Association Between Serum Potassium and Discontinuation of Renin-Angiotensin Aldosterone System Blocker Medication in Patients With Chronic Kidney Disease

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Introduction

- Chronic kidney disease (CKD) patients are at high risk of cardiovascular events and for progression to end-stage renal disease. In both respects, patients may benefit from treatment with medications that inhibit the renin-angiotensin-aldosterone system (RAAS).
- CKD patients are predisposed to hyperkalemia, and RAAS-blocking medications, or RAAS inhibitors, increase such predisposition.[1,2]
- Physicians my respond to patients' hyperkalemia by discontinuing RAAS blocker, thereby denying affected patients the potential cardio and renal protection afforded by RAAS blockade.

Objectives

The purpose of this study was to evaluate the association between serum K concentration and discontinuation of RAAS-inhibiting medications among CKD patients stratified by underlying severity of disease.

Methods

Study data. Demographic, comorbid disease, laboratory, and mortality data were taken from the electronic health record of DaVita HealthCare Partners containing data from nearly 1 million patients annually. Medication utilization was abstracted from pharmacy claims files. Demographic patient data are organized according to the time of patient study entry.

Study patients. We considered patients who were aged ≥18 years, had estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2 measured between 01 January 2009 and 30 June 2013, and who subsequently or concurrently had serum K measured while receiving a RAAS blocker. Patients who had received a kidney transplant or dialysis prior to their serum K index date were excluded.

Exposure status. Results of generalized additive models examining the nonlinear association between K were used to guide the discrete categorization of K for subsequent analyses (<3.5, 3.5-3.9, 4.0-4.4, 4.5-4.9, 5.0-5.4, 5.5-5.9, and ≥6.0 mEq/L), including the serum K category used for risk comparisons (4.5-4.9 mEq/L). Other covariates of interest (including eGFR) were also updated as of the time of each K measurement.

Outcome. The primary outcome of interest was discontinuation of RAAS blocker. Patients who discontinued RAAS blocker and later resumed treatment were eligible to re-enter the study provided inclusion criteria were otherwise met.

Analysis. Patient time at-risk and outcome events were attributed to serum K and eGFR (Figure 1). Associations between serum K and RAAS discontinuation were estimated using time-updated Poisson regression models. Estimates were adjusted for patient age, sex, race, diabetes, congestive heart failure, coronary artery disease, cerebrovascular accident, beta blocker use, non-dihydropyridine calcium channel blocker use, loop diuretic use, and thiazide diuretic use, and are reported as adjusted incidence rate ratios (aIRR). Variance estimates were corrected for multiple observations made over time within each patient.

Results

Table 1. Patient Demographics

Variable	Serum K (mEq/L) N = 32,136							
	<3.5 n = 557	3.5 - 3.9 n = 3359	4.0 - 4.4 n = 11,071	4.5 - 4.9 n = 10,910	5.0 - 5.4 n = 1208	5.5 - 5.9 n = 371	≥6.0 n = 281	*P*
Age (years) mean ± SD	72.0 ±11.9	74.1 ±11.1	74.7 ±11.2	75.0 ±11.1	75.0 ±11.1	74.3 ±11.7	73.9 ±12.7	< 0.001
Female, %	66.6	68.5	62.8	55.6	52.0	52.0	50.2	< 0.001
Diabetes, %	16.9	16.5	17.2	20.0	21.4	23.8	26.3	< 0.001
CHF, %	10.2	6.5	5.6	5.3	6.0	5.2	8.2	< 0.001
CAD, %	8.4	9.3	9.3	10.4	10.4	11.4	12.1	0.01
CVA, %	5.8	5.1	5.0	4.5	4.6	5.5	6.1	0.3
Loop diuretic, %	10.1	5.5	4.0	3.6	3.6	3.3	5.0	< 0.001
Thiazide diuretic, %	26.8	18.6	8.7	4.7	3.5	4.7	1.8	< 0.001
Beta blocker, %	11.7	13.6	11.1	10.3	9.8	11.4	10.7	< 0.001
ND-CCB, %	5.0	4.8	3.4	2.5	1.8	2.3	2.5	< 0.001

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CVA, cerebrovascular accident; K, potassium; ND-CCB, non-dihydropyridine calcium channel blocker

Figure 1. Schema for Patient Eligibility and Time-updating of Exposure Status, Shown for One Hypothetical Patient

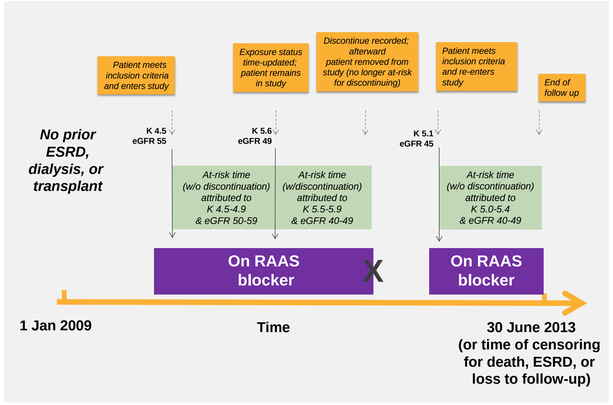


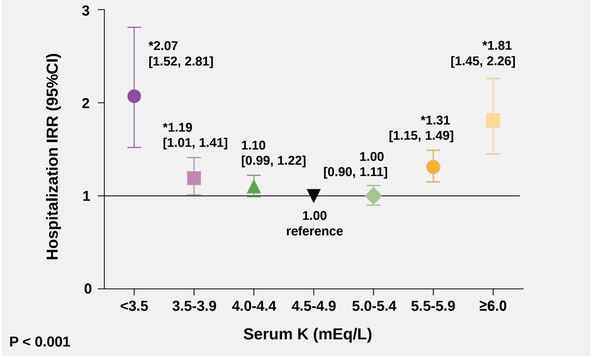
Table 2. Adjusted Incidence Rate Ratios for RAAS Discontinuation

eGFR mL/min/1.73m^2	Serum K (mEq/L) <3.5	3.5 - 3.9	4.0 - 4.4	4.5 - 4.9	5.0 - 5.4	5.5 - 5.9	≥6.0	*P*
<30	**2.07 [1.52, 2.81]**	**1.19 [1.01, 1.41]**	1.10 [0.99, 1.22]	Ref	1.00 [0.90, 1.11]	**1.31 [1.15, 1.49]**	**1.81 [1.45, 2.26]**	<0.001
30-39	**1.69 [1.26, 2.26]**	**1.28 [1.14, 1.44]**	1.07 [0.99, 1.16]	Ref	1.08 [0.99, 1.17]	**1.38 [1.22, 1.57]**	**1.71 [1.33, 2.20]**	<0.001
40-49	**1.50 [1.19, 1.91]**	**1.13 [1.03, 1.25]**	1.05 [0.98, 1.11]	Ref	1.06 [0.99, 1.15]	**1.45 [1.28, 1.65]**	**2.21 [1.68, 2.90]**	<0.001
50-59	**1.37 [1.09, 1.72]**	**1.13 [1.03, 1.23]**	1.00 [0.94, 1.06]	Ref	1.03 [0.95, 1.11]	**1.39 [1.20, 1.61]**	**1.70 [1.13, 2.56]**	<0.001

Incidence rate ratios were adjusted for age, sex, race, diabetes, congestive heart failure, coronary artery disease, cerebral vascular accident, beta blocker use, and non-dihydropyridine calcium channel blocker use, loop diuretic use, and thiazide diuretic use. Associations were estimated using mixed effects Poisson models, with random intercept terms representing individual patients and fixed effects terms as described.

- Percent patient-time spent with hypokalemia (<3.5 mEq/L) was similar across eGFR strata (range 0.7-0.9% of time); percent patient-time spent with hyperkalemia (>5.0 mEq/L) increased with decreasing eGFR (range 16.0%-35.4% of time) (data not shown).

Figure 2. Adjusted Incidence Rate Ratios for RAAS Discontinuation: <30 mL/min/1.73m^2



Estimates based on Poisson models that were time updated as per Figure 1.
P-value is for an omnibus test that adjusted for how discontinuation rates vary across categories of K.
* Indicates that adjusted discontinuation rate was statistically significantly different versus referent K 4.5-4.9 mEq/L.

Discussion

- Our study findings demonstrate that hyperkalemia is relatively common in unhospitalized CKD patients. Of the 32,136 patients prescribed RAAS inhibitors at study entry:
  - 5.7% were hyperkalemic (>5.0 mEq/L)
  - 1.7% were hypokalemia (<3.5 mEq/L)
- Higher serum K was associated with discontinuation of RAAS inhibitors; the highest adjusted rates of discontinuation were observed during patient-time spent with K ≥6.0 versus K 4.5-4.9 mEq/L.
- A limitation of the study is that the reasons for discontinuation were not captured.

Conclusions

- Future studies should be designed to determine whether RAAS discontinuation due to hyperkalemia is associated with poor outcomes and to establish whether maintenance of normokalemia might positively affect patient outcomes.

References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3(1):1-150.
2. Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol.* 2010;5(3):531-548.

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