## Low Rates of Evidence-Based HFrEF Medical Therapies at Discharge by eGFR



## Despite elevated risk of mortality, patients with HFrEF and CKD are not optimally treated with GDMT, even when not contraindicated by severity of kidney dysfunction

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist. Patel RB, et al. *J Am Coll Cardiol*. 2021;78(4):330-343.



### **Receiving RAAS Inhibitors**

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ABSTRACT

Hyperkalemia increases the risk of death and limits the use of inhibitors of the From the Division of Nephrology, Departrenin-angiotensin-aldosterone system (RAAS) in high-risk patients. We assessed the school of Medicine, Battmore (M.W.) safety and efficacy of patiromer, a nonabsorbed potassium binder, in a multicenter, University of Chicago Medicine, Depart prospective trial.

Patients with chronic kidney disease who were receiving RAAS inhibitors and who (G.L.B.): Division of Nephrology, Capacity of Mechanics and who rauceuts with childrand Roundy discusse ment of Medicine, University of Rochester, had serum potassium levels of 5.1 to less than 6.5 mmol per liter received patiromer Rochester, NY (D.A.B.); Relyosa, Redwood (at an initial dose of 4.2 g or 8.4 g twice a day) for 4 weeks (initial treatment phase); City, CA (M.R.M., D.G., Y.S., L.B.); Statisthe primary efficacy end point was the mean change in the serum potassium level tics Collaborative, Washington, DC (JW., from baseline to week 4. Eligible patients at the end of week 4 (those with a baseline Arbor (8.P). Address reprint requests to potassium level of 5.5 to <6.5 mmol per liter in whom the level decreased to 3.8 to Dr. Weir at N3W143 Nephrology, Univerpotassium level of 5.5 to <6.5 minol per liter in whom the level decreased to 5.6 to <5.1 minol per liter) entered an 8-week randomized withdrawal phase in which they sty of Maryland Medical Center, 22.5. Greene St., Baltimore, MD 21201, or at were randomly assigned to continue patiromer or switch to placebo; the primary mweir@medicine.umaryland.edu. efficacy end point was the between-group difference in the median change in the serum potassium level over the first 4 weeks of that phase.

In the initial treatment phase, among 237 patients receiving patiromer who had at least one potassium measurement at a scheduled visit after day 3, the mean (±SE) change in the serum potassium level was  $-1.01\pm0.03$  mmol per liter (P<0.001). At week 4, 76% (95% confidence interval, 70 to 81) of the patients had reached the target potassium level (3.8 to <5.1 mmol per liter). Subsequently, 107 patients were 2014, at NEJM.org. randomly assigned to patiromer (55 patients) or placebo (52 patients) for the randomized withdrawal phase. The median increase in the potassium level from base Dot: 10.1056/NEJMea1410853 DOI: 10.009/FREJ MODELA 100033 Line of that phase was greater with placebo than with patiromer (P<0.001); a recur-Capying € 2014 Manuschuutts Malical Society. rence of hyperkalemia (potassium level, ≥5.5 mmol per liter) occurred in 60% of the patients in the placebo group as compared with 15% in the patiromer group through week 8 (P<0.001). Mild-to-moderate constipation was the most common adverse event (in 11% of the patients); hypokalemia occurred in 3%.

Packham DK, et al. N Engl J Med. 2015;372(3):222-231.

Weir MR, et al. N Engl J Med. 2015;372(3):211-221.

In patients with chronic kidney disease who were receiving RAAS inhibitors and who had hyperkalemia, patiromer treatment was associated with a decrease in serum potassium levels and, as compared with placebo, a reduction in the recurrence of hyperkalemia. (Funded by Relypsa; OPAL-HK ClinicalTrials.gov number, NCT01810939.)

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\*A complete list of investigators and committee members in the Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia (OPAL-HK) is provided in the Supplementary Appendix, available at NEJM.org.

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N Engl J Med 2015;372:211-21.

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etts Medical Society.

### CONCLUSIONS

Patients with hyperkalemia who received ZS-9, as compared with those who received placebo, had a significant reduction in potassium levels at 48 hours, with normokalemia maintained during 12 days of maintenance therapy. (Funded by ZS

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The NEW ENGLAND

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creased mortality among patients with heart failure, chronic kidney disease, or Melbourne, and the Depart. Behology, Royal Melbourne and Melbourne diabetes. We investigated whether sodium zirconium cyclosilicate (ZS-9), a novel logi, Royal Melbourne universe, we investigated whether sound another evolution evolution of the sound of the nd the University of Texas Center at San Antonio METHODS

8 Center at San Antonio mal Associates (P,P), San In this multicenter, two-stage, double-blind, phase 3 trial, we randomly assigned in Texas: Boston Blostatis. Texas; Boston Biostatis. audation, Framingham, For 10 e) or plocebo three times deity for 40 hours Defense for 40 hours D undation, Framingham,  $r_{33}$  patients with hyperkalentia to receive entree 2.5% (at a unse of 1.2.2 g, 4.3 g, 5.3 g) define (Medical Research or 10 g) or placebo three times daily for 48 hours. Patients with normokalenia (serum potassium level, 3.5 to 4.9 mmol per liter) at 48 hours were randomly assigned iverside (8,5.) — both Denner Nephrologists, to receive either ZS-9 or placebo once daily on days 3 to 14 (maintenance phase). The enver Nephrologists, to receive claims and place or place or once using on uses 5 to 14 unanticulative place, line (sess reprint requests primary end point was the exponential rate of change in the mean serum potassium the Melbourne Benal trust to 40 knows. or at dmpackham@

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At 48 hours, the mean serum potassium level had decreased from 5.3 mmol per and an November 21, the to the section portant portans with rever that decreased from 3.5 minuto per n January 15, 2015, at liter at baseline to 4.9 mmol per liter in the group of patients who received 2.5 g of 25-9, 4.8 mmol per liter in the 5-g group, and 4.6 mmol per liter in the 10-g group, for mean reductions of 0.5, 0.5, and 0.7 mmol per liter, respectively (P<0.001 for all comparisons) and to 5.1 mmol per liter in the 1.25-g group and the placebo group (mean reduction, 0.3 mmol per liter). In patients who received 5 g of ZS-9 and those who received 10 g of ZS-9, serum potassium levels were maintained at 4.7 mmol per liter and 4.5 mmol per liter, respectively, during the maintenance phase, as compared with a level of more than 5.0 mmol per liter in the placebo group (P<0.01 for all comparisons). Rates of adverse events were similar in the ZS-9 group and the placebo group (12.9% and 10.8%, respectively, in the initial phase; 25.1% and 24.5%, respectively, in the maintenance phase). Diarrhea was the most common complica-

## **Potassium Binders in Patients on Dialysis**

- 2016 Patiromer<sup>1</sup>
  - Clinical research center study
  - 6 patients with HK on hemodialysis (HD)
  - Results Decrease in sK<sup>+</sup> and sPO4 levels and increased fecal potassium
- 2019 Sodium Zirconium Cyclosilicate<sup>2</sup>
  - DIALIZE Randomized (1:1), double-blind, placebo-controlled study
  - Patients with HK on dialysis
  - Results Effective in reducing sK+ in patients on HD
- 2018 First Real-World Study with Patiromer<sup>3</sup>
  - Retrospective cohort study using EHR data from a large dialysis provider in the US
  - Median follow-up 141 days; patiromer (n = 527), no potassium binder (n = 8,747)
  - Results Patients had significant K<sup>+</sup> reductions following patiromer initiation; the relative proportion of patients with severe HK (ie, >6.0 mEq/L) was reduced by 50% after patiromer initiation

EHR, electronic health records; HK, hyperkalemia; sK<sup>+</sup>, serum potassium; sPO4, serum phosphate. 1. Bushinsky DA, et al. *Am J Nephrol.* 2016;44(5):404-410.

2. Fishbane S, et al. J Am Soc Nephrol. 2019;30(9):1723-1733.

3. Kovesdy CP, et al. *Kidney Int Rep.* 2018;4(2):301-309.

# **Hemodialysis Patient Case**

58-year-old male

- Poorly treated hypertension
- Obese
- 2 prior myocardial infarctions
- CABG
- HFrEF (LVEF ~30%)

Medications

- Carvedilol
- Eplerenone
- Dapagliflozin
- Lisinopril
  - 30 mg reduced to 10 mg due to HK and then stopped

Goal

- Increase lisinopril
- Receive good dietary counseling

Recommendation

- Start patiromer to lower potassium
- Increase lisinopril to improve chances of survival

CABG, coronary artery bypass grafting; HFrEF, heart failure with reduced ejection fraction; HK, hyperkalemia; LVEF, left ventricular ejection fraction.

# Quote by David Bushinsky, MD

"...it's critical to educate people that they have a tool that can bind the potassium and allow the use of these agents which will improve cardiac and renal survival."

### **DIAMOND Trial: Study Design**



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; D, day; HK, hyperkalemia;

RAASi, renin-angiotensin-aldosterone system inhibitor; W, week.

Follow-up after the end-of-study visit included a K<sup>+</sup> assessment visit within 2 weeks of patiromer/placebo discontinuation and/or follow-up phone call

at least 2 weeks after the end-of-study visit.

<sup>a</sup> ≥50% recommended dose of ACEI/ARB/ARNI.

<sup>b</sup> 50 mg of MRA (spironolactone or eplerenone).

Butler J, et al. Eur J Heart Fail. 2022;24(1):230-238.

### **DIAMOND Trial Primary Endpoint:** Change in Serum K<sup>+</sup> Levels from Baseline (Randomization)



Association of Serum Potassium with All-Cause Mortality in Heart Failure, Chronic Kidney Disease, and/or Diabetes



CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor. Collins AJ, et al. *Am J Nephrol.* 2017;46(3):213-221.

# Key Takeaway: Lars Lund, MD

"Hyperkalemia is a big problem in heart failure and it's now treatable with novel potassium binders."

"With potassium binders there's data to support enablement of MRA use, and this enablement will translate into improved outcomes for our patients."

