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Focus on Hyperkalemia Management: Expert Consensus and Economic Impacts

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Table of Contents

Focus on Hyperkalemia Management: Expert Consensus and Economic Impacts

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Disclosures

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Clinical and Economic Impact of Hyperkalemia in Patients with Chronic Kidney Disease and Heart Failure

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ABSTRACT

BACKGROUND: Hyperkalemia (HK) is a concern for patients with chronic kidney disease (CKD) and heart failure (HF), and for those receiving treatments that inhibit the renin-angiotensin-aldosterone system (RAASi). An analysis of 1.7 million medical records of patients in the United States revealed that among individuals with more than 2 potassium values during 2007 to 2012, HK was detected in 34.6% of patients with CKD and 30.0% of patients with HF.

OBJECTIVE: To evaluate the association of HK and use of RAASi therapies at optimal and suboptimal doses in patients with CKD and/or HF with health care resource utilization and overall cost of care in a diverse cohort of commercially insured patients.

METHODS: This retrospective cohort study was conducted using medical and pharmacy claims from multiple regional health plans. Qualifying patients were ≥18 years old, continuously enrolled for 6 months before and throughout the study period (January 1, 2014, to December 31, 2015) and had an ICD-9-CM or ICD-10-CM diagnosis code of CKD and/or HF. Health care resource utilization, including hospital visits, length of stay, office visits, and associated medical and pharmacy costs, were assessed according to the 3 cohorts (CKD alone, HF alone, and concomitant CKD and HF). For the 3 cohorts, the results were also compared between patients with and without HK and between patients with and without RAASi use at optimal and suboptimal doses. Generalized linear models were used to further examine the predictors of medical and overall costs.

RESULTS: In this study, 15,999 patients met inclusion criteria. Among patients using RAASi therapy, 26.8% received the optimal dose. Optimal dosing of RAASi was associated with decreased median outpatient office visits (8, 10, and 15, respectively, for patients with CKD, HF, and both CKD and HF) compared with suboptimal dosing of RAASi (12, 15, and 23, respectively). Similarly, optimal dosing of RAASi was associated with decreased overall median medical costs ($2,092, $4,144, and $7,762, respectively, for patients with CKD, HF, and both CKD and HF) compared with suboptimal dosing of RAASi ($3,121, $8,289, and $12,749, respectively). Patients with CKD, HF, or both CKD and HF, all in combination with HK, had higher overall costs, compared with those without HK.

CONCLUSIONS: The results of this real-world analysis suggest that HK and suboptimal dosing of RAASI were associated with a median increase in outpatient office visits as well as increased overall medical costs among patients with CKD and/or HF. This evaluation of median costs suggests effective HK management may potentially reduce costs in patients with CKD and/or HF, including those currently receiving RAASi therapy.

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What is already known about this subject

- Hyperkalemia (HK) may result from various chronic conditions, particularly chronic kidney disease (CKD) and heart failure (HF).
- Renin-angiotensin-aldosterone system inhibitors play a key role in managing patients with CKD and HF but present a challenge in managing those patients with a predisposition to HK.

What this study adds

- This study evaluated the clinical and economic impact of HK on patients with CKD and/or HF.
- The findings highlight the opportunity for cost savings and clinical care improvement in effectively managing HK in this patient population.

Hyperkalemia (HK), which is typically defined as a serum potassium concentration greater than 5.2 millimoles per liter (mmol/L), is a serious medical condition that, left untreated, can lead to life-threatening conditions. HK may result from various acute and chronic conditions that affect potassium renal excretion and commonly occurs among patients with chronic kidney disease (CKD) and other comorbidities such as heart failure (HF), diabetes mellitus (DM), and hypertension.[1,2] Among individuals with more than 2 documented potassium values during 2007 to 2012, HK was detected in 34.6% of patients with CKD and 30.0% of patients with HF.[3] Additionally, a retrospective study that evaluated the 5-year prevalence of HK in an estimated 1.7 million patients revealed that 47.6% of patients with concomitant stage 3 to 4 CKD and HF had at least 1 medical record of HK compared with 8.5% of patients without CKD or additional comorbidities.[4] Of note, due to the progressive nature of CKD, patients who have CKD with or without comorbidities are at risk for recurrent HK.[4]

The renin-angiotensin-aldosterone system (RAAS) plays a critical role in the pathophysiology of CKD and HF.[3,5] Patients are treated with angiotensin-converting enzyme (ACE) inhibitors as a first-line approach to therapy, with angiotensin II receptor blockers (ARBs) used either in conjunction with ACE inhibitors or as an alternative to ACE inhibitors in certain patient populations.[1,5,6] Treatment guidelines recommend that RAAS inhibitor (RAASi) agents be titrated up to moderate to high doses in order for patients to derive optimal treatment benefits.[6] RAASi therapies are crucial to managing individuals with CKD and/or HF; however, these therapies may also present a challenge in managing patients with a predisposition to HK due to their mechanisms of action, which may contribute to elevated serum potassium levels.[6]

Regional length of stay (LOS) and cost differences for HK admissions were examined using discharge data from the National Inpatient Sample, Healthcare Cost and Utilization Project, from the Agency for Healthcare Research and Quality. These data indicated that in 2014, there was an estimated $1.2 billion in total annual hospital charges for patients admitted with a primary diagnosis of HK, with an average LOS of 3.3 days and mean charges of $29,181 per stay.[7] Collectively, these factors speak to the potential clinical and economic value of HK management in individuals with HF and/or CKD.

The objective of this retrospective study was to evaluate the impact of HK and use of RAASi therapies at optimal and suboptimal doses in patients with CKD and/or HF on health care resource utilization and overall cost of care in a diverse cohort of commercially insured patients.

Methods

Study Design and Data Sources

This retrospective study examined medical and pharmacy claims data from multiple regional health plans in a real-world cohort of patients with CKD and/or HF and determined the extent of concomitant HK and use of RAASi therapies and their impact on LOS and total costs of care for this population. In particular, the factors evaluated included demographics, comorbidities (Charlson Comorbidity Index [CCI]), medical utilization, medical costs, pharmacy utilization, and pharmacy costs.

Study Population Selection

Patients were included in this study if they were ≥ 18 years of age at index date and had continuous enrollment for 6 months before the study period for baseline assessment and throughout the study period. Patients in this analysis were required to have a diagnosis of CKD and/or HF with > 1 claim of a qualifying *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or ICD-10-CM (*Tenth Revision*) diagnosis code (Appendix A). Patients were excluded from the study if they did not meet all the inclusion criteria. The study period for this analysis spanned January 1, 2014, to December 31, 2015.

For patients with CKD and/or HF without diagnosis codes indicative of HK, pharmacy claims were reviewed. Pharmacy claims records were also evaluated for all patients with a diagnosis code of HF and/or CKD for whom a prescription for RAASi therapy was documented and for whom a prescription for RAASi therapy was not documented. RAASi therapy was identified using the First Databank's hierarchical ingredient code list sequence number (Appendix B).

Patients must have been eligible for both medical and pharmacy benefits throughout the study and comorbidity assessment baseline periods. The sample size for this study was limited to the number of members within the health plan databases meeting the inclusion criteria.

Study Measures

The primary objective of this study was to evaluate and compare the medical and pharmacy costs and utilization for patients with and without HK in each of the 3 cohorts (CKD alone, HF alone, and both CKD and HF). In the categories of patients with and without HK, comparisons were made between patients who were using RAASi therapy and those who were not, and further comparisons were made between patients receiving an optimal dose and a suboptimal dose (Appendix B).

Patients were categorized as receiving optimal dosing if they were receiving the maximum U.S. Food and Drug Administration (FDA)-recommended dose, whereas patients who were receiving any dose below that were categorized as receiving suboptimal dosing. This categorization is based on findings by Epstein et al. (2015), which note that "patients on maximum doses of RAAS inhibitor therapies experienced fewer cardiorenal adverse outcomes or mortality compared with patients on submaximum doses or who discontinued RAAS inhibitors."[6]

Patient characteristics that were measured included age, gender, and CCI. The CCI score was calculated by identifying comorbidities in the 6 months before the study period began.

Statistical Analysis

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC). Means, standard deviations (SDs), and medians were reported for continuous variables, and frequencies (percentages) were reported for categorical variables. The relationship between age, gender, CCI, HK, RAASi dosing level (optimal vs. suboptimal), and medical as well as overall total costs were estimated using generalized linear models in each cohort. The assumption of this study was similar to that of other health care cost studies that assume that the distribution of the cost data is skewed.[8] Therefore, gamma regression with a log-link function was chosen to best estimate the parameters, as it allows for violations of homoscedasticity.

Results

Patient Characteristics

In this study population of 15,999 patients, 46.8% were female, and there was a median age of 72 years across all cohorts. Among patients included in the study population, 34.5% had a CCI of zero while 23.3% had a CCI of 3 or more. Table 1 displays patient baseline characteristics measured and segmented into the study cohorts.

Medical and Pharmacy Utilization and Cost

The use of RAASi was observed in 44.8% of the CKD group, 42.2% in the HF group, and 41.2% in patients with both CKD and HF. Optimal dosing of RAASi in the 3 groups was

TABLE 1 Patient Baseline Characteristics

Characteristics		CKD Patients		HF Patients		Patients with CKD and HF	
		RAASi Patients n = 2,774	No RAASi n = 3,423	RAASi Patients n = 3,426	No RAASi n = 4,699	RAASi Patients n = 691	No RAASi n = 986
Age, years n (%)	Mean (SD) [median]	69.3 (12.7) [71.0]	68.9 (13.4) [70.0]	69.5 (13.4) [71.0]	69.5 (14.8) [71.0]	73.7 (11.5) [76.0]	74.1 (11.5) [75.0]
	18-19	0	3 (0.1)	2 (0.1)	13 (0.0)	0	0
	20-29	13 (0.5)	19 (0.6)	8 (0.2)	46 (0.1)	2 (0.3)	0
	30-39	43 (1.6)	64 (1.9)	45 (1.3)	73 (1.6)	0	5 (0.5)
	40-49	148 (5.3)	200 (5.9)	178 (5.2)	214 (4.6)	19 (2.8)	26 (2.6)
	50-59	411 (14.8)	526 (15.4)	598 (17.5)	868 (16.7)	78 (11.3)	80 (8.1)
	60-69	691 (24.9)	828 (24.2)	777 (22.7)	947 (20.2)	135 (19.5)	176 (17.9)
	70-79	845 (30.5)	943 (27.5)	887 (25.9)	1,169 (24.9)	223 (32.3)	342 (34.7)
	80+	623 (22.5)	840 (24.6)	931 (27.2)	1,369 (29.1)	234 (33.9)	357 (36.2)
Gender n (%)	Female	1,300 (46.9)	1,580 (46.2)	1,498 (43.7)	2,405 (51.2)	298 (43.1)	413 (41.9)
	Male	1,474 (53.1)	1,843 (53.8)	1,928 (56.3)	2,294 (48.8)	393 (56.9)	573 (58.1)
CCI n (%)	Mean (SD) [median]	1.4 (1.6) [1.0]	2.0 (1.8) [2.0]	1.1 (1.4) [1.0]	1.3 (1.5) [1.0]	2.2 (1.9) [2.0]	2.7 (2.0) [3.0]
	0	1,080 (38.9)	1,000 (29.2)	1,365 (39.8)	1,786 (38.0)	152 (22.0)	140 (14.2)
	1	480 (17.3)	481 (14.1)	1,019 (29.7)	1,374 (29.3)	147 (21.3)	159 (16.1)
	2	564 (20.3)	854 (25.0)	586 (17.1)	790 (16.8)	122 (17.7)	171 (17.4)
	3+	650 (23.4)	1,088 (31.8)	456 (13.3)	749 (15.9)	270 (39.1)	516 (52.3)

CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation.

associated with decreased overall median medical costs (Table 2). When segmented further, the management of individuals who were receiving RAASi therapy and had CKD and HK; HF and HK; and the combination of CKD, HF, and HK was associated with higher median medical costs compared with patients without HK (Tables 3 and 4).

The management of patients with CKD and HK who were being treated with optimal RAASi therapy was associated with a median medical cost of $12,671 and median LOS of 6 days compared with $1,894 and 3 days, respectively, for patients without HK (Table 3). Similarly, patients with HF and HK who were being treated with optimal RAASi therapy had a higher median medical cost of $33,469 compared with $3,974 for patients without HK (Table 3). For patients with CKD, HF, and HK who were being treated with optimal RAASi therapy, the median medical cost was $27,075 compared with $6,064 for patients without HK (Table 3).

Across all patient subgroups in which patients were receiving RAASi therapy, only 26.8% of patients (n = 1,850) were receiving the optimal dose, while 73.2% of patients were not receiving an optimal dose. For patients with CKD and HK who were receiving RAASi therapy at an optimal dose, the overall medical cost was higher compared with patients who were receiving a suboptimal dose. Similarly, patients with HF and HK who were receiving RAASi therapy at an optimal dose had higher overall median medical costs compared with patients who were receiving a suboptimal dose ($P < 0.05$). However, for patients with CKD and HF with a diagnosis of HK who were receiving RAASi therapy at an optimal dose, the overall medical cost was lower for patients who were receiving a suboptimal dose ($27,075 vs. $28,293, respectively). In both the CKD and the HF cohorts, the overall median medical cost was higher for patients with HK compared with patients without HK (Table 3).

Overall medical costs and LOS were compared for patients with HK in the 3 groups between those receiving RAASi therapy and those not receiving RAASi treatment. The management of patients with CKD and HK who were receiving an optimal RAASi regimen resulted in a median medical cost and median LOS of $12,671 and 6 days, compared with $10,063 and 4 days, respectively, for patients who were not receiving treatment with a RAASi regimen ($P < 0.05$). Patients with HF and HK who were receiving optimal RAASi therapy had an overall median medical cost of $33,469, compared with $15,475 for patients who were not being treated with a RAASi regimen ($P < 0.05$). For patients with CKD, HF, and HK who were receiving optimal RAASi therapy, the median medical costs were $27,075, compared with $23,189 for patients who were not receiving treatment with a RAASi regimen ($P < 0.05$).

Table 3 demonstrates that there were mixed results with respect to optimal RAASi dosing. Patients with optimal RAASi dosing in the CKD cohort had significantly higher overall costs than with suboptimal dosing ($P = 0.0086$); the difference in the HF cohort was significant ($P < 0.05$). The cohort of patients with both CKD and HF who were receiving optimal

TABLE 2 Patients on Renin-Angiotensin-Aldosterone System Inhibitor Therapy

Measure		CKD Patients			HF Patients			Patients with CKD and HF		
		Optimal Dose n = 850	Suboptimal Dose n = 1,924		Optimal Dose n = 816	Suboptimal Dose n = 2,610		Optimal Dose n = 184	Suboptimal Dose n = 507	
Medical utilization mean (SD) [median]	Inpatient visits	1.0 (0.0) [1.0]	1.2 (0.4) [1.0]		1.4 (1.1) [1.0]	1.5 (0.8) [1.0]		1.0 (0) [1.0]	1.1 (0.3) [1.0]	
	LOS	7.2 (6.8) [6.0]	6.2 (5.4) [4.0]		11.6 (9.2) [9.0]	6.8 (6.6) [5.0]	[b]	15.0 (0) [15.0]	7.4 (3.9) [7.0]	
	ED visits	1.9 (1.7) [1.0]	2.0 (1.6) [1.0]		2.5 (2.3) [2.0]	2.4 (2.2) [2.0]		2.9 (2.4) [2.0]	3.0 (2.5) [2.0]	
	Office/OP visits	12.8 (12.1) [8.0]	14.8 (12.9) [11.5]	[b]	14.2 (12.4) [10.0]	18.8 (14.0) [15.0]	[b]	18.9 (15.0) [15.0]	25.8 (16.9) [23.0]	[b]
Medical cost[a] mean (SD) [median]	Overall cost, $	9,747 (37,108) [2,092]	10,259 (26,453) [3,121]		12,752 (22,907) [4,144]	19,230 (41,350) [8,289]	[b]	22,672 (37,180) [7,762]	30,956 (69,275) [12,749]	[b]
Overall pharmacy cost[a] and utilization mean (SD) [median]	Fills per patient	54.6 (36.1) [48.0]	43.1 (29.8) [35.0]	[b]	49.7 (32.9) [41.0]	38.6 (27.6) [32.0]	[b]	55.8 (37.0) [47.0]	47.4 (33.3) [39.0]	[b]
	Cost per fill, $	142.7 (767.8) [18.8]	142.1 (639.6) [16.8]		114.8 (522.3) [15.2]	124.7 (644.5) [12.2]		117.1 (701.6) [17.1]	105.6 (345.9) [14.8]	

[a] *Costs reported in U.S. dollars.*

[b] *Indicates statistical significance ($P < 0.05$).*

CKD = chronic kidney disease; ED = emergency department; HF = heart failure; LOS = length of stay (in days); OP = outpatient; SD = standard deviation.

RAASi dosing had lower overall costs compared with patients who were receiving suboptimal dosing ($27,075 vs. $28,293), although the difference was not statistically significant

Table 4 presents gamma distributed regression results for the separate groups. In all the cohorts, decreasing age and increasing CCI were significant predictors of overall costs, whereas gender was not a significant predictor in the CKD and HF cohorts. Patients with CKD alone, HF alone, or both CKD and HF, all in combination with HK, had higher overall costs than did those without HK.

Discussion

Treatment with RAASi agents has been shown to reduce morbidity and mortality in patients with CKD, HF, or both, and treatment guidelines recommend their use in these patient populations.[5,6,9-11] Among patients treated with RAASi therapies, the results of this study demonstrate that RAASi optimal dosing was associated with higher pharmacy costs and lower overall median costs (Table 2). These results are consistent with the findings of a study by Epstein et al. (2016), which demonstrated that patients receiving RAASi therapies at maximum doses incurred lower total costs per patient compared with those who had been prescribed RAASi therapies at submaximum doses.[3]

While the use of RAASi therapies is recommended and continues to demonstrate lower overall health care costs, the use of these treatments in these patients also poses challenges due to their potential to exacerbate HK.[6,12] The results of this analysis demonstrate that managing patients with HK was associated with higher median medical costs compared with individuals without HK. These results are similar to a recent study in which authors concluded that HK imposes a large economic burden to the U.S. health care system.[12] One potential explanation for the differences in cost and LOS is that the management of HK may require pharmacological treatment in order to normalize the serum potassium level and may complicate management of the underlying conditions for which patients are admitted. Additionally, given the potential for fatal complications, such management likely requires hospital admission, thereby potentially contributing to the observed increases in overall medical costs for these patients.

Further, the results of this study show that HK was associated with higher costs compared with individuals without HK, regardless of whether they were receiving RAASi therapy. Variations in RAASi therapy dosing had an impact on the median medical cost for patients with HK among these subgroups. For patients with CKD and HK who were being treated with RAASi therapy, the median medical costs were higher and LOS was longer compared with patients without HK. Patients

TABLE 3 Patients with Chronic Kidney Disease, Heart Failure, and Both

Measure		RAASi Population						No RAASi		
		Hyperkalemia			No Hyperkalemia					
		Optimal Dose	Suboptimal Dose		Optimal Dose	Suboptimal Dose		Hyperkalemia	No Hyperkalemia	
Chronic Kidney Disease										
Patient count		45	158		805	1,766		321	3,102	
Medical utilization mean (SD) [median]	Inpatient visits	1.0 (0.0) [1.0]	1.0 (0.0) [1.0]		1.0 (0.0) [1.0]	1.3 (0.5) [1.0]		1.4 (0.8) [1.0]	1.3 (0.7) [1.0]	b
	LOS	10.3 (7.5) [6.0]	8.5 (9.2) [8.5]	b	2.5 (0.7) [2.5]	5.7 (4.9) [4.0]	b	5.3 (3.6) [4.0]	6.1 (6.5) [4.0]	b
	ED visits	1.9 (1.2) [2.0]	2.2 (1.8) [2.0]		1.9 (1.8) [1.0]	1.9 (1.6) [1.0]		2.4 (2.2) [2.0]	2.0 (1.7) [1.0]	b
	Office/OP visits	24.4 (16.8) [22.0]	22.6 (12.4) [20.0]		12.2 (11.4) [8.0]	14.1 (12.7) [10.0]		26.5 (17.7) [23.0]	19.0 (14.6) [16.0]	b
Medical cost[a] mean (SD) [median]	Overall cost, $	58,097 (139,595) [12,671]	20,645 (31,501) [9,065]	b	7,044 (15,795) [1,894]	9,329 (25,761) [2,785]	b	28,891 (55,076) [10,063]	15,895 (47,638) [5,278]	b
Overall pharmacy cost[a] and utilization mean (SD) [median]	Fills per patient	50.6 (36.8) [44.0]	36.6 (23.6) [32.0]		54.8 (36.1) [49.0]	43.7 (30.2) [36.0]		31.6 (24.0) [26.0]	32.2 (25.2) [26.0]	
	Cost per fill, $	115 (314) [12]	126 (356) [12]	b	144 (784) [19]	143 (655) [17]		221 (935) [16]	178 (867) [15]	b
Heart Failure										
Patient count		11	90		805	2,520		144	4,555	
Medical utilization mean (SD) [median]	Inpatient visits		1.8 (1.3) [1.0]		1.4 (1.1) [1.0]	1.4 (0.7) [1.0]		2.0 (0.8) [2.0]	1.2 (0.5) [1.0]	b
	LOS		10.4 (12.8) [6.0]		11.6 (9.2) [9.0]	6.1 (4.5) [5.0]		5.0 (2.8) [4.0]	6.6 (7.2) [5.0]	
	ED visits	3.3 (1.6) [4.0]	3.3 (2.9) [2.0]		2.5 (2.3) [2.0]	2.4 (2.2) [2.0]		3.3 (3.7) [2.0]	2.4 (2.6) [2.0]	
	Office/OP visits	28.5 (19.3) [27.0]	25.3 (13.6) [23.5]		14.0 (12.2) [10.0]	18.6 (14.0) [15.0]	b	22.6 (16.1) [19.0]	20.8 (15.0) [17.0]	
Medical cost[a] mean (SD) [median]	Overall cost, $	48,403 (38,207) [33,469]	33,495 (43,099) [20,433]	b	12,264 (22,274) [3,974]	18,721 (41,204) [8,017]	b	36,923 (64,304) [15,475]	18,969 (38,566) [8,806]	b
Overall pharmacy cost[a] and utilization mean (SD) [median]	Fills per patient	43.7 (18.7) [37.0]	40.7 (27.4) [36.0]		49.8 (33.1) [41.0]	38.6 (27.6) [32.0]		29.2 (23.1) [23.0]	31.2 (22.5) [25.0]	
	Cost per fill, $	58 (130) [12]	142 (464) [12]	b	115 (525) [15]	124 (650) [12]		150 (729) [13]	163 (740) [12]	
Chronic Kidney Disease and Heart Failure										
Patient count		26	94		158	413		178	808	
Medical utilization mean (SD) [median]	Inpatient visits		1.0 (0.0) [1.0]		1.0 (0) [1.0]	1.1 (0.3) [1.0]		2.8 (2.6) [2.0]	1.6 (0.9) [1.0]	
	LOS		11.0 (5.7) [11.0]		15.0 (0) [15.0]	6.8 (3.5) [6.0]		5.5 (2.1) [5.0]	5.4 (2.9) [5.0]	
	ED visits	2.6 (1.5) [2.0]	3.3 (2.7) [3.0]		3.0 (2.6) [2.0]	2.9 (2.5) [2.0]		2.9 (2.4) [2.0]	2.8 (2.5) [2.0]	
	Office/OP visits	24.9 (18.1) [20.5]	28.2 (15.6) [27.5]		18.0 (14.2) [15.0]	25.2 (17.1) [22.0]	b	30.6 (16.7) [28.0]	28.8 (18.7) [25.0]	
Medical cost[a] mean (SD) [median]	Overall cost, $	49,845 (55,267.00) [27,075]	58,682 (93,346.30) [28,293]		18,200.50 (31,344.50) [6,064]	24,645 (60,924.70) [11,267]	b	50,029 (72,305.10) [23,189]	33,614 (66,157.20) [14,304]	b
Overall pharmacy cost[a] and utilization mean (SD) [median]	Fills per patient	42.6 (24.6) [39.5]	45.9 (30.8) [35.5]		58.0 (38.3) [48.5]	47.8 (33.9) [39.0]	b	37.6 (27.6) [31.0]	34.2 (22.1) [30.0]	
	Cost per fill, $	201 (1,536.50) [18]	111 (274.00) [13]		108 (541.80) [17]	105 (359.10) [15]		157 (692.20) [14]	149 (516.40) [14]	

[a]*Costs reported in U.S. dollars.*

[b]*Indicates statistical significance ($P < 0.05$).*

ED = emergency department; LOS = length of stay (in days); OP = outpatient; RAASi = renin-angiotensin-aldosterone system inhibitor; SD = standard deviation.

TABLE 4 Generalized Linear Model Regression Results

	Variable	Estimate[a]	Standard Error	*P* Value
CKD Cohort				
Medical costs	Gender (male)	-0.0068	0.0326	0.8343
	Age	-0.0321	0.0012	<0.0001
	CCI	0.2072	0.0094	<0.0001
	Hyperkalemia	0.6994	0.0588	<0.0001
	RAASi (optimal)	-0.4190	0.0473	<0.0001
Overall costs	Gender (male)	0.0221	0.0276	0.4222
	Age	-0.0031	0.0011	<0.0001
	CCI	0.1497	0.0077	<0.0001
	Hyperkalemia	0.3567	0.0495	0.0001
	RAASi (optimal)	0.1050	0.0399	0.0086
HF Cohort				
Medical costs	Gender (male)	0.0448	0.0255	0.0783
	Age	-0.0233	0.0009	<0.0001
	CCI	0.1990	0.0086	<0.0001
	Hyperkalemia	0.6044	0.0741	<0.0001
	RAASi (optimal)	-0.3415	0.0421	<0.0001
Overall costs	Gender (male)	0.0203	0.0223	0.3628
	Age	-0.0224	0.0008	<0.0001
	CCI	0.1850	0.0075	<0.0001
	Hyperkalemia	0.4772	0.0649	<0.0001
	RAASi (optimal)	-0.0450	0.0370	0.2231
CKD and HF Cohort				
Medical costs	Gender (male)	0.1066	0.0554	0.0545
	Age	-0.0357	0.0024	<0.0001
	CCI	0.1445	0.0144	<0.0001
	Hyperkalemia	0.3978	0.0725	<0.0001
	RAASi (optimal)	-0.5638	0.0892	<0.0001
Overall costs	Gender (male)	0.1116	0.0468	0.0171
	Age	-0.0353	0.0021	<0.0001
	CCI	0.1216	0.0118	<0.0001
	Hyperkalemia	0.2837	0.0612	<0.0001
	RAASi (optimal)	-0.2604	0.0752	0.0005

[a]*Parameter was estimated by maximum likelihood.*

CCI = Charlson Comorbidity Index; CKD = chronic kidney disease; HF = heart failure; RAASi = renin-angiotensin-aldosterone system inhibitor.

with HF and HK who were being treated with RAASi therapy had increased median medical costs compared with those without HK. In this group, those who were receiving RAASi therapy at an optimal dose were the most costly patients studied across all patient groups with respect to optimal dosing. However, the population associated with optimal RAASi dosing is small, and therefore, further studies are needed to fully evaluate this finding.

These higher costs for the patient groups with concomitant CKD and HK and concomitant HF and HK may be attributed to the greater potential for the occurrence of HK when the RAASi therapies are given at maximum recommended doses and may represent a potential area for greater monitoring among patients with HK and concomitant CKD or HF. Of note, for patients with both CKD and HF who had a diagnosis of HK and were receiving RAASi therapy at an optimal dose, median medical costs were $1,218 lower compared with patients who were receiving a suboptimal dose; however, it is important to note that the treatment of patients in the optimal dose group resulted in higher emergency department visits.

Managing HK in patients with CKD, HF, or a combination of the two poses a challenge for clinicians. Clinical guidelines recommend the use of RAASi therapies for these patients. Electing to not use RAASi treatment in this patient population may lead to increased health care costs associated with poor health outcomes, whereas using RAASi at the recommended optimal dosing is associated with increased health care costs due to HK precipitated by RAASi treatment.

Until the FDA approval of patiromer in 2015, the HK treatment landscape had remained unchanged for approximately 50 years. This novel potassium binder exerts its effect by exchanging calcium for potassium in individuals with HK. This treatment was studied in patients with type 2 DM in the AMETHYST-DN trial (N = 304), which demonstrated that treatment with patiromer lowered potassium and reduced the recurrence of HK up to 52 weeks in patients receiving treatment with a RAASi therapy.[13]

Novel potassium-binding agents are being developed for use in individuals with HK. One investigational treatment, ZS-9 (zirconium salicylate), is undergoing FDA review as of this writing. ZS-9 was studied in the 28-day HARMONIZE study and demonstrated favorable outcomes via its mechanism of action, exchanging sodium for potassium in patients with HK.[13] Further studies are needed to evaluate the potential for these agents to decrease health care costs due to HK events.

Limitations

This retrospective analysis is based on paid claims data from regional health plans. Plans with significantly different patient populations or benefit structures may not share the same trends. Available claims information will be limited for patients who do not choose to seek routine care. Patients groups who are using drug therapy such as RAASi therapies likely have baseline differences. Services performed but not billed are not captured in the data. These services may include physician samples for pharmaceutical products or services performed pro bono. They may also include prescription drugs that were not billed to the health plan but were instead paid for through a discount prescription drug program or cash payments. Additionally, not all pertinent information can be captured from claims data, and other external factors may have contributed to the results observed through this study.

Data outside the study period were not evaluated. Given that this study relies on the accuracy of submitted claims data, there is the potential that diagnosis codes may have been submitted

incorrectly. This study was not designed to detect differences for median medical costs and median LOS at various dosing levels among each dosing group. Therefore, observed differences in medical costs and LOS exist between the maximum recommended dose and any doses below the maximum recommended dose. Additionally, the population in the optimal dosing group was small and therefore not powered to show consistent statistically significant differences.

Conclusions

The results of this real-world analysis suggest that HK and suboptimal dosing of RAASi therapy were associated with a median increase in outpatient office visits as well as increased overall medical costs among patients with CKD and/or HF. This evaluation of median costs suggests that effective HK management may potentially reduce medical costs among patients with CKD and/or HF or both CKD and HF, including those currently receiving RAASi therapy. To this end, the development of a quality improvement program structured around the management of HK in individuals with HF and/or CKD may be warranted. Additional studies are needed to establish the relationship between suboptimal dosing of RAASi and increased medical costs for patients among these subgroups.

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DISCLOSURES

This study was conducted by Magellan Rx Management and funded by Relypsa. Brenner, Alvarez, and Oestreicher were employed by Relypsa during the development of this study and the writing of this manuscript. Polson, Lord, Kangethe, Speicher, and Farnum are employees of Magellan Rx Management, which received funding from Relypsa for conducting the retrospective study and writing the manuscript.

Study concept and design were contributed by Lord, Polson, Brenner, Alvarez, and Oestreicher. Data collection and interpretation were performed by Polson and Kangethe, with assistance from Lord. The manuscript was written by Farnum, with assistance from Kangethe and Speicher and revised by all authors.

REFERENCES

1. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med.* 2009;169(12):1156-62.

2. An JN, Lee JP, Jeon HJ, et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care.* 2012;16(6):R225.

3. Epstein M, Alvarez PJ, Reaven NL, et al. Evaluation of clinical outcomes and costs based on prescribed dose level of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care.* 2016;22(11 Suppl):S311-24.

4. Latts LM, Reaven NL, Funk SE, et al. Hyperkalemia is prevalent in patients with cardiorenal comorbidities. Poster presented at: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 20th Annual International Meeting; May 16-20, 2015; Philadelphia, PA. Available at: https://www.ispor.org/research_pdfs/49/pdffiles/PCV33.pdf.

5. Sayer G, Bhat G. The renin-angiotensin-aldosterone system and heart failure. *Cardiol Clin.* 2014;32(1):21-32, vii.

6. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care.* 2015;21(11 Suppl):S212-20.

7. Healthcare Cost and Utilization Project (HCUP). National Inpatient Sample (NIS) overview. 2017. Agency for Healthcare Research and Quality. Rockville, MD. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed March 29, 2017.

8. Briggs A, Gray A. The distribution of health care costs and their statistical analysis for economic evaluation. *J Health Serv Res Policy.* 1998;3(4):233-45.

9. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2016;134(13):e282-93.

10. National Kidney Foundation. NKF KDOQI guidelines. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Available at: https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_7.htm. Accessed March 29, 2017.

11. Kovesdy CP. Management of hyperkalemia: an update for the internist. *Am J Med.* 2015;128(12):1281-87.

12. Dunn JD, Benton WW, Orozco-Torrentera E, Adamson RT. The burden of hyperkalemia in patients with cardiovascular and renal disease. *Am J Manag Care.* 2015;21(15 Suppl):S307-15.

13. Pitt B, Bakris G. New potassium binders for the treatment of hyperkalemia. *Hypertension.* 2015;66:731-38. Available at: http://hyper.ahajournals.org/content/66/4/731.full. Accessed March 29, 2017.

APPENDIX A Diagnosis Definitions

Condition	ICD-9-CM Codes	ICD-10-CM Codes
Chronic kidney disease	585.3, 585.4, 585.5	N18.3, N18.4, N18.5
Heart failure	428.x	I50.x
Hyperkalemia	276.7	E87.5

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = Tenth Revision.

APPENDIX B Optimal RAASi Dosing

Class	Product	Maximum Dose (mg)	FDB Designation
ACE inhibitors	Benazepril	80	010041, 006113, 008962
	Captopril	450	000128, 000127
	Enalapril	40	016845, 000130, 012660, 000129
	Fosinopril	40	006106, 018610
	Lisinopril	40	000132, 000131
	Moexipril	30	009934, 014293
	Perindopril	8	013911
	Quinapril	80	007631, 007826
	Ramipril	10	006080
	Trandolapril	8	008991, 012230
Direct renin inhibitor	Aliskiren	300	034493, 035338
ARBs	Azilsartan	80	038370, 037444
	Candesartan	32	016913, 021280
	Eprosartan	800	016920, 024744
	Irbesartan	300	015576, 018963
	Losartan	100	009829, 009863
	Olmesartan	40	035042, 023490, 037089, 025446
	Telmisartan	80	018839, 036697, 021873
	Valsartan	320	034433, 036305, 042256, 012204, 017084
MRAs	Eplerenone	100	024316
	Spironolactone	25	002901, 002900
Combination products	Aliksiren/valsartan	300/320	036626

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; FDB = First Databank; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

Expert Panel Recommendations for the Identification and Management of Hyperkalemia and Role of Patiromer in Patients with Chronic Kidney Disease and Heart Failure

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SUMMARY

Virtual panel meetings were conducted among 7 physicians, all of whom are independent experts, including 3 nephrologists, 2 cardiologists, and 2 emergency medicine physicians (the panel). The panel met with the purpose of discussing the current treatment landscape, treatment challenges, economic impact, and gaps in care for patients with hyperkalemia that is associated with heart failure and chronic kidney disease. The stated goal of the panel discussion was to develop practical solutions in the identification and management of hyperkalemia in this patient population.

The panel noted that hyperkalemia is a serious condition that can lead to life-threatening complications, yet the treatment paradigm for hyperkalemia has remained without major advances for approximately 50 years, until the approval of patiromer.

A number of issues still exist in the management of this patient population, including the lack of uniform treatment guidelines and consensus regarding the approach to treatment. As part of its effort, the panel developed an algorithm, the Proposed Diagnostic Algorithm for Hyperkalemia Treatment in the Acute Care Setting/Chronic Care. The panel agreed that patiromer appears to be a viable option for the management of hyperkalemia in patients with chronic kidney disease and/or heart failure and in patients who experience chronic hyperkalemia.

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Hyperkalemia is a life-threatening condition that can present acutely or chronically and is characterized by elevated serum potassium levels greater than 5.0 or 5.5 mEq/L.[1,2] Severe hyperkalemia is defined as having a serum potassium level greater than 6.0 mEq/L.[2] Hyperkalemia is associated with serious medical conditions such as cardiac arrhythmias, ventricular fibrillation, and sudden cardiac death.[1] Hyperkalemia can be the result of various acute and chronic conditions that affect potassium homeostasis and commonly occurs in patients with chronic kidney disease (CKD), heart failure (HF), and diabetes mellitus (DM).[2,3] Even when treated rapidly and appropriately, mortality for patients with severe hyperkalemia may be greater than 30%.[3]

Methods for Creation of this Document

Virtual panel meetings were conducted among a total of 7 physicians, all of whom are independent experts, including 3 nephrologists, 2 cardiologists, and 2 emergency medicine physicians (the panel). The panel met with the purpose of discussing the current treatment landscape, treatment challenges, economic impact, and gaps in care for patients with hyperkalemia that is associated with HF and CKD. The stated goal of the panel discussion was to develop practical solutions in the identification and management of hyperkalemia in this patient population. One large challenge in the treatment of this condition is that there is a lack of consensus regarding its management, particularly in the acute and chronic settings. This is problematic, as the treatment of this condition is costly, and wide variability among treatment approaches has the potential to result in unnecessary increases in treatment costs. The panel explored the role of traditional management strategies and pipeline and recently introduced treatments such as patiromer (Veltassa, Relypsa) in the treatment of hyperkalemia in patients with HF and CKD. Resources that may be of use to providers in the treatment of this patient population were also discussed.

Epidemiology

Patients who are at the highest risk of hyperkalemia are those with CKD stages 3-4, DM, HF, and any combination of these conditions, as well as patients who are being treated with drugs that inhibit renal potassium excretion, such as renin-angiotensin-aldosterone system (RAAS) inhibitors.[2,4] In a study conducted by Latts et al. (2015), which evaluated the 5-year prevalence of hyperkalemia in approximately 1.7 million patients, 47.6% of patients in stages 3 or 4 CKD with HF had at least 1 episode of hyperkalemia compared with 8.5% of patients in the comparison group, which was composed of patients who did not have CKD stage 2 or higher, end-stage renal disease (ESRD), HF, or DM.[4] Overall, of the 15.8% of patients who experienced at least 1 hyperkalemia event, 9.8% had at least 1 mild hyperkalemia event and 6.1% had moderate/severe events.[4] Hyperkalemia was classified as mild (K^+ 5.1 to 5.4 mEq/L) or moderate/severe ($K^+ \geq 5.5$ mEq/L) based on the highest measured value.[4] Additionally, 8.5% of individuals in the control group experienced a hyperkalemia event compared to 23.5% of patients with HF, 29.5% with CKD stages 3-4, and 47.6% with HF and CKD stages 3-4.[4]

The prevalence of hyperkalemia was generally higher in patients 65 years of age and older than in individuals with similar comorbidities who were younger than 65 years of age.[4] In addition, patients with DM, HF, CKD stages 3-4, and combinations of these conditions were 2.5 to 5.6 times more likely to experience hyperkalemia versus the cohort without any of these conditions.[4] The authors of the study concluded that as medical comorbidity increases, either through declining renal function or through the development of other concomitant conditions, the prevalence of hyperkalemia also increases.

TABLE 1 2014 National Statistics. First-Listed Diagnosis Only: Outcomes by ICD-9-CM Code 276.7, Hyperpotassemia[7]

	All ED Visits	ED Visits with Admission to the Same Hospital	Discharged from the ED
Total number of visits	76,028	35,166	40,862
ED visits with admission to the same hospital, n (%)	35,166 (46.25)	35,166 (100.00)	[a]
Died during ED visit, n (%)	168 (0.41)	N/A	168 (0.41)
Died during hospital stay, n (%)	482 (1.37)	482 (1.37)	N/A

[a]*Statistics based on estimates with a relative standard error (standard error/weighted estimate) greater than 0.30 or with standard error = 0 in the nationwide statistics (NIS, NEDS, and KID) are not reliable. These statistics are suppressed.*
ED = emergency department; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; KID = Kids' Inpatient Database; N/A=not applicable; NEDS = Nationwide Emergency Department Sample; NIS = National Inpatient Sample.

TABLE 2 2014 National Statistics. Principal Diagnosis Only: Outcomes by ICD-9-CM Code 276.7, Hyperpotassemia[8]

	276.7 Hyperpotassemia	Standard Errors
Total number of discharges	40,380	989
LOS, days (mean)	3.3	0.072
LOS, days (median)	2.0	N/A
Charges, $ (mean)	29,181	789
Charges, $ (median)	17,411	N/A
Costs, $ (mean)	7,472	178
Costs, $ (median)	4,863	N/A
Aggregate costs, $	302,665,865	8,478,278
Aggregate charges, $ (the "national bill")	1,181,305,044	36,352,360
In-hospital deaths, n (%)	615 (1.52)	57 (0.14)
Routine discharge, n (%)	27,335 (67.69)	853 (0.74)
Another short-term hospital, n (%)	335 (0.83)	42 (0.10)
Another institution (nursing home, rehab), n (%)	5,960 (14.76)	193 (0.49)
Home health care, n (%)	4,655 (11.53)	177 (0.43)
Against medical advice, n (%)	1,440 (3.57)	99 (0.22)
Missing discharge status, n (%)	[a]	[a]

[a]*Statistics based on estimates with a relative standard error (standard error/weighted estimate) greater than 0.30 or with standard error = 0 in the nationwide statistics (NIS, NEDS, and KID) are not reliable. These statistics are suppressed.*
ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; LOS = length of stay; KID = Kids' Inpatient Database; N/A = not applicable; NEDS = Nationwide Emergency Department Sample; NIS = National Inpatient Sample.

Although the incidence and prevalence of hyperkalemia in the general population have not been extensively studied, some studies conducted among hospitalized patients have estimated the prevalence to be between 1 and 10 per 100 patients.[5] In addition, some retrospective analyses have reported that the prevalence of hyperkalemia is between 2.5% and 3.2% in populations with diverse risk factors, although the actual prevalence is dependent upon the patient population being studied and the serum potassium threshold used to determine hyperkalemia.[2,6] Nonetheless, the presence of CKD is consistently associated with hyperkalemia.

Economic Impact

In the United States, hyperkalemia represents a considerable economic, societal, and health system burden. The financial burden of the condition is largely a result of the costs associated with emergency department (ED) visits, inpatient stays, pharmacological treatments, and disease-related mortality. Additionally, there are considerable costs associated with adverse outcomes that occur as a result of suboptimal use of RAAS inhibitor therapy, which may be due to discontinuation or down-titration of the treatment based on concerns about hyperkalemia.

ED visits for hyperkalemia or hyperpotassemia were examined using discharge data from the Nationwide Emergency Department Sample (NEDS), Healthcare Cost and Utilization Project (HCUP), and Agency for Healthcare Research and Quality (AHRQ). Data indicated that there were 76,028 visits to the ED with a primary diagnosis of hyperkalemia (hyperpotassemia; *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 276.7) in 2014. Of these visits, 35,166 were ED visits with admission to the same hospital, and 40,862 represented discharges from the ED (Table 1).[7] In addition, regional cost differences for hyperkalemia admissions were examined using discharge data from the National Inpatient Sample (NIS), HCUP, and AHRQ.[8] For the patients admitted, there was an average length of stay of 3.3 days, with an average charge of $29,181 per stay (Table 2).[8] These data suggest that hyperkalemia is associated with increased ED visits and hospitalizations, both of which result in increased costs. Additionally, hyperkalemia predominantly affects the Medicare population compared to patients with other types of insurance (Table 3).[8] National and state statistics differences by payer type were examined using discharge data from the NIS, HCUP, and AHRQ.[8] These data from 2014 indicated that where hyperkalemia was listed as the primary diagnosis, 66.42% of the patients were Medicare beneficiaries, and over $821 million of the national bill was accounted for by these individuals' costs.[8]

A study conducted by Jain et al. (2012) further emphasized that hospitalization rates and mortality were higher in patients with hyperkalemia and cardiovascular disease (CVD) than in those without CVD.[9] In this retrospective analysis that evaluated all-cause mortality in patients with CVD who were receiving treatment with antihypertensive drugs, patients who

TABLE 3 2014 National Statistics. Principal Diagnosis: Outcomes for ICD-9-CM Principal Diagnosis Code 276.1, Hyperpotassemia[8]

	All Payers Combined	Medicare	Medicaid	Private Insurance	Uninsured
Total number of discharges, n (%)	40,380 (100.00)	26,820 (66.42)	6,795 (16.83)	4,510 (11.17)	1,585 (3.93)
LOS, days (mean)	3.3	3.5	3.0	2.9	2.5
LOS, days (median)	2.0	2.0	2.0	2.0	1.0
Charges, $ (mean)	29,181	30,543	27,181	25,432	21,536
Charges, $ (median)	17,411	18,167	16,925	15,719	12,710
Aggregate charges, $ (the "national bill")	1,181,305,044	821,122,977	184,893,947	115,314,419	34,134,190

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; LOS = length of stay.

had hyperkalemia demonstrated higher rates of hospitalization compared to those with normokalemia (7.80% vs. 5.04%, respectively; $P = 0.0001$) and higher mortality rates (6.25% vs. 2.92%, respectively; $P = 0.0001$).[9]

In a retrospective analysis performed by Einhorn et al. (2009), researchers evaluated the occurrence of hyperkalemia among 245,808 Veterans Affairs patients with and without CKD in the ambulatory and hospital settings.[2] The results of the analysis indicated that among patients receiving RAAS inhibitors, specifically angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs), hyperkalemia occurred at a higher rate in patients with CKD than in those without (7.67 vs. 2.30 per 100 patient-months; $P < 0.001$).[2]

ACE inhibitors and ARBs are commonly used in the treatment of patients with CKD, DM, and/or HF; however, due to concerns over the development of hyperkalemia, these RAAS inhibitors may be prescribed at suboptimal doses or not at all, which may be detrimental to long-term outcomes and contribute to increased medical expenditures.[10,11] A budget impact model was developed to estimate the potential benefits of losartan by modeling a patient cohort similar to the treatment groups included in the RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial.[11] The model was developed to simulate the 10-year cost savings and outcome improvements of renoprotective therapy, specifically losartan, for a cohort of privately insured patients with diabetes and advanced CKD, compared to no treatment.[11] For the best-case scenario, which assumed a patient cohort that matched the patient population observed in the RENAAL trial, the estimated annual cost savings were $10,990 per patient after 10 years of treatment with losartan.[11] For the conservative scenario, which assumed a patient cohort of less acutely ill patients, the estimated annual cost savings were $5,659 per patient by year 10 among patients treated with losartan.[11]

Current Approaches to Treatment and Gaps in Care

The panel indicated that there are no clear, specific, standardized guidelines for the management of hyperkalemia in patients with CKD and/or HF, which is problematic given that hyperkalemia can often be a life-threatening condition. The panel noted that the approach to treatment can be highly variable and may be affected by a variety of factors. For example, nephrologists and cardiologists stated that if a patient has a serum potassium level of 5.8 mEq/L, the provider may decide not to treat immediately but instead wait a few weeks, repeat the test, and potentially initiate treatment based on the subsequent lab results. These panel participants further explained that their colleagues who treat a patient with the same potassium level may decide to utilize a different approach and initiate treatment immediately.

Physicians on the panel who work in the ED indicated that elevated potassium levels typically result in immediate treatment, followed by a referral based on the specific level. If the potassium level is 6 mEq/L or greater, the patient will receive an emergency referral to nephrology for dialysis; however, if the level is less than 6 mEq/L, non-ESRD patients are typically discharged home for outpatient follow-up with their primary care physician. The panel also indicated that internal medicine physicians may want to manage hyperkalemia without referral to a specialist. The panel discussions revealed that approaches to treatment may depend on the site of care, physician specialty, and comfort level of the physician in treating hyperkalemia in patients with baseline renal dysfunction and medical comorbidities.

Among the medications that can lead to or worsen hyperkalemia, RAAS inhibitors are major contributors. This is problematic as these medications have been shown to reduce morbidity and mortality in patients with CKD, DM, and CVD.[12-14] RAAS inhibitors, irrespective of dose but especially at higher doses, can cause hyperkalemia, thereby limiting their use at optimal doses for cardiorenal protection.[15] In patients with hypertension who do not have risk factors for hyperkalemia, treatment with RAAS inhibitor monotherapy is associated with an incidence of hyperkalemia below 2% but increases to 5% when dual RAAS inhibition is used.[16] The incidence of hyperkalemia is even greater in patients with HF or CKD and ranges from 5% to 10%.[16]

In a study performed by Epstein et al. (2015), patients receiving RAAS inhibitors who had hyperkalemia were subject

TABLE 4 Treatment Options for Hyperkalemia in Emergency, Subacute/Nonemergent/Intermediate, and Chronic/Maintenance Settings

Treatment Strategy	Mechanism of Action	Advantages	Limitations	Clinical Setting
Beta2-adrenergic receptor agonists	K^+ redistribution into the intracellular space	Onset of action (~30 minutes) Effect is independent of insulin and aldosterone	Short duration, inconsistent effect (2-4 hours) Does not reduce total K^+ levels Use with caution in ischemic heart disease (risk of tachycardia)	Emergency treatment
Insulin glucose	K^+ redistribution into the intracellular space	Onset of action within 30 minutes Effects last 4-6 hours	Risk of hypoglycemia Does not reduce total K^+ levels	Emergency treatment
Calcium gluconate	Membrane stabilization	Onset of action in 1-3 minutes Efficacy can be monitored with ECG and dose can be repeated if no changes observed	Short duration of effect (30-60 minutes) Serum K^+ level is unaffected Avoid in patients receiving digoxin (risk of digoxin toxicity) Risk of hypercalcemia	Emergency treatment
Sodium bicarbonate	K^+ redistribution into the intracellular space When administered by infusion over 4-6 hours, it may enhance urinary K^+ excretion	Evidence is mixed Recommended when acidosis is the cause of hyperkalemia	No immediate reductions in serum K^+; effects may be observed after 4-6 hours Risk of metabolic alkalosis and volume overload Longer follow-up data were not available from RCTs	Intermediate/nonemergent/ subacute care setting Adjunct treatment in emergent setting once emergency treatments have been started
Diuretics	K^+ elimination	Onset of action depends on start of diuresis Beneficial in patients with volume expansion	Efficacy depends on residual renal function (until diuresis is present) Increased risk for gout and volume depletion May produce volume contraction, decreased distal nephron flow, worsening of kidney function, and reduced K^+ excretion	Intermediate/nonemergent/ subacute care setting (loop diuretics) Adjunct treatment in emergent setting once emergency treatments have been started Chronic/maintenance treatment (loop or thiazide diuretics)
Dialysis (hemodialysis, peritoneal dialysis)	K^+ elimination	Onset of action within minutes Effects lasting until end of dialysis or longer	Limitations and complications inherent to each dialysis modality (i.e., arrhythmias with hemodialysis)	Intermediate/nonemergent/ subacute care setting Adjunct treatment in emergent setting once emergency treatments have been started Chronic/maintenance treatment
Sodium polystyrene sulfonate	K^+ elimination	Efficacy of 6.9 days Effects may last 4-6 hours longer depending on ongoing potassium intake or cellular redistribution	No consistent evidence of efficacy Serious GI AEs reported, including fatal cases of intestinal necrosis Caution with sodium loads in patients with CHF, hypertension, or edema	Adjunct treatment in emergent setting once emergency treatments have been started Chronic/maintenance treatment
Low-potassium diet	Reducing potassium intake	May improve metabolic acidosis in CKD	Difficult to adhere to a low-potassium diet Limiting K^+ rich foods can cause constipation Contradicts the DASH diet; may worsen chronic hypertension	Chronic/maintenance treatment
Discontinuation/ dose reduction of RAAS inhibitors	Identification and interruption of hyperkalemia-inducing medications	Prevention of recurrent hyperkalemia events	Stopping or suboptimal utilization of renal/cardioprotective RAAS inhibitor therapy	Chronic/maintenance treatment
Patiromer for oral suspension	K^+ elimination	Onset of action 7 hours Management of hyperkalemia	Can take 3 hours before or after any medication Patiromer decreased the systemic exposure of coadministered ciprofloxacin, metformin, and levothyroxine. However, there was no interaction when patiromer and these drugs were taken 3 hours apart[30] No data to date to show efficacy in the acute setting	Adjunct treatment in emergent setting once emergency treatments have been started Chronic/maintenance treatment

AE = adverse event; CHF = congestive heart failure; CKD = chronic kidney disease; DASH = Dietary Approaches to Stop Hypertension; ECG = electrocardiographic; GI = gastrointestinal; RAAS = renin-angiotensin-aldosterone system; RCT = randomized controlled trial.

TABLE 5 Drugs Known to Cause Hyperkalemia

Drugs that promote transmembrane potassium shift	• Nonselective beta-blockers (e.g., propranolol, bucindolol, carvedilol)
	• Digoxin intoxication
	• Intravenous cationic amino acids
Drugs that affect aldosterone secretion	• ACE inhibitors (e.g., benazepril, lisinopril, ramipril)
	• ARBs (e.g., candesartan, irbesartan, losartan)
	• Direct renin inhibitors (e.g., aliskiren)
	• NSAIDs and COX-2 inhibitors (e.g., ibuprofen, naproxen, celecoxib)
	• Calcineurin inhibitors (e.g., cyclosporine, tacrolimus)
	• Heparin
Drugs that cause tubular resistance to the action of aldosterone	• Aldosterone antagonists (e.g., spironolactone, eplerenone) and other potassium-sparing diuretics (e.g., amiloride, triamterene)
	• Trimethoprim
	• Pentamidine
Agents that contain potassium	• Salt substitutes and alternatives
	• Penicillin G
	• Stored blood products

Adapted from Ben Salem C, Badreddine A, Fathallah N, et al. Drug-induced hyperkalemia.[41]

ACE = angiotensin-converting enzyme; ARB = angiotensin-II receptor blocker; COX = cyclooxygenase; NSAID = nonsteroidal anti-inflammatory drug.

to RAAS inhibitor dose reduction or permanent discontinuation of RAAS inhibitor therapy.[15] In this study, medical records were evaluated to assess the frequency of adverse outcomes among 205,108 patients with serum potassium levels >5.0 mEq/L who had at least 1 prescription for an RAAS inhibitor prior to the beginning of the study.[15] Adverse outcomes consisted of CKD progression, ESRD, stroke, acute myocardial infarction, coronary artery bypass, percutaneous coronary intervention, or death and were correlated with RAAS inhibitor dose levels, which were classified as maximum, submaximum, or discontinued during a 3-year follow-up period.[15]

Among HF patients, 44.3% of patients who received maximum doses of an RAAS inhibitor experienced an adverse outcome compared to 52.3% of patients who received submaximum doses and 59.8% of patients in whom a RAAS inhibitor had been discontinued.[15] There may also be a relationship between mortality and dosing levels, as demonstrated by mortality risks of 13.7%, 27.7%, and 30.1% for patients receiving maximum, submaximum, and discontinued doses, respectively.[15] To further assess the risk associated with RAAS inhibitors, one retrospective real-world observational study evaluated over 2,000 patients receiving an RAAS inhibitor in a single Veterans Affairs medical center. The results of the study indicated that 20.4% of patients receiving an ACE inhibitor and 31.0% of patients receiving an ARB experienced hyperkalemia.[17]

HF patients are especially susceptible to hyperkalemia resulting from HF-associated reductions in renal blood flow, the presence of comorbidities such as DM, and treatment regimens that include RAAS inhibitors. In the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) study, the use of an ARB, either as monotherapy or in combination with an ACE inhibitor, was evaluated in patients with symptomatic HF, including those with both preserved and decreased left ventricular ejection fraction (LVEF).[18] The greatest risk factors for hyperkalemia were male gender, age ≥75 years, DM, prior use of ACE inhibitors or spironolactone, baseline creatinine ≥2 mg/dL, and baseline K^+ ≥5.0 mEq/L.[18] The authors of this study reported that although these patient groups received clinical benefits from treatment with candesartan, treatment with this agent increased the rate of hyperkalemia, which was associated with hospitalization or death in some patients.[18]

The panel stated that a significant finding of the aforementioned studies was that patients who were receiving submaximal doses or who discontinued RAAS inhibitors had poorer cardiorenal outcomes and higher mortality than patients who were receiving maximum doses. The results of these studies present a challenge behind RAAS inhibitor prescribing decisions: attempting to balance the risk of developing hyperkalemia with the benefits on cardiorenal morbidity and mortality. These decisions are further complicated by the fact that patients with CKD with concomitant DM and/or HF who are most likely to experience the greatest benefit from these drugs are the same patients who are at highest risk of developing hyperkalemia.

The panel emphasized the differences between acute and chronic treatment and how critical this difference is in the management of hyperkalemia. Acute hyperkalemia is typically a clinical emergency that warrants immediate interventions, such as cardiac monitoring, administration of medications that will lower potassium, or emergency dialysis.[5] Generally, potassium levels >5.5 mEq/L are thought to be clinically significant.[1,19] The primary goals for managing severe, acute hyperkalemia are to stabilize cardiac membrane potential and prevent cardiac arrhythmias, induce a shift of serum potassium from the extracellular to the intracellular space, and decrease total body serum potassium levels.[5]

The treatment options for the management of acute hyperkalemia may be further divided into the following categories: (a) those with an onset of action within minutes and are more appropriate for emergency management and (b) those with an onset of action of a few hours to exert therapeutic effects and are suitable for intermediate or subacute care. Examples of treatments used can be found in Table 4. Treatments include nebulized or inhaled beta-2-receptor agonists (e.g., albuterol, salbutamol); intravenous (IV) insulin and glucose, which stimulate intracellular potassium uptake; and IV calcium gluconate salt for membrane stabilization. Sodium bicarbonate, loop diuretics, dialysis, and the potassium-binding resins patiromer and the sodium polystyrene sulfonate (SPS) Kayexalate have

played a role in the subacute management of hyperkalemia as adjunct therapies, once emergent treatments have been started.

In the chronic management setting of hyperkalemia, it is important to identify any underlying causes for an episode of hyperkalemia and to manage these factors/causes on an ongoing basis. Dietary potassium restriction and oral administration of sodium bicarbonate and loop diuretics can be utilized. SPS will occasionally be given in the chronic setting, but due to the poor taste, profound diarrhea, associated side effects, and salt load, patients may be nonadherent to treatment. In patients with ESRD, longer dialysis sessions, reduced potassium in the dialysate, and dietary restriction can be utilized. With regard to the identification of any underlying causes, the drugs listed in Table 5 have been known to cause hyperkalemia.[20]

The panel commented that current options to manage hyperkalemia on a chronic basis are limited, and robust evidence supporting their efficacy and safety in the outpatient setting is lacking. The panel recommended that more clinical trials be conducted. Before the approval of patiromer in 2015, SPS, an ion-exchange resin designed to bind potassium in exchange for sodium in the colon, was the only approved treatment for hyperkalemia.[21] SPS was approved by the U.S. Food and Drug Administration (FDA) in 1958, 4 years before the passing of the Kefauver-Harris Drug Amendment, which required that drug manufacturers prove the safety and efficacy of drugs.[21,22]

More recently, Lepage et al. (2015) conducted a small randomized controlled trial (RCT) in 33 patients to evaluate the efficacy of SPS in patients with CKD and mild hyperkalemia.[23] Patients were randomly assigned to receive either placebo or 30 grams of SPS orally 1 time per day for 7 days.[23] The primary outcome was the mean difference of serum potassium levels between the day after the last dose of treatment and baseline.[23] The results of the study indicated that the mean duration of treatment was 6.9 days and that SPS was superior to placebo in the reduction of serum potassium levels (mean difference between groups: -1.04 mEq/L; 95% confidence interval, -1.37 to -0.71).[23] A higher proportion of patients in the SPS group attained normokalemia at the end of their treatment compared with those in the placebo group, but the difference was not statistically significant (73% vs. 38%; $P = 0.07$).[23] There was a higher rate of electrolyte disturbances and gastrointestinal (GI) side effects in the SPS group, and SPS was considered superior to placebo in reducing serum potassium over 7 days in patients with mild hyperkalemia and CKD.[23]

The use of SPS is limited by its propensity to cause GI adverse events (AEs) (e.g., diarrhea, nausea, and vomiting) and other systemic toxicities, including sodium loading, hypomagnesemia, hypocalcemia, and colonic necrosis.[24-27] Historically, SPS was administered with sorbitol, a laxative, because of the potential for constipation to develop and because of the ability of sorbitol to further increase potassium elimination; however, in 2009, the FDA issued a warning with regard to the concomitant use of SPS and sorbitol following reports of colonic necrosis and other serious GI AEs.[28]

The panel expressed the opinion that SPS is not the ideal drug to use in the treatment of hyperkalemia because of its unfavorable safety and efficacy profile, safety warning for colonic necrosis, poor tolerability, and unpalatable taste. These aforementioned factors present a challenge to patients and providers, and the approval of new agents could aid in the treatment of hyperkalemia. The panel also stated that physicians must carefully assess uncontrolled studies demonstrating benefit versus risk with SPS. Therefore, the panel recommended that all other treatment options be exhausted prior to using this potentially harmful therapy with little evidence of efficacy.

The Role of Patiromer

Until recently, treatment options for patients with chronic hyperkalemia have been limited to nonpharmacological interventions (e.g., low dietary potassium intake), loop diuretics with or without sodium bicarbonate, and/or dose adjustments or discontinuation of RAAS inhibitor therapies. Some physicians have even given fludrocortisone. These limited options are not optimal for most patients. Thus, there is an unmet need for a safe, efficacious, and well-tolerated chronic strategy to control hyperkalemia. Before the availability of patiromer, physicians generally considered the following management strategies:

- If diet alone could not control potassium, doses of diuretic medications were increased and bicarbonate replacement was considered; however, these treatments ultimately lose their effectiveness as patients lose kidney function.
- When RAAS inhibitor dose reduction did not achieve desired results, RAAS inhibitor therapy was eventually discontinued.
- Some physicians have even given fludrocortisone with its risk for hypertension and vascular injury.

On October 21, 2015, patiromer received FDA approval for the treatment of hyperkalemia.[29] Patiromer is a polymer that exchanges calcium for potassium.[30] It has been shown to lower and maintain serum potassium levels in patients with CKD who are receiving RAAS inhibitors.[31] This treatment is not indicated to prevent hyperkalemia.[30] Additionally, due to its delayed onset of action, patiromer is not intended for use as an emergency treatment for life-threatening hyperkalemia.[30] Patiromer has the potential to bind to orally administered medications, which could reduce their absorption and effectiveness.[30] As a result, it is recommended that other oral medications should be administered at least 3 hours before or 3 hours after patiromer.[30]

The 2 main clinical trials that contributed to the approval of patiromer were OPAL-HK and AMETHYST-DN.[32,33] The multinational, single-blind, 2-phase OPAL-HK study evaluated the efficacy of patiromer in patients with CKD who were receiving RAAS inhibitors.[32] In phase 1, all participants received a starting dose of patiromer of 8.4 grams or 16.8 grams daily in 2 divided doses, depending on the severity of hyperkalemia, at baseline for 4 weeks.[32] The results of the study demonstrated an average decrease in serum potassium concentration of 1.01 mEq/L, and 76% of patients had serum potassium levels within the target range of 3.8 to ≤5.1 mEq/L at the end of 4 weeks.[32] In phase 2, the 8-week randomized withdrawal phase explored the effects of continuation of patiromer versus switching to placebo.[32] The results of the phase 2 portion demonstrated that there was no change in potassium levels in participants who continued patiromer; however, for patients who switched to placebo, an average increase of 0.72 mEq/L in serum potassium levels over the first 4 weeks of the phase was observed.[32] These results demonstrate the need for continuous treatment in this patient population and support the benefit of chronic use of patiromer to maintain safe potassium levels.

The 52-week, multi-center, open-label randomized AMETHYST-DN study evaluated the safety and efficacy of patiromer in hypertensive patients with DM or CKD.[33] Patients were stratified according to baseline serum potassium levels and received 1 of 3 randomized starting doses ranging from 8.4 g to 33.6 g daily, administered in 2 divided doses.[33] The doses were titrated to achieve and maintain serum potassium levels ≤5.0 mEq/L.[33] Observed decreases in serum potassium levels ranged from 0.35 mEq/L for patients on the lowest dose to 0.92 mEq/L for patients on the highest dose.[33] There was no evidence of loss of efficacy over 1 year of treatment.[33] The medication was also well tolerated with few dropouts.[33]

A third study, PEARL-HF, was a double-blind, randomized, placebo-controlled trial that was designed to assess the safety and efficacy of patiromer over 4 weeks in chronic HF patients who were candidates for spironolactone and had a serum potassium level between 4.3 and 5.1 mEq/L.[34] Enrolled patients must have also had a history of documented hyperkalemia resulting in discontinuation of an aldosterone antagonist, ACE inhibitor, ARB, or beta-blocker or CKD with an estimated glomerular filtration rate <60 mL/minute. A mean decrease in serum potassium of 0.22 mEq/L from baseline was observed in the patiromer group compared to a mean increase of 0.23 mEq/L from baseline in the placebo group.[34] When spironolactone was administered concomitantly, treatment with patiromer prevented increases in potassium levels.

The panel indicated that, based on their clinical experience, they view patiromer as a viable treatment option for patients with hyperkalemia, especially in the chronic management setting, and that SPS and patiromer may be used as adjunct therapies once emergency treatments have been initiated. However, more evidence is needed to support their use in the emergency setting. The panel also stated that an advantage of patiromer over SPS is the more favorable side effect profile, flavorless formulation, and use of calcium instead of sodium as the exchange ion, all of which have the potential to improve patient adherence. Based upon the 2%-3% incidence of hyperkalemia in the general population, 6.4 to 9.6 million people in the United States may qualify for treatment with patiromer.[9]

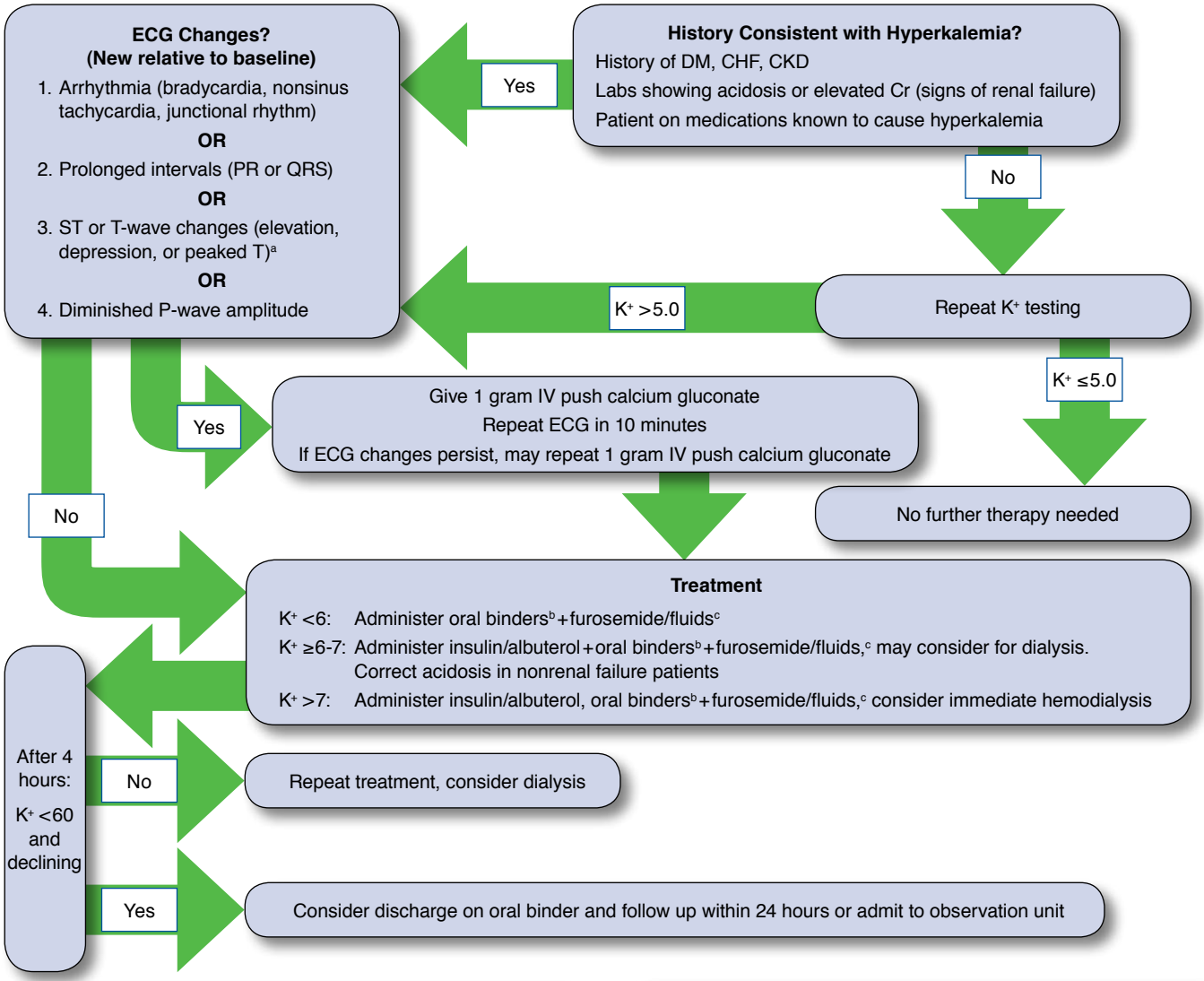
Panel Insights and Recommendations

The panel noted that hyperkalemia is a serious condition that can lead to life-threatening complications, yet the treatment paradigm for hyperkalemia has remained without major advances for approximately 50 years until the approval of patiromer.[35] Additionally, hyperkalemia can occur without clinical manifestations, which further complicates its diagnosis.[36] Cardiac conduction defects and both depolarization and repolarization abnormalities can occur with hyperkalemia.[37] Hyperkalemia can cause widening of the QRS complex, which increases pacing thresholds and can lead to failure to capture, and oversensing of, the spaced or spontaneous T-wave by implantable cardioverter-defibrillators, which can result in inappropriate shocks.[38] Finally, hyperkalemia has caused electrocardiographic (ECG) changes that were mistaken for malfunction of pacemakers and implantable cardioverter-defibrillators.[39,40]

ECG changes associated with hyperkalemia can vary between patients, and even normal ECGs have been observed in patients who have severe hyperkalemia. The panel commented that some physicians may review an ECG and determine that the abnormalities are due to hyperkalemia while others may not. This is problematic, as there is no consensus on how to use ECGs in the diagnosis and treatment of hyperkalemia. The panel noted that a potential solution to this problem is the development of a diagnostic algorithm that eliminates ECG measurements as a precise indicator of hyperkalemia. The proposed diagnostic algorithm, developed by the panel, is shown in Figure 1.

The panel noted that a need exists for the development of a differentiation strategy for the identification and management of hyperkalemia in acute and chronic settings. The panel agreed that patiromer would be ideal in the chronic management setting; however, there are no clinical studies published supporting use in the emergency setting. Physicians in this setting must rely on calcium, insulin, bicarbonate, furosemide, or other treatments for patients presenting with emergent, life-threatening hyperkalemia. Of note, approximately, 5 million doses of SPS are given yearly, despite the unfavorable safety and tolerability profile.[25] Patiromer may present a better tolerability and safety option for these patients; however, neither SPS or patiromer are indicated for the management of emergent

FIGURE 1 Proposed Diagnostic Algorithm for Hyperkalemia (K^+ >5.0 mEq/L) Treatment in the Acute Care Setting/Chronic Care



Recommended Doses for Treatment in the Acute Care Setting	
Calcium gluconate	1 gram
Insulin (regular)/ dextrose	5 units (insulin-naïve); 10 units (not naïve)/D50, 1 amp. Repeat POC glucose in 30 mins
Albuterol	10 mg nebulizer over 1 hour
Furosemide	20 mg (naïve and CKD stage <3), 40 mg (not naïve or CKD stage ≥3)
SPS	15 grams daily[d]
Patiromer	8.4 grams daily

Recommended Doses for Treatment in the Chronic Care Setting	
Furosemide	20-80 mg daily or more in single or divided doses as indicated
SPS	15-30 grams daily[e]
Patiromer	8.4-25.2 grams daily

[a]*History not consistent with myocardial ischemia.*
[b]*Hypokalemic effect of binders may be significantly delayed.*
[c]*Furosemide: use when patient has functional kidneys; administer fluids when patient has functional kidneys and no HF.*
[d]*Concern for lower GI toxicity and tolerability/compliance.*
[e]*Concern for lower GI toxicity and tolerability/compliance (continue low-potassium diet, discontinue potentially offending pharmaceutical agents, and avoid NSAIDs and COX-2 inhibitors).*
CHF = congestive heart failure; CKD = chronic kidney disease; COX = cyclooxygenase; Cr = creatinine; DM=diabetes mellitus; ECG = electrocardiography; GI = gastrointestinal; HF = heart failure; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; POC = point of care; SPS = sodium polystyrene sulfonate.

hyperkalemia, but both agents may be used to facilitate potassium lowering once emergent treatments have been initiated.

The panel also indicated that there is an educational deficit among patients and providers regarding patiromer use. Patient education about the correct use of patiromer is crucial, as many of these patients may be receiving treatment with patiromer and an RAAS inhibitor therapy concomitantly. This patient population must be counseled about the importance of treatment adherence. There is a risk of developing hyperkalemia with discontinuation of treatment with patiromer while continuing RAAS inhibitor therapy. Patients who discontinue treatment with an RAAS inhibitor may not receive the maximal clinical benefit of reduced morbidity and mortality with RAAS inhibitor treatment and should therefore be instructed to speak with their physician before discontinuing treatment with either therapy.[12-14]

Presently, many physicians are unfamiliar with the availability and administration of patiromer, and the panel suggested that a payer-, manufacturer-, or health care provider-initiated educational campaign may be beneficial in addressing this educational gap. Members of the panel indicated that the educational campaign should be targeted toward nephrologists, internal medicine, family medicine, and emergency medicine physicians, as they are the initial or first-line providers and treat the majority of these patients. Educational campaigns should also be directed toward cardiologists and physicians who work in the ED setting, as this is the setting in which most patients with hyperkalemia are treated and subsequently referred to primary care or a specialist. The panel felt that the clinical uptake of patiromer will be influenced by physicians' existing level of comfort with other therapies, the hesitancy to use new products prior to receiving adequate education or having experience with new-to-market agents, and the potential for beneficial outcomes among patients in their own practice.

Future Implications/Considerations

The panel agreed that patiromer appears to be a viable option for the management of hyperkalemia in patients with CKD and HF and in patients who experience chronic hyperkalemia. A number of issues still exist in the management of this patient population, including the lack of uniform treatment guidelines and consensus regarding the approach to treatment, the limited data demonstrating the safety and effectiveness of patiromer in the emergent setting, and the educational gap among patients and providers surrounding the availability and administration of this product. To address the lack of data supporting use in the acute setting, the panel recommended that a study be conducted in the ED setting to evaluate the role of patiromer as a treatment for life-threatening hyperkalemia. If such a trial is conducted, this would require changes to the hospital formulary in order for patients and prescribers to gain access to treatment with patiromer.

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REFERENCES

1. Garth D. Hyperkalemia in emergency medicine. Medscape. Updated September 2, 2016. Available at: http://emedicine.medscape.com/article/766479-overview. Accessed April 18, 2017.

2. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med.* 2009;169(12):1156-62.

3. An JN, Lee JP, Jeon HJ, et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care.* 2012;16(6):R225.

4. Latts LM, Reaven NL, Funk SE, McGaughey KJ, Adamson RT. Hyperkalemia is prevalent in patients with cardiorenal comorbidities. Poster presented at: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 20th Annual International Meeting; May 16-20, 2015; Philadelphia, PA.

5. Hollander-Rodriguez JC, Calvert JF Jr. Hyperkalemia. *Am Fam Phys.* 2006;73(2):283-90.

6. Drawz PE, Babineau DC, Rahman M. Metabolic complications in elderly adults with chronic kidney disease. *J Am Geriatr Soc.* 2012;60(2):310-315.

7. HCUP Nationwide Emergency Department Sample (NEDS). Healthcare Cost and Utilization Project (HCUP). 2014. Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/nedsoverview.jsp. Accessed April 18, 2017.

8. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2014. Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed April 18, 2017.

9. Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol*. 2012;109(10):1510-13.

10. Kovesdy CP. Management of hyperkalemia: an update for the internist. *Am J Med*. 2015;128(12):1281-87.

11. Reaven NR, Funk SE, Bakris GL. The economics of renoprotective therapy in advanced diabetic kidney disease. *Am J Pharm Benefits*. 2014;6(6):e169-e76.

12. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345(12):861-69.

13. Lewis EJ, Hunsicker LG, Clarke WR, et al.; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-60.

14. Yusuf S, Sleight P, Pogue J, et al.; The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):145-53.

15. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care*. 2015;21(11 Suppl):S212-S220.

16. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol*. 2010;5(3):531-48.

17. Sadjadi SA, McMillan JI, Jaipaul N, Blakely P, Hline SS. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Ther Clin Risk Manag*. 2009;5(3):547-52.

18. Desai AS, Swedberg K, McMurray JJ, et al.; CHARM Program Investigators. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM Program. *J Am Coll Cardiol*. 2007;50(20):1959-66.

19. Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. *Pediatr Nephrol*. 2011;26(3):377-84.

20. Ben Salem C, Badreddine A, Fathallah N, Slim R, Hmouda H. Drug-induced hyperkalemia. *Drug Saf*. 2014;37(9):677-92.

21. Hagan AE, Farrington CA, Wall GC, Belz MM. Sodium polystyrene sulfonate for the treatment of acute hyperkalemia: a retrospective study. *Clin Nephrol*. 2016;85(1):38-43.

22. U.S. Food and Drug Administration. Significant dates in U.S. food and drug law history. December 19, 2014. Available at: http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm. Accessed April 18, 2017.

23. Lepage L, Dufour AC, Doiron J, et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol*. 2015;10(12):2136-42.

24. Chaitman M, Dixit D, Bridgeman MB. Potassium-binding agents for the clinical management of hyperkalemia. *P.T.* 2016;41(1):43-50.

25. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med*. 2013;126(3):264.e9-24.

26. Sterns RH, Rojas M, Bernstein P, Chennupati S. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol*. 2010;21(5):733-35.

27. Kayexalate (sodium polystyrene sulfonate). Sanofi-Aventis U.S. 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011287s022lbl.pdf. Accessed April 18, 2017.

28. Abraham SC, Bhagavan BS, Lee LA, Rashid A, Wu TT. Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol*. 2001;25(5):637-44.

29. U.S. Food and Drug Administration. FDA news release. FDA approves new drug to treat hyperkalemia. October 21, 2015. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm468546.htm. Accessed April 18, 2017.

30. Veltassa (patiromer) for oral suspension. Relypsa. Updated November 2016. Available at: https://www.veltassa.com/pi.pdf. Accessed April 18, 2017.

31. Bushinsky DA, Williams GH, Pitt B, et al. Patiromer induced a rapid onset and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. *Kidney Int*. 2015;88(6):1427-33.

32. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211-21.

33. Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium levels in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-61.

34. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ; PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J*. 2011;32(7):820-28.

35. Sterns R, Grieff M, Bernstein P. Treatment of hyperkalemia: something old, something new. *Kidney Int*. 2016;89(3):546-54.

36. Lederer E. Hyperkalemia. Medscape. January 11, 2016. Available at: http://emedicine.medscape.com/article/240903-overview. Accessed April 18, 2017.

37. Youssef M. First in a series on hyperkalemia: hyperkalemia, the sodium potassium pump and the heart. E-Journal of Cardiology Practice. Vol. 14, no. 11. May 24, 2016. Available at: http://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-14/First-in-a-series-on-Hyperkalemia-Hyperkalemia-the-sodium-potassium-pump-and-the-heart. Accessed April 18, 2017.

38. Kiamanesh O, et al. Inappropriate shocks by subcutaneous implantable cardioverter-defibrillator due to T-wave oversensing in hyperkalemia leading to ventricular fibrillation. *Heart Rhythm Case Reports*. 2015;1(4):257-59.

39. Martindale J, deSouza IS. Managing pacemaker-related complications and malfunctions in the emergency department. *Emerg Med Pract*. 2014;16(9):1-21. Available at: http://www.slremeducation.org/wp-content/uploads/2015/02/0914-Pacemakers.pdf. Accessed April 18, 2017.

40. Bortnik M, et al. Transient hyperkalemia-induced T-wave oversensing as a cause of inappropriate ICD charges. *J Cardiol Cases*. 2013;8(5):164-67.

41. Ben Salem C, Badreddine A, Fathallah N, et al. Drug-induced hyperkalemia. *Drug Saf*. 2014;37(9):677-92.

Notes

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