OPEN

Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics

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Objective: Recurrent hyperkalemia frequently limits use of renin–angiotensin–aldosterone system inhibitors (RAASi) in chronic kidney disease (CKD) patients with hypertension, diabetes, and/or heart failure. Patiromer is a sodium-free, nonabsorbed potassium (K^+)-binding polymer approved by the US Food and Drug Administration for the treatment of hyperkalemia. This post-hoc analysis of OPAL-HK examined the effectiveness and safety of patiromer in reducing serum K^+ in hyperkalemic CKD patients on RAASi, with hypertension, receiving diuretic therapy versus those not on diuretics.

Methods: Depending on the degree of hyperkalemia at baseline, CKD patients with serum K^+ from 5.1 to less than 6.5 mmol/l on RAASi ($n = 243$) were assigned to a patiromer of total dose 8.4 or 16.8 g, divided twice daily. Changes in serum K^+, and tolerability and safety were assessed over 4 weeks in patients on and not on diuretics.

Results: At baseline, 132 patients used diuretics and 111 were not on diuretics, mean age was 64.3 and 64.0 years, respectively, and 63 and 51% were men. Similar reductions in serum K^+ were seen over 4 weeks in both subgroups. At week 4, serum K^+ fell by -0.95 ± 0.04 mmol/l with any diuretic and -1.04 ± 0.05 mmol/l with no diuretic. Patiromer was well tolerated, with mild-to-moderate constipation reported as the most common adverse event (7.6 and 14.4% of patients on any diuretic or no diuretic, respectively). Hypokalemia (s-K^+ <3.5 mEq/l) was reported in 2.3% of patients on any diuretic and in 3.7% not on diuretics.

Conclusion: The serum K^+-lowering efficacy and safety profile of patiromer in hyperkalemia patients with CKD was not compromised by diuretic therapy.

Keywords: chronic renal insufficiency, diuretics, hyperkalemia, patiromer

Abbreviations: AASK, African-American Study of Kidney Disease; ACE, angiotensin-converting enzyme; ACR, urine albumin/creatinine ratio; AMETHYST-DN, A Multicenter, Randomized, Open-Label, Dose Ranging Study to Evaluate the Efficacy and Safety of Patiromer in the Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy Receiving Angiotensin-converting Enzyme Inhibitor (ACEI) and/or Angiotensin II Receptor Blocker (ARB) Drugs, With or Without Spironolactone; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; eGFR, estimated glomerular filtration rate; K^+, potassium; MMRM, Mixed Model for Repeated Measures; MRA, mineralocorticoid receptor antagonist; OPAL-HK, Two-Part, Single-Blind, Phase 3 Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor; SPS, sodium polystyrene sulfonate

INTRODUCTION

Treatment guidelines recommend the use of renin–angiotensin–aldosterone system inhibitors (RAASi) for the treatment of hypertension, proteinuria, and heart failure [1–3]. However, the use of guideline-recommended doses of RAASi therapy is limited by hyperkalemia in patients with chronic kidney disease (CKD) and/or heart failure due to reduced renal potassium (K^+) excretion [4]. Hyperkalemia can cause life-threatening cardiac arrhythmia [4,5], and until recently, long-term treatment options for hyperkalemia were limited and frequently suboptimal [6]. As a result, down-titration or discontinuation of RAASi is frequently required to minimize recurrent or chronic hyperkalemia [7].

Potassium restricted diets and diuretic therapy with thiazide, loop, or combinations of diuretics have long been

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employed to treat hyperkalemia [7,8], but have limited effectiveness in patients with advanced CKD [9,10]. Diuretic-induced kaliuresis is dependent on kidney function, adequate extracellular volume, and delivery of sodium to the cortical collecting tubule [7,11,12], all of which may be impaired in patients with advanced renal insufficiency and/or heart failure [13]. Additionally, adverse effects such as orthostatic hypotension, syncope, gout, ototoxicity, and increasing azotemia secondary to volume depletion can limit the use of high dose or combination diuretic therapy [14–18].

Patiromer, a novel, sodium-free nonabsorbed polymer designed to bind and remove K^+, was approved by the US Food and Drug Administration (FDA) in 2015 for the treatment of hyperkalemia [19] and is under evaluation by the European Medicines Agency. Patiromer exchanges calcium for K^+ in the gastrointestinal tract, thereby increasing fecal K^+ excretion and decreasing serum K^+ in patients with hyperkalemia [20]. In a phase 3 trial (OPAL-HK), patiromer provided significant reductions in serum K^+ in CKD patients receiving RAASi and reduced the rapid recurrence of hyperkalemia during a placebo-controlled withdrawal phase [21]. Furthermore, long-term (1 year) control of hyperkalemia was demonstrated in the AMETHYST-DN study in patients with diabetic kidney disease and hypertension [22]. Thus, patiromer has been shown to provide clinically meaningful reductions in serum K^+ in hyperkalemic populations generally thought to benefit from RAASi.

We sought to determine if the magnitude of K^+ reduction with patiromer might be altered in patients receiving chronic diuretic therapy. CKD patients commonly require chronic diuretic therapy for control of hypertension, edema, and excess fluid volume [8]. Overtreatment of hyperkalemia may lead to hypokalemia, which similarly carries a significant risk for cardiac arrhythmia [23,24]. Therefore, it is important to examine the potential benefits and risk of adding a K^+-binder to patients receiving chronic diuretic therapy.

Here, we report the results of a post-hoc analysis of OPAL-HK designed to determine the efficacy and safety of patiromer for the treatment of hyperkalemia in a RAASi-treated CKD population with high rates of comorbid disease including hypertension, diabetes, proteinuria, and/or heart failure receiving diuretics versus those not receiving diuretics.

METHODS

Study design and participants

The study design of OPAL-HK has been previously described as a sequential, two-part, placebo-controlled, 12-week phase 3 study, evaluating patiromer treatment in 243 patients with CKD, stage 3 or greater, and hyperkalemia on RAASi medications [21]. The current analysis involves the initial 4-week treatment phase of the study (Fig. 1). Analyses are presented only for the initial treatment phase, as patient numbers in the randomized withdrawal phase do not support meaningful comparisons between the two diuretic subgroups. Eligible patients were adults with CKD stage 3 or 4 [estimated glomerular filtration rate (eGFR) 15 to less than 60 ml/min per 1.73 m^2), serum K^+ levels of 5.1 to less than 6.5 mmol/l at screening based on local laboratory measurement. In addition, patients were required to be on stable dose of RAASi, diuretics, and other permitted medications for at least 28 days before screening, and the doses of these medications were not anticipated to change during study participation. However, by protocol, doses of diuretics and other medications could be adjusted/up-titrated in patients with symptomatic heart failure. Patiromer starting doses at the beginning of the initial 4-week treatment phase were based on screening serum K^+ levels: 8.4 g total dose (divided twice daily) for mild hyperkalemia (5.1 to less than 5.5 mmol/l) and 16.8 g (divided twice daily) for moderate-to-severe hyperkalemia (5.5 to less than 6.5 mmol/l). The dose was adjusted according to a prespecified algorithm to maintain serum K^+ within the range 3.8 to less than 5.1 mmol/l. During this phase, adjustment of RAASi therapy was not allowed unless medically necessary, but could be discontinued if serum K^+ was $\geq$6.5 mmol/l (or $\geq$5.1 mmol/l while on maximum doses of patiromer).

Laboratory assessment of serum K^+ was conducted at baseline (day 1), on day 3 of both treatment phases, and weekly thereafter until the end of the study.

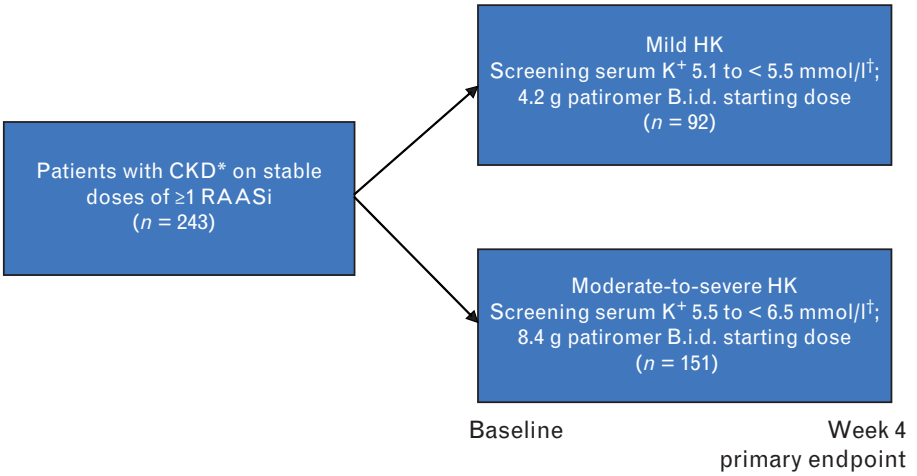

FIGURE 1 Study design for the initial treatment phase of OPAL-HK (single-blind, 4 weeks). (*) Estimated glomerular filtration rate (eGFR) 15 to less than 60 ml/min per 1.73 m^2 (central lab value) (†) Based on local lab value. B.i.d., twice a day; CKD, chronic kidney disease; HK, hyperkalemia; K^+, potassium; RAASi, renin–angiotensin–aldosterone system inhibitors.

Serum K^+ results during the initial treatment phase are presented for 132 patients prescribed diuretics and 111 patients on no diuretics at baseline. Use of a diuretic prior to study enrollment and at baseline and the type of diuretic were at the discretion of the investigator. Of those on diuretics, 62 were receiving loop diuretics, 55 were on thiazide/thiazide-like diuretics, and 15 were taking loop and thiazide/thiazide-like diuretics.

Statistical methods

To evaluate mean change in serum K^+ for each diuretic subgroup, mixed models for repeated measures (MMRMs) using restricted likelihood estimation and unstructured covariance matrix were fit to the weekly change from baseline in serum K^+ measurements. The models included the baseline serum K^+ measurement as a continuous covariate and three categorical covariates: study week; presence/absence of type II diabetes mellitus; and presence/absence of heart failure. Six patients who had no postbaseline serum K^+ measurement after day 3 were excluded from these models (two from the group using no diuretics and four from the group using diuretics). Additionally, the serum K^+ means [standard errors (SEs)] have been plotted at each time point, by group, using all available data.

Descriptive statistics for baseline demographic and medical characteristics have been summarized as mean (SD) for continuous variables, or as proportions for categorical variables. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Study participants

Demographic and baseline results were generally similar between patients on diuretics and those not on diuretics (Table 1), although there were some differences in prevalence of reported comorbidity and in the number of RAASi medications taken. Most patients in the study population were men (63% on diuretics, 51% not on diuretics), and nearly all were white (98% on diuretics, 99% not on diuretics). The mean ± SD age at baseline was 64.3 ± 9.5 and 64.0 ± 11.6 for the diuretics and no diuretics subgroups, respectively.

Hypertension was not a requirement for study entry. However, 96% on diuretics and 98% not on diuretics had a history of hypertension. Additional comorbidities included: 60 and 54%, respectively, with type II diabetes; 46 and 37% with heart failure; and 24 and 26% with a previous myocardial infarction. All patients were receiving at least one RAASi at baseline, and 23% of patients on diuretics and 11% of patients not on diuretics were on more than one RAASi.

Table 1 shows CKD stage at baseline, as determined by the central laboratory eGFR value; 46% of patients in both the any diuretic and no diuretic subgroups had stage 3 CKD, and nearly 45% in both groups had stage 4/5 disease. Final classification of CKD stage was determined on the basis of central laboratory measurements, and 9% of the patients in each diuretic subgroup were reclassified to stage 2 CKD as a result. The patients on diuretics tended to have a more advanced CKD stage than those not on diuretics (75 versus 66% had CKD stage 3b or greater).

TABLE 1. Demographic and clinical characteristics at baseline

	Any diuretic ($n = 132$)	No diuretic ($n = 111$)
Male, *n* (%)	83 (62.9)	57 (51.4)
Age, years, mean (SD)	64.3 (9.5)	64.0 (11.6)
White, *n* (%)	129 (97.7)	110 (99.1)
Hyperkalemia stratum, *n* (%)[a]		
Mild (5.1 to <5.5 mmol/l)	50 (37.9)	42 (37.8)
Moderate-to-severe (5.5 to <6.5 mmol/l)	82 (62.1)	69 (62.2)
Type 2 diabetes, *n* (%)	79 (59.8)	60 (54.1)
Heart failure, *n* (%)	61 (46.2)	41 (36.9)
Hypertension, *n* (%)	127 (96.2)	109 (98.2)
Prior myocardial infarction, *n* (%)	31 (23.5)	29 (26.1)
Sitting blood pressure, mmHg, mean (SD)		
Systolic	142.4 (16.5)	140.0 (17.7)
Diastolic	79.2 (11.6)	78.2 (9.9)
CKD stage (eGFR range), *n* (%)		
Stage 2 (60 to <90 ml/min per 1.73 m^2)	12 (9.1)	10 (9.0)
Stage 3A (45 to <60 ml/min per 1.73 m^2)	21 (15.9)	28 (25.2)
Stage 3B (30 to <45 ml/min per 1.73 m^2)	40 (30.3)	23 (20.7)
Stage 4/5 (<30 ml/min per 1.73 m^2)	59 (44.7)	50 (45.0)
RAASi medication, *n* (%)	132 (100.0)	111 (100.0)
ACE inhibitor	90 (68.2)	80 (72.1)
ARB	56 (42.4)	36 (32.4)
Aldosterone antagonist	15 (11.4)	7 (6.3)
Renin inhibitor	2 (1.5)	0
>1 RAASi medications	30 (22.7)	12 (10.8)

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular rates; RAASi, renin–angiotensin–aldosterone system inhibitors.
[a]Based on local laboratory measurement.

TABLE 2. Central laboratory baseline values

	Any diuretic ($n=132$)	No diuretics ($n=111$)	Diuretic subgroups		
			Loop only ($n=62$)	Thiazide/thiazide-like only ($n=55$)	Loop and thiazide/thiazide-like ($n=15$)
Serum sodium (mmol/l)	139.9 ± 2.3	139.6 ± 2.3	140.0 ± 2.5	139.9 ± 3.6	139.7 ± 2.8
Serum potassium (mmol/l)[a]	5.56 ± 0.41	5.56 ± 0.48	5.57 ± 0.42	5.51 ± 0.43	5.64 ± 0.37
Serum bicarbonate (mmol/l)	24.1 ± 3.7	24.0 ± 3.9	23.5 ± 3.2	24.5 ± 4.1	25.0 ± 4.2
Serum magnesium (mmol/l)	1.09 ± 0.14	1.10 ± 0.15	1.11 ± 0.14	1.06 ± 0.14	1.08 ± 0.18
Serum creatinine (μmol/l)	189.2 ± 74.6	184.8 ± 103.7	202.4 ± 77.7	177.7 ± 72.9	173.3 ± 61.7
eGFR (ml/min per 1.73 m^2)	34.4 ± 15.1	36.6 ± 17.5	31.6 ± 14.6	37.1 ± 15.6	36.4 ± 14.1
ACR (mg/mmol creatinine)[b]	86.8 ± 136.2	84.9 ± 177.9	77.3 ± 121.5	93.8 ± 134.1	101.1 ± 196.7

All values are mean ± SD.
ACR, urine albumin/creatinine ratio; eGFR, estimated glomerular filtration rate.
[a]For no diuretics, $n=108$; for loop and thiazide/thiazide-like diuretics, $n=13$.
[b]For no diuretics, $n=107$; for loop diuretics only, $n=61$; for thiazide/thiazide-like diuretics only, $n=51$.

At baseline, the percentage of patients with mild versus moderate-to-severe hyperkalemia was the same in the diuretic and no diuretic subgroups, as 38% had mild hyperkalemia (5.1 to less than 5.5 mmol/l) and 62% had moderate-to-severe hyperkalemia (5.5 to less than 6.5 mmol/l) in each subgroup. The mean ± SD serum K^+ level at baseline was 5.56 ± 0.41 and 5.56 ± 0.48 mEq/l for the any diuretic and no diuretic subgroups, respectively. Baseline laboratory values for the patients on any diuretic, no diuretic, and those receiving different classes or combinations of diuretic appear in Table 2. Central laboratory values were similar between the diuretic and the no diuretic subgroups. Mean (SD) systolic/diastolic blood pressure was 142.4 (16.5)/79.2 (11.6) mmHg in patients on any diuretics and 140.0 (17.7)/78.2 (9.9) mmHg in patients on no diuretics.

Classes of diuretic, specific selection and dose of diuretic, and dosage regimens varied in the diuretic subgroup. Mean ± SD weekly doses were 364.6 ± 517.7 mg for furosemide ($n=58$), 135.3 ± 55.7 mg for hydrochlorothiazide ($n=39$), 10.8 ± 3.9 mg for indapamide ($n=33$), 46.9 ± 80.4 mg for torsemide ($n=17$), and 8.8 ± 7.4 mg for bumetanide ($n=2$).

Efficacy in the initial treatment phase

The observed mean ± SEs of serum K^+ for patients on and off diuretics over time are plotted in Fig. 2. Using the MMRM model, the estimated mean ± SE change in serum K^+ levels from baseline to week 4 for the patients receiving diuretics at baseline was −0.95 ± 0.04 mmol/l (−1.03 to −0.86; $P<0.001$); for patients not on diuretics at baseline the estimate was −1.04 ± 0.05 mmol/l (−1.13 to −0.94; $P<0.001$). These results were also mirrored in the diuretic subgroup by type of diuretic medication (i.e. loop diuretics and thiazide/thiazide-like diuretics). For those taking only loop diuretics, the estimate was −0.99 ± 0.06 mmol/l (−1.11 to −0.87; $P<0.001$), for thiazide/thiazide-like diuretics it was −0.97 ± 0.05 mmol/l (−1.07 to −0.87; $P<0.001$), and for both loop and thiazide/thiazide-like diuretics it was −0.69 ± 0.19 mmol/l (−1.11 to −0.28; $P<0.004$).

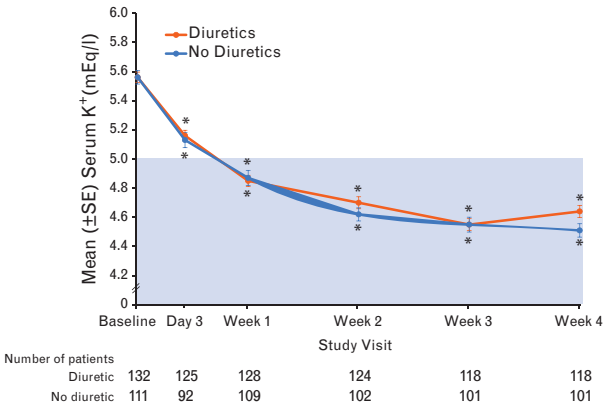

FIGURE 2 Serum potassium decreased over 4 weeks in hyperkalemic patients on patiromer on and off diuretics. Six patients who had no postbaseline serum potassium measurement after day 3 were excluded (four from the group using diuretics and two from the group using no diuretics). *$P<0.0001$ versus baseline.

The mean total daily dose of patiromer during the initial treatment phase was 12.6 g (mild hyperkalemia) and 21.7 g (moderate-to-severe hyperkalemia) for patients taking any diuretic, and 13.0 g (mild hyperkalemia) and 21.2 (moderate-to-severe hyperkalemia) for those taking no diuretics.

Safety

Patiromer adverse events have previously been described [23]. One or more adverse event was reported in 52 and 41% of patients in the diuretic and no diuretic subgroups, respectively (Table 3). Mild-to-moderate constipation was the most common adverse event, occurring in 8 and 14% of patients on any diuretics and not on diuretics, respectively. No serious gastrointestinal events were recorded. Adverse events leading to discontinuation of patiromer treatment occurred in 7 and 5% in the diuretic and no diuretic subgroups, respectively. Few patients discontinued due to constipation (1% in patients on any diuretics and not on diuretics). Three patients had a total of six serious adverse events. These patients were taking only loop diuretics at baseline. None of the serious adverse events were fatal, and all were considered by the investigators not to be related to patiromer treatment.

During the initial treatment phase, the incidence of hypokalemia (prespecified as serum K^+ levels <3.5 mmol/l) was 2.3 and 3.7% in the patients on any diuretic and not on diuretics, respectively. Serum K^+ levels in these patients ranged from 3.2 to 3.4 mmol/l, and were most often transient following adjustment of the patiromer dose. Mean serum magnesium level remained within the normal range. A small mean decrease in mean serum magnesium from baseline to week 4 of −0.18 mg/dl was observed in patients on any

TABLE 3. Adverse events the first 4 weeks of patiromer treatment

Adverse event	Any diuretic ($n = 132$)	No diuretic ($n = 111$)
Reporting any AE, *n* (%)	68 (51.5)	46 (41.4)
Serious[a]	3 (2.3)	0
Leading to discontinuation	9 (6.8)	6 (5.4)
Most common AEs, *n* (%)[b]		
Constipation (none severe)	10 (7.6)	16 (14.4)
Diarrhea (none severe)	7 (5.3)	1 (0.9)

AE, adverse event.
[a]None of the serious AEs were considered related to patiromer by the investigators.
[b]Occurring in 5% or more of patients in either subgroup.

diuretics and not on diuretics. A prespecified serum magnesium level of less than 1.4 mg/dl occurred in five (3.9%) patients on any diuretics and in three (2.8%) patients not on diuretics during the initial treatment phase; none of these patients had serum magnesium levels below 1.2 mg/dl.

At week 4, mean (SE) systolic/diastolic blood pressure decreased from baseline by −5.1 (1.7)/−4.5 (1.1) in patients on any diuretics and by −6.5 (1.6)/−3.2 (1.1) in patients not on diuretics (Table 4).

DISCUSSION

The post-hoc analysis of OPAL-HK demonstrated that patiromer, a new K^+-binding medication, was well tolerated and effective in reducing serum K^+ in hyperkalemia patients with CKD and hypertension, and multiple comorbidities receiving RAASi irrespective of whether background concomitant diuretic therapy was used. Overall, the results in patients on and not on a diuretic were consistent with those reported in the primary analysis [21]. The primary endpoint for this subanalysis was the change in serum K^+ from baseline at 4 weeks. Significant reductions in mean serum K^+ were seen at the first postbaseline visit (day 3, 48 h after the first dose), and serum K^+ fell to less than 5.0 mmol/l by week 1 in both patients on and off diuretics. Decreases in mean serum K^+ were significant at all postbaseline time points. By week 4, the observed mean ± SE changes in serum K^+ were similar in both the diuretic and no diuretic subgroups (-0.95 ± 0.04 and -1.04 ± 0.05 mmol/l, respectively). Hypokalemia (predefined as serum K^+ <3.5 mmol/l) was infrequent, occurring in 2.3% of patients on any diuretic and in 3.7% of patients on no diuretic. Adverse effects leading to discontinuation of study drug were reported in 6.8% of patients in the diuretic subgroup and in 5.4% of patients in the no diuretic subgroup.

TABLE 4. Mean (SE) systolic and diastolic blood pressure at baseline and change from baseline during the first 4 weeks of patiromer treatment

Systolic/diastolic blood pressure (mmHg)	Any diuretic ($n = 132$)	No diuretic ($n = 111$)
Baseline	142.4 (1.4)/79.2 (1.0)	140.0 (1.7)/78.2 (0.9)
Change from baseline to		
Day 3	−4.2 (1.3)/−2.8 (0.7)	−3.7 (1.4)/−1.7 (0.9)
Week 1	−4.7 (1.4)/−3.4 (0.9)	−5.0 (1.6)/−2.5 (1.0)
Week 2	−5.3 (1.6)/−3.9 (1.0)	−4.7 (1.6)/−2.0 (1.0)
Week 3	−3.4 (1.7)/−3.5 (1.0)	−6.0 (1.7)/−3.2 (1.1)
Week 4	−5.1 (1.7)/−4.5 (1.1)	−6.5 (1.6)/−3.2 (1.1)

The demographic characteristics and comorbidities of the population studied in this OPAL-HK subanalysis were typical of those seen in hyperkalemic patients in clinical practice. Patients at greatest risk for hyperkalemia were those with impaired renal function and diabetes receiving RAASi medication [7].

Blood pressure, pulmonary congestion, and edema in patients with CKD and heart failure can be managed by the addition of potent and/or long-acting diuretics [25]. Over half of the OPAL-HK population with hyperkalemia on RAASi therapy at baseline were taking diuretics (loop, thiazide/thiazide-like, or combinations of diuretics). Non-potassium sparing diuretics combined with a low K^+ diet may reduce the risk of hyperkalemia with RAASi therapy [7]. However, patients with advanced kidney disease may be relatively resistant to the effects of diuretic therapy [11]. Counter-regulatory rebound sodium retention secondary to volume depletion may reduce distal delivery of sodium to the cortical collecting tubule and require dosage adjustment or supplemental sodium, thus limiting diuretic effectiveness in lowering serum K^+ [11]. The diuretic subgroup appeared to have more advanced kidney disease and comorbidity than the no diuretic subgroup. Although mean eGFR was similar in both subgroups, a greater percentage of the OPAL-HK diuretic subgroup had more advanced renal impairment on the basis of CKD staging. In addition, a greater percentage of the diuretic subgroup reported heart failure, and received more than one RAASi medication at baseline when compared with the no diuretic group.

In a safety assessment, we noted a reduction in systolic blood pressure in both the diuretic and no diuretic subgroups in our OPAL-HK analysis. Clinically meaningful reductions in systolic and diastolic blood pressure were also observed in the AMETHYST-DN study over 52 weeks [22]. However, the changes observed in this analysis in patients on and not on diuretics during the initial treatment phase and in AMETHYST-DN study should be interpreted cautiously, given the absence of a placebo group.

Adverse effects related to diuretics may limit their use for treating hypertensive hyperkalemic patients. Careful monitoring of renal function, serum electrolytes, and fluid status during diuretic therapy is required to prevent or detect hyponatremia, hypovolemia, and/or worsening kidney function in patients with CKD [2]. Although the reported frequency of hyperkalemia was low in the African-American Study of Kidney Disease (AASK) trial, it was highest in the ramipril group. A loop diuretic, furosemide, was utilized to treat hyperkalemia in AASK, and a higher frequency of adverse effects, including dizziness (50.1%), lightheadedness (49.2%), and syncope (6.7%), were observed in the ramipril cohort [26], possibly secondary to exaggerated diuretic therapy.

Hyperkalemia secondary to RAASi therapy has been reported to occur in 10–38% of hospitalized patients, and in approximately 10% of outpatients within 1 year following initiation of therapy [7]. The addition of a mineralocorticoid antagonist (MRA) to an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker

for control of hypertension has been reported to double the risk for hyperkalemia [11]. All patients in our analysis were on RAASi, 42 of whom were on more than one RAASi medication. Clinically, the development of hyperkalemia during the treatment of hypertension, CKD, and/or heart failure poses a therapeutic dilemma, as patients at highest risk for this RAASi-induced complication are the same patients who derive the greatest cardiovascular benefit from these drugs [7,27].

Heretofore, the development of hyperkalemia in RAASi-treated patients on diuretics given in conjunction with a low K^+ diet frequently led to down-titration or discontinuance of guideline recommended RAASi therapy [7]. In the AMETHYST-DN study, patiromer was found to be well tolerated and effective in treating hyperkalemia over 52 weeks in a high-risk population with diabetic kidney disease on RAASi [22]. With the availability of patiromer following US FDA approval [19], US clinicians now have another option to manage chronic or recurrent hyperkalemia in high-risk patient populations, while maintaining RAASi therapy.

We recognize the limitations of this post-hoc analysis. Our study was limited to the initial treatment phase of OPAL-HK, which lasted 4 weeks, and this phase was not placebo controlled. No attempts were made to increase diuretic therapy to determine if diuretic resistance to additional K^+ reduction was present prior to the initiation of patiromer therapy.

In summary, 54% of hyperkalemic CKD patients in OPAL-HK presented with hypertension and/or multiple comorbidities on RAASi therapy while receiving diuretic therapy at baseline. Patiromer significantly reduced mean serum K^+ levels over 4 weeks regardless of diuretic use. Patiromer was generally well tolerated in patients on and not on diuretics, and hypokalemia was infrequent in patients on any diuretic. Thus, the efficacy and safety of patiromer was not compromised by concomitant administration of diuretics.

Hyperkalemia limits the use of optimal RAASi therapy in patients with CKD. ACE inhibitors and angiotensin receptor blockers are recommended as first-line therapy for hypertension in patients with CKD because of their cardioprotective and renoprotective effects [1,28,29]. Despite these recommendations, RAASi medications are underutilized in patients with CKD, in part secondary to the risk of recurrent hyperkalemia, and they are less likely to be prescribed than in patients with preserved renal function [28]. As a result, a widening gap has emerged between guideline-recommended RAASi therapy and real-world experience, leading to clinical inertia. Patiromer has been demonstrated to be well tolerated and effective for the treatment of hyperkalemia in CKD patients with hypertension and multiple comorbidities on RAASi, alone or in conjunction with other K^+-lowering interventions.

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Conflicts of interest

M.R.W. reports personal fees from Relypsa, Janssen, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Akebia, and MSD (scientific advisor). M.R.M., D.G., S.A.A., and D.J.W. report employment by Relypsa. L.B. reports employment by Relypsa and other from Relypsa. In addition, L.B. has a patent WO 2014/058905 pending. D.B. reports personal fees from Relypsa, Amgen, Sanofi Aventis/Genzyme, Tricida, Fresenius Medical Care, and OPKO Health. He also has stock options in Relypsa and Tricida. M.E. reports personal fees for consulting with Bayer, OPKO Health, and Relypsa, Inc.

REFERENCES

1. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al.* 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
2. Kidney Disease Outcomes Quality Initiative. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43 (5 Suppl 1):S1–S290.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 62:e147–e239.
4. Kuijvenhoven MA, Haak EA, Gombert-Handoko KB, Crul M. Evaluation of the concurrent use of potassium-influencing drugs as risk factors for the development of hyperkalemia. *Int J Clin Pharm* 2013; 35:1099–1104.
5. McMahon GM, Mendu ML, Gibbons FK, Christopher KB. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med* 2012; 38:1834–1842.
6. Fordjour KN, Walton T, Doran JJ. Management of hyperkalemia in hospitalized patients. *Am J Med Sci* 2014; 347:93–100.
7. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 2004; 351:585–592.
8. Hollander-Rodriguez JC, Calvert JF Jr. Hyperkalemia. *Am Fam Physician* 2006; 73:283–290.
9. Ingelfinger JR. A new era for the treatment of hyperkalemia? *N Engl J Med* 2015; 372:275–277.
10. Kovesdy CP. Management of hyperkalemia: an update for the internist. *Am J Med* 2015; 128:1281–1287.
11. Rossignol P, Massy ZA, Azizi M, Bakris G, Ritz E, Covic A, *et al.* The double challenge of resistant hypertension and chronic kidney disease. *Lancet* 2015; 386:1588–1598.
12. Shankar SS, Brater DC. Loop diuretics: from the Na-K-2Cl transporter to clinical use. *Am J Physiol Renal Physiol* 2003; 284:F11–F21.
13. Perez GO, Pelleya R, Oster JR, Kem DC, Vaamonde CA. Blunted kaliuresis after an acute potassium load in patients with chronic renal failure. *Kidney Int* 1983; 24:656–662.
14. Sica DA. Diuretic-related side effects: development and treatment. *J Clin Hypertens (Greenwich)* 2004; 6:532–540.
15. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. *Arthritis Rheumatol* 2014; 66:185–196.
16. Wang DJ, Gottlieb SS. Diuretics: still the mainstay of treatment. *Crit Care Med* 2008; 36 (1 Suppl):S89–S94.
17. Greenberg A. Diuretic complications. *Am J Med Sci* 2000; 319:10–24.

18. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, *et al*. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356:366–372.
19. *Veltassa® (patiromer) for oral suspension [package insert]*. Redwood City, CA, USA: Relypsa Inc.; 2015.
20. Li L, Harrison SD, Cope MJ, Park C, Lee L, Salaymeh F, *et al*. Mechanism of action and pharmacology of patiromer, a nonabsorbed cross-linked polymer that lowers serum potassium concentration in patients with hyperkalemia. *J Cardiovasc Pharmacol Ther* 2016; 21:456–465.
21. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, *et al*. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; 372:211–221.
22. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, *et al*. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. *JAMA* 2015; 314:151–161.
23. Helfant RH. Hypokalemia and arrhythmias. *Am J Med* 1986; 80 (4A):13–22.
24. Hollifield JW, Slaton PE. Thiazide diuretics, hypokalemia and cardiac arrhythmias. *Acta Med Scand Suppl* 1981; 647:67–73.
25. KDOQI. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *Am J Kidney Dis* 2007; 49 (2 Suppl 2):S12–S154.
26. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, *et al*. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; 288:2421–2431.
27. Epstein M. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. *Kidney Int Suppl* 2016; 6:20–28.
28. Chang TI, Zheng Y, Montez-Rath ME, Winkelmayer WC. Antihypertensive medication use in older patients transitioning from chronic kidney disease to end-stage renal disease on dialysis. *Clin J Am Soc Nephrol* 2016; 11:1401–1412.
29. Wheeler DC, Becker GJ, Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? *Kidney Int* 2013; 83:377–383.