

Evaluation of Clinical Outcomes and Costs Based on Prescribed Dose Level of Renin-Angiotensin-Aldosterone System Inhibitors

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Renin-angiotensin-aldosterone system (RAAS) inhibitors, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and mineralocorticoid receptor antagonists, have been shown to reduce mortality and slow disease progression in patients with heart failure (HF), chronic kidney disease (CKD), and diabetes.¹⁻⁶ Current evidence-based guidelines consider RAAS inhibitors as integral components in the management and treatment of patients with HF^{7,8} and CKD^{9,10} and of patients with diabetes and comorbid hypertension or renal impairment.^{11,12} However, concerns related to hyperkalemia risk and other risks with the use of RAAS inhibitors have contributed to sub-therapeutic dosing, discontinuation, and avoidance of RAAS inhibitors when clinically indicated.¹³⁻¹⁵ As a result, there is a large gap between guideline recommendations and real-world clinical practice in the use of RAAS inhibitors.¹⁶⁻²¹

To better elucidate this treatment gap, we recently published a comprehensive retrospective analysis of an electronic medical records database covering more than 1.7 million patients to evaluate 3 pivotal concerns: (1) whether RAAS inhibitors are being prescribed according to treatment guidelines for HF, CKD, and diabetes; (2) what happens to prescriptions for RAAS inhibitors after hyperkalemia events; and (3) whether clinical outcomes are affected in patients who are prescribed doses below guideline recommendations or whose RAAS inhibitors are discontinued.²² We identified a substantial gap between guideline recommendations and real-world prescribing patterns for RAAS inhibitors, with 58% to 65% of patients prescribed lower-than-recommended doses and approximately 15% discontinued from RAAS inhibitor therapy. The prescribing patterns for RAAS inhibitors appeared to be significantly altered by the development of hyperkalemia. An association was found between RAAS inhibitor dose and the development of serious adverse outcomes or death, favoring the use of RAAS inhibitors at guideline-recommended doses, when possible. Taken together, these findings highlight the challenge behind RAAS inhibitor prescribing decisions in which clinicians attempt to balance treatment benefits against the risk of provoking hyperkalemia.

ABSTRACT

Objectives: This study examined associations among renin-angiotensin-aldosterone (RAAS) inhibitor dose level, clinical outcomes, and costs in a US patient population.

Study Design: De-identified medical records (Humedica: 1.7 million records) were analyzed for patients with 2 or more serum potassium readings between 2007 and 2012; 1 or more RAAS inhibitor prescriptions before July 1, 2009 (index date); and 12 months of data before and 90 days' data after the index date.

Methods: Patients (N = 198,775) were assigned to payer category based on age (≥ 65 years, Medicare; < 65 years, commercial insurance) and classified by comorbidities (chronic kidney disease, heart failure, or diabetes) at index and prescribed postindex RAAS inhibitor dose levels. Postindex adverse cardiovascular and renal outcomes and mortality were evaluated. Costs from a US medical claims database were assigned to observed all-cause utilization and were annualized and compared by RAAS inhibitor dose level. Multivariate regression was used to examine predictors of annualized total costs.

Results: Patients on the maximum recommended dose of RAAS inhibitors had lower rates of adverse outcomes/mortality and incurred significantly lower annualized total costs than patients receiving submaximum doses in all disease cohorts in both Medicare and commercial insurance populations ($P < .001$ for all cost comparisons). Although cost differences were not statistically significant, the maximum dose groups also had better clinical outcomes than those whose RAAS inhibitors were discontinued, possibly reflecting a lower level of engagement with the healthcare system by patients in whom therapy was discontinued. Multivariate analysis identified preindex hyperkalemia as a strong predictor of postindex costs, raising them by 21% to 64%, depending upon disease cohort and payer category.

Conclusions: Patients prescribed the maximum recommended doses of RAAS inhibitors had better clinical outcomes and incurred lower total costs than those prescribed lower-than-recommended doses.

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For author information and disclosures, see end of text.

This treatment decision process takes place in a healthcare environment with juxtaposing objectives of balancing therapeutic quality with spiraling medical costs. To balance these objectives, there is a need to better understand the implications of *care* on costs. Therefore, in the current study, we expanded our previous investigation by examining medical system costs in relation to RAAS inhibitor use in the same patient populations, as well as the influence of hyperkalemia as a determinant of RAAS inhibitor use and cost. We compared annualized all-cause medical and pharmacy costs from a payer perspective for patients classified by whether they were prescribed the recommended dose of RAAS inhibitor per each agent's product label, were prescribed a lower-than-recommended dose, or had been discontinued from their RAAS inhibitors.

Methods

Study Population and Cohorts

The original study²² involved selecting patients who had at least 2 potassium test results between 2007 and 2012 from a large US database of electronic health records (EHRs) (Humedica). Records from patients with sufficient data and without preindex end-stage renal disease (ESRD), who had one or more RAAS inhibitor prescriptions prior to the fixed index date of July 1, 2009, were examined (specific medications and their dose levels included in each dose category are listed in **eAppendix Box 1**, available at www.ajmc.com). The current analysis further excluded patients with less than 90 days of postindex data and those to whom RAAS inhibitor doses exceeding the maximum recommended dose listed in the package insert were prescribed.

Age was used to assign patients to 2 payer categories: those covered by Medicare (age ≥ 65 years) and those covered by commercial insurance (age < 65 years, including 373 patients whose ages were unspecified). Nonexclusive cohorts of patients with CKD (stages 3a, 3b, or 4, identified by estimated glomerular filtration rate [eGFR] or diagnosis code), HF (by diagnosis code), or diabetes (by single diagnosis code, glycated hemoglobin [A1C] $\geq 6.5\%$, or single outpatient written prescription for a hypoglycemic agent) were analyzed separately for each payer category. (All hypoglycemic agents used to identify diabetes are listed in **eAppendix Box 2**, available at www.ajmc.com. Only 4% of diabetes was identified through a drug prescription alone.)

As in the previous study, adverse outcomes included stroke, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, CKD progression, or progression to ESRD. Death was documented according to the Social Security Death Register or from the EHR. RAAS inhibitor prescriptions were classified by dose level as "maximum" (the recommended labeled dose), "submaximum" (any lesser amount), or "discontinued" (> 390 days elapsed since the most recent prescription, with this time period allowing 30 days past

the longest common prescription length for patients to seek prescription renewal). RAAS inhibitor dose level was classified as of the patient's first adverse outcome or death (if applicable) or the dominant dose level of RAAS inhibitor prescriptions during the postindex period (in the absence of adverse outcomes or death), as defined in published supplemental data.²² Hyperkalemia was defined as a serum potassium level between 5.1 and 10.0 mEq/L (mild, 5.1 to 5.4 mEq/L; moderate-to-severe, ≥ 5.5 mEq/L).

Classification of Services and Medications

In the EHR data, healthcare services were grouped by calendar day and classified as inpatient (IP) admissions or emergency department (ED) visits or by type of outpatient (OP) services (inclusive of OP hospital surgeries, diagnostics, or visits, along with office, laboratory, or home visits). Medications prescribed in the OP setting were identified by generic name of the primary ingredient, irrespective of dose, brand, or formulation.

Cost of Services in Claims Data

Average health plan-allowed cost was obtained from 2013 commercial insurance and Medicare claims data (OptumInsight, Minneapolis, MN) as follows: per IP day, for multiple categories of surgical and nonsurgical admissions; per visit, for multiple categories of hospital/facility OP visits; and per calendar day for physician services in office, hospital OP, and hospital IP settings. Costs were normalized to 2016 US dollars at 3% per annum.

All-Cause Costs: Application of Cost of Services in Claims Data to Services Identified in Medical Records Data

The relevant cost per service derived from commercial and Medicare insurance claims was applied to each service event among patients in the commercial and Medicare groups, respectively. For IP costs, the average allowed cost per day of hospital plus IP physician care was applied to each hospitalization day using length-of-stay information and whether the claims were for medical or surgical admissions. The length of time in the intensive care unit was accounted for. Base costs were adjusted depending upon patient comorbidities (HF, diabetes, CKD stages 3/4). For OP/ED costs, the relevant average allowed cost per hospital visit plus the average allowed cost per day of physician services in the hospital OP setting was applied to each ED visit and other hospital OP visits. Relevant costs per visit were applied to each office visit (average allowed cost per day of physician services in the office setting), home health visit, and laboratory visit.

Cost of OP Medications

Data on the average cost per filled prescription and percent refills were obtained from 2013 commercial insurance and Medicare

claims (OptumInsight) for 120 medications, which, together, made up 75% of all postindex OP prescriptions. The average cost per prescription (original + average refills) was calculated and applied to written OP prescriptions for each evaluated medication. The average cost per prescription for all evaluated medications combined was assigned for all other prescriptions.

Outcomes and Descriptive Analyses

The primary clinical end point was a composite of any adverse outcome or mortality; the secondary end point was mortality alone. Both end points were assessed from July 1, 2009, through the patient's last interaction or December 31, 2012 (postindex period; median follow-up, 3.4 years). Additional end points included mean annualized all-cause cost per patient, measured during the postindex period for all patients and further stratified by the presence or absence of the primary or secondary clinical end points. Costs of all postindex services and medications were summed by category (IP, ED, OP, and prescriptions), totaled for each patient, and annualized (postindex cost divided by number of days from index date to patient's last interaction with the healthcare provider). For each clinical and cost end point, results were assessed separately within the commercial and Medicare groups for each disease cohort and the total population, stratified by RAAS inhibitor dose level. For cost analyses, median, 25th, and 75th percentile values were also analyzed. Post hoc exploratory analyses were used to assess the factors driving findings regarding patients on discontinued versus submaximum RAAS inhibitor doses.

Patient engagement was assessed by the number of office/clinic visits in the patient's last 12 months of interaction with the healthcare provider system (including preindex data, if necessary) and was classified as disengaged (0 to one visits) or engaged (≥ 2 visits). Mean cost per patient per year was stratified by level of engagement in the CKD cohort. Additionally, in-hospital deaths were identified by discharge status, and the proportion and impact of in- versus out-of-hospital deaths were assessed.

The percentage of patients with hyperkalemia during the preindex period was assessed in the total original study population ($N = 201,655$).²² The frequency of RAAS inhibitor dosing changes following mild and moderate-to-severe hyperkalemia events was evaluated for all hyperkalemia events in the preindex period in patients on maximum recommended or submaximum RAAS inhibitor doses at the time, comparing the pre-event RAAS inhibitor dose with the first RAAS inhibitor dose level after the hyperkalemia event.

Statistical Analyses

Statistical comparisons were made by χ^2 for the primary and secondary clinical end points and by an analysis of variance (ANOVA) for the annualized total postindex cost per patient between RAAS inhibitor dose levels (overall and pairwise) among patients within

each disease cohort and payer classification. Comparisons of postindex costs per patient among, and between patients within RAAS inhibitor dose categories, who did or did not experience the primary composite end point (adverse outcome/death) or the secondary end point (death), were similarly performed. Pairwise statistical comparisons between RAAS inhibitor dose levels were made by ANOVA and adjusted using the Bonferroni correction of Holm. RAAS inhibitor dosing response was evaluated by ANOVA for mild versus moderate hyperkalemia events, segmented by pre-event RAAS inhibitor dose level.

Multivariate regression analyses were conducted within each disease cohort (segmented by payer) to assess predictors of annualized total cost (log-transformed). Independent variables, evaluated with a stepwise selection procedure (using $\alpha = 0.05$), included RAAS inhibitor dose category (forced into all models), age, gender, preindex hyperkalemia, eGFR, number of target comorbidities, and interaction terms. *P* values less than 0.05 were considered significant. All statistical analyses were carried out using SAS/STAT[®] software, version 9.2, of the SAS[®] System for Windows.

Results

Study Population Characteristics

Patient demographics and characteristics for both commercial (<65 years) and Medicare (≥ 65 years) databases are presented in **Tables 1A** and **1B**. Of the 201,655 patients included in the published outcomes study,²² 707 were above the maximum recommended dose level and were excluded from this analysis. For the remaining 200,948 patients, 2173 had less than 90 days of postindex data and were excluded, leaving 198,775 for the cost-study population. The commercial cohort (<65 years) consisted of 107,877 patients (50% female; mean age, 53 years), and the Medicare (≥ 65 years) cohort included 90,898 patients (56% female; mean age, 75 years).

Rates of Adverse Outcomes or Death by Comorbidity and RAAS Inhibitor Dose

Overall, patients to whom the maximum recommended dose of RAAS inhibitors was prescribed experienced better clinical outcomes, as manifested by lower adverse outcomes/death rates compared with patients prescribed submaximum doses or those with discontinued RAAS inhibitor treatment in each disease cohort for both commercial and Medicare cohorts ($P < .0001$ for each payer, within each cohort). For patients younger than 65 years, no significant difference was seen in rates of adverse outcomes or death for maximum compared with submaximum doses for CKD stages 3-4 (34.7% vs 36.8%; $P = \text{NS}$) and diabetes (20.6% vs 19.8%; $P = \text{NS}$); however, in the HF group, the maximum-dose group had lower rates of adverse outcomes or death (31.6% vs 35.7%; $P = .0103$) (**Figure 1A**). Rates of adverse outcomes or death for maximum compared with discontinued doses were lower for CKD stages 3-4 (34.7% vs

TABLE 1A. Study Population Characteristics by Payer Among Patients Younger Than 65 Years (Commercial)^a

Cohort:	CKD Stages 3-4					Heart Failure					Diabetes					Total Commercial Population				
	Max	Submax	Discont'd	Total	Total	Max	Submax	Discont'd	Total	Total	Max	Submax	Discont'd	Total	Total	Max	Submax	Discont'd	Total	
RAAS Inhibitor Dose:																				
Patients (N)	2457	5910	2236	10,603	1148	3817	1267	6232	9033	24,935	6119	40,087	21,353	68,597	17,927	107,877				
Gender ^b																				
Female	42.4%	43.8%	44.8%	43.7%	45.9%	41.1%	46.3%	43.1%	49.0%	48.8%	51.8%	49.3%	48.0%	48.4%	53.7%	49.2%				
Male	56.9%	55.2%	54.2%	55.4%	53.5%	58.0%	52.2%	56.0%	50.7%	50.8%	47.5%	50.3%	51.7%	51.2%	45.9%	50.4%				
Age (mean), years	56.5	56.1	55.0	56.0	54.7	54.2	53.1	54.1	54.6	53.5	52.5	53.6	53.8	52.6	51.3	52.6				
Race																				
African American	33.0%	22.1%	24.1%	25.1%	37.0%	19.6%	26.4%	24.2%	23.2%	15.8%	16.2%	17.5%	18.6%	12.9%	14.0%	14.2%				
Comorbidity count (mean)																				
Comorbidity count ^c	1.8	1.8	1.7	1.8	1.9	1.8	1.9	1.8	1.4	1.5	1.5	1.5	0.9	0.9	0.9	0.9				
RAAS inhibitor therapy category																				
ACE inhibitor only	46.6%	72.4%	0.0%	51.2%	57.1%	67.6%	0.0%	51.9%	49.1%	78.3%	0.0%	59.8%	44.8%	77.3%	0.0%	58.0%				
ARB only	48.4%	18.3%	0.0%	21.4%	36.4%	15.5%	0.0%	16.2%	47.1%	16.9%	0.0%	21.1%	52.1%	18.3%	0.0%	22.0%				
Insurance type ^d																				
Commercial	61.9%	48.1%	41.8%	49.9%	59.8%	42.0%	39.3%	44.7%	65.3%	54.7%	46.4%	55.8%	65.3%	57.2%	49.0%	57.4%				
Medicare	16.7%	20.1%	20.0%	19.3%	19.5%	22.4%	24.3%	22.3%	10.5%	12.3%	12.9%	12.0%	8.2%	8.7%	10.0%	8.8%				
Medicaid	2.2%	4.0%	4.5%	3.7%	2.3%	5.4%	5.4%	4.9%	1.7%	3.1%	3.7%	2.9%	1.3%	2.3%	3.2%	2.3%				
Other/uninsured/unknown	19.3%	27.9%	33.7%	27.1%	18.4%	30.2%	30.9%	28.2%	22.5%	30.0%	37.0%	29.4%	25.2%	31.8%	37.8%	31.5%				
Hyperkalemia																				
Preindex serum potassium	28.5%	35.6%	38.6%	34.6%	24.5%	30.1%	34.6%	30.0%	16.6%	18.4%	20.9%	18.4%	12.6%	13.2%	14.7%	13.3%				
≥5.1 mEq/L																				

^aACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; RAAS, renin-angiotensin-aldosterone system.

^bCosts of services were obtained for commercial and Medicare plans only. Except in the insurance type detail section, "commercial" indicates patients younger than 65 years or age unknown; "Medicare" indicates patients 65 years and older.

^cGender was unspecified for 0.2% of the total study population (n = 373).

^dComorbidity count is based on HF, CKD stages 3-5, and diabetes (range, 0-3).

^eInsurance type detail is reported as of the last preindex date on which an insurance type other than "unknown" was identified.

42.3%), HF (31.6% vs 42.3%), and diabetes (20.6% vs 26.9%), with $P < .0001$ for all pairwise comparisons. Rates of adverse outcomes or death in the diabetes cohort for all doses (range 19.8%-26.9%) were much lower compared with HF (range 31.6%-42.3%) and CKD stages 3-4 (range 34.7%-42.3%).

For patients 65 years and older, maximum recommended dosing was associated with fewer adverse outcomes or deaths compared with submaximum and discontinued dosing for CKD stages 3-4 (45.3% vs 50.1% vs 57.7%), HF (50.2% vs 58.7% vs 66.1%), and diabetes (39.0% vs 42.8% vs 53.9%), respectively (Figure 1B), with $P < .0001$ for all pairwise comparisons. Adverse outcomes or deaths for the diabetes cohort were generally lower than the CKD stages 3-4 or HF cohorts for all doses. Maximum recommended dosing was associated with the lowest mortality in each disease cohort for both age groups; all mortality comparisons, $P < .0001$ (eAppendix Figure 1, available at www.ajmc.com).

Associated Costs by RAAS Inhibitor Dosing and Comorbidity

In the younger-than-65-years population, the average cost in the maximum recommended dose group was significantly lower compared with the submaximum group for CKD stages 3-4 (\$21,972 vs \$32,184), HF (\$26,308 vs \$38,188), and diabetes (\$15,448 vs \$18,527), respectively; $P < .0001$ for all. Similarly, maximum dose was associated with significantly lower costs compared with the discontinued group in patients with CKD stages 3-4 (\$21,972 vs \$28,344) and diabetes (\$15,448 vs \$17,428); $P < .01$ for both. Of note, however, is that the difference was not statistically different for those with HF (\$26,308 vs \$30,703; $P = NS$) (Figure 2A). In the diabetes cohort, observed cost differences between the submaximum

TABLE 1B. Study Population Characteristics by Payer Among Patients 65 Years and Older (Medicare)^a

Cohort: RAAS Inhibitor Dose:	CKD Stages 3-4				Heart Failure				Diabetes				Total Medicare Population			
	Max	Submax	Discont'd	Total	Max	Submax	Discont'd	Total	Max	Submax	Discont'd	Total	Max	Submax	Discont'd	Total
Patients (N)	6604	17,719	7223	31,566	2216	8045	3341	13,602	8977	21,805	6911	37,693	18,822	53,921	18,155	90,898
Gender ^b																
Female	58.9%	54.1%	53.2%	54.9%	56.3%	51.3%	54.5%	52.9%	57.0%	52.5%	51.0%	53.3%	59.1%	55.8%	55.5%	56.4%
Male	41.1%	45.9%	46.8%	45.1%	43.7%	48.7%	45.5%	47.1%	43.0%	47.5%	49.0%	46.7%	40.9%	44.2%	44.5%	43.6%
Age (mean), years	76.1	76.8	77.6	76.9	75.9	76.8	77.9	77.0	73.6	74.0	75.1	74.1	74.1	74.4	75.8	74.6
Race																
African American	22.0%	11.1%	10.8%	13.3%	22.0%	8.9%	9.9%	11.3%	19.4%	10.7%	10.4%	12.7%	15.5%	8.3%	8.2%	9.8%
Comorbidity count (mean)	1.8	1.9	1.8	1.9	2.1	2.1	2.2	2.2	1.8	1.9	1.9	1.9	1.2	1.4	1.4	1.3
Comorbidity count ^c	1.8	1.9	1.8	1.9	2.1	2.1	2.2	2.2	1.8	1.9	1.9	1.9	1.2	1.4	1.4	1.3
RAAS inhibitor therapy category																
ACE inhibitor only	47.7%	68.6%	0.0%	48.5%	52.7%	64.7%	0.0%	46.9%	49.1%	71.9%	0.0%	53.3%	47.4%	72.1%	0.0%	52.6%
ARB only	48.7%	23.1%	0.0%	23.2%	42.5%	21.0%	0.0%	19.4%	47.4%	22.0%	0.0%	24.0%	49.8%	22.4%	0.0%	23.6%
Insurance type ^d																
Commercial	6.7%	6.8%	7.0%	6.8%	6.5%	7.3%	6.8%	7.0%	7.9%	8.0%	7.1%	7.8%	8.2%	7.9%	7.9%	8.0%
Medicare	70.1%	60.8%	56.0%	61.6%	71.4%	59.8%	56.3%	60.8%	66.3%	59.8%	54.2%	60.3%	64.9%	58.1%	54.0%	58.7%
Medicaid	0.2%	0.5%	0.7%	0.5%	0.2%	0.7%	0.9%	0.7%	0.2%	0.5%	0.8%	0.5%	0.2%	0.3%	0.6%	0.4%
Other/Uninsured/Unknown	23.1%	32.0%	36.3%	31.1%	21.9%	32.3%	36.1%	31.5%	25.6%	31.8%	37.9%	31.4%	26.7%	33.6%	37.5%	33.0%
Hyperkalemia																
Preindex serum potassium ≥5.1 mEq/L	32.3%	35.5%	38.0%	35.4%	30.7%	37.3%	40.6%	37.0%	25.7%	28.5%	31.4%	28.4%	21.3%	22.4%	24.9%	22.7%

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; HF, heart failure; RAAS, renin-angiotensin-aldosterone system.

^aCosts of services were obtained for commercial and Medicare plans only. Except in the insurance type detail section, "commercial" indicates patients younger than 65 years or age unknown; "Medicare" indicates patients 65 years and older.

^bGender was unspecified for 0.2% of the total study population (n = 373).

^cComorbidity count is based on HF, CKD stages 3-5, and diabetes (range, 0-3).

^dInsurance type detail is reported as of the last preindex date on which an insurance type other than "unknown" was identified.

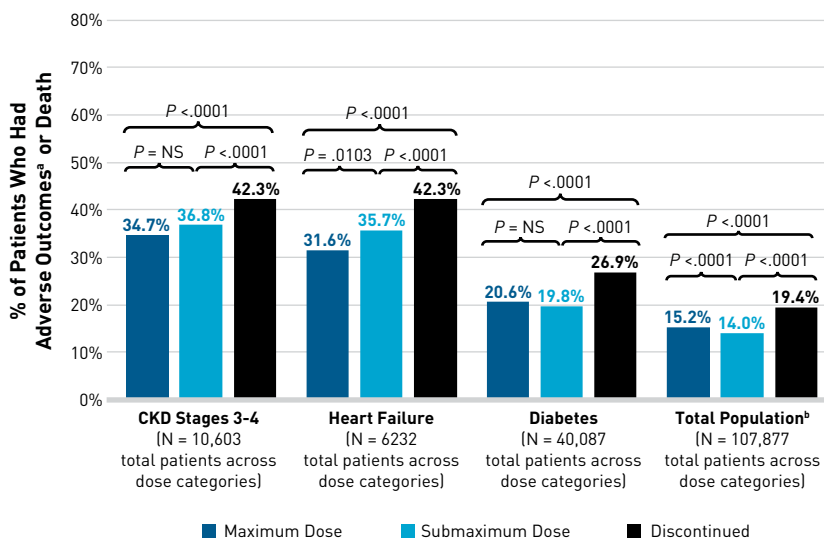
and discontinued dose groups were not significantly different. The most costly population was the HF cohort; the least costly was the diabetes group.

For patients 65 years and older, the cost in the maximum recommended dose group was significantly lower than that in the submaximum group for patients with CKD stages 3-4 (\$18,600 vs \$23,589), HF (\$24,241 vs \$31,167), and diabetes (\$17,114 vs \$20,862), respectively (all *P* < .0001) (Figure 2B). The cost in the submaximum group was also significantly higher compared with the discontinued group for CKD stages 3-4 (\$23,589 vs \$18,438), HF (\$31,167 vs \$22,271), and diabetes (\$20,862 vs \$17,935), respectively; *P* < .0001. Costs for all disease cohorts were not significantly different between the maximum and discontinued groups. Similar to the younger-than-65-years population, HF was the mostly costly disease cohort.

Adverse Outcomes/Death as a Determinant of Cost

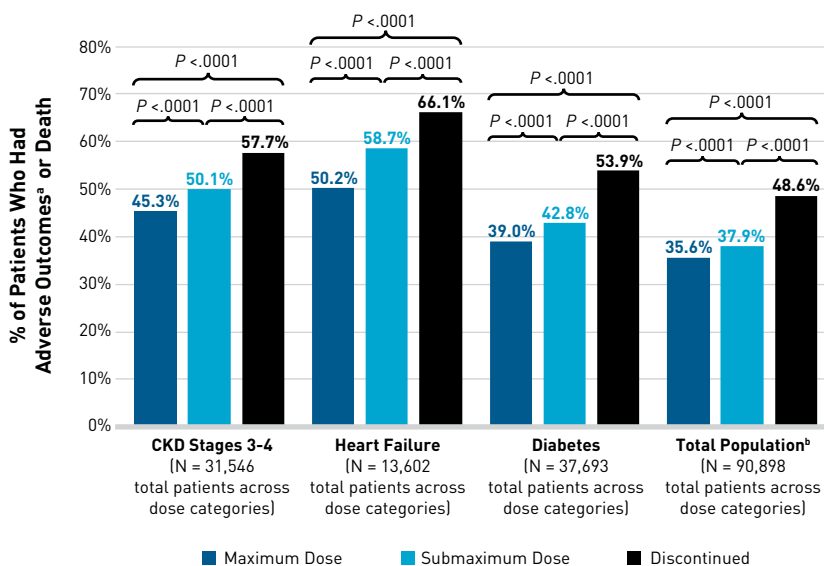
Within all groups, costs were substantially higher for patients who experienced adverse outcomes/death (*P* < .0001; Figures 3A and 3B; see Appendix Table 1 [available at www.ajmc.com] for median cost and 25th and 75th percentiles of the annualized total cost). For the commercial group (<65 years; Figure 3A), the maximum recommended dose group was consistently associated with lower costs compared with the submaximum dose group for CKD stages 3-4 (\$40,985 vs \$62,789), HF (\$53,786 vs \$79,059), and diabetes (\$33,874 vs \$49,548; *P* < .001 for all comparisons) for patients with adverse outcomes/death. For those who did not have adverse outcomes/death, costs for maximum doses were significantly lower for CKD stages 3-4 (\$11,879 vs \$14,336) and trended lower in HF (\$13,602 vs \$15,461; *P* = NS). On average, the incremental cost impact of adverse

FIGURE 1A. Rates of Adverse Outcomes or Death by Payer, Disease Cohort, and RAAS Inhibitor Dose Level Among Patients Younger Than 65 Years (Commercial)



CKD indicates chronic kidney disease; NS, not significant; RAAS, renin-angiotensin-aldosterone system. ^aAdverse outcomes included stroke, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or CKD progression. ^bTotal population also includes all patients younger than 65 years meeting inclusion criteria who were prescribed RAAS inhibitor treatment but had no evidence of CKD stages 3-4, heart failure, or diabetes.

FIGURE 1B. Rates of Adverse Outcomes or Death by Payer, Disease Cohort, and RAAS Inhibitor Dose Level Among Patients 65 Years and Older (Medicare)



CKD indicates chronic kidney disease; RAAS, renin-angiotensin-aldosterone system. ^aAdverse outcomes included stroke, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or CKD progression. ^bTotal population also includes all patients 65 years and older meeting inclusion criteria who were prescribed RAAS inhibitor treatment but had no evidence of CKD stages 3-4, heart failure, or diabetes.

outcomes/death was lowest in the maximum dose group across all disease cohorts.

For patients 65 years and older with CKD stages 3-4 or HF, the discontinued dose group was consistently associated with significantly lower costs compared with both the submaximum and maximum recommended dose groups, irrespective of whether or not patients experienced adverse outcomes/death (Figure 3B; $P < .05$ for all). The average cost among patients with adverse outcomes/death was significantly lower in the maximum dose group compared with the submaximum dose group in patients with diabetes (\$34,505 vs \$27,046; $P < .0001$). The maximum dose group showed the lowest incremental cost impact of adverse outcomes/death for the CKD stages 3-4 and the diabetes disease cohorts.

Associated Costs per Patient by Service Category

Among all cohorts in both age groups, the maximum recommended dose of RAAS inhibitor was associated with higher pharmacy costs and lower IP costs than submaximum doses, resulting in lower total cost. A similar pattern of lower IP costs and higher pharmacy costs was observed in all comparisons of maximum dose to discontinued dose, except for Medicare patients with HF. Among patients with CKD stages 3-4, IP costs predominated and were lowest among patients on the maximum dose; submaximum dosing was associated with the highest costs (Figure 4). Costs were higher for patients with HF than for those with CKD stages 3-4, but the patterns of cost distribution between service categories and dose levels were similar to the CKD stages 3-4 findings for both age groups.

Among Medicare patients with diabetes, total cost was higher for patients on submaximum doses and was similar between the maximum and discontinued dose groups; patients on maximum doses had lower IP but higher prescription costs. Also, in the Medicare cohort, patients in whom therapy was discontinued had costs for IP services that were higher than for patients on maximum doses with CKD stages 3-4 or diabetes

but lower for those with HF. Overall, service costs were highest for patients with HF across both age groups and disease states, and higher for IP versus other service categories. For complete service costs data, see [eAppendix Figures 2A-2C](#), available at www.ajmc.com.

Role of Hyperkalemia in the Study Population

Of the original study population, 18% (n = 35,735) of patients (~1 in 5) experienced hyperkalemia (serum potassium ≥5.1 mEq/L) during the preindex period, and 41% (n = 11,173 of 27,603) of patients with preindex hyperkalemia and full dosing information experienced a dosing change subsequent to a hyperkalemia event (discontinuation, 31% of patients; down-titration, 5%; up-titration, 9%).

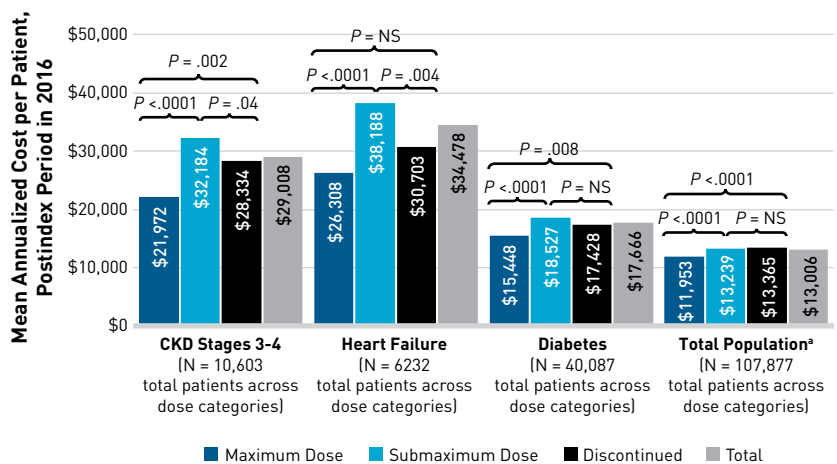
Among hyperkalemia events in patients on the maximum recommended RAAS inhibitor dose at the time of the event, more than 40% of all mild hyperkalemia events in the preindex period were followed by discontinuation or down titration versus half of all moderate-to-severe hyperkalemia events (P = .0009). Subsequent to hyperkalemia events in patients on submaximum RAAS inhibitor doses at the time of the event, a significant percent (34%) of moderate-to-severe hyperkalemia events were followed by discontinuation compared with 29% of mild events (P <.0001). In addition, 67% of all mild hyperkalemia events in the preindex period resulted in no dosage change.

Hyperkalemia as a Predictor of Cost in All Disease Cohorts

Although regression analyses were not undertaken in the first outcomes analysis,²² multivariate regression analyses were completed in the cost analysis to evaluate confounding factors that may explain the relationship between dose group and cost.

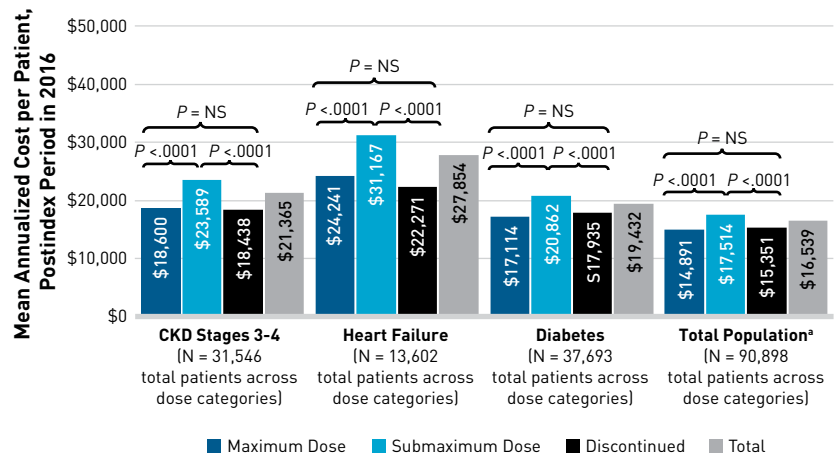
Hyperkalemia reported during the preindex period was a strong predictor of postindex costs, after controlling for other variables ([Figures 5A-5B](#)). Regardless of RAAS inhibitor dose category, in patients with HF, hyperkalemia was associated with a 50% increase in costs for patients younger than 65 years and a 29% increase for those 65 years and older. In patients with CKD stages 3-4 (<65 years), hyperkalemia was associated with a 27% cost

FIGURE 2A. Mean Annualized Cost per Patient According to Payer, Disease Cohort, and RAAS Inhibitor Dose Level Among Patients Younger Than 65 Years (Commercial)



CKD indicates chronic kidney disease; NS, not significant; RAAS, renin-angiotensin-aldosterone system. Mean annualized cost differs among dose levels in a 3-way comparison within each disease cohort, P <.0001. *Total population also includes all patients younger than 65 years meeting inclusion criteria who were prescribed RAAS inhibitor treatment but had no evidence of CKD stages 3-4, heart failure, or diabetes.

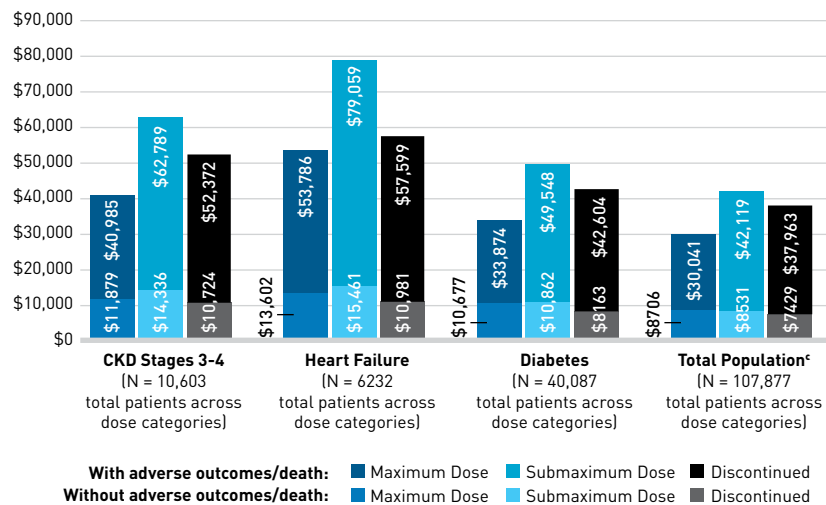
FIGURE 2B. Mean Annualized Cost per Patient According to Payer, Disease Cohort, and RAAS Inhibitor Dose Level Among Patients 65 Years and Older (Medicare)



CKD indicates chronic kidney disease; NS, not significant; RAAS, renin-angiotensin-aldosterone system. Mean annualized cost differs among dose levels in a 3-way comparison within each disease cohort, P <.0001. *Total population also includes all patients 65 years and older meeting inclusion criteria who were prescribed RAAS inhibitor treatment but had no evidence of CKD stages 3-4, heart failure, or diabetes.

increase for the maximum recommended dose group, 48% for the submaximum dose group, and 64% for the discontinued group; in patients 65 years and older who had CKD stages 3-4, hyperkalemia was associated with a 26% cost increase irrespective of RAAS inhibitor dosing category. In patients with diabetes (<65 years), hyperkalemia was associated with a 21% cost increase in the maximum dose group, 31% in the submaximum group, and 50% in the

FIGURE 3A. Incremental Mean Annualized Cost of Adverse Outcomes^a or Death (Compared With No Adverse Outcomes or Death) per Patient, Postindex, by Payer, Disease Cohort, and RAAS Inhibitor Dose Level^b Among Patients Younger Than 65 Years (Commercial)



ANOVA indicates analysis of variance; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system.

$P < .0001$ for the comparison of mean annualized postindex cost per patient for all cohorts and RAAS inhibitor dose levels, for patients with versus without adverse outcomes/death, assessed by ANOVA.

^aAdverse outcomes included stroke, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or CKD progression.

^bRAAS inhibitor dose level of the patient's active RAAS inhibitor prescription as of their first adverse outcome or death, or the dominant dosage level of RAAS inhibitor prescriptions during the postindex period.

^cTotal population also includes all patients younger than 65 years meeting inclusion criteria who were prescribed RAAS inhibitor treatment but had no evidence of CKD stages 3-4, heart failure, or diabetes.

discontinued group; in patients with diabetes who were 65 years and older, hyperkalemia was associated with a 22% cost increase irrespective of RAAS inhibitor dosing category.

Increasing comorbidity, female sex, and declining kidney function were all significant as independent predictors of increased cost or were significant in interaction with RAAS inhibitor dose level or hyperkalemia in one or more regression models, in addition to RAAS inhibitor dose level and hyperkalemia. In all cohorts, increasing comorbidity had a substantial impact on costs among patients on the maximum recommended or submaximum RAAS inhibitor doses, while its effect was less pronounced among the discontinued group. Gender contributed independently to cost only in the commercial HF and diabetes models. Age, gender, and kidney function were all less powerful than preindex hyperkalemia in predicting cost within the disease cohorts studied.

Discussion

The present study demonstrates that patients to whom RAAS inhibitors at maximum recommended doses were prescribed incurred lower total costs per patient compared with those prescribed

submaximum doses across disease cohorts (HF, CKD, and diabetes) and payers (Medicare and commercial insurance). These findings are consistent with our earlier results, showing lower rates of adverse outcomes/death among patients prescribed maximum RAAS inhibitors compared with those who received submaximum doses.²² These findings may be expected, in that patients who are able to tolerate maximum RAAS inhibitor doses may have fewer complications and, consequently, incur lower costs.

Patients in whom RAAS inhibitor therapy was discontinued were also evaluated. In the original study, these patients had higher adverse outcome/death rates than those to whom maximum or submaximum doses of RAAS inhibitors were prescribed.²² In the present analysis, patients discontinued from RAAS inhibitors had similar total costs (Medicare cohort) or somewhat higher total costs (commercial cohort) compared with those to whom maximum doses were prescribed. However, the discontinued group had lower total costs than the group to whom submaximum doses were prescribed.

The apparent difference between the outcome and cost data for the discontinued group compared with the other groups, particularly with the submaximum group, is unexpected. A possible explanation may be attributable to differences in patients' engagement with the healthcare system.²³ Using office/clinic visits as a proxy for patient engagement, patients in the discontinued group were more likely to have minimal engagement, defined by 0 or one visit during their last 12 months in the healthcare system compared with patients in the maximum recommended or submaximum dose RAAS inhibitor groups. This finding was particularly evident for discontinued patients with CKD stages 3-4 who eventually died during the postindex period; the proportional death rate was substantially higher in the discontinued group compared with the maximum and submaximum groups (eAppendix Figure 3, available at www.ajmc.com). Related analyses (not shown) revealed that a modestly higher proportion of minimally engaged patients died outside of the hospital setting, and these patients incurred lower costs than those who died in IP or ED settings.

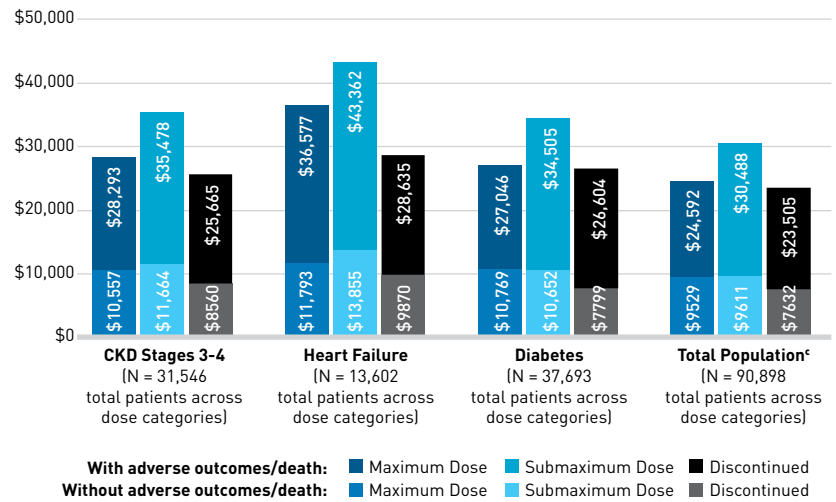
Among all patients, lower engagement with the healthcare system was associated with lower total costs, as is shown for the CKD stages 3-4 cohort in Figure 6 (and for HF and diabetes cohorts in eAppendix Figures 4A-4B, available at www.ajmc.com). Thus, it

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appears that patients in whom RAAS inhibitors were discontinued were more likely to be disengaged from the healthcare system and, consequently, were likely to receive fewer medical services overall. This factor lowers medical costs incurred by the discontinued group despite their high adverse outcomes/death rates.

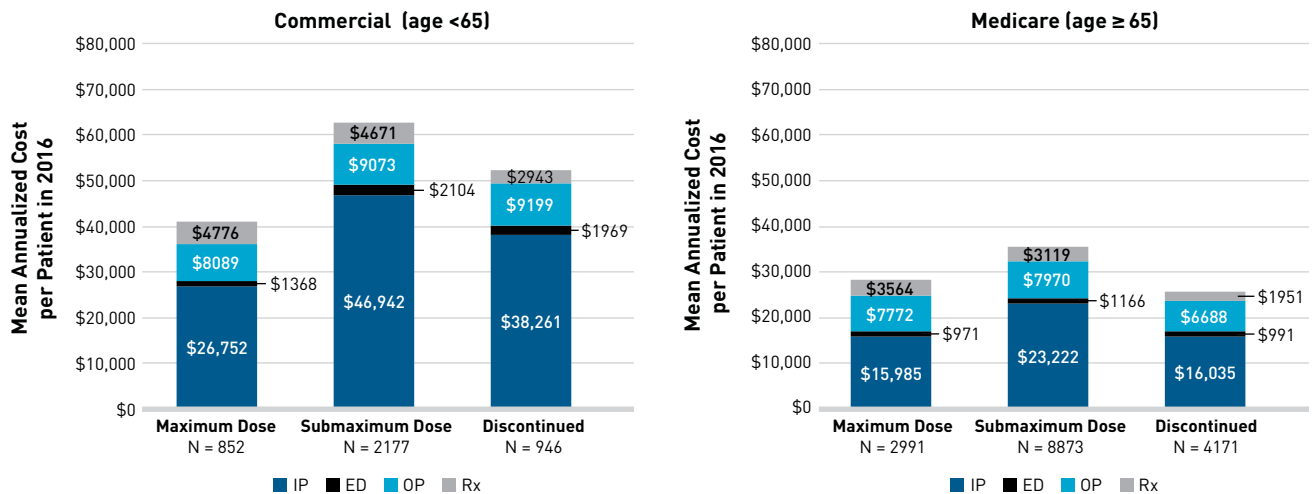
Adverse outcome/death was a significant driver of total costs, with IP costs being the largest determining factor in total costs for patients with adverse outcomes. IP costs were determined using length-of-stay information, with costs applied to each hospital stay based on whether the claims were for medical or surgical admissions, and costs adjusted depending on patient comorbidities (HF, CKD, diabetes). By developing costs at the individual patient level based on services actually received, this study fully reflects many important differences in IP costs for patients with one or multiple comorbidities, including admission frequency, length of stay, and the mix of surgical and medical admissions. The average annualized cost per patient is therefore adjusted for these factors, with no attempt made to distinguish between single

FIGURE 3B. Incremental Mean Annualized Cost of Adverse Outcomes^a or Death (Compared With No Adverse Outcomes or Death) per Patient, Postindex, by Payer, Disease Cohort, and RAAS Inhibitor Dose Level^b Among Patients 65 Years and Older (Medicare)



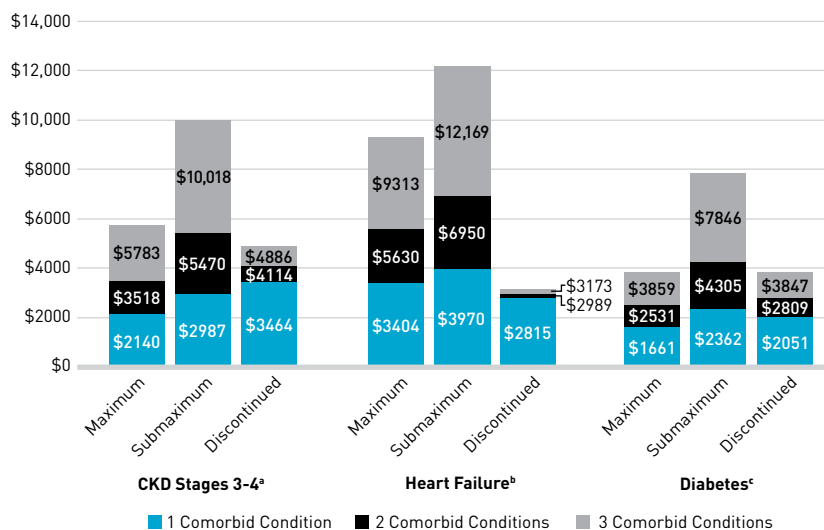
ANOVA indicates analysis of variance; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system. *P* < .0001 for the comparison of mean annualized postindex cost per patient for all cohorts and RAAS inhibitor dose levels, for patients with versus without adverse outcomes/death, assessed by ANOVA. ^aAdverse outcomes included stroke, acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or CKD progression. ^bRAAS inhibitor dose level of the patient's active RAAS inhibitor prescription as of their first adverse outcome or death, or the dominant dosage level of RAAS inhibitor prescriptions during the postindex period. ^cTotal population also includes all patients 65 years and older meeting inclusion criteria who were prescribed RAAS inhibitor treatment but had no evidence of CKD stages 3-4, heart failure, or diabetes.

FIGURE 4. Components of Mean Annualized Cost Per Patient With Adverse Outcomes/Death in the Postindex Period by RAAS Inhibitor Dose Level and Service Category Among Patients With CKD Stages 3-4



CKD indicates chronic kidney disease; ED, emergency department; IP, inpatient; OP, outpatient; RAAS, renin-angiotensin-aldosterone system; Rx, pharmacy.

FIGURE 5A. Incremental Costs Associated With Hyperkalemia as Predicted by Regression Analysis Comparing Patients Without and With Hyperkalemia by Payer, Number of Comorbid Conditions, RAAS Inhibitor Dose, and Disease Cohort Among Patients Younger Than 65 Years (Commercial)



CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

Values shown reflect the predicted added cost of hyperkalemia. Each cohort was modeled separately within each payer group; characteristics that were significant independent predictors in the specific model are reported and are included at mean values.

Modeling of costs assumes the following patient characteristics for commercial patients: ^aCKD stages 3-4 with eGFR of 66.2 and 55.4% male; ^bheart failure with eGFR of 86.5, 56.0% male, and an age of 54.1; ^cdiabetes with eGFR of 93.1, 50.3% male, and an age of 53.6.

and multiple comorbid patients. Across all disease cohorts and both commercial and Medicare payers, IP costs were consistently lower for the maximum recommended dose RAAS inhibitor group compared with the submaximum dose group. These findings suggest that the ability to maintain patients on maximum, or at least near-maximum, doses of RAAS inhibitor therapy may help to prevent adverse outcomes while reducing total and IP costs.

Multivariate regression analyses were not undertaken in the original study of outcomes, but were conducted in the present cost analysis to evaluate confounding factors that may explain the relationship between RAAS inhibitor dose group and total cost. The multivariate analysis suggested that hyperkalemia is a strong independent predictor of cost in each disease cohort. Hyperkalemia drives clinical decisions regarding RAAS inhibitors, often resulting in dose reductions to submaximum levels or discontinuation of treatment.¹³⁻¹⁵

Mechanistically, hyperkalemia influences cell membrane polarization, which may lead to a variety of physiological effects—including muscle weakness, cardiac conduction abnormalities, and arrhythmias—prompting ED visits, clinic visits, and IP hospitalizations, and, in turn, contributing to increased costs.^{24,25} In 2013, hyperkalemia was responsible for 70,394 ED visits; approximately 50% of these patients were admitted to the hospital, with

a mean length of stay of 3.1 days and mean in-hospital charges of \$27,802.²⁶ In the present study, hyperkalemia occurred in nearly one of every 5 patients during the preindex period and commonly was followed by down-titration or discontinuation of RAAS inhibitor. Notably, hyperkalemia during the preindex period was a strong independent predictor of postindex costs across disease cohorts.

The results of these analyses are hypothesis generating and suggest that therapy prescribed to manage hyperkalemia may better enable optimal use of RAAS inhibitors and may potentially reduce mortality, morbidity, and associated costs. Patiromer and sodium zirconium cyclosilicate (ZS-9) are newly developed, orally administered agents that bind potassium in the gastrointestinal tract in exchange for calcium (patiromer) or sodium (ZS-9), leading to increased fecal potassium excretion and lower serum potassium levels. Patiromer has been shown to lower serum potassium levels and reduce recurrence of hyperkalemia for up to 52 weeks in patients developing hyperkalemia during treatment with RAAS inhibitors²⁷⁻³⁰ and has been approved by the FDA for the treatment of hyperkalemia.³¹ ZS-9 has shown

efficacy in clinical studies lasting up to 28 days.^{32,33} Further studies are warranted to determine whether controlling hyperkalemia with patiromer or ZS-9 will allow continued use of maximum dose RAAS inhibitors and, in turn, translate into a cost benefit for health plans and improved clinical outcomes for patients.

As new agents are developed and integrated into the treatment of HF, CKD, and diabetes, it will be important to ascertain whether these agents reduce the risk of hyperkalemia compared with standard RAAS inhibitors. One new treatment for HF is a product containing the neprilysin inhibitor sacubitril in combination with the ARB valsartan. In PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial), the incidence of hyperkalemia (serum potassium >5.5 mmol/L) with the combination product was similar to that for the ACE inhibitor enalapril (16% and 17%, respectively).³⁴

Limitations

First, these analyses were undertaken to evaluate observational associations, but do not establish causality between RAAS inhibitor dose level and costs, which is typical for a retrospective data-

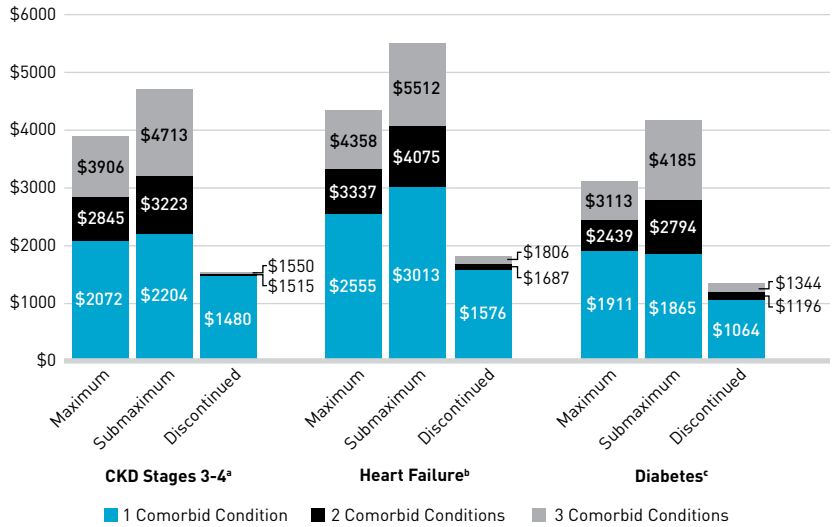
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base analysis. Second, the HF cohort included patients with and without preserved ejection fraction, whose results may differ. The available data in the EHR were insufficient to differentiate HF patients by New York Heart Association class or by ejection fraction level. Third, CKD progression, a component of the primary clinical outcome, may have been underestimated because proteinuria differences were not evaluated in the CKD cohort. Fourth, hyperkalemia may also have been underestimated because it was identifiable only from the EHR when potassium levels were measured during the course of clinical care. Fifth, services provided in long-term care facilities, free-standing dialysis centers, or home settings may not have been integrated into the available EHR and thus may be underreported in the cost analysis. Finally, the cost analysis methodology assumed that all written prescriptions were filled.

Conclusion

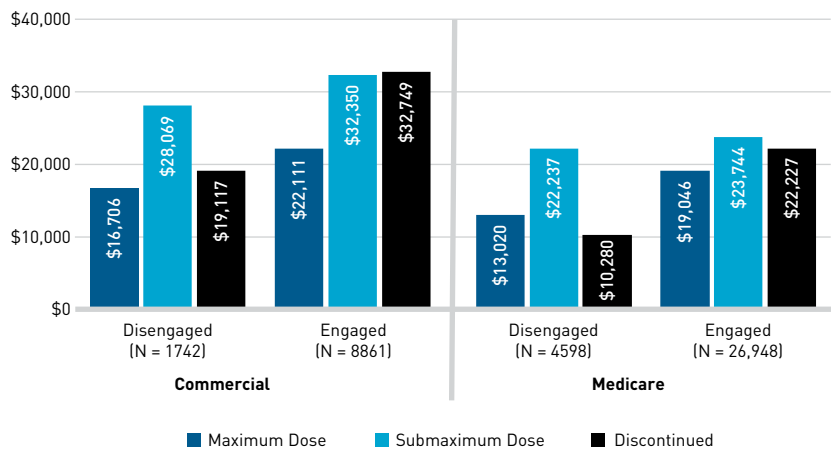
Patients prescribed the maximum recommended dose of RAAS inhibitors incurred lower total costs per patient compared with those prescribed submaximum doses, regardless of disease cohort or payer category. Patients for whom RAAS inhibitor therapy was discontinued were more likely to be disengaged from the healthcare system (as measured by office/clinic visits during their last 12 months), which lowered their medical costs to levels similar to or slightly higher than those to whom maximum doses were prescribed. Adverse outcomes/death was a significant driver of costs, with IP costs being the largest determining factor for total costs among patients with adverse outcomes. It is important to note that patients who were engaged were more commonly on maximal RAAS inhibitor doses and had lower costs related to IP care and adverse outcomes. Across each disease cohort, maximum-dose RAAS inhibitor was generally associated with the lowest risk of adverse outcomes/death and with the lowest total and IP costs. Finally, hyperkalemia was a significant factor in predicting total costs in each disease cohort and across RAAS inhibitor dose levels.

FIGURE 5B. Incremental Costs Associated With Hyperkalemia as Predicted by Regression Analysis Comparing Patients Without and With Hyperkalemia by Payer, Number of Comorbid Conditions, RAAS Inhibitor Dose, and Disease Cohort Among Patients 65 Years and Older (Medicare)



CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system. Values shown reflect the predicted added cost of hyperkalemia. Each cohort was modeled separately within each payer group; characteristics that were significant independent predictors in the specific model are reported and are included at mean values. Modeling of costs assumes the following characteristics for Medicare patients: ^aCKD with age of 76.9; ^bheart failure with age of 77.0; ^cdiabetes with eGFR of 73.7 and age of 74.1.

FIGURE 6. Average Cost by RAAS Inhibitor Dose Level for Patients with CKD Stages 3-4 by Level of Patient Engagement^a and Payer



CKD indicates chronic kidney disease; RAAS, renin-angiotensin-aldosterone system. ^aLevels of patient engagement, as measured by 0 to 1 [disengaged] versus 2 or more [engaged] office visits in the patient's last year of interaction with the healthcare provider.

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REFERENCES

- Garg R, Yusuf S; Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273(18):1450-1456.
- Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341(10):709-717.
- Cohn JN, Tognoni G; The Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-1675.
- Maschio G, Alberti D, Janin G, et al; The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med*. 1996;334(15):939-945.
- Balamuthusamy S, Srinivasan L, Verma M, et al. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J*. 2008;155(5):791-805. doi: 10.1016/j.ahj.2008.01.031.
- 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):861-869.
- Yancy CW, Jessup M, Bozkurt B, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-e327.
- McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail*. 2012;14(8):803-869. doi: 10.1093/eurjhf/hfs105.
- The National Kidney Foundation. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. National Kidney Foundation website. http://www2.kidney.org/professionals/KDOQI/guidelines_bp/guide_11.htm. Published May 2004. Accessed April 21, 2016.
- National Institute for Health and Care Excellence (NICE). Chronic kidney disease in adults: assessment and management. NICE website. <http://www.nice.org.uk/guidance/cg182>. Published July 2014. Accessed April 21, 2016.
- American Diabetes Association. Standards of medical care in diabetes-2016 abridged for primary care providers. *Clin Diabetes*. 2016;34(1):3-21. doi: 10.2337/diaclin.34.1.3.
- Epstein M. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. *Kidney Int Suppl*. 2016;6(1):20-28.
- Epstein M. Hyperkalemia as a constraint to therapy with combination renin-angiotensin system blockade: the elephant in the room. *J Clin Hypertens*. 2009;11(2):55-60. doi: 10.1111/j.1751-7176.2008.00071.x.
- Chang AR, Sang Y, Leddy J, et al. Antihypertensive medications and the prevalence of hyperkalemia in a large health system. *Hypertension*. 2016;67(6):1181-1188. doi: 10.1161/HYPERTENSIONAHA.116.07363.
- Yildirim T, Arici M, Piskinpassa S, et al. Major barriers against renin-angiotensin-aldosterone system blocker use in chronic kidney disease stages 3-5 in clinical practice: a safety concern? *Ren Fail*. 2012;34(9):1095-1099. doi: 10.3109/0886022X.2012.717478.
- Winkelmayer WC, Fischer MA, Schneeweiss S, Wang PS, Levin R, Avorn J. Underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. *Am J Kidney Dis*. 2005;46(6):1080-1087.
- Berger AK, Duval S, Manske C, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. *Am Heart J*. 2007;153(6):1064-1073.
- Krantz MJ, Ambardekar AV, Kallenbach L, Hernandez AF, Heidenreich PA, Fonarow GC; Get With the Guidelines Steering Committee and Hospitals. Patterns and predictors of evidence-based medication continuation among hospitalized heart failure patients (from Get With the Guidelines-Heart Failure). *Am J Cardiol*. 2011;107(12):1818-1823. doi: 10.1016/j.amjcard.2011.02.322.
- Curtis LH, Mi X, Qualls LG, et al. Transitional adherence and persistence in the use of aldosterone antagonist therapy in patients with heart failure. *Am Heart J*. 2013;165(6):979-986.e1. doi: 10.1016/j.ahj.2013.03.007.
- Maggioni AP, Anker SD, Dahlström U, et al; Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;15(10):1173-1184. doi: 10.1093/eurjhf/hft134.
- Allen LA, Fonarow GC, Liang L, et al; American Heart Association's Get With the Guidelines Heart Failure (GWTG-HF) Investigators. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. *Circulation*. 2015;132(14):1347-1353. doi: 10.1161/CIRCULATIONAHA.115.014281.
- 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(suppl 11):S212-S220.
- Kimball AB, Corey KC, Kvedar JC. Engaging patients to decrease costs and improve outcomes. *Med Econ*. 2015;92(2):36-37.
- 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(suppl 15):S307-S315.
- Campese VM, Adenuga G. Electrophysiological and clinical consequences of hyperkalemia. *Kidney Int Suppl*. 2016;6(1):16-19.
- Agency for Healthcare Research and Quality. Healthcare cost and utilization project. Data on ICD-9-CM first-listed diagnosis code 276.7 hyperpotassemia. AHRQ website. <http://hcupnet.ahrq.gov/HCUFnet.jsp>. Accessed May 24, 2016.
- Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang LZ; 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):820-828. doi: 10.1093/eurheartj/ehq502.
- Weir MR, Bakris GL, Bushinsky DA, et al; OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211-221. doi: 10.1056/NEJMoa1410853.
- Bakris GL, Pitt B, Weir MR, et al; METHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The METHYST-DN randomized clinical trial. *JAMA*. 2015;314(2):151-161. doi: 10.1001/jama.2015.7446.
- Pitt B, Bakris GL, Bushinsky DA, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalemia in patients with heart failure and chronic kidney disease on RAAS inhibitors. *Eur J Heart Fail*. 2015;17(10):1057-1065. doi: 10.1002/ehfj.402.
- Veltassa (patiromer) for oral suspension [prescribing information]. Redwood City, CA: Relypsa, Inc; 2016.
- Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med*. 2015;372(3):222-231. doi: 10.1056/NEJMoa1411487.
- Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*. 2014;312(21):2223-2233. doi: 10.1001/jama.2014.15688.
- McMurray JJ, Packer M, Desai AS, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077. ■

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