Part 1: Rationale and Design

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Hypertension is a recognized community health problem of immense magnitude. The association between elevated blood pressure and premature mortality has been demonstrated consistently in the United States and other countries.  1,8 The efficacy of sustained and rigorous treatment in reducing excess deaths due to hypertension has also been proved. 9,14 Most trials have dealt with the problem of diastolic hypertension; that is, elevated diastolic blood pressure (DBP) has been the focus of attention and consideration. Findings of epidemiological studies show, however, that SBP is also a significant predictor of mortality and morbidity, especially among older persons. 1,4,7,14-20 Moreover, these studies demonstrate that elevated SBP with normal DBP (i.e., isolated systolic hypertension [ISH]) is associated with increased long-term risks of cardiovascular disease. Ability of antihypertensive treatment to alleviate the potential risks of ISH has not been clarified.

In most populations, blood pressure is generally progressively higher with increasing age. However, SBP and DBP follow different patterns in this regard. When hypertension is defined on the basis of DBP (i.e., DBP of 90 mm Hg or more), the prevalence rate in the general population increases steadily with age into middle age (e.g., 50-54 or 55-59 years), reaches a plateau, and then tends to decrease with older age. However, when SBP is used as the criterion of hypertension (i.e., SBP of 140 mm Hg or more), prevalence continues to increase well beyond the 55-59-year-old age group. It has been estimated that for persons of age 80 compared with persons of age 60, average SBP is higher by about 20 mm Hg. As a consequence of these age-specific patterns of SBP and DBP, prevalence of ISH is progressively higher in later life. Thus, in persons less than 55 years old, ISH (SBP of 160 mm Hg or more and DBP less than 90 mm Hg) prevalence is low; it increases markedly among persons 55 years old and older. 1 In the National Health and Nutrition Examination Survey of 1976-1980 (NHANES-II) involving a probability sample of the US population, prevalence of ISH among Americans aged 55-74 years was higher in women than in men (6.3% versus 4.5%) and higher in blacks than in whites (8.1% versus 5.2%) (Table 1.1). 2

Prevalence of Isolated Systolic Hypertension

The SHEP pilot study (SHEP-PS) provided additional data on prevalence of ISH among older Americans. In the SHEP-PS, prevalence of ISH was 6% in the 60-69-year-old age group, 11% in the 70-79-year-old age group, and 18% in those 80 years old or older. 1,23 Population-based surveys have recorded even higher prevalence rates of ISH among Americans 60-69 years old. 2,24

In 1985, 12% (28.6 million people) of the US population was 65 years old or older. This percentage is predicted to increase to 19.5%, or 58.7 million people, by 2025. 25 Furthermore, the fastest growing segment of the population is the "oldest old," those 80 years old or older. This group included 6.2 million people in 1985 and is projected to increase to 14.5 million by 2025. 16,18

Based on these demographic data and the findings of the SHEP-PS on ISH prevalence by age, the number of people with ISH in the United States in 1985 and 2025 in the age groups of 60-69, 70-79, and 80+ years can be readily estimated (Table 1.2). 25 There will probably be close to 8 million people 60 years old or older with ISH by 2025.

Mortality Risks With Isolated Systolic Hypertension

Rates of morbidity and mortality in a given population increase progressively with higher levels of SBP. 1 ISH in older persons is an established risk factor for major cardiovascular diseases, including nonfatal and fatal stroke. Both prospective epidemiological investigations and life insurance actuarial studies in the United States demonstrate the risk associated with ISH. 1-4,7,14,16,20 For example, data from the Build and Blood Pressure Study by the Society of Actuaries show a mortality ratio (i.e., ratio of actual to expected mortality x 100) of 238 among men in the 60-69-year-old age group with SBP of 158-167 mm Hg and DBP of 88-92 mm Hg. 1 For women in the same age group and with similar blood pressure ranges, the corresponding mortality ratio was 174. In another prospective study of persons 65-74 years old, ISH at baseline (here defined as

\[\text{Deceased.}\]
SBP of 180 mm Hg or more and DBP less than 95 mm Hg) was associated with a twofold increase in risk of cardiovascular death and an almost threefold increase in risk of stroke. Such excess risks due to ISH prevail not only for older persons but also for middle-aged persons. In another prospective investigation, white men 40–59 years old with ISH (SBP of 140 mm Hg or more and DBP less than 90 mm Hg) who were followed for 15 years had 1.7-fold the mortality rate from all causes as those with a normal blood pressure (SBP less than 140 mm Hg and DBP less than 90 mm Hg) (actual incidence, 277 per 1,000 versus 163 per 1,000), 1.9-fold the mortality rate from cardiovascular diseases (156 per 1,000 versus 83 per 1,000), and 2.0-fold the mortality rate from coronary heart disease (118 per 1,000 versus 58 per 1,000). Similar findings are available from the 6-year follow-up of the approximately 350,000 US men 35–57 years old screened in 1973–1975 for eligibility for the Multiple Risk Factor Intervention Trial (MRFIT). Clearly, given its current and expected prevalence rates and associated risks, ISH is a substantial problem. There is a paucity of information on the efficacy of treatment of ISH with antihypertensive drugs. No adequate trial has been completed to determine the effects of antihypertensive treatment on the risks of morbidity and mortality in elderly persons with ISH. The purpose of SHEP is to resolve this problem.

### Table 1.1

| Prevalence of Isolated Systolic Hypertension (SBP > 160 mm Hg and DBP < 90 mm Hg) in the Age Group 55-74 Years, by Sex and Race* |
| United States, 1976-1980 |
| Prevalence of ISH (%) |
| Age Group (years) | Men | Women |
| White | Black | White | Black |
| 55-74 | 4.5 | 4.2** | 5.8 | 11.3 |

* Data from the National Health and Nutrition Examination Survey (NHANES-II)²¹.

** Numbers are too small to meet standard of reliability or precision.

### Table 1.2

| Estimated Number of Persons with ISH* in the United States, by Age Group, for the Years 1985 and 2025** |
| Year 1985 | Year 2025 |
| Age Group (years) | No. of persons (in 1,000) | No. with ISH (in 1,000) | No. of persons (in 1,000) | No. with ISH (in 1,000) |
| 60-69 | 20,157 | 1,209 | 37,899 | 2,274 |
| 70-79 | 13,197 | 1,452 | 26,071 | 2,868 |
| 80 and over | 6,204 | 1,116 | 14,467 | 2,604 |

* ISH = Isolated systolic hypertension (SBP ≥ 160 mm Hg and DBP < 90 mm Hg)

** Based on prevalence of ISH in respective age groups from the SHEP Pilot Study (unpublished data) and the population projection for each age group by the U.S. Bureau of the Census²².
Historical Background of SHEP

SHEP traces its origins to the US Public Health Service Hospitals and the Veterans Administration Cooperative Studies trials in hypertension, whose leadership and policy advisory boards had overlapping membership. As early as 1973, hypertension in the elderly was identified as a high priority area, and both groups recommended a randomized, double-blind trial. Preliminary sample size calculations indicated the need for at least 10 centers with a total of 4,500 participants (300 for each center, except one that has 200), based on incidence of fatal and nonfatal stroke as the primary end point. Five US Public Health Service Hospital centers and six additional medical centers collaborated in the development of an investigator-initiated grant application that was submitted to the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Aging (NIA), and the National Institute of Mental Health (NIMH) in 1978. This grant application addressed the question of whether the treatment of predominantly ISH in men and women 60 years old or older with currently available pharmacological agents would significantly reduce the risks of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke. The application was also designed to assess the effects of this treatment on the incidence of dementia and depression as part of the disease process or as a consequence of pharmacological process. The application was reviewed by NHLBI in 1978, and revisions were suggested.

In January 1979, NHLBI sponsored a workshop on hypertension in the elderly that addressed the appropriate goal of SBP reduction, the optimum pharmacological regimen in the elderly, the impact of anti-hypertensive treatment on behavioral and cognitive functions, and the problem of adherence to drug regimens in the elderly. The conference concluded that a trial should be undertaken on the efficacy of drug treatment for older persons with ISH.

A revised application for the study was submitted in February 1979, and a reverse site visit occurred in June. Approval was recommended after further review by a special ad hoc committee of the NHLBI Advisory Council, which considered protocol issues. A specific recommendation was made to include only individuals with DBP less than 90 mm Hg. Other concerns included the choice of drugs, starting dosages, and potential consequences of side effects in older persons. It was further recommended that if the pilot study was successful, the full-scale study should be done via the institutes' contract mechanism.

SHEP Pilot Study

In February 1980, the NHLBI and NIA advisory councils unanimously recommended approval of the grant application but only for the pilot phase. The NIMH also provided financial support for the pilot study.

Detailed planning for implementation of the pilot study began in 1980. The Steering Committee comprised the principal investigators of the five clinical centers (Kaiser Permanente Center for Health Research, Portland, Ore.; Washington University, St. Louis; University of Pittsburgh; Rush-Presbyterian-St. Luke's Medical Center, Chicago; and the University of Alabama at Birmingham) and the Coordinating Center at the University of California, San Francisco. The NHLBI program staff participated actively in the planning process.

Objectives. SHEP-PS was designed to test the feasibility of a full-scale trial. The specific objectives of SHEP-PS were 1) to assess the feasibility of recruiting and retaining 500 elderly participants with ISH in a long-term, double-blind, placebo-controlled trial and to estimate and compare the yield of participants for randomization from various community groups with the use of different recruitment techniques; 2) to estimate adherence to the visit schedule and to prescribed double-blind treatment regimens; 3) to estimate the efficacy of the prescribed antihypertensive medications for reduction of high SBP; 4) to estimate unwanted effects of such medication in older people; 5) to evaluate feasibility and effectiveness of periodic behavioral assessment of the participants; and 6) to develop and test methods for determination of stroke and other disease end points.

Recruitment. The feasibility of recruiting an elderly population for the study was successfully demonstrated. Recruitment began in July 1981 and was completed 1 year later with each center having enrolled more than 100 participants from a total of 27,299 persons screened. The five clinical centers randomized a total of 551 participants. Among untreated but otherwise selected age-eligible persons, 2% of screened participants were enrolled in the study; in selected samples, the yield was greater. More than one third of persons screened for SHEP-PS were on hypertensive treatment; among those willing to be taken off therapy, almost one fifth of the participants were randomized.

Adherence. SHEP-PS participants adhered very well to the visit schedule. During the first year, approximately 90% of visits occurred within the established visit window. Self-report, pill count, and urinalysis data indicated that almost 90% of active SHEP-PS participants were excellent adherers to the treatment regimen throughout the first year of follow-up.

Percentage termination from SHEP medication during the first year was estimated at 18.5%, with a somewhat higher proportion in the placebo group (20%) than in the active treatment group (17%). Approximately one half of all terminations were at the request of the participant. Alteration in SHEP-PS medication without termination occurred in 7.1% of the group on active drug and 4.0% of the placebo group.

Diuretic efficacy. A satisfactory SBP response to medication was considered a decrease of 20 mm Hg or to below 160 mm Hg, whichever was lower. Three
months after randomization, 75% of those on chlorthalidone were at or below the goal compared with 34% of those on placebo. The decrease in SBP was 17 mm Hg greater in those on chlorthalidone than in placebo recipients at 3 months; the DBP decrease was 3 mm Hg greater. Thus, there was a prompt response to diuretic that predominantly involved SBP, and this difference was maintained at 12, 24, and 36 months.

Adverse effects. When specifically queried, approximately one half of both active and placebo participants reported symptoms at each visit, including visits before treatment began. Few symptoms were deemed troublesome by more than 10% of either group, and only 2% of the entire group reported intolerable symptoms.

There were shifts toward lower mean serum potassium and higher mean uric acid levels in the chlorthalidone group compared with the placebo group, but no differences were noted in other laboratory parameters. The frequency of ectopic beats and other arrhythmias was low and comparable for the two groups.

Behavioral assessment. Behavioral assessment consisting of an evaluation of cognitive, emotional, and physical functions was well accepted by the participants, and logistics was not a problem.

End point determination. Methods for determining stroke and other disease end points were developed and found to be feasible.

Transition From SHEP Pilot Study to SHEP Trial
With the successful completion of recruitment for SHEP-PS and promising early intervention results, NHLBI and NIA initiated the planning process for a full-scale trial. After having obtained concurrence from their respective national advisory councils, the institutes circulated requests for proposals soliciting candidate organizations to serve as clinical centers or as a coordinating center for SHEP. From a large number of proposals, 17 (later reduced to 16) institutions were selected as clinical centers, and a contract was awarded to a coordinating center to provide data management, statistical, central laboratory, and administrative support. Development of the detailed definitive protocol formally began in July 1984.

SHEP Trial
SHEP was planned as a randomized clinical trial to be performed in multiple centers to achieve the needed large sample size. Men and women 60 years old or older who had ISH were to be recruited into a double-blind, placebo-controlled, stepped-care treatment program and followed for an average of 5 years (range, 4–6 years). The primary end point of the trial is fatal plus nonfatal stroke.

Objectives
Primary hypothesis. The primary hypothesis to be tested in SHEP is whether long-term administration of antihypertensive therapy to older persons with ISH (SBP of 160 mm Hg or more and DBP less than 90 mm Hg) reduces the combined incidence of fatal and nonfatal stroke during a 5-year period. Incidence of total stroke (fatal and nonfatal) was selected as the primary end point because it is the major cardiovascular complication most strongly associated with level of SBP, and it is the event most conclusively affected by drug treatment of hypertension. To accomplish this objective, 4,800 persons with ISH were to be recruited into the clinical trial. One half the participants were to be randomly assigned to a stepped-care regimen of antihypertensive drug therapy, and one half were to be assigned to identical placebo.

Secondary objectives. SHEP also aims to assess the cardiovascular, including coronary, effect of long-term antihypertensive therapy on morbidity and mortality in older people with ISH; the effect of long-term antihypertensive therapy on other selected morbidity (e.g., dementia, clinical depression, deterioration of cognitive function) and on mortality from any cause; the possible adverse effects of long-term use of antihypertensive drug treatment in the participants; the effect of therapy on quality-of-life indexes such as hospital and nursing home admissions, days of restricted activity, level of functional impairment, and incidence of fracture of hip, wrist, or vertebra; and the natural history of ISH in the placebo group.

Subgroup hypotheses. In addition to the primary hypothesis, two prior subgroup null hypotheses were formulated: The change in incidence of total stroke due to treatment of ISH is the same in those not on antihypertensive medication at time of initial screening as in those on such medication; and the change in incidence of sudden cardiac death or of cardiac death plus nonfatal myocardial infarction is the same in those with resting electrographic abnormalities as in those with normal electrocardiograms. Although other subgroup hypotheses regarding presence or absence of prior cardiovascular diseases and demographic and personal characteristics were considered, plausible expected differences in relative effects of treatment gave a power of less than 50%. Therefore, they were not included as formal prior subgroup hypotheses.

Other Aspects of SHEP Design
Power calculations and sample size for the primary hypothesis. To test the primary hypothesis, a sample size of 4,800 participants was estimated for SHEP. This number was based on the following: 1) The primary end point is fatal plus nonfatal stroke (one third fatal and two thirds nonfatal); 2) the average follow-up period is to be 5 years (6 years for the first randomized participant); 3) based on the SHEP-PS experience, the annual rate for fatal plus nonfatal stroke in the placebo group will be 1.6% (or a 5-year rate of 7.75%); 4) the proportion of participants on active medication who terminate or substantially reduce study medication (drop-out rate) will be 7% in the first year and 3.5% in each of the second
Table 1.3

Major SHEP Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong> ≥ 60 years</td>
<td>Atrial fibrillation or flutter, A-V block, multifocal VPBs, heart rate less than 50 beats per minute, or permanent pacemaker</td>
</tr>
<tr>
<td><strong>Baseline BP:</strong> SBP 160-219 mm Hg, DBP &lt; 90 mm Hg</td>
<td>Stroke with residual paresis, myocardial infarction or coronary bypass surgery during the past six months, insulin dependent diabetes, dementia, or alcohol abuse</td>
</tr>
</tbody>
</table>

* Average of Baseline Visits 1 and 2.

through fifth years; 5) the proportion of participants on placebo who are placed on antihypertensive treatment (drop-in rate) will be 9% in the first year and 4.5%, 5.0%, 5.5%, and 6.0% in each of the remaining 4 years, respectively; 6) after allowance for drop-out in the active group and drop-in in the placebo group, the anticipated net reduction in total stroke rate for the active group decreases from 40% to 32%; 7) based on US vital statistics data, the competing risk of nonstroke death will be 15.4%\(^3\); and 8) a two-tailed significance level (α) of 0.05 and a power (1-β) of 0.90 were used. These considerations yield a sample size of approximately 4,800 persons 60 years old or older with ISH to be enrolled into the program.

Power calculations for the two subgroup hypotheses. Those taking antihypertensive drugs at first screening and qualifying for the trial after medication withdrawal may represent in part individuals with diastolic hypertension whose blood pressure did not increase to pretreatment levels during drug evaluation visits to the SHEP clinics. If the net reduction in primary end point for those not on medication when initially screened is 40% and the net reduction for those initially on medication is only 10%, then the power to detect the difference in treatment effect is 80% at a two-sided α of 0.05. This power will be similar for detecting the 30–40% effect among participants not on antihypertensive medication (i.e., 80%).

The assumption for the second subgroup hypothesis for participants with certain baseline electrocardiographic abnormalities is that they may be at increased risk for sudden death when treated with antihypertensive agents. If the estimate is that the 5-year sudden death rate will be 1.3% among all participants randomized to the control group, 35% of participants will have electrocardiographic abnormalities, the reduction in rate of sudden death among those with normal electrocardiograms will be 20%, and the sudden death rate in the treated group with electrocardiographic abnormalities is 20% higher than among controls, then the power to detect this difference in treatment effects between those without and those with electrocardiographic abnormalities is 60% at a two-sided α of 0.05. It should be noted that doses of chlorthalidone used in SHEP are lower than those used in previous trials.

Entry criteria. SHEP entry criteria were designed to allow inclusion of age-eligible persons meeting the blood pressure criteria and likely to be able to participate in the study, while excluding individuals with serious comorbid or other factors likely to cause problems with participation or confound the eventual results. A summary of SHEP inclusion and exclusion criteria is given in Table 1.3.

Inclusion criteria. Study inclusion criteria were age of 60 years or older; mean SBP of 160–219 mm Hg and DBP less than 90 mm Hg (average of baseline visits 1 and 2); willingness to comply with study protocol, including scheduled visits, assigned medications, and clinical, laboratory, and behavioral evaluations; and no anticipated change in residence of more than 50 miles (Tables 1.3 and 1.4).

Exclusion criteria. Study exclusion criteria were evidence of atrial fibrillation or flutter, second- or third-degree atrioventricular (AV) block, multifocal ventricular premature beats (VPBs), VPBs in pairs or runs or VPBs more frequent than 10% of beats, or heart rate of less than 50 beats/min; 2) permanent pacemaker; 3) history of stroke with residual paresis or other neurological disability; 4) suspected or established significant renal dysfunction; 5) alcohol abuse (based on clinical judgment); 6) history of coronary bypass surgery or myocardial infarction within the past 6 months; 7) current treatment with insulin, anticoagulants, or drugs having antihypertensive activity; 8) uncontrolled congestive heart failure; 9) malignant neoplasm or other life-threatening dis-
Table 1.4
SHEP Blood Pressure Eligibility Criteria for Persons Not On Antihypertensive Medications and for Persons On Antihypertensive Medications at Initial Contact

<table>
<thead>
<tr>
<th>Visit</th>
<th>Persons Not on Antihypertensive Medication</th>
<th>Persons on Antihypertensive Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Contact</strong></td>
<td>SBP 160-219 mm Hg  DBP &lt; 100 mm Hg</td>
<td>SBP 130-219 mm Hg  DBP &lt; 85 mm Hg</td>
</tr>
<tr>
<td><strong>Drug Evaluation Visit 1</strong></td>
<td></td>
<td>SBP 130-219 mm Hg  DBP &lt; 85 mm Hg</td>
</tr>
<tr>
<td><strong>Drug Evaluation Visit 2</strong></td>
<td></td>
<td>SBP 160-219 mm Hg  DBP &lt; 100 mm Hg</td>
</tr>
<tr>
<td><strong>Baseline Visit 1</strong></td>
<td>SBP 150-219 mm Hg  DBP &lt; 95 mm Hg</td>
<td>SBP 160-219 mm Hg  DBP &lt; 90 mm Hg</td>
</tr>
<tr>
<td><strong>Baseline Visit 2</strong></td>
<td>SBP 150-219 mm Hg  DBP &lt; 95 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and average of BL1 and BL2:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBP 160-219 mm Hg  DBP &lt; 90 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

* Mean of second and third readings of DBP and SBP values at Initial Contact and all Drug Evaluation Visits; mean of two determinations at Baseline Visits 1 and 2.

** Or subsequent visit in evaluation period, up to 8 weeks after withdrawal of antihypertensive medications; participants with SBP less than 160 mm Hg should continue to be followed until SBP is in eligible range, SBP or DBP rise above eligible levels, or the 8-week evaluation period ends.

*** Allow one more visit to qualify if SBP > 220.

... (rest of the text)
pertensive medication and whose single SBP was less than 150 mm Hg were not to be evaluated further. If the first SBP reading was 150 mm Hg or more, two additional blood pressure measurements were to be taken (Table 1.4). For persons meeting blood pressure eligibility criteria at initial contact, initial historical information was to be sought regarding potential exclusions (listed above). Persons still eligible and interested were to be referred to the SHEP clinic for baseline visits.

SHEP design further stipulated that persons who were receiving pharmacological therapy for high blood pressure and were potentially eligible may, with the consent of their personal physicians, undergo drug withdrawal and be followed off antihypertensive medication for as long as 8 weeks (drug evaluation visits). Drug discontinuation could begin during the visit or at any subsequent interim visit in the follow-up period. It was expected that randomization of such a person prescribed medication for known diastolic hypertension. Informed consent was to be required specifically for withdrawal from medications. Three blood pressure determinations were to be taken with the use of a standard mercury sphygmomanometer. Drug withdrawal could begin during drug evaluation visit 1 if the average of the second and third SBP readings was 130–219 mm Hg and DBP was less than 85 mm Hg. It was recognized and incorporated into the protocol that several visits might be necessary, based on the SHEP clinician’s judgment, to completely withdraw medications. During the drug withdrawal period, if SBP was 220 mm Hg or more or DBP was 100 mm Hg or more, the participant was ineligible and was to be referred back to his or her usual source of care or the original medication was to be restarted. Those taken off antihypertensive medication completely were to be given an appointment to be seen in 2 weeks. If at that visit or at any subsequent interim visit in the following 2–6 weeks, the average of the second and third SBP readings was 160–219 mm Hg and average DBP was less than 100 mm Hg, the person was eligible for baseline visit 1. If SBP was 220 mm Hg or more or DBP was 100 mm Hg or more, the participant was ineligible and was to be referred back to his or her usual source of care or the original medication was to be restarted. Medication could be discontinued for as long as 8 weeks to establish blood pressure eligibility. Individuals not qualifying at this time because their blood pressure was not high enough were to be referred back to their usual sources of care. If they remained off hypertensive medication, they were eligible to be rescreened.

The two baseline visits were to establish eligibility based on study inclusion and exclusion criteria (described above), provide orientation to the program, and allow collection of baseline data. At these clinic visits, blood pressure was to be measured with a random-zero device. SBP was defined as the pressure at the first recognized Korotkoff sound. DBP was defined as the pressure at the fifth phase or the last Korotkoff sound heard. Two seated readings were taken at each visit, with the average of the two to be used for eligibility determination.

At baseline visit 1, procedures included a medical and medication history, electrocardiogram, physical examination, and urinalysis. Further detailed description of the design and purpose of the trial was to be given to the potential participant. If the individual was still eligible at baseline visit 2, he or she was to undergo blood pressure measurement, behavioral evaluation, detailed side effects history, and further orientation to the study. If the person was still eligible and willing to participate, randomization was to take place at this visit after a thorough process of informed consent.

Randomization. Immediately after completion of baseline visit 2, eligible participants were to be randomly allocated to either the active or the placebo treatment regimen. Randomization was to be stratified by clinical center and by antihypertensive medication status at initial contact. The random assignment to one of the two study groups was to be made by the Coordinating Center and transmitted to the clinical center by telephone after verification of eligibility (inclusion and exclusion criteria). Each participant was to be assigned a drug bottle number for the first step and dosage of the treatment program. A randomization report was then to be mailed to each clinical center.

Blocked randomization was to be used to ensure approximately equal sample sizes in the active and placebo treatment groups during the recruitment period. It was expected that randomization of such a large sample would produce comparable study groups with respect to baseline prognostic factors. Small imbalances could be taken into account at the time of analysis with the use of appropriate statistical methods. All analyses are to be based on the participants’ original treatment group assignments, as described in Part 10 ("intention-to-treat" principle).33

Treatment program. Participants were to be randomized at each center to either chlorthalidone or matching placebo in a double-blind manner. Baseline SBP was to be used to establish a goal blood pressure for each participant. For individuals with a baseline SBP of more than 179 mm Hg, the goal was to be 159 mm Hg; for those with a baseline SBP of 160–179 mm Hg, a reduction of 21 mm Hg was to be the goal. Each participant was to be assigned a drug bottle number, and the dosages and the type of drugs were to be stepped up until either the goal or the maximum allowable dose of medication was reached.
Intolerable side effects or potentially serious blood chemistry changes (collectively termed "adverse effects") might require either stopping short of maximum dosage or prescribing a different study drug.

All randomized participants were to be started on a low dosage of chlorthalidone (12.5 mg/day) or matching placebo. After randomization, a participant was to return in 4 weeks for a first visit and then again 4 weeks later. If the participant was at or below the SBP goal at 8 weeks, he or she was to return at the regularly scheduled quarterly visit. If the goal had not been reached at the end of 8 weeks, the dosage was to be increased to 25 mg/day chlorthalidone or matching placebo. The participant was to continue to return at 4-week intervals for blood pressure checks. If at 16 weeks the participant was still above the goal on 25 mg/day of step 1 drug, then the step 2 drug, atenolol 25 mg/day, or matching placebo was added. The same type of visit sequence was to apply to persons for whom the step 2 drug was added: two visits at 4-week intervals, with dosage increase of atenolol to 50 mg/day or matching placebo at 8 weeks for persons not reaching the goal.

Participants with contraindications to atenolol at initiation of step 2 or experiencing intolerable side effects to the step 2 drug would instead receive reserpine or matching placebo in dosages of 0.05 or 0.1 mg/day, to be prescribed in analogous manner.

In summary, a participant above the SBP goal at two consecutive monthly visits would be given an increased dosage or the next step drug until reaching the maximum step or dosage. Other reasons identified for stepping up medications would be if a participant was at escape blood pressure (see below) or if otherwise necessary in the clinician's judgment. Figure 1.1 depicts clinic flow and treatment schedule by randomization assignment.34

SHEP protocol also stipulated that potassium supplementation is indicated if, on two consecutive scheduled visits, serum potassium is less than 3.5 meq/l. If serum potassium is 3.2–3.5 meq/l once, the level is to be rechecked on the next scheduled visit. If it is less than 3.2 meq/l, the participant is to be recalled within 1 week of notification for a local recheck of serum potassium level. Oral potassium supplementation is to be Micro-K in 10-meq tablets in doses high enough to increase serum potassium to 3.5 meq/l or more.

Standardized general information on nutrition, smoking, and exercise is to be given to all participants. Moderation of salt intake and emphasis on foods high in potassium are to be recommended. Avoidance or reduction of obesity and regular gradual exercise are to be advised.

**Follow-up procedures.** SHEP participants are to be seen frequently until their blood pressure reaches the SBP goal or until the maximum level of stepped care is reached. All participants are also to have quarterly visits after the date of randomization. All quarterly visits are to include measurements of blood pressure,
heart rate, and weight and a general interval history including screening questions for stroke or other end points and use of concomitant medications. A pill count and compliance self-report are to be done at visits after a medication change and every 6 months. If positive responses are obtained from the general interval history, a complete side effects questionnaire is to be administered. Components of the behavioral evaluation, involving rapid screening for depression and dementia, are to be administered at semiannual visits. The schedule for administering laboratory tests and electrocardiograms is given in Table 1.5.

On each anniversary date of the original randomization, each participant is to undergo an extensive annual evaluation including a more comprehensive history and physical examination, a complete side effects questionnaire, a neurological examination, and the complete behavioral evaluation. In addition to the required visits described above, other visits may be scheduled in the SHEP clinic if the participant is above the SBP goal, the participant is at escape SBP or DBP levels, the participant's serum potassium level is not within the normal range, or the clinician or participant feels that a visit is necessary.

If at any visit the participant reports being prescribed any antihypertensive agent by a non-SHEP physician, the SHEP physician is to contact the prescribing physician, review the SHEP study medication with him or her, and discuss whether the participant may discontinue the newly prescribed drug. If the prescribing physician declines, the SHEP medications may be reduced or stopped if it is deemed necessary in the judgment of the SHEP physician.

Monitoring for “escape” blood pressure levels and other possible adverse effects. An “escape” blood pressure was defined as an SBP or DBP alert level indicating a special action. SBP and DBP escape criteria were predefined (Tables 1.6 and 1.7). If conditions occur that may be harmful and are considered drug related (adverse effects; e.g., symptoms suggesting postural hypotension, depression, asthma or bronchospasm, Raynaud's phenomenon, or serious lethargy), the medication thought to be associated with that adverse effect may be stepped down to progressively lower levels (or reduced immediately to a specified lower level if deemed appropriate by the severity of adverse effects). If clinically advisable, medication may be discontinued. Whenever study medication is reduced or discontinued, consideration is to be given to represcribing it if blood pressure is above the goal and the participant is willing.

If SBP decreases to 110 mm Hg or less, medication may be stepped down to the next lower step or dosage at the direction of the SHEP clinician. If SBP is above the goal at any subsequent visit, medication is to be stepped up again.
**Table 1.6**

**SHEP Systolic Blood Pressure Escape Criteria**

<table>
<thead>
<tr>
<th>Situation</th>
<th>SBP Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anytime</td>
<td>&gt; 240 mm Hg</td>
<td>Individual open-label therapy should be initiated.</td>
</tr>
<tr>
<td>Participant not on maximum dosage of study drugs</td>
<td>220-239 mm Hg</td>
<td>Return in two weeks; if SBP remains above 220 mm Hg, move to next drug dose or step.</td>
</tr>
<tr>
<td>Participant on maximum dosage of study drugs</td>
<td>220-239 mm Hg</td>
<td>Return in two weeks; if SBP remains above 220 mm Hg, individual open-label therapy should be initiated.</td>
</tr>
</tbody>
</table>

**Behavioral evaluation.** SHEP investigators were aware that lowering SBP levels in elderly participants could have either adverse or beneficial effects on overall quality of life or on specified areas of physical, cognitive, affective, and social functions. Therefore, a comprehensive behavioral assessment was developed to evaluate these matters as well as the participant’s global self-assessment of his or her quality of life.

To accomplish this goal, SHEP design stipulated that certain critical functions are to be assessed semiannually in all 16 clinics with a behavioral assessment package called Behavioral Part I. This battery of tests includes SHORT-CARE, a series of questions that screen for the presence of depression or dementia, and the Center for Epidemiologic Studies Depression Scale (CES-D), a scale that tests for depressive symptoms. The Activities of Daily Living scale, a scale that tests an expanded range of physical function from basic self-care to the ability to lift heavy objects, and the Social Network Question-

**Table 1.7**

**SHEP Diastolic Blood Pressure Escape Criteria**

<table>
<thead>
<tr>
<th>Situation</th>
<th>DBP Level</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anytime</td>
<td>&gt; 115 mm Hg</td>
<td>Individual open-label therapy should be initiated.</td>
</tr>
<tr>
<td>Participant not on maximum dosage of study drugs</td>
<td>95-114 mm Hg</td>
<td>Return in 1-2 weeks; if DBP remains 95-114, move to next drug dose or step; return in 1-2 weeks and repeat step-up until DBP is less than 95 or maximum dose of study drugs reached.</td>
</tr>
<tr>
<td>Participant on maximum dosage of study drugs</td>
<td>90-94 mm Hg</td>
<td>On two consecutive monthly visits; move to next drug dose or step; repeat until DBP &lt; 90 or maximum dose of study drugs reached.</td>
</tr>
<tr>
<td>Participant on maximum dosage of study drugs</td>
<td>95-114 mm Hg</td>
<td>Return in one or two weeks; if DBP still 95-114, initiate individual open-label therapy.</td>
</tr>
<tr>
<td>Participant on maximum dosage of study drugs</td>
<td>90-94 mm Hg</td>
<td>On three consecutive monthly visits; initiate open-label drugs or non-pharmacologic therapy.</td>
</tr>
</tbody>
</table>
Table 1.8

Definitions of Major Cardiovascular Events

<table>
<thead>
<tr>
<th>ICD* Number</th>
<th>Type of Event</th>
<th>Criteria for Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertensive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>430-438</td>
<td>Stroke</td>
<td>Abrupt onset of new neurologic deficit lasting 24 hours, with specific localizing finding confirmed by unequivocal physical or laboratory examination, and without evidence for an underlying non-vascular cause.</td>
</tr>
<tr>
<td>428-429</td>
<td>Left Ventricular Failure</td>
<td>Third heart sound or increased jugular pressure, plus basilar rales or increased markings, plus dyspnea or fatigue.</td>
</tr>
<tr>
<td>435</td>
<td>Transient Ischemic Attack</td>
<td>Reliably observed transient (less than 24 hours) neurologic deficit of abrupt onset, without evidence for an underlying non-vascular cause.</td>
</tr>
<tr>
<td><strong>Atherosclerotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>410-414</td>
<td>Myocardial Infarction</td>
<td>Definite ECG evidence for an acute myocardial infarction, or probable ECG evidence plus transient abnormal enzymes, or prolonged cardiac pain plus transient abnormal enzymes, or definite autopsy evidence.</td>
</tr>
<tr>
<td>410</td>
<td>Sudden Death</td>
<td>Death within 24 hours of first evidence of acute cardiovascular disease, and unrelated to other known pre-existing disease.</td>
</tr>
<tr>
<td>413</td>
<td>Angina Pectoris</td>
<td>Positive Rose Questionnaire at annual visit.</td>
</tr>
</tbody>
</table>

* ICD, International Classification of Diseases.

Determination of nonfatal and fatal trial end points. Mortality and morbidity end points are listed, with a brief definition of each, in Table 1.8. Rules stipulated in the design as to reporting and adjudication of events are described below.

A clinical center is to report any suspected fatal or nonfatal SHEP event to the Coordinating Center within 48 hours. Within 6 weeks, a final report is to be completed and submitted and must include all available information necessary or useful for determination of the diagnosis. If available, the complete hospital record is to be included whenever a significant cardiovascular event is suspected. Furthermore, with suspected stroke, special review is to be done of results of computed tomography (CT) scans or magnetic resonance imaging and notes by neurologists. If a myocardial infarction is suspected, then electrocardiograms, cardiac enzyme data, and notes by cardiologists are to be systematically reviewed. For hospitalizations for other causes, only the “face sheet” is to be collected.

naire, a questionnaire that assesses the strength of the social support network, were administered annually. Behavioral Part I was designed to assess the most critical behavioral functions that the investigators felt needed to be monitored on a studywide basis.

In addition to these functions, an expanded behavioral battery, Behavioral Part II, was to be administered at baseline and annually to participants at six of the 16 clinics. The purpose was to provide tests of cognitive function that would be more sensitive to subtle changes over time and to add a global assessment of quality of life as well as a more detailed assessment of participants’ social activities.

Use of SHORT-CARE to monitor possible development of clinically significant dementia or depression was to be pursued with proviso for follow-up. Thus, when certain scores on the scales for dementia or depression were recorded, participants would be referred to a psychiatrist or neurologist for clinical assessment and treatment when appropriate.
At the Coordinating Center, individual case reports are to be checked, and any missing data are to be requested. All complete case reports are adjudicated by the SHEP Morbidity and Mortality Coding Group; its nine members remain blinded to treatment assignment. This group includes two neurologists, three cardiologists, and four other physicians. Each case is reviewed by three members of the group. If there is disagreement, the entire group is to consider the case in detail at a semiannual meeting. At this meeting, final diagnoses are to require concurrence by a majority, with a neurologist having to concur in any stroke diagnosis. Alternatively, all coding may be done by the entire membership of the adjudication working group at periodic meetings.

**Governance, Organization, and Administration**

SHEP design provided that the participating units of the trial—16 clinical centers, Coordinating Center, electrocardiogram laboratory, central laboratory, CT scan center, drug distribution center, and project office—are to be administratively tied together through a structure designed to enhance effective communication and collaboration as well as to monitor and maintain operations of the trial (Figure 1.2). Each of the participating units was involved in the planning and development phase of the trial and contributed to the writing of the protocol and operations manual. All are committed to conducting the study in a consistent and uniform manner with adherence to a common protocol.

The Steering Committee, comprising a chairman, SHEP principal investigators, NHLBI and NIA staff, and the Clinic Coordinators Subcommittee chairperson, was stipulated as the decision-making body for the scientific and technical conduct of the study. Agendas and recommendations for the Steering Committee are to be developed by an executive committee comprising the chairman of the Steering Committee, and representatives of the Coordinating Center, principal investigators, and NHLBI and NIA project offices. This committee also is to provide direction between Steering Committee meetings. Provisions were made for several working subcommittees (Figure 1.2), all of which are responsible and report to the Steering Committee.
To facilitate communication, provision was made for a distributed data entry system. Remote data entry via microcomputers at each clinical center are to provide the means for consolidating collection, entry, verification, and validation of data before transmission to the Coordinating Center. Important features anticipated from the use of distributed data processing were reduction in error rates, potential for more complete data, and promotion of timeliness of receipt of data at the Coordinating Center.

The design also provided for appointment by the institutes of a data and safety monitoring board comprising scientists who are experts in fields relevant to the trial but are not investigators in the trial. The board is to review and evaluate study progress. It is to meet semiannually and review and assess data, including data on recruitment, quality control, adherence, adverse effects, and fatal and nonfatal events.

Conclusion

ISH is highly prevalent in the older US population. It is associated with a significantly increased risk of mortality and morbidity. Whether pharmacological treatment confers benefit, in terms of reduced incidence of total stroke, other major cardiovascular events, and life expectancy, is unknown. There is also a need to determine whether such treatment has an effect (favorable or unfavorable) on multi-infarct dementia, psychosocial status, and quality of life. Other completed and ongoing clinical trials that have dealt with the efficacy of drug treatment for hypertension in older people—the European Working Party on High Blood Pressure in the Elderly Trial,15 the randomized trial of treatment of hypertension in elderly patients in primary care,20 the Swedish Trial in Old Patients with Hypertension (STOP Hypertension),51 and the HDFP with its subgroup aged 60–69 years at entry—do not address the same set of questions as SHEP, which is focused on the unresolved issues of efficacy of long-term drug use for older persons with ISH. The results of SHEP are expected to be available in the early 1990s and should resolve these issues that are important to medical practice and public health because of the increasing number of older persons in the population.

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