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Hypertension in the very elderly: Brief review of management

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Abstract

This brief review discusses pharmacological management of hypertension in very elderly patients, a very powerful and rapidly growing subpopulation of patients.

It is well known that age is the most powerful risk factor for death, cardiovascular death and hypertension. Blood pressure reduction is effective in preventing major vascular events including stroke and heart failure. However, earlier trials were inconclusive as to whether treatment of this age group is beneficial. One of these trials, subgroup meta-analysis (1999) which enrolled 1,670 patients in seven clinical trials, showed a 36% lower risk of stroke and a 39% lower risk of heart failure, but slightly increased all-cause mortality.

More recently, however, data coming from the Hypertension In the Very Elderly Trial (HYVET) has resolved the clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients over 80 years old. HYVET studied a relatively healthy 3,845 patients, who were assigned to indapamide ± perindopril vs. *placebo ± placebo. There was a significant reduction in cardiovascular morbidity and mortality. What was unexpected was that overall mortality reduced as well in actively treated individuals.*

No specific guidelines exist for hypertension management for this particular population. Data from clinical trials including HYVET favor thiazide diuretics, angiotensin converting enzyme inhibitors and calcium channel blockers for either mono-therapy or combination therapy for hypertension in the elderly. (Cardiol J 2009; 16, 4: 379–385)

Key words: hypertension, very elderly, HYVET, diuretics

Introduction

According to the World Health Organization, hypertension is the commonest cause of preventable death in developed countries and is increasingly significant in developing countries [1]. The prevalence of hypertension increases with age. Based on US Census Bureau data, the numbers of very elderly people (those aged 80 or older) is expected to reach 15 million, or 4.5% of the US population, within the next 20 years [1, 2].

Age is the most powerful risk factor for hypertension, death, and cardiovascular death [1]. Blood pressure reduction has been shown to be effective in preventing major vascular events including stroke and heart failure in hypertensive individuals [3]. However, it has remained unclear whether treatment of hypertension in the very elderly is

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Table 1. Cardiovascular risk factors and end-organ damage in hypertension (based on the Seventh Report of the Joint Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure — the JNC 7 Report).

Risk factor	End-organ damage
Hypertension	CAD
Tobacco use	LVH
Obesity	CHF
Dyslipidemia	Stroke/TIA
Sedentary lifestyle	Chronic kidney disease
Diabetes mellitus	Peripheral artery disease
Microalbuminuria	Retinopathy
Age:	
Men: above 55	
Women: above 65	
Family history of CAD:	
Men: below 55	
Women: below 65	

CAD — coronary artery disease; LVH — left ventricular hypertrophy; CHF — congestive heart failure; TIA — transient ischemic attack

beneficial [4, 5]. Early clinical trials enrolled few individuals aged 85 or older. The most likely reason for this was concern about their short life expectancy [6, 7]. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) made no exceptions to the target blood pressure recommendations in the very elderly group of individuals [8] (Table 1).

The patterns of blood pressure elevation change with age. Systolic blood pressure initially rises in adolescence and continues throughout life, while diastolic blood pressure initially increases, then begins to decrease after the age of 60. This leads to a widening of the pulse pressure, which is indicative of central arterial stiffening. However, in people who develop isolated systolic hypertension, there is no antecedent diastolic hypertension. These distinct patterns suggest different etiologic and hemodynamic mechanisms for these two entities [9]. Hypertension left untreated accelerates the development of arterial stiffness, regardless of subtype. This, in turn, accentuates age-related arterial stiffening.

In patients with sustained hypertension, there is no change in cardiac output or blood flow to the organs due to autoregulation despite an increase in vascular resistance. Autoregulation is maintained both by short-term mechanisms (myogenic response and metabolic control) and long-term mechanisms (thickening of vessels and reduction in the number of capillaries). Increases in blood pressure lead to an activation of autoregulatory responses, resulting in increased oxygen delivery to tissues, decreased concentration of active metabolites, increased myogenic constriction, and decreased release of endothelial vasodilatory factors.

Clinical trials

The commonest form of hypertension in elderly people is isolated systolic hypertension. In the Framingham Heart Study, 90% of participants with normal blood pressure at the age of 55 developed hypertension as they aged. It was found that 57% of men and 65% of women between 65 and 89 years developed systolic hypertension [1, 10]. Most isolated systolic hypertension is caused by decreased elasticity and increased stiffness of large arteries as a consequence of arteriosclerosis. In addition, elevations in blood pressure cause direct damage to the endothelium and impaired vasodilatation. Systolic hypertension has been identified as a risk factor for cardiovascular and renal disease [11].

The importance of isolated systolic hypertension and its treatment has been addressed in several clinical trials (Table 2). Systolic Hypertension in the Elderly Program (SHEP) included 4,736 individuals over the age of 65 with identified hypertension. The patients were assigned to treatment with chlorthalidone or a placebo. Chlorthalidone therapy decreased the risk of stroke of any kind by 36%, cardiovascular risk by 25% and risk of heart failure by 49% compared to the placebo. Furthermore, the effect of treating blood pressure to a goal of 150 mm Hg was superior to that of aiming for a goal of lower than 160 mm Hg [12]. The results of the SHEP trial were supported by similar results from two large clinical trials: European Trial in Systolic Hypertension (Syst-Euro Trial) and Systolic Hypertension in China (Syst-China Trial). In these, treatment with nitrendipine, a calcium channel blocker, was associated with a significantly reduced incidence of stroke, coronary artery disease and congestive heart failure [10, 13, 14]. A meta-analysis of eight clinical trials involving 15,693 elderly patients with isolated systolic hypertension showed that antihypertensive therapy reduced the risk of stroke by 30%, coronary artery disease by 23%, and cardiovascular risk by 26%. All-cause mortality was reduced by 13% and cardiovascular mortality by 18% [10, 15].

A recent retrospective cohort analysis by Oates et al. [16] involved 4,071 patients, of whom 84.5%

Table 2. Summary of clinical trials involving elderly population of patients; N = number of individuals involved in the study.

Trial	Population	Intervention	Results
SHEP	N = 4376; age: above 65	Chlorthalidone *vs*. placebo	Stroke risk reduction (–36%, CI 18–50; p = 0.001) Cardiovascular risk reduction (–34%) Heart failure risk reduction All cause mortality reduction (–13%)
SYST-EUR	N = 4695; age: above 60	Nitrendipine ± enalapril/ /hydrochlorothiazide *vs*. placebo	Stroke risk reduction (–42%, CI –60 to –18; p = 0.002) Cardiovascular risk reduction (–26%, CI –43 to –2; p = 0.03) Cardiovascular mortality reduction (–27%, CI –46 to –3; p = 0.07)
STOP- HYPERTENSION	N = 6614; age: above 70	*BB/diuretic *vs*. lisinopril/ /enalapril *vs*. felodipine/ /isradipine	Cardiovascular mortality similar in all three groups Heart failure risk reduction similar in all three groups Stroke risk reduction (all types): ACEI and CCB superior *vs*. BB/diuretic (–25%, CI 0.58–0.97; p = 0.027)
ALLHAT	N = 33 357; age: above 55 N = 19 013; age: above 65	Chlorthalidone *vs*. amlodipine/lisinopril	Heart failure prevention: chlorthalidone superior *vs*. amlodipine/lisinopril (7.7% *vs*. 10.2%/8.7%) Diuretic/CCB (RR 1.38, CI 1.25–1.52, p = 0.001) Diuretic/ACEI (RR 1.19, CI 1.07–1.31, p = 0.001) Stroke risk reduction: chlorthalidone superior *vs*. lisinopril (5.6% *vs*. 6.3%; RR 1.15, CI 1.02–1.3, p = 0.02) Cardiovascular risk: chlorthalidone superior *vs*. lisinopril (30.9% *vs*. 33.3%; RR 1.10, CI 1.05–1.16, p = 0.001)
HYVET	N = 3845; age: above 80	Indapamide ± perindopril *vs*. placebo	Stroke risk reduction (–30%, CI –1 to 51, p = 0.05) All cause mortality reduction (–21%, CI 4–35, p = 0.02) Cardiovascular mortality reduction (–23%, CI –1 to 40, p = 0.06) Cardiovascular risk reduction (–34%, CI 18–47, p = 0.001) Heart failure risk reduction (–64%, CI 42–78, p = 0.001)

*BB/diuretic: atenolol, metoprolol, pindolol/hydrochlorothiazide + amiloride; **95% confidence interval (CI); BB — beta-blocker; ACEI — angiotensin--converting enzyme inhibitors; CCB — calcium channel blocker; SHEP — Systolic Hypertension in the Elderly Program; SYST-EURO — European Trial in Systolic Hypertension; STOP-HYPERTENSION — the Swedish Trial in Old Patients with Hypertension; ALLHAT — the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; HYVET — the Hypertension In the Very Elderly Trial

were receiving blood pressure lowering agents. It showed a shorter survival in patients with systolic blood pressure lower than 140 mm Hg. A subgroup meta-analysis by Gueyffier et al. [17] (INDANA subgroup) enrolled 1,670 patients in seven clinical trials that compared active drug therapy versus a placebo or no treatment. Active drug therapy showed a 36% risk reduction of stroke, 39% reduction in heart failure and a 22% reduction in major cardiovascular events. On the other hand, results showed a 14% increase in risk of death from any cause. The risk of cardiovascular death was shown to be slightly higher as well. The treatment regimens used in trials involved in INDANA were based on high doses of diuretics and beta-blockers.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large randomized control trial that proved that

one of the benefits of blood pressure lowering therapy is the prevention of heart failure. These findings were extended to the subgroup of elderly patients [18, 19]. ALLHAT compared the effects of chlorthalidone, amlodipine and lisinopril in the prevention of heart failure. Chlorthalidone was found to be superior to amlodipine and lisinopril in heart failure prevention. Chlorthalidone was also shown to be more effective than lisinopril in lowering blood pressure, preventing stroke, and decreasing combined cardiovascular events. ALLHAT demonstrated that chlorthalidone had a significantly higher risk of hyperglycemia compared with amlodipine or lisinopril. Despite the higher incidence of hyperglycemia, the cardiovascular risk at the long-term follow-up favored chlorthalidone. Chlorthalidone remained the best medication for treatment in diabetic patients for the combined endpoints of heart failure and cardiovascular events [18].

To date, the most encouraging data supporting aggressive management of hypertension in the elderly population comes from the Hypertension In the Very Elderly Trial (HYVET). The goal of HYVET was to resolve the clinical uncertainty of antihypertensive treatment in patients over 80 [20]. It was designed as a randomized, double-blind placebo trial that enrolled 3,845 patients from 195 centers in Europe, China, Australia, and North Africa. The patients were assigned to receive treatment with either indapamid or a placebo. The patients who did not achieve a blood pressure goal of 150/80 mm Hg were then assigned perindopril or a placebo. The primary endpoint was stroke of any kind. Secondary endpoints were death from any cause, death from cardiovascular causes, death from cardiac causes, and death from stroke. The median duration of the follow-up was 1.8 years. Results showed a 30% reduction in stroke rate. The rate of fatal stroke was reduced by 39%. With regard to secondary endpoints, there was a 21% reduction in the rate of death from any cause, the rate of death from cardiovascular causes was reduced by 23%, but the rate of death from cardiac causes was not reduced significantly in the actively treated group. There was a significant reduction of the rate of fatal or nonfatal heart failure (64%), and the rate of any cardiovascular event (death from cardiovascular events or stroke, myocardial infarction, heart failure, 34%) [20].

There were no significant differences in serum potassium levels between the groups as well as in serum glucose, creatinine or uric acid. The number of serious events was lower in the actively treated group [20].

The significant reduction in the risk of heart failure demonstrated in HYVET strongly supports the ALLHAT conclusions. The lowest rates of fatal events and hospitalizations for heart failure were found in patients treated with diuretic or angiotensin converting enzyme inhibitors (ACEI). Heart failure remains the most frequent reason for hospital admissions among patients over 65 in the United States, with the one-year mortality rate ranging from 20 to 50%. Hypertension remains one of the most powerful risk factors for heart failure. ALLHAT and HYVET results stress the importance of blood pressure control in preventing heart failure.

The data from HYVET, which demonstrates risk reduction in death from any cause in the actively treated group, outweighs the results of INDANA meta-analysis. The blood pressure regimen used in the studies involved in INDANA consisted of high doses of diuretics and beta-blockers. Diuretics used as a single drug are associated with high risk of hypokalemia and related arrhythmias. A combination of diuretic and ACEI may have a balanced effect on serum potassium levels [20].

Data from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) showed beta-blockers to be less effective in the treatment of hypertension [21]. These observations may partially explain the unfavorable results of the INDANA meta-analysis.

HYVET and the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) trial both demonstrated the mortality benefit of blood pressure management [22, 23].

Discussion

A therapeutic approach to the management of hypertension in the very elderly should start with lifestyle modifications. This remains the case regardless of age. Lifestyle modifications include weight reduction, dietary modifications (i.e. reduction of salt intake and increases in fruit and vegetable intake), increase in physical activity and moderate alcohol consumption. Clinical trials have identified five classes of medication that have been successfully used in elderly patients. These classes are: thiazide diuretics, ACEI, beta-blockers, angiotesin-receptor antagonists and calcium channel blockers.

Joint National Committee 7 guidelines recommend thiazide-type diuretics as initial drug therapy for most patients with hypertension, regardless of age (Table 3). Thiazides can be administered once daily and are efficient in low doses in the elderly.

Table 3. Existing guidelines for general population of patients.

Guidelines	Area of concern	Target BB [mm Hg]	Drug of choice
JNC 7	General population	< 140/80	Thiazide diuretic# unless other medical conditions preexist
	DM, CKD	< 130/80	ACEI or ARB
AHA and ESH/ESC	General population/ /primary CAD prevention	< 140/80	Any group
	High CAD risk*	< 130/80	ACEI *or* ARB *or* CCB *or* thiazide diuretic *or* combination
	Stable angina	< 130/80	BB *and* ACEI *or* ARB
	ACS**	< 130/80	BB *and* ACEI *or* ARB
	Left ventricular dysfunction	< 120/80	ACEI *or* ARB *and* BB *and* aldosterone antagonist *and* thiazide diuretic *or* loop diuretic *and* hydralazine/isosorbide dinitrate

#without compelling indication: heart failure, post-myocardial infarction, CKD, DM etc. (see text); *DM, CKD, known coronary artery disease (CAD) or CAD equivalent (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm) or 10-year Framingham risk score ≥ 10%; **unstable angina, STEMI, NSTEMI; JNC7 — the Seventh Report of the Joint Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure; ESH — European Society of Hypertension; ESC — European Society of Cardiology; ACS — acute coronary syndrome; ACEI — angiotensin-converting enzyme inhibitors; ARB — angiotensin receptor blockers; BB — beta-blocker; CCB — calcium channel blocker; DM — diabetes mellitus; CKD — chronic kidney disease

Additionally, they can be successfully combined with other classes of anti-hypertensive medications with additive effects and minimal side effects. Known side effects of diuretics include hypokalemia, hyperglycemia, hypomagnesaemia and hyperuricemia. None of these side effects has been associated with increased short-term mortality in clinical trials [9].

Certain classes of antihypertensive medication are indicated if significant medical conditions coexist, e.g. hypertension with coexisting chronic kidney insufficiency is an indication for ACEI or angiotensin-receptor blocker; a history of myocardial infarction is an indication for beta-blockers. The American College of Cardiology and the American Heart Association recommend ACEI as first-line agents in all stages of heart failure. ACEI improve exercise tolerance and reduce death from heart failure in all patients, including elderly patients. The mechanism of action is based on decreasing production of angiotensin II and reducing sympathetic nervous system activity. The sympatholytic actions in heart failure increase the ventricular filling time and improve contractile efficiency. The most common side effects of ACEI are: cough, hyperkalemia, angioedema and reversible functional renal insufficiency secondary to reduced renal perfusion pressure.

The benefits of beta-blockers therapy for elderly patients with hypertension have been questioned recently [10]. A meta-analysis of intervention trials for hypertension showed a 16% higher incidence of stroke among patients treated with beta-blockers (primarily atenolol) compared to those treated with other antihypertensive medications [24]. The lack of benefit from beta-blockers could be attributed to a smaller reduction in blood pressure compared with other medication classes. The most important mechanisms responsible for antihypertensive beta-blockers include: inhibition of renin release, central nervous system effect, reduction of heart rate and cardiac output, reduction in peripheral vascular resistance, and reduction in vasomotor tone. Beta-blockers may worsen glucose intolerance or mask the symptoms of hypoglycemia and should be used with caution in patients with insulin-dependant diabetes mellitus. Elderly patients are at high risk of developing orthostatic hypotension with beta-blockers. Beta-blockers are most appropriate for the management of hypertension accompanied by ischemic heart disease, heart failure and arrhythmias and their use in elderly patients should probably be limited to those with these pre-existing conditions. It is unclear whether such restrictions should also apply to newer beta-blockers with peripheral vasodilator effects.

The main differences between the treatment of older as opposed to younger individuals are careful monitoring of elderly patients towards postural and postprandial hypotension before initiation of treatment. Elderly patients may have sluggish baroreceptors and sympathetic nervous responsiveness as well as impaired cerebral autoregulation. Thus the reduction of blood pressure

Table 4. General guidelines for treatment of hypertension in the very elderly (age above 80).

Blood pressure goal [mm Hg]	Drug of choice	Special precautions
General population: < 140/80 High CAD risk: < 130/80	Thiazide diuretic *and/or* ACEI, *and* CCB in combination to reach target blood pressure	Dose: carefully, use low initial doses to minimize side effects
Left ventricular dysfunction: < 120/80	Avoid beta-blocker as primary therapy unless specific indication exists (e.g. status post MI, CHF)	Assess for postural/ /postprandial hypotension before initiating therapy Note that trials involved relatively fit and active individuals, apply carefully to frail patients

ACEI— angiotensin-converting enzyme inhibitors; CAD — coronary artery disease; CCB — calcium channel blocker; CHF — congestive heart failure; MI — myocardial infarction;

should be gradual to minimize the risk, and these patients may require lower initial doses of medication. We also emphasize that trials showing benefits from the treatment of hypertension in the elderly were performed in relatively fit patients. Greater caution should be applied to the therapy of frail individuals.

Treatment of hypertension in the elderly shows a significant benefit, regardless of the medication group (Table 4). All the guidelines (The Joint National Committee, American Medical Association, American Heart Association, American Society of Hypertension, European Society for Hypertension, and European Society of Cardiology) emphasize that the major benefits of therapy are related to lowering blood pressure and controlling hypertension [25]. Thiazide diuretics and ACEI seem to be optimal drugs to safely achieve blood pressure reduction and may provide survival benefits and reduce the risk of stroke or heart failure [20]. Calcium channel blockers can be sequentially added or substituted. Data suggests that beta-blockers should not be used as primary therapy for hypertension in the elderly. They do not appear to be better than other groups in primary prevention of myocardial infarction in this population, and may be less effective in stroke prevention than other agents. Unless indicated (post-myocardial infarction or coronary heart failure) beta-blockers should be avoided in very elderly patients.

Summary

Existing data, specifically the HYVET trial results, indicates an overall benefit of hypertension treatment in the very elderly. Treatment of hypertension is likely to prevent heart failure, reduce stroke and prolong life. The target blood pressure in the very elderly needs to be further established, but based on the HYVET trial, a blood pressure target of less than 150/80 mm Hg seems both effective and safe [20]. More aggressive goals, such as those of the JNC-7, may be similarly appropriate for the very elderly.

Current evidence favors the use of diuretics (indapamide or chlorthalidone) as the initial drugs used in the management of hypertension in this subpopulation. However, as shown in ALLHAT and HYVET, single drug therapy may not be sufficiently effective to achieve target blood pressure goals and ACEI would be a reasonable option for combination therapy [1, 18].

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