Special Article

Implications of the Systolic Hypertension in the Elderly Program

The Systolic Hypertension in the Elderly Program Cooperative Research Group

Several imperatives drive the need to establish the merit of treating isolated systolic hypertension in the elderly. These include its higher prevalence with age, the associated excess cardiovascular risks, and the rapid aging of the population. The Systolic Hypertension in the Elderly Program demonstrated a significant reduction in stroke incidence (fatal and nonfatal) (36%, equivalent to preventing 30 strokes per 1,000 participants per 5 years). A 27% reduction in coronary heart disease incidence and a 32% reduction in all major cardiovascular events were also achieved (equivalent to the prevention of 16 and 55 events per 1,000 participants per 5 years, respectively). These results were associated with a treatment regimen in which the primary agent was low-dose chlorthalidone. The benefits accrued to all subgroups identified based on baseline age, race and sex, blood pressure, serum cholesterol levels, and electrocardiographic abnormalities. The reduction in coronary disease is consistent with predictions based on prospective epidemiological studies and is concordant with other recent intervention trials. It is a reasonable inference from the Systolic Hypertension in the Elderly Program findings that middle-aged as well as older people with isolated systolic hypertension, and people with less severe degrees of this condition, particularly when other risk factors are present, would benefit from such therapy. Another reasonable implication of the trial relates to the matter of preferred drug treatment regimens for diastolic hypertension, in middle-aged as well as older people. A low-dose diuretic regimen is clearly the initial treatment of choice for most hypertensive patients, based on demonstrated reduction in risk for major cardiovascular events, including coronary heart disease, and its safety, patient acceptance, and low cost. (Hypertension 1993;21:335–343)

Key Words • hypertension, systolic • age factors • clinical trials • antihypertensive therapy

The Systolic Hypertension in the Elderly Program (SHEP) clinical trial was designed to determine whether pharmacological treatment of isolated systolic hypertension (ISH) in people aged 60 years and older reduces the risk of total stroke (fatal and nonfatal).1-3 Secondarily, it examined the effect on coronary heart disease (CHD), all cardiovascular events, and total mortality, although it was recognized that the sample size of the SHEP trial afforded insufficient power to test total mortality as an end point. Such a study was required because, despite well-documented excess cardiovascular risk associated with ISH, medical practice suffered from a legacy of belief that ISH was benign and from concerns that pharmacological therapy may be neither safe nor effective.

There were other imperatives as well. The number and percentage of older individuals in the United States and many other countries are increasing because of improvement in life expectancy and decline in birth rates. The US population aged 65 and older is projected to double over the next three decades. Given the higher prevalence of hypertension with age, including isolated or predominantly systolic hypertension, the control of systolic hypertension is a major medical care and public health issue. Screening data from the SHEP pilot study indicated a prevalence of ISH of 8% in the age stratum of 60–69 years, rising to 22% for those aged 80 or older.5 Based on population data from the US census and blood pressure data at a single visit of the US National Health and Nutrition Survey (NHANES-II), it has been estimated that nearly 4 million Americans aged 60 and older have ISH, i.e., systolic blood pressure (SBP) ≥160 mm Hg and diastolic blood pressure (DBP) <90 mm Hg.5

In the early years of the last decade, the SHEP pilot or feasibility study demonstrated the effectiveness of a diuretic-based regimen in safely lowering SBP in people with ISH aged 60 and older.6-7 Although the pilot study was not designed to have adequate statistical power to demonstrate significant reduction in subsequent cardiovascular events, the final results showed favorable trends in the incidence of stroke and overall cardiovascular disease in those patients on active drug treatment. The stage had therefore been set for a definitive clinical trial.

Study Design

The SHEP trial was a randomized, placebo-controlled, double-blind trial.1-3 Its primary end point was incidence of stroke, nonfatal plus fatal. The estimated sample size of 4,800 participants was required to detect
an observed difference of at least 32% in stroke incidence during a mean follow-up of 5 years, with 90% power and a two-sided alpha of 0.05. For a person to be eligible for randomization, the average of four seated SBP measurements, two at each of two baseline visits, had to be between 160 and 219 mm Hg and the average DBP <90 mm Hg. Patients receiving antihypertensive medication at initial screening contact, with SBP between 130 and 219 mm Hg and DBP <85 mm Hg, and free of major illness were withdrawn from their antihypertensive medication after informed consent for drug withdrawal and permission for trial participation were obtained from them and their personal physicians. These people were required to meet blood pressure eligibility within an 8-week period of close follow-up while not taking medication.

Criteria for exclusion were major cardiovascular disease such as recent myocardial infarction or stroke; other major disease such as cancer, alcoholic liver disease, or renal dysfunction; or the presence of medical management problems such as insulin-dependent diabetes mellitus or clinically apparent depression. Participants eligible at the end of the second baseline visit, after giving informed consent, were randomly allocated to either active drug or matching placebo.

Randomization was by clinical center and by whether or not the participant was on antihypertensive medication at initial contact. Each participant had a goal blood pressure established as follows: people with SBP ≥180 mm Hg had a goal reduction to <160 mm Hg, and those whose SBPs were between 160 and 179 mm Hg had a goal reduction of at least 20 mm Hg; e.g., a person with a baseline SBP of 165 had a goal of 145 mm Hg.

Drugs used were chlorthalidone, 12.5 mg/day (step 1), or matching placebo. If this step 1 medication did not achieve goal, drug dosage was doubled. If goal was not achieved at this maximal dose of step 1 medication, then 25 mg/day atenolol or matching placebo was added as the step 2 drug unless it was contraindicated, in which case 0.05 mg/day reserpine could be substituted. If necessary, the step 2 dose could be doubled.

Monthly visits were required until participants reached goal SBP or until the maximal level of stepped-care treatment was attained. If blood pressure rose above predefined escape levels despite maximal stepped-care therapy, then “open-label” therapy, i.e., known active drug, was prescribed. The escape criteria were SBP ≥240 mm Hg or DBP ≥115 mm Hg at a single visit, or sustained SBP ≥220 mm Hg or sustained DBP ≥90 mm Hg. All participants had quarterly and annual visits at which blood pressure, heart rate, body weight, medical history, and information on medication use were obtained. Questionnaires related to depression and dementia were administered at semiannual and annual visits. Detailed medical history, complete physical examination, laboratory tests, and behavioral assessments were done annually.

Nonfatal plus fatal stroke, the SHEP primary end point, was defined as rapid onset of a new neurological deficit attributed to obstruction or rupture of a vessel in the arterial system of the brain, persisting for at least 24 hours unless death supervened. Confirmation by neurological examination and brain computed tomographic scan was required and obtained in most stroke cases. Fatal stroke was established either by autopsy or from the death certificate and/or from preterminal hospitalization data. Other end points included sudden cardiac death (death within 1 hour of onset of severe cardiac symptoms), rapid cardiac death (death within 1–24 hours of onset of severe cardiac symptoms), or nonfatal myocardial infarction based on typical symptoms of acute myocardial infarction plus either typical electrocardiographic (ECG) changes or significant enzyme elevations but not including silent myocardial infarction. For fatal myocardial infarction, diagnosis was based on autopsy, death certificate, and/or preterminal hospitalization data. Other end points are described in detail elsewhere. Occurrence of nonfatal and fatal events was confirmed by a panel of three physicians blinded to treatment and blood pressure status, including two neurologists for neurological events and one cardiologist for cardiac events.

Results

The SHEP trial randomized 4,736 men and women aged 60 or older with ISH found eligible among 447,921 people screened. The mean age of the participants at baseline was 72 years; 13.7% were 80 years or older; 57% were women; and blacks composed 14% of the group. Of the 4,736, one third were on antihypertensive medication at initial contact; 61% had baseline ECG abnormalities; and 14% reported a history of stroke, 5% a history of heart attack, and 10% a history of diabetes. Mean baseline SBP and DBP were 170 and 77 mm Hg, respectively. The active and placebo-treated groups were comparable on multiple baseline characteristics.

Most participants randomized to active drug therapy remained on antihypertensive medication (either as prescribed by the SHEP or another medical provider) during the trial—89% at year 3 and 90% at year 5. At year 5, nearly half (44%) were receiving diuretic alone, whereas 17% were receiving a step 2 drug (atenolol or reserpine) in addition to diuretic and 5% were receiving a step 2 drug alone. Of those randomized to the placebo group, 33% were prescribed active antihypertensive therapy at year 3 and 45% at year 5.

Patients under active treatment experienced an average reduction in SBP of nearly 26 mm Hg and in DBP of more than 9 mm Hg throughout the trial. Their level of SBP and DBP, respectively, averaged between 11 and 14 mm Hg and 3 and 4 mm Hg lower than the level of the placebo group (Figure 1). After 5 years of treatment and follow-up, unadjusted cumulative stroke rates based on life table analysis were 5.1/100 for the active treatment group and 7.9/100 for the placebo group, representing a reduction in nonfatal plus fatal stroke of 36% (p = 0.0003). This 36% reduction in stroke rate is equivalent to the prevention of 30 strokes per 1,000 participants per 5 years. In the case of CHD events (27% reduction in nonfatal myocardial infarction plus CHD death) and all major cardiovascular events (32% reduction), these represent the prevention of 16 and 55 events per 1,000 participants per 5 years, respectively. Given that a substantial majority of all CHD deaths occur in the population aged 60 and older, it is relevant to note also that the CHD death rate was 20% lower for the active treatment compared with the placebo group in SHEP.
Implications

The fundamental reasons for conducting major controlled clinical trials are to provide definitive information on which to base the care of individual patients, to confirm or augment epidemiological understanding of disease causation, and to enhance the basis for improving the public's health. All of these were part of the reasons for conducting the SHEP trial. It must be remembered, however, that the circumstances of the well-controlled clinical trial differ from those of clinical practice. Physicians must be assured that the results are applicable to their patients, whose mix and individual characteristics may differ in varying degrees from those in the trial. The implications (applicability) of the SHEP results are discussed here in the form of responses to specific questions, focused for the most part on the generalizability to the care of patients.

Should People With Isolated Systolic Hypertension Be Identified and Treated?

This question addresses whether the SHEP results can be generalized to people aged 60 and older in the general population who meet the SHEP eligibility criteria. At the outset, it should be noted that the low yield from screening (1.06% of 447,921) is not relevant to the

Table 1. Cumulative Stroke Rates for SHEP Age, Race-Sex, and Baseline Systolic Blood Pressure Subgroups by Treatment Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active Events/n</th>
<th>5-year rate/100 (SE)</th>
<th>Placebo Events/n</th>
<th>5-year rate/100 (SE)</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>34/972</td>
<td>3.9 (0.7)</td>
<td>47/992</td>
<td>5.2 (0.8)</td>
<td>0.71 (0.45–1.11)</td>
</tr>
<tr>
<td>70–79</td>
<td>48/1,062</td>
<td>5.4 (0.8)</td>
<td>74/1,060</td>
<td>8.6 (1.0)</td>
<td>0.70 (0.48–1.02)</td>
</tr>
<tr>
<td>80+</td>
<td>21/331</td>
<td>7.5 (1.6)</td>
<td>38/319</td>
<td>14.0 (2.3)</td>
<td>0.51 (0.29–0.89)</td>
</tr>
<tr>
<td>Race-Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White women</td>
<td>39/918</td>
<td>5.0 (0.8)</td>
<td>64/911</td>
<td>8.4 (1.1)</td>
<td>0.62 (0.41–0.92)</td>
</tr>
<tr>
<td>White women</td>
<td>48/1,120</td>
<td>4.9 (0.7)</td>
<td>66/1,130</td>
<td>6.7 (0.8)</td>
<td>0.75 (0.51–1.10)</td>
</tr>
<tr>
<td>Black men</td>
<td>9/116</td>
<td>9.4 (3.2)</td>
<td>8/101</td>
<td>11.6 (4.2)</td>
<td>0.82 (0.30–2.25)</td>
</tr>
<tr>
<td>Black women</td>
<td>7/211</td>
<td>3.9 (1.5)</td>
<td>21/229</td>
<td>10.8 (2.3)</td>
<td>0.36 (0.14–0.92)</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>160–169</td>
<td>471/2,363</td>
<td>4.1 (0.6)</td>
<td>78/1,370</td>
<td>7.0 (0.8)</td>
<td>0.59 (0.41–0.86)</td>
</tr>
<tr>
<td>170–179</td>
<td>30/617</td>
<td>5.8 (1.1)</td>
<td>56/659</td>
<td>9.4 (1.3)</td>
<td>0.61 (0.39–0.96)</td>
</tr>
<tr>
<td>180+</td>
<td>26/385</td>
<td>7.6 (1.5)</td>
<td>25/342</td>
<td>8.8 (1.7)</td>
<td>1.00 (0.57–1.76)</td>
</tr>
<tr>
<td>Total</td>
<td>103/2,365</td>
<td>5.1 (0.5)</td>
<td>159/2,371</td>
<td>7.9 (0.6)</td>
<td>0.66 (0.51–0.85)</td>
</tr>
</tbody>
</table>

SHEP, Systolic Hypertension in the Elderly Program; n, number of people in subgroup; SBP, systolic blood pressure. Relative risks are adjusted for age, sex, race, smoking, baseline SBP, baseline diastolic blood pressure, baseline total serum cholesterol, history of myocardial infarction, history of stroke, history of diabetes, and years of education.
TABLE 2. Fatal Plus Nonfatal Stroke, Coronary Heart Disease, and Cardiovascular Disease During SHEP by Treatment Group and Baseline Serum Cholesterol Level

<table>
<thead>
<tr>
<th>Baseline cholesterol (mg/dl)</th>
<th>Active</th>
<th>Placebo</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/n</td>
<td>5-year rate/100 (SE)</td>
<td>Events/n</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;216</td>
<td>39/726</td>
<td>6.0 (1.0)</td>
<td>57/727</td>
</tr>
<tr>
<td>216–251</td>
<td>32/759</td>
<td>4.6 (0.8)</td>
<td>36/734</td>
</tr>
<tr>
<td>&gt;251</td>
<td>30/741</td>
<td>5.0 (0.9)</td>
<td>52/741</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;216</td>
<td>35/726</td>
<td>5.5 (0.9)</td>
<td>49/727</td>
</tr>
<tr>
<td>216–251</td>
<td>42/759</td>
<td>6.7 (1.1)</td>
<td>58/734</td>
</tr>
<tr>
<td>&gt;251</td>
<td>52/741</td>
<td>8.1 (1.2)</td>
<td>66/741</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;216</td>
<td>89/726</td>
<td>13.4 (1.4)</td>
<td>117/727</td>
</tr>
<tr>
<td>216–251</td>
<td>86/759</td>
<td>12.9 (1.4)</td>
<td>132/734</td>
</tr>
<tr>
<td>&gt;251</td>
<td>99/741</td>
<td>16.0 (1.6)</td>
<td>133/741</td>
</tr>
</tbody>
</table>

SHEP, Systolic Hypertension in the Elderly Program; n, number of people in subgroup. Relative risks are adjusted for age, sex, race, smoking, baseline SBP, baseline diastolic blood pressure, baseline total serum cholesterol, history of myocardial infarction, history of stroke, history of diabetes, and years of education. None of the tests for interaction of cholesterol and treatment results were statistically significant. Note: 308 people are missing baseline cholesterol values.

question. Ninety percent of those excluded from SHEP were ineligible because they did not meet the blood pressure criteria specified for ISH. The remainder, nearly all of whom had ISH, were not randomized either because they manifested exclusion criteria such as recent or current major cardiovascular disease; other major noncardiovascular disease such as cancer, alcohol-related hepatic disease, or renal insufficiency; or they declined to participate, either on their own or on their physician’s recommendation.

We conclude from the SHEP trial that older people with ISH, as defined in SHEP, should be identified and treated. As noted above, the incidence of stroke was reduced by 36%, representing the prevention of 30 strokes per 1,000 people per 5 years. Moreover, the reduction of CHD events and total cardiovascular events was 16 and 55 per 1,000 people per 5 years, respectively. Given the high prevalence of ISH and the high risk of cardiovascular diseases in those aged 60 years and older, considerable potential exists for decreasing morbidity and disability associated with ISH.

Based on application of the SHEP results to the approximately 4 million people aged 60 and older estimated to have ISH in the United States, the public health impact of the treatment used in SHEP could be the annual prevention of approximately 24,000 strokes, 44,000 major cardiovascular events, and 84,000 admissions to hospitals and nursing homes.

Life table data from SHEP show that the absolute difference in stroke rate between the two SHEP groups increased progressively over the 5 years of the trial. Such favorable influence of treatment would be expected to continue over several subsequent years. Moreover, the results of SHEP may be an underestimate of the effect of lowering SBP on risk of disease, because 33% of the control placebo group reported active drug treatment at 3 years (44% at 5 years), limiting to some degree the comparison between treatment and non-treatment groups. It is probable that the differences between treated and control groups with regard to risk of stroke and heart disease would have been even greater than observed if none of the control patients had been treated with antihypertensive agents.

Finally, the consistency of results across all subgroups, including three age strata, four sex-race strata, three baseline blood pressure strata, three baseline serum cholesterol strata, and participants with and without baseline ECG abnormalities further establishes the generalizability of the SHEP results to the population that meets the SHEP eligibility criteria.

Is There a Subgroup With Isolated Systolic Hypertension at Highest Risk for Whom Therapy Could Be Targeted?

This question assumes such a group would stand to benefit the most from treatment and that those at lesser risk might avoid treatment altogether. To our knowledge, no data exist for testing this hypothesis. SHEP data indicate no significant difference in the beneficial effects of treatment across age–race–sex subgroups or between those already taking a drug at initial contact and those not previously treated. There was also no difference between subgroups with and without ECG abnormalities at baseline. Also, in the Hypertension and Detection and Follow-up Program (HDFP), intensive stepped-care treatment did not result in a greater percentage reduction in 5-year mortality for subgroups at much greater risk due to end-organ damage at baseline compared with subgroups free of end-organ damage. By inference, it seems reasonable at this time not to exclude from treatment groups who are assessed to be at potentially lower risk.

Are the SHEP Results Generalizable to Other Strata of the Population With Isolated Systolic Hypertension?

Such strata include sicker people aged 60 and older with ISH, people with less severe ISH, and younger people with ISH as defined by SHEP. Five percent of SHEP participants had a history of myocardial infarction, 1.4% a history (but no residual) of stroke, 10% a history of diabetes, and 61% an abnormal ECG at
baseline. By every measure of target-organ damage at baseline, participants at higher risk responded as well as those without such findings. Thus, although management of more complex cases of ISH in the practice setting may be more difficult, the SHEP data do not suggest that they will benefit less from a well-managed antihypertensive regimen using low-dose medication. It seems reasonable to infer that the presence of other morbid conditions does not constitute a contraindication to judicious treatment of ISH in older patients.

Borderline ISH has been defined as SBP between 140 and 159 mm Hg with DBP <90 mm Hg. Does SHEP provide evidence for the use of pharmacological therapy in people in this blood pressure stratum? Not explicitly. The SHEP procedure after initial screening (two baseline visits, four pressures), suitable for clinical practice, identified a cohort with ISH ≥160 mm Hg SBP and <90 mm Hg DBP; therefore, we have no trial data on ISH with 140–159 mm Hg SBP. Data on the Multiple Risk Factor Intervention Trial (MRFIT) screeners and other cohort studies such as the Framingham Study indicate that SBP has a curvilinear relation to risk, with SBP <120 mm Hg being optimal.12-14 In fact, data on the approximately 350,000 men screened for the MRFIT study show that less severe ISH (SBP 140–159 mm Hg, DBP <90 mm Hg) may actually carry as much cardiovascular risk as “mild-to-moderate” systolic-diastolic hypertension. Given that older people with ISH of 140–159 mm Hg are more common in the general population than those with ISH of 160 mm Hg or higher, the population risk attributable to this blood pressure stratum (SBP 140–159 mm Hg) is greater. The implication is that serious consideration must be given to treating at least some patients with SBP in the range of 140–159 mm Hg, especially if they have other risk factors or evidence of target-organ damage. We deem this a reasonable generalization from the favorable SHEP results.

The excess mortality rate for men in the 35–57-year age group with ISH was documented in the MRFIT screenee data referred to above, but the question of benefit from treatment for these younger age strata was not addressed in the SHEP study. Until data are available, it is recommended that decisions be tailored to the individual patient, taking into consideration the presence of other risk factors and comorbidity. Certainly, nonpharmacological intervention is appropriate, and it seems reasonable that some patients will benefit from pharmacological therapy.

Was a J-Shaped Relation Between the Lowering of Blood Pressure and Coronary Mortality Observed in the SHEP Trial?

The J-shaped curve refers to an increasing risk of CHD events at lower ranges of blood pressure, especially in people with preexisting CHD. Such a relation has been reported, particularly for DBP, both in prospective observational studies15 and in a randomized controlled therapeutic trial in an elderly cohort.16 The authors of the former report suggested that overly vigorous therapy could be harmful. The latter study found a J-shaped relation for both treatment and control groups. A plausible explanation for these observations is that patients with the lowest levels of blood pressure may have serious underlying myocardial disease, accounting for both their lower pressures and higher mortality.

In time-dependent analyses controlled for multiple possible confounding variables, the SHEP data show no evidence for a J-shaped relation of DBP reduction to risk of stroke, CHD, cardiovascular events, or to risk of all-cause mortality for either the active treatment group, the placebo group, or the two groups combined (unpublished observations). This lack of a J-finding with DBP reduction seems especially meaningful given the baseline mean DBP level of 77 mm Hg and the average reductions in DBP during the 5 years of the trial of 9 ±10 and 5 ±12 mm Hg for the active treatment and the placebo group, respectively. There was also no evidence of a significant J-shaped relation of SBP reduction to risk of stroke or all-cause mortality for either the active treatment group, the placebo group, or the two groups combined. There was a significant J-shaped relation of SBP fall to CHD and cardiovascular events in the placebo group and in both groups combined but not in the active treatment group alone. The absence of a J-finding in the active treatment group in relation to either degree of DBP or SBP reduction is concordant with the overall SHEP data on the efficacy of its low-dose antihypertensive drug regimen for the control of ISH. Further analyses of this matter are in progress by the SHEP Cooperative Research Group, including level of DBP and SBP attained during the trial as the independent variable.

How Far Should the Systolic Blood Pressure Be Lowered?

The design of SHEP did not address this question directly, nor do the results provide more than an inferential conclusion. Certainly, the stated goal of lowering SBP to <160 mm Hg or by 20 mm Hg, depending on the baseline level, is a validated objective. What about to <140 mm Hg? On average, the active treatment group achieved and maintained a SBP level of approximately 142 mm Hg associated with the benefits discussed above. The standard deviation around that mean level was 19.4 mm Hg. Clearly, many individuals achieved SBP levels well below 140 mm Hg. Therefore, a favorable influence of treatment might be expected at levels lower than 140 mm Hg.

A related question is whether or not SBP should be the primary basis for setting a therapeutic goal for treatment of people with hypertension. SBP is an important independent predictor of excess risk, probably more so than DBP in people aged 45 and older.12-14 As reported in recent prospective studies of large representative community-based cohorts from four areas of the United States, SBP is also a much more powerful predictor of cardiovascular events after age 65, with the impact of DBP as a risk factor diminishing dramatically with advancing age.17

When treating diastolic or “combined” (systolic/diastolic) hypertension, should antihypertensive medication be increased or altered to normalize SBP even when DBP has been lowered to <90 mm Hg? Although not addressed directly in SHEP, the beneficial consequences of lowering SBP in the absence of high DBP were clearly demonstrated, results consistent with findings from observational epidemiological studies.
Is Isolated Systolic Hypertension Unique From a Pharmacotherapeutic Perspective?

It would be a mistake to infer from SHEP that people with ISH are unique, at least from the standpoint of their response to pharmacotherapy. Despite pathophysiological and epidemiological differences, ISH may be considered a variant of hypertension in the elderly generally, in which the hallmarks are increased peripheral resistance and a disproportionate elevation of SBP apparently due to loss of distensibility of the aorta and major tributaries. The reason why some older individuals develop higher SBP than others is unknown. In any case, the SHEP results, together with recent epidemiological data on risks with elevated SBP, compel rethinking of the primacy of DBP elevation. Thus, until now, no criteria or goals have been established for assessing the efficacy of drug treatment aimed at lowering SBP.

However, one only has to look at data from trials on treatment of diastolic hypertension to find that SBP was lowered at least proportionately by whatever drug was effective in lowering DBP. All drugs approved for treatment of mild and moderate hypertension have been effective against both SBP and DBP, and, in fact, the major classes of drugs have been shown to be effective in ISH. Thus, the SHEP results, achieved with low-dose chlorthalidone as the step 1 and principal antihypertensive medication, should not be interpreted as limiting the choice of drugs for the treatment of ISH, either because of the choice of drugs made for the study or because of the pathophysiology of ISH.

Is the SHEP Regimen the Preferred Approach to Treating Isolated Systolic Hypertension?

What are the relative merits of using diuretics versus other available antihypertensive agents? What about concerns regarding putative adverse effects of diuretics on CHD that have been voiced in recent years, including the tendency to increase serum total cholesterol levels by up to 8%, at least in the short term, and the alleged potential for inducing sudden cardiac death? These concerns have been advanced as possible reasons for the less than expected reduction in CHD reported by some clinical trials that tested efficacy of diuretic therapy in hypertension, and not on an a priori hypothesis that was tested.

Collins and colleagues have stated that the often-cited effects of diuretics or β-blockers on glucose and lipoprotein metabolism would seem to be insufficient to cause a dilution in observed benefit of the magnitude indicated by the point estimate from the combined results of the randomized trials before SHEP. In any case, effective control of blood pressure, as accomplished in the SHEP trial, reduced risk of stroke, coronary, and total cardiovascular events across all strata of baseline cholesterol.

Hypokalemia with resultant increased risk of cardiac arrhythmia has also been invoked as a mechanism for the results of these clinical trials with regard to CHD. Post hoc subgroup analyses of data from MRFIT raised a question as to whether use of diuretics in people with baseline ECG abnormalities leads to greater risk of CHD events than for those without such abnormalities. This issue was posed particularly because the diuretic dosages in MRFIT were 50–100 mg/day of either hydrochlorothiazide or chlorthalidone. However, the MRFIT data demonstrated no relation between either the participants’ most recent potassium level or the presence of ventricular premature beats and CHD mortality, although statistical power was low for exploration of these issues. Additional reasons for questioning the significance of the MRFIT data include the fact that this analysis was post hoc, and the findings could well have been due to chance alone.

In SHEP, based on the question posed by the MRFIT post hoc analyses, an a priori subgroup hypothesis was stated as part of the SHEP protocol: “Would treatment of ISH reduce the incidence of sudden cardiac death or coronary death plus nonfatal myocardial infarction similarly in those free of baseline ECG abnormalities and those with such abnormalities?” An ECG abnormality was present in nearly 61% of SHEP participants at baseline. The reduction in CHD for those with baseline ECG abnormalities was 31% (95% confidence interval [CI] −50% to −6%), whereas the reduction for those without such abnormalities was 18% (95% CI, −47% to +29%). Such widely overlapping confidence intervals in this comparison suggest that these results are representative of similar treatment effects, as confirmed by formal statistical testing. Although small numbers of events precluded testing a hypothesis on sudden death and sudden plus rapid death, analyses indicated no trend of increased risk for those with ECG abnormalities at baseline.

Thus, the question posed by the MRFIT post hoc subgroup analyses, as to possible increased CHD risk in hypertensive men with ECG abnormalities treated with diuretics, was answered in the negative when tested as a prior hypothesis by SHEP. Moreover, in an ancillary study involving ambulatory ECG recording, done at a few SHEP centers, low-dose diuretic use was not associated with an increase in premature ventricular contractions. The difference in diuretic dosage in the SHEP and MRFIT studies should be noted again, along with the fact that the SHEP protocol stipulated potassium supplementation for participants with serum potassium levels <3.5 mg/dL on two consecutive visits. Additionally, a SHEP ancillary study observed in participants in the active treatment group a reduction in left ventricular mass, a known predictor of cardiovascular risk.

The 27% overall reduction in CHD incidence in SHEP, the absence of any overall adverse effect on mortality, and the demonstrated benefit of therapy in people with baseline ECG abnormalities all challenge the validity of concerns previously expressed regarding the risk/benefit ratio of diuretic treatment. Whatever the reasons for the prior uncertainty about the mix of benefit and risk, the positive experience in SHEP underscores the efficacy of low-dose diuretics.

Are the Results Attributable to a Protective Effect of Atenolol?

With the use of time-dependent life table regression analyses, with control for several factors, the addition of either atenolol or reserpine to chlorthalidone did not enhance the favorable findings for chlorthalidone alone for any of the outcomes. The relative risk for atenolol versus no atenolol for CHD events was 1.08 (95% CI, 0.59–1.94). Thus, the beneficial effects seen for several
outcomes of SHEP were due to its treatment regimen based primarily on low-dose chlorthalidone therapy for lowering SBP.

What About the Newer Classes of Antihypertensive Agents?

Calcium channel blockers and angiotensin converting enzyme inhibitors are known to be effective in lowering both SBP and DBP in the elderly. Drugs that lower SBP by diluting small and medium-sized arteries, thereby reducing pulse wave velocity and augmented aortic SBP (total impedance) via reflected wave transmission, may have special applicability to the treatment of hypertension in the elderly. However, their effect on morbidity and mortality has not been established by clinical trial; hence, any assumed advantage over the SHEP regimen is unproved. They could be better, worse, or the same; chlorthalidone is the only agent for which efficacy on morbidity and mortality is established for older people with ISH.

SHEP was not designed to determine the optimum way to treat ISH. It was a clinical trial to test the hypothesis of whether a standard treatment, known to be effective in lowering SBP, would reduce stroke and other cardiovascular risks. The results support the need for a trial comparing the risk-reducing potential of several classes of antihypertensive agents. The Treatment of Mild Hypertension Study (TOHMS) was designed to be such a trial through implementation of its phase II protocol. A full-scale trial of this type remains to be carried out.

Do the SHEP Results Have Any Implications for Preferred Drug Treatment Regimens for Diastolic Hypertension?

Uncertainty continues regarding optimal initial drug therapy, especially for so-called mild hypertension. The SHEP results are congruent with the combined results of previous trials of drug treatment for diastolic hypertension. Collins and colleagues reported an overview of antihypertensive therapy in DBP-lowering trials, and MacMahon and colleagues reported the results of prospective epidemiological studies on the relation of usual DBP to risk of CHD and stroke during long-term follow-up. The epidemiological studies suggest that there should be a 20–25% reduction in CHD associated with a 5–6 mm Hg lower DBP. CHD events were actually reduced by 14% (95% CI, 4–22%) in the overview of the 14 unconfounded randomized trials, which had an average reduction in DBP of 5–6 mm Hg. Thus, the difference between the projected and the observed reduction could be a result of chance. As detailed above, adverse actions of some pharmacological agents used in the various DBP-lowering trials have been suggested as the reason for a reduced benefit seen on the CHD outcome, but this remains unsubstantiated.

Results of the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) were recently reported for its 1,627 participants aged 70–84 years, with diastolic hypertension and combined systolic/diastolic hypertension, but specifically excluding those with ISH. Three different \( \beta \)-blocker regimens were used with a diuretic regimen as the fourth active drug regimen in this placebo-controlled trial. Mean baseline SBP in the trial was 190 mm Hg, and mean DBP was 104 mm Hg. A SBP/DBP net reduction of 19.5/8.1 mm Hg was observed in comparison with the 12.2/3.9 mm Hg reduction observed in SHEP. The investigators reported a 40% reduction in the primary end point (total stroke plus myocardial infarction and other fatal cardiovascular disease in those on active therapy compared with placebo). Fatal and nonfatal myocardial infarction plus sudden death were reduced by 27% (40 versus 29), with a 66% reduction in sudden death (13 versus 4). The proportion of patients successfully managed with monotherapy was not reported, nor was there a comparison of those receiving only diuretics versus all other drugs; no light is shed on the relative efficacy of the individual agents or the classes of drugs.

The Medical Research Council (MRC) Treatment Trial of Hypertension in Older Patients\(^\text{34}\) had stroke, CHD, and deaths from all causes as primary end points in a hypertension trial including many with ISH. Participants numbered 4,396 between the ages of 65 and 74 years. Two drug regimens used were hydrochlorothiazide (50 mg) plus amiloride (5 mg) versus placebo, and atenolol (50 mg) versus placebo. Half of those randomized to the diuretic regimen were allocated to a regimen with a half dose of each of the diuretics; after 1985, all randomized to the diuretic arm were transferred to the lower dose. The first drug of each regimen could be used as the second drug for the opposite active regimen if goal blood pressure was not achieved. A SBP/DBP net reduction of 16/7 mm Hg was accomplished. With a 25% loss to follow-up, a 19% reduction in CHD events was reported (159 placebo versus 128 active treatment, \( p=0.08 \)). The reduction in CHD was seen in the diuretic-treated group (12.7 per 1,000 patient years placebo versus 7.7 diuretic, 39% reduction); the CHD rate in the \( \beta \)-blocker group was 12.8 per 1,000 patient years versus 12.7 in the placebo group.

Thus, in these three recent trials, there is substantial evidence of a reduction in CHD associated with treatment of hypertension, both ISH and diastolic hypertension or combined systolic/diastolic hypertension, much more in keeping with the results predicted from the prospective epidemiological studies. The lesser benefits suggested by the earlier studies were from cohorts who were identified as hypertensive based on diastolic criteria and who were younger in age. The demonstrated benefit appears to be present whenever diuretics are used and whether or not baseline ECG abnormalities are present when treatment is started. Benefit attributable to \( \beta \)-blockers is less certain in these studies. The efficacy demonstrated in the SHEP trial indicates that low-dose chlorthalidone is as useful as initial treatment of hypertension as any agent available. Consideration of the comparative costs of diuretics and newer agents lends further importance to this judgment. Antihypertensive drug therapy should not be withheld from people because of ECG abnormalities. Significant broad benefits for CHD outcomes, as well as for stroke and other cardiovascular end points, are associated with the use of diuretics in the treatment of hypertension in the elderly. There are no trial data on ability of the newer antihypertensive drugs to prevent nonfatal plus fatal cardiovascular disease events.

Returning to the question on choosing the initial drug in the treatment of ISH in older people, are there other considerations? In the elderly, more than any other...
group of people with hypertension, coexisting disease and other risk factors may influence the choice. Patients with concurrent illnesses such as symptomatic myocardial ischemia, left ventricular dysfunction, diabetes mellitus, or renal dysfunction may warrant consideration of other agents as initial therapy. However, in the absence of compelling concerns, the SHEP results indicate that a low-dose diuretic is the agent of choice for treating older patients with systolic hypertension. Other studies suggest this is also the case for diastolic hypertension.32–36

Concluding Commentary

The list of questions addressed in this report is lengthy but not exhaustive. Some questions await further analyses of the data, and others may be addressed only partially (if at all) by the SHEP results. Examples of the former include whether there are predictors at baseline that identify those of differing resistance to reduction of cardiovascular or cerebrovascular disease risk; whether change in blood pressure correlates with cognitive function and quality of life; and whether reduction in stroke incidence varies by stroke type.

The SHEP study did not address the issues of whether ISH can be prevented or the role of nonpharmacological therapy in the treatment of ISH in older people. The available SHEP data do not clarify whether less multi-infarct dementia will emerge over a longer period of time as a result of treatment of ISH. Should systolic hypertension in elderly individuals who have had a recent myocardial infarction be treated aggressively? Afterload reduction would seem desirable in such cases, and no J-shaped phenomenon has emerged for any cardiovascular disease incidence end point in the SHEP active treatment group. Similar questions remain concerning treatment for recent transient ischemic attack or stroke. These questions, although not addressed in the SHEP study, provide direction for further research.

What is clear is that ISH should be treated in older people and probably in the middle-aged as well. Significant numbers of strokes as well as other major cardiovascular events, including CHD, will be prevented. The treatment need not be expensive. In the SHEP study, the results were achieved using a diuretic in low dose as the primary agent. The regimen was safe, well tolerated, and not associated with an increase in depression or dementia.

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References


10. Langford HG, Stamler J, Wassesheit-Smoller S, Prineas RJ: All-cause mortality in the Hypertension Detection and Follow-up Program: Findings for the whole cohort and for persons with less severe hypertension, with and without other traits related to risk of mortality. Prog Cardiovasc Dis 1986;24(suppl 1):29–54


reductions in blood pressure: Overview of randomized drug trials in their epidemiological context. Lancet 1990;335:827–838


35. Hypertension Detection and Follow-up Program Cooperative Group: Five-year findings of the Hypertension Detection and Follow-up Program 1: Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979;242:2562–2571

Implications of the systolic hypertension in the elderly program. The Systolic Hypertension in the Elderly Program Cooperative Research Group.

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