Potassium binders as enablers of Neuro-Hormonal blockade/modulation in HF-REF

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Disclosures

- FDA, CDRH, Medical Reviewer
- Advisory Board, Relypsa
- Research Steering Committee, Novartis
Introduction

• RAAS inhibitors reduce morbidity and mortality in patients with CKD and in patients with HF

• However, these patients often do not receive the maximal/optimal dose of RAAS inhibitor because of the increased risk for hyperkalemia

• The importance to maintain appropriate RAAS inhibitor use in patients with CKD and HF

• Practical messages to identify patients with hyperkalemia, and prevent it
Patient Case: The Zone of Uncertainty

- FP is a 69-year-old Italian man referred to outpatient heart failure (HF) team after 2 recent hospitalizations for acute decompensated HF
  - Hyperkalemia documented in EMR as an “allergy” to ACE inhibitors

| Past Medical History | Hypertension  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Heart failure with reduced ejection fraction</td>
</tr>
<tr>
<td></td>
<td>• NYHA Class III EF 25% s/p AICD</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease stage 3A</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
</tr>
</tbody>
</table>

| Labs                  | Serum creatinine: 1.6 mg/dL                           |
|                       | Estimated GFR: 45 mL/min/m²                            |
|                       | Potassium: 4.9 mEq/L                                  |
|                       | NT-proBNP: 4500 pg/mL                                  |
|                       | Digoxin level: 0.4 ng/mL                               |

| Vitals                | BP: 144/96                                          |
|                       | HR: 76                                              |

| Medications           | Carvedilol 12.5 mg BID                               |
|                       | Hydralazine 25 mg TID                                |
|                       | Isosorbide dinitrate 20 mg TID                       |
|                       | Naproxen 500 mg BID as needed                         |
|                       | Digoxin 125 mcg daily                                 |
|                       | Torsemide 40 mg BID                                   |
Angiotensin-Converting Enzyme Inhibitor–Associated Elevations in Serum Creatinine: *Is This a Cause for Concern?*

An inverse correlation between the amount of renal function loss at baseline and the subsequent rate of annual decline in renal function following randomization to a regimen that contained ACEI.

Data for Aldosterone Antagonism

- **RALES**
- **EPHESUS**
- **EMPHASIS-HF**
- **TOPCAT**

**Issues**

A. 30-day event rate
B. Mechanism
   (K⁺ vs fibrosis)
C. Patient selection
D. HFrEF vs HFpEF

**Results**

- **RALES**¹ (Severe HFrEF)
  - 30% Risk Reduction
  - RR=0.70
  - \(P<0.001\)

- **EPHESUS**² (Post-MI)
  - 15% Risk Reduction
  - RR=0.85
  - \(P=0.008\)

- **EMPHASIS**³ (Mild HFrEF)
  - 22% Risk Reduction
  - RR=0.78
  - \(P=0.01\)

Post Hoc Analysis of TOPCAT by Region Indicated Possible Clinical Benefits of Spironolactone in the Americas

Cardiovascular death, heart failure hospitalization, or aborted cardiac arrest in patients.

Among 12,565 patients eligible for MRA therapy, 4087 (32.5%) received a mineralocorticoid receptor antagonist at discharge, and there was a modest increase in treatment from 28% to 34% over the study period.

Hyperkalaemia Is a Leading Reason for Not Starting or Discontinuing RAASi in Patients With CKD

279 patients with baseline mean GFR 33.3 mL/min/1.73 m² and serum K⁺ 4.73 mEq/L.
Using Maximum vs Submaximum Doses of RAAS Inhibitors Is Associated With Reductions in Mortality

Mortality, %

CKD stages 3-4

Maximum dose 42.6 47.4 54.4
Submaximum dose 43.3 52.3 59.8
Discontinued

HF

Maximum dose 29.9 30.9 41.3
Submaximum dose
Discontinued

Diabetes

Maximum dose
Submaximum dose
Discontinued

Total population

Maximum dose 24.9 24.9
Submaximum dose
Discontinued

(n = 43,288) (n = 20,529) (n = 79,087) (n = 201,655)

BIOSTAT- HF: Uptitration of ACEI/ARB

Outcomes Based on Achieving Different Levels of Treatment Dose

Better Renal Outcomes With Higher Doses of ACE Inhibitors/ARBs

Withdrawal of pharmacological treatment for HF in patients with recovered dilated cardiomyopathy: TRED-HF (cont)

KM Curve of Primary Endpoint: Relapse of dilated cardiomyopathy within 6 months

Event rate 45.7% (95% CI 28.5–67.2); p=0.0001

Number at risk

<table>
<thead>
<tr>
<th>Months since randomisation</th>
<th>Control group</th>
<th>Treatment withdrawal group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>13</td>
</tr>
</tbody>
</table>

Evidence-based guidelines are consistent in recommending RAAS inhibitors in patients with HF\[^{[a-c]}\]

- ACE inhibitors are recommended, in addition to a BB, for symptomatic patients with HFrEF
- ARBs are recommended when ACE inhibitors are not tolerated
- MRAs are recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE inhibitor and a BB
- Sacubitril/valsartan is recommended as an ACE inhibitor replacement in patients with HFrEF who remain symptomatic despite optimal treatment with an ACE inhibitor, BB, and MRA

Highest tolerated targeted doses recommended\[^{[a,b]}\]

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MRA and Hyperkalemia

Clinical Trials Data vs “Real-world” Data
Hyperkalemia (>6.0) Rates Were Relatively Low with MRAs in HF Trials with Careful Patient Selection and Monitoring

- **RALES**
  - Renal exclusion (mg/dL): SrCr > 2.5
  - Potassium exclusion (mEq/L): K+ > 5
  - Treatment: Spironolactone 25–50 mg qd + ACEI, placebo + ACEI

- **EMPHASIS**
  - GFR < 30
  - Treatment: Eplerenone 25–50 mg qd + ACEI and/or ARB, placebo + ACEI and/or ARB

- **EPHEBUS**
  - SrCr > 2.5
  - K+ > 5
  - Treatment: Eplerenone 25–50 mg qd + ACEI or ARB, placebo + ACEI or ARB

---

**SrCr**, serum creatinine.

Hyperkalemia (≥6.0) Rates Are Higher in CHF Patients on MRA in Real-world Studies

Studies by Drs. Shah and Bozkurt were real-world, observational studies.
*Out of a total of 840 patients enrolled, 551 patients with follow-up laboratory values were determined.

Less than a quarter of HF patients initiating MRA receive guideline-recommended potassium monitoring

The SCREAM project (N=4036)

A real-world cohort study on the quality of potassium and creatinine monitoring during initiation of mineralocorticoid receptor antagonists in patients with heart failure
How to Manage Hyperkalemia
Management of Chronic Hyperkalemia before Era of New $K^+$ Binders

- Assess renal function
- Prescribe low-$K^+$ diet
- Titrate or discontinue RAASi
- Prescribe diuretic therapy

FACT

• Hyperkalemia is a common cause of RAAS inhibitor down-titration and discontinuation in patients with heart failure
• Heart failure patients, especially with comorbidities such as diabetes and CKD, are at high-risk for hyperkalemia

FICTION

• Previous occurrence of hyperkalemia is an absolute contraindication to subsequent RAAS inhibition
• Sodium polystyrene sulfonate (SPS) is safe and effective in the management of recurrent hyperkalemia
The K/DOQI guidelines recommend the following before initiating ACE inhibitor or ARB treatment in patients with CKD for management of blood pressure:

- No intervention if baseline serum potassium level is ≤4.5 mEq/L
- Dietary counseling if serum potassium level is 4.6–5 mEq/L
- Dietary counseling and initiation of potassium-lowering medications and ARB or ACE inhibitor if serum potassium level is 5.1–5.5 mEq/L
- Immediate initiation of potassium-lowering medications before initiating ACE inhibitor or ARB if serum potassium level is >5.5 mEq/L

K/DOQI Guidelines
Monitoring of Serum Potassium before Initiating RAASi Therapy

K/DOQI, Kidney Disease Outcomes Quality Initiative.

Limitations of Long-term Hyperkalemia Management Strategies

<table>
<thead>
<tr>
<th>Treatment Focuses on Diet Changes, Removal of Therapies That Increase Serum $K^+$, and SPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAASi reduction</strong></td>
</tr>
<tr>
<td>• Limiting the dose of or discontinuing treatment with drugs known to be effective in these populations$^1$</td>
</tr>
<tr>
<td><strong>SPS$^2$</strong></td>
</tr>
<tr>
<td>• Warnings related to serious GI AEs and colonic necrosis</td>
</tr>
<tr>
<td>• Precaution related to Na$^+$</td>
</tr>
<tr>
<td><strong>Dietary $K^+$ restriction of 50 to 75 mEq/day</strong></td>
</tr>
<tr>
<td>• $K^+$ is a common ingredient in many foods$^3$</td>
</tr>
<tr>
<td>• Restricts consumption of healthy foods (eg, the DASH Diet)$^3$</td>
</tr>
<tr>
<td>• Low-$K^+$ diet often expensive$^4$</td>
</tr>
</tbody>
</table>

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$^2$SPS Prescribing Information;

$^3$https://www.kidney.org/sites/default/files/02-10-0410_EBB_Potassium.pdf;

# Counsel Patients to Avoid Foods High in K⁺

<table>
<thead>
<tr>
<th>Food</th>
<th>Portion</th>
<th>K⁺ Content, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beans—black, canned</td>
<td>½ cup</td>
<td>903</td>
</tr>
<tr>
<td>Beans—lima, canned</td>
<td>1 cup</td>
<td>987</td>
</tr>
<tr>
<td>Brussels sprouts—frozen, boiled</td>
<td>1 cup</td>
<td>446</td>
</tr>
<tr>
<td>Clams—moisture cooked</td>
<td>19 small</td>
<td>665</td>
</tr>
<tr>
<td><strong>Guacamole—with tomatoes</strong></td>
<td>½ cup</td>
<td>458</td>
</tr>
<tr>
<td>Lentils—boiled</td>
<td>1 cup</td>
<td>731</td>
</tr>
<tr>
<td>Mango</td>
<td>1 medium</td>
<td>564</td>
</tr>
<tr>
<td>Milk—coconut</td>
<td>8 fl oz</td>
<td>497</td>
</tr>
<tr>
<td><strong>Orange juice</strong></td>
<td>8 oz</td>
<td>496</td>
</tr>
<tr>
<td>Oysters—raw</td>
<td>6 medium</td>
<td>504</td>
</tr>
<tr>
<td>Plantain—cooked</td>
<td>1 cup</td>
<td>716</td>
</tr>
<tr>
<td>Potato—baked</td>
<td>1 medium</td>
<td>926</td>
</tr>
<tr>
<td>Raisins</td>
<td>1 cup</td>
<td>1086</td>
</tr>
<tr>
<td>Spinach—frozen, boiled</td>
<td>1 cup</td>
<td>574</td>
</tr>
<tr>
<td><strong>Tomato paste, canned, no added salt</strong></td>
<td>6 oz</td>
<td>1724</td>
</tr>
</tbody>
</table>

## Review for Medications That May Cause Increase in Serum Potassium Levels

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Herbal remedies (eg, alfalfa, dandelion, hawthorn berries, horsetail, milkweed, nettle, noni juice, Siberian gensing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliskiren</td>
<td>Hyperosmolar solutions (eg, mannitol glucose)</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Intravenous cationic amino acids</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>NSAIDs</td>
</tr>
<tr>
<td>Azole antifungals (eg, ketoconazole, fluconazole, itraconazole)</td>
<td>Pentamidine</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Suxamethonium</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Drospernione</td>
<td>Suxamethonium</td>
</tr>
<tr>
<td>Eplerenone and finerenone</td>
<td></td>
</tr>
<tr>
<td>Heparin and its derivatives</td>
<td></td>
</tr>
</tbody>
</table>
Potassium Lowering Drugs
### Overview of Potassium Binders

<table>
<thead>
<tr>
<th>Mechanism of action&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sodium Polystyrene Sulfonate</th>
<th>Patiromer</th>
<th>Sodium Zirconium Cyclosilicate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific cation binding in exchange for sodium</td>
<td>Nonspecific cation binding in exchange for calcium</td>
<td>Selective potassium binding in exchange for sodium and hydrogen</td>
<td></td>
</tr>
<tr>
<td>Time to normokalaemia</td>
<td>Unconfirmed efficacy</td>
<td>Achieves normokalaemia within 1 wk&lt;sup&gt;b&lt;/sup&gt; 84% achieved potassium target at 24 h and 98% at 48 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>84% of patients normokalemic within 24 h&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>Unknown (generally h to d)</td>
<td>K+ levels reduced significantly 7 h after first dose&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Median time to significant reduction 2.2 h&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>Interactions with antacids, laxatives, digitals, sorbitol, lithium, and thyroxine&lt;sup&gt;e&lt;/sup&gt; Must be taken 3 h apart from other oral drugs&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Should be taken at least 3 h apart from other oral drugs&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Must be taken 2 h apart from oral medications with clinically meaningful gastric pH– dependent bioavailability&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Location of potassium binding&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Colon</td>
<td>Distal colon predominantly</td>
<td>Likely to be upper and lower GI tract (not proven)</td>
</tr>
<tr>
<td>Safety/tolerability</td>
<td>Poor tolerability/adherence, associated with colonic necrosis, hypokalaemia, electrolyte disturbances, and GI side effects&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Well tolerated, but may cause hypomagnesaemia and GI side effects, such as mild to moderate constipation&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Well tolerated, but may cause oedema (more common at 15 g QD dose), mild to moderate GI effects, and hypokalaemia&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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Sodium Polystyrene Sulfonate (SPS)

1958—Approved by FDA 4 years before requirement to prove safety and effectiveness. (Kefauver-Harris Drug Amendments)

2009—FDA Black Box Warning
Cases of colonic necrosis and other serious GI adverse events.
Concomitant administration of sorbitol is not recommended.

“We can find no convincing evidence that SPS increases fecal potassium losses in experimental animals or humans.”
“There is growing concern, however, that suspensions of SPS in sorbitol can be harmful.”
• Reports of highly fatal upper and lower GI transmural necrosis with SPS combined with 70% sorbitol
• Occurs in 0.1%–0.3% of patients
POTASSIUM-BINDING AGENTS FOR THE TREATMENT OF HYPERKALAEMIA: IS ENABLEMENT POSSIBLE?

Patiromer^[a]\n
- Nonabsorbed, sodium free potassium binder
- Binds potassium in exchange for calcium ions
- Works primarily in the colon

SZC^[b]\n
- Inorganic, crystalline potassium binder
- Sodium-based, potassium-selective, cation exchanger
- Primarily active in the GI tract

---

PATIROMER BINDS K⁺ IN THE COLON

Patiromer controls K⁺ levels without increasing the sodium load

- **Novel, high-capacity K⁺ binder**

- Spherical polymer with an average bead size (100 μM) is **too large to be absorbed**

- Site of action is primarily from the colon where K⁺ is the most abundant cation and residence time of the polymer is the longest

Patiromer travels through the GI tract over 24–72 hours

- Patiromer is fully ionised at the physiologic pH of the colon for optimal ion exchange

- Carboxylate groups of patiromer bind to K⁺, which is primarily in the colon due to upregulation of BK channels in colonic epithelial cells

- Patiromer beads are excreted, leading to removal of excess K⁺ and reduction of serum K⁺ levels

---

OPAL-HK: PATIROMER IN PATIENTS WITH CKD AND HYPERKALAEMIA RECEIVING RAAS INHIBITORS

Patients with CKD* on RAASi (n = 243)

- **Wk 4**
  - **Part A** primary and secondary endpoints
  - **Part B** randomised withdrawal phase

**Mild hyperkalaemia** (sK⁺ 5.1 to <5.5 mEq/L): patiromer 4.2 g BID (n = 92)

**Moderate to severe hyperkalaemia** (sK⁺ 5.5 to <6.5 mEq/L): patiromer 8.4 g BID (n = 151)

- **Wk 4**
  - **primary endpoint**
  - **secondary endpoints**

**Patiromer† continued RAASi** (n = 55)

**Placebo continued RAASi** (n = 52)

- **Wk 8**
  - **Part B** secondary endpoints

Mild hyperkalaemia:
- sK⁺: 3.8 to <5.1 mEq/L (ie, normokalaemia)
- Still on patiromer
- Still on RAASi (n = 107)

Moderate to severe hyperkalaemia:
- Patients with CKD* on RAASi (n = 243)
- sK⁺ 5.5 to <6.5 mEq/L: patiromer 8.4 g BID (n = 151)

* eGFR 15 to <60 mL/min/1.73 m²; †Dose adjusted as needed by treating physician.

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Patiromer is effective for the initial treatment of hyperkalaemia: OPAL-HK (Part A)

Primary Efficacy Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Mild HK</th>
<th>Moderate/Severe HK</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in serum potassium, mEq/L</td>
<td>-0.65 (95% CI: -0.74, -0.55)</td>
<td>-1.23 (95% CI: -1.31, -1.16)</td>
<td>-1.01 (95% CI: -1.07, -0.95)</td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

76% of patients had sK\(^+\) in the target range (3.8 to < 5.1 mmol/L) at wk 4

OPAL-HK: RAASi enablement with patiromer in hyperkalemic HF-CKD patients

*P<0.001. †Requiring any adjustment of RAASi (i.e., down-titration or discontinuation) or patiromer dose increase due to hyperkalaemia at any time during Part B.
‡Receiving any dose of a RAASi at the end of Part B. RAASi, renin-angiotensin-aldosterone system inhibitors
Phase 2, open-label, dose-ranging randomised clinical trial evaluating patiromer in patients (N = 306) with T2DM, hyperkalaemia, and CKD (eGFR 15 to <60 L/min/1.73 m²) who were receiving RAAS inhibitors.
PEARL-HF: Objectives and endpoints

- **Objectives:**
  - To evaluate efficacy and safety of patiromer when used for the prevention of hyperkalaemia in normokalaemic CHF patients treated with RAASi, during initiation and uptitration of spironolactone

- **Primary endpoints:**
  - Mean change in sK⁺ from baseline to day 28

- **Key secondary endpoints:**
  - Proportion of patients with sK⁺ >5.5 mEq/L at any time during the study
  - Proportion of patients whose spironolactone dose could be increased to 50 mg/day
• **Primary Endpoint**

- Spironolactone initiated at 25 mg once daily on day 1
- Spironolactone increased to 50 mg once daily on day 15 if sK⁺ ≤ 5.1

*vs placebo

- Spironolactone (n=55)
- Placebo (n=49)

- **Incidence of hyperkalemia, sK⁺ > 5.5 mEq/L**

  - Placebo (n=49)
  - Patiromer (n=55)

  - Patients able to uptitrate spironolactone dose to 50 mg daily, %

  - **P = .019**

  - **P = .015**

PEARL-HF: Majority of patients had spironolactone dose increased

Frequency of hyperkalemia and proportion of patients* on 50 mg/day of spironolactone

Number of patients (%)

<table>
<thead>
<tr>
<th>Hyperkalaemia (&gt;5.5 mEq/L)</th>
<th>Patiromer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Increase of spironolactone dose to (50 mg)

| 91%                         | 74%       |

*Patients with heart failure with reduced ejection fraction.
† P=0.015; ‡ P=0.019

**AMBER: STUDY DESIGN**

CKD patients with rHTN
- Systolic AOBP 135-160 mm Hg
- eGFR 25-45 mL/min/1.73 m²
- sK⁺ 4.3-5.1 mEq/L

Additional antihypertensive medication as needed

Spironolactone + blinded patiromer

Spironolactone + blinded placebo

Day 1: start spironolactone 25 mg once daily, 8.4 g/day patiromer or placebo

**Screening/run-in up to 4 weeks***

**Double-blind treatment period 12 weeks**

**Safety follow-up 2 weeks**

---

*To ensure eligibility criteria, stable medication, and competent use of HBP monitor.
†Stratified by local K⁺ (4.3-<4.7 vs 4.7-5.1) and history of diabetes.

AOBP: automated office blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; f/u: follow-up; HBP: home blood pressure; rHTN: resistant hypertension; sK⁺: serum potassium.

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AMBER
Primary Endpoint: Patients Who Remained on Spironolactone at Week 12

Patients Who Remained on Spironolactone at Week 12, % (95% CI)

LS mean (95% CI) difference between groups: 20% (95% CI 10, 29)

\( P < 0.0001 \)
PROPORTION OF PATIENTS REQUIRING DISCONTINUATION OF SPIRONOLACTONE

Time to Early Discontinuation of Spironolactone
ITT Population

Circles indicate censored observations
- Spironolactone + Placebo
- Spironolactone + Patiromer

Proportion of Patients Requiring Discontinuation of Spironolactone

Study Week

Number at Risk
- Spironolactone + Patiromer: 147, 146, 143, 140, 135, 133, 127, 126

Log-rank
P=0.0001

Study Week

Number at Risk

ITT: intention-to-treat.


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SODIUM ZIRCONIUM CYCLOSILICATE (SZC)
TREATMENT AMONG OUTPATIENTS WITH HYPERKALAEMIA: HARMONIZE

• Phase 3, multicentre, randomised, double-blind, placebo-controlled trial evaluating SZC vs placebo in outpatients with hyperkalaemia (sK⁺ ≥ 5.1 mEq/L)
• Patients (n = 258) received SZC 10 g, 3 times daily, in the initial 48-h open-label phase
• Patients (n = 237) achieving normokalaemia (3.5-5.0 mEq/L) were then randomly assigned to receive SZC 5 g, 10 g, or 15 g, or placebo once daily (QD) for 28 d
Randomized Phase
Mean Potassium Levels Over Time

No. of patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>5-g dose</th>
<th>10-g dose</th>
<th>15-g dose</th>
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<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>45</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>45</td>
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<td>7</td>
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<td>17</td>
<td>74</td>
<td>42</td>
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<tr>
<td>19</td>
<td>73</td>
<td>39</td>
<td>38</td>
<td>43</td>
</tr>
</tbody>
</table>

**SZC: EFFICACY AND SAFETY**

**HARMONIZE- SZC-005[a]**
- Phase 3 study in patients with hyperkalaemia and CKD (N = 751)
- Mean serum K\(^+\) (≤ 5.1 mEq/L or ≤ 5.5 mEq/L) were maintained in the extended phase in 88% and 99%, respectively, of patients from mo 3 to mo 12

**Most Common AEs in Clinical Trials[b]**
- Hypokalaemia (2.3%)
  - Resolved with discontinuation of drug
- Oedema-related AEs (5.7%)
  - Fluid overload, fluid retention, generalised oedema, peripheral oedema, hypervolaemia
- A dose-dependent increase in serum bicarbonate levels has been observed

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### SZC REDUCES SERUM POTASSIUM IN PATIENTS WITH OTHER COMORBIDITIES: SUBANALYSIS OF HARMONIZE

Patients received SZC 10 g 3 times daily for 48 hours in the induction phase. Those achieving normokalaemia (3.5 to 5.0 mEq/L) were randomised to SZC once daily (5g, 10g, 15g) vs placebo for 28 days.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Baseline K⁺ (mEq/L)</th>
<th>K⁺ at 48 Hours (mEq/L)</th>
<th>Median Time to Normalisation (Hours)</th>
<th>Proportion of Patients Normalised (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 Hours</td>
</tr>
<tr>
<td>All</td>
<td>258</td>
<td>5.6</td>
<td>4.5</td>
<td>2.2</td>
<td>84</td>
</tr>
<tr>
<td>HF</td>
<td>94</td>
<td>5.6</td>
<td>4.4</td>
<td>2.0</td>
<td>90</td>
</tr>
<tr>
<td>CKD</td>
<td>179</td>
<td>5.6</td>
<td>4.5</td>
<td>2.3</td>
<td>82</td>
</tr>
<tr>
<td>DM</td>
<td>170</td>
<td>5.6</td>
<td>4.5</td>
<td>2.0</td>
<td>82</td>
</tr>
</tbody>
</table>
SUMMARY

• Clinical studies of patiromer and SZC demonstrated a dose dependent potassium-lowering effect and good tolerability for both these agents.

• They may be helpful in optimizing RAASi therapies in patients with hyperkalaemia.
Do they work in all patient sub-groups?
Treatment for hyperkalemia in HF patients receiving maximal, submaximal or no RAASi

Pooled analysis from two Phase III trials

Proportion of HF patients achieving normokalemia

Distribution of RAASi therapy classes among HF patients receiving maximal and submaximal RAASi therapy

So it stands to reason...

- Use novel K\textsuperscript{+} binders to optimize RAASi therapy

- Enabling therapy not new in medicine
  - Antiemetic and chemotherapy
  - Diuretics and ACEi
  - PPI and DAPT
The questions is:

- NOT discussing patients not studied (e.g. GFR <30 or HFpEF)

- In those population where RAASi proven to be efficacious
  - Those who develop hyperkalemia likely older, more comorbid, and lower GFR (still over 30) etc.
  - Is this group unresponsive? Hyper-responsive?

  - Maybe benefit is due to hyperkalemia?
Will RAASi enablement with PATIROMER through potassium control in HFrEF patients potentially result in better CV outcomes?

**INCLUSION CRITERIA**

- ~2400 Patients with Heart Failure (HFrEF)
- With or without CKD (eGFR >30 mL/min/1.73m²)
- ~ 418 sites across the globe
- sK+ > 5.0 mEq/L
- History of HK in the past 12 months => RAASi discontinuation
- Hospitalization for HF (or equivalent) within 12 months

**RUN-IN PHASE**

- (single blided, up to 12 weeks)
- Initiate patiromer
- Start at 8.4 g/day and up-titrates as necessary up to 25.2 g/day
- Optimise ACEi/ARB/ARN i
- Initiate/optimise MRA †

**TREATMENT PHASE**

- (double blinded)
- Patiromer Continued
- Placebo (withdraw patiromer)

**Primary endpoint:**

- Time to first occurrence of CV death or CV hospitalization (or equivalent in outpatient clinic)

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*Start at 8.4 g/day and up-titrates as necessary up to 25.2 g/day. Subject must return within 1 week (± 3 days) after patiromer initiation or dose adjustment to assess potassium levels.

†Initiate selected MRA; up-titrates to 50 mg/day. ††If there are changes to ACEi, ARB, ARNi and/or MRA dose or serum potassium varies outside the intended range, unscheduled weekly or monthly visits should occur until stability returns.

§If the potassium Assessment Visit is at 2 weeks after the EOS Visit, then follow-up Phone call is not required.
The Zone of Uncertainty: 1 Week Later

- After dietary counseling, discontinuation of naproxen and digoxin, and pre-authorization for patiromer, enalapril 5 mg BID initiated

- FP reports “feeling great” with the following labs and vitals during clinic visit

| Labs          | Serum creatinine: 1.5 mg/dL → 1.7 mg/dL  
|               | Estimated GFR: 45 mL/min/m² → 40 mL/min/1.73m²  
|               | Potassium: 4.9 mEq/L → 5.3 mEq/L  
|               | NT-proBNP: 4500 pg/mL → 2700 pg/mL  |
| Vitals        | BP: 144/96 → 132/84  
|               | HR: 76 → 74  |
| Medications   | Carvedilol 12.5 mg BID  
|               | Hydralazine 25 mg TID  
|               | Isosorbide dinitrate 20 mg TID  
|               | Enalapril 5 mg BID  
|               | Torsemide 40 mg BID  |
The Uncertain: 2 Weeks Later

- With prior authorization already obtained patiromer 8.4g daily is immediately started

- FP reports “no taste, no problems” and repeats blood work 5 days later

<table>
<thead>
<tr>
<th>Labs</th>
<th>Serum creatinine: 1.5 mg/dL → 1.7 mg/dL → 1.7 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated GFR: 45 mL/min/m² → 40 mL/min/1.73m² → 40 mL/min/1.73m²</td>
</tr>
<tr>
<td></td>
<td>Potassium: 4.9 mEq/L → 5.3 mEq/L → 4.6 mEq/L</td>
</tr>
<tr>
<td></td>
<td>Magnesium: 2.0 mEq/L</td>
</tr>
<tr>
<td></td>
<td>NT-proBNP: 4500 pg/mL → 2700 pg/mL → 2500 pg/mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitals</th>
<th>BP: 144/96 → 132/84 → 130/82</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR: 76 → 74 → 76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th>Carvedilol 12.5 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hydralazine 25 mg TID</td>
</tr>
<tr>
<td></td>
<td>Isosorbide dinitrate 20 mg TID</td>
</tr>
<tr>
<td></td>
<td>Enalapril 5 mg BID</td>
</tr>
<tr>
<td></td>
<td>Patiromer 8.4 g daily</td>
</tr>
<tr>
<td></td>
<td>Torsemide 40 mg BID</td>
</tr>
</tbody>
</table>
Summary and Conclusions

• The treatment of patients with HF or CKD include RAAS inhibitors that are associated with an improved prognosis

• Hyperkalemia is associated with a decreased use of RAASi and a poorer prognosis

• A close follow-up of potassium level is recommended in patients with HF, CKD or taking a RAASi

• New potassium-binding drugs -- patiromer and SZC – are highly effective at lowering serum potassium, while maintaining a favorable safety profile
We're a little concerned about your potassium levels.