Current Hypertension Reports (2019) 21: 82
https://doi.org/10.1007/s11906-019-0987-y

ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (ME ERNST, SECTION EDITOR)

From Clinical Trials to Bedside: the Use of Antihypertensives in Aged Individuals. Part 1: Evaluation and Evidence of Treatment Benefit

Eric J. MacLaughlin[1] · Michael E. Ernst[2]

Published online: 10 October 2019

Abstract

Purpose of Review Use of antihypertensives in older adults can be complicated by the potential for undesired effects on comorbidities, adverse effects of the drugs, and overall medication burden. The purpose of this two-part review is to discuss contemporary issues encountered in the management of hypertension in aged individuals, with a particular focus on the individualization of treatment. In part 1, we discuss the evaluation of the aged hypertensive patient and review the clinical trial evidence for treatment benefit of hypertension in the elderly.

Recent Findings Elderly patients with suspected hypertension need careful evaluation of their blood pressure, as errors in measurement technique, inaccurate devices, or overreliance on office blood pressure readings may lead to under- or over-treatment, thereby increasing risks of adverse medication effects and/or cardiovascular events. Epidemiologic evidence in older adults suggests a link between low blood pressure and increased mortality. However, key prospective hypertension trials such as HYVET and SPRINT, which were focused in mostly healthy, community-dwelling elderly cohorts, have unequivocally demonstrated benefits of lowering blood pressure in reducing cardiovascular events in the very elderly. Recent evidence also suggests benefit in reducing the risks of cognitive impairment.

Summary Hypertension is a major modifiable risk factor and the benefits of treatment in lowering cardiovascular events are realized for most individuals, even at advanced ages.

Keywords Hypertension · Elderly · Antihypertensive agents · Aged

Introduction

Elevated blood pressure is an important modifiable risk factor for cardiovascular disease, and hypertension is estimated to affect over 1.1 billion individuals globally [1]. Although not exclusively a disease of the elderly, there is a strong correlation between age and the development of hypertension, making it one of the most common conditions encountered with advancing age. The overall prevalence of hypertension (using the traditional threshold of 140/90 mmHg) increases from 30 to 45% of adults, to more than 60% in those older than 60 years [2]. These numbers increase substantially, from 75.6% of those aged 65–74 years to 82.3% of those > 75 years of age, when applying the more recent 2017 guideline thresholds [3]. Regardless of which threshold is applied, older adults encompass a progressively growing sector of the population, and it is estimated that the prevalence of hypertension will increase by 15–20%, to nearly 1.5 billion individuals, by 2025 [4].

The management of hypertension in older adults has many challenges owing to relatively limited studies conducted in populations of advanced aged, and an almost universal exclusion of those with significant or extensive comorbidities. While benefits observed in clinical trials predominately populated with younger and middle-aged individuals would

This article is part of the Topical Collection on *Antihypertensive Agents: Mechanisms of Drug Action*

✉ Michael E. Ernst
michael-ernst@uiowa.edu

1 Department of Pharmacy Practice, Jerry H. Hodge School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, TX, USA

2 Department of Pharmacy Practice and Science, College of Pharmacy; and, Department of Family Medicine, Carver College of Medicine, The University of Iowa, 01291-A PFP, 200 Hawkins Dr, Iowa City, IA 52242, USA

generally be expected to extend to older individuals sharing the same disease processes, advancing age produces a heterogenous spectrum of phenotypes ranging from robust to frail, and the approach to management of hypertension in older individuals must reflect these individualized considerations. Questions such as what the upper age boundaries for initiation of treatment should be, agreement on target blood pressure levels in those treated, selecting pharmacological interventions which balance risk and benefit, and when to de-escalate antihypertensives and treatment goals exemplify some of those encountered on a regular basis.

This review will focus on the personalization of antihypertensive use in individuals of advanced age. Because there is no consensus definition for "elderly," "aged," or "older" individuals with respect to hypertension (although generally, clinical trials have recognized subjects aged 60–79 years as "old" and those 80 years and older as "very old"), this review is written with attention to the biologic or phenotype of the aged hypertensive rather than restricted to an exclusive chronological age categorization. We will use the descriptors of "elderly," "aged," and "older" persons interchangeably, recognizing that the interaction between chronologic age and biological function resides on a continuum without absolute demarcations. In general, issues addressed in this review are most likely to be commonly encountered in those aged 75 years and older, as these are the widely heterogenous group for which the risks and benefits of treatment are finely balanced and individualization of treatment is most warranted.

Pathophysiology of the Aging Hypertensive and Implications for Treatment

The underlying architecture of hypertension in aging individuals shares some commonalities with that of younger persons, particularly in the contribution of lifestyle. Increased rates of obesity due to adoption of more sedentary behaviors, use of concomitant medications that cause sodium retention (e.g., non-steroidal anti-inflammatory drugs) or direct vasoconstriction (e.g., sympathomimetic agents), excessive alcohol intake, smoking, and high dietary sodium intake all contribute to elevation of blood pressure, irrespective of age.

While lifestyle factors such as several of those mentioned above are amenable to modification even in the elderly, perhaps more importantly, aging vasculature undergoes distinct and unavoidable physiologic changes which also drive the progressive elevation of blood pressure. Blood pressure patterns in older individuals are predominated by the high prevalence of isolated systolic hypertension, characterized by the increase in systolic blood pressure accompanied by a fall in diastolic blood pressure, and a widening of pulse pressure [5]. This is believed to result from loss of elastic tissue in large arteries accompanied by increased central arterial stiffening, a theory supported by hemodynamic studies showing increased pulse wave velocity for the forward and reflected waves in the arterial system [6]. The earlier wave reflection occurs prior to closure of the aortic valve during systole (as opposed to after closure in younger persons), which augments systolic pressure and opposes systolic output. Throughout the remainder of this review, any reference to elevated blood pressure will be done so with systolic blood pressure as the focal point.

Because all antihypertensives have the potential to lower both systolic and diastolic blood pressure, the drop in diastolic blood pressure in older individuals can adversely impact coronary blood flow. In younger individuals, coronary artery blood flow is enhanced by the boost in central aortic pressure provided by the reflected arterial wave in diastole [6]. As this boost is lost in older adults, those with underlying coronary ischemia may be particularly susceptible to the effects of antihypertensives in lowering the diastolic blood pressure. Epidemiologic observations of a U-shaped curve showing higher mortality in older persons with lower blood pressure further complicate treatment decisions in elderly [7•]. However, several recent studies have suggested these epidemiologic observations may be largely the result of a reverse causality bias, as the trajectory of blood pressure levels decline in most individuals in the years leading up to and immediately prior to death, independent of the use of antihypertensives [8, 9].

In addition to changes specific to the pathophysiology of hypertension, aging itself is often accompanied by a myriad of other physiologic and clinical issues which have implications for treatment of hypertension, both in overall decisions about how intensively to manage but in choice of specific medications and regimens as well. Older adults may have cognitive impairment, underlying renal insufficiency, orthostatic intolerance, urinary symptoms, electrolyte disturbances, gait/balance problems, and problems with medication adherence. Table 1 summarizes these issues along with considerations for use of antihypertensives when they are encountered.

Importance of Appropriate Blood Pressure Measurement in Older Adults

Appropriate blood pressure measurement and monitoring for the diagnosis and management of hypertension, while important for all patients with high blood pressure, is critical in aged individuals. Errors in measurement technique or failure to obtain out-of-office readings may lead to under- or over-treatment, thereby increasing the risk of an adverse drug event or atherosclerotic cardiovascular disease. There are several issues that merit particular consideration in older patients at it relates to blood pressure monitoring.

Table 1 Potential age-related challenges in the management of hypertension in older adults, and implications for antihypertensive use

Potential age-related challenge	Implications for use of antihypertensives
Cognitive impairment	
•Older adults may have underlying cognitive impairment which can impact learning new tasks such as adhering to changes in medication regimens •Depending on severity, existence of cognitive impairment in the presence of multimorbidity may portend limited remaining life expectancy	•Need for simplification of regimen; fixed-dose combinations, avoiding breaking tablets if possible •Consider goals of care discussion with caregivers and evaluation of risk/benefit of treatment and intensity of blood pressure treatment goals
Renal insufficiency	
•Potential for increased adverse effects with several antihypertensive classes	•Insure doses (of all medications, not just antihypertensives) are correct for renal function •Monitor labs (Na, K, SCr) regularly
Orthostasis	
•Older adults often do not keep well hydrated, or have coexisting conditions or take other medications which can predispose them to orthostasis •Impaired hemodynamic and neurovascular responses (blunting of baroreceptor response)	•Check orthostatic blood pressures as part of routine office blood pressure measurement •Ask about symptoms of lightheadedness and falls •Cautiously use diuretics and alpha-1 blockers
Uropathy	
•Decreased bladder emptying, increased frequency; incontinence	•Consider alpha-1 blockers in men with prostatic hyperplasia •Cautious use of diuretics
Electrolyte perturbations	
•Related to other conditions/medications or decreased free water intake	•Cautious use of ACEi/ARBs, diuretics •Consider calcium channel blockers
Balance/gait abnormalities	
•Postural instability—potential for falls	•Avoid aggressive BP goals •Cautious use of diuretics
Medication adherence	
•May be a function of underlying cognitive impairment or medication burden if multimorbidity present	•Need for simplification of regimen •Assess whether adverse effects or costs are contributing to non-adherence •Assess whether patient does not understand the benefit of treating hypertension

Clinical Blood Pressure Measurements

Clinical blood pressure measurements, defined as measurements taken in the office or institutional setting, remain a standard of care for the detection and evaluation of high blood pressure. However, as noted below, they should not be the sole method used, especially in older, community-dwelling patients. Correct measurement technique is essential, and has been well-described [10]. Factors such as lack of adequate resting time, incorrect cuff placement, wrong cuff size, measurement over clothing, unsupported back, crossed legs, full bladder, or talking during measurement may result in erroneous measurements.

As previously noted, older patients with high blood pressure typically have isolated systolic hypertension and widened pulse pressure due to increased arterial stiffening. Stiffening of the brachial artery due to advanced atherosclerosis has been associated with falsely elevated blood arterial pressure called "pseudohypertension," as first described by Sir William Osler in 1892 [11]. The "Osler's maneuver," which is performed by inflating the blood-pressure cuff above the systolic pressure and palpating the radial or brachial artery to determine if the arteries remained palpable, has been described as a method to assess for the presence of pseudohypertension [11]. However, further evaluation of the Osler's maneuver, which was increasingly more common as patients aged, had poor reproducibility and low test reliability, making it of little clinical value for routine evaluation [12].

Another aspect when considering blood pressure measurement in older patients, particularly those with increased levels of frailty, is an assessment for possible orthostatic hypotension. Orthostatic hypotension is defined as a decrease in SBP greater than 20 mmHg or 10 mmHg in DBP within 3 min of standing, or in those with supine hypertension and an SBP decrease greater than 30 mmHg [13]. The presence of orthostatic hypotension significantly increases the risk of falls and injury and increases with age. While the prevalence in community-dwelling elderly is approximately 6%, the rate of orthostatic hypotension increases substantially in institutionalized elderly, with rates estimated to be as high as 70% [13].

Several age-related changes such as a reduction in baroreceptor sensitivity, α_1-adrenergic receptor response, cardiac and vascular compliance, and efficiency in skeletal muscle pump may result in an increased risk of orthostatic hypotension [13, 14]. Therefore, in older patients, it may be advisable to assess for orthostatic hypotension, depending on the clinical situation. For instance, any patient with complaints of postural dizziness or lightheadedness, unexplained fall or syncope, suspected or diagnosed neurodegenerative disorder (e.g., Parkinson's disease, dementia with Lewy Bodies), and those greater than 70 years of age and frail or on multiple medications should be routinely screened [15].

Out-of-Office Measurements

Out-of-office blood pressure measurements for the initial detection, evaluation, and treatment of high blood pressure are strongly recommended [10]. Detection of white coat hypertension (WCH), which is when blood pressure readings in the office setting are elevated but not outside the clinic setting [10], while critical in all patients with hypertension, is particularly noteworthy in older individuals. While the prevalence of WCH in the general population averages between 13 and 35%, WCH increases with age [10]. In a sub-study of 284 patients enrolled in the Hypertension in the Very Elderly Trial (HYVET) who underwent ambulatory blood pressure monitoring, the prevalence of WCH was 50% [16]. Lack of recognition of the white coat effect in older patients, if not detected, may result in a higher frequency of incorrect diagnosis of hypertension and possible over-treatment, resulting in adverse sequelae, particularly in this at-risk population. Likewise, masked hypertension (MH), which is when blood pressure is normal in the clinic setting but elevated outside the clinic and is associated with a significant increase in the risk of CV events [10], is common in the elderly. In a cross-sectional study of 1814 community-based seniors 75 years of age and older, the frequency of MH in patients with a normal office BP was 40% [17]. Therefore, confirmation of elevated clinic blood pressure readings with the use of home blood pressure monitoring (HBPM) or ambulatory blood pressure monitoring (ABPM) is essential.

Considering cost, wide availability of validated monitors, ease of use, and ability to monitor and adjust therapy using telemedicine principles, HBPM is the most common method used to obtain out-of-office readings. Table 2 outlines some practical tips for obtaining out-of-office readings in aged individuals.

Table 2 Practice tips for out-of-office readings in aged individuals

Monitor selection	•Use a validated device with a large display that is easy to read.
	•Choose a monitor that has a memory feature.
	•Automated upper arm devices preferred over wrist monitors because of accuracy.
	•Validated wrist monitors with position sensors can be considered for patients in whom automated upper arm devices are too difficult to use (e.g., lack of manual dexterity for appropriate cuff placement) or for patients whose anatomy precludes their use (e.g., severe obesity, short upper arm).
	•Avoid manual BP measurement devices due to complexity and skill required for appropriate use and effort required to manually inflate the cuff.
	•Ensure a monitor with the correct cuff size is used.
Training and use	•Train the patient on appropriate use and confirm their ability to use the device correctly.
	•Periodically validate the monitor in the clinic setting.
	•During initial evaluation to confirm WCH or MH, have the patient monitor their BP twice daily, once in the morning upon awaking and once in the afternoon for 7–10 days.
	•Periodic monitoring such as once daily or every-other-day at different times of the day can be considered when evaluating treatment effects.
	•Two readings should be taken when monitoring BP, with the second BP reading recorded.
Recording results	•Provide BP monitoring log sheets that have large font sizes and are easy to read and use.
	•For patients with a smartphone, consider using built-in health monitoring apps.
	May consider use of devices that can automatically transmit data to the clinician.

Evidence for Treatment Benefit in Aged Hypertensives

Several major landmark randomized controlled trials (RCTs) have established that the treatment of high blood pressure in older patients significantly decreases the risk of cardiovascular disease and death [18–22]. However, while these trials unequivocally proved that treatment of hypertension decreases cardiovascular outcomes, and included patients that were on average "elderly" (as typically defined as ≥ 65 years of age), most had relatively few patients that would be considered "very old," target BPs varied, and no large outcome trial to date has included institutionalized, frail elderly. Therefore, there is little guidance when it comes to the treatment of very old, institutionalized patients. Table 3 outlines outcomes-based RCTs that included older patients.

The first large, outcome-based trial designed to assess the benefit of treatment of high blood pressure specifically in very old patients (e.g., ≥ 75 years) was the Hypertension in the Very Elderly Trial (HYVET) [24]. In HYVET, 3845 patients ≥ 80 years of age with persistent hypertension, defined as an SBP ≥ 160 mmHg, were randomized to indapamide or matching placebo. Perindopril or matching placebo was added if needed to attain a BP goal of < 150/80 mmHg. After 2 years, the trial was terminated early due to a reduced risk of fatal or nonfatal stroke (hazard ratio [HR] = 0.70; 95% CI 0.49–1.01; number needed to treat [NNT] = 94) and death from any cause (HR = 0.79; 95% CI 0.65–0.95; NNT = 40) with active treatment. Treatment was also associated with a reduced risk of death from stroke (HR = 0.61; 95% CI 0.38–0.99; NNT = 119), any heart failure (HR = 0.36; 95% CI 0.22–0.58; NNT = 53), and any CV event (HR = 0.66; 95% CI 0.53–0.82; NNT = 30).

There are some fundamental aspects of HYVET that should be noted. First, while patients included in the trial would be considered very old, with age at study entry of 80 up to 105 years, they were ambulatory and healthier than most patients in the general population [24]. Therefore, the results from HYVET cannot be extrapolated to frail, institutionalized older patients. In addition, while the BP goal in the active treatment arm was < 150/80 mmHg, the BP achieved at 2 years was 144/78 mmHg. Also, while active treatment was associated with a decline in serum potassium levels compared with placebo (− 0.02 mmol/L vs. + 0.03 mmol/L; $p = 0.009$), there was no significant difference in creatine (+ 0.04 mg/dL vs. + 0.03 mg/dL), and the number of serious adverse events was paradoxically less common in the active treatment group vs. placebo (358 vs. 448 respectively; $p = 0.001$). Therefore, despite the fear of adverse effects and potential for an increased risk of CV events associated with treatment in the very elderly, HYVET demonstrated that treatment is well tolerated and decreases the risk of stroke, death from any cause, heart failure, and any CV event.

While HYVET unequivocally demonstrated that treatment of high blood pressure in ambulatory patients who were very old is beneficial, the ideal treatment goal for these patients had been a question for many years. The 2014 Eighth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommended a relaxed BP goal in patients ≥ 60 years, due to the inclusion criteria used of available outcomes-based RCTs at the time [28]. This recommendation was controversial, with several members of the JNC8 panel publishing a "minority report" that disagreed with raising the BP goal in older patients, citing concerns on lack of inclusion of some studies and the significant adverse impact that raising the BP goal in older patients would have on a large proportion of the population [29].

The question of what BP goal to select for patients, including those with advanced age, was recently assessed in the Systolic Blood Pressure Intervention Trial (SPRINT) and SPRINT-Senior [30, 27••]. SPRINT was designed to assess if intensive BP lowering (SBP < 120 mmHg) was more effective in reducing CV outcomes than standard BP lowering (SBP < 140 mmHg) in patients who had a SBP of > 130 mmHg and either had CVD or were at high-risk of ASCVD [30]. The main SPRINT population including 9361 patients ≥ 50 years of age and had either clinical ASCVD or a 10-year Framingham Risk of CHD of > 15%, chronic kidney disease, or were ≥ 75 years of age or older. Patients with a history of diabetes and stroke were excluded. SPRINT was stopped early after a mean follow-up of 3.26 years due a 25% decrease risk in the primary composite outcome of MI, other ACS, stroke, HF, or death from CV causes (NNT = 61) and 27% decrease in all-cause mortality (NNT = 90) associated with intensive BP lowering.

A unique aspect of SPRINT was that it was designed and funded to include a large portion of patients ≥ 75 years of age, and the protocol included measures of functional status and frailty [27••]. The SPRINT-Senior subgroup analysis included 2363 patients with a mean age of 79.9 years. Of note, in addition a history of stroke or diabetes, patients were excluded if they had symptomatic heart failure in the past 6 months or left ventricular ejection fraction of < 35%, dementia, life expectancy of fewer than 3 years, unexpected weight loss of > 10% in the last 6 months, had an SBP of < 110 mmHg after 1 min of standing, or resided in a nursing home. Similar to the overall SPRINT population, patients in SPRINT-Senior derived benefit with more intensive therapy and had an even greater reduction in the primary composite outcome (NNT = 27) and all-cause mortality (NNT = 41). Exploratory analysis based on levels of frailty and gait speed suggested similar benefits. Regarding adverse effects, intensive treatment was associated with a greater risk of an emergency room visit or serious adverse events due to hypotension (3.3% vs. 2.0%, $p = 0.039$; number need to harm [NNH] = 77) and sodium < 130 mmol/L (5.2% vs. 3.4%, $p = 0.02$; NNT = 56).

Table 3 Major hypertension outcome trials in older patients

Trial	Study design	Age	Results
Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) [20]	•Multicenter RCT of 1627 Swedish patients with mean supine BP 195/102 mmHg and mean standing BP 188/104 mmHg •Patients randomized to active treatment with β-blocker (atenolol, metoprolol, or pindolol) and/or diuretic (HCTZ plus amiloride therapy or matching placebo) •Average follow-up 2.1 years	•Age inclusion criteria, 70–84 years •Mean age, 75.7 years	•Mean achieved supine BP in treatment group was 166/87 mmHg vs. 188/97 mmHg in placebo •Active treatment decreased the risk of the primary composite outcome of all MI, all stroke, and other CV death (40%), all stroke (47%), fatal stroke (73%), and total deaths (43%)
Systolic Hypertension in the Elderly Program (SHEP) [21]	•Multicenter RCT of 4736 ambulatory patients with mean BP 170/77 mmHg •Patients randomized to chlorthalidone, with atenolol add if needed or placebo •Average follow-up 4.5 years	•Age inclusion criteria, ≥ 60 years •Mean age, 71.6 years	•Mean achieved SBP in treatment group was 143 mmHg vs. 155 mmHg in placebo •Active treatment decreased the risk of stroke (36%), clinical nonfatal MI plus coronary death (27%), major CV events (32%), and death from all cause (13%)
Systolic Hypertension in Europe (Syst-Eur) [22]	•Multicenter RCT of 4695 ambulatory patients with mean sitting BP 174/86 mmHg and mean standing BP 169/87 mmHg •Patients randomized to nitrendipine, with addition of enalapril and HCTZ or matching placebo •Median follow-up 2 years	•Age inclusion criteria, ≥ 60 years •Mean age, 70.2 years	•Mean achieved sitting SBP in treatment group was 151 mmHg vs. 161 mmHg in placebo •Active treatment decreased the risk of stroke (42%), nonfatal stroke (44%), fatal and nonfatal cardiac endpoints including sudden death (26%), nonfatal cardia endpoints (33%), and all fatal and nonfatal CV endpoints (31%)
Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) [23]	•Prospective, randomized, open-label study with blinded endpoints of 4418 ambulatory Japanese patients with mean sitting BP 172/89 mmHg •Patients randomized to strict (SBP < 140 mmHg) or less strict (< 160 but > 140 mmHg) •Median follow-up 1.8 years	•Age inclusion criteria, 65–85 years •Mean age, 73.6 years	•Mean BP in strict group 136/75 mmHg vs. 146/78 in less strict •No difference in the primary outcome of combined incidence of cerebrovascular disease, cardiac and vascular disease, and renal failure (9% vs. 8% for strict vs. less strict BP treatment). •No difference in withdraw due to adverse events (36 each group)
Hypertension in the Very Elderly Trial (HYVET) [24]	•International RCT of 3845 ambulatory patients with mean sitting BP 173/91 mmHg and mean standing BP 168/89 mmHg •Patients randomized to indapamide, with addition of perindopril to achieve BP target of < 150/80 mmHg •Trial terminated early (median follow-up 1.8 years) due to ethical reasons	•Age inclusion criteria, ≥ 80 years •Mean age, 83.6 years	•Mean achieved sitting SBP in treatment group was 144/78 mmHg vs. 159/84 mmHg in placebo •Active treatment decreased the risk of death from stroke (39%), death from any cause (21%), and heart failure (23%) •Fewer adverse events reported in active group vs. placebo (358 vs. 448)
Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica (CARDIO-SIS) [25]	•Open-label RCT of 1111 non-diabetic ambulatory patients in 44 centers in Italy with mean BP of 163/90 mmHg •Patients randomized to tight SBP goal of < 130 mmHg or usual care SBP < 140 mmHg •Median follow-up 2 years	•Age inclusion criteria, ≥ 55 years •Mean age, 67 years	•Mean BP in tight SBP group 136/80 mmHg vs. 140/81 in usual care •Tight BP control decreased the primary outcome of rate of electrocardiographic left ventricular hypertrophy (47%) and composite CV outcome of death from any cause, MI, stroke, TIA, atrial fibrillation, admission for HF, angina, coronary revascularization (50%)
Valsartan in Elderly Isolated Systolic Hypertension (VALISH) [26]	•Prospective, randomized, open-label, blinded-endpoint study of 3260 ambulatory patients from 460 centers in Japan with sitting SBP 160–190 mmHg and DBP < 90 mmHg	•Age inclusion criteria, 70–84 years •Mean age, 76.1 years	•Mean BP in strict control BP group 136.6/74.8 mmHg vs. 142.0/76.5 mmHg in moderate BP group. •No difference in the primary composite outcome of sudden death, fatal and nonfatal stroke, fatal and nonfatal MI, HF death, other CV death, unplanned hospitalization because of

Table 3 (continued)

Trial	Study design	Age	Results
	•Patients randomized to strict BP control (SBP) < 140 mmHg or moderate BP control (SBP < 150 mmHg) with valsartan used as first step therapy •Median follow-up 3.1 years		CV diseases, renal dysfunction between strict and moderate BP control (3.04% vs. 3.39%). •Study underpowered with less than 50% observed incidence of primary endpoints as expected
Systolic Blood Pressure Intervention Trial (SPRINT-Senior) [27••]	•Pre-specified subgroup analysis of 2636 community-dwelling patients ≥ 75 years of age enrolled in SPRINT •Patients randomized to intensive treatment group (SBP < 120 mmHg) vs. standard treatment group (SBP < 140 mm) •Trial terminated early (median follow-up 3.14 years in subgroup of patients ≥ 75 years of age) due to ethical reasons	•Age inclusion criteria, ≥ 75 years •Mean age, 70.9 years	•Mean SBP in intensive group 123.4 mmHg vs. 134.8 mmHg in standard group. •Intensive BP control decreased the primary composite outcome of nonfatal MI, ACS not resulting in a MI, nonfatal stroke, nonfatal acute decompensated HF, and death from CV causes (34%), all-cause mortality (33%), primary outcome plus all-cause mortality (32%), and HF (38%) •Exploratory analysis by frailty level and gait speed favored intensive treatment group

ACS, acute coronary syndrome; *BP*, blood pressure; *CV*, cardiovascular; *DBP*, diastolic blood pressure; *HCTZ*, hydrochlorothiazide; *HF*, heart failure; *MI*, myocardial infarction; *RCT*, randomized controlled trial; *SBP*, systolic blood pressure; *TIA*, transient ischemic attack

However, there was no significant increased risk of serious adverse events (48.4% vs. 48.3%; $p = 0.90$). Also, while numerically higher, there was also no significant increased risk of hypotension (2.4% vs. 1.4%, $p = 0.066$), syncope (3.0% vs. 2.4%, $p = 0.401$), electrolyte abnormalities (4.0% vs. 2.7%, $p = 0.058$), or acute kidney injury or acute renal failure (5.5% vs. 4.0%, $p = 0.061$), although the lack of statistical significance of these outcomes may be due to lack of power. Therefore, SPRINT-Senior demonstrated that more intensive BP lowering in the very elderly decreases not only the risk of adverse CV outcomes but also the risk of death and is generally well tolerated.

Another noteworthy aspect of SPRINT was a pre-planned study to assess the effects of intensive BP lowering on the risk of dementia, cognitive dysfunction, and cerebral small vessel ischemic disease [30]. Results of the SPRINT Memory and Cognition IN Decreased hypertension (SPRINT MIND) study found that while intensive BP lowering did not result in a statistically significant reduction in the primary outcome of adjudicated probable dementia, it was associated with a reduced risk of mild cognitive impairment (MCI; 19%, $p = 0.01$) and MCI plus probable dementia (15%, $p = 0.02$) [31•]. The lack of a statistically significant reduction in the primary cognitive outcomes was likely due to the short period of follow-up, as the primary study was terminated early and there were fewer cases of dementia than expected. Results from a sub-study of 454 patients who underwent follow-up magnetic resonance imaging presented at the 2018 Alzheimer's Association International Conference found that intensive BP lowering was associated with a significantly smaller increase in white matter lesion volume and a smaller decrease in total brain volume [32]. Both white matter lesions volume and total brain volume are markers associated with the risk of vascular dementia and risk potential risk of Alzheimer's Disease. While the preliminary results of SPRINT MIND and potential implications are significant, longer-term studies are needed to definitively demonstrate that more intensive BP lowering reduces the risk of dementia. Intensive BP lowering could be the first disease-modifying intervention to demonstrate reduced risk of MCI and dementia, which are expected to grow significantly in the coming years due to the growth in the aging population.

Conclusion

Hypertension is widely prevalent in older patients, with most developing high blood pressure as they advance in age. The pathophysiology of hypertension and response to drug therapy change with aging, with the majority developing isolated systolic hypertension. Older patients have a higher risk of hypotension and adverse effects of treatment compared with younger hypertensive individuals. Out-of-office measurements can be beneficial to assess patients with, or at risk for, high blood pressure, and monitoring of therapy. Data from well-done randomized controlled trials have unequivocally demonstrated that treating high blood pressure, even in the very elderly, decreases the risk of adverse cardiovascular events. In addition, data are emerging that more intensive blood pressure goals may decrease the risk of dementia. However, hypertension trials in older adults that have been performed to date included ambulatory, community-dwelling patients, and there is significant variability in phenotypes and differences in patients' physiologic vs. chronologic age. Part 2 of this review will address the individualized approach to treating hypertension in the elderly, with considerations provided when assessing the potential treatment benefit, severity of hypertension, and risk of adverse effects across various elderly phenotypes.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017;389(10064):37–55.
2. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310(9):959–68.
3. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, et al. Potential U.S. population impact of the 2017 ACC/AHA high blood pressure guideline. J Am Coll Cardiol. 2018;71(2):109–18.
4. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–23.
5. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation. 1997;96(1):308–15.
6. O'Rourke MF. From theory into practice: arterial haemodynamics in clinical hypertension. J Hypertens. 2002;20(10):1901–15.
7.• Lv YB, Gao X, Yin ZX, Chen HS, Luo JS, Brasher MS, et al. Revisiting the association of blood pressure with mortality in oldest old people in China: community based, longitudinal prospective study. BMJ. 2018;361:k2158. **In this large cohort of 144,403 participants aged 80 years and older, systolic blood pressure trajectories showed an accelerated decline in the last 2 years of life which did not appear due to intensification of antihypertensive therapy. This suggests that epidemiological associations of low systolic BP with higher mortality may be due to reverse causation bias.**
8. Delgado J, Bowman K, Ble A, Masoli J, Han Y, Henley W, et al. Blood pressure trajectories in the 20 years before death. JAMA Intern Med. 2018;178(1):93–9.
9. Ravindrarajah R, Hazra NC, Hamada S, Charlton J, Jackson SHD, Dregan A, et al. Systolic blood pressure trajectory, frailty, and all-cause mortality >80 years of age: cohort study using electronic health records. Circulation. 2017;135(24):2357–68.
10. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):e13–e115.
11. Messerli FH, Ventura HO, Amodeo C. Osler's maneuver and pseudohypertension. N Engl J Med. 1985;312(24):1548–51.
12. Tsapatsaris NP, Napolitana GT, Rothchild J. Osler's maneuver in an outpatient clinic setting. Arch Intern Med. 1991;151(11):2209–11.
13. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci. 2011;161(1–2):46–8.
14. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. Am J Med. 2007;120(10):841–7.
15. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol. 2017;264(8):1567–82.
16. Bulpitt CJ, Beckett N, Peters R, Staessen JA, Wang JG, Comsa M, et al. Does white coat hypertension require treatment over age 80?: results of the hypertension in the very elderly trial ambulatory blood pressure side project. Hypertension. 2013;61(1):89–94.
17. Cacciolati C, Hanon O, Alperovitch A, Dufouil C, Tzourio C. Masked hypertension in the elderly: cross-sectional analysis of a population-based sample. Am J Hypertens. 2011;24(6):674–80.
18. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA. 1967;202(11):1028–34.
19. Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial. Lancet. 1985;1(8442):1349–54.
20. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet. 1991;338(8778):1281–5.
21. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265(24):3255–64.
22. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) trial investigators. Lancet. 1997;350(9080):757–64.

23. JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res 2008;31(12):2115–2127.

24. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887–98.

25. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet 2009;374(9689):525–533

26. Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension 2010;56(2):196–202.

27.•• Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA. 2016;315(24):2673–82. **This pre-planned analysis of patients ≥ 75 years of age that were enrolled in SPRINT found that an intensive SBP goal of < 120 mmHg decreased the primary cardiovascular composite outcome as well as all-cause mortality compared with the standard SBP goal of < 140 mmHg in ambulatory, community-dwelling seniors.**

28. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20.

29. Wright JT Jr, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. Ann Intern Med. 2014;160(7):499–503.

30. Sprint Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.

31.• SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA. 2019;321(6):553–61. **This sub-study of SPRINT found that treating to an intensive SBP goal of < 120 mmHg was associated with a decreased risk of mild cognitive impairment and the combined rate of mild cognitive impairment or probable dementia. While there was no decrease in the primary cognitive outcome of adjudicated dementia, it is important to note that this outcome was likely underpowered as SPRINT was stopped early and there were fewer cases of dementia than expected.**

32. Nasrallah IM, Pajewski NM, Auchus AP, Chelune G, Cheung AK, Cleveland ML; 2 SPRINT MIND Investigators for the SPRINT Research Group. Association of intensive vs standard blood pressure control with cererbral white matter lesions. JAMA 2019;322(6):524–534.