REPORT

Managing Hyperkalemia in High-Risk Patients in Long-Term Care

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ABSTRACT

Hyperkalemia is common among elderly patients and is associated with an increase in morbidity and mortality. Patients at highest risk for developing hyperkalemia are those with chronic kidney disease (CKD) and heart failure (HF), particularly those on guideline-recommended inhibitors of the renin-angiotensin-aldosterone system (RAAS). Hyperkalemia remains a challenge for clinicians practicing in the long-term care setting as they are often faced with the difficult decision of down-titrating or discontinuing RAAS inhibitors in response to hyperkalemia in the very patients who derive the greatest benefit from these agents. In the past, options to chronically manage hyperkalemia were limited. Patiromer was approved for the treatment of hyperkalemia in 2015 and has been shown to maintain normokalemia for up to 52 weeks in patients with CKD and/or HF on RAAS inhibitors. With the emergence of a new hyperkalemia treatment, there could be a paradigm shift away from the discontinuation of guideline recommended therapies, allowing the continuation of RAAS inhibitor therapy to effectively manage HF symptoms and reduce the risk of rehospitalization in patients with HF, and slow the progression to end-stage renal disease in patients with CKD.

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For author information and disclosures, see end of text.

Hyperkalemia is clinically one of the most important electrolyte abnormalities that can lead to cardiac arrhythmias and sudden cardiac death. Elderly patients, because of many underlying conditions, are particularly predisposed to develop this electrolyte disturbance.[1] A combination of age-associated reductions in glomerular filtration rate (GFR) and disturbances in the renin-angiotensin-aldosterone system (RAAS) and renal tubular function lead to this predisposition.[1,2] The prevalence of hyperkalemia in the general population has been estimated at 2% to 3%.[3] However, studies in older patients with chronic kidney disease (CKD) show much higher frequencies of hyperkalemia—as high as 50%—particularly in those with advanced stages of CKD, diabetes, and heart failure (HF) and in patients treated with RAAS inhibitors (RAASIs).[3-5]

Background and Significance

The number of elderly people (aged ≥65 years) in the world is estimated to increase more than two-fold from 420 million (6.9% of the world population) in the year 2000 to 973 million (12.0%) in 2030.[6] In the United States, the number of elderly people doubled from 1960 to 2000, and it is estimated to double again to 71 million by 2030.[6,7]

The projected medical and economic burden of the aging population on the healthcare system is significant.[8] The aging population requires a focus on chronic diseases, such as heart disease, cancer, respiratory disease, cerebrovascular disease, dementia, diabetes, and kidney disease.[9] Chronic diseases are often associated with disability, which leads to an increased use of long-term care services, such as nursing homes, assisted living facilities, and home healthcare.[10] Over two-thirds of individuals who reach 65 years of age are projected to need long-term care in their lifetime—for an average of 3 years.[11,12] Nursing home residents, because of their chronic conditions, take an average of 6.7 different medications per day.[13] Chronic diseases are a significant medical burden, potentially leading to hospitalizations, invasive medical procedures (eg, dialysis), poor quality of life, and increased mortality in the community and in long-term care settings.[10]

This article reviews the current understanding of how elderly patients with CKD and/or HF may develop hyperkalemia, and how

the recent advent of new treatment strategies may be helpful in improving clinical outcomes in these patients.

CKD

The prevalence of CKD and end-stage renal disease (ESRD) in the United States, especially in older individuals, is high and growing.[14] The 2015 United States Renal Data System annual data report revealed the prevalence of CKD and ESRD in the Medicare population to be approximately 11%.[15] Interestingly, although the incidence of ESRD has generally plateaued in the last decade, its prevalence has continued to rise by approximately 21,000 cases per year.[15] Consistent with this, the prevalence of patients receiving dialysis (hemodialysis and peritoneal dialysis) increased by 4%, and of those receiving a renal transplant, it increased by 3.1%.[15] This increase in prevalence has generally been attributed to increased longevity.[15]

The decision of whether or not to start dialysis in patients with advanced CKD can be difficult, especially in elderly patients with multiple comorbidities.[16-18] Advanced age, poor functional assessment, disabilities, and conditions such as dementia and depression should be taken into consideration. In a recent retrospective national cohort analysis of more than 28,000 patients with a sustained estimated GFR (eGFR) less than 15 mL/min/1.73 m^2, it was found that the proportion of patients who received, or were preparing to receive, renal replacement therapy differed significantly between younger and older populations: 96% for patients aged less than 45 years and 53% for those 85 years and older.[19] Consistent with this finding, the patients deciding against dialysis were significantly older (mean age, 75 years) and had a significantly higher Gagne comorbidity score (mean, 6.1), including greater rates of dementia and stroke.[19]

Reducing overactivity of the RAAS with RAASIs has shown significant renoprotective benefit in patients with CKD in multiple clinical trials, including RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) and IDNT (Irbesartan Diabetic Nephropathy Trial).[20-24] Although no RAASI clinical trial has assessed mortality as the primary end point in patients with CKD, a large observational study showed an association between RAASI use and lower mortality in patients with CKD.[25] For these reasons, use of RAASIs is recommended by guidelines.[26,27] The National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommend using angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) at moderate-to-high doses in patients with diabetic or nondiabetic kidney disease with proteinuria, with or without hypertension.[28] More recent hypertension guidelines (Eighth Joint National Committee) also support the use of RAASIs in adult patients with CKD and hypertension.[27] The major incentive for using RAASIs in patients in the long-term care setting goes beyond blood pressure control and includes a reduction in intraglomerular pressure and proteinuria, thereby slowing the progression of CKD to ESRD. However, because these patients are typically elderly, have renal insufficiency, and are taking multiple medications, providers may be concerned about the risk versus benefit of prescribing RAASIs in these patients for fear of increased serum creatinine, reduced GFR, or hyperkalemia.

RAAS inhibition with an ACEI or ARB can result in an acute increase in serum creatinine and/or fall in eGFR in patients with CKD.[29] The rise in serum creatinine may lead physicians to discontinue or reduce the dose of these disease-delaying medications.[29] Many physicians view this rise in serum creatinine as a contraindication for future RAASI use. Clinical trial data demonstrate that serum creatinine rises transiently and stabilizes relatively quickly in patients with diabetic or nondiabetic kidney disease.[29] It is now generally accepted that an elevation in serum creatinine of up to 30% to 35% that stabilizes within the first 2 months of RAASI therapy is associated with good prognosis and long-term preservation of kidney function.[29,30]

Another major concern related to usage of RAASIs is hyperkalemia. Patients with CKD on RAASI therapy, especially the elderly, commonly develop this electrolyte abnormality.[2,31-33] RAASI-induced hyperkalemia has been associated with an increased risk of adverse renal outcomes in patients with diabetic nephropathy.[34] Hyperkalemia has also been associated with an increased risk of sudden death in patients undergoing chronic dialysis.[35] In large retrospective analyses, hyperkalemia in patients with CKD and/or on dialysis was correlated with an increased risk of death.[4,36-38] Therefore, it is recommended that serum potassium (K^+) level be closely monitored, as follows in patients with CKD who are on RAASI therapy: every 2 to 4 weeks if baseline serum K^+ level (at initiation or dose increase of RAASI) is 4.6 to 5.0 mEq/L, and every 2 weeks or less if the baseline serum K^+ level is greater than 5.0 mEq/L.[28,39] The K/DOQI guidelines recommend reducing the dose of an ACEI or ARB by 50% if hyperkalemia (serum K^+ level >5.0 mEq/L) develops and re-evaluating serum K^+ level every 5 to 7 days.[28] If serum K^+ level does not return to baseline in 2 to 4 weeks, RAASI therapy should be discontinued.[28] It should be noted, however, that these guidelines were developed before the recent advent of new and more tolerable therapies for the treatment of hyperkalemia.

HF

HF is a leading cause of death, hospitalizations, and rehospitalizations in patients 65 years and older in the United States.[9,40,41] A study assessing hospitalizations for HF in the Medicare population (mean age, 80 years) during a 5-year period showed that approximately one in 4 patients were readmitted to a hospital within 30 days of the initial hospitalization, and the most common cause of readmission was cardiovascular disease.[40] Another study showed that the most frequent reason for all-cause 30-day hospital readmissions in the elderly—costing approximately $1.7 billion—was congestive HF.[42] In a 2004 national survey of skilled nursing facilities (SNFs), 4%

to 5% of the long-term residents were reported to have a primary diagnosis of HF, with many more having HF as a secondary diagnosis.[43,44] Although the exact prevalence of HF in SNF residents is unknown, it has been estimated to be approximately 30% to 40%.[45,46] Furthermore, an observational study assessing the clinical outcomes in Medicare patients hospitalized for HF showed that the rates of rehospitalization and death were significantly higher in patients who were discharged to a SNF versus home.[47]

RAASI therapy is well known to reduce the risk of death and hospitalization in patients with HF and reduced ejection fraction (HFrEF).[48-52] Available data suggest that ACEIs and ARBs have similar effects in the young and the elderly. A study of ACEIs showed previously that the reduction in mortality and hospitalizations was consistent among older and younger age groups and more evident in patients with a left ventricular ejection fraction (LVEF) of 25% or less.[53] In a more recent study (CHARM [Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity]), candesartan (an ARB) resulted in similar relative reductions in the risk of cardiovascular death or hospitalization, regardless of age.[1,54] ARBs seem to be better tolerated than ACEIs.[55-57] The ELITE II trial compared losartan (an ARB) and captopril (an ACEI) in older patients (mean age, 71 years) with an LVEF of 40% or less, and showed that the two drugs were equally effective in improving survival, but losartan was better tolerated.[56]

The benefit of blocking the RAAS does not end with the ACEIs and ARBs. The mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone also provide an increased benefit in the elderly patients with HF. The Randomized Aldactone Evaluation Study (RALES) demonstrated a 30% reduction in mortality when spironolactone was added to standard-of-care treatment in patients with severe HF.[48] Following the publication of results from RALES, there was a significant increase in the use of spironolactone in older patients, with a corresponding increase in hyperkalemia and hyperkalemia-related hospitalizations and deaths.[58,59] The EMPHASIS HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial showed that eplerenone decreased the risk of cardiovascular death and hospitalization even in patients with mild, New York Heart Association (NYHA) class II HF, and these benefits remained in subgroups of older patients.[50] However, in the older patients and in those with CKD, there was a noted increase in the incidence of moderate hyperkalemia (serum K^+ level >5.5 mEq/L).[60]

The American Heart Association (AHA) guidelines for the management of HF recommend using an ACEI or ARB with a beta-blocker in patients with HFrEF.[61,62] If the patient remains NYHA class II or greater, provided that eGFR is greater than 30 mL/min/1.73 m^2 and serum K^+ level is less than 5.0 mEq/L, it is further recommended to add an MRA to the treatment regimen.[61,62] The guidelines of the European Society of Cardiology (ESC) also recommend prescribing an ACEI or ARB, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.[63] An MRA is recommended for patients with HFrEF who remain symptomatic.[63]

Recently, the AHA and the Heart Failure Society of America developed specific guidelines for the management of HF in SNFs. These guidelines, similarly, recommend ACEIs, ARBs, and MRAs as preferred therapy in patients with HFrEF, in addition to restricting sodium to achieve euvolemia (**Table 1**[44]).[44] In all guidelines, caution is advised when prescribing these therapies in patients with low blood pressure, increased serum creatinine, or elevated serum K^+.[44,61-63] Current guidelines recommend RAASI dose modifications with increasing serum K^+ levels. The most recent 2016 ESC guidelines recommend a short-term cessation of K^+-retaining agents and RAASIs to manage severe hyperkalemia (serum K^+ level >6.0 mEq/L).[63] However, this should be minimized and the RAASI therapy should be carefully reintroduced as soon as possible to resume its beneficial effects.[63]

Treatments for Acute Hyperkalemia

Treatment strategies for acute hyperkalemia are designed to prevent or minimize the adverse electrophysiological effects on the heart and remove the patient from immediate danger.[64] These include intravenous administration of calcium to restore the resting membrane potential of cardiac cells when electrocardiographic changes are present, and pharmacologic treatments such as insulin and beta-adrenergic agonists that shift K^+ to the intracellular space.[64] The effect of these agents can be observed within 30 minutes, but they do not decrease total body K^+, thus necessitating the removal of K^+ through other nonacute approaches. These approaches include dialysis, increased renal excretion through forced diuresis, and increasing the gastrointestinal (GI) removal with short-term use of a K^+-binding agent. These measures are useful emergency and in-hospital therapies for acute hyperkalemia, but are unsuitable for the chronic hyperkalemia that is typically seen in patients with CKD and/or HF who are on RAASIs.

Management of Chronic Hyperkalemia

The strategy to manage chronic hyperkalemia in the elderly is fundamentally different from the strategy for acute hyperkalemia. The management of chronic hyperkalemia usually begins with the elimination of any potential causes, including high dietary K^+ and medications such as nonsteroidal anti-inflammatory drugs and RAASIs.[3] Other interventions include dietary education, a thorough review of prescribed and other medications, and alkali replacement, if acidotic.[3] Unfortunately, the class of medication most associated with hyperkalemia—RAASIs—is also the most beneficial to patients with CKD and HF.

Treatment guidelines for the management of CKD and HF outline the importance of RAAS inhibition in these patient populations

TABLE 1. Medical Management of HF in Long-Term[a] SNF Residents[44]

Intervention	Recommendation
Assessment of LVEF	Preferable, needs to be individualized
Sodium restriction to achieve euvolemia	Preferable, needs to be individualized
Diuretic agents to achieve euvolemia	Yes
ACEI/ARB	Yes for HFrEF, low dose preferable, avoid low SBP
Beta-Blocker[b]	Yes for HFrEF, as tolerated by BP, HR, and fatigue
MRA	Yes for HFrEF NYHA class II–IV[c] and in NYHA class III with IHD; avoid in those with eGFR <30 mL/min/1.73 m^2
Hydralazine-nitrates (and in patients with contraindications or intolerance to an ACEI/ARB)	Yes for HFrEF in self-identified black patients, only if already receiving an ACEI or ARB, a beta-blocker, and an MRA or if they have contraindications
Digoxin	Yes for HFrEF, only if symptomatic despite treatment with an ACEI or ARB, a beta-blocker, and an MRA; low dose (≤0.125 mg/d)
Implantable cardioverter defibrillator	Not indicated
Cardiac resynchronization therapy	Not indicated
Left ventricular assist device	No
Identify preferences for end of life	Yes
Assess and treat symptoms of HF	Yes

[a]Residents who are expected to remain in a SNF until death.
[b]Carvedilol, metoprolol succinate extended release, and bisoprolol are the only evidence-based, guideline-recommended beta-blockers for systolic HF. If patients are taking other beta-blockers, they should be converted to 1 of the 3 listed above. Data support improved function and reduced HF symptoms with these drugs in the long run, but there are no data for patients with HF who are ≥80 years of age or living in SNFs.
[c]NYHA class improved for 40% in RALES (Randomized Aldactone Evaluation Study). Only 20% of real-world octogenarians with HF (eg, patients seen in routine clinical practice) would have been eligible to participate in RALES; 59% of RALES patients were ≥65 years old, 9% were 80-90 years old, none were ≥91 years old, and none were from SNFs.
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; SNF, skilled nursing facility.
Adapted with permission from Jurgens CY, Goodlin S, Dolansky M, et al. *J Card Fail*. 2015;21(4):263-299.

and provide some guidance on managing hyperkalemia when it develops.[26,28,61,62] There is an urgent need to update the guidelines, as the current guidelines were written prior to the advent of newer K^+ binders that can be taken on a daily basis. In the past, chronic hyperkalemia in patients with CKD and/or HF was typically managed by reducing or discontinuing RAASIs. The following sections review the standard approaches to hyperkalemia management, and newly approved and investigational therapies for the daily management of hyperkalemia.

Potassium-Restricted Diet

A K^+-restricted diet is often recommended[28] but is not a long-term and effective therapeutic approach to chronic hyperkalemia management. The dietary approach is difficult to comply with and may adversely affect nutrition in patients who may benefit the most from a healthy diet, such as the Dietary Approaches to Stop Hypertension diet.[65] Moreover, the clinical utility of this approach has not been tested in randomized controlled trials.[66]

Diuretics

Although loop and/or thiazide diuretics have long been used to treat hyperkalemia, and may be a feasible choice in some patients with CKD, use of these agents may not be possible or may be inappropriate in others.[32,66-68] Factors such as extracellular volume, distal delivery of sodium, and kidney function may play a role in the effectiveness of diuretic-induced K^+ excretion but are impaired in patients with advanced CKD and/or HF.[32,69-71] In addition, a high dose or combination of diuretics may cause adverse effects such as volume depletion and gout.[72,73] Diuretics may be overused in the elderly[74] and contribute to adverse effects and drug-drug interactions in this patient population.[75,76]

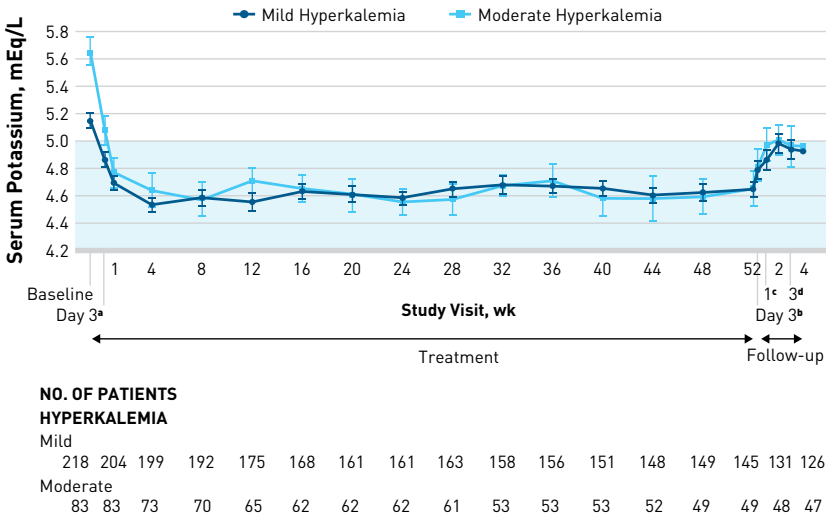
Potassium Binders

Until recently, the only available treatment option specifically indicated for hyperkalemia in the United States was sodium polystyrene sulfonate (SPS).[77] Although SPS was developed more than 50 years ago, it lacks sufficient clinical trial data with appropriate controls and its efficacy has not been rigorously evaluated.[78-80] A short-term (7 days) and small placebo-controlled study (n = 33) assessed the efficacy and safety of SPS in treating mild-to-moderate hyperkalemia (serum K^+ level 5.0-5.9 mEq/L) in outpatients with CKD.[81] Treatment with SPS resulted in a significantly greater reduction in serum K^+ level compared with placebo, but the percentage of patients achieving normokalemia at the end of treatment was similar in the 2 groups.[81] The rates of electrolyte disturbances and

GI adverse events (AEs) were higher in the SPS group, but the small sample size precluded broad conclusions.

A prominent concern about the safety of SPS appears in its prescribing information, which includes a warning for the infrequent but potentially fatal AE of intestinal necrosis.[77,82,83] A systematic review of biomedical databases identified 58 cases of severe GI AEs associated with SPS use in 30 reports; these included 36 (62%) cases of intestinal necrosis and 5 (9%) cases of perforation.[83] Necrosis was reported with the use of SPS given both with and without sorbitol. Additionally, death due to GI injury was reported in 33% of these cases.[83] The prescribing information further warns to reserve the use of SPS for patients who have normal bowel function and to avoid use in patients who are at risk of developing constipation or impaction. Another important concern is the presence of sodium as the counter-exchange ion in SPS, which may contribute to volume overload in patients who cannot tolerate even a small increase in sodium load, such as those with severe HF or hypertension.[65]

FIGURE 1. Least Squares Mean (95% CI) Serum Potassium Levels Over 52 Weeks and During Posttreatment Follow-Up in Patients With Mild or Moderate Hyperkalemia (Post Hoc Mixed-Effects Models for Repeated-Measures Analysis)[91]



All serum potassium analyses are based on central laboratory values; 3 patients (2 with mild hyperkalemia [potassium concentration >5.0-5.5 mEq/L] and 1 with moderate hyperkalemia [potassium concentration >5.5 to <6.0 mEq/L]) did not have a central laboratory serum potassium value at baseline and therefore are not included in the analysis at this time point. At all points, $P<.001$ (2-sided t test) for least squares mean changes from baseline and week 52 (or from last dose of patiromer received during the study). Least squares means and their 95% CIs are based on a mixed-effects repeated-measures model with central laboratory serum potassium value as the dependent variable, timepoint and starting dose as fixed-effect predictors, baseline central laboratory serum potassium value as a continuous covariate, and patient as a random effect. An unstructured correlation matrix was fit. Least squares means and their 95% CIs for the follow-up period are based on the same model above, while the baseline covariate used was the last potassium value before study termination. Tinted region indicates serum potassium reference range.

[a]At treatment day 3, there were 202 patients with mild hyperkalemia and 82 with moderate hyperkalemia.
[b]At follow-up day 3, there were 163 patients with mild hyperkalemia and 58 with moderate hyperkalemia.
[c]At follow-up week 1, there were 154 patients with mild hyperkalemia and 57 with moderate hyperkalemia.
[d]At follow-up week 3, there were 126 patients with mild hyperkalemia and 48 with moderate hyperkalemia.
Reprinted with permission from Bakris GL, Pitt B, Weir MR, et al. *JAMA*. 2015;314(2):151-161.

Newly Approved and Investigational K^+ Binders

Patiromer

Patiromer is a K^+-binding polymer approved by the FDA to treat hyperkalemia with a once-daily dosing regimen.[84] Patiromer exchanges K^+ for calcium and promotes fecal excretion of K^+ in a dose-dependent manner, leading to a concordant reduction in serum K^+ level.[85-87] The exchange occurs throughout the gut, but predominantly in the colon where the K^+ concentration is high and pH is optimal for exchange.[87] Animal studies using the radiolabeled drug have shown that patiromer is not absorbed into the systemic circulation.[87] A rigorously designed study of patients with CKD admitted to a clinical research unit showed that a single dose of patiromer reduces serum K^+ level significantly within 7 hours following administration.[88] Patiromer is administered as a powder mixed with 1/3 cup of water.[84]

Patiromer uses calcium rather than sodium as the counter-exchange ion to bind K^+, thus avoiding sodium overload.[84,87,89] The calcium released from K^+ binding with patiromer has the potential to be absorbed or to bind to phosphate. In healthy volunteers, a total daily dose of patiromer 25.2 g (the maximum recommended dose) led to an increase in urine calcium of 73 mg/d and a decrease in urine phosphate of 64 mg/d.[90] These data suggest that only a small fraction of calcium released from patiromer is available for absorption and some binds to intestinal phosphate.

Clinical Efficacy of Patiromer in the Treatment of Hyperkalemia

In a multicenter, open-label, randomized, 52-week study (AMETHYST-DN), patiromer was shown to significantly reduce the serum K^+ level in hyperkalemic patients with diabetic nephropathy and hypertension with or without HF who were taking RAASIs (**Figure 1**[91]).[91] Daily administration of patiromer resulted in the reduction of mean serum K^+ to normokalemic levels (<5.0 mEq/L) in approximately 48 hours for patients with mild hyperkalemia and in one week for patients with moderate hyperkalemia. Serum K^+ level was significantly decreased at week 4 and remained in the target range (3.8–5.0 mEq/L) through week 52.

OPAL-HK was a multicenter, single-blind, randomized study that comprised 2 phases: a 4-week, single-group initial treatment

phase and an 8-week, placebo-controlled, randomized withdrawal phase.[86] In the treatment phase, hyperkalemic patients with CKD who were on a stable dose of RAASI therapy were treated with patiromer. This resulted in a significant decrease in mean serum K^+ level from baseline to week 4. In the randomized withdrawal phase, the median serum K^+ level remained unaltered from the start of the withdrawal phase to week 4 in patients who continued taking patiromer, whereas it increased by 0.72 mEq/L in patients who switched to placebo. By week 8 of the withdrawal phase, a significantly higher proportion of patients given placebo had at least one event of recurrent hyperkalemia compared with those given patiromer. Of note, a significantly higher proportion of patients who received patiromer (94%) remained on RAASI therapy compared with those who received placebo (44%).[86] Similar findings were observed in a prespecified analysis of the subgroup of patients with HF in OPAL-HK, with 100% of patients with HF taking patiromer still receiving RAASI therapy at the end of the randomized withdrawal phase, compared with 55% of patients taking placebo.[89]

Safety and Tolerability of Patiromer in the Treatment of Hyperkalemia

In OPAL-HK, patiromer was reported to be generally safe and well tolerated, with 47% of patients reporting at least one AE during the initial patiromer treatment phase, and 47% of the patients who continued taking patiromer and 50% of those who switched to placebo reporting at least one AE during the withdrawal phase.[86] Serious AEs—none determined by the investigators to be related to patiromer—were reported in 1% of patients during the treatment phase and in 2% of patients given placebo and none given patiromer during the withdrawal phase.[86] In the AMETHYST-DN study, the most common AEs over 52 weeks of patiromer treatment were worsening of CKD (9%; none related to patiromer), hypomagnesemia (9%; related to patiromer, 7%), worsening of hypertension (8%; related to patiromer, 0.3%), constipation (6%; related to patiromer, 5%), and diarrhea (6%; related to patiromer, 3%).[91] None of the patients developed severe hypomagnesemia (serum magnesium level <1.0 mg/dL) and none had cardiac arrhythmias or neuromuscular abnormalities temporally associated with hypomagnesemia.[91]

To assess safety and tolerability in patients (n = 666) treated with patiromer across all clinical studies, an integrated safety analysis was conducted.[65] The results were generally consistent with those from OPAL-HK and AMETHYST-DN. Of the 666 patients, 219 (32.9%) received patiromer daily for at least 6 months and 149 (22.4%) for at least one year. Patiromer was generally well tolerated in these patients, including those with CKD, HF, and/or diabetes. The majority of AEs were mild or moderate. The most common individual AEs that resulted in discontinuation of patiromer were GI-related (2.7%), including vomiting (0.8%), diarrhea (0.6%), flatulence (0.5%), and constipation (0.5%). Based on prespecified laboratory criteria, hypokalemia (serum K^+ level <3.5 mEq/L) occurred in 4.7% of patients; no patient developed a serum K^+ level less than 3.0 mEq/L.[65] A serum magnesium level less than 1.2 mg/dL was reported in 2.0% of patients; no patient developed a serum magnesium level less than 1.0 mg/dL. There were no patiromer-related serious AEs or deaths in any of the trials.[65,86,88,91] There were no clinically meaningful changes in renal function or mean serum electrolyte (calcium, sodium, magnesium, phosphate) levels.[65]

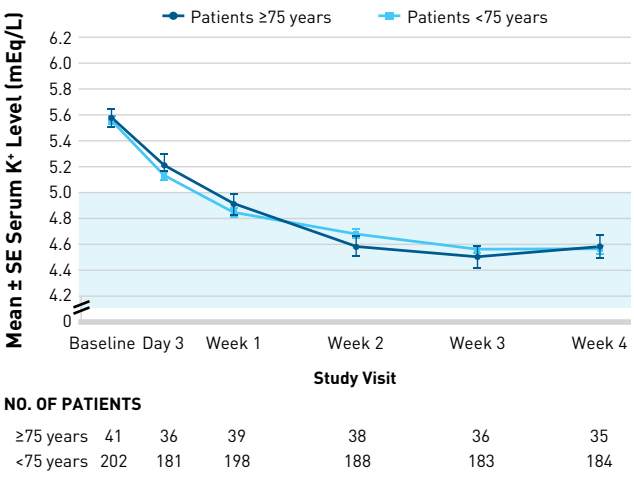
Patiromer is not systemically absorbed[87]; therefore, the potential for drug-drug interactions related to effects on cytochrome P450 isoenzymes or systemic drug transporters is not a clinical concern when patiromer is coadministered with other drugs. Recently, in a series of in vivo studies in healthy volunteers, patiromer was evaluated for potential drug-drug interactions with 12 drugs administered at the same time as patiromer or 3 hours apart. The 12 drugs were selected based on results of in vitro tests, in which patiromer had demonstrated potentially clinically relevant binding in 14 of 28 drugs.[84] Results from the phase one studies revealed that no reduction in absorption was observed for any of the 12 drugs tested with a 3-hour dose separation from patiromer. Based on these study results, the FDA recently approved a supplemental New Drug Application for patiromer with important updates to the prescribing information, which no longer includes a boxed warning regarding the separation of patiromer and other oral medications, and recommends that patients take patiromer at least 3 hours before or 3 hours after other oral medications.[84]

Efficacy and Safety of Patiromer in Elderly Patients

An additional post hoc analysis of 41 patients at least 75 years of age from the OPAL-HK study assessed the same end points as in the primary study.[86] Treatment with patiromer resulted in a mean (standard error [SE]) decrease in serum K^+ level of −0.99 (0.10) mEq/L (95% CI, −1.19 to −0.80; P <.001) from baseline to week 4 of the initial treatment phase. **Figure 2** shows mean serum K^+ level during the initial treatment phase for patients 75 years and older and those less than 75 years of age. In the randomized withdrawal phase, serum K^+ level was essentially unchanged from the start of the phase to week 4 in patients aged 75 years and older who remained on patiromer (median change [quartiles], −0.10 [−0.3, 0.3] mEq/L), whereas it increased considerably (0.60 [0.40, 1.10]) in patients who were switched to placebo; the difference in the median change between the groups (0.70; 95% CI, 0.06-1.34) was signficant (P <.001) (**Figure 3**). The results were generally similar in patients less than 75 years of age (Figure 3).

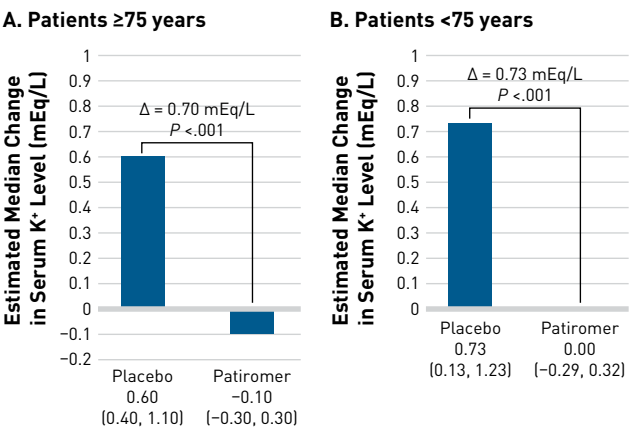
Treatment with patiromer was generally safe and well tolerated in patients 75 years and older and those less than 75 years of age. **Table 2** summarizes the safety parameters during the initial treatment phase. A total of 46% of patients 75 years and older and 47% of those less than 75 years of age had at least one AE. Mild-to-moderate constipation was the most common AE and it was the most common patiromer-related AE in these patients (Table 2). AEs led to study

FIGURE 2. Mean ± Standard Error Serum Potassium Level in Patients Aged ≥75 Years and <75 Years During Initial Treatment Phase of OPAL-HK



K+ indicates potassium; SE, standard error.

FIGURE 3. Median Change in Serum Potassium Level From Start to Week 4 of Randomized Withdrawal Phase of OPAL-HK in Patients Aged ≥75 Years (A) and <75 Years (B) Who Were Given Placebo Versus Patiromer



K+ indicates potassium.

discontinuation in 10% of patients 75 years and older and in 5% of those less than 75 years of age. Serious AEs—none considered to be related to patiromer—occurred in 2% of patients 75 years and older and 1% of those less than 75 years of age. Hypokalemia (predefined as a serum K^+ level <3.5 mEq/L) occurred in 8% of patients 75 years and older and in 2% of those less than 75 years of age (Table 2).

Zirconium Cyclosilicate

Sodium zirconium cyclosilicate (ZS-9) is an inorganic cation-exchange crystal currently undergoing clinical evaluation as a potential treatment for hyperkalemia. It is an orally administered compound composed of zirconium and silicate that exchanges sodium and hydrogen for K^+ and ammonium as it moves through the GI tract.[92-94] Based on recovery of zirconium in feces of ZS-9-treated rats, the drug appears to not be systemically absorbed.[93] The silicate compound is administered as a powder mixed in 240 mL (approximately one cup) of water with each dose.[95]

Clinical Efficacy, Safety, and Tolerability of ZS-9 in the Treatment of Hyperkalemia

In randomized, double-blind, placebo-controlled trials, ZS-9 was effective in reducing serum K^+ levels in hyperkalemic patients with CKD, HF, and/or diabetes.[94,95] Starting doses in clinical trials ranged from 0.3 to 10 g three times daily (TID), with maintenance doses between 1.25 and 15 g once daily.[93-95] In the phase 3 study by Packham and colleagues,[94] 754 patients with a serum K^+ level of 5.0 to 6.5 mEq/L at baseline were treated with 1.25 to 10 g of ZS-9 TID or placebo for 48 hours; those achieving serum K^+ level between 3.5 and 4.9 mEq/L were then randomized to receive ZS-9 1.25 to 10 g once daily or placebo from day 3 through day 14. The primary end point (exponential rate of change in serum K^+ level during the first 48 hours) showed reductions of 0.11% to 0.30% per hour across ZS-9 dose groups versus 0.09% per hour for placebo (P <.001 for the comparison with the 3 highest dose groups). During the maintenance phase, the 5 g and 10 g doses were significantly better than placebo at maintaining normal K^+ levels.

In a phase 3 study evaluating the safety and efficacy of ZS-9 for 4 weeks in outpatients with hyperkalemia (serum K^+ level ≥5.1 mEq/L), 258 patients received 10 g of ZS-9 TID for 2 days.[95] Those achieving normokalemia (n = 237) were then randomized to ZS-9 (5, 10, or 15 g) or placebo once daily for 28 days.[95] The primary end point (mean K^+ level in each dose group vs placebo during days 8-29) was met, with significantly lower serum K^+ levels in all 3 dose groups (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [4.4-4.6], and 4.4 mEq/L [4.3-4.5] for 5 g, 10 g, and 15 g doses, respectively, vs 5.1 mEq/L [5.0-5.2] for placebo; P <.001 for all comparisons; **Figure 4**[95]).[95]

Studies reported in the literature to date have followed patients for up to 28 days of maintenance therapy with ZS-9,[93-95] although a recent congress abstract reported data in 421 patients treated with ZS-9 for up to 24 weeks and 149 patients treated for up to 52 weeks in the open-label extension phase of the 28-day maintenance study.[96] Mean serum K^+ level was 4.7 mEq/L for patients treated for at least 24 weeks, and 89% of patients had a mean serum K^+ level of 5.1 mEq/L or less between week 12 and week 52.[96]

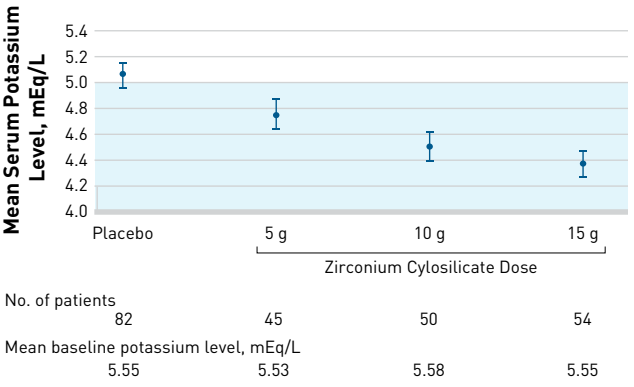
Regarding the safety and tolerability of ZS-9, in the 28-day maintenance phase of the study by Kosiborod and colleagues, 45% to 53% of patients given ZS-9 reported at least 1 AE versus 32% of patients given placebo.[95] Edema was the most common AE with ZS-9,

TABLE 2. Safety Summary During Initial Treatment Phase of OPAL-HK

Parameter	≥75 years	<75 years
Adverse Event, n (%)	**n = 41**	**n = 202**
At least 1 AE	19 (46.3)	95 (47.0)
Most common AEs[a]		
Constipation	8 (19.5)	18 (8.9)
Anorexia	3 (7.3)	0
Diarrhea	2 (4.9)	6 (3.0)
Nausea	2 (4.9)	6 (3.0)
Hypomagnesemia	2 (4.9)	6 (3.0)
Anemia	2 (4.9)	5 (2.5)
Hypokalemia	2 (4.9)	1 (0.5)
Pruritus	2 (4.9)	1 (0.5)
Renal failure, chronic	0	7 (3.5)
Most common patiromer-related AEs[a]		
At least 1 patiromer-related AE	14 (34.1)	39 (19.3)
Constipation	8 (19.5)	16 (7.9)
Diarrhea	2 (4.9)	5 (2.5)
Hypomagnesemia	2 (4.9)	5 (2.5)
Hypokalemia	2 (4.9)	1 (0.5)
Anorexia	2 (4.9)	0
AEs leading to discontinuation	4 (9.8)	11 (5.4)
At least 1 serious AE	1 (2.4)	2 (1.0)
Prespecified laboratory values of interest	**n = 39[b]**	**n = 198[b]**
Serum Mg^{2+} level <1.4 mg/dL[c]	1 (2.6)	7 (3.0)
Serum K^+ level <3.5 mEq/L	3 (7.7)	4 (2.0)

[a]Occurring in >3% of patients in any subgroup; presented in descending order of incidence.
[b]Patients with at least 1 postbaseline serum Mg^{2+}/K^+ result.
[c]No patient had serum Mg^{2+} level <1.2 mg/dL.
AE indicates adverse event; K^+, potassium; Mg^{2+}, magnesium.

FIGURE 4. Serum Potassium Levels During the Randomized Phase (Days 8-29) According to Study Group[95]



The primary end point was the mean serum potassium level over days 8 to 29 of the randomized phase in which patients received placebo or 1 of 3 doses of zirconium cyclosilicate (5 g, 10 g, or 15 g). Error bars indicate 95% CI; the shaded region, normal potassium range.
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with rates increasing with dose (2.2% with 5 g, 5.9% with 10 g, and 14.3% with 15 g).[95] Hypokalemia was observed in 10.7% of patients treated with 15 g ZS-9. Across all patients given ZS-9 in the long-term extension, AEs of worsening of hypertension were reported in 8.2%, peripheral edema in 7.6%, and constipation in 5.0%.[96]

The New Drug Application for ZS-9 was first submitted to the FDA in May 2015 and resubmitted in 2016.[97,98] An FDA response to the resubmission is expected in the first half of 2017.

Effects of New K^+ Binders on Serum Aldosterone and Blood Pressure

While K^+ contributes to regulation of aldosterone synthesis and secretion,[99] the relationship between serum K^+ levels and aldosterone response is complex.[100] In a prespecified exploratory analysis of OPAL-HK, it was reported that mean serum aldosterone levels decreased significantly (−1.99 ± 0.51 [SE] ng/dL; P = .0001) and concordantly with serum K^+ levels in the intital patiromer treatment phase.[101] In the randomized withdrawal phase, the initial decrease in aldosterone levels was sustained (+0.23 ± 1.07 ng/dL) in patients continuing with patiromer, whereas levels increased significantly (+2.78 ± 1.25 ng/dL; $P \leq .03$) in those given placebo.[101] Because aldosterone activates mineralocorticoid receptors, the decreased aldosterone levels associated with patiromer treatment could represent an additional benefit of the drug.[101]

With regard to blood pressure, in OPAL-HK, mean systolic and diastolic blood pressures decreased significantly in the initial treatment phase, and during the randomized withdrawal phase in patients receiving patiromer.[101] Although AMETHYST-DN was not designed to study the effect of patiromer on blood pressure, mean systolic and diastolic blood pressures decreased considerably.[91] The reductions in blood pressure were observed at day 3 (first postbaseline visit) and continued through week 52 of treatment.[91] Data presented in an abstract suggest that ZS-9 does not produce any clinically meaningful changes in blood pressure,[102] although other preliminary data suggest that ZS-9 is associated with a reduction in aldosterone levels.[103]

Conclusion

Elderly patients in the long-term care setting characteristically have several disease states and take multiple medications. These patients typically have long-standing hypertension, reduced renal function, and/or HF that puts them at a much greater risk for medication-induced changes in potassium homeostasis. The overactivity of the RAAS plays a major role in the development of

end-organ damage and these chronic conditions, so it is logical to target this system. Over the years, the use of RAASIs has been shown to improve clinical outcomes in patients with hypertension, CKD with or without diabetes, and HF, but these benefits come with the risk of hyperkalemia. Physicians practicing in the long-term care setting may be reluctant to add or increase the dose of a guideline-recommended RAASIs because of this risk.

New therapies for the treatment of hyperkalemia will provide clinicians with more options to address this potentially life-threatening electrolyte abnormality. Beyond the treatment of hyperkalemia, these agents may also enable more patients to be maintained on or add guideline-recommended RAASI therapy. New K^+ binders could also be appropriate for the older patients with stage 5 CKD who may not be suitable for or refuse dialysis.[16,18,19] Hyperkalemia is and continues to be a challenging clinical problem in the elderly patient. A much-needed paradigm shift from the periodic management of hyperkalemia to preventative measures aimed at avoiding these episodes and enabling the continued use of standard of care medications seems to be in sight. ■

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