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Focus on Hyperkalemia Management: Expert Consensus and Economic Impacts

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Disclosures
The retrospective cohort study included in this supplement was conducted by Magellan Rx Management and funded by Relypsa.

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

Michael Polson, PharmD, MS; Todd C. Lord, PharmD; Anne Kangethe, MPH, PhD; Lindsay Speicher, JD; Carolyn Farnum, BS; Melanie Brenner, PharmD, BCPS; Nina Oestreicher, PhD, MS; and Paula Alvarez, RPh, MBA, MPH

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

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.

LOS was longer compared with patients without HK. Patients 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

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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.

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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.

Notes

Supplement

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