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Research Paper

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Research Paper

Healthcare resource utilization and costs associated with hyperkalemia in a large managed care population

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Abstract

Background Hyperkalemia is a serious metabolic condition and can lead to life-threatening cardiac arrhythmias and sudden death. Guideline-directed medications that affect the renin-angiotensin-aldosterone axis can increase serum potassium and may limit their use. Hyperkalemia has been shown to drive healthcare resource utilization (HRU) and costs for patients with cardiorenal conditions.

Objectives To describe hyperkalemic patient characteristics and quantify patient HRU and costs relative to normokalemic patients from a large US health plan.

Methods A retrospective cohort study that identified and evaluated a hyperkalemic patient population from a large administrative claims database. The observation period was 1 January 2015 to 31 May 2018, with a 1-year follow-up period after the index date (the earliest service/claim with evidence of hyperkalemia). Primary patient outcomes included inpatient admissions, emergency department (ED) visits, primary care physician (PCP)/specialist visits, length of stay (LOS) and associated medical and pharmacy costs. This hyperkalemic cohort was stratified by renin-angiotensin-aldosterone system inhibitor (RAASi) utilization and chronic kidney disease (CKD) stage for the economic analysis.

Key findings 86,129 adult patients with hyperkalemia were evaluated in the study cohort (median age: 69 years). There were more males [45,155 (52%)], with the majority of patients located in the Southern United States [45,541 (51%)] and a 70/30 split of Medicare to a commercial health plan. Most patients had CKD, hypertension and hyperlipidemia; ≥80% of the patients had ≥4 comorbidities. Over 40% of patients were not receiving RAASi therapy, and potassium binder use was low (<5%). Patients using optimal-dose RAASi with proportion of days covered ≥80% were observed to have the lowest HRU for inpatient admissions, ED and PCP visits and LOS days.

Conclusions Hyperkalemia is associated with substantial HRU and costs. The development of a quality improvement program structured around the management of hyperkalemia in individuals with heart failure, diabetes and/or CKD may be necessary.

Keywords: health economics; pharmaco-economics; managed care; outcomes research; quality of care; hyperkalemia

Introduction

Hyperkalemia is a common electrolyte abnormality that can be severe and life threatening.[1] An estimated 3.7 million US adults had an episode of hyperkalemia in 2014.[2] About half of all patients with hyperkalemia have either chronic kidney disease (CKD) and/or heart failure (HF), and the annual prevalence of hyperkalemia in this population was 6.35%.[3]

The management and prevention of hyperkalemia requires a multidisciplinary approach that entails reducing intake of high potassium foods, adjusting hyperkalemia-inducing medications and adding medications that reduce the plasma potassium concentration.[4, 5] Hyperkalemia is associated with both clinical and economic consequences, including increased emergency department (ED) visits, hospitalizations and mortality. These have a direct bearing on the overall cost of managing patients, especially in a managed care setting.[6]

Patients with CKD may be predisposed to hyperkalemia for a variety of reasons. Principal causes include patients' impaired glomerular filtration rate combined with a frequently high dietary potassium intake relative to residual renal function, a commonly observed extracellular shift of potassium caused by the metabolic acidosis of renal failure.[6–8] Other disease states and therapies that place patients at increased risk for hyperkalemia include diabetes, HF and use of renin-angiotensin aldosterone system inhibitor (RAASi) therapy, which includes angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, direct renin inhibitors and mineralocorticoid-receptor antagonists. Randomized clinical trials have demonstrated that RAASi therapy can reduce the risk of death and slow the disease progression in patients with HF, CKD and diabetes.[2, 9] Increased serum potassium is a common electrolyte change associated with medications that affect the renin-angiotensin-aldosterone axis, limiting their use.[7, 8]

Hyperkalemia drives healthcare resource utilization (HRU) and costs for patients with cardiorenal conditions. In 2011, the estimated total annual hospital charges for Medicare admissions with hyperkalemia as the primary diagnosis were approximately $697 million (US).[6] In 2014, there was an estimated $1.2 billion in total annual hospital charges for patients admitted with a primary diagnosis of hyperkalemia, with an average length of stay (LOS) of 3.3 days and mean charges of $29,181 per stay. Collectively, these factors speak to the potential clinical and economic value of hyperkalemia management in individuals with HF and/or CKD.[10] Patients who are prescribed and tolerate RAASi therapy at maximum recommended doses have been observed to have lower rates of adverse outcomes/death and incur lower total costs compared with patients prescribed submaximum doses across disease cohorts (HF, CKD and diabetes) and payers (Medicare and commercial insurance).[11, 12]

The goal of this study was to describe the characteristics of hyperkalemic patients and quantify HRU and costs relative to normokalemic patients using data from a large US health plan. Comorbid conditions and multiple comorbidity patterns among hyperkalemic patients were also assessed.

Methods

Study design

A retrospective cohort study identified and evaluated patients with hyperkalemia from a large administrative claims database from 1 January 2015 to 31 May 2017. The observation period was 1 January 2015 to 31 May 2018, including a 1-year follow-up period after the index date (defined as the earliest service/claim with evidence of hyperkalemia). This cohort was stratified by RAASi therapy utilization and CKD stage for the economic analysis. All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations. As this study used only statistically de-identified patient records, it was exempted from institutional review board approval.

Patient selection

Individuals were included in this study if they were aged ≥18 years and enrolled in an Aetna fully insured commercial health plan or Medicare Advantage health plan with medical and pharmacy benefits for at least 12 months after the index date. Medical and/or pharmacy claims and laboratory results with service dates from 1 January 2015 to 31 May 2017 were used to identify the hyperkalemic population. Qualifying criteria were:

(1) Two or more potassium lab tests >5.0 mEq/L on different dates (via Logical Observation Identifiers Names and Codes (LOINC; Supplementary Table S1);
(2) OR Two or more diagnosis codes of hyperkalemia (ICD-9-CM code of 276.7 or one ICD-10-CM code of E87.5);
(3) OR One diagnosis code of hyperkalemia and one lab potassium value >5.0 mEq/L;
(4) OR Evidence of a National Drug Code number for either patiromer or sodium polystyrene sulfonate (SPS; Figure 1).

Statistical analyses

Means, standard deviations and medians were reported for continuous variables, and frequencies (percentages) were reported for categorical variables. Comparisons of patient characteristics and outcomes between patients with and without RAASi therapy were performed using the chi-square test (categorical variables) and the Wilcoxon rank-sum test (continuous variables). Multicomorbidities were measured by the number of comorbidities. To evaluate sensitivity of the cutoff point of blood potassium level >5.0 mEq/L for hyperkalemia, a sensitivity analysis was conducted to examine the total healthcare costs using >5.0 to 5.5, >5.5 to 6.0 and >6.0 mEq/L compared with CKD patients with normokalemia. We also performed subgroup analyses to assess the economic impact of hyperkalemia in patients with diabetes and HF. All data management and statistical analyses were conducted using SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC, USA). All P values were two-sided, with $P < 0.05$ considered statistically significant.

Primary endpoints

The primary patient outcomes evaluated in this study included inpatient admissions, ED visits, primary care physician (PCP) visits, specialist visits, LOS and associated medical and pharmacy costs.

Results

A total of 86,129 adult patients were evaluated in the cohort of hyperkalemic patients. Patient characteristics are given in Table 1. Overall, there were more males [45,155 (52%)] in the study population, with the majority of the population located in the Southern United States [45,541 (51%)]. Medicare patients made up 70% of the study population, with the remaining 30% being commercial

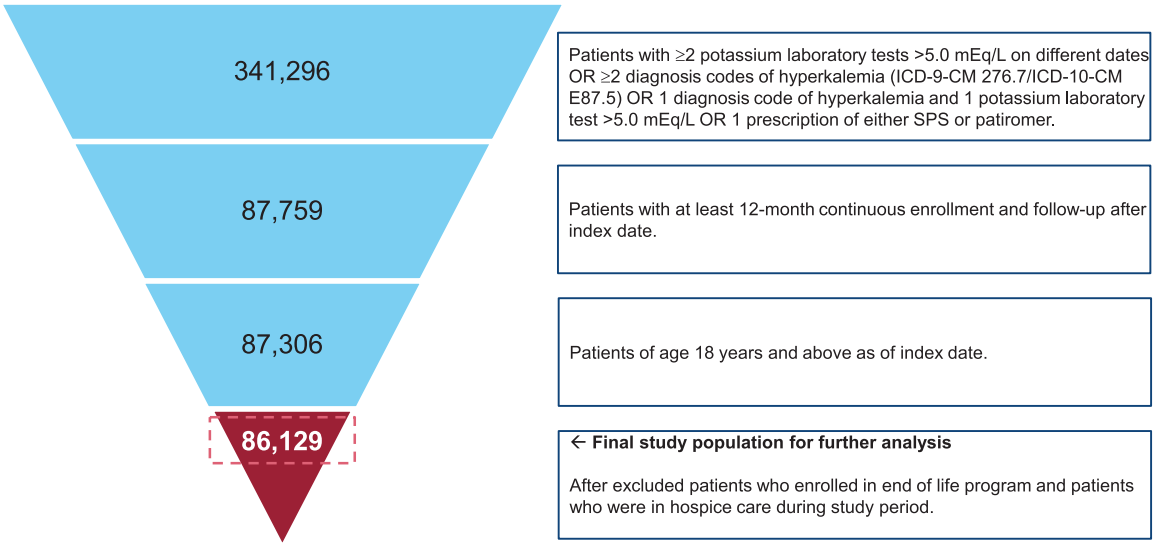

Figure 1 Patient selection and data flow. ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; ICD-10-CM, ICD, Tenth Revision, CM.

patients. The majority of patients had CKD (*n* = 79,084; 92%), hypertension (*n* = 70,146; 81%) and hyperlipidemia (*n* = 68,532; 80%). At least 80% of the study population had ≥4 comorbidities. Over 40% of patients (*n* = 35,536) were not receiving RAASi therapy, including diabetic (*n* = 11,088) and HF (*n* = 6479) patients.

Of the patients using RAASi therapy (*n* = 50,593), approximately 17% (8461) were using the optimal dose with proportion of days covered (PDC) ≥80%. These patients were observed to have the lowest HRU for inpatient admissions (*n* = 1783; 21%), ED visits (*n* = 2267; 27%), PCP visits (*n* = 6983; 83%) and LOS days (*n* = 1.70; 6%; Table 2).

The total healthcare costs [per member per year (PMPY)] by CKD stage [normokalemia (potassium 3.8–5.0 mEq/L) vs. hyperkalemia] 1-year post-index date are given in Figure 2. On average, hyperkalemic patients were more than twice as costly ($20,029) as patients with normal serum potassium ($8570). Nominal (<5%) potassium binder therapy (patiromer/SPS) use was observed in these hyperkalemic patients (Figure 3).

Figure 4 shows the total mean costs (PMPY) for patients both utilizing and not utilizing RAASi therapy. In the RAASi group, total costs (PMPY) were $25,340, whereas the no-RAASi group observed a cost of $26,412. When evaluating patients receiving optimal and suboptimal RAASi doses with a PDC <80%, the total mean costs were $32,739 and $32,831, respectively (Figure 5). In patients with a PDC ≥80%, each group observed lower overall costs, whereas the suboptimal dose showed marginally increased costs [$20,435 and $19,529 (suboptimal RAASi and optimal RAASi dose, respectively)].

The sensitivity analyses showed that the total mean costs (PMPY) increased remarkably by blood potassium level (Supplementary Figure S1). Patients with potassium levels >5.0 to 5.5 mEq/L were more than twice as costly as patients with potassium levels ≤5.0 mEq/L ($18,667 vs. $8570, respectively). Patients with potassium levels >6.0 mEq/L had the highest costs ($30,052 PMPY).

Supplementary Figure S2 shows that hyperkalemic patients without diabetes and HF had the lowest costs ($16,836 PMPY) compared to hyperkalemic patients with diabetes, HF, or both diabetes and HF ($21,451, $35,303 and $46,286 PMPY, respectively).

Discussion

This retrospective cohort study used administrative claims data to construct a large, comprehensive cohort of patients diagnosed with hyperkalemia to profile patients based on demographics, comorbidities, HRU and costs. There are limited published studies characterizing the economic burden of hyperkalemia. A study by Dunn *et al.* in 2015 identified a mean inpatient cost of $24,178 per episode and an average LOS of 3.2 days among patients admitted from EDs to hospitals for elevated potassium levels.[6] In a retrospective database study by Betts *et al.*, patients with hyperkalemia had significantly higher HRU and healthcare costs compared with matched controls.[13] Those with hyperkalemia incurred approximately $4100 more in total healthcare costs over 30 days ($5994 vs. $1865) and approximately $16,000 more in total healthcare costs over 1 year ($31,844 vs. $15,861).[13] Our current study showed that hyperkalemia is associated with substantial HRU and healthcare costs. CKD patients with hyperkalemia utilized more healthcare resources and incurred on average more than twice the healthcare costs of CKD patients without hyperkalemia ($20,029 vs. $8570 annually). More specifically, patients with hyperkalemia and stage 5 CKD receiving dialysis had an observed total cost of $67,758, while normokalemic dialysis patients incurred $37,094.[13] This is also consistent with a study by Polson *et al.*, which showed that hyperkalemic patients with CKD, HF or both CKD and HF had higher overall costs.[10]

Older patients with an advanced stage of CKD, diabetes and/or HF are at higher risk for hyperkalemia. In our study, hyperkalemic patients without diabetes and HF observed lower costs than hyperkalemic patients with diabetes or HF (Supplementary Figure S2). The highest costs were observed in hyperkalemic patients with

Table 1 Patient characteristics

Characteristics	Overall N = 86,129	RAASi use n = 50,593 (58.74%)	No RAASi n = 35,536 (41.26%)	P value
Age				<0.0001
Mean (SD)	67.48 (13.43)	69.36 (11.75)	64.81 (15.11)	
Median, years (interquartile range)	69 (59–77)	70 (62–78)	66 (55–76)	
Gender, n (%)				<0.0001
Male	45,155 (52.43)	27,514 (54.38)	17,641 (49.64)	
Female	40,972 (47.57)	23,078 (45.62)	17,894 (50.35)	
Geographic region, *n* (%)				<0.0001
Midwest	14,955 (17.37)	9346 (18.48)	5609 (15.79)	
Northeast	22,775 (26.46)	13,324 (26.35)	9451 (26.61)	
South	45,541 (50.58)	25,294 (50.02)	18,247 (51.37)	
West	4815 (5.59)	2601 (5.14)	2214 (6.23)	
Urban–rural, *n* (%)				<0.0001
Urban	36,029 (41.83)	20,678 (40.87)	15,351 (43.20)	
Rural	28,164 (32.70)	17,037 (33.67)	11,127 (31.31)	
Median household income ($)				<0.0001
Mean (SD)	61,136 (22,523)	59,909 (21,832)	62,883 (23,360)	
Median (interquartile range)	56,076 (45,037–73,308)	55,269 (44,469–71,913)	57,306 (45,581–76,471)	
Line of business, *n* (%)				<0.0001
Commercial	25,218 (29.28)	11,667 (23.06)	13,551 (38.13)	
Medicare advantage	60,911 (70.27)	38,926 (76.94)	21,985 (61.87)	
Retrospective ERG risk scores				<0.0001
Mean (SD)	4.50 (6.39)	4.68 (6.20)	4.24 (6.64)	
Median (interquartile range)	2.35 (0.63–5.78)	2.69 (0.84–6.15)	1.89 (0.42–5.18)	
Number of comorbid conditions				<0.0001
Mean (SD)	7.32 (3.89)	8.05 (3.64)	6.29 (4.01)	
Median (interquartile range)	7 (4–10)	8 (5–10)	6 (3–9)	
Comorbid condition				
CKD any	79,084 (91.82)	49,098 (92.72)	32,179 (90.54)	<0.0001
CKD stage 1	8632 (10.02)	3415 (6.75)	5127 (14.68)	
CKD stage 2	27,471 (31.90)	14,349 (28.36)	13,122 (36.93)	
CKD stage 3	28,807 (33.45)	20,469 (40.46)	8338 (23.46)	
CKD stage 4	8164 (9.48)	5578 (11.03)	2586 (7.28)	
CKD stage 5	5328 (6.19)	2704 (5.34)	2624 (7.38)	
CKD unspecified	682 (0.79)	393 (0.78)	289 (0.81)	
Hypertension	70,146 (81.44)	49,430 (97.70)	20,716 (58.30)	<0.0001
CKD	79,084 (91.82)	46,908 (92.72)	32,176 (90.54)	<0.0001
Resistant hypertension*	592 (0.69)	429 (0.85)	163 (0.46)	<0.0001
Hyperlipidemia	68,532 (79.57)	44,267 (87.50)	24,265 (68.28)	<0.0001
Diabetes mellitus	41,181 (47.81)	30,093 (59.48)	11,088 (31.20)	<0.0001
Ischemic heart disease	24,336 (28.26)	16,879 (33.36)	7457 (20.98)	<0.0001
Heart failure	22,123 (25.69)	15,644 (30.92)	6479 (18.23)	<0.0001
Medications				
RAASi				
MRAs	5033 (5.84)	5033 (9.95)	0	–
ACEis	32,228 (37.42)	32,228 (63.70)	0	–
ARBs	18,745 (21.76)	18,745 (35.05)	0	–
Direct renin inhibitors	50 (0.06)	50 (0.10)	0	–
Potassium binders	3638 (4.22)	2061 (4.07)	1577 (4.44)	0.0094
NSAIDs	15,944 (18.51)	9258 (18.30)	6686 (18.81)	0.0554
Calcineurin inhibitors	1145 (1.33)	530 (1.05)	615 (1.73)	<0.0001
Potassium-sparing diuretics	1107 (1.29)	751 (1.48)	356 (1.00)	<0.0001
Digoxin	1896 (2.20)	1391 (2.75)	505 (1.42)	<0.0001
Beta-blocker	28,939 (33.60)	19,182 (37.91)	9757 (27.46)	<0.0001

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; ERG, episode risk group; MRA, mineralocorticoid-receptor antagonist; NSAID, non-steroidal anti-inflammatory drug.

*Resistant hypertension was identified by >1 claims with ICD-9/ICD-10 (997.91, I16.0, I16.1, I16.9) at least 7 days apart.

both diabetes and HF (Supplementary Figure S2). These findings are similar to the study by Betts *et al*. that reported a significant economic burden associated with hyperkalemic patients with comorbidities.[13]

Treatment with RAASi agents has been shown to reduce morbidity and mortality in patients with CKD, HF or both, and treatment guidelines recommend the use of these medications at optimal

Table 2 HRU for RAASi use by PDC and optimal dose

HRU	No RAASi (n = 35,536)	Total RAASi use (n = 50,593)	P value	Optimal RAASi dose and PDC ≥80% (n = 8461)	Optimal RAASi Dose and PDC <80% (n = 4831)	P value
Patients with at least one visit, n (%)						
Inpatient admission	9048 (25.46)	14,501 (28.66)	<0.0001	1783 (21.07)	1762 (36.47)	<0.0001
ED visit	10,357 (29.15)	15,758 (31.15)	<0.0001	2267 (26.79)	1762 (36.47)	<0.0001
PCP visit	29,862 (84.03)	42,480 (83.96)	0.7916	6983 (82.53)	4031 (83.69)	0.0933
Specialist visit	30,040 (84.53)	43,345 (85.66)	<0.0001	7244 (85.62)	4141 (85.72)	0.8977
Number of visits, mean (SD)						
Inpatient admission	0.49 (1.16)	0.54 (1.18)	<0.0001	0.32 (0.78)	0.73 (1.45)	<0.0001
ED visit	0.64 (1.75)	0.67 (1.69)	<0.0001	0.52 (1.24)	0.81 (1.87)	<0.0001
PCP visits	4.16 (4.43)	4.65 (4.78)	<0.0001	4.26 (4.23)	4.78 (5.02)	<0.0001
Specialist visit	6.35 (7.49)	6.65 (7.31)	<0.0001	6.25 (6.91)	7.02 (7.51)	<0.0001
LOS, days mean (SD)	3.25 (10.69)	3.31 (10.17)	<0.0001	1.70 (5.86)	4.86 (13.60)	<0.0001

ED, emergency department; HRU, healthcare resource utilization; LOS, length of stay; PCP, primary care physician; PDC, proportion of days covered; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation.

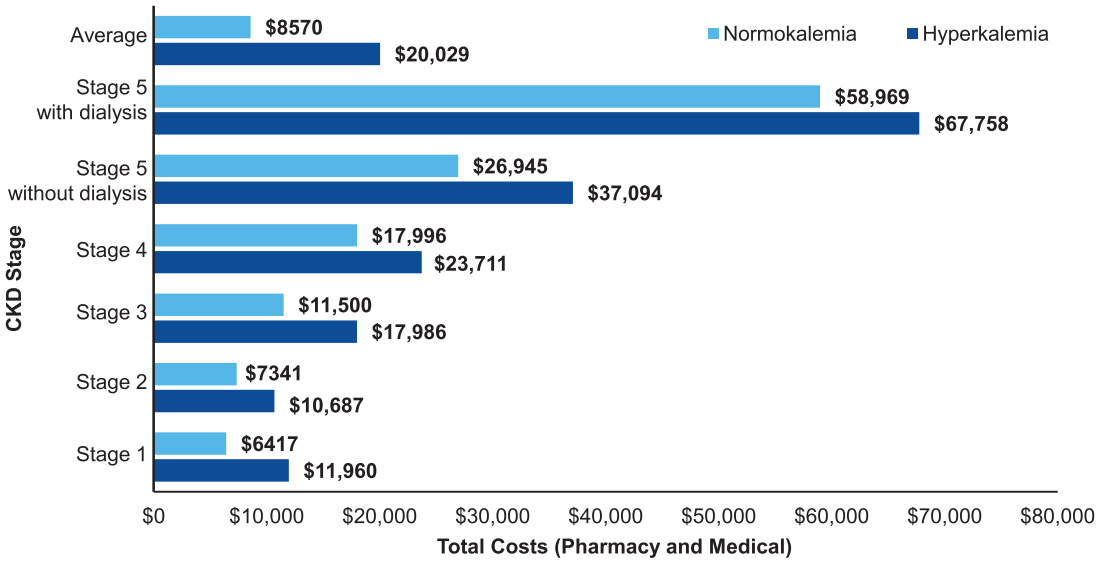

Figure 2 Total health care costs (PMPY) by CKD stage: normokalemia vs hyperkalemia (post-index 1 year).

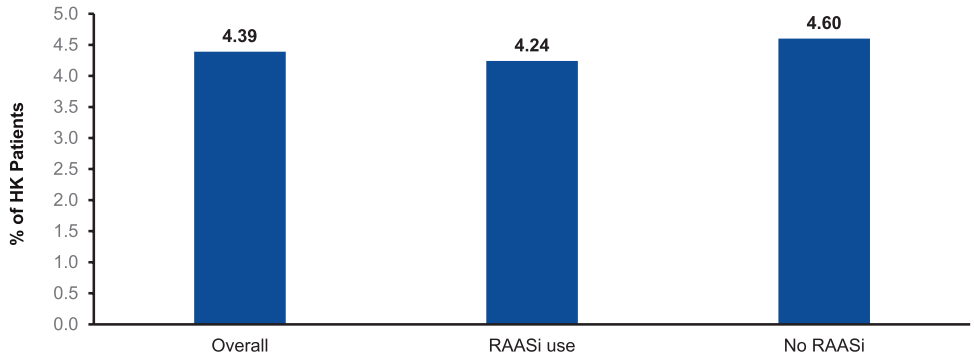

Figure 3 Potassium-binder utilization (%) by RAASi use.

doses to manage these patients.[12,14] This analysis found a significant percentage CKD patients with cardiorenal comorbidities are not receiving guideline-directed medical therapies, revealing an important opportunity to improve treatment. In our study, we observed that only 26% of patients received an optimal dose of their RAASi medication. Of these patients, 64% achieved a PDC ≥80%. When evaluating this patient profile (optimal-dose RAASi and PDC ≥80%), there was an observed decrease in inpatient admissions, ED visits and PCP/specialist visits. These results are consistent with the findings of a study by Epstein *et al.*, which demonstrated

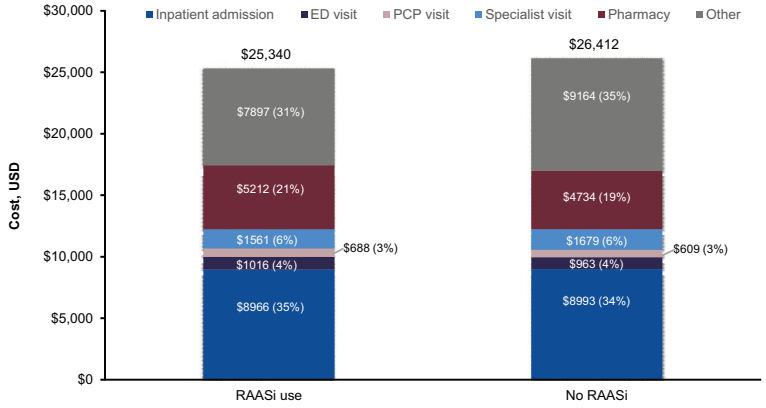

Figure 4 Total mean costs (PMPY) by RAASi versus no RAASi utilization. USD, US dollars.

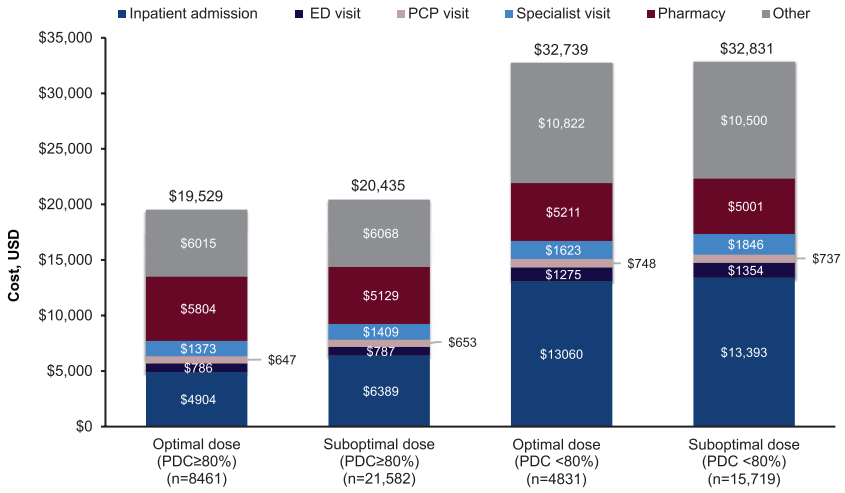

Figure 5 Total mean costs (PMPY) for RAASi use by PDC and optimal dose. USD, US dollars.

that patients receiving RAASi therapies at maximum doses incurred lower total costs than patients prescribed RAASi therapies at submaximum doses.[11]

Managing hyperkalemia in patients with cardiorenal diseases poses a challenge for clinicians. Electing to not use RAASi treatment in this patient population may lead to poor health outcomes and increased healthcare costs. One option for meeting this challenge is chronic treatment of hyperkalemia with contemporary potassium binders such as patiromer and sodium zirconium cyclosilicate. The consistency of results across prospective clinical trials supports the chronic use of novel potassium binders up to 1 year.[5, 15] However, we observed that potassium-binder therapy continues to be underutilized with only 4.4% of patients prescribed a binder during the study period.

Limitations

This is a descriptive observational study; therefore, no causal relationships can be derived. We have assumed that patients were taking the medications that were dispensed. The identification of hyperkalemia depended in part on the serum potassium laboratory data. It is possible that some laboratory tests performed were not present in the claims data. For example, tests done in hospitals or ED visits would be bundled in ED visit or inpatient claims. However, these patients would be identified using ICD-9-CM or ICD-10-CM codes from the claims data. Comorbidities were identified using ICD-9-CM and ICD-10-CM codes, which are used for administrative purposes. As a result, certain comorbidities may be underestimated.

Conclusions

Hyperkalemia is associated with substantial HRU and healthcare costs and remains a significant healthcare burden. In this study, patients with hyperkalemia were more likely to be hospitalized, visit the ED or see a PCP or specialist as an outpatient. The development of a quality improvement program structured around the management of hyperkalemia in individuals with CKD, HF and/or diabetes may be necessary to optimize RAAS inhibitor treatment and reduce costs.

Supplementary Material

Supplementary data are available at *Journal of Pharmaceutical Health Services Research* online.

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Author Contributions

All authors fully contributed to the content of this manuscript, including meeting the four criteria of the Internal Committee of Medical Journal Editors. All authors had full access to all of the data in the study and take full responsibility for the integrity of the work and the accuracy of the data analysis, from inception to published article.

Conflict of Interest

A.S. reports serving as a clinical investigator for and employment by Healthagen, an affiliate of Aetna Inc., part of the CVS Health family of companies, New York, NY, which conducted research funded by Relypsa, Inc., a Vifor Pharma Group Company, Redwood City, CA. P.J.A., S.D.W. and J.F. report employment by Relypsa, Inc., a Vifor Pharma Group Company, and stock in Vifor Pharma, Glattbrugg, Switzerland. D.D. reports serving as a lead scientist for and employment by Healthagen, an affiliate of Aetna Inc., part of the CVS Health family of companies, New York, NY, which conducted research funded by Relypsa, Inc., a Vifor Pharma Group Company.

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