HYPERTENSION IN THE ELDERLY

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Introduction:

Over the last 3 decades, the population older than 65 years old has increased, leading to a significant increase of hypertensive patients, with predominance of systolic hypertension, of greater cardiovascular risk and more difficult to control. Moreover, aging is associated to an increase in cardiovascular and general co-morbidity.

In our country, this aging represents a Public Health problem, since people older than 65 years old are a 10-12% of the population. Official data from our country indicate that the current life expectancy is 73 years old, that the increase of people of more than 80 years old has increased a 56% over the last 2 decades, and that those that today reach 80 years old have an additional life expectancy of 6.8 years old. The prevalence of hypertension (HTN) increases with age, and in patients older than 65 years old, it fluctuates between 60 to 70% in different series. It is well known that cardiovascular diseases are the main cause of death in individuals older than 65 years old.

Hypertension is an important and treatable factor of cardiovascular risk in this population, and the one that most contributes to the development of the main causes of morbi-mortality: coronary artery disease and stroke.

In hypertensive patients, isolated systolic hypertension is the most common form of presentation(1), with the worsening factor that systolic pressure (SP) and pulse pressure (PP) (difference between SP and diastolic pressure (DP)) are cardiovascular risk markers more significant than PD. In the studies that have focused on evaluating the value of PP it is concluded that for a given level of SP there is an inverse correlation between DP and cardiovascular risk.

Isolated systolic HTN (SP above 140 mmHg with DP equal or under 90 mmHg) is frequent in the elderly by increase of rigidity of the great vessels, representing a good prognostic marker

of cardiovascular morbi-mortality. Table 1 describes the current classification of blood pressure according to mmHg level.

Table 1. Baseline characteristics of the population studied in the HYVET

	Placebo (%)	**Activo (%)**
Cardiovascular disease	12.0	11.5
Known hypertension	89.9	89.9
Antihypertensive treatment	65.1	64.2
Stroke	6.9	6.7
Myocardial infarction	3.2	3.1
Age (years)	83.5	83.6
Women	60.3	60.7
Diabetes	6.9	6.8
Total cholesterol	207.8	207.8
SP sitting (mm Hg)	173.0	173.0
DP sitting (mm Hg)	90.8	90.8
Orthostatic hypotension	8.8	7.9
Isolated systolic hypertension	32.6	32.3
Heart failure	2.9	2.9
Serum creatinine (mg%)	1.01	1.0
Body mass index (Kg/m2)	24.7	24.7
Smoking	6.6	6.4

Pathophysiological reflections

Blood pressure may be defined as the force (or pressure) that blood exerts against arterial walls. This depends on the existence of energy, whether potential (pressure) or kinetic (blood velocity), with the heart being the one that adds such energy during systole. From the hemodynamic point of view, blood pressure is defined as the product of cardiac output (CO) multiplied by peripheral vascular resistance (PVR): blood pressure = CO x PVR.

In adults older than 65 years old a series of structural and functional changes occur in the arteries and the heart that lead to significant variations in blood pressure behavior. For this reason, we will make a brief summary of normal function and in elderly people of such components of the cardiovascular system.

Arteries can be classified in two types:

-elastic arteries: such as the aorta and its main branches, made up mostly by elastic tissue, mainly by collagen and elastin. Arterial adjustment to cardiac ejection depends on them, thus determining the compliance and distensibility of the system. While progressing to the arteries with a lesser diameter (arterioles), the pulsatility of the flow decreases progressively, in such a way that blood reaches the tissues continously. Their main structural component, elastin, has elliptical fenestrations that increase several times their number and size during post-natal growth. The growth of fenestrations occurs while lamellas accumulate great amounts of new elastin(2,3). By creating or enlarging arterial tissue fenestrations, they increase their distensibility when pressure grows, altering their geometry; but this process is reduced in the elderly when these elastin fibers are replaced by collagen tissue, increasing the rigidity of the arterial wall.

-predominantly muscular arteries: the remaining ones (second and third level of arteries, peripheral arteries and arterioles), the main element of which in the middle tunic is the smooth muscle. They have the chance to contract or expand and generate peripheral vascular response. By increasing the thickness of the middle muscular layer, vascular lumen is reduced, thus generating that for the same degree of shortening of smooth muscular fibers, peripheral resistance is increased. This process also explains in part the increase in blood pressure in the elderly. In some cases, the hypertrophy of the middle layer leads to arterial occlusion leading to a process of capillary rarefaction, openly and directly associated to aging. All arteries are internally covered by the endothelium, constituted by a basal layer, collagen, proteoglycans, loose connective tissue, fibroblasts, collagen of type IV and AB_2, and smooth muscle cells. Endothelial cells may contract by the action of angiotensin, histamine, serotonin, and other drugs. Cells are oriented in the direction of blood flow, and by having a negative charge they repel blood components with the same electrical charge. To the

traditionally known effect of preventing intravascular coagulation and protecting the rest of the wall from incoming of harmful substances (for instance microparticles of LDL cholesterol), the fact is added that it constitutes a real organ for internal secretion (renin, angiotensin, prostaglandins, etc.) that contribute to regulating arterial tone. The endothelial function is progressively altered over time, and dysfunctions are frequent in hypertensive elder patients.

Finally, arteries are coated on the outside by the adventitia, made up by collagen and elastic fibers, fibroblasts, mast cells, and smooth muscle cells. Through it travels the vascular innervation that is introduced later in the middle layer. The vasa vasorum that nourish the artery go through it. Innervtion of adventitia causes vascular contraction or expansion, modifying its diameter.

Peripheral vascular resistance (summation of forces that oppose blood flow) is determined by compliance or distensibility of the great arteries, due to the resistance generated in the middle and small arteries and in the reflect wave (Figure 1).

Figure 1. Components of arterial impedance (I)

Normally, the reflect wave originates in the aortic bifurcation and is transmitted in a centripetal fashion to the aortic root. While years go by, this reflect wave accelerates and instead of reaching the aortic root coinciding with the end of diastole, it makes it so coinciding with the systole, thus instead of contributing to the maintenance of pressure during

diastole, the systole is added and it is one of the main causes for the increase of the systolic pressure in adults older than 65 years old (Figure 2).

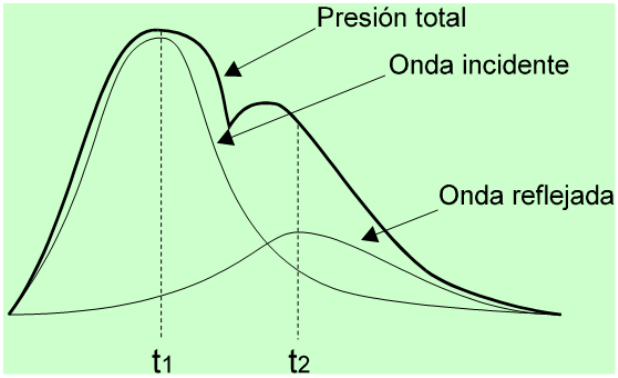


Figure 2. Pulse wave components: incident and reflected wave that determine the final format of it. (Brandani L y col: "Evaluación no invasiva de la función Arterial en humanos". Capítulos de Cardiologia. Hipertensión Arterial.Soc Arg de Cardiologia (Edit), 2000)

For this reason, with a greater age systolic hypertension is often seen in the isolated form, since without the support of a more delayed reflect wave, diastolic pressure tends to decrease in a parallel way to the increase of systolic pressure. For this reason, pulse pressure (difference between systolic and diastolic pressure) increases in elderly people, thus predicting high cardiovascular risk. It is worth highlighting that the reflect wave is altered in hypertension, advancing its onset because its origin is shifted from the bifurcation until any sector of the aortic wall where a modification in its diameter occurs, whether by changes in distensibility (increase of rigidity, presence of atheromatous plaques) or by changes in vascular tone.

In hypertension in elderly people, structural alterations associated to the effect of neurohormonal and cytochemical agents induce a progressive loss of arterial distensibility that causes on the one hand, that BP values are greater for the same degree of arterial distension (Figure 3), with such tension increase producing at the level of the left ventricle an increase of post-ventricular load.

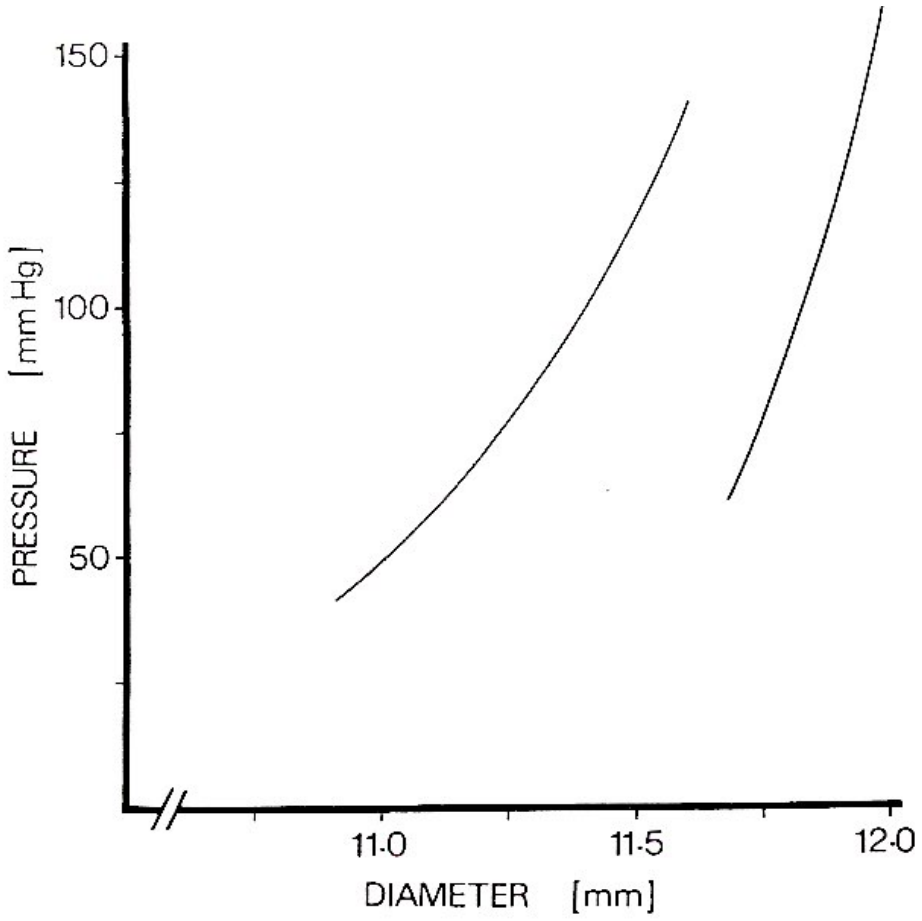


Figure 3. Relationship between blood pressure and arterial diameter in a normotensive and a hypertensive patient. The curve at the left corresponds to the normotensive and the one at the right to the hypertensive patient. Check the greater initial diameter in the hypertensive patient and how the curve slope in the latter is greater, indicating that an increase in diameter generates a greater increase of BP by loss of arterial elasticity.

This phenomenon is associated to an increase of vascular impedance.

A measurement of great usefulness in elderly patients is pulse wave velocity (PWV) that is accepted as the best method to measure arterial rigidity (4). Measuring it is easy, using in general the trajectory between the homolateral carotid and femoral arteries. At a greater velocity of the pulse wave, the greater the rigidity of the system, and therefore, the lesser the distensibility, with age and blood pressure level being the best factors that correlate with its value. Other factors that also influence it are smoking, African-American ethnicity, diabetes mellitus, and LDL cholesterol increase.(5)

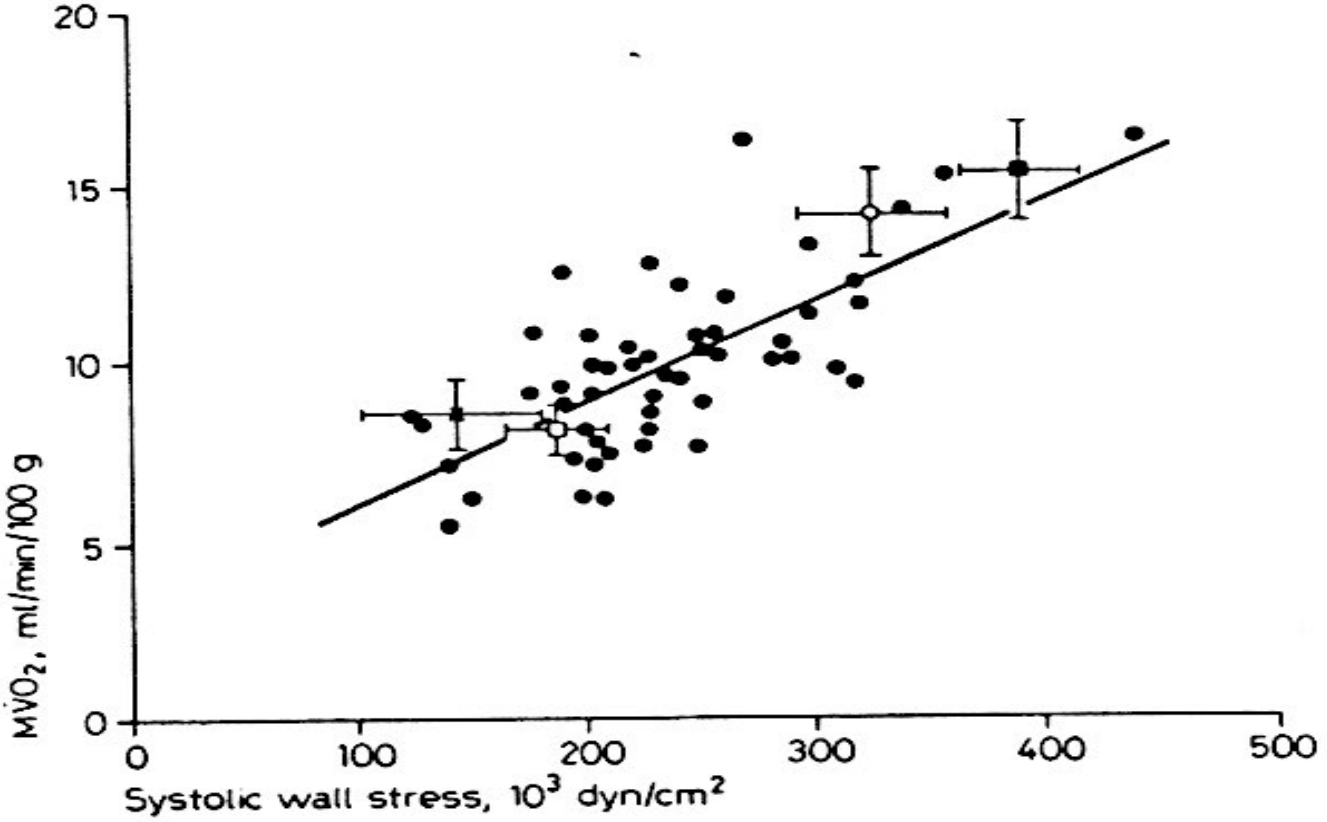
The severity of hypertension conditions the progression to arterial rigidity(6), and in turn it is associated to alteration of the cognitive function and microalbuminuria, frequent in elderly patients.(7)

Hypertension generates a pressure overload that compromises the heart, especially the left ventricle that in the long run leads to alteration both of systolic and diastolic function. The relationship between LV function as ejecting pump and buffering of pulsatility of the flow ejected in the aorta is also compromised; this interaction is called ventriculo-aortic coupling. (8) In elderly adults it is frequent to detect left ventricular hypertrophy, left atrial enlargement, ventricular relaxation alteration, and biochemical changes in the parietal structure. This set of alterations is acknowledged as hypertensive heart disease.

Left ventricular hypertrophy usually begins in the basal septum, extending later to the ventricular free wall, and expresses the increase in mass or ventricular weight. Cardiomyocytes increase their size, by increase of protein synthesis and changes in structure. (9) Ventricular hypertrophy shows two forms: 1-concentric; secondary to pressure overload; and 2-eccentric, by volume overload (valve failure, etc.) In the former, there is an association of sarcomeres in parallel, with lateral growth of cardiomyocytes. In the latter, the sarcomeres align in a series, with a longitudinal cell growth.(10) The hypertrophy is associated to an increase in myocardial oxygen consumption, existing in a direct relationship between the behavior of both variables (Figure 4), which added to a decreased coronary reserve, vascular rarefaction, arteriolar remodeling, perivascular fibrosis, and diastolic pressure reduction at the aortic root, generate a state of relative chronic ischemia, particularly noticeable in elderly hypertensive patients.(11)

Some hormonal factors are significant in the genesis of ventricular hypertrophy; we can mention angiotensin II, aldosterone, and the level of catecholamines. This fact partially explains the beneficial effect of blood pressure reduction with drugs that inhibit the renin-angiotensin system, such as ACEI and AT1 receptor antagonists.

Diastolic dysfunction (DD) is frequent in hypertensive patients with an advanced age, being a direct consequence of the increase of post-load, ventricular hypertrophy, and myocardial fibrosis. At least 50% of elderly patients with heart failure maintain a preserved ejection



estimated that decreasing SP 10 to 12 mmHg and DP 5 to 6 mmHg in hypertensive patients reduces the relative risk of stroke in approximately 40%, of coronary artery disease in approximately 20%, and overall mortality in approximately 15%.

Besides increasing systolic BP and decreasing diastolic BP, aging increases BP variability, which contributes to making a correct diagnosis and management of these patients more difficult. These BP variations could be spontaneous or conditioned by posture changes or food ingestion. In some patients, HBP is exaggerated in a supine position and "normalizes" or drops to values of hypotension when standing, or after a copious ingestion. Particularly in very old patients, in diabetic ones, or in those who suffer Parkinson disease, and in those with history of syncope or falls, it is a good practice to measure BP in a supine posture and standing before starting or reinforcing the treatment. It is also important to evaluate patients who achieved a "very well controlled" BP (<140 mmHg while sitting), in a standing position. When faced with a patient with orthostatic hypotension, we should investigate the consumption of drugs such as alpha-1 adrenergic blockers, carvedilol, methyldopa, and others

with alpha-blocking effect. Although the priority is preventing orthostatic hypotension, supine hypertension should also be researched and if possible, reduced.

Certain details of hypertension in elderly individuals may contribute to a greater diagnostic inaccuracy. For instance, blood pressure is more variable, alert reactions (hypertensive response during the medical interview) are greater, elderly patients often display autonomic dysfunction that favors orthostatic hypotension, and excessive rigidity of the arterial wall may generate falsely high pressure values (pseudo-hypertension). This requires special precautions to measure blood pressure: it is necessary to determine more data in both arms if possible, to gather data obtained outside the medical office, to make measurements at home or ambulatory, to make up for the greater variability and alert reactions. As a routine, blood pressure should be measured in a lying position, sitting and standing to detect orthostatism. Finally, it is convenient to perform the Osler maneuver (radial or humeral artery, palpable after inflating the cuff above systolic pressure) that may help to suspect pseudo-hypertension, although a confirmation is only valid with intraatrial measurement.

Although hypertension in the elderly is predominantly primary or essential, secondary causes should be investigated when hypertension begins after 60 years of age, is refractory to treatment, is difficult to manage in previously controlled individuals, in those who present atherosclerotic cardiovascular co-morbidity and/or suffer pulmonary edema without clear cardiological cause. In the latter renovascular disease is frequent.

In elderly people with spontaneous hypokalemia or induced by diuretic agents, and in all patients with severe hypertension, refractory to 3 antihypertensive drugs, even with normal kalemia values, primary hyperaldosteronism should be ruled out. Pheochromocytoma is exceptional in hypertensive patients older than 75 years old.

Carotid arteries should be systematically examined by auscultation and eventually by echo doppler, mostly before starting an intensive antihypertensive management, to prevent ischemic phenomena secondary to blood pressure drop in individuals with severe obstructive lesions. In elderly hypertensive patients, often (30-60%) ischemic lesions are observed in the cerebral white matter, which may be associated to neurocognitive disorders.

Prior studies:

The STOP-H(12), SHEP(13), MRC(14), and SYST-CHINA(15) studies contributed solid evidence as to the benefit of treating hypertension in elderly people with an age above 65 years old, by showing considerable reductions in the incidence of stroke (25-47%), coronary events (13-30%), heart failure (29-55%), and cardiovascular death (16-40%), but evidence in individuals older than 75 years old is limited.

The STOP 2(16) study included patients with isolated systolic hypertension and systo-diastolic hypertension in both sexes and between 70 and 84 years old (median 75.8 years old) with favorable results similar to those obtained in younger individuals. In this study and in the ASCOT study(17), in one arm diuretic agents and beta blockers were used, and in the other ACEI and calcium antagonists. It was concluded that the two last groups of drugs have at least the same or better efficacy as classical drugs. Patients with inhibition of the renin-angiotensin system showed a lower number of complications by heart failure and myocardial infarction in comparison to those receiving calcium-antagonists; however, in terms of reducing cardiovascular morbi-mortality, there were no significant differences between these families of drugs.

The blood pressure endpoint to reach is similar to the one in younger patients (<140/90 mmHg), but it is more difficult to reach. The lowest value tolerated by the patient is considered acceptable. In elderly patients with isolated systolic hypertension, it has been advised to limit the decrease of systolic pressure if diastolic pressure reaches values below 65 mmHg.

Recently, the HYVET study(18) randomized 3,845 hypertensive patients older than 80 years of age. This population is characterized by their advanced age, but at the same time by keeping a relatively good state, since only self-sufficient patients were included, and who had no entities that would significantly reduce their life expectancy. Table 1 shows the baseline characteristics of the population studied. From them, 1,912 were assigned to the control arm with placebo, while 1,933 were assigned to group with active management with long-acting indapamide 1.5 mg/day, while if necessary perindopril 2 mg/day was added, and increased to 4 mg/day in another step. The BP fall in the active management arm was 29.5 mmHg for systolic pressure and 12.9 mmHg for diastolic pressure, while the placebo arm showed a decrease of 14.5 and 6.8 mmHg for systolic and diastolic pressure, respectively. We can also

state that at the end of the study, 75% of the patients of the active management arm were receiving the combination of indapamide and perindopril.

The results were remarkable since a 30% reduction was observed for total stroke, 21% for total mortality, 39% for fatal stroke, and 64% of heart failure; and in all cases the difference in comparison to the control arm was statistically significant.(Figure 5)

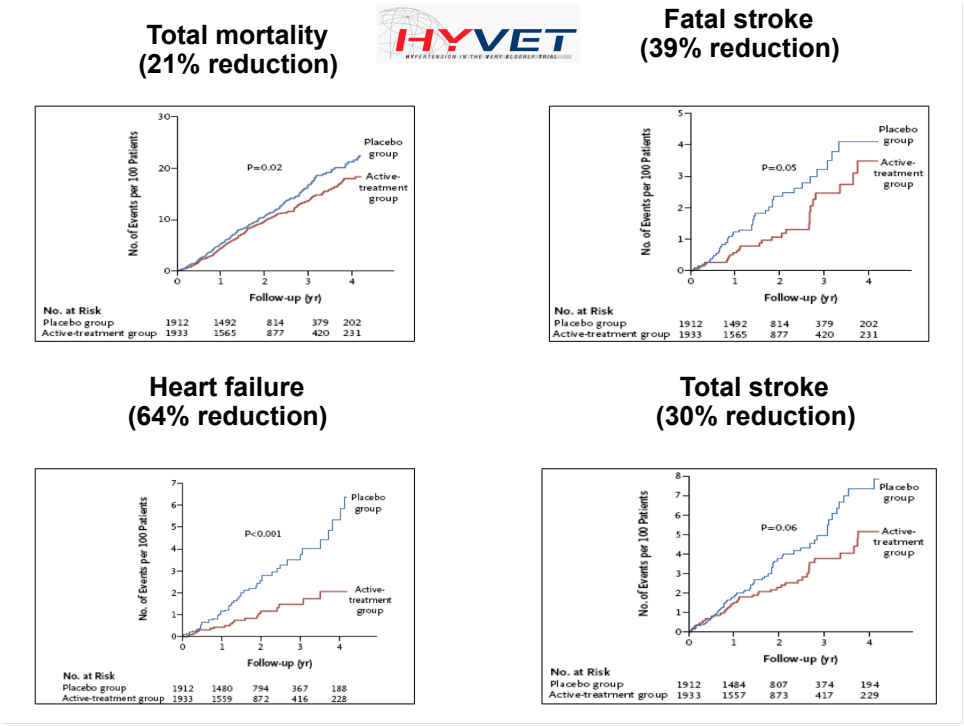


Figure 5. Main results of the HYVET study.

The treatment was well tolerated in both arms, and the collateral effects reported were relatively scant, with no differences at 2 years in kalemia, uricemia, glycemia, and creatininemia.

Finally, it is worth mentioning that in all studies conducted in hypertensive patients older than 65 years old, patients in stage 2 were included, i.e. with systolic pressure equal or greater than 160 mmHg, so there is a void of information about the benefit of the treatment in these individuals in stage 1 (systolic pressure between 140 and 159 mmHg). The way we see it, even with information missing, the treatment of these patients would be appropriate in stage 1, especially when other risk factors are associated that increase total cardiovascular risk.

Primary prevention of HTN:

It is possible by modifying life habits such as smoking, sedentarism, excessive consumption of salt and alcohol, and high calorie consumption leading to obesity. Since one of the goals of primary prevention is reducing the increase of BP with age, it is essential to provide advice as to healthy life habits to all patients coming to the office, emphasizing young patients with the aim of reducing hypertension in elderly people.

Nonpharmacological treatment:

It is similar to that of younger patients, and the recommended physical activity is hiking or swimming, since they are less risky for these patients. Beyond the antihypertensive effect of exercise, this has a special significance since it promotes a better mood state and it is beneficial for the prevention or treatment of multiple pathologies of different kinds, highly prevalent in this population. The elderly are usually sensitive to salt, so that a discrete reduction of sodium in the diet (40 mEq/day) correlates with an evident decrease in blood pressure(19,20). An increase in the potassium contribution to the diet is also recommended.

For this, the following measures are advised, isolated or jointly with pharmacological treatment:(21)

1. Shedding weight in case of overweight.
2. Sodium consumption around 100 mmol/day by suppressing the use of salt shakers in the table, and avoiding eating pre-cooked and canned food, and cold meats. Up to 1.5 g of salt per day is accepted, and using it on the food once cooked is preferable, instead of using it while cooking it.
3. Increase of potassium consumption (fresh fruits, vegetables, and cereals)
4. Increase of calcium in the diet (100 mg of cheese provide between 700 and 1,180 mg of calcium, depending on the type).
5. Walking more than ½ hour per day, preferably between 1 and 2 hours. In non-trained people, the goal should be reached gradually.
6. Do not ingest more than 30 g of alcohol/day (equivalent to 300 ml of wine, 500 of beer, or a liquor cup).

7. The indication of nonpharmacological measure should take into account the socio-economic conditions of the patient.
8. The simultaneous and moderate application of several nonpharmacological measures, should yield a therapeutic result better than the strict application of a single one of them.
9. Assess sensibly the therapeutic benefit/loss in quality of life ratio before starting changes in elderly people's diet and lifestyle.

Pharmacological management

Five families of drugs have been used successfully in the management of essential hypertension: thiazide diuretics, beta blockers, calcium antagonists, ACEI and angiotensin II AT1 receptor antagonists. Different studies have proven with all of them, a reduction in cardiovascular events(12,13,22,23). When used in the appropriate doses, the average decrease of BP is very similar between the five types of drugs, although there are important individual differences for each of them.

When selecting antihypertensive drugs, we should consider the frequent co-morbidities in this population: glaucoma, constipation, gout, osteoarthritis, sexual dysfunction, dyslipidemia, diabetes, chronic obstructive pulmonary disease, prostatic hypertrophy, coronary artery disease, valvulopathy, peripheral arterial disease, sinus node disease, heart failure, stroke, and extrapyramidal disorders. Polypharmacy due to co-morbidities increases the risk of medication interaction. To avoid hypotensive complications, it is important to take into account the chance of overdose due to slower drug elimination, overestimating usual tension values due to the alert reaction, undetected postprandial or orthostatic hypotension, limitation of flow self-regulation mechanisms and hypovolemia states added or induced by diuretic agents. The treatment should begin progressively adjusting the dose each two to four weeks, controlling adverse effects and orthostatic hypotension.

There is evidence of a greater benefit in the elderly with hypertension without complications with the use of low-dose diuretics and calcium antagonists of long-lasting half life. Thiazide diuretics are particularly efficient in elderly people with isolated systolic hypertension, although they may induce glucose intolerance and diabetes(25), especially in patients with

hypokalemia. However, the clinical significance of this fact is still uncertain, and a specific study to clarify this issue is necessary.

Loop diuretics are not commonly used in uncomplicated essential hypertension, acquiring relevance except in the case of renal or heart failure. Several studies showed the usefulness and good tolerance of calcium antagonists, both in the short and the long term, as well as ACEI and AT1 receptor antagonists (ASCOT, VALUE, LIFE, HOPE, and EUROPA). (17,26,27,28,29)

An interesting additional datum was observed in the ASCOT study (Anglo-Scandinavian Cardiac Outcomes Trial)(30); patients randomized to the amlodipine-perindopril combination as basic treatment, had lower central aortic pressure values than those assigned to atenolol-thiazide diuretics, in spite of no significant differences appearing in the traditional measurements of blood pressure in the arm. (Figure 6)

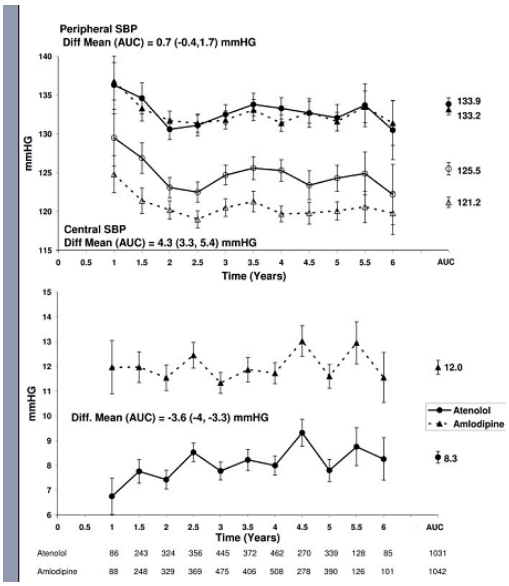


Figure 6. ASCOT study (Anglo-Scandinavian Cardiac Outcomes Trial).
Evolution of brachial and central (aortic) systolic pressure over the period of the study with both treatments.(30)

Moreover, aortic pressure was significantly associated to cardiovascular and renal events.

In patients with prostatic hypertrophy alpha blockers could be used, being cautious with the hypotensive effect of the first dose.

The use of BB is currently being questioned for different reasons. A recent meta-analysis of 13 randomized studies of patients with essential hypertension with a total of 105,951 patients, has compared their protective effect on the target organ in comparison to other drugs. The relative risk of stroke was 16% greater in the beta blocking group (95% CI 4-30%) than with other drugs, and there were no differences in myocardial infarctions.(24) Particularly, in the group of elderly patients beta blockers were inferior to the other groups of hypertensive drugs to reduce cardiovascular events and they increase the risk of developing new diabetes, especially when associated to thiazide diuretics. Canadian and British guidelines do not consider the use of these drugs as an initial alternative for the treatment of uncomplicated hypertension in individuals older than 65 years old, while the European and American guidelines keep them as an option, but limited to situations that would clearly justify their use. As a conclusion, beta blockers should not be considered as first-choice drugs for the management of uncomplicated essential hypertension in elderly people.

Blocking the renin-angiotensin system is particularly indicated in diabetic patients, or in those with prior cardiovascular event, as has been proven in the HOPE and LIFE studies(27,28) in patients in high risk, or else with left ventricular hypertrophy. Although it is frequently mentioned that these drugs are more useful in younger individuals, there is no evidence of a different antihypertensive response in comparison to older patients. Recently, the ONTARGET study,(31) did not show differences in reducing cardiovascular events when comparing one ACEI (ramipril) with one AT1 receptor antagonist (telmisartan), with the addition that the combination of both not only did not produced a better result, but was also associated to a greater number of collateral effects. To this group of drugs, aliskiren has recently been added, which is the first direct renin inhibitor that has shown to be an effective antihypertensive agent, with a security profile equal to placebo and with an antiproteinuric effect additional to the maximal conventional therapy.(32)

If there are associated risk factors, hypertension complications, or other concomitant diseases, the choice of drug should be made based in the accompanying pathology. Drugs with a long-lasting half life and a single daily intake are preferred.

Aspirin and other antiplatelet aggregation agents reduce the risk of fatal or nonfatal coronary episodes, stroke and cardiovascular death in patients with coronary or cerebrovascular disease. The HOT study,(33) showed the benefit of aspirin in low doses (75-100 mmHg) in hypertensive patients with ages ranging from 50 to 80 years old, as long as they have a controlled BP and no particular risk of bleeding.

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