Effect of Patiromer on Hyperkalemia Recurrence in Older Chronic Kidney Disease Patients Taking RAAS Inhibitors

BACKGROUND:

- The use of renin-angiotensin-aldosterone system inhibitors (RAASi) has been shown to slow the progression of diabetic and nondiabetic chronic kidney disease and to reduce morbidity and mortality in patients with heart failure.
- Lowering serum K levels in hyperkalemic patients taking renin-angiotensin-aldosterone system inhibitors (RAASi) may improve clinical outcomes by preventing hyperkalemia-associated cardiac adverse effects and allowing continuation of guideline-recommended RAASi therapy.
- Patiromer has demonstrated to be effective in lowering serum K levels and generally safe in hyperkalemic patients with chronic kidney disease taking RAASi, many of whom also had heart failure, diabetes, and/or hypertension.

OBJECTIVE:

- The objective was to study the efficacy and safety of patiromer in a prespecified subgroup of patients aged ≥65 years from OPAL-HK (a phase 3 study).

METHODS:

- **Design:** Single-blind, Randomized, parallel, experimental study
- **Inclusion Criteria:**
  - 18-80 years old
  - Chronic kidney disease stage 3 or 4 (eGFR 15 - <60)
  - Hyperkalemia (serum K 5.1 - <6.5 by local lab measurement)
  - Taking stable dose of ≥1 RAASi medication for ≥28 days at screening
- **Exclusion Criteria:** Not explicitly listed
- **Primary Outcome Measure:**
  Part A: change in serum K from baseline to week 4 of the initial treatment phase
  Part B: between-group difference in change in serum K from start to week 4 of the randomized withdrawal
- **Secondary Outcome Measures:**
  Part A: proportion of patients with serum K in the normal range (3.8 - <5.1 mEq/L) at any time
  Part B: proportion of patients with serum K ≥5.5 and serum K ≥5.1 at any time during part B, time to recurrent hyperkalemia, time to RAASi discontinuation, proportion of patients requiring intervention to manage hyperkalemia (patiromer dose increase or RAASi discontinuation for patients taking patiromer, RAASi dose decrease of ≥50%, or RAASi discontinuation for patients taking placebo), and safety was evaluated by adverse events, change in BP, change in serum Mg, and proportions of patients with serum Mg <1.4 or serum K <3.5
- **Number Enrolled:**
  Part A: 243 patients met eligibility criteria
  - 131 people age ≥65 (87% competed part A)
  - 112 people age <65 (94% completed part A)

  Part B: 107 patients met eligibility criteria
  - 60 people age ≥65
    - 40 persons completed study
      - 22/29 taking patiromer (76% completed part B)
      - 18/31 taking placebo (58% competed part B)
  - 47 people age <65
    - 35 persons completed study
      - 23/26 taking patiromer (88% completed part B)
      - 12/21 taking placebo (57% completed part B)
- Data handling method was intent-to-treat

RESULTS:

- **Primary Outcome Measure:**
  Part A: The estimated mean ± SE change in serum K from baseline to week 4 in patients who received ≥1 dose of patiromer and had ≥1 serum K measurement after day 3 was −1.01 ± 0.05 mEq/L (95% CI, −1.10, −0.92) for patients ≥65 years (n = 126) and −0.96 ± 0.05 mEq/L (95% CI, −1.05, −0.88) for those <65 years (n = 111; $P < .001$ for both); $P = .50$ for difference between age groups.
  Part B: Differences between the patiromer versus placebo groups in the median (95% CI) change in serum K were 0.81 (0.49, 1.14) mEq/L ($P < .001$) in patients ≥65 years and 0.57 (0.11, 1.03) mEq/L ($P = .006$) in patients <65 years.
- **Secondary Outcome Measure:**

Part A: Patients with ≥1 centrally measured serum K+ value after baseline, the proportion that achieved normokalemia (serum K 3.8-<5.1 mEq/L) at any time was 97%, both for patients aged ≥65 years (122 of 126) and for those <65 years (108 of 111).

Part B:

- Patients aged ≥65 years taking patiromer versus placebo, 11% versus 64% ($P < .001$) had at least 1 serum K value ≥5.5 mEq/L, and 30% versus 92% ($P < .001$) had at least 1 serum K value ≥5.1 mEq/L.
- The proportion of patients aged ≥65 years who required an intervention to manage hyperkalemia was 10% for patiromer versus 71% for placebo.
- All patients ≥65 years (100%) receiving patiromer, compared with 48% of those taking placebo, continued to be receiving RAASi at the end of part B.
- Two (6.9%) patients aged ≥65 years who were taking patiromer reported constipation; in both, the adverse event was related to patiromer but was not severe or serious.
- Two patients (3.3%) ≥65 years (1 patiromer, 1 placebo) and none <65 years reported an adverse event that led to study discontinuation.
- Hypomagnesemia was reported as an adverse event in 3 patients (serum Mg 1.7-1.8 mg/dL at the time of the event; 2 patients were ≥65 years [1 taking patiromer, 1 taking placebo], and 1 patient was <65 years and taking placebo); and a decrease in blood Mg was reported in 1 patient ≥65 years receiveing placebo (serum Mg 1.7 mg/dL at the time of the event).

- **Author's Conclusions:** Patiromer significantly decreased serum K in hyperkalemic patients aged ≥65 years with chronic kidney disease taking renin-angiotensin-aldosterone system inhibitors (RAASi) and reduced the risk of recurrent hyperkalemia. A significantly larger proportion of patients taking patiromer continued to receive RAASi medications compared with those receiving placebo. Patiromer was well tolerated in patients aged ≥65 years and <65 years.

STRENGTHS:

- The study demonstrates that daily patiromer is needed to maintain normokalemia in patients taking RAASi.

LIMITATIONS:

- Short-term
- Single-blind study
- The number of patients in the 2 age groups that received patiromer or placebo during the randomized withdrawal phase was relatively small
- The dosages of patiromer in part A and B were reported, but the administration technique was not, and neither were reported for the placebo treatment
    - Patiromer is a reconstituted solution and it would be important to know how and when the drug was reconstituted for use.
- Examples of bias are seen throughout the study, specifically in instances were standard error is reported instead of standard deviation to make the spread of the individual study responses appear less than it actually is.

CONCLUSIONS:

- In conclusion, keeping patients normokalemic while on RAASi therapy to slow the progression of diabetic and nondiabetic chronic kidney disease and to reduce morbidity and mortality in patients with heart failure is an important therapeutic intervention to improve clinical outcomes by preventing hyperkalemic-associated cardiac adverse effects. Even though the study concluded that patiromer was well tolerated in patients aged ≥65 years and <65 years, because the mean ages were 77.1 and 55.5, respectively, one should not feel comfortable as of now to extrapolate it to a younger population of stage 3 or 4 CKD patients. This would be a good area to test the efficacy of patiromer compared to placebo.
- Future Research:
    - Since the results of the study concluded daily patiromer is needed to maintain normokalemia, a randomized, double-blind study should be done that looks at how long patiromer would be effective to keep CKD patients normokalemic.

Reference: Weir MR, Bushinsky DA, Benton WW, Woods SD, Mayo MR, Arthur SP, Pitt B, Bakris GL. Effect of Patiromer on Hyperkalemia Recurrence in Older Chronic Kidney Disease Patients Taking RAAS Inhibitors. The American Journal of Medicine. 2018; 131 (5): 555-564.

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