The Relationship Between Serum Potassium Concentration and Discontinuation of Renin–Angiotensin–Aldosterone System Inhibitors in UK Patients With CKD

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Introduction

- Patients with chronic kidney disease (CKD) have a high risk of hypokalemia and hyperkalemia, which are associated with higher rates of major adverse cardiovascular events and death[1]
- Hyperkalemia may occur in the absence of renin–angiotensin–aldosterone system inhibitors (RAASis), but RAASi use may increase the likelihood of hyperkalemia.[1,2] Although RAASis improve cardiovascular function, they may be discontinued in patients with hyperkalemia[1,2]
- Both hypokalemia and hyperkalemia have been associated with higher rates of RAASi discontinuation among patients with CKD in the United States (US),[1] but this phenomenon has been poorly documented in other populations
- This retrospective, observational cohort study evaluated the real-world incidence of RAASi discontinuation over a range of baseline serum potassium (K^+) levels and renal function severities among patients with CKD in England

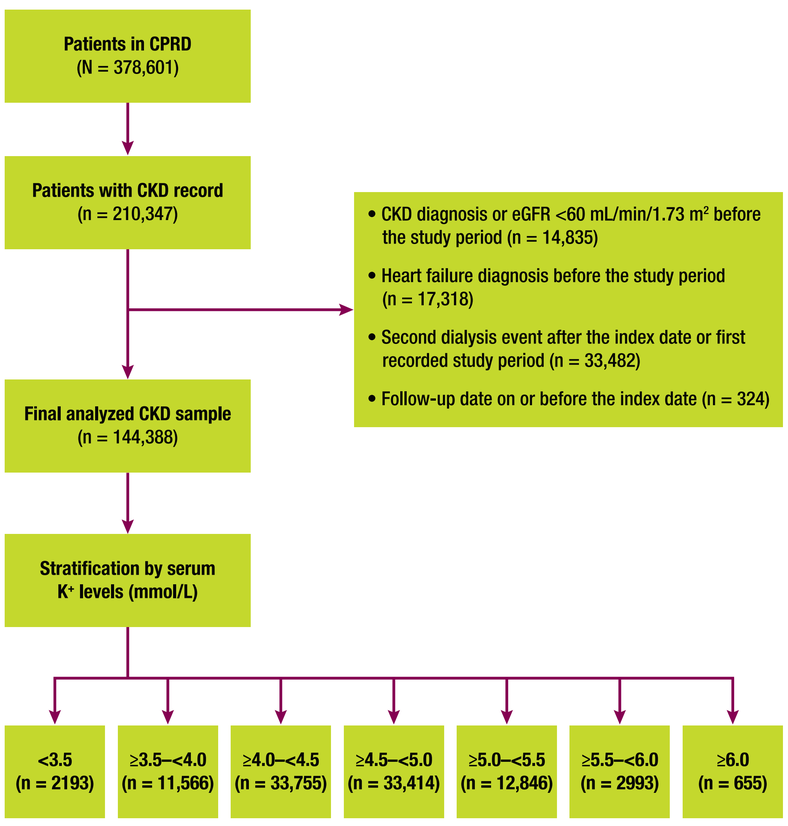
Methods

- Primary care and hospital data from January 1, 2006 to December 31, 2015 were extracted from the linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases
  - CPRD is an electronic primary care database of anonymous longitudinal medical records for >11 million individuals from 674 primary care practices across the UK and has established linkages to HES[3]
  - The HES dataset provides information on hospital/emergency department admissions and outpatient appointments provided at National Health Service hospitals in England[4]
  - The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research
- Inclusion criteria:
  - Age ≥18 years
  - First record of estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2, first diagnosis of stage ≥3 CKD, or undergoing dialysis, with or without diabetes, during the study follow-up period
- Exclusion criteria:
  - Kidney dialysis as the first recorded renal event during the study follow-up
  - History of heart failure before the study period
- Patients were followed and their records extracted for all observations up to and including the first occurrence of death, loss to follow-up, or end of the study period (December 31, 2015)
- Patients given a RAASi prescription within ±3 months of the index date were considered to be on RAASi therapy
- RAASi discontinuation was defined as the first ≥90-day gap without a prescription after an estimated end date of a RAASi prescription
- Statistical analyses
  - Patients were stratified by serum K^+ (<3.5, ≥3.5–<4.0, ≥4.0–<4.5, ≥4.5–<5.0 [reference serum K^+ strata], ≥5.0–<5.5, ≥5.5–<6.0, and ≥6.0 mmol/L) and eGFR levels (<30, 30–45, and 46–60 mL/min/1.73 m^2)
  - Serum K^+ and eGFR were captured every 3 months after the index date, creating a series of patient intervals. RAASi discontinuations during each interval were attributed to the serum K^+ level and adjusted for eGFR level at the interval start
  - Incidence rate ratios and 95% confidence intervals were calculated using Poisson regression, using time-updated eGFR and serum K^+ measurements and adjusting for age, sex, diabetes status, eGFR (overall CKD cohort only), cerebrovascular accident, and the use of medications (diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and calcium channel blockers)

Results

- A total of 144,388 patients comprised the analyzed CKD population and were followed for a mean (standard deviation) of 2.9 (2.4) years (**Figure 1**)

Figure 1. Identification of Study Participants



CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; K^+, potassium.

- Baseline patient characteristics and demographics, including comorbidities and concomitant medications, are shown in **Table 1**
  - Baseline characteristics and demographics were similar among the serum K^+ level strata, as were baseline comorbidities, except that more patients with higher K^+ concentrations had diabetes than patients with lower K^+ concentrations
  - At baseline, about one-half of all patients were taking RAASi therapy
    - Higher use of RAASi therapy was observed at baseline (49-69%) as baseline serum K^+ levels increased

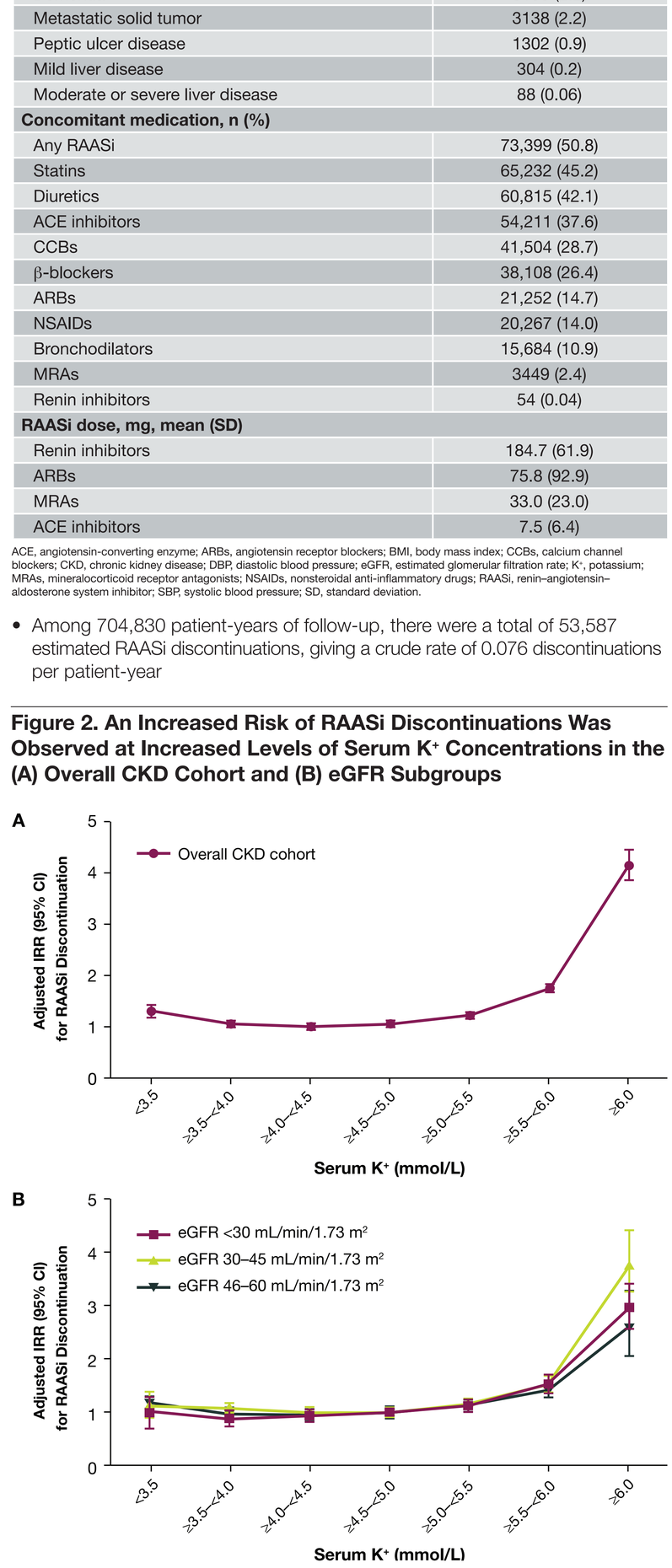
Table 1. Baseline Patient Characteristics and Demographics

	Overall CKD Cohort (N = 144,388)
Age, years, mean (SD)	73.7 (11.7)
Female, n (%)	87,272 (60.4)
BMI, kg/m², mean (SD)	28.5 (5.8)
SBP, mm Hg, mean (SD)	140.4 (19.9)
DBP, mm Hg, mean (SD)	77.9 (11.4)
Serum K^+, mmol/L, mean (SD)	4.5 (0.5)
eGFR, mL/min/1.73 m², mean (SD)	49.7 (9.2)
Comorbidities, n (%)	
Diabetes without chronic complications	18,969 (13.1)
Chronic pulmonary disease	13,450 (9.3)
Any malignancy, including leukemia and lymphoma	12,890 (8.9)
Cerebrovascular disease	9570 (6.6)
Rheumatologic disease	4971 (3.4)
Myocardial infarction	4903 (3.4)
Renal disease	4674 (3.2)
Diabetes with chronic complications	4050 (2.8)
Peripheral vascular disease	3747 (2.6)
Dementia	3198 (2.2)
Metastatic solid tumor	3138 (2.2)
Peptic ulcer disease	1302 (0.9)
Mild liver disease	304 (0.2)
Moderate or severe liver disease	88 (0.06)
Concomitant medication, n (%)	
Any RAASi	73,399 (50.8)
Statins	65,232 (45.2)
Diuretics	60,815 (42.1)
ACE inhibitors	54,211 (37.6)
CCBs	41,504 (28.7)
β-blockers	38,108 (26.4)
ARBs	21,252 (14.7)
NSAIDs	20,267 (14.0)
Bronchodilators	15,684 (10.9)
MRAs	3449 (2.4)
Renin inhibitors	54 (0.04)
RAASi dose, mg, mean (SD)	
Renin inhibitors	184.7 (61.9)
ARBs	75.8 (92.9)
MRAs	33.0 (23.0)
ACE inhibitors	7.5 (6.4)

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; K^+, potassium; MRAs, mineralocorticoid receptor antagonists; NSAIDs, nonsteroidal anti-inflammatory drugs; RAASi, renin–angiotensin–aldosterone system inhibitor; SBP, systolic blood pressure; SD, standard deviation.

- Among 704,830 patient-years of follow-up, there were a total of 53,587 estimated RAASi discontinuations, giving a crude rate of 0.076 discontinuations per patient-year

Figure 2. An Increased Risk of RAASi Discontinuations Was Observed at Increased Levels of Serum K^+ Concentrations in the (A) Overall CKD Cohort and (B) eGFR Subgroups



CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; K^+, potassium; RAASi, renin–angiotensin–aldosterone system inhibitor.

Limitations

- Emergency care data and laboratory values for hospitalized patients were not available for the study
- Clinical diagnoses were not adjudicated

Conclusions

- In this real-world analysis in England, one-half of patients with CKD were treated with RAASi therapy
- Physicians in England were more likely to discontinue RAASi therapy in CKD patients with high serum K^+, particularly in those with K^+ ≥6.0 mmol/L
- Results are consistent with those of a prior study in the US population[1]
- Future research is warranted to examine the role of RAASi discontinuation in the prevention or treatment of hyperkalemia in England

References

1. Luo J, et al. *Clin J Am Soc Nephrol*. 2016;11(1):90–100.
2. Weir MR, Rolfe M. *Clin J Am Soc Nephrol*. 2010;5(3):531–548.
3. Herrett E, et al. *Int J Epidemiol*. 2015;44(3):827–836.
4. Hospital Episode Statistics. http://www.hscic.gov.uk/hes. Accessed April 14, 2017.

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