Current challenges in antihypertensive treatment in the elderly

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KEY WORDS
blood pressure goal, cardiovascular risk, elderly, hypertension, nursing home patients

ABSTRACT
Arterial hypertension affects more than 25% of the global population, and its prevalence is increasing with age. Arterial stiffening occurs with aging and results in a pattern of increased systolic and decreased diastolic blood pressure (BP). In the elderly population, elevated BP has been related with increased cardiovascular risk. Trials on this population have shown great benefits for morbidity and mortality from reducing systolic BP (SBP) levels to less than 150 mmHg. Most guidelines for the management of elderly hypertensive patients agree on BP reduction to less than 150/90 mmHg. However, there is still uncertainty whether further BP reduction could provide beneficial results. The recently published SPRINT trial demonstrated that reducing SBP to between 120 and 125 mmHg in patients over the age of 75 years is related with increased survival and is expected to affect future recommendations. On the contrary, the limited data that are available for patients aged 80 years or older and frail nursing home patients create concerns for more aggressive BP strategies in these subgroups, and thus they should be treated more conservatively. Among the various antihypertensive classes of drugs, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were proved beneficial in the elderly and are favored as first choices for the management of elderly hypertensive individuals. Given the common coexistence of other comorbidities and polypharmacy, physicians should be careful when initiating or uptitrating treatments to avoid potential adverse events or interaction with other drugs or diseases.

Introduction
Hypertension is a public health problem that affects almost 1 billion adults worldwide, and this number is estimated to reach 1.5 billion by 2025. The global prevalence of hypertension is increasing with age; approximately half of the population aged between 60 and 69 years and more than 60% of those over the age of 70 years are hypertensive.\(^1\) Data from the Framingham study\(^2\) suggest that normotensive men and women at the age of 55 years have a 93% and 91% lifetime risk of developing hypertension, respectively. Increased blood pressure (BP) has been independently associated in all ages with increased incidence of cardiovascular (CV) events, such as stroke, coronary artery disease, myocardial infarction, sudden death, and heart failure.\(^3\) In the elderly population, systolic BP (SBP) and pulse pressure were shown to be better predictors of CV outcomes than diastolic BP (DBP). This is attributed to the gradual increase in SBP that comes with aging, whereas DBP tends to decline after 60 years of age, and thus the majority of elderly hypertensive patients have increased pulse pressure and isolated systolic hypertension.\(^4,5\)

Many aspects of hypertension treatment are similar in younger and older patients. However, given the unique features of hypertension in the elderly, several challenges arise that physicians have to deal with in daily clinical practice.\(^6\) Target BP and optimal hypertensive treatment seem to be different between young and old patients. Trials in the elderly population using BP-reducing treatment seem to have provided a safe BP threshold of less than 150 mmHg to reduce morbidity and mortality events in fit elderly patients; on the contrary, data are inconclusive for the optimal antihypertensive strategies in frail elderly patients and those residing in nursing homes.\(^7\)
Furthermore, the high prevalence of comorbidities among elderly patients dictates the need for greater caution when choosing antihypertensive treatment in order to optimize the results for all concomitant conditions and to avoid treatment-related adverse effects. The purpose of the present review was to comprehensively analyze data for the management of elderly hypertensive patients and discuss the challenges of the currently recommended antihypertensive approaches in elderly patients.

**Pathophysiology of hypertension in the elderly** Age-related BP elevations derive mainly from changes in arterial structure and function that accompany the aging process. Loss of vascular smooth muscle cells, calcification in the intima–media complex (together with atherosclerosis), fatigue fractures, and increased collagen deposition in the vessel wall are associated with an increase in the vessel diameter and intima–media thickness, resulting in increased arterial stiffening, which is a common finding among elderly hypertensive patients. Arterial stiffness is not only a product of structural changes, but is also attributed to endothelial dysfunction that leads to decreased bioavailability of vasodilating nitric oxide.

Along with arterial stiffening, age-related renal alterations are also implicated in the pathogenesis of hypertension. The progression of glomerulosclerosis and interstitial fibrosis in the aging kidney is associated with a decline in glomerular filtration rate and disrupted renal homeostatic mechanisms. These deteriorating renal mechanisms are unable to regulate increased dietary sodium load. Membrane sodium/potassium and calcium adenosine triphosphate pumps show an age-related decline in activity, leading to excess of intracellular calcium and sodium and increased vasoconstriction and vascular resistance. Decreased activity of the sodium pump and polymorphisms of the angiotensin-converting enzyme gene have also been implicated in increased salt sensitivity in the elderly.

Neurohormonal changes are also observed in this patient group. The activity of the renin–angiotensin–aldosterone system declines with aging. Nephrosclerosis of the juxtaglomerular apparatus is responsible for a decrease in the renin activity of 40% to 60% at the age of 60 years, as compared with younger adults. In addition, sympathetic nervous system activity and peripheral plasma norepinephrine concentrations have been shown to gradually increase with advancing age.

**Diagnostic challenges** Several aspects have to be taken into account by clinicians when evaluating elderly patients for the presence of hypertension. White-coat hypertension is described as the presence of elevated office BP measurements and normal home or ambulatory BP measurements (mean 24-hour ambulatory BP below 135/85 mmHg). This condition is more common in the elderly and especially in centenarians. Masked hypertension, defined as normal office BP values and high BP levels on home or ambulatory measurements, is more frequent in aged patients and is related with increased CV risk. False high BP measurements (pseudohypertension) can also be observed in patients with sclerotic, calcified arteries or other vascular lesions associated with aging. The Osler maneuver (the presence of radial artery pulse after cuff inflation above SBP) should be performed if pseudohypertension is suspected; however, it has low sensitivity and specificity. Lastly, when considering resistant hypertension, one should first exclude the reasons that may explain the persistence of increased BP (incorrect technique in measuring BP, pseudohypertension, nonadherence, suboptimal therapy) and then consider potential secondary hypertension causes (hyperaldosteronism, Cushing syndrome or other endocrine disorders, chronic kidney disease, use of drugs, such as nonsteroidal anti-inflammatory drugs, or alcohol, pheochromocytoma, and others).

**Isolated systolic hypertension** As described above, aging is associated with a progressive derangement of the human vascular system that results in the presence of isolated systolic hypertension, which is defined as an SBP greater than 140 mmHg with a DBP lower than 90 mmHg. The proportion of hypertensive patients with isolated systolic hypertension increases with aging, from 65% of patients with hypertension older than 60 years to over 90% in those older than 70 years of age.

SBP is a strong independent risk factor for incident CV events in all decades of life. Increased SBP has been associated with increased CV morbidity and mortality. Reducing high SBP is related with substantial reductions in morbidity and mortality rates. The Systolic Hypertension in the Elderly Program (SHEP) evaluated CV outcomes in more than 4700 hypertensive patients older than 60 years with an SBP greater than 160 mmHg and a DBP lower than 90 mmHg. Patients were randomized to receive active treatment with chlorthalidone (and atenolol if BP goals were not achieved) or placebo for 4.5 years. At the end of the study, BP was decreased from 170.5/76.7 mmHg and 170.1/76.4 mmHg at baseline to 144.0/67.7 mmHg and 155.5/71.1 mmHg in the active treatment and placebo groups, respectively. Stroke rate was significantly decreased by 37% in the active treatment compared with the placebo groups. BP reduction resulted also in risk reduction for a myocardial infarction by 33% and a CV event by 32%.

The Systolic Hypertension in European Trial (Syst-Eur) randomized approximately 4700 patients older than 60 years with isolated systolic hypertension (SBP greater than 160 and DBP lower than 95 mmHg) on nitrendipine or placebo; nitrendipine was combined with or replaced by enalapril, hydrochlorothiazide, or both if patients were nonadherent or BP remained above...
### TABLE 1 Treatment initiation and blood pressure goals in elderly patients with uncomplicated hypertension

<table>
<thead>
<tr>
<th>Guidelines, year</th>
<th>Initiation of treatment</th>
<th>BP target</th>
</tr>
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<tbody>
<tr>
<td>ACCF/AHA, 2011</td>
<td>general elderly: SBP &gt;140 mmHg, DBP &gt;90 mmHg</td>
<td>elderly &lt;79 y: SBP &lt;140 mmHg elderly ≥80 y: &lt;140 mmHg but if 140–145 mmHg is tolerated can be acceptable</td>
</tr>
<tr>
<td>NICE, 2011</td>
<td>elderly &lt;80 y: SBP ≥140 mmHg, DBP ≥90 mmHg and 1 or more of the following: target organ damage, established cardiovascular disease, renal disease, diabetes, a 10-year cardiovascular risk equivalent to 20% or greater general elderly: SBP ≥160 mmHg, DBP ≥100 mmHg</td>
<td>elderly &lt;80 y: SBP &lt;140 mmHg, DBP &lt;90 mmHg elderly ≥80 y: SBP &lt;150 mmHg, DBP &lt;90 mmHg</td>
</tr>
<tr>
<td>ESH/ESC, 2013</td>
<td>general elderly: SBP ≥160 mmHg, DBP ≥90 mmHg</td>
<td>general elderly: SBP 140–150 mmHg, DBP &lt;90 mmHg fit elderly &lt;80 y: SBP ≥140 mmHg elderly ≥80 y: SBP ≥160 mmHg frail elderly: individualized fit elderly &lt;80 y: SBP &lt;140 mmHg, DBP &lt;90 mmHg elderly ≥80 y: SBP ≥140 mmHg, DBP ≥90 mmHg frail elderly: individualized</td>
</tr>
<tr>
<td>ASH/ISH, 2014</td>
<td>elderly &lt;80 y: SBP ≥140 mmHg, DBP ≥90 mmHg</td>
<td>elderly &lt;80 y: SBP &lt;140 mmHg, DBP &lt;90 mmHg elderly ≥80 y: SBP ≥140 mmHg, DBP ≥90 mmHg</td>
</tr>
<tr>
<td>JNC8, 2014</td>
<td>general elderly: SBP ≥150 mmHg, DBP ≥90 mmHg</td>
<td>general elderly: SBP &lt;150 mmHg, DBP &lt;90 mmHg expert opinion: “In the general population aged 60 years or older, if pharmacologic treatment for high BP results in lower achieved SBP (for example, &lt;140 mmHg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.”</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACCF/AHA, American College of Cardiology Foundation / American Heart Association; ASH/ISH, American Society of Hypertension / International Society of Hypertension; BP, blood pressure; DBP, diastolic blood pressure; ESH/ESC, European Society of Hypertension / European Society of Cardiology; JNC8, Eighth Joint National Meeting; NICE, National Institute of Health and Care Excellence; SBP, systolic blood pressure

The goal. After 2 years, sitting SBP and DBP had fallen by 13/2 mmHg in the placebo group and by 23/7 mmHg in the active-treatment group. Nonfatal stroke, fatal and nonfatal stroke, and cardiac endpoints were significantly decreased in the active-agent group (44%, 42%, and 33%, respectively). Of note, active treatment resulted in a reduction in all fatal and nonfatal CV events by 31%.14

Another trial of Asian patients over the age of 60 years with isolated systolic hypertension randomized approximately 2400 patients on nitrendipine along with captopril and/or hydrochlorothiazide if a BP goal was not achieved. In the active-treatment group, BP was reduced from 170.2/85.9 mmHg to 150.2/80.9 mmHg. The risk for a nonfatal or fatal CV event and the risk for stroke were significantly reduced by 37% and 38%, respectively. All-cause death, CV death, and death from stroke were also significantly decreased by 39%, 39%, and 58%, respectively.15

**Treatment initiation** All the above data have shown benefits in treating elderly hypertensive patients with an SBP greater than 160 mmHg. Indeed, the 2013 European Society of Hypertension and European Society of Cardiology (ESH/ESC) guidelines for the management of hypertension recommend, in elderly hypertensive patients, the initiation of antihypertensive treatment when SBP is greater than 160 mmHg. Furthermore, it is stated that antihypertensive drug treatment can be considered in fit elderly patients younger than 80 years when SBP is over 140 mmHg and provided that antihypertensive treatment is well tolerated.16 On the other hand, the Eighth Joint National Committee (JNC8) concluded in stricter recommendations, suggesting the use of antihypertensive agents if SBP is greater than 150 mmHg and/or DBP is greater than 90 mmHg in patients older than 60 years.37 The Clinical Practice guidelines for the Management of Hypertension in the Community by the American Society of Hypertension and the International Society of Hypertension (ASH/ISH), published also in 2014, recommend initiation of treatment if SBP is greater than 140/90 mmHg for all ages. In patients older than 80 years, the threshold of 150/90 mmHg is suggested for treatment initiation. These recommendations, however, suggest that in patients over 80 years of age and with other CV-related comorbidities such as diabetes or kidney disease, antihypertensive therapy should begin at BP levels over 140/90 mmHg.38 The American College of Cardiology Foundation / American Heart Association (ACCF/AHA) consensus recommends initiation of treatment in patients with BP greater than 140/90 mmHg.39 Lastly, the guidelines of the National Institute for Health and Care Excellence in the United Kingdom suggest the initiation of treatment in patients aged under 80 years with stage 1 hypertension who have target organ damage, established CV disease, renal disease, diabetes, and/or a 10-year CV risk of 20% or higher irrespectively of age, as well as in individuals of any age with stage 2 hypertension (TABLE 1).40

**Target blood pressure: where to stop?** It has to be highlighted though that all trials in the elderly population were conducted in patients with baseline SBP values over 160 mmHg and the average achieved SBP never attained values lower...
than 140 mmHg. Among the trials of BP-lowering regimens in the elderly, two studies were designed to evaluate CV-related outcomes of intensive vs standard treatment strategies. The Japanese trial to assess optimal SBP in elderly hypertensive patients, JATOS, compared intensive (SBP goal below 140 mmHg) vs standard treatment (SBP goal between 140 and 160 mmHg) for 2 years in patients with essential hypertension, aged between 65 and 85 years old, with an SBP above 160 mmHg. More than 4400 patients received enalapril as the initiation treatment, and more drugs were added to achieve the BP target in each group. At the end of the trial, BP was 135.9/74.8 mmHg in the strict-treatment group and 145.6/78.1 mmHg in the standard-treatment group. The composite endpoint of CV disease and renal failure did not differ between the groups. Insignificant differences were also observed in cerebrovascular disease, cardiac and vascular disease, and renal failure rates. Another Japanese trial of 3260 patients aged from 70 to 84 years with isolated systolic hypertension evaluated the CV outcomes of strict vs moderate BP control with valsartan plus other BP-lowering agents. After 3 years, BP was 136.6/74.8 mmHg and 142.0/76.5 mmHg in the intensive- and standard-treatment groups, respectively. The incidence of the composite endpoint was similar between the groups. The incidence of each event separately (all-cause death, CV death, sudden death, fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, unplanned hospitalization, and renal insufficiency) were also similar.

The above studies have examined the effect of BP decrease in study populations that included patients aged 60 years or older and using antihypertensive drugs, as compared with other treatments or placebo. However, patients older than 80 years were not represented adequately in these trials. Data for the optimal BP target in the very elderly (age greater than 80 years) comes from the Hypertension in the Very Elderly Trial (HYVET). More than 3845 participants who were aged 80 years or older, with an SBP of 160 mmHg or more, received either the diuretic indapamide (plus perindopril to achieve target BP) or placebo. The difference in BP after 2 years (from 173 mmHg to approximately 158 mmHg of SBP) in the active treatment group resulted in significant reductions in the rates of death from stroke (39%), death from any cause (21%), heart failure (64%), and marginally insignificant reductions in the rates of fatal or nonfatal stroke (30%) and death from CV causes (23%). These findings are in agreement with the earlier published meta-analysis of the Individual Data Analysis of Antihypertensive Drug Intervention Trials (INDANA) group, which suggested that treatment of 1670 participants aged 80 years or more prevented 34% of stroke, 22% of major CV, and 39% of heart failure events.

Collectively, the available data evaluating the effects of lowering BP below 140 to 150/90 mmHg in the elderly population is limited and without sings of significant benefits; thus, most international guidelines agree on targeting a BP of 150/90 mmHg and below. The 2013 ESH/ESC guidelines propose reducing SBP to below 150 and 140 mmHg. In octogenarians or older patients with an initial SBP of more than 160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg. In fit elderly patients younger than 80 years, already on antihypertensive treatment, SBP should be reduced below 140 mmHg if the treatment is well tolerated. The JNC8 recommendations suggest lowering SBP below 150 mmHg and DBP below 90 mmHg. The recommendation for an SBP goal of less than 140 mmHg in the JNC7 was supported by some members of the JNC8, thus concluding with the joint statement that if “pharmacologic treatment for high BP results in lower achieved SBP (for example, <140 mmHg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted”.

The ACCF/AHA recommendations propose reducing BP below 140/90 mmHg in all hypertensive elderly patients. However, due to lack of strong data regarding the elderly over 80 years, guidelines state that in these patients SBP levels of “140 to 145 mmHg, if tolerated, can be acceptable”. The ASH/ISH guidelines suggest that in patients aged 80 years or older, BP should be below 150/90 mmHg. The British guidelines propose a BP goal of less than 140/90 mmHg in patients younger than 80 years; in older patients, BP should be reduced to less than 150/90 mmHg.

The SPRINT trial: the lower the better? The recently published Trial of Intensive versus Standard Blood-Pressure Control (SPRINT) has examined, in patients with high CV risk, the impact of lowering SBP below 120 mmHg compared to a less aggressive reduction of SBP to lower than 140 mmHg. More than 9000 patients with an SBP between 130 and 180 mmHg, aged more than 50 years, were randomized to receive intensive vs standard BP-lowering therapy. The study was terminated prematurely due to rapid and sustained between-group differences in CV outcomes after approximately 3.2 years. A significant 33% reduction of the combined primary outcome incidence (myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from CV causes) was observed with intensive treatment in 2636 participants older than 75 years compared to standard treatment. Total mortality was also reduced in the elderly on intensive vs standard treatment by 32%. On the contrary, in patients below the age of 75 years, intensive treatment did not provide such substantial benefits, although an insignificant trend towards CV and survival benefits was observed. It has to be noted that patients with diabetic mellitus and overt cerebrovascular disease were not included in the SPRINT trial; therefore, study findings do not apply for these patients.
Recently, the detailed report of the SPRINT outcomes in the elderly was published and provided a clearer picture of the more aggressive BP reduction effect in morbidity and mortality in the elderly population of the study and in several elderly subgroups individually. In the intensive-treatment group, BP did not reach the target of lower than 120 mmHg (123.4/62.0 mmHg). However, the difference from the achieved BP in the standard-treatment group (134.8/67.2 mmHg) was substantial. The incidence of the primary outcome was significantly lower with intensive compared to standard treatment by 34%. Aggressive BP reduction resulted also in a significantly lower rate of heart failure events (38%), nonfatal heart failure events (37%), and all-cause mortality (33%). The combined incidence of the primary outcome and all-cause death was also remarkably decreased by 32%. Furthermore, the analysis of the results according to frailty status resulted in greater benefits with intensive treatment in the less fit and frail individuals. The primary outcome and all-cause mortality were significantly lower in the less fit elderly (a decrease of risk by 37% and 52%, respectively); in frail elderly, these outcomes reached a marginal insignificant result, suggesting a potential benefit of aggressive BP reduction in this specific subgroup. Indeed, the incidence of these two outcomes combined was significantly decreased in both less fit and frail elderly patients (risk reductions of 40% and 33%, respectively). All these data support that reduction of BP beyond the suggested limit of 140 mmHg might ameliorate the morbidity and mortality risk of patients above 75 years of age. Furthermore, it seems that intensive BP reduction may benefit the less fit and fragile elderly, in whom physicians are reluctant to treat hypertension even to the suggested BP goals. It is expected that future guidelines will take under consideration the findings of the SPRINT study. However, the extent of potential alterations to the guidelines is still to be seen.

**Lifestyle interventions**

Lifestyle modifications are suggested for both delaying the development of hypertension and as adjunctive therapy in hypertensive patients. In the Randomized Controlled Trial of Nonpharmacologic Interventions in the Elderly (TONE), 585 obese participants (aged 60–80 years) with BP lower than 145/85 mmHg were randomized to reduced sodium intake, weight loss, combination of both, or usual care; 390 nonobese participants of the same age and with the same BP levels were randomized to reduced (1800 mg/d) sodium intake or usual care. Diagnosis of high BP, treatment with antihypertensive medication, or occurrence of a CV event was significantly less frequent in the group with reduced compared to usual sodium intake (risk reduction of 31%). Similar results were observed with weight loss of 3.5 to 4.5 kg in obese patients (risk reduction of 30%), compared to the 0.9-kg reduction in the control group. Compared to usual care, reduced sodium intake, weight loss, and their combination, resulted in a significant reduction of the combined outcome (40%, 36%, and 53%, respectively). Along with sodium intake restriction and weight loss, other lifestyle modification measures are suggested including smoking cessation, aerobic physical activity, restriction of dietary fat and cholesterol, avoidance of excessive caffeine and alcohol intake, and adequate dietary potassium intake.

**Pharmacological therapy: which is the optimal choice?**

The available antihypertensive drug armamentarium includes a variety of classes that can be used for all the steps of the management of hypertensive elderly (TABLE 2). Data from several trials are available for their efficacy in reducing BP and optimizing the CV profile of the elderly population. The first available data for diuretics in older hypertensive patients come from the European Working Study group and the Medical Research Council working group. In the first one, use of hydrochlorothiazide and triamterene in the double-blind arm of the study resulted in a significant decrease of CV mortality (38%), cardiac deaths (47%), deaths from myocardial infarction (60%), study-terminating morbid CV events (60%) and nonterminating cerebrovascular events (52%) in hypertensive patients older than 60 years with entry SBP between 160 and 239 mmHg and DBP between 90 and 119 mmHg. The Medical Research Council study showed significant reductions in the rates of stroke, coronary events, and all CV events (31%, 21%, and 35%, respectively) with the use of hydrochlorothiazide or amiloride in old hypertensive patients (age, 65–74 years) with a baseline SBP of 160 to 209 mmHg and a DBP below 115 mmHg. On the contrary, β-blockers were unable to decrease the risk of these endpoints, despite the observed BP reduction. The SHEP and HYVET trials also provide encouraging data for the use of chlorthalidone and indapamide, respectively, in the elderly population.

Data favoring the use of β-blockers come from the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension), which evaluated CV outcomes in 1627 patients between 70 and 84 years of age, with an SBP between 180 and 230 mmHg and a DBP between 105 and 120 mmHg, who received randomly either active treatment (one of 3 β-blockers or 1 diuretic) or placebo. After treatment, BP was 186/96 mmHg in the placebo group and 167/87 mmHg in the actively treated group vs 195/102 mmHg for both groups at baseline. All stroke events and fatal stroke deaths were significantly decreased with treatment compared to placebo (47% and 76%, respectively). The number of total deaths was also significantly reduced with treatment (risk reduction of 43%). Further data come from a British study in primary care, where the use of atenolol and bendrofluzid in patients aged from 60 to 79 years for more than 4 years resulted in a 30% reduction in the rate of fatal stroke in the treatment group compared to...
controls. Fatal and nonfatal stroke incidence was also decreased by 58%.56

The above mentioned trials, Syst-Eur54 and Syst-China,55 have favored the use of calcium channel blockers (CCB) for the treatment of elderly hypertensive patients. Additionally, the STOP-Hypertension 2 trial57 suggested the similarity in the efficacy of CCBs to diuretics or β-blockers in prevention of CV events in hypertensive individuals aged from 70 to 84 years. Compared with the use of angiotensin-converting enzyme inhibitor (ACEI), a significant difference in the risk for myocardial infarction and congestive heart failure was noted, favoring the use of the CCBs. However, in all the other CV outcomes examined, CCBs were equally efficient.57

Of major importance, a large meta-analysis of 31 trials and 190,606 hypertensive patients did not note any differences between the effects of different classes of antihypertensive drugs in older compared with younger adults either in BP reduction efficacy or CV outcomes. The comparison of different drug regimens in patients older than 65 years did not show any differences in the efficacy between the drug classes.

Based on these findings, the ESH/ESC 2013 guidelines recommend the use of either an ACEI or angiotensin receptor blocker (ARB), CCB,
diuretic, or a β-blocker for the management of hypertension in the elderly. However, it is stated that diuretics and CCBs may be preferred in isolated systolic hypertension.26

The JNC8 recommendations favor the use of either a thiazide-type diuretic, an ACEI, an ARB, or a CCB in all nonblack patients. The use of β-blockers is not suggested based on the results of the LIFE study. In this trial, more than 9000 patients with essential hypertension and left ventricular hypertrophy aged from 50 to 80 years randomly received either atenolol- or losartan-based therapy. While BP reduction was rather similar between the two groups after 4.8 years, losartan treatment resulted in fewer fatal and nonfatal CV events and was better tolerated.28 Based on these finding, the JNC8 did not include the β-blocker class as an option for the treatment of hypertension in any age group.29 Similarly, the ACCF/AHA guidelines propose the use of ACEIs, ARBs, CCBs, diuretics, or their combination in elderly patients with uncomplicated hypertension.30

In contrast, the ASH/ISH and British guidelines suggest a different approach. Based on the differences in renin levels according to age and race, the British version uses age and race as surrogates for renin in order to overcome existing difficulties with renin determination.31 Renin levels are more likely to be higher in patients younger than 55 years and lower in patients older than 55 years.32 Favoring this theory, a randomized crossover study sought to determine which of the common groups of antihypertensive drugs is the most effective in lowering SBP in elderly patients (aged 65–86 years). ACEIs and β-blockers resulted in a milder BP decrease compared to diuretics or CCBs; the percentage of patients who achieved the target SBP was higher with diuretics or CCBs.61

The Identification of the Determinants of the Efficacy of Arterial blood pressure Lowering drugs (IDEAL) trial13 evaluated the effect of age and sex on BP response to indapamide and perindopril. The study included 112 untreated, middle-aged hypertensive patients who were randomized to one of the two drugs in a crossover manner. It was found that SBP response to indapamide increased by 3 mmHg for every 10 years of age gradient in women. Furthermore, SBP response to perindopril decreased by 2 mmHg for every 10 years of age gradient in both sexes.62

The British guidelines suggest initiation of treatment with a CCB and then proceed to treatment with ACEIs or ARBs; in patients aged 80 years and over, the same antihypertensive drug treatment should be used, but the physician should consider any existing comorbidities.40 The ASH/ISH guidelines suggest initiation with either a CCB or a diuretic.38 As in the JNC8 recommendations, β-blockers are not included as the first-line options, mainly based on the results of the LIFE study63 and the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) study,64 in which the amlodipine-based treatment prevented more CV events than the atenolol-based treatment.59,63-65

Lastly, it has to be stated that due to the common presence of other comorbidities in the elderly population,35 treatment should be adjusted according to these conditions. Choices for initiation or additional antihypertensive treatment should have an ameliorating effect on the concomitant diseases as well (TABLE 3).

Management of hypertension in nursing home patients Nursing home patients constitute a particular subgroup of the elderly population of increased frailty status. They are usually aged 80 years or more. In these patients, the strategies to treat hypertension are complicated by the presence of other comorbidities; the subsequent polypharmacy (including antihypertensive drugs) increases the risk of adverse drug reactions, drug–drug or drug–disease interactions, and nonadherence.66 Most international guidelines recommend treating robust stage 2 hypertensive patients older than 80 years to achieve a BP level of less than 150 mmHg. However, older individuals with frailty and multiple morbidities are generally excluded from clinical trials that are the basis for current guidelines. Even the HYVET study,63 which specifically addressed the elderly over 80 years, did not include patients with a requirement of nursing care. Therefore, it is questionable whether these guidelines can be applied to frail institutionalized patients.

The Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population (PARTAGE) study67 has examined the relation between BP and overall mortality and major CV events in 1126 nursing home patients. Surprisingly, a 10-mmHg increase in SBP, DBP, or mean BP resulted in a significant decrease in the risk of total mortality by 9%, 16%, and 15%, respectively. The highest mortality was observed in patients with an SBP of less than 130 mmHg, even after adjustment for potential confounding factors such as age, sex, history of previous CV disease, cognitive function, and daily living activities.67 Further analysis of the data showed more than a 2-fold increase of the mortality rate in patients with an SBP of less than 130 mmHg on 2 or more antihypertensive drugs, as compared with the remaining study population. The groups with similarly low SBP and receiving no or 1 antihypertensive drug, as well as patients with an SBP greater than 130 mmHg with various numbers of medications presented significantly lower mortality risk compared with those on more than 1 drug and an SBP higher than 130 mmHg. In addition, these associations remained unchanged after adjustment for heart failure, cancer, other major CV disease, and the Charlson Comorbidity Index score.68

Frail nursing home patients are usually characterized by decreased walking speed, a known marker of frailty status.69 A study of 2340 patients older than 65 years examined the association
between BP and mortality according to walking speed. Among faster walkers (>0.8 m/s), BP higher than 140 mmHg was related with a 35% greater mortality risk. On the contrary, in slowly walking patients (<0.8 m/s), neither elevated SBP nor DBP was associated with mortality rates. Of particular importance, in patients that did not complete the walking test, SBP greater than 140 mmHg and DBP greater than 90 mmHg were strongly and independently associated with a 62% and 90% decreased mortality risk, respectively.70

These data suggest that in frail elderly patients, a slightly increased BP might prevent fatal events. This elderly subgroup is more prone to the development of orthostatic hypotension and organ hypoperfusion due to impaired autoregulation,66 and strict antihypertensive therapy to achieve a BP below 150/90 mmHg may increase the rate of such events. The PARTAGE study67 concluded that even in patients with low SBP and no antihypertensive treatment, the mortality rates were significantly lower than in the similar BP group on more than 2 medications. Conclusively, current data are insufficiently powered to determine the strategies to manage hypertension in this elderly subgroup. Physicians should be careful when treating such individuals and provide less aggressive BP goals with regimens that cause lower adverse events and reactions with other drugs or diseases.

Orthostatic hypotension and syncope Orthostatic hypotension combined with dizziness and syncope are more common in elderly patients owing to a blunted baroreflex response that occurs with standing.71 Such conditions are considered as significant adverse events of antihypertensive treatment, and the risk for these conditions should be taken into account when prescribing treatment for hypertension.72 Any of the available antihypertensive agents may potentially contribute to the manifestation of symptomatic postural hypotension, postprandial hypotension, syncope, or falls.73-75 The use of some classes, however, has been related to higher event rates than the use of others. Diuretics that seem to be

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>BP target</th>
<th>Drug choice for treatment initiationa</th>
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<tbody>
<tr>
<td>diabetes mellitus</td>
<td>&lt;130/80 mmHg, if tolerated (ACCF/AHA)</td>
<td>ACEI, ARB, CCB, thiazide-type diuretic, or β-blocker (ACCF/AHA)</td>
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<tr>
<td></td>
<td>&lt;140/85 mmHg (ESH/ESC)</td>
<td>All drugs are recommended; ACEI or ARB may be preferred especially in the presence of proteinuria or microalbuminuria (ESH/ESC).</td>
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<tr>
<td></td>
<td>&lt;140/90 mmHg (ASH/ISH)</td>
<td>ACEI or ARB (ASH/ISH) thiazide-type diuretic, ACEI, ARB, or CCB in patients without CKD (JNC8)</td>
</tr>
<tr>
<td></td>
<td>&lt;140/90 mmHg (JNC8)</td>
<td></td>
</tr>
<tr>
<td>chronic kidney disease</td>
<td>&lt;130/80 mmHg, if tolerated (ACCF/AHA)</td>
<td>ACEI or ARB (ACCF/AHA)</td>
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<td></td>
<td>CKD no proteinuria &lt;140/90 mmHg (ESH/ESC)</td>
<td>ACEI or ARB (ESH/ESC)</td>
</tr>
<tr>
<td></td>
<td>CKD + proteinuria &lt;130/90 mmHg (ESH/ESC)</td>
<td>ACEI or ARB (ASH/ISH)</td>
</tr>
<tr>
<td></td>
<td>&lt;140/90 mmHg (ASH/ISH)</td>
<td>ACEI or ARB alone or in combination with other drugs (JNC8)</td>
</tr>
<tr>
<td></td>
<td>&lt;140/90 mmHg (JNC8)</td>
<td></td>
</tr>
<tr>
<td>heart failure</td>
<td>&lt;130/80 mmHg for patients with HF and CAD (ACCF/AHA)</td>
<td>Thiazide-type diuretic plus β-blocker, ACEI, ARB, CCB, or aldosterone antagonist (ACCF/AHA)*</td>
</tr>
<tr>
<td></td>
<td>The other guidelines do not provide specific recommendations for this subgroup.</td>
<td></td>
</tr>
<tr>
<td>coronary artery disease</td>
<td>SBP &lt;140 mmHg (ESH/ECS)</td>
<td>β-blocker, ACEI, aldosterone antagonist, ARB (post MI); thiazide-type diuretic, β-blocker, ACEI, CCB (CAD or high CVD risk); β-blocker plus CCB (angina) (ACCF/AHA)</td>
</tr>
<tr>
<td></td>
<td>The other guidelines do not provide specific recommendations for this subgroup.</td>
<td>β-blocker (recent MI); all antihypertensive agents; β-blocker and CCB are preferred (other CAD) (ESH/ESC)</td>
</tr>
<tr>
<td></td>
<td>&lt;140/90 mmHg (ASH/ESC)</td>
<td>β-blocker plus ARB or ACEI (clinical CAD) (ASH/ISH)</td>
</tr>
<tr>
<td>history of cerebrovascular event</td>
<td>&lt;140/90 mmHg (ESH/ESC)</td>
<td>Diuretic plus an ACEI, ARB or CCB (ACCF/AHA)*</td>
</tr>
<tr>
<td></td>
<td>The other guidelines do not provide specific recommendations for this subgroup.</td>
<td>ACEI, ARB, CCB, diuretic, or β-blocker (ESH/ESC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACEI or ARB (ASH/ISH)</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; HF, heart failure; LV, left ventricular; MI, myocardial infarction; others, see TABLES 1 and 2
particular effective in older patients can cause volume depletion-induced syncope. Especially in older patients with chronic heart failure who are predisposed to volume depletion, excessive diuretic use may cause orthostatic phenomena.75 On the other hand, vasodilators such as ACEIs or ARBs, CCBs, hydralazine, nitrates, and α-blockers may cause venodilation and reduction in systemic vascular resistance. The initiation of ACEIs is associated with the presence of acute hypertension.76 Data suggest that patients with drug-resistant hypertension and renovascular disease are prone to the development of symptomatic hypertension after an initial dose of 25 mg of captopril.77 Furthermore, the risk for hypotension events is significantly increasing with aging. Regarding β-blockers, it seems that their use is associated with increased risk of syncope under the presence of some comorbidities, such as sinoatrial disease, severe sinus bradycardia, and first-, second-, and third-degree atroventricular block.78 Alpha-blockers have been associated with increased risk for syncope, through first-dose and chronic-postural effects, especially in individuals receiving diuretics or vasodilator drugs, such as PDE-5 inhibitors.71,79 To avoid such events, initiation of α-blockers with low doses and with the patient in the supine position, especially in patients at high risk for hypotension (sodium-depleted patients with high pretreatment BP levels, concomitant therapy with β-blockers) is indicated. Lastly, elderly patients on antihypertensive agents are more prone to syncope secondary to dehydration during summer months.80 Downtitration of the therapy, and especially of diuretics, which should be avoided.

**References**


**Other considerations when treating the elderly**

Initiation of treatment should generally be at low doses with gradual adjustments. When making treatment alterations, standing BP measurement may prevent hypotensive episodes.71 Additionally, the prevalence of other comorbidities is increasing with age; therefore, polypharmacy is a common phenomenon in this age group.66,81 When initiating or adding a drug, one should always bear in mind possible drug–drug or drug–disease interactions. Due to the large number of medicacion that the elderly receive on daily basis, they are more prone to nonadherence.67,83 Given the gradual cognitive decline with aging,84 nonadherence phenomena are multiplied.85-87 Furthermore, among the drugs used, there are several agents that can result in an increase in BP, such as non-steroidal anti-inflammatory drugs, nasal decongestants containing sympathomimetics, corticosteroids, erythropoietin, amphetamines, and steroids, which should be avoided.66-80

**Conclusions**

The necessity to treat hypertensive elderly patients to reduce morbidity and mortality has been convincingly demonstrated. Based on the data from large clinical studies, most guidelines seem to agree that BP should be reduced below 150/90 mmHg. However, it is still debatable whether this threshold has to be reduced even more. Most outcome-investigating studies did not reach BP levels below 140 mmHg. The SPRINT trial was able to achieve SBP levels of 120 to 125 mmHg in the elderly subgroup, which resulted in a significant risk reduction and will probably be taken under consideration in future recommendations. Regarding the frail elderly and nursing patients, data are very limited; future studies are needed to determine the optimal target BP and antihypertensive agents in these groups. CCBs and diuretics are favored by several recommendations as first-line treatment in uncomplicated hypertension in the old population, while ACEIs and ARBs are suggested either as first or second-ary options. Physicians should always consider the presence of comorbidities and administrate agents that will benefit all diseases and will present fewer drug–disease or drug–drug interactions. Initiation of treatment should be made after verifying that patients are indeed adherent, and white-coat hypertension or pseudohypertension have been excluded. Lastly, initiation or up-titration of treatment should be gradual and patients should be under close observation to prevent the occurrence of adverse events.
Hypertension in the elderly


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Problemy w leczeniu nadciśnienia u osób w podeszłym wieku

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STRESZCZENIE

Nadciśnienie tętnicze dotyczy ponad 25% populacji świata, a częstotliwość jego występowania rośnie z wiekiem. W miarę starzenia zwiększa się sztywność tętnic, co powoduje wzrost skurczowego, a spadek rozkurczowego ciśnienia tętniczego krwi. U osób w wieku podeszłym wysokie ciśnienie tętnicze wiąże się ze zwiększoną ryzykiem sercowo-naczyniowym. Badania kliniczne prowadzone w tej populacji wykazały duże korzyści w zakresie chorobowości i umieralności z obniżenia skurczowego ciśnienia tętniczego (systolic blood pressure – SBP) do poziomu <150 mm Hg. Większość wytycznych postępowania u osób starszych z nadciśnieniem zgadza się co do obniżenia ciśnienia tętniczego <150/90 mm Hg. Wciąż nie ma jednak pewności, czy dalsze obniżanie ciśnienia może dać korzystne efekty. W niedawno opublikowanym badaniu SPRINT wykazano, że obniżenie SBP do 120–125 mm Hg u chorych w wieku >75 lat wiąże się z wydłużeniem przeżycia, co, jak można oczekiwać, wpłynie na przyszłe zalecenia. Z drugiej jednak strony, ograniczone dane na temat osób w wieku ≥80 lat i mieszkańców domów opieki z zespołem słabości, których leczono agresywniej, są niepokojące i sugerują bardziej zachowawcze cele leczenia. Spośród wielu grup leków hipotensyjnych korzystne działanie u osób w wieku podeszłym wykazano dla diuretyków, blokerów kanału wapniowego, inhibitorów konwertazy angiotensyny i blokerów receptoru angiotensynowego; są one preferowanymi lekami pierwszego wyboru w leczeniu nadciśnienia u tych chorych. Pamiętając o współistnieniu innych chorób i polifarmakoterapii, lekarze powinni ostrożnie włączać leki lub zwiększać ich dawki, aby uniknąć potencjalnych działań niepożądanych lub interakcji z innymi lekami albo chorobami.