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Hypertension in the elderly

Ipertensione nell'anziano

Giuliano Pinna^{a,*}, Claudio Pascale^a, Micaela La Regina^b,
Francesco Orlandini^b

^a Ospedale Cottolengo, Torino

^b Ospedale S. Andrea, Presidio Unico del Levante Ligure, La Spezia

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KEYWORDS

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Summary

Introduction: There is a high prevalence of hypertension in the elderly, as evidenced by clinical and health behavioral policies. Still, there are uncertainties on the treatment of hypertension, especially treatment of the very elderly. These considerations have largely been ignored in clinical trials due to concern regarding contamination by other pathologies that are difficult to frame and manage.

Methods: We performed an effective and ample literature review and provided reflections on the Consensus Conference ACCF/AHA 2011 on the principle types of hypertension found in the elderly. We also considered the associated principle pathologies for various treatments and related organs.

Discussion: Even if the goal of treatment of elevated blood pressure in the elderly is same as in younger population, it is no longer certain that a target systolic blood pressure (SBP) <140 mmHg should be persistently reached in the very elderly. It is important to note that for all studies these values have never been reached. In the treatment of isolated systolic hypertension (ISH) the preferred target is a SBP >160 mmHg. Treating hypertension in the elderly and very elderly reduces the risk of stroke and heart failure, though the evidence is inconclusive for all-cause mortality.

Conclusion: Hypertension in the elderly is very common and needs to be treated with criteria that consider the patient's age, comorbidities, lifestyle and adherence.

Above all, in the very elderly, therapeutic treatment should be personalized according to the above criteria. Where possible pharmaceutical therapy should be limited at the preference of healthy lifestyle changes (physical activity, diet, etc.).

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* Corresponding author: Via Bertola 86 - 10122 Torino, Italy.
E-mail: giuliano.pinna@gmail.com (G. Pinna).

Introduction

In industrialized countries, the mean age of the population is rapidly increasing. Likewise, the prevalence of high blood pressure (HBP) is also on the rise: 60% of people older than 60 years of age and 65% of men and 75% of women older than 70 have HBP [1]. These data are especially important, considering that HBP is the primary cardiovascular risk factor in elderly adults and is even stronger than hypercholesterolemia and diabetes [2]. Although there is great interest in this topic, both in the clinical and public policy settings, there are no certainties about treatment in elderly adults, and especially in the very elderly. These patients are often ignored by large clinical trials because they have multiple medical comorbidities and are difficult to manage.

Epidemiology

In the Framingham Heart Study (FHS), 90% of subjects who had normal blood pressure (BP) at age 55 subsequently developed hypertension [3]. According to ACCF/AHA Consensus Conference (2011) data, from 1995 to 2005 hypertension-related deaths increased by 25.4% in the US, due to aging of the population and an increasing prevalence of hypertension in the elderly [4]. Surprisingly, there are more Europeans with HBP than North Americans, according to a multicenter study of 6 industrialized countries across two continents [5]. Among European countries, Germany has the highest rates of HBP and Italy has more intermediate rates (Fig. 1). In Italian epidemiological studies conducted on people over 65 years of age, HBP prevalence varied from 67% (the ILSA study dating as far back as 1997) [6] to 72% (ICAR and Dicomano Study) [7] and up to 80% in older samples. These studies used a cutoff of 140 mmHg according to guidelines (CASTEL study) [8].

Pathophysiology

Somewhere around 50 and 55 years of age, systolic blood pressure (SBP) begins to increase while diastolic blood pressure (DBP) decreases (Fig. 1). With aging, large arteries develop important changes. Arterial walls stiffen because of the diminution of elastin and non-extensible collagen content along with an increase in afterload. The result is an increase in pulse wave velocity (PWV), which causes an increase in SBP and enhanced demand for myocardial oxygen. In the meantime, DBP decreases. During systole, large arteries distend with blood as their elastic walls stretch. During diastole, the walls rebound, propelling the blood. In this way, the arteries act as a pressure reservoir that maintains a constant flow of blood through the capillaries despite pressure fluctuations during the cardiac cycle. With aging, arterial stiffness increases causing an increase in SBP and DBP decreases because of the lack of arterial elasticity.

In elderly people, during the blood pressure cycle, reflected waves come back to the heart early causing a systolic peak, with an increase in SBP called the "augmentation index". The area under the curves, or the mean blood pressure (MBP), for younger and older people is equal, but the SBP and pulse pressure (PP) are higher while the DBP is lower in elderly subjects (Fig. 2) [9]. Increased PP is a strong coronary risk factor in elderly adults, even more so than SBP, DBP and MBP [10]. Stiffening of the arterial wall is due to altered endothelial activity, diminished flow-mediated arterial dilation, and an altered neuro-hormonal profile. The altered neuro-hormonal profile produces autonomic dysfunction [4], which results in orthostatic hypotension (with an associated risk increase for falls and syncope) and relevant cardiovascular risk factors. Kidney involvement occurs via progressive nephroangiosclerosis. It is important to stress that these changes are not physiological. The so-called "normal aging changes" of arteries are more commonly

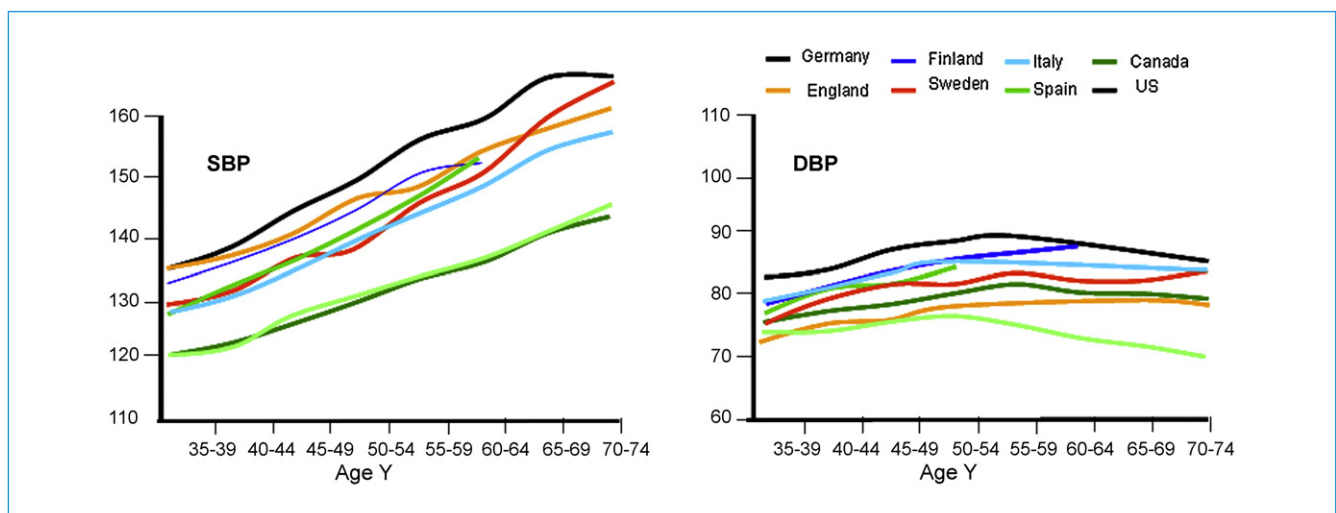


Figure 1 Mean systolic and diastolic blood pressures in 6 European and 2 north American countries, men and women combined, by age. Modified from Wolf-Maier, K. et al. [5].

Wolf-Maier, K. Cooper S, Banegas JR, Giampaoli S, Hense HW, Joffres M et al. Hypertension prevalence and blood pressure levels in 6 european countries, Canada, and the United States. JAMA 2003; 289:2363-2369.

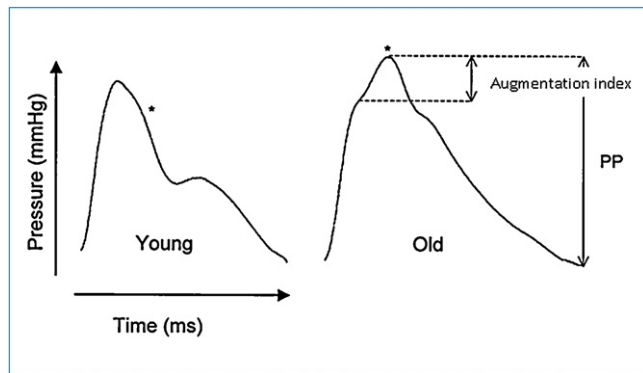


Figure 2 Traditional aspects of the shape of the aortic blood pressure curve in young (<64 years) and old (>65 years) subjects. Modified from Safar [9].

Safar ME. Systolic hypertension in the elderly: arterial wall mechanical properties and the renin–angiotensin–aldosterone system. *J Hypertens*. 2005, 23: 673–681.

found in people who consume high sodium or high calorie diets, are sedentary and are obese [4]. It is also important to take into consideration that, with ageing, comorbidities and organ damage are more common. It was estimated that 69% of patients with myocardial infarction, 77% of those with stroke and 74% of those with heart failure suffered from HBP. In addition, HBP is a major risk factor for the development of diabetes, atrial fibrillation and renal failure [11].

Isolated Systolic Hypertension

Until the 1980's SBP was considered to be less important than DBP as a cardiovascular risk factor. Its relevance was recognized after the publication of the Framingham [12] and MRFIT (Multiple Risk Factor Intervention Trial) studies [13]. After the publication of SHEP [14] and Syst-Eur [15] studies, researchers began to consider it a major cardiovascular risk factor. This finding was emphasized by the JNC 7, which stated “in persons older than 50 years, SBP is a much more important cardiovascular risk factor than DBP” [16]. Isolated systolic hypertension (ISH) is, perhaps, the most peculiar form of hypertension in elderly people. Up to 90% of people over 70 years of age with hypertension have ISH. Coronary blood flow occurs mainly in diastole. Very low DBP inhibits this flow, especially with concomitant coronary disease [17], which is commonly seen in elderly people. The so-called “J-curve phenomenon” describes the increase in cardiovascular deaths associated with decreased DBP, but it is not universally accepted [18]. Elevated PP, a marker of arterial stiffness, is associated with cardiovascular risk, but it is an epiphenomenon and is not in itself responsible for cardiovascular alterations [19]. Race does not seem to affect risk for ISH, but women seem to be more affected [11]. Some suspect that, in the post-menopausal period, changes in estrogen levels increase arterial stiffness [20] and, as a result, risk for ISH. However, this assumption is not universally accepted [21]. Osteoporosis and chronic renal failure, conditions that involve calcification of arterial walls, are associated with ISH [22]. The severity of these conditions and their degree of treatment-resistance correlate with

aortic calcifications. Therefore, these conditions are responsible for ISH and increased PP [23]. The Framingham Heart Study revealed that, after adjusting for age, sex, BMI, diabetes and smoking, subjects with untreated ISH and DBP < 70 mmHg, have a cardiovascular risk that is equivalent to that of people with a SBP of 20 mmHg more and a DBP of 70–89 mmHg [24]. It is also interesting that people with systolic pre-hypertension and a DBP < 70 mmHg have an increased cardiovascular risk. In fact, that risk is similar to the risk of subjects with stage I hypertension and a DBP of 70–89 mmHg [25]. Another finding of the Framingham study was that most people with ISH do not develop essential diastolic hypertension. However people with normal or high-normal blood pressure do develop ISH, mainly due to the different mechanisms involved. Specifically, increased stiffness of the large arteries is responsible for ISH, and increased peripheral resistance is the cause of idiopathic hypertension. A significant minority, approximately 40%, of people with essential hypertension develop ISH. This is due to stiffening of the arteries in the presence of pre-existing increased peripheral resistance, so-called “burned-out” diastolic hypertension [26].

Conditions frequently associated with HBP in elderly people

Alterations in glucose metabolism

It is well known that arterial hypertension and diabetes increase cardiovascular mortality. They are often comorbid, for they share some common pathogenetic factors including insulin-resistance, endothelial dysfunction, generation of reactive oxygen species, sympathetic hypertonia, and RAS hyperactivity. DAI study (*Diabetes and Informatics Study Group, Italian Association of Diabetologists and Italian National Institute of Health*), the longest Italian study on diabetic people (14,4232 subjects) reported a HBP prevalence of 84% in patients with type 2 diabetes [27]. Data obtained from the National Health Nutrition Examination Survey (NHANES, 1999–2006) showed that people with ISH and DBP <70 mmHg had a high cardiovascular risk and a high risk for diabetes [26]. Among elderly people with type 2 diabetes, high SBP (either in the office or during a state of arousal) is an independent predictor of albuminuria. Albuminuria is very common in patients with diabetes who have micro- or macro-vascular damage and an increased risk of death [28]. Diabetes can enhance cardiovascular risk and contributes to arterial stiffness. In fact, people with type 1 diabetes, which is not associated with obesity or hypertension (at least in early stages of the disease), develop ISH about 15 years earlier than people who do not have diabetes [29]. Elderly people with HBP and diabetes have a higher risk of cardiovascular and all-cause mortality than do people who do not have diabetes. This risk is higher than the risk for people with diabetes and hypercholesterolemia and holds true for women and men [27]. The INVEST (INTERNATIONAL Verapamil SR-Trandolapril) study examined a population with a mean age of 66 years. It demonstrated a relationship between blood pressure levels and primary outcomes, which included a composite of occurrence of all-cause mortality, nonfatal myocardial infarction or nonfatal stroke, in a cohort

of adults with diabetes [30]. The ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) study enrolled patients with diabetes on suboptimal therapy who were randomized to receive either combination perindopril and indapamide or placebo. This study reported that the absolute risk reductions for the primary outcome (a composite of major macrovascular and microvascular disease) and for mortality were higher in subjects older than 75 years than in those younger than 65. Furthermore, active treatment was well tolerated in patients older than 75 years [31]. In a discussion of the association between diabetes and hypertension, one cannot ignore the responsibility of some antihypertensive agents, such as diuretics and beta-blockers (BB), which are independent risk factors for diabetes, as shown in the next sections [32]. Despite the common comorbidity of dyslipidemia and hypertension, this association has not been well-studied [33]. If one considers the dangerous increase in cardiovascular risk in the presence of both conditions, one must be very aggressive in treating hypercholesterolemia. Statins, even with their own limits, are the gold standard for treating hyperlipidemia and have a synergistic effect with antihypertensive agents [34].

Obesity

Obesity (BMI >30) is a cardiovascular risk factor and may be associated with increases in left ventricular wall thickness and heart volume and mass, independent of the effects of BP. It is well known obese people experience sympathetic hyperactivity. Additionally, people over 50 years of age have increased plasma norepinephrine, which continues to increase with age. Also, a reduction in baro-reflexes, common in elderly people, can stimulate norepinephrine production [35]. Elderly adults and obese people experience activation of the tissue renin-angiotensin system (RAS), which can contribute to ISH development. Angiotensin II activates inflammation and causes fibrosis, atherosclerosis and organ damage [36].

However, whether obesity worsens the prognosis of elderly adults with hypertension is not clear. An analysis from the INVEST study demonstrated that high BMI was associated with lower morbidity and mortality compared to normal BMI in a well-treated group of elderly adults with hypertension and coronary artery disease (CAD) [37].

Cerebrovascular disease

The relationship between hypertension, especially ISH, and ischemic and hemorrhagic stroke is well known, and treatment of hypertension appears to be effective in reducing the risk of stroke. In the SHEP study [38] (treatment of ISH with chlorthalidone + atenolol or reserpine versus chlorthalidone + placebo), patients in the active treatment group had a lower incidence of ischemic and hemorrhagic stroke compared to placebo (37% and 54%, respectively). Similar results were reported in the PROGRESS study (perindopril + indapamide versus placebo for 4 years) where ischemic and hemorrhagic stroke were reduced by 24% and 50% [39]. The Syst-Eur study (nitrendipine and enalapril and/or hydrochlorothiazide versus nitrendipine + placebo) was stopped after 2 years because of a 42% total stroke

reduction in the active treatment group ($P < 0.003$). In the very elderly, the relationship is less clear. Data for adults ≥ 80 years of age are lacking and mortality endpoints are often less important than quality of life outcomes (for example, myalgia, polypharmacy, cost, etc.).

Dementia

HBP is an important risk factor for atherosclerosis, and it may contribute to the development of vascular dementia. Furthermore, atherosclerosis and narrowing of the arterioles that penetrate the subcortical regions of brain is common. This process can lead to demyelination of subcortical white matter, micro-infarctions and other lesions that cause cognitive impairment. Microvascular brain damage, lesions of the large arteries and changes in crosstalk between large and small arteries are strong risk factors for cognitive deterioration and the development of dementia in older people [40]. Observational studies have reported the presence of chronic ISH with paradoxical BP reduction in the years immediately before dementia development [41]. Frequently, we do not distinguish vascular dementia from Alzheimer's disease, even though they are very different conditions with different pathogenesis. These conditions are only clinically similar during the late stages of disease. A recent Japanese study followed 668 older, community-dwelling Japanese adults without dementia, up for 17 years to examine the association between mid- and late-life hypertension and vascular dementia and Alzheimer's disease. The researchers found that hypertension was an important risk factor for the development of vascular dementia but not for Alzheimer's disease. In particular, mid-life hypertension was associated with vascular dementia, independently of late-life blood pressure [42]. Antihypertensive treatment improves dementia outcomes, though the effect is not very impressive. In the Syst-Eur [43] and PROGRESS studies [39] active treatment reduced the incidence of dementia by 50% and 19%, respectively. The SCOPE study [44], which investigated Candesartan in very elderly subjects, reported a significantly lower incidence of dementia only in a post-hoc analysis of patients that had a minor cognitive impairment at the beginning of the study ($p < 0.04$). In other studies, like the SHEP [38] and HYVET-COG [45] studies, the findings were only slightly significant or not significant at all. In conclusion, although antihypertensive treatment does reduce the risk of ischemic and hemorrhagic stroke, it is not yet clear if a blood pressure reduction, which poses a risk of decreasing cerebral blood flow, is useful in dementia prevention. It may be effective in earlier stages, as shown by the SCOPE and PROGRESS studies.

Cardiac diseases

Coronary artery disease (CAD)

It has been demonstrated that elderly people with hypertension are at higher risk of myocardial infarction (MI). Hypertension is found in most elderly patients with MI and angina. Hypertension may be a risk factor for angina, as it contributes to coronary atherosclerosis and increases myocardial oxygen demand. As we have already pointed out the J curve phenomenon may be relevant. Because coronary blood flow occurs almost entirely during diastole, subjects affected

by coronary artery disease (CAD), may experience an interruption in coronary flow if perfusion pressure drops below 40-50 mmHg (the so called zero-flow pressure). Furthermore, capillary density decreases with left ventricular hypertrophy, a finding typical of long-standing hypertension. This reduction limits coronary auto-regulation, especially in the sub-endocardium. The J curve phenomenon can occur in the setting of antihypertensive treatment. A decrease in blood pressure (particularly a decrease in DBP) can compromise the perfusion of hearts affected by CAD. Patients with low DBP often present with high SBP and high PP, and current guidelines recommend treating ISH [46,47]. The result is a further decrease in DBP that can be dangerous in patients with CAD. We commonly correlate the J curve phenomenon with ISH, but isolated diastolic hypertension can also produce the J curve phenomenon, as the Cardiovascular Health study, which was performed on subjects >65 years of age with a median follow-up >12 years, reported. This study showed that, like ISH, isolated diastolic hypotension is a significant independent risk factor for heart failure among community-dwelling older adults [48]. As we reported above, scientists do not agree on the existence of the J curve. Many believe that elderly patients with a low DBP are already compromised, due to comorbid diseases, diabetes, CAD, cancer, other systemic diseases and age. In other words, a low BP was not the cause of the increased cardiovascular risk in these patients, as their baseline cardiovascular risk was already very high. A large meta-analysis by Wang has provided evidence against the J curve [49]. It included 8 studies of 3 populations of different ages (30-49, 60-79, and >80 years). It concluded that the best outcomes resulted when DBP was lowered to less than 70 mmHg, regardless of SBP or age. They did not observe any differences between the younger and elderly participants in terms of cardiovascular events. However, a follow-up period of 4-5 years may be too short for young study participants and too long for elderly ones. At this point, it is important to mention the last update of the European guidelines on hypertension, based on major trials conducted from 2007 to 2009 [46]. Even with the limitations of post-hoc analyses, those individuals who developed the guidelines noted a progressive reduction in cardiovascular events when SBP is less than 120 mmHg and DBP is less than 75 mmHg. Benefits in terms of organ damage were observed at these blood pressure levels, even though the benefits of further blood pressure reduction have been rather scarce. Thus, the J curve phenomenon is not completely understood, but it likely occurs in patients with advanced atherosclerotic disease. Arterial hypertension is also a risk factor for sudden cardiac death. ECG and US scans showing left ventricular hypertrophy (LVH) are predictive of this outcome [50]. Nevertheless, antihypertensive treatment reduces the incidence of sudden cardiac death in the elderly [51].

Heart failure (HF)

Hypertension can lead to heart failure through different, though often overlapping, mechanisms, such as LVH, impaired left ventricular (LV) filling, and increased wall thickness. These factors are more common, especially when diabetes, obesity, atrial fibrillation, and CAD coexist. In the elderly, older age and hypertension lead to stiffening of the

arteries. Initially, this is the result of impaired systolic and diastolic cardiac reserve and impaired sensitivity to catecholamines. Left ventricular dilation occurs only at later stages. Therefore, in elderly adults with hypertension, we can observe HF with decreased or preserved LV function. In this latter case, HF can be attributed to impaired diastolic function [4].

Atrial fibrillation (AF)

Atrial fibrillation is a common dysrhythmia in elderly adults, with a prevalence of 10% in 80-year-olds [52]. Hypertension, HF, obesity and diabetes are all major risk factors for AF. A well-controlled BP is associated with low incidence or recurrence of AF in people affected by HBP. In the STOP study [53], ACE-inhibitors (ACEIs) and calcium-channel blockers (CCBs) were more effective than diuretics and beta-blockers in preventing stroke, even if there were more new cases of AF in patients treated with the newer agents, especially CCBs (RR 1.53; 95% CI: 1.05-2.21).

Other diseases

Gout and osteoarthritis are other diseases that are common in older age, and they can contribute to the development of hypertension. Serum uric acid is an independent predictor of cardiovascular events in elderly people with HBP [54]. Like diabetes, diuretics cause hyperuricemia, and hypertension and diuretics are both independent risk factors for gout [55]. That is why one must be cautious when using diuretics in patients with gout. Arthritis is very common in older age, as well. It affects about 10% of men and 20% of women older than 60 years of age [56]. The chronic inflammation of rheumatoid arthritis (RA) causes an increase in arterial stiffness and SBP. Additionally some drugs used to treat RA, such as NSAIDs [57], Cox-2 inhibitors [58], cyclosporine and leflunomide [59], can lead to HBP. In a recent Finnish study, an association between ISH, increased PP and Parkinson's disease was found, but only in elderly women [60].

Treatment

Elderly adults, and in particular the very elderly, are not simply older adults. Age in and of itself is not a determinant factor. Rather, health in elderly people is a product of many factors, including life-style, previous and concomitant diseases, socioeconomic status, religion, etc. Therefore when deciding on a treatment, one should consider all of these factors. As we have mentioned, making treatment decisions for the very elderly person is a separate issue. Even if the BP goal for elderly adults is similar to that of younger adults, we still do not know the best course for the very elderly over 85 years of age. In very elderly adults with a SBP of 140 to 159 mmHg, large-scale trials to assess the effect of antihypertensive treatment have not been performed. Therefore, existing recommendations are based mainly on observational studies that documented an increase in cardiovascular events with increasing SBP. A recent outcome trial, the HYVET study [61], showed that antihypertensive treatment is beneficial in patients \geq 80 years of age. In particular, patients treated with indapamide had a 30% risk reduction in fatal or non-fatal stroke ($P = 0.06$). However, the study presents many limitations. None of the studies achieved a SBP <140 mmHg, and it

is important to recall that the treatment of ISH was beneficial if SBP was higher than 160 mmHg. Chaudry et al. performed a systematic review of studies from 1966 to 2004, identifying 1064 trials. They reported that the treatment of very elderly people with a SBP of 140 to 159 mmHg is controversial [62]. In a recent meta-analysis of randomized controlled trials of patients 75 years and older treated for at least 12 months, it was reported that the treatment of healthy elderly subjects with moderate to severe HBP lowered the risk of non-fatal stroke, cardiovascular morbidity and mortality and heart failure. However, BP treatment did not affect total mortality, and the mean blood pressure achieved at the end of the studies was 164/83 mmHg in the placebo group and 150/83 mmHg in the treatment group [63].

There is no consensus, as two more studies demonstrate. An Italian study, the Cardio-Sis trial [64] compared two antihypertensive treatments in subjects that did not have diabetes but did have at least one other risk factor. The outcome of interest was reduction of left ventricular hypertrophy after 2 years. This study showed that tight blood pressure control (SBP < 130 mmHg) versus more lenient control (SBP < 140 mmHg) reduced adverse events, with the maximal reduction occurring in patients younger than 70 years of age. On the other hand, the ACCORD BP (Action to control Cardiovascular Risk in Diabetes) study, which was

limited to high-risk patients with diabetes, reported an increased number of adverse events in patients older than 65 years of age when the BP target was 120 mmHg. This study demonstrated a clear J effect [65]. Therefore, in the reappraisal of the ESH-ESC guidelines (2009) the goal SBP goal of < 140 mmHg was maintained, though the fragility of these patients was stressed. We must remember that age-induced pharmacokinetic changes (including changes in fat deposits and mild renal and hepatic failure, etc.) can affect absorption, distribution and drug metabolism. Furthermore, we cannot ignore the importance of adherence and pharmacological interactions, as elderly people are often subject to polypharmacy. So, which, if any, antihypertensives are most appropriate? At present, we do not have conclusive results from clinical trials. Besides, we know that this question is mainly theoretical as elderly patients with HBP rarely present with non-complicated hypertension and are rarely treated with only one drug (Fig. 3).

Diuretics

Diuretics are the most commonly used drugs because they are usually well tolerated (even if the rate of withdrawal from diuretics is the highest of all the antihypertensive drugs), are

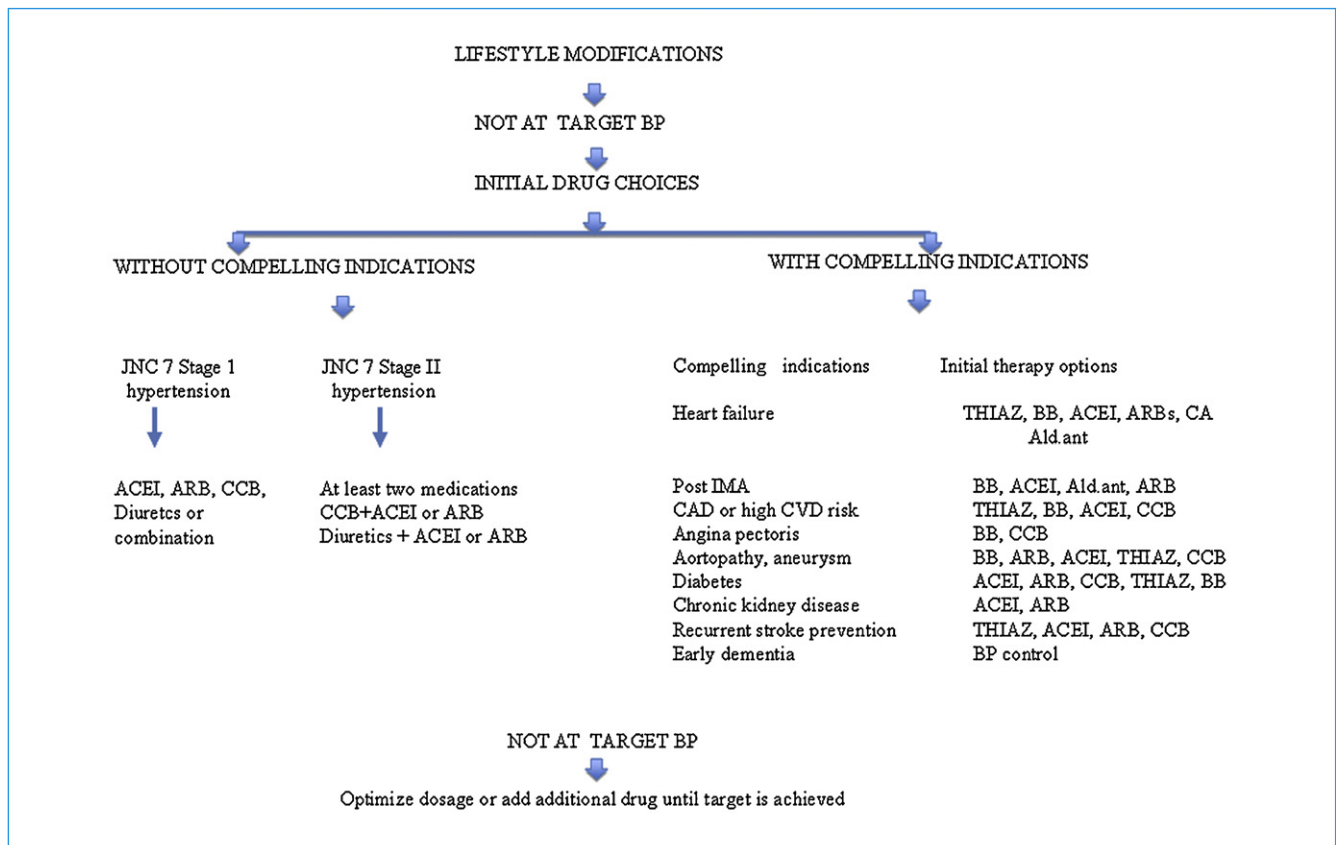


Figure 3 Algorithm for treatment of hypertension in the elderly. ACEI indicates angiotensin-converting enzyme inhibitors; Ald.ant aldosterone antagonists; ARBs, angiotensin II receptor blockers; BB, beta blockers; CCBs, calcium antagonists; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; RAS, renin-angiotensin system; SBP, systolic blood pressure; and THIAZ, thiazide diuretics. *Modified from Chobanian [16].*

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo, JL et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003; 42:1206–1252.

less expensive and have been validated by several studies. They cause an initial reduction of intravascular volume and peripheral vascular resistance, causing a reduction in blood pressure. Obviously, not all diuretics are equal, and even among the thiazides there are some differences, mainly pharmacodynamic differences. Chlorthalidone differs from hydrochlorothiazide (HCTZ) because of its longer action and stronger potency, but adverse metabolic effects can be more common with chlorthalidone. It can cause hyperuricemia and lipid alterations. However, with the exception of hyperuricemia that can require treatment, the other metabolic alterations do not seem relevant over the long term. Drug withdrawal rates range from 3.5 to 15% [66]. Indapamide, a non-thiazide sulfonamide diuretic, was utilized in many trials (HYVET, PROGRESS, etc.). It can induce hyperglycemia and hyponatremia, but not hyperuricemia. Potassium-sparing diuretics and epithelial sodium channel antagonists (amiloride and triamterene) appeared useful, mainly in combination, in these patients.

Beta-blockers (BB)

Despite being heavily used, the evidence for beta-blockers is less convincing in elderly people, except when there are other indications, such as arrhythmias, headache, CAD or heart failure. Usually, beta-blockers are used with diuretics, for their synergic action. Of the newest BBs, nebivolol appears to be the most promising and best-tolerated, as it avoids the typical adverse effects of its class. Nebivolol produced beneficial outcomes in the SENIORS trial (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors), which included patients >70 years of age with HF, most of who had also HBP [67].

Calcium-channel blockers (CCBs)

CCBs represent a large class of effective and well-tolerated drugs. However, this class is heterogeneous. It is essential to distinguish between dihydropyridinic and non-dihydropyridinic CCBs which have very different effects. Edema and headache are common and well-known adverse effects, but verapamil and diltiazem can precipitate heart block in elderly subjects with pre-existing conduction defects. Furthermore, first generation CCBs (nifedipine, verapamil and diltiazem) should not be used in patients with LV systolic dysfunction.

ACE-inhibitors (ACEIs)

With aging, angiotensin levels decline, and theoretically, ACEIs should be less effective than other drugs. However, many studies have shown different findings. Decreased morbidity and mortality have been seen in patients with MI and heart failure with reduced systolic function [68,69], as well as slowing of diabetic nephropathy progression and hypertension nephrosclerosis. Available data support ACEIs as drugs of choice in elderly people with hypertension associated with HF and/or diabetes or chronic renal disease [4].

Angiotensin Receptor Antagonists (ARBs)

ARBs have almost the same indications as ACEIs and are commonly prescribed. There are some reports of their advantages in delaying Alzheimer's disease and dementia [70]. Also in elderly people with hypertension and diabetes, ARBs are indicated as the therapy of choice and as an alternative to ACEIs in intolerant patients.

Renin inhibitors

At present, Aliskiren is the only available renin inhibitor, though it seems promising. The AGELESS study demonstrated that, compared to ramipril, Aliskiren decreases systolic blood pressure by an additional 2.3 mmHg in patients ≥ 65 [71]. Aliskiren is also helpful in combination with other agents. For example, in combination with HCTZ, ramipril or amlodipine it produces a greater BP reduction than do any of these agents alone [72].

Alpha-blockers

After the ALLHAT study [73], alpha-blockers were no longer used as monotherapy for treatment for hypertension, even if they could be useful for relieving the symptoms of prostatic hypertrophy. We consider alpha-blockers to be third or fourth line agents in the treatment of ISH in elderly people because they can cause orthostatic hypotension. It is important to stress that, in elderly people, uncomplicated hypertension is rare. Therefore, when one is deciding on a treatment, comorbid diseases must be considered. Combination therapies have more success, either by acting synergistically or by improving compliance. Fixed combination

Table 1 Dose adjustments for elderly patients. Reprinted from Frishman W. Appendices in Cardiovascular Pharmacotherapeutics. New York, NY: McGraw-Hill; 2003:1033–6. (modified).

Drugs	Dose Adjustment
Alpha-adrenergic agonists, centrally acting	start with the lowest doses and increase on the ground of the response
Diuretics	start with full dose
Calcium-channel blockers	start with low doses and increase on the ground of the response
Beta-blockers	start with low doses and increase on the ground of the response (Nebivolol does not require progressive dose adjustments)
ACE-inhibitors	start with low doses and increase on the ground of the response (Captopril and benazepril do not require progressive dose adjustments)
Angiotensin II receptor blockers	start with full dose

Table 2 Rationale of combination antihypertensive therapy in elderly people.

PROs	
1.	Major antihypertensive efficacy (synergic and adjunctive effects)
2.	Minor doses of single agents
3.	Better pharmacokinetic
4.	Better protection of target-organ
5.	Less expensive
6.	Better compliance
CONs	
1.	Fixed doses combination are few flexible

therapies are less flexible, but there are exceptions in which there are an increasing number of combinations of the same drugs in different proportions. Altogether, the advantages seem to outweigh the challenges of dosing (Tables 1 and 2).

Conclusions

Antihypertensive treatment in the elderly and the very elderly reduces the incidence of stroke and heart failure. However, the mortality data are conflicting: positive findings have been reported by the HYVET study and negative findings have been reported by many other studies. Surely, prevention strategies, such a healthy diet and active lifestyle, are very important. Elderly adults and especially very elderly adults must be considered as a particular category of patient, and every intervention (therapeutic or not) must be tailored to the individual patient, taking into consideration his or her associated diseases and his/her personal history (Table 3). Compliance is another issue, crucial in this class of patients, that is heterogeneous and peculiar. At the end, we should reflect on how far we should go in trying to reach the established goals or if a less aggressive approach would be better.

Table 3 General indications to antihypertensive treatment in elderly people.

1.	Antihypertensive drugs must be started with low doses that can be progressively and slowly increased
2.	The highest dose must be lower than in younger people; the duration of action is usually longer
3.	Choose drugs useful also for other comorbidities (according to general guidelines)
4.	Do not reduce diastolic blood pressure too much
5.	Do not change medication too often
6.	Use simple therapeutic schedules (too complex therapies are often disregarded)
7.	Check all the drugs taken by the patients, also over-the-counter medications
8.	Adjust therapy in case of undercurrent events (infections, hydro-electrolyte imbalance, anemia, etc.) or concomitant administration of hypotensive agents

Conflict of interest

The authors have no conflicts of interest to disclose.

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