>NR</td>
<td>3 (3)</td>
<td>5 (3)</td>
<td>NR</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>NR</td>
<td>4 (4)</td>
<td>2 (1)</td>
<td>NR</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>NR</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>NR</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>NR</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>NR</td>
</tr>
<tr>
<td>Anemia</td>
<td>NR</td>
<td>4 (4)</td>
<td>3 (2)</td>
<td>NR</td>
</tr>
<tr>
<td>Edema</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>
Outline of the Presentation

1. Chronic hyperkalemia: a common and serious problem in CKD patients
   - Patients at risk
   - Risks and complications

2. Chronic hyperkalemia: indirect consequences – clinical concerns
   - Limit usage of medications protecting kidney and cardiovascular system

3. Monitoring of chronic hyperkalemia: pitfalls and errors

4. Managing chronic hyperkalemia in CKD patients
   - Traditional ways
   - New tools

5. Take home message
Limitations and Remaining Questions

- No head-to-head randomized, controlled trials of two or more agents (novel agent vs novel agent or versus sodium polystyrene sulfate)
- Acute emergency treatment of hyperkalemia have not been tested with these novel agents
- In the setting of acute kidney injury, effects of patiromer or ZS-9 have not been evaluated
- Alternative routes of administration (nasogastric tube or rectal administration, enema) for these novel agents have not been tested to date
- Long term treatment (months to year) of hyperkalemia with these novel K binders has not explored
- Most common clinical indications of hyperkalemia that requires treatment have not been evaluated in clinical trials
- Long-term safety and efficacy of these new K binders cannot be inferred today
- Cost-effectiveness has not been addressed
Conclusions

• Novel therapies, including the polymer **patiromer sorbitex calcium** and **sodium zirconium cyclosilicate** trap, are promising both as acute medications and as adjunctive therapies for hyperkalemia.

• Novel therapies may allow greater use of **RAAS** (ACE inhibitors, ARBs, and MRAs) and **Aldosterone Blockade** in vulnerable patients (hypertensive, CKD, Cardiac...).

• Remaining questions to be addressed in long term studies:
  - Patient acceptance,
  - Long term safety,
  - Best use,
  - Cost-effectiveness