Systolic Hypertension in Older Persons

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SYSTOLIC HYPERTENSION (SH), defined as systolic blood pressure (SBP) of at least 140 mm Hg and diastolic blood pressure (DBP) of less than 90 mm Hg, is a major public health issue that predominately affects older individuals.\(^1\) A major message of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure emphasizes the importance of systolic hypertension (SH), defined as systolic blood pressure (SBP) of at least 140 mm Hg and diastolic blood pressure less than 90 mm Hg, in older persons (\(\geq 60\) years).\(^2\)

Objective To systematically review the literature on clinical management of SH in older persons.

Data Sources We performed a MEDLINE search of English-language literature from 1966-2004 to identify reports about SH in older persons, with particular emphasis on data from randomized clinical trials.

Study Selection and Data Extraction We selected 1064 studies by using the search terms **hypertension** combined with the terms **systole** (or **systolic** and **aged**).

Data Synthesis There is strong evidence from clinical trials to support the treatment of SH in older persons with SBP of at least 160 mm Hg. Large-scale trials to assess the value of antihypertensive therapy for older patients with SBP of 140 to 159 mm Hg have not been performed, and recommendations to treat these patients are based on observational studies that show a graded relationship of cardiovascular risk with increasing SBP. The studies most strongly support the use of thiazide diuretics and long-acting calcium channel blockers as first-line therapy to treat SH.

Conclusions Treatment of SH in older patients with SBP of at least 160 mm Hg is supported by strong evidence. The evidence available to support treatment of patients to the level of 140 mm Hg or those with baseline SBP of 140 to 159 mm Hg is less strong; thus, these treatment decisions should be more sensitive to patient preferences and tolerance of therapy.
sidered, we present data from randomized controlled trials and observational studies. In selecting trials for this review, we preferentially included studies that correlated SBP level with morbidity or mortality. In choosing observational studies for inclusion, we required that subgroup analyses on patients with SH be available in the published literature. A total of 36 articles met our criteria.

**EVIDENCE SYNTHESIS**

**What Is the Evidence for Blood Pressure (BP) Reduction for Patients With SBP at Least 160 mm Hg and DBP Less Than 90 mm Hg?**

As early as the 1970s, epidemiologic studies strongly suggested that SH was a risk factor for cardiovascular disease. With the publication of the SHEP trial in 1991, high-level randomized clinical trial evidence became available to support routine treatment of this condition. The Systolic Hypertension in Europe (Syst-Eur) and Systolic Hypertension in China (Syst-China) trials further supported treatment for SH. The primary objective of all 3 of these trials was to determine whether treatment of SH in older persons could reduce the risk of stroke. Treatment of SH has not been shown to reduce either all-cause or cardiovascular mortality because none of these 3 trials was adequately powered to demonstrate differences in these fatal end points. The key features of these trials are discussed below and summarized in Table 1.

**Systolic Hypertension in the Elderly Program.** Participants in SHEP were given the thiazide diuretic chlorthalidone (12.5-25 mg/d) or matching placebo. Atenolol (25-50 mg/d) was added next, if needed to achieve target SBP. Of the participants in the active treatment group, 46% received chlorthalidone only. The 5-year incidence of stroke (fatal and nonfatal combined) was 8.2% in the placebo group and 5.2% in the active treatment group, with a relative risk (RR) of 0.64 (95% confidence interval [CI], 0.49-0.82). There was a statistically significant 32% reduction in the incidence of cardiovascular disease (fatal and nonfatal combined).

Although the development of new cases of diabetes was not significantly greater in the active treatment group compared with the placebo group (8.6% vs 7.5%, respectively, \( P = .25 \)), serum glucose, uric acid, and cholesterol levels were out of the specified ranges more frequently in the active treatment group.

**Systolic Hypertension in Europe.** Active treatment in Syst-Eur consisted of the long-acting dihydropyridine calcium channel blocker (CCB) ni-trendipine (10-40 mg/d), with the addition of enalapril (5-20 mg/d) and then hydrochlorothiazide (12.5-25 mg/d) as needed to lower the SBP to goal. After 2 years, nitrendipine was the only treatment given to 59% of the pa-

| Table 1. Studies of Treating Systolic Hypertension With Systolic Blood Pressure ≥160 mm Hg |
|---------------------------------|----------|----------|----------|
| **SHEP** | **Syst-Eur** | **Syst-China** |
| No. of patients | 4736 | 4989 | 2394 |
| Definition of SH, mm Hg | 160-190 | 160-219 | 160-219 |
| Diastolic BP | <90 | <95 | <95 |
| Initial BP, mean (SD), mm Hg | | | |
| Systolic | 170 (9) | 174 (10) | 170 (11) |
| Diastolic | 77 (10) | 85 (6) | 86 (7) |
| BP reduction, mean (SD), mm Hg | | | |
| Systolic | 27* | 23 (16) | 20 (16) |
| Diastolic | 9* | 7 (8) | 5 (8) |
| Stroke risk reduction | | | |
| Relative risk (95% CI) | 0.64 (0.49-0.82) | 0.58 (0.41-0.84) | 0.69 (0.48-1.02) |
| Absolute risk (95% CI) | 0.02 (0.01-0.04) | 0.01 (0.01-0.02) | 0.02 (0.00-0.03) |
| Total cardiovascular risk reduction | | | |
| Relative risk (95% CI) | 0.68 (0.58-0.79) | 0.71 (0.57-0.87) | 0.72 (0.53-0.96) |
| Absolute risk (95% CI) | 0.03 (0.03-0.07) | 0.02 (0.01-0.04) | 0.02 (0.00-0.04) |

Abbreviations: BP, blood pressure; CI, confidence interval; SH, systolic hypertension; SHEP, Systolic Hypertension in the Elderly Program; Syst-China, Systolic Hypertension in China; Syst-Eur, Systolic Hypertension in Europe. *SDs not available.
Participants in the active treatment group. Treatment significantly reduced the risk of stroke by 42%, from 3.35%, with an RR of 0.58 (95% CI, 0.41-0.84) in the placebo group to 1.96% in the active treatment group. Cardiovascular disease was also significantly reduced by 30% with active treatment. The active treatment group had half the incidence of dementia compared with the placebo group (7.7 vs 3.8 cases per 1000 patient-years).13 and this reduction in dementia persisted during extended follow-up after termination of the original trial.14

Over a 2-year period, 15% of study participants discontinued nitrendipine, 20% discontinued enalapril, and only 6% discontinued hydrochlorothiazide. The most common reasons for stopping nitrendipine were edema and flushing; for stopping enalapril, cough.15

Systolic Hypertension in China. Active treatment in Syst-China was started with nitrendipine (10 or 20 mg/d or 20 mg twice daily), with the possible addition of captopril (12.5 mg/d or twice daily or 25 mg twice daily), hydrochlorothiazide (in the same dosages as captopril), or both to achieve target SBP. Nitrendipine was the only medication given in 74% of the active treatment group. In the placebo group the rate of stroke was 5.17%, and in the active treatment group the rate was 3.59%. The RR for stroke was not statistically significant at 0.69 (95% CI, 0.48-1.02). Significant reductions were observed in total cardiovascular events.

Meta-analysis. The benefit of antihypertensive drug treatment in patients with SH was further evaluated in a clinical trial meta-analysis.16 The analysis included all patients in the SHEP, Syst-Eur, and Syst-China trials and a subset of older patients with SH enrolled in 5 other hypertension trials. In the control group, 835 major cardiovascular events occurred, whereas in the treatment group 647 events occurred. Across all trials, treatment was associated with a 26% (95% CI, 17%-34%) difference in cardiovascular events.

CONTROVERSIES

What Is the Evidence for BP Reduction in Patients With SBP of 140 to 159 mm Hg and DBP of Less Than 90 mm Hg?

To date, no large-scale clinical trial has been performed to assess the value of therapy for SH in those with SBP between 140 and 159 mm Hg, so-called stage 1 SH. Analysis of data from the National Health and Nutrition Examination Survey III shows that most cases labeled “uncontrolled hypertension” in the United States are in fact stage 1 SH in older adults.17 Clarification of the benefit of treatment for these patients is therefore critical. The evidence available to guide clinicians in treating stage 1 SH consists primarily of observational data. One trial examining treatment of stage 1 SH compared 1 year of treatment with felodipine to placebo and examined BP control and quality of life, but no cardiovascular end points were examined.18 This trial enrolled only 171 patients, and the group receiving active treatment achieved lower SBP at the end of the trial and had higher quality-of-life scores.

Observational studies supporting treatment of stage 1 SH did not assess effectiveness of therapy for stage 1 SH; they only documented increased risk of stage 1 SH. The observational studies discussed were chosen from all observational studies available because they are prominent and representative of the literature, and subgroup analyses on SH have been published.

Framingham Heart Study. Analysis of participants in the Framingham Heart Study who had stage 1 SH revealed a greater risk for development of cardiovascular disease (RR, 1.47; 95% CI, 1.24-1.74), coronary heart disease (RR, 1.44; 95% CI, 1.18-1.77), stroke (RR, 1.42; 95% CI, 1.03-1.93), and heart failure (RR, 1.60; 95% CI, 1.15-2.22) compared with those with normal BP.19 Mortality from cardiovascular disease was greater compared with that of normotensive participants (RR, 1.57; 95% CI, 1.24-2.00). The total number of people with stage 1 SH was relatively small (n = 351), and only 90 participants were aged at least 60 years at the beginning of the study. This study suggests that stage 1 SH is associated with increased risk for cardiovascular disease.

Physicians’ Health Study. In this study, 1266 of 22071 male physicians had stage 1 SH at baseline, with a mean SBP of 142.3 mm Hg and a mean age of 59 years.20 When compared with normal BP, stage 1 SH was associated with significantly increased risks of cardiovascular disease (RR, 1.32; 95% CI, 1.09-1.59), stroke (RR, 1.42; 95% CI, 1.04-1.93), cardiovascular death (RR, 1.56; 95% CI, 1.13-2.15), and all-cause mortality (RR, 1.22; 95% CI, 1.01-1.47).

What Is the Evidence for Treating the Oldest Old?

Patients older than 85 years are commonly considered the “oldest old.”21 With life expectancy increasing in western societies, this population is expanding.22 Issues that must be considered when treatment decisions are made with these patients are increased susceptibility to adverse reactions from pharmacologic treatment, competing risks from non–BP-related causes, and higher cardiovascular event rates.23 In SHEP, though, the benefit of active treatment compared with placebo increased with age, reaching its maximum in the 650 patients in the oldest age group (those >80 years). The RR for stroke in actively treated patients in the oldest age group was 0.53 (95% CI, 0.32-0.88), compared with 0.74 (95% CI, 0.48-1.14) in the group aged 60 to 69 years.9 Although the risk reduction in the 2 groups may not actually be different, the evidence suggests that the older patients may still benefit from treatment. Subgroup analysis of Syst-Eur revealed that active treatment prevented cardiovascular complications, stroke, and cardiac end points. The small size of the oldest age group (n = 441) limited its power to draw statistically significant conclusions.24

Should “White Coat” Hypertension Be Treated?

Whether isolated office hypertension with nonelevated BP readings at home
should be treated has been the subject of much debate. Although some studies have suggested increased risk of future cardiovascular events with such “white coat” hypertension,25 others have suggested no important associated risk.26 Opinion about utility of treatment remains sharply divided among hypertension experts.27 Informed patient preference and tolerance of therapy should guide treatment decisions for these patients.

**What Is the Management Approach for Older Persons With Hypertension?**

**Initial Evaluation.** The initial evaluation of the older hypertensive patient should focus on defining the severity of hypertension, assessing other risk factors for cardiovascular disease, and identifying possible secondary causes for hypertension. The JNC 7 recommends a complete medical history and physical examination, a urine examination, a clinical chemistry, and an electrocardiogram for initial diagnostic evaluation. For a diagnosis of hypertension to be established, BP should be measured on at least 2 occasions after the initial determination unless it is more than 160/105 mm Hg on the first reading.

**Lifestyle Modification.** Although no long-term trials have been designed to assess the impact of lifestyle intervention on morbidity and mortality, JNC 7 supports lifestyle interventions as an important component of treating patients with SH. Because cardiovascular risk factors often cluster, hypertensive persons tend to have an increased prevalence of dyslipidemia and insulin resistance. Lifestyle interventions, therefore, should address not only hypertension but also overall cardiovascular risk (FIGURE). Although weight reduction in overweight persons, limitation of alcohol and sodium intake, increased physical activity, and adequate potassium intake are all recommended to reduce BP, the role of these strategies in older persons has not been adequately tested. The original Dietary Approaches to Stop Hypertension (DASH) trial demonstrated that a diet high in fruits, vegetables, and fiber and limited intake of red meats, sweets, total and saturated fat, and cholesterol lowers BP significantly compared with a typical American diet.26 An analysis of the DASH diet in stage 1 SH demonstrated its effectiveness in...

**Figure. An Approach to Systolic Hypertension in Older Adults**

<table>
<thead>
<tr>
<th>ASSESS</th>
<th>Identification of Systolic Hypertension (SBP ≥ 140 mm Hg; DBP &lt; 90 mm Hg) Confirm on 2 Separate Occasions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assess Lifestyle Identify Major Hypertension Risk Factors, Target Organ Damage, or Disorders That Might Affect Prognosis or Treatment</td>
</tr>
<tr>
<td></td>
<td>Identifiable Cause Present? No</td>
</tr>
<tr>
<td></td>
<td>Sleep Apnea Renovascular Disease Cushing Syndrome Thyroid/Parathyroid Disease Drug Induced Primary Aldosteronism Pheochromocytoma Coarctation</td>
</tr>
<tr>
<td></td>
<td>SBP 140-159 mm Hg DBP &lt; 90 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Compelling Indication* Present? No</td>
</tr>
<tr>
<td>ADVISE</td>
<td>Therapy Guided by Patient Preference Lifestyle Modification Thiazide Diuretic or CCB for Most May Consider ACE Inhibitor, ARB, β-Blocker, or Combination Therapy</td>
</tr>
<tr>
<td></td>
<td>Lifestyle Modification Where Appropriate Strongly Consider Pharmacological Treatment Select Drug(s) Based on Compelling Indication(s) Other Antihypertensive Drugs (Diuretics, ACE Inhibitor, ARB, β-Blocker, CCB) as Needed</td>
</tr>
<tr>
<td></td>
<td>Thiazide Diuretic or CCB for Most Patients May Also Consider ACE Inhibitor, ARB, β-Blocker Based on Presence of Compelling Indication(s) May Require Combination Therapy Based on Target Blood Pressure</td>
</tr>
<tr>
<td>AGREE</td>
<td>Inform Patient of Recommended Treatment Approach Provide Balanced, Evidence-Based Information About Treatment, Including Benefits, Harms, Alternatives, and Areas of Uncertainty</td>
</tr>
<tr>
<td></td>
<td>Elicit Patient’s Values and Treatment Goals and Determine Preferences Negotiate and Agree on a Treatment Plan</td>
</tr>
<tr>
<td>ASSIST</td>
<td>Review Treatment Decision and Document Decision Making Process Deliver/Prescribe Agreed Upon Plan</td>
</tr>
<tr>
<td>ARRANGE</td>
<td>Arrange Follow-up or Plan to Revisit Discussion in the Future</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin–converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure. *Compelling indications include heart failure, post-myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention.† See also Table 2.
lowering SBP.29 However, this subgroup was relatively small (only 72 individuals), and the mean age of the group receiving the DASH diet was 54.7 years. There has not been a large-scale trial of the impact of this diet on morbidity or mortality or in older adults with any stage of SH.

Medications. Given the wide range of therapeutic options available for treatment of SH, it is prudent to consider the data available about reduction in morbidity and mortality, costs, patient tolerance of therapy, and comorbidity in selecting an agent for initial therapy of SH. Thiazide diuretics are an appealing option for first-line therapy, as advocated by JNC 7. It is important to note that the thiazide used in SHEP was chlorthalidone, but hydrochlorothiazide is the form most widely used in the United States today. No data exist on whether the benefits demonstrated with chlorthalidone are attainable with hydrochlorothiazide. Long-acting CCBs are also a reasonable first-choice for treatment of SH, especially given that 2 of the 3 major SH trials used this form of therapy. The recently performed SHELL (Systolic Hypertension in the Elderly: Lacidipine Long-Term) study30 compared the effect of a dihydropyridine CCB (lacidipine) with chlorthalidone in 1882 patients with a mean age of 72 years and found no difference in the incidence of cardiovascular events or mortality between treatment groups, with similar reductions in BP.

A substudy of the Losartan Intervention For Endpoint Reduction (LIFE)31 trial examined whether losartan improves outcomes to a greater degree than atenolol in 1326 older patients (mean age, 70 years) with left ventricular hypertrophy and SH. The main outcome of interest was a composite of cardiovascular events, death, stroke, or myocardial infarction. The adjusted main outcome rate was 25.1 events per 1000 patient-years with losartan compared with 35.4 with atenolol (RR, 0.75; 95% CI, 0.56-1.01). Losartan decreased electrocardiographic left ventricular mass more than atenolol (P<.001) and was better tolerated. Furthermore, in a meta-analysis of 10 trials involving more than 16000 persons aged 60 years or older (50% of whom had SH), diuretic therapy was superior to β-blockade with regard to all end points and was effective in preventing cerebrovascular events. β-Blocker therapy was ineffective in preventing coronary heart disease, cardiovascular mortality, and all-cause mortality.32 β-Blockers should therefore not be viewed as appropriate first-line therapy for uncomplicated SH in the elderly patient. Many patients with SH require more than 1 medication to adequately control SBP, and JNC 7 emphasizes the need for early combination therapy in most hypertensive patients.3 In selecting a second medication, it is important to choose an agent with a mechanism of action complementary to that of the first medication. For instance, β-blockers and an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker both act by blocking renin release, so there is less additive benefit in using these agents together.33,34 Similarly, there is little synergy between thiazide diuretics and the dihydropyridine CCBs.35,36 Reasonable evidence-based combinations might be a diuretic and an ACE inhibitor or ACE inhibitor and CCB.

What Is the Risk of Causing Widened Pulse Pressure When Treating SH?

Recent analyses of data from the Syst-Eur and Syst-China trials showed that a higher pulse pressure at enrollment was strongly correlated with a worse cardiovascular prognosis.37 If treatment of SH lowers DBP to a greater extent than SBP, pulse pressure will be increased. Whether this sort of treatment-induced widened pulse pressure is associated with cardiovascular outcome was investigated by using SHEP data.38 In the treatment group, an increase of 10 mm Hg in pulse pressure on therapy was independently predictive of significant increases in the risks of stroke (24% increased risk) and heart failure (32% increased risk). Further analysis of SHEP data demonstrated a strong dose-response effect: lower DBP was associated with increased risk of cardiovascular disease, reaching significance first at 70 mm Hg and becoming even stronger at 60 mm Hg or lower.39

How Can Treatment Decisions in Older Persons With SH Be Optimized?

The decision whether to lower BP in older patients is often challenging. Although JNC 7 states that a BP higher than 140/90 mm Hg warrants pharmacologic therapy irrespective of age, no randomized clinical trial evidence is available to demonstrate that reducing a BP of 140 to 159 mm Hg in older persons reduces morbidity or mortality. Additionally, few clinical data are available to guide treatment in the oldest old or among those with “white coat” hypertension. Compounding clinical uncertainty, the long duration and complexity of therapy, asymptomatic nature of the condition, and lack of immediate or perceived benefits are important considerations in care decisions. Further, age-related physiologic and metabolic alterations, increased prevalence of risk factors and comorbidities, and heterogeneity among older persons complicate the decision making process for the older hypertensive patient and may cause the substantial variation in treatment rates.37

Hypertension treatment decisions, particularly in older persons, must often rely on extrapolations and fall into a gray area in which optimal choice for an individual patient may be unclear. In these instances, patients must understand the probable outcomes of options, consider the personal value they place on benefits vs risks, and share decision making with their practitioners. Shared decision making occurs when the doctor and patient share all stages of the decision making process and agree on the final treatment decision.40

The primacy of patient-centered care has been supported by the Institute of Medicine41 and the US Preventive Services Task Force,42 which have proposed a realignment of health care ac-
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CONCLUSIONS

There is strong evidence to guide treatment of SH in patients with SBP of at least 160 mm Hg. Guidelines have been widely disseminated, and effective, readily available therapies should be advocated and routinely prescribed by physicians. Furthermore, recent work demonstrates the long-term (11 to 14 years) effectiveness of treating SH in reducing cardiovascular events. Despite this effectiveness, poor control of SH among patients seeking treatment for hypertension is increasing.

The evidence behind JNC 7 guidelines about treatment of older patients with SBP of 140 to 159 mm Hg and SH among the oldest old is less strong. No large-scale clinical trials have been performed to assess the effectiveness of treatment for SH in patients with SBP of 140 to 159 mm Hg. Current evidence suggests that physicians should not withhold therapy solely according to advanced age, and this is a group of patients with especially high cardiovascular risk. Therapy in these patient populations should be determined by balancing potential benefits of treatment with individual patient preference and tolerance of therapy. Similarly, although JNC 7 states that patients should be treated to targets of less than 140 mm Hg in most cases and less than 130 mm Hg if they have diabetes mellitus or chronic renal disease, there are no clinical trial data to support this recommendation. Of the 3 major SH trials discussed, SHEP achieved the lowest mean SBP, at 143/68 mm Hg. There is no evidence from clinical trials for lowering SBP in patients with SH to targets less than 140 mm Hg.

The evidence available suggests that there are risks to treatment-induced widened pulse pressure, especially when the DBP decreases to less than 60 mm Hg. Data from large-scale trials on treatment of hypertension suggest that thiazide diuretics are more effective in reducing pulse pressure than CCBs and ACE inhibitors. Furthermore, recent analysis of data from the Third National Health and Nutrition Examination Survey showed that older hypertensive patients who used diuretics alone or in combination with -blockers had lower pulse pressure than patients using -blockers alone.

Many questions remain unresolved in the treatment of SH in older persons, leaving patients and clinicians uncertain about how best to balance risks and benefits. In addition, in this age group, decisions about treatment invariably involve tradeoffs of substantial risk. A possible approach to older patients with SH uses the 5 a’s framework (assess, advise, agree, assist, and arrange), which the US Preventive Services Task Force and Institute of Medicine have supported for behavioral counseling interventions (Figure and Table 2).

There is little guidance in the literature about how best to approach modification of asymptomatic risk factors in the very elderly or how to engage these patients in shared decision making. Given the scope of the problem and the growing size of the elderly population, there remains an acute need for more study.

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REFERENCES


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