Long-Term Fatal Outcomes in Subjects With Stroke or Transient Ischemic Attack
Fourteen-Year Follow-Up of the Systolic Hypertension in the Elderly Program

Alpesh B. Patel, MD; John B. Kostis, MD; Alan C. Wilson, PhD; Michael L. Shea, MD; Sara L. Pressel, MS; Barry R. Davis, MD, PhD

Background and Purpose—Epidemiologic studies have demonstrated that hypertension increases the risk of stroke, and clinical trials have shown that antihypertensive therapy reduces this risk. Incident stroke was significantly decreased by treatment in the Systolic Hypertension in Elderly Program (SHEP) Trial, but the reduction in fatal events was not statistically significant.

Methods—Vital status was determined for 4736 SHEP participants by matching to the National Death Index. We assessed the impact of antihypertensive treatment, stroke, and transient ischemic attacks (TIAs) during SHEP on long-term (mean, 14.3 years) mortality.

Results—Treatment with a chlorthalidone-based antihypertensive regimen significantly reduced the risk of cardiovascular death (adjusted relative risk [RR] = 0.86; 95% CI, 0.76 to 0.98; \( P \leq 0.026 \)) in the SHEP cohort without a significant \( (P = 0.39) \) interaction with stroke status. Patients who sustained a stroke during SHEP had significantly higher all-cause mortality at the 14.3-year mean follow-up: 65.6% compared with 40.6% among those free of stroke or TIA (adjusted RR = 1.97; 95% CI, 1.67 to 2.33). They also were at higher risk for cardiovascular death (RR = 2.00; 95% CI, 1.58 to 2.53) and stroke death (RR = 2.94; 95% CI, 1.87 to 4.64). TIA was not significantly associated with increased total mortality (RR = 1.13; 95% CI, 0.88 to 1.44), cardiovascular death (RR = 1.30; 95% CI, 0.94 to 1.81), or stroke death (RR = 1.76; 95% CI, 0.95 to 3.26).

Conclusions—In SHEP, chlorthalidone-based treatment reduced the risk of cardiovascular death after 14 years of extended follow-up. Nearly two thirds of elderly persons with isolated systolic hypertension who experienced stroke died within 14 years. (Stroke. 2008;39:000-000.)

Key Words: antihypertensive agents ■ hypertension ■ stroke ■ transient ischemic attack

Stroke remains a common vascular event with high mortality and morbidity.1–3 Epidemiologic studies have demonstrated that hypertension increases the risk of stroke, and clinical trials have shown that antihypertensive therapy reduces such risk.4–9 In the Systolic Hypertension in the Elderly Program (SHEP), chlorthalidone-based antihypertensive therapy decreased the risk of stroke among older patients with isolated systolic hypertension.10–12

Of the 262 SHEP participants with stroke, 24 (9.2%) died of stroke, 4.5% were admitted to skilled nursing facilities or intermediate-care nursing homes, <10% were confined to bed (on average, for <1 day), and only 3.1% remained confined to bed at the last trial report. Of the 222 SHEP participants with stroke who had brain images adequate for evaluation, 122 (55%) had no visible lesions related to the stroke.12 These findings may imply that the majority of nonfatal strokes in SHEP were not severe and highlight the need for long-term follow-up. The present article reports on the extended follow-up (average, 14.3 years) of SHEP participants with and without stroke or transient ischemic attack (TIA) during the clinical trial and examines the long-term impact of 4.5 years of an antihypertensive chlorthalidone-based regimen.

Subjects and Methods

SHEP was a double-blind, randomized, placebo-controlled trial of treatment for isolated systolic hypertension in 4736 men and women aged 60 and above. Isolated systolic hypertension was defined as a diastolic blood pressure <90 mm Hg and a systolic blood pressure in the range 160 to 240 mm Hg.10 Patients were randomized to receive chlorthalidone-based, stepped-care therapy beginning with chlorthalidone (12.5 mg/d) or matching placebo doubled to chlorthalidone (25 mg/d) or matching placebo, if needed, to achieve blood pressure...
control. A second drug was atenolol (25 mg/d to 50 mg/d) or low-dose reserpine in patients with a contraindication to β-blockers. Blood pressure control was defined as a systolic blood pressure <160 mm Hg and a decrease by 20 mm Hg. Patients were excluded if they had a history of major cardiovascular disease. Details of the protocol, baseline characteristics, and results of SHEP (49% reduction in heart failure, 36% reduction in stroke, and 27% reduction in coronary heart disease) have been reported elsewhere.10,11

Matching
To extend the follow-up of vital status and cause of death, we used the National Death Index Plus service. Information for the 2281 participants who were alive at the end of SHEP were submitted by the Coordinating Center to the National Center of Health Statistics to be matched against the National Death Index for the years 1991 through 2000 according to a probabilistic algorithm. Matching variables included social security number, birth date, the initial letters of the last and first names, and middle initial. Likely matches were evaluated clerically. The median length of the extended follow-up after the end of the double-blind phase of SHEP was 119 months. This corresponds to a total of 172 months (14.3 years) from the beginning of SHEP. The only data available from the follow-up extension were date of death and cause of death. Deaths coded with International Classification of Diseases–10 diagnosis codes were converted to the corresponding International Classification of Diseases–9 codes according to the World Health Organization crosswalk. The institutional review boards of Robert Wood Johnson Medical School and the University of Texas School of Public Health approved the follow-up study.

Strokes (Fatal and Nonfatal) and TIAs
During the SHEP clinical trial, participants who developed acute neurologic deficits were hospitalized and reviewed in the acute phase if possible by a consulting neurologist who evaluated the event by

Table 1. Occurrence of Cerebrovascular Events During SHEP

<table>
<thead>
<tr>
<th>Cerebrovascular Event</th>
<th>Active Treatment Group, n=2365</th>
<th>Placebo Group, n=2371</th>
<th>Total, N=4736</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal stroke</td>
<td>96</td>
<td>149</td>
<td>245</td>
</tr>
<tr>
<td>Fatal stroke*</td>
<td>10</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Total stroke</td>
<td>106</td>
<td>163</td>
<td>269</td>
</tr>
<tr>
<td>TIA</td>
<td>62</td>
<td>82</td>
<td>144</td>
</tr>
<tr>
<td>TIA complicated by stroke</td>
<td>13</td>
<td>9</td>
<td>22</td>
</tr>
</tbody>
</table>

*Seven participants had both a nonfatal and a fatal stroke: 3 in the active arm and 4 in the placebo arm.

Figure 1. Kaplan–Meier survival curves for cardiovascular disease mortality among SHEP participants by treatment group overall, during the double-blind trial (A), and during the follow-up extension (B). For active treatment (solid line) compared with assignment to placebo, the overall log-rank P was 0.016 (main plot). The vertical axis represents the proportion remaining of those alive at the start of SHEP (main plot and A) or those alive at the end of the double-blind trial (B).
clinical and imaging methods according to the appropriate algorithms defined by the SHEP Endpoints Committee, who were responsible for the final diagnosis of stroke. Stroke was defined as abrupt onset of a new neurologic deficit lasting \( \leq 24 \) hours, with specific localizing finding confirmed by unequivocal physical or laboratory examination and without evidence of an underlying nonvascular cause. A participant had the diagnosis of TIA if he or she had a reliably observed transient (\( \leq 24 \) hours) neurologic deficit of abrupt onset, without evidence of an underlying nonvascular cause.4

Statistical Analysis
The data were analyzed with SAS software, version 9.1 (SAS Inc, Cary, NC). Survival analysis was performed with the Kaplan–Meier method (LIFETEST procedure). Adjusted hazard ratios were computed by Cox proportional-hazards regression analysis (PHREG procedure), with stroke and TIA during SHEP as time-dependent variables. The following factors were included in the multivariate models: demographics (age, race, and sex), smoking, diabetes, baseline systolic and diastolic blood pressures, years of education, body mass index, history of myocardial infarction, and baseline alcohol consumption, as well as treatment assignment.

Results
The SHEP clinical trial began in March 1985 and ended in February 1991 with an average follow-up of 4.5 years. The study included 4736 participants (43.2% male and 13.9% black). At randomization, the average age was 71.6 years with 42% of the participants in their 60s, 45% in their 70s, and 14% in their 80s or 90s. By history, 1.4% of the participants had a previous stroke, 4.9% had a prior myocardial infarction, and 10% had diabetes mellitus. Patients with atrial fibrillation were excluded at randomization. Average baseline blood pressure was 170/77 mm Hg with 57% of the participants having a systolic blood pressure between 160 and 169 mm Hg, 27% with a systolic blood pressure of 170 to 179 mm Hg, and 15% with a systolic blood pressure of \( \geq 180 \) mm Hg. At the end of the trial, 46% of participants randomized to active treatment were receiving the step 1 drug only and 23% were receiving step 1 and step 2 drugs; 89% to 90% of participants in the active treatment group were receiving some active drug at all 5 annual visits. The percentage of participants in the placebo group taking active antihypertensive drug(s) increased progressively from 13% at year 1 to 44% at year 5. During the trial, the decrease in blood pressure from pretreatment baseline averaged 26/9 mm Hg for participants in the active treatment group and 15/4 mm Hg for those in the placebo group; the amount of decrease changed little during the trial. At the 5-year visit, 65% of participants in the treatment group and 40% in the placebo group were at goal systolic blood pressure.

Double-Blind Trial Follow-Up
During the double-blind period of SHEP, 159 participants in the placebo group had strokes and 82 participants developed TIAS. In the active treatment group, 103 participants had a stroke and 62 developed a TIA; 122 participants had a TIA.
Table 3. Mortality Rates by Treatment Assignment and Nonfatal Stroke Status in the SHEP Trial and the SHEP Extension

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment Group, n=2365</th>
<th>Placebo Group, n=2371</th>
<th>Stroke vs No Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonfatal Stroke, n=103*</td>
<td>No Stroke, n=2262</td>
<td>Nonfatal Stroke, n=159</td>
</tr>
<tr>
<td>All-cause death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>61</td>
<td>909</td>
<td>111</td>
</tr>
<tr>
<td>Percent</td>
<td>59.2</td>
<td>40.2</td>
<td>68.8</td>
</tr>
<tr>
<td>Cardiovascular disease death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>33</td>
<td>418</td>
<td>61</td>
</tr>
<tr>
<td>Percent</td>
<td>32.0</td>
<td>18.5</td>
<td>38.4</td>
</tr>
<tr>
<td>Stroke death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>12</td>
<td>76</td>
<td>27</td>
</tr>
<tr>
<td>Percent</td>
<td>11.7</td>
<td>3.4</td>
<td>17.0</td>
</tr>
</tbody>
</table>

*Seven participants had both a nonfatal and a fatal stroke: 3 in the active arm and 4 in the placebo arm.
†Values are adjusted hazard ratios (95% CI) according to Cox’s model. Explanatory factors in addition to stroke and TIA as time-dependent variables were body mass index, baseline systolic blood pressure, baseline diastolic blood pressure, sex, race, smoking status, education, alcohol use, diabetes, and prior myocardial infarction.

without stroke (Table 1). Active therapy significantly reduced the risk of cardiovascular death among participants (adjusted relative risk [RR]=0.86; 95% CI, 0.76 to 0.98, *P*=0.026). Treatment with a chlorthalidone-based regimen was associated with lower all-cause death and stroke death, but the decreases were not statistically significant (adjusted RR=0.93; 95% CI, 0.85 to 1.02, *P*=0.13 and adjusted RR=0.91; 95% CI, 0.68 to 1.21; *P*=0.51, respectively).

**Mortality During Follow-Up Extension**

As shown in Figure 1, the number of deaths after 14 years was lower in the active treatment group compared with the control group (970 vs 1020, *P*=0.16), and the number of cardiovascular deaths was significantly lower (451 vs 517, *P*=0.016). Among all participants, as shown in Table 2, antihypertensive drug therapy based on chlorthalidone during SHEP was associated at 14.3 years of follow-up with a significantly decreased risk of cardiovascular death (adjusted hazard ratio=0.85; 95% CI, 0.75 to 0.97) as well as a lower risk of stroke death (which did not reach statistical significance). There were more deaths from noncardiovascular causes in the active treatment group than in the control group during the follow-up extension, but the difference was not significant.

Stroke during SHEP was associated with higher all-cause mortality during the extended follow-up and with a higher probability of cardiovascular death or death attributed to stroke. During the extended follow-up, 172 (65.6%) of the 262 participants who developed stroke during SHEP died compared with 1818 (40.6%) of the 4474 who did not develop stroke in SHEP (*P*<0.0001; Table 3, Figure 2). The majority of deaths among those who developed stroke during SHEP were attributed to cardiovascular causes (94 of 172, 54.7%) including a significant proportion attributed to stroke (39 of 172 deaths, 22.7%). The Cox adjusted hazard ratios for total mortality, cardiovascular mortality, and stroke mortality among participants who had stroke compared with those who did not are also shown in Table 3. For participants who developed stroke, the adjusted RRs for all-cause, cardiovascular, and stroke death were 1.97 (95% CI, 1.67 to 2.33), 2.00 (95% CI, 1.58 to 2.53), and 2.94 (95% CI, 1.87 to 4.64), respectively.

As shown in Table 4, TIA during SHEP was not significantly associated with an increased chance of cardiovascular or all-cause death during the extended follow-up. Of the 122 participants who developed TIA without stroke, 58 (47.5%) died compared with 40.4% (1760 of 4474, *P*=0.12) who did not develop TIA (or stroke) during the clinical trial. Overall, TIA during SHEP was associated with a trend toward higher mortality attributed to stroke during the extended follow-up (RR=1.76; 95% CI, 0.95 to 3.26, *P*=0.07) after adjustment for stroke, comorbidities, and other variables as detailed in Methods.

In the multivariate Cox regression model, other significant predictors of all-cause death among the 245 SHEP participants who survived stroke included age (RR=1.07; 95% CI, 1.07 to 1.08, *P*<0.0001), white race (RR=0.80; 95% CI, 0.74 to 0.86, *P*<0.0001), smoking (adjusted RR=1.74; 95% CI, 1.53 to 1.98, *P*<0.0001), and diabetes (RR=1.34; 95% CI, 0.51 to 0.66, *P*<0.0001), as well as education (RR=0.98; 95% CI, 0.97 to 0.99, *P*=0.009) and systolic blood pressure (RR per mm Hg increase =1.01; 95% CI, 1.01 to 1.01,
control of all modifiable risk factors may decrease long-term mortality in stroke survivors.\textsuperscript{14} These considerations imply that intensive therapy based on chlorthalidone was lower than that in the control group. The association of active treatment with a decreased risk of cardiovascular death among all participants persisted after adjustment.

The long-term results described herein are important because the SHEP trial will not be reproduced and because it would be unethical to assign subjects to placebo treatment. After 14 years of follow-up, the number of all-cause and cardiovascular deaths among the group assigned to antihypertensive drug therapy based on chlorthalidone was lower than that in the control group. The association of active treatment with a decreased risk of cardiovascular death among all participants persisted after adjustment.

Analysis of 14.3-year mortality among subjects who developed stroke during the double-blind phase of SHEP confirms the poor prognosis of patients who have a stroke. This article indicates that the strokes that occurred in SHEP were not trivial. In the majority of subjects, death was due to cardiovascular rather than cerebrovascular events. These data are similar to those reported by Wijk and associates.\textsuperscript{13} The long follow-up of this study imply a better prognosis for TIA than generally assumed. However, questions have been raised on the reliability of ascertainment of the TIA end point in clinical trials. It is possible that symptoms due to noncerebrovascular causes are attributed to TIA in some instances.\textsuperscript{15,16}

Limitations of this study are its retrospective nature and the lack of information on nonfatal end points, pharmacological therapy, and blood pressure after the end of the double-blind phase of the SHEP and the use of an administrative database to adjudicate vital status and cause of death. It is unlikely that these factors would have exerted sufficient bias to invalidate the conclusions of the study. The reliability of the National Death Index and the matching algorithm has been verified in previous studies.\textsuperscript{17,18} In addition, this study did not allow evaluation of the outcomes of elderly patients with different stroke subtypes and the impact of blood pressure control on each of these. Furthermore, the effect of TIA on long-term prognosis should be validated in younger populations.

In summary, this study emphasizes the importance of preventing stroke with antihypertensive drug treatment to prevent cardiovascular accidents.

Sources of Funding

This study was supported in part by contracts with the National Heart, Lung, and Blood Institute and the National Institute on Aging.

Disclosures

None.

References

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Stroke. published online February 28, 2008; Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2008/02/28/STROKEAHA.107.500777.citation

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