Potassium Binding to Improve Guideline Directed Treatment

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Case Presentation

• 55 y/o male with known ischemic CM and EF of 0.20 admitted for progressive HF symptoms over past 4 weeks.
• Hx of CAD with stents in LAD and LCfx and VT arrest treated with ICD.
• Markedly limited due to DOE and fatigue.
• Current meds: carvedilol 3.125 mg bid, ASA 81 mg, clopidogrel 75 mg, atorvastatin 40 mg, NTG SL prn.

Physical Examination

• BP 126/84, HR 101, RR 16, SpO2 96%
• GEN: no acute distress
• Lungs: clear to auscultation, no wheezing
• Cards: RRR, S3 present and Gr I-II/VI apical systolic murmur, JVP 15 cm
• Ext: 2+ edema, warm

Treatment and Hospital Course

• Patient was clearly congested on admission and bumetanide 1 mg IV twice daily started with excellent results as the patient loses 15 lbs over the next 5 days.
• Lisinopril 2.5 mg bid is added to his regimen and increased to 7.5 mg bid over the next few days.

What are the next steps to consider?

• Uptitrate beta blocker, uptitrate ACEI or switch to sacubitril-valsartan, add aldosterone blocking agent
Labs

- Na 140
- K 5.5
- Cl 101
- Cr 1.42
- Ca 9.6
- WBC 9.4
- Hgb 16
- plt 187
- BNP 463

Hyperkalemia Prevalence

- Incidence and prevalence of hyperkalemia unknown
  - 1–10% of hospitalized patients
  - Up to 11% of outpatients on ACE inhibitor at a VA outpatient clinic
- CKD most common predisposing factor
  - Frequency in CKD population is as high as 45–50%
- Comorbid conditions and accompanying treatments contribute to increased risk
  - Heart failure
  - Type 2 diabetes mellitus (T2DM)
  - Advanced age
  - Use of RAAS inhibitors

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Hyperkalemia Prevalence Increases as Kidney Function Declines

5-Year Database Prevalence of HyperK⁺ in Pts ≥ 65 Years

<table>
<thead>
<tr>
<th>Percent Patients with Hyperkalemia</th>
<th>Control</th>
<th>CKD Stage 3a</th>
<th>CKD Stage 3b</th>
<th>CKD Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>11.7%</td>
<td>23.5%</td>
<td>23.9%</td>
<td>47.7%</td>
</tr>
</tbody>
</table>

Hyperkalemia Prevalence Increases as Kidney Function Declines

Drug-Induced Hyperkalemia

Medications Associated with Hyperkalemia

- ACEi’s, ARB’s and sacubitril-valsartan combination
- K⁺-sparing diuretics, spironolactone
- Bactrim (trimethoprim), pentamidine
- NSAIDs
- Beta blocker (both non-selective and B2 selective)
- Heparin
- Digoxin (supratherapeutic levels)
- Succinylcholine (intubation in ICU, Surgery)
- Calcineurin inhibitors (cyclosporine, tacrolimus [FK506])

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The Addition of MRA to RAS Therapy Increases Hyperkalemia (≥6.0) Risk in HF Patients

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

- Clinical trials
- Real-world

<table>
<thead>
<tr>
<th></th>
<th>N=422</th>
<th>N=1,336</th>
<th>N=945</th>
<th>N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>2</td>
<td>2.5</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>EMPHASIS</td>
<td>1.0</td>
<td>1.2</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Shah 2005</td>
<td>1.5</td>
<td>1.8</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Buxton 2003</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Hyperkalemia and the RALES Study

- Publication of RALES sparked an increase in prescriptions for spironolactone
- Also a parallel increase in hospital admissions and death from hyperkalemia


MRA-Eligible HF Patients Are Undertreated:
Get With the Guidelines–HF Registry

- Among 12,565 pts eligible for aldosterone antagonist therapy, only 4,087 (32.5%) received an aldosterone antagonist at d/c

<table>
<thead>
<tr>
<th>Quarter</th>
<th>A-II Antagonist Prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 2005</td>
<td>40.0</td>
</tr>
<tr>
<td>3-4 2005</td>
<td>40.0</td>
</tr>
<tr>
<td>1-2 2006</td>
<td>40.0</td>
</tr>
<tr>
<td>3-4 2006</td>
<td>40.0</td>
</tr>
<tr>
<td>1-2 2007</td>
<td>40.0</td>
</tr>
<tr>
<td>3-4 2007</td>
<td>40.0</td>
</tr>
</tbody>
</table>

| No. of patients | 1,098 | 1,965 | 2,613 | 2,727 | 2,593 | 1,569 |


Hyperkalemia Was Common in PARADIGM-HF

<table>
<thead>
<tr>
<th></th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
<td></td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.5 mmol/liter</td>
<td>674 (16.1)</td>
<td>727 (17.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;6.0 mmol/liter</td>
<td>183 (4.3)</td>
<td>236 (5.6)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

→ Doesn’t count those excluded for high K+ during run-in period!

McMurray et al. NEJM. 2014.
Long-Term Hyperkalemia Management Strategies – old version

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Limitation</th>
</tr>
</thead>
</table>
| Dietary K+ restriction of 40-60 mmol/day | Potassium is common ingredient in many foods  
Restricted consumption of healthy foods  
Low K+ diet often expensive |
| RAASi reduction           | Limiting the prescription of drugs known to be effective in these populations |
| Kayexalate                | Warnings related to serious gastrointestinal (GI) adverse events  
Precaution related to sodium |

Low K+ Diet Is the First Step in Chronic Management, but Compliance Is Difficult

Potassium-Rich Foods

KAYEXALATE (Sodium Polystyrene Sulfonate) Is Problematic – do not use

- Can cause intestinal necrosis (esp. when used with sorbitol)
- Should not be used in pts without normal bowel function or in pts at risk for constipation or impaction
- Administration = obligatory salt and water load
  - 1g of SPS contains 100mg of Na+; avg daily dose 15-60 g/day

→ Do NOT use in chronic hyperK+ in pts without hyperK+ emergency!

Long-Term Hyperkalemia Management Strategies – NEW version

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Examples</th>
</tr>
</thead>
</table>
| GI Cation Exchanger | Patiromer  
Zirconium cyclosilicate (ZS-9) |
Patiromer (VELTASSA) Oral Suspension

**Patiromer**

- Free-flowing powder of small, spherical beads (~100 µm)
- Active moiety, patiromer, is nonabsorbed
- Calcium (rather than sodium) is exchanged for potassium
- Site of action is the GI tract, mainly in the lumen of the colon
  - K⁺ is the most abundant cation
  - Residence time of the polymer is the longest


**Electron Microscopy Image**

**Baseline serum K⁺ 5.1-<5.5 mEq/L (Mild Hyperkalemia)**

**Baseline serum K⁺ 5.5-<6.5 mEq/L (Moderate/Severe Hyperkalemia)**

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

**Starting Patiromer Dose**

- 8 g per day (total daily dose) (n=242)
- 16 g per day (total daily dose) (n=242)

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

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

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: Primary and Secondary Efficacy Endpoints**

**Mean Serum K⁺ (mEq/L)**

- Overall: 62%
- Mild hyperkalemia: 16%
- Moderate-to-severe hyperkalemia: 10%

Study included 243 patients with CKD who were taking a RAAS blocker

**Part B: Exploratory Endpoints**

- Requiring any adjustment of RAAS (ie, dose titration or discontinuation) or patiromer dose increase due to hyperK⁺
- Receiving any dose of a RAAS at the end of Part B

*P < 0.001*
Mean Change in Serum Potassium Over 1 Year (AMETHYST-DN)


<table>
<thead>
<tr>
<th>Study Visit (week)</th>
<th>Follow-Up (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Serum K+</td>
<td>Baseline Serum K+</td>
</tr>
<tr>
<td>≥5.0 – 5.5 mEq/L</td>
<td>≥5.5 – &lt;6.0 mEq/L</td>
</tr>
</tbody>
</table>

BL: Baseline
N=301 (start of study)
N=173 (study end)

Patiromer: Adverse Reactions

The most common adverse reactions (incidence ≥ 2%) are:
- Constipation (7.2%)
- Hypomagnesemia (5.3%)
- Diarrhea (4.8%)
- Nausea (2.3%)
- Abdominal discomfort (2.0%)
- Flatulence (2.0%)

Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with patiromer and included edema of the lips.

Patiromer (VELTASSA)

Indication
- Indicated for the treatment of hyperkalemia

Limitation of Use
- Patiromer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action

Contraindications
- Patients with a history of a hypersensitivity reaction to patiromer or any of its components

Patiromer: Dosing and Administration

Dosing:
- 8.4 grams of patiromer once daily (recommended starting dose)
- Administer at least 3 hours before or after other oral meds

Dose Titration:
- Monitor serum K+ and ↑ or ↓ dose as necessary
- Up-titrate based on serum K+ level at 1-week or longer intervals, in increments of 8.4 grams.
- Max dose 25.2 grams once daily
ZS-9: Inorganic Crystalline Compound Designed Specifically to Trap $K^+$

- First in class inorganic crystalline zirconium silicate compound
- Exchanges $K^+$ for $Na^+$ in the intestine
- Highly selective for $K^+$ trapping (>150 times more than $Na^+$)
- Insoluble, stable, does not expand in water
- Not systematically absorbed

*SPS: sodium polystyrene sulfonate

Illustration of ZS-9 Action in Gastrointestinal (GI) Tract

ZS-9 is thought to begin working immediately in the small intestine, selectively trapping potassium

HARMONIZE study: Mean Serum K+ Levels Over 48h With ZS-9

Rapid drop within 4 hours

Dose-Dependent Serum K+ Reduction Over 48 Hours in HF Patients on RAASi

Serum K+ during Open-Label Phase (48h)
- A. Mean K+ levels over time in pts treated with ZS-9 10 g, tid x 48h (then switch to QD)
- B. Mean K+ levels at 0 and 48h by subgroups

Shaded region represents nl K+ range

Dose-Dependent Serum K+ reduction Over 48 Hours in HF Patients on RAASi

Rapid drop within 4 hours

Source: El-Shahawy M, et al. Oral Presentation During a Late-Breaking Clinical Trial Session at the Heart Failure Society of America (HFSA) 18th Annual Scientific Meeting, Sep 15, 2014.
Maintenance: 1x Daily ZS-9 10g Maintained Normal Range of Mean K+ Levels vs Placebo: HF Patients on RAASi

Packham et al. NEJM 2015.

New Therapies For Hyperkalemia

- Hyperkalemia is common in patients with HF, CKD and/or diabetes.
- High levels of potassium may lead to dose reduction or discontinuation of RAAS inhibitors.
- There are problems with current treatments for hyperkalemia.
- New agents that are safe and effective to treat hyperkalemia are (patiromer) or will be (ZS-9) available.
- Use of these new agents are likely to become important adjuncts to heart failure/CAD therapy.