Clinical Significance of Incident Hypokalemia and Hyperkalemia in Treated Hypertensive Patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Michael H. Alderman, Linda B. Piller, Charles E. Ford, Jeffrey L. Probstfield, Suzanne Oparil, William C. Cushman, Paula T. Einhorn, Stanley S. Franklin, Vasilios Papademetriou, Stephen T. Ong, John H. Eckfeldt, Curt D. Furberg, David A. Calhoun, Barry R. Davis, for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group

Abstract—Concerns exist that diuretic-induced changes in serum potassium may have adverse effects in hypertensive patients. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, a large practice-based clinical trial, made it possible to examine consequences of observed changes in potassium during care in conventional practice settings. Normokalemic participants randomized to chlorthalidone (C) versus amloidipine or lisinopril as a first-step drug were stratified by year-1 potassium. Postyear-1 outcomes among hypokaleemics (potassium, <3.5 mmol/L) and hyperkaleemics (potassium, >5.4 mmol/L) were compared with normokaleemics (potassium, 3.5–5.4 mmol/L). Year-1 hypokalemia incidence was 6.8%; incidence in C (12.9%) differed from amloidipine (2.1%; P<0.001) and lisinopril (1.0%; P<0.01). Hyperkalemia incidence (2.0%) was greater in lisinopril (3.6%) than in C (1.2%; P<0.01) or amloidipine (1.9%; P<0.01). Coronary heart disease occurred in 8.1% with hypokalemia, 8.0% with normokalemia, and 11.1% with hyperkalemia. Overall, mortality was higher in hypokaleemics than in normokaleemics (Cox hazard ratio, 1.21 [95% CI, 1.02–1.44]) with statistically significant (interaction, P<0.01) disparity in hazard ratios for the 3 treatment arms (hazard ratios, C=1.21, amloidipine=1.60, lisinopril=3.82). Hyperkalemia was associated with increased risk of combined cardiovascular disease (hazard ratio, 1.58 [95% CI, 1.15–2.18]) without significant treatment interactions. In conventional practice settings, the uncommon appearance of hyperkalemia was associated with increased cardiovascular disease risk. Hypokalemia was associated with increased mortality; however, the statistically significant heterogeneity in hazard ratios across treatment groups strongly suggests that the observed increase in mortality is unrelated to the specific effects of C. Thus, for most patients, concerns about potassium levels should not influence the clinician’s decision about initiating hypertension treatment with low-moderate doses of thiazide diuretics (12.5–25.0 mg of C). (Hypertension. 2012;59:926-933.) • Online Data Supplement

Key Words: hypertension ■ hypokalemia ■ hyperkalemia ■ diuretic ■ calcium-channel blocker ■ angiotensin-converting enzyme inhibitor

Concerns have been raised that low and high serum potassium (K⁺) concentrations may be associated with adverse cardiovascular effects in hypertensive patients. Although variations in serum K⁺ have been implicated in the development and progression of coronary heart disease (CHD), new-onset diabetes mellitus, and myocardial infarction, the main concern has been the potential of diuretic-induced hypokalemia to provoke cardiac arrhythmia and sudden death.

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Received August 4, 2011; first decision August 23, 2011; revision accepted February 29, 2012. From the Department of Epidemiology and Social Medicine (M.H.A.), Albert Einstein College of Medicine, Bronx, NY; Coordinating Center for Clinical Trials (L.B.P., C.E.F., B.R.D.), The University of Texas School of Public Health, Houston, TX; Clinical Trials Service Unit J.L.P.), University of Washington, Seattle, WA; Division of Cardiovascular Disease (S.O., D.A.C.), University of Alabama at Birmingham, Birmingham, AL; Memphis Veterans Affairs Medical Center (W.C.C.), Memphis, TN; Division of Cardiovascular Sciences (P.T.E.), National Heart, Lung, and Blood Institute, Bethesda, MD; Department of Medicine (S.S.F.), University of California, Irvine, CA; Veterans Affairs Medical Center Washington (V.P.), Washington, DC; Ong Medical Center (S.T.O.), Oxon Hill, MD; University of Minnesota Hospital and Clinic (J.H.E.), Minneapolis, MN; Wake Forest University School of Medicine (C.E.F.), Winston-Salem, NC.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00000542).

The online-only Data Supplement is available with this article at http://hyper.ahajournals.org lookup/suppl/doi:10.1161/HYPERTENSIONAHA.111.180554/D1C1.

Correspondence to Charles E. Ford, The University of Texas School of Public Health, 1200 Herman Pressler Dr, W-940, Houston, TX 77030. E-mail Charles.E.Ford@uth.tmc.edu

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Hypertension is available at http://hyper.ahajournals.org

DOI: 10.1161/HYPERTENSIONAHA.111.180554
Diuretics, an antihypertensive mainstay for >50 years, produces hypokalemia more frequently than do other antihypertensive agents. Concerns have also been raised about the potentially adverse effects of hyperkalemia induced by angiotensin-converting enzyme inhibitor therapy, such as increased risk of cardiovascular disease (CVD) mortality in hypertensive patients.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a double-blind, practice-based hypertension treatment trial, randomized 42,418 high CVD risk patients to an initial treatment with chlorthalidone (C), lisinopril (L), amlodipine (A), or doxazosin. The doxazosin arm was discontinued early and is not considered in this report. Chlorthalidone was at least as effective as comparator drugs in preventing cardiovascular events and all-cause mortality and superior to all in preventing new-onset heart failure. It was also superior to the angiotensin-converting enzyme inhibitor in preventing combined CVD and, in black participants, stroke. With its large size and long follow-up, ALLHAT offers a unique opportunity to determine the relative effects of these treatments on year-1 K⁺ and the potential impact of these perturbations on long-term (3–7 years) cardiovascular morbidity and mortality in patients treated in diverse clinical practice settings. Data are not available to assess clinical behaviors that occurred in response to these findings. Thus, our data describe associations of hypokalemia and hyperkalemia with the CVD outcomes but do not detail clinical practice responses (potassium supplementation, change in therapy, etc) that may have contributed to these results. Specifically, we report the association of new-onset hypokalemia (<3.5 mmol/L) and hyperkalemia (>5.4 mmol/L) determined at year-1 of follow-up by a central laboratory with major clinical end points, overall and by randomized treatment assignment.

Methods

ALLHAT Design

The design of ALLHAT has been reported. The primary outcome was nonfatal myocardial infarction (MI) or CHD mortality. Secondary end points included fatal and nonfatal stroke, heart failure (HF), combined CVD, and total mortality.

ALLHAT Participants

ALLHAT enrolled men and women (47%) aged ≥55 years with hypertension and ≥1 additional CVD risk factor; 35% of participants were black; 19% were Hispanic. Recruitment was accomplished by testing for treatment-covariate interaction with the Cox PH model. Proportional hazards (PH) regression models (hazard ratios [HRs] and 95% CIs) were used to compare hypokalemia/normokalemia and hyperkalemia/normokalemia (overall and within randomized drug groups) while adjusting for age, race, sex, history of diabetes mellitus, CHD and atherosclerotic CVD, cigarette smoking, baseline systolic BP and K⁺, and estimated year-1 glomerular filtration rate. To account for the possible differences in follow-up BP and K⁺, Cox PH regression analyses with time-dependent covariates were also performed.

The PH assumption was examined with log-log plots and Schoenfeld residual analysis; the assumption was violated once, for HF among C participants, and a logistic model was used to obtain odds ratios and CIs. Heterogeneity of effects in subgroups was examined by testing for treatment-covariate interaction with the Cox PH regression model using P<0.05, indicating statistical significance. However, given the many multivariate, subgroup, and interaction analyses performed, statistical significance at this level should be interpreted with caution.

Results

The study cohort was derived from 33,357 ALLHAT participants randomized to C, A, or L (Figure S1, available in the online-only Data Supplement). It was composed of participants (n=19,731 [59%]) who had normal baseline K⁺ values (3.5–5.4 mmol/L) and valid year-1 values (2.5–7.0 mmol/L); of these, 13,511 (6.8%) had hypokalemia, 17,982 (91.1%) had normokalemia, and 398 (2.0%) had hyperkalemia at year 1. Baseline characteristics were similar between this and the overall ALLHAT cohort (Table S1). In comparison with normokalemic subjects, those who became hypokalemic were
more likely to be black, to be women, and to have received antihypertensive medications before enrollment, whereas they were less likely to have a history of CHD and/or diabetes mellitus, to be taking aspirin, or to be a past smoker. In addition, persons with hypokalemia tended to have higher baseline systolic BP and diastolic BP, lower fasting glucose, higher high-density lipoprotein cholesterol levels, and lower triglyceride concentrations than those with normokalemia. Persons who became hyperkalemic by year 1 tended to be older, have lower DBP, have modestly lower estimated glomerular filtration rate, and were less likely to be in the lipid-lowering trial component than those with normokalemia.

Mean levels of $K^+$ and BP at baseline and by follow-up year are presented in Table S1 by serum $K^+$ group. During follow-up, systolic BP was similar among these groups, whereas diastolic BP in hypokalemics was slightly higher than in those with normal $K^+$ and was lowest in hyperkalemics.

Randomization to C was associated with increased risk of hypokalemia (1185 of 9159 [12.9%]) compared with A (113 of 5371 [2.1%]) and L (53 of 5201 [1.0%]; Table 1 footnote). Severe hypokalemia ($K^+ < 3.2$ mmol/L) occurred in 277 C participants (3.5%), 17 A (0.3%), and 8 L (0.2%). Overall, participants who developed hypokalemia by year 1 did not experience greater CHD, stroke, or HF than those who remained normokalemic (Table 2). The rate for combined

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### Table 1. Cumulative No. of Events, 5-Y Kaplan-Meier Event Rates per 100, Cox Proportional HRs, Corresponding 95% CIs, and $P$ Values for Hypokalemia and Normal Y-1 $K^+$ Subgroups Within Drug Groups

<table>
<thead>
<tr>
<th>Outcome by Drug Group*</th>
<th>No. of Events</th>
<th>5-y Rate per 100</th>
<th>Unadjusted, HR (95% CI; $P$ Value)$†$</th>
<th>Adjusted, HR (95% CI; $P$ Value)$‡$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>90</td>
<td>639</td>
<td>$9.13$ (10.51)</td>
<td>$0.91$ (0.73–1.14; 0.43)</td>
</tr>
<tr>
<td>A</td>
<td>15</td>
<td>411</td>
<td>$13.25$ (10.09)</td>
<td>$1.78$ (1.06–2.98; 0.03)</td>
</tr>
<tr>
<td>L</td>
<td>4</td>
<td>384</td>
<td>$8.61$ (10.02)</td>
<td>$1.19$ (0.44–3.18; 0.73)</td>
</tr>
</tbody>
</table>

Stroke

| C                      | 47           | 322             | $5.04$ (5.41) | $0.95$ (0.70–1.29; 0.73) | $1.03$ (0.75–1.41; 0.86) |
| A                      | 4            | 177             | $5.09$ (4.19) | $1.07$ (0.40–2.87; 0.90) | $1.19$ (0.44–3.25; 0.74) |
| L                      | 2            | 209             | $4.32$ (5.31) | $1.05$ (0.26–4.23; 0.94) | $1.07$ (0.26–4.34; 0.93) |

HF

| C                      | 45           | 401             | $4.75$ (6.87) | $0.73$ (0.54–1.01; 0.06)§ | $0.77$ (0.56–1.06; 0.11) |
| A                      | 12           | 350             | $11.33$ (8.95) | $1.62$ (0.91–2.88; 0.10) | $2.19$ (1.22–3.95; <0.01) |
| L                      | 6            | 263             | $12.85$ (6.53) | $2.51$ (1.12–5.64; 0.03) | $3.10$ (1.36–7.08; <0.01) |

CCVD

| C                      | 234          | 1890            | $23.23$ (28.79) | $0.79$ (0.69–0.90; <0.001) | $0.86$ (0.75–0.99; 0.04) |
| A                      | 30           | 1247            | $30.70$ (28.77) | $1.13$ (0.79–1.63; 0.50) | $1.48$ (1.03–2.14; 0.04) |
| L                      | 13           | 1238            | $26.61$ (29.55) | $1.14$ (0.66–1.97; 0.64) | $1.30$ (0.75–2.25; 0.35) |

Death

| C                      | 161          | 965             | $16.48$ (15.16) | $1.08$ (0.92–1.28; 0.34) | $1.21$ (1.02–1.43; 0.03) |
| A                      | 17           | 585             | $15.63$ (13.73) | $1.38$ (0.85–2.24; 0.19) | $1.60$ (0.98–2.61; 0.06) |
| L                      | 15           | 578             | $30.66$ (14.07) | $2.88$ (1.72–4.80; <0.001) | $3.82$ (2.26–6.44; <0.001) |

CVD deaths

| C                      | 68           | 422             | $7.29$ (6.77) | $1.05$ (0.81–1.36; 0.70) | $1.12$ (0.86–1.46; 0.39) |
| A                      | 10           | 286             | $9.32$ (6.93) | $1.65$ (0.88–3.10; 0.12) | $2.10$ (1.10–4.00; 0.02) |
| L                      | 7            | 276             | $14.28$ (7.07) | $2.79$ (1.32–5.91; <0.01) | $3.93$ (1.83–8.45; <0.001) |

Non-CVD deaths

| C                      | 85           | 492             | $9.12$ (8.28) | $1.12$ (0.89–1.41; 0.34) | $1.28$ (1.01–1.62; 0.04) |
| A                      | 7            | 274             | $6.96$ (6.66) | $1.22$ (0.58–2.28; 0.60) | $1.26$ (0.61–2.70; 0.55) |
| L                      | 6            | 274             | $14.35$ (6.84) | $2.44$ (1.09–5.48; 0.03) | $2.97$ (1.31–6.77; <0.01) |

A indicates amlodipine; C, chlorthalidone; CCVD, combined cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; L, lisinopril.

*Sample sizes for $K^+ < 3.5$ and $3.5 < K^+ < 5.4$ groups, respectively, are as follows: C = 1185 and 7864; A = 113 and 5155; L = 53 and 4963.

†Unadjusted Cox model for each outcome included only terms for the $K^+ < 3.5$ group and the $K^+ > 5.4$ groups relative to the normal potassium group. The corresponding data for $K^+ > 5.4$ are given in Table 3.

‡The adjusted Cox model for each outcome included main effects terms for hypokalemia/normal, hyperkalemia/normal, baseline characteristic: age (decades of life), sex (male/female), race (black/nonblack), type 2 diabetes mellitus (yes/no), history CHD (yes/no), history of other atherosclerotic CVD (yes/no), cigarette smoker (yes/no); baseline systolic blood pressure and serum potassium; and estimated glomerular filtration rate at y 1.

§Odds ratio was from a logistic model; proportional hazards assumption was violated.

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928 Hypertension May 2012
CVD was actually lower for hypokalemics compared with normokalemics (HR, 0.88), and the result was significantly different for C versus A (P for interaction = 0.02; HR_C, 0.86; HR_A, 1.48; Tables 1 and 2). Total death rates for all of the hypokalemic exceed that of normokalemic (HR, 1.21; P = 0.03) with an absolute risk difference of 2.5% and with significantly different results for L compared with C (P for interaction < 0.01; HR_C, 1.21, P = 0.03; HR_L, 1.60, P = 0.06; HR_A, 3.82, P < 0.001). Adjustment for follow-up systolic BP, diastolic BP, and K^+ in Cox PH regression analyses with time-dependent covariates, including fixed covariates examined previously, did not appreciably alter these HRs. In hypokalemic, the adjusted HR for stroke slightly increased from 1.01 to 1.02, for total deaths from 1.21 to 1.22, and for CVD deaths from 1.18 to 1.19. Similarly, in hyperkalemic, the adjusted HR for stroke slightly increased from 1.25 to 1.26, for total deaths from 1.15 to 1.16, and for CVD deaths from 1.23 to 1.24. The interaction HRs, likewise, did not change appreciably.

Overall mortality in hypokalemic compared with normokalemic was composed of an 18% higher risk of CVD death (P = 0.20) and a 23% higher risk of non-CVD death (P = 0.08; Table 2). Mortality from CHD causes accounted for 54% of the CVD deaths but did not differ significantly between hypokalemic and normokalemic groups (3.99/100 versus 3.78/100; HR, 1.32; P = 0.11). Notably, mortality from cancer causes, which composed 52% of non-CVD deaths, was significantly higher in hypokalemic compared with normokalemic (5.48/100 versus 3.74/100; HR, 1.52; P < 0.01).

There was also heterogeneity between drug groups in several CVD outcomes. Specifically, those assigned to A who developed hypokalemia, compared with those remaining normokalemic, had significantly increased risk for CHD (HR, 2.41), HF (HR, 2.19), combined CVD (HR, 1.48), and CVD death (HR, 2.10). These results for A are significantly different than C, with all of the interaction P values < 0.03. For those assigned to L, there was a significantly increased risk for hypokalemia compared with normokalemic at year 1 for HF (HR, 3.10) and CVD death (HR, 3.93). These results for L were significantly different than C, with all of the interaction P values < 0.01.

Development of hyperkalaemia was far less frequent than hypokalaemia (398 versus 1351) and was more common among L participants (3.6%) than C (1.2%) or A (1.9%). In L participants, those developing hyperkalaemia were at increased risk of death (HR, 1.49 [1.05–2.12]; P = 0.02) compared with normokalemic (Table 3). Overall (Table 4), hyperkalemias were at significantly increased risk of combined CVD compared with normokalemic (HR, 1.58), but there were no significant interactions with treatment.

Potassium supplementation was available (Table S2), and 36% of participants with K^+ < 3.2 mmol/L at their first follow-up visit (1–3 months after randomization) were reported to be on supplementation at the next visit (within 3 months); 28% of those with a K^+ < 3.5 mmol/L and 2% of
those with a K⁺ ≥3.5 mmol/L were on supplementation. These percentages increased by year 4 to 71% of those with K⁺ <3.2 mmol/L and 62% of those <3.5 mmol/L. At year 1, an open-label diuretic was prescribed for 3% of C hypokalemics, 19% of A hypokalemics, and 23% of L hypokalemics. For hyperkalemics, open-label angiotensin-converting enzyme inhibitor was prescribed for 4% of C, 6% of A, and 5% of L.

Discussion

ALLHAT data show that, in conventional practice settings, notice of incident hypokalemia was not associated with adverse cardiovascular outcomes, and, although associated with increased total mortality, the observed increase showed heterogeneity across treatment groups, with HR in C significantly different from L. This large study with careful ascertainment of clinical outcomes provides further assurance that appearance of hypokalemia is not likely to compromise the proven cardiovascular benefit of diuretic therapy. In addition, ALLHAT data show that hyperkalemia, although relatively rare and most common in patients randomized to L, was associated with increased total CVD outcomes.

Our analysis was limited to ALLHAT participants, randomized to C, A, or L, who had normal baseline K⁺ concentrations (3.5–5.4 mmol/L) and repeat measurements between 10 and 14 months later. These participants did not markedly differ from the entire trial population in demo-
It has been suggested that hypokalemia, by contributing to atherosclerosis, platelet aggregation, and cardiac arrhythmia, may offset the benefits of BP reduction (thus perhaps increasing cardiovascular morbidity) and help explain a putative deficit in coronary event prevention (as evidenced by the increased cancer mortality [HR, 1.52; P<0.01]) and transient conditions such as gastrointestinal disturbances (not documented in ALLHAT). The lowest risk in the diuretic arm was possibly because of admixture of the hypokalemia directly related to the effects of the drug, which in some patients may be corrected by homeostatic mechanisms and in others addressed by potassium supplementation per usual clinical standards. Thus, it appears that non-CVD mortality, specifically cancer deaths, contributes significantly to the excess mortality in hypokalemia. This experience in ALLHAT exceeds, in magnitude and data quality, any similar observational data

Table 4. Overall Cumulative No. of Events and 5-Y Kaplan-Meier Event Rates per 100 for the Hyperkalemic and Normal Y-1 Potassium Subgroups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Events</th>
<th>5-Y Rate per 100</th>
<th>Cox Proportional Hazard Models</th>
<th>Hypokalemia/Normal×Drug Interaction Adjusted, HR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺&lt;3.5</td>
<td>1.46 (1.08–1.97; 0.01)</td>
<td>1.34 (0.76–2.37; 0.32)</td>
<td>0.97 (0.43–2.23; 0.95)</td>
<td>1.01 (0.49–2.08; 0.98)</td>
</tr>
<tr>
<td>K⁺&lt;3.5</td>
<td>1.27 (0.81–2.01; 0.30)</td>
<td>1.25 (0.56–2.80; 0.59)</td>
<td>1.37 (0.44–4.33; 0.59)</td>
<td>0.62 (0.23–2.07; 0.50)</td>
</tr>
<tr>
<td>K⁺&gt;3.5</td>
<td>1.58 (1.11–2.23; 0.01)</td>
<td>1.71 (0.91–3.20; 0.10)</td>
<td>0.63 (0.25–1.62; 0.34)</td>
<td>0.79 (0.35–1.78; 0.56)</td>
</tr>
<tr>
<td>Death</td>
<td>1.48 (1.16–1.89; &lt;0.01)</td>
<td>1.15 (0.71–1.86; 0.57)</td>
<td>1.04 (0.52–2.11; 0.91)</td>
<td>1.28 (0.71–2.31; 0.41)</td>
</tr>
<tr>
<td>CVD deaths</td>
<td>1.50 (0.51–2.48; 0.56)</td>
<td>0.93 (0.33–2.59; 0.88)</td>
<td>1.13 (0.48–2.69; 0.77)</td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>1.71 (1.08–2.70; 0.02)</td>
<td>1.49 (0.61–3.61; 0.38)</td>
<td>0.61 (0.14–2.58; 0.50)</td>
<td>1.22 (0.41–3.57; 0.72)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.34 (0.50–3.25; 0.52)</td>
<td>1.50 (0.37–6.15; 0.57)</td>
<td>0.68 (0.06–7.68; 0.75)</td>
<td>0.56 (0.08–4.12; 0.57)</td>
</tr>
<tr>
<td>HF</td>
<td>1.32 (0.18–9.66; 0.78)</td>
<td>1.32 (0.18–9.66; 0.78)</td>
<td>3.16 (0.31–31.95; 0.33)</td>
<td>0.52 (0.03–8.69; 0.65)</td>
</tr>
<tr>
<td>Non-CVD deaths</td>
<td>1.33 (0.92–1.93; 0.13)</td>
<td>0.94 (0.45–1.99; 0.87)</td>
<td>0.91 (0.29–2.90; 0.87)</td>
<td>1.72 (0.70–4.19; 0.24)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.35 (0.81–2.26; 0.26)</td>
<td>0.56 (0.14–2.27; 0.42)</td>
<td>1.14 (0.16–8.20; 0.90)</td>
<td>3.65 (0.80–16.70; 0.10)</td>
</tr>
<tr>
<td>Other</td>
<td>1.31 (0.77–2.24; 0.31)</td>
<td>1.26 (0.52–3.07; 0.60)</td>
<td>0.84 (0.20–3.59; 0.82)</td>
<td>0.89 (0.27–2.98; 0.85)</td>
</tr>
</tbody>
</table>

Also depicted are Cox proportional HRs, corresponding 95% CIs, and P values for the hyperkalemia/normal comparisons and for the drug group by y-1 serum potassium interaction tests: hyperkalemia/normal×A/C and hyperkalemia/normal×L/C. Participants with baseline potassium <3.5 mmol/L or >5.4 mmol/L were excluded. A indicates amlodipine; C, chlorthalidone; CCVD, combined cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; L, lisinopril.

*Sample size: K⁺<3.5, n=398; 3.5≤K⁺<5.4, n=17 982.
†Unadjusted Cox model for each outcome included only terms for the K⁺<3.5 group and the K⁺>5.4 group relative to the normal potassium group; K⁺>5.4, n=398; 3.5≤K⁺<5.4, n=17 982.
‡The adjusted Cox model for each outcome included main effects terms for hypokalemia/normal, hyperkalemia/normal, baseline characteristic: age (decades of life), sex (male/female), race (black/nonblack), type-2 diabetes mellitus (yes/no), history CHD (yes/no), history of other atherosclerotic CVD (yes/no), cigarette smoker (yes/no); baseline systolic blood pressure and serum potassium, estimated glomerular filtration rate at y, drug treatment effects (A/C and L/C), and 4 interaction terms: the 2 potassium main effects (hypokalemia/normal, hyperkalemia/normal) with each of the 2 drug main effects (A/C and L/C).

graphical and clinical characteristics. As expected, modest year-1 hypokalemia (3.2–3.4 mmol/L) was primarily an experience of participants randomized to C (9.5% compared with 1.7% in A and 0.8% in L). Development of severe hypokalemia (<3.2 mmol/L) was less frequent (3.5% in C). By contrast, hyperkalemia (K⁺>5.4) occurred primarily in L participants (3.6%) and was least common among C participants (1.2%). Potassium supplements were prescribed to ~10% of participants. The availability and use of potassium supplements suggest that clinical care, in ALLHAT, is likely to mirror conventional care, and, thus, the CVD outcomes of interest in regard to incident hypokalemia are likely to be generally applicable in settings where clinicians are free to respond appropriately to this laboratory finding.

It has been suggested that hypokalemia, by contributing to atherosclerosis, platelet aggregation, and cardiac arrhythmia, may offset the benefits of BP reduction (thus perhaps increasing cardiovascular morbidity) and help explain a putative deficit in coronary event prevention achieved in clinical trials of diuretic therapy compared with that predicted from epidemiological data.13 Thus, concerns have primarily been directed at diuretic-induced hypokalemia and its CVD consequences.

Thirteen percent of C participants were hypokalemic at year 1. Their subsequent CVD morbidity and mortality did not exceed those of normokalemic participants in any cardiovascular outcome, and they actually had lower rates of cardiovascular events than the hypokalemic, normokalemic, or hyperkalemic subgroups of either L or A participants. For CVD outcomes, HF seems to be responsible for most of the heterogeneity as opposed to CHD or stroke. There was less HF in C compared with A or L. Overall mortality among hypokalemic C participants was significantly higher than normokalemics. However, when stratified by CVD and non-CVD causes, only the latter remained statistically significant. The risk of death in hypokalemics compared with normokalemics was the highest in L participants (HR, 3.82; P<0.01), intermediate in A (HR, 1.60; P=0.06), and lowest in C (HR, 1.21; P=0.03). This heterogeneity across treatment groups suggests that hypokalemia likely represents chronic conditions associated with potassium loss and high mortality (as evidenced by the increased cancer mortality [HR, 1.52; P<0.01]) and transient conditions such as gastrointestinal disturbances (not documented in ALLHAT). The lowest risk in the diuretic arm was possibly because of admixture of the hypokalemia directly related to the effects of the drug, which in some patients may be corrected by homeostatic mechanisms and in others addressed by potassium supplementation per usual clinical standards. Thus, it appears that non-CVD mortality, specifically cancer deaths, contributes significantly to the excess mortality in hypokalemia. This experience in ALLHAT exceeds, in magnitude and data quality, any similar observational data.
linking K⁺ concentrations to subsequent cardiovascular morbidity in a treated hypertensive population.

Of interest in the ALLHAT analyses of hypokalemia and hyperkalemia and their potential association with clinical events is the degree of persistence of these clinical states during the remainder of the trial. The administration of K⁺ supplements was encouraged for all of the participants who had K⁺ <3.5 mmol/L persistently. In this large trial, incidental K⁺ measurements done as part of routine patient care were not recorded centrally. Of the 19731 ALLHAT participants included in this report, 16213 (82%) had central K⁺ measures at 3, 12, and 24 months. Only 9.6% of the 1117 who were hypokalemic at 12 months were hypokalemic at all 3 of the time points. The majority of participants with hypokalemia were assigned C. In like fashion, only 1.3% of the 309 who were hyperkalemic at 12 months were hyperkalemic at all 3 of the time points. The largest proportion was assigned L. The available data do not permit an explanation for the association of potassium abnormalities with CVD events or total mortality. However, the data do imply that the clinical response to learning that abnormalities in K⁺ had occurred was both appropriate and sufficient and that hypokalemic or hyperkalemic states detected in ALLHAT participants were not allowed to persist.

Altogether, clinical studies linking K⁺ concentrations to subsequent events have yielded inconsistent results.⁴,¹⁴,¹⁵ The limitations of methodology and observational nature of most studies make this inconsistency understandable. The potassium-losing effects of diuretics, particularly when higher doses were in fashion, have been widely described, as have the reverse effects of agents blocking the renin-angiotensin system.¹⁶–¹⁸

Meta-analyses of clinical trials consistently indicate that, as was the case in ALLHAT, no other antihypertensive agent produces cardiovascular protection superior to that achieved when therapy is initiated with a diuretic.¹⁹ Diuretic dosage in ALLHAT, 12.5 to 25.0 mg of C per day, can be considered moderate. The incidence of hypokalemia here was consistent with that seen in placebo-controlled clinical trials in which CVD prevention was achieved.¹⁹

This report of the ALLHAT is a post hoc observational analysis of subjects’ experience not protected by randomization and is, therefore, despite robust multivariable analysis, subject to residual confounding. This applies particularly to the drug subgroup analyses. We lack precise interval information on the course of both therapy and potassium concentrations and, thus, cannot assess interval interventions or potassium levels proximal to events. It should also be noted that the data here reflect the relatively short-term impact of treatment-induced variations in potassium in older hypertensive patients. At the same time, ALLHAT provides a very large experience to determine the midterm CVD consequences in routine clinical practice when evidence of incident hypokalemia or hyperkalemia has been systematically made available to treating physicians.

In summary, these results reveal that severe drug-induced alterations of K⁺ affect a small minority of treated patients. Hyperkalemia, although infrequent, usually occurred among angiotensin-converting enzyme inhibitor–treated patients, and signals increased cardiovascular risk. On the other hand, much more common hypokalemia, affecting ≈13% of C participants at year 1, was not associated with adverse cardiovascular consequences and likely represents chronic conditions associated with potassium loss and high mortality and transient conditions.

**Perspectives**

Diuretics have been demonstrated in multiple clinical trials to provide low-cost clinical benefit in the treatment of hypertension. Yet, many physicians have been reticent about prescribing diuretics because of concerns of diuretic-induced hypokalemia. Until now, little has been known about clinical ramifications of this hypokalemia. Several pertinent lessons can be learned from ALLHAT data. First, although the majority of the participants with hypokalemia at some time point during ALLHAT were assigned to the diuretic C, the hypokalemia seldom persisted throughout the study, likely attributed in large part to potassium supplementation, a need easily detected and therapy commonly prescribed in general medical practice. Critically, the appearance of hypokalemia in the diuretic group was not associated with increased cardiovascular outcomes; to the contrary, the risk of adverse cardiovascular outcomes including mortality among hypokalemic participants was lower in the diuretic arm than in either of the other 2 arms. Regardless of treatment group, participants with hyperkalemia fared worse than those with hypokalemia. Treating hypertension is fundamental, and treatment should often include a thiazide-type diuretic. Clinicians should feel reassured that hypokalemia associated with low-to-moderate dose diuretics (12.5–25.0 mg of C a day) affected <13% of patients and was easily remedied. Hyperkalemia, although infrequent, may present a more alarming cardiovascular risk and deserves additional study.²⁰ What is clear, however, is that the cardioprotective actions of diuretic use are unaffected by consequent but treatable alterations in serum potassium.

**Acknowledgments**

For a complete list of members of the ALLHAT Collaborative Research Group, see Reference.⁶

**Sources of Funding**

This research was supported by contract number N01-HC-35130 from the National Heart, Lung, and Blood Institute. The ALLHAT investigators acknowledge contributions of study medications supplied by Pfizer, Inc (amlodipine); AstraZeneca (atenolol and lisinopril); and Bristol-Myers Squibb (pravastatin), as well as financial support by Pfizer, Inc.

**Disclosures**

M.H.A. has received research grants from Sankyo. D.A.C. has consulted for Eli Lilly and Novartis. W.C.C. has consulted for Daiichi Sankyo, Novartis, Noven, Sanofi Aventis, Takeda, and Theravance, has received honoraria from Bristol-Meyer Squibb, Daiichi Sankyo, Novartis, and Sanofi-Aventis, and has received research grants from GlaxoSmithKline and Novartis. B.R.D. has consulted for Eli Lilly and Novartis. S.T.O. has received honoraria from Novartis and has received research grants from Amarin, Amylin, Daiichi Sankyo, Forest Pharmaceuticals, GlaxoSmithKline, Johnson and Johnson, Luitpold, Novartis, Pfizer, Roche, Sanofi Aventis, Takeda, and XOMA. S.O. has consulted for Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Forest Laboratories, Forest Pharmaceuticals, NicOx, Novartis, Omron Healthcare, Pfizer, and Schering Plough and has received research grants from Amgen, and...
Daiichi Sankyo, Gilead, Merck, and Takeda. V.P. has received honoraria from Astra-Zeneca and Forest Pharmaceuticals. J.L.P. has received research grants from Abbott Laboratories, Boehringer Ingelheim, GlaxoSmithKline, and Sanofi Aventis.

References


Clinical Significance of Incident Hypokalemia and Hyperkalemia in Treated Hypertensive Patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

Hypertension. 2012;59:926-933; originally published online March 19, 2012; doi: 10.1161/HYPERTENSIONAHA.111.180554
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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CLINICAL SIGNIFICANCE OF INCIDENT HYPOKALEMIA AND HYPERKALEMIA IN TREATED HYPERTENSIVE PATIENTS IN ALLHAT

SUPPLEMENTAL MATERIALS

Michael H Alderman, MD1, Linda B Piller, MD, MPH2, Charles E Ford, PhD2, Jeffrey L Probstfield, MD3, Suzanne Oparil, MD3, William C Cushman, MD3, Paula T Einhorn, MD, MS4, Stanley S Franklin, MD5, Vasilios Papademetriou, MD6, Stephen T Ong, MD, MPH6, John H Eckfeldt, MD, PhD10, Curt D Furberg, MD, PhD11, David Calhoun, MD4, Barry R Davis, MD, PhD2, for the ALLHAT Collaborative Research Group12.

Affiliations: 1Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, NY; 2Coordinating Center for Clinical Trials, The University of Texas School of Public Health, Houston, TX; 3Clinical Trials Service Unit, University of Washington, Seattle, WA; 4Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL; 5Memphis Veterans Affairs Medical Center, Memphis, TN; 6Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD; 7Department of Medicine, University of California, Irvine, CA; 8Veterans Affairs Medical Center Washington, Washington, DC; 9Ong Medical Center, Oxon Hill, MD; 10University of Minnesota Hospital and Clinic, Minneapolis, MN; 11Wake Forest University School of Medicine, Winston-Salem, NC; 12For a complete list of members of the ALLHAT Collaborative Research Group, see JAMA 2002; 288(23):2981-2997.
Table S1. Baseline and follow-up characteristics of participants overall and by year-1 serum potassium (K+) strata for participants with known baseline and year-1 serum potassium levels, excluding those with baseline K+<3.5 or >5.4 mmol/L.

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>ALLHAT Cohort</th>
<th>Cohort in analysis</th>
<th>Cohort by Potassium Strata (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>K+&lt;3.5 n (%)</td>
</tr>
<tr>
<td>Sample size</td>
<td>33357 (100.0)</td>
<td>19731 (100.0)</td>
<td>1351 (100.0)</td>
</tr>
<tr>
<td>Black vs. Non-black</td>
<td>11792 (35.4)</td>
<td>6184 (31.3)</td>
<td>513 (38.0)*</td>
</tr>
<tr>
<td>Women</td>
<td>15638 (46.9)</td>
<td>8505 (43.1)</td>
<td>713 (52.8)*</td>
</tr>
<tr>
<td>AHT Treated†</td>
<td>30089 (90.2)</td>
<td>17900 (90.7)</td>
<td>1266 (93.7)*</td>
</tr>
<tr>
<td>Lipid trial participants</td>
<td>8162 (24.5)</td>
<td>5744 (29.1)</td>
<td>398 (29.5)</td>
</tr>
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<td>On aspirin</td>
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<td>7650 (21.1)</td>
<td>294 (21.8)</td>
</tr>
<tr>
<td>On estrogen</td>
<td>2752 (17.6)</td>
<td>1687 (19.8)</td>
<td>154 (21.6)</td>
</tr>
<tr>
<td>Cigarette smoker</td>
<td>7303 (21.9)</td>
<td>4171 (21.1)</td>
<td>294 (21.8)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>13448 (40.3)</td>
<td>8444 (24.8)</td>
<td>529 (39.2)*</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>12063 (36.2)</td>
<td>6817 (34.6)</td>
<td>332 (24.6)*</td>
</tr>
<tr>
<td>History of CHD</td>
<td>8415 (25.4)</td>
<td>5109 (26.1)</td>
<td>315 (23.5)*</td>
</tr>
<tr>
<td>Age, years</td>
<td>n Mean (SD)</td>
<td>n Mean (SD)</td>
<td>n Mean (SD)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
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<td>19731 66.7 (7.4)</td>
<td>1351 66.6 (7.7)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>33357 84.0 (10.1)</td>
<td>19731 83.7 (10.1)</td>
<td>1351 84.6 (9.7)</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>33252 29.8 (6.2)</td>
<td>19683 29.8 (6.0)</td>
<td>1349 29.5 (5.7)</td>
</tr>
<tr>
<td>Fasting serum glucose, mg/dl</td>
<td>24742 123.2 (57.3)</td>
<td>15612 121.4 (54.4)</td>
<td>1064 111.6 (46.2)</td>
</tr>
<tr>
<td>Estimated GFR† serum glucose, mg/dl</td>
<td>31897 77.7 (19.7)</td>
<td>19731 77.9 (19.0)</td>
<td>1351 78.4 (18.9)</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>29801 135.8 (37.1)</td>
<td>18490 135.8 (36.5)</td>
<td>1282 136.5 (36.8)</td>
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<tr>
<td>HDL, mg/dl</td>
<td>31752 46.8 (14.7)</td>
<td>19630 46.3 (14.5)</td>
<td>1344 47.7 (14.8)</td>
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<tr>
<td>Fasting triglycerides, mg/dl</td>
<td>25660 172.7 (133.6)</td>
<td>16228 172.1 (130.4)</td>
<td>1110 163.3 (105.7)</td>
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<td>Serum K+; mmol/L§ Baseline</td>
<td>31776 4.31 (0.51)</td>
<td>19731 4.30 (0.40)</td>
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<tr>
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<td>1351 3.26 (0.16)</td>
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<tr>
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<td>16324 4.23 (0.68)</td>
<td>1121 3.71 (0.55)</td>
</tr>
<tr>
<td>Year-4</td>
<td>17850</td>
<td>4.32 (0.71)</td>
<td>13557</td>
</tr>
<tr>
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<tr>
<td>Follow-up SBP, mmHg</td>
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<tr>
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<td>18712</td>
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<tr>
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<td>16939</td>
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<td>Year-4</td>
<td>16857</td>
<td>134.8 (15.9)</td>
<td>12490</td>
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<td>Year-5</td>
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<td>Follow-up DBP, mmHg</td>
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<tr>
<td>Year-1</td>
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<td>18712</td>
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<td>16939</td>
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<tr>
<td>Year-4</td>
<td>16854</td>
<td>76.3 (9.8)</td>
<td>12490</td>
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<td>Year-5</td>
<td>9220</td>
<td>75.1 (10.0)</td>
<td>6901</td>
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</table>

<table>
<thead>
<tr>
<th>Year-4</th>
<th>17850</th>
<th>4.32 (0.71)</th>
<th>13557</th>
<th>4.32 (0.69)</th>
<th>934</th>
<th>3.85 (0.60)</th>
<th>12374</th>
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<th>249</th>
<th>4.68* (0.75)</th>
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<tr>
<td>Follow-up SBP, mmHg</td>
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<td></td>
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<td>Year-1</td>
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<td>877</td>
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<td>132.9 (18.0)</td>
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<td>18712</td>
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<td>1161</td>
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<td>6253</td>
<td>74.6 (9.8)</td>
<td>119</td>
<td>73.4 (10.2)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body-mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; *p<0.05; comparisons are between hypokalemic and normal potassium groups or hyperkalemic and normal potassium groups † AHT = Treated with antihypertensive medication prior to trial entry. ‡ ml/min/1.73 m². § Serum potassium values <2.5 and >7.0 mmol/L were excluded.
### Table S2. Hypokalemia status and subsequent potassium supplementation during follow-up.

<table>
<thead>
<tr>
<th>Serum Potassium (K⁺), mmol/L</th>
<th>Baseline</th>
<th>1-3 months</th>
<th>12 months</th>
<th>24 months</th>
<th>48 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>&lt;3.2</td>
<td>0 (0%)</td>
<td>193 (100)</td>
<td>302 (100)</td>
<td>254 (100)</td>
<td>114 (100)</td>
</tr>
<tr>
<td>On K⁺ supp at next visit*</td>
<td>0 (0%)</td>
<td>70 (36)</td>
<td>112 (37)</td>
<td>107 (42)</td>
<td>45 (40)</td>
</tr>
<tr>
<td>Ever on K⁺</td>
<td>0 (0%)</td>
<td>152 (79)</td>
<td>220 (73)</td>
<td>187 (74)</td>
<td>81 (71)</td>
</tr>
<tr>
<td>&lt;3.5</td>
<td>0 (0%)</td>
<td>941 (100)</td>
<td>1,351 (100)</td>
<td>1,094 (100)</td>
<td>580 (100)</td>
</tr>
<tr>
<td>On K⁺ supp at next visit</td>
<td>0 (0%)</td>
<td>262 (28)</td>
<td>399 (30)</td>
<td>387 (35)</td>
<td>195 (34)</td>
</tr>
<tr>
<td>Ever on K⁺</td>
<td>0 (0%)</td>
<td>620 (66)</td>
<td>823 (61)</td>
<td>687 (63)</td>
<td>357 (62)</td>
</tr>
<tr>
<td>≥3.5</td>
<td>19,731 (100)</td>
<td>15,789 (100)</td>
<td>18,380 (100)</td>
<td>15,119 (100)</td>
<td>12,889 (100)</td>
</tr>
<tr>
<td>On K⁺ supp at next visit</td>
<td>379 (2)</td>
<td>256 (2)</td>
<td>727 (4)</td>
<td>1,021 (7)</td>
<td>1,080 (8)</td>
</tr>
<tr>
<td>Ever on K⁺</td>
<td>3,996 (20)</td>
<td>2,829 (18)</td>
<td>3,173 (17)</td>
<td>2,749 (18)</td>
<td>2,554 (20)</td>
</tr>
</tbody>
</table>

* Next visit = 3, 6, 16, 28, 52 months.
Figure S1 ALLHAT participants comprising cohort for serum potassium analyses.

ALLHAT
42,418 Randomized Participants, From 623 Clinical Sites in North America

Excluded From Analysis:
- Randomized to Doxazosin (n=9661)
- Missing Baseline Serum Potassium (K⁺) Measure (n=1,472)
- Died Before Year-1 Visit (n=554)
- No Serum K⁺ Value Within Year-1 Visit Window (n=10,216)
  - Baseline K⁺ < 3.5 mmol/L (n=649)
  - Baseline K⁺ ≥ 5.4 mmol/L (n=615)
  - Year-1 K⁺ < 2.5 mmol/L (n=3)
  - Year-1 K⁺ > 7.0 mmol/L (n=116)

Included in Analysis (n = 19,731)

- Hypokalemic: Serum K⁺ < 3.5 mmol/L
  - 1,351 Included in Analysis
- Normokalemic: 3.5 ≤ Serum K⁺ ≤ 5.4 mmol/L
  - 17,981 Included in Analysis
- Hyperkalemic: Serum K⁺ > 5.4 mmol/L
  - 398 Included in Analysis