Challenges in RAASi optimization: Hyperkalemia Management

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A case of hyperkalaemia during RAASi use

- 78-year old female
- 6 years history of severe heart failure with reduced ejection fraction post AMI
- Chronic AF – rate ~65/min
- Blood pressure: 124/72 mmHg
- Renal function and electrolytes:
  - eGFR: 45 ml/min/1.73 m², Na⁺ 136 mmol/L, K⁺ 5.7 mmol/L (was 4.8 mmol/L before Spironolactone)

Treatment:
Perindopril 4 mg od; furosemide 80 mg od;
bisoprolol 5 mg od; warfarin 2 mg od; atorvastatin 20 mg od;
spironolactone 50 mg od

What would you do?
— Stop spironolactone?
— Reduce dose of spironolactone?
— Something else?
Patient’s treatment in line with ESC HFrEF guidelines 2016

- Patient with symptomatic HFrEF
  - Therapy with ACEi and beta-blocker (Up-titrate to maximum tolerated evidence-based doses)
    - Still symptomatic and LVEF ≤35%
      - Yes: Add MR antagonist (Up-titrate to maximum tolerated evidence-based dose)
      - No: Consider reducing diuretic dose
  - Still symptomatic and LVEF ≤35%
    - Yes: These above treatments may be combined if included
    - No: No further action required

- Diuretics to relieve symptoms and signs of congestion
  - If LVEF ≤35% despite OMT or a history of symptomatic VT/NF, implant ICD

- Diuretics to relieve symptoms and signs of congestion
  - If LVEF ≤35% despite OMT or a history of symptomatic VT/NF, implant ICD

- Consider digoxin or H-ISDN or LVAD, or heart transplantation

Adding a mineralocorticoid (MRA) to an ACE improves patient outcomes

RALES and EMPHASIS – Heart Failure
MRA Improved Survival in HF Patients

MRA use increases the risk of HK, especially in patients with CKD and a decline in renal function after RAASi initiation.

RALES study

- **Baseline Renal Function**
  - Baseline eGFR ≥60: 6.0%
  - Baseline eGFR <60: 8.5%
  - No WRF: 6.7%
  - WRF: 13.3%

- **Intra-study Change in Renal Function**
  - Placebo: 15.4%
  - Spironolactone: 25.6%
  - Placebo: 18.2%
  - Spironolactone: 30.2%

eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonists; WRF, worsening renal function.

Hyperkalaemia at hospital admission: CKD and/or RAASi


Event rate adjusted for: race, gender, age, CCI, cancer, diabetes, CVD, and RAAS blocker treatment within 30 days. CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CVD, cardiovascular disease; RAASi, renin-angiotensin-aldosterone system inhibitor

*p <0.0001 versus no CKD
The risk for HK is increased with age and comorbidities

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

* 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.

The risk of HK is limiting RAASi use

Hyperkalemia: a threat to RAAS inhibition?

The renin–angiotensin–aldosterone system (RAAS) has a pathogenetic role in several edematous disorders, including cardiac disease, liver disease, drug-resistant hypertension, chronic kidney disease (CKD), the metabolic syndrome, and diabetes mellitus (Schrier, R. W. et al. Clin. J. Am. Soc. Nephrol. in press). The finding that angiotensin II and aldosterone are pro-inflammatory, profibrotic, and can cause oxidative injury, has led to the development of several agents that inhibit the RAAS. These agents include angiotensin-converting-enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), mineralocorticoid-receptor antagonists, and direct renin inhibitors, all of which can induce hyperaldosteronism in patients with advanced heart failure and the finding from the ADHERE study that nearly 50% of hospitalized patients with decompensated heart failure are discharged with no improvement in symptoms of congestion (Fonarow, G. C. et al. Arch. Intern. Med. 165, 1469–1477; 2005). By contrast, in patients with decompensated cirrhosis and ascites, natriuretic doses of spironolactone are the primary diuretic of choice because of the association of this entity with secondary hyperaldosteronism.

In patients with decompensated cirrhosis, diuretic resistance is defined as no change in urinary sodium excretion after administration of 400 mg of spirono-

"An extensive study of patients with CKD or heart failure who were treated with RAAS inhibitors revealed an incidence of hyperkalemia of 5–10%"

European healthcare professionals are withholding RAASi due to HK

PARADIGM-HF study: Despite novel approaches to RAASi therapy, hyperkalaemia is still an issue with ARNIs

- PARADIGM-HF selected a population at low risk for hyperkalemia prior to randomization
- Excluded patients with eGFR <30 mL/min/1.73 m²
- Excluded patients with a serum [K⁺] of more than 5.2 mEq/L at screening (or >5.4 mEq/L at randomization)
- Had a run-in phase on ACEi that excluded 6% of patients due to AEs, then a run-in phase on LCZ-696 that excluded another 6% of patients due to AEs, which selected a population that would be at low risk for hyperkalaemia

- But hyperkalaemia rates remained high despite a carefully selected population
- >5.5 mEq/L: 16.1% LCZ-696 vs 17.3% ACEi (P=0.15)
- >6.0 mEq/L: 4.3% LCZ-696 vs 5.6% ACEi (P=0.007)

1 mEq/L = 1 mmol/L
AE, adverse event; ACEi, angiotensin converting enzyme inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitor ARNI, angiotensin receptor-neprilysin inhibitor

The incidence of hyperkalaemia in real-world studies far exceeds that seen in clinical trials\(^1\)

Hyperkalaemia with spironolactone in real-world vs clinical trials in patients with heart failure

Patients who experience HK once are at greater risk of recurrent HK events

~50% of patients with hyperkalaemia* had 2 or more recurrences within 1 year

Some patients experienced >20 recurrent episodes within 1 year†

HK, hyperkalaemia
*Hyperkalaemia was defined as serum [K⁺] ≥5.5 mEq/L (1 mEq/L = 1 mmol/L); †70 individuals (0.21%) had more than 20 episodes in 1 year

Hyperkalemia Contributes to ED Visits, Hospitalizations, and Health Care Costs

- In 2011, the estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis were ~$697 million
- Average Medicare LOS was 3.2 days; mean charges of $24,085 per stay
- One-third were discharged to another short-term hospital, institution, or home health care

ED: emergency department, LOS: length of stay.
Hyperkalemia Is a Leading Reason for Not Starting RAASi and the Major Reason for Discontinuation of RAASi in CKD Patients

- 279 CKD patients
- Baseline mean GFR was 33.3 mL/min/1.73 m² and the serum $K^+$ was 4.73 mEq/L

Poor monitoring of serum $[K^+]$ levels after the initiation of MRA therapy in real-world studies

- Evaluation of 10,443 Medicare beneficiaries with heart failure and incident MRA therapy
  - 91.6% of patients had serum $[K^+]$ first measured in the 120 days prior to MRA initiation
  - However, only 13.3% had guideline suggested measurement of serum $[K^+]$ in the early (1–10 days) follow-up period (11–90 days after MRA initiation)
  - Overall, 55% of patients did not receive any monitoring of serum $[K^+]$ in the early post-initiation period and 22.3% did not receive any monitoring of serum $[K^+]$ during the extended follow-up period

Regular monitoring of serum $[K^+]$ is needed in clinical practice after patients start MRA therapy

MRA, mineralocorticoid receptor antagonist

Guidelines recommend dose reduction or discontinuation if HK is a problem during RAASi therapy

- Serum K\(^+\) (mEq/L)
  - >6.0
  - >5.5
  - >5.0

KDIGO Guidelines do not provide recommendations

- NICE\(^5\): Stop RAASi if >6.0
- ESC HF,\(^2\) K/DOQI\(^6\): Reduce dose of/stop ACEi/ARB, MRA if >5.5
- HFSA\(^3\): MRA not recommended >5.0
- ACA/AHA HF\(^1\): Maintain AA 4.0-5.0
- K/DOQI\(^6\): don’t start RAASi if > 5.0
- NICE\(^5\): don’t start RAASi if >5.0

Serum K\(^+\) Threshold Before Change in RAASi Guidelines Recommendation

References:
Current treatment options for hyperkalaemia: No effective long term option

- Calcium gluconate salt
- Hypertonic solution
- Insulin
- β- andrenoreceptor antagonists
- Dialysis
- Loop diuretics
- Sodium bicarbonate
- SPS/CPS
- RAASi reduction
- Low K+ diet
- Membrane stabilization
- K+ redistribution
- K+ elimination
- Removal / reduction of drugs that ↑ serum K+

Onset of action
- Immediate
- 15-30 minutes
- >1 hour
- >6 hours
- Maintenance

Therapy
- Acute
- Subacute
- Chronic

Note: SPS, sodium polystyrene sulfonate; CPS, calcium polystyrene sulfonate

Many Patients Are Already on Low Carb and Low Salt: Hyperkalemia Now Adds Potassium Restrictions

What’s Left to Eat?

- Track fluid intake
- Avoid alcohol
- Limit caffeine
- Low protein in severe CKD
Loop diuretics are effective in lowering serum potassium

• However, Loop diuretics are associated with hypochloremia (serum chloride <96 meq/L) resulting in:
  – Diuretic Resistance
  – Renal Dysfunction
  – If persistent 14 days after hospitalization for Acute HF reduced survival
Hyperkalemia

• Reducing the dose or discontinuing the use of a RAASi is an effective strategy to reduce serum K$^+$ and the clinical consequences of hyperkalemia

• However discontinuing a RAASi in a patient with HFREF and or CKD places the patient at increased risk of CV death
### Potassium Lowering Drugs

#### Table 2. Comparison of Existing and New Potential Therapies for Chronic Hyperkalemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Kayexylate</th>
<th>Patiomer</th>
<th>ZS-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical pharmacology</td>
<td>Cation-exchange resin, exchanges sodium for H⁺ in stomach, then exchange for H⁺ for other cations in large intestine</td>
<td>Nonabsorbed organic polymer, preferentially binds K⁺ in the colon</td>
<td>Inorganic polymer; negative charge to framework enables cation exchange</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Observed decreases in serum potassium between 0.82 and 1.14 mEq/L depending on dose</td>
<td>Mean reduction in serum potassium at week 4 = 1.01 mmol/L; 76% with normokalemia after 4 wk; 60% placebo vs 15% patiomer had recurrent serum K⁺ ≥ 5.5 mmol/L during 8-week withdrawal phase</td>
<td>Mean initial reduction in serum potassium (48 h) = –0.46 to –1.1 mEq/L depending on dose; 98% achieved normokalemia within 48 h; 71%–85% depending on ZS-9 dose maintained normokalemia during 28 day follow-up vs 48% with placebo</td>
</tr>
<tr>
<td>Safety</td>
<td>Risk of acute bowel necrosis, hypernatremia, diarrhea, and gastrointestinal intolerance</td>
<td>Mild-to-moderate constipation most commonly reported (11% during initial treatment phase and 4% patiomer vs 0% placebo during 8-wk randomized withdrawal phase), hypokalemia (5–6%), hypomagnesemia (3% in OPAL-HK, 7.2% in AMETHYST-DN, and 24% in PEARL-HF)</td>
<td>Gastrointestinal disorder reported in 2.1%–8.7% of ZS-9 patients (depending on dose and period of study) vs 2.4%–7.4% of placebo patients, hypokalemia (∼10% depending on dose), edema (2.4%)</td>
</tr>
</tbody>
</table>
SPS (Kayexalate) and CPS are the only current drugs that remove excess potassium from the body

- Sodium polystyrene sulfonate was approved for the treatment of hyperkalaemia by the FDA in 1958 and in France in 1980

- SPS is a cation-exchange resin that is administered orally or rectally
- In 2009, the FDA added gastrointestinal safety warnings and precautions to the label
- Intestinal necrosis (particularly with concomitant sorbitol) which may be fatal, and other serious gastrointestinal adverse reactions
- Resin is a source of sodium – caution is advised in patients who cannot tolerate increases in sodium load (i.e. severe CHF, severe HTN, marked oedema or renal damage)
- Not an option for long-term use

CHF, congestive heart failure; FDA, Food and Drug Administration; HTN, hypertension; SPS, sodium polystyrene sulfonate SPS sodium polystyrene sulfonate CPS, calcium polystyrene sulfonate

Sodium Polystyrene Sulfonate (SPS)

- SPS removes 0.5-1.0 mg of K⁺ in exchange for 2-3 mg of Na⁺
- A single daily dose of SPS contains approximately 60 mg of Na⁺
- Administration of SPS to patients with renal failure and hyperkalemia is associated with:
  - Worsening edema
  - Weight gain
  - Poor blood pressure control

Nasir, K. et al; J. Ayub Med Coll Abbottabad 2014; 26:455
Patients who benefit the most from RAASi therapy are the patients at greatest risk of hyperkalaemia

Catch 22: Hyperkalemia vs RAASi benefits?

Prescribe RAASi and accept the presence of hyperkalemia?

Discontinue/ down-titrate RAASi and lose the benefits on clinical outcomes?

CATCH-22

RAASi, renin-angiotensin-aldosterone system inhibitor

ECS Guidelines for heart failure 2016: New option?

“Two new potassium binders (patiromer and sodium zirconium cyclosilicate) are currently under consideration for regulatory approval. Initial results from patients with HF are available and confirm the efficacy of these therapies in reducing serum potassium and preventing recurrent hyperkalemia in patients with HF and CKD in the context of treatment with RAAS inhibitors.”
Patiromer (RLY5016) is a polymer that binds potassium in the colon.

**Hyperkalemia**

Hyperkalemia is most commonly caused by chronic kidney disease (CKD), or the use of RAAS blockade drugs that limit urinary $K^+$ excretion and increase serum $K^+$ level.

**Patiromer (RLY5016)**

- Patiromer is a non-absorbed $K^+$ binding polymer.
- Patiromer binds $K^+$ in colon (not dietary $K^+$).
- Patiromer acts as a “sink” to increase colonic $K^+$ excretion.

_Future Cardiol. © Future Medicine (2012)_

_Buyssse JM et al. 2012 Future Cardiol. 8:17-28_
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

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

Mean age 64yrs, eGFR: 35, $K^+$ 5.6mmol/L

$K^+$ decreased by 1.01mmol/L, 76% Final $K^+$ 3.8 – 5.1 p<0.001

K$^+$ rise to ≥5.5mmol/L: Placebo 60%, Patiromer 15%, p<0.001

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

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

<table>
<thead>
<tr>
<th></th>
<th>Heart failure</th>
<th>No Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>-0.5±0.05</td>
<td>-0.5±0.04</td>
</tr>
<tr>
<td>Week 1</td>
<td>-0.8±0.05</td>
<td>-0.7±0.04</td>
</tr>
<tr>
<td>Week 2</td>
<td>-0.9±0.05</td>
<td>-0.9±0.04</td>
</tr>
<tr>
<td>Week 3</td>
<td>-1.1±0.05</td>
<td>-1.0±0.04</td>
</tr>
<tr>
<td>Week 4</td>
<td>-1.1±0.05</td>
<td>-1.0±0.04</td>
</tr>
</tbody>
</table>

Mean (±SE) Serum K+ (mEq/L)

- Heart Failure: Mean ± SE = 5.6 ± 0.0
- No Heart Failure: Mean ± SE = 5.5 ± 0.0

Mean Baseline Serum K+ (mEq/L)

- Heart Failure: 5.6
- No Heart Failure: 5.5

Treatment Phase Primary Endpoint: Mean Change from Baseline to Week 4

<table>
<thead>
<tr>
<th></th>
<th>Heart Failure</th>
<th>No Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEq/L</td>
<td>-1.06 (95% CI, -1.16, -0.95)</td>
<td>-0.98 (95% CI, -1.06, -0.90)</td>
</tr>
<tr>
<td>N</td>
<td>100</td>
<td>137</td>
</tr>
</tbody>
</table>

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

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

OPAL-HK Part B: Effect of Continuing Versus Discontinuing Patiromer on Mean Serum Aldosterone

Exploratory Endpoint

![Graph showing the effect of continuing versus discontinuing patiromer on mean serum aldosterone levels.](Image)

- **Initial Treatment Phase**: Patiromer (n=107)
- **Randomized Withdrawal Phase**: Switched to placebo (n=52), Continued patiromer (n=55)

\[ \dagger P<0.01 \text{ vs Part A week 4.} \]

OPAL-HK Part B: Effect of Continuing Versus Discontinuing Patiromer on Mean Serum Systolic and Diastolic BP

AMETHYST-DN: Least Squares Mean (95% CI) Serum K+ Levels Over 52 Weeks and During Posttreatment Follow-up

All serum K⁺ analyses are based on central lab values; 3 patients (2 with mild HK and 1 with moderate HK) did not have a central lab serum K⁺ value at baseline and therefore are not included in the analysis at this timepoint. * At all timepoints, p<0.001 (2-sided t-test) for least squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study). BL: baseline, F/Up: follow-up, HK: hyperkalemia.

PEARL-HF Study Design

Subjects with a history of chronic HF, aged 18 or older, clinically indicated to receive spironolactone with a serum K⁺ at screening between 4.3 – 5.1 mEq/L and:

1. CKD (eGFR <60 mL/min) and on ≥ 1 ACEi or ARB or βB; OR
2. Documented Hx hyperK⁺ < 6 mo* that led to discontinuation of AA, ACEi or ARB or βB

Endpoints

1°:
Mean change in serum K⁺ from BL at Day 28

2°:
% of patients with serum K⁺>5.5 mEq/L at any time
% of patients eligible for dose titration to Spiro 50 mg


Note: In the publication, 15g BID (30g total) is reported which refers to dosing calculation that incorporates the weight of the exchange ion and sorbitol complex; Current dosing reflects the active moiety only where 15g BID = 12.6g BID (25.2g total)

* Leading to d/c of RAASI or βB.

**PEARL-HF Primary Efficacy Endpoint: Change From Baseline in Serum K+ (LOCF) by Study Visit**

<table>
<thead>
<tr>
<th>Serum K⁺ (mEq/L)</th>
<th>Patiromer (n=55)</th>
<th>Placebo (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.69</td>
<td>4.65</td>
<td>0.664</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.22</td>
<td>+0.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference Patiromer vs placebo</td>
<td>-0.45</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Spironolactone initiated at 25 mg/d on Day 1

Spironolactone increased to 50 mg/day on Day 15 if K ≤ 5.1

LOCF: last observation carried forward.

PEARL-HF Secondary Efficacy Endpoint: Proportion of Subjects Able to Increase Spironolactone Dose to 50 mg/day

<table>
<thead>
<tr>
<th></th>
<th>Patiromer (n=55)</th>
<th>Placebo (n=49)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects able to titrate up spironolactone dose</td>
<td>50 (91%)</td>
<td>36 (74%)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

### Chemical and Physical Properties of ZS-9

#### ZS-9

- **An orally administered, non-absorbed, selective potassium binder** \(^1\)

- A selective, high-capacity, inorganic crystalline lattice that selectively traps monovalent cations (e.g., potassium) over divalent cations in the gastrointestinal tract \(^1\)

- Has its greatest effects in the **duodenum** \(^2\)

#### Structure of ZS-9

Blue spheres = oxygen atoms; red spheres = zirconium atoms, green spheres = silicon atoms

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**ZS-9**, sodium zirconium cyclosilicate.

<table>
<thead>
<tr>
<th>Trial, First Author, Year (Ref #)</th>
<th>Type of Study</th>
<th>Number of Patients (n)</th>
<th>Intervention</th>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZS-003 Pacifia et al., 2015 (71)</td>
<td>RCT, Double-blinded Phase III</td>
<td>253 patients with K+ 5.0-6.5 mmol/L, 561 patients had eGFR &lt; 60 ml/min/1.73 m², 502 patients had diabetes, and 300 patients had history of HF</td>
<td>Patients were randomly assigned to twice-daily: 1. ZS-9 treatment with 1.25, 2.5, 5, or 10 g or 2. placebo for 48 h. Patients with K+ 3.5-4.9 mmol/L at 48 h were randomly assigned to once-daily ZS-9 or placebo on days 3-14.</td>
<td>Potassium levels through 48 h</td>
<td>Reduction of 0.46, 0.54, and 0.73 in the 2.5-, 5-, and 10-g groups, respectively, and 0.25 mmol/L with placebo. At 1 h, a significant reduction was seen with the 10-g dose (p = 0.009). At 48 h, 99% of patients treated with 10 g i.d. and 94% with 5 g i.d. achieved normal K+. In the maintenance phase, the patients who received 5 g and 10 g ZS-9, serum K+ levels were maintained at 4.76 mmol/L and 4.58 mmol/L, respectively, compared with &gt;5.40 mmol/L in the placebo group (p &lt; 0.01) after ZS-9 withdrawal. Adverse events: Initial phase (ZS-9 group 12.9%, and placebo group 10.8%). Maintenance phase (ZS-9 group 25.1%, and placebo group 24.5%).</td>
</tr>
<tr>
<td>ZS-002 Ash et al., 2015 (70)</td>
<td>RCT, Double-blinded Phase II</td>
<td>90 patients with K+ 5.0-6.5 mmol/L</td>
<td>Patients were randomly assigned to twice-daily: 1. ZS-9 treatment with 0.3 (n = 12), 3.0 (n = 24), or 10 g (n = 24) or 2. Placebo (n = 30) for 48 h</td>
<td>Potassium levels through 48 h</td>
<td>Mean baseline serum K+ was 5.1 mmol/L. Serum K+ was significantly decreased by 0.92 ± 0.52 mmol/L at 48 h. Urinary potassium excretion significantly decreased with 10-g ZS-9 as compared with placebo at day 2 (+15.8 ± 21.8 mmol/L/24 h vs. -8.9 ± 23.9 mmol/L/24 h). Mild GI adverse events in 20% patients in treatment group vs. 10% in placebo group. Only 90 patients in study.</td>
</tr>
<tr>
<td>ZS-004 or HARMONIZE Kosiborod et al., 2014 (69)</td>
<td>RCT, Double-blinded Phase III</td>
<td>258 patients with K+ &gt;5.0 mmol/L</td>
<td>All patients treated with twice-daily 10 g ZS-9 for 48 h. Patients with normokalemia (3.5-5.0 mmol/L) at 48 h were randomly assigned to receive once-daily 10 g, 15 g, or placebo for 28 days</td>
<td>Potassium levels through 8 to 29 days in each group</td>
<td>In the open-label phase, mean K+ levels decreased from 5.6 to 4.5 mmol/L at 48 h. Median time to normalization was 2.2 h. 84% achieved normal K+ by 24 h and 98% by 48 h. In the randomized phase, K+ level declined though days 8-29 with all ZS-9 doses vs. placebo (4.8 mmol/L, 4.5 mmol/L, and 4.4 mmol/L for 3 g, 10 g, and 15 g, respectively). 5.1 mmol/L for placebo. The proportion of patients with mean K+ &lt;5.1 mmol/L during days 8-29 was higher in all treatment groups vs. placebo (80%, 90%, and 94% for the 5-, 10-, and 15-g groups, respectively, vs. 46% with placebo). Edema was more common in the 25-g, 15-g group (2%, 2%, and 14% in placebo, 5-g, 10-g, and 15-g groups, respectively). Hyponatremia developed in 10% and 11% in the 10-g and 15-g treatment groups, respectively, vs. none in the 3-g or placebo group.</td>
</tr>
<tr>
<td>HARMONIZE HF subgroup Anker et al., 2015 (73)</td>
<td>Double-blinded Phase III</td>
<td>94 patients with K+ &gt;5.0 mmol/L, 60 receiving RAASi</td>
<td>All patients treated with twice-daily 10 g ZS-9 for 48 h. Patients with normokalemia (3.5-5.0 mmol/L) at 48 h were randomly assigned to receive once-daily 5 g, 10 g, or 15 g or placebo for 28 days</td>
<td>Potassium levels through 8 to 29 days in each group</td>
<td>In the randomized phase, despite constant RAASi doses, K+ level declined though days 8-29 with all ZS-9 doses vs. placebo (4.7 mmol/L, 4.5 mmol/L, and 4.4 mmol/L for 3 g, 10 g, and 15 g, respectively). 5.2 mmol/L for placebo. The proportion of patients with mean K+ &lt;5.1 mmol/L during days 8-29 was higher in all treatment groups vs. placebo (83%, 89%, and 92% for the 5-g, 10-g, and 15-g dose groups, respectively, vs. 40% with placebo). Edema was more common in the maintenance phase, occurring in 1, 2, and 5 patients in the 5-g, 10-g, and 15-g dose groups, respectively, vs. 1 patient in the placebo group.</td>
</tr>
</tbody>
</table>
### ZS-003: Phase 3 study

<table>
<thead>
<tr>
<th>AEs</th>
<th>Placebo (all arms)</th>
<th>ZS-9 (all arms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=219</td>
<td>n=326</td>
</tr>
<tr>
<td><strong>Any event, n (%)</strong></td>
<td>53 (25%)</td>
<td>82 (25%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorder, n (%)</strong></td>
<td>8 (4%)</td>
<td>18 (6%)</td>
</tr>
<tr>
<td><strong>Cardiac disorder, n (%)</strong></td>
<td>2 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td><strong>Urinary tract infection, n (%)</strong></td>
<td>3 (1%)</td>
<td>9 (3%)</td>
</tr>
</tbody>
</table>

AEs, adverse events; ZS-9, sodium zirconium cyclosilicate.

# ZS9: Tolerability in Heart Failure Patients on RAASi from a Phase 3 Study

Incidence of Adverse Events with ZS9 and placebo

<table>
<thead>
<tr>
<th></th>
<th>Acute Maintenance Phase</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10g ZS9</td>
<td>Placebo</td>
<td>5g ZS9</td>
<td>10g ZS9</td>
<td>15g ZS9</td>
</tr>
<tr>
<td>N=256</td>
<td>N=85</td>
<td>N=45</td>
<td>N=51</td>
<td>N=56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>2 (2.4%)</td>
<td>1 (2.2%)</td>
<td>3 (5.9%)</td>
<td>8 (14.3%)</td>
</tr>
</tbody>
</table>

Peripheral edema
Potassium Binders: Potential Future Clinical Trials

• Evaluate their effectiveness in reducing CV events in patients with CKD, DM, HF and or resistant hypertension in whom RAAS-I have been shown to be effective but who have discontinued a RAAS-I due to hyperkalemia

• Enable the use of RAAS-Is, especially MRAs in patients with an eGFR <30-/>=15 ml/min/1.73 m2

• Prevent the occurrence of hyperkalemia and CV events in patients known to benefit from RAAS-Is but who have not been started due to the fear of inducing hyperkalemia
Are Potassium Binders the Solution?

Summary/Conclusions

• Potassium binders are effective in reducing serum potassium and allowing the maintenance or reintroduction of RAASi, especially MRAs in patients with HF and or CKD.

• The long term effectiveness in reducing CV death vs discontinuing or reducing the dose of a RAASi remaining to be determined.