Diuretic-Based Treatment and Cardiovascular Events in Patients With Mild Renal Dysfunction Enrolled in the Systolic Hypertension in the Elderly Program

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**Background:** It is expected that the treatment of hypertension in patients with renal disease decreases the risk of cardiovascular events, but the evidence in these patients is lacking.

**Objective:** To assess the effect of diuretic-based treatment on cardiovascular events in patients with isolated systolic hypertension and renal dysfunction.

**Methods:** A total of 4336 persons aged 60 years and older with systolic blood pressures of 160 mm Hg and higher and diastolic blood pressures of less than 90 mm Hg were randomly assigned to receive either placebo or chlorthalidone (12.5-25.0 mg/d), with the addition of atenolol (25-50 mg/d) or reserpine (0.05-0.10 mg/d) if needed, and observed for 5 years. The risk of first-occurring cardiovascular events, including stroke, transient ischemic attack, myocardial infarction, heart failure, coronary artery bypass surgery, angioplasty, aneurysm, endarterectomy, sudden death, or rapid death, was stratified according to baseline serum creatinine levels (35.4-84.0, 84.1-101.6, 101.7-119.3, and 119.4-212.2 µmol/L [0.4-0.9, 1.0-1.1, 1.2-1.3, and 1.4-2.4 mg/dL]).

**Results:** Systolic blood pressure reduction was not affected by baseline serum creatinine levels. Active treatment did not affect the risk of serum creatinine levels becoming elevated during follow-up. The risk of hypokalemia with active treatment decreased significantly with increasing baseline serum creatinine levels. In the 4 baseline serum creatinine groups, the relative risk (95% confidence interval) of cardiovascular events developing with active treatment was 0.73 (0.54-0.97), 0.63 (0.49-0.82), 0.62 (0.44-0.87), and 0.59 (0.38-0.91). The results were similar for the outcomes of stroke or coronary artery events and in analyses stratified by sex or age.

**Conclusion:** Diuretic-based treatment of patients with isolated systolic hypertension prevents the development of cardiovascular events in older persons with mild renal dysfunction.

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Increased serum creatinine levels, a marker of renal dysfunction, are an independent predictor of cardiovascular events such as stroke and coronary artery events. Hypertension can accelerate renal dysfunction, and renal dysfunction can cause or worsen hypertension. Both increase the risk of cardiovascular complications. In about 1 of 3 patients with hypertension, renal dysfunction develops that is characterized by abnormal serum creatinine levels, and hypertension is a major cause of renal failure, second only to diabetes mellitus.

Several studies of patients with renal dysfunction have investigated the effects of antihypertensive treatment on surrogate outcomes such as serum creatinine levels, urine protein concentrations, and glomerular filtration rate. In such patients, however, the available evidence from studies that examine the effects of treatment on the incidence of major morbidity events is extremely limited. It is expected that lowering the blood pressure (BP) in hypertensive patients with renal dysfunction produces the same benefits on cardiovascular outcomes as in those with normal renal function. Although such evidence is lacking, 2 trials provided controversial results. In the Hypertension Detection and Follow-up Program, there was a 16% reduction in mortality with optimal BP control with mainly diuretic therapy among patients who had baseline serum creatinine levels of less than 150.3 µmol/L (<1.70 mg/dL) and only an 8% reduction among those who had higher creatinine levels. Although this difference in effect was not statistically significant, the findings of the Hypertension De-
PATIENTS AND METHODS

DESIGN AND PARTICIPANTS

The SHEP was a randomized, double-blind, placebo-controlled clinical trial jointly funded by the National Heart, Lung, and Blood Institute and the National Institute on Aging, Bethesda, Md. The methods of the SHEP have been described in detail elsewhere. The primary end point of the trial was the combined incidence of fatal and nonfatal stroke during a 5-year period. Secondary end points were the incidences of myocardial infarction, fatal coronary artery disease, and major cardiovascular morbidity and mortality. The events were adjudicated independently by members of an end-point adjudication committee who used predetermined standardized adjudication criteria and who were unaware of the treatment and BP status. Beginning in 1985, 447,921 persons aged 60 years and older were screened from the community in 16 clinical centers, and among them, 4736 participants with isolated systolic hypertension were recruited. The medical history and the results of an electrocardiogram and a physical examination were assessed at baseline. The seated BP was measured by trained technicians according to a standardized protocol. The BP inclusion criteria were a systolic BP of 160 to 219 mm Hg and a diastolic BP of less than 90 mm Hg assessed as the average of 4 measurements (2 measurements were obtained at each of the 2 baseline visits).

Exclusion criteria were a systolic BP of 220 mm Hg or higher, a recent myocardial infarction or stroke, or the presence of a major illness such as cancer, alcoholic liver disease, renal failure, insulin-treated diabetes mellitus, and depression. Participants who were receiving an antihypertensive treatment and Follow-up Program may raise questions about the efficacy of diuretic-based antihypertensive treatment in patients with renal dysfunction. In another trial of patients with renal failure, the use of angiotensin-converting enzyme inhibitor benazepril improved renal function and BP, but was associated with a significant increase in the risk of all-cause mortality. To our knowledge, no randomized study has examined whether diuretic-based treatment of isolated systolic hypertension in patients with renal dysfunction decreases the risk of major cardiovascular events. The aim of this secondary analysis is to determine whether antihypertensive treatment as used in the Systolic Hypertension in the Elderly Program (SHEP) is as effective in preventing cardiovascular events among persons with increased baseline serum creatinine levels as it is among those with normal or low serum creatinine levels.

RESULTS

BASELINE CHARACTERISTICS

The baseline characteristics of the participants stratified according to treatment and serum creatinine levels are shown in Table 1. The participants with higher creatinine levels were older, more likely to be men, of the black race, and more likely to have a history of heart attack. Among the baseline serum creatinine strata, there were no significant differences in baseline BP, body mass index, or percentage of participants who were using antihypertensive medications at the initial contact visit or who had a history of stroke or diabetes mellitus. In all creatinine subgroups, the baseline characteristics of the patients randomly allocated to receive placebo were similar to those assigned to active treatment.

BP CONTROL

The reduction of systolic BPs achieved with active treatment was similar across serum creatinine levels (Figure 1). In a series of general linear models that tested the effect of baseline serum creatinine levels and treatment on changes of systolic BPs during follow-up, only the effect of treatment was statistically significant (P <.001). Although the baseline mean diastolic BP was similar in all creatinine subgroups, a slightly greater diastolic BP reduction with active treatment was achieved in participants who had lower creatinine levels than in those who had higher creatinine levels (Figure 1). For example, on average, the diastolic BPs during follow-up of the active treatment group with baseline serum creatinine levels of 35.4 to 84.0 µmol/L (0.40-0.95 mg/dL) were 2 mm Hg lower than the diastolic BPs of the active treatment group with baseline serum creatinine levels of...
the administration of chlorthalidone, 12.5 mg/d. The dosage was doubled if the goal BP was not achieved. If the goal BP was not reached at the first step, atenolol, 25 mg/d, was added (second step). If atenolol therapy was not tolerated, reserpine, 0.05 mg/d, could be substituted. The dosage of the second-step drugs could be doubled if the goal BP was not reached. No active antihypertensive agent was given to the participants randomly allocated to receive placebo. An open-label potassium supplement was given to the participants in both treatment arms who had serum potassium concentrations below 3.5 mmol/L.

**FOLLOW-UP**

All participants were observed monthly until the BP goal was reached and quarterly thereafter until the end of follow-up. Blood specimens were drawn routinely at baseline and at each annual clinic follow-up visit. The blood specimens were centrifuged and sent by overnight mail to a central laboratory for analysis (MetPath, Teterboro, NJ). Serum creatinine, uric acid, urea nitrogen, sodium, and potassium levels were part of the blood test battery.

**DATA ANALYSIS**

The patients allocated to active treatment were compared with those receiving placebo. Their characteristics were compared by means of the χ² test and analysis of variance as appropriate. For analysis, the participants were stratified according to tertiles and values above normal of the baseline serum creatinine as follows: 35.4 to 84.0 µmol/L (0.4-0.9 mg/dL) (lowest tertile, n=1595), 84.1 to 101.6 µmol/L (1.0-1.1 mg/dL) (median tertile, n=1536), 101.7 to 119.3 µmol/L (1.2-1.3 mg/dL) (upper tertile less values above normal, n=812), and 119.4 to 212.2 µmol/L (1.4-2.4 mg/dL) (values above normal in the general population corresponding to the upper decile, n=393). These cutoff points have been chosen to obtain a sufficient number of participants and events in each stratum and a sufficient number of strata to allow analyses of trend. No participants had baseline serum creatinine levels of less than 35.4 µmol/L or greater than 212.2 µmol/L (<0.40 or >2.40 mg/dL). In separate analyses, the participants were stratified according to 4 similar levels (3 tertiles and the lower decile) of creatinine clearances. For men, the creatinine clearance (milliliters per minute) was calculated with the following formula: (140 – age) × weight in kilograms)/(72 × serum creatinine level in milligrams per deciliter).12 For women, the value was reduced to 89% of that estimated with this equation.

The Kaplan-Meier method was used to plot survival free of cardiovascular events, and the log-rank test was used to compare treatments.13 Cox proportional hazards regression models were used to estimate the hazard ratio and 95% confidence intervals for the effect of treatment on the outcomes of interest.14 The assumption of proportionality of hazards was assessed with log−log plots and by testing the interaction of exposure with time.15 To test the trend of drug effect with increasing baseline serum creatinine levels, the interaction of treatment with baseline serum creatinine levels as a continuous variable was assessed in separate proportional hazards models after adjusting for the main effect of treatment, baseline serum creatinine levels, age, sex, ethnicity, systolic and diastolic BPs, body mass index, and history of stroke, heart attack, and diabetes mellitus. General linear models for repeated measures were used to analyze the variation of BP and serum creatinine levels according to treatment.

### Table 1. Baseline Characteristics of the Participants According to Treatment and Baseline Serum Creatinine Levels*

<table>
<thead>
<tr>
<th>Baseline Serum Creatinine, µmol/L†</th>
<th>Placebo (n = 790)</th>
<th>Active Treatment (n = 805)</th>
<th>Placebo (n = 778)</th>
<th>Active Treatment (n = 858)</th>
<th>Placebo (n = 411)</th>
<th>Active Treatment (n = 401)</th>
<th>Placebo (n = 177)</th>
<th>Active Treatment (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.8 ± 6.7</td>
<td>71.0 ± 6.5</td>
<td>71.4 ± 6.5</td>
<td>71.4 ± 6.7</td>
<td>72.3 ± 6.5</td>
<td>72.2 ± 6.7</td>
<td>74.1 ± 7.0</td>
<td>73.9 ± 6.7</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>16.2</td>
<td>16.9</td>
<td>46.9</td>
<td>48.0</td>
<td>70.3</td>
<td>66.3</td>
<td>80.2</td>
<td>82.4</td>
</tr>
<tr>
<td>Ethnic origin, %</td>
<td>White</td>
<td>81.8</td>
<td>82.2</td>
<td>78.3</td>
<td>78.4</td>
<td>77.6</td>
<td>74.8</td>
<td>77.4</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>9.6</td>
<td>9.1</td>
<td>15.2</td>
<td>14.0</td>
<td>16.1</td>
<td>20.9</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>5.7</td>
<td>6.6</td>
<td>3.6</td>
<td>3.8</td>
<td>4.1</td>
<td>2.0</td>
<td>2.8</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>27.2 ± 5.3</td>
<td>27.3 ± 5.4</td>
<td>27.9 ± 5.0</td>
<td>27.9 ± 4.7</td>
<td>27.4 ± 4.7</td>
<td>27.7 ± 4.5</td>
<td>27.0 ± 4.1</td>
<td>27.4 ± 4.7</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>170 ± 9</td>
<td>171 ± 9</td>
<td>170 ± 10</td>
<td>170 ± 9</td>
<td>170 ± 8</td>
<td>171 ± 10</td>
<td>172 ± 10</td>
<td>172 ± 1</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76 ± 9</td>
<td>77 ± 10</td>
<td>77 ± 9</td>
<td>77 ± 9</td>
<td>77 ± 10</td>
<td>77 ± 11</td>
<td>77 ± 10</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>Antihypertensive medication at initial contact, %</td>
<td>31.4</td>
<td>35.4</td>
<td>35.5</td>
<td>31.8</td>
<td>35.0</td>
<td>31.9</td>
<td>38.4</td>
<td>33.8</td>
</tr>
<tr>
<td>History of myocardial infarction, %</td>
<td>2.5</td>
<td>1.7</td>
<td>1.3</td>
<td>1.1</td>
<td>6.3</td>
<td>5.0</td>
<td>5.1</td>
<td>5.6</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>1.3</td>
<td>2.2</td>
<td>2.1</td>
<td>2.4</td>
<td>1.5</td>
<td>2.2</td>
<td>3.4</td>
<td>4.2</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>9.1</td>
<td>9.0</td>
<td>11.7</td>
<td>9.5</td>
<td>9.7</td>
<td>12.0</td>
<td>12.5</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Values are mean ± SD unless otherwise indicated.
†To convert serum creatinine values from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 88.4.

119.4 to 212.2 µmol/L (1.35-2.40 mg/dL). In a series of general linear models that tested the effect of baseline serum creatinine levels and treatment on changes of diastolic BPs during follow-up, the effects of serum creatinine levels and treatment were statistically significant (P=.03 and P<.001, respectively).

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The active treatment group when compared with the placebo group had a small but statistically significant (P<.001) increase in mean serum creatinine levels following randomization, but all the differences had occurred by 1 year and were stable thereafter (Figure 2). A similar pattern was observed when the data were stratified according to the 4 baseline serum creatinine groups and for the outcome of serum urea nitrogen and uric acid concentrations (data not shown). There were no significant differences between the placebo and active treatment groups in the number of patients who had elevated serum creatinine values during follow-up. During follow-up, 9 patients receiving placebo and 5 patients receiving active treatment had 1 or more serum creatinine values of greater than 265.2 µmol/L (>3.0 mg/dL), and 44 patients in each group had 1 or more serum creatinine values of greater than 176.8 µmol/L (>2.0 mg/dL).

It has been previously described in SHEP that the patients receiving active treatment had significantly lower serum potassium levels during follow-up than those receiving placebo and that the patients receiving active treatment were significantly more likely to have hypokalemia any time during follow-up (serum potassium level <3.2 mmol/L). In the present stratified analyses, the proportion of actively treated participants having hypokalemia decreased progressively with increasing baseline serum creatinine levels (Figure 3) (P<.001 for trend). The proportion of patients having hypokalemia in the placebo group did not vary significantly according to baseline serum creatinine levels. Consequently, the difference in the risk of hypokalemia between the active treatment group and the placebo group decreased with increasing baseline creatinine levels.

**CARDIOVASCULAR EVENTS**

As expected, the proportion of participants having either any cardiovascular event, stroke, coronary events, or death increased with increasing creatinine level (P<.001, P=.002, P<.001, and P<.001, respectively, with the Mantel-Haenszel test for linear association) (Table 2). In all baseline serum creatinine subgroups, the participants receiving active treatment were significantly less likely to have cardiovascular events than those receiving placebo (Figure 4). The beneficial effect of active treatment on cardiovascular events was significant in each baseline serum creatinine stratum and tended to increase progressively with increasing baseline serum creatinine level. The P value for trend, however, did not reach statistical significance after adjustment for the main ef-
Table 2. Hazard Ratio (HR) of Cardiovascular Events in Group With Active Treatment Compared
With Placebo Group According to Baseline Serum Creatinine Values*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Group</th>
<th>Baseline Serum Creatinine, µmol/L*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n = 1595)</td>
<td>35.4-84.0 (n = 1536)</td>
</tr>
<tr>
<td>Any cardiovascular event</td>
<td>0.73 (0.54-0.97)</td>
<td>0.63 (0.49-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.65 (0.41-1.03)</td>
<td>0.50 (0.32-0.80)</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>0.80 (0.51-1.27)</td>
<td>0.73 (0.50-1.05)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.92 (0.64-1.33)</td>
<td>0.77 (0.55-1.09)</td>
</tr>
</tbody>
</table>

*To convert serum creatinine values from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 88.4. Data are given as HR (95% confidence interval) and number (percentage) of events.

These analyses show that diuretic-based treatment of isolated systolic hypertension significantly decreases the risk of cardiovascular events in older persons with mild renal dysfunction. During follow-up, the average systolic BP in the placebo and the active treatment groups did not vary according to baseline serum creatinine levels, and diastolic BPs in the treatment group tended to be slightly higher in participants with higher baseline serum creatinine levels than in those with lower serum creatinine levels.

Active treatment did not appear to adversely affect renal function. Although the serum creatinine levels of actively treated participants increased slightly following randomization, during follow-up, average serum creatinine levels remained stable, and the small number of participants who had marked creatinine elevations during follow-up was similar in the active treatment and placebo groups. If the diuretic-based treatment had had an adverse effect on renal function, a progressive increase in average serum creatinine levels and more participants having elevated creatinine levels over time would be expected. The observed initial increase in serum creatinine levels was most likely related to the reduction of intravascular volume and consequent modest hemococoncentration caused by the diuretic therapy. This interpretation is supported by the corresponding initial increase in serum urea nitrogen and uric acid concentrations in the actively treated group.

Hypokalemia might partially offset the benefits of diuretic antihypertensive treatment. It has been suggested that hypokalemia may be responsible for the adverse effect of treatment, baseline serum creatinine level, age, sex, race, baseline systolic and diastolic BPs, body mass index, and history of stroke, myocardial infarction, and diabetes mellitus (Table 2) (P=.96 for trend). In separate analyses that used 4 levels of estimated baseline creatinine clearance instead of 4 levels of serum creatinine to stratify the participants, the results were unchanged. Similar results were found when the incidences of stroke and coronary artery events were analyzed according to treatment and serum creatinine levels (Table 2) and when the data of men, women, participants aged 60 to 69 years, and those aged 70 years and older were analyzed separately (data not shown). The findings remained unchanged when the participants were stratified according to quartiles of baseline serum creatinine levels or according to levels of serum creatinine of less than 115 and 115-212.2 µmol/L, and higher, instead of the 4 groups presented in Table 2. The reduction in all-cause mortality with active treatment was significant only in the group with baseline serum creatinine levels of 101.7 to 119.3 µmol/L (1.2-1.3 mg/dL). Three persons died of renal disease—1 in the placebo group among the patients with creatinine levels of 101.7 to 119.3 µmol/L and 2 in the treated group in the highest creatinine stratum.
verse outcomes associated with the use of high doses of diuretic agents. The present analyses show that increasing baseline serum creatinine levels were associated with a lower risk of hypokalemia with diuretic therapy. The lower propensity for hypokalemia to develop among patients with renal dysfunction could partially explain the enhanced efficacy of diuretic treatment in those with increased baseline serum creatinine levels.

This study has limitations. First, because the serum creatinine level might not be an accurate indicator of renal function in older persons who have a reduced muscle mass, some participants with reduced muscle mass and mild renal dysfunction might have been grouped with participants with normal renal function. Such misclassification is likely to be conservative because it would underestimate the proportion of participants with renal dysfunction. Second, only a small proportion of screened persons have been ultimately randomly allocated. The SHEP protocol excluded participants with major morbidity and severe renal failure. Therefore, in this cohort, the highest value of the baseline serum creatinine was limited to 212.2 µmol/L (2.40 mg/dL). The results of this study cannot be generalized to patients with severe renal failure, congestive heart failure, unstable angina, or with recent stroke or myocardial infarction and to those who have contraindications to the use of diuretic agents or β-blockers. Finally, the post hoc design of the present analyses does not allow a definitive cause-and-effect statement.

Few randomized studies have examined the effects of antihypertensive agents on morbidity or mortality events in patients with renal dysfunction. In the Hypertension Detection and Follow-up Program trial, there was no significant difference in mortality reduction with optimal BP control with mainly diuretic therapy among patients with baseline serum creatinine levels of less than 150.3 µmol/L (<1.70 mg/dL) compared with those with higher creatinine levels. In a trial of patients with insulin-dependent diabetic nephropathy, the administration of captopril significantly decreased the combined end point of mortality or need of dialysis or renal transplantation. In another trial of patients with renal insufficiency caused by various disorders, the administration of benazepril prevented the progression of renal failure as assessed by serum creatinine levels and decreased BPs but was associated with a significant excess mortality. Compared with conventional treatment, in a 7-year extended follow-up of a trial of patients with chronic nephropathy, enalapril maleate treatment was associated with a significantly lower incidence in the combined end point of death or renal replacement therapy. Most of these studies have shown beneficial effects of antihypertensive treatment on mortality or end-stage renal disease. They provide little information, however, on the efficacy of treatment in preventing cardiovascular events in patients with renal dysfunction.

The present findings have important clinical relevance. Serum creatinine levels tend to increase with increasing age in healthy persons, and even small increases in the serum creatinine level are associated with a significant increase in the risk of cardiovascular events. There is emerging evidence that diuretic-based treatment of isolated systolic hypertension is effective in preventing major cardiovascular events in subgroups of high-risk older patients such as those with type 2 diabetes mellitus or renal dysfunction, as described herein. It is not known yet whether modern antihypertensive agents, such as angiotensin-converting enzyme inhibitors that are more effective than diuretic agents in improving secondary measures of renal function, are also more effective in preventing major morbid events in patients with mild renal dysfunction. The present findings are in agreement with the recommendations of the 1995 update of the Working Group Reports on Chronic Renal Failure and Renovascular Hypertension and strongly support the use of diuretics for the treatment of hypertension in patients with mild renal dysfunction.

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