New Therapeutic Options for the Treatment of Hyperkalemia

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Case Presentation

- 65 YO Caucasian male.
- History of hypertension for last 10 years.
- CKD stage 3A.
- Extensive anterior MI 2 years ago.
- LVEF 25%.
- ICD for primary prevention 1 year ago.
Case Presentation

- VS: HR 76 bpm, BP 122/82 mmHg.
- Functional class II, no signs of volume overload.
- Meds: ASA 81 mg/d, Carvedilol 25 mg bid, furosemide 40 mg bid, enalapril 5 mg bid (dose reduced from 10 mg bid due to increase in Scr from 1.4 to 1.8 and K to 5.3).
- Labs: Na 140, K 5.0, Scr 1.4, GFR 52.
Should the patient be started on spironolactone?

Should the patient be switched from enalapril to sacubitril/valsartan (Entresto) and if yes (for both) which one first? and at what dose?
Pharmacological Treatment for Stage C HFrEF

Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or eGFR>30 mL/min/1.73m2) and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.

Main Causes for Hyperkalemia in Patients with Heart Failure

- Medications-induced hyperkalemia: ACEI/ARB, Spironolactone, Eplerenone, Entresto, Beta blockers, NSAID.
- Impaired renal excretion of K.
- Decreased renal perfusion.
### Trials With Aldosterone Antagonist

**Primary Endpoint:** All-Cause Mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Aldosterone Antagonist</th>
<th>Hazard Ratio</th>
<th>Log-rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPHESUS Post-MI</td>
<td>554/3,319</td>
<td>478/3,313</td>
<td>.85 (.75, .96)</td>
<td>.008</td>
</tr>
<tr>
<td>RALES Advanced HF</td>
<td>386/841</td>
<td>284/822</td>
<td>.70 (.60, .82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EMPHASIS Milder HF</td>
<td>356/1373</td>
<td>249/1364</td>
<td>.76 (.62, .93)</td>
<td>.008</td>
</tr>
</tbody>
</table>

Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV, LVEF of \( \leq 35\% \), to reduce morbidity and mortality.

Aldosterone antagonists after MI
Rassi AN et al. JACC 2013;61:35

11,255 patients post MI eligible for AA

Figure 2
**Trends in Use of Aldosterone Antagonist Therapy in Post-MI Patients With EF <40% Without Documented Contraindications**

EF = ejection fraction; HF = heart failure (medical history); MI = myocardial infarction.
RAAS Inhibitors and Hyperkalemia
Rate of Hyperkalemia after publication of RALES

Jurleenk DN et al NEJM 2004;351:543

Number of prescriptions of sironolactone in patients with HF on ACE-I

Number of admissions for hyperkalemia in patients with HF on ACE-I

Death due to hyperkalemia in patients with HF on ACE-I
Incidence of Hyperkalemia ($\geq 6.0$) in CHF Patients Receiving ARA

Hyperkalemia with spironolactone in Real-world vs Clinical-trial HF patients

**Clinical trials**

- **RALES**
  - N=822
  - Hyperkalemia 2%

- **EMPHASIS**
  - N=1,336
  - Hyperkalemia 2.5%

**Real-world**

- **Svensson 2004 (Norway)**
  - 125 pts
  - Mean age 73 yrs
  - BL Mean serum K 4.2
  - During F/U 10% >6.0
  - Hyperkalemia 12%

- **Bozkurt 2003**
  - N=104
  - Hyperkalemia 6%

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214 patients with class II-IV HF on ACE-I.

- Placebo: 5%
- 12.5 mg: 5%
- 25 mg: 13%
- 50 mg: 20%
- 75 mg: 50%

Predictors of hyperkalemia: BL Scr and serum K levels.
Hyperkalemia (>5.5) Rates in HF Patients Increase as Renal Function Declines

**RALES**

<table>
<thead>
<tr>
<th>Baseline Renal Function</th>
<th>Intra-study Change in Renal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline eGFR ≥60</td>
<td>Placebo 6.0 15.4</td>
</tr>
<tr>
<td>Baseline eGFR &lt;60</td>
<td>Spironolactone 25.6</td>
</tr>
<tr>
<td>No WRF</td>
<td>Placebo 6.7 18.2</td>
</tr>
<tr>
<td>WRF</td>
<td>Spironolactone 13.3</td>
</tr>
</tbody>
</table>

Impaired renal function increases the risk of hyperkalemia in both placebo and MRA-treated patients.

eGFR: estimated glomerular filtration rate; HF: heart failure; MRA: mineralocorticoid receptor antagonist; WRF: worsening renal function.

Hyperkalemia Is a Major Reason for MRA Discontinuation

- 134 HF patients followed in a Portuguese HF clinic
- Spironolactone use in patients with sCr ≤2.5 mg/dL and K⁺ ≤5 mEq/L
- 25% of patients withdrew from spironolactone therapy (19/76)

*Severe hyperkalemia (≥6 mEq/L) occurred in 7 patients who withdrew from spironolactone therapy (9.2%).

Changes in RAAS Inhibitor Dose Subsequent to Hyperkalemia Events

Among Patients on RAAS Inhibitor at Maximum Dose

- **Mild Hyperkalemia (Potassium 5.1-5.4 mEq/L)**
  - Maintained Dose: 52%
  - Down-titrated Dose: 16%
  - Discontinued: 22%

- **Moderate-to-Severe Hyperkalemia**
  - Maintained Dose: 41%
  - Down-titrated Dose: 21%
  - Discontinued: 26%

Percent Mortality by Prior RAAS Inhibitor Dose

- **Maximum Dose**
- **Submaximum Dose**
- **Discontinued**

<table>
<thead>
<tr>
<th>Condition</th>
<th>N (%)</th>
<th>Maximum Dose</th>
<th>Submaximum Dose</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stages 3-4 (N = 43,288)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure (N = 20,529)</td>
<td></td>
<td>22.4%</td>
<td>27.7%</td>
<td>30.1%</td>
</tr>
<tr>
<td>Diabetes (N = 79,087)</td>
<td></td>
<td>9.8%</td>
<td>13.7%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Total Population (N = 201,655)</td>
<td></td>
<td></td>
<td>8.2%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

Total Patients across dose categories:
- CKD Stages 3-4: 43,288
- Heart Failure: 20,529
- Diabetes: 79,087
- Total Population: 201,655
PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from CV causes
20% risk reduction

HF hospitalization
21% risk reduction

### Hyperkalemia in PARADIGM-HF

<table>
<thead>
<tr>
<th>Event</th>
<th>LCZ696 (N = 4187)</th>
<th>Enalapril (N = 4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated serum potassium</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>5.5 mmol/liter</td>
<td>181 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Patients Excluded Due to Elevated K⁺ Levels During Run-in Period Veils
Number of Patients with Elevated K⁺ Due to Treatment

### Sodium Polystyrene Sulfonate (Kayexalate) Warnings and Precautions Highlighted in FDA-approved Label

<table>
<thead>
<tr>
<th>2009</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warning</strong></td>
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</tr>
<tr>
<td>Cases of <em>colonic</em> necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use</td>
<td>Cases of <em>intestinal</em> necrosis, which may be fatal, and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use</td>
</tr>
<tr>
<td>The majority of these cases reported the concomitant use of sorbitol</td>
<td>Do not use in patients who do not have normal bowel function. This includes postoperative patients who have not had a bowel movement post surgery.</td>
</tr>
<tr>
<td>Risk factors for gastrointestinal adverse events were present in many of the cases including prematurity, history of intestinal disease or surgery hypovolemia, and renal insufficiency and failure</td>
<td>Do not use in patients who are at risk for developing constipation or impaction (including those with history of impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, or bowel obstruction)</td>
</tr>
<tr>
<td>Concomitant administration of sorbitol is not recommended</td>
<td>Discontinue use in patients who develop constipation</td>
</tr>
<tr>
<td><strong>Precaution</strong></td>
<td><strong>Precaution</strong></td>
</tr>
<tr>
<td>Do not administer repeated doses in patients who have not passed a bowel movement</td>
<td>Concomitant use of sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal</td>
</tr>
</tbody>
</table>

**References:**
- FDA: Food and Drug Administration
### Sodium Polystyrene Sulfonate (Kayexalate)

**Warnings and Precautions Highlighted in FDA-approved Label**

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<td>Warning</td>
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Cases of intestinal necrosis, which may be fatal, and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use.

**Concomitant use of sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal**

Precaution: Concomitant use of sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal.

**FDA:** Food and Drug Administration


Unmet need for a safe and effective chronic therapy for prevention and treatment of hyperkalemia in HF patients on ACE-I, ARBs, MRA, and ARNI therapies.
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*

Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.
New Drugs for Hyperkalemia

Patiromer

Gut Lumen

K+

Colon

Upper/Lower GI

ZS-9

Na+
# Characteristics of New Potassium Binding Agents

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patiromer</th>
<th>Zirconium Cyclosilicate (ZS-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI Absorption</td>
<td>Non-absorbable</td>
<td>Non-absorbable</td>
</tr>
<tr>
<td>Molecular structure</td>
<td>Organic polymer</td>
<td>crystalline inorganic cation exchange compound</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Ca-K exchange</td>
<td>Na-K exchange</td>
</tr>
<tr>
<td>Relative K Affinity</td>
<td>-</td>
<td>25-fold &gt; Na</td>
</tr>
<tr>
<td>Site of Action</td>
<td>Colon</td>
<td>Upper/Lower GI tract</td>
</tr>
<tr>
<td>K selectivity relative to SPSS</td>
<td>-</td>
<td>120-fold</td>
</tr>
<tr>
<td>Onset of [K]p lowering</td>
<td>7 hours</td>
<td>2 hours</td>
</tr>
</tbody>
</table>
## Patiromer (Veltassa) Oral Suspension

**Patiromer**

- Free-flowing powder of small, spherical beads (~100 µm)\(^1\)
- Active moiety, patiromer, is nonabsorbed\(^1,2\)
- Calcium (rather than sodium) is exchanged for potassium\(^1,2\)

**Site of action is the gastrointestinal tract, mainly in the lumen of the colon where\(^1\)**

- \(\text{K}^+\) is the most abundant cation

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Part A: 4-week Treatment Phase (Single-Blind)

Starting Patiromer Dose

<table>
<thead>
<tr>
<th>Baseline serum K⁺ 5.1-&lt;5.5 mEq/L (Mild Hyperkalemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4g per day (total daily dose)†</td>
</tr>
<tr>
<td>(n=92)</td>
</tr>
</tbody>
</table>

Primary endpoint:
- Mean change in serum potassium from Baseline to Week 4

Secondary endpoint:
- Proportion of patients with serum potassium level of 3.8 mEq/L to < 5.1 mEq/L at Week 4

Week 4 Part A

<table>
<thead>
<tr>
<th>Baseline Part A</th>
<th>Week 4 Part A</th>
</tr>
</thead>
</table>

All patients were on stable dose of at least one RAAS inhibiting agents
*estimated glomerular filtration rate 15-60 ml/min/1.73m²
†dose titrated as needed to maintain target serum K⁺ 3.8 mEq/L to < 5.1 mEq/L

OPAL-HK Study Part A: Efficacy Results

**Primary Endpoint:**

<table>
<thead>
<tr>
<th>Patiromer Starting Dose</th>
<th>Overall Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline K+ [Mean (SD)]:</td>
<td></td>
</tr>
<tr>
<td>5.31 mEq/L (0.57)</td>
<td>5.74 mEq/L (0.40)</td>
</tr>
<tr>
<td>(n=90)</td>
<td>(n=147)</td>
</tr>
<tr>
<td></td>
<td>5.58 mEq/L (0.51)</td>
</tr>
<tr>
<td></td>
<td>(n=237)</td>
</tr>
</tbody>
</table>

**Change in Serum Potassium (mEq/L)**

- **Mild HK:** -0.65 (95% CI: -0.74, -0.55)
- **Moderate/Severe HK:** -1.23 (95% CI: -1.31, -1.16)
- **Total:** -1.01 (95% CI: -1.07, -0.95)

**Secondary Endpoint:**
76% (95% CI: 70%, 81%) achieved target serum potassium at Week 4.

Time to First Recurrence of Hyperkalemia during the Randomized Withdrawal Phase.

Baseline K level 4.5 mmol/L for both 60% of the Placebo group and 15% of the Patiromer group had at least one K value > 5.5
OPAL- HK Study
Use of RAASi during the study

Down-titration or discontinuation of patiromer dose due to hyperkalemia at any time during Part B

- Placebo: 62%
- Patiromer: 16%

Receiving any dose of a RAASi at the end of Part B

- Placebo: 44%
- Patiromer: 94%

P<0.001*

**Open-Label Study**

- **Mild HK**
  - \( K^+ > 5.0 - 5.5 \)
  - \( n = 222 \)

- **Moderate HK**
  - \( K^+ > 5.5 - 6.0 \)
  - \( n = 84 \)

**Dose titrated to K level < 5.0 mEq/L**

- Initial dose of 8.4 g/day (total daily dose)
- Mean daily dose was 14 g

- Initial dose of 16.8 g/day (total daily dose)
- Mean daily dose was 20 g

**N=306**

Subjects with CKD* and T2DM on stable RAASi dose

GFR 15-60

**Screening ≤10 days**

**Run-in ≤4 wk**

**Baseline**

**Wk 4†**

**Wk 8**

**Wk 52**

Mean reduction in serum K level from BL to 4 and 8 weeks

Figure 2. Least Squares Mean Reduction in Serum Potassium Level From Baseline to Weeks 4 and 8 or Time of First Patiromer Titration, by Starting Dose

<table>
<thead>
<tr>
<th>Stratum 1</th>
<th>Stratum 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Patiromer dose, g/d</td>
<td>8.4</td>
</tr>
<tr>
<td>(mild hyperkalemia)</td>
<td>(moderate hyperkalemia)</td>
</tr>
</tbody>
</table>

| No. of patients | 73 | 72 | 72 | 26 | 27 | 30 |

Change in Serum Potassium From Baseline, mEq/L

- Baseline to week 4
- Baseline to week 8

P < .001 for all changes compared with baseline by hyperkalemia strata and by starting dose groups within strata. Stratum 1 indicates mild hyperkalemia (serum potassium level >5.0 to 5.5 mEq/L); stratum 2, moderate hyperkalemia (serum potassium level >5.5 to <6.0 mEq/L). Error bars indicate 95% CIs.
Mean Change in Serum Potassium Over 1 Year (AMETHYST-DN)

Mean (95% CI) Serum Potassium over 52 weeks

<table>
<thead>
<tr>
<th>Study Visit (week)</th>
<th>Serum Potassium over 52 weeks (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL 2 4 6 8 12 16 20 24 28 32 36 40 44 48 52 14 28</td>
<td></td>
</tr>
</tbody>
</table>

Baseline Serum $K^+ > 5.0 - 5.5$ mEq/L
Baseline Serum $K^+ > 5.5 - < 6.0$ mEq/L

N = 301 (start of study)
N = 173 (study end)

Patiromer

Adverse Events

• OPAL-HK
  • Constipation (7.2%)
  • Diarrhea (4.8%)
  • Nausea (2.3%)
  • Abdominal discomfort (2.0%)
  • Flatulence (2.0%)
  • Hypomagnesemia (5.3%)

• AMETHYST-DN
  • Constipation (4.6%)
  • Diarrhea (2.7%)
  • Nausea (2.3%)
  • Hypomagnesemia (7.2%)
  • Hypokalemia < 3.5 mEq/L (5.6%)
Patiromer: Dosing and Administration Summary

- Taken as oral suspension once a day with food.
- Do not heat, add to heated foods or liquids or take in its dry form.
- Store in the refrigerator.
- Use within 3 months if stored at room temperature.
8.4 grams of patiromer once daily (recommended starting dose)
Administer at least 3 hours before or 3 hours after other oral medications
Monitor serum potassium and increase or decrease dose as necessary.

- Up-titrator based on serum potassium level at 1-week or longer intervals, in increments of 8.4 grams.
- Maximum dose of 25.2 grams once daily.
Sodium Zirconium Cyclosilicate in Hyperkalemia

David K. Packham, M.B., B.S., M.D., Henrik S. Rasmussen, M.D., Ph.D., Philip T. Lavin, Ph.D., Mohamed A. El-Shahawy, M.D., M.P.H., Simon D. Roger, M.D., Geoffrey Block, M.D., Wajeh Qunibi, M.D., Pablo Pergola, M.D., Ph.D., and Bhupinder Singh, M.D.
Multicenter, two-stage, DB, phase III trial.

753 patients with hyperkalemia received either ZS-9 (at a dose of 1.25 g, 2.5 g, 5 g, or 10 g) or placebo tid for 48 hours.

Patients with normokalemia (K 3.5-4.9 mmol/L at 48 h), were randomly assigned to receive either ZS-9 or placebo once daily on days 3-14.
Patients with hyperkalemia who received ZS-9, had a significant reduction in K levels at 48 hours, with normokalemia maintained during 12 days of maintenance therapy.
Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia
The HARMONIZE Randomized Clinical Trial

Mikhail Kosiborod, MD; Henrik S. Rasmussen, MD, PhD; Philip Lavin, PhD; Wajeh Y. Qunibi, MD; Bruce Spinowitz, MD; David Packham, MD; Simon D. Roger, MD; Alex Yang, MD; Edgar Lerma, MD; Bhupinder Singh, MD

JAMA 2014;312(21):2223-2233.

N=258 on ZS-9 and 85 placebo
One third with HF
Effect of Sodium Zirconium Cyclosilicate on Potassium after 28 days in Patients With Hyperkalemia

Effect of Sodium Zirconium Cyclosilicate on Potassium after 48 hours in Patients With Hyperkalemia

Hyperkalemia is a common electrolyte disorder and frequent reason for reduction or discontinuation of RAAS inhibitors.

Severe hyperkalemia is associated with serious cardiac arrhythmias and increased mortality.
Patiromer and has been shown to be effective in reducing and maintaining desirable levels of serum K.

It is tolerated by ~ 90% of patients.
Summary

• It should be used in patients with hyperkalemia to allow the use or prevent the discontinuation of life saving therapy such as ACE inhibitors, Aldosterone receptor antagonists and Entresto.