

## Hypertension in the Older Patient: Practical Clinical Management

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**Abstract:** Hypertension is an important risk factor for cardiovascular morbidity and mortality in the elderly. Isolated systolic hypertension is particularly prevalent, because of structural and functional changes of the arteries and alterations in salt sensitivity and neural function with aging. Blood pressure lowering therapy has been shown to reduce the morbidity and mortality in the elderly. There is little doubt that a healthy lifestyle including diet, physical activity and ideal body weight is the foundation of hypertension management. Adequate lifestyle changes may reduce the need for antihypertensive drugs, but most older people with elevated BP will require a combination of antihypertensive drugs for ideal blood pressure control. An achieved systolic blood pressure of less than 150 mmHg seems to be effective and safe to date, while stricter goals may be appropriate, if tolerated. Careful attention should be required to postural and postprandial hypotension. Optimal blood pressure goal for the elderly remains inconclusive and needs to be further investigated.

**Keywords:** hypertension, elderly, cardiovascular risk

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## Introduction

In the developed countries of the world, life expectancy is continuously increasing; as a result, the proportion of elderly people in these population has increased rapidly in recent decades. Data from the National Health and Nutrition Examination Survey from 1999 to 2004 show that 60% of all adults aged 60 to 69 years and up to 77% of those aged 80 years or older have hypertension.<sup>1</sup> According to the World Health Organization, hypertension is a common cause of premature death in developed countries and is increasingly significant in developing countries.<sup>2</sup> The prevalence of hypertension increases with age.<sup>3</sup>

Age is a strong risk factor for hypertension, cardiovascular death and death. Blood pressure (BP) reduction has been shown to be effective in preventing major cardiovascular events in hypertensive subjects.<sup>4</sup> Because of the continued increase in the proportion of older people in developed countries, further increases in cardiovascular and renal complications of hypertension can be predicted for the next few decades.<sup>5–7</sup> Indeed, hypertension in the elderly is one of the main topics in antihypertensive treatment. However, both the effectiveness of BP lowering and the BP goal in the elderly have remained unclear.<sup>8–11</sup>

## Pathophysiology of Hypertension in the Elderly

In older people, changes in the arterial structure—namely, a decrease of vascular smooth muscle cells— increase collagen in the vessel wall; together with the

disruption of elastic fibers and calcium deposition that occur with aging, this results in the large elastic vessels becoming less distensible.<sup>12</sup> Functional changes in vessels also contribute to the increase in arterial stiffness. Endothelial dysfunction is more common in older people with hypertension, and derives from the decreased bioavailability of nitric oxide. Nitric oxide plays key roles in the promotion of vasodilatation and the inhibition of platelet aggregation.<sup>13</sup> The increase in arterial stiffness limits expansion of the vessels and thus the system's ability to effectively buffer the pressures from the heart, leading to elevations in systolic blood pressure (SBP), while the loss of recoil in the diastolic phase leads to a diastolic blood pressure (DBP) plateau in the fifth and sixth decades of life, with slow declines thereafter (Fig. 1).<sup>8,14</sup> Consequently, isolated elevated SBP (ie, isolated hypertension) is more prevalent in older people.<sup>3</sup> These changes lead to elevated pulse pressure, which damages vessels and organs, and as a result, increased cardiovascular risk. Hence, SBP should be recommended as a primary target for the diagnosis and care of older subjects with hypertension.<sup>8–11,14</sup>

Hypertension is common among older people with kidney disease.<sup>1,15,16</sup> A stepwise increase in the prevalence of isolated hypertension has been found at each stage of chronic kidney disease.<sup>16</sup> An inverse relationship between pulse pressure and glomerular filtration rate (GFR) has been also reported.<sup>17</sup> These findings highlight the importance of the relationship between blood pressure and kidney function in the elderly.

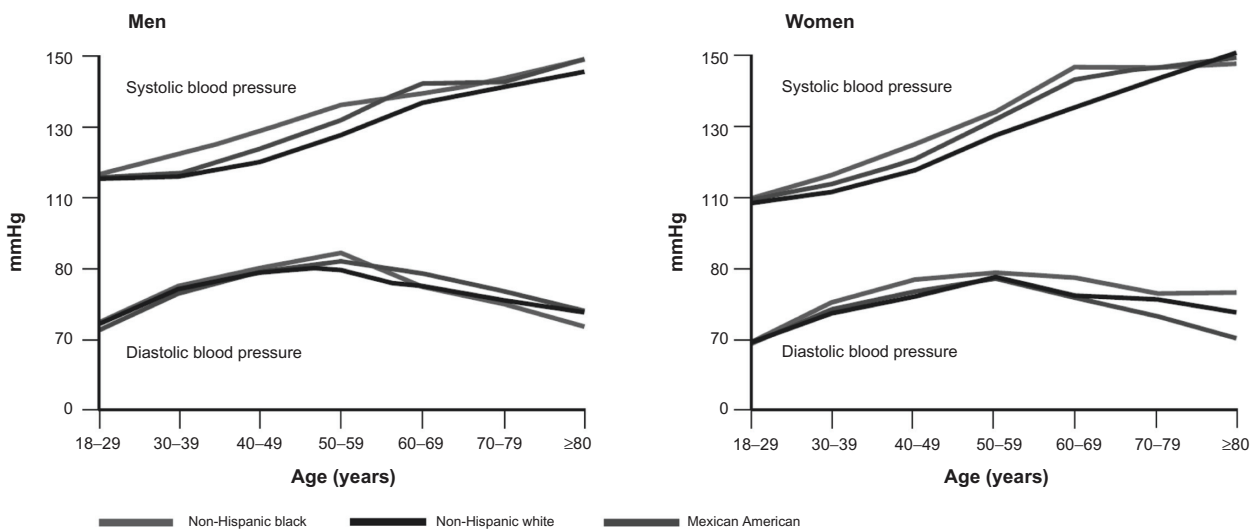


Figure 1. Changes in systolic and diastolic blood pressure with age.<sup>8</sup>



Geriatric hypertension is generally of a salt-sensitive nature with a disproportionate frequency of isolated systolic hypertension.<sup>18,19</sup> Age-related increases in salt sensitivity result, in part, from a reduced ability to appropriately excrete salt loads and subsequent sodium expansion, due to a decline in renal function and reduced generation of natriuretic substances such as prostaglandin E<sub>2</sub>, dopamine and atrial natriuretic peptide. Declines in the activity of membrane sodium/potassium-adenosine triphosphatase may also contribute to hypertension in older people, because this results in increased intracellular sodium, which may cause reduced sodium-calcium exchange and thereby increase intracellular calcium and vascular resistance. Likewise, reduced calcium-ATPase activity may also cause an increase in intracellular calcium and vascular resistance. Age-related reduced renal tubular mass provides fewer transport pathways for potassium excretion; thus, elderly hypertensive patients are prone to hyperkalemia.

The available experimental evidence indicates that tonic whole-body sympathetic nervous system activity increases with age.<sup>20</sup> The tone of the sympathetic nervous system for the heart is increased; and, although the mechanisms underlying the age-associated increases in its activity have not been established, this appears to be due in part to reduced neuronal reuptake of norepinephrine and increased sympathetic drive in subcortical central nervous system. These changes in sympathoadrenal function with advancing age may have a number of important physiological and pathophysiological consequences for human health and disease. On the contrary, elderly people are likely to have sluggish baroreflex response and impaired cerebral autoregulation, which increase risks of postural and postprandial hypotension, falls, syncope, and cardiovascular events.

## Clinical Trials

### Effects of lifestyle modification in the elderly

Lifestyle modification is an important BP-lowering therapy for older people with hypertension. Several lines of evidence have suggested that lifestyle modifications such as maintaining ideal body weight, restricting salt intake, regular aerobic activity for at least 30 minutes three times a week, and limiting alcohol intake reduce BP levels.<sup>21–23</sup> A recent expert

consensus document on hypertension in the elderly also recommended comprehensive lifestyle modifications such as smoking cessation, reduction in excess body weight and mental stress, modification of excessive salt and alcohol intake, and increased physical activity to reduce anti-hypertensive agent doses in the elderly.<sup>24</sup>

The Trial of Nonpharmacologic Interventions in the Elderly (TONE), is a randomized control trial conducted in 975 hypertensive patients aged 60 to 80 years, which investigated whether weight loss of 4.5 kg or greater, sodium restriction to less than 1.8 g per day, and a combination of both would reduce BP levels and the risk of cardiovascular events during a 30-month follow-up.<sup>22</sup> In their findings, weight loss reduced SBP/DBP levels to  $-4.0/-1.3$  mmHg from baseline, and was associated with 30% lower risk of cardiovascular events as compared with nonintervention. In this study, weight loss of 4.5 kg or greater was achieved by regular exercise and diet therapy and was well tolerated. Therefore, maintaining ideal body weight with regular exercise and avoidance of excessive calorie intake should be encouraged among elderly subjects to reduce BP levels. The TONE study also suggested the importance of sodium restriction in the management of hypertension. Sodium restriction reduced SBP/DBP values by 3.4/1.9 mmHg compared to baseline. People with sodium restriction had a 31% lower cardiovascular risk than those without sodium restriction. Similar findings were demonstrated in another clinical trial performed in United Kingdom, in which restricting salt from 10 g/day to less than 5 g/day was associated with 7.2/3.2 mmHg lower SBP/DBP levels in elderly normotensive and hypertensive subjects.<sup>23</sup> Additionally, recent evidence has suggested that a diet rich in fruits and vegetables, or a combination diet rich in fruits, vegetables, and low-fat dairy products and with reduced saturated and total fat in addition to sodium restriction were likely to have a benefit on BP lowering.<sup>25,26</sup> Dietary modification, that is salt sodium restriction and additional nutritional approaches, is an important strategy in preventing and treating hypertension.

### Efficacy of pharmacological antihypertensive treatment in the elderly

The efficacy of pharmacological therapy in older people with systolic and diastolic hypertension or with

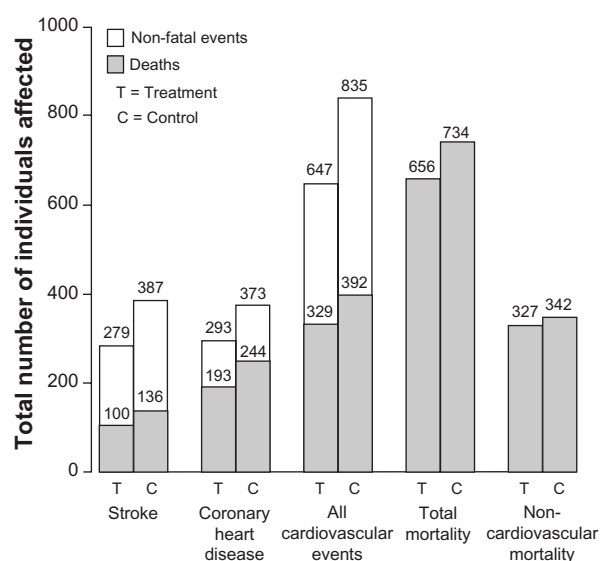
isolated systolic hypertension, in terms of reducing cardiovascular morbidity and mortality, has been widely confirmed by many controlled and randomized controlled trials.<sup>27–35</sup> The Systolic Hypertension in the Elderly Program (SHEP) study showed the benefit of antihypertensive treatment in 4,736 subjects aged 60 years and over with isolated hypertension during an average 4.5-year follow-up, in which a chlorthalidone-based regimen with or without atenolol reduced the risk of cardiovascular death by 32% ( $P < 0.001$ ), stroke by 36% ( $P < 0.001$ ), myocardial infarction by 27% ( $P < 0.001$ ), and heart failure by 54% ( $P < 0.001$ ), as compared with a placebo.<sup>27</sup> Major cardiovascular events were reduced, with a 5-year absolute benefit of 55 events per 1,000 patients. In the European Trial on Systolic Hypertension in the Elderly (SYST-EUR), 4,695 patients aged 60 years and over with isolated hypertension were randomly assigned to treatment with the calcium channel blocker (CCB) nitrendipine (with the possible addition of enalapril and/or hydrochlorothiazide) or a matching placebo.<sup>28</sup> At a median of 2-year follow-up, the CCB-based regimen lowered the SBP by 23 mmHg and the DBP by 7 mmHg. Active treatment was associated with a reduction in the risk of total stroke by 42% ( $P = 0.003$ ), and all fatal and non-fatal cardiac endpoints, including sudden death, by 26% ( $P = 0.03$ ). Treatment of 1,000 patients for 5 years with a CCB-based regimen may prevent 29 strokes or 53 cardiovascular endpoints. A similar trial, the Systolic Hypertension in China (SYST-CHINA) trial, was conducted in Chinese people aged 60 years or older, also using nitrendipine versus a placebo. SBP/DBP values were reduced by 20/5 mmHg in the active-treatment group. CCB-based treatment reduced total strokes by 38% ( $P = 0.01$ ), all fatal and nonfatal cardiovascular endpoints by 37% ( $P = 0.004$ ), cardiovascular death by 39% ( $P = 0.03$ ), and all-cause death by 39% ( $P = 0.003$ ).<sup>29</sup> Active treatment was estimated to prevent 55 deaths, 39 strokes or 59 major cardiovascular endpoints per 1,000 Chinese patients over 5 years. In a meta-analysis of eight trials including 15,693 older people with isolated systolic hypertension, 1,482 major cardiovascular events and 1,390 deaths during an average 3.8 years of follow-up, active treatment was shown to reduce all-cause death by 13% ( $P = 0.02$ ), cardiovascular death by 18% ( $P = 0.01$ ), all cardiovascular complications by 26% ( $P = 0.001$ ), stroke by 30% ( $P = 0.001$ ), and coronary

events by 23% ( $P = 0.001$ ) (Fig. 2).<sup>36</sup> The number of patients who would have to undergo 5-year treatment for one major cardiovascular event to be prevented was lower in men (18 vs. 38), in patients at or above age 70 (19 vs. 39), and in patients with previous cardiovascular complications (16 vs. 37), suggesting that the absolute benefit is greater in men, in patients 70 years or older and in those with previous cardiovascular complications.

### Class of antihypertensive agents

Thiazide-type diuretics, either alone or in combination with other agents, is recommend as a first-line treatment for older people with hypertension by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), unless other comorbid medical conditions exist.<sup>8</sup> However, other guidelines have stated that any of the five classes of antihypertensive agents including thiazide diuretics, CCBs, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) and beta-blockers are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination.<sup>9–11</sup> Differences in the efficacy, safety and tolerability across classes of antihypertensive drugs are summarized in Table 1.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),



**Figure 2.** Effects of antihypertensive treatment in the older people with isolated systolic hypertension: the summarized results from 8 randomized controlled trials of antihypertensive treatment.<sup>36</sup>



**Table 1.** Efficacy and adverse effects of antihypertensive drugs in the elderly.

	<b>Thiazide diuretics</b>	<b>Beta-blockers</b>	<b>ACEIs</b>	<b>ARBs</b>	<b>CCBs</b>
Efficacy	Isolated systolic hypertension Heart failure Hypertension in blacks	Angina pectoris Post-myocardial infarction Heart failure Tachyarrhythmias Glaucoma	Heart failure LV dysfunction Post-myocardial infarction Diabetic nephropathy Non-diabetic nephropathy Proteinuria/albuminuria LV hypertrophy Carotid atherosclerosis Atrial fibrillation Metabolic syndrome	Heart failure Post-myocardial infarction Diabetic nephropathy Proteinuria/albuminuria Left ventricular hypertrophy Carotid atherosclerosis Atrial fibrillation Metabolic syndrome ACEI-induced cough	(Dihydropyridines) Isolated systolic hypertension Angina pectoris LV hypertrophy Carotid Atherosclerosis Hypertension in blacks (Non-dihydropyridines) Angina pectoris Carotid atherosclerosis Supraventricular tachycardia (Dihydropyridines) Peripheral edema Reflex tachycardia Heart failure (Non-dihydropyridines) AV block Bradycardia Heart failure Constipation Gastroesophageal reflux Gingival hyperplasia Cyclosporine Grapefruit juice
Adverse effects	Hypokalemia Hyponatremia Hypomagnesemia Dehydration Renal impairment Postural hypotension Hyperuricemia Gout Hyperglycemia Sexual dysfunction	AV block Bradycardia Bronchospasm Heart failure Confusion Depression Fatigue Hyperglycemia Sexual dysfunction	Cough Hyperkalemia Renal impairment Angioedema Rash Altered taste sensation	Hyperkalemia Renal impairment	
Drug interactions	Digoxin NSAIDs	Digoxin Non-dihydropyridines CCBs	NSAIDs potassium-sparing diuretics	NSAIDs potassium-sparing diuretics	

**Abbreviations:** ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; CCBs, calcium channel blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; LV, left ventricular; AV, atrioventricular.



a total of 42,418 participants aged 55 years or older with hypertension and at least 1 other cardiovascular risk factor were randomly assigned to receive chlorthalidone, amlodipine, lisinopril, or doxazosin and followed-up for an average of 4.9 years.<sup>37</sup> Chlorthalidone was found to be superior to amlodipine and lisinopril in heart failure prevention. Chlorthalidone was also shown to be more effective than lisinopril in lowering BP, preventing stroke, and decreasing combined cardiovascular events. The doxazosin arm was discontinued eventually, because of an excess of cardiovascular events and heart failure as compared with the chlorthalidone arm. These findings extended to the subgroup of elderly patients. It has been known that thiazide diuretics induce various metabolic side effects such as hypokalemia, hyponatremia, dyslipidemia, hyperuricemia, and glucose intolerance.<sup>38</sup> ALLHAT demonstrated that chlorthalidone use entailed a significantly higher risk of hyperglycemia compared with amlodipine or lisinopril. Despite the higher incidence of hyperglycemia, the cardiovascular risk at the long-term follow-up favored chlorthalidone.<sup>39</sup> In addition, thiazide diuretics are prone to increase the incidence of postural hypotension in older people with hypertension, because of contracted intravascular volumes and impaired baroreflexes. Thus, physicians should check postural hypotension and suggest measures for preventing falls.

The benefits of beta-blocker therapy for older people with hypertension have been questioned. A meta-analysis of 13 intervention trials for hypertension ( $n = 105,951$ ) showed that the relative risk of stroke was reduced by 19% ( $P < 0.01$ ), for all beta blockers, when the effect of beta blockers was compared with that of a placebo or no treatment. However, patients treated with beta-blockers had 16% ( $P < 0.01$ ) higher incidence of stroke than those treated with other classes of antihypertensive drugs. There was no difference for myocardial infarction among drug classes.<sup>40</sup> The lack of benefit from beta-blockers may be attributed to less BP reduction as compared with other medication classes. Also, beta-blockers may worsen glucose intolerance or mask the symptoms of hypoglycemia. In contrast, beta-blockers have several benefits for hypertensive treatment: inhibition of renin release, central nervous

system effect, reduction of heart rate and cardiac output, reduction in peripheral vascular resistance and pulse pressure, and reduction in vasomotor tone. Beta-blockers would be suitable for the management of hypertension with comorbidities such as ischemic heart disease, heart failure, and arrhythmias.

Other classes of antihypertensive drugs—namely, ACEIs and CCBs—are also indicated. The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) investigated the effects of antihypertensive drugs on cardiovascular death and morbidity among subgroups of age, including assessments of the comparative effects of drugs, using data of 190,606 individual patients from 31 randomized controlled trials.<sup>41</sup> This meta-analysis showed that the ACEI-based regimens and CCB-based regimens significantly reduced the risk of major cardiovascular events by 17% ( $P < 0.01$ ) and by 26% ( $P < 0.01$ ), respectively, in subjects aged 65 years or older as compared with a placebo. In the overviews of trials comparing blood pressure-lowering regimens based on different drug classes in the elderly, there was no strong evidence of differences in beneficial effects on cardiovascular risk among different classes of antihypertensive drugs: ACEIs vs. diuretics or beta-blockers, CCBs vs. diuretics or beta-blockers, and ACEIs vs. CCBs. In the meta-regression analysis, there was no difference in the risk reduction achieved per unit reduction in blood pressure for individuals aged less than 65 as compared with those 65 years or older for major cardiovascular events. Therefore, this study suggests that the favorable effects of antihypertensive drugs can be attributed mainly to the BP reduction achieved rather than the class of drug and failed to reveal any strong evidence to support the use of one specific class of drug over another for the treatment of hypertension in the elderly.

On the contrary, the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study provides evidence of the benefits of a losartan-based regimen on cardiovascular events as compared with an atenolol-based regimen in 9,193 subjects with hypertension and left ventricular hypertrophy (mean age, 70 years).<sup>42</sup> Patients assigned to the Losartan group had a 13% ( $P = 0.02$ ) lower risk of the composite endpoint of death, myocardial infarction, or stroke rather than those assigned to atenolol, despite only



1 mmHg difference in the average BP levels during the follow-up period between treatment groups, raising the possibility that Losartan conferred benefits beyond reduction in BP. Furthermore, several lines of evidence have demonstrated that renin-angiotensin-aldosterone system (RAS) inhibitors such as ACEIs and ARBs improve the degree of albuminuria and reduce the risk of end-stage kidney disease in diabetic patients.<sup>43–46</sup> Accordingly, RAS inhibitors should be recommended as a first-line drug for hypertensive patients with coexisting chronic kidney disease, diabetes, or target organ damage. The most common side effects of RAS inhibitors are cough, hyperkalemia, angioedema and reversible functional renal insufficiency secondary to reduced renal perfusion.

Older people with hypertension are prone to need a combination of antihypertensive drugs to control BP. Common regimens involve RAS inhibitors combined with diuretics or CCB. Some trials have sought to find good combinations of different classes of antihypertensive agents. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure-Lowering Arm (ASCOT-BPLA), which was a randomized controlled trial in 19,257 high-risk subjects with hypertension aged 40–79 years, found that an amlodipine-based regimen (with or without perindopril) prevented more major cardiovascular events (relative risk reduction, 16%,  $P < 0.001$ ), reduced all-cause death (11%,  $P = 0.03$ ) and less frequently induced diabetes (30%,  $P < 0.001$ ) than the atenolol-based regimen (with or without bendroflumethiazide) with a similar degree of BP reduction.<sup>47</sup> The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial was conducted in 11,506 high-risk subjects with hypertension who were randomly allocated to receive treatment with either benazepril plus amlodipine or benazepril plus hydrochlorothiazide. This study demonstrated that initial antihypertensive therapy with benazepril plus amlodipine was superior to benazepril plus hydrochlorothiazide in preventing the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization, representing a relative risk reduction with benazepril-amlodipine therapy of 20% ( $P < 0.001$ )

in the absence of a BP difference between treatment groups.<sup>48</sup> An ideal antihypertensive treatment for the elderly would provide significant BP-lowering effects, would be metabolically neutral, and would be well-tolerated. The combination of an RAS inhibitor plus CCB may meet these conditions.

### Very elderly trial

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension), which was a prospective, randomized, and double-blind intervention study comparing the effects of active antihypertensive therapy (atenolol, metoprolol, pindolol, or hydrochlorothiazide plus amiloride) and placebo on the risk of fatal and non-fatal stroke and myocardial infarction and other cardiovascular death in hypertensive Swedish people aged 70–84 years, demonstrated that active treatment significantly reduced the number of primary endpoints ( $P = 0.003$ ) and stroke morbidity and mortality ( $P = 0.008$ ).<sup>30</sup> The Hypertension in the Very Elderly Trial (HYVET), a randomized control trial conducted in 3,845 patients from Europe, China, Australasia, and Tunisia who were 80 years of age or older and had a sustained systolic blood pressure of 160 mmHg or more, compared treatment groups receiving either the diuretic indapamide or a matching placebo.<sup>31</sup> The ACEI perindopril (2 or 4 mg) or matching placebo was added if necessary to achieve the target blood pressure of 150/80 mmHg. The primary endpoint was fatal or nonfatal stroke; median follow-up was 1.8 years. Active treatment was associated with a 30% ( $P = 0.06$ ) reduction in the rate of fatal or non-fatal stroke, a 39% ( $P = 0.046$ ) reduction in the rate of death from stroke, a 21% ( $P = 0.02$ ) reduction in the rate of death from any cause, a 23% ( $P = 0.06$ ) reduction in the rate of death from cardiovascular causes, and a 64% ( $P < 0.001$ ) reduction in the rate of heart failure. Fewer serious adverse events were reported in the active-treatment group (358, vs. 448 in the placebo group;  $P = 0.001$ ). Further, a meta-analysis of data from 1,670 participants aged 80 years or older in randomized controlled trials of antihypertensive drugs, conducted by the Individual Data Analysis of Antihypertensive Drug Intervention Trials (INDANA) group, suggested that active treatment reduced the risk of stroke by 34% ( $P = 0.01$ ), major cardiovascular events by 22% ( $P = 0.01$ ) and heart failure by 39%



( $P = 0.01$ ) of heart failure.<sup>49</sup> The treatment regimens used in the trials analyzed in INDANA were generally high-dose diuretics and beta-blockers. These studies provide evidence that antihypertensive treatment in persons 80 years of age or older is beneficial for the prevention of cardiovascular disease and premature death.

Dementia and cognitive impairment occurs commonly among very elderly adults. The relation of blood pressure level with cognitive function and dementia has received much attention from epidemiological research.<sup>50</sup> Longitudinal studies have yielded diverse results that largely depend on the age at which blood pressure is measured and the time interval between blood pressure and outcome assessments.<sup>51</sup> Additionally, some studies have suggested that midlife high blood pressure is a risk factor for late-life cognitive impairment and dementia, especially vascular dementia.<sup>52,53</sup> However, several randomized controlled trials provide limited evidence for the protective effect of antihypertensive therapy against dementia and stroke-related cognitive decline among the elderly so far. In the SYST-EUR, antihypertensive treatment was associated with a risk reduction of the incidence of dementia by 50% ( $P = 0.05$ ) in 2,418 subjects aged 60 year or over with isolated hypertension.<sup>54</sup> On the basis of this finding, 19 cases of dementia might be prevented among 1000 hypertensive patients treated with antihypertensive drugs for 5 years. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS), a randomized control trial in 6,105 patients with a history of cerebrovascular disease, demonstrated that the risks of dementia with recurrent stroke and of cognitive decline with recurrent stroke were reduced by 34% ( $P = 0.03$ ) and 45% ( $P < 0.001$ ), respectively, with no clear effect on either dementia or cognitive decline in the absence of recurrent stroke.<sup>55</sup> On the contrary, the SHEP study and the HYVET failed to reveal the benefit of antihypertensive treatment on the prevention of dementia.<sup>56,57</sup> Long exposure to poorly controlled hypertension presumably worsens arteriosclerotic changes and lipohyalinosis in the deep subcortical white matter circuit, which may be less reversible by BP reduction once these changes are established.<sup>53,58,59</sup> If this is indeed the case, optimal management of hypertension as early as possible in

the life cycle should be recommended to prevent late-life dementia.

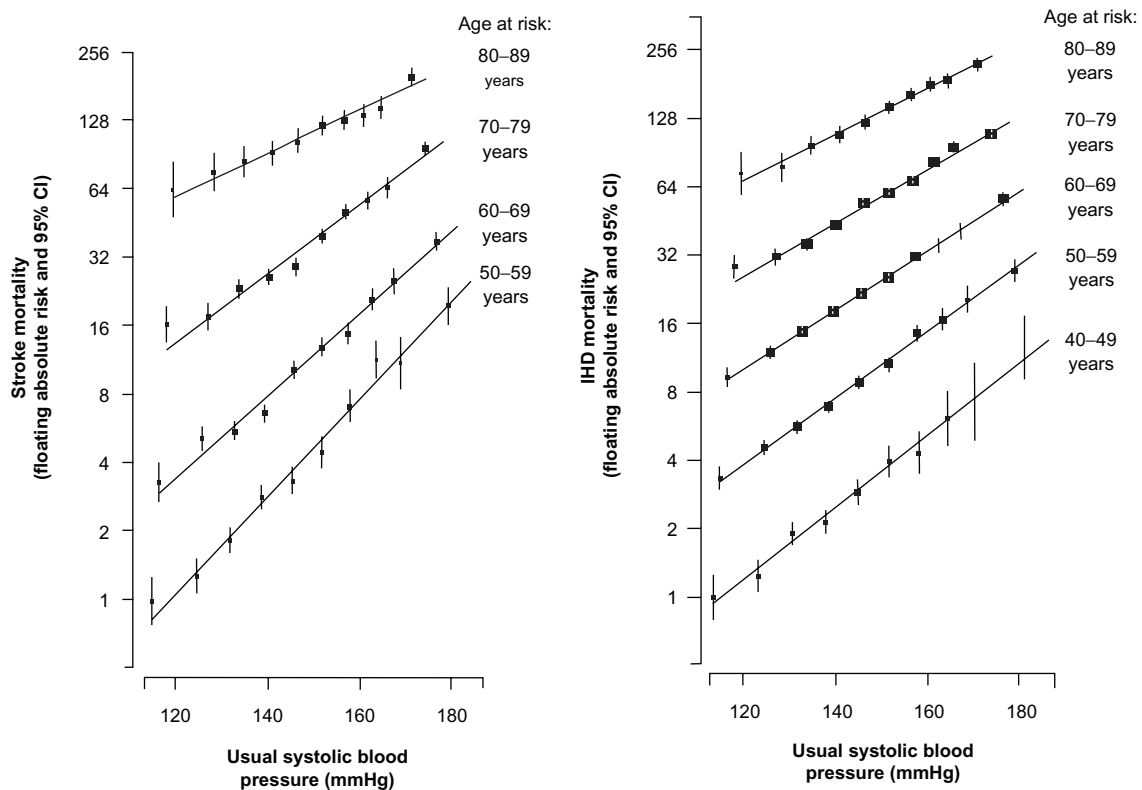
## Safety of Antihypertensive Treatment in the Elderly

Data on the safety and efficacy of lower BP levels in the elderly have been inconclusive. Observational analyses of clinical trials have documented a J curve relationship between a low BP and an increased risk of cardiovascular events and death in the elderly,<sup>60,61</sup> On the other hand, the results from a meta-analysis of individual participant data from 61 prospective cohort studies suggested that greater SBP was associated linearly with an increased risk of stroke or ischemic heart disease mortality without evidence of an excess risk at lower SBP levels in the BP range from 115/72 to 180/110 mmHg among older people as well as middle-aged people (Fig. 3).<sup>62</sup> Likewise, randomized control trials have provided no definitive evidence of an increase in the risk of adverse outcomes from aggressive use of antihypertensive therapy in elderly.<sup>63</sup>

The HYVET demonstrated that BP lowering could successfully reduce mortality with relative safety, as well as cardiovascular events, among very elderly people.<sup>31</sup> In the INDANA meta-analysis, antihypertensive treatment showed a tendency to increase the risk of all-cause death by 6%, but this effects was not significant.<sup>49</sup> In the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS), which evaluated the optimal BP target in elderly hypertensive patients aged 65–85 years, there were no differences between the strict-treatment group (SBP maintained at less than 140 mmHg) and the mild-treatment group (SBP maintained at 140–159 mmHg) in terms of the 2-year incidence of primary endpoints of cardiovascular disease and renal failure.<sup>64</sup> Likewise, the strict treatment, maintaining SBP of less than 140 mmHg, did not show any added risk of adverse events.

The safety and efficacy of BP lowering to below 130/80 mmHg has not been examined sufficiently among older people with diabetes mellitus or chronic kidney disease. The post-hoc analysis of Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study failed to reveal significant evidence of





**Figure 3.** Absolute risks of death from stroke or ischemic heart disease in relation to systolic blood pressure according to age: the result from prospective studies collaboration.<sup>62</sup>

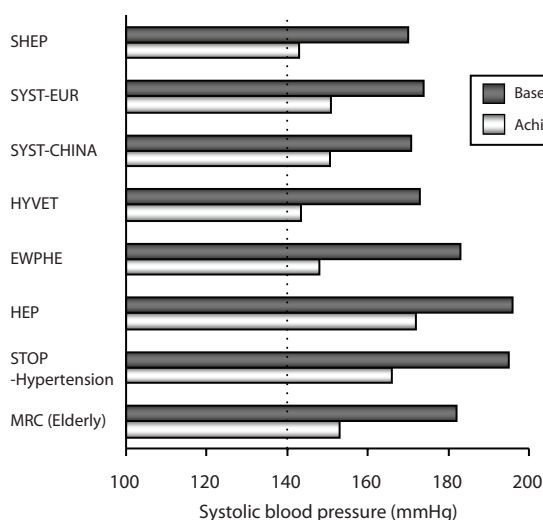
**Note:** The Y axis is log-transformed. The vertical bars represent 95% confidence intervals.

**Abbreviations:** CI, confidence interval; IHD, ischemic heart disease.

heterogeneity in the favorable effects of a fixed combination of perindopril and indapamide in terms of major clinical outcomes including macro- and microvascular disease and death between middle-aged and older people with type-2 diabetes at high cardiovascular risk.<sup>65</sup> In this study, the mean SBP/DBP levels achieved over time in the active-treatment groups were 133/77, 135/74 and 137/72 mmHg for patients aged <65, 65–74 and ≥75 years old, respectively. As expected, the proportion of patients permanently discontinuing study treatment increased with age group, but was similar in the active-treatment and placebo groups. Compared with the placebo group, the active-treatment group was more likely to discontinue study treatment due to cough, hypotension or dizziness. Serious adverse events and hyperkalemia were reported in similar proportions in both treatment groups. In this trial, importantly, the absolute benefits of active treatment on major clinical outcomes appeared to outweigh the risk of side effects in older people. On the other hand, in the BP arm of the Action to Control Cardiovascular Risk in

Diabetes (ACCORD) trial among 4,733 patients with type 2 diabetes at high cardiovascular risk, results of a target SBP of 120 mmHg or lower as compared with that 140 mmHg or lower suggested important benefits connected with the significant reduction of stroke in the intensive-treatment group, but it also showed the lack of advantage of such therapy on other endpoints.<sup>66</sup> The same was true among the subgroup of 1,617 patients aged 65 years or over. In fact, the ACCORD Trial also showed an increased risk of adverse events including hypotension, hyperkalemia and kidney impairment when intensive treatment was used in this group of patients.

The findings from clinical trials seem to support the safety and efficacy of antihypertensive treatment in the elderly, but these clinical trials have been performed among relatively fit patients who tended to have the ability to tolerate the study treatment. Furthermore, the average SBP levels achieved in active-treatment groups were generally more than 140 mmHg among the randomized control trials which revealed the beneficial effects of active treatment as compared with



**Figure 4.** Baseline and achieved systolic blood pressure levels in active treatment group among randomized placebo-controlled trials for elderly patients with hypertension.

**Abbreviations:** SHEP, The Systolic Hypertension in the Elderly Program;<sup>27</sup> SYST-EUR, The European Trial on Systolic Hypertension in the Elderly;<sup>28</sup> SYST-CHINA, The Systolic Hypertension in China;<sup>29</sup> HYVET, The Hypertension in the Very Elderly Trial;<sup>31</sup> EWPHE, European Working Party on High Blood Pressure in the Elderly;<sup>32</sup> HEP, The trial on Hypertension in Elderly Patients in Primary Care;<sup>33</sup> STOP-Hypertension, The Swedish Trial in Old Patients with Hypertension;<sup>30</sup> MRC (Elderly), Medical Research Council Trial of treatment of hypertension in older adults.<sup>34</sup>

placebo among the elderly (Fig. 4). The results from JATOS may indicate that strict treatment for elderly hypertensive patients has little effect in enhancing the suppression of the onset of cardiovascular events as compared with mild treatment. Additionally, evidence of the benefit of more aggressive BP treatment on cardiovascular events and death in older people with diabetes or target organ damage is limited, and caution should be applied to the use of more aggressive treatment in the elderly, which may increase the risk of adverse events.

## Patient Preference

Treatment adherence is an important contributor to the efficacy of BP control treatments, and its lack is often a cause of failure. Many older people with hypertension may be taking multiple pharmacologic agents for chronic conditions such as diabetes mellitus, hypercholesterolemia, heart disease or arthritis. Polypharmacy causes several problems: for example, the complexity of the regimen can easily lead to confusion about dose, especially for patients with impaired cognitive function; there is an increased risk of side effects; and the high total cost may force the discontinuance of one or more medications. These

problems can adversely affect adherence to treatment. Concomitant medications for other chronic disease may also interfere with the pharmacological effects of an antihypertensive drug. Non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors, which are used for the pain control of osteoarthritis among the elderly, are notorious for worsening BP control by inhibiting prostaglandin E2 and prostacyclin production by the kidney, resulting in sodium retention and vasoconstriction.<sup>67</sup> Therefore, patients at risk for hypertension should be monitored for changes in BP levels during the usage of NSAIDs or COX2 inhibitors. Incidentally, low-dose aspirin, which is commonly used in the prevention of cardiovascular events, has not been shown to have a significant influence on BP control in the elderly.<sup>68</sup> Postural and postprandial hypotension, which is associated with symptoms such as dizziness, difficulty walking, frequent fall, and syncope, is another reason for nonadherence to antihypertensive treatment in the elderly. Thus, the titration of drug doses along with routine checks for relevant symptoms and standing BP is necessary. The use of alpha-blockers in older people is discouraged.

## Management of Hypertension in the Elderly

Because there is limited information for evidence-based guidelines to manage older people with hypertension, the following recommendations are based on expert opinion.

For the diagnosis of hypertension among older people, who are likely to have wide fluctuations in BP, BP should be measured at least twice after the patient has been seated quietly for 5 minutes using an appropriately sized cuff. BP should be also measured in both sitting and standing positions in older people to evaluate the presence of postural hypotension. Before determining a therapeutic strategy for hypertension in the elderly, it would be most important to evaluate the following issues: the duration and severity of the hypertension, the existence of reversible and treatable causes, the contribution of other cardiovascular risk factors and target organ damage (Table 2), adverse effects such as fainting and hypotension, and treatment adherence. Several laboratory tests are recommended: eg, urinalysis (albuminuria or proteinuria); serum chemistries (serum creatinine, eGFR, and



**Table 2.** Cardiovascular risk factors and target organ damage in older subjects with hypertension.

Risk factors	Target organ damage
Tobacco use	Coronary artery disease
Obesity	Left ventricular hypertension
Dyslipidemia	Congestive heart failure
Sedentary lifestyle	Stroke/transient ischemic attack
Diabetes mellitus	Chronic kidney disease
Microalbuminuria	Peripheral artery disease
Family history of cardiovascular disease	Retinopathy

potassium); lipids (total cholesterol, high-density lipoprotein cholesterol, triglycerides); glucose tolerance (fasting glucose concentration, hemoglobin A1c); and electrocardiography and echocardiography findings.

The aim of antihypertensive treatment is to reduce cardiovascular and renal morbidity and mortality. Current guidelines recommend a BP goal of less than 140/90 mmHg in uncomplicated hypertensive subjects.<sup>8–11</sup> The BP goal in hypertensive subjects with diabetes mellitus or chronic kidney disease is less than 130/80 mmHg. However, the BP goal for elderly hypertensive people has been questioned because evidence for the benefit of lowering SBP below 140 mmHg is limited. Nonetheless, an SBP target of less than 150 mmHg seems to be both effective and safe in the elderly, on the basis of previous clinical trials, as stated previously. An achieved SBP of less than 140 mmHg, if tolerated, would be recommended. The main difference in antihypertensive treatment of older people as opposed to younger people is the need for careful attention to postural and postprandial hypotension in older people. Thus, the antihypertensive drug should be started at the lowest dose and be titrated to the maximum tolerable dose, with particular attention to potential adverse responses and excessive BP lowering. Any of five classes of antihypertensive agents including thiazide diuretics, CCBs, ACEIs, ARBs and beta-blockers could be selected as a first-line drug depending on the patient's medical conditions and side effects (Table 1). ACEIs or ARBs would be strongly recommended for hypertensive patients with chronic kidney disease, diabetes or target organ damage.

Hypertension in the elderly has been known to be more difficult to control in the elderly, and most older people with hypertension require treatment with a combination of antihypertensive drugs to reduce BP.<sup>69</sup> Generally, when BP lowering is inadequate after using the maximum tolerable dose of one drug, a second antihypertensive drug from another class should be added. However, combination therapy with lower doses of drugs having complementary active mechanisms may be more effective at reducing BP levels with fewer side effects than maxing out one drug.<sup>70</sup> The use of two or three drugs that act by different mechanisms may provide improved BP lowering efficacy and a lower risk of adverse events because one drug may offset the potential adverse effects of the other.<sup>70</sup> For example, combination therapy with both diuretics and a CCB has been shown to be significantly more effective in reducing SBP and pulse pressure than either monotherapy, and also reduced peripheral edema better than monotherapy with a CCB.<sup>71</sup> For older people with refractory hypertension (eg, taking more than 6 prescription drugs), it would also be important to examine possible reasons for inadequate BP response before adding new antihypertensive drugs: nonadherence, inadequate lifestyle modification, and potential drug interaction.

## Conclusion

Hypertension is an important risk factor for cardiovascular morbidity and mortality in the elderly. Isolated systolic hypertension is particularly prevalent, and is attributable to structural and functional changes of the arteries and alterations in salt sensitivity and neural function with aging. Accumulated evidence indicates the overall benefit of antihypertensive treatment in the elderly. Treatment of hypertension is likely to prevent cardiovascular events and prolong life. Although the BP goal for the elderly needs to be further investigated, an achieved SBP of less than 150 mmHg seems to be effective and safe, while stricter goals, if tolerated, may be appropriate. Careful attention should be required to postural and postprandial hypotension, which is one of the causes of nonadherence in the elderly. Therefore, treatment decisions should be guided by the presence of a comorbidity such as diabetes, heart disease itself, and by tolerability of



the treatment. There is little doubt that a healthy lifestyle including diet, physical activity and ideal body weight is the foundation of hypertension management. Adequate lifestyle changes may reduce the need for antihypertensive drugs, but most older people with elevated BP will require a combination of antihypertensive drugs for ideal BP control.

## Author Contributions

Wrote the first draft of the manuscript: TN. Contributed to the writing of the manuscript: TN. Author reviewed and approved of the final manuscript.

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