

REVIEW ARTICLES

Clinical Trials in Isolated Systolic Hypertension in the Elderly

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The presence of isolated systolic hypertension in elderly subjects predisposes to the development of coronary artery disease, myocardial infarction, heart failure, cardiovascular events, stroke and cardiovascular mortality. Whether pharmacologic management of isolated systolic hypertension in the elderly is justified or not has not received attention until the recent years. In this era of the practice of evidence based medicine it is important to review the results of clinical trials about the

management of isolated systolic hypertension involving thousands of elderly patients. The main trials and their results will be presented. These demonstrate a 17 % reduction in total mortality, 25 % reduction in cardiovascular mortality, 37% reduction in stroke and a 25 % reduction in myocardial infarction for those patients under pharmacologic treatment.

Key words: Isolated systolic hypertension, Elderly, Clinical trials, Pharmacologic management.

In the 1970's, elderly individuals suffering from isolated systolic hypertension were often left untreated because of the prevailing impression that hypertension in older adults was a normal and natural response to aging and that lowering the blood pressure could cause damage by reducing the perfusion of the heart, brain or kidney (1).

Studies and trials conducted on hypertensive patients prior to 1985 had demonstrated that adequate antihypertensive treatment significantly reduced the incidence of fatal and non-fatal strokes as well as fatal and non-fatal coronary heart disease events when compared to placebo (2). During that time elderly hypertensive patients were either not included or were only a minor component of the populations investigated. Fortunately, the results of a number of intervention trials devoted to elderly hypertensives have become available since 1985. The purpose of this publication is to present the present knowledge concerning the benefit of antihypertensive treatment in older patients with isolated systolic hypertension.

Systolic hypertension rises almost linearly between the ages 30 and 80 years, whereas diastolic blood pressure rises until approximately age 50, levels off, and then declines (3). It has been extensively reported that arterial stiffness increases with aging principally the central arteries so causing aortic stiffness which is considered a main factor in the development of systolic hypertension (4). Isolated systolic hypertension is a distinct pathophysiological entity in which the rise in systolic blood pressure is mainly due to a decrease in the elasticity of the large arteries and is not necessarily accompanied by a rise in mean arterial blood pressure or in peripheral resistance (5). The prevalence of isolated systolic hypertension averages 8 % in sexagenarians and exceeds 25% beyond 80 years of age (6).

For many years, it has been established that systolic blood pressure is a better predictor of cardiovascular disease events than diastolic blood pressure (7). It has emerged as the single greatest risk factor other than age for cardiovascular disease (8). Two recent guidelines: the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNCVI) (9) and the World Health Organization / International Society of Hypertension (10) have agreed that both systolic and diastolic blood pressure should be used for classification of hypertension, but they have included isolated systolic hypertension as a new item in their classification. They state that isolated systolic hypertension is present with a systolic blood pressure of ≥ 140 mm Hg and a diastolic blood pressure < 90 mm Hg.

It is known that isolated systolic hypertension in the elderly leads to coronary artery disease, stroke, congestive

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heart failure and other cardiovascular events. Being a frequent finding in the elderly and associated to stiffening of the aorta, reduction in the elasticity of the large arteries, and concurrent reduction in the diastolic blood pressure, which decreases coronary blood flow during diastole, it is important to be aware of the result of clinical trials related to the management of elderly patients with isolated systolic hypertension.

There has been 3 main clinical trials conducted in elderly patients with isolated systolic hypertension. These are: 1) Systolic Hypertension in the Elderly Program (SHEP) (11) that includes 4,736 elderly hypertensives with an average age of 71.5 years; 2) Systolic Hypertension in Europe (Syst-Eur) (12) that includes 4,695 hypertensive elderly with an average age of 70 years and 3) Systolic Hypertension in China (Syst-China) (13) including 2,394 hypertensive patients with an average age of 67 years. These 3 studies provided 11,825 elderly systolic hypertensive patients of which 6016 were treated and 5809 served as controls. Staessen and Wang (14) pooled the results of the three trials revealing a 17% reduction in total mortality, a 25% reduction in cardiovascular mortality, a 37% reduction in stroke and 25% reduction in myocardial infarction in those treated. Table 1 presents additional information about each one of those three studies.

Table 1. Treatment of Isolated Systolic Hypertension in the trials SHEP, Syst-Eur and Syst-China.

	SHEP (11)	SYS-EUR (12)	SYST-CHINA (13)
Subjects	4736	4695	2394
Treated	2365	2398	1253
Age (yrs)	71.5	70	66.5
Follow-Up	4.5 yrs	2 yrs	3 yrs
Therapy	chlorthalidone	nitrendipine	nitrendipine
Other Rx	atenolol	enalapril	captopril
Reduction			
Stroke	36%	42%	38%
Coronary Disease	27%	30%	37%
Heart Failure	55%	29%	-
CV Disease	32%	31%	37%

The data presented in these three clinical trials demonstrate that adequate pharmacologic intervention in isolated systolic hypertension constitutes an effective secondary prevention approach for coronary artery disease, cardiovascular complications, stroke and death. Besides these three studies, including elderly patients with isolated systolic hypertension, there has been an analysis of 3868 elderly patients with isolated systolic hypertension

that were included as a part of the samples in five studies on all types of hypertensive patients: European Working Party on High Blood Pressure in the Elderly (EWPHE), Hypertension in the Elderly Patients in Primary Care (HEP), the Swedish Trial on Old Patients with Hypertension (STOP), the Medical Research Council trial in mild hypertension (MRC1) and in adults (MRC2). Across all these trials active treatment reduced total mortality, cardiovascular disease, coronary events and strokes (6). Besides the benefit obtained by pharmacologic treatment there is evidence pointing to the fact that elderly patients do not develop more secondary side effects from the use of antihypertensive therapy as compared to younger patients. (15)

Physicians frequently express some concern about the capacity of elderly people to cooperate and follow advice oriented to altering their lifestyle habits. The TONE Study (16), that included 900 patients, revealed that elderly patients were able to follow instructions to lose weight and to reduce the ingestion of salt, thus dissipating the concern that the elderly can not modify their usual habits. A clinical trial on non-pharmacological intervention in patients aged 60 to 85 with mild hypertension addressing weight reduction, sodium restriction, and increased physical activity demonstrated the effectiveness of such measures in elderly persons (17).

Older hypertensives are somewhat different from other groups for different reasons. They have a higher risk for cardiovascular events compared to young individuals, they have a higher prevalence of isolated systolic hypertension and they are more likely to have concomitant medical conditions that directly affect the choice of antihypertensive drug therapy (18). Compared to younger hypertensives, older persons are more likely to have dyslipidemia, arthritis, heart failure, osteoporosis, renal dysfunction, diabetes, benign prostatic hypertrophy and many other conditions. These medical problems often directly influence the choice of the initial antihypertensive drug therapy, as it is often possible to treat both the hypertension and the other condition with a single medication. Contrariwise there are some conditions in which specific antihypertensive therapy may worsen the concomitant condition. For example, if a hypertensive also suffers from gout a thiazide should not be the initial antihypertensive therapy.

Today the target blood pressure for uncomplicated hypertensives is < 140/90 mm Hg. The JNCVI has recommended that diabetics and hypertensives with renal impairment have a target goal of 130/85 mm Hg. The American Diabetes Association recommends a blood pressure goal of < 130/80 mm Hg for diabetics. The JNCVI suggests a target of < 125/75 mm Hg for patients with

associated renal impairment and more than 1 gram of proteinuria per day.

The elderly patients often metabolize drugs differently from younger persons, because of alterations in hepatic blood flow and renal function with aging. Thus, the recommended starting dose and maximum dose of drugs used in older subjects are characteristically lower than in other age groups. Frequently, the starting dose of medications used is half of the one used in younger patients and the clinician should increase the dose after each dosage has had enough time to be effective. Physicians always wonder if a specific class of antihypertensive medication should be the starting one for all older hypertensives if there is no other concomitant condition that can be treated with a particular drug. Different clinical trials are now available which indicate that with the exception of initial therapy with an alpha blocker all of the well tolerated antihypertensive drugs have similar beneficial effects on the long term cardiovascular mortality and morbidity (18). JNC-VI guidelines recommended starting treatment of uncomplicated hypertension with a long acting diuretic or B-blocker or both, and emphasize the importance of individualizing treatment according to concomitant disease and other factors. Several studies comparing ACE inhibitors or calcium antagonists with placebo have also shown the benefits of the use of these drugs in older individuals. (Syst-Eur and Syst-China). Nevertheless the best drug is the one that reduces the blood pressure and that the patient can afford and use.

One of the areas of concern, in a era in which lifespan is becoming longer and longer, is whether there is an upper age limit to the benefit of antihypertensive treatment. The group of patients >80 years of age included in our elderly sample populations has been small. The sub-group analysis suggests a benefit in this population, but the final conclusion should wait until the results of the Hypertension in the Very Elderly Trial (HYVET) are completed (19).

Life style modifications remain a cornerstone of long term antihypertensive therapy. These include losing weight if overweight, limiting alcohol ingestion to 1 oz of ethanol per day, 30 to 45 minutes of aerobic exercise most days of the week and reduction of sodium intake to 6g of sodium chloride per day. Ten pounds of weight loss are sufficient to elicit changes in blood pressure in the overweight patient.

Conclusion

Isolated systolic hypertension is frequent in the elderly partly due to the increase in arterial stiffness, which occurs

with aging. Its prevalence exceeds 25% in subjects beyond 80 years of age. Untreated isolated systolic hypertension in the elderly leads to damaging complications such as coronary artery disease, stroke, myocardial infarction, congestive heart failure and other cardiovascular events.

In the last 10 years important clinical trials have been conducted in thousands of elderly patients with isolated systolic hypertension in order to appraise the effect of blood pressure lowering by pharmacologic management versus placebo.

A summary of the results of the 3 largest clinical trials: SHEP, Syst-Euro and Syst-China has been presented with an integrated analysis of the 11,825 subjects which demonstrated a 17% reduction in total mortality, 25% reduction in cardiovascular mortality, 37 % reduction in stroke and a 25 % reduction in myocardial infarction in those treated. As isolated systolic hypertension is associated with increased risk for cardiovascular morbidity and mortality, emphasis is presented on the importance of treating all the elderly with isolated systolic hypertension until a normal blood pressure level is obtained.

Resumen

La presencia de hipertensión sistólica aislada predispone al desarrollo de la enfermedad coronaria, infarto del miocardio, fallo cardíaco, eventos cardiovasculares, apoplejía y mortalidad cardiovascular. No es hasta los últimos años que se le ha brindado atención a si el tratamiento farmacológico de la hipertensión sistólica aislada está justificado o no. En esta era donde se práctica la medicina basada en evidencia es importante revisar los resultados de los ensayos clínicos sobre el manejo farmacológico de la hipertensión sistólica aislada en miles de pacientes de edad avanzada. Se presentan los ensayos clínicos más prominentes y sus resultados. Estos demuestran una reducción de 17% en la mortalidad total de, 25% en mortalidad cardiovascular, de 37% en apoplejía y de 25% en el infarto del miocardio en los pacientes bajo tratamiento farmacológico.

References

1. García-Palmieri, MR. Primary and secondary prevention of cardiovascular disease in the elderly. Bol Asoc Med P R 2000; 92:3-8
2. Collins R, Peto R, Mac Mahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2. Short term reduction in blood pressure: Overview of randomized drug trials in their epidemiological context. Lancet 1990;335:827-838.
3. Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. Circulation 1997;96:308-315.

4. Laurent B P, Benetos A. Pathophysiology of hypertension in the elderly. *Am J Geriatr Cardiol* 2002;11:34-39.
 5. Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. *J Hypertens* 1990;8:393-405.
 6. Staessen J, Gasowki J, Wang JC, Lutgarde T. et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000;355:865-872.
 7. Black HR. Isolated systolic hypertension in the elderly: Lessons from clinical trials and future directions. *J Hypertens* 1999;17(suppl 5):549-554
 8. Garcia-Palmieri, MR. Cardiovascular disease prevention in the elderly *Clin Geriatr* 2001;9:69-77.
 9. The Sixth Report of the National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Int Med* 1997;157:2413-2446.
 10. Guidelines Subcommittee. World Health Organization-International Society of Hypertension Guideline for the Management of Hypertension. *J. Hypertens* 1999;17:151-183.
 11. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP) *JAMA* 1991;265:3255-3264.
 12. Staessen JA, Fagard R, Thijs L. et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;350:757-764.
 13. Liu L, Wang JG, Gong L. et al. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. *J Hypertens* 1998;16:1823-1829.
 14. Staessen JA, Wang JG. Benefit of antihypertensive treatment in older patients with isolated systolic hypertension. *Eur Heart J* 1999;11(suppl P):3-8.
 15. Holzgreve H. Managing the elderly hypertensive beyond blood pressure reduction. *J Hypertens* 1995;13:S103-S107.
 16. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons. A randomized controlled trial of non-pharmacologic interventions in the elderly (TONE): Collaborative Research Group *JAMA* 1998;279:839-846.
 17. Appelgate WB, Miller ST, Elam JT et al. Non-pharmacologic intervention to reduce blood pressure in older patients with mild hypertension. *Arch Intern Med* 1992;152:1162-1166.
 18. Elliot WJ, Black HR. Treatment of hypertension in the elderly. *Am J Geriatr Cardiol* 2002;11:11-22.
 19. Leonetti G, Zanchetti A. Results of antihypertensive treatment trials in the elderly. *Am J Geriatr Cardiol* 2002;11:41-47.
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