Rational For New Approaches For Treatment Of Hyperkalemia In Heart Failure

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

- VS: HR 76 bpm, BP 122/82 mmHg.
- Functional class II, no signs of volume overload.
- Labs: Na 140, K 5.0, Scr 1.4, GFR 52 mL/min/1.73 m²
- Meds: ASA 81 mg/d, enalapril 10 mg bid, Carvedilol 25 mg bid, furosemide 40 mg bid.
Case Presentation

- Could/should the patient be started on spironolactone?
- Could /should the patient be switched from enalapril to sacubitril/valsartan (Entresto) and if yes (for both) which one first? and at what dose?
Aldosterone antagonists are not recommended when:

- creatinine is > 2.5 mg/dL in men and >2.0 in women (or creatinine clearance is < 30 ml/min/1.73 m2)
- serum potassium is > 5.0 mmol/L
- in conjunction with other potassium-sparing diuretics.

Strength of Evidence = A
Figure 1. Kaplan–Meier Estimates of Death from Any Cause.
CI denotes confidence interval.
EMPHASIS - Results

A. CV mortality/HF hospitalizations

B. All cause mortality

C. All cause hospitalizations

D. HF hospitalizations
EMPHASIS - Results

- Results

CV mortality/HF hospitalizations

All cause mortality

23% survival benefit with ICD in 45 months

24% survival benefit in 23 months
Should patients with CRD be treated with RAAS inhibitors?
### 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><strong>ACEi</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AIRE SAVE</td>
<td>SOLVD</td>
<td>CONSENSUS</td>
<td>PEP-CHF (perindopril)</td>
</tr>
<tr>
<td><strong>MRA</strong></td>
<td>EPHESUS&lt;sup&gt;1&lt;/sup&gt; (eplerenone)</td>
<td>EMPHASIS&lt;sup&gt;1&lt;/sup&gt; (eplerenone)</td>
<td>RALES&lt;sup&gt;1&lt;/sup&gt; (spironolactone)</td>
<td>TOPCAT&lt;sup&gt;2&lt;/sup&gt; (spironolactone)</td>
</tr>
<tr>
<td><strong>ARB</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>OPTIMAAL VALIANT</td>
<td>ELITE-II HEALL VAL-HeFT CHARM</td>
<td></td>
<td>CHARM-Preserved I-PRESERVE</td>
</tr>
<tr>
<td><strong>ARNI</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PARADIGM-HF (LCZ-696)</td>
<td></td>
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<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.

Renal Insufficiency should not preclude use of ACEI for pts with AMI and low EF

- 20902 Medicare patients with LVEF < 40% following confirmed AMI.
- One year survival in patients with and without renal insufficiency (Scr ≥ 3.0 mg/Dl) receiving ACEI.

141,413 US veterans with nondialysis CKD. GFR <60 in 90% and <44 in 30%. 90% hypertension and 15% Heart failure.

Hazard ratio in the as treated patients: 0.37, 95% CI 0.34-0.41

Prognostic Importance of Early WRF After Initiation of ACE Inhibitors

6337 SOLVD patients
WRF = \( \downarrow \) GFR ≥ 20%
Pts continued on enalapril in spite WRF HR 0.66 P = 0.02

Conclusions

- Early WRF associated with initiation of ACE inhibitors is free of adverse prognostic significance.
- Patients with WRF in the setting of initiation of ACEI/ARB do not seem to lose the survival benefits of these drugs.

AHA/ACC guidelines 2013:
ACE inhibitors should be prescribed with caution in patients with markedly increased Scr (> 3 mg/dL).
Benefits of Mineralocorticoid Receptor Antagonists (MRAs) in Patients With Heart Failure and Reduced Ejection Fraction (HF-REF)
Influence of Baseline and Worsening Renal Function on Efficacy of Spironolactone in Patients With Severe Heart Failure

Insights From RALES (Randomized Aldactone Evaluation Study)

Orly Vardeny, PHARM D, MS,* Dong Hong Wu, PHD,† Akshay Desai, MD, MPH,† Patrick Rossignol, MD,‡ Faiez Zannad, MD,‡ Bertram Pitt, MD,§ Scott D. Solomon, MD,† for the RALES Investigators

RALES
Randomized ALdactone Evaluation Study

- NYHA class III or IV HF with decreased LV function
- Added spironolactone (25 mg) or placebo to standard HF therapy
- Spironolactone significantly decreased mortality by 30%
- 10-11% of patients were on beta-blocker therapy
- 94-95% were on ACE inhibitors

Randomized 2737 pts >55 years with NYHA Class II-III symptoms, LVEF <0.30 (or 0.30-0.35 if QRS >130msec) and serum K+ ≤5.0 mmol/l within 6 months of a CV hospitalization to either eplerenone (up to 50 mg daily) or placebo in addition to standard therapy.
Aldosterone antagonists reduce morbidity and mortality in patients with EF <0.35 and severe heart failure (RALES) or following an MI (EPHESUS).

Whether these agents are effective in patients with reduced EF and milder degrees of heart failure is uncertain.
EMPHASIS - Results
## 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</td>
<td>554/3,319</td>
<td>478/3,313</td>
<td>.85 (.75, .96)</td>
<td>.008</td>
</tr>
<tr>
<td>Post-MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RALES</td>
<td>386/841</td>
<td>284/822</td>
<td>.70 (.60, .82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Advanced HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPHASIS</td>
<td>356/1373</td>
<td>249/1364</td>
<td>.76 (.62, .93)</td>
<td>.008</td>
</tr>
<tr>
<td>Milder HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aldosterone receptor antagonists are recommended in patients with NYHA class II-IV, LVEF of ≤35%, to reduce morbidity and mortality. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists.

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.

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

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.
### Efficacy of Spironolactone by baseline GFR and WRF

<table>
<thead>
<tr>
<th></th>
<th>eGFR &lt;60 ml/min/1.73 m² (n = 792)</th>
<th>eGFR ≥60 ml/min/1.73 m² (n = 866)</th>
<th>Efficacy of Spironolactone Comparing Treatment Group With WRF With Placebo Group Without WRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0.68 (0.56-0.84)</td>
<td>0.71 (0.57-0.90)</td>
<td>0.72 (0.54-0.98)</td>
</tr>
<tr>
<td>Death or HF hospital stay</td>
<td>0.67 (0.56-0.81)</td>
<td>0.64 (0.52-0.77)</td>
<td>0.82 (0.64-1.04)</td>
</tr>
</tbody>
</table>

Vardeny O et al JACC 2012;60:2082
Analysis from the RALES study
Influence of BL GFR on Efficacy of Spironolactone

Figure 1  Baseline Mortality and Hospital Stay

(A) Mortality by baseline estimated glomerular filtration rate (eGFR) and randomized treatment. (B) Mortality and hospital stay for heart failure (HF) by baseline eGFR and treatment. Baseline renal function did not modify the efficacy of spironolactone on all-cause mortality and the combined endpoint of mortality and hospital stays for HF.

Influence of WRF on Efficacy of Spironolactone

Figure 2: Kaplan-Meier Curves and Forest Plots for WRF

Spironolactone, GFR and WRF

- Patients with HF and reduced GFR exhibit similar risk reduction with Spironolactone compared with patients with higher GFR.
- Individuals randomized to spironolactone derive benefits regardless of whether renal function worsens during treatment.
Renin–Angiotensin System Inhibition, Worsening Renal Function, and Outcome in Heart Failure Patients With Reduced and Preserved Ejection Fraction

A Meta-Analysis of Published Study Data

Iris E. Beldhuis, BSc; Koen W. Streng, MD; Jozine M. Ter Maaten, MD, PhD; Adriaan A. Voors, MD, PhD; Peter van der Meer, MD, PhD; Patrick Rossignol, MD, PhD; John J.V. McMurray, MD; Kevin Damman, MD, PhD

Background—Renin–angiotensin aldosterone system (RAAS) inhibitors significantly improve outcome in heart failure (HF) patients with reduced ejection fraction (HREF), irrespective of the occurrence of worsening renal function (WRF). However, in HF patients with preserved ejection fraction (HFPEF), RAAS inhibitors have not been shown to improve outcome but are still frequently prescribed.

Methods and Results—Random effect meta-analysis was performed to investigate the relationship between RAAS inhibitor therapy, WRF in both HF phenotypes, and mortality. Studies were selected based on literature search in MEDLINE and included randomized, placebo controlled trials of RAAS inhibitors in chronic HF. The primary outcome consisted of the interaction analysis for the association between RAAS inhibition–induced WRF, HF phenotype and outcome. A total of 8 studies (6 HREF and 2 HFPEF, including 28,961 patients) were included in our analysis. WRF was more frequent in the RAAS inhibitor group, compared with the placebo group, in both HREF and HFPEF. In HREF, WRF induced by RAAS inhibitor therapy was associated with a less increased relative risk of mortality (relative risk, 1.19 (1.08–1.31); P<0.001), compared with WRF induced by placebo (relative risk, 1.48 (1.35–1.62); P<0.001; P for interaction 0.005). In contrast, WRF induced by RAAS inhibitor therapy was strongly associated with worse outcomes in HFPEF (relative risk, 1.78 (1.43–2.21); P<0.001), whereas placebo-induced WRF was not (relative risk, 1.25 (0.88–1.77); P=0.21; P for interaction 0.002).

Conclusions—RAAS inhibitors induce renal dysfunction in both HREF and HFPEF. However, in contrast to patients with HREF where mortality increase with WRF is small, HFPEF patients with RAAS inhibitor–induced WRF have an increased mortality risk, without experiencing improved outcome with RAAS inhibition.

(Circ Heart Fail. 2017;10:e003588. DOI: 10.1161/CIRCHEARTFAILURE.116.003588.)
RAAS Inhibitors and Hyperkalemia
Rate of Hyperkalemia after publication of RALES

Jurleenk DN et al NEJM 2004;351:543

Number of prescriptions of srironolactone in pts with HF on ACE-I

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

Death due to hyperkalemia in pts with HF on ACE-I
### Table 5: Adverse Events and Drug Discontinuation During Titration

<table>
<thead>
<tr>
<th></th>
<th>Baseline eGFR &lt;60</th>
<th>Baseline eGFR ≥60</th>
<th>No WRF</th>
<th>WRF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PL (n = 402)</td>
<td>SP (n = 390)</td>
<td>PL (n = 781)</td>
<td>SP (n = 683)</td>
</tr>
<tr>
<td>Hyperkalemia (K &gt; 5.5 mmol/l or AE)*</td>
<td>8.5%</td>
<td>25.6%</td>
<td>6.0%</td>
<td>15.4%</td>
</tr>
<tr>
<td></td>
<td>OR † 3.7 (2.5-5.7)</td>
<td>OR 2.9 (1.8-4.6)</td>
<td>OR 3.1 (2.2-4.4)</td>
<td>OR 3.8 (1.2-6.4)</td>
</tr>
<tr>
<td>Dose reduction or discontinuation during titration</td>
<td>3.0%</td>
<td>6.7%</td>
<td>1.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>OR 2.3 (1.2-4.7)</td>
<td>OR 1.3 (0.48-3.5)</td>
<td>OR 1.8 (0.9-3.6)</td>
<td>OR 1.1 (0.4-3.3)</td>
</tr>
</tbody>
</table>

*Variable was defined as hyperkalemia > 5.5 mmol/l or an investigator-reported adverse event (AE), occurring at any time during the trial; †comparison between placebo (PL) and spironolactone (SP) groups within each category of renal function.

eGFR = estimated glomerular filtration rate; K = potassium; OR = odds ratio; WRF = worsening renal function.
Incidence of Hyperkalemia (≥6.0) in CHF Patients Receiving ARA

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

<table>
<thead>
<tr>
<th>Clinical trials</th>
<th>Real-world</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES 1</td>
<td>Bozkurt 2003 4</td>
</tr>
<tr>
<td>N=822</td>
<td>N=104</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>EMPHASIS 2</td>
<td>Shah 2005 3</td>
</tr>
<tr>
<td>N=1,336</td>
<td>N=840</td>
</tr>
<tr>
<td>2.5</td>
<td>6</td>
</tr>
</tbody>
</table>

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

- 214 patients with class II-IV heart failure.
- On ACE inhibitors.
- 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>Condition</th>
<th>Placebo</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline eGFR ≥60</td>
<td>6.0</td>
<td>15.4</td>
</tr>
<tr>
<td>Baseline eGFR &lt;60</td>
<td>8.5</td>
<td>25.6</td>
</tr>
<tr>
<td>No WRF</td>
<td>6.7</td>
<td>18.2</td>
</tr>
<tr>
<td>WRF</td>
<td>13.3</td>
<td>30.2</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)

Reason for spironolactone suspension (%)

- Hyperkalemia
- Renal function decline
- Gynecomastia
- Other


*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

Percent Mortality by Prior RAAS Inhibitor Dose

- **CKD Stages 3-4** (N = 43,288 total patients across dose categories)
  - Maximum Dose: 9.8%
  - Submaximum Dose: 22.4%
  - Discontinued: 20.2%

- **Heart Failure** (N = 20,529 total patients across dose categories)
  - Maximum Dose: 13.7%
  - Submaximum Dose: 27.7%
  - Discontinued: 30.1%

- **Diabetes** (N = 79,087 total patients across dose categories)
  - Maximum Dose: 5.0%
  - Submaximum Dose: 13.1%
  - Discontinued: 10...

- **Total Population** (N = 201,655 total patients across dose categories)
  - Maximum Dose: 4.1%
  - Submaximum Dose: 8.2%
  - Discontinued: 11.0%
## Hyperkalemia in PARADIGM-HF

### Patients Excluded Due to Elevated K⁺ Levels During Run-in Period Veils

<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>no (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>

### Number of Patients with Elevated K⁺ Due to Treatment

Main Causes of Hyperkalemia in Patients with Heart Failure

- Medications-induced hyperkalemia. ACEI/ARB, Entresto, BB, NSAID.
- Impaired renal excretion of K. Renal failure.
- Decreased renal perfusion.
Hyperkalemia

Diagnosis
Diagnosis
R/O Spurious K Elevation

- Drawing blood from a vein or line into which K is being infused.
- Lab error.
- Hemolysis.
- Leukocytosis or thrombocytosis.
- Repeat clenching of the fist during phlebotomy.
Hyperkalemia is usually asymptomatic but can be associated with muscular weakness, flaccid paralysis, ileus and characteristic ECG changes.

About half of patients with K level >6.0 mEq have normal ECG.

Hyperkalemia can lead to life threatening arrhythmias even if the ECG is normal.
### ECG in Hyperkalemia

<table>
<thead>
<tr>
<th>Serum potassium</th>
<th>Typical ECG appearance</th>
<th>Possible ECG abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (5.5-6.5 mEq/L)</td>
<td><img src="image" alt="Mild ECG" /></td>
<td>Peaked T waves</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged PR segment</td>
</tr>
<tr>
<td>Moderate (6.5-8.0 mEq/L)</td>
<td><img src="image" alt="Moderate ECG" /></td>
<td>Loss of P wave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prolonged QRS complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ST-segment elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ectopic beats and escape rhythms</td>
</tr>
<tr>
<td>Severe (&gt;8.0 mEq/L)</td>
<td><img src="image" alt="Severe ECG" /></td>
<td>Progressive widening of QRS complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sine wave</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular fibrillation</td>
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<td></td>
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<td>Asystole</td>
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<tr>
<td></td>
<td></td>
<td>Axis deviations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bundle branch blocks</td>
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<tr>
<td></td>
<td></td>
<td>Fascicular blocks</td>
</tr>
</tbody>
</table>
ECG in Hyperkalemia
Diagnosis

- Hyperkalemia is usually asymptomatic but can be associated with muscular weakness, flaccid paralysis, ileus and characteristic ECG changes.
- About half of patients with K level >6.0 mEq have normal ECG.
- Hyperkalemia can lead to life threatening arrhythmias even if the ECG is normal.
### Strategies to Minimize the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine is >1.6 mg/dL. In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance is >30 mL/min/1.73 m² is recommended.

2. Aldosterone antagonists would not ordinarily be initiated in patients with baseline serum potassium >5.0 mEq/L.

3. An initial dose of spironolactone of 12.5 mg or eplerenone 25 mg is typical, after which the dose may be increased to spironolactone 25 mg or eplerenone 50 mg if appropriate.

4. The risk of hyperkalemia is increased with concomitant use of higher doses of ACE inhibitors (captopril ≥75 mg daily; enalapril or lisinopril ≥10 mg daily).

5. In most circumstances, potassium supplements are discontinued or reduced when initiating aldosterone antagonists.

6. Close monitoring of serum potassium is required; potassium levels and renal function are most typically checked in 3 d and at 1 wk after initiating therapy and at least monthly for the first 3 mo.

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Table 17. Strategies to Minimize the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

*Although the entry criteria for the trials of aldosterone antagonists included creatinine <2.5 mg/dL, the majority of patients had much lower creatinine; in 1 trial, 95% of patients had creatinine ≤1.7 mg/dL. ACE indicates angiotensin-converting enzyme.
Careful monitoring of potassium, renal function 3 days and 1 week after initiation and than monthly.

Figure 1. The laboratory monitoring follow-up of patients with heart failure started with spironolactone. One-third of the patients did not have serum potassium checked within three months of drug initiation.
Laboratory Monitoring for Spironolactone
Shah KB et al. JACC 2005;46:845

Figure 1. The laboratory monitoring follow-up of patients with heart failure started with spironolactone. One-third of the patients did not have serum potassium checked within three months of drug initiation.
Low K⁺ Diet Is the First Step in Chronic Management, but Compliance Is Difficult

Potassium-Rich Foods

- Artichoke
- Beets
- Clams
- French fries
- Lentil
- Milk
- Grapefruit
Cases of colonic necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use. The majority of these cases reported the concomitant use of sorbitol. 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. Concomitant administration of sorbitol is not recommended.

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. 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. 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). Discontinue use in patients who develop constipation.

Do not administer repeated doses in patients who have not passed a bowel movement.

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

- Unmet need for a safe and efficacious chronic treatment used with ACE, ARB, MRA, and ARNI therapies to address hyperkalemia in order to implement GDMT for HF patients.
PARADIGM-HF: Primary outcome
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

At risk

<table>
<thead>
<tr>
<th></th>
<th>Enalapril:</th>
<th>LCZ696:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4212</td>
<td>4187</td>
</tr>
<tr>
<td>180</td>
<td>3883</td>
<td>3922</td>
</tr>
<tr>
<td>360</td>
<td>3579</td>
<td>3663</td>
</tr>
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<td>540</td>
<td>2922</td>
<td>3018</td>
</tr>
<tr>
<td>720</td>
<td>2123</td>
<td>2257</td>
</tr>
<tr>
<td>900</td>
<td>1488</td>
<td>1544</td>
</tr>
<tr>
<td>1080</td>
<td>853</td>
<td>896</td>
</tr>
<tr>
<td>1260</td>
<td>236</td>
<td>249</td>
</tr>
</tbody>
</table>

Cumulative Proportion of Patients with Primary End Point (%)

Days after Randomization

HR: 0.80 (0.73, 0.87)
p = 0.0000004

Primary Endpoint: CV mortality and HF hospitalizations

Enalapril (n=4212)
LCZ696 (n=4187)
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

PARADIGM-HF
Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial

Death from any cause
16% risk reduction

HR: 0.84 (0.76, 0.93)
P = 0.0009

How These Binders Work

Patiromer

Gut Lumen

K+

ZS-9

Colon

Upper/Lower GI

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-reabsorbable</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 Oral Suspension**

**Patiromer**

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

OPAL-HK Study

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

**Starting Patiromer Dose**

<table>
<thead>
<tr>
<th>Dose</th>
<th>(total daily dose)†</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.4g per day</td>
<td>(total daily dose)†</td>
<td>(n=92)</td>
</tr>
<tr>
<td>16.8g per day</td>
<td>(total daily dose)†</td>
<td>(n=151)</td>
</tr>
</tbody>
</table>

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

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

N=237

**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

Subjects with CKD* on RAASi (n=243)

8.4g per day  
(total daily dose)†
(n=92)

16.8g per day  
(total daily dose)†
(n=151)

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>(n=90)</td>
<td>(n=237)</td>
</tr>
<tr>
<td>5.31 mEq/L (0.57)</td>
<td>5.58 mEq/L (0.51)</td>
</tr>
<tr>
<td>5.74 mEq/L (0.40)</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Change in Serum Potassium (mEq/L)</th>
<th>Mild HK</th>
<th>Moderate/Severe HK</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.65 (95% CI -0.74, -0.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.23 (95% CI -1.31, -1.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1.01 (95% CI -1.07, -0.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Endpoint:**

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

---

OPAL-HK 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

Effect of Withdrawing Patiromer on Serum Potassium Control

Part B: 8-week Randomized Withdrawal Phase (Single-Blind)

<table>
<thead>
<tr>
<th>Subjects with Part A baseline K⁺ 5.5 to &lt; 6.5 and who completed Part A and:</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Serum K⁺ 3.8 to &lt;5.1 mEq/L at Part A Week 4</td>
</tr>
<tr>
<td>▪ Still on RAASi</td>
</tr>
<tr>
<td>(n=107)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patiromer*, continued RAASi (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo, continued RAASi (n=52)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Part B</th>
<th>Week 4 Part B⁺ 1° Endpoint</th>
<th>Week 8 Part B 2° Endpoint</th>
</tr>
</thead>
</table>

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

**Panel A**
Time to First Serum Potassium Level ≥5.5 mmol/liter

**Panel B**
Time to First Serum Potassium Level ≥5.1 mmol/liter

<table>
<thead>
<tr>
<th>Week of Withdrawal Phase</th>
<th>Placebo</th>
<th>Patiromer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week of Withdrawal Phase</th>
<th>Placebo</th>
<th>Patiromer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>23</td>
</tr>
</tbody>
</table>
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)

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

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

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Placebo</th>
<th>Patiromer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺ ≥ 5.1 mEq/L</td>
<td>91%</td>
<td>43%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[95% CI: 83%, 99%]</td>
<td>[95% CI: 30%, 56%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K⁺ ≥ 5.5 mEq/L</td>
<td>60%</td>
<td>15%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[95% CI: 47%, 74%]</td>
<td>[95% CI: 6%, 24%]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OPAL-HK Study

Use of RAASi during the study

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

- **Requiring any adjustment of RAASi (i.e., down-titration or discontinuation) or patiromer dose increase due to hyperkalemia at any time during Part B:**
  - Placebo: 16%
  - Patiromer: 62%

- **Receiving any dose of a RAASi at the end of Part B:**
  - Placebo: 44%
  - Patiromer: 94%

*P < 0.001*

Subjects with CKD* and T2DM on stable RAASi dose (n=306)

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

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

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

The most common treatment related adverse reactions (incidence ≥ 2%) are:

- Constipation (4.6%)
- Hypomagnesemia (7.2%)
- Diarrhea (2.7%)
- Nausea (2.3%)
- Hypokalemia < 3.5 mEq/L (5.6%)
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
Patiromer 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 patiromer. Choose patiromer or the other oral medication if adequate dosing separation is not possible.

Indication

- Patiromer is 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:
Warnings and Precautions

Worsening of Gastrointestinal Motility

– Avoid use of patiromer in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders
– Patiromer 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

- Patiromer 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 patiromer. 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

### Dose Titration:
- Monitor serum potassium and increase or decrease dose as necessary
- Up-titrante 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

### Administration:
- 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])*
CRD and WRF are common in patients with HF treated with ACEi/ARBs, ARA and ARNI.

Mortality benefit of RAAS inhibitors is maintained in spite of CRD or WRF.
Hyperkalemia is a common electrolyte disorder and frequent reason for reduction or discontinuation of RAAS inhibitors.

Hyperkalemia is associated with serious cardiac dysrhythmias and increased mortality.
Summary

- Patiromer has been shown to be relatively safe and effective for chronic treatment of hyperkalemia and is likely to become an important adjunct to heart failure therapy.
Thank You

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