Current Hypertension Reports (2019) 21: 83
https://doi.org/10.1007/s11906-019-0988-x

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

From Clinical Trials to Bedside: the Use of Antihypertensives in Aged Individuals. Part 2: Approach to Treatment

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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 considerations for the individualization of treatment. In Part 2, we discuss the individualized approach to treating hypertension in the elderly.

Recent Findings Achieving lower blood pressure goals in older adults has the potential to increase risks for complications such as hypotension and acute renal insufficiency, especially in those less healthy. Because elderly exhibit many different phenotypes, a one-size-fits-all approach to treatment goals and choice of antihypertensives is problematic. Many areas of uncertainty remain, including what the optimal goal blood pressure should be in frail or institutionalized elderly, whether there is an upper age limit for treatment initiation where benefits and risks overlap, and when de-escalation of antihypertensives should be considered.

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. Areas of uncertainty in the management of hypertension in this group mandate a cautious, individualized approach to treatment which relies on careful assessment of biologic or phenotypic age, rather than chronologic age alone.

Keywords Hypertension · Elderly · Antihypertensive agents · Aged

Introduction

The management of hypertension in older adults presents a myriad of challenges for clinicians because there have been limited studies conducted in populations of advanced aged; of those performed, most have included only those individuals residing in the upper ranges of good health. However, aging results in a varied spectrum of phenotypes ranging from robust to frail, and the approach to management of hypertension in older individuals must bear this in mind.

Part 2 of this review will focus on the personalization of antihypertensive use in individuals of advanced age. As in Part 1, this review is written with attention to the biologic or phenotype of the aged hypertensive rather than restricted to exclusive chronological age categorizations. The terms "elderly," "aged," and "older" persons may be mixed interchangeably, as the interface of chronologic age and biological function exists on a continuum. In general, many of the issues addressed in this review will be encountered in those aged

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

For additional background information on this topic, the reader is referred to the accompanying prior manuscript, "From Clinical Trials to Bedside: the Use of Antihypertensives in Aged Individuals. Part 1: Evaluation and Evidence of Treatment Benefit."

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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 goals and therapy is most necessary.

Guidelines—"There to Guide, Not to Mandate"

Contemporary high blood pressure guidelines from the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology/European Society of Hypertension (ESC/ESH) outline recommendations for treatment in older patients. The 2017 ACC/AHA guideline recommends a systolic BP goal of < 130 mmHg in older (≥ 65 years), non-institutionalized, community-dwelling patients, with no upper limit in age [1]. The 2018 ESC/ESH guideline recommends a SBP goal of 130–139 mmHg and DBP of < 80 mmHg if tolerated in patients > 65 years of age [2].

While both guidelines recommend lower SBP goals than have traditionally been used, there is also an emphasis in both regarding the need to individualize therapy. The ACC/AHA guideline specifically recommends that in older patients with a limited life expectancy and high level of comorbidity, clinician judgment, patient preference, and a team approach to weighing are needed when determining the intensity of treatment [1]. Likewise, the ESC/ESH guideline also recommends a potential relaxed BP goal in some patients. While relaxed goals may be considered in older patients, particularly those who are very frail or institutionalized, it is important to recognize that any amount of BP lowering is likely to be helpful in reducing CV events [2].

Treatment Approaches—Population Versus Individual Considerations

The benefits of treating elevated blood pressure, even at advanced ages, are well documented (Table 3, in Part 1). As SPRINT is considered widely representative of community-dwelling older adults [3], with a sizable proportion of those community-dwelling aged 75 and older fitting SPRINT entry criteria, evaluation of the hypertensive older person should begin with this key trial as a frame of reference. However, as with many conditions of aging, the management of hypertension in the elderly should not be defined by a "one-size-fits-all approach," because there is distinct phenotypic heterogeneity in the group. Absolute versus relative benefits of treatment differ across individuals, and while treatment may provide relative benefit overall in a population of individuals enrolled in the clinical trial, absolute benefit may be much smaller and the average individual may not benefit (or could be harmed) [4]. This paradox underscores the need for individualization of treatment decisions when data from clinical trials are generalized into the real world.

Geriatric decision-making is an inherently individualized process, and amalgamating evidence-based guidelines with good clinical reasoning should form the backbone of an overall sensible approach to using antihypertensives in older adults. In general, the potential benefits of a treatment will increase as the severity of the disease increases; however, because more treatments are often required in more severe disease, and addition of treatments may amplify risk of adverse effects, the risk/benefit ratio can narrow quickly. The underlying health status of the individual can further alter this dynamic between treatment and harm. For example, frailty is a phenotype defined by multiorgan decreased functional reserve with increased vulnerability to stressors and is often observed in older adults who also have hypertension. Several observational studies have reported higher mortality in frail older hypertensive adults treated to lower blood pressures [5, 6]. In contrast, an estimated one-third of those aged 75 and older in SPRINT met criteria for frailty, along with substantial prevalence of mild cognitive impairment; and yet, clear reductions in cardiovascular events occurred in this subgroup [7••]. A frailty index has also been applied to the HYVET study cohort, which concluded that the benefit of treatment was not diminished in frail individuals [8], although the overall prevalence of frailty was low in this trial.

Figure 1 shows a conceptual model of the potential risk/benefit of treatment of hypertension by disease severity and three different aging phenotypes. Aged individuals who are otherwise healthy, ambulatory, community-dwelling, and free of dementia or disability and independent in their activities of daily living should be treated similarly to their younger counterparts whenever possible. The likelihood of adverse events remains small across all levels of disease severity, and the risk remains justifiable, with a high ceiling for benefit of treatment across disease severity. Close monitoring is essential to avoiding or minimizing the impact of adverse events and maximizing the potential for treatment benefit. In contrast, frail, hospitalized individuals may have less potential benefit, with benefits possibly annulled by higher risk for adverse events. In these individuals, treatment should still occur but potentially less intensively (e.g., SBP goal of < 150 mmHg or < 140 mmHg if tolerated).

It should be acknowledged that elderly individuals may not always rank quantity above quality of remaining life, especially if prolonging life comes at the expense of greater disability [9]. Despite lower cardiovascular events in SPRINT, functional outcomes of gait speed and mobility were similar but with more adverse events (hypotension, syncope, electrolyte abnormalities, and acute kidney injury) as previously noted in the intensively treated group [10]. Clinical trials in hypertensive elderly should consider these geriatric-relevant endpoints in

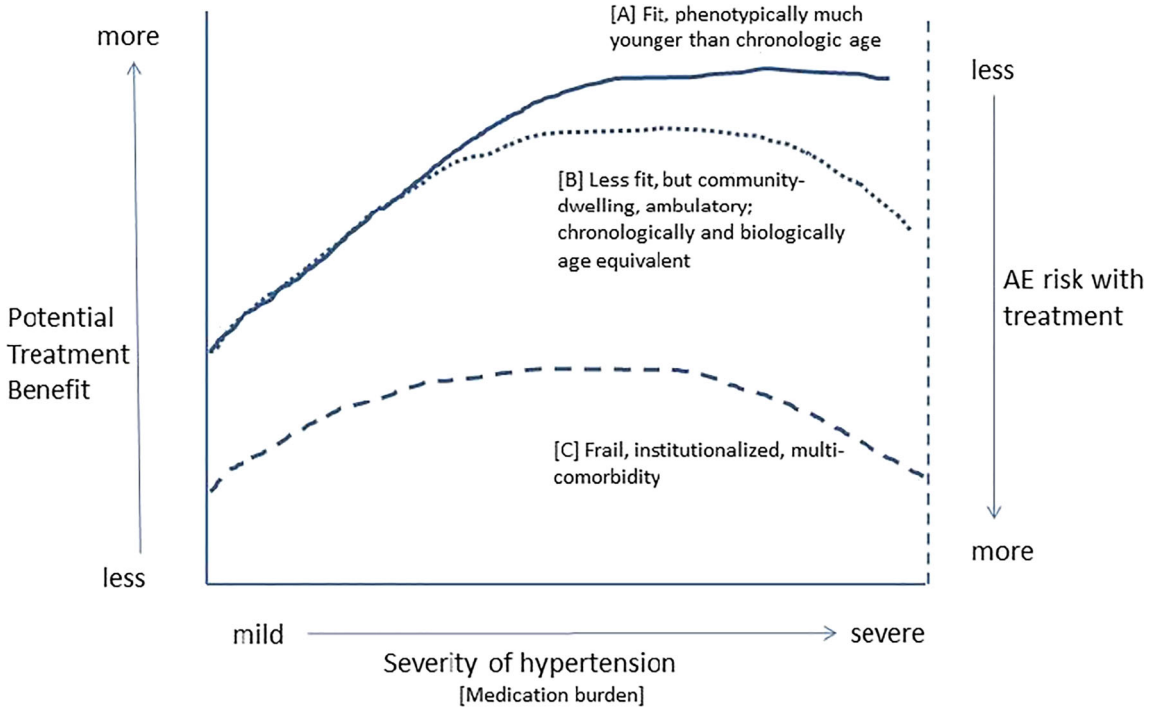

Fig. 1 Conceptual model for evaluating potential risk/benefit of antihypertensive use in elderly. Although older individuals present a continuum of health phenotypes, potential risk/benefit of antihypertensive treatment is presented across 3 distinct phenotypes: **[A]: Fit**—these individuals are the most robust of the elderly (top 10–20%). Phenotypically, they are much younger than their chronologic age indicates. They are otherwise healthy, free of major illnesses, community-dwelling, ambulatory individuals without disability. They maintain significant homeostatic reserve, can respond adequately to physiologic stressors, and are on the highest spectrum of function. Treatment in these individuals is of benefit across the severity spectrum of hypertension, and risk of adverse effects remains low. Risk of adverse effects may even diminish over time, likely due to survivor bias (i.e., those remaining on antihypertensives are a selected group who remain free of adverse events despite the addition of more medication to treat more severely elevated blood pressure). **[B]: Less Fit, or "pre-frail"**—these individuals represent the "average" or majority (50%) of older individuals. They are phenotypically equivalent to their chronological age. They are community-dwelling, ambulatory, free of significant illness that would limit their lifespan to < 5 years, but they have some comorbidities, some medication burden, and possibly some relatively minor disability. They maintain homeostatic reserve, although response to stressors is less robust. Treatment in these individuals is generally beneficial across the severity spectrum of hypertension, and risk of adverse effects remains low except for more severe disease whereby medication burden increases risk of adverse events and may cause diminishing returns as the homeostatic reserve is perturbed and eventually exhausted. **[C]: Frail**—these individuals are in the lower 20–25% relative to their peers. They have diminished capacity, may be institutionalized or require assistance for activities of daily living, and harbor significant comorbidity burden. Treatment of these individuals will likely provide marginal benefit, due to the impact on other comorbidities and their overall shortened remaining life expectancy relative to the time needed to observe benefits of treatment

addition to specific hard outcomes. Regardless of whether prospective, or post hoc, outcome data are available from randomized trials, risk/benefit as it relates to the quantity and quality of remaining lifespan should always be carefully considered when approaching goals of treatment in the geriatric hypertensive patient.

Antihypertensive Medication Selection in the Elderly

Together, the shifting lifestyle patterns and pathophysiologic changes which predispose older adults to development of hypertension can also influence response to antihypertensive medication. Population-level approaches to the selection of antihypertensives, such as the modified Cambridge "AB/CD" method, are pathophysiologically grounded in this notion and advocate for vasodilator drugs such as calcium channel blockers and volume drugs like diuretics ("C/D") as preferred treatments of hypertension in older persons [11]. These approaches reflect the observation of decreased renin levels in older individuals and the possibility of decreased responsiveness to agents blocking the renin-angiotensin system when used as monotherapy. Likewise, older adults exhibit greater salt sensitivity, suggesting they may respond better to volume-mediating drugs like diuretics. Table 1 summarizes the classes of antihypertensives and geriatric specific considerations for their use. Discussed below are some additional considerations when approaching the use of antihypertensives in the elderly.

Single Agent Versus Combinations

Although it is important to consider the underlying pathophysiology contributing to hypertension in older adults,

Table 1 Pearls for antihypertensive use in older adults

Drug class	Geriatric pearls	
	Conditions potentially benefited	Conditions potentially harmed
Renin-angiotensin system blockers (ACEi/ARB)	Diabetes, heart failure, chronic kidney disease	Hyperkalemia, renal insufficiency
Beta blockers	Ischemic heart disease, heart failure	COPD, bradycardia
Diuretics (thiazide and loop)	Edematous states; high sodium intake	Gout, uropathy may worsen, hyponatremia, hypokalemia, hypomagnesemia, falls (loops)
Diuretics (potassium-sparing)	Correct underlying cause of hypokalemia; less gastric irritation than supplemental potassium chloride	Hyperkalemia (especially in the setting of chronic kidney disease, concurrent NSAIDs, or hypoperfusion)
Calcium channel blockers	Tachyarrhythmias, angina	Constipation
Peripheral alpha-1 blockers	Benign prostatic hyperplasia	Fluid retention, hypotension, falls
Centrally acting agents	Resistant to other antihypertensives	Sedation, dry mouth, confusion, dementia
Arteriolar vasodilators	Heart failure	Fluid retention; drug-induced lupus (hydralazine)

contemporary guidelines recommend any of the four major classes of antihypertensives as initial therapy [1, 2]. More importantly, because most individuals will require more than one antihypertensive to achieve their goal blood pressure, stepped care approaches (initial therapy, titrated to moderate/maximal dose, followed by addition of a second agent) have yielded to recommendations to initiate with combination therapies targeting multiple mechanisms of action for most individuals. While this is a reasonable strategy in otherwise healthy elderly, and can be accomplished thanks to a number of readily available, low-dose combinations, the desire to achieve simplicity and begin with single agent antihypertensive is still a reasonable approach, especially in less healthy elderly or the very elderly. Forthcoming adjustments to a low-dose combination product when a second agent is needed can then occur. In either case, given the risk of adverse events with increased doses for most agents, the addition of a second agent should occur when the first agent is at a low-moderate dosage as opposed to escalating to a maximal dosage.

One potentially promising strategy, but needing more study in elderly patients, is the use of ultralow-dose combinations of several agents (i.e., a "polypill" or "quadpill"). Studies have evaluated the safety and efficacy of initial therapy with these combinations but have been limited primarily to younger populations [12, 13]. Efficacy appears to be even greater than the individual agents themselves, at minimal risk of adverse effects. However, the lack of commercial availability and the need for investigation in older cohorts make it unlikely this strategy will be adopted in the immediate future.

Dosing

When initiating antihypertensives in older persons, it is important to start with the lowest available strength for most elderly patients. Aging baroreceptors lead to hemodynamic response that may be inadequate to buffer significant drops in blood pressure [14], thus contributing to orthostasis and increased risk of falls. Furthermore, if the tablet can be halved, it should be considered for those who are frail, who have postural instability, or who already have significant medication burden. Doses can be gradually titrated every 2–4 weeks up to a moderate dose; although consideration can be made to maximize the dose (in order to minimize tablet burden), the best balance for efficacy and adverse effects is generally at the low-moderate dose. Thus, there should be strong consideration to adding an agent with a complementary mechanism of action once the initial agent is in the mid dose range.

Monitoring

All antihypertensives require close monitoring in the elderly, not just those associated with a need for specific laboratory monitoring of electrolytes and renal function. This is true for both efficacy and adverse effects. Patients should have their blood pressure rechecked by a healthcare professional within 2 weeks of initiation of treatment, escalation of dose, or intensification of the regimen. As discussed previously, home blood pressures should be obtained if possible, or other outside readings if the patient resides in assisted living or nursing home. Patients should be queried about possible side effects of the medication, and attention paid to the impact of antihypertensive use on their overall quality of life.

Compelling Indications

As with younger individuals, consideration must be made in choosing agents for which there are compelling indications that may benefit from the antihypertensive class chosen. Some examples include ACE inhibitors or ARBs for those with heart failure with reduced ejection fraction, or chronic kidney disease, and beta blockers for those with established coronary artery disease. Concern for polypharmacy and

overtreatment should not lead to undertreatment of otherwise healthy older individuals. Although not necessarily compelling indications, it is also beneficial to select antihypertensives that may have favorable effects on other comorbidities of the patient, in an attempt to keep the medication burden low. Examples include peripheral alpha-1 blockers for men with benign prostatic hyperplasia and non-dihydropyridine calcium channel blockers for those with tachyarrhythmias.

Contraindications

Contraindications to medication use can be absolute or relative. Absolute contraindications are reasonably obvious, but the more common and challenging situations involve relative contraindications because they are subjective and depend on an individualized assessment of potential risk/benefit of the therapy. A prime example related to antihypertensive use in the elderly is the case of thiazide diuretics in patients with a history of gout or uropathy. Elderly individuals generally respond well to thiazides, but the increase in uric acid may precipitate a gout attack. Likewise, lower urinary tract symptoms may be worsened by the increased diuresis. If the patient is already on uric acid–lowering therapy, then the thiazide is probably okay. If they have a history of gout flares, consideration should be made for an alternate agent, especially in the absence of a recent uric acid level to gauge the potential risk. A similar risk-benefit assessment should occur with regard to the severity of the uropathy symptoms.

Antihypertensives to Avoid (Mostly)

Because of more pronounced adverse effects, several antihypertensive classes should be avoided in the outpatient setting in most elderly as the risk/benefit is much narrower. Examples include central alpha agonists (dry mouth, sedation), direct arteriolar vasodilators (e.g., hydralazine—fluid retention and risk of lupus-like syndrome), alpha-1 receptor blockers (orthostasis, falls), and loop diuretics (falls), unless needed for underlying conditions.

Antihypertensives as Part of a Comprehensive Cardiovascular Risk Factor Approach

Cardiovascular risk factors do not exist in silos, so it is important to remember to address other risk factors simultaneously in older patients. In some cases, one might be less aggressive with blood pressure targets if it means balancing medication burden with treatment of other conditions. Alternatively, the failure to control important risk factors such as diabetes, or inability to tolerate statins, may be situations where intensifying blood pressure goals could yield more substantive benefits to offset the lack of control of the other risk factors. More research is necessary to evaluate this potential approach.

A Practical Approach to Blood Pressure Thresholds and Treatment Goals in Elderly—"Ceilings and Floors"

With ongoing debate about the target blood pressure in older persons, it should be noted that the magnitude of benefit in lowering blood pressure is generally determined by how elevated it is to begin with and the degree of difference achieved with treatment [15•, 16, 17]. Absolute benefit likely decreases the lesser the elevation is to begin with (i.e., there is greater benefit in lowering from systolic 170 down to 140 mmHg than from 140 to 130 mmHg). Thus, not all elderly need to get systolic blood pressure to < 130 mmHg to receive any benefit of treatment. This is an important consideration when balancing treatment decisions in the context of other comorbidities and deciding whether to add that next drug or intensify doses.

One way to operationalize the notion of specific blood pressure targets in older persons is to consider whether the targeted blood pressure is a "ceiling" or a "floor." If it is a floor, then the goal is to get down to it, but if it is a ceiling, then the goal is to get down and stay below it as much as possible. For some individuals depending on their phenotype, 130 mmHg may be a ceiling, and for others, a floor.

In otherwise healthy elderly, a blood pressure threshold for treatment of 140 mmHg is sensible, with a target goal blood pressure of < 130 mmHg (as a ceiling in otherwise healthy—e.g., phenotype A in the figure; and a floor for phenotype B). Likewise, < 150 mmHg may be the goal (as a ceiling) in less healthy elders, and < 140 mmHg as a floor.

Remaining Uncertainties in Management

Prospective hypertension intervention studies conducted in elderly cohorts have answered important and yet a limited scope of questions. Given the heterogeneity of aging and the commonality of hypertension in the aged group, clinicians will undoubtedly continue to face additional relevant questions for which they need to use good clinical reasoning. Some of these questions are highlighted below.

Is there an upper age limit for initiation of treatment where benefit will likely be observed during remaining life expectancy?

There may be an upper age limit for initiation of treatment, but there is little research evidence to evaluate this. Antihypertensive treatment has shown benefit across a wide spectrum of ages in meta-analysis of trials [14, 15•, 16]. Age thresholds are undoubtedly unique to each individual and should be based on overall functional assessment and biological age, not just chronological age. Remaining life expectancy at any specific point in one's age can be derived from population models but is a discrete outcome that does not

factor overall function. Likewise, having a systolic blood pressure of 145 mmHg not on treatment may not confer the same risk as someone who needs multiple medications to have the same blood pressure level.

How much emphasis should blood pressure receive in elders hospitalized for other reasons (e.g., urosepsis with delirium), and when should antihypertensives be reintroduced (and how intense, especially if the hospitalization included an acute kidney injury)?

In contrast to healthy community-dwelling elders, there appears to be little evidence to support intensive blood pressure in hospitalized patients. It is reasonable to target < 150–160 mmHg, and consider slow reintroduction as the condition improves in those who had antihypertensives held, and reassessment of the maintenance regimen in the outpatient setting.

What is the optimal goal blood pressure in frail older adults, such as those in nursing homes, or with significant cognitive impairment?

In individuals with limited remaining life expectancy, the risks of overtreatment with antihypertensives must be guarded against. Goals of care as they relate to aggressiveness of treatments are important to establish in this setting of competing disease risks, and there may be a need to lessen the focus on achieving a specific goal BP but rather a strategy to avoid the highest readings. In general, when treatment is desired, a goal SBP of < 150 mmHg is likely reasonable for many; if tolerated and consistent with treatment goals, it may be advanced to < 140 mmHg.

When should clinicians consider de-escalation of antihypertensives?

When to de-prescribe is a challenging question. Close monitoring is necessary in those individuals with progression of frailty or multimorbidity. If a patient is clearly being harmed by their antihypertensives, then they should be reduced. If there is significant progression of frailty or multimorbidity, it may be prudent to de-escalate treatment and goals with closer monitoring, in an attempt to avoid future problems, minimize medication burden, and preserve the best obtainable quality of life under the circumstances.

Conclusion

Hypertension trials including significant proportions of elderly have collectively demonstrated the benefits of lowering blood pressure to reduce cardiovascular events. For many otherwise healthy older persons, these benefits come at minimal increased risks of treatment. Contemporary guidelines have shifted thresholds lower for both the initiation of treatment and optimal targets, including in the ambulatory community-dwelling elderly. There are challenges to adoption of strict thresholds for treatment and goals across the entire spectrum of geriatric individuals, including undesired effects on comorbidities, adverse effects of the drugs, and medication burden. Because of wide variance in geriatric phenotypes related to functional ability, a number of questions remain that will not likely be answered by data from randomized trials. The presence of these factors necessitates a cautious, personalized approach to treatment that balances available evidence and clinical reasoning. Use of antihypertensives in aged individuals epitomizes the personalization required of geriatric pharmacotherapy.

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.

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