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Original Article

ORIGINAL ARTICLE

Patiromer utilization in patients with advanced chronic kidney disease under nephrology care in Germany

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ABSTRACT

Background. Hyperkalemia (HK) is a frequent condition in patients with chronic kidney disease (CKD) that is associated with high morbidity and mortality. Patiromer has recently been introduced as a potassium binder. Data on patiromer use in patients with CKD in the real-world setting in Europe are lacking. We describe time to discontinuation and changes in serum potassium levels among German CKD stage 3–5 patients starting patiromer.

Methods. Duration of patiromer use was estimated by Kaplan–Meier curve, starting at patiromer initiation and censoring for death, dialysis, transplant or loss to follow-up. Serum potassium levels and renin–angiotensin–aldosterone system inhibitor (RAASi) use are described at baseline and during follow-up, restricted to patients remaining on patiromer.

Results. We identified 140 patiromer users within our analysis sample [81% CKD stage 4/5, 83% receiving RAASi, and median K+ 5.7 (5.4, 6.3) mmol/L]. Thirty percent of patiromer users had prior history of polystyrene sulfonate use.

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Overall, 95% of patiromer users stayed on treatment past 1 month, with 53% continuing for over a year. Mean serum potassium levels decreased after patiromer initiation and remained stable under treatment during follow-up (up to 180 days). Among these patients, 73%–82% used RAASis during the time periods before and after patiromer initiation, with no obvious trend indicating discontinuation.

Conclusion. Real-world evidence of patiromer use in Germany shows that, in line with what has been observed in clinical trials, patients on patiromer have a reduction in serum potassium when used long-term. Moreover, most patients on patiromer do not discontinue treatment prior to 1 year after initiation.

Keywords: chronic kidney disease, hyperkalemia, patiromer, potassium binders

INTRODUCTION

Hyperkalemia (HK), usually defined as potassium concentrations ≥5 mmol/L [1], is associated with increased risk of adverse events, and the management of this electrolyte disorder is challenging, leading to the introduction of a variety of management strategies, including discontinuing drugs that can induce hyperkalemia as a side-effect [non-steroidal anti-inflammatory agents, beta-blockers and renin–angiotensin–aldosterone system inhibitors (RAASi)], dietary advice to reduce potassium rich foods, and medications such as loop diuretics, bicarbonate and potassium binders [2].

RAAS inhibition clearly improves outcomes in patients with heart failure and reduced ejection fraction [3], and in patients with proteinuric kidney disease, including diabetes, though its role in advanced chronic kidney disease (CKD) is less clear, based on evidence from a single trial of 224 participants with proteinuric advanced CKD [4]. There is increasing evidence that discontinuation of RAASi has led to worsening outcomes in patients with CKD and heart failure; this has led to the recommendation from recent guidelines that this should be considered the last resort in this group of patients [5]. Also, the potential impact of dietary restriction on quality of life and overall negative impact on the healthy diet profile limits the universal application of this approach [1]. Therefore, the use of pharmacological interventions to reduce the risk of hyperkalemia has been introduced to clinical practice.

Polystyrene sulfonate (PS) has been for many years the only oral HK therapy in its sodium or calcium formulations; however, PS was neither studied nor commonly used for chronic HK management or prevention. Patiromer is a potassium binder recently introduced in clinical practice, with long-term (up to 1 year) safety and efficacy supported by randomized trial evidence in people with normal or reduced estimated glomerular filtration rate (eGFR) [6]. In observational cohorts, hyperkalemia is associated with reduction or cessation of RAASi, while an exploratory analysis of 107 people with CKD receiving RAASi and hyperkalemia controlled with patiromer found only 44% of those randomized to withdrawal from patiromer continued on RAASi compared with 94% of those randomized to ongoing patiromer [7]. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial [8].

Descriptions of patiromer utilization in patients with moderate to advanced CKD in the real-world setting are still scarce in Europe, where a more effective strategy to avoid discontinuation of RAASi (compared with the practice pattern in the Americas) has been reported in our previous studies [9]. The objective of the present study is to explore the current practice patterns in the utilization of patiromer among German CKD patients not on dialysis under nephrology care.

MATERIALS AND METHODS

Study design and data collection

The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) is an ongoing prospective cohort study of non-dialysis, advanced CKD patients in national samples of nephrology clinics in Brazil, France, Germany, Japan and the USA [10]. In Germany, data are collected by Wissenschaftliches Institut für Nephrologie (WiNe) of the Verband Deutsche Nierenzentren (DN, Network of Germany Kidney Centers) [11]. Nephrology clinics from the DN were included in the study as a representative national sample of clinics, guaranteed by stratification by geographic location and center size. This analysis included patients treated in these clinics, with eGFR between 15 and 60 mL/min/1.73 m^2 at screening, and who had provided written consent. The eGFR was calculated using the Modification of Diet in Renal Disease Study equation. Patients with a serum potassium concentration <4 mEq/L were excluded. Patient follow-up prior to April 2018 was also excluded, since patiromer received pricing approval in Germany only in April 2018.

An electronic data collection system, Qualitätssicherung Nephrologie und Transplantation (QuaNT), was used to collect individual patient-level information. Data include demographic characteristics, comorbid conditions, medications, hospitalizations and laboratory values measured during routine clinical care. Data were assessed for data quality standards by study coordinators and transmitted quarterly from the DN to the CKDopps data coordinating center in Ann Arbor, MI, USA for inclusion in CKDopps. The current study includes German patients enrolled from 2013 Quarter 1 through 2016 Quarter 2, with longitudinal data through 2021 Quarter 2. The study was conducted with adherence to the Declaration of Helsinki and received research ethics board approval from Ethical and Independent Review Services (study number: 14004-05).

Patient characteristics

Comorbidities, including hypertension, diabetes and other cardiovascular conditions, were determined based on reported International Classification of Diseases, Tenth Revision codes. Potassium, phosphate, calcium, blood pressure and body mass index (BMI) were taken from the closest measurement to the maximum of either study entry or 1 April 2018 for the non-patiromer users or the start of patiromer use within 6 months prior. RAASi and PS prescriptions were recorded during this period as well. The group 'PS, but not patiromer' was defined by patients who received PS at some point during follow-up but who never received patiromer.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of patients at baseline. Time on medica-

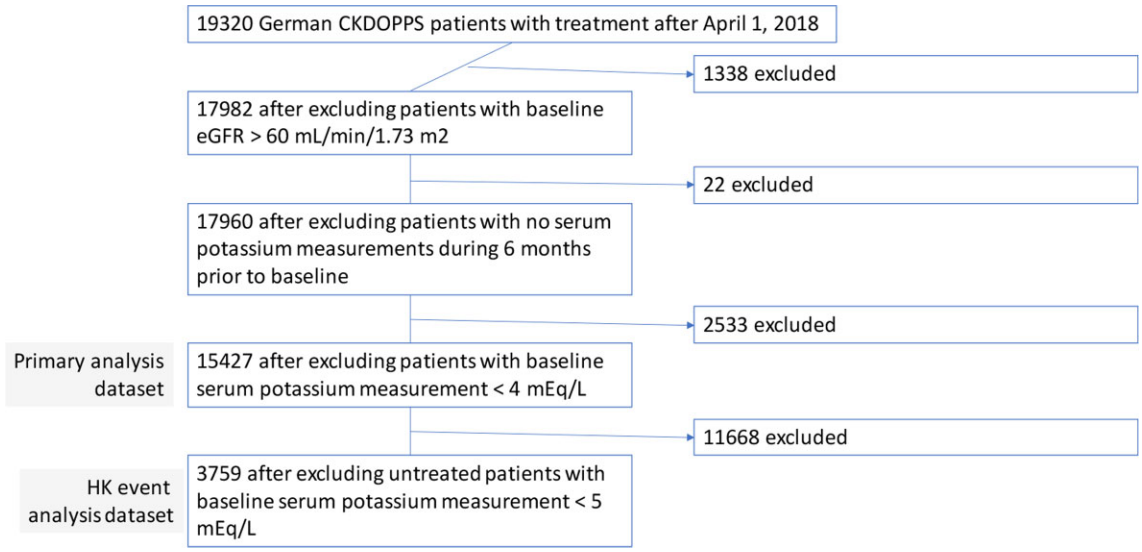

Figure 1: STROBE inclusion/exclusion chart.

tion use was determined using Kaplan–Meier curves, censored at loss to follow-up, including transplant, start of dialysis, death or other departure from the study. Patiromer use and PS use were each modeled using logistic regressions based on Firth's penalized likelihood to mitigate possible biases caused by analyses of rare events. Patients who never received either patiromer or PS were used as the comparison group. RAASi use and potassium levels within each time period relative to baseline (180 days prior to baseline, baseline to baseline + 30 days, 31–90 days after baseline, 91–180 days after baseline) were calculated using available data. Patients who discontinued patiromer did not have their serum potassium levels after this point included in the analyses of serum potassium level. Intermittent use of RAASi is defined as having at least 1 day during each time period where RAASi was prescribed and at least 1 day during the time period after RAASi use had been reported as having ended or at least 1 day during the time period prior to start of RAASi use. Time periods with incomplete follow-up (e.g. for a patient whose baseline was shortly before the data update) were excluded from these analyses.

Hyperkalemic events during the year prior to baseline were determined by the number of laboratory values at or above 5 mEq/L. If a lab indicated a hyperkalemic event occurred within 7 days of a prior hyperkalemic event, it was considered a continuation of an ongoing event, and not counted separately.

RESULTS

After applying the exclusion criteria, there were 15 427 patients in the sample, including 140 patients who received patiromer at some point during follow-up, of which 490 had not received patiromer but did receive PS during follow-up after 1 April 2018, and 14 797 patients who never received either kind of hyperkalemia treatment (Fig. 1).

Table 1 compares patients who never received HK treatment (either patiromer or PS) who had baseline serum potassium levels <5 mEq/L, patients who never received hyperkalemia treatment who had baseline serum potassium levels ≥5 mEq/L, patients who were prescribed patiromer (whether or not they had also been prescribed PS) and patients who had only been treated with PS. Table 1 shows that patients given patiromer tend to be in later CKD stages and tend to have higher serum potassium levels (see also Supplementary data, Fig. S1), which would in turn affect many unadjusted comparisons in the table. Thirty percent of patiromer users had been started on polystyrene sulfonate first. This may also explain the higher prevalence of constipation drugs among patiromer users, as these are commonly prescribed along with polystyrene sulfonate.

Table 2 shows the results of separate logistic models on patiromer or PS use, compared with no hyperkalemia treatment during follow-up. Serum potassium levels are very strong predictors of both PS and patiromer use, with higher serum potassium levels being associated with adjusted odds ratios of 3.8 and 4.4 for PS and with 96 and 200 initiations, respectively, for patiromer or associated with serum potassium levels 6-6.4 and >6.5+ mEq/L compared with levels of 4–4.9. CKD stage has an independent association with both PS and patiromer use, with patients in stage 4 and 5 more likely to receive either treatment. Male sex was associated with increased odds of both PS and patiromer use, and congestive heart failure (CHF) was associated with decreased odds of both PS and patiromer use, independent of the other factors in the model.

Figure 2 shows the duration of patiromer use, based on the cumulative incidence of discontinuation of patiromer over time, censoring for other events such as dialysis. Only 5% of patients who initiated patiromer discontinued use within the first month. Absent a competing event such as death or dialysis, over 50% of patients who started patiromer were still on patiromer a year later (Fig. 2).

Lab values were generally taken shortly before patiromer use, especially serum potassium levels. The median time between the serum potassium lab date and the initiation of patiromer use was 4 days. Among patients who did not initiate patiromer use, the median time between the most recent serum potassium lab and baseline for data collection (usually based on patient start in the CKDopps) was 45 days. Figure 3 shows the distribution of serum potassium levels before and after the start of patiromer use. The median serum potassium level dropped from 5.8 to 5.2–5.5 mEq/L after initiation of patiromer. The

Table 1: Description of population starting patiromer use versus nonusers, restricted to patients with potassium ≥4 mEq/L and eGFR <60 mL/min/1.73 m^2.

	No HK treatment				
Characteristics	SK <5	SK 5+	Patiromer users	PS[a] users	% Miss
	(*n* = 11421)	(*n* = 3376)	(*n* = 140)	(*n* = 490)	
Gender (% male)	49	55	64	63	0
Age (years)	76.9 (68.0, 81.4)	77.0 (68.4, 82.0)	76.0 (64.8, 81.3)	77.1 (67.9, 82.1)	0
BMI (kg/m^2)	29.2 (25.9, 33.3)	29.0 (25.6, 33.0)	27.8 (24.2, 32.5)	28.1 (24.9, 31.8)	1
Labs					
Serum potassium (mEq/L)	4.5 (4.2, 4.7)	5.3 (5.1, 5.5)	5.7 (5.4, 6.3)	5.0 (4.7, 5.4)	0
Serum potassium (category %)					0
4–4.4 mEq/L	51	0	2	14	
4.5–4.9 mEq/L	49	0	7	34	
5–5.9 mEq/L	0	95	56	47	
6–6.4 mEq/L	0	4	20	4	
≥6.5 mEq/L	0	1	15	1	
Days from potassium to baseline	12 (0, 75)	11 (0, 66)	1 (0, 6)	31 (9, 66)	0
eGFR (mL/min)	39.3 (30.2, 48.2)	33.0 (24.5, 42.2)	21.1 (13.2, 28.3)	23.9 (16.6, 33.3)	0
CKD stage (category %)					0
3	75	59	19	34	
4	22	34	48	46	
5	3	8	33	21	
Hemoglobin (g/dL)	12.8 (11.8, 13.8)	12.3 (11.2, 13.4)	11.6 (10.7, 12.5)	11.9 (10.9, 13.0)	0
Serum albumin (g/dL)	4.2 (4.0, 4.5)	4.2 (3.9, 4.4)	4.0 (3.8, 4.3)	4.1 (3.9, 4.4)	50
Serum phosphorus (mg/dL)	3.4 (3.0, 3.8)	3.7 (3.2, 4.1)	4.1 (3.6, 5.2)	3.8 (3.3, 4.4)	10
Serum phosphorus ≥4.5 mg/dL (%)	6	13	37	23	10
Systolic blood pressure (mmHg)	138 (123, 150)	140 (125, 153)	140 (122, 152)	140 (125, 150)	11
Diastolic blood pressure (mmHg)	75 (69, 82)	75 (67, 81)	76 (66, 83)	70 (65, 80)	11
Prescriptions (%)					
ACEi	31	38	38	33	24
ARB	49	47	47	52	24
Renin inhibitor	0	0	0	0	24
Aldosterone antagonist	11	12	16	6	24
Any RAASi	81	84	83	84	24
Sodium bicarbonate	0	0	0	0	24
Diuretic—any	70	69	82	78	24
Diuretic—loop	52	54	73	68	24
Polystyrene sulfonate	0	0	30	100	24
Constipation drug	5	5	17	11	24
Comorbidities (%)					
Diabetes	45	49	43	48	0
Hypertension	90	89	88	91	0
Coronary artery disease	29	32	25	33	0
Congestive heart failure	14	16	8	11	0
Cerebrovascular disease	10	10	11	13	0
Peripheral vascular disease	20	21	20	24	0
Other cardiovascular disease	29	27	25	30	0
Lung disease	8	9	7	7	0
Cancer (excluding non-melanoma skin)	17	17	9	19	0
GI bleeding	2	1	0	3	0
Recurrent cellulitis/gangrene	3	2	1	2	0
Neurologic disease	2	2	3	2	0
Psychiatric disorder	5	5	4	3	0

Note: all percentages rounded to nearest integer, e.g. a value <0.5% would be rounded to '0%'. Data are presented as median (interquartile range) or precentage.
[a]PS users, excluding patients that used patiromer.
% Miss: percentage missing data; ARB: angiotensin-receptor blocker; ACEi: angiotensin-converting enzyme inhibitor; GI: gastrointestinal.

P-value for the pre-patiromer serum potassium level versus any of the post-patiromer time periods was <.0001. Table 3 shows the distribution of hyperkalemic events (serum potassium ≥5 mEq/L) by hyperkalemic treatment arm, over the course of the year preceding the baseline. These data are limited to patients with a baseline measure of ≥5 mEq/L serum potassium, so all patients have at least one hyperkalemic event. A history of hyperkalemic events was more frequent among patients treated with patiromer than among patients treated with PS. Both PS and patiromer utilization were independently associated with having a history of hyperkalemic events. When the data are not limited to patients with baseline serum potassium ≥5 mEq/L,

Table 2: Odds ratios of PS or patiromer initiation from logistic models with selected covariates.

	PS vs none		Patiromer vs none	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Potassium, 4–4.9 mEq/L	1.00 (ref)		1.00 (ref)	
Potassium, 5–5.9 mEq/L	2.54 (2.09–3.07)	<.0001	14.25 (8.00–25.38)	<.0001
Potassium, 6–6.4 mEq/L	4.43 (2.69–7.29)	<.0001	96.36 (48.31–192.19)	<.0001
Potassium, ≥6.5 mEq/L	3.84 (1.59–9.30)	0.0028	199.89 (90.87–439.72)	<.0001
CKD Stage 3	1.00 (ref)		1.00 (ref)	
CKD Stage 4	3.54 (2.88–4.36)	<.0001	4.52 (2.87–7.11)	<.0001
CKD Stage 5	8.77 (6.67–11.54)	<.0001	10.83 (6.43–18.23)	<.0001
Male	1.74 (1.43–2.11)	<.0001	1.63 (1.12–2.37)	0.0108
Age (per 5 years)	1.03 (0.99–1.08)	0.1236	1.02 (0.94–1.10)	0.6484
Diabetes	1.09 (0.91–1.32)	0.3566	0.88 (0.61–1.26)	0.4767
CAD	1.13 (0.92–1.39)	0.2531	0.90 (0.59–1.38)	0.6354
CHF	0.68 (0.51–0.91)	0.0092	0.48 (0.25–0.91)	0.0247

Limited to patients with enrollment GFR <60 mL/min/1.73 m^2, baseline serum potassium 4+ mEq/L. Does not include any use of PS prior to October 2017.
PS vs none omits patiromer only, while patiromer vs none omits PS only.
OR: odds ratio; CI: confidence interval; CAD: coronary artery disease; CHF: congestive heart failure.

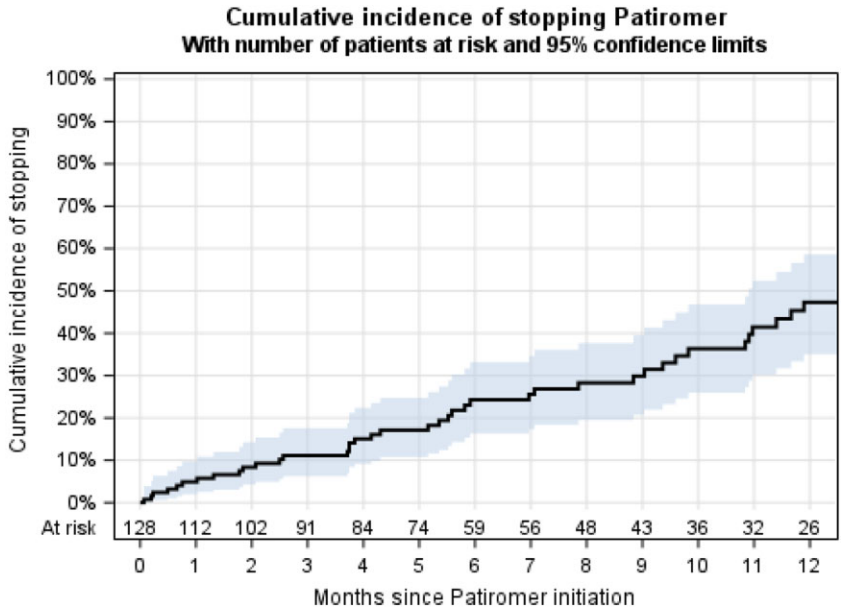

Figure 2: Time to discontinuation of patiromer.
Note: 12 patients omitted due to insufficient follow-up data after patiromer initiation.

most of the patients who had received no hyperkalemic treatment had zero hyperkalemic events (results not shown).

Figure 4 shows RAASi use prior to patiromer and during the follow-up period after patiromer initiation. We observed that 73%–82% of patiromer users were on RAASi therapy during the observation period, with no obvious trend indicating discontinuation.

DISCUSSION

Hyperkalemia is a frequent condition in patients with CKD; it is associated with high morbidity and mortality and is a common reason for RAASi discontinuation and dose down titration. In addition to PS, which has been used for decades as the only oral medication to treat hyperkalemia, new potassium binders have recently been introduced to clinical practice and data from practice patterns in the real world are emerging. This is the first European description of patiromer utilization in patients with moderate-to-advanced CKD in a real-world setting using data from the CKDopps. Our main findings are that hyperkalemia was commonly observed in this cohort of patients with moderate-to-advanced CKD under nephrology care, and long-term treatment strategies, such as the use of potassium binders, were underutilized. Also, we provide real-world observational evidence that patiromer prescription can be maintained for chronic use in the majority of patients with advanced CKD, and its initiation is associated with a reduction in serum potassium levels in a population with a sustainedly high proportion of RAASi utilization.

There is a high prevalence of hyperkalemia in the population with advanced CKD, and relatively low implementation

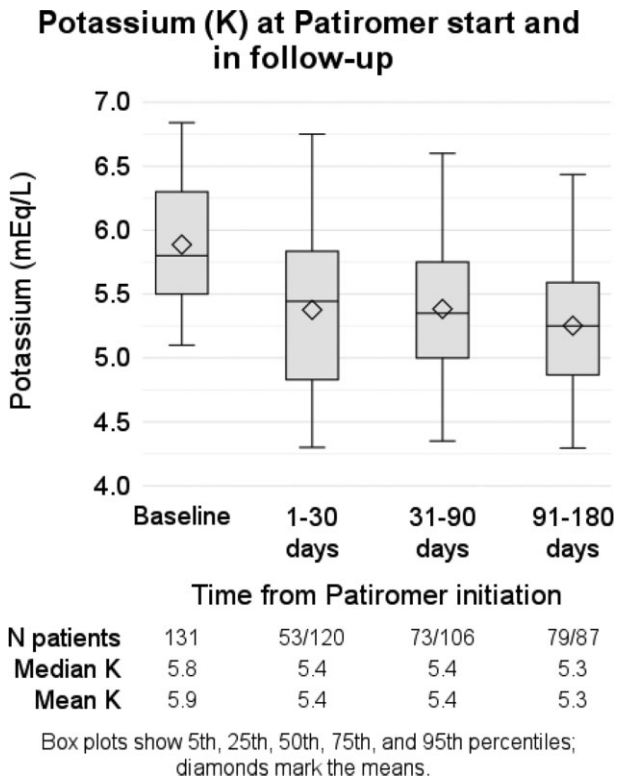

Figure 3: Reduction in serum potassium after patiromer start.

Table 3: Hyperkalemic events (serum potassium ≥5 mEq/L) during the year preceding baseline, by hyperkalemia treatment category, among patients with serum potassium ≥5 mEq/L at baseline.

	HK events (>5 mEq/L) in prior year			
	No treatment	Patiromer	PS, no patiromer	All
5th percentile	1	1	1	1
25th percentile	1	2	2	1
50th percentile	1	3	3	1
75th percentile	2	4	4	2
95th percentile	4	9	7	4
Overall *N*	2840	107	211	3158

Limited to patients with at least one non-missing serum potassium lab strictly within the period of 1 year prior to baseline.

of mid- and long-term strategies to proactively manage hyperkalemia; they are clearly under-implemented in our study and in previous observations [9]. It is noticeable that, despite the observation that the majority of patients starting patiromer were maintained on therapy for up to 1 year, a large number of patiromer users discontinued the treatment during the follow-up, pointing to a practice pattern of periodic use rather than chronic therapy. Since there is no evidence of an economic barrier to chronic prescription, the reasons for this practice pattern need to be addressed in future studies. However, it is possible that patiromer may be discontinued once the acute hyperkalemia episode is controlled, hypothetically, by interventions such as dietary counselling, treatment of metabolic acidosis and/or other non-reported mechanisms.

Compared with a population who at the same range of potassium levels did not receive patiromer, users tend to be in later CKD stages and have more hyperkalemic events. About a third of patiromer users had been started on PS first, and these patients had a higher prevalence of anti-constipation drugs that are commonly prescribed along with PS to treat side effects. In combination, these findings may suggest that in the real world, patiromer may be used in patients with hyperkalemia that are refractory to treatment with current standards of care, or in those who do not tolerate PS. It is important to highlight that the population included in this analysis comprises patients with moderate to severe CKD and describes practices reflecting nephrology care due to the study design and setting.

Mean serum potassium concentration reductions following patiromer initiation were similar in our study as those in the randomized controlled trial data, where the mean change in the serum K^+ concentration was -1.01 ± 0.03 mmol/L [12–16]. A history of hyperkalemic events was more frequent among patients treated with patiromer than among patients treated with PS. However, statistically, PS and patiromer are independently associated with having a history of hyperkalemic events. Consistent with phase 3 trials with up to 1 year of follow up, our data support the feasibility of the chronic utilization of patiromer, with the majority of patients continuing on treatment through 1 year of observation.

Also aligned with previous clinical trial findings, our data show RAASi continuation in approximately 80% of patients with continuous patiromer exposure, which is much higher than observed in a previous report of cohorts of advanced CKD patients [9]. In fact, in our previous analysis of CKDopps, the drop in RAASi utilization can be noted more strikingly at the same level of GFR that characterizes the patiromer-user cohort in the current report. Furthermore, in the AMBER trial, patients with resistant hypertension and CKD were enabled to continue spironolactone therapy in 86% of patients receiving patiromer compared with 60% receiving a placebo at 12 weeks [8]. Since our analysis includes patients with low eGFR, this high proportion of patients on therapy during the treatment with patiromer in our study may be an indication that the drug may be enabling RAASi therapy also in the real world, although the lack of a comparison with controls limits the interpretation of our results.

Like all observational studies, the present study has limitations. The single-arm, within-patient (i.e. pre-versus-post) K^+ concentration analyses do not provide causal conclusions regarding the effectiveness of patiromer. The observed results may be associated with continuous patiromer exposure, but other concomitantly employed HK management strategies cannot be excluded. Further research with a suitable comparator group and comparative methodology is warranted to fully assess patiromer's real-world effectiveness. Describing adverse events related to patiromer utilization was not an aim of this analysis and these data were not available to the authors. Furthermore, the effectiveness of patiromer in patients continuously exposed as opposed to those discontinued at each time interval was not an aim but would be of interest and warrants future research.

This study provides a novel assessment of real-world HK management among German patients with advanced CKD under nephrology care in Europe. The observed serum potassium reductions were consistent with well-controlled prospective clinical trials. The successful management of HK may have contributed to the observed high rate of RAASi therapy continuation during the observation period.

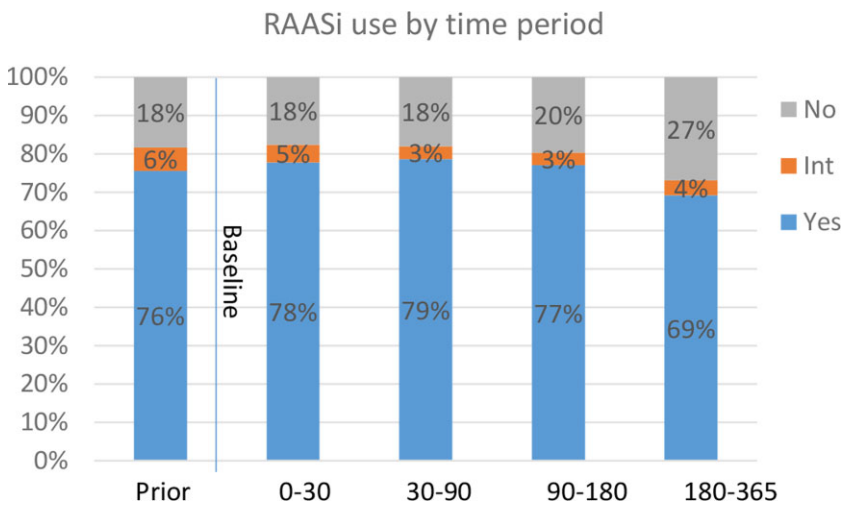

Figure 4: RAASi use by time period after patiromer initiation baseline.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST STATEMENT

J.B. is an employee of Vifor Pharma. V.C.-S. reports consulting fees from Baxter Brazil; honoraria from Baxter Brazil; participates on and is in leadership roles in Brazilian Society of Nephrology, International Society of Nephrology, Latin America Chapter-International Society of Peritoneal Dialysis. C.M.Q. is an employee of Vifor Pharma; holds a patent for Avb8 antibody for the treatment of CKD; and owns stocks in AstraZeneca and Vifor Pharma. D.F. serves as the ERA Renal Science Chair. Z.A.M. reports grants and contracts from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Genzyme/Sanofi, Lilly, Otsuka, and Government support for CKD REIN PROJECT AND EXPERIMENTAL PROJECTS; and honoraria from AstraZeneca, Boheringer and GSK. F.-P.T., J.G., H.R., A.R.d.A. and J.D. have no conflicts of interest to declare. K.M., D.M., B.B., R.P.-F. and B.M.R. are employees of Arbor Research Collaborative for Health, which administers the DOPPS Programs. In addition, B.M.R. has received consultancy fees or travel reimbursement since 2019 from AstraZeneca, GlaxoSmithKline, Kyowa Kirin Co. and Monogram Health, all paid directly to his institution of employment. Also, R.P.-F. reports research grants from National Council for Scientific and Technological Development; consulting fees from Fresenius Medical Care, Bayer, AstraZeneca, Fibrigen and Akebia paid to his employer; honoraria from Fresenius Medical Care, Bayer, AstraZeneca, Novo Nordisk, Fibrigen and Akebia paid to his employer; and is in a leadership role at KDIGO, ISN and ISPD.

APPENDIX

CKDopps Steering Committee and Country Investigators: Antonio Lopes, Roberto Pecoits-Filho, Viviane Calice da Silva (Brazil); Christian Combe, Ziad Massy, Benedicte Stengel, Elodie Speyer (France); Danilo Fliser, Helmut Reichel (Germany); Junichi Hoshino, Kunihiro Yamagata (Japan); Ron Pisoni, Bruce Robinson (United States). Additional CKDopps Research Group: Viviane Calice da Silva, Ricardo Sesso (Brazil); Elodie Speyer (France); Koichi Asahi, Junichi Hoshino, Ichiei Narita (Japan); Rachel Perlman, Friedrich Port, Nidhi Sukul, Michelle Wong, Eric Young, Jarcy Zee (USA).

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