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Hypokalemia Associated With Diuretic Use and Cardiovascular Events in the Systolic Hypertension in the Elderly Program

Lonneke V. Franse, Marco Pahor, Mauro Di Bari, Grant W. Somes, William C. Cushman, William B. Applegate

Abstract—The treatment of hypertension with high-dose thiazide diuretics results in potassium depletion and a limited benefit for preventing coronary events. The clinical relevance of hypokalemia associated with low-dose diuretics has not been assessed. To determine whether hypokalemia that occurs with low-dose diuretics is associated with a reduced benefit on cardiovascular events, we analyzed data of 4126 participants in the Systolic Hypertension in the Elderly Program (SHEP), a 5-year randomized, placebo-controlled clinical trial of chlorthalidone-based treatment of isolated systolic hypertension in older persons. After 1 year of treatment, 7.2% of the participants randomized to active treatment had a serum potassium <3.5 mmol/L compared with 1% of the participants randomized to placebo ($P<0.001$). During the 4 years after the first annual visit, 451 participants experienced a cardiovascular event, 215 experienced a coronary event, 177 experienced stroke, and 323 died. After adjustment for known risk factors and study drug dose, the participants who received active treatment and who experienced hypokalemia had a similar risk of cardiovascular events, coronary events, and stroke as those randomized to placebo. Within the active treatment group, the risk of these events was 51%, 55%, and 72% lower, respectively, among those who had normal serum potassium levels compared with those who experienced hypokalemia ($P<0.05$). The participants who had hypokalemia after 1 year of treatment with a low-dose diuretic did not experience the reduction in cardiovascular events achieved among those who did not have hypokalemia. (*Hypertension*. 2000;35:1025-1030.)

Key Words: hypokalemia ■ diuretics ■ myocardial infarction ■ stroke ■ clinical trials

Thiazide diuretics tend to deplete potassium in a dose-dependent fashion. It has been suggested that this adverse effect may increase the risk of sudden cardiac death and limit the benefit of high-dose diuretic treatment on coronary events. In the Puget Sound Group Health Cooperative case-control study, the use of high-dose thiazide diuretics (100 mg daily) was associated with an increased risk (odds ratio=3.6) of primary cardiac arrest compared with the use of low-dose thiazide diuretics (25 mg daily).¹ In the Multiple Risk Factor Intervention Trial, in the subgroup with abnormal resting ECG at baseline, the use of high-dose diuretics (50 to 100 mg per daily) was associated with a 2.4 times increased risk of sudden cardiac death compared with "usual care."² More recent trials that used low-dose diuretics found a greater reduction in coronary events than those using high doses.³⁻⁵ In a meta-analysis of 18 randomized, placebo-controlled trials, high-dose diuretic therapy did not prevent coronary heart disease, whereas low-dose diuretic therapy was associated with a 28% reduction in coronary heart disease.⁶

The effects of low-dose diuretics on potassium depletion are considered mild, but, to the best of our knowledge, the clinical relevance of hypokalemia associated with low-dose diuretics has not been assessed. In the Systolic Hypertension in the Elderly Program (SHEP), participants randomized to low-dose chlorthalidone-based treatment had significantly lower serum potassium levels during follow-up and were more likely to have hypokalemia than those receiving placebo.^{3,7} The aim of this secondary analysis in SHEP was to determine whether hypokalemia associated with randomly assigned diuretic treatment affects the cardiovascular benefit of antihypertensive treatment.

Methods

Design and Participants

The SHEP was a randomized, double-blind, placebo-controlled clinical trial on the efficacy of diuretic-based antihypertensive drug treatment of isolated systolic hypertension in persons ≥ 60 years of

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age. Isolated systolic hypertension was defined as a systolic blood pressure of 160 to 219 mm Hg, with diastolic blood pressure <90 mm Hg. The follow-up was 5 years. The criteria for enrollment, adjudication of end points, and primary findings of SHEP were reported in detail elsewhere.³ The participants gave informed consent, and the study was approved by the institutional review boards of the study sites.

For this study, 4126 patients who had a valid measurement of serum potassium at the clinic visit 1 year after randomization were included in the analyses. A total of 610 patients (of whom 58 died) who had been randomized into the SHEP but for whom serum potassium was not available at the first annual clinic visit were excluded from the analyses. The 610 patients who were excluded were older (72.8 years); had a higher baseline systolic blood pressure (171 mm Hg); had a higher serum creatinine (93.7 $\mu\text{mol/L}$); were more likely to be randomized to placebo treatment (55.5%); and were more likely to be black (20.3%), to be a current smoker (16.4%), and to have a history of diabetes (12.3%) compared with those who had a valid serum potassium measurement.

This article reports primarily on the first occurring major cardiovascular event, which included stroke, transient ischemic attack, myocardial infarction, heart failure, coronary artery bypass surgery, angioplasty, aneurysm, endarterectomy, and sudden death or rapid cardiac death (within 1 to 24 hours of the onset of severe cardiac symptoms unrelated to their known cause). In addition, fatal and nonfatal coronary heart disease (which included myocardial infarction, coronary procedures, and cardiac death), fatal and nonfatal stroke, and all-cause mortality were analyzed separately.

Intervention

The participants were randomized to active treatment or placebo. A stepped-care treatment approach was used. The treatment goal was systolic blood pressure <160 mm Hg or a ≥ 20 mm Hg reduction in systolic blood pressure. In the active treatment group, the first step was chlorthalidone 12.5 mg/d. The dosage was doubled if the goal blood pressure was not achieved. If the goal was not reached at the first step, atenolol 25 mg/d was added (second step). If atenolol was not tolerated, reserpine 0.05 mg/d was substituted. The dosage of the second step drugs could be doubled if the goal blood pressure was not reached. Potassium supplements were given to all participants who had serum potassium concentrations <3.5 mmol/L at 2 consecutive visits. No active antihypertensive agent was given to the participants randomized to placebo.

Data Analysis

During follow-up, differences in potassium decrease between the active and placebo group and among participants with different doses of chlorthalidone were tested with ANOVA.⁸ A dose trend was tested by the polynomial linear contrasts ANOVA. Baseline and year 1 characteristics of the participants according to treatment group and hypokalemia after 1 year were compared by means of the χ^2 test and ANOVA test as appropriate.⁸

Cox proportional hazards regression models were used to estimate the hazard ratio and 95% CI for the effect of hypokalemia (<3.5 mmol/L) after 1 year of active treatment on the outcomes of interest.⁹ Only events occurring after the first year were considered in the analyses of the effect of hypokalemia observed after 1-year treatment. The 1-year change was chosen because serum potassium decreased the most in the first year and did not decrease significantly in the active treatment group thereafter (Figure 1). The assumption of proportionality of hazards was assessed with log-log plots and by testing the interaction of exposure with time.⁸ To assess independent associations of hypokalemia at year 1 and subsequent outcomes, potential confounding factors were entered into a summary model if they changed the β of hypokalemia by $\geq 10\%$ in a bivariate Cox regression model. The same adjustments were used in all models that analyzed the 4 outcomes. A variable that changed the β by 10% for any 1 of the 4 outcomes was included in all multivariate models.

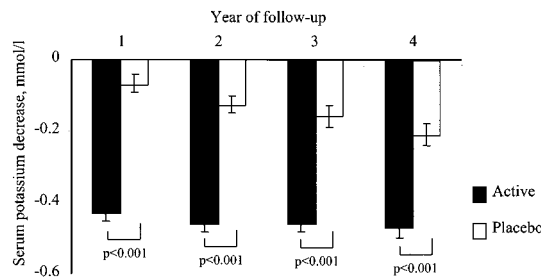


Figure 1. Serum potassium decrease during follow-up compared with baseline according to treatment.

Results

At baseline, the average serum potassium was 4.52 mmol/L (± 0.46) for both active treatment and placebo groups; 6 participants in the active treatment group and 9 in the placebo group had hypokalemia (serum potassium <3.5 mmol/L) ($P=0.30$). During follow-up, and especially in the first year, potassium levels decreased significantly more in the active treatment group compared with the placebo group (Figure 1). After 1 year, the average serum potassium was 4.09 mmol/L (± 0.48) in the active treatment group and 4.45 mmol/L (± 0.43) in the placebo group ($P<0.001$); 151 (7.2%) participants in the diuretic group had hypokalemia compared with 21 (1.0%) in the placebo group ($P<0.001$).

Chlorthalidone dose prescribed at the last clinic visit before the first annual visit was inversely associated with serum potassium levels at the first annual visit (P for trend <0.001) (Figure 2). The use of 6.25, 12.5, or 25.0 mg of chlorthalidone per day was associated with a significantly lower serum potassium level than the use of placebo.

Baseline characteristics according to treatment group and hypokalemia after 1 year are shown in Table 1. In the active treatment group, participants who experienced hypokalemia after 1 year were at baseline younger; had a slightly higher diastolic blood pressure; were more likely to be treated with antihypertensive medication at initial contact; had lower serum potassium, serum creatinine, and serum glucose levels; and were less likely to report a history of diabetes compared with those who did not experience hypokalemia. In the placebo group, virtually the same differences in characteristics were observed between those who were hypokalemic after 1 year and those who were not, but because of the small numbers, the difference did not always reach statistical significance. Furthermore, participants in the placebo group

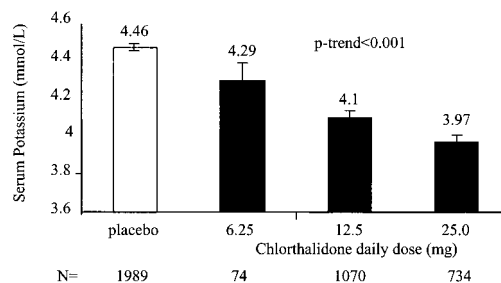


Figure 2. Serum potassium at year 1, according to chlorthalidone dose. The numbers at the bottom of the figure indicate the number of participants in each group.

TABLE 1. Baseline Characteristics of the Participants According to Treatment and Hypokalemia After 1 Year

Risk Factors	Active Treatment		Placebo	
	1-Year K \geq 3.5 (n=1951)	1-Year K<3.5 (n=151)	1-Year K \geq 3.5 (n=2003)	1-Year K<3.5 (n=21)
Demographic				
Age, y	71.6 \pm 6.6	70.4 \pm 6.5*	71.3 \pm 6.5	67.6 \pm 5.4*
Male gender, %	44.1	37.1	43.5	47.6
Ethnic origin				
White, %	79.3	80.8	80.6	61.9
Black, %	13.3	13.9	12.3	28.6
Asian, %	4.7	2.6	4.6	4.8
Lifestyle indicators				
Alcohol intake nearly every day, %	15.8	17.9	15.7	23.8
Smoking, current %	12.2	9.3	12.2	23.8*
Health status indicators				
Body mass index, kg/m ²	27.6 \pm 4.9	28.0 \pm 5.3	27.6 \pm 5.1	28.6 \pm 5.9
Systolic blood pressure, mm Hg	170 \pm 9	171 \pm 9	170 \pm 9	175 \pm 12
Diastolic blood pressure, mm Hg	77 \pm 10	78 \pm 9*	76 \pm 10	79 \pm 10
Antihypertensive medication at initial contact, %	33.3	43.0*	33.7	42.9
Serum potassium, mmol/L	4.5 \pm 0.5	4.2 \pm 0.4**	4.5 \pm 0.4	4.3 \pm 0.8*
Serum creatinine, mmol/L†	92.8 \pm 20.3	88.4 \pm 17.7*	91.9 \pm 20.3	84.9 \pm 17.7
Serum glucose, mmol/L‡	6.1 \pm 1.9	5.6 \pm 1.0*	6.0 \pm 1.8	5.5 \pm 1.1
Serum cholesterol, mmol/L§	6.14 \pm 1.14	6.19 \pm 1.61	6.11 \pm 1.11	5.62 \pm 1.09
Serum triglycerides, mmol/L¶	1.75 \pm 1.03	1.90 \pm 1.54	1.80 \pm 1.08	1.59 \pm 0.99
Serum HDL-cholesterol, mmol/L§	1.40 \pm 0.39	1.40 \pm 0.39	1.40 \pm 0.39	1.40 \pm 0.36
Serum uric acid, mmol/L	0.32 \pm 0.08	0.32 \pm 0.08	0.32 \pm 0.08	0.33 \pm 0.08
Comorbidity				
History of heart attack, %	3.6	4.0	4.2	0.0
History of stroke, %	2.4	2.0	1.5	4.8
History of diabetes, %	10.5	4.6*	9.5	9.5

K indicates serum potassium mmol/L.

* P <0.05; ** P <0.001 significantly different from nonhypokalemic, corresponding treatment group.

†To convert to mg/dL divide by 88.4.

‡To convert to mg/dL divide by 0.056.

§To convert to mg/dL divide by 0.026.

¶To convert to mg/dL divide by 0.011.

††To convert to mg/dL divide by 0.058.

who experienced hypokalemia after 1 year also had a higher systolic blood pressure and were more likely to smoke at baseline.

At year 1, participants in the active treatment group who experienced hypokalemia had higher levels of serum triglycerides and serum uric acid compared with those who did not experience hypokalemia (Table 2). Both active treatment subgroups had the same proportion of participants on open-label antihypertensive medications, but those who were hypokalemic were more likely to use a higher dose of chlorthalidone (prescribed at the last clinic visit before the first annual clinic visit). In the placebo group at year 1, the participants who were hypokalemic had a lower systolic blood pressure, a higher serum uric acid level, and a greater proportion of them used open-label antihypertensive medications compared with those who were not hypokalemic.

During the 4 years after the first annual visit, 451 participants experienced any cardiovascular event, 215 experienced coronary heart disease, 177 experienced stroke, and 323 died (Table 3). Participants in the placebo group who had no hypokalemia, experienced more cardiovascular events (P <0.001) and strokes (P <0.001) than the corresponding participants in the active treatment group. In the active treatment group, unadjusted rates of cardiovascular events, coronary heart disease, and stroke were significantly higher (P <0.05) among those who were hypokalemic after 1 year compared with those who were not. Sudden cardiac death occurred in 18 participants of the active, nonhypokalemic subgroup; in 2 participants of the active, hypokalemic subgroup; and in 9 participants of the placebo, nonhypokalemic subgroup (P =0.29). After adjustment for age; gender; race; body mass index; alcohol use; smoking; history of heart

TABLE 2. Characteristics of the Participants After 1 Year, According to Treatment and Hypokalemia After 1 Year

	Active Treatment		Placebo	
	1-Year K \geq 3.5 (n=1951)	1-Year K<3.5 (n=151)	1-Year K \geq 3.5 (n=2003)	1-Year K<3.5 (n=21)
Systolic blood pressure, mm Hg	143 \pm 16	140 \pm 13	157 \pm 17	145 \pm 18*
Diastolic blood pressure, mm Hg	70 \pm 10	69 \pm 11	73 \pm 12	72 \pm 11
Serum creatinine, mmol/L†	97.2 \pm 24.8	93.7 \pm 22.1	92.8 \pm 23.0	88.4 \pm 22.1
Serum glucose, mmol/L‡	6.4 \pm 2.4	6.4 \pm 2.2	6.1 \pm 1.9	6.3 \pm 2.3
Serum cholesterol, mmol/L§	6.24 \pm 1.22	6.42 \pm 1.22	6.14 \pm 1.11	5.58 \pm 1.01
Serum triglycerides, mmol/L¶	1.93 \pm 1.19	2.12 \pm 1.33*	1.80 \pm 1.06	1.55 \pm 0.89
Serum HDL-cholesterol, mmol/L§	1.42 \pm 0.41	1.45 \pm 0.39	1.42 \pm 0.39	1.50 \pm 0.41
Serum uric acid, mmol/L††	0.37 \pm 0.10	0.41 \pm 0.11**	0.33 \pm 0.09	0.42 \pm 0.09**
Chlorthalidone dose, n (%)				
12.5 mg/d	1009 (51.7)	61 (40.4)**
25.0 mg/d	654 (33.5)	80 (53.0)**
Open-label antihypertensives, n (%)	77 (3.9)	5 (3.3)	227 (11.3)	14 (66.7)**

K indicates serum potassium mmol/L. Chlorthalidone dose and open-label antihypertensives as prescribed the last visit before the first annual visit; 10 participants who were hypokalemic at year 1 used 6.25 mg of chlorthalidone per day (n=1), an unknown dose of chlorthalidone per day (n=6), or no chlorthalidone (n=3).

* $P<0.05$; ** $P<0.001$ significantly different from nonhypokalemic, corresponding treatment group.

†To convert to mg/dL divide by 88.4.

‡To convert to mg/dL divide by 0.056.

§To convert to mg/dL divide by 0.026.

¶To convert to mg/dL divide by 0.011.

††To convert to mg/dL divide by 0.058.

attack, stroke, and diabetes; baseline potassium; year 1 serum creatinine, serum glucose, serum cholesterol, serum triglycerides, serum HDL-cholesterol, serum uric acid; and study drug dose, the hazard ratios HR of stroke and any cardiovascular event were significantly lower for normokalemic (K \geq 3.5 mmol/L) participants in the active treatment group compared with normokalemic participants in the placebo group (Table 4). But, participants in the active treatment group who were hypokalemic after 1 year experienced a similar risk of coronary heart disease, stroke, and any

cardiovascular event as those in the placebo group. No significant difference was found in the relative risk of all-cause mortality. A direct comparison within the active treatment group showed that those who did not experience hypokalemia after 1 year had a significantly lower risk of coronary heart disease, stroke, and any cardiovascular event compared with those who were hypokalemic (Table 4). The findings were virtually unchanged after stratification on chlorthalidone dose or when the analyses were restricted to the participants who had a compliance with study drugs

TABLE 3. Number and Rates (Unadjusted) of Cardiovascular Events, Coronary Heart Disease, Stroke, and All-Cause Mortality After 1 Year, According to Hypokalemia After 1 Year

		Active Treatment		Placebo	
		1-Year K \geq 3.5 (n=1951)	1-Year K<3.5 (n=151)	1-Year K \geq 3.5 (n=2003)	1-Year K<3.5 (n=21)
Any cardiovascular event	n	172	24	254	1
	rate*	27.9	50.0†	41.2†	14.8
Coronary heart disease	n	91	13	110	1
	rate*	14.2	25.8†	16.8†	14.8
Stroke	n	58	11	108	0
	rate*	9.1	22.3†	16.5‡	...
All-cause mortality	n	161	7	152	3
	rate*	24.5	13.5	22.5	44.3

K indicates serum potassium mmol/L; and n, number of events.

*Per 1000 person years.

†Significantly different ($P<0.05$) from active treatment, nonhypokalemic.

‡Significantly different ($P<0.001$) from active treatment, nonhypokalemic.

TABLE 4. Hazard Ratio of Cardiovascular Events, Coronary Heart Disease, Stroke, and All-Cause Mortality According to Hypokalemic Status at Year 1

Treatment Group	Any Cardiovascular Event, HR (95% CI)	Coronary Heart Disease, HR (95% CI)	Stroke, HR (95% CI)	All-Cause Mortality, HR (95% CI)
Placebo, K \geq 3.5 (n=2003)	1	1	1	1
Active treatment, K<3.5 (n=151)	1.18 (0.73–1.76)	1.46 (0.79–2.67)	1.43 (0.74–2.74)	0.73 (0.34–1.58)
Active treatment, K \geq 3.5 (n=1951)	0.61 (0.50–0.75)	0.75 (0.56–1.01)	0.51 (0.36–0.71)	1.06 (0.84–1.34)
Within the active treatment group				
Active treatment, K<3.5 (n=151)	1	1	1	1
Active treatment, K \geq 3.5 (n=1951)	0.49 (0.31–0.76)	0.45 (0.24–0.83)	0.28 (0.14–0.57)	1.33 (0.62–2.88)

*Data has been adjusted for age; gender; race; body mass index; alcohol use; smoking; history of heart attack, stroke, or diabetes; baseline potassium; year 1 serum creatinine, serum glucose, serum cholesterol, serum triglycerides, serum HDL-cholesterol, and serum uric acid; and study drug dose. K indicates serum potassium mmol/L; and HR, hazard ratio.

\geq 80% as determined by pill count (data not shown). There were too few participants in the placebo group with hypokalemia to analyze events.

Discussion

The 7.2% of participants in the active treatment group who experienced hypokalemia had a similar risk of CVD, CHD, and stroke as those randomized to placebo. Within the active treatment group, the risk of cardiovascular events was \approx 50% lower among those who had normal serum potassium levels compared with those who experienced hypokalemia. These associations remained unchanged and significant after adjustment for or stratification on a broad range of cardiovascular risk factors and study drug doses and were not explained by differences in blood pressure control. No conclusions can be drawn on the effects of hypokalemia on all-cause mortality because the number of deaths in the low-potassium group was small and the hazard ratios had wide confidence intervals.

According to the SHEP protocol, patients received potassium supplements after 2 determinations of serum potassium <3.5 mmol/L. Several factors can account for the finding that, despite this intervention, 7.2% of the patients in the active treatment group had hypokalemia at the first annual follow-up visit: potassium supplements may have been ineffective or insufficient, patients may have not been compliant with potassium supplement therapy, or in some participants, this may have been the first detection of hypokalemia.

Studies of the safety of commonly used medicines are subject to confounding by indication for the specific therapy.¹⁰ Although in SHEP the treatment was randomly assigned, the dose of chlorthalidone prescribed was dependent on a person’s blood pressure response. It is possible that participants who need higher doses of chlorthalidone to control hypertension have an increased cardiovascular risk. However, adjustment for or stratification on study drug dose did not modify the association of hypokalemia with the risk of cardiovascular events. Furthermore, hypokalemia was not associated with an increased cardiovascular risk profile at baseline or poorer blood pressure control during follow-up.

The 610 participants excluded from the analyses because of missing potassium measurements had a worse cardiovas-

cular risk profile and were more likely to be randomized to placebo compared with those included in the analyses. Consequently, the present analyses included relatively healthier participants. Confounding, if any, could only have diluted the association of hypokalemia with cardiovascular disease. Additionally, the data were analyzed according to the intention-to-treat principle by using the participant’s original treatment assignment. Again, this conservative analytical approach might have diluted the findings.

Hypokalemia induced by high-dose diuretics has been associated with ventricular arrhythmias and cardiac arrest.^{11–13} This effect might explain the lack of benefit of blood pressure lowering on the risk of coronary heart disease found in earlier studies.^{1,6} In SHEP, low-dose thiazide treatment without a potassium-sparing drug was not associated with a reduced risk of sudden cardiac death.³ However, an ancillary study of 186 SHEP participants showed that chlorthalidone did not increase the occurrence of ventricular premature complexes, although potassium levels were lower among participants randomized to diuretic treatment compared with those receiving placebo.¹⁴ Because of there were few sudden cardiac deaths among those with hypokalemia, we could not analyze this outcome.

Studies on diet support the view that potassium levels may affect the risk of stroke and cardiovascular events. The association between potassium and stroke has been investigated in several epidemiological^{15–17} and animal studies,^{18–22} showing that high intake of potassium is protective for the risk of stroke. High-potassium intake has been associated with modest reductions in blood pressure,^{23,24} especially among hypertensive persons,²⁵ but the effect is variable^{26,27} and does not fully explain the strong inverse association with stroke.¹⁶ We did not find a higher blood pressure in participants with hypokalemia, and their higher risk of stroke could not be explained by differences in blood pressure.

A mechanism that may explain the association between low potassium and cardiovascular events includes free radical formation from vascular endothelial cells.²⁸ Physiological increases in potassium concentration inhibit the rate of superoxide anion formation by cell lines derived from the endothelium. Physiological increases in potassium concentra-

tion also reduce the proliferation of cultured vascular smooth muscle cell proliferation²⁹ and inhibit platelet aggregation and arterial thrombosis.^{30,31} Raising extracellular potassium concentration by 1 mmol/L increments from 3 to 7 mmol/L caused a highly significant decrease of free radical formation, smooth muscle proliferation, and thrombus formation, with the greatest decrement between 3 and 4 mmol/L.^{28–31} The clinical relevance of these animal or in vitro studies, however, remains to be established.

In conclusion, 7.2% of the participants in SHEP who received active treatment were hypokalemic at the first annual visit and did not experience the beneficial effect of blood pressure lowering on the risk of cardiovascular events as seen among those with potassium ≤ 3.5 mmol/L. The current guidelines of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of high blood pressure recommend diuretics as the preferred agents in older persons with isolated systolic hypertension.³² The present findings support the importance of monitoring serum potassium during low-dose diuretic treatment to identify the few patients who may not benefit from diuretic treatment.

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