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Real-world use of patiromer in patients with hyperkalaemia: A retrospective study from the Valencian Community

Uso en vida real de patirómero en pacientes con hiperpotasemia: estudio retrospectivo en la Comunidad Valenciana

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ABSTRACT

Background and objective: Hyperkalaemia is common in patients with chronic kidney disease (CKD) treated with renin-angiotensin-aldosterone system inhibitors (RAASi) and mineralocorticoid receptor antagonists (MRAs). Although new potassium binders have demonstrated efficacy in clinical trials, evidence from real-world clinical practice remains limited.

Materials and methods: We present a retrospective, observational, multicentre, non-interventional study aimed at evaluating the use of patiromer in patients with hyperkalaemia under routine clinical conditions in the Valencian Community. Patients who received patiromer for at least 3 months due to hyperkalaemia were included. The primary objective was to assess the evolution of serum potassium at 1, 3, 6, and 12 months after initiation of treatment. Secondary objectives included describing baseline patient characteristics, changes in RAASi and MRA therapy, and patiromer-related adverse events.

Results: A total of 59 patients were included. The baseline serum potassium level was 5.72 mmol/L, showing significant reductions at 1, 3, 6, and 12 months (5.02, 5.17, 5.11, and 5.01 mmol/L, respectively; all $P < .001$). Patiromer treatment enabled continuation of RAASi in 94.9% of patients and MRAs in 98.3%. The most frequent adverse events were gastrointestinal. Patiromer was discontinued in 8 patients (13.5%), with adverse effects accounting for half of these cases.

Conclusions: Our study provides real-world evidence on the effectiveness, safety, and RAASi/MRA maintenance potential of patiromer in patients with CKD and hyperkalaemia under routine care. In this setting, patiromer proved effective and well tolerated for managing hyperkalaemia and preserving RAASi/MRA therapy.

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Palabras clave:
Hiperpotasemia
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Inhibidor del sistema renina–angiotensina–aldosterona
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RESUMEN

Introduccion y objetivos: La hiperpotasemia es frecuente en pacientes con ERC tratados con inhibidores del sistema renina-angiotensina-aldosterona (iSRAA) y antagonistas del receptor de mineralocorticoides (ARM). Aunque los nuevos quelantes han mostrado eficacia en ensayos clínicos, falta evidencia en práctica clínica real.

Materiales y métodos: Presentamos un estudio retrospectivo observacional, multicéntrico, no intervencionista con el objetivo de evaluar el uso de patirómero en pacientes con hiperpotasemia en condiciones de práctica clínica habitual en la Comunidad Valenciana. Se incluyeron pacientes que hayan recibido patirómero al menos 3 meses por haber presentado hiperpotasemia. El objetivo primario del estudio fue evaluar la evolución del potasio sérico a los meses 1, 3, 6 y 12 del inicio del tratamiento. Los objetivos secundarios fueron definir las características basales de los pacientes, las modificaciones en el tratamiento con iSRAA y ARM y los efectos secundarios relacionados con patirómero.

Resultados: Se incluyeron 59 pacientes. El valor inicial de potasio sérico fue de 5,72 mmol/L, mostrando descensos significativos al mes, 3, 6 y 12 meses (5,02 mmol/L, 5,17 mmol/L, 5,11 mmol/L y 5,01 mmol/L al año respectivamente. Todos $P < .001$). El tratamiento con patirómero permitió mantener los iSRAA en el 94,9% de los pacientes y los ARM en el 98,3%. Los efectos adversos más frecuentes fueron de carácter gastrointestinal. El patirómero fue suspendido en 8 pacientes (13,5%), siendo la causa los efectos adversos solo en la mitad de ellos.

Conclusiones: Nuestro estudio proporciona evidencia real sobre la eficacia, seguridad y capacidad de mantenimiento de iSRAA y ARM utilidad de patirómero en pacientes con ERC e hiperpotasemia tratados en condiciones habituales. En ese escenario patirómero ha demostrado eficacia y seguridad en el tratamiento de la hiperpotasemia y en el mantenimiento de iSRAA y ARM.

Introduction

Hyperkalemia (HK) is defined as a serum potassium concentration above the normal limit (approximately 5 mmol/L), although levels above 5.5 mmol/L are considered clinically relevant. HK is a serious disorder since it can cause potentially fatal arrhythmias[1] and is especially common in patients with chronic kidney disease (CKD) and/or heart failure (HF). It is estimated that approximately 28% of patients with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 present with HK during follow-up.[2]

The treatments recommended for patients with HF and/or CKD include inhibitors of the renin-angiotensin-aldosterone system (RAASi), as well as, in certain cases, mineralocorticoid receptor antagonists (MRAs). These therapies have been shown to reduce cardiovascular morbidity, slow the progression of kidney disease and improve overall survival in these patients.[3,4] However, their use is associated with an increased risk of HK,[2] therefore, despite their nephroprotective and cardioprotective benefits, long-term maintenance therapies are not always possible, especially in patients with severe renal dysfunction or advanced comorbidities that increase the risk of HK.[5]

Historically, the only treatments available for the chronic management of HK were cation exchange resins, such as sodium or calcium polystyrene sulfonate. However, their use has important clinical side effects, such as frequent gastrointestinal effects, especially constipation, and the risk of severe intestinal necrosis and hypokalemia; moreover, there is a lack of controlled trials and robust data on the efficacy and long-term safety of these treatments.[6,7]

Clearly, there is an unmet clinical need for HK treatment, especially for patients who cannot receive or be maintained on optimal doses of RAASis or MRAs. A reduction in or interruption of these drugs due to the risk of HK is associated with a significant increase in cardiovascular and renal morbidity and mortality.[8] In recent years, new therapeutic alternatives, including sodium zirconium cyclosilicate (Lokelma®) and patiromer (Veltassa®), have emerged. Patiromer is a non-absorbable polymer that exchanges calcium for potassium in the colon, facilitating the elimination of potassium and effectively reducing its serum levels. This compound has shown sustained efficacy and a favorable safety profile in clinical studies and in real practice, allowing the optimization of treatment with RAASis with adequate control of serum potassium. In this context, we propose evaluating the use of the patiromer complex in patients with HK under conditions of routine clinical practice in our study population, with the aim of characterizing its effectiveness, safety and impact on treatment with RAASi and MRAs.[9,10] To achieve this, a real-life study was conducted to analyze the change in serum potassium levels during the months after the start of patiromer as the primary objective. As secondary objectives, we considered 1) baseline patient characteristics, 2) modifications in treatment with RAASi and MRAs, and 3) side effects related to patiromer use.

Material and methods

Study design

This is an observational, retrospective, multicenter, noninterventional study to evaluate the real-life use of patiromer (Veltassa®) in patients with chronic HK treated under routine clinical practice conditions in the Valencian community (Spain). The study was designed following the recommendations of Real Decreto 957/2020 on observational studies with medications.

Sample size

The minimum sample size for detecting a mean difference of 0.5 mmol/L in serum potassium levels with a standard deviation of 0.9, using a two-tailed paired *t*-test for a single sample, assuming an alpha risk of 0.05 and a statistical power of 95% was estimated at 45 patients. This calculation was based on variability data from previous studies of the prevention and treatment of HK[11,12] and on the consideration of a clinically relevant difference as defined by the research team. Considering a loss rate of 10%, it was estimated that at least 50 patients would need to be included to analyze the primary objective of the study. The calculations were performed using G*Power *software* version 3.1.9.7.[13]

Population and inclusion criteria

Adult patients (≥18 years) who started treatment with patiromer between September 1, 2019 and January 20, 2021 were included. Inclusion criteria included a minimum duration of treatment of three months and the presence of chronic HK, defined as ≥2 episodes of serum potassium ≥ 5.0 mmol/L separated by at least two weeks in the

previous 12 months. Patients with pseudohyperkalemia (marked leukocytosis, thrombocytosis or hemolysis in the sample), congenital adrenal hyperplasia, Addison's disease, large burns or treatment with potassium supplements were excluded. The information necessary to apply these criteria was obtained through a specific questionnaire and review of the medical history at the time of inclusion in the database.

Data collection

The clinical data were obtained retrospectively from the electronic medical records of the patients in a web-based database developed by the INCLIVA research institute with security and anonymization characteristics according to current legislation. Sociodemographic data, anthropometric data, comorbidities, analytical parameters, and information on concomitant treatments, especially RAASi and MRAs, were collected.

The change in serum potassium level was evaluated longitudinally at different follow-up points (months 1, 3, 6 and 12). Similarly, changes in the therapeutic regimen with RAASi and MRAs were documented; the dose and adherence to treatment with patiromer were also considered when this information was available.

Study variables

The primary outcome was the change in serum potassium concentration during the months after the start of patiromer treatment. The following were analyzed as secondary outcomes: 1) baseline characteristics of the patient, 2) modifications in treatments with RAASi and MRAs, and 3) side effects related to patiromer. In the writing of this manuscript, the study data have been described according to the STROBE guidelines for retrospective studies.[14]

Statistical analysis

Quantitative variables are presented as the mean and standard deviation or median and interquartile range, according to the normality of their distribution. Changes over time (prescription, first month, third month, sixth month and final visit) in the primary outcome variable and the other analytical parameters were studied using a linear mixed effects model with the value at each time point as a dependent variable, time as an independent variable and the indicator of the individual as a random factor. Statistical analysis was performed using R *software* (version 3.6.1). Values of $P < .05$ were considered indicative of statistical significance.

Ethical considerations

The study was approved by the Drug Research Ethics Committee (CEIm) of the University Clinical Hospital of Valencia (Code: HK-01-21; number: 17/22). All procedures were carried out in accordance with the Declaration of Helsinki and the guidelines of good clinical practice. Written informed consent was obtained for the use of clinical data. For patients who died or were lost to follow-up, this requirement was waived according to current regulations.

Results

Patient characteristics

A total of 59 patients who were diagnosed with HK and who started treatment with patiromer during the follow-up period at six hospitals in the Valencian community were included. The mean age was 73.8 ± 11.6 years, the median age was 76 (67–83) years, and 59% of the patients were men. The etiologies of CKD in our sample were vascular or unknown in 26 (44%) patients, diabetic kidney disease in 22 (37%) patients and glomerulopathy in 11 (19%) patients. The mean follow-up duration was 11.1 ± 4.7 months (range: 3–28), and the median was 11.9 (7.3–13) months.

The majority of the prescriptions originated from nephrology units (45 [76%] patients); of these patients, 15 were also being followed up with cardiology or cardiorenal units, one was being followed up with an internal medicine and cardiology unit, and one was being followed up with an internal medicine unit. Cardiology was the prescribing specialty for 8 (14%) patients, and internal medicine was the prescribing specialty for 6 (10%) patients; both specialties were within cardiorenal units. The baseline characteristics of the patients, as well as the baseline analytical data, are summarized in Table 1. Before starting the study, nine patients received MRAs, three of whom suspended this treatment at the time of starting the patiromer. Thus, during the study, only six patients were receiving MRAs (10%). For one patient, MRA treatment was suspended at the 3-month visit, and another patient started treatment with an MRA at the 6-month visit. Treatment with patiromer allowed 85% of patients receiving MRAs to maintain this treatment and allowed MRA treatment to be restarted in a new patient who had suspended treatment before starting the study.

Only one patient had a history of HK that required hospitalization, whereas 33 (56%) patients had presented with HK at the previous follow-up in the last year. Prior to the start of the study, 23 (39%) patients had received exchange resins, 20 (87%) of whom discontinued treatment because of intolerance or lack of efficacy.

Changes in potassium levels and biochemical parameters

All patients started treatment with 8.4 g patiromer/day. Treatment with patiromer significantly decreased serum potassium levels during follow-up (P value $< .001$) (Fig. 1). In the linear mixed model analysis (Table 2), the initial estimated serum potassium level was 5.72 mmol/L, against which significant decreases were observed ($P < .001$) at multiple follow-up points: 5.02 mmol/L at one month, 5.17 mmol/L at three months, 5.11 mmol/L at six months and 5.01 mmol/L at one year ($P < .001$ in all cases compared to baseline). These results reflect an average decrease of between 0.55 and 0.71 mmol/L with respect to baseline, with sustained efficacy throughout follow-up.

In the analysis of individual trajectories, 83% of the patients achieved potassium levels less than 5.5 mmol/L at the end of the study.

The evolution of the analytical parameters is shown in Table 3. There was no significant increase in the levels of plasma calcium or sodium. In addition, the NT-proBNP levels remained stable during follow-up.

Modifications in patiromer treatment

The initial dose of patiromer was 8.4 g in 57 (96%) patients and 16.8 g in two (4%) patients. The initial dose of patiromer was maintained in 47 (79.8%) patients, increased in 3 (5%) patients and decreased in 1 (1.6%) patient; treatment was suspended in 8 patients. The changes in the patiromer dose are shown in Fig. 2.

The changes in treatments with RAASi and MRAs in the study patients are shown in Fig. 3. Treatment with patiromer allowed the maintenance of RAASi in 94.9% of patients and of MRAs in 98.3%. RAASi were suspended in only 2 (3.4%) patients; MRA treatment was suspended in only one (1.7%) patient and restarted in a patient for whom it had been suspended before the baseline visit of the study. This finding is interesting, given that in previous retrospective real-life studies, a high percentage of patients had to suspend treatment with cardioprotective and nephroprotective drugs.[15,16]

Fig. 4 shows the proportion of serum potassium ranges during the different study visits.

Table 1
Baseline characteristics of the study patients.

Characteristics	n = 59
Age (years), median (IQR)	76 (67–83)
Male sex, n (%)	35 (59)
Mean follow-up, months, mean ± SD	11.1 ± 4.7
BMI, kg/m^2, mean ± SD (n = 51)	28.5 ± 4.2
Prescribing specialist department, n (%)	
Nephrology	45 (76)
Cardiology	8 (14)
Internal Medicine	6 (10)
Etiology of CKD, n (%):	
Glomerular	11 (19)
Vascular	14 (24)
Diabetic nephropathy	22 (37)
Other	12 (20)
Current smoking status, n (%)	11 (19)
DM, n, (%)	37 (63)
History of HF with hospitalization, n (%)	19 (32)
eGFR ranges, n (%)	
eGFR < 15,	6 (10)
eGFR 15–29,	23 (39)
eGFR 30–59,	27 (46)
eGFR > 60,	3 (5)
GFR, mL/min/1.73m^2, mean ± SD	32.3 ± 16.4
Creatinine, mg/dL, mean ± SD	2.3 ± 0.9
Baseline hyperkalemia (>5.5 mmol/L), n (%)	33 (56)
Baseline serum K $^+$, mmol/L, mean ± SD	5.7 ± 0.5
Last K $^+$ value before study entry, mean ± SD	5.3 ± 0.6
Number of K $^+$ determinations in the last 2 years, mean ± SD	18 ± 13
NYHA Grade II–IV, n (%)	21 (36)
LVEF, %, n (%)	
Normal (≥50%)	28 (48)
Average (41%–49%)	5 (8)
Reduced (≤40%)	5 (8)
Not available	21 (36)
LVEF, %, median, (IQR)	60 (37)
Ischemic heart disease, n (%)	20 (34)
AF, n (%)	12 (20)
Peripheral vascular disease, n (%)	15 (25)
HTN, n (%)	55 (93)
Previous patient follow-up, n (%)	Nephrology 48 (81) Cardiology 30 (51) Internal medicine 13 (22)
Previous prescription of exchange resins, n (%)	37 (63)
RAASi or ANRI treatment, n (%)	59 (100)
Maximum RAASi dose, n (%)	16 (27)
MRAs treatment, n (%)	6 (10)
Maximum MRAs dose, n (%)	4 (7)
Previous chelator (resin) prescription, n (%)	23 (39)
Systolic blood pressure, mmHg, mean ± SD	138 ± 15
Diastolic blood pressure, mmHg, mean ± SD	70 ± 8
Total cholesterol, mg/dL mean ± SD	151 ± 32
LDL-c, mg/dL, mean ± SD	86 ± 26
HDL-c, mg/dL, mean ± SD	45 ± 11
Triglycerides, mg/dL, mean ± SD	155 ± 83
Uric acid, mg/dL, mean ± SD	6.6 ± 1.7
Sodium, mmol/L, mean ± SD	140 ± 3.6
Hemoglobin, g/dL, mean ± SD	12.3 ± 1.6
Calcium, mg/dL, mean ± SD	9.4 ± 0.5
Magnesium, mg/dL, mean ± SD	2.1 ± 0.2
Urine albumin/creatinine ratio, mg/g median (IQR), (n = 31)	170 (5–537)
NT-proBNP, pg/mL median, (IQR), (n = 21)	1433 (822–4383)

The results are shown as the frequency and percentage or as the mean ± standard deviation (SD) or median and interquartile range (IQR), depending on the distribution of the variables.
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; K: potassium; BMI: body mass index; AHT: arterial hypertension; RAASi: renin angiotensin-aldosterone system inhibitor; ANRI: angiotensin-neprilysin receptor inhibitor; MRA: mineralocorticoid receptor antagonist; DM: diabetes mellitus; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association heart failure scale; AF: atrial fibrillation; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol.
The number of patients for whom certain variables were not collected is shown in parentheses after the name of the variable.

Adverse effects and safety

Table 4 shows the side effects that occurred during follow-up, the visit in which they occurred and whether or not they motivated the suspension of treatment with patiromer.

The majority of adverse effects were mild and did not motivate discontinuation of the drug. During follow-up, 8 (13.5%) patients discontinued their patiromer treatment. The causes included low but otherwise normal potassium levels in two patients, hypercalcemia in two patients (physician's decision for both), renal progression with the need for dialysis (initiation of dialysis and correction of HK) in one patient, a lack of therapeutic compliance in one patient and gastrointestinal disorders in two patients (constipation in one and vomiting in the other).

During the follow-up period, 15 (25.4%) patients were hospitalized. Ten hospitalizations were due to cardiovascular causes, and the rest were due to neoplasia (1), infection (1), renal deterioration with the start of dialysis (1), hepatopathy (1) or hyperosmolar coma (1). During the course of their conditions, 2 (3.4%) patients died—one from an infection and another from renal deterioration with multiorgan failure. In neither case was HK the cause of death.

Discussion

This retrospective multicenter study, conducted under routine clinical practice conditions in the Valencian community, demonstrated that the use of patiromer in patients with CKD is associated with a significant, sustained and clinically relevant reduction in serum potassium with a favorable safety profile. In addition, most patients were able to stay on maintenance treatment with therapies such as RAASi and MRAs, with good treatment tolerance and little need for dose modification or discontinuation.

Our work provides additional evidence on the usefulness of patiromer in routine clinical practice in Spain for outpatient medicine and for patients with clear indications for RAAS blockade and/or MRA treatment and a high risk of progression of renal disease or cardiovascular events. In this context, published data on the actual use of this drug are scarce. Aside from clinical trials, only two studies have analyzed real-life data concerning the use of patiromer in patients with CKD, with specific data on the efficacy of potassium reduction and the assessment of adverse effects. One study was on a population of patients with CKD and not on dialysis, similar to ours,[17] while the other was on a population on hemodialysis[18]; notably, both involved the U.S. Veteran's database.

In both our study and the other two real-life studies, the use of patiromer was associated with a significant reduction in serum potassium levels at the first follow-up visit (−1 mmol/L in the study by Kovesdy et al.,[17] −1.03 mmol/L in the study by Pinnell et al.[18] and −0.55 to −0.71 mmol/L in our study). These potassium reductions with respect to baseline are consistent with those observed in the AMETHYST-DN[12] and OPAL-HK[10] studies.

This effect was achieved in most cases with a standard initial dosage of 8.4 g/day, without frequent adjustments, which reinforces its clinical utility. In the study by Kovesdy et al.,[17] 96% of the participants received a dosage of 8.4 g/day, and 4% received 16.8 g/day. In our study, 86.4% of the participants received 8.4 g/day, 10.2% received 16.8 g/day, and 3.4% received 25.2 g/day. In the study by Pinnel et al., which involved hemodialysis patients, the dosages were more variable, but only 15.3% received more than 8.4 g/day. A total of 69% of the patients received 8.4 g/day, and the remaining patients received lower doses every other day.

The data on the percentage of comorbidities among the patients in the three studies were very similar, but our study was performed on an older population (73.8 years in our study vs. 70 and 66 years on

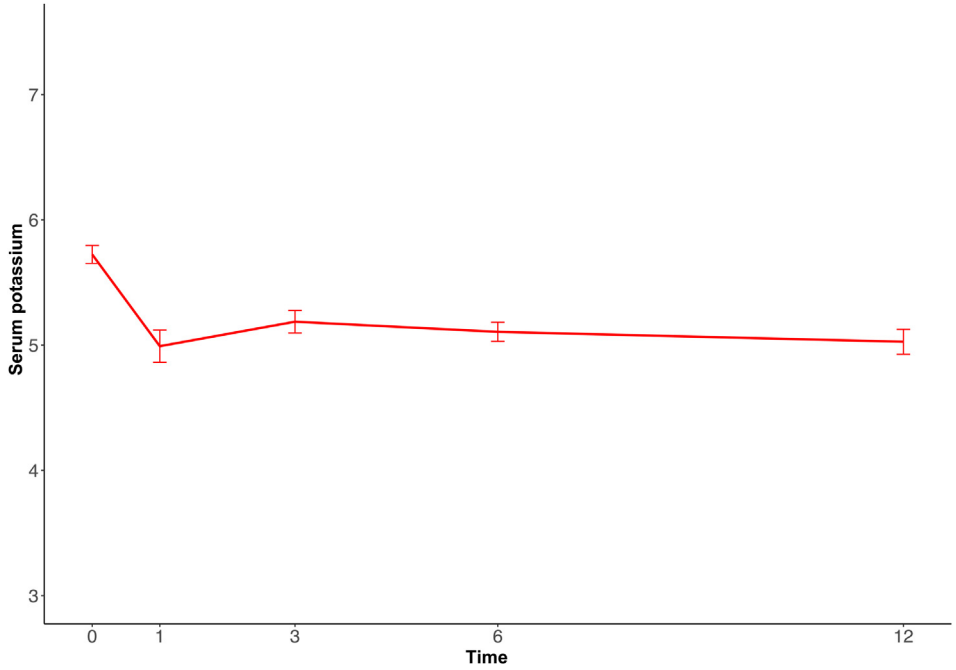


Fig. 1. Changes in potassium levels during the study period.

Table 2
Changes in serum potassium levels during the study period. The analysis was performed using a linear mixed-effects model with the value at each time point as a dependent variable (Fig. 1).

	Estimator	95% CI	*P*
Baseline potassium, mmol/L	5.72	5.56–5.88	
Potassium at visit 1	−0.70	−0.93 to −0.48	< .001
Potassium at visit 2	−0.55	−0.75 to −0.35	< .001
Potassium at visit 3	−0.61	−0.82 to −0.41	< .001
Potassium in final visit	−0.71	−0.93 to −0.49	< .001

average in the other two real-life studies). This distinction reinforces the applicability of our results to real care scenarios.

Notably, in our study, therapy with RAASi and MRAs was maintained in 94.9% and 98.3% of patients, respectively. These data represent an improvement relative to retrospective series, such as that of Trevisan, who analyzed 36,011 patients with CKD stages 3–5, where HK contributed to the suspension of blockade treatment in more than 30% of cases.[19]

Both our study and that of Kovesdy et al.[17] demonstrate a low rate of discontinuation of patiromer treatment (13.5% and 20%, respectively), which contrasts with the high rate of discontinuation in the study that analyzed patients on hemodialysis, which reached 50% despite a mean sustained reduction in potassium level of 1 mmol/L. The latter may be related to the substantial changes in potassium levels in patients on hemodialysis, many of which are influenced by, among other factors, the dose of dialysis, which rapidly normalizes potassium levels and may even result in hypokalemia. The inclusion criterion of at least three months of patiromer use in our study may have excluded patients who discontinued treatment early. The contribution of patiromer to the maintenance of basic nephroprotective therapies is especially relevant in this context, where the suppression of RAASi/MRA treatment is a frequent cause of kidney disease progression.[16,19]

Safety is highly important in treatments with chelators or potassium exchangers, where the side effects, especially gastrointestinal effects, have limited the use of cardio- and nephroprotective drugs. This also has implications for morbidity, mortality and renal progression in patients with CKD,[20] for whom the use of calcium or sodium polystyrene sulfonate is limited because of its limited effectiveness and safety issues.[21] The main side effects described in pivotal studies with patiromer (AMETHYST-DN[12] and OPAL-HK[10]) include constipation (4.6%–11%), diarrhea (2.7%–5%), hypomagnesemia (up to 7.2%) and other minor gastrointestinal side effects, such as nausea and abdominal pain (2%–4%). In our study, the presence of

Table 3
Changes in the different analytical parameters during follow-up period.

	Prescription (n = 59)	1 month (n = 34)	3 months (n = 46)	6 months (n = 48)	1 year (n = 37)	*P*
Creatinine, mg/dL	2.3 ± 0.9	2.4 ± 1.1	2.5 ± 1.1	2.5 ± 1.2	2.6 ± 1.2	< .001
GFR, mL/min/m^2	31.2 ± 16.4	29.3 ± 14.9	29.6 ± 16.5	29.4 ± 16.4	25.2 ± 12.2	< .001
Sodium, mmol/L	140 ± 4	140 ± 3	141 ± 3	141 ± 3	140 ± 4	.217
Calcium, mg/dL	9.4 ± 0.5	9.2 ± 0.7	9.4 ± 0.5	9.3 ± 0.5	9.4 ± 0.7	.339
Magnesium, mg/dL	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.3	2.1 ± 0.2	2.1 ± 0.3	.757
Hemoglobin, g/dL	12.3 ± 1.6	11.8 ± 1.9	12.2 ± 1.8	12.2 ± 1.8	12.3 ± 1.8	.094
Hematocrit, %	38.5 ± 5.0	36.7 ± 6.0	38.3 ± 5.3	38.1 ± 5.4	38.5 ± 5.9	.062
NT-proBNP, pg/mL	3762 ± 5399	9368 ± 12,515	7006 ± 9342	4230 ± 6705	3565 ± 6444	.172
Albuminuria, mg/g	296.5 (468.5)	252.3 (505.7)	201.4 (331.8)	178.9 (271.9)	152.1 (247.5)	.678

The values are shown as the mean ± standard deviation or median (IQR) according to the distribution of the variable.
eGFR: estimated glomerular filtration rate.

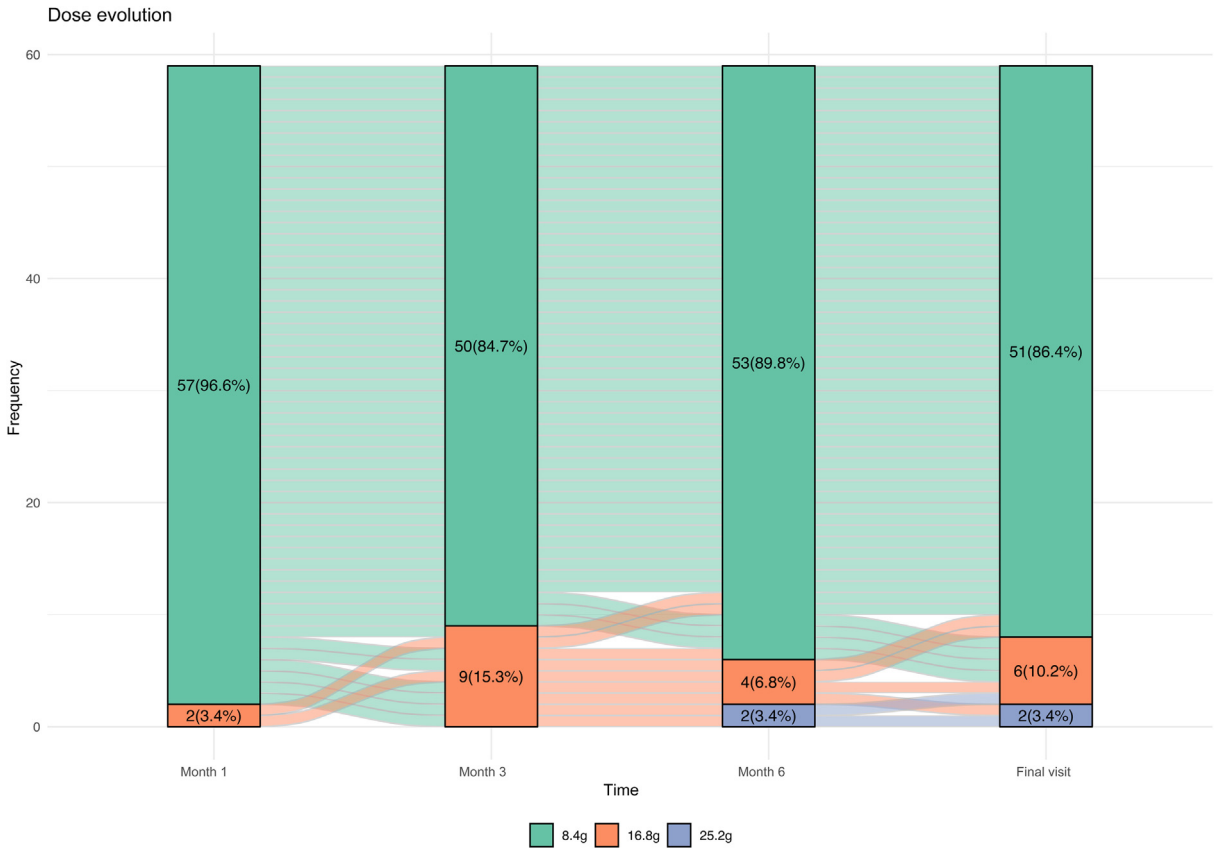


Fig. 2. Changes in the patiromer dose across visits. Most patients were maintained on a patiromer dose of 8.4 g throughout the study. At the end of the study, 86.4% of the patients achieved control of hyperkalemia with 8.4 g/day. A total of 10.2% required a dosage of 16.8 g/day, and only 3.4% required a dosage of 25.2 g/day.

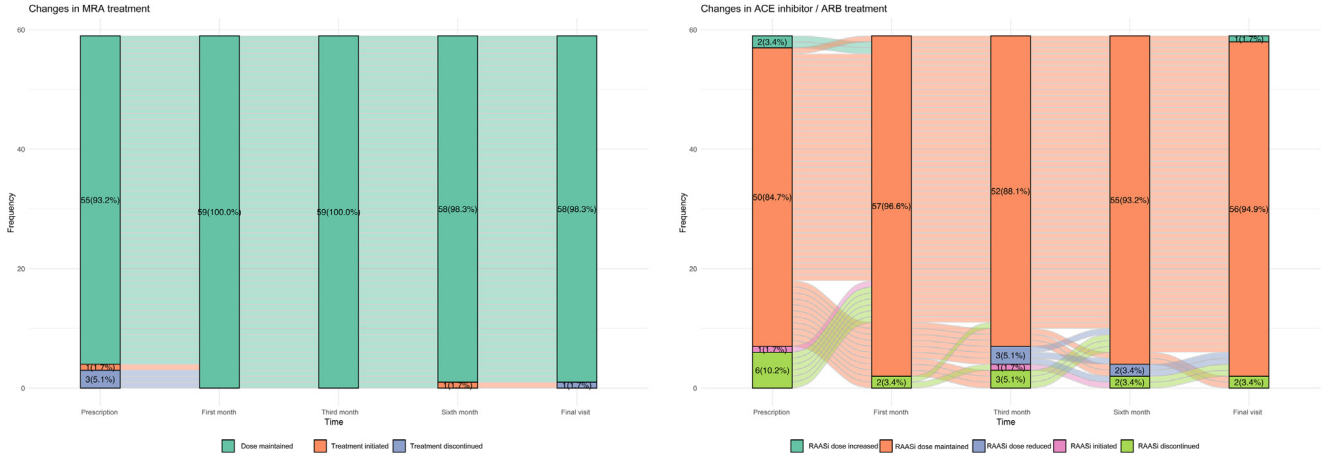


Fig. 3. Changes in treatment with RAASi (left) and MRAs (right). At the end of the study, the RAASi dose was maintained in 94.9% of the patients; the dose was increased in 1.7% of the patients, and the treatment was suspended in only 3.4%. The right panel shows that 98.3% of the patients in the study maintained their MRA doses and that MRA treatment was only suspended in one patient.

gastrointestinal side effects was lower than that described in the pivotal trials, which may be related to the retrospective nature of the analysis. No cases of hypomagnesemia were detected, despite the monitoring of magnesium levels in the majority of patients during nephrology follow-up.

The identification of two patients with hypercalcemia is noteworthy, which, although mild, led to the suspension of patiromer. Although hypercalcemia was not identified in pivotal trials of patiromer, some isolated clinical cases with this complication have been described, especially among patients with advanced CKD.[22–24]

The proposed mechanism for this hypercalcemia is based on the ion exchange properties of the drug itself: patiromer (also known as calcium patiromer) releases calcium by binding to potassium in the intestinal lumen, which can increase the systemic absorption of calcium in susceptible patients, especially those with a reduced glomerular filtration rate, in whom the urinary excretion of calcium is compromised, resulting in its accumulation. Other factors, such as the

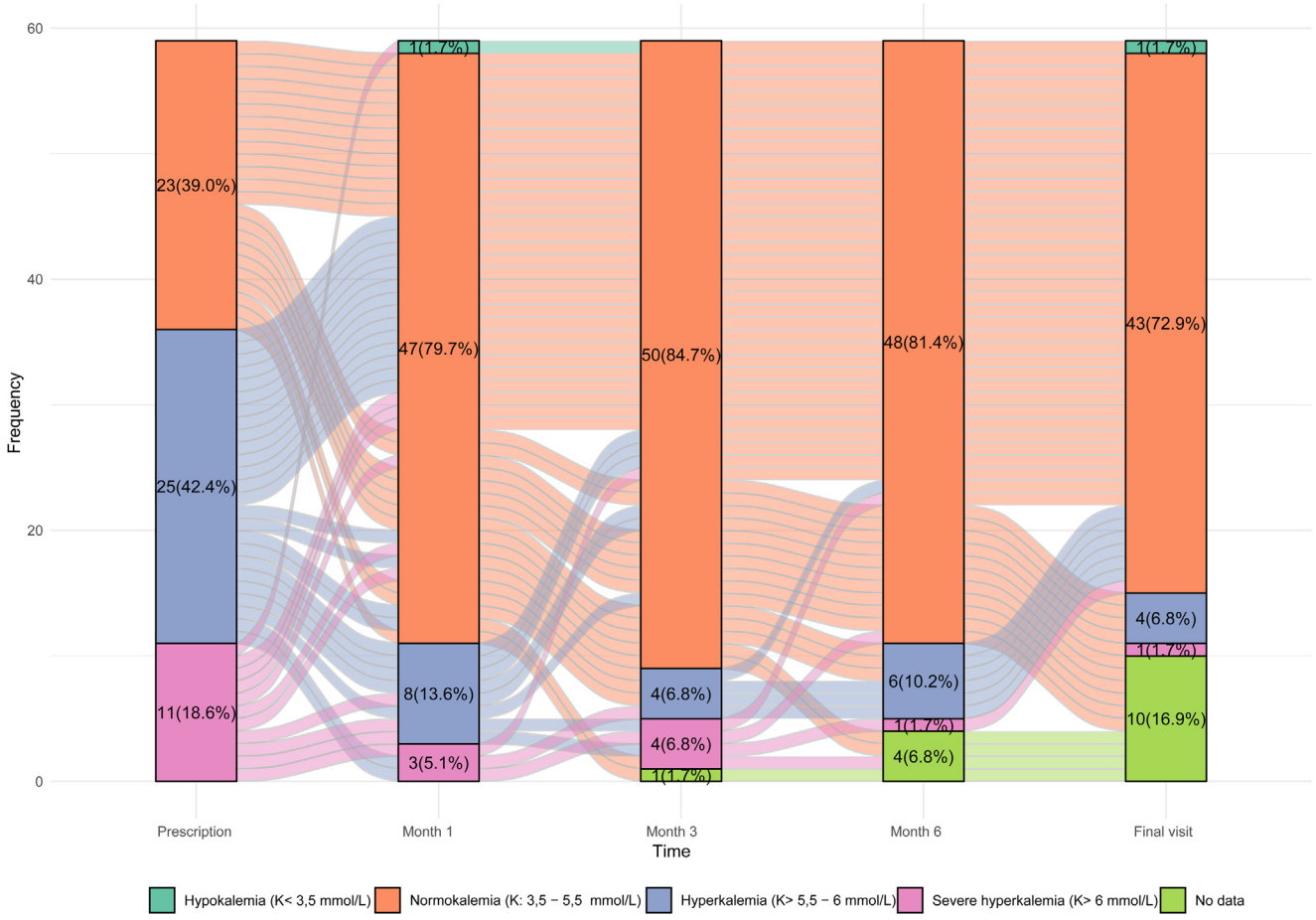


Fig. 4. Proportion of serum potassium ranges during the different study visits. Ranges: <3.5 mmol/L (hypokalemia); 3.5–5.5 (normokalemia); 5.5–6 mmol/L (hyperkalemia); >6 mmol/L (severe hyperkalemia). No data: Patients whose potassium levels were not determined or who had exited the study for some reason.

Table 4
Side effects recorded during follow-up and causes of patiromer discontinuation.

	First Month	Third month	Sixth month	Final Visit	Side effects, total, n (%)	Suspension
Hypomagnesemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Constipation	1 (1.7%)	2 (3.4%)	2 (3.4%)	2 (3.4%)	2 (3.4%)	1 (1.7%)
Nausea	0 (0%)	1 (1.7%)	2 (3.4%)	0 (0%)	2 (3.4%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	1 (1.7%)	0 (0%)	1 (1.7%)	1 (1.7%)
Nonspecific GI alterations	0 (0%)	2 (3.4%)	0 (0%)	0 (0%)	2 (3.4%)	0 (0%)
Hypercalcemia	0 (0%)	0 (0%)	2 (3.4%)	2 (3.4%)	2 (3.4%)	2 (3.4%)
Other reasons*	0 (0%)	1 (1.7%)	2 (3.4%)	1 (1.7%)	4 (7.0%)	4 (7.0%)
Patiromer suspensions, months	1 (1.7%)	3 (5.2%)	4 (7.0%)	0 (0%)	8 (13.5%)	8 (13.5%)
Motivated discontinuation of patiromer	0 (0%)	2 (3.4%)	6 (10.2%)	5 (8.5%)	8 (13.5%)	8 (13.5%)

GI: gastrointestinal.
* Other reasons for suspension: renal deterioration with initiation of dialysis (1), lack of compliance and treatment suspension by the patient (1) and treatment suspension due to normokalemia (2).

use of thiazide diuretics, secondary hyperparathyroidism, and vitamin D supplementation, may increase calcium absorption. In the published cases, hypercalcemia was resolved by discontinuing patiromer treatment and recurred when patiromer was reintroduced. Although infrequent, this adverse effect should be considered when determining whether to administer patiromer, and serum calcium should be monitored during prolonged treatments.[22–24]

It is also notable that the majority of treatment discontinuations were not due to side effects *per se* but to other situations, such as renal deterioration with the start of dialysis, lack of compliance by the patient or suspension by the doctor due to the presence of normokalemia. These findings indicate that the real prevalence of patiromer discontinuation due to adverse side effects may actually be lower than that reported, with most of the side effects being mild and not causing discontinuation of treatment, reinforcing patient tolerance of the drug.

Our study has several limitations. One of them is inherent to its retrospective and observational design, which prevents the establishment of strong, causal relationships between the use of patiromer and the changes observed in serum potassium level or in the continuity of treatment with RAASi/MRA, as well as the possible omission of any adverse effects, especially mild ones, as they were not reported in the clinical history. Second, the relatively limited sample size (59 patients) could restrict the generalization of the findings compared with that of previous studies with larger populations, such as those of Kovesdy et al.[17] (n. = 288) or Pinnell et al.[18] (n. = 458). Nevertheless, ours is a

representative cohort of outpatient nephrology patients with advanced CKD, which provides clinical value and applicability to the findings. Another limitation is the absence of a control group, which also prevents the establishment of direct causal relationships between treatment with patiromer and the change in potassium levels. Although significant and sustained reductions in serum potassium were observed, the influence of other concomitant factors, such as dietary adjustments, changes in medication or spontaneous clinical variability—which may have contributed to the observed effect—cannot be ruled out.

Despite these limitations, the study presents several relevant strengths. First, it offers a detailed evaluation of the safety of patiromer under routine clinical practice conditions, including the adverse effects experienced by the patients. In addition, prolonged follow-up, with a median of 12 months, allows us to assess not only the initial efficacy but also the therapeutic persistence and stability of potassium control in the long term, providing useful information for clinical decision-making.

Finally, this is one of the first studies conducted in Europe in outpatients with CKD and cardiorenal syndrome treated with patiromer, which contributes to expanding the available evidence and supports the implementation of this drug in nephrology practice in our environment.

We would like to emphasize that most of the participating centers were parts of cardiorenal units, where there is a more integrated approach aligned with clinical guidelines. From a clinical perspective, the results reinforce the usefulness of patiromer as a tool to facilitate a comprehensive approach to treating cardiorenal disease. Its use can avoid forced therapeutic decisions, such as a reduction or suppression of renin–angiotensin axis blockade, in patients who could benefit from these treatments, especially those in advanced stages of CKD where the therapeutic margin is limited. This strategy is in line with the current recommendations of the KDIGO and HF guidelines, which emphasize the importance of maintaining optimized treatment whenever possible,[4,25,26] in this case through the use of patiromer. In addition to the recommendations of the guidelines, the use of patiromer in patients with HK and CKD or HF has been associated with a reduction in costs, generating annual savings between € 3127 and € 3466 per patient.[27]

It should be noted that funding does not always correspond to clinical indications. In Spain, the cost of patiromer is reimbursed only for patients with advanced CKD and grade III–IV HF with mild–moderate HK (5.5–6.4 mmol/L), for those treated with RAASi whose continuation is essential, and those for whom ion exchange resins failed or produced intolerance. Since financing criteria differ across countries and health systems, the generalizability of our results may be limited.

We believe that the new potassium exchangers, such as patiromer, could play a preventive role in the stabilization of potassium and facilitate the maintenance of cardiorenal drugs, even before episodes of severe HK.

In conclusion, this study provides real evidence of the efficacy, safety and usefulness of patiromer in patients with CKD and HK treated under routine conditions. Its ability to reduce and stabilize serum potassium levels in the long term, along with its good tolerance profile and its contribution to the maintenance of treatment with RAASi and MRAs, make it a valuable tool in nephroprotection. Prospective studies designed specifically to evaluate the clinical impact of this strategy would be desirable.

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Declaration of competing interest

BGC declares having received honoraria for presentations from CSL VIFOR, AstraZeneca and Laboratorios Rubió. JPS declares having received honoraria for presentations from CSL VIFOR and AstraZeneca. MS declares having received honoraria for presentations from AstraZeneca. PSP has received help from CSL VIFOR to attend congresses. JP declares having received honoraria for presentations from AstraZeneca. MJP declares having received honoraria for presentations from AstraZeneca and CSL VIFOR, aid to attend congresses of CSL VIFOR and aid in research through the INCLIVA Research Institute. RGM declares having received honoraria for presentations from AstraZeneca and aid to attend congresses from CSL VIFOR and collaboration from Laboratorios Rubió. RDLE declares having received fees for presentations from AstraZeneca and CSL VIFOR and fees for consulting and research support from AstraZeneca.

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