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## Serum Potassium Predicts Time to Blood Pressure Response Among African-Americans with Hypertensive Nephrosclerosis

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### Abstract

It is not known whether serum potassium levels affect blood pressure response to anti-hypertensive medication. The African American trial of Kidney disease and Hypertension (AASK) Genomics Study (N=828) is a subset of the AASK trial that randomized 1,094 African American men and women with hypertensive nephrosclerosis to ramipril, amlodipine or metoprolol. Participants were also randomized to a usual (102–107 mmHg) or low ( < 92 mmHg) mean arterial pressure (MAP) treatment goal. Time-to-event analyses were used to determine the relationship between serum potassium prior to randomization and time (days) to reach an MAP of 107 mmHg. Mean baseline serum potassium was 4.22 (standard deviation +/- 0.56 and range 2.8–6.0) mmol/L and the median days to reach target MAP was 32 (interquartile range 8–95) days. The adjusted hazard ratio (HR) for each 1mmol/L increase in serum potassium was 1.31 (95%CI: 1.08–1.59) in the usual MAP group, and 1.21 (95%CI: 1.02–1.44) in the low MAP group. Secondary findings suggested that women in the usual MAP group on amlodipine were more likely to reach target MAP compared to women randomized to ramipril (HR: 2.05, 95%CI: 1.30–3.21). Older subjects in the low MAP group ( < 55 years) were also more likely to reach target MAP on amlodipine compared to ramipril (HR: 1.57, 95%CI: 1.03–2.38). Serum potassium appears to be a significant predictor of time to blood pressure response, independent of drug class. Results also suggest a benefit of using amlodipine when more rapid blood pressure control is clinically indicated among women and more aggressively managed older subjects.

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### Conflicts of Interest

None to declare.

## Keywords

Hypertension; Serum potassium; Blood Pressure; Antihypertensives; Nephrosclerosis; Survival Analysis

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## Introduction

The prevalence of hypertension in the adult US population is 28.9% according to estimates from the National Health and Nutrition Examination Survey (NHANES) 1999–2004.<sup>1</sup> The burden of hypertension is seen to be disproportionately higher in non-Hispanic blacks (32.4%) compared to non-Hispanic whites (23.3%) or Mexican-Americans (22.6%).<sup>2</sup> In addition to earlier onset hypertension, blood pressure control is inadequate in a majority of African-American patients, with significantly higher blood pressure observed among African Americans in comparison to Caucasian Americans.<sup>3</sup> This might partly explain the higher risk for end-stage renal disease<sup>4</sup> and other end-organ disease observed among African-American hypertensive patients.<sup>4, 5</sup>

Previous research has shown blood pressure to vary inversely with dietary potassium intake.<sup>6, 7</sup> Older placebo-controlled studies have also linked oral potassium supplementation (not necessarily changes in serum potassium) with a reduction in blood pressure in patients with essential hypertension<sup>8–10</sup> Studies have also recently associated higher potassium intake with lower risks of cardiovascular mortality and stroke.<sup>11, 12</sup>

However, the effect of serum potassium on blood pressure has been less well studied. The African American study of Kidney disease and hypertension (AASK) was a randomized study designed to examine the effect of blood pressure control and initial anti-hypertensive drug choice (metoprolol, ramipril or amlodipine) on the rate of decline of renal function in African-American men and women with hypertensive nephrosclerosis.<sup>13, 14</sup> While our previous pharmacogenetic work with the AASK Genomics dataset suggested that serum potassium was an independent predictor of blood pressure response among those randomized to metoprolol, the relationship between serum potassium on blood pressure response to anti-hypertensive medications has been not been formally studied.<sup>15</sup> The objectives for this analysis were to explore the relationship between serum potassium levels and time to blood pressure response and to determine whether this relationship was independent of drug class based on data from the AASK Genomics Study. In this study, time-to-event analyses were used to determine the relationship between serum potassium and days to reach a mean arterial pressure (MAP) of 107 mmHg, a primary end point in the AASK study.

## Materials and Methods

### Study Design and Participants

The AASK Genomics Study (N=828 with complete data, 96% of the study cohort) was a follow-up cohort representative of the original AASK trial (N=1094). Protocol approval and informed consent were obtained according to the requirements of the University of California San Diego Human Subjects Protection Program. The AASK trial was a 3×2

factorial randomized study of hypertensive kidney disease in African American men and women aged 18–70 years with a glomerular filtration rate (GFR) between 25 and 70 mL/min per 1.73 m<sup>2</sup>. Participants were randomized to receive one of three drugs: an angiotensin converting enzyme inhibitor (ACE-I) ramipril, a dihydropyridine calcium-channel blocker (CCB) amlodipine or a beta-adrenergic receptor blocker (beta-blocker) metoprolol. Additional anti-hypertensive drugs were sequentially added to realize the assigned MAP goal. Participants were also randomized to a usual (102–107 mmHg) or low (<92 mmHg) MAP goal. Allocation to usual or low MAP goal was known to both subjects and investigators (unblinded); randomization to drug class, however, was double-blinded. Additional details of the original AASK study design and population have been previously published.<sup>4, 14</sup>

### Statistical Methods

Data from the AASK Genomics Study were analyzed to study the association between baseline serum potassium levels and days to reach a target MAP of 107 mmHg. Because few reached the lower blood pressure goal in the low MAP group (<92 mmHg), 107 mmHg was also used as the end point in the low MAP group. Serum potassium was drawn at baseline, off study drugs (amlodipine, ramipril and metoprolol); because participants may have been on diuretics, diuretic use was considered as a potential confounder. Associations ( $p < 0.25$ , Kruskal-Wallis or Fisher-exact tests) between serum potassium and baseline characteristics of the study population were considered in the multivariate analysis described below.

Serum potassium was modeled as a continuous variable with 1 mmol/L increments. An alternate analysis modeled serum potassium tertiles (<4.0, 4.0–4.4 and >4.4). Other covariates included demographic variables (i.e., gender, age, body mass index and education), and other baseline variables (baseline MAP, glomerular filtration rate, number of co-morbidities, smoking status and serum lipids). Additional medications (aside from ACE-I, CCB and beta-blocker) were to be used to manage blood pressure as dictated by the AASK protocol. Thus, the average number of medications per day was used as a proxy measure to control for these additional anti-hypertensive medications.

Univariate Cox proportional hazards model stratified by low or usual MAP group was used to assess baseline association between serum potassium and days to reach an MAP of 107 mmHg. Associations between covariates with days to reach target MAP were also assessed. Variable associated at  $p \leq 0.25$  were considered in further analysis. Cox proportional hazards models were also used for multivariate analyses to estimate adjusted hazard rate (and 95% confidence intervals, CI) of reaching a target MAP of 107 mmHg stratified by low and usual MAP goal. In addition to potassium, age and gender were included in the base model.

A stepwise approach was used to identify variables contributing significantly ( $p < 0.05$ ) to the prediction of time to reach target MAP. Correlations between potential covariates were analyzed and the partial likelihood ratio test was used to identify variables to be included in the final model. Average medications per day were highly correlated with baseline MAP ( $p < 0.0001$ ); therefore, only baseline MAP was considered in the analysis.

All possible two-way interactions between variables were assessed, and those significant at  $p < 0.05$  were retained in the model. Variables affecting estimated coefficients by more than 10% were included as confounders. Variables in the final model were tested to assure they satisfied the proportional hazards assumption. If a variable violated the proportional hazards assumption, the model was either stratified by that variable or a variable by time interaction term was included in the model. The effects of influential observations on estimated parameters were assessed by score residuals.<sup>16</sup>

Statistical analyses were done using SAS statistical software, version 9.1, programming package (SAS Institute, Inc., Cary, N.C. USA).

## Results

### Participant Characteristics

The study population consisted of 503 men (mean age  $53.8 \pm 10.9$  years) and 325 women (mean age  $54.4 \pm 10.3$  years) with 410 (49.5%) randomized to usual MAP goal and 418 (50.5%) to low MAP goal. Mean baseline GFR was  $47.98 \pm 12.72$  mL/min per  $1.73 \text{ m}^2$  in men and  $44.69 \pm 12.79$  mL/min per  $1.73 \text{ m}^2$  in women ( $p=0.0001$ ). Mean baseline serum potassium was 4.22 (standard deviation  $\pm 0.56$  and range 2.8 to 6.0) mmol/L and the median days to reach target a MAP of 107 mmHg was 32 (interquartile range 8 to 95) days. Among subjects in the low MAP group, 4.3% did not reach the target MAP of 107 mmHg after one year of randomization compared to 7.8% in the usual group ( $p=0.041$ ; results not shown).

There was a univariate association between serum potassium and days to target MAP in both the low and usual MAP groups ( $p=0.03$  and  $p=0.002$ , respectively; Table 1). Age, baseline MAP, average number of medications and education level were significantly associated with time to reach target MAP in both the low and usual MAP groups (Table 1). Baseline renal function (serum creatinine and GFR) were only associated with time to reach target MAP in the usual MAP group (Table 1).

Serum potassium was found to be significantly associated with baseline BMI ( $p=0.002$ ), GFR ( $p<0.0001$ ), serum creatinine ( $p<0.0001$ ), diuretic use ( $p<0.0001$ ) and serum glucose ( $p<0.0001$ ; results not shown). Participants with higher serum potassium levels required fewer medications to control blood pressure ( $p<0.001$ ) and had fewer comorbid conditions ( $p=0.005$ ; results not shown).

### Adjusted Cox Model: Usual MAP

Cox proportional hazards analysis suggested a significant association between serum potassium and days to reach a target MAP ( $p < 0.001$ ) after adjustment for gender, drug class and baseline MAP. Baseline MAP ( $p<0.0001$ ) and randomization to amlodipine (compared to ramipril;  $p=0.002$ ) were also significant predictors of time to reach target MAP. There was a significant interaction between gender and drug randomization group ( $p=0.005$ ). The proportional hazards assumption was satisfied in the model (results not shown).

A 1.0 mmol/L increase in serum potassium was significantly associated with the odds of reaching a target MAP of 107 mmHg: Adjusted HR 1.31 (95% CI: 1.08–1.59) (Table 2). Similar results were found comparing the highest serum potassium tertile (>4.4 mmol/L) to the lowest tertile (<4.0 mmol/L): Adjusted HR 1.36 (95% CI 1.06 to 1.75; results not shown). Baseline MAP was inversely associated with reaching target MAP: Adjusted HR 0.97 (95% CI: 0.96–0.98; Table 2). Females were more likely to reach the target MAP on a CCB compared to those on an ACE inhibitor: Adjusted HR 2.05 (95% CI: 1.30–3.21; Table 2). However, there was no significant difference in response among male subjects randomized to a CCB compared to males randomized to an ACE-I: Adjusted HR 0.84 (95% CI: 0.58–1.22; Table 2).

### Adjusted Cox Model: Low MAP

Baseline MAP violated the proportional hazards assumption; therefore, a baseline MAP by time interaction variable was included in the final Cox proportional hazards model. HDL appeared to be a confounder and was left in the multivariate model. There was a significant association between days to reach target MAP and serum potassium after adjustment for age, drug class, baseline MAP-time interaction and serum HDL ( $p=0.03$ ). A significant interaction was found between drug class and age at randomization ( $p=0.03$ ); thus, hazard ratios were calculated for subjects above and below 55 years, the median age for this study population.

A 1.0 mmol/L increase in serum potassium was significantly associated with the odds of reaching a target MAP of 107 mmHg: The adjusted HR was 1.21 (95% CI: 1.02–1.44; Table 2). Though only marginally significant, similar results were found comparing the highest serum potassium tertile (>4.4 mmol/L) to the lowest tertile (<4.0 mmol/L): Adjusted HR 1.21 (95% CI 0.95 to 1.55; results not shown). The odds of reaching an MAP of 107 mmHg was also increased for older subjects (> 55 years) on amlodipine in comparison to those on ramipril: Adjusted HR 1.57 (95% CI: 1.03–2.38; Table 2). There was no significant difference in response by drug class among subjects <55 years: Adjusted HR 0.69 (95% CI: 0.47–1.02; Table 2).

## Discussion

This is a unique study exploring the role of serum potassium in blood pressure response to three different classes of antihypertensive medication among African-Americans with early hypertensive nephrosclerosis. Serum potassium was a predictor of time to blood pressure response independent of the antihypertensive drug classes (ramipril, amlodipine and metoprolol) studied in the AASK trial. Secondary results suggested an interaction between gender and drug class among participants in usual MAP: Women on amlodipine were more likely to reach target MAP compared to women on ramipril. Among participants in the more aggressively managed low MAP group, there was also an interaction between drug class and age: Older participants (> 55 years) on amlodipine were more likely to reach target MAP in comparison to older participants on ramipril.

Chronically exaggerated sympathetic vasoconstrictor response may increase the risk for developing hypertension,<sup>17</sup> and this has been shown to decrease after potassium

supplementation (100 mmol/day) in borderline hypertensive patients.<sup>18</sup> The low dietary potassium intake in African-Americans has been linked with an enhanced vasopressor response to stress and cold, and may contribute to the higher prevalence of hypertension in this group.<sup>17,19</sup> Changes in serum potassium on blood pressure and cardiovascular outcomes, however, have been less well studied.

Our results suggest that higher serum potassium within the physiological normal range may be an independent predictor of blood pressure treatment response. There is also increasing evidence suggesting that serum potassium in the upper physiological range may be not be detrimental in pre-dialysis CKD patients. In the pre-dialysis RRI-CKD Cohort Study, low-normal serum potassium (<4.0 mmol/L) was associated with increased cardiovascular risk, and a higher serum potassium level (5.0 to 5.9 mmol/L) was not associated with an increased risk of death in comparison to eukalemic study participants.<sup>20</sup> Another recent cohort study of pre-dialysis CKD patients found that hypokalemia was also associated with CKD progression. While both hypokalemia and hyperkalemia were associated with death, hypokalemia (as opposed to hyperkalemia) was a stronger predictor of mortality among Black study participants.<sup>21</sup> However, given the observational design of these studies, future research should consider interventions designed to maintain serum potassium in the upper physiological range in order to clarify the long-term effects of serum potassium on cardiovascular and blood-pressure related outcomes prior to making clinical recommendations.

### Secondary Findings

Older African-American subjects in this study were more likely to respond to amlodipine in comparison to ramipril, while the response to metoprolol and ramipril was similar among younger and older study participants. The hypertensive state in African-American patients has been associated with low plasma renin,<sup>22, 23</sup> salt sensitivity and expanded plasma volume.<sup>23</sup> Low plasma renin activity (PRA) is also associated with low cardiac output that leads to increased peripheral resistance,<sup>23</sup> and possibly enhanced blood pressure lowering response to amlodipine in African American patients. On the other hand, reduced arterial compliance in old age contributes to increased blood pressure, and relaxation of resistance vessels by amlodipine and the subsequent fall in peripheral resistance may be more pronounced in older subjects. This suggests a specific advantage of using amlodipine or other dihydropyridine calcium channel blockers in elderly patients when it is imperative to achieve quick blood pressure control, as in heart failure and dissecting aortic aneurysm. However, calcium channel blockers may not be the preferred treatment in elderly stroke patients since lower blood pressure and consequent reduced cerebral blood flow may result in further brain injury.<sup>24</sup>

As shown in our previous work, women in the usual MAP group responded faster to a CCB in comparison to ramipril suggesting a gender-specific effect. P-glycoprotein, a cellular transporter of drugs and other xenobiotics, is important for drug response as it affects their tissue distribution, absorption and elimination and has been demonstrated to be 2–3 times higher in men than in women.<sup>25</sup>

## Study advantages and limitations

This is the first study to our knowledge to examine the association of serum potassium with days to reach target blood pressure on three different classes of antihypertensive medications using data from a large clinical trial. In contrast to pre-post blood pressure measurements, we utilized blood pressure measurements over a one-year time period to define blood pressure response.<sup>26</sup> However, serum potassium was only measured at baseline, which may not accurately reflect potassium levels throughout the one-year study period especially in the setting of ongoing and possibly worsening renal disease.

In addition, results cannot be extrapolated beyond the serum potassium range studied here.

Study participants were African Americans with early hypertensive nephrosclerosis, so the results may not be readily applicable to other racial/ethnic groups and to patients without hypertensive renal nephrosclerosis. Analysis was limited to the first year of randomization, since declining renal function with time can impact response to anti-hypertensive medication. Average medications per day was a proxy measure for additional anti-hypertensive medications used for blood pressure control, but was not included in the analysis since it was highly correlated with baseline MAP.

Serum potassium appears to be a predictor of blood pressure response among African-American patients with early hypertensive nephrosclerosis, independent of the anti-hypertensive medication class. From both a clinical and public health perspective, serum potassium levels in the upper physiological limit of normal may be beneficial with respect to blood pressure control. These findings warrant clinical intervention study of serum potassium and blood pressure response in different patient study populations.

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**What is known about this topic**

- Previous research has shown an inverse relationship between serum potassium and blood pressure and the prevalence of hypertension.
- The effect of serum potassium levels on blood pressure response to anti-hypertensive medication has yet to be studied.

**What this study adds**

- To our knowledge, this is the first study to examine the association of serum potassium with response to different classes of antihypertensive medications using data from a large clinical trial.
- In contrast to before-and-after blood pressure measurements, we used survival methodology to examine a one-year follow-up period to more accurately capture the time to blood pressure response.
- This study suggests that patients with higher serum potassium within the normal physiological range were more likely to reach target blood pressure goals independent of anti-hypertensive medication class.

**Table 1**

Univariate Cox Proportional Hazards Model: Associations with Time to Reach Target MAP for Selected Covariates

<b>P-value</b>	<b>Low MAP</b>	<b>Usual MAP</b>
Baseline serum potassium (mmol/L)	0.03	0.002
Gender	0.94	0.63
Age (years)	0.001	<0.0001
Body mass index (kg/m <sup>2</sup> )	0.06	0.06
Baseline MAP (mmHg)	<0.0001	<0.0001
Baseline GFR (ml/min/1.73 m <sup>2</sup> )	0.28	0.007
Serum creatinine (mg/dL)	0.97	0.002
Baseline diuretic use	0.17	0.32
Serum CHOL (mg/dL)	0.58	0.59
Serum HDL (mg/dL)	0.72	0.11
Serum LDL (mg/dL)	0.57	0.99
Serum triglycerides (mg/dL)	0.35	0.61
Serum glucose (mg/dL)	0.90	0.59
Serum sodium (mmol/L)	0.30	0.63
Urine sodium (g/d)	0.42	0.54
Urine potassium (g/d)	0.57	0.49
Average number of medications	<0.0001	<0.0001
Number of comorbidities	0.17	0.52
Smoking status	0.35	0.47
Alcohol Use	0.67	0.44
Employment Status	0.47	0.65
Education	0.01	0.02
Income	0.91	0.26
Private Health Insurance	0.34	0.86

**Table 2**

Adjusted Hazard Ratios and 95% Confidence Intervals

Variable	Hazard Ratio	95% CI
<b>Usual Treatment Goal (MAP: 102–107 mmHg)</b>		
Serum Potassium (1 mmol/L increase)	1.31	1.08–1.59
Drug class		
- CCB vs. ACE (Females)	2.05	1.30–3.21
- CCB vs. ACE (Males)	0.84	0.58–1.22
Baseline MAP	0.97	0.96–0.98
<b>Low Treatment Goal (MAP&lt;92 mmHg)</b>		
Serum Potassium (1 mmol/L increase)	1.21	1.02–1.44
Drug class		
- CCB vs. ACE ( ≥ 55 years)	1.57	1.03–2.38
- CCB vs. ACE (< 55 years)	0.69	0.47–1.02

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