Systolic Hypertension in the Elderly: Addressing an Unmet Need

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ABSTRACT

Systolic hypertension is a major public health issue in the elderly and is often under-recognized and under-treated. The concept that systolic blood pressure increases with age should be considered a pathophysiologic concept. Aging of the cardiovascular system is accompanied by endothelial dysfunction, activation of the renin-angiotensin system and, consequently, vascular remodeling. This process leads to an increase in large artery stiffness and an increase in arterial wave reflections to the heart. These processes in daily clinical practice translate to an increase in systolic blood pressure, which is associated with increased cardiovascular morbidity and mortality. Evidence-based medicine recommendations to treat systolic hypertension in the elderly are based on landmark and recent clinical trials, which clearly demonstrated that treatment of isolated systolic hypertension is associated with significant decreases in cardiovascular morbidity and mortality. However, treatment of systolic hypertension in older adults remains disappointing because therapeutic goals often are not reached. Therefore, emphasis should be placed on the treatment of systolic hypertension in the elderly, and there is need for more effective, individualized antihypertensive therapy.

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KEYWORDS: Angiotensin II; Arterial stiffness; Elderly; Renin; Systolic hypertension; Vascular remodeling

Systolic hypertension, the most frequent type of uncontrolled hypertension in the elderly, is a major public health issue. Increased systolic blood pressure has been acknowledged as a more important risk factor for cardiovascular disease and appears to play a greater role than elevated diastolic blood pressure in determining eligibility for antihypertensive therapy. Despite the availability of effective antihypertensives, poor control of systolic hypertension appears to be increasing, especially in the older population.

There is not often consistency in use of the term “elderly.” Generally it is considered as an age of 65 years and older, while middle age is considered between 50 and 65 years of age. Therefore, in all the major studies discussed here, either age range or mean age of the study population is given.

AGING AND SYSTOLIC HYPERTENSION

After the age of 50 or 60 years, increase in blood pressure occurs primarily in systolic blood pressure (Figure 1). Diastolic blood pressure tends to spontaneously decrease with increasing age while systolic blood pressure increases, mainly as a result of the functional and structural changes in the arterial vasculature. In large arteries, aging results in progressive deposition of calcium salts, fraying and fragmentation of elastin, and an increase in the number and cross-linking of collagen fibers that increase the rigidity of the vessel wall. A rigid aorta is less able to buffer the pulsatile output from the heart, so increases occur in systolic blood pressure and ventricular afterload, while diastolic blood pressure and coronary perfusion decrease.

These age-related changes in arterial stiffness and systolic blood pressure are strongly associated with organ damage, cardiac and vascular disease, and an increased risk of morbidity and mortality.

Results from large epidemiologic studies have confirmed the association between increased systolic blood pressure and the increased risk of morbidity and mortality. A meta-analysis of 61 prospective studies of blood pressure and...
mortality showed that, between the ages of 40 and 69 years, an increase in systolic blood pressure of 20 mm Hg was associated with a more than 2-fold increase in the death rate due to stroke and in the death rates from ischemic heart disease and other vascular causes. Relatively small decreases in mean systolic blood pressure were associated with large absolute reductions in strokes and premature deaths. A 2-mm Hg mean lower systolic blood pressure was equivalent to a 7% lower risk of death from ischemic heart disease and a 10% lower risk of stroke.

**ROLE OF THE RENIN-ANGIOTENSIN SYSTEM**

The renin-angiotensin system appears to be one of the most significant contributors to systolic hypertension. It plays an important role in the regulation of blood pressure, water and salt balance, and tissue growth. It functions both as a circulating endocrine system and as a tissue paracrine/autocrine system, most notably in the heart, brain, kidney, and vasculature.

Angiotensin II is a powerful vasoconstrictor that triggers the release of aldosterone, causing the kidneys to retain sodium and water. This increases blood volume and maintains normal blood pressure in hypotensive situations.

Under pathophysiologic conditions, activation of the renin-angiotensin system at the tissue level contributes to the pathogenesis of cardiovascular and renal disease. Angiotensin II triggers vascular inflammation and fibrosis in the heart and kidney, and is associated with the development of atherosclerosis in large vessels.

Chronic stimulation of the renin-angiotensin system leads to growth- and fibrosis-promoting processes, which lead to further deleterious effects, including organ damage (Figure 2).

Antihypertensive drugs that block the renin-angiotensin system at any one of several points have been shown not only to attenuate organ damage associated with hypertension but also to decrease cardiovascular morbidity and mortality. These include the angiotensin-converting enzyme inhibitors, the angiotensin II receptor blockers, and the aldosterone antagonists.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been found to be more effective than beta-blockers and diuretics for regression of left ventricular hypertrophy, a common problem among elderly patients with isolated systolic hypertension that is linked to morbidity and mortality.

Multiple placebo-controlled trials of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have shown significant slowing of renal damage in diabetic and nondiabetic nephropathies. A recent substudy analysis of 918 patients with isolated hypertension showed that the angiotensin II receptor blocker telmisartan afforded significantly greater lowering of urinary albumin excretion than hydrochlorothiazide after 6 weeks, regardless of the baseline urinary albumin excretion and despite comparable reductions in systolic blood pressure with both drugs.

**EVIDENCE-BASED MEDICINE IN THE TREATMENT OF SYSTOLIC HYPERTENSION**

The evaluation and treatment of hypertension should focus on lowering blood pressure and reducing the risk of cardiovascular and renal morbidity and mortality. Effective therapy should slow or reverse abnormal structural changes in arterial circulation that are associated with systolic hypertension in the elderly. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure recommends that systolic blood pressure become the major criterion for diagnosis, staging, and therapeutic management (including lifestyle modification and pharmacotherapy) of hypertension, particularly in middle-aged Americans. For most patients, target blood pressure is <140/90 mm Hg. For patients with multiple cardiovascular risk factors, established organ damage, or specific comorbidities (eg, diabetes or renal insufficiency), the target
is below 130/80 mm Hg. For older hypertensive patients, including those with isolated systolic hypertension (defined as systolic blood pressure $\geq 140$ mm Hg and diastolic blood pressure $<90$ mm Hg), treatment recommendations should follow the same principles outlined for the general management of hypertension, although multiple drugs are often necessary to achieve blood pressure targets in the majority of these patients.\(^{13}\)

While blood pressure control can be difficult, it is often achievable through the use of lifestyle modification and combinations of medications. Selection of first-line medication is predicated on a variety of factors, including target organ damage, compelling indications, and other factors such as cost. The value of blood pressure reduction in patients with isolated hypertension has been demonstrated in numerous clinical trials, and studies are ongoing to determine the best interventions.

**LANDMARK CLINICAL TRIALS**

A literature search was done in PubMed for isolated systolic hypertension, elderly, clinical trials, and cardiovascular complications from 1980 until now. Only randomized double-blind clinical trials that aimed to study the effect of antihypertensive agents on cardiovascular complications (defined as fatal and nonfatal stroke, fatal and nonfatal coronary heart disease, and other fatal and nonfatal vascular disorders as defined in each trial) in elderly with a mean age above 60 years old with systolic hypertension were withheld for discussion.

This literature search gives clinical evidence from several large randomized trials that emerged in the early 1990s, providing convincing support for the routine treatment of systolic hypertension in elderly patients. The Table, available online, summarizes these trials, and absolute and relative outcome results are given.

The Systolic Hypertension in the Elderly Program (SHEP) study showed that active blood pressure treatment significantly reduced rates of nonfatal stroke by 36%, total coronary heart disease by 25%, and left ventricular failure by 53% in 4736 elderly patients with systolic hypertension (aged $\geq 60$ years; mean blood pressure 171/77 mm Hg) who were followed for an average of 4.5 years.\(^{14}\) A recent follow-up analysis of the SHEP participants showed that treatment improved long-term outcomes, especially among patients who had diabetes.\(^{15}\) At a mean follow-up of 14.3 years, the cardiovascular mortality rate was significantly lower, 19% in the treatment group versus 22% in the placebo group. Further, patients who developed diabetes during treatment had no significant increase in cardiovascular events and had a better prognosis than those who had preexisting diabetes. In a study of a smaller SHEP cohort ($n=268$) of patients with isolated systolic hypertension, placebo treatment was associated with a 90% greater risk of death or a cardiovascular event during a 14-year period when compared with active treatment.\(^{16}\)

The Systolic Hypertension in Europe (Syst-Eur) and the Systolic Hypertension in China (Syst-China) trials were 2 other large trials in elderly patients with isolated systolic hypertension, yielding outcomes similar to those of SHEP.\(^{17,18}\) Each assessed the effect of therapy based on the calcium channel blocker nitrendipine. The European trial included 4695 patients (aged $\geq 60$ years; mean blood pressure 174/86 mm Hg), and showed that nitrendipine-based therapy significantly reduced stroke by 42% and cardiovascular outcomes by 31%.\(^{17}\) Likewise, in the Chinese trial, nitrendipine therapy prevented stroke and other cardiovascular complications in 2394 older patients (aged $\geq 60$ years) with isolated systolic hypertension.\(^{18}\) Active treatment reduced total stroke by 38%, all-cause mortality by 39%, cardiovascular mortality by 39%, stroke mortality by 58%, and all fatal and nonfatal cardiovascular end points by 37%.

A meta-analysis that examined a subset of patients with isolated systolic hypertension from the SHEP, Syst-Eur, and Syst-China trials showed that there was a 23% reduction in cardiovascular events associated with treatment of systolic hypertension compared with no treatment in elderly patients.\(^{19}\)

**RECENT CLINICAL TRIALS**

Following the encouraging findings of the early trials in treating systolic hypertension in older subjects, many new trials have focused on elucidating the effects of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and other blood pressure-lowering drugs on mortality and major cardiovascular morbidity (Table, available online).\(^{20-23}\) The Losartan Intervention For Endpoint reduction (LIFE) trial was a randomized, double-blind study that examined the effects of the angiotensin receptor blocker losartan on cardiovascular
mortality, stroke, and myocardial infarction. In a subgroup analysis of the LIFE trial, 1326 elderly patients with isolated hypertension (mean age 70 years; mean blood pressure 174/83 mm Hg) and left ventricular hypertrophy received once-daily losartan or atenolol (with hydrochlorothiazide as the second agent in both arms) for a mean of 4.7 years. The composite end point of cardiovascular death, stroke, or myocardial infarction was reduced by 25% with losartan compared with atenolol. Patients receiving losartan also had significant reductions in left ventricular hypertrophy as measured by electrocardiography.

The Study of Cognition and Prognosis in the Elderly (SCOPE), a prospective, double-blind, randomized, parallel-group study, examined the effects of the angiotensin receptor blocker candesartan on cardiovascular events, stroke, and cognition in 4964 elderly patients with mild hypertension (aged 70-89 years; systolic blood pressure 160-179 mm Hg or diastolic blood pressure 90-99 mm Hg). Although this was not a study of isolated systolic hypertension specifically, 30% of the patients had isolated systolic hypertension. After a mean follow-up of 3.7 years, the angiotensin receptor blocker-based treatment reduced nonfatal stroke by 27.8% and stroke by 23.6%. There were no significant differences in myocardial infarction and cardiovascular mortality, and cognitive function was well maintained in both the treatment and placebo groups.

Several other studies have lent support to the use of calcium channel blockers as a treatment option for elderly patients with isolated systolic hypertension. The Systolic Hypertension in the Elderly Long-term Lacidipine (SHELL) study compared the effect of lacidipine and chlorthalidone in 1882 elderly patients with isolated systolic hypertension (age >60 years; mean blood pressure 178/87 mm Hg) followed for 32 months. Both drugs markedly reduced systolic blood pressure. The overall incidence of the primary end point, a composite of cardiovascular and cerebrovascular events, was 9.3% in both groups.

The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) study included 6321 elderly patients (aged 55-80 years) with hypertension and at least 1 additional cardiovascular risk factor. Although not a selective isolated systolic hypertension trial, INSIGHT contained a subgroup of 1498 patients with isolated systolic hypertension (mean blood pressure 173/88 mm Hg) that was analyzed separately. In the subgroup analysis, the calcium channel blocker nifedipine gastrointestinal therapeutic system was compared with the diuretic combination co-amilozide, and it evaluated a composite end point of death due to cardiovascular and cerebrovascular causes and nonfatal stroke, myocardial infarction, and heart failure. Both treatments had similar effects on blood pressure lowering and on the primary outcome (6.0% with nifedipine, 6.6% with co-amilozide).

Several short-term studies compared the blood pressure-lowering effects and safety of angiotensin receptor blockers and calcium channel blockers in elderly patients with isolated systolic hypertension. Valsartan and Amlodipine for the Treatment of Isolated Systolic Hypertension in the Elderly (Val-Syst), a 24-week randomized, double-blind study, compared the risk/benefit profiles of the angiotensin receptor blocker valsartan with the calcium channel blocker amlodipine in 421 elderly (aged 60-80 years) patients with isolated systolic hypertension. The results showed that valsartan, given alone or in combination with hydrochlorothiazide, showed similar efficacy but better tolerability than amlodipine-based treatment. Overall, adverse events were observed in 31.9% of those receiving amlodipine versus 20.2% of the patients receiving valsartan (P < .003), with peripheral edema rates of 26.8% and 4.8%, respectively.

Another randomized, double-blind, placebo-controlled 12-week study compared the effects of the diuretic indapamide with the angiotensin receptor blocker candesartan and the calcium channel blocker amlodipine in 1758 patients (aged 40-80 years) with hypertension. In a subgroup of patients with isolated systolic hypertension (n = 388, mean age 64 years), the 3 treatments significantly reduced systolic blood pressure; although, indapamide did not change diastolic blood pressure and, thus, reduced pulse pressure significantly. All 3 drugs were well tolerated.

The findings from these clinical trials demonstrate that blockade of the renin-angiotensin system at various points in the cascade are effective blood-pressure-lowering medications. Studies listed comparing angiotensin receptor blockers to other regimens showed a lower incidence of stroke, but not of other cardiovascular outcomes, with renin-angiotensin-directed regimens, and equivalence of non-renin-angiotensin-treatments in reducing events (calcium channel blockers, diuretics) based on degree of blood pressure lowering. In these randomized clinical trials, the discrepancy in outcome can be due to a difference in reached target blood pressure; for example, in Syst-Eur, 43% of the nitrendipine group reached target blood pressure, but only 21% of the control group did so. Therefore the results of these randomized trials should be interpreted in an appropriate perspective.

FUTURE PERSPECTIVES AND DIRECTIONS

Potential new markers are being identified to help detect preclinical disease. There is evidence that high-sensitivity C-reactive protein, for example, a marker for acute and low-grade inflammation, may indicate reductions in large-artery elasticity, which subsequently leads to elevated systolic blood pressure. This information may be useful when performing primary prevention cardiovascular screening in asymptomatic individuals.

Central aortic blood pressure measurement, which interprets the shape of pulse waves measured at the wrist, may also be a better predictor of stroke or myocardial infarction than peripheral blood pressure measurement and may be more indicative of how well a drug is performing. Regardless of reductions in cuff blood pressure, beneficial effects on central arterial pressure may still occur, which may
explain the apparent “pressure-independent” effects of drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. In the Conduit Artery Function Evaluation study, different blood pressure-lowering treatment regimens had different effects on central aortic pressures, despite similar effects on brachial pressure.\textsuperscript{28} The use of both peripheral and central aortic assessments may be more sensitive for detecting cardiovascular disease than cuff blood pressure alone and is increasingly more common in office practice.

Future pharmacological treatments are most likely to affect the early mechanisms of vascular disease and focus on reducing arterial stiffness. Clearly, renin-angiotensin system blockade protects against cardiovascular events and reduces mortality, as demonstrated by the success of the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in clinical trials. However, pharmacological renin-angiotensin blockade is possible at other renin-angiotensin sites as well.\textsuperscript{29} A promising new strategy is the direct inhibition of renin, which catalyzes the first, rate-limiting step in the renin-angiotensin system pathway. Although a number of renin inhibitors were developed in the past 2 decades, they were not clinically useful drugs because of poor pharmacokinetics and potency. Encouraging results have recently been reported with aliskiren, the first representative of a new class of nonpeptide, orally active renin inhibitors that was recently approved by the United States Food and Drug Administration as monotherapy or in combination with other antihypertensive agents.\textsuperscript{29} Clinical data have demonstrated that once-daily aliskiren achieves dose-dependent reductions in plasma renin activity and systolic blood pressure over 4-week\textsuperscript{30} and 8-week study periods with no rebound effects on blood pressure after treatment withdrawal.\textsuperscript{31} Additionally, aliskiren is safe and well tolerated in the patient populations assessed.\textsuperscript{30,31}

Recently, the first large-scale study designed to assess the effects of dual renin system blockade with the direct renin inhibitor aliskiren and the angiotensin receptor blocker valsartan versus each drug alone in 1797 patients with mild-to-moderate (stage 1-2) diastolic hypertension was published.\textsuperscript{32} Aliskiren in combination with valsartan significantly lowered mean sitting systolic and diastolic blood pressure compared with either agent alone in this patient population. Currently, there is an ongoing clinical trial, the AGELESS trial, assessing the efficacy of aliskiren compared with ramipril in systolic hypertension in patients aged \( \geq 65 \) years. Additional studies are ongoing and continue to explore the safety and efficacy of aliskiren, as well as other renin inhibitors, and also the possibility of inhibiting multiple steps in the renin-angiotensin system with combination therapies.

CONCLUSION
Systolic hypertension is the most frequent type of hypertension in the elderly. Age-related changes in arterial stiffness and systolic hypertension are strongly associated with organ damage, cardiac and vascular disease, and an increased risk of morbidity and mortality. Although treatment of systolic hypertension in older adults has resulted in substantial reductions in mortality and cardiovascular events, current hypertension control rates remain disappointing.

The renin-angiotensin system plays a significant role in the pathogenesis and progression of systolic hypertension. Currently, there is a good scientific rationale for using agents that act on the renin-angiotensin system in the treatment of systolic hypertension, and ongoing studies are investigating the best use of these agents-alone and in combination.

New definitions for hypertension may serve to better identify elderly patients who are at higher cardiovascular risk and may be candidates for early intervention. Better tools, such as ambulatory blood pressure monitoring, are becoming more readily available to accurately assess and monitor hypertension. Ongoing large-scale studies are assessing the effects of various classes of antihypertensive agents on the vascular tree—beyond just lowering blood pressure—and may lead to improved treatment algorithms for isolated systolic hypertension in the elderly.

References


<table>
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<tr>
<th>Trial Name and Design</th>
<th>Patients n</th>
<th>Mean Age (Years)</th>
<th>Median Follow-up (Years)</th>
<th>Mean Initial SBP/DBP (mm Hg)</th>
<th>Regimens and End Points</th>
<th>Outcomes</th>
<th>Absolute</th>
<th>Relative</th>
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<tr>
<td>SHEP&lt;sup&gt;15&lt;/sup&gt; (1991) Randomized, double-blind, placebo-controlled</td>
<td>4736</td>
<td>71.6</td>
<td>4.5</td>
<td>170/77</td>
<td>Chlorthalidone with atenolol or reserpine if necessary Primary end point: nonfatal and fatal (total) stroke</td>
<td>Total stroke: 5.2% (123/2365), treatment group 8.2% (194/2371), placebo group All coronary heart disease events: 5.9% (140/2365), treatment group: 7.7% (184/2371), placebo group All fatal and nonfatal cardiovascular events: 12.2% (289/2365), treatment group 17.5% (414/2371), placebo group Depression: 4.4% (104/2365), treatment group 4.7% (112/2371), placebo group No significant difference between groups</td>
<td>Total stroke: 36% reduction in the treatment group compared with the placebo group RR = 0.64, 95% CI, 0.50-0.82 P = .0003 All coronary heart disease events: 25% reduction in the treatment group compared with the placebo group RR = 0.75, 95% CI, 0.60-0.94 All fatal and nonfatal cardiovascular events: 32% reduction in the treatment group compared with the placebo group RR = 0.68, 95% CI, 0.58-0.79</td>
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<td>SHEP&lt;sup&gt;15&lt;/sup&gt; Extension (2005)</td>
<td>4732</td>
<td>71.6</td>
<td>14.3</td>
<td>170/77</td>
<td>Chlorthalidone with atenolol or reserpine if necessary Primary end point: long-term mortality</td>
<td>Cardiovascular mortality: 19% (450/2363), treatment group 22% (515/2369), placebo group Subjects who developed diabetes during treatment had no significant increase in cardiovascular events and had a better prognosis than those who had pre-existing diabetes</td>
<td>HR 0.854, 95% CI, 0.751-0.972 P &lt;.05</td>
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<td>Syst-Eur&lt;sup&gt;17&lt;/sup&gt; (1997) Randomized, double-blind, placebo-controlled</td>
<td>4695</td>
<td>70.3</td>
<td>2.0</td>
<td>174/86</td>
<td>Nitrendipine combined with or replaced by enalapril, hydrochlorothiazide, or both if necessary Primary end point: Nonfatal and fatal (total) stroke</td>
<td>All stroke: 7.9 events per 1000 patient-years, treatment group 13.7 events per 1000 patient-years, placebo group Nonfatal stroke: 5.7 events per 1000 patient-years, treatment group 10.1 events per 1000 patient-years, placebo group All fatal and nonfatal cardiovascular events: 23.3 events per 1000 patient-years, treatment group 33.9 events per 1000 patient-years, placebo group</td>
<td>All stroke: 42% reduction in the treatment group compared with the placebo group 95% CI, .17-.60 P = .003 Nonfatal stroke: 44% reduction in the treatment group compared with the placebo group 95% CI, .14-.63 P = .007 All fatal and nonfatal cardiovascular events: 31% reduction in the treatment group compared with the placebo group 95% CI, .14-.45 P = .001</td>
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<tr>
<td>Trial Name and Design</td>
<td>Patients n</td>
<td>Mean Age (Years)</td>
<td>Mean Median Follow-up (Years)</td>
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<td>Outcomes</td>
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| Syst-China\(^1\%\) (1998)               | 2394       | 66.4             | 3.0                           | 171/86                      | Nitrendipine with captopril, hydrochlorothiazide, or both if necessary Primary end point: Nonfatal and fatal (total) stroke | All stroke: 13.0 events per 1000 patient-years, treatment group 20.8 events per 1000 patient-years, placebo group  
All fatal and nonfatal cardiovascular events: 21.4 events per 1000 patient-years, treatment group 33.3 events per 1000 patient-years, placebo group  
Total mortality: 17.4 events per 1000 patient-years, treatment group 28.4 events per 1000 patient-years, placebo group  
Cardiovascular mortality: 9.4 events per 1000 patient-years, treatment group 5.2 events per 1000 patient-years, placebo group  
Stroke mortality: 2.9 events per 1000 patient-years, treatment group 6.9 events per 1000 patient-years, placebo group | All stroke: 38% reduction in treatment group compared with placebo group 95% CI, .09-.58  
All fatal and nonfatal cardiovascular events: 37% reduction in treatment group compared with placebo group 95% CI, .14-.53  
Total mortality: 39% reduction in treatment group compared with placebo group 95% CI, .16-.57  
Cardiovascular mortality: 39% reduction in treatment group compared with placebo group 95% CI, .04-.61  
Stroke mortality: 58% reduction in treatment group compared with placebo group 95% CI, .14-.80 | \(P = .01\)  
\(P = .004\)  
\(P = .003\)  
\(P = .03\)  
\(P = .02\) |
| LIFE\(^2\) substudy (2002)              | 1326       | 70               | 4.7 (mean) 174/83 (mean)      | Losartan or atenolol with hydrochlorothiazide if necessary Primary end point: Composite of cardiovascular death, stroke, or myocardial infarction | Cardiovascular death, stroke, or myocardial infarction: 25.1 events per 1000 patient-years, losartan group 35.4 events per 1000 patient-years, atenolol group | Cardiovascular death, stroke, or myocardial infarction: 25% reduction with losartan compared with atenolol RR 0.75, 95% CI, 0.56-1.01 | \(P = .06\)  
Losartan decreased ECG-LVH more than atenolol \((P < .001)\) |

\(1\) Life Extension Study of Antihypertensive Drugs in the Elderly

\(2\) Losartan Intervention ForEndpoint Reduction in Hypertension
<table>
<thead>
<tr>
<th>Trial Name and Design</th>
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<th>Outcomes</th>
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<th>Relative</th>
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<tr>
<td>SCOPE&lt;sup&gt;21&lt;/sup&gt; (2003) Prospective, double-blind, randomized, parallel-group</td>
<td>4964 (30% were ISH)</td>
<td>76.4</td>
<td>3.7</td>
<td>166/90</td>
<td>Candesartan with open-label active antihypertensive therapy added as needed. Primary end points: Major cardiovascular events, a composite of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction. Secondary end points: Cardiovascular death, nonfatal and fatal stroke, and myocardial infarction, cognitive function measured by the MMSE and dementia.</td>
<td>First major cardiovascular event: 26.7 events per 1000 patient-years, candesartan group 30.0 events per 1000 patient-years, control group. Nonfatal stroke: 7.4 events per 1000 patient-years, candesartan group 10.3 events per 1000 patient-years, control group. All stroke: 9.7 events per 1000 patient-years, candesartan group 12.8 events per 1000 patient-years, control group.</td>
<td>First major cardiovascular event: 10.9% reduction with candesartan compared with control 95% CI, −6.0-25.1. Nonfatal stroke: 27.8% reduction with candesartan compared with control 95% CI, 1.3-47.2. All stroke: 23.6% reduction with candesartan compared with control 95% CI, −0.7-42.1.</td>
<td>P = .19</td>
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<td>SHELL&lt;sup&gt;22&lt;/sup&gt; (2003) Prospective, open design</td>
<td>1882</td>
<td>72</td>
<td>2.6</td>
<td>178/87</td>
<td>Chlorthalidone or lacidipine Primary end point: composite of cardiovascular and cerebrovascular events.</td>
<td>Composite of cardiovascular and cerebrovascular events: 9.4% (88/940), chlorthalidone group 9.6% (90/942), lacidipine group. All-cause mortality: 13.0% (122/940), chlorthalidone group 15.4% (145/942), lacidipine group.</td>
<td>Composite of cardiovascular and cerebrovascular events: HR 1.01, 95% CI, 0.75-1.36. All-cause mortality: HR 1.23, 95% CI, 0.97-1.57.</td>
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<td>INSIGHT&lt;sup&gt;23&lt;/sup&gt; subanalysis (2004) Prospective, randomized, double-blind</td>
<td>6321 (with 1498 ISH)</td>
<td>55-80 (range)</td>
<td>3.0</td>
<td>173/88</td>
<td>Nifedipine or co-amilozide (hydrochlorothiazide plus amiloride) with addition of atenolol or enalapril Primary end points: Cardiovascular death, myocardial infarction, heart failure, or stroke.</td>
<td>Cardiovascular death, myocardial infarction, heart failure, or stroke: Patients with ISH: 6.0% (44/738) nifedipine 6.6% (50/760) co-amilozide. Patients without ISH: 6.4% (156/2419) nifedipine 5.5% (132/2404) co-amilozide.</td>
<td>Cardiovascular death, myocardial infarction, heart failure, or stroke: OR 0.90, 95% CI, 0.59-1.37. OR 1.19, 95% CI, 0.93-1.51.</td>
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SBP = systolic blood pressure; DBP = diastolic blood pressure; SHEP = Systolic Hypertension in the Elderly Program; RR = relative risk; CI = confidence interval; HR = hazards ratio; Syst-Eur = Systolic Hypertension in Europe; Syst-China = Systolic Hypertension in China; LIFE = Losartan Intervention for Endpoint; ECG-LVH = electrocardiographic-left ventricular hypertrophy; SCOPE = Study on Cognition and Prognosis in the Elderly; ISH = isolated systolic hypertension; MMSE = Mini Mental State Examination; SHELL = Systolic Hypertension in the Elderly Long-term Lacidipine; INSIGHT = International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment; OR = odds ratio.