

Evaluation of the Treatment Gap Between Clinical Guidelines and the Utilization of Renin-Angiotensin-Aldosterone System Inhibitors

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Abstract

Objectives: This study examined renin-angiotensin-aldosterone system (RAAS) inhibitor dose levels in a US patient population and investigated the impact of hyperkalemia on RAAS inhibitor dose and the association between dose levels and clinical outcomes.

Study Design: De-identified medical records from a large database of electronic health records (Humedica) for patients 5 years of age or older with at least 2 serum potassium readings were analyzed (N = 205,108 patients; 1.7 million records).

Methods: Inclusion criteria required 1 RAAS inhibitor prescription and 12 months' data prior to July 1, 2009 (index date). Patients were classified by comorbidities (chronic kidney disease, heart failure, or diabetes) and RAAS inhibitor dose level at index date, as determined by prescription information. Additional analyses examined RAAS inhibitor dose changes following hyperkalemia and the frequency of cardiorenal adverse outcome/mortality or mortality alone by post index dose level.

Results: Dose level was similarly distributed irrespective of patient comorbidity status, with RAAS inhibitors prescribed at maximum dose in 19% to 26% of patients and submaximum dose in 58% to 65% of patients; RAAS inhibitors were discontinued in 14% to 16% of patients. RAAS inhibitor dose was down-titrated after 16% to 21% of hyperkalemia events and discontinued after 22% to 27% of hyperkalemia events. Cardiorenal adverse event/mortality and mortality occurred in 34.3% and 11.0% of patients who discontinued RAAS inhibitors, 24.9% and 8.2% of patients on submaximum doses, and 24.9% and 4.1% of patients on maximum doses, respectively.

Conclusions: Relatively few patients were prescribed maximum doses of RAAS inhibitors, and dose and usage declined following hyperkalemia. Patients on submaximum doses or who discontinued RAAS inhibitors had worse outcomes than patients on maximum doses.

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For author information and disclosures, see end of text.

INTRODUCTION

Renin-angiotensin-aldosterone system (RAAS) inhibitors comprise a large class of drugs, which includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), direct renin inhibitors, and mineralocorticoid receptor antagonists (MRAs). Numerous randomized clinical trials have clearly demonstrated that RAAS inhibitors can reduce the risk of death and slow disease progression in

patients with heart failure (HF), chronic kidney disease (CKD), and diabetes (DM).¹⁻⁷ Based on these results, evidence-based treatment guidelines recommend the use of RAAS inhibitors for patients with HF^{8,9} or CKD^{10,11}, and for DM patients with hypertension and/or renal insufficiency.¹² The guidelines specifically recommend that RAAS inhibitors be titrated up to moderate to high doses, as used in clinical trials, in order for patients to derive optimal treatment benefits.⁸⁻¹² However, the use of these drugs may be limited by their potential to cause hyperkalemia.

Although usually asymptomatic, clinical manifestations of hyperkalemia include muscle fatigue, paralysis, and the more serious manifestations of cardiac arrhythmia and cardiac arrest.^{13,14} Treatment guidelines provide several recommendations for minimizing the risk of hyperkalemia, including: avoiding RAAS inhibitor therapy in patients who may be at risk of developing hyperkalemia, performing regular potassium monitoring, titrating the dose of the RAAS inhibitor, and discontinuing drugs that can interfere with renal potassium excretion prior to initiating RAAS inhibitors.⁸⁻¹² Discontinuing or lowering the dose of the RAAS inhibitor is recommended if hyperkalemia develops after initiating therapy.⁸⁻¹²

Several observational and retrospective studies have reported a large gap between recommendations in guidelines and real-world practice in the use of RAAS inhibitor therapies.¹⁵⁻¹⁸ A retrospective analysis of data from the American Heart Association's Get With the Guidelines–Coronary Artery Disease database showed that less than 10% of eligible HF patients hospitalized for myocardial infarction were prescribed an aldosterone agonist at discharge,¹⁷ and a large European registry has reported that while 67% to 92% of hospitalized HF patients were prescribed the recommended RAAS inhibitor therapy, less than 30% were up-titrated to the recommended target dose.¹⁸ In order to better elucidate this apparent treatment gap, this study undertook a comprehensive analysis of a large database of electronic medical records (>7 million patients) to evaluate: (1) whether RAAS inhibitors are being prescribed according to treatment guidelines, (2) what happens to RAAS inhibitor prescriptions after hyperkalemia events, and (3) what the clinical outcomes are in patients whose RAAS inhibitors are discontinued or prescribed at doses lower than recommended in guidelines.

METHODS

Data Source and Patient Selection

De-identified medical records (2007-2012) for patients 5 years of age or older with at least 2 potassium readings were obtained from Humedica, a large US database of electronic health records (www.humedica.com). A total of 1.7 million patient records met these criteria. Study patients were individuals receiving care from providers in integrated health delivery networks across the United States, including those insured by commercial insurance, Medicare, Medicaid, other health insurance, or no insurance. For all study patients, the data include any services provided in hospitals as well as office and outpatient

care. Medication data include written prescriptions and medication administrations that occurred in-clinic and/or in-hospital. Results were available for a limited number of lab tests.

Inclusion criteria required at least 1 outpatient RAAS inhibitor prescription and 12 months of data prior to July 1, 2009 (index date). RAAS inhibitors included ACE inhibitors, ARBs, direct renin inhibitors, and select MRAs. To ensure continuity, evidence that patient engagement with the healthcare provider began at least 12 months prior to the index date and continued up to the index date was required. This requirement is analogous to requiring continuous enrollment in a claims data study.

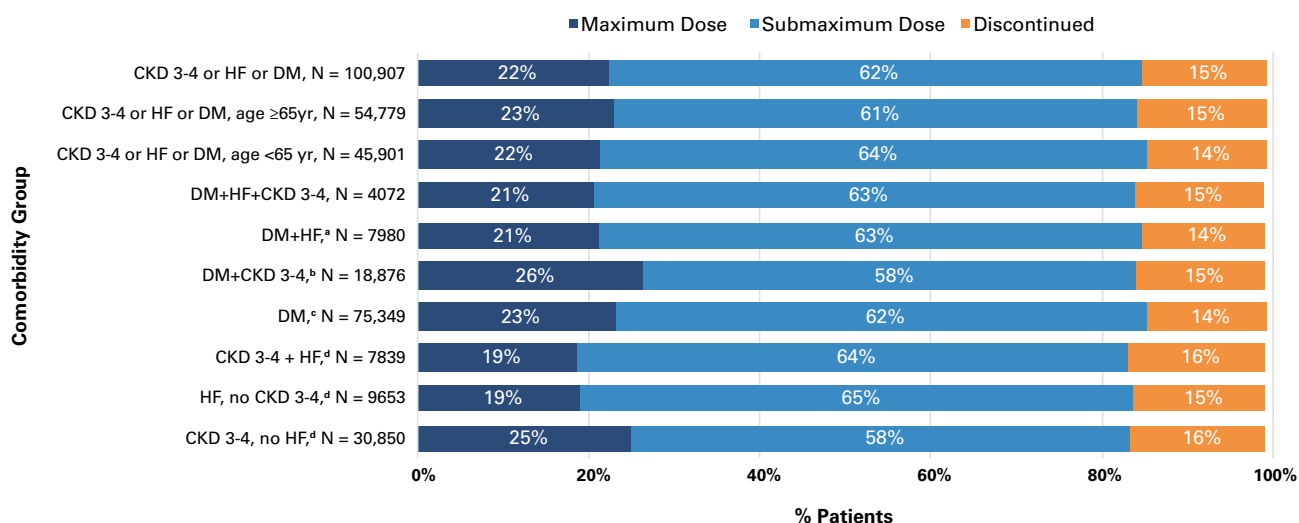
Patients with end-stage renal disease (ESRD) at the index date were excluded from the analysis of dose distribution and outcomes. The dose distribution analysis further excluded patients with CKD stage 5 and acute kidney injury. Response to hyperkalemia events was evaluated for each hyperkalemia event in the data (2007-2012) without restriction by patient comorbidity status.

Classification of Patient Comorbidity and RAAS Inhibitor Dose Category

Patients were classified by disease comorbidity (CKD stages 3-4 and/or HF or DM [types 1 and 2]) and age (<65 vs ≥65 years) prior to the index date using *International Classification of Diseases, Ninth Edition (ICD-9)* diagnosis codes; results of testing for estimated glomerular filtration rate (eGFR), left ventricular ejection fraction, and glycated hemoglobin (if available); and prescriptions for anti-DM medications. If multiple values were available for a particular biomarker, the value indicating greatest severity was utilized. A condition was deemed present if identified by 1 or more indicators in the medical record, irrespective of setting of care. Diagnosis codes used in defining comorbidities generally reflect definitions used by the US Renal Data System (USRDS) and are listed in [eAppendix 1](#) (available online at www.ajmc.com).¹⁹

RAAS inhibitor prescriptions were classified by dose level using the following dose categories: “supramaximum,” defined as any RAAS inhibitor dose above the labeled dose; “maximum,” defined as the labeled dose; “submaximum,” defined as any RAAS inhibitor dose lower than the labeled dose; or “discontinued,” defined as the absence of RAAS inhibitor prescriptions for a period of more than 390 days subsequent to prior prescription. The 390-day period allows 360 days (longest common prescription length in the database) plus 30 additional days for patients to see or contact their healthcare provider for

■ **Figure 1.** Distribution of RAAS Inhibitor Dose Levels by Comorbidity Group



CKD indicates chronic kidney disease; DM, diabetes mellitus; HF, heart failure; RAAS, renin-angiotensin-aldosterone system.

^aComorbidity group does not exclude CKD stage 3 to 4.

^bComorbidity group does not exclude HF.

^cComorbidity group does not exclude CKD stage 3 to 4 or HF.

^dDM was not excluded from these comorbidity groups.

a refill. Specific medications and their dose levels included in each dose category are listed in [eAppendix 2](#) (available online at www.ajmc.com). Results are not reported for the small group of patients on supramaximum doses.

Dose Distribution Study

A patient-level analysis was performed to examine RAAS inhibitor dose distribution as of the index date. The distribution (number and percent) of patients by dose category was assessed for the total study population and for each of 10 comorbidity groups as listed in [Figure 1](#).

Determining RAAS Inhibitor Dose Subsequent to Hyperkalemia Event

An event-level analysis was used to examine RAAS inhibitor dose changes following hyperkalemia. Hyperkalemia was defined as any serum potassium measurement above 5.0 mEq/L. All laboratory-reported events of serum potassium of 5.1 mEq/L or higher were classified by severity (mild, 5.1-5.4 mEq/L; moderate-to-severe, ≥5.5 mEq/L). RAAS inhibitor prescription status was assessed before and after each hyperkalemia event, with a 390-day follow-up period for assessing RAAS inhibitor dose following hyperkalemia. (The 390

days corresponds to the time period required to identify discontinued RAAS inhibitor prescriptions.) Post hyperkalemia event dosing was compared with the last pre-hyperkalemia dose (or prescription expiration) before the hyperkalemia event. Outcomes were described as the percent of hyperkalemia events for which the next RAAS inhibitor dose represented maintenance of dose, down titration, or discontinuation. Results were segmented by RAAS inhibitor dose category (submaximum or maximum) at the time of the hyperkalemia event and severity of the hyperkalemia event (mild or moderate-to-severe).

Outcomes Study

In this patient-level analysis, differences in clinical outcomes between patients with submaximum or discontinued RAAS inhibitor versus those remaining on maximum doses were evaluated in the total study population and within disease categories (CKD 3-5, HF, or DM). Adverse outcomes evaluated were CKD progression and progression to ESRD (by eGFR laboratory value, diagnosis code, or chronic dialysis by procedure code); stroke and acute myocardial infarction (by diagnosis code during inpatient hospitalization); and coronary artery bypass and percutaneous coronary intervention (by procedure

■ **Table 1.** Study Population Characteristics

	Total dosing study population	Patients with hyperkalemia event(s)	Outcomes study population
Total	195,327	66,862	201,655
Age, years, mean (SD)	62.5 (13.36)	66.2 (12.71)	62.7 (13.39)
Gender, n (%)			
Female	102,777 (52.6)	33,084 (49.5)	105,788 (52.5)
Male	92,180 (47.2)	33,587 (50.2)	95,464 (47.3)
Unknown	370 (0.2)	191 (0.3)	403 (0.2)
CKD stages 3-4, without HF, n (%) ^a	30,850 (15.8)	16,644 (24.9)	33,113 (16.4)
HF, without CKD stages 3-4, n (%) ^a	9653 (4.9)	5613 (8.4)	10,354 (5.1)
CKD 3-4 + HF, n (%) ^a	7839 (4)	6674 (10)	10,175 (5)
DM, n (%) ^b	75,349 (38.6)	33,322 (49.8)	79,087 (39.2)
DM + CKD stages 3-4, without HF	18,876 (9.7)	13,012 (19.5)	21,594 (10.7)
DM + HF, without CKD stages 3-4	7980 (4.1)	6917 (10.3)	9836 (4.9)
DM + CKD stages 3-4 + HF	4072 (2.1)	3855 (5.8)	5483 (2.7)

CKD indicates chronic kidney disease; DM, diabetes mellitus; HF, heart failure.
^aDM was not excluded from these comorbidity groups.
^bComorbidity group does not exclude CKD stages 3-4 or HF.

code); or all-cause mortality (from Social Security or hospital records). Code sets were consistent with USRDS methodology and are supplied in eAppendix 1 and eAppendix 3 (available online at www.ajmc.com).¹⁹

End points included a composite measure of any adverse outcome or mortality and mortality alone and were assessed from July 1, 2009, until the patient's last interaction or December 31, 2012 (post index period; median follow-up 3.4 years). Date of death was not available; therefore, it was not possible to ascertain time frames from last prescription/expiration to death.

For the composite end point, the most frequently prescribed dose level of RAAS inhibitor was identified for each patient during the post index period. RAAS inhibitor dose category was reevaluated and adjusted for patients who experienced an adverse outcome to ensure that the dominant dose category did not reflect data occurring after the adverse outcome; this adjustment resulted in a higher or lower RAAS inhibitor dose category for 1.6% and 3.5% of patients, respectively. For the end point of mortality alone, all patients were classified according to their last RAAS inhibitor dose level in the data.

Chi-square tests were carried out to compare differences in the proportion of adverse outcomes or death between the various RAAS inhibitor dose groups. *P* values for the 3 contrast comparisons were adjusted using the step-down Bonferroni procedure of Holm to protect the family-wise error rate at 0.05.²⁰

RESULTS

Study Population Characteristics

Table 1 shows the age, gender, and comorbidity classifications for the patient populations included in each analysis. A total of 205,108 patients met the inclusion criteria; of these, 66,862 (32.8%) experienced 1 or more hyperkalemia events. Of the patients who experienced hyperkalemia events, 58,520 (28.5%) experienced 1 or more mild hyperkalemia events and 30,912 (15.1%) experienced 1 or more moderate-to-severe hyperkalemia events. After excluding patients with ESRD, 201,655 patients were included in the outcomes analyses. After further excluding patients with CKD stage 5 and acute kidney injury, 195,327 patients were included in the dose distribution study.

RAAS Inhibitor Dose Distribution

RAAS inhibitor dose level was similarly distributed irrespective of patient comorbidity status. Maximum doses were prescribed in 19% to 26% of patients, over half of the patients (58%-65%) were prescribed submaximum doses, and 14% to 16% of patients discontinued treatment with RAAS inhibitors as of the index date (Figure 1). Supramaximum doses were prescribed in less than 1% of patients (data not shown). The distribution of patients by dose category was similar between patients younger than 65 years and 65 years and older. Patients

Report

with HF were least likely to be prescribed maximum doses of RAAS inhibitors (19%-21%), irrespective of comorbidities (Figure 1).

RAAS Inhibitor Dosing Subsequent to Hyperkalemia Events

Laboratory records included 218,813 hyperkalemia events (144,800 mild and 74,013 moderate-to-severe) in 66,862 patients. Analysis of RAAS inhibitor dosing before and after these hyperkalemia events revealed that a substantial proportion of patients had changes in their dose following an instance of elevated serum potassium, with dose changes occurring more frequently after moderate-to-severe hyperkalemia events. Patients on a maximum dose of a RAAS inhibitor were down-titrated to a submaximum dose or discontinued the RAAS inhibitor nearly half the time (47%) after moderate-to-severe hyperkalemia events and 38% of the time after mild events (Figure 2A). Among patients on submaximum doses of RAAS inhibitors, moderate-to-severe hyperkalemia events were followed by submaximum dose maintenance in 55% of patients and discontinuation in 27% of patients, compared with dose maintenance after 61% of mild hyperkalemia events and discontinuation after 24% of mild events (Figure 2B). In the remaining events, the data period following the hyperkalemia event was insufficient to determine subsequent RAAS inhibitor dose level.

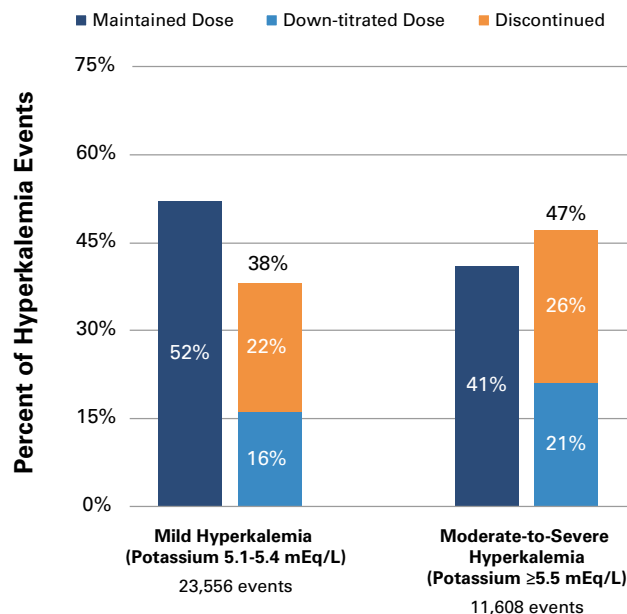
Dose changes subsequent to hyperkalemia were similar in patients younger and older than 65 years (data not shown). Patients 65 years or older on maximum dose of RAAS inhibitor were down-titrated to submaximum doses or discontinued 46% of the time after a moderate-to-severe hyperkalemia event compared with 49% of the time for patients younger than 65 years. In patients in both age groups on submaximum doses, moderate-to-severe events were followed by RAAS inhibitor discontinuation in 27% of patients.

Cardiorenal Outcomes and Mortality by RAAS Inhibitor Dose

Patients on submaximum doses or who continued RAAS inhibitor therapy showed consistently worse outcomes compared with patients on maximum doses, irrespective of comorbidity status (Figure 3) or patient age. Over 50% of patients with CKD stages 3 to 4 who discontinued RAAS inhibitors experienced an adverse outcome or died compared with 47.4% of patients on submaximum doses and 42.6% of patients on maximum doses (all comparisons $P < .05$) (Figure 3). Nearly 60% of

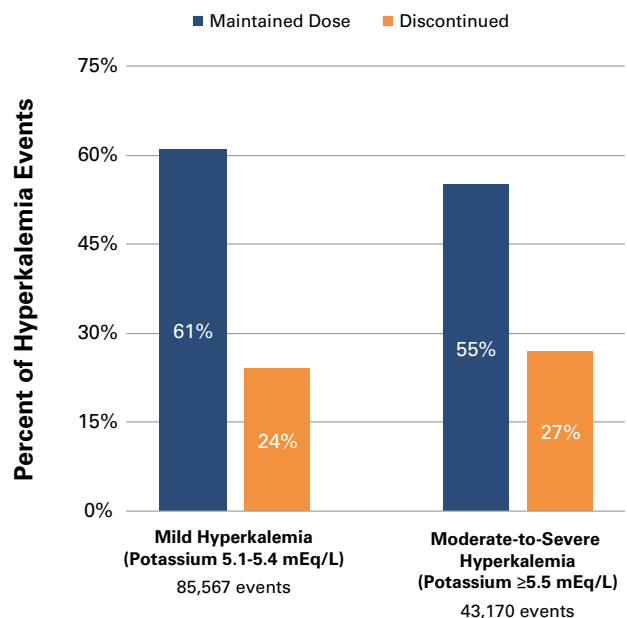
Figure 2. Changes in RAAS Inhibitor Dose Subsequent to Hyperkalemia Events

Figure 2A. Among Patients on RAAS Inhibitor at Maximum Dose



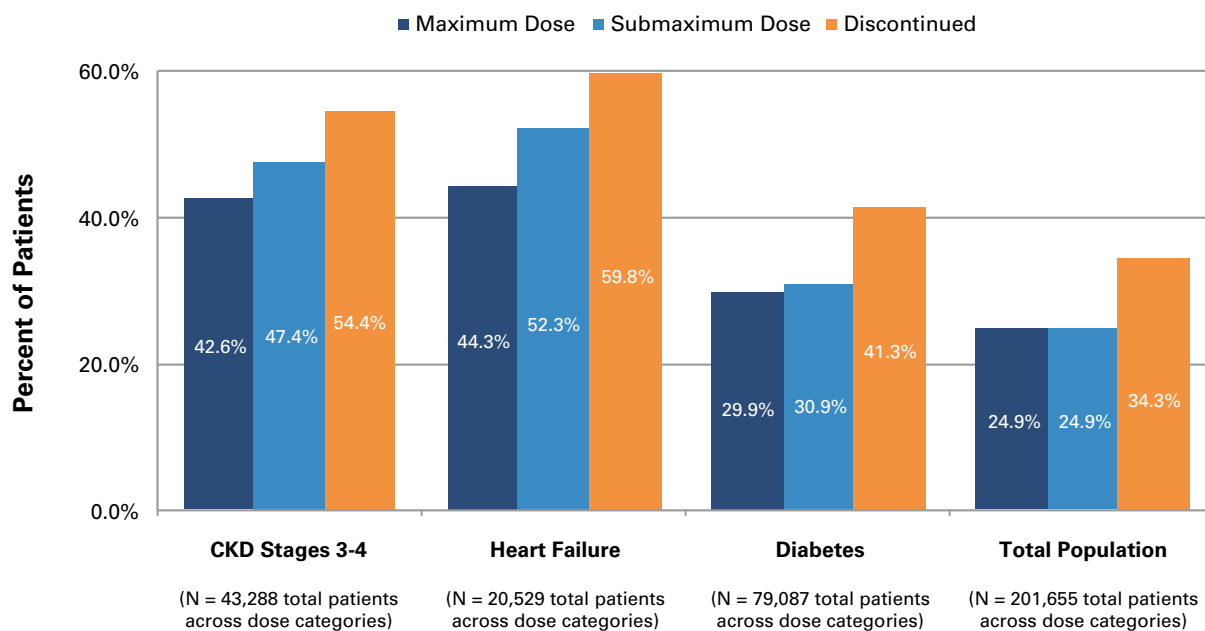
RAAS indicates renin-angiotensin-aldosterone system.

Figure 2B. Among Patients on RAAS Inhibitor at Submaximum Dose



RAAS indicates renin-angiotensin-aldosterone system.

■ **Figure 3.** Percent of Patients Who Experienced Adverse Outcomes or Mortality by Prior RAAS Inhibitor Dose



CKD indicates chronic kidney disease; RAAS, renin-angiotensin-aldosterone system.

patients with HF who discontinued RAAS inhibitors experienced an adverse outcome or mortality compared with 52.3% of patients on submaximum doses and 44.3% of patients on maximum doses (all comparisons $P < .05$) (Figure 3). Patients with DM had better outcomes than patients in the HF or CKD stage 3 to 4 comorbidity groups. A total of 41.3% of DM patients who discontinued RAAS inhibitors experienced an adverse outcome or mortality compared with 30.9% of patients on submaximum doses and 29.9% of patients on maximum doses (all comparisons $P < .05$) (Figure 3). A comparison of patients younger than 65 years versus patients 65 years and older (data not shown) suggested that patients on submaximum doses or who discontinued RAAS inhibitors had consistently worse outcomes compared with patients on maximum dose regardless of age group, with the exception of patients with DM who were younger than 65 years in whom maximum and submaximum RAAS inhibitor doses were associated with similar levels of adverse outcomes or mortality (20.5% and 19.8%, respectively).

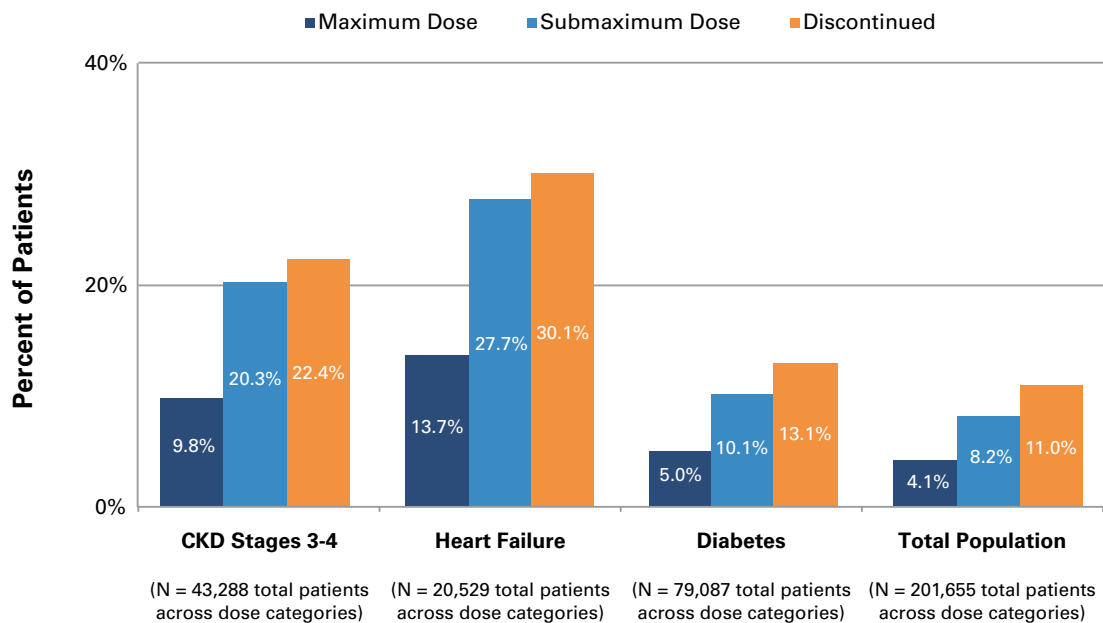
Patients on submaximum dose or who discontinued RAAS inhibitors died twice as frequently as patients on maximum dose irrespective of comorbidity status (Figure 4) or patient age. Mortality was recorded for 9.8% of patients

with CKD stage 3 to 4 on maximum doses of RAAS inhibitors compared with 20.3% of patients on submaximum doses and 22.4% of patients who discontinued therapy. Among patients with HF, mortality was recorded for 13.7% of patients on maximum doses of RAAS inhibitors, compared with 27.7% on submaximum doses and 30.1% of patients who discontinued. Patients in the DM category had the lowest mortality rates, with mortality recorded for 5.0% of patients on maximum doses, 10.1% of patients on submaximum doses, and 13.1% of patients who discontinued RAAS inhibitor therapy.

DISCUSSION

Overall, the results of these analyses indicate that there is a substantial gap between the recommendations in treatment guidelines and the real-world prescribing patterns for RAAS inhibitors. Among patients with cardiorenal comorbidities for which RAAS inhibitors are recommended by the guidelines, this retrospective analysis showed that more than half were prescribed lower than recommended doses and roughly 14% to 16% discontinued RAAS inhibitors. This observed discordance with treatment guidelines is corroborated by evidence

■ **Figure 4.** Percent Mortality by Prior RAAS Inhibitor Dose



CKD indicates chronic kidney disease; RAAS, renin-angiotensin-aldosterone system.

from the USRDS, which reported RAAS inhibitor use in 52.5% of Medicare patients with CKD,²¹ and similar results have been documented in registries designed to prospectively evaluate adherence to treatment guidelines for patients with HF.¹⁵⁻¹⁸

Although several studies have investigated RAAS inhibitor prescribing patterns, the current study is the first to our knowledge to investigate the association between RAAS inhibitor prescribing patterns and hyperkalemia and the association between RAAS inhibitor dose and clinical outcomes in a large database. A specific strength in our evaluation of RAAS inhibitor treatment patterns is that we were able to examine what prescriptions physicians wrote, in contrast to earlier studies that based their conclusions on prescription fills. Our results suggest that the prescribing patterns for RAAS inhibitors may be altered by the development of hyperkalemia. Moderate-to-severe hyperkalemia events (serum potassium ≥ 5.5 mEq/L) were followed by down-titration or discontinuation of RAAS inhibitor therapy in nearly half of the patients on maximal doses and discontinuation in nearly one-third of patients on submaximal doses.

An extremely important observation of this study is that patients on submaximum doses or who discontin-

ued RAAS inhibitors had worse cardiorenal outcomes and higher mortality than patients on maximum doses. Taken together, these results highlight the extraordinary challenge behind RAAS inhibitor prescribing decisions: attempting to balance the risk of provoking hyperkalemia with the benefits to cardiorenal morbidity and mortality. These decisions are further confounded by the fact that those patients who are known to derive the most benefit from these drugs (CKD patients with concomitant DM or HF) are the same patients who are at highest risk of developing hyperkalemia.²²

Current and Emerging Treatments for Hyperkalemia

Treatment for hyperkalemia often occurs in the acute setting. Emergency treatments typically include insulin or β -adrenoceptor agonists to quickly redistribute serum potassium into cells and sodium gluconate to restore the normal resting membrane potential of cardiac myocytes.^{13,14} Loop diuretics can also be prescribed to promote renal excretion of potassium and hemodialysis can be administered to eliminate serum potassium.^{13,14}

Sodium-containing polystyrene sulfonate (SPS), a potassium exchange resin that eliminates potassium in the gut lumen, is an option for treating chronic hyper-

kalemia.^{13,14} However, the efficacy of SPS has never been studied in a controlled clinical trial, and its use is limited due to serious safety concerns, including a risk for life-threatening intestinal necrosis.^{13,14,23} Use of this product is further limited because it contains sodium as the counter ion. Caution is advised in patients who cannot tolerate even small increases in sodium loads, such as patients with HF, severe hypertension, or marked edema, all of which are common comorbidities in patients with CKD.^{13,14}

Two newly developed potassium-binding drugs, patiromer and sodium zirconium cyclosilicate (ZS-9), have recently reported positive clinical trial results for the management of hyperkalemia. Patiromer and ZS-9 are cation exchangers that bind potassium in the gastrointestinal tract in exchange for calcium (patiromer) or sodium (ZS-9), thereby increasing fecal potassium excretion and lowering serum potassium.²⁴⁻²⁷ Both drugs have demonstrated the ability to restore normal serum potassium in patients with hyperkalemia and to maintain normokalemia after 28 days (ZS-9 and patiromer), and patiromer has also shown safety and efficacy over 52 weeks.²⁴⁻²⁷ The adverse effects reported in the clinical trials for ZS-9 and patiromer were generally similar to those for placebo.²⁴⁻²⁷ These products could represent a much-needed advancement in the treatment of hyperkalemia.

Limitations

As is typical for retrospective database analyses, this study evaluates associations but does not establish causality between hyperkalemia events and RAAS inhibitor dose changes or between RAAS inhibitor dose and adverse outcomes. A further limitation of the hyperkalemia analyses is the long follow-up period (390 days) for identifying RAAS inhibitor dose changes, which was dictated by the length of time required to identify prescription discontinuations. It is also important to note that the comorbid patient cohort identified in this analysis did not exclude all patients for whom RAAS inhibitor therapy is not guideline-recommended, such as DM patients without cardiac or renal comorbidities or patients who developed severe hyperkalemia after initiating a RAAS inhibitor. Finally, these data do not allow for an examination of at-risk patients who are never prescribed RAAS inhibitors (eg, patients with contraindications to RAAS inhibitor therapy). Despite these limitations, the direction and magnitude of the observed associations are important results that merit further investigation.

CONCLUSIONS

Despite the presence of serious comorbidities, relatively few patients are prescribed maximum guideline-recommended doses of RAAS inhibitors, and hyperkalemia associated with RAAS inhibitor therapy was frequently followed by reduction in dosage or discontinuation of therapy. 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. These findings warrant further evaluations of the relationship between hyperkalemia and subsequent RAAS inhibitor dosing, as well as between RAAS inhibitor dose levels and adverse outcomes.

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