Overview of Hyperkalemia in Heart Failure (HF)
Case Presentation

- 55 y/o male with known ischemic CM and EF of 0.20 admitted for HF management.
- 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, no MRG, JVP 15 cm with + HJR

• Ext: 2+ edema, warm
Treatment and Hospital Course

• Benazepril 10 mg daily and Bumex 1 mg IV twice daily started.

• Patient experiences vigorous diuresis and loses 15 lbs over 5 days.

• Patient feels markedly improved.

• Repeat echo shows enlarged LV with EF 0.20.

On CPET patients peak O$_2$ cons is PeakVO2 16.9 ml/kg/min.

What are the next steps to consider?
Labs

- Na 140
- K 5.5
- Cl 101
- Scr 1.42
- Ca 9.6
- WBC 9.4
- Hgb 16
- Plt 187
- BNP 463
Serum Potassium Cutoff Values to Define Hyperkalemia Vary 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 hyperkalemia

K+: potassium.

Rates of Hyperkalemia (≥6.0) in HF Patients on Mineralocorticoid Receptor Antagonists (MRA)

- RAASi clinical trials populations are carefully selected to exclude patients at high risk for hyperkalemia\(^1\)
- Incidence of hyperkalemia in community-based practice far exceeds that observed in clinical trials\(^1\)

Hyperkalemia With Spironolactone in Real-World vs Clinical Trial HF Patients\(^2-4\)

<table>
<thead>
<tr>
<th></th>
<th>Clinical Trials</th>
<th>Community-Based</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RALES n=822</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>EMPHASIS n=1,336</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Shah 2005 n=840</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Bozkurt 2003 n=104</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

HF: heart failure; RAASi: renin-angiotensin-aldosterone system inhibitor.
Hyperkalemia (>5.5) Rates in HF Patients Increase as Renal Function Declines

<table>
<thead>
<tr>
<th>Baseline eGFR ≥60</th>
<th>Baseline eGFR &lt;60</th>
<th>No WRF</th>
<th>WRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.0</td>
<td>8.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>15.4</td>
<td>25.6</td>
<td>18.2</td>
</tr>
<tr>
<td></td>
<td>30.2</td>
<td></td>
<td>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.

De-identified medical records (2007-2012) of individuals with at least 2 serum K⁺ readings were collected from Humedica database, Cambridge, MA.

Comorbidities were identified using ICD-9 diagnosis codes.

Mortality evaluated through hospital discharge records/Social Security registry.

### CV Comorbidities Analysis


<table>
<thead>
<tr>
<th>CV Comorbidities (DM, HF, CKD, CVD/HTN)</th>
<th>No CV Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=510,169</td>
<td>n=197,489</td>
</tr>
</tbody>
</table>

Spline analysis performed to assess mortality at 0.1 mEq/L increments of K⁺ after adjusting for all covariates (age, gender, CVD, HTN, AMI, HF, DM, RAASi use within previous 12 months, CKD stage) and interactions.

Comorbidities analysis also adjusted for interactions for patients aged ≥45 y.


Adjusted Mortality* by Serum K\(^+\) Level in Patients 45 to 64 Years and ≥65 Years With and Without Comorbid Illness

Increases in mortality remained after adjustments for demographic characteristics and comorbidities

*Evaluated through de-identified medical records (2007-2012) of individuals with ≥2 mEq/L serum K\(^+\) readings (Humedica, Cambridge, MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K\(^+\) after adjusting for covariates and interactions. Comorbid patients are those with diabetes, heart failure, CKD stages 3-5, cardiovascular disease, or hypertension.

CKD: chronic kidney disease; K\(^+\): potassium.

Benefits of Mineralocorticoid Receptor Antagonists (MRAs) in Patients With Heart Failure and Reduced Ejection Fraction (HF-REF)
RAASi Have Been Extensively Studied in Patients With Heart Failure (HF) and Post-Myocardial Infarction (MI)

<table>
<thead>
<tr>
<th></th>
<th>Post-MI Low EF</th>
<th>Mild-Mod CHF Low EF</th>
<th>CHF Severe HF</th>
<th>CHF Preserved EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi¹</td>
<td>AIRE SAVE</td>
<td>SOLVD</td>
<td>CONSENSUS</td>
<td>PEP-CHF (perindopril)</td>
</tr>
<tr>
<td>MRA</td>
<td>EPHESUS¹ (eplerenone)</td>
<td>EMPHASIS¹ (eplerenone)</td>
<td>RALES¹ (spironolactone)</td>
<td>TOPCAT² (spironolactone)</td>
</tr>
<tr>
<td>ARB¹</td>
<td>OPTIMAAL VALIANT</td>
<td>ELITE-II HEALL VAL-HeFT CHARM</td>
<td>CHARM-Preserved I-PRESERVE</td>
<td></td>
</tr>
<tr>
<td>ARNI³</td>
<td></td>
<td>PARADIGM-HF (LCZ-696)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; CHF: chronic heart failure; EF: ejection fraction; MRA: mineralocorticoid receptor antagonist; RAASi: renin-angiotensin-aldosterone inhibitor.

RALES: The Landmark Trial of Spironolactone in Severe Heart Failure

NYHA III or IV heart failure
LVEF ≤35%
ACEi + loop diuretic ± digoxin

Spironolactone
25 mg/day
(n=822)

3 years

Placebo
(n=841)

Primary End Point
Total mortality
Key Secondary End Points
Cardiac mortality
Cardiac hospitalization
Changes from baseline in NYHA classification

*History of NYHA IV within 6 months before first dose.

ACEi: angiotensin-converting enzyme inhibitor; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association.
RALES Demonstrated Clear Survival Benefit of Spironolactone in Patients With Severe Heart Failure

Primary end point:
Risk reduction 30%;
P<0.001

ACE: angiotensin-converting enzyme.

EPHESUS Was Landmark Trial of Eplerenone in Patients With LV Dysfunction Post-MI

3-14 days post-AMI, HF, LVEF ≤40%, or diabetes
Standard therapy

Mean 16 months

Eplerenone
Up to 50 mg/day
(n=3319)

Placebo
(n=3313)

Two co-primary end points
Total mortality
CV mortality/CV hospitalizations

Key secondary end points
All-cause death or hospitalization
CV death

EPHESUS Demonstrated Robust Mortality Benefit of Eplerenone in Patients With LV Dysfunction Post-MI

Eplerenone

Placebo

Months Since Randomization

Cumulative Incidence (%)

LVEF ≤40%
3-14 days post-AMI

RR = 0.85 (95% CI, 0.75-0.96)
p = 0.008

Placebo

Eplerenone

AMl: acute myocardial infarction; CI: 95% confidence interval; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; RR: relative risk.

EMPHASIS Evaluated Eplerenone in Patients With Mild Heart Failure (NYHA Class II)

NYHA II heart failure
LVEF ≤35%
ACEi or ARB + β-Blocker

Median 21 months

Eplerenone
Up to 50 mg/day
(n=1364)

Placebo
(n=1373)

Primary end point
CV death, or first hospitalization for HF

Key secondary end points
All-cause death or hospitalization for HF
All-cause death
CV death
Hospitalization for HF


EMPHASIS Demonstrated Significant Reductions in Key Clinical End Points

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CV: cardiovascular; HF: heart failure; MRA: mineralocorticoid receptor antagonist.

Hyperkalemia in Landmark MRA Trials in Patients With Heart Failure
Hyperkalemia (>6.0) Rates Were Relatively Low With MRAs in HF Trials With Careful Patient Selection and Monitoring

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; MRA: mineralocorticoid receptor antagonist; GFR: glomerular filtration rate; HF: heart failure; K⁺: potassium; qd: once daily; SrCr: serum creatinine.

Hyperkalemia Can Limit Implementation of Guideline-Recommended Therapy in Heart Failure
Mineralocorticoid Receptor Antagonists Are Level I Recommendation for Many Patients With Heart Failure

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mineralocorticoid receptor antagonists are recommended in patients with NYHA class II-IV HF who have LVEF ≤35%</td>
<td>I</td>
</tr>
<tr>
<td>Mineralocorticoid receptor antagonists are recommended in patients following an acute MI who have LVEF ≤40% with symptoms of HF or DM</td>
<td>I</td>
</tr>
<tr>
<td>Inappropriate use of mineralocorticoid receptor antagonists may be harmful</td>
<td>III: Harm</td>
</tr>
</tbody>
</table>


Guidelines Recommend RAASi Dose Modifications With Increasing Serum K$^+$

**Serum K$^+$ Threshold Before Change in RAASi Guideline Recommendation**

- **>6.0**
  - NICE$^5$: don’t start RAASi if >5.0
  - ESC HFA$^2$, K/DOQI$^6$: Reduce dose of/stop ACEi/ARB, MRA if >5.5

- **>5.5**
  - HFSA HF$^3$: MRA not recommended >5.0

- **>5.0**
  - ACC/AHA HF$^1$: MRA not recommended >5.0

KDIGO Guidelines do not provide recommendations$^4$


Hyperkalemia Is a Reason for Discontinuation of Mineralocorticoid Receptor Antagonists (MRA)

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

Reason for spironolactone suspension (%)

- Hyperkalemia: 17.1%
- Renal function decline
- Gynecomastia
- Other

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

DC: discontinuation; HF: heart failure; srCr, serum creatinine.
Hyperkalemia was common with both ACEIs and LCZ696 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></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>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.

McMurray et al., NEJM. 2014.
Current Treatment Options for Hyperkalemia

- **Emergency Therapy**
  - Calcium gluconate\(^{1,2,3}\)
  - Insulin + Dextrose\(^{1,2,3}\)
  - \(\beta_2\)-adrenergic receptor agonists\(^{1,2,3}\)

- **Intermediate Therapy**
  - Dialysis\(^{1,2,3}\)
  - Sodium bicarbonate\(^{1,2,3}\)
  - Sodium polystyrene sulfonate (SPS)\(^{1,2,3}\)
  - Loop diuretics\(^{1,2,3}\)

- **Maintenance Therapy**
  - RAASi reduction\(^{2,4}\)
  - Low K\(^+\) diet\(^4\)

- **Membrane stabilization**
- **K\(^+\) redistribution**
- **K\(^+\) elimination**
- **Removal/reduction of food or drugs that ↑ serum K\(^+\)**

---

## Long-Term Hyperkalemia Management Strategies

<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  
Restricts 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 Not the Answer

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

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warning</strong></td>
<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></td>
<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></td>
<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></td>
<td>Concomitant administration of sorbitol is not recommended</td>
<td>Discontinue use in patients who develop constipation</td>
</tr>
<tr>
<td></td>
<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:**

## Kayexalate: Additional Considerations for HF Patients

<table>
<thead>
<tr>
<th>Heart Failure Society of America (HFSA) Recommendations¹</th>
<th>Kayexalate Administration²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt;2 g/day sodium in patients with moderate to severe HF</td>
<td>• Average daily dose of SPS is 15-60 g/day: 100 mg of Na⁺/1 g of SPS*</td>
</tr>
<tr>
<td>• Restriction of daily fluid intake to &lt;2,000 mL is recommended in patients with severe hyponatremia (serum sodium &lt;130 mEq/L)</td>
<td>• Standard SPS dose contains 20-100 mL of water; 1 to 4x/day</td>
</tr>
</tbody>
</table>

## Patiromer (VELTASSA) Oral Suspension

<table>
<thead>
<tr>
<th>Patiromer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free-flowing powder of small, spherical beads (~100 µm)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Active moiety, patiromer, is nonabsorbed&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Calcium (rather than sodium) is exchanged for potassium&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Site of action is the gastrointestinal tract, mainly in the lumen of the colon where&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- K&lt;sup&gt;+&lt;/sup&gt; is the most abundant cation</td>
</tr>
<tr>
<td>- Residence time of the polymer is the longest</td>
</tr>
</tbody>
</table>

Phase 3 Pivotal Study in HK Patients With CKD on RAASi: Special Protocol Assessment With FDA

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

- **Mild HK**
  - Screening serum $K^+ 5.1$-$5.5$ mEq/L;
  - 4.2 g BID starting dose (n=92)

- **Moderate to Severe HK**
  - Screening serum $K^+ 5.5$-$6.5$ mEq/L;
  - 8.4 g BID starting dose (n=151)

Subjects with CKD* on RAASi (n=243)

**Part B:**
Randomized Withdrawal Phase (Single-Blind)

- Patients with Part A baseline $K^+ \geq 5.5$ mEq/L who completed Part A and
  - Serum $K^+ 3.8$-$5.1$ mEq/L, at Part A, Week 4
  - Still on patiromer
  - Still on RAASi (n=107)

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

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

Baseline Part A ➔ Week 4 Part A Primary Endpoint ➔ Baseline Part B

Week 4 Part B Primary Endpoint ➔ Week 4 Part B Secondary Endpoints

*Randomization

**Protocol**


*BID: twice daily; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FDA: Food and Drug Administration; HK: hyperkalemia; $K^+$: potassium; RAASi: renin-angiotensin-aldosterone system inhibitors.
Part A: Treatment Phase (Single-Blind)

**Mild HK**
Screening serum K$^+$ 5.1-5.5 mEq/L; 4.2 g BID starting dose (n=39 with HF) (n=53 without HF)

**Moderate to Severe HK**
Screening serum K$^+$ 5.5-6.5 mEq/L; 8.4 g BID starting dose (n=63 with HF) (n=88 without HF)

Subjects with HF (n=102)
Subjects without HF (n=142)

Baseline Part A

Week 4 Part A Primary Endpoint

Part B: Randomized Withdrawal Phase (Single-Blind)

Patients with Part A baseline K$^+$ ≥5.5 mEq/L who completed Part A and
- Serum K$^+$ 3.8-<5.1 mEq/L at Part A, Week 4
- Still on patiromer
- Still on RAASi
  - (n=49 with HF) (n=58 without HF)

Patiromer, continued RAASi (n=27 with HF) (n=28 without HF)

Placebo, continued RAASi (n=22 with HF) (n=30 without HF)

Baseline Part B

Week 4 Part B Primary Endpoint

Week 8 Part B Secondary Endpoints

Determined by history of HF based on investigator assessment (Patients with New York Heart Association (NYHA) class IV were excluded).

BID: twice daily; eGFR: estimated glomerular filtration rate; HF: heart failure; HK: hyperkalemia; K$^+$: potassium; RAASi: renin-angiotensin-aldosterone system inhibitors.

The aim of this subgroup analysis is to study the effects of patiromer in HF patients in the OPAL-HK study

- **Primary objectives**
  - Treatment phase: to determine the mean change in serum K⁺ level from baseline to week 4 in patients who received ≥1 dose of patiromer and had at least 1 K⁺ measurement after day 3
  - Randomized withdrawal phase: to analyze the difference between the patiromer and placebo groups in the median change in serum K⁺ from baseline to either week 4—if serum K⁺ stayed in target range—or the earliest visit when serum K⁺ was outside that range

- **Secondary objectives**
  - Treatment phase: to determine the proportion of patients whose serum K⁺ was within target range (3.8-<5.1 mEq/L) at week 4
  - Randomized withdrawal phase: proportions of patients with a recurrence of hyperkalemia according to 2 definitions: serum K⁺ of ≥5.1 or ≥5.5 mEq/L

HF: heart failure; K⁺: potassium.
## Baseline Demographic and Clinical Characteristics for HF and Non-HF Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Heart Failure n=102</th>
<th>No Heart Failure n=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>56 (55%)</td>
<td>84 (60%)</td>
</tr>
<tr>
<td>Age (yr), mean (SD)</td>
<td>67.4 (8.6)</td>
<td>61.9 (11.1)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>102 (100%)</td>
<td>137 (97%)</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73 m²), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 to ≤90 [Stage 2]</td>
<td>9 (9%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>45 to &lt;60 [Stage 3A]</td>
<td>20 (20%)</td>
<td>29 (21%)</td>
</tr>
<tr>
<td>30 to &lt;45 [Stage 3B]</td>
<td>28 (27%)</td>
<td>35 (25%)</td>
</tr>
<tr>
<td>&lt; 30 [Stage 4/5]</td>
<td>45 (44%)</td>
<td>64 (45%)</td>
</tr>
<tr>
<td>Serum K⁺ (mEq/L), mean (SD)</td>
<td>5.6 (0.6)</td>
<td>5.5 (0.4)</td>
</tr>
<tr>
<td>Type 2 diabetes, n (%)</td>
<td>55 (54%)</td>
<td>84 (60%)</td>
</tr>
<tr>
<td>Time since T2DM diagnosis (yr), mean (SD)</td>
<td>12.0 (9.9)</td>
<td>14.0 (8.9)</td>
</tr>
</tbody>
</table>

| NYHA heart failure class,* n (%)|                     |                        |
| I                               | 19 (19%)            | NA                     |
| II                              | 66 (65%)            | NA                     |
| III                             | 17 (17%)            | NA                     |
| Myocardial Infarction, n (%)    | 33 (32%)            | 27 (19%)               |
| Hypertension, n (%)             | 97 (95%)            | 139 (99%)              |

*NYHA class IV heart failure patients were excluded.
eGFR: estimated glomerular filtration rate; HF: heart failure; K⁺: potassium; NYHA: New York Heart Association; SD: standard deviation; T2DM: type 2 diabetes mellitus

Baseline RAASi, Beta Blocker, and Diuretic Use for HF and Non-HF Patients

<table>
<thead>
<tr>
<th>Medication</th>
<th>Heart Failure n=102</th>
<th>No Heart Failure n=141</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAASi medication, n (%)</strong></td>
<td>102 (100%)</td>
<td>141 (100%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>70 (69%)</td>
<td>100 (71%)</td>
</tr>
<tr>
<td>ARB</td>
<td>37 (36%)</td>
<td>55 (39%)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>20 (20%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Renin inhibitor</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Dual RAASi blockade,* n (%)</td>
<td>25 (25%)</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>On maximal RAASi dose,** n (%)</td>
<td>42 (41%)</td>
<td>64 (45%)</td>
</tr>
</tbody>
</table>

**Non-RAASi antihypertensive, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure n=102</th>
<th>No Heart Failure n=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blocker</td>
<td>60 (59%)</td>
<td>68 (48%)</td>
</tr>
</tbody>
</table>

**Non-RAASi diuretic, n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure n=102</th>
<th>No Heart Failure n=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide</td>
<td>27 (26%)</td>
<td>43 (30%)</td>
</tr>
<tr>
<td>Loop</td>
<td>44 (43%)</td>
<td>33 (23%)</td>
</tr>
</tbody>
</table>

*Any combination of two or more of the following: ACE inhibitor, ARB, aldosterone antagonist, renin inhibitor.

†As judged by the investigator in accordance with local standards of care.

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; HF: heart failure; RAASi: renin-angiotensin-aldosterone system inhibitors.

Primary Endpoint: Mean Change in Serum K⁺ From Baseline to Week 4 During the Treatment Phase (Part A)

### Treatment Phase Primary Endpoint:

**Mean Change from Baseline to Week 4**

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure (mEq/L)</th>
<th>No Heart Failure (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 1</strong></td>
<td>-0.5±0.05</td>
<td>-0.7±0.04</td>
</tr>
<tr>
<td><strong>Week 2</strong></td>
<td>-0.8±0.05</td>
<td>-0.9±0.04</td>
</tr>
<tr>
<td><strong>Week 3</strong></td>
<td>-0.9±0.05</td>
<td>-1.0±0.04</td>
</tr>
<tr>
<td><strong>Week 4</strong></td>
<td>-1.1±0.05</td>
<td>-1.0±0.04</td>
</tr>
</tbody>
</table>

**Mean (±SE) Serum K⁺ change from baseline (mEq/L)**

- **HF**: -1.06 (95% CI, -1.16, -0.95)
- **No HF**: -0.98 (95% CI, -1.06, -0.90)

*p* < 0.001 for interaction

Secondary endpoint: 76% and 75% of patients with and without HF, respectively, had serum K⁺ 3.8 to < 5.1 mEq/L at week 4

Cl: 95% confidence interval; HF: heart failure; K⁺: potassium; SE: standard error.

Primary Endpoint: Difference Between Treatments in the Median Change in Serum $K^+$ After 4 Weeks (Part B)

**HF Patients**

- **Placebo:** Estimated Median Change = 0.74 mEq/L ($n = 22$)
- **Patiromer:** Estimated Median Change = 0.10 mEq/L ($n = 27$)

\[ \Delta = 0.64 \text{ mEq/L} \]

(95% CI, 0.29, 0.99)*

**Non-HF Patients**

- **Placebo:** Estimated Median Change = 0.78 mEq/L ($n = 30$)
- **Patiromer:** Estimated Median Change = -0.05 mEq/L ($n = 28$)

\[ \Delta = 0.83 \text{ mEq/L} \]

(95% CI, 0.42, 1.24)*

*p = 0.50 for interaction between HF vs no HF

**Notes:**
- *p < 0.001 for between-group difference in mean ranks of change.
- CI: 95% confidence interval; HF: heart failure; $K^+$: potassium.

Exploratory Endpoint: Effect of Patiromer on Time to First Recurrence of Hyperkalemia in Patients With Heart Failure During the Withdrawal Phase (Part B)

Time to hyperkalemia (serum K⁺ ≥5.1 mEq/L) recurrence, patients with HF

Secondary endpoint: Recurrent hyperkalemia, when defined by ≥1 serum K⁺ ≥5.1 mEq/L, occurred in 95% of placebo patients with HF compared with 36% of patiromer patients with HF (p<0.001)

BL: baseline of withdrawal phase; HF: heart failure; K⁺: potassium.

OPAL-HK

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

Starting Patiromer Dose

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

- Subjects with CKD* on RAASi (n=243)
- Baseline serum K⁺ 5.1-<5.5 mEq/L (Mild Hyperkalemia)
- Starting Patiromer Dose: 8.4g per day (total daily dose)† (n=92)

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

- Baseline serum K⁺ 5.5-<6.5 mEq/L (Moderate/Severe Hyperkalemia)
- Starting Patiromer Dose: 16.8g per day (total daily dose)† (n=151)

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

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

Change in Serum Potassium (mEq/L)

- Mild HK: -0.65
- Moderate/Severe HK: -1.23
- Total: -1.01

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

---

Phase 3 Part A: Primary and Secondary Efficacy Endpoints

Secondary Efficacy Endpoint: 76% of subjects had serum $K^+$ in the target range (3.8 to <5.1 mEq/L) at week 4.

Phase 3 Part B: Exploratory Endpoints

![Bar chart showing the proportion of subjects requiring any adjustment of RAASi or patiromer dose increase due to hyperkalemia and receiving any dose of a RAASi at the end of Part B.]

- **Requiring any adjustment of RAASi (or down-titration or discontinuation) or patiromer dose increase 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: 94%

Effect of Withdrawing Patiromer on Serum Potassium Control

Part B: 8-week 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 to < 5.1 mEq/L at Part A Week 4
- Still on RAASi

(n=107)

Patiromer*, continued RAASi
(n=55)

Placebo, continued RAASi
(n=52)

Baseline Part B

Week 4 Part B†
1º Endpoint

Week 8 Part B
2º Endpoint
OPAL-HK Study Part B: Efficacy Results

- **Primary Endpoint:**
  - Estimated median change in serum potassium from Part B baseline*

  ![Graph showing change in serum potassium](image)

  \[ \Delta = 0.72 \text{ mEq/L} \]
  \[ p < 0.001 \]

- **Secondary Endpoint:**
  - Exceeded serum potassium threshold at any time during Part B

<table>
<thead>
<tr>
<th>Serum Potassium (mEq/L)</th>
<th>Placebo</th>
<th>VELTASSA†</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ ≥ 5.1 mEq/L</td>
<td>91% [95% CI: 83%, 99%]</td>
<td>43% [95% CI: 30%, 56%]</td>
<td>≤0.001</td>
</tr>
<tr>
<td>K⁺ ≥ 5.5 mEq/L</td>
<td>60% [95% CI: 47%, 74%]</td>
<td>15% [95% CI: 6%, 24%]</td>
<td>≤0.001</td>
</tr>
</tbody>
</table>

AMETHYST-DN

Open-Label Study

Subjects with CKD* and T2DM on stable RAASi dose (n=304)

Mild HK (K⁺ >5.0–5.5) n=222

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

Moderate HK (K⁺ >5.5–<6.0) n=84

- Initial dose of 17g/day (total daily dose)
- Mean daily dose was 20 g

Screening ≤10 days
Run-in ≤4 wk
Baseline
Wk 4† Wk 8
Wk 52

Mean Change in Serum Potassium Over 1 Year (AMETHYST-DN)

Mean (95% CI) Serum Potassium over 52 weeks

Baseline Serum K⁺ >5.0 – 5.5 mEq
Baseline Serum K⁺ >5.5 – <6.0 mEq/L
Mean Change in Serum Potassium Over 1 Year (AMETHYST-DN)

Mean change in serum potassium over 1 year (AMETHYST-DN)

Mean (95% CI) Serum Potassium over 52 weeks

Study Visit (week)

Follow-Up (day)

Baseline Serum K⁺ >5.5 – <6.0 mEq/L

N= 301
(start of study)

N= 173
(study end)
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.
Warning: Binding to Other Oral Medications
VELTASSA binds to many orally administered medications, which could decrease their absorption and reduce their effectiveness. Administer other oral medications at least 6 hours before or 6 hours after VELTASSA. Choose VELTASSA or the other oral medication if adequate dosing separation is not possible.

Indication
• VELTASSA is indicated for the treatment of hyperkalemia
• **Limitation of Use:** VELTASSA 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 VELTASSA or any of its components
orsening of Gastrointestinal Motility

- Avoid use of VELTASSA in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders
- VELTASSA may be ineffective and may worsen gastrointestinal conditions
- Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in clinical studies

Hypomagnesemia

- VELTASSA binds to magnesium in the colon, which can lead to hypomagnesemia
- In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with VELTASSA
- Approximately 9% of patients in clinical trials developed hypomagnesemia with a serum magnesium value < 1.4 mg/dL
- Monitor serum magnesium
- Consider magnesium supplementation in patients who develop low serum magnesium levels
Patiromer: Dosing and Administration Summary

**Dosing:**
- 8.4 grams of patiromer once daily (recommended starting dose)
- Administer at least 6 hours before or 6 hours after other oral medications
- Monitor serum potassium and increase or decrease dose as necessary
- Up-titrate 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
- Taken as oral suspension once a day with food
- Do not heat, add to heated foods or liquids or take in its dry form

**Storage:**
- Store in the refrigerator at 2°C to 8°C (36°F to 46°F)*
- Use within 3 months if stored at room temperature (25°C ± 2°C [77°F ± 4°F])*

*Note: Temperatures are approximate and may vary.*
ZS-9: A Novel First-in-Class Inorganic Crystalline Compound Designed Specifically to Trap $K^+$

- First in class inorganic crystalline zirconium silicate compound
- Exchanges $K^+$ for $H^+$ and $Na^+$ in the intestine
- Highly selective for $K^+$ trapping (>125 times more than SPS)
- Insoluble, stable, does not expand in water
- Not systemically absorbed

*SPS: sodium polystyrene sulfonate

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

Lower GI tract (transit time)

Stomach | Duodenum | Jejunum | Ileum | Colon/Rectum | Exit

- Monovalent: $K^+$, $H^+$, $Na^+$
- Divalent: $Ca^{2+}$, $Mg^{2+}$

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

Adapted from: Stravos et al. PLOSONE 2014
In Vitro, ZS-9 is More Selective for Potassium than Kayexalate (SPS)

Potassium, Calcium, and Magnesium Concentration Ratio (1:1:1)

**ZS-9 Ion Binding**
- K+: 96
- Ca2+: 2**
- Mg2+: 2**

**Kayexalate Ion Binding**
- K+: 18
- Ca2+: 59
- Mg2+: 24

**KEY OBSERVATIONS**
- ZS-9 is more selective for K+ even in the presence of other ions
- SPS is more selective for Ca2+ than K+
- ZS-9 is >125 times more selective for K+ than SPS
- ZS-9 has 9.3 times more K+ binding capacity than SPS

SPS: Sodium Polysterene Sulphonate
*Selectivity Ratio = [K+] / [Ca2+] + [Mg+2]
**Exchange capacity of Ca2+ and Mg2+ was below the set detection limit of 0.05 mEq/g; therefore, 0.05 mEq/g assumed for calculation purposes.

*Stavros et al., submitted manuscript

Adapted from: Stravos et al. PLOSONE 2014
ZS003 Phase 3 Study Design

Rate of Change in Serum Potassium from Baseline to 48 Hours

Rate of Change in Serum [K⁺] from Baseline to 48 Hours

Rate of Change in Serum Potassium from 48 Hours to Day 14

Rate of Change in Serum [K⁺] from 48 Hours to Day 14

ZS-9 Reduces Potassium Levels

Mean Serum Potassium Levels Over 48 Hours With ZS-9

Serum Potassium Levels During the Open-Label Phase (48 Hours)

A, Mean serum potassium levels over time in patients treated during the open-label phase with zirconium cyclosilicate, 10 g, 3 times daily for 48 hours. B, Mean serum potassium levels at 0 and 48 hours across prespecified subgroups of chronic kidney disease (CKD) (by patient history and by estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²), heart failure, diabetes mellitus, concomitant renin-angiotensin-aldosterone system inhibitor (RAASi) use, and baseline potassium levels. Error bars indicate 95% confidence intervals; shaded region, normal potassium range.

Effects of ZS-9 on Serum Potassium Levels

Serum Potassium Levels During the Randomized Phase (Days 8-29) According to Study Group A. Primary end point: mean serum potassium over days 8-29 of the randomized phase in the placebo and 5-g, 10-g, and 15-g doses of zirconium cyclosilicate. B, Serum potassium levels during the randomized phase: patients received placebo or zirconium cyclosilicate, 5 g, 10 g, or 15 g, once daily for 28 days. Error bars indicate 95% confidence interval; shaded region, normal potassium range.

Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia: The HARMONIZE Randomized Clinical Trial JAMA. 2014;312(21):2223-2233.
Dose-Dependent Serum K+ Reduction Over 48 Hours in HF Patients on RAASi

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,
Once Daily ZS-9 10g Maintained Normal Range of Mean Serum K+ Levels Compared With Placebo: HF Patients on RAASi

Mean Serum K⁺ (Extended Treatment, HF on RAASi) – 10g vs. Placebo

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,
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 (Veltassa) or will be (ZS-9) available.

- Use of these new agents are likely to become important adjuncts to heart failure therapy.