Hypertension in the Geriatric Population

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Abstract

Hypertension is one the most common conditions that physicians encounter on a daily basis. Because this is highly prevalent in the geriatric population, and this is the largest growing segment of society, this chronic and asymptomatic disorder proves to be a challenge for physicians to effectively monitor, diagnose, treat, control and even improve. In order to improve morbidity and mortality within the geriatric population, it is fundamental to combat this "silent killer".

The elderly experience a great number of changes in the body due to the aging process that cannot be controlled. These changes include altered metabolism along with altered renal, hepatic and cardiovascular functions that will all influence the body´s homeostasis. This also means that drug metabolism will vary, thus multiple drug interactions and side effects could occur that will alter treatment, and control. These physical alterations interact directly with various genetic and environmental conditions and so can cause and even aggravate hypertension.

Hypertension has various causes but in the majority of cases these are not identifiable. In the 5-20% that have a specific cause, these are treated accordingly. In the rest, treatment is symptomatic and aimed at stabilizing and lowering blood pressure. Prevalence of hypertension can be related to obesity, increased salt intake, alcohol consumption, low ingestion of potassium and calcium, low physical activity along with stress. There also seems to be an environmental component. This means that in order for adequate control to be achieved, there needs to be treatment that targets both lifestyle as well as physiological components that influence this condition. Despite all the information that is known about this

disorder, it continues to be uncontrolled in a great number of elderly patients, thus physician education to try explain why prevalence is continually increasing and why control is poor is important. It is beneficial to develop strategies that fight this noncompliance and enable effective treatment and control of this disorder. It has been shown that there is no age limit for hypertension treatment and even in the elderly, successful blood pressure control can improve cardiovascular and renal disease along with a reduction in dementia and cognitive decline: treatment is always beneficial.

Hypertension control is the great challenge of our century. Awareness and education are the best tools to combat this chronic fatal condition that is so universal and is blissfully and quietly ignored by patients.

Keywords: Hypertension; Geriatric; Aging; Antihypertensive treatment; blood pressure control;

Hipertensão na População Geriátrica

Resumo

A hipertensão arterial é das patologias mais recorrentes com que os médicos se deparam diariamente. Devido à sua elevada prevalência na população geriátrica, e sendo esta um segmento crescente da sociedade, esta patologia crónica assintomática prova ser um desafio em parâmetros como a monitorização, diagnóstico, tratamento e controlo eficazes. Para melhorar a morbilidade e mortalidade na população geriátrica é fundamental o combate deste "assassino silencioso".

Na verdade, envelhecimento acarreta uma serie de alterações físicas incontroláveis que estão, na maior parte dos casos, associados à hipertensão. Estas alterações incluem modificações das funções renais, hepáticas e cardíacos que irão influenciar o equilíbrio funcional do organismo. Isto significa que o metabolismo dos medicamentos pode variar afectando as interacções medicamentosas e efeitos secundários que podem ocorrer, alterando, assim, o tratamento e controlo desta patologia. Estas alterações físicas interagem directamente com vários factores genéticos e ambientais, que podem causar e até mesmo agravar a hipertensão arterial.

A Hipertensão arterial tem varias causas, mas na maioria dos casos, estas são idiopáticas. Nos 5-20% dos casos que têm uma causa específica, estes são tratados de acordo com essa especificidade. No entanto, nos casos de causa desconhecida, o tratamento é sintomático e visa a estabilização e redução da pressão arterial.

A prevalência da hipertensão pode estar relacionada com a obesidade, o aumento da ingestão salina, o consumo de álcool, a baixa ingestão de potássio e cálcio, a baixa actividade física, juntamente com o stress. Para um controlo adequado, é necessário haver alterações no estilo

de vida, bem como no tratamento farmacológico. Apesar dos avanços da medicina, esta doença continua a ser uma patologia mal controlada. Por esta razão, é importante apostar na informação e educação médica para tentar explicar o aumento desta prevalência e as possíveis razões da sua falta de controlo. Será benéfico desenvolver estratégias para combater esta falta de adesão terapêutica para se obter um tratamento e controlo eficaz desta condição. Estudos revelam que não há limite de idade para tratamento da hipertensão arterial e, até mesmo em idosos, um controlo eficaz da pressão arterial pode melhorar a doença cardiovascular e renal, bem como a redução de demências: o tratamento é sempre benéfico.

O controlo da hipertensão arterial é o grande desafio do nosso século. A consciencialização e a educação são as melhores ferramentas para combater esta doença crónica, fatal que é tão universal e quietamente ignorada pelos pacientes.

Palavras-chave: Hipertensão Arterial; Geriatria; Envelhecimento; Idoso; Tratamento antihipertensivo, controlo tensão arterial

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Glossary of abbreviations

ABPM- ambulatory blood pressure monitoring

ACEI- Angiotensin-converting enzyme inhibitors

ARB- Angiotensin II receptor blockers

BB- Beta blocker

BP- Blood pressure

CCB- calcium channel blockers

CNS- Central nervous system

ALLHAT - the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial;

DASH-dietary approaches to stop hypertension

DBP- diastolic blood pressure

GI- Gastrointestinal

HTN- Hypertension

HYVET -the Hypertension In the Very Elderly Trial

ISH- Isolated systolic hypertension

JNC 7 - The Seventh Report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure

NHANES -National health and nutritional examination survey

NSAID- Non-steroidal anti inflammatory

OSA -Obstructive sleep apnea

RAA- Renin-angiotensin-aldosterone

SBP- Systolic Blood pressure

SHEP-Systolic Hypertension in the Elderly Program

SNS- sympathetic nervous system

STOP-HYPERTENSION - the Swedish Trial in Old Patients with Hypertension;

SYST-EURO -European Trial in Systolic Hypertension

TONE- Trial of non pharmacological intervention in the elderly

VALISH- Valsartan in Elderly Isolated Systolic Hypertension

Hypertension in the geriatric population

Introduction

Hypertension poses an increasing challenge for modern society. This is especially true as the population ages and health issues multiply at an astounding rate. Society in general is aging and thanks to the evolution of modern day medicine, it is possible to allow society to reach the extremes of age, and prolong life. However, this comes at a price, and just as the structure of the population changes, medicine has to evolve with the times, in order to treat and control the aging society that come with the multiple pathologies interacting with numerous medications in an already frail and elderly body.

Since hypertension is one of the "silent killers", it is important to understand and appreciate some of the recent findings that have been made in this area, as it is through better education of the physician that it is possible to achieve healthier results within the population. HTN is a modifiable risk factor for cardiovascular morbidity and mortality, as well as other arterial, heart and kidney diseases, and even diseases like dementia.

High systolic BP represents a challenge for the modern world and awareness is an initial and vital step in controlling this problem. One of the most cost effective health interventions available was found to be the improvement of blood pressure control (Jones et. al. (2008).

Initially it was thought that high blood pressure was a side effect of the aging process and it could not be avoided. However, according to Padiyar (2009), studies show that secluded populations such as cloistered nuns and even primitive societies like the San Bushmen of Southern Africa, despite the increase in age, do not exhibit such elevations in blood pressure. Furthermore results show that within migrating populations, from underdeveloped to urban

areas, the population show patterns similar to those belonging to the urban area into which they are settling as compared to the rural population from which they came. This begins to prove that hypertension is strongly affected by lifestyle and influenced by environmental factors, and shows that the foundations of treatment need to take all these factors into account if adequate control of this disorder is to be achieved.

Definition and diagnosis

Hypertension can be defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure > 90mmHg noted on at least 2 visits during several weeks. Recommended blood pressure in the general population is less than 140/90 mmHg and should be lower among diabetics or patients with chronic kidney disease, thus target BP should be around 130/80 mmHg (Chobanian et al. (2003); Wolff & Miller (2007). **Table 1** shows the classification of HTN according to BP values.

Table 1: Blood pressure classification adapted from (Aronow (2006); Acelajado & Oparil (2009);Aronow (2009).

Blood pressure classification	Systolic Blood pressure	Diastolic Blood pressure
Normal	<120 mm Hg	<80 mm Hg
Pre-hypertension	120-139 mm Hg	80-89 mm Hg
Stage 1 HTN	140-159 mm Hg	90-99 mm Hg
Stage 2 HTN	≥160 mm Hg	≥100 mm Hg

Within the geriatric population, physicians need to be educated in treatment and correct diagnosis. Blood pressure should be measured in both arms, and the higher of the two readings should be treated. Measurements should also be taken in both the sitting and

standing position after the patient has been seated quietly for 5 minutes and a lower limb measurement should also be taken for comparison (Koka et al. (2007). Cuffs must be the right size and properly calibrated, and the arm should be supported and remain at the level of the heart during arterial pressure measurement. The patient should have abstained from caffeine, smoking, and exercise half an hour before BP measurement. It is possible to confirm a diagnosis of HTN, after an elevated BP has been found as an average of two readings per visit on 2 or more clinic visits. Ideally an ambulatory BP monitoring (ABPM) reading for the 24hrs is done to determine a possible circadian pattern of BP increase (Llisterri et al. (2009); Rafey (2009) .

Once diagnosis has been established, a full medical history is necessary to assess lifestyle in search of other cardiovascular risk factors including pre-existing medical conditions that could possibly affect prognosis and treatment. Physical examination is very important and should include a fundoscopic examination to evaluate and assess the signs associated with secondary hypertension. It is also important to search for target organ damage and a probable cause that could possibly explain the HTN.

Before initiating treatment, routine laboratory examinations should be done to determine plasma and electrolyte concentrations, as well as, urine microscopy, blood glucose, hematocrit, creatinine, serum potassium and calcium levels as well as a lipoprotein profile, renin, aldosterone and catecholamine excretion in 24hr urine along with plasma metanephrine levels, ECG, and even renal ultrasound with duplex if necessary. After target pressure is reached, follow-up check-ups should be every 3-6 months along with regular routine electrolyte monitoring. Successful treatment can provide positive quality of life outcomes for this problem (Acelajado& Oparil (2009); Corrigan (2009); Rafey (2009); Stokes (2009).

One of the problems with diagnosis in the elderly is that true intra-arterial BP is substantially lower than the inappropriately measured cuff pressure due to excessive arteriosclerosis and arterial stiffness common in this age group. On inflation of the BP cuff, thickened and calcified arteries are not compressed adequately, due to arteriosclerosis, thus resulting in an inaccurate measurement. For the most precise and definitive diagnostic test it is necessary to measure the pressure intra arterially (Rafey (2009).

The obviously sclerotic arteries that do not collapse during inflation of the cuff result in a falsely high systolic BP referred to as pseudohypertension. With ageing, there is an increase in the stiffness of the artery caused by structural alterations within the arterial media resulting from the degradation and calcification of the elastic fibers along with the changes in the quantity and nature of the collagen that becomes calcified and has increased interstitial fibrosis. These changes could partly explain the increase in systolic BP that occurs in the elderly (Lakatta (1989).

Resistant hypertension refers to a "blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally one of the three agents should be a diuretic, and all agents should be prescribed at optimal dose amounts. Recent American Heart association guidelines also include patients who are well controlled but require 4 or more medications as having resistant hypertension" (Rafey (2009).

Goal blood pressure in isolated systolic hypertension, common in the elderly remains a debate, and clinical trials in this area have not yet achieved goal blood pressures of less than 140 mmHg (Rafey (2009). Previously older people were excluded from clinical trials, possibly due to limited life expectancy (Zeglin et al. (2009).

Isolated systolic hypertension (ISH) is characterized by systolic BP ≥140 mm Hg with diastolic BP <90 mm Hg and consequently high pulse pressure (Izzo et al. (2000); Franklin et al. (2001); Chobian et al. (2009); Stokes (2009). But the mechanisms of systolic and diastolic HTN are distinct and have different etiologies as in most cases, people who develop ISH, have no preceding or accompanying diastolic HTN (Zeglin et al. (2009). This type of HTN is the most common among the geriatric population and the widening of the pulse pressure could be due to the stiffening of the arteries that occurs with aging.

Prevalence and different population studies

The general prevalence of this disorder is seen to be increasing on a global scale, not only in developed countries but also in developing countries. There are various hypotheses to try and explain this, and one such explanation revolves around the changes in lifestyle along with dietary patterns. The National Health and Nutrition Examination survey from 1999 to 2004 showed that 60 % of all adults aged 60-69, and around 77% - 80% of those older than 80 years have HTN (Acelajado& Oparil (2009). Isolated systolic HTN accounts for 60-75% of cases (Chobanian et al. (2003). HTN accounts for 6% of deaths worldwide (Kotchen (2008).

Cardiovascular risk doubles for every 20/10 mm Hg increase in blood pressure. 80-95% of HTN is considered to be essential, primary or idiopathic in which case the cause is unknown (Kotchen (2008).The rest of the 5% - 20% of the elderly have a secondary cause for their hypertension, and the majority of cases are renovascular in nature (Ogihara et al. (2003).

Resistant HTN occurs across all age groups but seems to be more prevalent in the elderly. However the research is not significant and there is no clear picture of prognosis as this

specific patient population do not have enough follow-up studies on this subject (Rafey (2009) .

In the US, HTN affects the lives of 65 million adults, and the highest rate of this condition occur in the population older than 75 years. Statistics show that 2/3 of the population older than 60 years of age have HTN, with prevalence continually rising and control remaining poor (Wolff & Miller (2007). Prevalence increases with age affecting 64% of men and 76% of women over the age of 75 years (Lloyd-Jones et al. (2009). By the age of 75, 90% of 55 year old normotensive individuals will have HTN according to the Framingham Heart study. Reasons for this include excess dietary sodium, excessive alcohol intake, weight gain from increased caloric intake overlapping with increasing sedentarism and psychological stress all contribute to the development of HTN. Data from various studies revealed insufficient nutrition and exercise counseling for the general population and especially for the elderly, when treating for HTN (Aronow (2009); Padiyar (2009); Zeglin et al. (2009).

Curiously the patterns in blood pressure change with age, as after 50 years of age, isolated systolic HTN predominates, diastolic pressure falls while systolic rises (Ogihara et al. (2003). Statistics predict that by the year 2030 there will be approximately 70 million in the US over 65, representing 20% of the total population. This means that more than 7 million people will be 85 and older (Rosenthal & Nussinovitch (2008) .

Gender also plays a role in the prevalence and control of HTN, as US statistics reveal that elderly women are more affected by HTN than elderly men, 76.6% versus 63.0% and are also more aware, and seek more treatment but curiously, elderly women are the least likely to have their HTN properly controlled by medication (42.9% in women versus 57.9% in men) and have greater difficulty in achieving target BP´s suggesting that perhaps it would be useful to have control programs specifically targeted toward women (McDonald et al. (2009). HTN

becomes more prevalent in women than in men after the age of 65 years as systolic BP peaks in middle age for men but for women there is a continuous rise until beyond the age of 80 (Ninios et al.(2008).

Contrary to the studies conducted in the US, an Indian study showed a HTN prevalence of 39.5%, with this condition being more frequent in men, affecting 41% of men when compared to women, affecting only 38% of women. Studies conducted on a resettlement colony of Delhi further show an awareness of 51%, treatment of 38.8% of the studied population but adequate control was only seen in 14%. These findings suggest that prevalence seems to be higher in developed countries rather than in developing countries (Yadav et al. (2008). But equally worrying are the low treatment rates and the even lower successful control rates.

The prevalence in China has increased by 42% since 1991, possibly due to the changing lifestyle including diet and a contributing factor could possibly also be due to an increase in life expectancy resulting from the recent economic development of China. The Shanghai Men´s Health study evaluated the association of dietary patterns with blood pressure, and discovered that a diet rich in fruit and milk as opposed to one rich in meat or rich in only vegetables was significantly and inversely associated with both lower systolic and diastolic blood pressures in men that took part in this study. This could be related to the intake of sodium. Chinese populations tend to eat vegetables that have been cooked with salt or have been pickled, instead of raw vegetables and thus this influences the BP as well as the antioxidant and vitamin content that would be lost in the cooking process. Thus food processing and cooking methods need to be considered as each culture will have their own traditions and this could influence diet and consequently BP (Lee et al. (2010).

The prevalence within the Spanish population is considerably high, approximately 45% and reaching 70% in the elderly. Curiously, around 50% of cardiovascular deaths are related to hypertension (Tornero Molina (2009). The proportion of elderly patients over the age of 80, has increased by 28.8% in the past 6 years, and estimations say that this will rise by 33% by the year 2015 and 44% by 2020. ¾ of patients over 80 are hypertensive, but similarly to other population studies, BP control is poor, as only 35.6% of patients achieve BP targets. Curiously BP control declines with advancing age, but in some studies has shown slight improvements over time in recent years possibly due to better information that has allowed for the improvement in HTN awareness and control and at the same time possibly due to the advances made in geriatric studies. Interestingly, BP control improved in patients older than 90 years of age. A possible explanation for this fact could be that systolic BP declines after 85 years, and because it is more likely that patients with poor BP control would have died from this or other causes (Rodriguez-Roca et al. (2009).

The prevalence of hypertension in various Greek studies of an elderly population above 65 years of age, was estimated around 83% - 89%, with a higher incidence in women (86%) as compared to men (79%). 89.8% of the hypertensive population studied were aware of their disease, 77% were receiving treatment, but effective control was only found in 42.5%. This means that less than half were correctly controlled. Awareness of hypertension was significantly higher among those with a high frequency of BP measurements and among those with a history of coronary or other chronic diseases thus suggesting perhaps increased awareness and monitoring could play a role in improving control (Ninios et al. (2008); Triantafyllou et al. (2010). Another reason could possibly be the fact that people with a significant medical history are more cautious and aware of their health issues.

Various population studies have been conducted in numerous countries with variable results that are specific to each population group studied, but are only useful in giving a general idea

of prevalence and control of HTN within these countries, as the studies varied considerably, with different ranges of age groups, and BP measurements and so do not allow for an accurate qualitative comparison as in some cases, sample size is small, and in other cases data was based upon a single BP measurement, which does not allow for diagnosis to be most accurate. However for estimation purposes, in the geriatric population above 65 years of age, data showed a prevalence of 80.5% of HTN in England (Primatesta & Poulter, (2004) with 69.4% prevalence in men compared to 65.8% in women. (Ninios et al. (2008). According to Macedo et al. (2005), Portugal seems to show a slightly lower prevalence of 79% in men and 78.9% in women, when compared to England, followed by France with 78.2% (Brindel et al. (2006), and then Italy with 64.8% all with similar gender results (Ninios et al. (2008); (Triantafyllou et al. (2010).

Aging and the cardiovascular system

The geriatric population which is defined as individuals over the age of 65 years comprises 13% of the US population and those older than 85 years of age make up the largest growing segment of that group (Corrigan, (2009). There is a high incidence of common diseases in this population group, ranging from heart disease, osteoporosis, renal disease, diabetes, GI problems, as well as immune system alterations and diminished responses to sensory and musculoskeletal disturbances. These changes, in conjunction with other risk factors, cause a rise in the risk of cardiovascular events (Rosenthal & Nussinovitch (2008).

"Cardiovascular disease is the leading cause of death among older Americans. Stroke, heart failure and premature death account for the associated morbidity and mortality with untreated and undertreated HTN" (Corrigan MV. (2009) . These patients exhibit a higher pulse pressure

and amplification of both the heart rate along with pulse wave velocity (Rosenthal & Nussinovitch. (2008).

Because the increase in systolic blood pressure, and pulse pressure cause a higher risk for cardiovascular events, and these tend to increase with age, cardiovascular risks also increase with age. According to Corrigan, (2009) recent advances show that there is no threshold age above which treatment should be discontinued, and effective treatment has been shown to decrease the incidence of adverse cardiovascular events by 36% in the geriatric population and 34% in those older than 80 years. More specifically, treatment reduced major cardiovascular events by 22%, stroke risk by 34% and heart failure by 39%.

Increased systolic blood pressure and pulse pressure can be partially explained in the elderly due to structural changes because of aging of the arteries. This includes loss of vascular smooth muscle cells, calcium deposition, increase in vessel wall collagen content and collagen fiber cross-linking, and disruption and thinning of the elastic fibers. These are more significant in the large elastic arteries such as the aorta, and cause increased arterial thickness resulting from the loss of the elastic properties and remodeling, leading to abnormal dilation of the vessel. This results in a stiff artery that has limited recoil and decreased capacitance, and consequently is unable to accommodate the changes that occur during the cardiac cycle. Thus this increases cardiac afterload, systolic pressure and amplifies the pulsatile nature of blood flow(Acelajado& Oparil (2009); Aronow (2009). Thus elderly with HTN are more likely to have decreased baroreceptor sensitivity, increased ventricular mass, increased peripheral resistance, decreased left ventricular early diastolic filling rate as well as volume, increased left atrial dimension with reduced cardiovascular response to catecholamines. These factors and the difficult adaptability of the aging body when being medicated with

antihypertensive agents make it more likely to develop orthostatic and postprandial hypotension (Corrigan, (2009).

Arteriosclerosis builds up with aging, this in conjunction with the decrease in elastin, result in the reduced compliance and loss of elasticity of large arteries in the elderly. The stiffening of the arteries as well as endothelial dysfunction underlies the pathology behind systolic HTN (Corrigan, 2009; Stokes, 2009).

In the elderly total peripheral resistance is increased and there is a decrease in baroreceptor sensitivity related to age. It is this fact that causes greater fluctuations in BP. Target organs like the brain, heart and kidneys all suffer from a dysfunction in autoregulation (Corrigan, (2009). Diminished adaptive capacity is important as there is a tendency to have exaggerated postural changes in BP that are not compensated by a reflex increase in cardiac output. As explained by Cooney & Pascuzzi,(2009), "the elderly have impaired baroreceptor reflex activity due to reduced sensitivity or function of the carotid sinus and aortic arch, and so there is a reduced cardiac response to stimulation."

In the presence of HTN in elderly patients, endothelial dysfunction occurs more frequently as there is a decrease in bioavailability of nitric oxide, which is important in regulation of vasomotor tone and thrombosis by promoting vasodilation and inhibiting platelet aggregation (Acelajado & Oparil (2009).

Body changes due to age include decreased renal function, decreased hepatic blood flow, increased body fat, decreased albumin , and decreased lean muscle mass with decreased body water. There are also changes within the GI system, like altered GI function, increased gastric pH, delayed gastric emptying and impaired intestinal motility. The volume of distribution of various medications can be altered by these changes. As cardiac output decreases, there is a

decrease in perfusion of the vital organs including kidneys and liver, thus this can decrease a body´s ability to metabolize and excrete medications. Lipid soluble drugs can have a larger volume of distribution, prolonged half life and increased duration of action. Changes in the metabolism of drugs can alter drug responses in the elderly. Elderly have roughly a 40% decrease in hepatic blood flow, and this causes a great decrease in first pass metabolism, thus medications subject to oxidative phase I metabolism have a decreased elimination ex. (propranolol, verapamil, nifedipine), however phase II metabolism is not affected by age (Rosenthal & Nussinovitch. (2008).

Unexpected pharmacodynamic changes can occur such as altered sensitivity to several classes of drugs like anticoagulants, cardiovascular and psychotropic drugs along with an increased volume of distribution of lipid soluble drugs that prolong elimination half-life. There is a reduced clearance of lipid soluble as well as water soluble drugs. Due to the reduced renal and hepatic clearance, drug metabolism in this population group is complicated. bioavailability of drugs that undergo first pass metabolism can be significantly increased due to the reduction in first pass metabolism of some drugs. On the other hand, the majority of ACEI pro-drugs (enalapril and perindopril) that undergo activation in the liver, may have an impaired biotransformation in patients with severe heart failure and hepatic dysfunction. Kidney function and excretion can be altered by age, resulting in a diminished renal blood flow, glomerular filtration rate, tubular secretion and renal mass due to the reduction in nephrons. These age related changes in glomerular filtration and tubular secretion are particularly detrimental to the excretion of several ACEI, thus resulting in their increased plasma concentration. Homeostatic regulatory mechanisms decline in the elderly, which may explain the greater incidence of postural hypotension, slower thermoregulation and slower capacity to compensate for the hypotensive effects of the antihypertensive drugs (Rosenthal& Nussinovitch, (2008). According to Cooney &Pascuzzi, (2009), because of the altered

pharmacokinetics and pharmacodynamics that occur in the elderly, they are prone to adverse drug reactions.

BP has a circadian variation in this population group. While asleep and in the afternoon, BP decreases and in the evening it increases, but is most pronounced in the early morning. This means that especially after 80 years of age, there is a reduction in nighttime dips of BP (Corrigan, (2009).

Older individuals have an increased salt sensitivity, thus the BP increases in response to a sodium load, as there is increased responsiveness of volume homeostasis, especially in hypertensive individuals as a result of an age-related decrease in renal function that limits the kidney´s ability to excrete a sodium load. There is also a decline in activity of membrane sodium-potassium and calcium adenosine triphosphate pumps, leading to an excess of intracellular calcium and sustained vasoconstriction, thereby increasing vascular resistance (Acelajado& Oparil, (2009); Stokes , (2009).

Aging also affects the neurohormonal mechanisms that control BP. There is a progressive decline in plasma renin activity along with renin secretion and a slow response by aldosterone to acute stimuli. By contrast, basal SNS activity increases with age (Acelajado& Oparil, (2009). There are also changes in the CNS, the autonomic nervous system in the cardiovascular and respiratory tract have reduced β- adrenergic receptor activity, thus elderly are less responsive to β-adrenergic agonists like formoterol and salmeterol as well as β-adrenergic blockers like atenolol, metoprolol and propranolol (Cooney& Pascuzzi, (2009).

Curiously there tends to be a reduction in both systolic and diastolic BP after 85 years. This could be due the consequent reduction of systolic function along with the decrease in muscle mass, along with malnutrition that is so typical of the last ages of life. Natural selection is

important as there seems to be preferential survival of normotensive individuals, while a premature death seems to come to those with HTN, due to a combination of environmental and genetic factors (Casiglia, (2009).

This population group has a high incidence of pathologies that are usually accompanied by a large quantity of medications taken together and interacting to try culminate the symptoms along with the possible control of some of the conditions. This polypharmacy is one of the great challenges posed to the physician as each individual drug needs to be given at the right dose, at the right time, and drug interactions need to be considered as this could affect treatment and compliance. Over the age of 65, ¼ of hospitalized patients are taking 6 or more drugs daily, while older adults average 13 prescriptions per year. 90 % of patients over the age of 75 take drugs regularly, and more than 1/3 take 3 or more a day. According to a survey in the US, the highest medication use is among women aged at least 65, of these, 23% used 5 medications and 12% used 10 or more different medications every day (Rosenthal & Nussinovitch. (2008). This is highly significant, and implies that caution needs to taken by physicians when prescribing for the elderly, as very often, the medications have side effects that cause new symptoms to appear and this can generate a vicious cycle of new conditions that aggravate rather than alleviate the quality of life of the patient.

Arterial stiffness greatly affects the capacitance function and also is responsible for the increase in the velocity of both the propagation wave and the reflected wave, which causes an earlier arrival of the reflected wave before the completion of the systole (DeLoach &Townsend (2008) ;Mitchell et al. (2004). Consequently the outcome is a widened pulse pressure that is the result of an increase in systolic and decrease in diastolic pressures. This increases the cardiac workload, reduces coronary perfusion during diastole and increases the consequent pressure that is transmitted to vital end organs like the brain and kidneys

(DeLoach &Townsend. (2008) ; Mitchell et al. (2004). Thus in this age group, widened pulse pressure (difference between systolic BP and diastolic BP≥50 mm Hg) may be a better marker for cerebrovascular and cardiovascular disease vulnerability rather than any individual average of systolic or diastolic BP.

There is an increase in systolic blood flow with the increased arterial stiffness which increases shearing forces. However the aortic stiffness integrates the total damage of CV risk factors on the arterial wall over a long period of time, whereas BP, glycemia, and lipids fluctuate continually over time and may not reflect the true values damaging the arterial wall.

Thus, lowering BP and lipid values and improving glycemia control in a few weeks may improve CV risk scores, but not attenuate arterial stiffness. Improving arterial stiffness may take a longer period of time, or may be partially irreversible, meaning that an improvement in CV mortality may not actually be seen despite lower CV risk scores (DeLoach &Townsend. (2008) (Lim &Townsend (2009) Laurent et al. (2006).

The longer the population lives, the more likely there will be degenerative central nervous system (CNS) disease, presenting clinically as dementia (such as Alzheimer's disease) or vascular dementia, a long-term complication of hypertension. Studies reveal that lowering BP can prevent stroke, but this does not imply that it is possible to simultaneously prevent microangiopathy, which is what causes white matter demyelinization. This process of demyelinization in conjunction with clinical cognitive deterioration is compatible with a diagnosis of vascular dementia. Thus it is recommended for the safety of the patient to reduce BP slowly as cerebral autoregulation is slower (Cherubini et al. (2010). It is also a well known fact that if BP is controlled during a younger age, cognitive decline is less likely and at a much slower rate above 65 years of age. This is another incentive for successful treatment and

control from the moment of diagnosis, so as to improve quality of life when reaching extremes of age, as this implies to a certain degree that the progression toward dementia could be controlled and possibly even avoided in some cases.

Causes of high blood pressure

When considering resistant HTN there are various causes that can be considered true causes but it is important to remember that false positives can occur as in the cases of an incorrect technique in measuring BP that could give altered results, "white coat effect", lack of patient adherence to medication, suboptimal therapy or incorrect treatment, food, and over the counter medications and even lack of adherence to lifestyle changes. All these factors need to be taken into account when diagnosing and searching for a possible cause for HTN.

When considering incorrect technique in BP measurement, it is important to consider the deflation rate of the BP cuff (recommended to be at a rate of 2-3 mm Hg/s), and an adequate cuff size because if the deflation is too fast or the cuff too small, the value could be altered and falsely elevated. The cuff width should be equal to 40% of the arm circumference, and the length should encircle at least 80% of the arm circumference. The values could also be altered if the patient ingests caffeine or pressor agents shortly before measurements, and thus these should be avoided before measurement (Chobanian et al. (2003); Pickering et al. (2005); Pickering et al. 2008).

The identifiable causes of hypertension include Chronic kidney disease; Renovascular Hypertension; Hyperaldosteronism; Cushing syndrome; Obstructive sleep apnea; Pheochromocytoma; Coarctation of the aorta; Increased intracranial pressure; Thyroid

/Parathyroide disease; CNS tumors; and Acromegaly among others (Acelajado & Oparil,(2009); Rafey, (2009).

Secondary causes account for less than 5% of HTN, with renal disorders like chronic kidney disease and renovascular disease being the most common of these. BP control can be worsened by impaired kidney function due to the reduction in the excretion rate of sodium and water which in turn results in overload and resistant HTN. According to Hansen et al.(2002), renal artery disease was found to be more prevalent in the elderly, in a study with renal duplex ultrasound, significant stenosis was found in 6,8% of individuals older than 65 years and this stenosis increases in prevalence with age. When there is renal artery stenosis the kidney suffers from a severe reduction in perfusion which in turn activates the RAA system and so leads to retention of water and sodium thus worsening BP control. This is often associated with atherosclerosis. Renal arteriogram is the gold standard for this diagnosis. The management of renovascular disease is complicated by the conflicting outcomes of studies comparing medical management with interventions including angioplasty of the renal artery stent placement (Rafey, (2009).

Depression and anxiety have previously been associated with development of HTN, however it is not clear if intervention targeting emotional health would be effective in the prevention of HTN. Even stress plays an important role in BP as women not under stress like nuns have lower BP´s when compared to women with a highly stressful lifestyle or job, like lawyers. Increase in systolic BP with age is a genetic base adaptation to the environment and thus an adaptation to physical and psychological stress is probable. This means that controlling BP in these cases would require adaptive measures to daily stress (Stokes (2009).

In the elderly OSA (Obstructive sleep apnea) is present in 37.5-62% of people older than 60 years of age (Ancoli-Israel et al.(1991). According to Gonçalves and colleagues (2007) ,

studies reveal a relationship between HTN and OSA. The mechanisms for this include altered chemoreceptor stimulation, chronic nighttime hypoxemia, and activation of sympathetic and rennin-angiotensin system. Regardless of the renin levels, aldosterone production also seems to be stimulated by hypercapnia along with nighttime hypoxia (Brooks et al. (1997). Treatment of the OSA with non-invasive positive pressure ventilator support also allows for an improvement in BP control (Campos-Rodriguez et al. (2007).

In patients suffering from primary aldosteronism, several studies have reported elevated serum levels of aldosterone in patients with resistant HTN (Benchetrit et al. (2002); Calhoun et al. (2002). Diagnosis of primary aldosteronism can be based on a history of spontaneous potassium decrease with serum potassium <3mEq/ L, while urine potassium increases >30mEq /24h, plasma rennin activity is reduced to less than 1ng/mL/h and plasma aldosterone levels achieve values greater than 22ng/dL. Because aldosterone plays a critical role in the regulation of potassium balance and extracellular fluid volume, a mineralcorticoid antagonists like spiranolactone is recommended in cases when surgery is not an option (Rafey, (2009).

Pheochromocytoma s are tumors that occur in the adrenal medulla or sympathetic ganglia and cause excess production of catecholamines. Clinically this manifests as extensively variable BP or persistent HTN. BP Elevations may be linked with headaches, palpitations, tremor and paleness, as well as diaphoresis. Detection can be done with plasma metanephrine levels and resting serum catecholamine levels along with 24hr urinary metanephrine levels and imaging studies include a CT scan and MRI. In these cases the treatment of choice is a laparoscopic adrenelectomy, along with “alpha blockade using selective postsynaptic alpha-1 adrenergic receptor antagonists such as Terazocin, a calcium channel blocker for cardiac protection and a betablocker if tachyarrythmias are present” (Rafey, (2009).

The “White coat effect”, is when BP is increased temporarily through an autonomic neural reaction triggered by the process of measurement and is often mistaken for ISH.

Complications

There is emerging evidence that cardiovascular disease, along with extremes of weight (such as obesity and extreme leanness) and hypertension have a negative impact on cognitive function in the elderly, as these can contribute to the onset and pathology of disorders like Alzheimer´s. Various studies have showed a “positive association between elevated blood pressure and cognitive impairment”. “age is the most critical factor when assessing the relationship between weight and cognitive function in hypertensive’s, and that risk at middle age may not be the same as risk at older age, especially very old age” (Beydoun & Beason-Held ,(2008).

Increased systolic blood pressure and pulse pressure are stronger risk factors for cardiovascular morbidity and mortality in the elderly. However the optimal BP in the very old requires further investigation. HTN is a major risk factor for coronary events, stroke, heart failure and peripheral heart disease and renal insufficiency (Aronow, (2009).

According to the Captoril Prevention Project, diuretics and beta blockers were independently linked to an increased risk of new onset diabetes in the elderly while the use of ACE inhibitors and α- blockers were found to be a better option as these caused a decreased risk of new onset diabetes (Liou et al. (2008).

Orthostatic hypotension is defined as a “supine to standing systolic blood pressure decrease greater than 20 mmHg or a diastolic blood pressure decrease greater than 10 mm Hg.” It has a prevalence of about 12-55%, and tends to increase with age and with increasing quantities of medication taken. The primary cause is attributed to an age-related decrease of baroreflex

activation that occurs with standing along with a slow and difficult physiological postural adaptation by the body to the different positions. The difficulties in autoregulation that occur with result in the typical symptoms of orthostatic hypotension which include dizziness, difficulty walking, frequent falls, history of myocardial infarction or transient ischemic attack, syncope and presence of carotid artery stenosis on ultrasonography (Acelajado & Oparil, (2009).

HTN plays a role in the pathogenesis of cognitive impairment in the elderly, as elevated BP in midlife is predictive of dementia in the later years. Risk factors for dementia include high systolic BP >180 mm Hg and low diastolic BP <70 mm Hg (Acelajado & Oparil, (2009).

Caution needs to be taken with lowering of BP as this may be harmful if inadequate organ perfusion occurs along with altered autoregulation, which can be detrimental especially in elderly patients with cardiovascular complications (Ogihara et al. (2010).

Treatment

The goal of antihypertensive treatment is to lower BP in order to reduce renal and cardiovascular morbidity and mortality. The BP goal within the older population is still a matter of debate; however the consensus at the moment is a BP of less than 140/90 mm Hg, in individuals with uncomplicated HTN, regardless of age. In patients with chronic kidney disease or diabetes mellitus, the goal BP is less than 130/80 mm Hg. But more research is needed to address this issue, as in the elderly population, if the systolic BP is reduced to less than 140 mm Hg, consequently this will result in an excessively low diastolic Bp, which is dangerous and is associated with an increase risk for death (Acelajado & Oparil, (2009).

Non-pharmacological treatment

Successful management of elderly patients includes awareness, screening and identification of possible causes and complications. Lifestyle changes are an important part of hypertension control. These include weight reduction, smoking cessation, change in diet to favor one rich in fruit and vegetables according to the Dietary Approach to Stop Hypertension (DASH),(Appel et al. (1997) lower salt intake, and regular exercise have all been shown to help in lowering BP and reducing the need for additional antihypertensive medications (Sacks et al. (2001); Stokes (2009) . Effective treatment to target level is seen with the use of multidisciplinary teams composed of physicians, nurses, dieticians and pharmacists. It is also important to educate the patient and include him in his care plan. The use of pill boxes as well as lifestyle modification with specific goals for changing diet in conjunction with exercise has been seen to be more beneficial than just general advice (Roumie et al. (2006).

Diet

There is a well recognized relationship between HTN, cardiovascular morbidity and obesity. Studies reveal a rise of 3,0mm Hg in systolic BP along with a diastolic rise of 2,3mm Hg for each 10kg increase in body weight. A 12% increased risk in coronary heart disease and a 24% increase in the risk of stroke is associated with every 10kg increase in body weight. This means that patients decreased their need for antihypertensive medication by 30% by reducing average body weight about 3,5 kg- 4,5 kg (Stanton & Lowenthal, (2000); Aronow (2009).

When analyzing diet, one of the important factors that need to be considered is the levels of micronutrients. Micronutrients like as K, Ca, Na, Mg, fiber etc could be linked to the levels of blood pressure as these along with antioxidants help prevent oxidative stress, thus fruits and vegetables which are abundant in these elements could be beneficial in controlling BP.

However, the Supplementation en vitamines et mineraux antioxydants-randomised trial could not demonstrate any beneficial effect of low-dose antioxidant supplementation on the total risk of hypertension. The Oxford Fruit and Vegetable Study along with the Dietary Approaches to Stop Hypertension intervention study have shown results of substantial lowering of both systolic and diastolic BP with a diet low in saturated fats and rich in vegetables, fruit and low-fat dairy. However further studies are needed as no causal association of dietary patterns and BP can be established directly, as no specific nutrients can be identified to impact on BP and the variation on diet is so vast that studies would have to be done in diverse populations as diet varies according to sex, socioeconomic status, ethnic group and culture (Lee et al.(2010).

Foods that increase BP like licorice and grapefruit juice that inhibit the 11β hydroxysteroid dehygrogenase enzyme, lead to an increase in intracellular cortisol thus worsening HTN (Walker & Edwards (1994); Lee et al. (1996); Sardi et al. (2002). NSAIDs (non-steroidal anti-inflammatory) , except aspirin, increase sodium retention and the pressor response worsen BP control as these along with other everyday non-prescription medications antagonize antihypertensive medications (Pope et al. (1993). Pseudoephedrine along with other sympathomimetic agents like phenylpropranoline raise BP while medications like steroids, cyclosporine and erythropoietin directly cause HTA or Beta agonists like albuterol antagonize the action of antihypertensive agents. Thus all these drugs would alter BP control.

Curiously in an industrialized country, the lowest average BPs was found among a population of strict vegetarians in Massachusetts. The group of individuals adhered to "Macrobiotics" consuming almost no animal products and instead relying upon whole grains, green leafy vegetables, squash and root vegetables (Sacks & Kass, (1988). Numerous studies have shown that a high intake of fruit and vegetables is associated with decrease not only in BP and in

change of BP with age but also in overall cardiovascular risk (Bazzano, et al. (2002). The DASH trial established that independently of sodium restriction or weight loss, HTN could be lowered with a diet rich in fruits, vegetables, low-fat dairy products and with reduced saturated and total fat. After 8 weeks of dietary modification, there was a BP reduction of 11,4 /5,5 mm Hg in HTN patients, as well as a reduction of BP in normotensive people by 3,5/2,1 mm Hg (Appel, et al. (1997); Acelajado & Oparil, (2009).

Thus in conjunction with sodium restriction, even greater reductions are possible if correct dietary modifications are instilled in order to improve eating patterns. Subjects eating more fish in comparison to other subjects of the same genetic strain that followed a more western lifestyle show a lower BP with a lower prevalence of HTN and show no BP increase with age (Stokes, (2009).

Salt

Diets rich in salt are one of the principal causes that aggravate HTN, and in many cases this problem is increased because elderly have a decreased taste sensitivity to food, so the salt is used to compensate this (Stokes, (2009). Reduced dietary sodium lead to a significant reduction of HTN in 56 randomized trials. Thus Low salt would have a more pronounced benefit in the elderly as it was noted that reductions were larger in trials with older individuals (Midgley, et al. 1996) . The most compelling of this evidence was seen in the TONE (Trial of nonpharmacological intervention in the elderly) trial as results revealed a 30% decrease in the need for antihypertensive drugs when dietary sodium was reduced by 40mmol/day in the elderly population (Appel, et al. 2001). Thus simply by changing the way food is cooked and processed in senior centers and retirement communities, a passive decrease in sodium is achievable. Dietary salt was initially recommended to be less than 2,4g daily but more recent

evidence has shown that by lowering this to 1,6g of sodium helps to reduce the number of antihypertensive medications by at least one medication. In fact, there has been noted a decrease efficacy and resistance to diuretics related to high salt intake (Wilcox, et al. (1989).

Alcohol

There is a well known association between alcohol consumption and BP. A study in Japan showed an average annual increase in systolic BP far greater in drinkers that consumed ≥300g/ week than among non-drinkers, thus showing the hypertensive effect of long term alcohol consumption (Lee et al. 2010). However this is a matter of debate, but it is established that alcohol affects BP only if taken in large quantities and chronically (Padiyar (2009). This means another measure for BP control includes limiting alcohol consumption.

Smoking

Smoking is thought to cause an acute increase in BP and heart rate. In some cases it has been associated with malignant hypertension probably because of nicotine acting as adrenergic agonist, mediating local and systemic catecholamine release of vasopressin. However, results are variable in this area as studies in England show a similar independent effect of smoking on BP, while a cross sectional Japanese study found lower BP among smokers (Lee et al. (2010) .

Exercise

Regular aerobic exercise has been shown not only to reduce BP but also to improve overall cardiovascular health. 180 minutes per week of moderate intensity physical activity is beneficial. Regular aerobic exercise with 30 minutes of interval training three times a week during 12 weeks of exercise showed a decrease in systolic blood pressure by 8,5 mm Hg.

After 6 months of lifestyle changes, a BP reduction of 4,2 /4,9 mm Hg was observed. Regular physical activity also improved lipid profile, glucose tolerance and total cardiovascular risk (Acelajado & Oparil, (2009).

Thus weight reduction, a diet rich in fruits, vegetables, low-fat dairy products with decreased content in saturated fats and total fat, salt reduction, regular aerobic activity, limiting alcohol consumption would all go a long way in helping reduce BP even before Pharmacological intervention (Chobanian et al. 2003; Stokes ,2009).

Advances in treatment

According to Esler et al. (2010), despite multiple lifestyle interventions in combination with numerous effective medications, BP remains higher than accepted and control is further complicated by physician inertia along with patient's antipathy to lifelong multidrug treatment for a predominantly asymptomatic disease. This means that despite current strategies, there is an underlying refractory pathophysiology that does not respond adequately to pharmacological intervention, and other strategies need to be developed. In the past, before antihypertensive medication was available, non-selective surgical sympathectomy was effectively used to control HTN. Most recently, endovascular catheter technology allows for selective denervation of the human kidney using radiofrequency energy on the nerves within the adventitia of the renal arteries. The clinical trial of this approach showed successful renal denervation with a reduction of sympathetic activity and rennin release along with reduced central sympathetic signaling. This procedure proved to be feasible and safe without substantial side effects. "Renal denervation led to a reduction in blood pressure of 10 mm Hg or more in 84% of treated patients. Furthermore, the renal denervation procedure was done

without any major adverse effects. Imaging of renal arteries for damage showed no evidence of renal artery stenosis or aneurismal dilatation during the 6-month follow-up". This is successful because renal sympathetic nerves play a significant role in the development and perpetuation of hypertension, and essential HTN causes activation of sympathetic signaling to the kidneys Increased tubular sodium re absorption, renin release and reduction in renal blood flow are all stimulated by an efferent sympathetic signal while afferent signals from the kidney modulate central sympathetic outflow and thereby directly contribute to neurogenic HTN (Esler et al. (2010).

Pharmacological treatment

One important geriatric principle is to avoid medications known to interfere with each other and to use the least possible number of medications to treat disease. There needs to be a balance between polypharmacy and abstaining from treatment, and it is important to consider quality of life. Diuretics are often the first line of choice in this population group (Corrigan, (2009). Antihypertensive pharmacologic treatment decreases the development of new coronary events, stroke and heart failure in the elderly. Successful treatment is associated with a decrease in cardiovascular events, renal insufficiency and a reduction in dementia (Aronow & Frishman , (2006). The decrease in strokes can be up to 36%. In the perindopril against recurrent stroke study, perindoril and indapamide reduced stroke related dementia by 34% and cognitive decline by 45% (Forette et al. (2002). In the systolic hypertension in Europe trial, nitrendipine decreased dementia by 55% at 3.9 years follow-up, while cognitive impairment decreased by 38% (Murray et al. (2002). The Rotterdam study showed that antihypertensive drugs decreased vascular dementia by 70% (Veld et al. (2001). HYVET showed in a substudy that the antihypertensive drug therapy reduced dementia by 14% but the effect was not significant (Peters et al. (2008). HYVET proved that antihypertensive therapy

is beneficial in the elderly, however the study did not provide data on target BP as in the study, target BP was 150/80 mm Hg, but the Joint National Committee on detection, evaluation and treatment of HTN 7th report, (JNC 7) recommend a target BP of 140/90 mm Hg. Further research is needed to answer this question. JNC 7 recommend that diuretics be the 1st choice for initial treatment in the elderly, but most patients will need 2 or more antihypertensive agents to control BP. "If the BP is more than 20/10 mm Hg above the goal BP, drug therapy should be initiated with 2 antihypertensive agents, one of which is a thiazide diuretic" (Chobanian et al. (2003); (Acelajado & Oparil, (2009).

Older patients are at more risk for adverse effects, including drug interactions related to the use of multiple medications (Chobanian et al. (2003). Falls or syncope could be caused by orthostatic or postprandial hypotension especially in this population group (Aronow , (1998). The changes with age to the kidney could predispose the elderly to electrolyte abnormalities including hypokalemia, hyponatremia and hypomagnesemia with both thiazide like and loop diuretics. There is a risk of hyperkalemia with potassium sparing diuretics and these need to be administered with caution especially in conjunction with ACEI or ARBs, as these can also cause a worsening in the renal function (Acelajado & Oparil, (2009).

Beta blockers depress the sinus and AV node, and therefore are not indicated in patients with severs sinus bradycardia, sinoatrial disease or atrioventricular block. These should also not be given to patients with asthma, lung disease or severe bronchospasm. In addition, beta blockers may cause fatigue, exercise intolerance or confusion (Rosendorff et al. (2007); Acelajado & Oparil, (2009).

Beta blockers are not generally recommended as they do not combat the effects of increased arterial stiffness, and they have been associated with increase insulin resistance and worsening glycemic control in diabetics. However, these are important agents for the use in

treatment of elderly with comorbidities such as coronary artery disease and should be used with caution and in conjunction with other agents (Acelajado & Oparil, (2009); Stokes, (2009).

Calcium channel blockers have the potential to increase cardiovascular events and should be avoided (Pahor et al. (1995). These are especially indicated in cases of refractory angina, otherwise they should be avoided in cases of decreased left ventricular systolic function (ejection fraction less than 40%), like beta blockers, verapamil and diltiazem depress the sinus and AV node and thus should not be used in cases of bradyarrhythmias (Aronow & Ahn, (2002).

Central acting agents such as clonidine, resperpine and guanethidine should not be used as monotherapy because they have a high incidence of adverse effects including sedation, depression and constipation. Direct vasodilators including hydralazine and minoxidil may cause headache, fluid retention, tachycardia and angina pectoris. Elderly patients with history of myocardial infarction should be treated with beta blockers and ACEI as these also decrease the incidence of new coronary events (Aronow & Ahn, (2002); Chobanian et al, (2003).

ACEIs and ARBs were found to be beneficial in the elderly with atrial fibrilhation in 2 randomized trials. ACEIs, calcium channel blockers and ARBs seem to offer significant neuroprotection in addition to BP reduction.

To control BP and restore cerebral blood flow Nifedipine, atenolol and valsartan are all effective as monotherapy. Evidence is emerging that the use of ARBs as first line of therapy for HTN as well as cognition protection in the elderly should be strongly considered. A recent observational study suggests that the use of ACEI in Alzheimers disease is associated with

slower rate of progression of the disease, but this requires further confirmation by clinical trials (Rosenthal & Nussinovitch. (2008).

According to Naya et al. (2007), there is evidence that "strongly indicates that olmesartan has beneficial effects on brain perfusion in hypertensive subjects over age 65 years. A cardiologic study of olmesartan also found that this ARB improves endothelium-dependent coronary dilation in hypertensive subjects, independent of blood pressure decrease. The advantages of olmesartan may help protect against brain damage in hypertensive subjects but further studies are needed".

The VALISH study found that calcium channel blockers and diuretics may be preferential drugs for older hypertensive patients when compared with drugs that inhibit the rennin-angiotensin system. Low doses of angiotensin receptor blocker (valsartan) was found to be less effective in US and European patients, however this was an asian study and so the results need to be considered carefully before extrapolating to a non-asian population (Ogihara et al. (2010).

Diuretic treatment, along with other medications, are important in improving cardiovascular outcomes according to the "Antihypertensive therapy and lipid lowering treatment to prevent heart attack trial" (Rafey, (2009). Often hyponatremia is a side effect of diuretic treatment especially in older women. Hydrochlorothiazide(12.5mg) and Chlorothalidone (6.25mg) are both effective diuretics with minimal side effects (Carter et al. (2004). In patients that have impaired renal function with glomerular filtrate rate less than 40ml/min, loop diuretics are more effective than thiazides, while Furosemide and others in the same group, require frequent dosage monitoring with higher doses being needed for optimal control of BP (Zamboli, et al. (2006).

In patients with chronic kidney disease, the antihypertensive medications of choice are ACEIs and ARBs along with a loop diuretic or in combination with a thiazide like diuretic (Rafey, (2009).

Monotherapy shows an overall similar efficacy, however there is a considerable variation in individual response thus indicating an alternative strategy of combining different antihypertensive agents to reach desirable BP targets is necessary. Effective combination therapy consists of drugs with different modes of action to achieve an additive antihypertensive effect, as well as to mitigate the compensatory mechanisms that limit the decrease in BP. Studies support efficacy of combination therapy in the elderly (Antonopoulos, et al. (2008). Evidence suggests that combination therapy should be done as follows: A calcium channel blocker like amlodipine 10mg or ACEI like imidapril 20mg with a diuretic like indapamide 2.5mg, as this is more effective than an ARB or a calcium channel blocker in monotherapy. Curiously, combining the CCB with the diuretic proved to be more effective than the ACEI with the diuretic. This is important considering that 2/3 of individuals with HTN cannot be controlled with 1 drug and will require 2 or more agents selected from different classes. Thus 1st line agent is usually a thiazide diuretic and 2nd line will be either a CCB or an ACEI (Acelajado & Oparil, (2009). Studies have found it to be more beneficial to introduce additional groups of medication instead of reaching extremely high doses of the individual drugs separately. This means that lower doses also decrease toxicity and this is preferable in the elderly due to the renal and hepatic changes that occur which affect pharmacodynamics.

Why is this disorder not being controlled in the elderly population?

There are many reasons why this disorder is not adequately controlled. These reasons include non-compliance of medication for various reasons as well as lifestyle changes that aggravate the condition. Inactivity tends to increase with age, as only 30% of patients older than 65years report regular exercise. This lack of physical activity leads to an increase in weight as well as further exacerbates the aging process. Studies have shown that regular physical exercise can actually slow down and counter the effects of aging and thus this could benefit HTN treatment. The lack thereof can be considered one of the multiple factors that counteract the BP control mechanisms.

Elderly people have to compensate the lack of taste sensitivity, so they add more salt to their meals and they also depend more on processed and prepackaged foods that are high in sodium rather than fresh foods that are low in sodium. This means that ultimately they have a higher salt intake.

The Framinghan study showed that the strongest patient characteristic that predicted uncontrolled HTN was older age. Less than 25% of those with an age superior to 75 years had BP controlled to goal (Lloyd-Jones, et al. 2005). Data from NHANES (National health and nutritional examination survey), show similar results with a much higher prevalence of uncontrolled HTN in older age groups as compared to younger ages (Franklin, et al. 2001). There are various reasons why there is more uncontrolled HTN in older individuals including suboptimal treatment. Until recently elderly individuals were usually excluded from patient trials and this could have influenced patient care and physician attitude. HYVET (Hypertension in the very elderly trial), was the first randomized controlled trial for the

elderly that clearly showed beneficial results with antihypertensive therapy. Other reasons for inadequate treatment in this population group include side effects from medication and fear of excessively low diastolic BP (Beckett, et al. (2008).

The Framinghan study proved that the problem behind the lack of HTN control was due to under-treatment. 61% of patients were receiving only 1 antihypertensive medication and even fewer were on a thiazide diuretic as is recommended. Trials show that optimal doses of 3 or 4 medications are generally required to improve BP control, and among these, there should be an appropriate diuretic present according to the renal function. Adherence to medication is poor and seems to be worse in the elderly due to factors like advanced age, cognitive impairment, memory loss, depression, potential for adverse effects, and certain attitudes that have been identified as barriers to adherence and optimal BP control. These include altered moods and behavior that accompany vascular dementia, and insomnia along with the deleterious effects of hypnotics used to treat insomnia. Because HTN is chronic and so often asymptomatic, it remains a challenge for doctors to measure, monitor and treat (Lee, et al. (2006); Simpson, (2006); Rosenthal & Nussinovitch. (2008).

Reasons for non-compliance that need to be considered in this age group include diminished understanding and memory; impaired eyesight and hearing; financial restrictions; general decline in the ability to cope, poor nutrition; simply being unable to remove the pills from the bottle and living far from family. Another important reason for this lack of HTN control includes the choice and will of the patient to comply, as often they choose not to take the medication because they feel cured, or simply because the prescription finished and they no longer think it necessary to continue medication. They could have difficulty in going to the chemist to get more medicine, as they may live far, have difficulty moving, do not have

adequate transportation or just the fact that they take so many types of medication makes it possible for them to not want any more drugs (Rosenthal & Nussinovitch. (2008).

With ageing, the CNS changes affecting memory and there is a decreased ability to process new information. This could be one of the reasons behind non-compliance and affect the patient's ability to adhere and understand the correct instructions for a new medication (Cooney & Pascuzzi, 2009). Because the patients rarely feel any type of symptoms with HTN, they do not feel the need to take medication and this is also affected by the patient's ability to read and understand prescription and instructions. In order to follow instructions and adhere to correct treatment schemes, there needs to be adequate visual acuity as well as hearing and manual dexterity as these are all important when listening to instructions, reading and opening medication vials (Cooney & Pascuzzi, 2009).

Only 20-50% of the antihypertensive patients who are identified, are treated, and even fewer of these actually manage to achieve adequate control. Non-delayed treatment could prevent 14% of strokes, and 20% of major cardiovascular events in 5 years (Casiglia et al. 2009).

A method to facilitate compliance could be the use if a multicompartment dispenser with clear plastic cover, through which each compartment holding tablets for a specified day of the week can be seen. This as well as explaining in simple understandable language the importance of taking medication correctly could all aid in this problem of non-compliance as well as the lack of control of HTN.

It could be beneficial to improve adherence strategies that include a multidisciplinary team approach incorporating patient education and ongoing support by health professionals

simplifying medication regime, systems like the polypill and self BP monitoring at home (Celis, et al. (2005) ; Simpson.(2006).

Elderly patients with multiple medical problems are often undertreated termed “treatment inertia”. Reports show that in more than 50% of patients with poorly controlled blood pressure, there have been no changes made in their medication regime by the physician (Moser & Setaro.(2008).

In some cases more medications are felt to be worse than the benefits they offer, and there is a severe problem with coverage of medication and the ability to afford more medication even if clinically indicated (Rochan & Gurwitz ,(1999). 24% of patients do not take medication as prescribed (Acelajado & Oparil, (2009). With the current financial crisis, this problem needs to be addressed with medical aid schemes, further coverage and reimbursement schemes to try culminate this difficulty. Physicians also should be aware of the patient’s financial situation and choose affordable drug schemes accordingly.

Prevalent comorbidities, polypharmacy and high cost of medication contribute to low control rates in the elderly. Polypharmacy, mistakes in selecting drugs and doses as well as taking medication prescribed for someone else all pose serious problems to the adequate control of this disorder (Gandelman , et al. (2004); Acelajado & Oparil, (2009).

Age related changes in pharmacokinetics and pharmacodynamics render them more susceptible to drug related problems. Improper control leads to increased toxicity in this age group. Inadequate control could also be due to failure by healthcare professionals to prescribe the indicated medications and perform adequate follow-up, as well as document the management of care, educate the patients correctly, and maintain continuity (Rosenthal & Nussinovitch. (2008).

Another important aspect is that of drug interactions as there could be interference by other medications like NSAID´s, cold formulations, decongestants, diet pills, appetite suppressants, and steroids, estrogen containing drugs, alcohol, EPO, herbal preparations and various types of pain medication (Acelajado & Oparil, (2009). NSAIDs cause salt and fluid retention and thus increase BP. They are frequently used for arthritic pain so common in this age group. As an alternative for pain treatment in these cases, they should consider acetaminophen as this does not affect BP (Cooney & Pascuzzi, (2009).

For the physician treating elderly patients with HTN, one of the first steps in successful BP control is the analysis of each case individually, and determining the circumstances of noncompliance and inadequate control for each patient and what can be done to improve the situation.

Benefits and recommendations of hypertension treatment of the elderly population

In practice, widening of pulse pressure with age was seen as compensatory to the hardening and aging of the arteries, and it was feared that lowering of the arterial pressure could cause circulatory collapse, and possibly affect the renal circulation (Stokes. (2009). However, thankfully medicine has evolved and with the aid of clinical trials and various studies, this is no longer the perception, as beneficial outcomes of active HTN treatment in the elderly population were clearly established with HYVET among others. Although this trial had a duration of 2 years and target BP was 150/80 mm Hg for 3845 hypertensive patients over the age of 80, with randomized treatment to indapamide and perindopril if necessary, it clearly demonstrated the benefits obtained with treatment as total mortality was reduced by 13%, cardiovascular mortality was reduced by 18%, coronary events were reduced by 23%,

incidence of stroke showed a reduction of 30%, while cardiovascular complications were reduced by 26%. At the end of the trial, the treatment group had lowered their BP by an average of 15.0/6.1 mm Hg when compared to the placebo group (Staessen, et al. (2000); (Beckett, et al. (2009). This trial finally demonstrated that active HTN treatment does not depend on age, and demonstrated improved cardiovascular outcomes. This was further proved by the "Blood Pressure Lowering treatment trialists collaboration", as any possible reduction in systolic BP from antihypertensive medication, granted cardiovascular protection in younger adults as well as older adults above 65 years of age (Turnbull, et al.(2008); Rafey,(2009). Table 2 summarizes some of the important trials that have been done and their results.

In the elderly population, especially over the age of 80, the prevalence of mortality caused by strokes is as high as 52%. HTN along with diabetes, and hyperlipidemia are major risk factors for stroke, and with the increasing prevalence of HTN, it is fundamental and beneficial especially in this population group to control BP along with these other risk factors and thus decrease the incidence of strokes and other cardiovascular events (Chobaniian, (2007).

The degree of systolic reduction explains the benefits as a reduction in systolic BP by 10mm Hg leads to a 25% relative risk reduction in coronary heart disease and 35-40% relative risk reduction in stroke (Law et al. (2009). Current guidelines suggest that systolic BP should be lowered below 140mm Hg in patients of all ages including the elderly, but this is controversial as in all the trials conducted, BP was always above this value, and targets were always slightly higher. The fear is that if pressure is reduced too significantly, vital organs could suffer from lower blood perfusion rates and the body could have trouble adapting to the new pressures, and these changes in BP could also affect the patient symptomatically (Chobanian, et al. (2003).

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)

Table taken from Zeglin et al. (2009)

*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

The advantages of HTN treatment in the elderly do not change with age, as the benefits of systolic reduction are well established. However further research is needed in the determining the appropriate target systolic BP, as the current guidelines recommend 140 mmHg but this is not completely supported, and more evidence is needed for the elderly population (Staessen, et al. (2000); Zanchetti, et al. (2009).

In order for treatment to be effective, it is also beneficial to evaluate lifestyle factors contributing to HTN, causes of increased BP, and possible reasons for the noncompliance with medication and unsuccessful treatment (Aronow, (2006); Moser& Setaro.(2008). Studies reveal that 24hr ambulatory blood pressure monitoring showed 42,2 % of HTN control as opposed to clinical monitoring which only achieved a 21,5% control. This implies that the key to effective control could mean tighter BP monitoring, along with effective active treatment (Llisterri, et al. (2009).

HYVET not only showed a large reduction in heart failure, but also showed a decrease in Alzheimers, as dementia seems to be lower in patients with a tightly controlled and adequately treated BP (Chobaniian, (2007). This means that controlling HTN in the elderly could also cause a decrease in cognitive decline and perhaps protect the elderly to a certain extent from developing dementia, or at least slowing the progression of such dementia.

Studies by Alpérovitch et al. (2009), clearly showed a significant relationship between seasonal external temperatures and BP. On average, SBP´s were seen to be 5.0mm Hg lower in summer than in winter. Accordingly, prevalence of high blood pressure (SBP- 160mmHg or DBP- 95mmHg) decreased from 33.4% to 23.8% between winter and summer. The 3C Study also provided for the opportunity to examine the possible relationship between BP and external temperature. It showed that in the elderly population, outdoor temperature strongly influenced BP, the mean SBP varied from 150.1mmHg to 142.1 mm Hg between the lowest

and highest measurements of external temperature. The data further suggested that the temperature-related variations in both SBP and DBP could be increased in very old people, which is an important consideration as low BP may be a risk factor for increased mortality among the elderly with environmental hyperthermia, thus monitoring of BP in older individuals could be an important issue under extreme weather conditions.

Systolic HTN is a modern problem and there is a great need to reduce it in order to improve survival in the elderly. This is currently one of the great challenges of our century that affects all physicians. Today it is difficult to reduce systolic BP more than diastolic, thus further research could satisfy this hope in the imminent future (Casiglia, (2009). It is through education and research that physicians can gain tools to fight the eternal battle against death, and disease, while simultaneously trying to help patients lead a healthier life.

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