Effect of Treating Isolated Systolic Hypertension on the Risk of Developing Various Types and Subtypes of Stroke

The Systolic Hypertension in the Elderly Program (SHEP)

H. Mitchell Perry, Jr, MD
Barry R. Davis, MD, PhD
Thomas R. Price, MD
William B. Applegate, MD
William S. Fields, MD
Jack M. Guralnik, MD
Lewis Kuller, MD
Sara Pressel, MS
Jeremiah Stamler, MD
Jeffrey L. Probstfield, MD
for the Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group

Context The Systolic Hypertension in the Elder Program (SHEP) demonstrated that treating isolated systolic hypertension in older patients decreased incidence of total stroke, but whether all types of stroke were reduced was not evaluated.

Objective To investigate antihypertensive drug treatment effects on incidence of stroke by type and subtype, timing of strokes, case-fatality rates, stroke residual effects, and relationship of attained systolic blood pressure to stroke incidence.

Design The SHEP study, a randomized, double-blind, placebo-controlled trial began March 1, 1985, and had an average follow-up of 4.5 years.

Setting and Participants A total of 4,736 men and women aged 60 years or older with isolated systolic hypertension at 16 clinical centers in the United States.

Interventions Patients were randomly assigned to receive treatment with 12.5 mg/d of chlorthalidone (step 1); either 25 mg/d of atenolol or 0.05 mg/d of reserpine (step 2) could be added (n=2,365); or placebo (n=2,371).

Main Outcome Measures Occurrence, type and subtype, and timing of first strokes and stroke fatalities; and change in stroke incidence for participants (whether in active treatment or placebo groups) reaching study-specific systolic blood pressure goal (decrease of at least 20 mm Hg from baseline to below 160 mm Hg) compared with participants not reaching goal.

Results A total of 85 and 132 participants in the active treatment and placebo groups, respectively, had ischemic strokes (adjusted relative risk [RR], 0.63; 95% confidence interval [CI], 0.48-0.82); 9 and 19 had hemorrhagic strokes (adjusted RR, 0.46; 95% CI, 0.21-1.02); and 9 and 8 had strokes of unknown type (adjusted RR, 1.05; 95% CI, 0.40-2.73), respectively. Four subtypes of ischemic stroke were observed in active treatment and placebo group participants, respectively, as follows: for lacunar, n=23 and n=43 (adjusted RR, 0.53; 95% CI, 0.32-0.88); for embolic, n=9 and n=16 (adjusted RR, 0.56; 95% CI, 0.25-1.27); for atherosclerotic, n=13 and n=13 (adjusted RR, 0.99; 95% CI, 0.46-2.15); and for unknown subtype, n=40 and n=60 (adjusted RR, 0.64; 95% CI, 0.43-0.96). Treatment effect was observed within 1 year for hemorrhagic strokes but was not seen until the second year for ischemic strokes. Stroke incidence significantly decreased in participants attaining study-specific systolic blood pressure goals.

Conclusions In this study, antihypertensive drug treatment reduced the incidence of both hemorrhagic and ischemic (including lacunar) strokes. Reduction in stroke incidence occurred when specific systolic blood pressure goals were attained.

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**METHODS**

**Summary of SHEP**

SHEP was a double-blind, randomized, placebo-controlled trial designed to test whether antihypertensive drug therapy reduces the frequency of new strokes in a multiethnic cohort of 4736 men and women aged 60 years or older with isolated systolic hypertension (SBP $\geq 160$ mm Hg and diastolic blood pressure $<90$ mm Hg).²

The cohort, recruited at 16 clinical centers, was 43.2% male and 13.9% black. Average age at randomization was 71.6 years, with 42% of participants in their 60s, 45% in their 70s, and 14% in their 80s or 90s. Baseline blood pressure averaged 170/77 mm Hg; 57% of participants had SBP from 160 to 169 mm Hg, 27% from 170 to 179 mm Hg, and 15% had 180 mm Hg or higher. Ten percent of participants had diabetes mellitus, 4.9% had experienced an MI, and 1.4% had experienced a previous stroke. Subjects with atrial fibrillation were excluded from the trial. Participants were randomly assigned to double-blind active treatment or placebo groups. Average follow-up in the trial was 4.5 years.³⁴⁵

The first treatment step was chlorthalidone (12.5 mg/d), which could be doubled if the participant’s SBP was not controlled at goal. The second step, if needed, was atenolol (25 mg/d) or low-dose reserpine (0.05 mg/d) for those with a contraindication to β-blockers. The second-step drug also could be doubled if control had not been achieved. 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; however, 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.³ At the 5-year visit, 65% of participants in the active treatment group and 40% in the placebo group were at goal SBP (decrease in baseline SBP of $\geq 20$ mm Hg to an SBP of $<160$ mm Hg).

**Stroke and TIA Definition and Ascertainment**

Participants with strokes were hospitalized during the acute phase and were examined by a trial neurologist who completed standardized forms describing the event. When examination was not feasible, pertinent records were reviewed by a trial neurologist and the forms completed. Transient ischemic attacks were handled similarly. Final decisions regarding TIA and stroke end points (including type and subtype) were made in a face-to-face unanimous decision process by 3 physicians on the end point subcommittee. Diagnoses were based on information from hospital charts, standardized forms giving findings on history and physical examination, evaluations of brain images (computed tomography or magnetic resonance imaging) by 2 neuroradiologists blinded to treatment groups, and the clinical center neurologist’s diagnosis. All strokes were evaluated, but only the first stroke was considered unless otherwise stated.

**Transient ischemic attack** was defined as the rapid onset of a focal neurological deficit lasting more than 30 seconds and less than 24 hours without evidence of an underlying nonvascular cause and presumed to be caused by cerebral ischemia.

**Stroke** was defined as the rapid onset of a new neurological deficit attributed to obstruction or rupture in the cerebral arterial system. The defined deficit had to persist at least 24 hours unless death supervened and had to include specific localizing findings confirmed by neurological examination and without evidence of an underlying nonvascular cause.

The method of determining stroke type (ischemic, hemorrhagic, or unknown) and subtype was similar to that used in the Stroke Data Bank.⁴ A patient was diagnosed as having a hemorrhagic stroke if intracranial bleeding was found on brain imaging, by lumbar puncture, or at autopsy, and there was no evidence on the brain image of late bleeding into an ischemic infarction. Ischemic stroke was diagnosed when a focal neurological deficit was present without blood in the brain image or lumbar puncture. Stroke, type unknown, was diagnosed when the definition of stroke was satisfied but there was insufficient evidence to determine whether it was hemorrhagic or ischemic.

Ischemic strokes were subdivided into lacunar, cardioembolic, atherosclerotic, or other/unknown on the basis of clinical information and brain imaging.

**Lacunar stroke** was diagnosed either when a small (<2 cm in diameter) lesion correlated with symptoms and/or signs of the stroke was seen in deep structures of the hemisphere or in the pons by brain imaging or if brain imaging showed no lesion responsible for the signs or symptoms and the patient had pure motor hemiparesis, pure sensory stroke, dysarthria-clumsy hand syndrome, or ataxia hemiparesis syndrome.

**Embolic stroke** was diagnosed when there was insufficient evidence of a lacune and a known source of embolism was present (eg, atrial fibrillation or recent MI).

**Atherosclerotic infarction** was diagnosed when there was evidence by noninvasive test (eg, carotid duplex) or by angiogram of at least 70% stenosis of the appropriate artery (eg, left carotid compromise with left cerebral hemisphere infarction).

**Ischemic infarction, other/unknown type** was diagnosed when no specific subtype was identified.

Hemorrhagic strokes were subdivided into subarachnoid hemorrhage if blood was seen in the subarachnoid space, or intraparenchymal hemorrhage if blood was seen within the brain substance.
Stroke Fatality Rates
All 18 participants who died within 30 days of their first stroke were considered stroke fatalities. Six additional participants died within 30 days of subsequent strokes; they too were considered stroke fatalities. None of the 24 stroke fatalities had other obvious causes of death. For the 38 participants with strokes who died more than a month after their strokes, other events were considered to be primary causes of death.

Stroke Imaging
Satisfactory brain images were obtained during hospitalization following 85% of first strokes. For strokes occurring early in the trial, adequate imaging was not available for 15 participants in the active treatment group and 25 in the placebo group, thus 222 participants had adequate images for evaluation. However, for 122 participants, no appropriate lesion was recognized, leaving 100 participants with strokes having identifiable lesions. For the 100 participants with visualized lesions, stroke volumes were approximated using the method of Kothari et al.5

Blood Pressure Measurement
Blood pressure levels were measured by trained, certified technicians using random-zero sphygmomanometers. All visit SBP levels were the average of 2 measurements made at that visit with the subject seated quietly. Baseline SBP was the average (between 160 and 219 mm Hg) of measurements at the first and second baseline visits. In-trial visit SBP levels were the average of measurements at that visit. The 1-year SBP was the value at the first annual visit. For participants with strokes, in-trial prestroke SBP was the average SBP at all visits before the first stroke.

Relationship of In-Trial SBP to Stroke Incidence
Relationships were sought between in-trial prestroke SBP and the likelihood of stroke. For this purpose, SBP was considered a dichotomous variable, with participants having average prestroke SBP above or below the cut point. All participants with strokes were divided into these 2 groups whether randomized to placebo group or active treatment group and whether taking antihypertensive drug or not. The nonstroke SHEP participants were also divided by the same cut points on the basis of SBP at 1 year (when in-trial SBP had been established), providing the groups from which participants with strokes came.

Stroke Residual
Three estimates of stroke residual were made. Admissions to skilled or intermediate care nursing homes were tabulated for all participants. Activities of daily living (ADL) data were obtained at baseline and annually for each SHEP participant, using a standardized questionnaire derived from the Barthel Index.6,7 Seven activities were assessed: walking across a small room, bathing, grooming oneself, dressing, eating, getting from bed to chair, and using the toilet. To evaluate stroke-induced changes in ADL, the last prestroke assessment and the first assessment more than 6 months after the stroke were compared. With the double-blind intact, participants reported the number of disability days of 2 types: days of reduced ordinary activity and days in bed (a subset of disability days) for the 2 weeks before each annual visit.

Statistical Analyses
All analyses were performed on an intention-to-treat basis, and unless specific exception is indicated, only first strokes were considered. Cumulative rates were calculated using life-table methods. Comparisons of active treatment and placebo groups with respect to stroke and its subtypes, and reductions in risk with control for baseline variables were determined using proportional hazards analyses.8 The proportional hazards assumption was tested using Schoenfeld’s approach.9 This assumption was not violated. Mean ADL scores were compared between treatment groups using t tests.10 Days of reduced activity and days in bed were compared between treatment groups using rank-order tests.11 A priori, there was relatively low power to detect differences between treatment groups for poststroke events. The numbers, percentages, and P values are a more descriptive guide.

The relationship between in-trial SBP during treatment and stroke incidence was examined using Cox proportional hazards regression models accounting for both time-constant and time-dependent covariates. Time-constant baseline variables included in the model were age, race, sex, antihypertensive medication status at initial contact, history of prior MI and/or stroke, history of diabetes, current smoking status, presence of specified electrocardiogram abnormalities, body mass index (BMI), BMI squared, heart rate, total serum cholesterol and high-density lipoprotein cholesterol levels, and years of education. The time-dependent variable was SBP, modeled as either a dichotomous or a continuous variable.

RESULTS
Stroke Reduction, Timing, and Fatality Rates
Treatment reduced the incidence of all strokes and of both stroke types (Table 1). There were significantly fewer ischemic strokes among participants in the active treatment group than among those in the placebo group (85 vs 132), fewer lacunar and other/unknown subtypes of stroke, and equal numbers of atherosclerotic strokes. Although there were fewer hemorrhagic strokes, both subarachnoid and intraparenchymal numbers were small and differences between participants in the active treatment and placebo groups were not significant. After the indicated adjustments, Table 1 provides risk ratios (RRs) and 95% confidence intervals (CIs) for stroke incidences.

During the first postrandomization year, there were 2 hemorrhagic strokes for participants in the active treatment group and 7 in the placebo group, suggesting a prompt treatment effect. The numbers of hemorrhagic strokes during the trial totaled 9 and 19, respectively. The numbers of ischemic
Table 1. Incidence of First Stroke by Randomized Group and by Type and Subtype

<table>
<thead>
<tr>
<th>Type of Stroke</th>
<th>Active (n = 2365)</th>
<th>Placebo (n = 2371)</th>
<th>Risk Ratio (95% Confidence Interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All first</td>
<td>103</td>
<td>159</td>
<td>0.63 (0.49-0.81)</td>
</tr>
<tr>
<td>Ischemic</td>
<td>85</td>
<td>132</td>
<td>0.63 (0.48-0.82)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>23</td>
<td>43</td>
<td>0.53 (0.32-0.88)</td>
</tr>
<tr>
<td>Embolic</td>
<td>9</td>
<td>16</td>
<td>0.56 (0.25-1.27)</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>13</td>
<td>13</td>
<td>0.90 (0.46-2.15)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>40</td>
<td>60</td>
<td>0.64 (0.43-0.96)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>9</td>
<td>19</td>
<td>0.46 (0.21-1.02)</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>1</td>
<td>4</td>
<td>0.25 (0.03-2.26)</td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>8</td>
<td>15</td>
<td>0.52 (0.22-1.22)</td>
</tr>
<tr>
<td>Unknown type</td>
<td>9</td>
<td>8</td>
<td>1.05 (0.40-2.73)</td>
</tr>
</tbody>
</table>

*Risk ratios indicate likelihood of a first stroke occurring in a participant in the active treatment group with the participant in the placebo group as a reference. Values are adjusted for age, race, sex, years of education, baseline body mass index, systolic and diastolic blood pressure, history of diabetes mellitus, smoking history, and prerandomization use of antihypertensive agents.

Seventeen strokes of unknown type are omitted. Three additional strokes were also omitted (1 for a participant in the active treatment group and 2 participants in the placebo group). These 3 strokes occurred after the participants had completed 5 years in the trial.

Two hundred twenty-two participants with strokes had brain images adequate for evaluation. Of these, 122 (55%) had no visible lesions related to their strokes, leaving 100 (42%) in the active treatment group and 58 in the placebo group with appropriately localized lesions ascribed to their first stroke. Hemorrhagic strokes were visualized more often (82%; 23/28) than ischemic strokes (40%; 77/194).

A total of 63 participants in the active treatment group and 98 in the placebo group developed symptomatic MI during the trial (P = .005). Fourteen of these 161 had strokes, and for 9 of them (4 participants in the active treatment group and 5 in the placebo group) the MI followed the first stroke.

Stroke Imaging

Two hundred twenty-two participants with strokes had brain images adequate for evaluation. Of these, 122 (55%) had no visible lesions related to their strokes, leaving 100 (42%) in the active treatment group and 58 in the placebo group with appropriately localized lesions ascribed to their first stroke. Hemorrhagic strokes were visualized more often (82%; 23/28) than ischemic strokes (40%; 77/194).

For the 100 visualized strokes, there were no obvious differences between participants in the active treatment group and those in the placebo group in their frequency or approximate stroke volumes. Lacunar strokes in both treatment groups were markedly smaller than other stroke subtypes. Combining both treatment groups, the median stroke volumes were lacunar, 52 mm³; embolic, 1500 mm³; atherosclerotic, 1470 mm³; subarachnoid, 1754 mm³; and intraparenchymal, 1960 mm³.

Relationship of In-Trial SBP to Stroke Incidence

Participants who attained specific initial, prestroke SBP goals had reduced likelihood of developing strokes (Table 3). One year after randomization, an SBP lower than 160 mm Hg had been achieved by two thirds (3162) of all SHEP participants; 1906 (60.3%) were in the active treatment group and 1256 (39.7%) were in the placebo group. Although more participants in the active treatment group than in the placebo group reached each SBP level of Table 3, reduction in stroke incidence for those who had reached a goal was similar for both treatment groups. At 1 year, some participants in the placebo group were taking active drug(s): 15% of those with SBP of lower than...
160 mm Hg and 18% of those with SBP of lower than 150 mm Hg.

Participants whose in-trial pre-stroke SBP was lower than 160 mm Hg experienced a significant reduction (33%) (adjusted RR, 0.67; 95% CI, 0.51-0.89) in total stroke incidence compared with participants having higher in-trial pre-stroke SBP (Table 3). Participants whose SBP was lower than 150 mm Hg experienced a 38% reduction in total stroke incidence compared with those having an SBP of 150 mm Hg or higher. For the smaller number of participants (1356) with an SBP lower than 140 mm Hg, the 22% reduction in stroke incidence was not statistically significant compared with those having an SBP of 140 mm Hg or higher. Data for all strokes and for ischemic and lacunar strokes are cited in Table 3.

Approximately half (2317) of SHEP participants reached the SHEP goal (decrease in SBP of ≥20 mm Hg from baseline to <160 mm Hg); they had a significant decrease (33%) in stroke incidence compared with participants who had not reached that goal (Table 3).

In a model using in-trial pre-stroke SBP as a continuous variable, for every millimeter of mercury decrease in SBP, stroke incidence decreased by 1%. At 1 year, two thirds of all SHEP participants had decreases in SBP of 10 mm Hg or more. Those who had achieved that goal had a significant decrease (10%) in total stroke incidence compared with those who had not achieved it (Table 3).

### Stroke Residual

Three estimates of stroke residuals were made. Within 6 months of their first stroke, 4 participants (4%) in the active treatment group and 8 (5%) in the placebo group were admitted to skilled or intermediate care nursing homes. By the end of the trial, 6 participants in the active treatment group and 15 in the placebo group were admitted to such nursing homes; the average interval between stroke and admission approximated 250 days for both treatment groups. For comparison, 82 (1.8%) of the 4474 nonstroke SHEP participants had such admissions during the trial follow-up at 4.5 years (average).

Of the 262 participants with stroke, 87 participants in the active treatment group had both pre-stroke and post-stroke ADL assessments. For them, the mean decrease in ADL score (indicating increased disability) was 1.3 for participants in the active treatment group and 1.5 for those in the placebo group. The ADL scores decreased in 1 or more of 7 tested domains for 31 participants (31%) in the active treatment group and 56 (35%) in the placebo group. Scores did not change for 51 participants (50%) in the active treatment group and 66 (42%) in the placebo group. Differences between treatment groups were not significant.

Self-reported days of reduced activity were consistently, but not significantly, fewer for participants in the active treatment group than for those in the placebo group at 3 poststroke intervals (Table 4). Days in bed were also consistently fewer for participants in the active treatment group than in the placebo group; moreover, at the last trial report, the difference in the average of 

### Table 2. Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group

<table>
<thead>
<tr>
<th>Type of Stroke</th>
<th>Participants</th>
<th>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Lacunar</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Embolic</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Hemorrhagic strokes</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
<tr>
<td>Unknown type strokes</td>
<td>Participants</td>
<td>Deaths of Participants With Stroke by Type and Subtype of Stroke and Treatment Group</td>
</tr>
</tbody>
</table>

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0.25 days in bed for 61 participants in the active treatment group and the average of 1.18 days for 92 participants in the placebo group was significant (P = .03) (Table 4).

**COMMENT**

**Stroke Reduction**

One in 10 of the 262 first strokes observed was hemorrhagic, slightly more than 8 in 10 were ischemic, and the remainder were of unidentified type. The frequency of stroke type and subtype diagnoses is similar to that observed in the Stroke Data Bank.4 In both SHEP and the Stroke Data Bank, no subtype diagnosis could be made for about 45% of ischemic strokes. Most ischemic strokes in SHEP (60%) were not visualized and the Stroke Data Bank had comparable difficulties with adherence. Finally, SHEP and the Stroke Data Bank used similar methods to identify stroke types. Although SHEP participants were older, case fatality rates were similar, with the 30-day rate for ischemic strokes being 5% for SHEP and 8% for the Stroke Data Bank, and the rates for hemorrhagic stroke being 39% and 30%, respectively.

**Stroke-Related Events**

Usually considered precursors of stroke, TIA and atrial fibrillation relatively rarely preceded first stroke in SHEP. Only 15 of 262 participants experienced TIA prior to their first strokes, and atrial fibrillation was recognized in only 6 prior to their first strokes.

**Relationship of Attained SBP to Stroke Incidence**

The fact that achieving specific SBP goals significantly decreased the incidence of stroke should encourage both the physician and patient to strive for such goals. Thus, decreasing the SBP to less than 160 mm Hg lowered the stroke rate by one third and decreasing SBP to less than 150 mm Hg lowered the rate even more. Decreasing the SBP to less than 140 mm Hg did not have a significant effect, perhaps because fewer participants achieved that goal. For those reaching a goal SBP, reduction was similar regardless of the participant’s randomization group, although more participants in the active treatment group than in the placebo group achieved that goal. This strongly suggests that the level of attained SBP rather than treatment or a particular antihypertensive drug was the paramount factor in reducing stroke incidence.

**Stroke Residual**

Three measures of stroke residual were examined in seeking differences between the 2 treatment groups. First, nursing home admissions were similar for both treatment groups. Second,
ADL scores worsened slightly, but not significantly more, for participants in the placebo group. Third, the consistently fewer days of reduced activity, including days in bed, suggest that participants in the active treatment group were less disabled by strokes than those in the placebo group. Although these data must be considered “soft,” they were self-reported with the double-blind intact.

Conclusions

Treatment induced a significant reduction in the incidence of all strokes in elderly patients with isolated systolic hypertension. There were also reductions in ischemic and hemorrhagic stroke types and in the lacunar subtype. Similar percentages of strokes in participants in the active treatment group and in the placebo group were fatal. The treatment effect may have appeared earlier for hemorrhagic than for ischemic strokes. Significant reduction in stroke incidence was observed for any participants reaching certain SBP levels: SHEP goal (20 mm Hg decrease in SBP to < 160 mm Hg), SBP below 160 mm Hg, and SBP decrease of 10 mm Hg. Certain stroke residuals may be less among participants in the active treatment group than in the placebo group. Elderly patients and their physicians should be diligent in treating isolated systolic hypertension to achieve a goal SBP.

Author Affiliations: Department of Medicine, Washington University, St Louis, Mo (Dr Perry); School of Public Health, University of Texas Health Science Center, Houston (Drs Davis and Fields and Ms Pressel); Department of Neurology, University of Maryland School of Medicine, Baltimore (Dr Price); Department of Medicine, Wake Forest University, Winston-Salem, NC (Dr Applegate); National Institute on Aging, Bethesda, Md (Dr Guralnik); Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pa (Dr Kuller); Department of Preventive Medicine, Northwestern University Medical School, Chicago, Ill (Dr Stanler); and Department of Medicine, University of Washington, Seattle (Dr Probisfield). A complete list of the SHEP Cooperative Research Group was published previously (JAMA. 1991;265:3255-3264).

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Art was made to disturb, science reassures. —Georges Braque (1882-1963)