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Hypertension in the elderly: evidence-based management

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Abstract

Hypertension is a common finding in elderly men and women; most of them have isolated systolic hypertension (ISH). Treatment guidelines define hypertension as blood pressure (BP) higher than 140/90 mm Hg, based on an average of at least two readings taken at two or more visits, after an initial screening visit. ISH, systolic blood pressure of 140 mm Hg or greater and diastolic BP of less than 90 mm Hg, affects up to 25% of people 80 years of age, and is primarily due to increased vessel wall thickness. Lifestyle modifications must be recommended to all patients regardless of BP stage, and may be the only treatment necessary in stage 1 with no target organ damage and no risk factors if a good control is reached. Medication is indicated in stages 2 and 3 as soon as the diagnosis is confirmed. Even though diuretics and betablockers are recommended as first line therapy, other drug classes may be used as first choice depending on coexisting comorbid conditions. Blood pressure must be lowered to $<140/90$ mm Hg, but randomized trials have demonstrated that even less strict BP control can improve outcomes in elderly people. Age should not be a contraindication to treating hypertension.

Keywords: Hypertension; Systolic; Elderly; Evidence-based; Management; Treatment

1. Introduction

Hypertension is a common finding in elderly men and women. The Sixth Joint National Committee Report on the Detection, Evaluation, and Treatment of Hypertension (JNC VI) defines systolic and diastolic hypertension in elderly persons as a blood pressure (BP) of 140/90 mm Hg or higher, based on an average of two or more blood pressure readings taken at each of two or more visits, after an initial screening visit [1]. The same document defines isolated systolic hypertension (ISH) as a systolic blood pressure of 140 mm Hg or greater and a diastolic pressure of less than 90 mm Hg [1]. Hypertension is present in more than half of all persons over 60 years of age, regardless of race [2,3]. The majority of

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hypertensive patients in this age group have ISH; its prevalence increases with age, from about 5% in persons aged 60 years to almost 25% of those aged 80 years, and is more prevalent in women than in men [4]. The prevalence of hypertension was 59% in 1360 women and 54% in 459 men followed in a geriatric center; ISH accounted for 38% of the cases in the female population [5].

Systolic BP rises throughout the lifespan in industrialized societies; this fact led to the erroneous assumption that this was a normal finding with advancing age, and attributable to decreased compliance of the major arteries. However, epidemiologic data accumulated from cross-sectional studies of nonindustrialized societies have failed to show an age-related raise in SBP, indicating that other factors such as environment, lifestyle, or other diseases might be involved. Elevated SBP was found to be a more potent risk factor than elevated DBP in the MRFIT trial [6], and doubled the risk for every increment of 10 mm Hg in the population's median systolic blood pressure in The Seven Countries Study [7]. Results from the Established Populations for Epidemiologic Studies in the Elderly (EPESE) have shown that, over the age of 65, elevations of DBP decline as a cardiovascular risk factor while increased SBP continues as an important risk well into advanced age [8].

Widened pulse pressure has also been associated with increased cardiovascular risk especially for coronary heart disease [9]. Patients with pretreatment pulse pressure in the upper tertile (≥ 63 mm Hg) had a greater incidence of myocardial infarction than those in the lower tertiles, and this relationship was stronger than SBP or DBP in a study conducted by Madhaven et al. [10]. Because prospective treatment trials have not used pulse pressure per se as an entry criterion, pulse pressure should not replace elevated SBP as an indication to initiate antihypertensive therapy. Widened pulse pressure may be used to assess risk, however.

2. Pathophysiology

The NAHNES III data show a progressive increase in the average systolic blood pressure with advancing age, whereas diastolic BP peaks during the sixth decade and falls thereafter [11]. These findings have been linked with an enlarged intima-medial wall thickness of the arteries due to the accumulation of collagenous fibers, calcium deposition, and loss of elastic fibers, resulting in increased stiffness of blood vessels, greater pulse wave velocity, and augmentation of the systolic blood pressure [12,13]. Because of the reduced vascular compliance, the pulse generated during systole is transmitted to the aorta and its tributaries, resulting in a steeper increase in vascular degeneration and acceleration of other senescent changes [6]. Even though artery stiffness is the main cause of ISH, an increase in cardiac output seen in the elderly may play an important role [14]. Structural changes in the vasculature associated with aging contribute to cardiovascular baroreflex dysfunction [15], lability of blood pressure, and propensity toward orthostatic hypotension [16].

Elderly hypertensive patients tend to have low plasma volume and relatively low levels of renin and aldosterone. Renal excretion of salt tends to be decreased in these patients making them more salt sensitive than younger people are. Low calcium levels, due to poor

dietary intake and increased calciuria, may raise peripheral resistance leading to hypertension [17].

3. Diagnosis

Recommendations for measurement of blood pressure in the elderly are similar to those for the rest of the population [1]. Blood pressures should be measured by determining the average of at least two seated blood pressures taken 2 min apart after the patient has rested quietly for at least 5 min in a chair, with the arm supported at heart level, the back supported, the legs uncrossed, and the feet resting firmly on the floor rather than dangling [18]. An essential step in measuring blood pressure is the use of an appropriately sized cuff fitted to a mercury sphygmomanometer [7]. Standing and supine BP should also be measured at the first visit to discover those patients who may be more likely to develop postural hypotension when antihypertensive therapy is used [6]. As many as 18% of untreated elderly patients with hypertension will have an asymptomatic decrease in SBP of ≥ 20 mm Hg after 1–3 min in the standing position [19].

Pseudohypertension should be considered in the elderly patient with ISH; this condition is associated with a rigid sclerotic brachial or radial artery that cannot be occluded by the sphygmomanometer cuff inflated above systolic pressure. The artery continues to be palpable despite being pulseless when the cuff is inflated (positive Osler's maneuver and Osler's sign) [20,21]. In pseudohypertension, BP measured by the cuff may be falsely elevated by 10 to 15 mm Hg when compared with directed measured intraarterial pressure. Pseudohypertension should be suspected in elderly patients who have apparent elevation of BP by cuff measurement, but who have rigid vessels, minimal hypertensive changes of heart and retina, and significant postural hypotension in spite of cautious therapy [6]. Some authors argue that the Osler's sign may not be as reliable an indicator of pseudohypertension as previously thought [21,22].

Essential hypertension is the most common cause of hypertension in the elderly. However, secondary hypertension is more common in the elderly than in younger patients. Renovascular hypertension is probably the most common cause of secondary hypertension and should be suspected in new-onset hypertension in patients 60 years or older or in those whose BP becomes difficult to control with multiple drug therapy [23].

Hypertension in the elderly should be classified as recommended in The Sixth Joint National Committee Report on the Detection, Evaluation, and Treatment of Hypertension (JNC VI) [1].

4. Evidence-based management

4.1. Lifestyle therapy

The Joint National Committee and the Society of Geriatric Cardiology emphasize that lifestyle modifications should be a part of the treatment of hypertension regardless of the age of the patient [1,24]. The strongest evidence favors weight loss, low alcohol intake

(1 oz or 30 ml per day), increase physical activity (30–45 min most days of the week), and sodium restriction as having a beneficial effect on blood pressure [25]. The Trial of Nonpharmacologic Interventions in the Elderly (TONE) was a randomized, controlled trial of sodium reduction, weight reduction, or both, in 875 hypertensive patients aged 60 to 80 years with SPB lower than 145 mm Hg and diastolic BP lower than 85 mm Hg who were on a single antihypertensive medication, and followed for 15 to 36 months. The occurrence of hypertension at one or more study visits following attempted withdrawal of antihypertensive medication, treatment with an antihypertensive drug, or occurrence of a clinical cardiovascular event (myocardial infarction, angina, congestive heart failure, stroke, coronary bypass grafting, or percutaneous transluminal coronary angioplasty), were the combined outcome measures assessed in this trial. These outcome measures were less frequent among those assigned to reduced sodium intake vs. no sodium reduction; relative hazard ratio 0.69; 95% CI 0.59–0.81, $p < 0.001$, and in obese patients assigned to weight loss vs. not assigned to weight loss; relative hazard ratio 0.70; 95% CI 0.57–0.87, $p < 0.001$. The development of hypertension or a clinical cardiovascular event was reduced 31% ($p < 0.001$) with low sodium intake and 30% ($p < 0.001$) with weight reduction in obese patients. They concluded that weight loss and reduction in sodium intake are feasible, effective, and safe non-pharmacologic therapies of hypertension in the elderly [26].

Patients with mildly or moderately elevated blood pressure should be allowed to try lifestyle modification for several months. For those with target-organ damage, as indicated by a history of myocardial infarction, stroke, or renal disease, pharmacologic therapy may need to be instituted sooner than for other patients [3].

4.2. Pharmacology treatment

Randomized trials in the elderly have documented a 34% reduction in strokes, a 19% reduction in coronary heart disease events, and a 23% reduction in vascular deaths after 5 years of follow-up with a 12 to 14 mm Hg change in systolic BP and 5 to 6 mm Hg in diastolic BP compared with placebo or control [23].

At least six randomized, placebo-controlled trials have confirmed that treating SBP of 160 mm Hg or greater, regardless of DBP levels, reduces cardiovascular morbidity and mortality in the elderly (Table 1). The European Working Party on Hypertension in the Elderly Trial (EWPHE) was the first trial to assess the effects of antihypertensive therapy on persons 60 years or older with a systolic BP of 160 to 239 mm Hg and a diastolic BP of 90 to 119 mm Hg [27]. Active therapy with one or two tablets of hydrochlorothiazide/triamterene (25/50 mg) a day, with addition of methyldopa (250–2000 mg) in 35% of subjects, reduced cardiac deaths by 38% ($p = 0.04$).

The Medical Research Council Trial in the Elderly (MRC) evaluated 4369 patients, aged 65 to 74 years, with SBP of 160 to 209 mm and diastolic BP of 115 or lower who were randomized to receive placebo, or amiloride hydrochloride (2.5 mg) plus hydrochlorotiazide (HCTZ) 25 mg daily, or atenolol (50 mg once daily) [28]. The treatment goal was SBP 150 to 160 mm Hg or less; 43% of patients had ISH. Both treatment arms reduced SBP compared with the placebo group. After three months, the diuretic therapy reduced blood pressure more than atenolol. However, after 2 years, systolic and diastolic

blood pressures were similar in the diuretics and atenolol groups. More patients randomized to atenolol required supplementary drugs to control hypertension than the diuretic group (52% vs. 38%). After adjusting for baseline characteristics, the diuretic group had reduced risks of stroke (31%, 95%CI 3%-51%), coronary events (44%, 95% CI 21%–60%), and all cardiovascular events (35%, 95%CI 17%–49%), compared with placebo. The atenolol group showed no significant reduction in these end points.

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) [29] was a randomized, double blind, placebo-controlled, multicenter study conducted in 1627 patients aged 70 to 84 years, with either a SBP of 180 to 230 mm Hg and a diastolic BP of 90 mm Hg or higher, or a DBP of 105 to 120 mm Hg. This was not an ISH trial. The patients were randomly assigned to receive placebo or one of four treatment regimes: atenolol 50 mg/day, HCTZ 25 mg/day + amiloride 2.5 mg/day, metoprolol 100 mg/day, or pindolol 5 mg/day. If blood pressure was > 160/95 mm Hg after two moths of therapy, diuretic therapy was added to the beta-blocker, and vice versa. Active treatment significantly reduced stroke, all cardiovascular disease events, deaths, and heart failure, but not coronary events alone (Table 1).

5. Isolated systolic hypertension

Three randomized, double blind, placebo-controlled studies address ISH in the elderly: SHEP, Syst-Eur, and Syst-China.

The Systolic Hypertension in the Elderly Program (SHEP) trial [30] randomized 4736 patients 60 years or older, with SBP of 160 to 219 mm Hg and diastolic BP < 90 mm Hg, to receive either placebo or chlorthalidone (12.5–25 mg/day) to reach a SBP of less than 160 mm Hg. If the pressure goal was not achieved, the diuretic dose was doubled and, if necessary, either atenolol (25 mg/day) or reserpine added. Compared with placebo, patients on active treatment had a significant reduction in strokes, heart failure, and myocardial infarction. Combination therapy was needed in 44% of patients. The diabetic patients who received active treatment experienced two times fewer cardiovascular events than non-diabetic subjects did.

The Systolic Hypertension in Europe (Syst-Eur) Trial [31] reported results from a double blind, placebo-controlled trial of 4695 patients aged 60 years or older with a SBP of 160 to 219 mm Hg, and diastolic blood pressure of less than 95 mm Hg (their definition of ISH). Patients were randomized to nitrendipine (10–40 mg/day) with the addition of enalapril (5–20 mg/day) and HCTZ (12.5–25 mg/day), if necessary, or matching placebos. After a 2-year follow-up period, patients on active treatment had reduced their BP by 10 mm Hg, their stroke rate by 42%, and all cardiovascular events by 31%. Reductions in heart failure (29%) and myocardial infarction (30%) were not statistically significant.

The Systolic Hypertension in China (Syst-China) trial [32] evaluated 2379 patients aged 60 years or older with a SBP of 160–219 mm Hg and a diastolic BP of less than 95 mm Hg. Subjects were randomly allocated to receive placebo or nitrendipine (titrated 10 mg at bedtime, 20 mg at bedtime, and 20 mg BID) and, if needed, either captopril (12.5–25 mg BID) or HCTZ (12.5–25 mg BID), or both. The target was a SBP of less than 150

mm Hg and a change in sitting systolic blood pressure of 20 mm Hg or greater. Active treatment reduced total mortality by 39% and stroke mortality by 58%. Fatal and non-fatal heart failure was reduced by 58% ($p = 0.13$), and fatal and non-fatal myocardial infarction increased by 6% ($p = 0.91$).

The Shanghai Trial of Nifedipine in the Elderly (STONE) [33] was a single blind, randomized, multicenter trial aimed to evaluate whether there was a difference between long-acting nifedipine and placebo in the development of cardiovascular events in hypertensive patients between 60 and 79 years of age. There was a significant decrease in risk of strokes and severe arrhythmias in patients receiving active medication; relative risk 0.41; 95% CI 0.27–0.61.

5.1. Overview of the treatment of hypertension in the elderly

Decisions about the management of patients with hypertension should not be based on the level of blood pressure alone, but also on the presence of other risk factors, concomitant diseases, and target-organ damage.

Some of the key issues in treating elderly hypertensive patients are: when to start a drug regimen, to what extent to lower BP, and what medication to select. Lifestyle modifications should be considered for all patients regardless of age or hypertension stage, as recommended by the VI JNC document and the World Health Organization–International Hypertension Society (WHO-ISH) Guidelines for the Management of Hypertension [1,34]. In stage 1 diastolic hypertension, if appropriate lifestyle changes are effective in reaching the individual's patient goal within 6 months, drug therapy may be postponed or avoided. In stage 2–3 diastolic hypertension, drug therapy should be initiated in days or weeks after confirming the diagnosis (Table 2).

Although stage 1 ISH is associated with increased risk of cardiovascular events, there are no prospective randomized, controlled trials completed testing whether treating SBP of 140–159 mm Hg reduces events or mortality [25]. There is evidence derived from epidemiologic data or retrospective analyses of controlled trials suggesting better outcomes in treated patients, however. JNC VI recommends drug therapy for patients with stage 1 systolic hypertension in risk group C (those with target organ damage, clinical cardiovascular disease, or diabetes) or in risk group B (other risk factors, including age ≥ 60) after a maximum of 6 months of lifestyle modifications, if SBP persists above 140 mm Hg. The WHO-ISH Guidelines advocates the initiation of drug treatment in patients with SBP ≥ 150 mm Hg and low risk after 6–12 months of unsuccessful lifestyle modifications [34]. Those in risk categories high and very high should start drug therapy immediately.

There is clear evidence from the randomized, controlled trials of systolic hypertension reviewed previously that SBP persistently greater than 160 mm Hg (stages 2–3) should be treated with antihypertensive drugs after confirming the diagnosis.

5.2. Goals in hypertension treatment

The SHEP trial specified a goal of less than 160 mm Hg and at least a 21-mm reduction in SBP, while the Syst-Eur had a goal of less than 150 mm HG and at least 20 mm Hg in

reduction. Those levels were associated with better outcomes, and there has not been evidence that lower SBP may result in additional improvement [25]. However, the VI JNC, the WHO-ISH, and the Guidelines of the Spanish Society of Cardiology on High Blood Pressure advocate a goal of less than 140/90 mm Hg for elderly patients [1,34,35]. Even if these levels cannot be achieved, the data shown in the studies reviewed support that still a less strict BP control can benefit elderly patients.

There has been controversy regarding how low DBP should be. Patients actively treated in the SHEP trial [30] had an average DBP of 68 mm Hg, with fewer coronary events than those in the placebo group. At 2 years, in the intention-to-treat analysis of patients in the Syst-Eur trial [31], DBP had fallen by a mean of 7 mm Hg in the treatment group. Even though a lesser result was seen in patients in the Syst-China trial (3 mm Hg) [32], patients on active treatment had better outcomes in both trials.

The Hypertension Optimal Treatment (HOT) [36] trial was designed to answer whether there is benefit or harm to lowering DBP to less than 90 mm Hg. Patients aged 50 to 80 years (mean 61.5 years) and diastolic BP 100 to 115 mm Hg were randomly assigned to a target DBP of 90 mm Hg or less, 85 mm Hg or less, or 80 mm Hg or less. There were no significant differences in major cardiovascular, coronary, or cerebrovascular events among the three groups. The results suggested increased risk at a BP of >90 mm Hg diastolic and >160 mm Hg systolic. Even though the HOT study did not have enough power to demonstrate whether those with the lowest goal did best, it was able to show that there was not an apparent harm with aggressive management [25].

In elderly diabetic patients, the HOT and UKPDS trials rendered evidence supporting a blood pressure goal of less than 150/85 mm Hg [36,37]. Nevertheless, an attempt to achieve BP levels recommended by the treatment guidelines should be made in all patients.

5.3. Choice of antihypertensive drug

Diuretics or beta-blockers are recommended as first choice therapy by JNC VI [1]; the WHO-ISH Guidelines and the Spanish Society of Cardiology Guidelines advise to tailor first choice therapy according to patient characteristics and comorbidity [34,35]. The diuretic-based therapy in SHEP and the diuretic arm of the MRC elderly trial reduced the incidence of stroke and other cardiovascular events [28,30] (Table 1), while atenolol did not [28]. This led to the indication not to use a beta-blocker as monotherapy in the elderly, unless there was a comorbid condition requiring this class of drug [1].

A systematic review of 10 randomized controlled trials in patients older than 60 years of age showed that 2/3 of the patients assigned to diuretics were well controlled on monotherapy, whereas less than a third of patients on beta-blockers were so. Diuretics were superior to beta-blockers with regard to stroke prevention (odds ratio [OR], 0.61), fatal stroke (0.67), coronary heart disease (0.75), cardiovascular mortality (0.75), and all-cause mortality (0.86). On the other hand, beta-blockers reduced cerebrovascular events only (0.75) but were ineffective in preventing coronary heart disease (1.01), cardiovascular mortality (0.98), and all-cause mortality (1.05) [38].

The calcium antagonist nitrendipine used in the Syst-Eur and Syst-China studies, and nifedipine used in the STONE trial consistently reduced the risk for stroke and showed

good BP control [31–33]. The International Nifedipine GITS Study (INSIGHT) compared nifedipine gits (30–60 mg/day) with a diuretic combination (HCTZ 25 mg + amiloride 2.5 mg) in patients 55–80 years of age and found that they were equally effective in preventing overall cardiovascular or cerebrovascular complications [39].

The ALLHAT and CONVINCE trials are two ongoing studies comparing different antihypertensive drugs in patients older than 55 years. ALLHAT is comparing chlorthalidone, amlodipine, lisinopril and doxazosin; and CONVINCE is comparing verapamil (crono) at bedtime, a diuretic, and a beta-blocker. When these results are available, the place of these drugs in treating elderly hypertensive patients will be more clearly defined.

In hypertensive type II diabetics, several relatively small controlled trials have reported lower cardiovascular event rates with an ACE inhibitor than with a calcium antagonist [25].

Some conditions require specific drugs. These compelling indications are based on randomized, controlled trials and are well established in treatment guidelines [1,34,35,40]. For systolic heart failure, ACE inhibitors and diuretics are appropriate initial choices. For myocardial infarction, beta-blockers without intrinsic sympathomimetic activity are recommended; if systolic dysfunction is also present, an ACE inhibitor should be added (Table 3).

5.4. Combination therapy

Combination therapy may often be necessary to provide additional efficacy in elderly patients. Among the causes for treatment failure when using monotherapy we have: noncompliance, drug-related—lack of efficacy, side effects—activation of counterregulatory mechanism, volume overload, secondary hypertension, and high pretreatment BP. In the MRC trial, [28] 52% of patients in the atenolol group and 38% in the diuretic group received more than one drug to control BP, 44% in the SHEP trial, at 5 years, used combination therapy [30], while 40% needed two agents in the Syst-Eur study [31]. By combining two drugs that work through different mechanisms, additive effects on BP reduction are often obtained. Besides, drug tolerability may improve if lower doses of each agent are used. Additionally, when used, fixed-dose combination can increase compliance and reduce costs. For patients with blood pressures of about 160/95 mm Hg, the usual reduction produced by monotherapy is about 7–13 mm Hg systolic and 4–8 mm Hg diastolic [34]. This reduction might not be enough to restore BP to optimal or nonhypertensive levels; a combination could be the first choice in such cases.

Currently, the fixed dose combinations of bisoprolol (a betablocker) plus low dose HCTZ and that of captopril plus HCTZ are approved for the initial treatment of hypertension. The remainder should be utilized after a trial of monotherapy [41].

5.5. Hypertension in the very old

Because elderly people have a greater risk of cardiovascular disease without treatment than younger people, the effect of reducing BP is greater in hypertensive people over 60 or 65 years of age. Nevertheless, there is no evidence that this is true in patients 80 years or older. A subgroup meta-analysis of randomized controlled trials found 34% lower rate of

fatal and nonfatal stroke (relative risk 0.66), and a benefit for major cardiovascular events and heart failure [42]. A non-significant trend of increased total mortality was also reported. The Hypertension in the Very Elderly Trial (HYVET), an ongoing study, will determine whether active treatment of hypertension in patients over 80 years can reduce the incidence of stroke [43]. Currently, there are no data of an age threshold above which hypertension should not be treated.

5.6. Conclusions

Hypertension is common in elderly men and women and most patients in this age group have isolated systolic hypertension. Elderly people are particularly susceptible to suffering orthostatic hypotension; this must be kept in mind when drug treatment is indicated. Lifestyle modifications must be instituted in all patients, regardless of hypertension stage, for 6 to 12 months before starting medication, unless there is target organ damage or other risk factors, when drug therapy must begin together with lifestyle changes. Blood pressure control in the elderly has been associated with reductions in coronary heart disease, strokes, and congestive heart failure, so an attempt to reduce hypertension to levels recommended in the treatment guidelines is mandatory in these patients.

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