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EDITORIAL

Hypertension in the elderly

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Abstract

The elderly are the most rapidly growing population group in the world. Data collected over a 30-year period have demonstrated the increasing prevalence of hypertension with age. The risk of coronary artery disease, stroke, congestive heart disease, chronic kidney insufficiency and dementia is also increased in this subgroup of hypertensives. Hypertension in the elderly patients represents a management dilemma to cardiovascular specialists and other practioners. During the last years and before the findings of the Systolic Hypertension in Europe Trial were published, the general medical opinion considered not to decrease blood pressure values similarly to other younger patients, in order to avoid possible ischemic events and poor oxygenation of the organs (brain, heart, kidney). The aim of this review article is to highlight the importance of treating hypertension in aged population in order to improve their quality of life and lower the incidence of the cardiovascular complications.

Key words: Hypertension; Elderly; Pathophysiology; Treatment

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INTRODUCTION

Aging is an inevitable part of life and brings along two inconvenient events: physiologic decline and disease state[1]. Hypertension is an important risk factor for cardiovascular morbidity and mortality, particularly in the elderly. It is a significant and often asymptomatic chronic disease, which requires optimal control and persistent adherence to prescribed medication to reduce the risks of cardiovascular, cerebrovascular and renal disease[2]. Hypertension in the elderly patients represents a management dilemma to cardiovascular (CV) specialists and other practioners. Furthermore, with the wide adoption of multiple drug strategies targeting subgroups of hypertensive patients with specific risk conditions to lower blood pressure (BP) beyond traditional goals, difficult questions arise about how aggressive elderly patients should be treated. "Is hypertension in the elderly an emergency state or not?", "Does the BP control lower the risks associated with cardiovascular disease and death in the geriatric population?", "What are the general principles of hypertension management in this population?" The purpose of the following article is to answer those questions through a review of pathophysiology of aging, clinical assessment

and diagnosis of hypertension and finally recommendations for its management.

EPIDEMIOLOGY

As our population ages, the importance of cardiovascular disease (CVD) as the leading cause of death in adults becomes increasingly clear[3]. One major reason for this trend is the patterns of BP changes and increasing hypertension prevalence with age (about 1 billion people worldwide)[4]. According to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7), hypertension occurs in more than two thirds of individuals after age of 65[5]. Data from the Framingham Heart Study, in men and women free of hypertension at 55 years of age indicate that the remaining lifetime risks for development of hypertension through 80 years are 93% and 91% respectively[6]. In other words, more than 90% of individuals who are free of hypertension at 55 years of age will develop it during their remaining lifespan.

From the standpoint of epidemiology and pathophysiology, there are some subgroups with particular characteristics such as elderly women and blacks that require additional focus. Hypertension prevalence is less in women than in men until 45 years of age, is similar in both sexes from 45 to 64 and is much higher in women than men over 65 years of age[3]. The severity of hypertension increases markedly with advancing age in women as well. After the age of 60 years, the majority of women (age 60-79 years: 48.8%; age ≥ 80 years: 63%) has stage 2 hypertension (BP ≥ 160/100 mmHg) or receives antihypertensive therapy[7-9]. Furthermore, BP control is difficult to achieve in elderly women[10]. Endothelial dysfunction, increased arterial stiffness, obesity, genetic factors, elevated total cholesterol and low high-density lipoprotein cholesterol levels have been implicated in menopause-related BP elevation rather than ovarian failure *per se*[11,12]. Hypertension among blacks is earlier in onset, more severe and uncontrolled and contributes to the highest coronary artery disease (CAD) mortality rates in the USA in addition to the highest morbidity and mortality attributable to stroke, left ventricular hypertrophy (LVH), heart failure (HF) and chronic kidney disease (CKD)[5]. Compared with whites, blacks are more likely to have hypertension, more likely to be aware of it and more likely to be pharmacologically treated, but less likely to achieve BP control[13]. Hypertension is an important factor in the disproportionate decreased life expectancy for blacks: African-American men 70.0 years *vs* 75.9 years for white men and African-American women 76.8 years *vs* 80.8 years for white women[14].

BP REGULATION

BP is regulated *via* several physiological mechanisms to ensure an adequate tissue blood flow. BP is determined by the rate of blood flow produced by the heart (cardiac output) and the resistance of the blood vessels to blood flow. The resistance is produced mainly in the arterioles and is known as the systemic vascular resistance. There are several physiological mechanisms that allow BP to maintain into normal range such as: (1) The autonomic nervous system is the most rapidly responding regulator of BP and receives continuous information from the baroreceptors situated in the carotid sinus and the aortic arch. This information is relayed to the vasomotor center. A decrease in BP causes activation of the sympathetic nervous system resulting in increased contractility of the heart (β receptors) and vasoconstriction of both arterial and venous side of the circulation (α receptors)[1]; (2) The capillary fluid shift mechanism refers to the exchange of fluid that occurs across the capillary membrane between the blood and the interstitial fluid. The fluid movement is controlled by the capillary BP, the interstitial fluid pressure as well as the colloid osmotic pressure of the plasma. Low BP results in fluid moving from the interstitial space into circulation, helping to restore blood volume and BP[6]; (3) Hormonal mechanisms exist both for lowering and raising BP. They act in various ways including vasoconstriction and vasodilation. The principal hormones raising BP are: (a) adrenaline and noradrenaline secreted from the adrenal medulla in response to sympathetic nervous system stimulation. They increase cardiac output and cause vasoconstriction; (b) renin-angiotensin-aldosterone production is increased in the kidney when stimulated by hypotension. Angiotensin is converted in the lung to Angiotensin Ⅱ which is a potent vasoconstrictor. In addition, these hormones stimulate the production of aldosterone from the adrenal cortex which decreases urinary fluid loss from the body (sodium retention-potassium loss). This system is responsible for the long-term maintenance of BP but is also activated very rapidly in the presence hypertension[5]; and (4) The kidneys help to regulate the BP by increasing the blood volume and also by the renin-angiotensin system (RAS) described above. They are the most important organs for the longterm control of the BP[5].

PATHOPHYSIOLOGY

Arterial stiffness

Elastic arteries show 2 major physical changes with age. They dilate and stiffen. Aorta and the proximal elastic arteries dilate by approximately 10% with each beat of heart in youth, while the muscular arteries dilate by only 3% with each beat[15]. Such difference in degree of stretch can explain differences in aging between proximal and distal arteries on the basis of fatigue[15]. Fracture of elastic lamellae is seen in the aorta with aging and can account for both dilation and for stiffening (through transfer of stresses to the more rigid collagenous components of the arterial wall)[15]. Autopsy studies of perfusion-fixed human arteries have shown that thickening is mostly confined to intimal hyperplasia[16]. The result is a stiff artery that has decreased capacitance and limited recoil and

is thus unable to accommodate the changes that occur during the cardiac cycle. Furthermore, during systole the arteriosclerotic arterial vessel exhibits limited expansion and fails to buffer effectively the pressures generated by the heart causing an increase in systolic BP (SBP). On the other hand, the loss of recoil during diastole results in reduction in diastolic BP (DBP)[17]. Thus, aging even in normotensive individuals is characterized by an increase pulse pressure, creating greater pulsatile stress on the arterial system[17]. Arterial stiffness is not only a product of structural changes in the arterial wall, but is also induced by endothelium-derived vasoactive mediators such as endothelin 1 and decreased bioavailability of nitric oxide (NO), which plays a key role in endothelial dysfunction[18,19]. According to a meta-analysis, aortic stiffness expressed as aortic pulse wave velocity (PWV) is a strong predictor for future cardiovascular events and all-cause mortality. The relative risk of total cardiovascular events, cardiovascular mortality and all-cause mortality were 2.26, 2.02 and 1.90, respectively for high *vs* low PWV subjects[20]. Aortic PWV is estimated noninvasively from the delay of pressure wave foot at the femoral site and from the distance traveled by the pulse. A typical value in a 20-year-old is 5 m/s and in an 80-year-old is 10-12 m/s (i.e., a 2, 4-fold increase over 60 years)[15]. In elderly individuals of 60-75 years old, an aortic PWV value below 10 m/s can be considered as a normal value. Values of 10-13 m/s can be considered as "high normal" or "borderline", whereas an aortic PWV above 13 m/s is frankly elevated[21]. In contrast to younger patients with hypertension in whom elevated BP is determined primarily by increased peripheral arterial resistance, the isolated systolic hypertension seen in elderly is due to increased arterial stiffness[22].

Neurohormonal and autonomic dysregulation

Neurohormonal mechanisms such as the renin-angiotensin-aldosterone system decline with age. Plasma renin activity at age of 60 years is 40% to 60% of the levels found in younger individuals[23]. This has been attributed to the effect of age-associated nephrosclerosis on the juxtaglomerular apparatus. Plasma aldosterone levels also decreases with age. Consequently, elderly patients with hypertension are more prone to drug-induced hyperkalemia[24]. In contrast, net basal sympathetic nervous system activity increases with advancing age. Peripheral plasma norepinephrine concentration in the elderly is double the level found in younger subjects[25]. The age-associated rise in plasma norepinephrine is thought to be a compensatory mechanism for reduction in β-adrenergic responsiveness with aging[25].

Decreased baroreflex sensitivity with age causes orthostatic hypotension in the elderly[26,27]. On the contrary, orthostatic hypertension, where BP increases with postural change, is also prevalent among the elderly[28]. The orthostatic hypertension is blocked by α-adrenergic blockade, indicating that α-adrenergic activity may be a predominant pathophysiological mechanism[28].

Table 1 Classification of blood pressure for adults according to JNC-7

Classification	SBP (mmHg)	DBP (mmHg)
Normal	⩽ 120	And ⩽ 80
Prehypertension	120-139	Or 80-89
Stage 1 hypertension	140-159	Or 90-99
Stage 2 hypertension	⩾ 160	Or ⩾ 100

SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Table 2 Classification of blood pressure for adults according to ESH/ESC 2007

Classification	SBP (mmHg)	DBP (mmHg)
Optimal	⩽ 120	And ⩽ 80
Normal	120-129	80-84
High normal	130-139	85-89
Hypertension		
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	⩾ 180	⩾ 100
Isolated systolic hypertension	⩾ 140	⩽ 90

SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

The aging kidney

The aging kidney is characterized by progressive development of glomerulosclerosis and interstitial fibrosis, which is associated with a decline in GFR and reduction of other homeostatic mechanisms[29]. Age-associated decline in activity of membrane sodium/potassium and calcium adenosine triphosphate pumps lead to an excess of intracellular calcium and sodium, thereby increase of vasoconstriction and vascular resistance[30]. Increased salt sensitivity characterized by an increase in BP in response to sodium overload occurs in older and obese subjects as a result of the limited renal ability of these subjects to excrete sodium overload.

DIAGNOSIS AND CLASSIFICATION OF HYPERTENSION

The JNC-7 has defined criteria for normal BP, prehypertension and stage 1 and 2 of hypertension[5] (Table 1). Guidelines from the European Society of Hypertension/European Society of Cardiology (ESH/ESC 2007 and 2009 update) stratify hypertension somewhat differently (Table 2). As with the previous ESH/ESC guidelines, the authors have again omitted the "prehypertension" category, as defined in JNC-7, because they believe that it implies that a large part of the population is "sick" and that this raises anxiety and leads to unnecessary physician visits. The authors also felt that the population of people who would fall into a prehypertension category would be so diverse to allow treatment recommendations for the whole group[31].

The diagnosis of hypertension should be based on at

Table 3 Causes of secondary hypertension

Hyperaldosteronism
Cushing syndrome
Coarctation of the aorta
Renovascular stenosis
Endocrine disorders (thyroid, parathyroid abnormalities)
Obstructive sleep apnea
Drugs (nonsteroidal antiinflammatory drugs, alcohol, estrogen)
Chronic kidney disease
Pheochromocytoma

Table 4 Causes of resistant hypertension

False positive or pseudoresistance
Incorrect technique in measuring blood pressure
Pseudohypertension
Lack of adherence to life style modifications
Lack of patient adherence to antihypertensive therapy
Suboptimal therapy
True resistant hypertension
Sleep apnea
Hypertension related to secondary etiology

least 3 different BP measurements taken on ≥ 2 separate office visits[5]. The majority of cases are due to essential hypertension. However, it is important to identify correctable causes of hypertension also known as secondary hypertension. History and examination may give clues to the presence of an underlying disease such as renal failure, renovascular disease, hyperaldosteronism, phaechromocytoma or Cushing syndrome. Other suggestive factors are lack of family history of hypertension, unusual course, early complications or resistance to therapy (Table 3).

Special definitions of hypertension

White-coat hypertension: A term reserved for those not on antihypertensive medications but with persistently elevated office BP (≥ 140/90 mmHg) together with a normal daytime ambulatory BP (≤ 135/85 mmHg), is also more common in the elderly and is more frequent among centenarians[32].

Masked hypertension: It is defined as normal BP at office associated with high BP at home, has been shown to be associated with an increased risk of cardiovascular events[33]. Masked hypertension is frequent in the elderly and is associated with a high vascular profile[34]. These results should encourage a more widespread use of home BP monitoring in this age segment.

Pseudohypertension: It is a falsely increased SBP caused by atherosclerotic and other vascular changes associated with age. The Osler maneuver (i.e. the presence of radial artery pulse that is still palpable after the cuff is inflated above the systolic pressure) should be performed if pseudohypertension is suspected, though it has low sensitivity and specificity[35]. Confirmation of pseudohypertension requires direct intraarterial measurement of BP[36].

Resistant hypertension: It is defined as BP that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the three agents should be a diuretic and all agents should be prescribed at optimal dose amounts. Like the American Heart Association statement, the JNC 7 guidelines also include patients who are well controlled but require 4 or more medications as having resistant hypertension[5]. Resistant hypertension is prevalent across all ages, but is more prevalent in elderly patients[37]. Several factors have been identified as contributors to resistant hypertension. Poor patient adherence, physical inertia, inadequate doses or inappropriate combinations of antihypertensive drugs, excess alcohol intake and sleep apnea are some of the most common causes of resistance. Secondary forms of hypertension represent another important contributor to drug resistance (Table 4).

Dipper or non-dipper patient: It is to say whether or not BP falls at night compared to daytime values. A night time fall is normal (nocturnal BP drop of 10%-20%, followed by an increase early in the morning). It correlates with variations in sympathetic activity but with other factors such as sleep quality, age, hypertensive status, marital status, and social network support[38]. In addition, nocturnal hypertension is associated with end organ damage and is a much better indicator than the daytime BP reading[39]. It should be noted that there is also a category of patients who, rather than non-dippers are extremely dippers (≥ 20% nocturnal BP fall) and this group may be at risk for silent and clinical cerebral ischemia through hypoperfusion during sleep[39]. The frequency of non-dippers is higher in the elder[40].

End-organ effects of hypertension in the elderly

Cerebrovascular disease and dementia: Hypertension in the elderly is a major risk factor for both ischemic stroke and cerebral hemorrhage. Isolated systemic hypertension (ISH) is an important component of BP-related stroke risk[41]. The benefit of BP reduction for stroke risk was demonstrated in Systolic Hypertension in the Elderly Program (SHEP), in which patients in the active treatment had reduced incidence of both ischemic (37%) and hemorrhagic stroke (54%)[42]. In the PROGRESS (Perindopril Protection Against Recurrent Stroke Study), patients under antihypertensive therapy had fewer recurrent ischemic strokes, 10% to 35% and hemorrhagic strokes 26% to 87% compared with placebo[43]. The Systolic Hypertension in Europe Trial (*Syst-Eur*), which comprised patients with ISH, confirmed stroke prevention with BP control using nitrendipine with possible addition of enalapril, hydrochlorothiazide (HCTZ) or both[44]. Patients in the aforementioned studies consisted of the "early elderly" (65-74 years). In Hypertension in the Very Elderly Trial (HYVET), patients in the "late elderly" group (≥ 80 years of age with elevated SBP) were randomized

to indapamide, with addition of perindopril if needed, or placebo. Patients in the indapamide group had a 30% risk reduction in fatal and non-fatal stroke[45]. It is unclear whether the benefits are related solely to BP reduction or whether there is additional benefit conferred by class of BP medication. Although there is consistent benefit in stroke reduction when drugs were compared with placebo, there is little difference between drug classes[46].

The prevalence of both hypertension and dementia increases with advancing age. Hypertension is an important risk factor for vascular dementia and Alzheimer's disease[47]. Poor BP control is associated with an even greater cognitive decline[48]. Four randomized studies evaluated dementia as an outcome with treatment of hypertension in elderly patients. In the Syst-Eur and PROGRESS, active treatment was associated with 50% and 19% reduction in dementia incidence respectively[43,49]. The SCOPE (Study on Cognition and Prognosis in Elderly) compared candesartan with placebo in 70 to 89 years old patients with hypertension and found no differences in cognitive outcome between the 2 groups[50]. The HYVET-COG trial found a non significant 14% decrease in dementia with active treatment *vs* placebo[51].

CAD: According to 2004 AHA statistics, 83% of CAD deaths occurred in persons ≥ 65 years of age[52]. Elderly patients with hypertension have higher prevalence of myocardial infarction than elderly patients without hypertension[53]. However, last recommendations to aggressively reduce BP in high risk patients, should be tempered particularly referring to myocardial infarction prevention. The old dogma "the lower the better" is not always true. This is what retrospective analysis of the International Verapamil-Trandolapril Study (INVEST) proved. The INVEST trial was designed to investigate two hypertension treatment strategies in patients with CAD. The study included a large number of individuals older than 80 years old and a secondary analysis of this group was performed to assess the effects of strict BP control by reporting a J-shaped mortality curve with BP control[54]. It is unclear whether the J-shaped mortality curve from this study is attributable to severe end stage disease alone or whether iatrogenesis plays a significant role. However, the data should cause one to be cautious in lowering BPs to below 130/70 mmHg in older patients, including those at high risk of adverse cardiovascular outcomes.

CKD: Hypertension and aging both impact renal function. Elderly patients are more likely to have CKD, usually defined by a measured estimated Glomerular Filtration Rate (eGFR) ≤ 60 mL/min per 1.73 m^2. 75% of the CKD population is ≥ 65 years of age[55]. SBP is a strong independent predictor of decline in kidney function among older patients with ISH[56].

Hypertension and age associated retinal changes: Retinal lesions prevalence increases with higher SBP, but not necessarily with DBP[57]. Persistent BP elevation produces intimal thickening, medial hyperplasia and hyaline degeneration (sclerosis)[58]. Aging itself is also associated with most of these changes which makes grading of retinal pathology in older patients less reliable *vs* younger patients[59]. Hypertension is an important risk factor for retinal artery occlusion and nonarteritic anterior ischemic optic neuropathy[60]. The final stages of retinal disease are caused by disruption of the retina/blood barrier and lipid exudates in severely elevated BP[61].

MANAGEMENT OF HYPERTENSION IN ELDERLY PATIENTS

The 2009 ESH/ESC update consider subclinical organ damage to be a very important component, because asymptomatic alterations of the cardiovascular system and the kidneys are important intermediate stages in the disease continuum that links risk factors such as hypertension to cardiovascular events and death. Moreover, multiple organ damage assessment is useful because of the evidence that in the presence of 2 signs of organ damage (even when present to the same organ), cardiovascular risk may be increased, upgrading the patient to the high cardiovascular risk category[62]. Reassessment of subclinical organ damage during treatment is also crucial because it offers information on whether the selected treatment is protecting patients from progressing organ damage and potentially from cardiovascular events[62]. Analysis of the data provided by some prospective studies indicate that in hypertensive patients, echocardiographic LVH is associated with an incidence of cardiovascular events equal or above 20% in 10 years[63,64]. Furthermore, the relationship of carotid intima-media thickness (IMT) and plaques with cardiovascular events, already discussed in the 2009 update, has been further reinforced by the European Lacidipine Study on Atherosclerosis trial, which have shown that IMT value at the bifurcations and the common carotid exerts an adverse prognostic effect in addition to that of high BP[65]. Finally, renal subclinical organ damage is associated with a 10-year risk of cardiovascular events of 20%. In a prospective cohort of Greek hypertensive patients, a low eGFR was associated with 20% incident cardiovascular event in 10 years[64].

A reappraisal of trials has underlined that no single trial on hypertension in the elderly has enrolled patients with grade 1 hypertension. Although not evidence based, the 2011 ACCF/AHA Expert Consensus Document suggest to initiate antihypertensive therapy in the elderly according to the same criteria used for younger adults and to use almost the same SBP goal as in younger patients[40]. Interestingly, although in almost all trials the groups of elderly patients randomized to treatment had lower incidence of cardiovascular outcomes, in no trial (except JATOS - the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients - with negative results[66]), the on-treatment SBP values were lowered to less than 140 mmHg. Thus, there is no randomized trial in support of lowering SBP to less than 140 mmHg[40].

Despite the known risk of uncontrolled hypertension in the elderly, there is poor adherence to guidelines. A meta-analysis in 2000 (largely from SHEP, Syst-Eur and Syst-China) pooled 15 693 patients older than 60 years (mean age 70 years) with ISH, SBP more than 160 mmHg, DBP less than 95 mmHg, analyzing the effect of hypertension treatment on cardiovascular outcomes[67]. Average BP was 174/83 mmHg and decrease in BP with treatment was 5.96% for SBP and 4.9% for DBP. Active treatment significantly reduced total mortality by 13%, chronic heart disease death by 18% and stroke by 26%. Clearly, we can conclude that treatment of hypertension in the elderly at least up to 70 years is beneficial to overall mortality. Treatment of hypertension in the elderly patients older than 80 years was not evaluated specifically in prospective trials until the HYVET study was published. The HYVET trial was a randomized prospective trial of 3845 participants older than 80 years[45]. The mean baseline BP was 173/91 mmHg (32% had ISH). Patients were randomized to diuretic or placebo. An angiotensin converting enzyme inhibitor (ACEI) was added if necessary to achieve a goal of BP of 150/80 mmHg. Active treatment was associated with a significant 30% relative risk reduction in fatal and non fatal stroke and 39% reduction in stroke death alone. CVD deaths were reduced by 23%. All cause mortality was also reduced by 23%. The HYVET trial answers a crucial question and gives an end to the dilemma whether hypertensive elderly patients should be treated or not. Physicians can feel comfortable prescribing anti-hypertensives for their elderly patients and know that there will be a mortality benefit. Another question regarding BP treatment in older individuals is whether severe hypertension constitutes an emergency and whether on the other hand there are levels that could be too low that might be associated with increases risk- known as the J-curve phenomenon.

Hypertensive emergency is defined as severely elevated BP in the setting of acute end organ damage[68]. Examples of hypertensive emergencies are acute myocardial infarction, pulmonary edema, cerebral ischemia or hemorrhage, aortic dissection, encephalopathy and progressive renal failure. Aside from the patient who has an obvious hypertensive emergency, how should patients who have asymptomatic severely elevated hypertension be treated? At what BP level does it become admirable to transfer the patient to the hospital? There is no evidence to support the idea that acute reduction of BP reduces cardiovascular events in the short or long term. In fact, many cases of harm have been documented. The mechanism by which acute reduction of BP leads to harm is related to auto regulation of blood flow. Patients, who have elevated BP, often have been present for many weeks or months. Any attempt to lower BP acutely may harm them by offsetting the patient's adaptive auto regulatory control[69]. Asymptomatic patients who do not have end-organ damage or significant comorbid illnesses should not have acute reduction of BP attempted. Instead, careful titration of antihypertensive medications should be undertaken with plans for close follow-up. Excessively lowering of the BP could be associated with poor outcome in long term (J-curve phenomenon). A Framingham Study in 2004 by Kannel *et al*[70] suggested that BP was responsible for the increased mortality and not DBP alone.

Table 5 Therapeutic strategies

Non-pharmacological strategy
Weight reduction
Dietary sodium reduction
Physical activity
Moderate alcohol consumption
Dash diet
Pharmacological strategy
Main Pharmacological agents
Thiazide diuretic: inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys →→ ↓ BP, ↓ stroke, ↓ CV mortality
ACEIs: block the conversion of angiotensin Ⅰ to angiotensin Ⅱ →→ ↓ SVR, ↓ BP, ↓ mortality in patients with MI and left ventricular dysfunction, ↓ progression of diabetic renal disease
ARBs: direct blockage of angiotensin Ⅱ receptors →→ vasodilation (↓SVR), ↓ secretion of vasopressin, ↓ aldosterone, ↓ BP, ↓ stroke. Generally, in patients who cannot tolerate ACEs
Calcium antagonists: disrupts the movement of calcium through calcium channels in cardiac muscle and peripheral arteries →→ vasodilation (↓ SVR), ↓ BP, ↓ CV complications in elderly patients with ISH
β blockers: ↓ heart rate, ↓ cardiac contractility, ↓ cardiac output, inhibit renin release, ↑ nitric oxide, ↓ vasomotor tone →→ ↓ BP
Other agents: direct renin inhibitors, aldosterone receptor antagonists, centrally acting agents, direct vasodilators, α-adrenergic blocking agents
Combination therapy
ACEIs or ARBs/Diuretic
ACEIs or ARBs/Calcium antagonist (especially in patients with high CV risk)

CV: Cardiovascular; BP: Blood pressure; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; SVR: Systemic vascular resistance.

The therapeutic strategies for hypertension in the elderly as well as the basic effects and the main cardiovascular benefits of the pharmacological agents are summurized in Table 5.

Non pharmacological management of hypertension in elderly patients

Non pharmacological management of hypertension is too often overlooked in the elderly. Lifestyle modifications may be the only treatment necessary for preventing or even treating milder forms of hypertension in the elderly. Weight reduction (results in a 5-20 mmHg decrease in SBP per 10kg less), dietary sodium reduction (2-8 mmHg decrease in SBP), physical activity (4-9 mmHg decrease in SBP), moderate alcohol consumption (2-4 mmHg decrease in SBP) and DASH (Dietary Approaches to Stop Hypertension) diet (8-14 mmHg decrease in SBP) should be the cornerstone of hypertension treatment in combination or not with active treatment[5].

Pharmacological management of hypertension in elderly patients

When lifestyle measures fail to lower BP to goal, pharmacotherapy should be initiated. The safety and efficacy of multiple medication classes has been studied in elderly patients over the last 30 years. Randomized controlled trials have consistently demonstrated that antihypertensive therapy in the elderly is effective in preventing total mortality, stroke and coronary events[5]. Another important consideration is that for most trials, the goal and achieved bp are higher than that recommended by JNC-7, while still showing a significant benefit of treatment.

General principles of pharmacological management: There is often a debate about which antihypertensive drug class should be used first in elderly patients with hypertension. Several classes of antihypertensive drugs are effective in preventing cardiovascular events. Treatment decisions should be guided by the presence of compelling indications such as diabetes mellitus, stroke or HF and by the tolerability of individual drugs or drug combinations. The initial antihypertensive drug should be started at the lowest dose and gradually increased depending on the BP response to the maximum tolerated dose[31]. If the antihypertensive response to the initial drug is inadequate after reaching full dose, a second drug from another class should be added. If the antihypertensive response in inadequate after reaching the full dose of 2 classes of drugs, a third drug from another class should be added[31].

A common question arising from current clinical practice refers to the threshold BP values for treatment initiation. As mentioned in the ESC 2007 document, the guidelines recommend to start drug treatment in grade 1 hypertensive patients at low or moderate risk when BP is equal or above 140/90 mmHg after lifestyle modifications. These thresholds which have been confirmed in the ESH 2009 update are similar in elderly hypertensives based on the results of the HYVET-trial[45]. Prompter treatment is recommended in grade 2 and 3 of hypertension[62]. In patients with high-normal BP ("pre-hypertension"), drug treatment should be delayed when overall cardiovascular risk is low. As far as goals of treatment are concerned, the ESH 2009 guidelines update document recommends to lower BP to values within the range 130-139 mmHg for systolic and 80-85 mmHg for diastolic, in all hypertensive patients[62]. Furthermore, the concept of lower BP goals in diabetics or very high risk patients is no longer recommended because there is no evidence of a greater benefit. On the other hand, the quantification of the total cardiovascular risk must also include a search for subclinical organ damage[62].

Pharmacological agents: The JNC-7 trial recommends a thiazide diuretic as initial drug therapy or in combination with other class[5]. Thiazide diuretics control hypertension by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by blocking the thiazide-sensitive Na^+-Cl^- symporter. The term "thiazide" is also often used for drugs with a similar action that do not have the thiazide chemical structure, such as chlorthalidone and metolazone. These agents are properly termed thiazide-like diuretics[71]. Thiazides are preferred because of an extensive volume of data showing that may decrease stroke and CV mortality in elderly patients with hypertension and because of their wide availability and low cost. These agents have benefits that are distinct from their effects on BP and CVD outcomes.

Their effect on calcium reabsorption constitutes the basis for their usefulness in preventing the formation of calcium containing renal stones and may also explain their protective effects on rates of bone mineral loss and prevention of hip fracture[72-74]. Unfortunately, thiazide treatment is associated with various metabolic side effects, including electrolyte abnormalities, dyslipidemia, insulin resistant and new-onset of diabetes mellitus[74]. Whether the metabolic effects of diuretics have adverse consequences for CVD outcomes has been questioned. In Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, there was no significant increase in any outcome (stroke, total mortality, CAD, HF, end stage renal disease) in subjects who developed incident diabetes mellitus[75]. In fact, thiazides remained unsurpassed in all clinical outcomes compared with the other drug classes[75]. Only the Avoiding Cardiovascular events through COMbination therapy in Patients LIving with Systolic Hypertension (ACCOMPLISH) trial favored ACEI/CCB combination over the ACEI/THIAZIDE combination in patients with hypertension who were at high risk for cardiovascular events[76]. However, the hydrochlorothiazide dose used (12.5-25 mg/dL) was half the dose used in other trials, indicating the need to titrate to higher doses[76]. Data support the following dosages of thiazides: hydrochlorothiazide 25 to 50 mg/d, indapamide 2.5 mg/d, chlorthalidone 12.5-25 mg/d[31].

ACEIs can also be considered for first-line or combination therapy, especially if diabetes, HF, post myocardial infarction or chronic disease is present. ACEI block the conversion of angiotensin I to angiotensin Ⅱ in multiple tissues and thus lower total peripheral vascular resistance reducing BP without reflex stimulation of heart rate and cardiac output. As aging occurs, angiotensin levels are lower and theoretically ACEIs should not be as effective as other therapies, but multiple studies have shown otherwise[77]. Among ACEIs benefits reduction in mortality in patients with MI and left ventricular dysfunction as well as reducing progression of diabetic renal disease are the most important[78,79]. When combination therapies are needed, often for high risk patients, JNC-7 guidelines indicate a strong preference for a thiazide diuretic[5]. The superiority of the amlodipine-based therapy (ACCOMPLISH trial) with respect to the clinical outcomes in this trial suggests that approaches that do not include thia-

zides may be better for some populations[76]. Nevertheless, these results should not cast doubt on the efficacy of diuretics in reducing the risk of cardiovascular events. In the HYVET trial, mortality was reduced with therapy that combined a diuretic with an ACE inhibitor as compared with placebo[45]. Moreover,patients with or at risk of sarcopenia may particularly benefit, as ACEIs have been shown to improve muscle strength and working speed in older hypertensive individuals[80]. Therefore, this group of hypertensive may be a good choice for the frail elderly. Finally, the main adverse effects of ACEIs include hypotension, chronic dry cough and rarely angioedema or rash. Renal failure can develop in those with renal artery stenosis. Hyperkalemia can occur in patients with renal insufficiency. Rarely, neutropenia or agranulocytosis can occur[81]. Therefore, close monitoring is suggested during the first months of therapy.

Hypertensive patients with diabetes mellitus, angiotensin receptor blockers (*ARBs*) are considered first line treatment and as an alternative to ACEIs in patients with hypertension and HF who cannot tolerate ACEIs[82]. Blockage of angiotensin Ⅱ receptors directly causes vasodilation, reduces secretion of vasopressin and reduces production and secretion of aldosterone. The combined effect reduces BP[83]. The LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study compared losartan with atenolol in patients (age 55 to 80 years) with hypertension and LVH, showing reduced stroke rate in the losartan treated group despite comparable BP reduction in both treatment groups[84]. In MOSES (Morbidity and Mortality after Stroke-Eprosartan compared with Nitrindipine in Secondary Prevention) study, eprosartan reduced stroke by 25% in patients with mean age 68 years[85]. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) trial showed similar efficacy between telmisartan and ramipril in elderly hypertensive subjects[86].

The usefulness of β blockers (reduce the heart rate and cardiac output, inhibit renin release, generate NO, reduce vasomotor tone)[87] as first line treatment of hypertension in older persons has been questioned. Although β-blockers have been used for hypertension in the elderly for years, evidence for benefit has not been convincing. Two large randomized trials, the LIFE study and the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, showed superiority of an angiotensin receptor antagonist and respectively an antihypertensive regimen of a calcium antagonist adding perindopril, over therapy initiated by a β-blocker as far as stroke (LIFE) or stroke and mortality (ASCOT) were concerned[84,88]. The 2 large trials have strongly influenced a recent meta-analysis which concluded that β-blocker should not remain first choice in the treatment of primary hypertension[89]. On the basis of a similar meta-analysis, the National Institute for health and Clinical Excellence in the United Kingdom has advised the use of β-blockers as fourth antihypertensive agent[90]. The adverse effects of β-adrenergic receptor blocking drugs can be divided in 2 categories: (1) those that result from known pharmacological consequences of β-adrenergic receptor blockade; and (2) other side-effect that do not appear to result from β-adrenergic receptor blockade. The first category includes bronchospasm, HF, prolonged hypoglycemia, bradycardia, heart block, intermittent claudication, and Raynaud's phenomenon. Neurological reactions include depression, fatigue, nightmares. Patient's age does not appear in itself, to be associated with more β-blocker side effects. Side effects of the second category are rare. They include an unusual oculomucocutaneous reaction and the possibility of oncogenesis[91].

In general, calcium antagonists appear well tolerated by the elderly. They are a heterogenous group of drugs with different effects on heart muscle, sinus node function, atrioventricular conduction, peripheral arteries and coronary circulation. Vascular smooth muscle is more dependent on external calcium entry for contraction whereas cardiac and skeletal muscles rely on a recirculating internal pool of calcium[92]. This preferential effect allows calcium antagonists to dilate coronary and peripheral arteries in doses that do not severely affect myocardial contractility and skeletal muscle. The Syst-Eur study investigated whether antihypertensive treatment could reduce cardiovascular complications in elderly patients with isolated systolic hypertension. It showed that antihypertensive drug-treatment, starting with the dihydropyridine calcium channel blocker nitrendipine, improves prognosis in elderly patients with isolated systolic hypertension[44].

Direct renin inhibitors, Aliskiren is an orally active direct rennin inhibitor approved for hypertension; 150 mg to 300 mg once daily appears as effective as ARBs and ACEIs for BP management[93]. Combining aliskiren with HCTZ, or amlodipine causes greater BP lowering than with either agent alone[94]. The major side effect is a low incidence of mild diarrhea[95]. Thus far, we know that dual RAS blockade with an ARB and an ACEI is not beneficial in patients like those in ONTARGET trial, and that it has questionable benefit in HF[86]. However, little was known about combining a direct renin inhibitor with either an ACEI or an ARB. The results of the halted ALTITUDE trial showed that the combination of aliskiren with ACEI or ARB in type 2 diabetic patients with high risk for cardiovascular and renal events is contraindicated because of the increased risk for non-fatal stroke, renal complications, hyperkalemia and hypotension in patients taking aliskiren after 18-24 mo[96,97].

Aldosterone receptor antagonists in hypertensive patients decrease BP to limit end-organ damage. Circulating aldosterone levels positively correlate with incident, resistant and obstructive sleep apnea-related hypertension[98]. Both spironolactone and eplerenone are each efficacious in reducing BP; however, there have been a limited number of comparison studies designed to establish drug superiority[99]. Eplerenone improves arterial compliance and reduces vascular stiffness by decreas-

ing the collagen to elastin ratio[100]. Both spironolactone and eplerenone have shown to decrease left ventricle mass[101]. In a small study of patients with resistant hypertension, 6 mo of spironolactone added to diuretic and ACEIs therapy reduced systolic and diastolic BP by 25 and 12 mmHg respectively and the magnitude of the response was not predicted by the plasma aldosterone level[102]. Spironolactone and eplerenone have different side effects profiles, although both share hyperkalemia as a serious side effect[103]. The incidence of spironolactone side-effect associated breast tenderness, gynecomastia, erectile dysfunction and menstrual irregularities increase the rates of medication non-compliance[104].

Centrally acting agents such as clonidine treats high BP by stimulating a2 receptors in the brain, which decreases cardiac output and peripheral vascular resistance, lowering thus BP. It has specificity towards the presynaptic a2 receptors in the vasomotor center in the brainstem. This binding decreases presynaptic calcium levels and inhibits the release of norepinephrine. The net effect is a decrease in sympathetic tone[105]. Reserpine is another centrally acting agent, whose antihypertensive action is a result of its ability to deplete catecholamines (among other monoamine neurotransmitter) from peripheral sympathetic nerve endings. Both clonidine and reserpine should not be used as monotherapy because they have been associated with a high incidence of adverse effects, including sedation, depression and constipation[106].

Direct vasodilators such as hydralazine (direct-acting smooth muscle relaxant, acting primarily in arteries and arterioles) and minoxidil may cause headache, fluid retention, tachycardia and angina pectoris[107]. Hydralazine may cause a lupus-like syndrome in 5%-10% of patients during longterm use[108]. Minoxidil (may act as a NO agonist), may cause hirsutism and pericardial effusion[109,110].

In the ALLHAT trial, an α-adrenergic blocking agent, the doxazosin (which inhibits the binding of noradrenaline to the α-1 receptors on the membrane of vascular muscle cells, leading to vasodilation and decreased BP) arm was stopped prematurely due to significant increases in HF (20%), stroke (19%), angina pectoris (16%)[111]. These drugs are used for prostate hypertrophy and caution should always be paid for orthostatic hypotension.

Monotherapy vs combination therapy

Both the 2009 updated ESH/ESC and the ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly recommend the combination of 2 drugs to be considered as initial treatment whenever hypertensive patients have high initial BP or are classified as being at high cardiovascular risk[40,62,76]. Trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an angiotensin receptor antagonist, and in recent trials for the ACE inhibitor/calcium antagonist combination (the angiotensin receptor antagonist/calcium antagonist combination also appears to be effective)[40,43,62,76]. Enhanced efficacy, reduced adverse effects, improved compliance as well as a potential organ protection are the key benefits of the combination therapy[40].

Medication compliance

Compliance is defined as the extent to which a patient takes medication as prescribed. Compliance rates are often reported as percentage of prescribed dose of medication taken over a period of time. Unfortunately, a large proportion of the elderly patients discontinues or takes the drugs inappropriately[112]. This noncompliance results in failing to reach guideline-recommended BP targets. Older age, low risk for cardiovascular events, competing health problems, low socioeconomic status, complexity (e.g., multiple dosing), side effects and cost of medication regimen predict noncompliance[113].

CONCLUSION

Hypertension is an important risk factor for cardiovascular morbidity and mortality, especially in the elderly. Multiple trials have been shown that not only is it safe to treat hypertension in the elderly, but also that will decrease stroke, HF, myocardial infarction and all-cause mortality. Hypertension treatment also reduces the incidence of cognitive impairment and dementia in the elderly. The adoption of a healthy lifestyle is one of the cornerstones of hypertension management. Evidence indicates that several classes of antihypertensive drugs are effective in preventing cardiovascular events, but usually no single drug is adequate to control BP in most elderly with hypertension. Individualization of the treatment should be guided by the presence of concomitant cardiovascular risk factors. The assessment of subclinical cardiovascular organ damage resulting to an earlier onset of antihypertensive therapy leads to a reduction of the total cardiovascular risk. For all those aforementioned reasons, physicians should treat hypertension in their patients regardless of their age.

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