Morbidity and Mortality in the Systolic Hypertension in the Elderly Program (SHEP) Pilot Study

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The pilot study of the Systolic Hypertension in the Elderly Program was a randomized, double-blind, placebo-controlled trial of drug therapy for isolated systolic hypertension. It followed 551 elderly participants with untreated blood pressures of >160/<90 mm Hg for an average of 34 months. Mean age of the participants was 72 years; 63% were women, and 82% were white. Pretreatment blood pressures averaged 172/75 mm Hg. Participants were randomly assigned to treatment with chlorthalidone or placebo as Step I medication. Blood pressures at annual visits averaged 141/68 and 157/73 mm Hg for the drug-treated and placebo-treated groups, respectively, with 60% and 33% of the survivors on blinded medication having systolic blood pressures of <160 mm Hg at their last annual visit. All-cause mortality rates for the drug-treated and placebo-treated groups were 25.4 and 22.7 deaths per 1,000 participant-years of risk, and rates for definite "first stroke" were 8.3 and 12.8 per 1,000 years of risk. Differences between groups were significant for systolic and diastolic blood pressure but not for death or stroke rates. A full-scale study has begun to determine the effects of drug therapy for isolated systolic hypertension on stroke and mortality rates. (Stroke 1989;20:4-13)

Isolated systolic hypertension (ISH) is conventionally characterized by systolic blood pressure of ≥160 mm Hg and diastolic blood pressure of <90 mm Hg. ISH is rare before the age of 50 years; thereafter, its incidence rises until by the age of 75 years it is present in more than a quarter of Americans. The most important complications of ISH are stroke, left ventricular failure, and myocardial infarction. Together these complications result in a severalfold excess risk of cardiovascular mortality. This excess risk is well established; the major unanswered question with respect to ISH in the elderly is whether available antihypertensive treatment can prevent or delay its catastrophic cardiovascular complications.

The pilot study of the Systolic Hypertension in the Elderly Program (SHEP-PS) was undertaken as the first step in seeking an answer to this question. In this randomized, double-blind, placebo-controlled trial, 551 participants 60 years of age or older who had ISH were followed for an average of 34 months. Treatment with diuretic, plus a second antihypertensive agent if needed, was compared with treatment with placebo. The major purpose of SHEP-PS was to test the feasibility of recruitment and the efficacy and acceptability of the treatment regimen. An analysis of the 1-year results demonstrated compliance with the study protocol and control of blood pressure; however, it did not consider the morbid events.1
SHEP-PS was not designed with a large enough sample or a long enough follow-up to provide definitive information on whether antihypertensive therapy diminished complications. It did, however, develop a surveillance system for discovering and assessing morbid events and deaths. Stroke was selected as the primary end point because it is a major cause of morbidity and mortality associated with ISH in the elderly and because trials involving the treatment of diastolic hypertension suggested that stroke was the complication most likely to respond favorably to treatment.2-7 All-cause mortality was also considered an important index of overall benefit.

Subjects and Methods

The design and general methodology of SHEP-PS, including the protocol, recruitment, and a description of the participants at randomization, have been reported2-8,9 and are therefore summarized only briefly here. Morbid events and deaths have not been considered previously and are therefore treated more fully. The 551 randomized participants were selected from a total of 27,199 individuals 60 years of age or older.9 Sixty-one percent of those screened denied taking antihypertensive medication. Of this untreated group, 16% had systolic blood pressures of ≥160 mm Hg and diastolic blood pressures of <100 mm Hg at screening and therefore qualified for the first baseline visit. After three baseline visits, 426 (2.6% of all untreated individuals screened) were randomized, having met blood pressure criteria (systolic blood pressure of 160-239 mm Hg and diastolic blood pressure of <90 mm Hg) and other eligibility criteria. The remaining randomized participants came from the 696 individuals taking antihypertensive drugs at screening who agreed (with their physician's permission) to carefully supervised withdrawal of medication. After meeting the same blood pressure and other eligibility criteria as the untreated participants, 125 of them were randomized.

Of those randomized, 63% were women, 18% were nonwhite, and 11% were smokers. The average baseline blood pressure of all participants after sitting for 5 minutes (average of four values obtained with a random-zero sphygmomanometer, two each at the second and third baseline visits) was 172/75 mm Hg, with 22% having systolic blood pressures of >180 mm Hg and 3% of >200 mm Hg. The mean age of the participants at randomization was 72.1 years; all were ≥60, 61% were >70, and 15% were >80 years of age. Their average baseline values for serum cholesterol, creatinine, and glucose concentrations were 238, 1.05, and 110 mg/dl, respectively, and for serum potassium 4.4 meq/l. There were no significant differences between the groups randomized to receive active drugs or placebo for any baseline parameter. Resting electrocardiograms (ECGs) at baseline and annual visits were assessed in the laboratory used for the Multiple Risk Factor Intervention Trial (MRFIT) using MRFIT criteria.10

Participants were randomly assigned in a double-blind fashion to receive 25 mg/day chlorthalidone or placebo; the ratio of assignment was 4:1 to permit the expected comparison among Step II medications. Randomization took place in five clinical centers between July 1981 and July 1982, with 443 participants being assigned to chlorthalidone and 108 to placebo. Clinic visits were scheduled at 4-week intervals until goal systolic blood pressure was achieved (systolic blood pressure of <160 mm Hg and >20 mm Hg below baseline level) on two consecutive visits, after which maintenance visits were scheduled at 8-week intervals. If goal systolic blood pressure was not achieved 4 weeks after randomization and if no adverse effects were noted, dosage was doubled. If goal systolic blood pressure was not achieved 12 weeks after randomization, the participant was randomized a second time to a Step II medication (hydralazine, reserpine, metoprolol, or placebo for those initially randomized to chlorthalidone; placebo for those initially randomized to placebo); if goal systolic blood pressure was not achieved in another 12 weeks, dosage of the Step II medication was doubled to give the maximum protocol dosage. For participants not at maximum dosage, medication was increased whenever systolic blood pressure was above goal for two consecutive visits. Of the 408 participants still taking study medications at the end of SHEP-PS, 41% of the drug-treated and 85% of the placebo-treated group were receiving doubled doses of Step I medication; 13% and 57%, respectively, were also receiving a Step II medication.

Hypertensive and atherosclerotic events are defined in Table 1. Hypertensive events included stroke, left ventricular failure, and transient ischemic attack. The criteria for stroke were a neurologic deficit that appeared acutely, persisted for at least 24 hours unless death supervened, and included specific localizing findings such as paresis, sensory deficit, or speech disturbance, combined with the reasonable exclusion of other diagnoses such as trauma or neoplasia; isolated nonspecific complaints such as dizziness or headache were insufficient for a diagnosis of stroke. Hospital records were available for all cases classified as stroke, and for half of them computed tomograms (CT scans) were available. Atherosclerotic events were myocardial infarction, sudden death, angina pectoris, coronary artery surgery, and peripheral vascular disease (Table 1). Noncardiovascular events included all other events that resulted in hospitalization, plus any additional events considered to be clinically significant.

For any participant with two or more events, one was designated the study event based on a hierarchical classification headed by death followed by four categories of nonfatal events in rank order of stroke, other hypertensive events, atherosclerotic
group assignment, each member made a diagnosis and two internists. Working independently and Morbidity and Mortality Committee (a neurologist event was assembled at the Coordinating Center, it was copied and mailed to the three members of the

When the necessary documentation for a morbid event was assembled at the Coordinating Center, it was copied and mailed to the three members of the Morbidity and Mortality Committee. Working independently and without knowledge of the participant’s treatment group assignment, each member made a diagnosis based on the criteria of Table 1. The diagnosis of “no event” was also acceptable and was the final diagnosis for five suspected morbid events. A diagnosis was accepted when the three members agreed unanimously. There were 33 events (of 278) without unanimous mail ballot agreement. For all 278 events, agreement among committee members ranged from a low of 80% for strokes to a high of 94% for other hypertensive events. These 33 nonunanimous cases were all resolved unanimously at semiannual meetings of the Morbidity and Mortality Committee.

Analysis was by intention to treat according to randomization to Step I medication (chlorthalidone or placebo), regardless of whether a Step II medication was added subsequently. Statistical significance of the difference in blood pressures between the drug-treated and placebo-treated groups was calculated using a t test. Follow-up time for each participant was taken as the time from randomization to either the study event or January 1, 1985, an average of 34, with a range of 29–42, months. Throughout this article, event rates are expressed as number per 1,000 participant-years of risk. Cumulative rates for the major study events and for death are based on the Kaplan-Meier (product-limit) survival curve estimate. Confidence intervals for the odds ratios were calculated using the methods described in Fleiss. All analyses were performed on the IBM 4341 mainframe computer at the University of California, Berkeley, using the Statistical Analysis System.

Results

At the end of SHEP-PS, the vital status of all participants was known; 512 were alive. The per-
percentage of survivors attending annual visits was similar for the two treatment groups. The percentage on blinded medication, however, tended to be greater for the drug-treated group, with 70% of those eligible still taking blinded medication at the third annual visit versus 60% of the placebo-treated group. Of those on blinded medication, the percentage of drug-treated participants with controlled systolic blood pressure (<160 mm Hg) was nearly twice that of placebo-treated participants (60% vs. 33%) (Table 2). (Of the 512 survivors at the end of SHEP-PS, 318 [62%], including 61 of the 92 not on blinded medication, had systolic blood pressures of <160 mm Hg and hence might have been expected to get the benefit of that degree of control.)

The decrease in blood pressure between baseline (172/75 mm Hg) and the first annual visit averaged 32/8 mm Hg for the drug-treated and 16/3 mm Hg for the placebo-treated groups. Thereafter, there was little change in blood pressure, and at the third annual visit, the decreases from baseline averaged 30/7 and 15/4 mm Hg, respectively, for the drug- and placebo-treated groups. The difference in the decrease between the drug-treated and placebo-treated groups was significant for both systolic and diastolic blood pressure at all three annual visits (p<0.005).

Figure 2 indicates the percentage of participants in systolic blood pressure ranges throughout SHEP-PS. The hatching emphasizes that, at 1 month after...
randomization, 82% of the drug-treated and 49% of the placebo-treated participants had systolic blood pressures of <160 mm Hg. At 3 months after randomization, these percentages had risen to 90% and 58%, after which there was little further change. This apparently prompt fall in blood pressure was confirmed by average decreases of 27/6 and 11/2 mm Hg at 1 month after randomization for drug- and placebo-treated participants, respectively; at 3 months after randomization, the average decreases were 30/7 and 14/3 mm Hg. The goal for each participant was a systolic blood pressure of both <160 mm Hg and >20 mm Hg below his/her baseline. At 1 month after randomization, 65% of the drug-treated and 24% of the placebo-treated participants had reached their goal systolic blood pressure; at 3 months after randomization, the comparable percentages were 77% and 33%, and at 1 year they were 80% and 40%.

Although eight participants (three receiving drug and five receiving placebo) had systolic blood pressures of ≥220 mm Hg on one visit, only four (one receiving drug and three receiving placebo) had systolic blood pressures as high as 200 mm Hg while on maximal study medication. No significant morbid event occurred while the systolic or diastolic blood pressure was >200 or >100 mm Hg, respectively. Two participants (both receiving drug) developed symptoms ascribed to postural hypotension and had their chlorthalidone dosage reduced to 12.5 mg/day.

During an average of 34 months of follow-up, the 551 study participants had a total of 278 adjudicated events, including 39 deaths. (Of the 39 deaths, eight did not involve hospitalization; of the remaining 239 nonfatal events, 11 were not associated with hospitalization.) Thirty-six events were categorized as hypertensive, 50 as atherosclerotic, and 192 as noncardiovascular. The incidence rates for these three categories were 25, 33, and 128 events per 1,000 participant-years of risk, respectively. The most common noncardiovascular event was neoplasia; there were a total of 37 cases of neoplasia, including 13 deaths.

Two thirds of the randomized participants had no event during SHEP-PS. One third (183 participants) had at least one event, and 63 had multiple events (with 39, 17, 6, and 1 having two, three, four, and five events, respectively). Fourteen participants with multiple events had at least one hypertensive complication, and five had two or more hypertensive complications. For every participant with multiple events, one event was selected as the study event for the purpose of comparing outcomes in the two treatment groups (see “Subjects and Methods”).

![Figure 2. Distribution of systolic blood pressure by Step I treatment groups, pilot study of the Systolic Hypertension in the Elderly Program. Hatched area, percentage of participants with systolic blood pressures of <160 mm Hg; numbers on right, levels of systolic blood pressure. Vertical distance between lines indicates percentage of participants with systolic blood pressures between levels. All participants whose blood pressures were obtained are included, regardless of whether they were on their randomized regimen.](http://stroke.ahajournals.org/)

Table 2. Follow-up Rates and Blood Pressure Control by Step I Treatment Group at Three Annual Visits, Pilot Study of the Systolic Hypertension in the Elderly Program

<table>
<thead>
<tr>
<th>Year</th>
<th>Eligible No.</th>
<th>Attended %</th>
<th>On blinded medication No.</th>
<th>Systolic blood pressure &lt;160 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-treated group (443 participants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>432</td>
<td>401</td>
<td>93</td>
<td>363</td>
</tr>
<tr>
<td>2</td>
<td>427</td>
<td>363</td>
<td>85</td>
<td>326</td>
</tr>
<tr>
<td>3</td>
<td>281</td>
<td>224</td>
<td>80</td>
<td>198</td>
</tr>
<tr>
<td>Placebo-treated group (108 participants)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>107</td>
<td>104</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>92</td>
<td>88</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>61</td>
<td>84</td>
<td>44</td>
</tr>
</tbody>
</table>
The 443 drug-treated participants had 140 study events, for a rate of 110.9 events per 1,000 participant-years of risk, whereas the 108 placebo-treated participants had 43 study events, for a rate of 139.7. Table 3 presents the numbers and incidence rates of hypertensive and atherosclerotic events. None of the tabulated differences is significant (p<0.05), nor were there significant or suggestive differences in the incidence of noncardiovascular events.

There were 19 strokes, 13 (two in one patient and one not a study event) in the drug-treated and six in the placebo-treated group. Thus, 17 of the 19 strokes were study events (Table 3). The drug-treated group had 11 definite “first strokes,” while the placebo-treated group had four, giving rates of 8.3 and 12.8 strokes per 1,000 participant-years, respectively, a difference that did not approach significance. If the three possible strokes are included (one in the drug-treated and two in the placebo-treated group), the incidence rates become 9.0 and 19.2, with a probability value of 0.14 (Table 4).

Eighteen study events categorized as hypertensive occurred in the drug-treated and 10 in the placebo-treated group, for rates of 14.3 and 32.5 per 1,000 participant-years. Twenty-six atherosclerotic study events occurred in the drug-treated and 10 in the placebo-treated group, for rates of 20.6 and 32.5. The rates for left ventricular failure, myocardial infarction, and sudden death ranged from 4.8 to 6.5 in each group (Table 3). If these three events are combined with strokes to form a combined major event category, 32 such events occurred in the drug-treated and 12 in the placebo-treated group, for rates of 26.2 and 38.9 (Table 4). Finally, the rates for all coronary heart disease events (myocardial infarction, sudden death, angina pectoris, and coronary artery surgery) were 18.9 and 21.7, respectively.

Figure 3 presents cumulative frequency curves for the combined major event category and for all fatal events. There was relatively little increase in either rate during SHEP-PS. For the combined major event category, the curve for the placebo-treated group was consistently above that for the drug-treated group, although the difference never reached significance. The all-cause mortality curves were very similar for the two treatment groups at all times.

Of the 39 fatal events, 32 occurred in the drug-treated and 7 in the placebo-treated group; the rates for all-cause mortality were 25.4 and 22.7 per 1,000 participant-years, respectively (Table 4). There were two fatal strokes in each treatment group. The only other fatal hypertensive complications were three episodes of left ventricular failure, all in the drug-treated group. There were 12 fatal atherosclerotic complications; all were either myocardial infarction or sudden death. Of these 12 participants, four had normal and eight had abnormal ECGs at baseline according to MRFIT criteria. Of the four participants with normal ECGs, two were in the drug-treated and two were in the placebo-treated group; of the eight participants with abnormal ECGs, seven were in the drug-treated and one was in the placebo-treated group.

Discussion

Lowering elevated diastolic blood pressure in patients 60 years of age or older lowers the incidence of cardiovascular events. Moreover, the incidence of first stroke, recurrent stroke, and heart failure may be closely related to how well hypertension is controlled. It is now generally accepted that diastolic hypertension should be...
TABLE 4. Death, Stroke, and Combined Major Events by Step I Treatment Groups, Pilot Study of the Systolic Hypertension in the Elderly Program

<table>
<thead>
<tr>
<th>Event</th>
<th>Drug-treated group (n=443)</th>
<th>Placebo-treated group (n=108)</th>
<th>Odds ratios (drug/placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all-cause)</td>
<td>32</td>
<td>7</td>
<td>1.12</td>
</tr>
<tr>
<td>Definite first stroke (fatal and nonfatal)</td>
<td>11</td>
<td>4</td>
<td>0.66</td>
</tr>
<tr>
<td>Definite first+possible stroke (fatal and nonfatal)</td>
<td>12</td>
<td>6</td>
<td>0.47</td>
</tr>
<tr>
<td>Combined major events</td>
<td>31</td>
<td>14</td>
<td>0.62</td>
</tr>
</tbody>
</table>

There were 19 strokes, with one drug-treated participant having two definite strokes; thus, 18 participants had strokes. Of these 18 participants, 15 had definite strokes and 3 (one drug-treated and two placebo-treated participants) had possible strokes. One definite stroke (in drug-treated participant) included in this table was not a study event because it was followed by a fatal myocardial infarction. Therefore, 17 strokes were study events (Table 3). Combined major events included stroke, left ventricular failure, myocardial infarction, and sudden death. There were 52 major events, but only 44 were study events, and except for one stroke (see above) only study events are considered here. Odds ratios of the differences are given in terms of point estimates and 95% confidence limits, by continuity-corrected $\chi^2$, approximate 0.60 for death, 0.14 for definite first+possible stroke, and 0.29 for combined major events.

SHEP-PS was not designed with sufficient power to provide definitive information on whether treatment of ISH reduced complications. Over the comparatively short average follow-up period of 34 months, 551 participants experienced 278 morbid events, including 39 deaths. One third of all participants experienced at least one morbid event, but only 12% had a cardiovascular event. The excess of participants with major cardiovascular events in the placebo-treated group compared with the drug-treated group (11% vs. 7%) did not reach significance in this relatively small sample. The surprisingly large decrease in the average systolic blood pressure of the placebo-treated group, which at the annual visits was more than half of the decrease for the drug-treated group, may have contributed to our failure to observe benefit from drug treatment. Most placebo-treated participants had systolic blood pressures of <160 mm Hg and hence had whatever benefit was associated with this degree of blood pressure control.

Despite uncertainty as to how well the elderly were likely to comply with an antihypertensive regimen, four fifths of all randomized participants continued through their last scheduled visit, an average of almost 3 years, and three fifths of the surviving participants in the the drug-treated group both remained on their blinded medication and had systolic blood pressures of <160 mm Hg. SHEP-PS clearly demonstrated that systolic blood pressure can be lowered easily and quickly; moreover, control can be achieved with moderate doses of chlorthalidone alone (59% of the drug-treated participants still on blinded medication were taking only 25 mg/day at the end of SHEP-PS). The regimen we used produced no serious adverse effects and no unusual or unexpected side effects, and it was well tolerated. With respect to safety, only one drug-treated participant had a systolic blood pressure of >200 mm Hg on maximum study drug, and there were no disturbing elevations of diastolic blood pressure. Only two drug-treated participants had a postural fall in blood pressure that required a change in medication.

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in the regimen. No events were associated with systolic or diastolic blood pressure escape or with postural hypotension.

There has been concern that antihypertensive therapy in the elderly might affect mood and cognition. Adverse effects of drugs are thought to increase with age and to be proportional to the intensity and frequency of drug exposure.25-28 In addition, there are indications that hypertensive subjects perform less well on tests of intellectual function and psychomotor response29,30; however, it has been suggested that administration of antihypertensive agents may reverse this pattern (B. Gurland, J. Teresi, W. McFate-Smith, D. Black, G. Hughes, and S. Edlavitch, unpublished observations). As reported in more detail elsewhere, active antihypertensive therapy had no adverse effect on mood or cognition of the SHEP-PS participants.31

The randomized participants were selected from a total screened population of 27,199 individuals 60 years of age or older. Those randomized were slightly older and more highly educated than those screened. Except for deliberate oversampling of blacks and those over 70 years of age, the randomized cohort resembled the population of the United States, although our selection criteria probably resulted in unusually healthy participants. Moreover, their elevations of systolic blood pressure tended to be mild, with 78% having baseline blood pressures of 160-180 mm Hg.9 Thus, it was expected that the morbidity and mortality experience of this cohort would compare favorably with that of the general population even without any benefit from antihypertensive therapy. The overall death rate of 2.5%/yr is less than predicted for a population of this age. The observed stroke rate in the placebo-treated group (1.7%/yr), though based on numbers too small to provide a precise estimate, is close to the predicted rate of 1.6%/yr used in calculating the sample size for the full-scale SHEP clinical trial now under way, a rate based in part on observations from the Framingham Study.19

The hypertension of the drug-treated participants responded rapidly to Step I of the treatment regimen. At least two-thirds of the decrease in blood pressure occurred during the first month, and most of the remaining decrease had occurred by the third month after randomization. Thereafter, the percentage of participants with controlled blood pressure remained relatively constant. Thus, the initial dose of diuretic was surprisingly effective, and the question arises whether progression to the second dosage of diuretic and then to a second drug may in part have been related to the algorithms for stepping up medications, which called for an increase whenever a participant's systolic blood pressure was above goal on two consecutive visits. For those participants who were close to goal, as the majority presumably were, random variation might have triggered medication step-ups without any real increase in blood pressure.

In an effort to identify as many hypertensive complications, particularly strokes, as possible, our surveillance system was designed to recognize and obtain information on every hospitalization and to make careful inquiry at every visit about symptoms and signs of possible events outside hospitalization. The observed preponderance of noncardiovascular events reflects the causes of hospitalization in this population. The surveillance system produced a data set that was 100% complete for vital status follow-up.

Conclusion

SHEP-PS demonstrated that appropriate patients could be recruited, that diuretic alone was very effective in controlling systolic blood pressure, that the patients complied well with such a regimen, which was well tolerated and not associated with any serious or unexpected adverse effects. SHEP-PS was not designed to have sufficient power to detect significant differences between treatment groups, and none was observed; however, depending on the criteria used, there was as much as a (nonsignificant) twofold difference in stroke rates favoring drug treatment.

The observed event rates were consistent with those reported in the literature and were used in estimating the sample size required for a definitive full-scale clinical trial to determine whether antihypertensive treatment can reduce the excess cardiovascular risk associated with ISH. In design, the full-scale clinical trial resembles the pilot study described here, with the major difference being that subjects were randomized in equal numbers to a placebo or a drug treatment regimen. Although the dosage of the Step I drug and the nature of the Step II drug is different, the drug regimen continues to have a maximum of four dosages, with the initial and doubled dose of chlorthalidone being 12.5 and 25 mg/day and the Step II drug being atenolol at doses of 25 and 50 mg/day or, for those unable to take atenolol, reserpine at a dose of 0.05 mg/day. In addition, there was concern that for patients whose treatment was discontinued before randomization, the washout period might not be long enough for persisting diastolic hypertension to recur; hence, such patients were required to have diastolic blood pressures of <85 mm Hg in order to be randomized. Finally, in the full-scale trial, an effort is being made to subdivide strokes into hemorrhagic, ischemic, and unknown types, although the primary end point will continue to be all strokes.

Until results of the full-scale trial are forthcoming, the decision to treat ISH must be individualized. General recommendations are not warranted in the absence of definitive data.

Appendix 1. Systolic Hypertension in the Elderly Research Group

Clinical Centers. University of Alabama at Birmingham, Birmingham, Alabama: H. Schnaper, MD (principal investigator), G. Hughes, PhD (coprin-
principal investigator); Rush—Presbyterian—St. Luke's Medical Center, Chicago, Illinois: J. Schoenberger, MD (principal investigator), G. Neri, MD (co principal investigator), E. Plank, RN (nurse coordinator); University of Pittsburgh, Pittsburgh, Pennsylvania: L. Kuller, MD, DPH (principal investigator), R. McDonald, MD (co principal investigator), B. Gahagan, RN (nurse coordinator); Kaiser Permanente Center for Health Research, Portland, Oregon: M. Green, PhD (principal investigator), T. Vogt, MD, MPH (co principal investigator), G. Bailey, RN (nurse coordinator), J. Wild, MD (coinvestigator), J. Bailey (coinvestigator); Washington University, St. Louis, Missouri: H. M. Perry, MD (principal investiga tor), G. Camel, MD (coprincipal investigator).

Coordinating Center. University of California, San Francisco, California: S. Hulley, MD, MPH (principal investigator), W. M. Smith, MD, MPH (past principal investigator), S. Edlitch, PhD (past co principal investigator), D. Feigal, MD, MPH (clinical epidemiologist), D. Black, PhD (statistician), A. Bagniewska, MA (data manager), C. Ireland, MA, MPH (deputy director), J. Smith, RN (nurse coordinator). Boston University School of Medicine, Boston, Massachusetts: P. A. Wolf, MD (consulting neurologist).

Behavior Evaluation Laboratory. Center for Geriatrics and Gerontology, Columbia University, New York, New York: B. Gurland, MD (principal investigator), J. Challop-Luhr, PhD, R. Golden, PhD. Electrocardiogram Laboratory. Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota, Minneapolis, Minnesota: R. Prineas, MD (principal investigator).

National Institutes of Health Project Offices. National Heart, Lung, and Blood Institute, Bethesda, Maryland: C. D. Furberg, MD (project officer), T. Blaszkowski, PhD, J. A. Cutler, MD; National Institute of Aging, Bethesda, Maryland: G. Steinberg, PhD; National Institute of Mental Health, Bethesda, Maryland: N. Miller, PhD.

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