Long-term Patiromer Use and Outcomes Among US Veterans With Hyperkalemia and CKD: A Propensity-Matched Cohort Study

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Rationale & Objective: Patiromer is a potassium binder approved for the long-term management of hyperkalemia. Although patiromer use among patients with advanced chronic kidney disease (CKD) has been shown to reduce the discontinuation of renin-angiotensin-aldosterone system inhibition therapy, it remains unclear whether patiromer can improve clinical outcomes. The aim of this study was to examine the association of long-term patiromer use with clinical outcomes among hyperkalemic patients with CKD.

Study Design: This was a longitudinal observational study.

Setting & Participants: We evaluated a national cohort of 854,217 US Veterans who had at least 1 serum potassium measurement of ≥5.1 mEq/L and were treated at US Department of Veterans Affairs health care facilities between January 2016 and September 2019.

Exposure: The exposure was long-term patiromer use.

Outcomes: The outcomes were as follows: (1) composite endpoint of kidney failure with replacement therapy (KFRT) or all-cause death and (2) all-cause death including the post-KFRT period.

Analytical Approach: Cox proportional Fine-Gray subdistribution hazard models were used in a propensity-matched cohort.

Results: Among 2,004 patients who ever used patiromer during the study period (0.2% of the cohort), 666 met the criteria for long-term patiromer use. We matched 308 long-term patiromer users to 308 nonusers based on propensity scores. The median estimated glomerular filtration rate was 23.5 mL/min/1.73m^2, and the median potassium level was 5.2 mEq/L. Approximately 45% were on renin-angiotensin system inhibitor(s) at baseline. During follow-up, 93 patients developed KFRT, and 134 patients died. Long-term patiromer users, when compared to nonusers, experienced a 26% lower risk of the composite outcome (HR, 0.74; 95% CI, 0.53-1.01; *P* = 0.06) and a 41% lower risk of all-cause mortality (HR, 0.59; 95% CI, 0.41-0.84; *P* = 0.003).

Limitations: The study cohort included mostly male veterans with relatively short follow-up periods.

Conclusions: Long-term patiromer use was associated with a lower risk of all-cause mortality among patients with CKD and hyperkalemia. Long-term potassium binder use for hyperkalemia may improve clinical outcomes in CKD.

H yperkalemia is a common complication of chronic kidney disease (CKD) due to impaired kidney potassium excretion in the setting of decreases in glomerular filtration rate, tubular flow, distal sodium delivery, or the expression of selective ion transporters located along the aldosterone-sensitive distal nephron.[1] In addition to decreased kidney function due to either CKD or acute kidney injury, heart failure, diabetes mellitus, metabolic acidosis, and the use of renin-angiotensin-aldosterone (RAAS) inhibitors, all of which are frequently observed among patients with CKD, are established risk factors for hyperkalemia.[2-8]

Hyperkalemia is associated with a higher risk of adverse clinical outcomes, including mortality, cardiovascular events, hospitalizations, and progression to kidney failure with replacement therapy (KFRT).[7,9-12] The association between hyperkalemia and adverse outcomes may be explained by its known cardiac electrophysiologic effects.[13] Severe hyperkalemia predisposes to both cardiac hyperexcitability and depression, either of which can lead

to fatal arrhythmias.[14] Dietary potassium restriction is commonly prescribed for nonemergent hyperkalemia, and such patients are generally discouraged from consuming heart-healthy diets containing fruits and vegetables.[15] Additionally, RAAS inhibitors, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and mineralocorticoid receptor antagonists (MRAs) have cardiorenal protective qualities and have proven clinical benefits in patients with CKD, diabetes mellitus, or congestive heart failure.[16] Hyperkalemia often hampers the utilization of these beneficial medications, which are frequently discontinued to prevent or treat hyperkalemia, despite the resulting inadequate reno- and cardioprotection.[17-19]

Patiromer is a potassium binder approved for the management of hyperkalemia.[20] Patiromer was well tolerated when administered for up to 1 year in clinical trials, has been shown to enable the use of RAAS inhibitors, and may allow the consumption of a heart-healthy diet.[21-25] Despite the hypothetical benefits of

PLAIN-LANGUAGE SUMMARY

Hyperkalemia is a common complication of chronic kidney disease (CKD) and can result in the discontinuation of renin-angiotensin-aldosterone system inhibition therapy, a cornerstone of CKD management. Patiromer is a new potassium binder approved for the long-term management of hyperkalemia, but it remains unclear whether patiromer can improve clinical outcomes. We examined a cohort of US Veterans with hyperkalemia between January 2016 and September 2019 and found that patiromer use was uncommon for treating hyperkalemia during this study period. We then matched 308 long-term patiromer users and 308 nonusers based on propensity scores. Long-term patiromer users, when compared to nonusers, experienced a 26% lower risk of the composite outcome and a 41% lower risk of all-cause mortality. These findings indicate that long-term potassium binder use for hyperkalemia may improve clinical outcomes in CKD.

these interventions, the impact of potassium binders on long-term clinical outcomes has not yet been examined in clinical trials or in observational studies. The aim of this study was to examine the association of long-term patiromer use with the following: (1) the composite endpoint of all-cause death or KFRT, (2) the development of KFRT, and (3) all-cause death in hyperkalemic patients with CKD. We hypothesized that long-term patiromer use would be associated with a lower risk of mortality and KFRT.

METHODS

This is a retrospective cohort study based on data obtained from the Department of Veterans Affairs (VAs) Corporate Data Warehouse (CDW). This study was approved by the Institutional Review Board of the Memphis VA Medical Center (IRB number: 1576407), with an exemption from informed consent. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for observational studies.

Demographics and Clinical Measurements

We collected data from the VA CDW on demographic and socioeconomic characteristics, comorbid conditions, medications, vital signs, and laboratory characteristics during the study period. We used race and ethnicity categories as reported in the VA CDW, including Black, Hispanic, White, and other, which included those who self-identified as Asian, American Indian, Pacific Islander, and others without further specification. Race and ethnicity data were included because these variables have known associations with kidney outcomes and are thus considered confounders. We collected information about prescribed medications from the Decision Support System National Data Extracts' outpatient and inpatient pharmacy files, including the date of dispensation, the dose, and the number of pills; we also collected information from Medicare Part D files for those eligible for such coverage.[26] We identified medications obtained outside VA pharmacies from non-VA medication files in CDW. We extracted information about comorbid conditions from the VA Inpatient and Outpatient Medical SAS Data files using the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) diagnostic and procedure codes and Current Procedural Terminology codes as well as from Centers for Medicare & Medicaid Services data files. We defined prevalent comorbid conditions based on the presence of at least 1 inpatient code or at least 2 outpatient codes recorded before the baseline date. We calculated the Charlson comorbidity index score using the Deyo modification for administrative data sets.[27] We collected information about relevant laboratory characteristics from the VA LabChem files[28] and calculated estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[29] We collected information about proteinuria, including urine protein-to-creatinine ratio, urine albumin-to-creatinine ratio (UACR), and urine dipstick protein, from the DSS National Data Extracts Laboratory Results file and the VA LabChem file in the CDW. Because UACR is the preferred method for defining and staging CKD, we converted urine protein-to-creatinine ratio and urine dipstick protein to UACR values using a validated conversion equation and categorized all available UACR values as <30 mg/g (normal to mildly elevated), 30 to <300 mg/g (moderately elevated), and ≥300 mg/g (severely elevated).[30] Missingness for race, smoking status, and albuminuria was used as a category of each variable in the propensity score calculation.

Exposure and Control

The exposure was long-term patiromer use, and the control was never-use or short-term patiromer use (collectively referred to as non-long-term users). We defined the start of long-term patiromer use as the date of patiromer prescription when a second prescription was dispensed, and the cumulative supply of outpatient patiromer exceeded 30 days. The other patiromer prescriptions were considered as short-term use.

Outcomes

Our primary outcomes were as follows: (1) the composite of all-cause pre-KFRT death or the development of KFRT, (2) development of KFRT, and (3) all-cause death during the entire follow-up time, including the post-KFRT period. Death data were obtained from the VA Vital Status Files and were available through September 30, 2019.[31] Data on the development of KFRT, defined as the initiation of maintenance dialysis therapy or preemptive
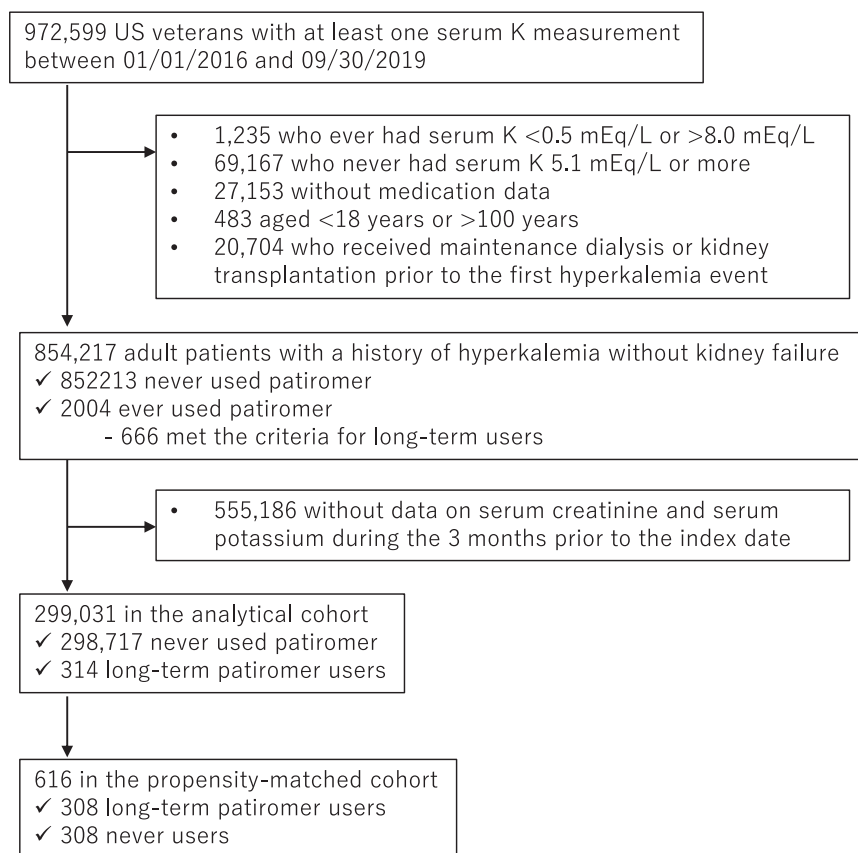
Figure 1. Study cohort construction. Abbreviation: K, potassium.

kidney transplantation, were obtained from the US Renal Data System and were available through December 31, 2018.

Cohort Definition

We evaluated a national cohort of 972,599 US Veterans receiving care from the VA Health Care System who had at least 1 serum potassium measurement between January 1, 2016, and September 30, 2019. This study period was determined given that patiromer became available at VA medical facilities shortly after its approval by the US Food and Drug Administration in October 2015. We excluded 1,235 patients who ever had potassium levels of <0.5 mEq/L or >8.0 mEq/L; 69,167 who did not experience any hyperkalemia event (potassium levels ≥ 5.1 mEq/L); 27,153 who did not have documented medication dispensations from a Department of VA pharmacy; 483 aged <18 years or >100 years; and 20,704 patients who received maintenance dialysis or kidney transplant before the first hyperkalemia event during the study period (Fig 1). Baseline was defined as the date of the hyperkalemia measurement before the first patiromer prescription among long-term users. For those never on long-term patiromer use, a random observation start date was generated to create comparable "excluded" times, accounting for the

immortal period created by the above definition of long-term users. We defined baseline laboratory data as the most recent available data during the 90 days preceding the baseline date and baseline medication use as the presence of at least 1 outpatient prescription of medication classes of interest for at least 30 days during the 365 days preceding the baseline date. We excluded 555,186 patients who did not have data on baseline eGFR and potassium, leaving 299,031 patients in the analytical cohort. We then matched long-term patiromer users and nonusers using propensity scores calculated from demographic characteristics, comorbid conditions, baseline eGFR, serum potassium level, proteinuria, and medications including RAAS inhibitors and prior use of sodium polystyrene sulfonate (SPS), all of which are shown in Table 1, as well as the above-defined start date.

Statistical Analyses

Patients' characteristics at the time of propensity score matching were compared between long-term patiromer users and nonusers using standardized difference.[32] We evaluated the longitudinal changes in patiromer and RAAS inhibitor utilization using Kaplan-Meier estimates. We defined drug discontinuation as interrupted dispensation before the end of patient follow-up or a break in prescriptions that lasted >30 days.

Table 1. Patient Characteristics Among 308 Long-term Patiromer Users Versus 308 Nonusers in the Propensity-Matched Cohort

Variables	Nonusers n = 308	Long-term Patiromer Users n = 308	Standardized Difference
Age (y), mean (SD)	70.8 (10.6)	70.8 (9.5)	0.003
Female, n (%)	13 (4.2%)	7 (2.3%)	0.110
Race, n (%)			
White	222 (72.1%)	219 (71.1%)	0.022
Black	74 (24.0%)	71 (23.1%)	0.023
Other + Multiple	6 (1.9%)	7 (2.3%)	−0.023
Missing	6 (1.9%)	11 (3.6%)	−0.099
Married, n (%)	162 (52.6%)	164 (53.2%)	−0.013
Service connected, n (%)	159 (51.6%)	165 (53.6%)	−0.039
Smoking status, n (%)			
Current	120 (39.0%)	129 (41.9%)	−0.060
Past	76 (24.7%)	69 (22.4%)	0.054
Never	52 (16.9%)	61 (19.8%)	−0.076
Unknown or missing	60 (19.5%)	49 (15.9%)	0.094
Comorbid conditions, n (%)			
Diabetes	244 (79.2%)	233 (75.6%)	0.086
Ischemic heart disease	39 (12.7%)	34 (11.0%)	0.099
Congestive heart failure	68 (22.1%)	67 (21.8%)	0.008
Cerebrovascular disease	61 (19.8%)	55 (17.9%)	0.050
Peripheral vascular disease	65 (21.1%)	73 (23.7%)	−0.062
Chronic pulmonary disease	21 (6.8%)	19 (6.2%)	0.000
Liver disease	71 (23.1%)	71 (23.1%)	−0.010
Peptic ulcer disease	15 (4.9%)	11 (3.6%)	0.014
Connective tissue disease	17 (5.5%)	16 (5.2%)	0.065
Cancer	1 (0.3%)	1 (0.3%)	−0.026
Charlson comorbidity index, median [IQR]	6 [4-7]	5 [4-7]	0.102
Medications, n (%)			
Prior SPS use	131 (42.5%)	138 (44.8%)	−0.046
Any antihypertensives	210 (68.2%)	207 (67.2%)	0.021
RAAS inhibitors	141 (45.8%)	138 (44.8%)	1.20
MRA	15 (4.9%)	19 (6.2%)	−0.057
Beta blockers	210 (68.2%)	201 (65.3%)	0.062
Alkalizing agents	99 (32.1%)	112 (36.4%)	−0.089
Erythropoiesis-stimulating agents	19 (6.2%)	11 (3.6%)	0.121
Proton pump inhibitors	101 (32.8%)	108 (35.1%)	−0.048
H2 blockers	22 (7.1%)	34 (11.0%)	−0.136
NSAIDs[a]	131 (42.5%)	124 (40.3%)	0.046
Thiazide	40 (13.0%)	45 (14.6%)	−0.047
Loop diuretics	181 (58.8%)	175 (56.8%)	0.039
Serum potassium level, median [IQR], mEq/L	5.2 [4.9-5.6]	5.3 [4.9-5.7]	−0.040
eGFR, median [IQR], mL/min/1.73 m²	23.4 [15.3-34.7]	23.5 [16.2-33.6]	−0.084
Albuminuria, n (%)			
Normal to mildly elevated	15 (4.9%)	21 (6.8%)	−0.083
Moderately increased	31 (10.1%)	24 (7.8%)	0.080
Severely increased	97 (31.5%)	88 (28.6%)	0.064
Missing	165 (53.6%)	175 (56.8%)	−0.065

Note: Values for categorical variables are given as percentages and those for continuous variables as mean ± standard deviation or median (IQR). Differences in patient characteristics between groups were compared by standardized difference, of which 80%, 50%, and 20% were considered large, medium, and small differences, respectively.[32]

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; SPS, sodium polystyrene sulfonate.

[a]Including aspirin.

Patients were followed up until the occurrence of either outcome, the last recorded VA encounter date, or the last available date (December 31, 2018 for KFRT and composite endpoint analyses, and September 30, 2019 for mortality analyses). Event rates were estimated by Poisson regression model. Survival without KFRT and the

cumulative incidence of KFRT were estimated using the Fine and Gray competing risk regression model because the Kaplan-Meier approach overestimates an incidence in the presence of competing risks. In the etiological association analyses for the study outcomes (ie, the composite endpoint, KFRT, and all-cause death), we used cause-specific Cox proportional hazard regression model.[33] In the analyses for all-cause death, we followed patients through the last date of the VA mortality data available to this study, irrespective of KFRT occurrence. Effect modifications were evaluated by including a product term between long-term patiromer use and any of the following variables: age, race, baseline RAAS inhibitor use, history of diabetes, Charlson comorbidity index, baseline eGFR, or baseline serum potassium levels. As sensitivity analyses, we adjusted for the same set of variables and the highest serum potassium level during the 3 months on or before the index date. The proportional hazard assumption was evaluated using Schoenfeld residuals. We defined statistical significance as P < 0.05 using two-tailed tests. We performed all statistical analyses using SAS 9.4 (SAS Institute, Inc, Cary, NC) and Stata version 17 (Stata Corp, College Station, Texas, USA).

RESULTS

Among 854,217 patients who had at least one hyperkalemia event, only 2,004 (0.23%) ever used patiromer during the study period of January 1, 2016 to September 30, 2019. A total of 666 (0.08% of the analytical cohort or 33% of ever-patiromer users) patients met the criteria for long-term patiromer use. Among 299,031 patients (298,717 non-long-term users and 314 long-term users) in the analytical cohort, long-term patiromer users, when compared to non-long-term users, were more likely Black (13% vs 24%) and had a higher prevalence of diabetes (46% vs 76%), congestive heart failure (12% vs 22%), and peripheral vascular disease (13% vs 24%) as well as a higher Charlson comorbidity index (median 4 vs 2) (Table S1). Long-term patiromer users had also higher prevalence of prior SPS use (45% vs 2%), higher serum potassium level (median 4.9 mEq/L vs 4.3 mEq/L), lower eGFR (median 16 vs 51 mL/min/1.73 m^2), and more severe albuminuria, but similar prevalence of RAAS inhibitor use (44% vs 41%). We then matched 308 long-term patiromer users to 308 nonusers based on propensity scores. Among the 616 matched patients, the mean age was 70.8 years, 3.2% were female, 24% were Black, and 77% had diabetes. The median eGFR was 23 mL/min/1.73 m^2 [interquartile range (IQR), 16-35], and the prevalence of normal or mildly elevated, moderately elevated, and severely elevated albuminuria was 6%, 9%, and 30%, respectively, whereas 55% of patients did not have data on baseline albuminuria. The median serum potassium level was 5.2 mEq/L (IQR, 4.9-5.6), and 44% used SPS during the 6 months before patiromer initiation. In total, 45% and 6% were on RAAS inhibitors and MRAs

at baseline, respectively. Baseline characteristics were similar between long-term patiromer users and matched nonusers, as shown in Table 1. However, the highest serum potassium level during the 91 days before the index date was higher in long-term patiromer users compared to matched non-long-term users {mean 5.8 [standard deviation (SD), 0.6] mEq/L vs 5.5 [SD, 0.6] mEq/L, P < 0.001}, which was included among the adjustment variables in the Cox proportional hazard regression as part of our sensitivity analyses.

Patiromer and RAAS Inhibitor Use

During the study period, the median number of outpatient patiromer refills was 2 (IQR, 1-4; range, 1-21) among the 308 long-term patiromer users. A total of 216 long-term users (70%) discontinued patiromer. Kaplan-Meier estimates showed that more than half of long-term patiromer users discontinued patiromer within 3 months, and approximately 25% and 15% remained on patiromer at 6 months and 1 year, respectively (Fig 2A). Of the 308 matched non-long-term users, 11 received short-term patiromer prescriptions, but none received long-term prescriptions.

Approximately 45% of patients in the matched cohort used RAAS inhibitors at baseline (137 and 138 among long-term patiromer users and nonusers, respectively). The median number of outpatient RAAS inhibitor refills was 2 (IQR, 1-5; range, 1-14) in the matched cohort. A total of 139 RAAS inhibitor users (16%) discontinued patiromer. Kaplan-Meier estimates showed that approximately 40% and 25% of baseline users remained on RAAS inhibitors at 1 year among long-term patiromer users and nonusers, respectively [hazard ratio (HR) for discontinuation = 0.79; 95% confidence interval (CI), 0.56-1.11; P = 0.17] (Fig 2B).

Composite Endpoint of KFRT or All-Cause Death

During a follow-up period of 429 patient-years, 159 patients developed the composite endpoint of KFRT or death (93 patients developed KFRT and 66 died without KFRT). The probabilities of KFRT and survival without KFRT among long-term patiromer users versus nonusers are shown in Fig 3. The incidence rate of the composite endpoint was 312 (95% CI, 244-401) per 1,000 patient-years among long-term patiromer users and 421 (95% CI, 345-514) per 1,000 patient-years among nonusers (HR, 0.74; 95% CI, 0.53-1.01; P = 0.06, Table 2). No significant effect modifications were found for age, race, baseline RAAS inhibitor use, history of diabetes, Charlson comorbidity index, baseline eGFR, or baseline serum potassium levels (P for interaction > 0.2 for all). Adjusted HR for the composite endpoint among long-term patiromer users (vs nonusers) was 0.69 (95% CI, 0.49-0.98; P = 0.04). The incidence rate of KFRT was 186 (95% CI, 135-257) and 243 (95% CI, 187-316) per 1,000 patient-years among long-term users versus non-long-term users, respectively (subhazard ratio, 0.76; 95% CI, 0.50-1.14;
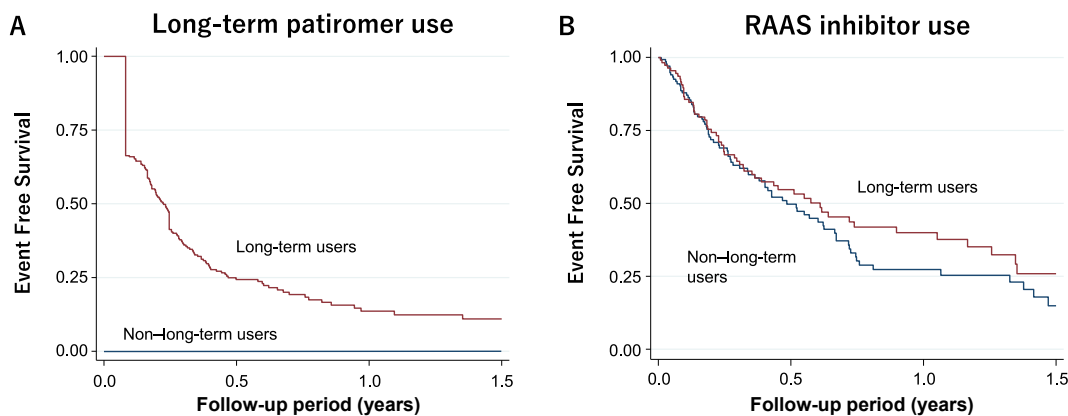
Figure 2. Longitudinal changes in the estimated probability of (A) patiromer use among 308 long-term patiromer users and (B) renin-angiotensin-aldosterone system inhibitor use among 141 long-term patiromer users versus 138 nonusers receiving renin-angiotensin-aldosterone system inhibitor at baseline. The follow-up time was from the date of matching after January 1, 2016 until the occurrence of death, end-stage kidney disease, the last recorded Veterans Affairs encounter date, or the last available date in our data file from the US Renal Data System (December 31, 2018).

P = 0.19, Table 2). The adjusted subhazard ratio for KFRT among long-term patiromer users (vs nonusers) was 1.13 (95% CI, 0.74-1.80; P = 0.59).

All-Cause Death

During a follow-up period of 864 patient-years, 134 patients died. The survival estimates among long-term patiromer users versus nonusers are shown in Fig 4. The all-cause mortality rate was 116 (95% CI, 88-154) per 1,000 patient-years among long-term patiromer users and 192 (95% CI, 155-234) per 1,000 patient-years among

Figure 3. Estimated probabilities of kidney failure with replacement therapy and survival without kidney failure with replacement therapy among 308 long-term patiromer users and 308 propensity-matched nonusers in the Fine & Gray competing risk regression model. The follow-up time was from the date of matching after January 1, 2016 until the occurrence of death, end-stage kidney disease, the last recorded Veterans Affairs encounter date, or the last available date in our data file from the US Renal Data System (December 31, 2018).

nonusers (HR, 0.59; 95% CI, 0.41-0.84; P = 0.003, Table 2). The finding remains significant after the multivariable adjustment (adjusted HR, 0.45; 95% CI, 0.31-0.66; P < 0.001).

DISCUSSION

In this national cohort of US Veterans with nondialysis CKD and hyperkalemia between January 2016 and December 2019, the prevalence of long-term patiromer use was rare. More than half of long-term patiromer users discontinued patiromer within 6 months. Long-term patiromer use was associated with lower all-cause mortality. Nominally fewer patients on long-term patiromer therapy experienced KFRT and discontinued RAAS inhibitors, but these differences did not reach statistical significance.

The prevalence of patiromer use was very low (0.23%) during the study period of January 1, 2016 to September 31, 2019, and its long-term use was ever rarer (0.08%). Patiromer became available for veterans without out-of-pocket expenses at VA medical facilities shortly after its approval by the US Food and Drug Administration on October 21, 2015. However, a trial of SPS before patiromer use was initially advised in the office setting. In addition, the drug label for patiromer states that other orally administered drugs should be given at least 3 hours apart from patiromer (previously stated as 6 hours apart in a boxed warning that appeared until November 25, 2016) given its possible drug-drug interaction.[34] This warning could make long-term patiromer use less practical because many patients with advanced CKD take multiple oral drugs, including antihypertensives, alkalizing agents, and diuretics.[35,36] Furthermore, another new potassium binder (sodium zirconium cyclosilicate) became available later in the study period. Together, these factors may have resulted in the observed low rates of long-term use and the high
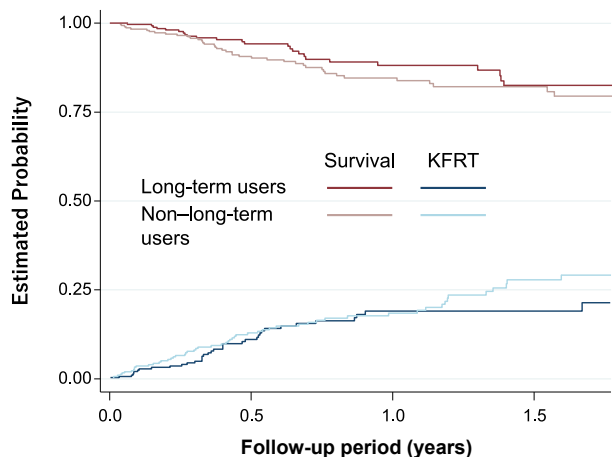
Table 2. Number of Events, Total Follow-Up Time, Event Rate, Unadjusted Risk, and Adjusted Risk for the Composite Endpoint of Kidney Failure With Replacement Therapy and All-Cause Death, Kidney Failure With Replacement Therapy, and All-Cause Death

		Long-term Users (N = 308)	Non-long-term Users (N = 308)
Composite endpoint	Number of events	62	97
	Total follow-up time, patient-years	198	230
	Event rate per 1,000 patient-years	312 (244-401)	421 (345-514)
	Unadjusted hazard ratio	0.74 (0.53-1.01), $P = 0.06$	
	Adjusted hazard ratio	0.69 (0.49-0.98), $P = 0.04$	
KFRT	Number of events	37	56
	Total follow-up time, patient-years	198	230
	Event rate, per 1,000 patient-years	186 (135-257)	243 (187-316)
	Unadjusted subhazard ratio	0.75 (0.50-1.14), $P = 0.19$	
	Adjusted subhazard ratio	1.13 (0.74-1.80), $P = 0.59$	
All-cause deaths	Number of events	49	85
	Total follow-up time, patient-years	421	442
	Event rate, per 1,000 patient-years	116 (88-154)	192 (155-238)
	Unadjusted hazard ratio	0.59 (0.41-0.84), $P = 0.003$	
	Adjusted hazard ratio	0.45 (0.31-0.66), $P < 0.001$	

Note: Event rate was estimated by Poisson regression. 95% confidence intervals are provided in parentheses.
Abbreviations: KFRT, kidney failure with replacement therapy.

discontinuation rate of patiromer, leading to the relatively limited statistical power of this study to detect between-group differences despite substantial nominal differences in the point estimates for some of the endpoints.

Patiromer may provide clinical benefit by allowing patients with advanced CKD to start or remain on RAAS inhibitors, which are recognized as a cornerstone of therapy in patients with CKD due to their beneficial cardiorenal effects.[9-12] In an exploratory analysis of the OPAL-

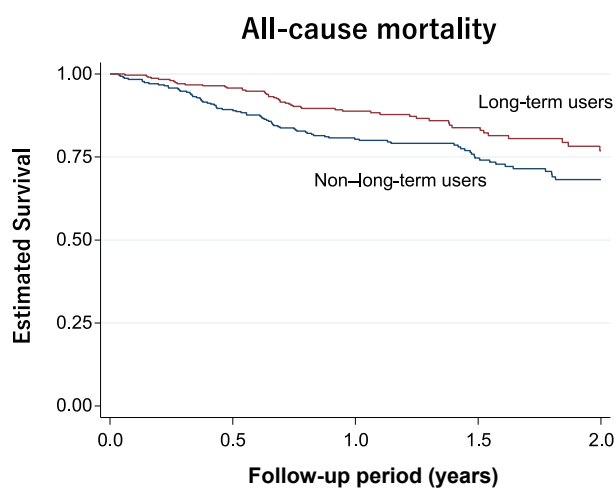**All-cause mortality**

Long-term users

Non–long-term users

Figure 4. Survival estimates among 308 long-term patiromer users and 308 propensity-matched nonusers. The follow-up time was from the date of matching after January 1, 2016 until the occurrence of death, the last recorded Veterans Affairs encounter date, or the last available date in our mortality data file from the Veterans Affairs (September 30, 2019).

HK 12-week study, 94% of patients assigned to patiromer remained on RAAS inhibitor or MRA therapy at week 12 versus 44% of placebo patients.[20] The AMBER and DIAMOND trials also demonstrated consistent findings.[22-24] Previous observational studies showed that RAAS inhibitor use is associated with favorable outcomes and that stopping RAAS inhibition among patients with advanced CKD was associated with higher risks of mortality and major adverse cardiovascular events, with no significant benefit in delaying the development of KFRT.[37,38] We also previously reported that the mortality benefit of pre-KFRT RAAS inhibitor use extended to the post-KFRT period.[18] The recently completed STOP ACEi trial also showed that discontinuation of RAAS inhibitors does not result in improved kidney outcomes despite a hypothesized short-term favorable effect on glomerular filtration rate, cautioning against routine discontinuation of RAAS inhibition in advanced CKD.[39]

Our study found significantly better survival among long-term patiromer users versus nonusers despite a small, unsignificant between-group difference in the prevalence of patients who remained on RAAS inhibition; hence, there may be other pathways in the survival benefit from patiromer use. Patiromer use may delay dialysis initiation simply by preventing the occurrence of severe hyperkalemia, which can be a trigger to initiate maintenance kidney replacement therapy in patients with advanced CKD even without associated adverse clinical events, such as arrhythmias. Mortality is particularly high during the first few months after dialysis initiation, and central venous dialysis catheter use has been identified as a risk factor for this early mortality after hemodialysis initiation in multiple studies.[40-45] A delay in the need for dialysis initiation and

preventing the need for emergency dialysis initiation may thus have benefits in patients treated with patiromer in the immediate postdialysis period by virtue of preventing the need of dialysis catheter use. Additionally, patiromer may provide a cardiovascular benefit by reducing aldosterone levels as shown in nondialysis CKD patients treated with RAAS inhibitors.[46] Other potential indirect benefits from patiromer use include less restriction on a potassium-rich diet, such as fruits, vegetables, and nuts, that have been proven to have multiple health benefits.[47,48]

Several limitations should be noted in this study. First, as mentioned above, our study had limited statistical power because of the relatively small number of long-term patiromer users. Second, our study cohort consisted of predominantly male US Veterans, and our findings should be validated in non-US Veterans and females. Second, we cannot prove causality between patiromer use and clinical outcomes because of the nature of observational study design that has inherent residual confounding and unmeasured confounders. Third, the mechanisms underlying the association between long-term patiromer use and mortality remain unclear because we lacked data on cause of death or reliable nutritional assessment. Fourth, we were unable to include sodium zirconium cyclosilicate in this study analysis. Compared with patiromer, sodium zirconium cyclosilicate has a similar safety profile but was approved later (May 18, 2018), and we excluded those patients who ever used sodium zirconium cyclosilicate because its use was even less frequent than patiromer during the study period.

In conclusion, in this cohort of US Veterans with CKD and hyperkalemia between January 2016 and September 2019, long-term patiromer use was associated with significantly lower all-cause mortality. The effectiveness of long-term potassium binder use on clinical hard outcomes among patients with CKD and hyperkalemia needs to be evaluated in sufficiently powered randomized clinical trials.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Patient Characteristics Among 314 Long-Term Patiromer Users Versus 298,717 Nonusers in the Analytical Cohort Before Propensity Score Matching.

ARTICLE INFORMATION

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Does patiromer use reduce all-cause mortality and need for kidney replacement therapy initiation in patients with CKD and hyperkalemia?

Kidney Medicine

Retrospective cohort study
US Department of Veterans Affairs
Jan 2016 – Sep 2019

299,031 adults with a history of hyperkalemia without kidney failure and data on baseline eGFR and serum potassium

	298,717 never used patiromer		314 long-term patiromer users
	51	Median eGFR	16
	40%	RAASi use	44%

Association between long-term patiromer use and clinical outcomes (*aHR, 95% CI)
308 long-term patiromer users matched with 308 non-users

Outcome	aHR	P value
Composite of KFRT or all-cause mortality	**0.69** 0.49 - 0.98	P = 0.04
Kidney failure with replacement therapy (KFRT)	**1.13** 0.74 - 1.80	P = 0.59
All-cause mortality	**0.45** 0.31 - 0.66	P < 0.001

*Adjusted for demographics, RAAS inhibitor use, history of diabetes, baseline eGFR, baseline and highest serum potassium

Conclusion: Long-term patiromer use was associated with a lower risk of all-cause mortality among patients with CKD and hyperkalemia. Long-term potassium binder use for hyperkalemia may improve clinical outcomes in CKD.

Obi Y, Thomas F, Dashputre AA, et al. Long-term patiromer use and outcomes among US veterans with hyperkalemia and CKD: a propensity-matched cohort study. *Kidney Medicine*, 2024.

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