ORIGINAL ARTICLE

Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

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ABSTRACT

BACKGROUND

Hyperkalemia increases the risk of death and limits the use of inhibitors of the renin–angiotensin–aldosterone system (RAAS) in high-risk patients. We assessed the safety and efficacy of patiromer, a nonabsorbed potassium binder, in a multicenter, prospective trial.

METHODS

Patients with chronic kidney disease who were receiving RAAS inhibitors and who had serum potassium levels of 5.1 to less than 6.5 mmol per liter received patiromer (at an initial dose of 4.2 g or 8.4 g twice a day) for 4 weeks (initial treatment phase); the primary efficacy end point was the mean change in the serum potassium level from baseline to week 4. Eligible patients at the end of week 4 (those with a baseline potassium level of 5.5 to <6.5 mmol per liter in whom the level decreased to 3.8 to <5.1 mmol per liter) entered an 8-week randomized withdrawal phase in which they were randomly assigned to continue patiromer or switch to placebo; the primary 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.

RESULTS

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±0.03 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 randomly assigned to patiromer (55 patients) or placebo (52 patients) for the randomized withdrawal phase. The median increase in the potassium level from baseline of that phase was greater with placebo than with patiromer (P<0.001); a recurrence 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%.

CONCLUSIONS

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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Hyperkalemia is associated with life-threatening cardiac arrhythmias and increased mortality.[1] Patients at the highest risk for hyperkalemia are those with stage 3 or higher chronic kidney disease, with or without diabetes or heart failure, who are being treated with drugs that inhibit renal potassium excretion, particularly inhibitors of the renin–angiotensin–aldosterone system (RAAS).[1-4]

Outpatient treatment of hyperkalemia is limited by the lack of effective agents.[4] Sodium polystyrene sulfonate and calcium polystyrene sulfonate may cause serious gastrointestinal adverse events[5-8] as well as less serious gastrointestinal side effects that may be difficult for patients to tolerate, which together typically limit their extended use.[4,9,10]

The active moiety of patiromer for oral suspension is a nonabsorbed polymer that binds potassium in exchange for calcium (see the Supplementary Appendix, available with the full text of this article at NEJM.org), predominantly in the distal colon, where the concentration of free potassium is highest, thus increasing fecal potassium excretion and lowering serum potassium levels.[11] Here we present the results of a multinational, single-blind, two-phase study evaluating the safety and efficacy of patiromer in patients with chronic kidney disease who were receiving at least one RAAS inhibitor and who had hyperkalemia.

Methods

Study Oversight

The protocol was approved by the local or central institutional review board or ethics committee for each participating center. All patients provided written informed consent; the study was performed in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice. All electrocardiograms were read at a core electrocardiographic laboratory; an independent safety review board adjudicated deaths from any cause and all potassium-related electrocardiographic changes that were identified by the core laboratory (see the Supplementary Appendix). The study was designed by the authors in collaboration with the sponsor (Relypsa). Worldwide Clinical Trials and Olander Clinical Consulting were both responsible for site management and monitoring; the former provided clinical data management and collected, processed, and reported data on adverse events. Investigators entered data directly into a central database. The authors had full access to the data, which are held by the sponsor. Statistics Collaborative analyzed the data. The first author wrote the introduction and discussion of the manuscript and oversaw all revisions; an employee of the sponsor wrote the preliminary draft of the Methods and Results sections under the direction of the first author. All the authors reviewed and edited the manuscript, vouch for the completeness and accuracy of the data and analyses, and testify to the fidelity of this report to the study protocol, which is available at NEJM.org.

Study Population

Patients were eligible for inclusion in the study if they were 18 to 80 years of age, had stage 3 or 4 chronic kidney disease (estimated glomerular filtration rate [eGFR], 15 to <60 ml per minute per 1.73 m^2 of body-surface area), had serum potassium levels of 5.1 to less than 6.5 mmol per liter at two screenings, and had been receiving a stable dose of one or more RAAS inhibitors for at least 28 days. Doses of antihypertensive drugs, loop and thiazide diuretics, and beta-blockers had to have been stable for 28 days before screening. Key exclusion criteria were potassium-related electrocardiographic changes, severe gastrointestinal disorders, uncontrolled or unstable arrhythmias or clinically significant ventricular arrhythmias, recent cardiac surgery, kidney or heart transplantation, acute coronary syndrome, transient ischemic attack or stroke within the previous 2 months, and confirmed systolic blood pressure of 180 mm Hg or higher or less than 110 mm Hg or diastolic blood pressure of 110 mm Hg or higher or less than 60 mm Hg. Other exclusion criteria were type 1 diabetes, emergency treatment for type 2 diabetes or for exacerbation of acute heart failure within the previous 3 months, and New York Heart Association class IV heart failure (see the Supplementary Appendix for additional details).

Study Procedures

The study had two phases — a 4-week single-group, single-blind initial treatment phase and an 8-week placebo-controlled, single-blind, randomized withdrawal phase. At the time of screening, patients who met all the entry criteria were as-

signed to one of two patiromer starting doses according to the severity of the hyperkalemia: patients with a potassium level of 5.1 to less than 5.5 mmol per liter (mild hyperkalemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5 to less than 6.5 mmol per liter (moderate-to-severe hyperkalemia) received 8.4 g of patiromer twice daily. Each dose was administered as an oral suspension in 40 ml of water with breakfast and dinner. During the initial treatment phase, the dose could be adjusted to reach and maintain a target potassium level according to a prespecified algorithm (Table S1 in the Supplementary Appendix). Doses of RAAS inhibitors were not adjusted; they were discontinued only if the potassium level was 6.5 mmol per liter or higher (≥5.1 mmol per liter in patients receiving the maximum dose).

Patients were eligible for the randomized withdrawal phase if they had had a serum potassium level of 5.5 mmol per liter or higher at baseline of the initial treatment phase and if their potassium level at the end of the initial treatment phase was within the target range (3.8 to <5.1 mmol per liter) while they were receiving patiromer and RAAS inhibitors. Qualifying patients were randomly assigned, in a 1:1 ratio, to continue receiving patiromer (at the same daily dose they were receiving at week 4 of the initial treatment phase) or to receive placebo (see the Investigational Product section in the Supplementary Appendix). Randomization, which was performed centrally, was stratified according to the serum potassium level at baseline of the initial treatment phase (5.5 to <5.8 mmol per liter [moderate hyperkalemia] or ≥5.8 mmol per liter [severe hyperkalemia]) and the presence or absence of type 2 diabetes.

During the randomized withdrawal phase, prespecified treatment algorithms (Tables S2 and S3 in the Supplementary Appendix) were developed to manage a recurrence of hyperkalemia, either by an increase in the dose of patiromer (patiromer group) or by modification of the RAAS-inhibitor regimen (placebo group) at the time of the first event of hyperkalemia. Subsequent events required discontinuation of the RAAS inhibitor. To facilitate interpretation of the primary end point, neither the first nor the second intervention was to be used during the time the primary end point was being evaluated (i.e., through week 4 of the randomized withdrawal phase) unless the serum potassium level was 5.5 mmol per liter or higher.

Serum potassium levels were measured at local and central laboratories at baseline and on day 3 of each phase and weekly thereafter. Local laboratory measurements were used for assessments of study inclusion criteria and for testing related to the clinical care of patients. Central laboratory measurements were used for assessments of baseline values, criteria for inclusion in the randomized withdrawal phase, and efficacy and safety. The central laboratory performed a visual inspection and a validated semiquantitative test on each blood sample as an assessment for hemolysis (see the Supplementary Appendix). Safety data were obtained at each visit. Diet was not controlled; however, patients were counseled at each visit to restrict their intake of high-potassium foods (>250 mg per 100 g) and to maintain a low-potassium diet (potassium intake of ≤3 g per day).[12]

Patients were followed in a safety follow-up period for 1 to 2 weeks after the discontinuation of treatment (including patients who withdrew early from either phase and those who did not qualify for the randomized withdrawal phase). To ensure careful monitoring of serum potassium levels, follow-up visits were scheduled at 3 days and 7 days after the discontinuation of patiromer; depending on the serum potassium level at that time, an additional follow-up visit at 14 days was required.

STUDY END POINTS

The primary efficacy end point for the initial treatment phase was the mean change in the serum potassium level from baseline to week 4; this end point was assessed in patients who received at least one dose of patiromer and had at least one serum potassium measurement at a scheduled visit after day 3. The secondary efficacy end point for the initial treatment phase was the proportion of patients who had a serum potassium level of 3.8 to less than 5.1 mmol per liter at week 4. The primary efficacy end point for the randomized withdrawal phase was the difference between the patiromer group and the placebo group in the median change in the serum potassium level from the start of that phase to week 4 of the phase or to the earliest visit at which the patient's serum potassium level, as measured in the local laboratory, was less than 3.8 mmol per

liter or 5.5 mmol per liter or higher; the secondary efficacy end points were the proportion of patients with a recurrence of hyperkalemia according to two definitions: a serum potassium level of 5.1 mmol per liter or higher and a serum potassium level of 5.5 mmol per liter or higher. A list of exploratory end points is provided in the Supplementary Appendix. Adverse events that occurred through the posttreatment follow-up period are summarized descriptively.

STATISTICAL ANALYSIS

The mean change in serum potassium levels and the associated 95% confidence intervals were estimated with the use of a longitudinal repeated-measures model that included as covariates the presence or absence of heart failure and type 2 diabetes and baseline serum potassium levels. For the primary efficacy end point in the randomized withdrawal phase, the estimated change in serum potassium levels from baseline and the comparison of

Table 1. Baseline Demographic and Clinical Characteristics.*

Characteristic	Initial Treatment Phase	Randomized Withdrawal Phase	
	Overall (N=243)	Placebo (N=52)	Patiromer (N=55)
Male sex — no. (%)	140 (58)	30 (58)	28 (51)
Age — yr	64.2±10.5	65.0±9.1	65.5±9.4
White race — no. (%)†	239 (98)	52 (100)	55 (100)
Type 2 diabetes — no. (%)	139 (57)	33 (63)	34 (62)
Heart failure — no. (%)	102 (42)	22 (42)	27 (49)
Myocardial infarction — no. (%)	60 (25)	14 (27)	18 (33)
Hypertension — no. (%)	236 (97)	50 (96)	54 (98)
Serum potassium — mmol/liter	5.6±0.5	5.9±0.4	5.9±0.6
Estimated GFR — ml/min/1.73 m^2‡	35.4±16.2	39.0±20.4	38.6±20.7
RAAS-inhibitor use — no. (%)‡	243 (100)	52 (100)	55 (100)
ACE inhibitor	170 (70)	38 (73)	37 (67)
Angiotensin II–receptor blocker	92 (38)	16 (31)	24 (44)
Aldosterone antagonist	22 (9)	4 (8)	4 (7)
Renin inhibitor	2 (1)	0	0
Dual RAAS blockade§	41 (17)	6 (12)	10 (18)
Receiving maximal dose¶	106 (44)	21 (40)	21 (38)
Non–RAAS-inhibitor diuretic use — no. (%)‡	132 (54)	27 (52)	28 (51)
Thiazide	70 (29)	11 (21)	16 (29)
Loop	77 (32)	20 (38)	16 (29)

* Plus–minus values are means ±SD; all laboratory values listed were measured in a central laboratory. There were no significant differences in baseline characteristics between the placebo group and the patiromer group in the randomized withdrawal phase (two-sided Fisher's exact test for categorical variables and two-sided t-test for continuous variables). Table S4 in the Supplementary Appendix provides more detailed information on baseline demographic and clinical characteristics in the initial treatment phase overall and according to patiromer dose group, and Table S5 in the Supplementary Appendix provides more detailed information on baseline demographic and clinical characteristics in patients randomly assigned to patiromer or placebo in the randomized withdrawal phase. ACE denotes angiotensin-converting enzyme, GFR glomerular filtration rate, and RAAS renin–angiotensin–aldosterone system.

† Race was determined by the investigators.

‡ The baseline values refer to values at the start of the randomized withdrawal phase.

§ Dual RAAS blockade refers to any combination of two or more of the following: ACE inhibitor, angiotensin II–receptor blocker, aldosterone antagonist, or renin inhibitor.

¶ The maximal dose was determined according to the judgment of the investigator in accordance with the local standard of care.

the two study groups were based on the ranks of the observed changes. Because the postbaseline values were constrained by clinical intervention, which could occur at different times for different patients, we ranked each change from lowest to highest at each time and carried forward to week 4 the ranks for patients with an intervention. We used these ranks to compare the treatment groups (see the Supplementary Appendix).[13] The difference between study groups in the median change (and associated 95% confidence intervals) from baseline was calculated with the use of the Hodges–Lehmann estimator.[14] The study groups were compared with the use of an analysis-of-variance model on the ranks, with adjustment for randomization stratification variables. Additional details are provided in the Supplementary Appendix.

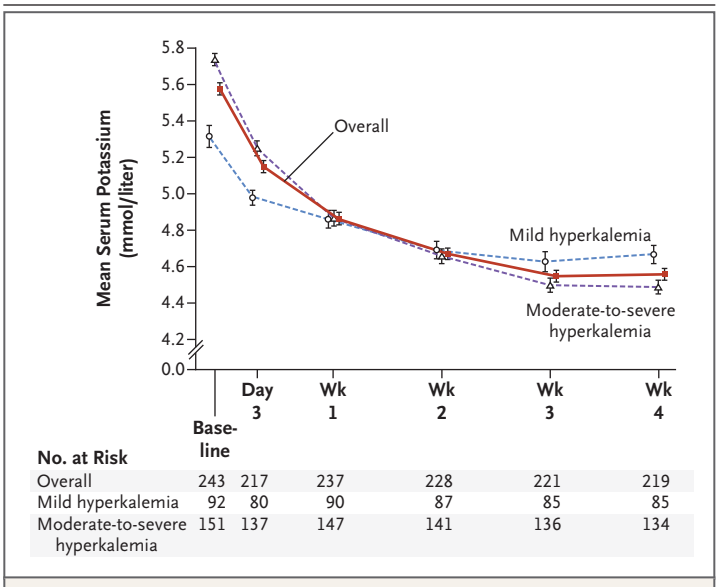

Figure 1. Serum Potassium Levels over Time during the Initial Treatment Phase.
Values are the observed mean values as measured in a central laboratory. During the 4-week initial treatment phase, all patients received treatment with patiromer; patients with a potassium level of 5.1 to less than 5.5 mmol per liter (mild hyperkalemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5 to less than 6.5 mmol per liter (moderate-to-severe hyperkalemia) received 8.4 g of patiromer twice daily. I bars indicate standard errors. Data points are staggered to make them more legible.

RESULTS

STUDY PATIENTS

A total of 243 patients were enrolled in the initial treatment phase (92 with mild hyperkalemia and 151 with moderate-to-severe hyperkalemia) at sites in Eastern Europe (24 sites), the European Union (21), and the United States (14). All the patients received at least one dose of patiromer; 24 patients (10%) discontinued this phase prematurely (Fig. S1 in the Supplementary Appendix).

Of the 219 patients who completed the initial treatment phase, 109 were not eligible to enter the randomized withdrawal phase, and 3 declined further participation in the study. The most common reason for ineligibility was a baseline potassium level of less than 5.5 mmol per liter, as measured at a central laboratory (97 patients [89%]). Eight patients (3 with mild hyperkalemia and 5 with moderate-to-severe hyperkalemia) were ineligible for randomization in the randomized withdrawal phase solely on the basis of a serum potassium level that was not in the control range at week 4 (Fig. S1 in the Supplementary Appendix). A total of 107 patients were randomly assigned to continue patiromer treatment (55 patients) or to switch to placebo (52 patients). All these patients received at least one dose of the study drug. Ten patients (18%) in the patiromer group and 22 (42%) in the placebo group discontinued the randomized withdrawal phase prematurely; the most common reasons for discontinuation were elevated potassium levels that met the prespecified withdrawal criteria (2 patients [4%] in the patiromer group and 16 [31%] in the placebo group) and potassium levels of less than 3.8 mmol per liter (3 patients [5%] in the patiromer group and 1 [2%] in the placebo group).

A majority of the patients in the study population were men, and most were white; the mean (±SD) age at baseline was 64.2±10.5 years (Table 1). Overall, 46% of the patients had stage 3 chronic kidney disease, and approximately 45% had stage 4 disease; 9% of the patients had stage 2 chronic kidney disease on the basis of measurements obtained at the central laboratory but had been included in the study because they had met entry criteria on the basis of measurements obtained at local laboratories. A total of 97% of the patients had hypertension; 57% had type 2 diabetes, 42% had heart failure, and 25% had had a myocardial infarction. All the patients were receiving at least one RAAS inhibitor at baseline. The use of non–RAAS-inhibitor diuretics was reported in 54% of the patients. The mean serum

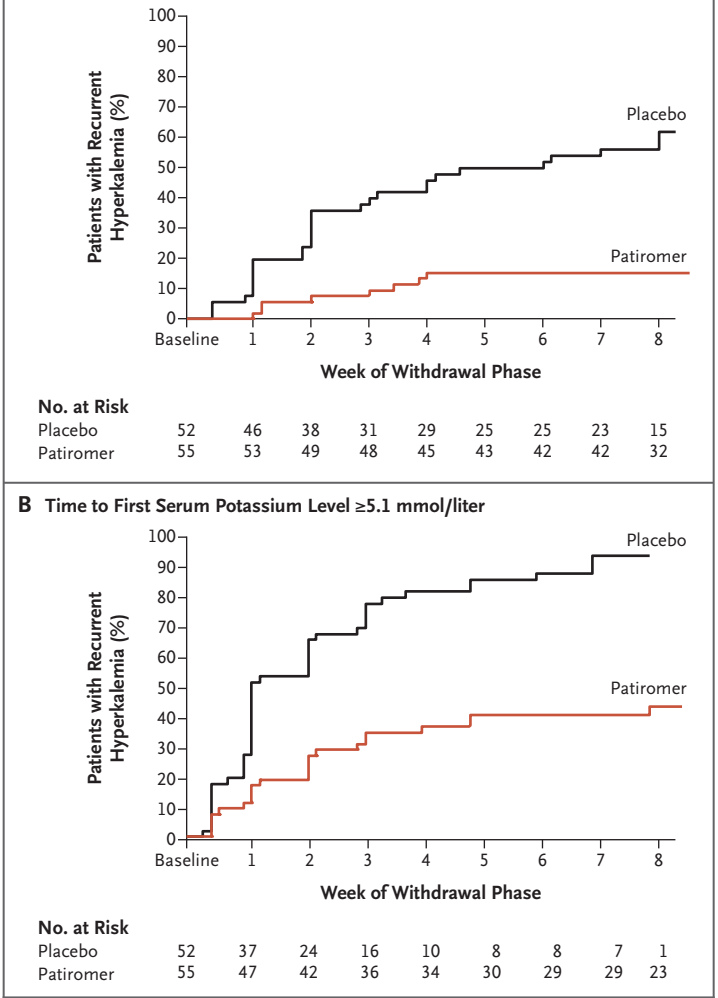

Figure 2. Time to First Recurrence of Hyperkalemia during the Randomized Withdrawal Phase.

Shown is the time to the first occurrence of a serum potassium level of 5.5 mmol per liter or higher (Panel A) and of 5.1 mmol per liter or higher (Panel B) among patients who were randomly assigned to continue patiromer treatment and those who were assigned to switch to placebo for the randomized withdrawal phase. Baseline refers to week 0 of the randomized withdrawal phase (week 4 of the study). The dose of the study drug was intended to be kept stable (i.e., not adjusted), and the doses of renin–angiotensin–aldosterone system (RAAS) inhibitors were not to be changed during the first 4 weeks of the randomized withdrawal phase in order to facilitate interpretation of the primary end point in this phase. After week 4 of the randomized withdrawal phase, an increase in the dose of patiromer was allowed at the first occurrence of a serum potassium level of 5.1 mmol per liter or higher.

potassium level at baseline was 5.6±0.5 mmol per liter (5.3±0.6 mmol per liter in patients with mild hyperkalemia and 5.7±0.4 mmol per liter in those with moderate-to-severe hyperkalemia). The baseline characteristics were similar in the two dose groups in the initial treatment phase (Table S4 in the Supplementary Appendix), and the characteristics of the patients in the patiromer and placebo groups in the randomized withdrawal phase were balanced at baseline (Table 1, and Table S5 in the Supplementary Appendix).

EFFICACY RESULTS FOR THE INITIAL TREATMENT PHASE

The mean (±SE) change in serum potassium levels from baseline to week 4 (in the 237 patients with at least one serum potassium measurement at a scheduled visit after day 3) was −1.01±0.03 mmol per liter (95% confidence interval [CI], −1.07 to −0.95; P<0.001). The change in patients with mild hyperkalemia was −0.65±0.05 mmol per liter (95% CI, −0.74 to −0.55), and the change in those with moderate-to-severe hyperkalemia was −1.23±0.04 mmol per liter (95% CI, −1.31 to −1.16). Figure 1 shows the observed mean serum potassium levels over time. The results of subgroup analyses of the primary efficacy end point are shown in Figure S2 in the Supplementary Appendix, and the results of sensitivity analyses are shown in Table S6 in the Supplementary Appendix.

The estimated proportion of patients with serum potassium levels in the target range (3.8 to <5.1 mmol per liter) at week 4 was 76% (95% CI, 70 to 81), with similar results in patients with mild hyperkalemia (74% [95% CI, 65 to 82]) and those with moderate-to-severe hyperkalemia (77% [95% CI, 70 to 83]). A total of 59 patients (24%) did not have serum potassium levels in the target range at week 4. Of these 59 patients, 24 withdrew early from the study and did not complete week 4, 8 had a serum potassium level of less than 3.8 mmol per liter at week 4, and 27 completed the phase with serum potassium levels of 5.1 mmol per liter or higher. Of these 27 patients, only 3 (1%) never had a serum potassium value that was less than 5.1 mmol per liter during the initial treatment phase (Fig. S3 in the Supplementary Appendix).

The mean daily dose of patiromer during the initial treatment phase was 12.8 g in patients with mild hyperkalemia and 21.4 g in patients with moderate-to-severe hyperkalemia, with a similar mean number of dose adjustments in the two groups (0.8 and 0.9, respectively). Of the 147 patients who required a dose adjustment, 91 (62%) required only one adjustment. Dose

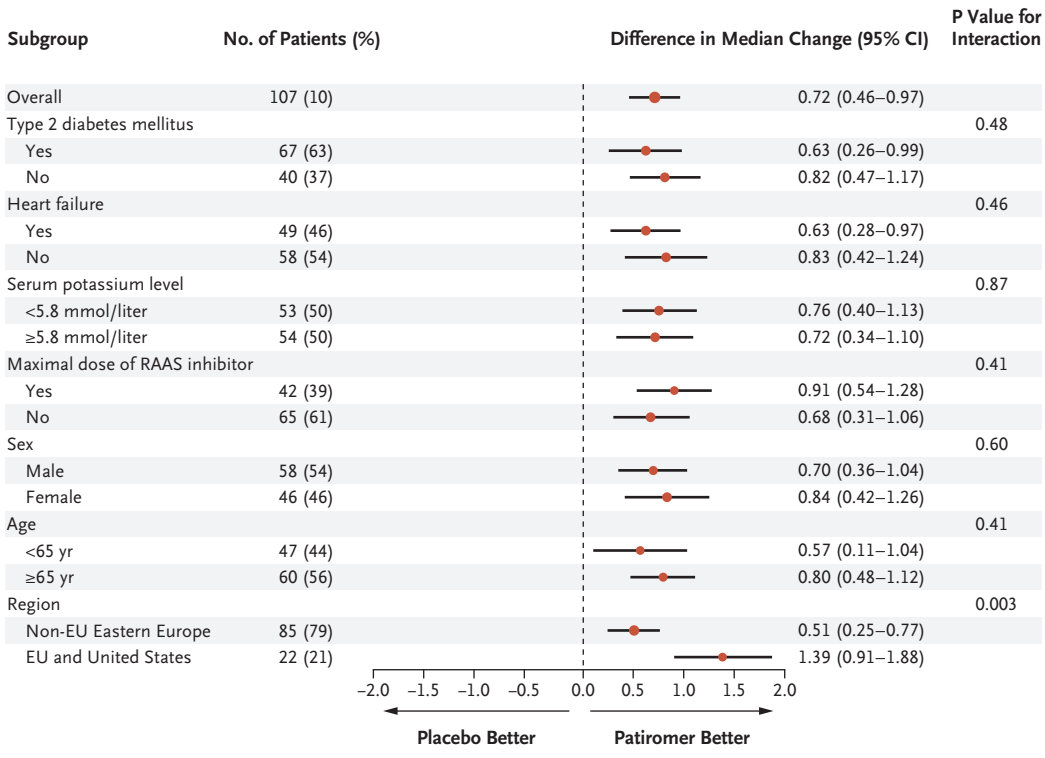

Figure 3. Primary Efficacy End Point in the Randomized Withdrawal Phase, According to Subgroup.

Shown is the difference between the placebo group and the patiromer group in the median change in serum potassium levels from the start of the randomized withdrawal phase to week 4 of that phase. The P values for interaction were calculated with the use of two-sided t-tests for the comparison of the differences between placebo and patiromer in the median change within each subgroup. EU denotes European Union.

adjustments were made most often at the day 3 visit (for 33% of the patients who required a dose adjustment) and the week 1 visit (for 25%).

EFFICACY RESULTS FOR THE RANDOMIZED WITHDRAWAL PHASE

At the start of the randomized withdrawal phase, which included patients whose serum potassium level had been well controlled while they were receiving patiromer in the initial treatment phase, the mean potassium level was 4.45 mmol per liter in the group that was randomly assigned to placebo (52 patients) and 4.49 mmol per liter in the group that was randomly assigned to continue patiromer treatment (55 patients). The estimated median change in the potassium level from the start of the randomized withdrawal phase to week 4 of the phase was 0.72 mmol per liter in the placebo group and 0 mmol per liter in the patiromer group, for a between-group difference of 0.72 mmol per liter (95% CI, 0.46 to 0.99; P<0.001).

A total of 60% (95% CI, 47 to 74) of the patients in the placebo group as compared with 15% (95% CI, 6 to 24) in the patiromer group had at least one potassium value of 5.5 mmol per liter or higher through week 8 of the withdrawal phase (P<0.001 for the between-group difference). Of the eight patients in the patiromer group who had at least one potassium value of 5.5 mmol per liter or higher, only two met protocol-specified withdrawal criteria for high serum potassium levels; one discontinued the RAAS inhibitor and beta-blocker medications, and the serum potassium level continued to be 5.5 mmol per liter or higher; in the other, concomitant medications were not changed, and two subsequent serum potassium values were less than 5.5 mmol per liter (see the Supplementary Appendix). A total of 91% (95% CI, 83 to 99) of the patients in the

Table 2. Adverse Events during the Initial Treatment Phase and through the Safety Follow-up Period for That Phase.*

Adverse Event	No. of Patients (%)
≥1 Adverse event†	114 (47)
Constipation	26 (11)
Diarrhea	8 (3)
Hypomagnesemia	8 (3)
Nausea	8 (3)
Anemia	7 (3)
Chronic renal failure	7 (3)
≥1 Serious adverse event‡	3 (1)

* The safety follow-up period was 1 to 2 weeks after discontinuation of the study drug. Events are listed if they occurred in at least 3% of the 243 patients overall. All the patients in the study received patiromer during the initial treatment phase; patients with a potassium level of 5.1 to less than 5.5 mmol per liter (mild hyperkalemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5 to less than 6.5 mmol per liter (moderate-to-severe hyperkalemia) received 8.4 g of patiromer twice daily. Table S7 in the Supplementary Appendix shows events and serious adverse events that occurred in at least 2% of the patients according to dose group.
† During the initial treatment phase (i.e., excluding the safety follow-up period), one or more adverse events were reported in 107 patients (44%), and one or more serious adverse events were reported in 2 patients (1%).
‡ The serious adverse events included atrial fibrillation (in 1 patient), enterococcal endocarditis (in 1), escherichia bacteremia (in 1), urinary tract infection (in 1), subtherapeutic anticoagulant blood levels (in 1), and chronic renal failure (in 1).

Table 3. Adverse Events during the Randomized Withdrawal Phase and through the Safety Follow-up Period for That Phase.*

Adverse Event	Placebo (N=52)	Patiromer (N=55)
	no. of patients (%)	
≥1 Adverse event	26 (50)†	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhea	0	2 (4)
Nausea	0	2 (4)
≥1 Serious adverse event	1 (2)‡	0

* The safety follow-up period was 1 to 2 weeks after discontinuation of the study drug. Adverse events are listed if they occurred in at least 4% of patients in the patiromer group.
† During the randomized withdrawal phase (i.e., excluding the safety follow-up period), one or more adverse events were reported in 24 patients (46%) in the placebo group.
‡ Mesenteric vessel thrombosis leading to death occurred in one patient. Additional details are provided in the Supplementary Appendix.

placebo group as compared with 43% (95% CI, 30 to 56) in the patiromer group had at least one potassium value of 5.1 mmol per liter or higher ($P<0.001$). Figure 2 shows the time to the recurrence of hyperkalemia. The results of the primary efficacy end point in prespecified subgroups were consistent with those in the overall population (Fig. 3). Analyses according to geographic region are provided in the Supplementary Appendix.

In exploratory analyses, 32 patients (62%) in the placebo group as compared with 9 (16%) in the patiromer group required an intervention to manage a recurrence of hyperkalemia; at the end of the randomized withdrawal phase, 44% in the placebo group as compared with 94% in the patiromer group were still receiving RAAS inhibitors. Figure S4 in the Supplementary Appendix shows the time to the discontinuation of RAAS inhibitors.

SAFETY

During the initial treatment phase and through its follow-up period, the proportion of patients with at least one adverse event was similar among patients with mild hyperkalemia and those with moderate-to-severe hyperkalemia (Table S7 in the Supplementary Appendix), with adverse events reported in 47% of the patients overall. The most common adverse events are shown in Table 2; mild-to-moderate constipation was the most common adverse event (occurring in 11% of the patients). The majority of gastrointestinal adverse events occurred in less than 2% of the patients. No serious gastrointestinal events occurred in this phase. Adverse events leading to discontinuation of patiromer occurred in 15 patients (6%). Three patients (1%) had a total of six serious adverse events (Table S7 in the Supplementary Appendix). None were fatal, and all were considered by the investigators not to be related to patiromer treatment.

During the randomized withdrawal phase and through its follow-up period, the proportion of patients with one or more adverse events was similar in the placebo group and the patiromer group (50% and 47%, respectively). Mild-to-moderate constipation, diarrhea, and nausea were the most common gastrointestinal events

reported with patiromer (each in 4% of the patients); these events occurred in none of the patients in the placebo group (Table 3). One patient (2%) in each study group discontinued the study drug owing to adverse events. One serious event (mesenteric vessel thrombosis leading to death) occurred in a patient in the placebo group; the investigator assessed it as unrelated to patiromer therapy (see the Supplementary Appendix for additional details).

During the initial treatment phase and through its follow-up period, the incidence of hypokalemia (serum potassium level <3.5 mmol per liter) was 3.0%. Potassium levels indicating hypokalemia ranged from 3.2 to 3.4 mmol per liter; the hypokalemia was most often transient after adjustment of the dose of patiromer. During the randomized withdrawal phase, withdrawal from the study was required if the serum potassium level was less than 3.8 mmol per liter; 5% of the patients in the patiromer group and 2% in the placebo group met this criterion.

The mean serum magnesium level remained within the normal range during both phases; a small mean decrease from baseline (−0.1 to −0.2 mg per deciliter [−0.04 to −0.08 mmol per liter]), with no apparent dose effect, was observed with patiromer in the initial treatment phase, and a small mean increase (0.1 mg per deciliter) was observed with placebo in the randomized withdrawal phase (Fig. S5 in the Supplementary Appendix). A serum magnesium level of less than 1.4 mg per deciliter (0.58 mmol per liter) occurred in eight patients (3%) during the initial treatment phase and through its follow-up period only; none of these patients had serum magnesium levels of less than 1.2 mg per deciliter (0.49 mmol per liter) during either phase. Magnesium-replacement therapy was initiated in nine patients (4%) in the patiromer group during the initial treatment phase. No clinically relevant changes in renal function or in levels of calcium, fluoride (Fig. S6 to S9 in the Supplementary Appendix), or other electrolytes (e.g., bicarbonate) were observed in either phase.

Two patients during the initial treatment phase and one patient in the patiromer group during the randomized withdrawal phase had electrocardiographic changes that were consistent with hyperkalemia, and none had changes consistent with hypokalemia, as assessed by the safety review board (see the Supplementary Appendix).

DISCUSSION

Among patients with chronic kidney disease who were taking RAAS inhibitors, treatment with patiromer was associated with a reduction from baseline in elevated serum potassium levels; normokalemia was subsequently maintained more effectively than it was among patients receiving placebo. The incidence of hypokalemia was low, there were few gastrointestinal side effects, and the dose of patiromer had to be adjusted infrequently.

Patients in whom persistent or sustained hyperkalemia develops typically have multiple risk factors, the most important of which are chronic kidney disease and diabetes and the concomitant use of RAAS inhibitors.[4] Approximately 85% of the patients in the current study had an eGFR of 15 to less than 60 ml per minute per 1.73 m^2; all were receiving RAAS inhibitors, and substantial proportions had hypertension, diabetes, heart failure, or coronary artery disease. Thus, the study population was representative of patients who generally benefit from RAAS-inhibitor therapy.[1,12,15-20] A range of elevated serum potassium levels (5.1 to <6.5 mmol per liter) was used to qualify patients for inclusion in the study, with 62% of the patients having a baseline potassium level of 5.5 mmol per liter or higher, a finding that is representative of the broad range of potassium elevations observed in patients with chronic kidney disease and hyperkalemia who are taking RAAS inhibitors.[1,4,12,20-22]

Overall, 76% of the qualifying patients with hyperkalemia who were treated with patiromer in the initial treatment phase had normal potassium levels at week 4. Among patients with moderate-to-severe hyperkalemia, the mean potassium level was less than 5.5 mmol per liter 2 days after the start of treatment, which was the time of the first postbaseline assessment. A serum potassium level of 5.5 mmol per liter is the threshold at which many clinicians initiate strategies to manage hyperkalemia.[4,21] Among patients with mild hyperkalemia, mean potassium levels were reduced to less than 5.1 mmol per liter after 2 days of treatment.

In the randomized withdrawal phase, the incidence of recurrent hyperkalemia (when defined as a potassium level ≥5.5 mmol per liter) was 4 times as high in the placebo group as in the patiromer group (60% vs. 15%), with hyperkale-

mia recurring more rapidly in the placebo group (Fig. 2). Almost 4 times as many patients in the placebo group as in the patiromer group required an intervention to lower the potassium level. In 56% of the patients in the placebo group as compared with 6% of patients in the patiromer group, discontinuation of RAAS-inhibitor therapy was required to control serum potassium levels adequately.

Mild-to-moderate constipation, the most common adverse event with patiromer (occurring in 11% of the patients during the initial treatment phase and in 4% during the randomized withdrawal phase), generally did not limit treatment. The rates of all other adverse events with patiromer were low and similar to those with placebo in the randomized withdrawal phase. Few serious adverse events occurred; investigators, who were aware of the treatment assignments, attributed none of these events to patiromer. Hypokalemia was uncommon and reversible, which suggests that it may be mitigated by monitoring serum potassium levels and adjusting the dose of patiromer as needed.

Although this study showed the benefit of patiromer in treating hyperkalemia and in reducing the risk of recurrence and also showed that more patients in the patiromer group than in the placebo group were able to continue taking RAAS inhibitors, additional data evaluating patiromer therapy in the long term (>12 weeks) are needed. Neither phase of the current trial was double-blind; however, the phlebotomy staff, medical monitors, and patients were unaware of the group assignments during both phases, and the statistical staff, the members of the core electrocardiographic laboratory, and the safety review board were unaware of the group assignments during the randomized withdrawal phase. Given that patients with serum potassium levels up to 6.5 mmol per liter were enrolled in the initial treatment phase, placebo control was considered to be unethical. The use of an active control (i.e., sodium or calcium polystyrene sulfonate) was not considered to be clinically appropriate because of the lack of prospective, controlled data on these agents, their potential to cause bowel necrosis,[5-8,10,23-31] and the absence of a standard of care for their use beyond the acute setting.

In conclusion, among patients with chronic kidney disease who were taking RAAS inhibitors and who had hyperkalemia, treatment with patiromer was associated with reductions in serum potassium levels and maintenance of normal potassium levels.

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