Quality of Life During Antihypertensive Treatment: Lessons from the SHEP Study

Based on a presentation by William B. Applegate, MD

Presentation Summary

The Systolic Hypertension in the Elderly Program (SHEP) study evaluated several quality-of-life parameters in patients being treated for hypertension. The study evaluated whether administration of a specific antihypertensive regimen (diuretic followed by a beta-blocker) to patients over the age of 60 with isolated systolic hypertension reduced their 5-year combined incidence of fatal and nonfatal stroke. Symptoms leading to discontinuation of therapy were experienced by 21% of patients in the placebo group and 28% of those in the treatment group, with no difference between the groups in unsteadiness and a slight increase in the treatment group in faintness, falls, fatigue, sexual dysfunction, muscle weakness, and self-reported memory problems. No differences were seen in dementia or depression.

Results of several behavioral analyses showed a slightly greater worsening in the placebo group for all scores. Global quality-of-life analysis showed a slight increase in the number reporting dissatisfaction in the placebo group, with no difference between the two groups in global perception of health.

When we consider health related quality-of-life (QoL) considerations, related William B. Applegate, MD, Professor of Preventive Medicine, University of Tennessee, Memphis, we look both at the effects of medication and the stresses associated with the disease. For hypertension, this can include effects on mood, energy/activity level, cognitive performance, mobility and physical function, and sexual activity. The SHEP (Systolic Hypertension in the Elderly Program) study, he continued, evaluated several of these. With cognitive performance, there was some concern that a reduction in systolic pressure would decrease perfusion of the brain. Mobility and physical function, even falls, are a significant concern in the elderly, particularly those on therapy with hypotensive effects. And, in both middle-aged and older patients, certain antihypertensive medications may affect sexual activity or function.

"The SHEP study," Dr. Applegate pointed out, "gives us a pure look at the effect of a specific antihypertensive regimen on QoL," since it did not compare different treatment regimens, but focused on a diuretic-based regimen followed by a beta-blocker. The primary question addressed in the SHEP study was whether administration of antihypertensive therapy to patients over the age of 60 with isolated systolic hypertension (ISH; >160 mm Hg systolic, ≤90 mm Hg diastolic) reduce their 5-year combined incidence of fatal and nonfatal stroke. In addition, the study evaluated whether this antihypertensive regimen had any subtle effects on cognition, mood, or physical performance.

One concern with the study was that older patients with high systolic pressures probably have some shift in cerebral autoregulation of flow, he explained, and the question was whether cerebral blood flow would decrease if systolic and diastolic pressures were lowered. Although cerebral blood flow was not tested, several well established, accurately measured QoL domains were, including:

- General well being (including anxiety and depression)
- Physical symptoms (both drug-related and overall)
- Cognition
- Mood
- Activities
- Physical function
- Social roles

In the SHEP study, patients on the antihypertensive regimen did have a lower incidence of stroke compared with placebo; this difference expanded over time, so that after 5 years the incidence of strokes was reduced in the treated group by 33 per 1,000 person-years.[1] One issue of concern, Dr. Applegate commented, was whether to include the patients who had had strokes in the QoL analysis. For instance, there is some evidence that depression may precede a vascular event.

QoL Results from the SHEP Study

Symptoms characterized as troublesome were reported by slightly more patients in the active treatment group than by those in the placebo group.[2] Intolerable problems, in which the drug was discontinued, were experienced by 21% of patients in the placebo group and 28% of those in the treatment group. There was no difference between the groups in unsteadiness, with a slight increase in the treatment group in faintness, falls, fatigue, sexual dysfunction, muscle weakness, and trouble with memory (self-reported). "Although these trends are small, they are consistent," he observed. "There is probably something here, but it can be managed on an individual basis."

Although the increase in self-reported memory problems is not meaningless, an objective measure of memory and cognitive function, dementia (as determined by a neurologist), was present in 1.6% of the treated group and in 1.9% of the placebo group, showing no difference between the two groups. Depression was measured both by an initial screen and determination by a psychologist; again, no difference was seen between the two groups (4.4% for the treated group and 4.8% for the placebo group).

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In addition to these clinical evaluations, several behavioral analyses were used, including:

- Short-CARE, which evaluates some symptoms of depression and some symptoms of possible dementia
- CES-D, which is a screen for depressive symptomatology
- Activities of daily living (ADLs)
- Social network questionnaire

These were administered at all clinical centers (total of 4,736 patients) at baseline and on an annual or semiannual basis. In a cohort of 2,000 patients at six centers, we used more sophisticated cognitive tests, including a speed test, an attention test, and an immediate recall test, in addition to questions about global QoL and leisure activities.

The results of these tests showed no differences at baseline in terms of cognitive function, depression, or ADLs, although the placebo group reported slightly more difficulty with modest impairment for basic and moderate ADLs. At the last evaluation in the study, the differences between the placebo and treated groups were very small and not statistically significant (Table 1). An increase in scores reflected a worsening of symptoms, while a positive difference

between placebo and treated scores reflected a greater worsening in the placebo group than in the treated group. All of the scores indicated a slightly greater worsening in the placebo group; for the CES-D score, this actually achieved statistical significance. Although there was perhaps slightly more deterioration in ADLs, again this was less so for the actively treated group. In almost no variable did the active group do worse than the placebo group, Dr. Applegate reported.

In terms of global QoL, reflecting patients' perceptions about life as a whole (delighted, pleased, somewhat dissatisfied, very dissatisfied), a slight increase was seen in the placebo group in the number reporting dissatisfaction, which is probably not clinically significant. Global perception of health (excellent, good, fair, poor, or bad) showed no difference between the two groups.

Interestingly, for all of the analyses, the results were not affected by inclusion or exclusion of patients who had had strokes, due to their small number. Although some differences could be seen when this group was analyzed separately, Dr. Applegate warned that "without some a priori hypothesis, this would undo the effects of randomization."

Conclusion

According to Dr. Applegate, the bottom line is that although individual patients can develop side effects or may become depressed or have QoL problems on medication, when you look at a large group of people at risk, treating ISH leads to a dramatic reduction in events, with a modest suggestion of improvement in QoL.

Table 1. Mean QoL Scores at the End of the SHEP Study

Parameter	QoL Score*
Cognitive impairment (Short-CARE)	+0.05
Depressive symptoms (Short-CARE)	+0.16
CES-D	+0.38**
Any basic ADL	+0.20
Moderate ADLs	+0.30
Advanced ADLs	+0.72
Any ADL	+0.97

*The difference between the change in placebo scores and the change in treated scores.
**P=0.05.

··· REFERENCES ···

1. Smith WM, Applegate WB, Berge K, et al. The SHEP cooperative research group: Implications of the systolic hypertension in the elderly program (SHEP). *Hypertension* 1993;21:335-343.
2. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991;265:3255-3264.