



Serum Potassium Levels and Risk of Sudden Cardiac Death Among Patients With Chronic Kidney Disease and Significant Coronary Artery Disease

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Introduction: Chronic kidney disease (CKD) patients have increased risks of sudden cardiac arrest and sudden cardiac death (SCA/SCD) that are not explained by traditional risk factors. We examined associations between serum potassium and SCA/SCD in a large cohort of patients with coronary artery disease (CAD) and moderate CKD.

Methods: Among 22,009 patients who underwent cardiac catheterization at our institution between 1999 and 2011, 6181 patients had an estimated glomerular filtration rate of ≤ 60 ml/min per 1.73 m^2 and were not receiving renal replacement therapy. The risk of SCA/SCD and all-cause mortality associated with potassium concentration was evaluated at the time of cardiac catheterization (baseline) and most proximate to SCA/SCD events. Covariate-adjusted Cox models were used to examine relationships between baseline potassium measurements and outcomes. A propensity score-matched, case-control design was used to assess risk associations of potassium measurements obtained proximate to SCA events.

Results: In the baseline potassium analysis, compared with levels in the normal range, there was no significant risk association between hyperkalemia ($>5 \text{ mEq/l}$) or hypokalemia ($<3.5 \text{ mEq/l}$) and SCA/SCD or all-cause death after covariate adjustment. In the proximate potassium analysis, hyperkalemia occurred more frequently than hypokalemia (16.7% vs. 3%), and was associated with a doubling in SCA/SCD risk (adjusted odd ratio: 2.37; 95% confidence interval: 1.33–4.23) whereas there was no significant relationship between hypokalemia and outcome.

Discussion: Among CKD patients with significant CAD, elevated serum potassium levels $>5.0 \text{ mEq/l}$ are common and are associated with an increased short-term risk of SCA/SCD. Early detection and treatment of hyperkalemia may reduce the high risk of SCD among CKD patients.

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KEYWORDS: cardiac arrhythmias; cardiovascular disease; chronic kidney disease; hyperkalemia; hypokalemia; sudden death

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More than 20 million Americans have chronic kidney disease (CKD) and have a markedly increased susceptibility to sudden cardiac arrest (SCA). Compared with patients with preserved kidney function, CKD patients with an estimated glomerular filtration rate (eGFR) ≤ 60 ml/min per 1.73 m^2 have a 4-fold increase in the risk of SCA.¹ Risk factors contributing to SCA in CKD patients are not well understood, but it is clear that traditional cardiovascular risk factors

such as left ventricular ejection fraction and hyperlipidemia have decreased usefulness in risk discrimination and risk prediction.² Thus, a better understanding of SCA risk factors unique to the CKD population is needed to improve outcomes.

Tight regulation of serum potassium levels is necessary for many physiologic processes, including normal cardiac conduction. The ability to maintain normal serum potassium levels is diminished among patients with CKD, both due to decreasing capacity to excrete potassium and increased exposure to medications that impair normal potassium handling in the kidney (e.g., renin-angiotensin-aldosterone system blockers and diuretics).^{3,4} Previous investigations

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among CKD patients have identified U-shaped associations between serum concentrations of potassium with increased risk of death and hospitalization^{5–7}; however, no study has specifically examined the role of serum potassium levels in relation to the risk of ventricular arrhythmias and SCA among patients with predialysis moderate CKD.

To further understand risk relationships among abnormal serum potassium levels, cardiac arrhythmias, and mortality, we explored the risk relationships between serum potassium disturbances and significant arrhythmic events among a large population of predialysis CKD patients with significant coronary artery disease (CAD) at high risk of SCA.

METHODS

Description of Data Source

Patients for this retrospective cohort study were identified using the Duke Databank for Cardiovascular Disease (DDCD), which has been described previously.^{1,8} In brief, this database compiled data on the clinical course of all patients who underwent a cardiac catheterization, an interventional cardiac procedure, or a coronary artery bypass surgery since 1969 at Duke University Medical Center. Patient information on physician-determined comorbidities, vital signs and symptoms at the time of cardiac procedure, and procedure results were collected at the time of treatment. Among patients with clinically significant CAD, the DDCD routinely collected follow-up data on mortality, cardiovascular events, and hospitalizations using mailed questionnaires and phone surveys at 6 months, 1 year, and annually thereafter. Linkage to the electronic medical record and the medical claims data across the health care system allowed for extraction of additional clinical and demographic variables. In addition, vital status was determined through a search of the National Death Index. The Duke University institutional review board committee reviewed and approved the study.

Study Subjects/Design

Consecutive patients who underwent cardiac catheterization between January 1, 1989 and June 30, 2014 and who were found to have clinically significant CAD (defined as ≥ 1 coronary arteries with $\geq 50\%$ stenosis) with available serum creatinine data within 3 months of cardiac catheterization were included for analysis. eGFR (reported in ml/min per 1.73 m^2) was determined using the CKD epidemiology collaboration (CKD-EPI) creatinine-based equation.⁹ All laboratory testing was performed at the core laboratories of a single institution. Serum creatinine was determined using the enzymatic Jaffé method. Patients were excluded from the study cohort if the cardiac

catheterization was performed to evaluate congenital or pericardial disease, hypertrophic cardiomyopathy, or for assessment before organ transplantation. Because we discovered that data on serum potassium values were only sporadically available before 1999, we further restricted the cohort to patients who underwent cardiac catheterization on or after January 1, 1999. Other specific exclusion criteria are shown in [Figure 1](#). A total of 6181 patients with reduced kidney function (defined as eGFR $< 60 \text{ ml/min per } 1.73 \text{ m}^2$) were included in the final study cohort.

Predictor

The main exposure of interest for this study was the serum potassium level. Because previous studies consistently described nonlinear U-shaped relationships between serum potassium and cardiovascular outcomes,^{5,6,10} we modeled potassium as a categorical variable split into clinically relevant categories: $< 3.5 \text{ mEq/l}$ (low), 3.5 to 5.0 mEq/l (normal), and $> 5.0 \text{ mEq/l}$ (high), based on normal reference values reported at our institution. Because potassium values vary over time, we assessed the association of serum potassium values with the risk of SCA examined at 2 different time points. First, we examined serum potassium levels at the time of cardiac catheterization (baseline) to assess the long-term predictive ability of potassium measurements. We defined baseline potassium measurement as the most recent measurement that occurred within 30 days before catheterization. For $< 9\%$ of our study cohort, there was no serum potassium measurement available in this time frame; instead, we used the closest potassium measurements that occurred up to 30 days after catheterization. Second, because of the more immediate effects of serum potassium levels on cardiac conduction and the risk of arrhythmia, we performed a matched case–control analysis (see Statistical Analysis) to assess risk associations with the last measured potassium value proximate to an event of interest. Although we considered performing a time-varying covariate analysis, we were concerned that unequal follow-up among patients might bias the results.

Primary Outcome

The outcome of interest was defined as a composite of sudden cardiac death (SCD) and resuscitated SCA. Two independent trained reviewers who were blinded to potassium values examined all deaths using data collected from family members, chart review of medical records, death certificate data, and query of the National Death Index. SCD was defined as deaths that were due to cardiac or unknown causes that occurred within 60 minutes of the onset of symptoms, as well as unobserved deaths that occurred in patients last seen

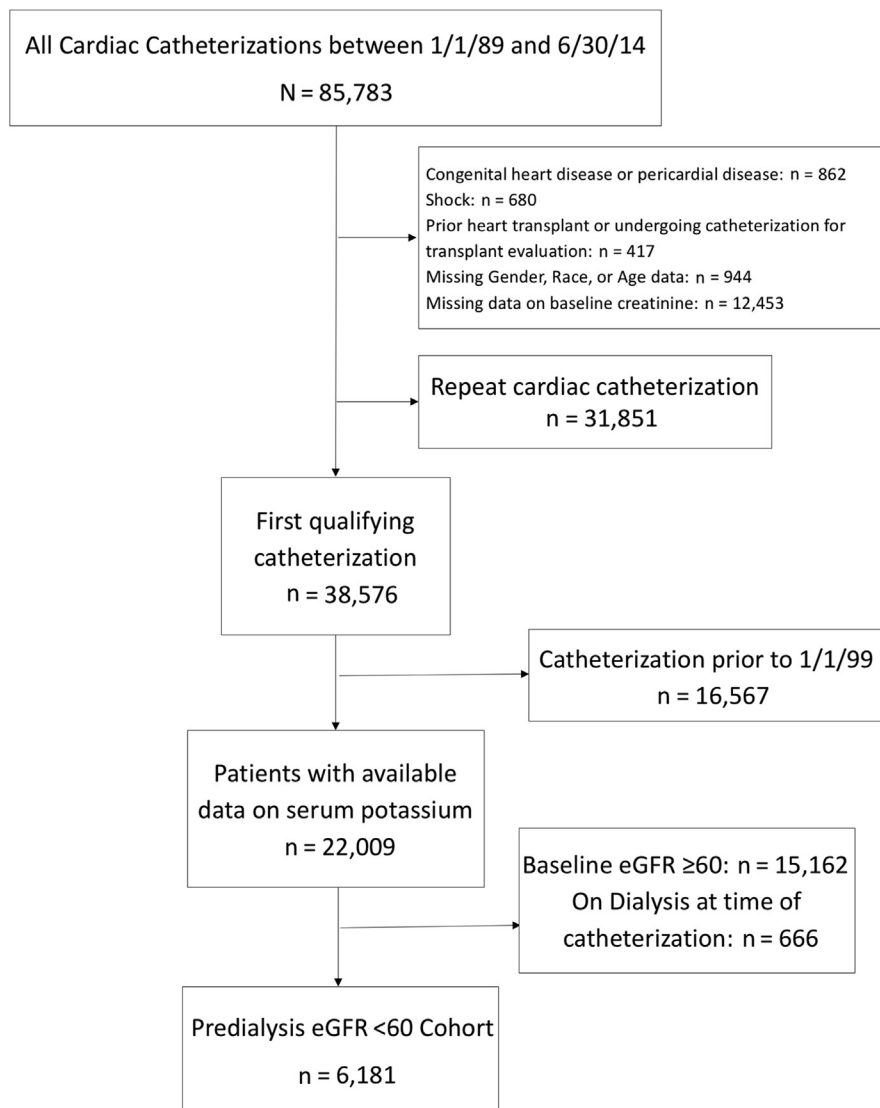


Figure 1. Study flow diagram. eGFR, estimated glomerular filtration rate.

alive >60 min before the discovery of death and the circumstances directly leading to the death were unknown. To identify resuscitated SCA events, we queried the medical claims database for the following diagnosis codes occurring at least 30 days after baseline cardiac catheterization: 427.5 (cardiac arrest), 427.4x (ventricular fibrillation/flutter), and 427.1 (ventricular tachycardia). Medical records linked to these diagnosis codes were then reviewed by 2 independent reviewers to (i) confirm the occurrence of a cardiac arrest event, and (ii) exclude cardiac arrests due to noncardiac causes, events that occurred in patients with implantable cardioverter-defibrillators, events among patients with a terminal diagnosis (life expectancy <3 months), and events that occurred in the setting of a preceding invasive procedure or intensive care unit admission. Disagreements were resolved by the first author, who was blinded to the results of the initial review.

Covariates

Data on covariates were collected at the time of cardiac catheterization. These included patient demographics (age, sex, race), vital signs (blood pressure, body mass index), symptoms at the time of cardiac catheterizations, and physician-determined comorbidities. Serum potassium altering medication use by drug category was assessed at time of cardiac catheterization or within 7 days after the procedure. Available covariate data also included severity of CAD (number of vessels with >50% stenosis), measures of left ventricular dysfunction (ejection fraction assessed either by ventriculogram performed at the time of catheterization or by echocardiogram within 1 year before catheterization or no more than 6 months after catheterization), and interventions performed around the time of catheterization (percutaneous intervention and coronary artery bypass grafting [CABG]), all which were associated with risk of SCA among CKD patients in previous analyses.¹

Statistical Methods

The outcome, primary predictor, and covariates were summarized by level of potassium using means and SDs for continuous variables and frequencies and percentages for categorical variables.

The composite SCD and SCA outcome was regressed on potassium level (categorized) at baseline using a Cox proportional hazards model, adjusted for all the previously described covariates. Patients entered the risk set at time of catheterization and were censored at the time of last follow-up. Covariates in the final Cox models consisted of eGFR, age, and body mass index at catheterization, sex, race (white, black, and other race), number of diseased vessels, history of diabetes, history of hyperlipidemia, history of smoking, and ejection fraction. Because overall mortality served as a competing event, we modeled the cause-specific hazards for SCD/SCA and overall mortality separately. Because of the absence of the important ejection fraction adjustor (21.4%) for all of the Cox models, we performed multiple imputation with fully conditional specification, with 5 imputations, and which included the primary predictor and all covariates.¹¹

For the proximate serum potassium risk association assessment, data were analyzed using case–control methods. Cases were defined as all patients who had a potassium measurement within 1 year of a SCD/SCA event and whose final eGFR measurement before the endpoint was <60 ml/min per 1.73 m². Because patients who received additional laboratory testing might differ from those who did not, all patients with SCD/SCA who met these criteria were propensity-score matched with 4 control subjects using a greedy matching algorithm.¹² Eligible control subjects for each SCD/SCA case included those patients still in the risk set within the year before the SCD/SCA and who also had a potassium measurement in that 1-year interval. The cases and control subjects were matched on eGFR before endpoint, CKD status before endpoint (dichotomized at eGFR: 60 ml/min per 1.73 m²), age at catheterization, body mass index at catheterization, sex, race, number of diseased vessels, history of diabetes, history of hyperlipidemia, and history of smoking. The patients were matched exactly on categorical variables, including the number of diseased vessels. For continuous variables, they were matched within 3 ml/min per 1.73 m² of eGFR, within 3 years of age, and within 3 kg/m² of body mass index. We then examined the relationship between the potassium level closest to the endpoint (categorized) and case (SCD/SCA) status using conditional logistic regression. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, North

Carolina), with matching performed using the % gmatch macro¹³ and imputation performed using PROC MI.

RESULTS

Figure 1 shows the development of the study cohort. After exclusions, 22,009 patients underwent a qualifying cardiac catheterization for CAD during the study period; of these, 6181 patients (28.1%) with a baseline eGFR <60 ml/min per 1.73 m² who were not receiving dialysis therapy met inclusion criteria and were included in the final study cohort. The median follow-up time was 4.14 years.

Table 1 shows the characteristics of the study cohort according to baseline potassium levels assessed at or near the time of cardiac catheterization. Hyperkalemia was more common than hypokalemia; 6.3% of the cohort had serum potassium >5.0 mEq/l, and 3.4% had a serum potassium <3.5 mEq/l. There was an increased prevalence of hyperkalemia (6.7%) and hypokalemia (4.8%) among black subjects compared with white subjects (6.2% and 3.1% respectively; $P = 0.03$). Compared with the group with normal serum potassium, patients with a serum potassium >5.0 mEq/l had a higher prevalence of diabetes and an increased severity of CAD as measured by the number of coronary vessels with significant stenosis. Conversely, patients with a serum potassium <3.5 mEq/l were more likely to be women, have a lower burden of comorbidity (diabetes, hyperlipidemia, and cigarette smoking), and have a decreased severity of coronary disease. eGFR was significantly lower among patients with high baseline serum potassium (37.6 ml/min per 1.73 m² vs. 45 ml/min per 1.73 m² among patients with normal potassium), whereas there was no difference in eGFR among patients with low potassium compared with those with normal potassium values. During the 15-year study period, there were 225 adjudicated SCD or SCA events and 3540 all-cause deaths. The overall SCD/SCA event rate was 7.5 per 1000 patient-years. Patients with serum potassium >5.0 mEq/l had a higher incidence of all-cause death and the composite outcome of SCD or SCA compared with other potassium groups.

In covariate-adjusted models, eGFR was independently associated with risk of both SCA/SCD (adjusted hazard ratio [aHR]: 1.16; 95% confidence interval [CI]: 1.05–1.29 per 10 ml/min per 1.73 m² decrease) and all-cause death (aHR: 1.29; 95% CI: 1.26–1.33) per 10 ml/min per 1.73 m² decrease). (See [Supplementary Table S1](#) for a full list of baseline factors associated with study outcomes). Figure 2 shows unadjusted cumulative incidence curves for SCD/SCA by the 3 baseline serum potassium categories. After accounting for differences

Table 1. Characteristics of patients by baseline serum potassium levels

| Variables | Serum Potassium Level | | | All Patients (N = 6181) ^a | P value |
|---|-------------------------|-----------------------------|--------------------------|---|---------|
| | <3.5 mEq/l (n = 208) | 3.5–5.0 mEq/l (n = 5538) | ≥ 5.0 mEq/l (n = 386) | | |
| Age at cardiac catheterization (yr) | 69.3 ± 11.1 | 71.3 ± 10.3 | 68.5 ± 11.8 | 71.1 ± 10.4 | <0.001 |
| Female | 114 (54.8) | 2427 (43.8) | 162 (42.0) | 2726 (44.1) | 0.005 |
| Race | | | | | 0.03 |
| White | 149 (71.6) | 4291 (77.5) | 291 (75.4) | 4774 (77.2) | |
| Black | 53 (25.5) | 971 (17.5) | 74 (19.2) | 1101 (17.8) | |
| Other | 6 (2.9) | 276 (5.0) | 21 (5.4) | 306 (5.0) | |
| Body mass index (kg/m ²) | 28.7 ± 6.3 | 28.8 ± 6.2 | 28.3 ± 6.5 | 28.8 ± 6.3 | 0.43 |
| Estimated GFR | 45.1 ± 12.0 | 45.0 ± 11.9 | 37.6 ± 14.6 | 44.6 ± 12.2 | <0.001 |
| Left ventricular ejection fraction | 48.9 (16.3) | 49.6 (15.3) | 48.6 (15.9) | 49.6 (15.3) | 0.52 |
| No. of diseased vessels with >50% stenosis | | | | | 0.006 |
| 1 | 92 (44.2) | 1846 (33.3) | 125 (32.4) | 2086 (33.7) | |
| 2 | 51 (24.5) | 1462 (26.4) | 90 (23.3) | 1616 (26.1) | |
| 3 | 65 (31.3) | 2230 (40.3) | 171 (44.3) | 2479 (40.1) | |
| History of diabetes | 66 (31.7) | 1976 (35.7) | 172 (44.6) | 2226 (36.0) | <0.001 |
| History of hyperlipidemia | 92 (44.2) | 3180 (57.4) | 213 (55.2) | 3517 (56.9) | <0.001 |
| History of cigarette smoking | 62 (29.8) | 1975 (35.7) | 139 (36.0) | 2198 (35.6) | 0.22 |
| Mean arterial blood pressure | 104.8 ± 18.9 | 102.0 ± 16.9 | 99.5 ± 18.8 | 101.9 ± 17.1 | <0.001 |
| PCI at time of catheterization | 118 (30.6) | 72 (34.6) | 1684 (30.4) | 1878 (30.4) | 0.43 |
| PCI within 30 d after catheterization | 168 (43.5) | 96 (46.2) | 2436 (44.0) | 2706 (43.8) | 0.81 |
| CABG within 30 d after catheterization | 79 (20.5) | 31 (14.9) | 1023 (18.5) | 1136 (18.4) | 0.25 |
| Potassium altering medication use at time of catheterization ^b | | | | | |
| ACE inhibitor | 220 (57.0) | 122 (58.7) | 3331 (60.1) | 3680 (59.5) | 0.44 |
| Angiotensin receptor blocker | 79 (20.5) | 54 (26.0) | 1197 (21.6) | 1333 (21.6) | 0.27 |
| Diuretic | 252 (65.3) | 157 (75.5) | 3298 (59.6) | 3714 (60.1) | <0.001 |
| Spironolactone | 18 (4.7) | 27 (13.0) | 355 (6.4) | 402 (6.5) | <0.001 |
| Death during study period | 120 (57.7) | 3144 (56.8) | 276 (71.5) | 3561 (57.6) | <0.001 |
| Sudden cardiac arrest or sudden death during study period | 5 (2.4) | 198 (3.6) | 22 (5.7) | 228 (3.7) | 0.06 |

ACE, angiotensin converting enzyme; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; PCI, percutaneous coronary intervention.

^aForty-nine patients were missing baseline potassium, and therefore were excluded from the low, normal, and high potassium columns.

^bMedication use at time of procedure or within 7 days following the procedure.

Data are mean ± SD or n (%).

in demographic variables, comorbidities, severity of coronary disease, ejection fraction, and estimated GFR, baseline serum potassium levels measured at the time of cardiac catheterization were not significantly associated with SCD/SCA or the secondary outcome of all-cause death (Table 2). There was no change in lack of significant association after repeating the analysis and excluding patients without a baseline potassium measurement occurring before or on the day of catheterization. There was also no significant interaction between eGFR and baseline potassium values on the risk of either SCD/SCA or all-cause death.

Because more proximate serum potassium measurements would be expected to more directly influence SCD/SCA events, we examined the association of the last recorded serum potassium measurement with these outcomes. Of 225 patients in the study cohort who experienced a SCD/SCA, 168 patients had available follow-up potassium measurements occurring within 1 year before the event (case cohort). The mean ± SD time between the last potassium measurement and SCD/SCA was 2.4 ± 3.4 months. Each patient was matched according to patient characteristics and propensity

score to approximately 3 control subjects who did not experience a SCD/SCA event but who also had available follow-up serum potassium measurements (655 total control subjects).

Table 3 shows the characteristics of the case and control cohorts. By the matched case–control design, the study groups had well-balanced demographic characteristics, baseline comorbidities, CAD severity, and eGFR; the overall mean ± SD eGFR was 42.1 ± 11.9 ml/min per 1.73 m². Regarding coronary interventions, the study groups were also well-matched for proportion that received PCI within 30 days after catheterization, but there was a higher proportion of control subjects who underwent CABG within 30 days (24.6%) compared with case patients (16.1%). Although hypokalemia (potassium <3.5 mEq/l) was similarly infrequent compared with the baseline potassium measurements (3% among SCD/SCA cases vs. 3.4% overall in baseline potassium analysis), hyperkalemia (potassium >5.0 mEq/l) was noted nearly 3 times more frequently among patients who experienced a SCD/SCA event (16.7%) compared with baseline potassium measures (6.3% overall).

Cause-specific SCD/SCA Cumulative Incidence Curve

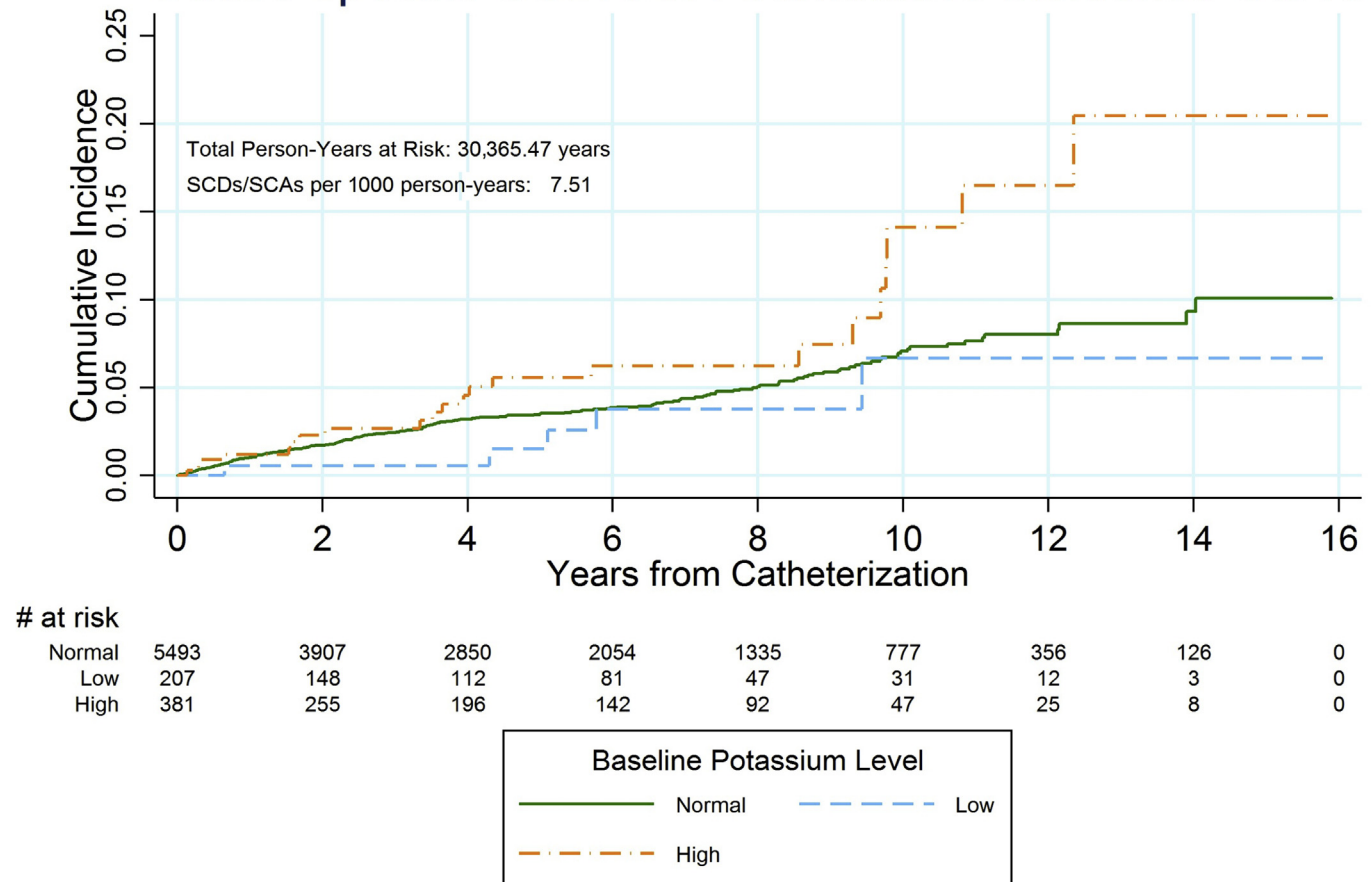


Figure 2. Unadjusted cumulative incidence curves for sudden cardiac death/sudden cardiac arrest (SCD/SCA) according to baseline serum potassium categories. High: >5.0 mEq/l; normal: 3.5 to 5.0 mEq/l; low: <3.5 mEq/l.

Figure 3 illustrates the association between the last measured potassium values and risk of SCD/SCA. Although there was no significant relationship between low serum potassium <3.5 mEq/l and outcome (OR: 1.74; 95% CI: 0.61–5.01), compared with controls, hyperkalemia was associated with a nearly 2-fold increase in the odds of SCD/SCA (OR: 1.98; 95% CI 1.21–3.24). In addition, when accounting for differences in measured ejection fraction, congestive heart failure severity, and proportion of patients who underwent CABG after catheterization, the relationship between hyperkalemia and SCD/SCA was further strengthened

(adjusted OR: 2.37; 95% CI: 1.33–4.23), whereas the relationship between hypokalemia and outcome remained nonsignificant (OR: 1.65; 95% CI: 0.40–6.90).

DISCUSSION

In this cohort of 6181 patients with significant CAD and CKD, we examined associations between abnormal serum potassium levels and the risk of SCA and all-cause mortality. We found that hyperkalemia was observed more frequently than hypokalemia, and hyperkalemia was observed nearly 3 times more

Table 2. Unadjusted and adjusted Cox proportional hazard models for sudden cardiac death/sudden cardiac arrest and all-cause death

| Baseline serum potassium level (mEq/l) | Unadjusted model | | | | Demographics-adjusted model ^a | | | | Fully adjusted model ^b | | | |
|--|------------------|---------|------------------|---------|--|---------|------------------|---------|-----------------------------------|---------|------------------|---------|
| | SCD/SCA | | All-cause death | | SCD/SCA | | All-cause death | | SCD/SCA | | All-cause death | |
| | Hazard Ratio | P value | Hazard Ratio | P value | Hazard ratio | P value | Hazard ratio | P value | Hazard ratio | P value | Hazard ratio | P value |
| 3.5–5.0 | Reference | | Reference | | Reference | | Reference | | Reference | | Reference | |
| <3.5 | 0.69 (0.28–1.68) | 0.41 | 1.04 (0.87–1.25) | 0.66 | 0.66 (0.27–1.61) | 0.36 | 1.09 (0.91–1.31) | 0.36 | 0.69 (0.28–1.68) | 0.41 | 1.11 (0.92–1.34) | 0.26 |
| >5.0 | 1.65 (1.06–2.56) | 0.03 | 1.29 (1.13–1.46) | <.01 | 1.64 (1.05–2.55) | 0.03 | 1.39 (1.22–1.58) | <.01 | 1.46 (0.93–2.29) | 0.10 | 1.11 (0.98–1.27) | 0.11 |

^aAdjusted for age at catheterization, sex, and race/ethnicity.

^bAdjusted for age at catheterization; year of catheterization, sex; race/ethnicity; body mass index; estimated glomerular filtration rate; history of diabetes, smoking, or hyperlipidemia; number of diseased vessels; year of catheterization; percutaneous intervention within 30 days following catheterization; coronary artery bypass grafting within 30 days following catheterization; and ejection fraction.

Table 3. Characteristics of sudden cardiac arrest patients (case) and control comparison patients at time of event

| Variable | Case (n = 168) | Control (n = 655) | Total (N = 823) |
|--|-------------------|----------------------|--------------------|
| Age at catheterization (yr) | 69.4 ± 10.5 | 69.7 ± 9.1 | 69.6 ± 9.4 |
| Female | 60 (35.7) | 230 (35.1) | 290 (35.2) |
| Race | | | |
| White | 134 (79.8) | 530 (80.9) | 664 (80.7) |
| Black | 33 (19.6) | 123 (18.8) | 156 (19.0) |
| Other | 1 (0.6) | 2 (0.3) | 3 (0.4) |
| Potassium (in each category) | | | |
| <3.5 mEq/l | 5 (3.0) | 12 (1.8) | 17 (2.1) |
| 3.5–5.0 mEq/l | 135 (80.4) | 581 (88.7) | 716 (87.0) |
| >5 mEq/l | 28 (16.7) | 62 (9.5) | 90 (10.9) |
| Potassium level | 4.5 ± 0.7 | 4.4 ± 0.5 | 4.4 ± 0.6 |
| eGFR | 39.6 ± 12.3 | 42.8 ± 11.8 | 42.1 ± 11.9 |
| Body mass index (kg/m ²) | 29.0 ± 6.2 | 28.9 ± 5.0 | 28.9 ± 5.3 |
| No. of diseased vessels with >50 stenosis | | | |
| 1 | 50 (29.8) | 194 (29.6) | 244 (29.6) |
| 2 | 39 (23.2) | 153 (23.4) | 192 (23.3) |
| 3 | 79 (47.0) | 308 (47.0) | 387 (47.0) |
| History of diabetes | 79 (47.0) | 306 (46.7) | 385 (46.8) |
| History of hyperlipidemia | 100 (59.5) | 394 (60.2) | 494 (60.0) |
| History of cigarette smoking | 70 (41.7) | 269 (41.1) | 339 (41.2) |
| Ejection fraction (%) | 46.7 ± 15.9 | 50.1 ± 15.3 | 49.4 ± 15.5 |
| CHF severity (NYHA class) | | | |
| 0 | 105 (65.6) | 470 (73.7) | 575 (72.1) |
| I | 6 (3.8) | 16 (2.5) | 22 (2.8) |
| II | 11 (6.9) | 42 (6.6) | 53 (6.6) |
| III | 24 (15.0) | 76 (11.9) | 100 (12.5) |
| IV | 14 (8.8) | 34 (5.3) | 48 (6.0) |
| Intervention at time of catheterization | 41 (24.4) | 175 (26.7) | 216 (26.2) |
| PCI within 30 d after catheterization | 71 (42.3) | 289 (44.1) | 360 (43.7) |
| CABG within 30 d after catheterization | 27 (16.1) | 161 (24.6) | 188 (22.8) |

CABG, coronary artery bypass graft; CHF, congestive heart failure; eGFR, glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Data are mean ± SD or n (%).

frequently proximate to an SCA/SCD event compared with at the time of cardiac catheterization. After accounting for differences in covariates, we did not observe a significant association between baseline serum potassium level and SCA/SCD or all-cause mortality. However, in an analysis that examined serum potassium levels drawn proximate to SCA/SCD events, we found a 2-fold increase in risk associated with hyperkalemia, whereas no significant risk association with hypokalemia was observed.

It is well appreciated that both hyperkalemia and hypokalemia are common among patients with CKD. Impaired potassium secretion from declining eGFR, use of medications that block the renin-angiotensin-aldosterone system, and metabolic acidosis all are potential contributors to the increased risk of hyperkalemia, whereas increased use of diuretics, poor oral intake, and malnutrition contribute to an increased risk of hypokalemia.^{3,4,14} The impact of serum potassium

levels on outcomes among patients with CKD has been the subject of several recent studies, with variable conclusions on the relative risks of hypokalemia and hyperkalemia. A study of 820 patients with moderate CKD found a U-shaped relationship between serum potassium and all-cause mortality, with mortality risk significantly greater at lower levels of potassium ≤ 4 mEq/l compared with patients with elevated potassium levels.⁶ More recently, Luo *et al.* examined risk of mortality and hospitalization among 55,266 patients with CKD who were not on dialysis, and found that both hyperkalemia and hypokalemia were independently associated with higher rates of death, major adverse cardiovascular events, and hospitalization.⁵ Although it did not explicitly examine the risk among CKD patients, a recent study by Hughes-Austin *et al.* that investigated 9651 patients enrolled in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS) community-based population cohorts, which consisted of approximately 13% of patients with eGFR ≤ 60 ml/min per 1.73 m² found a higher risk of all-cause mortality, cardiovascular death, and noncardiovascular death among patients with serum potassium concentrations ≥ 5.0 mEq/l compared with those with serum potassium concentrations between 4.0 and 4.4 mEq/l; no significant relationships with these outcomes were seen among patients with serum potassium levels < 4.0 mEq/l.¹⁵ The relationship was not modified in interaction analyses based on eGFR levels.

Although these studies varied in their conclusions emphasizing either hypokalemia or hyperkalemia as a more influential risk factor for mortality, it is important to acknowledge that both dyskalemiacs are plausible direct risk factors for death. Because of the role of potassium in maintaining resting cell membrane potential, there are significant risks for fatal cardiac arrhythmias at both extremes of the serum potassium spectrum.^{16,17} It is also important to note that the association between serum potassium abnormalities and mortality could be confounded by other associated conditions that predispose towards increased risk. For example, hypokalemia is a characteristic of the malnutrition-inflammation-cachexia syndrome, and hyperkalemia is often accompanied by other metabolic abnormalities associated with decreased kidney function (e.g., hyperphosphatemia and acidosis). All of these factors that underlie abnormal potassium values have been associated with increased risk of all-cause death.¹⁸ Although the possibility of confounding still exists, an important strength of our study was that it was one of the only studies to specifically examine risk between serum potassium levels and rigorously

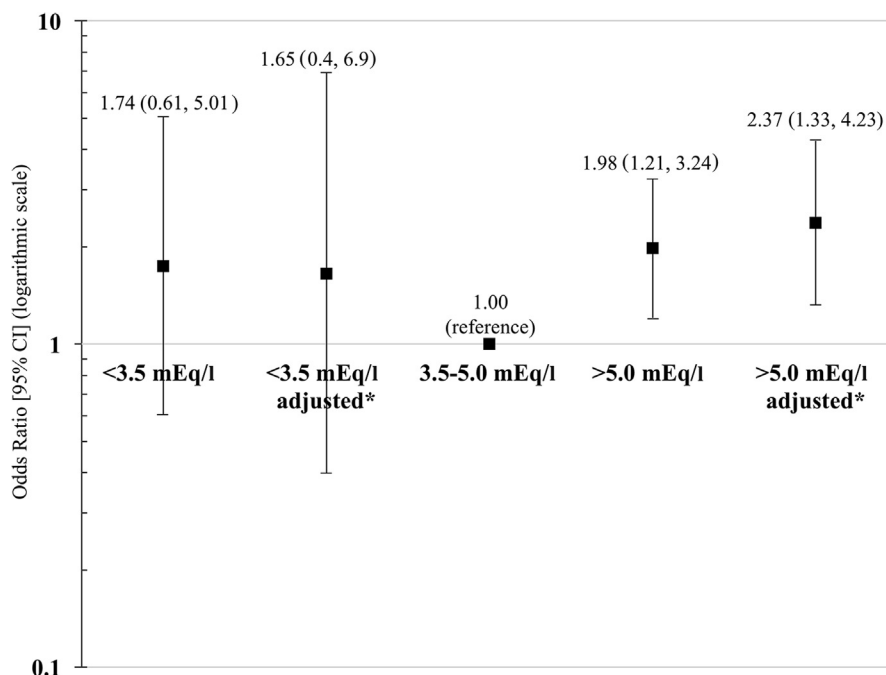


Figure 3. Risk of sudden cardiac death/sudden cardiac arrest according to the last recorded serum potassium value before the event. Odds ratio estimates are shown with 95% confidence intervals (CI) within each serum potassium category. *Adjusted for ejection fraction, congestive heart failure severity, and proportion of patients who underwent coronary artery bypass grafting after catheterization.

adjudicated arrhythmic mortality (SCA/SCD) that would be more directly influenced by the effect of potassium, and the first study that specifically examined these relationships among CKD patients. In addition, the direct influence of abnormal potassium levels on mortality would be expected to be manifested as an increase in short-term arrhythmic event risks; thus, because of day-to-day variations in potassium levels, associations between a single baseline potassium level and long-term outcomes were likely to be confounded by other factors. In contrast to similar studies that only examined SCD outcomes that occurred many years after potassium measurements were obtained,^{15,19} another strength of our analysis was that we examined both long- and short-term SCA/SCD risk associations. In our analysis, although baseline potassium levels did not have a significant association with long-term mortality or SCA/SCD, significant risk associations with potassium were noted in our proximate exposure analysis.

Multiple studies confirmed that patients with even moderate levels of CKD are at an increased risk for SCD compared with patients without CKD, and the increased risks appear to be independent of an increased burden of coronary heart disease and traditional coronary heart disease-related risk factors.^{1,20,21} Our study confirmed the independent association between estimated eGFR and risk of SCE observed by others, but it further suggested that the increased prevalence of hyperkalemia among patients with CKD³ might underlie the increased risk seen among patients with moderate CKD. The doubling in short-term SCD

risk we observed among hyperkalemic CKD patients compared with normokalemic patients suggested a potentially actionable means to reduce risk through early detection, rapid correction, and careful follow-up of elevated potassium levels. Although it was possible that the reason we did not observe a significant association between hypokalemia and SCD risk in CKD patients was due to the smaller number of events, it was noteworthy that relatively few (3%) SCD events were preceded by hypokalemia compared with the number of SCD events (16.7%) preceded by hyperkalemia. The greater overall prevalence of hyperkalemia compared with hypokalemia among CKD patients was consistent with previous reports,⁵ and suggested hyperkalemia might be a more important risk factor for SCD due to a larger population attributable risk.

Our study had important limitations. First, we included only patients with known, significant CAD in our study. Although this might limit generalizability because it was possible that a different relationship might exist among patients without significant CAD, a large proportion of CKD patients have significant CAD,²² and our study findings highlighted the importance of serum potassium levels among a population with a high risk of SCD. Second, we examined outcome associations with serum potassium levels measured at 2 single time points: at the time of cardiac catheterization, and for a subset of patients, proximate to a SCA/SCD event. Because of the expected variation of potassium levels over time,

this could have led to bias toward the null; despite this, we were able to demonstrate significant associations in our proximate time point analysis. Third, the lack of data on other covariates, such as serum magnesium and bicarbonate levels, time-updated ejection fraction measurements, and data on intervening nonfatal cardiac events between baseline catheterization and outcomes could have resulted in residual confounding; however, we adjusted our analyses using highly granular data on coronary anatomy, interventions performed at the time of catheterization, and other cardiac variables known to influence SCD risk. Fourth, although the number of SCA/SCD events ($n = 225$) was large relative to other similar observational studies, this could have limited our power to detect significant differences between groups and also limited our ability to examine relationships between narrower categories of serum potassium; nevertheless, we were able to examine and detect significant associations among 3 clinically relevant categories of serum potassium levels. Finally, as with all observational studies, causative relationships could not be demonstrated.

In summary, elevated serum potassium levels >5.0 mEq/l are common among patients with moderate CKD and significant CAD, and are associated with an increased short-term risk of SCA and SCD. Close monitoring of serum potassium levels and aggressive treatment of hyperkalemia among CKD patients with CAD may reduce the high risk of SCD.

DISCLOSURE

PHP and JPM received consultancy fees from Relypsa, Inc. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Fully-adjusted Cox proportional hazards model, all variables displayed.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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