Quality of Life During Antihypertensive Treatment
Lessons From the Systolic Hypertension in the Elderly Program
William B. Applegate

As physicians treating hypertension in the elderly, we should be concerned about the possible negative impact of antihypertensive medicines on the patient’s quality of life, as well as their probable beneficial effect on morbidity and mortality. There are two types of hypertension in the elderly. In addition to the traditional systolic-diastolic hypertension that occurs at all ages, there is an isolated systolic hypertension (ISH) that is virtually limited to the elderly.¹

Until recently little attention was paid to ISH; however, as it became recognized that ISH had the same catastrophic complications as systolic-diastolic hypertension, it became important to learn the effects—good and bad—of antihypertensive drugs in patients with ISH. The first question was whether the drugs designed to treat systolic-diastolic hypertension could also control ISH. The available antihypertensive drugs had been designed for and were effective in controlling diastolic hypertension due to excess arteriolar constriction, rather than systolic hypertension due to the loss of large vessel compliance found in ISH. The second question was that, even if control was achieved, would it diminish the number of hypertensive complications, as significant atherosclerosis was already in place. The final concern was that treatment might be associated with significant adverse effects.²

In this context, the Systolic Hypertension in the Elderly Program (SHEP) was designed to determine the effect of diuretic and β-blocker-based antihypertensive treatment on ISH. Would systolic blood pressure be satisfactorily controlled with such a regimen; if control was achieved, would it decrease cardiovascular complications and would it produce new adverse effects? There was particular concern about three possible adverse effects on the quality of life. The greatest fear was that lowering systolic blood pressure might lead to insufficient perfusion of the brain and resultant diminished mental function.³ There was the additional concern that even occasional hypotension might result in falls that could be disastrous for elderly people.¹ Finally, there was the worry that sexual activity might be further decreased in an elderly population where it had already been diminished by age and disease.¹ The SHEP trial provided a straightforward look at the effect of a specific antihypertensive regimen on quality of life. It compared the effect of a placebo and a diuretic-based regimen, with the addition of a β-blocker, if necessary, or reserpine if the β-blocker could not be tolerated.⁴

GENERAL DESCRIPTION OF SHEP

SHEP was a randomized double-blind placebo-controlled trial with participants followed for an average of 5 years at 16 academic clinical trial centers. The requirements for a trial participant was an age ≥60 years and a blood pressure ≥160/90 mm Hg. The 4736 randomized participants who met these requirements were selected from almost 100 times that many screenees. Inappropriate age and blood pressure were the main reasons for failure to meet the screening requirements.

Prerandomization systolic blood pressure for SHEP participants averaged 170 mm Hg and ranged from 160 to 219 mm Hg, while diastolic blood pressure averaged 77 mm Hg and was required to be below 90

From the Department of Preventive Medicine, University of Tennessee, Memphis, Tennessee.
Address correspondence and reprint requests to William B. Applegate, MD, Department of Preventive Medicine, University of Tennessee, 66 N Pauline, Suite 232, Memphis, TN 38105.

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Published by Elsevier Science, Inc.
mm Hg. Fifty-seven percent of the participants were women and 14% were black. The average age was 72 years, with a range from 60 to 94 years. The average number of years of education was 11.7. Thirteen percent of the participants were current smokers, 10% were diabetic, 1.4% had had a stroke, 5% had had a myocardial infarction, and 61% had a prerandomization electrocardiographic abnormality. At first contact, 3161 (67%) of the participants were not receiving antihypertensive medication. With the consent of both patient and physician, the antihypertensive medications of the remainder were discontinued.

Participants were randomized to active antihypertensive drug therapy or matching placebo. Active treatment consisted of 12.5 mg chlorthalidone, or 25 mg if necessary, as step 1; while step 2, if necessary, consisted of 25 or 50 mg atenolol. If atenolol was contraindicated, 0.05 or 0.1 mg of reserpine was used for the second-step drug. At the 5-year mark, 90% of active treatment participants were on SHEP drugs, 46% on diuretic alone and 23% on diuretic plus \( \beta \)-blocker, with 6% on diuretic plus reserpine. One year after randomization, 13% of the placebo group were taking antihypertensive medication, although the consent of both patient and physician, the antihypertensive medications of the remainder were discontinued.

Data from Systolic Hypertension in the Elderly Program (SHEP),\(^5\) giving the number and relative risks with their 95% confidence intervals of catastrophic cardiovascular events for active treatment and placebo participants.

<table>
<thead>
<tr>
<th>Number of Cardiovascular Events</th>
<th>Active Treatment Group (n = 2365)</th>
<th>Placebo Group (n = 2371)</th>
<th>Relative Risk for Treatment versus Placebo (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal first stroke</td>
<td>96</td>
<td>149</td>
<td>0.63 (0.49–0.82)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>50</td>
<td>74</td>
<td>0.67 (0.47–0.82)</td>
</tr>
<tr>
<td>Nonfatal left ventricular hypertrophy</td>
<td>48</td>
<td>102</td>
<td>0.46 (0.33–0.65)</td>
</tr>
<tr>
<td>Nonfatal renal dysfunction</td>
<td>7</td>
<td>11</td>
<td>—</td>
</tr>
<tr>
<td>Total cardiovascular deaths</td>
<td>90</td>
<td>112</td>
<td>0.80 (0.60–1.05)</td>
</tr>
<tr>
<td>Total noncardiovascular deaths</td>
<td>109</td>
<td>103</td>
<td>1.05 (0.80–1.38)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke, nonfatal myocardial infarction, or coronary heart disease death</td>
<td>199</td>
<td>289</td>
<td>0.67 (0.56–0.80)</td>
</tr>
</tbody>
</table>

Of the 2365 participants randomized to active treatment, 4.36% had a stroke during the 4.5 years of postrandomization follow-up. In contrast, 6.71% of the 2371 placebo participants had a stroke. The 5-year cumulative stroke rates were 5.2 per 100 for active treatment participants and 8.2 for placebo participants. The \( P \) value of the difference was .0003.\(^5\)

The beneficial effects of treating ISH were not limited to decreasing the stroke rate. As indicated in Table 1, nonfatal stroke, myocardial infarction (excluding silent infarction), and left ventricular failure were all significantly decreased in the active treatment group.

Total deaths during the trial were 213 for active treatment and 242 for placebo participants. There were 90 cardiovascular deaths in the active treatment and 112 in the placebo group, with 59 and 73 due to coronary causes. Although these differences did not reach statistically significant levels, the trend clearly favored active treatment. For noncardiovascular deaths there was no such trend. Next to death from cardiovascular disease, neoplastic deaths were the most common category, and they showed no such trend; there were 75 and 78 “cancer” deaths in the active treatment and placebo groups, respectively.\(^5\)

Finally, for the combination of all strokes and all coronary heart disease events, fatal and nonfatal (199 in active treatment and 289 in placebo participants), the difference was highly significant (risk ratio 0.67, 95% confidence interval [CI] 0.56 to 0.8) (Table 1). There were no apparent differences in benefit based on gender, ethnicity, or age. Although there had been some question about the appropriateness of treating octogenarians with ISH, they benefited from treatment as much as younger patients and had no additional adverse effects.\(^5\)
BEHAVIORAL EVALUATION PROCEDURES

A major question about treating ISH was whether it would have any subtle but still significant effect on mentation and other vital aspects of quality of life. Would treatment interfere with thinking and with other important activities in an elderly population whose age already put serious limitations on what they could do? SHEP undertook a very careful search for such adverse effects.

The SHEP behavioral evaluation was administered promptly after randomization but before therapy began; components of the evaluation were subsequently administered semiannually or annually. Twice a year all participants received a 20 min evaluation for cognitive impairment, depression, and mood disorder. Once a year all were questioned about activities of daily living (ADL) and their social network. In addition, at six clinical centers, participants (n = 2034) annually received more detailed tests of cognitive function including psychomotor speed, attention span, visual scanning, mental calculations, expressive language function, verbal memory, and hypothesis testing. There were also questions on quality of life, expression of anger, and leisure activities.6

Because of the importance attached to behavioral evaluation, strenuous efforts were made to standardize the procedures. At the beginning of the trial all behavioral raters were centrally trained. They were certified following evaluation of their rating of a standardized videotaped interview and observed practice interviews with age-eligible individuals. Quality control over rater performance was maintained by annual refresher courses and recertification. All raters periodically submitted audiotapes and hard copies of interviews for review. Raters at the six centers where more detailed tests were done were visited on site and observed while administering interviews with study participants. Cognitive impairment and depressive symptoms (Short Care)7 and mood changes (Centers for Epidemiologic Studies Depression [CES-D] Scale)8 were all measured in arbitrary units. In all seven lines of Table 2, the results have been simplified so that a positive value indicates that the result was better in the active treatment group. Although the trend continually favors the active treatment group, the only difference that was statistically significant was in “Mood changes” where P = .05.

Finally, it was hypothesized that data on social support might be a covariate of functional status at the end of the study.10 The only data on sexual function were collected as a single question on the side effects questionnaire and were published in the main study results.

BEHAVIORAL RESULTS

At baseline there were no differences between the active treatment and the placebo groups in cognitive function, depressive symptoms, or mood disorder, but there were modest differences in the basic and moderate levels of activities of daily living (ADL). More placebo than active treatment participants had some impairment in basic ADL (P = .02) and in moderate ADL (P = .05); however, considering all three levels of ADL together, there was no significant difference between the two treatment groups. Basic ADL tasks included bathing, personal grooming, dressing, eating, walking, using the toilet, and moving from bed to chair. Moderate ADL tasks included writing, handling small objects, walking up and down stairs, extending the arms above shoulder level, and walking 0.5 mile. Advanced ADL tasks included the ability to carry groceries, move furniture, lift and carry weights (4.5 kg), pull or push large objects, and crouch or kneel.6 The changes in ADL that occurred during the trial, although small, all favored the active treatment participants. Thus the active treatment participants did better than the placebo participants not only in the overall ADL, but in each of the three levels of ADL: basic, moderate, and advanced (Table 2). More importantly, the changes in cognitive function and depressive symptoms that occurred during the trial were not

### TABLE 2. DIFFERENCES BETWEEN TREATMENT GROUPS IN QUALITY OF LIFE CHANGES DURING THE SHEP TRIAL

<table>
<thead>
<tr>
<th>Quality of Life Measure</th>
<th>Differences Between Placebo Change and Active Treatment Change During the Trial</th>
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<tbody>
<tr>
<td>Cognitive impairment</td>
<td>+0.05</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>+0.16</td>
</tr>
<tr>
<td>Mood changes</td>
<td>+0.38</td>
</tr>
<tr>
<td>Any ADL</td>
<td>+0.97</td>
</tr>
<tr>
<td>Basic ADL</td>
<td>+0.20</td>
</tr>
<tr>
<td>Moderate ADL</td>
<td>+0.30</td>
</tr>
<tr>
<td>Advanced ADL</td>
<td>+0.72</td>
</tr>
</tbody>
</table>

ADL, activities of daily living (see text).

The results of the Behavioral Evaluation have been simplified in this table so that a positive value indicates that the result was better in the active treatment group. Although the trend continually favors the active treatment group, the only difference that was statistically significant was in “Mood changes” where P = .05.
significantly different for the two treatment groups, although the trend in both of these favored the active treatment group. Moreover, the results for these two parameters, ie, lack of significant difference between the two treatment groups, were the same whether or not participants with strokes or myocardial infarctions were included in the analysis. Therefore the results reported here are for all participants, using the last available evaluation data. Both treatment groups had some loss in cognitive function and both had some increase in depressive symptoms, with the placebo group having the biggest changes (Table 2). For mood change during the trial, there was a significant difference, with a greater deterioration in mood for the placebo group than for the active treatment group ($P = .05$) (Table 2).

Although not shown in a table, various data were collected on leisure activities, including active sports, taking walks, working in the yard, doing physical exercise, preparing meals, devoting time to hobbies, shopping, enjoying outside entertainment, watching television, taking day or overnight trips, doing volunteer work, and playing games, such as cards or bingo. In general, participants showed modest decreases over time in the more strenuous or complex activities. Thus taking walks decreased in both groups, but at their last treatment visit more patients in the active treatment group (85.4%) than in the placebo group (81.3%) reported that they were still walking. Likewise, working in the yard was reported more frequently by the former group (70.6% v 65.4%), and day or overnight trips were also taken by more of the former group (62.4% v 56.8%). These three activities showed significantly ($P < .05$) less reduction in the treatment group. For most of the less vigorous leisure activities, the level of activity remained fairly constant over the course of the study, and there were no differences between treatment groups.

Change in the participants’ global assessment of quality of life in the six clinics that did more extensive evaluations did not differ by treatment group (Table 3). Actually, global assessment of life, health, and happiness remained remarkably stable for the both treatment groups throughout the trial, with the large majority of participants considering themselves to be at least in the moderately satisfied, healthy, and happy categories. At the end of the trial, only 5% to 8% were unhappy or indicated general dissatisfaction with their overall lives, and only about 2% felt that their general health was bad.

**MINOR POTENTIAL ADVERSE EFFECTS**

Symptoms characterized as troublesome were reported by slightly more patients in the active treatment group than by those in the placebo group. Intolerable problems, in which the drug was discontinued, were experienced by 21% of patients in the placebo group and 28% of those in the active treatment group.

**OVERALL RESULTS OF ACTIVE TREATMENT**

As indicated, our analyses demonstrate that active treatment of isolated systolic hypertension in the
SHEP cohort did not have a perceptible negative effect on measures of cognitive, physical, or emotional function. In fact, we observed a significant positive effect on mood, ie, a smaller deterioration in the active treatment group than in the placebo group. The total lack of negative effect is reassuring since the SHEP trial did demonstrate highly significant and substantial reductions in cerebrovascular and cardiovascular morbidity. The active treatment group experienced significant reductions in all strokes and in all cardiovascular events, ie, decreases of 30 strokes and 55 cardiovascular events per 1000 participants over a 5-year period, when compared to the placebo group.

CONCLUSION

SHEP demonstrated that medical treatment of isolated systolic hypertension decreases the incidence of catastrophic cardiovascular events without causing significant adverse effects and specifically without causing deterioration in cognition, emotional state, physical function, or leisure social activities.

REFERENCES