European Society of Hypertension Scientific Newsletter:
Update on Hypertension Management
2001; 2: No.6

ISOLATED SYSTOLIC HYPERTENSION: Cardiovascular risk and treatment benefits

Csaba Farsang, 1st Department of Internal Medicine, St. Emeric Hospital, Budapest, Hungary and Peter Sleight, Department of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford, United Kingdom.

Introduction

Definition of isolated systolic hypertension (ISH) according to JNC-VI (1) and 1999 WHO/ISH (2): systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure <90 mmHg. Accordingly, the different grades of ISH are defined as follows:

Grade 1:	SBP < 160 mm Hg
subgroup borderline	SBP < 150
Grade 2:	SBP < 180 mm Hg
Grade 3:	SBP ≥ 180 mm Hg

Pathogenetic factors: Age-related vascular and neurohumoral changes are important factors leading to the development of hypertension and particularly of ISH. Arterial compliance deteriorates because of structural and functional changes and increases is collagen, extracellular protein matrix, ground substance, elastin that occur with age. These changes create structural and mechanical alterations in the vessel intima and media. Calcium binds to the elastin, and undifferentiated muscle cells of the media proliferate and migrate through the elastic laminae to the intima. The proliferation of the connective tissue results in intimal thickening and fibrosis, increases the stiffness of the vessels with partial loss of contractility. Consequently, arterial compliance diminishes and the so called „windkessel function" of the large arteries decreases. Pulse pressure and pulse wave velocity increase with an earlier reflection of pressure waves from the periphery, to a disproportionate increase in systolic blood pressure. Consequently, systolic blood pressure increases while diastolic blood pressure does not change or decreases particularly over the age of 60 (3, 4, 5).Cardiac output, stroke volume, intravascular volume, renal blood flow and plasma renin activity decrease, while left ventricular mass (prevalence of left ventricular hyperthrophy - LVH), circulating catecholamines, particularly noradrenaline, and total peripheral vascular resistance increase. Baroreceptor sensitivity to blood pressure changes also decreases causing a higher blood pressure variability.

ISH as cardiovascular risk

There are little data on the prevalence of ISH, using the latest definition of ≥140/<90 mm Hg. Prevalence of ISH (old definition) increases with age (Table 2). It becomes the most common type of hypertension in the elderly, and it is the most prevalent type of untreated hypertension among older people over 60 yrs of age (6).

Table 2.
Prevalence of ISH (old definition of ≥160/<90 mm Hg)

Age	(%)
50	0.8
60	5.0
70	8-12.6
80+	23-25

According to the cumulative 24-year data from the Framingham Study (also using the old definition) the incidence of ISH is high both in women (533/1000) and in men (418/1000) over the age of 65 years. ISH was the most common type of diagnosed hypertension (57.4% in men, 65.1% in women) at the age over 65 yrs (7). Subjects with Grade-1 ISH (old definition: borderline ISH) were found to be at increased risk of progression to definite (Grade 2) hypertension and the development of cardiovascular disease (7). Several studies have demonstrated the increased risk for cardio- or cerebrovascular diseases, and death (including sudden death) of patients with ISH. ISH increases cardiovascular morbidity and all-cause mortality twofold or more and triples cardiovascular mortality. In the MRFIT study of 316 099 men it was found that systolic blood pressure was a stronger predictor of outcome than diastolic blood pressure, and an excess risk of cardiovascular diseases exists in subjects with stage I (borderline) ISH (8, 9, 10, 11, 12). Untreated ISH patients showed a high prevalence of LVH with a concentric remodelling (13), which has been shown to have a poor cardiovascular prognosis (14). The meta-analysis of 8 outcome trials involving 15,693 patients with ISH and a follow-up period of 3.8 years (median) showed that the relative hazard rates associated with a 10 mm Hg higher initial systolic blood pressure were 1.26 for total mortality, 1.22 for stroke, but only 1.07 for coronary events. Independent of systolic blood pressure, diastolic blood pressure was inversely correlated with total mortality, stressing the role of pulse pressure as risk factor (21).

Treatment benefits

Randomised clinical trials provided compelling evidence that treatment of ISH results in significant benefits. The landmark trial of Systolic Hypertension in the Elderly Program (SHEP) in 4716 patients first proved the benefit on CV morbidity and mortality of antihypertensive treatment with chlorthalidone (with the option of adding atenolol or reserpine). Non-fatal stroke was reduced by 37 %, non-fatal myocardial infarction by 33 %, and left ventricular failure by 54 %. There were strong trends to decrease in transient ischemic attacks (25 %), and in total (13 %), cardiovascular (20 %), cerebrovascular (29 %) and coronary (20 %) mortality (15). This trial also pointed out that serum uric acid independently predicts cardiovascular events in patients with ISH. These patients experienced the same benefit from diuretic-based treatment as those with low baseline serum uric acid levels (16). The Systolic Hypertension in Europe (Syst-Eur) was the first large (4695 patients with ISH) study of the effect of a longer-acting calcium antagonist, nitrendipine (with optional add-on enalapril and/or hydrochlorothiazide), on long-term morbidity and mortality risks. Total strokes were reduced by 42 % (17). In the Syst-Eur trial the rate of vascular dementia was also reduced by 50 % (18), while it was not changed by the chlorthalidone-based therapy in the SHEP (16), therefore a specific neuroprotecive effect of dihydropyridine-type calcium antagonist, nitrendipine was hypothesized. The Syst-China trial confirmed the beneficial effect of nitrendipine in patients with ISH as it reduced total strokes by 38 %, stroke mortality by 58 %, all-cause mortality

by 39 %, cardiovascular mortality by 39 %, fatal and non-fatal CV events by 37 % (19). Subgroup analysis of the recently published INSIGHT trial showed that patients with ISH were slightly more responsive than ordinary hypertension to treatment by long-acting nifedipine-GITS as significantly less patients required addition of a second drug. An important result from this study showed that patients with ISH whose diastolic blood pressure significantly decreased with increasing therapy were smokers with existing evidence of atherosclerosis (20). Staessen's meta-analysis showed that active treatment reduced total mortality by 13 %, cardiovascular mortality by 18 %, all cardiovascular complications by 26 %, stroke by 30 % and coronary events by 23 %. The absolute benefit was larger in men, in patients aged 70 yrs. or more, and in those with previous cardiovascular complications or wider pulse pressure. Therapy prevented strokes more effectively than coronary events (21).

Efficacy trials showed that thiazide-based treatment is superior to beta-blockers for reduction of blood pressure and prevention of cardiovascular complications (22, 23, 24). Recent trials with newer antihypertensive agents, such as ACE-inhibitors, angiotensin AT1 receptor antagonists have also demonstrated improved blood pressure control of patients with ISH (25, 26). The new class of antihypertensive drugs, the vasopeptidase inhibitors such as omapatrilate, may have a particular importance in the treatment of patients with ISH because its effect on systolic blood pressure is greater than on diastolic blood pressure (27).

Guidelines for management of ISH: Lifestyle modifications (physical exercise, reduction in salt intake, weight reduction in obese patients, stop smoking) are advised as first-line therapy for the patients with ISH (1, 2). The recommended target systolic blood pressure is to or below 140 mm Hg (with a possible interim goal to below 160 mm Hg). If lifestyle modifications fail to reach the target, drug therapy is advised to control blood pressure. Diuretics and long-acting dihydropyridine-type calcium antagonists are considered first-line treatment of patients with ISH. ACE-inhibitors, angiotensin AT1 receptor antagonists are also effective drugs for ISH, but there are less data available regarding their effects on cardiovascular mortality and morbidity in patients with ISH. The results of several ongoing trials are expected to provide further information on possible additional advantage of newer promising agents.

References

1. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Sixth Report. Arch Intern Med 1997;157:2413-46.
2. Guidelines Subcommittee. 1999 World Health Organization - International Society of Hypertension Guidelined for the management of hypertension. J Hypertens 1999;17:151- 83.
3. Messerli FH. Essential hypertension in the elderly. Triangle 1985;24:35-47.
4. Messerli FH, Ventura HO, Glade LB et al. Essential hypertension in the elderly: haemodynamics, intravascular volume, plasma renin activity, and circulating catecholamine levels. Lancet 1983;2:983-86.
5. Grassi G, Seravalle G, Bertinieri G et al. Sympathetic and reflex alterations in systo-diastolic and systolic hypertension of the elderly. J Hypertens 2000;18:587-593.
6. Staessen J., Amery A., Fagard R. Isolated systolic hypertension in the elderly. J Hypertens 1990;8:393-405.
7. Wilking SVB, Belanger A, Kannel WB et al. Determinants of isolated systolic hypertension. JAMA 1988;260:3451-55.
8. Black HR. Individualized selection of antihypertensive drug therapy for older patients. Am J Hypertens 1998;11:62S-67S.
9. Curb JD, Borhani NO, Entwisle G et al. Isolated systolic hypertension in 14 communities. Am J Epidemiol 1985;121:362-70.
10. Kannel WB, Dawber TR, McGee DL. Perspectives on systolic hypertension: the Framingham Study. Circulation 1980;61:1179-82.
11. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992;152:56-64.
12. Himmelmann A, Hedner T, Hansson L. Isolated systolic hypertension: an important cardiovascular risk factor. Blood Pressure 1998; 7:197-207.
13. Heesen WF, Beltman FW, May JF et al. High prevalence of concentric remodelling in elderly individuals with isolated systolic hypertension from a population survey. Hypertension 1997;29:539-43.
14. Koren MJ, Devereux RB, Casale PN et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med 1991;114:345-52.
15. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older person with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991; 265:3255-64.
16. Franse LV, Pahor M, Di Bari M et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000;18:1149-54.
17. Staessen JA, Fagard R, Thijs L et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. Lancet 1997; 350:757-64.
18. Forette F, Seux ML, Staessen JA et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352:1347-51.
19. Liu L, Wang JG, Gong L, Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. J Hypertens 1998;16:1823-29.
20. Brown MJ, Castaigne A, de Leeuw PW et al. Influence of diabetes and type of hypertension on response to antihypertensive treatment. Hypertension 2000; 35:1038-42.
21. Staessen JA, Gasowski J, Wang JG et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000;355:865-72.
22. Kostis JB, Pressel SL, Cutler JA et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1997; 278:212-6.
23. Avanzini F, Alli B, Betteli G et al. Antihypertensive efficacy and tolerability of different drug regimens in isolated systolic hypertension in the elderly. Eur Heart J 1994;14:206-12.
24. Messerli FH, Grossman E, Goldbourt U. Are β-blockers efficacious as first-line therapy for hypertension in the elderly? A systematic review. JAMA 1998;279:1903-7.
25. Tonkin A, Wing L. Management of isolated systolic hypertension. Drugs 1996; 51:738-49.
26. Farsang C, Garcia-Puig J, Niegowska J et al. for Losartan Investigators Group. The efficacy and tolerability of losartan versus atenolol in patients with isolated systolic hypertension. J Hypertens 2000; 18:795-802.
27. Larochelle P, Smith DHG, Ouellet J et al. Efficacy and safety of omapatrilate in subjects with isolated systolic hypertension. Ann Meeting of Internat Soc Hypertens 2000, Chicago. Vasopeptidase Inhibition 2:110-1.
28. Sagie A, Larson MG, Levy D. The natural history of borderline isolated systolic hypertension. N Engl J Med 1993; 329:1912-7.