

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 m² 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 mEq/l) or hypokalemia (<3.5 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 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 m² 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 was 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 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-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

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