Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons With Isolated Systolic Hypertension

Final Results of the Systolic Hypertension in the Elderly Program (SHEP)

SHEP Cooperative Research Group

Objective.—To assess the ability of antihypertensive drug treatment to reduce the risk of nonfatal and fatal (total) stroke in isolated systolic hypertension.

Design.—Multicenter, randomized, double-blind, placebo-controlled.

Setting.—Community-based ambulatory population in tertiary care centers.

Participants.—4736 persons (1.06%) from 447,921 screenees aged 60 years and above were randomized (2365 to active treatment, 2371 to placebo). Systolic blood pressure ranged from 160 to 219 mm Hg and diastolic blood pressure was less than 90 mm Hg. Of the participants, 3161 were not receiving antihypertensive medication at initial contact, and 1575 were. The average systolic blood pressure was 170 mm Hg; average diastolic blood pressure, 77 mm Hg. The mean age was 72 years, 57% were women, and 14% were black.

Interventions.—Participants were stratified by clinical center and by antihypertensive medication status at initial contact. For step 1 of the trial, dose 1 was chlorthalidone, 12.5 mg/d, or matching placebo; dose 2 was 25 mg/d. For step 2, dose 1 was atenolol, 25 mg/d, or matching placebo; dose 2 was 50 mg/d.

Main Outcome Measures.—Primary.—Nonfatal and fatal (total) stroke. Secondary.—Cardiovascular and coronary morbidity and mortality, all-cause mortality, and quality of life measures.

Results.—Average follow-up was 4.5 years. The 5-year average systolic blood pressure was 155 mm Hg for the placebo group and 143 mm Hg for the active treatment group, and the 5-year average diastolic blood pressure was 72 and 66 mm Hg, respectively. The 5-year incidence of total stroke was 5.2 per 100 participants for active treatment and 8.2 per 100 for placebo. The relative risk by proportional hazards regression analysis was 0.64 (P = .0003). For the secondary end point of clinical nonfatal myocardial infarction plus coronary death, the relative risk was 0.70. Major cardiovascular events were reduced (relative risk, 0.68). For deaths from all causes, the relative risk was 0.87.

Conclusion.—In persons aged 60 years and over with isolated systolic hypertension, antihypertensive stepped-care drug treatment with low-dose chlorthalidone as step 1 medication reduced the incidence of total stroke by 36%, with 5-year absolute benefit of 30 events per 1000 participants. Major cardiovascular events were reduced, with 5-year absolute benefit of 55 events per 1000.

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This article presents the final results of the Systolic Hypertension in the Elderly Program (SHEP), a double-blind, randomized, placebo-controlled trial of treatment for isolated systolic hypertension (ISH) in persons 60 years of age and older. The full-scale SHEP study began in 1984, set as its primary objective "the determination of whether antihypertensive drug treatment reduces risk of total stroke (nonfatal and fatal) in a multi-ethnic cohort of men and women age 60 years and older with ISH.' Previous trials have demonstrated beneficial effects of antihypertensive treatment of diastolic hypertension on major morbidity and mortality, but none has investigated the ability to influence these events for persons with ISH.

For editorial comment see p 3301.

Isolated systolic hypertension is increasingly prevalent with age, especially in those aged 60 years and above. Epidemiologic studies have demonstrated an increase in risk of stroke, other cardiovascular diseases, and death for those with ISH, independent of other risk factors.

The SHEP pilot study demonstrated the feasibility of undertaking trials in older people with ISH, including ability to recruit participants. It also established ability of drug therapy to reduce blood pressure among persons with ISH. For SHEP, ISH was defined as systolic blood pressure (SBP) greater than 160 mm Hg and diastolic blood pressure (DBP) less than 90 mm Hg, based on the average of four measurements at two baseline visits.

Secondary objectives included assessment of the relationship of antihypertensive treatment to (1) multiple cardiovascular morbidity and mortality end points, including cardiac end points; (2) cause-specific and all-cause mortality; (3) multi-infarct dementia, clinical depression, and deterioration of cognitive function; (4) possible adverse effects; (5) hospitalizations and intermediate care services; (6) falls and fractures; and (7) multiple indexes of quality of life.

The SHEP protocol also stipulated two other questions for investigation as subgroup hypotheses: (1) Would treatment of ISH reduce the frequency of total stroke (fatal and nonfatal) similar-
ly in those receiving and not receiving antihypertensive medication at initial contact? (2) Would treatment of ISH reduce the incidence of sudden cardiac death or of coronary death plus nonfatal myocardial infarction similarly in those free of baseline electrocardiographic (ECG) abnormalities and in those with such abnormalities?

METHODS
The design and methods of SHEP have been reported in detail elsewhere.31,32 They are summarized here.

Sample Size
The SHEP design specified a sample size of 4600 participants to test the primary hypothesis.30 This sample size was used to detect a difference of at least 32% in total stroke incidence with 90% power and a two-sided alpha of .05.

Recruitment and Screening
For recruitment, SHEP used primarily mass mailing and community screening techniques.30 All identified potential participants underwent an initial contact to exclude individuals ineligible by age, blood pressure, and other criteria.30 One seated blood pressure reading was taken. All blood pressures during screening and trial follow-up were measured by trained, certified technicians using standardized techniques with a Hawksley random-zero manometer.31 The SBP was defined as the reading at the first Korotkoff sound and DBP as the reading at the last Korotkoff sound. For persons not receiving antihypertensive drugs who had a first SBP reading greater than 160 mm Hg, two more readings were taken. When the mean of the last two readings was between 160 and 219 mm Hg for SBP and less than 100 mm Hg for DBP, the person was eligible for the first baseline visit.

Persons receiving antihypertensive medication at initial contact who had SBPs between 130 and 219 mm Hg and DBPs less than 85 mm Hg and who were free of major illness were eligible for a drug withdrawal procedure. They were asked to obtain permission from their personal physicians and to sign an informed consent form for drug withdrawal. They were then monitored at multiple drug evaluation visits during a 2- to 8-week period to determine blood pressure eligibility off medication.

The baseline phase consisted of two visits. Eligibility was determined based on study inclusion and exclusion criteria. When the average of four seated blood pressure measurements, two at each of these visits, was between 160 and 219 mm Hg for SBP and less than 90 mm Hg for DBP, the participant was eligible for the trial. Persons were excluded on the basis of history and/or signs of specified major cardiovascular diseases.43 Other major diseases, eg, cancer, alcoholic liver disease, established renal dysfunction, with competing risk for the SHEP primary end point or the presence of medical management problems, were also exclusions. Screeners also underwent a physical examination and a 12-lead ECG was done, with a 2-minute rhythm strip.

Those remaining eligible at the second baseline visit underwent behavioral assessment (including cognition, mood, and activities of daily living), signed an additional informed consent form for participation in the trial, and had blood drawn.

Randomization
At the completion of the second baseline visit, after verification of eligibility, screeners were randomly allocated by the coordinating center to one of two treatment groups. Randomization was stratified by clinical center and by antihypertensive medication status at initial contact.

Treatment Program
Participants were randomized in a double-blind manner to a once-daily dose of either active drug treatment or matching placebo. Baseline SBP (average of four seated blood pressure readings at the first and second baseline visits) was used to establish a goal blood pressure for each participant. For individuals with SBPs greater than 160 mm Hg, the goal was a reduction to less than 160 mm Hg. For those with SBPs between 150 and 179 mm Hg, the goal was a reduction of at least 20 mm Hg.

The objective of the stepped-care treatment program was to use the minimum amount of medication to maintain SBP at or below the goal. All participants were given chlorthalidone, 12.5 mg/d, or matching placebo (step 1 medication). Drug dosage was doubled (including matching placebo) for participants failing to achieve the SBP goal at follow-up visits. If the SBP goal was not reached at the maximal dose of step 1 medication, atenolol, 23 mg/d, or matching placebo was added as the usual step 2 drug. When atenolol was contraindicated, reserpine, 0.05 mg/d, or matching placebo could be substituted. When required to reach the blood pressure goal, the dosage of the step 2 drug could be doubled. Potassium supplements were given to all participants who had serum potassium concentrations below 8.5 mmol/L at two consecutive visits.

Follow-up Procedures
The SHEP participants were followed up monthly until SBP reached the goal or until the maximum level of stepped-care treatment was reached.30 All patients had quarterly visits from the date of randomization, at which they underwent measurement of blood pressure (average of two readings), heart rate, and body weight, and a general medical history and detailed review of medication use (prescribed and over the counter) were done. At semiannual visits, standardized questionnaires were administered to screen for depression and dementia.31-32 Annual visits also included (1) a detailed medical history, (2) a complete physical examination, (3) laboratory tests, and (4) behavioral assessment. An ECG was also done at the second and final annual visits. Other visits were scheduled when indicated, eg, SBP above the goal, SBP or DBP above the escape criteria (see below), low serum potassium concentration (<3.2 mmol/L), or as requested by the clinician or participant. Blood pressure above a priori escape criteria, despite maximal stepped-care therapy, was an indication for prescribing known active drug therapy. Escape criteria included SBP greater than 240 mm Hg at a single visit, DBP greater than 155 mm Hg at a single visit, sustained SBP greater than 220 mm Hg, or sustained DBP greater than 90 mm Hg.

When adverse conditions occurred that were considered drug related, the dosage of the study medication could be reduced, or therapy could be discontinued. Whenever the dosage was reduced or therapy was discontinued, consideration was given to resuming drug therapy when it appeared safe, when the participant's blood pressure was above the goal, and when the participant agreed.

Ascertainment of End Points
Total stroke was the primary end point. Stroke was defined as rapid onset of a new neurologic deficit attributable to obstruction or rupture in the arterial system.30 The defined deficit had to persist for at least 24 hours unless death supervened and had to include specific localizing findings confirmed by neurologic examination or brain scan, with no evidence of an underlying nonvascular cause. Determination of fatal stroke was based on either autopsy or death certificate plus data on perterminal hospitalization with a definite diagnosis of stroke. Definitions of individual secondary end points were (1) sudden cardiac death—death within 1 hour of the onset of severe cardiac symptoms, unrelated
to other known causes; (2) rapid cardiac death—death within 1 to 24 hours of the onset of severe cardiac symptoms, unrelated to other known causes; (3) nonfatal myocardial infarction—typical symptoms consistent with acute myocardial infarction, plus either typical ECG changes (including new Q waves) or significant enzyme elevation (1.25 times normal), but not including silent myocardial infarction; (4) fatal myocardial infarction—autopsy diagnosis or death certificate diagnosis plus postmortem hospitalization, with a definitive or suspected diagnosis of myocardial infarction within 4 weeks of death; (5) left ventricular failure—a symptom, such as significant dyspnea, plus a chest roentgenogram characteristic of congestive heart failure, or an abnormal physical sign, such as rales or 2+ (moderate) ankle edema; (6) other cardiovascular death—presumed myocardial infarction that did not meet diagnostic criteria, or other cardiovascular causes; (7) transient ischemic attack—rapid onset of a focal neurologic deficit lasting more than 50 seconds and less than 24 hours, presumed to be due to cerebral ischemia, with no evidence of an underlying nonvascular cause; (8) coronary artery therapeutic procedures—coronary artery bypass graft or coronary angioplasty; and (9) renal dysfunction—serum creatinine concentration greater than 265 μmol/L. For combined end points, participants with multiple end points were counted only once.

Information related to study end points was collected by clinic staff. For suspected stroke and transient ischemic attack, a standardized neurological evaluation was carried out by a SHEP neurologist. For suspected stroke, this evaluation and notes by the attending neurologist and nurses of other studies of the brain were forwarded to the coordinating center. For participants with suspected myocardial infarction or left ventricular failure, data requested included ECGs, cardiac enzymes, chest roentgenogram reports, and other clinical information. Death certificates and autopsy reports were obtained for deceased. For hospitalizations and nursing home admissions, discharge or admission sheets were obtained.

Occurrence of study events listed above was confirmed by a coding panel of three physicians blinded to randomization allocation. For a neurological event, the coding panel included two neurologists. For myocardial infarction, left ventricular failure, and all causes of death, the panel included at least one cardiologist.

Possible adverse clinical and biochemical effects of the SHEP treatments were evaluated by (1) using a standardized questionnaire that asked participants questions about side effects at annual visits, at visits after the administration of study drugs was started or stepped up, and at visits at which complaints were thought to be due to SHEP medication and by (2) examining serum chemistry data from annual laboratory evaluations.

The behavioral assessment included a questionnaire to detect depression and dementia, administered at baseline and semiannually. Based on specified questionnaire scores, participants were referred for expert diagnostic evaluation in accordance with American Psychiatric Association criteria. A diagnosis of dementia had to be confirmed by the SHEP coding panel, including two neurologists. A diagnosis of depression was not reviewed centrally.

**Statistical Analyses**

Comparability of baseline characteristics of the two treatment groups was ascertained by χ² tests for categorical variables and standard normal (z) tests for continuous variables. The primary hypothesis was assessed with the logrank test using time to first stroke as the variable of interest. Cumulative event rates were calculated using life table methods. Relative risks and percentage differences were calculated by proportional hazards regression analy-
taking antihypertensive medication was 1.24% and for those taking medication was 0.82%. Of those ineligible, 90% were excluded because of failure to meet blood pressure criteria.

Randomization and Baseline Characteristics of SHEP Participants

Randomization.—Stratified randomization by antihypertensive drug treatment status at initial contact and by center produced two SHEP groups—assigned to active treatment and placebo—comparable at baseline (Table 1).

Baseline Characteristics.—Mean age of participants was 72 years, 57% were women, and 14% were black (Table 1). Included among the whites were 204 Orientals (5% of whites); 84 Hispanics (2% of whites); and 41 classified as “other” (1% of whites). Of all participants, 1.4% reported a history of stroke, and 5% reported a history of myocardial infarction. On physical examination, 7% had carotid bruits. About 61% had an ECG abnormality. As a group, the cohort was overweight, with a body-mass index averaging 27.5 kg/m² (almost 30% overweight by actuarial criteria); 6% had hypoglycemia; and 11% had a diabetes mellitus, hypertension, and smoking history. About 8% had a history of cardiovascular disease.

Antihypertensive Drug Treatment Status by Year of Follow-up

Active Treatment Group.—Most of the participants randomized to the active treatment group received active antihypertensive medication (either according to the SHEP protocol or by prescription) throughout the trial—88% of participants at year 1 and 90% of participants at year 5 (Table 2). About 8% of active treatment group participants were assigned to receive placebo for the first 3 years, and then were randomized to the active treatment group. A total of 128 participants were randomized to the active treatment group, and 124 were assigned to receive active antihypertensive medication. Of those assigned to receive active antihypertensive medication, 123 were taking active antihypertensive medication at the end of year 1; 122 were taking active antihypertensive medication at the end of year 5; and 117 were taking active antihypertensive medication at the end of year 10. The number of participants dropping out in years 2 and 4 mainly due to follow-up time.

RESULTS

Recruitment

Recruitment was done at 16 clinical centers between March 1, 1980, and January 15, 1985. Details of recruitment results have been published elsewhere.28 Altogether, 447,921 individuals aged 60 years and above were identified and contacted; 11.6% met initial criteria, and 2.7% completed baseline visit 1. Of those individuals, 64% were eligible for baseline visit 2; of those, 76% were eligible for randomization; of those, 80% were randomized.

Screening blood pressure criteria and not receiving antihypertensive medication proceeded directly through baseline visits; 3161 such participants were randomized. Those taking medication (188,820 persons [43.2%]) and meeting blood pressure criteria underwent drug withdrawal as previously described; 1575 such participants were randomized. A total of 4765 participants were randomized into the trial, two thirds of whom were not receiving antihypertensive medication at initial contact. The yield from initial contact to randomization for those not
cation only; 11% were receiving step 2, dose 1 medication; 12% were receiving step 2, dose 2 medication; 21% were receiving other active medication; and 9% were receiving no antihypertensive drug. Thus, almost half of the participants were receiving the step 1 drug only, and more than two thirds of the participants were receiving the step 1 and/or step 2 drug only.

Placebo Group.—The majority of participants randomized to the placebo group continued to receive no active antihypertensive medication throughout the trial (Table 2). However, the percentage for whom active antihypertensive drug therapy was prescribed increased progressively, from 13% at year 1 to 38% at year 3 and 44% at year 5 (Table 2). Throughout the trial, about 16% of placebo group participants were assigned to receive active therapy because their blood pressure met the escape criteria (mostly due to DBP); medication was stopped in 7% due to side effects.

The proportion of participants receiving active antihypertensive medication was consistently higher throughout the trial for persons in the active treatment group than for those in the placebo group—89% vs 33% at 3 years and 90% vs 44% at 5 years (Table 2).

Mean SBP and DBP by Treatment Group and Year of Follow-up

Throughout the trial, the mean SBP of the active treatment group was substantially lower than at baseline, by about 26 mm Hg overall (Table 3 and Fig 1).
The mean DBP of the active treatment group was lower by about 9 mm Hg throughout the trial compared with baseline. For the placebo group, the mean SBP was consistently lower than at baseline, by about 15 mm Hg. The mean DBP of the placebo group was lower than at baseline by about 4 to 5 mm Hg. During the trial, the SHEP goal blood pressure was reached by 65% to 72% of persons in the active treatment group but only by 42% to 40% of those in the placebo group.

Mean SBP levels were substantially lower throughout the trial for the active treatment group than for the placebo group, by 11 to 14 mm Hg (Table 3 and Fig 1). Mean DBP was reduced more in the active treatment group than in the placebo group, by about 3 to 4 mm Hg.

### Total Stroke Incidence

All Participants.—With a mean follow-up of 4.5 years, incident stroke, the primary end point of the trial, was diagnosed in 103 persons in the active treatment group and 159 persons in the placebo group (Table 4). By life table analyses, 5-year cumulative stroke rates were 5.2 per 100 participants for the active treatment group and 8.2 per 100 for the placebo group. The cumulative rates for the total period of follow-up (70 months) were 5.6 per 100 participants for the active treatment group and 9.2 per 100 for the placebo group. Based on proportional hazards regression analysis, relative risk was 0.64 (95% confidence interval [CI], 0.36 to 0.78; P = .0002) (Table 4 and Fig 2). The absolute reduction in 5-year risk of stroke was 30 events per 1000 participants. There were few stroke deaths—10 in the active treatment group and 14 in the placebo group. The cumulative difference in total stroke incidence rates, with rates lower in the active treatment group than in the placebo group, increased progressively over the 5 years of the trial (0.2, 1.1, 1.2, 2.0, and 3.0 events per 100 participants) (Table 4). Seventeen of 96 people in the active treatment group and 28 of 149 people in the placebo group who had a nonfatal stroke died during the trial—about 20% in each group.

### By Age, Sex, Race, and Baseline SBP

Stroke incidence was lower in those randomized to active treatment than in those randomized to placebo for all baseline age groups: 60 to 69 years, 54 vs 57 events; 70 to 79 years, 48 vs 74 events; and 80 years or older, 21 vs 38 events. A favorable effect of active treatment was also noted for three of the four major sex-race groups: white men, 39 vs 64 events; white women, 48 vs 65 events; and black women, 7 vs 21 events. The apparent lack of any trend for the small number of black men was based on few events (nine vs eight events). With proportional hazards regression using SBP as a continuous variable, the favorable trend in stroke incidence for the active treatment compared with the placebo group prevailed irrespective of baseline SBP.

### By Antihypertensive Drug Treatment Status at Initial Contact

One of the two SHEP subgroup hypotheses was related to the effects of active treatment on participants receiving and not receiving antihypertensive medication at initial contact. Randomization was stratified by whether or not participants were receiving antihypertensive medication at initial contact. For the subgroup not receiving antihypertensive medication at initial contact, relative risk of stroke for active treatment compared with placebo was 0.89 (95% CI, 0.51 to 0.95) (Table 5). For participants receiving antihypertensive medication at initial contact, relative risk for stroke was 0.67 (95% CI, 0.38 to 0.83). Thus, SHEP primary end point analysis indicates a high degree of consistency in favorable findings for the active treatment group.

### Table 6. Morbidity and Mortality by Cause and Treatment Group

<table>
<thead>
<tr>
<th>No. of Events</th>
<th>Active Treatment Group (n = 2365)</th>
<th>Placebo Group (n = 2321)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>213</td>
<td>242</td>
<td>0.87 (0.73-1.06)</td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
<td>14</td>
<td>0.71 (0.31-1.65)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>59</td>
<td>73</td>
<td>0.96 (0.70-1.31)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>23</td>
<td>28</td>
<td>1.00 (0.56-1.76)</td>
</tr>
<tr>
<td>Rapid death</td>
<td>24</td>
<td>24</td>
<td>0.87 (0.45-1.66)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15</td>
<td>26</td>
<td>0.57 (0.30-1.08)</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>21</td>
<td>23</td>
<td>0.87 (0.43-1.55)</td>
</tr>
<tr>
<td>Ventricular failure</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>18</td>
<td>0.71 (0.35-1.46)</td>
</tr>
<tr>
<td><strong>Noncardiovascular</strong></td>
<td>109</td>
<td>103</td>
<td>1.05 (0.83-1.36)</td>
</tr>
</tbody>
</table>

*Relative risk assessments were done for all types of events except those with lower than 20 events and indeterminate cause of death.

1. The mean DBP of the active treatment group was lower by about 9 mm Hg throughout the trial compared with baseline. For the placebo group, the mean SBP was consistently lower than at baseline, by about 15 mm Hg. The mean DBP of the placebo group was lower than at baseline by about 4 to 5 mm Hg. During the trial, the SHEP goal blood pressure was reached by 65% to 72% of persons in the active treatment group but only by 42% to 40% of those in the placebo group.

Mean SBP levels were substantially lower throughout the trial for the active treatment group than for the placebo group, by 11 to 14 mm Hg (Table 3 and Fig 1). Mean DBP was reduced more in the active treatment group than in the placebo group, by about 3 to 4 mm Hg.
Table 7—Prevalence of Symptoms Ever Characterized as Troublesome or Intolerable by Treatment Group

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Active Treatment Group</th>
<th>Placebo Group</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue or standing</td>
<td>1.9</td>
<td>1.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Feelings of unsteadiness or imbalance</td>
<td>32.9</td>
<td>9.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Loss of consciousness/passing out</td>
<td>2.2</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Heart beating fast or skipping beats</td>
<td>8.2</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Heart beating unusually slowly</td>
<td>2.1</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Chest pain or heartburn</td>
<td>21.9</td>
<td>18.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Unusual shortness of breath</td>
<td>11.0</td>
<td>11.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Unusual tiredness</td>
<td>23.8</td>
<td>23.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Cold or numb hands</td>
<td>19.8</td>
<td>18.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Ankle swelling</td>
<td>19.5</td>
<td>15.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Psychosocial Problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unusual worry or anxiety</td>
<td>25.5</td>
<td>24.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Trouble with memory/concentration</td>
<td>23.4</td>
<td>14.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Depression that interfered with activities</td>
<td>12.3</td>
<td>9.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Problems in sleeping</td>
<td>26.4</td>
<td>24.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4.2</td>
<td>4.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Problems in sexual function</td>
<td>4.8</td>
<td>3.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>6.4</td>
<td>5.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fails</td>
<td>12.6</td>
<td>19.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Fractures</td>
<td>2.4</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Muscle weakness or cramping</td>
<td>26.4</td>
<td>26.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Unusual palpitation</td>
<td>10.3</td>
<td>8.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Change in bowel habits</td>
<td>15.4</td>
<td>11.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Excessive thirst</td>
<td>7.9</td>
<td>6.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Nauseas or vomiting</td>
<td>9.7</td>
<td>8.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Terrible stools or red blood in stools</td>
<td>2.2</td>
<td>2.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Skin rash or bruising</td>
<td>12.5</td>
<td>10.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Unusual joint pain</td>
<td>36.4</td>
<td>31.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Stevens's nodes</td>
<td>7.8</td>
<td>8.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Waking frequently at night to urinate</td>
<td>14.6</td>
<td>12.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Any specified problem</td>
<td>91.8</td>
<td>80.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Any specified problem characterized as intolerable</td>
<td>78.1</td>
<td>79.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Morbidity and Mortality From Cardiovascular and Noncardiovascular Causes

Nonfatal Cardiovascular Events.—The number of nonfatal cardiovascular events was consistently lower for active treatment than for placebo, with relative risks ranging from 0.46 for left ventricular failure to 0.98 for angina pectoris (Table 6). The difference observed in total deaths from coronary heart disease was largely due to the difference in the number of fatal myocardial infarctions. The number of deaths from neoplastic diseases, second only to cardiovascular disease as a main cause of mortality for SHEP participants, was similar (75 and 78 deaths) for the active treatment and placebo groups.

Combined Nonfatal and Fatal Cardiovascular Events.—Nonfatal and fatal major cardiovascular events were consistently lower for active treatment than placebo. The number of deaths from coronary heart disease events, nonfatal plus fatal, was lower for the active treatment group (140) compared to the placebo group (154; Table 6). The main cause of death in the active treatment group was myocardial infarction, and the 5-year absolute benefit of active treatment compared to placebo was 86 events per 1000 participants. All nonfatal and fatal cardiovascular events numbered 263 in the active treatment group and 305 in the placebo group. This represented 32% fewer events in the active treatment group, with an 5-year absolute risk reduction estimated at 16 events per 1000 patients. All nonfatal and fatal cardiovascular events numbered 263 in the active treatment group and 305 in the placebo group. This represented 32% fewer events in the active treatment group, with an 5-year absolute benefit estimated at 16 events per 1000 participants.

Adverse Effects

At baseline, the number of clinical complaints was comparable in the active treatment and placebo groups. During the trial, reported rates of certain problems were greater in the active treatment group than in the placebo group (Table 7). The mean serum potassium, uric acid, glucose, cholesterol, and sodium levels out of the specified ranges were reported more frequently in the active treatment group than in the placebo group (Table 8). During follow-up, the mean serum potassium concentration was lower in the active treatment group than in the placebo group; the mean serum uric acid, glucose, and cholesterol concentrations were higher in the active treatment group; and the mean serum sodium concentration was similar in the two groups (Table 8).

About 1% of persons in the active treatment and placebo groups met questionnaire referral criteria for expert evaluation of possible dementia (Table 9). For more than 90% of these people a referral was completed; the main reason for failure to achieve referral was participant refusal. Thirty-seventeen patients (1.6%) receiving active treatment and 44 (1.9%) receiving placebo had a diagnosis of dementia made and confirmed by the coding panel. During the trial, 14% of persons in the active treatment group and 15% in the
placebo group met the questionnaire referral criteria for expert evaluation of possible depression (Table 9). For more than 75% of these people, a referral was completed, the main reason for failure to achieve referral was participant refusal. Of participants in the two groups, 104 (4.4%) randomized to active treatment and 112 (4.7%) randomized to placebo had a diagnosis of depression.

**COMMENT**

The SHEP antihypertensive drug treatment regimen significantly reduced the risk of total stroke, the primary end point, in people aged 60 years and older with ISH. During the entire 70 months of study follow-up, the total stroke incidence was reduced by 36% in the active treatment group and 31% in the placebo group. This was observed even though 35% of those assigned to placebo took the antihypertensive medications during the trial.

The SHEP trial was the first trial to test the efficacy of antihypertensive drug treatment on clinical end points for persons with ISH. The significant positive outcome on its primary end point of stroke was consistent with the trend found in the SHEP pilot study. The 36% reduction in stroke incidence is similar to that found in trials of drug therapy for diastolic hypertension, including the Hypertension Detection and Follow-up Program, the Medical Research Council trial, and 12 smaller trials combined. Overall, these previous trials recorded a 42% reduction in stroke incidence (95% CI, 30% to 54%). Findings from SHEP and other trials suggest that antihypertensive drug treatment is broadly effective, with similar reductions in the stroke rate for people with either diastolic hypertension or ISH.

Moreover, the SHEP decrease of 27% in incidence of nonfatal myocardial infarction plus coronary heart disease death for the active treatment group is similar to results of the Hypertension Detection and Follow-up Program and greater than those in other trials. Combined results of all diastolic hypertension trials indicate that sustained net decrease in blood pressure recorded for active intervention produced an overall reduction in incidence of major coronary events of 14% (95% CI, 4% to 24%).

For the coronary heart disease end point, SHEP recorded a favorable trend for participants with and without baseline ECG abnormalities. The SHEP medication regimen showed no evidence of adverse effect on coronary risk for people with baseline ECG abnormalities. In fact, for SHEP participants with baseline ECG abnormalities (61% of those randomized), the incidence rate of nonfatal myocardial infarction plus coronary heart disease death was 21% lower for active treatment.

The positive SHEP outcome was achieved with minimum effective doses of antihypertensive drugs in a stepped-care regimen structured to achieve and maintain a goal blood pressure at least 20 mm Hg below baseline and below 140 mm Hg. It used low-dose chlorthal-dione, 12.5 mg/d, as the step 1 medication.
This was increased to a maximum of 25.0 mg if needed. The step 2 medication—usually low-dose atenolol, 25 mg/d, or, if atenolol was contraindicated, low-dose reserpine, 0.6 mg/d—was added as needed, and the dosage of either drug could have been doubled.

High level adherence to this regimen was maintained throughout the 5 years of the trial. Based on the effects of this regimen (plus regression to the mean and adaptation to clinic assessment), the average SBP of the active treatment group was lower during the trial by about 20 mm Hg, and it was about 11 mm Hg lower than the placebo group SBP. The average DBP of the active treatment group was about 3 to 4 mm Hg lower than the placebo group DBP.

These data demonstrate an ability to achieve and maintain control of ISH in older persons with a low-dose, stepwise-care drug regimen. This regimen was associated with only an infrequent excess of adverse effects and no evidence of increase in dementia or depression.

Also the SHEP results may have implications for current uncertainties about optimal drug treatment regimens for diastolic hypertension, especially "mild" hypertension. The SHEP findings are congruent with the combined results of previous trials of drug treatment for diastolic hypertension in efficacy of preventing not only stroke but also coronary heart disease and all cardiovascular disease. In all these trials an oral diuretic was the step 1 treatment. The SHEP was unique in two respects: it used low-dose chlorothalidone, and its participants were older people with ISH. The favorable SHEP results suggest that a low-dose oral diuretic, particularly chlorothalidone, may be as efficacious for step 1 drug treatment of high blood pressure as any other drug available. Data from large-scale, long-term randomized trials are needed—such data are needed. The importance of this question is underscored by data on the comparative costs of oral diuretics and newer drugs.

In conclusion, SHEP demonstrated significant efficacy of active antihypertensive drug treatment in preventing stroke in persons aged 60 years and older with ISH. This result was achieved (1) with use of stepped-care treatment, starting with low-dose chlorothalidone as the step 1 medication; (2) with the majority of participants assigned to active drug therapy being at or below the goal blood pressure; (3) with a low-order excess of adverse effects; and (4) with no excess incidence of depression or dementia. Favorable findings were demonstrated for multiple secondary end points of the trial, including the incidence of major cardiac and cardiovascular events. These findings indicate a considerable potential for decreasing morbidity and disability by effective sustained drug treatment of ISH, given its prevalence and the high rates of cardiovascular diseases in those aged 60 years and older.

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