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HYPERTENSION IN THE ELDERLY — PATHOPHYSIOLOGY AND MANAGEMENT

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Every Man Desires To Live Long, But No Man Would Be Old
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Life can only be understood backwards,
but it must be lived forwards
– Sφren Kierkegaard

I. INTRODUCTION

Functional limitations and disease patterns in our society are related to the underlying demography of the older adult population. No other segment of the U.S. population is undergoing as significant a change with as many health care policy and practice implications. At the present, the most predominant demographic trend is that our population is aging. In the last 75 years, the percentage of men over the age of 60 has more than doubled. The percentage of women has more than tripled. At the upcoming turn of the century, 20% of our population will be over 60 years of age. These trends are significant because those over 60 impose a greater burden on the health care system than the other age groups.

In the last 30 years, while the total population grew by just 39 percent (Campion, 1994), the number of Americans 85 years or older increased by 232 percent and the number of Americans 65 years or older increased by 89 percent. Today, 3.5 million Americans are 85 years or older. On the basis of current mortality rates, 55 percent of girls and 35 percent of boys should live long enough to celebrate their 85th birthday. Despite these impressive trends, frailty is common in the aging population. It is difficult to know to what extent the frailty is the result of disease, the aging process itself, or a combination thereof.

The geriatric population of the U.S. (i.e. > 65 years of age) is expected to increase to more than 65 million over the next 40 years. This represents more than two and one-half times the number of elderly recorded in the 1980 U.S. census (Bureau of the Census, 1993).

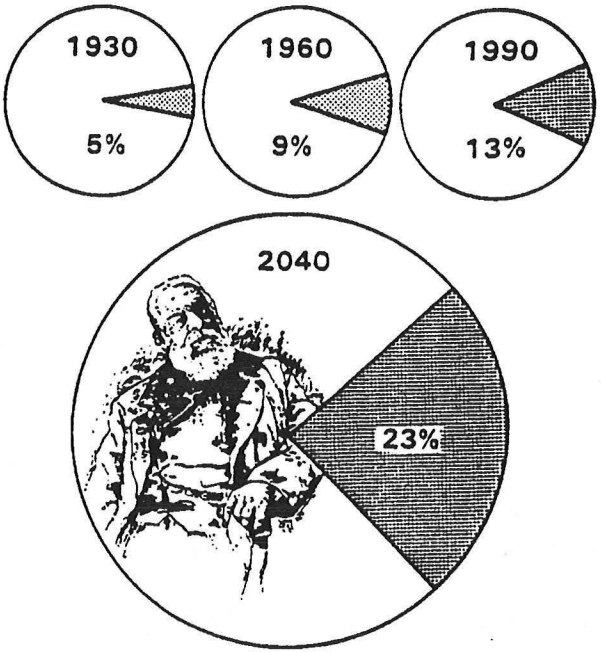


Figure 1: Increase in the percentage of elderly population over the past 50 years; projected changes for the future.

Although the mortality due to cardiovascular diseases has been steadily declining in the last two decades, they remain the most frequent single cause of death among persons over 65 years of age. Diseases of the cardiovascular system account for a growing proportion of hospitalizations and health care costs among the elderly. Eighteen percent of the U.S. citizen's lifetime medical expenses are spent in the last year of his/her life.

II. AGING AND BLOOD PRESSURE - PATHOPHYSIOLOGICAL CONSIDERATIONS

VASCULAR CHANGES

In the arterial intima, with advancing age, the endothelial cells become more heterogenous in size and in shape, thus, increasing the number of sites for lipid deposition; the intra-luminal blood flow also becomes less laminar (Wei, 1992). The subendothelial layer thickens due to increased deposition of calcium and lipids. In the media, increased fragmentation of elastin and calcium leads to the thickening of smooth muscle layer. These age related changes increase the stiffness of the vessel wall (Hallock and Benson, 1937). Arterial stiffening is manifested as an increase in pulse wave velocity. The increase in systolic pressure, even within the clinically normal range, is a result of this age-associated increase in arterial stiffness (Tables 1 and 2). If the arterial stiffness is blunted, the arterial pressure increase seen with age is also blunted. Increased arterial stiffness may not be related solely to age-associated structural changes, but may also relate to increased vascular tone mediated by calcium-dependent and adrenergic mechanisms.

Table 1: Determinants of Blood Pressure in the Elderly
Determinants of mean arterial pressure
Cardiac output
Total peripheral resistance
Determinants of systolic arterial pressure
Cardiac output
Total peripheral resistance
Stroke volume
Left ventricular ejection velocity
Arterial distensibility (compliance

Table 2
Anatomic and Hemodynamic Alterations of the Cardiovascular System with Age

Collagen degeneration	
loss of elastin	
fatty streaks	
atheromata	
calcification	
Wide pulse pressure: ↑ systolic ↓ diastolic	
Loss of body water	
Decreased myocardial contractility	↓ ejection fraction
Decreased heart rate	↓ cardiac output
Increased left ventricular stiffness	↓ maximal work capacity
Electromechanical dissociation	
Increased afterload	
Decrease in number and sensitivity of adrenergic receptors	

AUTONOMIC MECHANISMS OF CARDIOVASCULAR FUNCTION

Augmented autonomic stimulation has been long recognized as a cause of the hyperkinetic circulatory state frequently observed in younger hypertensive subjects. With advancing age, baro-receptor function becomes blunted and impaired communication exists between the circulatory and central nervous systems (Lakatta, 1989). The increase of plasma catecholamines seen with aging may be partially responsible for blunted baro-receptor sensitivity (Table 3). In the elderly, elevated plasma catecholamine levels do not correlate with the level of blood pressure. The age associated increase in catecholamines is further exaggerated during stress (Sowers and Mohanty, 1988; Sowers, et al, 1983) (Figure 2). At maximal exercise,

Table 3: Neuroendocrine changes with age	
Baroreflex sensitivity	↓
Noradrenaline	↑
Adrenaline	↔
Dopamine	↔
Renin-angiotensin-aldosterone	↓
Atrial natriuretic peptide	↑
Arginine vasopressin	↑
Thirst	↓

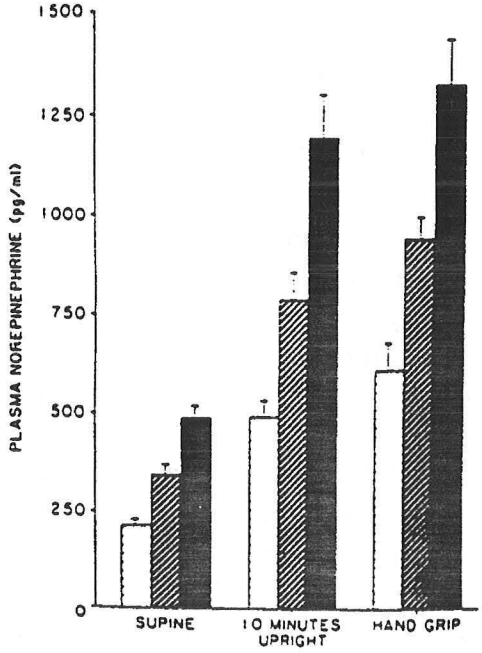


Figure 2: Effect of age (independent of obesity) on plasma norepinephrine responses to 10 min of upright posture and 5 min of isometric handgrip exercise. □, <55 years (n=20); ▨, 55-65 years (n=12); ■, 65-75 years (n=7). (From Sowers & Mohanty, 1988).

heart rate is lower in the elderly population. The hemodynamic changes which occur in older individuals during stress are probably due to diminished post-synaptic beta-adrenergic response. This diminished response could be related to reduced baro-receptor stimulation as well as due to a deficient baro-reflex (Lakatta, 1993; Gribbin et al, 1971) (Figure 3). The attenuated autonomic response that occurs with aging becomes more apparent in the presence of sodium or volume depletion (Lakatta, 1986; Shannon RP, et al, 1986). In older patients, there is a progressive reduction of ß-adrenoreceptor sensitivity and/or reactivity (Table 4). This defective ß-adrenergic response in conjunction with unopposed *α*-adrenoreceptor mediated vasoconstriction may contribute to hypertension (Bertel O, Bühler FR, Kiowski W, et al, 1980). It is noteworthy that *α*-adrenergic responses are unchanged with aging (O'Malley K, et al, 1988; Duckles SP, et al, 1985; Stevens MJ, et al, 1982).

Table 4: Physiologic Changes in Elderly Patients

- Reduced aortic distensibility
- Reduced cardiac output
- Reduced baroreceptor sensitivity
- Lower plasma renin levels
- Increased plasma norepinephrine levels

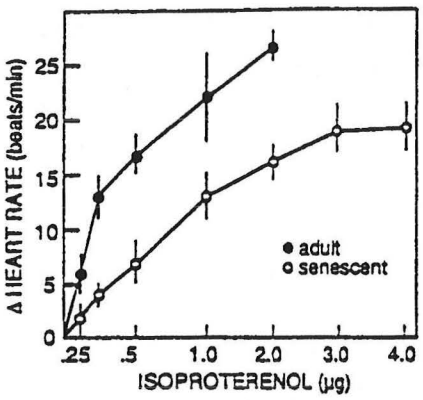


Figure 3: Effect of bolus intravenous isoproterenol infusions to increase heart rate in healthy young and older men at rest. (From Lakatta, 1993).

RENIN SECRETION AND AGE

The possible role of the renin-angiotensin system in the pathogenesis of hypertension has been extensively studied; evidence indicates that a majority of elderly patients have either normal or low renin levels (Weber et al, 1989). Group of patients with suppressed renin have kindled special interest since Laragh and colleagues have proposed that the level of plasma renin may have prognostic significance (Laragh, 1984a; 1984b). According to their view, a high-renin state is a renin-dependent vasoconstriction mediated form of hypertension with poor prognosis; whereas, a low-renin state is characterized by volume expansion that does not bestow poor prognosis. This hypothesis has consistently met severe criticisms. Among the criticisms is the fact that in low-renin hypertension, volume expansion is not a consistent phenomenon and that patients with low-renin hypertension are not immune to cardiovascular and other blood pressure related complications. Several reports have commented on the inverse relationship between the age and the plasma renin activity in patients with essential

hypertension (de Leeuw and Birkenhager, 1989). Indeed, an inverse relationship between age and renin has also been noted in normotensive individuals. Thus, there is compelling evidence to indicate that age is a determinant of plasma renin activity. Although it is not completely clear whether the suppression of plasma renin activity is due to reduced secretion or due to enhanced clearance, the former is the most likely explanation. Neurogenic mechanisms modulating renin secretion are down-regulated with increasing age. It is possible, but not proven, that structural intrarenal vascular changes (nephrosclerosis) may also play a role in reduced renin secretion.

There are at least two possibilities to explain the high prevalence of low renin levels in the elderly population. The first explanation is that ß-adrenergic mechanisms governing the renin release are impaired; secondly, is that renin release is suppressed due to sodium and volume retention. There is no clear explanation for the tendency of older individuals to retain sodium. Presumably, the pressure-natriuresis relationship that modulates sodium excretion may be reset in the elderly population.

AGING KIDNEY AND BLOOD PRESSURE

A number of abnormalities of renal function and structure are associated with advancing age. The glomerular filtration rate (GFR) which is approximately 140 ml/min/1.73m^2 until age 30 subsequently declines by 8 ml per decade (Davies and Shock, 1950) (Figure 4). The rate of decline in GFR is somewhat higher in individuals with urologic or renal disease or hypertension. In patients with hypertension, age related decline in GFR therefore is further compounded. It is difficult to determine in this context whether the elevated blood pressure is responsible for loss of renal function or vice-versa. GFR declines with age in parallel with and as part of an age-related decrease in muscle mass (metabolic mass). The fall in creatinine clearance with aging has a special significance.

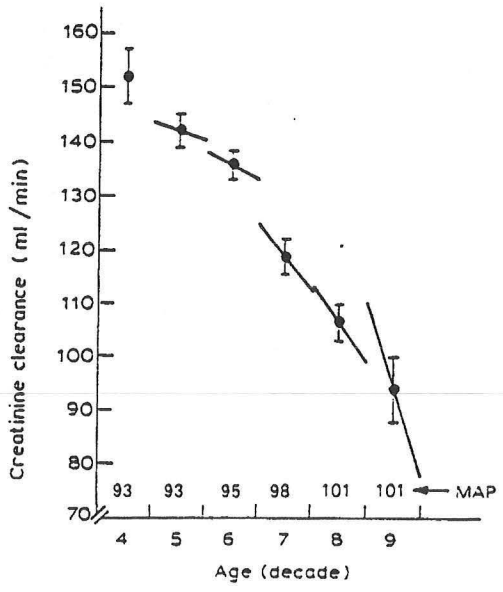


Figure 4: Changes in creatinine clearance and mean blood pressure (MAP) by age decades in subjects without evidence of renal or urinary tract pathology (n=254). The slope of the regression of creatinine clearance versus age increases with age. (From de Leeuw & Birkengager, 1989).

The relationship of serum creatinine to creatinine clearance changes with age. The resultant effect is constancy of serum creatinine concentration at a time when GFR is declining. For example, a serum creatinine level of 1 mg/100 mL may reflect a creatinine clearance of 120 mL/min at age 30, but it would be only 60 mL/min at age 75. Since 24 hour urine creatinine is often used to judge the accuracy of urine collections, failure to recognize the fall in creatinine excretion with aging may lead to erroneous interpretational conclusions.

Renal blood flow (RBF) which is maintained at about 650 ml/min until the fourth decade and declines thereafter by 10% per decade (Watkin and Shock, 1985) (Figure 5). This may cause blunted vasodilatory responsiveness to sodium load. The reduction in RBF is not fully explicable by reduction in renal mass, since there is proportionate decrease in RBF per unit of kidney mass. Cortical RBF is affected the most, and the redistribution of flow from the cortex to the medulla accounts for the increase in filtration fraction.

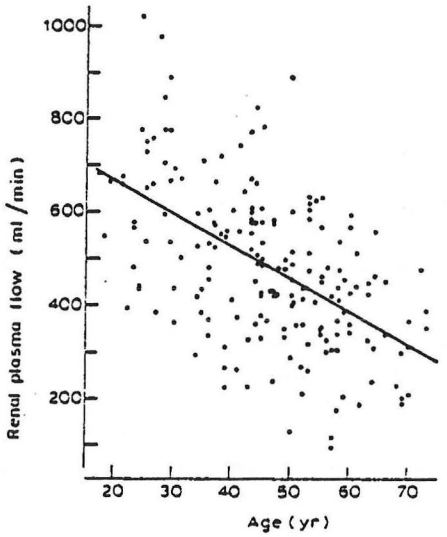


Figure 5: Relationship between renal plasma flow and age (n = 185; r = -0.53; P <0.001). (From de Leeuw & Birkengager, 1989).

Elderly subjects have a tendency to excrete a sodium load much more slowly than younger subjects (Luft et al, 1979; Luft et al, 1987). Older patients may also have difficulty in conserving sodium when placed on a low sodium diet. The concentration of atrial natriuretic peptide increases in the aging man. This could be due to sodium retention.

III. HEMODYNAMIC CHANGES IN THE ELDERLY

The pathophysiologic mechanisms of blood pressure elevation differ significantly between older and younger subjects with hypertension. Aging, per se, affects the cardiovascular hemodynamics and leads to certain age-specific changes. Long-standing hypertension produces distinct pathologic changes in the heart and the blood vessels which contribute to acceleration of age-induced hemodynamic consequences.

In general, it has been demonstrated that with advancing age, the cardiac output declines even in healthy individuals free of cardiac disease (Lewis, 1938). Sixty years ago, it was shown that cardiac index decreases with age at a rate of about 8 ml/minute/m^2/year (Starr et al, 1934; Stead et al, 1945). Assuming that arterial pressure remains unchanged, a reduced cardiac output will result in elevated total peripheral vascular resistance. At any given level of blood pressure in the elderly, cardiac output is lower and peripheral vascular resistance higher than in the young population (Table 5). Longitudinal studies performed by Lund-Johansen (1985) over a period of more than 20 years have shown that with advancing age, there is a progressive fall in cardiac output at rest as well as during exercise. Others have confirmed this hemodynamic pattern in the aging population.

Table 5: Pathophysiologic differences in hypertensive patients (mean ± SD)

	Elderly	Young	P-Values
Age (yr)	73±7	32±7	by design
Systolic pressure (mmHg)	182±32	153±23	$<10^{-5}$
Mean arterial pressure (mmHg)	114±17	113±16	by design
Diastolic pressure (mmHg)	81±11	93±14	$<10^{-5}$
Cardiac output (l/min)	4.70±1.04	6.22±1.20	$<10^{-5}$
Total peripheral resistance (units)	26±7	19±4	$<10^{-5}$
Stroke volume (ml)	71±18	88±23	<0.001
Heart rate (beats/min)	67±10	72±8	<0.02
Total blood volume (l)	4.10±0.8	4.64±1.0	<0.05
Renal blood flow (ml/min)	674±92	1110±296	<0.001
Renal vascular resistance (units)	1691±153	1012±33	$<10^{-5}$
Norepinephrine (pg/ml)	418±209	331±182	NS
Epinephrine (pg/ml)	95±89	98±76	NS
Dopamine (pg/ml)	63±78	62±63	NS
Plasma renin activity ($\mu g \cdot ml^{-1} \cdot min^{-1}$)	0.454±0.38	1.154±0.87	<0.05

NS = not significant. (From Messerli et al, 1983)

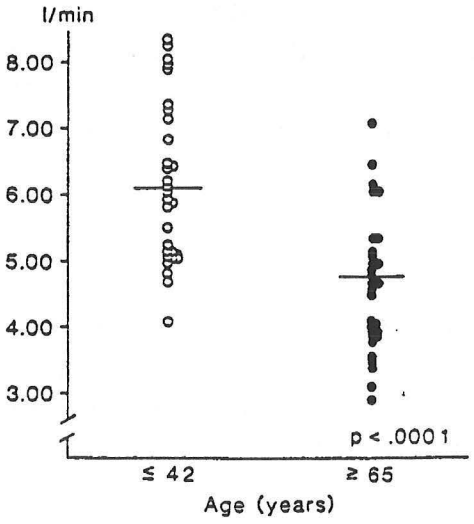


Figure 6: Cardiac output was found to be lower in elderly hypertensive patients when compared with younger patients having similar levels of arterial pressure. (Adapted from Messerli et al, 1983).

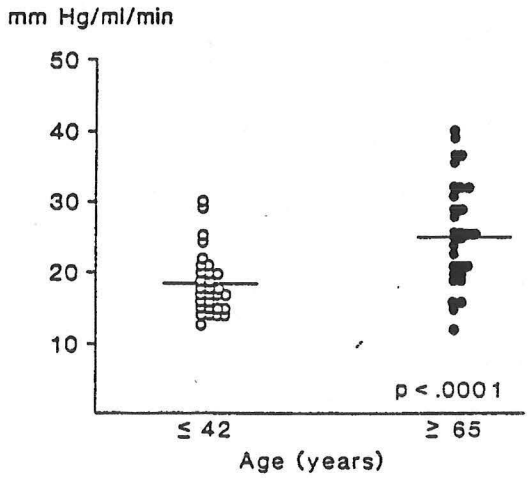


Figure 7: Total peripheral resistance was found to be elevated in elderly hypertensive patients when compared with younger patients having similar levels of mean arterial pressure. (Adapted from Messerli et al, 1983).

In a study conducted by Messerli and co-workers, hemodynamic assessment was carefully made in older and younger subjects (Messerli et al, 1983). In this cross-sectional study, stroke volume, heart rate, and cardiac output were significantly lower and total peripheral vascular resistance significantly higher in the elderly than in the younger subjects. The former also had contracted intravascular volume and reduced RBF.

There are several explanations for the age-related progressive decline in cardiac output and the reciprocal rise in total peripheral vascular resistance. Metabolic requirements decrease with age; vascular impedance increases with age (Figure 8); diastolic ventricular filling and myocardial contractility decrease and responsiveness to catecholamines decreases. Importantly, an increased afterload may further decrease the cardiac output in the elderly. The hemodynamic changes that accompany the aging process are also shared by hypertension (Table 6).

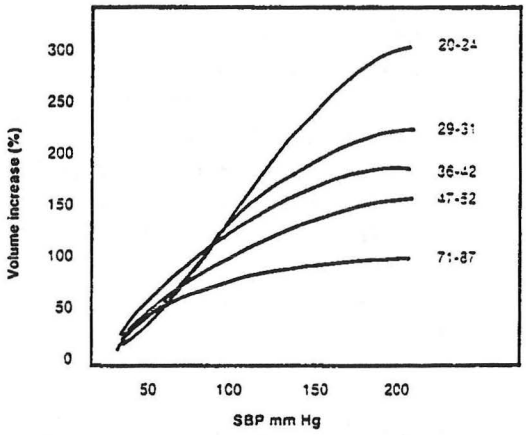


Figure 8: Changes in pressure-volume relation (human aorta). (From Hallock & Benson, 1937)

Table 6: Hemodynamic Characteristics Shared by the Aging Process and Hypertension

Characteristics	Aging Process	Hypertensive Disease
Progression with time	X	X
Elevated systolic pressure over time	X	X
Increased total peripheral resistance	X	X
Increased left ventricular impedance	X	X
Asymptomaticity	X	X
Reduced hemodynamic function	X	X
Reduced renal function	X	X
Increased vascular thickening	X	X
Reduced adrenergic participation with time	X	X
Decreased ejection fraction	X	X
Increased cardiac mass	X	X
Increased ventricular wall thickness	X	X
Decreased Plasma volume	X	X
Decreased vascular distensibility	X	X

IV. EPIDEMIOLOGY AND PREVALENCE OF HYPERTENSION IN THE ELDERLY

The new classification of hypertension proposed by the Joint National Committee is shown in Table 7.

TABLE 7: CLASSIFICATION OF BLOOD PRESSURE FOR ADULTS AGE 18 AND OLDER*

Category	Systolic (mm Hg)	Diastolic (mm Hg)
Normal†	<130	<85
High normal	130-139	85-89
Hypertension**		
STAGE 1 (Mild)	140-159	90-99
STAGE 2 (Moderate)	160-179	100-109
STAGE 3 (Severe)	180-209	110-119
STAGE 4 (Very Severe)	≥210	≥120

*Not taking antihypertensive drugs and not acutely ill. When systolic and diastolic pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For instance, 160/92 mm Hg should be classified as Stage 2, and 180/120 mm Hg should be classified as Stage 4. Isolated systolic hypertension (ISH) is defined as SBP ≥140 mm Hg and DBP <90 mm Hg and staged appropriately (e.g., 170/85 mm Hg is defined as Stage 2 ISH).

†Optimal blood pressure with respect to cardiovascular risk is SBP <120 mm Hg and DBP <80 mm Hg. However, unusually low readings should be evaluated for clinical significance.

** Based on the average of two or more readings taken at each of two or more visits following an initial screening.

Note: In addition to classifying stages of hypertension based on average blood pressure levels, the clinician should specify presence or absence of target-organ disease and additional risk factors. For example, a patient with diabetes and a blood pressure of 142/94 mm Hg plus left ventricular hypertrophy should be classified as "Stage 1 hypertension with target-organ disease (left ventricular hypertrophy) and with another major risk factor (diabetes)." This specificity is important for risk classification and management.

The prevalence of hypertension is a reflection of the number of subjects with the condition at a given moment in time. Prevalence observations, however, do not give an estimate of the incidence of hypertension, i.e., the number of persons developing high blood pressure over a given time frame. The earlier large studies analyzing the prevalence of hypertension in the elderly had two disadvantages: first, they only looked at single occasion blood pressure levels, and, second, they could not estimate the incidence. For example, Hawthorne et al found that prevalence of diastolic hypertension fell from 15.6% to only 5.5% on re-

examination (Hawthorne et al, 1974).

The average diastolic blood pressure decreases with advancing age and the systolic blood pressure increases concomitantly. Consequently, the prevalence of systolic hypertension in the elderly increases with age. Tables 8 and 9 show the prevalence of hypertension in the age group 65-74 as noted in the National Health and Nutrition Examination Surveys II and IV (NHANES II and NHANES III) for the time periods 1976-80 and 1988-91 (National High Blood Pressure Education Program, 1994). The overall prevalence of hypertension declined sharply in the last decade because of methodological improvements and hypertension treatment efforts.

Table 8: Prevalence of hypertension among noninstitutionalized men and women, black and white, aged 65 to 74 years, 1976-1980

	BP ≥160/95 mm Hg, %[a]	BP ≥140/90 mm Hg, %[b]
Black women	72.8	82.9
Black men	42.9	67.1
White women	48.3	66.2
White men	37.5	59.2
Total blacks	59.9	76.1
Total whites	43.7	63.1
Total (all races)[c]	45.1	64.3

[a]Defined as the average of 3 BP measurements 160 mm Hg or greater (systolic) and/or 95 mm Hg or greater (diastolic) taken on a single occasion or the self-reported taking of antihypertensive medication.

[b]Defined as the average of 3 BP measurements 140 mm Hg or greater (systolic) and/or 90 mm Hg or greater (diastolic) taken on a single occasion or the self-reported taking of antihypertensive medication.

[c]Includes races in addition to blacks and whites. (From The Working Group on Hypertension in The Elderly, 1986. Statement on hypertension in the elderly. JAMA 1986;256:70-74.

Table 9: Trends in Hypertension* Prevalence by Gender and Ethnicity in the Civilian, Noninstitutionalized Population, Aged 65 to 74, During 1976-80 and 1988-91

Gender and Ethnic Group	1976-80, %	1988-91, %
Women	67.5	52.5
African Americans	82.9	71.9†
Whites	66.2	51.2†
Mexican Americans	...	53.1
Men	60.2	56.4
African Americans	67.1	71.6†
Whites	59.2	54.9†
Mexican Americans	...	56.9
Totals	64.3	54.3
African Americans	76.1	71.8†
Whites	63.1	52.9†
Mexican Americans	...	54.9

From the Centers for Disease Control and Prevention. National Center for Health Statistics, Hyattsville, MD: the second National Health and Nutrition Examination Survey (NHANES II), 1976-80 (Vital Health Stat. 1986. US Dept of Health and Human Services publication PHS 86-1684); and unpublished data from Hispanic HANES, 1982-84, and NHANES III, 1988-1991. Totals include racial and/or ethnic groups not shown separately.

*Defined as the average of three BP measurements ≥140 mm Hg (systolic and/or ≥90 mm Hg (diastolic) on a single occasion or taking antihypertensive medication. Estimates based on three BP measurements taken by physicians in the HANES mobile examination center.

†Non-Hispanics.

Table 10: Percent Distribution of Blood Pressure Levels by JNC V Categories in the U.S. Population With Hypertension, Aged 60 and Older, by Sex

	Isolated Systolic Hypertension (≥140 and <90	Hypertensive*			
		Controlled† (<140 and <90)	Stage 1 (140-159 or 90-99)	Stage 2 (160-179 or 100-109	Stage 3-4‡ (≥180 or ≥110)
Total	64.8	25.6	49.6	18.2	6.5
Total men	63.3	21.8	54.9	18.1	5.1
60-74	58.9	23.7	54.9	17.3	4.1
75 and older	74.6	16.9	55.1	20.2	7.8
Total women	65.9	28.2	46.0	18.3	7.5
60-74	61.0	32.7	47.9	14.7	4.7
75 and older	73.7	21.1	43.0	24.0	11.9

From the Centers for Disease Control and Prevention, National Center for Health Statistics, NHANES III (1988-1991). Totals may not be equal to 100% due to rounding.

JNC V indicates the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure; BP blood pressure.

*When systolic and diastolic pressures fall into different categories, the higher category should be selected to classify the individual's blood pressure status. For instance, 160/92 mm Hg should be classified as stage 2.

†Controlled with medication.

‡Stages 3 and 4 are collapsed due to insufficient sample size

The status of blood pressure levels in persons > 60 years, regardless of the treatment status, is shown in Table 10. Among the people with elevated blood pressure, nearly 50% have Stage I hypertension, 18.2% have Stage II hypertension, and 6.5% have Stage III or IV hypertension. Isolated systolic hypertension (systolic blood pressure > 140; diastolic blood pressure < 90) is present in 65% of people > 60 years.

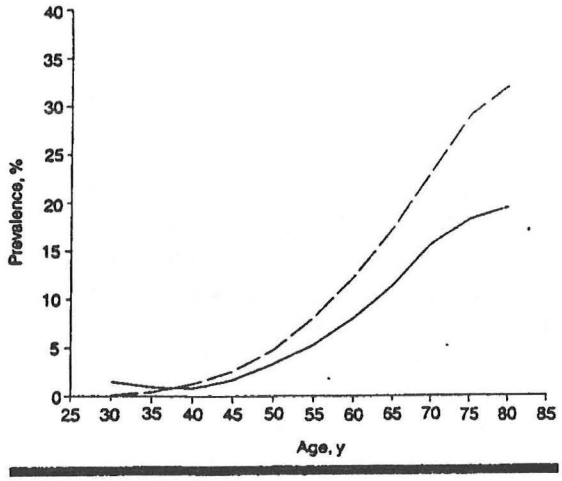


Figure 9: Prevalence of isolated systolic hypertension by age and sex — 30-year follow-up, Framingham Heart Study. Solid lines indicates men; broken lines, women.

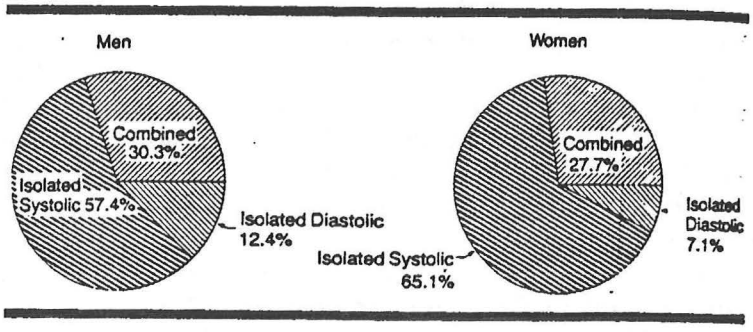


Figure 10: Distribution of hypertension among Framingham Heart Study elderly aged 65 to 89 years. Systolic hypertension defined as blood pressure of ≥160 mm Hg; diastolic hypertension, blood pressure of ≥95 mm Hg.

The prevalence of isolated systolic hypertension, defined as systolic blood pressure ≥ 160 , diastolic blood pressure ≤ 90 in industrialized nations has been shown to rise with age (Silagy and McNeill, 1992) — 5% at age 60; 12.6% at age 70; and 23.6% at 80. Casual blood pressure measurements likely overestimate the prevalence of isolated systolic hypertension. Twenty-four hour ambulatory blood pressure readings have shown marked disparity between the clinic levels and the ambulatory blood pressure levels (Cox et al, 1991).

V. THE RISKS OF HYPERTENSION IN THE ELDERLY

Cardiovascular diseases are the most common cause of morbidity and mortality in persons older than 65 years of age. More than half of mortality beyond age 65 is attributable to cardiac and cerebrovascular diseases. Figures 11 and 12 demonstrate the dangers of hypertension in the elderly as noted in the Framingham Study (Kannel, 1976; Kannel et al, 1988). The cardiovascular risk of the elderly increases proportionately to the level of blood pressure (Figure 13).

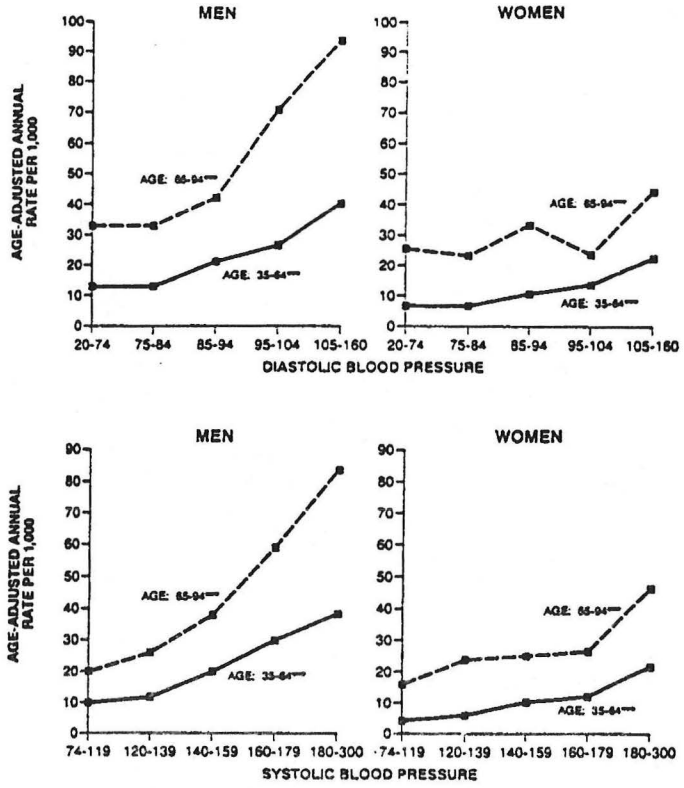


Figure 11: Line graphs show risk of cardiovascular disease by age, sex, and level of diastolic or systolic blood pressure from a 30-year follow-up in the Framingham Heart Study. The relation of systolic and diastolic blood pressure to cardiovascular events is generally more pronounced in people aged 65 to 94 years compared with those aged 35 to 64. Increased evidence of cardiovascular disease occurs at a diastolic blood pressure of 75 mm Hg or greater in men but is not definitively evident until 95 mm Hg in women. ***P<.001.

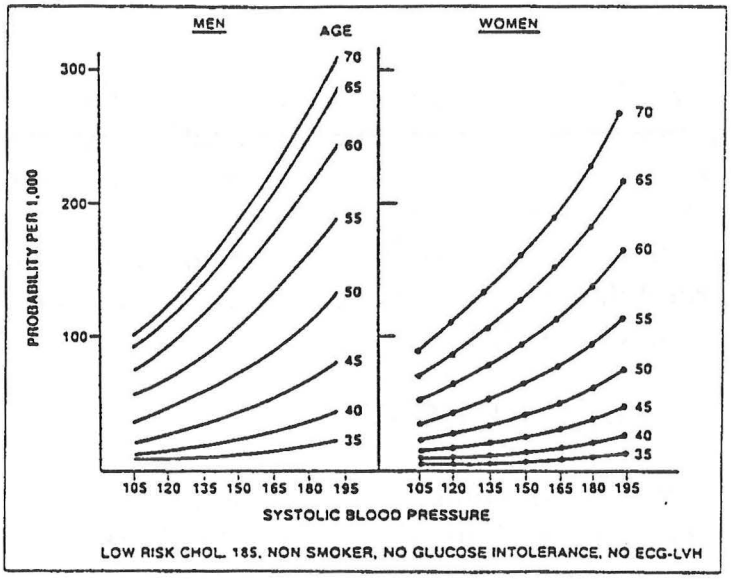


Figure 12: Risk of coronary heart disease among non-smoking men and women with low-risk cholesterol (CHOL.) levels (185 mg/dl) not intolerant to glucose (no electrocardiogram-left ventricular hypertrophy (ECG-LVH).

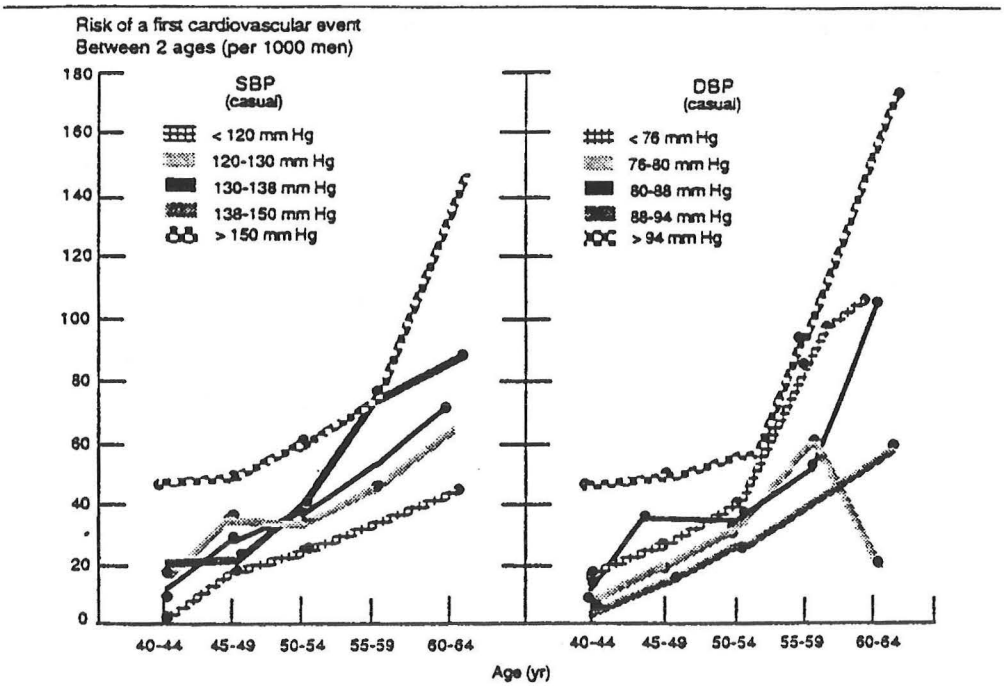


Figure 13: Risk of a first cardiovascular event as a function of age and BP. From Final Report of the Pooling Project: J Chronic Dis 1978;31:201.

Other studies have demonstrated a high (40%) prevalence of cardiac disease in people 65-74 years. More than 50% of older individuals have EKG abnormalities (Caird and Kennedy, 1976; Campbell et al, 1974). Aging also worsens the survival after the occurrence of a cardiovascular event. Mortality rates from myocardial infarction creep up with advancing age — 38% for ages 60-69; 43% for ages 70-79 and 58% for 80 years and above (Ostfeld, 1978). Only a fifth of stroke survivors over the age of 60 can expect a good recovery. Cardiovascular mortality increases

by eight-fold in older hypertensive women and by two-fold in older hypertensive men compared to normotensive elderly subjects (Kannel and Sorlie, 1975). The risk of hypertension is due to elevation of both the systolic and diastolic blood pressure. However, with advancing age, the systolic blood pressure has a greater impact on the risk of stroke, left ventricular hypertrophy (LVH), and congestive heart failure (CHF) than does the diastolic blood pressure. In the elderly, the risk doubles when systolic blood pressure increases from 140 to 185 mm Hg. In the Framingham Study, 73% of men and 81% of women who died had a blood pressure > 140/90 (Kannel et al, 1980). Hypertension markedly increases the risk for CHF, stroke, coronary disease, and peripheral vascular disease. Even mild hypertension (Stages I and II) increases the cardiovascular mortality by four-fold in men and by two-fold in women in the age group 65-74 years compared to age-matched normotensives.

Isolated systolic hypertension bestows a significant risk for cardiovascular disease. In the Framingham Study the presence of isolated systolic hypertension increased the stroke risk in elderly men by four-fold and more than two-fold in women compared to their normotensive counterparts. In persons with isolated systolic hypertension, for each mm rise in blood pressure, the corresponding all cause-mortality increases by 1%. In many individuals with isolated systolic hypertension, subclinical cardiovascular diseases may be frequently detected (Psaty et al, 1992).

VI. POST-PRANDIAL HYPOTENSION IN THE ELDERLY

Although nearly 40 years ago Smirk observed that hypertensive patients given a ganglion blocking drug (pentolinium) had a further pronounced fall in blood pressure after meals (Smirk, 1953), it was only recently that the phenomenon of postprandial hypotension has been recognized as a real problem in the elderly. Lipsitz and colleagues reported impressive postprandial blood pressure reductions in both the debilitated as well as the healthy elderly (Lipsitz et al, 1983; Lipsitz and Fullerton, 1986; Peitzman and Berger, 1989) (Figure 14). The nadir of blood pressure drop in these studies occurred within 60 minutes of meal ingestion. The blood pressure change was noted only after ingestion of solid food but not water. The exact mechanisms involved in the causation of post-prandial hypotension are not fully known. Several possibilities have been proposed — blunted autonomic regulation, food components (carbohydrates > fat > proteins), influence of vasoactive peptides such as VIP, somatostatin, etc. Whatever the pathophysiologic basis may be, the phenomenon of post-prandial hypotension in the elderly may have a number of serious consequences. It may be responsible for syncope and related complications like hip fractures, cerebrovascular catastrophes, etc. Many older patients receive antihypertensive drugs guided by office (preprandial) blood pressure measurements. If a post-prandial hypotensive effect does occur in such individuals,

blood pressure levels may vary substantially in relation to the timing of food intake. Physicians and nurses should be aware of this phenomenon. This important clinical observation warrants further investigation.

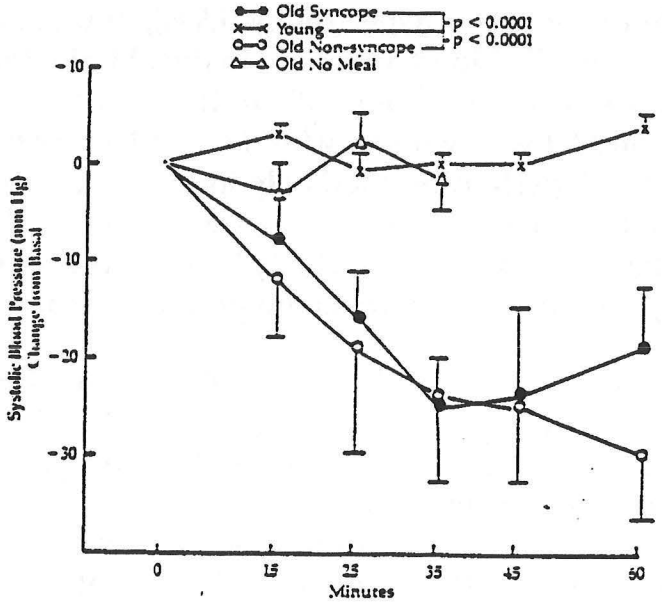


Figure 14: The change in systolic blood pressure following a meal in 10 elderly ... subjects with syncope (●), 10 elderly subjects without syncope (0) (mean age = 87±1 years for both groups), and 11 healthy young subjects (x) (mean age = 27±1 years). In 9 elderly subjects (△) no meal was given. Postprandial changes in systolic blood pressure for elderly subjects with and without syncope were similar to each other but differed significantly from postprandial blood pressure changes in young subjects ($p < .0001$) and elderly subjects not given a meal ($p < .0001$). (From Lipsitz et al, 1983).

VII. ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is observed more frequently in the elderly compared to the younger population. Therefore, in the evaluation of elderly patients, standing blood pressure should always be measured. With the patient recumbent, pulse and blood pressure should be measured. The examiner should next have the patient stand, and after 20 seconds or so, the blood pressure and heart rate should be checked. A normal response at one minute is a decrease of less than 7 mm Hg diastolic blood pressure and an increase of at least 8 beats/minute of heart rate. Orthostatic hypotension is defined as a decline of 20 mm Hg or more in systolic blood pressure or 10 mm Hg or more in diastolic blood pressure on the assumption of an upright posture. Studies have found that as high as 20% of patients ≥ 65 years and 30% of those ≥ 75 have orthostatic hypotension (Caird et al, 1973). The high prevalence of orthostatic hypotension, its day-to-day variability and frequent

absence of associated symptoms raise important questions about the clinical significance of this phenomenon. Given these limitations, it is reasonable to attach significance to postural hypotension only on the basis of accompanying symptoms. Epidemiologic studies have shown that orthostatic hypotension is a risk factor for falls and syncope (Lipsitz et al, 1986; Tinetti et al, 1976).

The prevalence of postural hypotension was examined in 8,574 persons (ages 25-74) who participated in the second National Health and Nutrition Examination Survey (Harris et al, 1991). The results of this study illustrate that the magnitude of postural drop in blood pressure is related to age and the level of systolic blood pressure. Whether treatment of isolated systolic hypertension causes amelioration of postural hypotension remains to be seen. Sodium depletion may aggravate age-related orthostatic hypotension (Shannon et al, 1986).

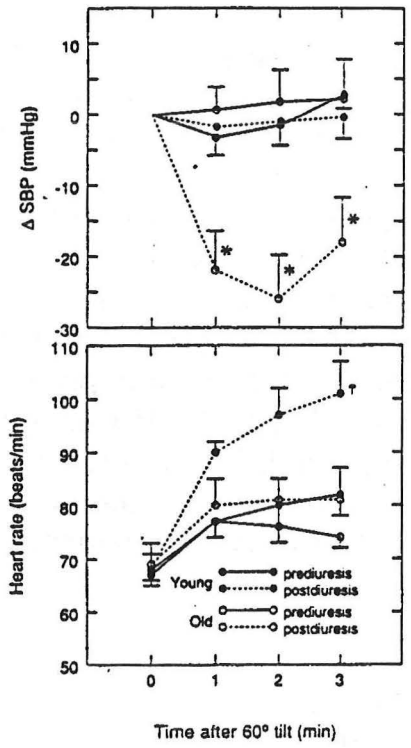


Figure 15: Alterations in systolic blood pressure (top panel) and heart rate (bottom panel) induced by 60° tilt. Note that both the young and old do not become orthostatic in the basal (prediuresis) state. The elderly, in contrast to the young, manifest a significant decline in systolic blood pressure when subjected to tilt in the volume depleted state ($P < .05$).* This is related to the ability of the young to raise the heart rate when so stressed ($P < .05$), ‡ whereas the elderly cannot mount this tachycardia. (From Shannon et al, 1986).

VIII. PSEUDOHYPERTENSION

"The physician cannot prescribe by letter, we must feel the pulse."
– Seneca

Pseudohypertension is a type of artefactual hypertension almost always occurring in elderly individuals. In this situation, the indirectly determined blood pressure with a sphygmomanometer cuff is much higher than the directly measured intra-arterial pressure. This disparity results from medial calcification of arteries

which decreases their collapsibility. Accurate determination of the blood pressure by indirect methods depends upon collapse of the artery when the pressure within the cuff exceeds that within the vessel. Stiffening of the artery by reducing its collapsibility results in erroneous overestimation of the blood pressure levels. The artefactual increase in pressure is as likely to affect the diastolic blood pressure level as the systolic blood pressure level. Pseudohypertension should be suspected in an elderly person with "hypertension" who shows no clinical evidence of target organ damage or dysfunction. Pseudohypertension is likely if the systolic blood pressure and diastolic blood pressure vary more than 10 mm Hg, respectively, compared to intra-arterial blood pressure levels. Pseudohypertension has been reported to occur in up to 40% of hypertensives without target organ damage (Spence et al, 1978), but this is clearly an overestimated figure.

More than a century ago, Sir William Osler wrote that if "the radial (artery) is compressed with the index finger (and), the artery can be felt beyond the point of compression, its walls are sclerosed." On the basis of this description, Messerli et al applied the term — Osler's maneuver — to detect the presence of pseudohypertension (Messerli et al, 1985; Messerli, 1986) (Figure 16). A patient is Osler-positive when either the radial or brachial artery remains palpable, although pulseless, after the blood pressure cuff has been inflated above systolic blood pressure. If the artery is not felt, the patient is Osler-negative. Although the Osler's maneuver was suggested as a useful screening tool to detect pseudohypertension, the procedure is unreliable and suffers from inter- and intra-subject variability. It has a low predictive value and has not lived up to its initial promise (Hla et al, 1988). If pseudohypertension is suspected, an oscillometric device (Dinamap or Infrasond) should be used to obtain readings closer to intra-arterial levels. Alternatively, direct intra-arterial blood pressure can be obtained. The risk of such invasive assessment is less dangerous than the risk of long-term unwarranted drug therapy.

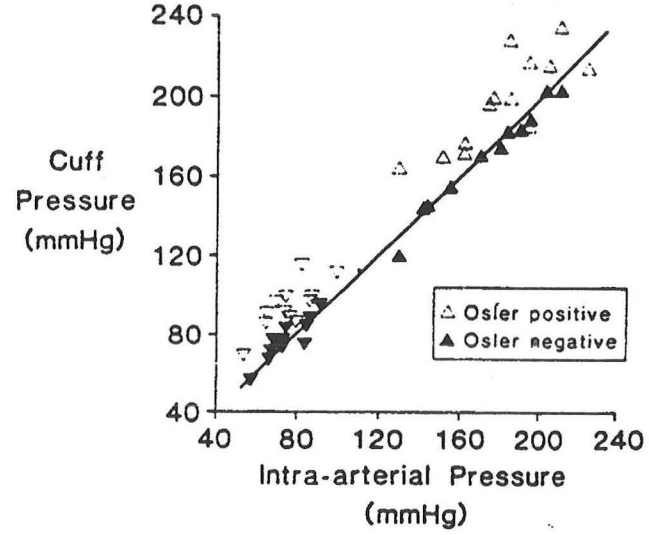


Figure 16: Discrepancy between cuff blood pressure measurements and intra-arterial values in Osler-positive (and Osler-negative) patients. (From Messerli et al, 1985).

IX. LEFT VENTRICULAR HYPERTROPHY (LVH) IN THE ELDERLY

LVH may occur in more than 50% of elderly patients with hypertension. At any given level of blood pressure, subjects with LVH have a more serious prognosis than those without LVH. The prevalence of echocardiographically-documented LVH increases with age. In the Framingham Study, LVH was found in 49% of women and 33% of men older than 70 years. LVH in the elderly is associated with increased incidence of cardiovascular and cerebrovascular complications (Aronow, 1992; Aronow et al, 1991). Cardiac function is markedly impaired in elderly patients with LVH. They are predisposed to diastolic dysfunction, complex cardiac arrhythmias, worsening of symptoms of coronary disease, etc. The recently published additional data from the Framingham Heart Study have confirmed the enhanced risk of stroke in elderly patients with increased left ventricular mass (Bikkina et al, 1994) (Figure 17). Not only diastolic hypertension but also isolated systolic hypertension is associated with the development of enhanced vascular wall thickness (Figure 18).

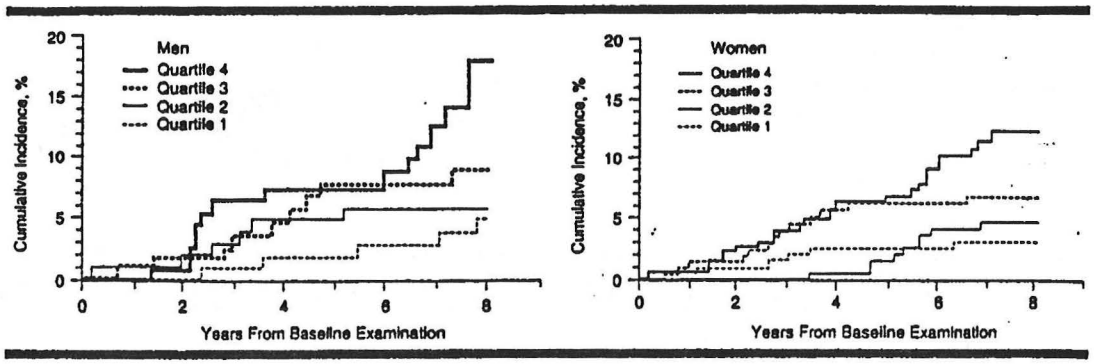


Figure 17: Eight-year age-adjusted cumulative incidence of stroke in men (left) and women (right), according to baseline quartile of left ventricular mass-to-height ratio.

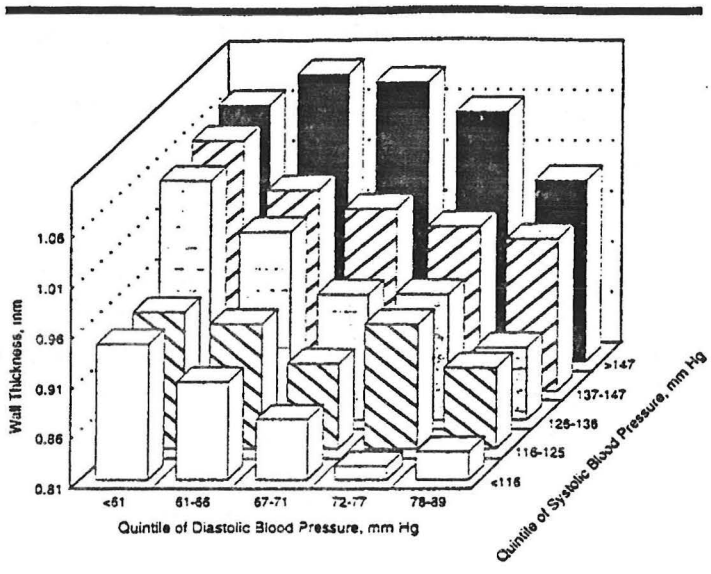


Figure 18: Maximum intima-media thickness of the common carotid artery according to quintiles of systolic and diastolic blood pressure among subjects with diastolic blood pressure <90 mm Hg, who were free of clinical cardiovascular disease and not taking antihypertensive medications. (From Psaty et al, 1992).

X. HYPERTENSION IN THE ELDERLY AND CAROTID DISEASE

Compared to elderly normotensive individuals, hypertensive subjects show a significantly higher prevalence of severe carotid disease (Figures 18 and 19). In a recent analysis of the Systolic Hypertension in the Elderly Program (SHEP), it was shown that 25% of patients with isolated systolic hypertension had significant carotid stenosis compared to only 7% of normotensive participants (Sutton-Tyrrell et al, 1993) (Figure 19). Each 10 mm Hg increment of systolic blood pressure is associated with nearly 2 times greater odds of carotid artery disease. In the same study it was shown that successful treatment of isolated systolic hypertension slowed the progression of carotid stenosis (Sutton-Tyrrell et al, 1994). If similar effects occurred in the intracranial vessels, it may explain the stroke protection seen in the patients successfully treated for isolated systolic hypertension in the SHEP study.

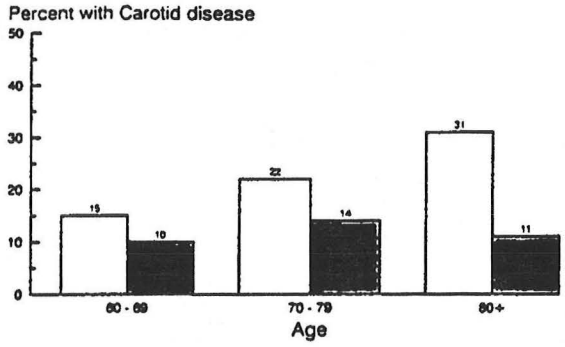


Figure 19: Bar graph presenting prevalence of internal carotid artery stenosis by age and sex. Carotid disease is defined as ≥40% reduction in diameter of internal carotid artery lumen, corresponding to ICA/CCA of ≥1.4. Open bars, male; shaded bars, female. (From Sutton-Tyrrell et al, 1993).

XI. THERAPEUTIC TRIALS OF ANTIHYPERTENSIVE THERAPY IN THE ELDERLY

Before considering therapy for hypertension in the elderly, we should review the clinical outcome in various trials designed to assess the value of blood pressure reduction in this population with hypertension — systolic, diastolic, or both..

THE VETERANS ADMINISTRATION COOPERATIVE STUDY ON ANTIHYPERTENSIVE AGENTS

In this landmark study, it was possible to extract data pertaining to the subgroup of older subjects who participated in the study (Veterans Administration Cooperative Study, 1982). All were male with diastolic blood pressure at entry averaging 90-129 mm Hg. The treatment consisted of a diuretic, reserpine, and hydralazine. Eighty-one subjects were 60 years and older (<75). The average blood pressure for this group was 178/102 mm Hg. The average follow-up period was 3.3 years. In the treated group, 28.9% developed morbid complications compared to 62.8% in the control group. The effectiveness of treatment was

directly proportional to the height of entry blood pressure level. Only one-fourth as many treated patients developed LVH during the trial as occurred in the control group. EKG regression of LVH was also more evident in the treated group.

THE HYPERTENSION DETECTION AND FOLLOW-UP PROGRAM (HDFP)

The HDFP was a 5-year, large community-based, controlled clinical trial which compared the consequences of customary treatment [referred-care - (RC)] with vigorous antihypertensive drug therapy [stepped-care - (SC)]. For those aged 60-69, and for all blood pressure levels, the mortality was 16.8% lower in the SC group than in the RC group. Blood pressure was effectively lowered in 82% of those aged 60-69 (Five year findings of the Hypertension Detection and Follow-up Program, 1979).

Table 11: Impact of drug treatment of hypertension on mortality in the elderly*

		Mortality rates‡								
		CHD			Stroke			All cause		
Study	Patients, n	Control	Treatment	Reduction‡, %	Control	Treatment	Reduction‡, %	Control	Treatment	Reduction‡, %
HDFP	2374	--	--	--	5.3	2.8	47§	30.5	25.5	16
ANBPS	582	3.6	0.9	75	0.9	0.9	0	8.1	6.3	22
EWPHE	840	23.6	14.9	37§	15.5	10.6	32	74.8	69.0	8
Coope and Warrender	884	13.6	13.6	0	7.3	2.2	70§	33.6	32.5	3
STOP	1627	4.5	3.4	24	8.4	2.3	73§	35.4	20.2	43§
SHEP-PS	551	9.8	7.1	28	6.5	1.6	75	22.7	25.4	-12
SHEP	4736	6.8	5.5	19	1.3	0.9	31	22.7	20.0	12
MRC	4396	8.6	6.7	22	3.3	2.9	12	24.7	23.9	3
Total	15,990									
Weighted means**		8.5	6.6	22§	4.4	2.5	43§	28.5	24.8	13§

*Coronary heart disease events include fatal myocardial infarction or sudden cardiac death.
†Mortality rates are deaths per 1000 patient-years of observation.
‡Percent reduction = 100 x (control rate minus treatment rate)/control rate.
§$P < 0.05$.
**Means are weighted according to study sample size.
ANBPS-Australian National Blood Pressure Study; CHD-coronary heart disease; EWPHE-European Working Party on High Blood Pressure in the Elderly; HDFP- Hypertension Detection and Follow-up Program; MRC-Medical Research Council; SHEP-Systolic Hypertension in the Elderly Program; SHEP-PS-Systolic Hypertension in the Elderly Program Pilot Study; STOP - Swedish Trial in Old Patients.

THE AUSTRALIAN NATIONAL BLOOD PRESSURE STUDY (ANBPS)

The ANBPS was planned to evaluate the outcome of treating subjects with mild (Stage I) hypertension. Of 4,000 patients studied, 582 subjects aged 60-69 were randomly assigned to single blind therapy with thiazide, beta-blockers, methyldopa, vasodilators, or placebo. Seventy percent of the active group and 28% of the placebo group achieved a diastolic blood pressure < 90 mm Hg during the 4 year trial period. Overall there was a 39% reduction in mortality and morbidity in the treated group (Management Committee, 1981).

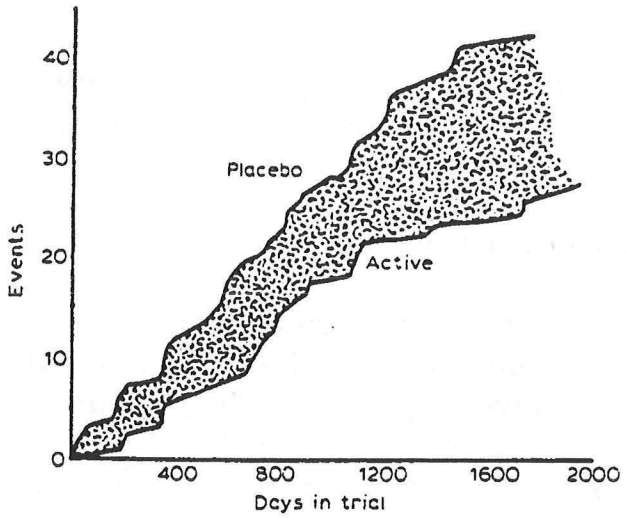


Figure 20: Trial end-points in the 'over 60 years' group, on treatment. (From Management Committee, 1981).

None of the above trials were designed specifically to evaluate the treatment of hypertension in the elderly, although sub-group analysis was indicative of therapeutic benefits in older patients. The following trials were designed specifically to assess the effects of antihypertensive therapy in the elderly.

THE EUROPEAN WORKING PARTY ON HIGH BLOOD PRESSURE IN THE ELDERLY TRIAL (EWPHE)

The EWPHE trial was a randomized, double-blind, placebo-controlled study to assess the effects of antihypertensive drug therapy in patients ≥ 60 years of age (Amery et al, 1985). The study population consisted of 840 men and women whose average entry blood pressure was 160-239/90-119 mm Hg. Initial therapy was HCTZ 25 mg + triamterene 50 mg or placebo. The "diuretic" dose was doubled, if necessary. Methyldopa was added to about one-third of subjects to achieve the goal blood pressure. After 5 years of therapy, blood pressure was reduced from $187 \pm 17/101 \pm 7$ to $150 \pm 20/85 \pm 9$ in the treated group. In the intention to treat group there was a 27% reduction in cardiovascular mortality due to a 38% and 32% reduction in cardiac and stroke mortality, respectively (Figure 21). In the double-blind portion of the trial, deaths from MI were reduced by 60%. There was a 52% reduction in cerebrovascular accidents, but not a significant reduction in mortality from these events with active therapy; there was also a 90% reduction in those developing severe hypertension. The beneficial effect of treatment seen in both men and women was more prominent in non-smokers. Compared to the placebo group, those on active treatment showed a tendency toward an increase in blood glucose and a decrease in serum potassium level. In contrast to trials in younger patients, there was a significant decrease in cardiac mortality as well in this study.

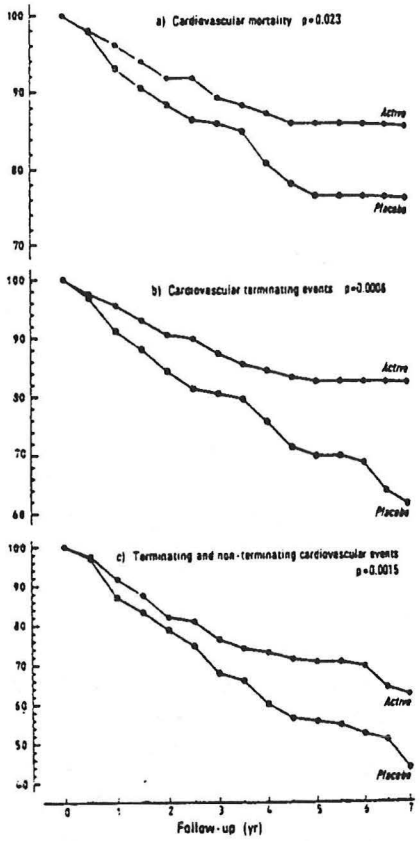


Figure 21: Cumulative percentage of survivors without events calculated for the patients on randomised treatment by life-table method. (From Amery et al, 1985).

THE STUDY BY COOPE AND WARRENDER FROM GENERAL PRACTICES IN U.K.

This was a single-blind, randomized trial of drug treatment (bendrofluazide and atenolol) in 884 patients whose average age was 69 years (Coope and Warrender, 1986). The entry blood pressure levels for the treatment and control group were 197/100 and 196/88, respectively. During the average follow-up of 4.4 years, there was a consistent difference of about 18 mm Hg in systolic blood pressure and 15 mm Hg of diastolic blood pressure between the treatment and control groups. The treatment group had a 30% reduction in the rate of fatal strokes, but there were no differences in the rates of MI or total mortality.

Table 12: Effects of Therapy in Older Patients With Hypertension

	Clinical Trial Name					
	Australian	EWPHE	Coope and Warrender	SHEP	STOP-Hypertension	MRC
No. of patients	582	840	884	4736	1627	4396
Age range, y	60-69	>60	60-79	60-≥80	70-84	65-74
Mean BP at entry, mm Hg	165/101	182/101	197/100	170/77	195/102	185/91
Relative risk of event (treatment vs control)						
Stroke	0.67	0.64	0.58†	0.67†	0.53†	0.75†
Coronary artery disease	0.82	0.80	1.03	0.73†	0.87‡	0.81
Congestive heart failure	...	0.78	0.68	0.45†	0.49†	...
All Cardiovascular disease	0.69	0.71†	0.76†	0.68†	0.60†	0.83†

†Statistically significant.
‡Myocardial infarction only; sudden deaths decreased from 13 to 4.

THE MEDICAL RESEARCH COUNCIL (MRC) TRIAL OF TREATMENT OF HYPERTENSION IN OLDER ADULTS

The MRC Study was a single-blind trial conducted at more than 200 primary care centers in the U.K (MRC Working Party, 1992). A total of 4396 men and women between the ages of 65 and 74 participated in the trial. The average follow-up was 5.8 years. Patients had a mean entry systolic blood pressure of 160-209 mm Hg and a mean diastolic blood pressure < 115 mm Hg during an 8 week run-in period. Patients were randomized to atenolol 50 mg daily; HCTZ 25-50 mg + amiloride 2.5-5 mg; or placebo. The regimens were adjusted to reach the goal therapy (based on initial blood pressure levels) — of systolic blood pressure 150-160 mm Hg.

Both treatments reduced blood pressure significantly compared to placebo. The actively treated group had a 25% reduction in stroke, 19% reduction in coronary events, and 17% reduction in all cardiovascular events (Figures 22 and 23). The diuretic group had a significant reduction in the risk of stroke (31%), coronary events (44%), and all cardiovascular events (35%) compared to placebo. The ß-blocker group showed no significant reduction in these end-points. The reduction in strokes was mainly observed in non-smokers on a diuretic regimen.

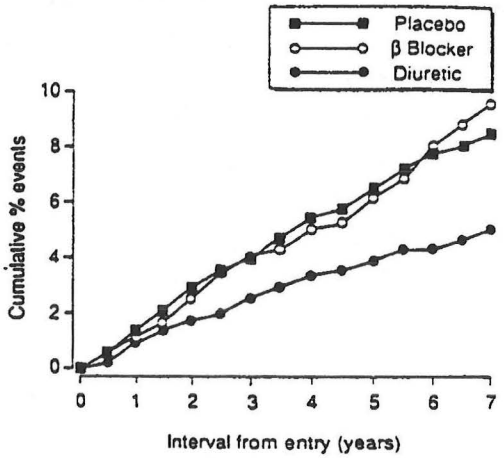


Figure 22: Cumulative percentage of patients receiving coronary events by randomized treatment. (From MRC Working Party, 1992).

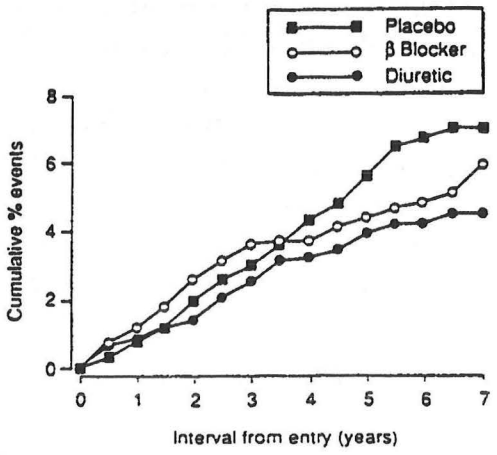


Figure 23: Cumulative percentage of patients experiencing stroke by randomized treatment. (From MRC Working Party, 1992).

A striking observation in this trial was that ß-blockers had no protective effect against any end-point, whereas, diuretics prevented even coronary mortality. Rational explanation for this observation is lacking. This study has some serious flaws, nevertheless. The majority of patients received both drugs, obviously confusing the analysis. If the intention was to compare the different classes of

drugs, they should not have combined them, but rather should have added a different class of agent when monotherapy was not sufficient. Secondly, 25% of the patients were "lost to follow-up," or did not adhere to the protocol. Nonetheless, the study findings are significant.

THE SWEDISH TRIAL IN OLD PATIENTS WITH HYPERTENSION (STOP-HYPERTENSION)

The STOP trial was a multicenter trial conducted in 116 centers in hypertensive patients between the ages of 70 and 84 years (Dahlof et al, 1991). A total of 1627 men and women with systolic blood pressure 180-230 mm Hg and a diastolic of ≥ 90 mm Hg; or a DBP > 105 mm Hg irrespective of systolic blood pressure were included in the study. Patients were randomized to receive a placebo or one of three ß-blockers (atenolol, metoprolol or pindolol) with or without HCTZ + amiloride. The average follow-up was 25 months. The mean difference between the systolic blood pressure of the treatment and placebo groups was 19.5 mm Hg, and the diastolic blood pressure difference was 8.1. Compared to placebo, active treatment was associated with a 40% reduction in the study end-points (Figure 24). Total mortality was reduced by 43% and stroke morbidity/mortality by 43%. Morbidity and mortality due to MI were reduced by 13% — not significant statistically. Increases in blood pressure were mainly seen in the placebo group. Not a single patient was lost to follow-up in this study.

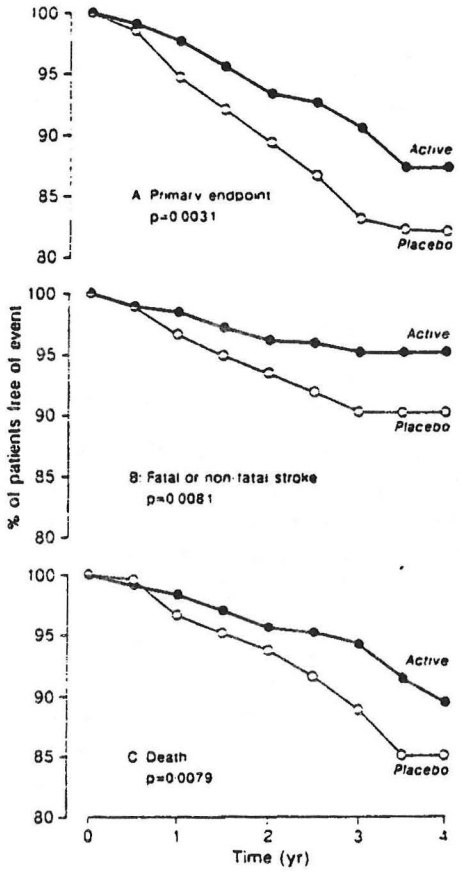


Figure 24: Percentages of patients who have escaped a primary endpoint (A), fatal or non-fatal stroke (B), or death (C) during 4 years of treatment. (From Dahlof et al, 1991).

THE SYSTOLIC HYPERTENSION IN THE ELDERLY PROGRAM (SHEP)

The SHEP trial was designed to assess the influence of anti-hypertensive drug treatment to reduce the risk of non-fatal and fatal strokes in patients with isolated systolic hypertension (SHEP Cooperative Research Group, 1991). For this multicenter, randomized, double-blind and placebo-controlled study, 4736 persons (out of 447,921 screenees) whose systolic blood pressure ranged between 160-219 mm Hg and diastolic blood pressure was < 90 mm Hg were randomized to receive a placebo or chlorthalidone ± atenolol. Average follow-up was 4.5 years. The 5-year average systolic blood pressure levels for the placebo and treatment groups were 155 and 143 mm Hg, respectively; the average diastolic blood pressure levels for the placebo and treatment groups were 72 and 68 mm Hg, respectively. In the treated group all of the major cardiovascular events were reduced, and the incidence of stroke was reduced by 36% (Figure 25). Towards the end of the trial, nearly a third of the patients were on both chlorthalidone and atenolol. Nearly half the placebo group had to be switched to active treatment because of an unacceptable rise in blood pressure. Despite these weak points, the SHEP results show a significant benefit for treating isolated systolic hypertension. Beneficial effects were observed in white men and women and in black women. The lack of demonstrated benefit in black men was likely due to the small number of subjects

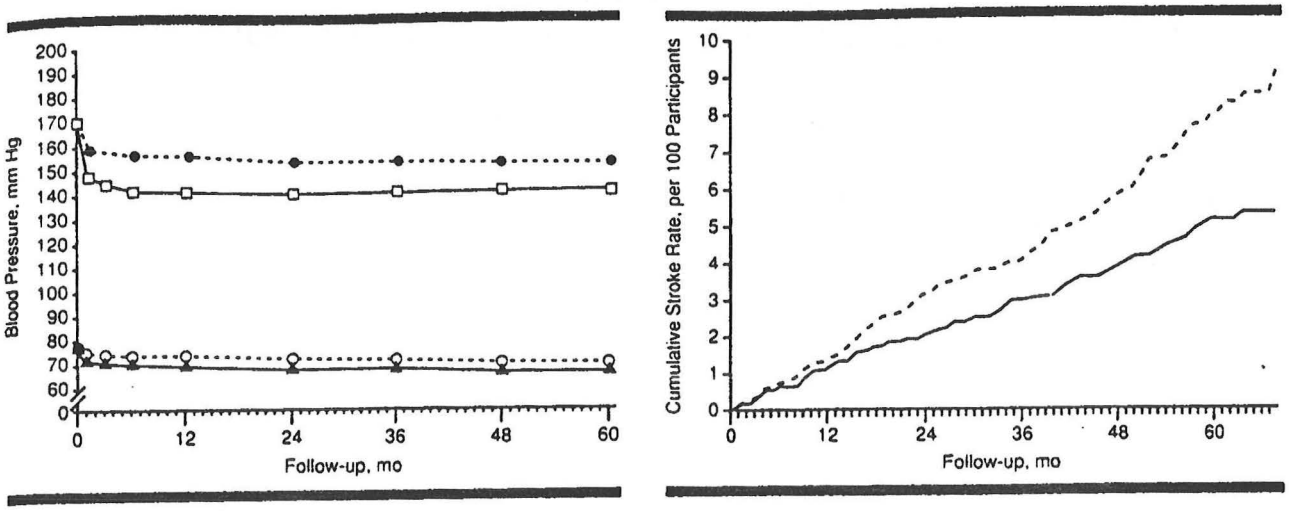


Figure 25: (A) Average systolic and diastolic blood pressure during the Systolic Hypertension in the Elderly Program follow-up plotted at 1, 3, 6, and 12 months and yearly thereafter. Solid line with open squares indicates average systolic blood pressure for the active treatment group; broken line with closed circles , average systolic blood pressure for the placebo group; solid line with triangles, average diastolic blood pressure for the active treatment group; and broken line with open circles, diastolic blood pressure for the placebo group.

(B) Cumulative fatal plus nonfatal stroke rate per 100 participants in the active treatment (solid line) and placebo (broken line) groups during the Systolic Hypertension in the Elderly Program.

in that group. All coronary disease events were reduced by 25% in the treated group but not in the placebo group. Similarly, all nonfatal and fatal cardiovascular events were reduced by 32% in the treated group. The treated group demonstrated typical biochemical abnormalities associated with chronic diuretic use. The treatment group also showed a favorable effect on the course of carotid lesions (Table 13).

Table 13: Progression and Regression* of Carotid Stenosis by SHEP Treatment Assignment

	N	*n*	%
Progression	129	28	21.7
Active	71	10	14.1
Placebo	58	18	31.0
*Regression**	49	8	16.3
Active	25	8	32.0
Placebo	24	0	0.0

*Regression could only be assessed in participants who had a stenosis (any location) at baseline.

XII TREATMENT OF HYPERTENSION IN THE ELDERLY

There is clear cut evidence that antihypertensive drug therapy in the elderly is not only effective but offers protection from cardiovascular and cerebrovascular morbidity and mortality. However, before initiating drug therapy in the elderly, consideration should be given for a trial of non-pharmacological therapy. These approaches should be offered as the first step for every hypertensive patient. Therapeutic response to non-pharmacological therapy may obviate the need for or lessen the doses of antihypertensive drugs.

OBESITY

A strong relationship exists between blood pressure and body weight in young and middle aged hypertensive individuals, but this correlation weakens after the age of 70. Weight loss is associated with a fall in blood pressure and improvement in glucose tolerance (Franssila-Kallunki et al, 1992; Anderson, 1978). In an open, uncontrolled study, weight loss in individuals > 70 years of age caused a significant drop in blood pressure; nearly a fifth of the hypertensive patients were able to stop antihypertensive drugs altogether. However, there was no correlation between the weight loss and the reduction in blood pressure. It is possible that exercise and reduced salt intake may have played a role in the observed studies. It seems reasonable, despite the lack of convincing evidence, that weight reduction should be recommended for obese, elderly hypertensives.

SODIUM RESTRICTION

In general, moderate sodium restriction has been shown to lower the blood pressure in the hypertensive population at large. Most studies included either younger subjects or no mention of age is made. A review of all studies of dietary sodium restriction suggests that greater hypotensive effect was observed in older subjects. A recent study concluded that moderate sodium restriction (80 mmol/day) lowered the 24 hour ambulatory blood pressure levels in elderly patients with chronic hypertension (Fotherby and Potter, 1993). Similarly, non-pharmacologic measures, including sodium restriction, lowered the systolic blood pressure and diastolic blood pressure levels in older patients with hypertension (Applegate et al, 1992) (Table 14). Since the therapeutic benefits of sodium restriction are not homogenous, the blood pressure may not change in some elderly hypertensive patients.

Table 14: Effect of Non-drug Treatment on Blood Pressure Levels in the Elderly. (From Applegate et al, 1992).

Observation	Systolic, mm Hg†		Diastolic, mm Hg‡	
	Experimental (N=21)	Control (N=26)	Experimental (N=21)	Control (N=26)
Baseline §	142.6±11.7	144.5±9.7	86.5±1.7	88.4±3.6
Change, mo				
1	-1.2	-1.7	-1.7	-1.3
2	-7.6	-4.3	-7.5	-1.7
3	-9.3	-1.5	-5.3	-0.9
4	-11.4	-1.6	-7.4	-0.8
5	-8.2	-3.9	-5.8	-3.7
6	-8.7	-4.5	-6.8	-1.9

*N=47.
†Group effect, P=.02; time effect, P=.20; and interaction effect, P=.22.
‡Group effect, P=.003; time effect, P=.09; and interaction effect, P=.10.
§Mean ± S.D.

INCREASED POTASSIUM INTAKE

Potassium supplementation has been shown to lower the systemic blood pressure in some therapeutic trials (MacGregor et al, 1982; Kaplan et al, 1985). However, these studies did not include many elderly subjects. Recently, Fotherby and Potter showed a significant drop in the blood pressure of elderly hypertensive patients given 60 mmol of potassium chloride daily. There is limited evidence to suggest that potassium supplementation may protect against stroke and may lessen the need for antihypertensive drugs. While this therapeutic modality can be applied to correct potassium depletion, at the present time, potassium supplementation is not recommended for routine treatment of hypertension.

CALCIUM

Several epidemiological studies have reported a relationship between hypertension and calcium. Some studies have even suggested that calcium supplementation lowers the blood pressure in essential hypertension. There does not appear to be consistent effect of calcium supplementation on systemic blood pressure, but a small subpopulation of patients may experience a therapeutic benefit. Although in a small number of elderly patients, calcium supplementation was shown to exert a modest blood pressure lowering effect, there is no evidence to recommend calcium supplements to reduce blood pressure in older patients (Morris and McCarron, 1992).

ALCOHOL

Excessive consumption of alcohol has been shown to increase the blood pressure in some individuals. Higher blood pressure levels were noted in the elderly population consuming > 80 g of alcohol/day. The prohypertensive effect of alcohol is more pronounced in the elderly compared to younger age groups (Schnall and Weiner, 1958). In one study, elderly hypertensive patients abstaining from alcohol had a remarkable fall in blood pressure. Thus, patients should be advised to restrict alcohol consumption to no more than 2 drinks/day.

EXERCISE

Several observations indicate that regular physical activity decreases the blood pressure in normotensives as well as in hypertensives. Aerobic exercise performed regularly may lower the blood pressure in elderly hypertensive patients. A high level of physical fitness is likely to be beneficial. It is important, especially in the elderly, to concentrate on isotonic rather than isometric forms of physical exercise. Isometric exercise may aggravate the pathophysiological factors responsible for hypertension. Gradual increase in isotonic physical exercises is likely to be helpful, not harmful.

GENERAL COMMENTS ON THE ROLE OF NON-PHARMACOLOGICAL TREATMENT

While there is little evidence that non-pharmacological therapy in the elderly prolongs life, it is now known that reducing the blood pressure in older hypertensive subjects is a worthwhile goal. Therefore, in theory, the elderly hypertensives should benefit from the non-pharmacological measures described above. We should be mindful that the effects of non-pharmacological interventions on blood pressure are inconsistent. Dietary and other life-style changes are feasible and should be given a trial in the initial therapy of hypertension in the elderly (Applegate et al, 1992). Moreover, drug therapy works best in conjunction with non-drug therapeutic modalities.

DRUG THERAPY OF HYPERTENSION IN THE ELDERLY

Only in the recent past has it become apparent that antihypertensive drugs exert a beneficial effect in the elderly. Several trials described above have demonstrated that not only diastolic but also systolic hypertension in the elderly should be treated (Ram, 1992). Since the elderly population is susceptible to adverse effects of therapy and since they may have other concomitant medical problems, drug selection and therapy should be chosen with considerable caution (Table 15) and the patients should be monitored closely. Inappropriate drug therapy may lead to serious sequelae, including death. Judicious use of antihypertensive drug therapy can offer major benefits in elderly patients with hypertension. Certain pharmacological principles are listed in Tables 16 and 17.

Table 15: Factors affecting side-effect incidence in the elderly

Polymedication
Altered pharmacokinetics
Altered pharmacodynamics
Baroreflex function
Sympathetic reactivity
Renal Na^+ and H_2O conservation
Plasma volume
Total body water
Pseudohypertension

Table 16: Major Concerns in Initiating Pharmacologic Treatment of Systolic Hypertension in the Elderly

Increased drug bioavailability (reduced metabolism or excretion)
Risk of postural fall in blood pressure
Presence of subclinical cerebrovascular or coronary disease
Drug side effects
Cost
Excessive lowering of diastolic blood pressure
Unnecessary treatment of patients with "white coat" hypertension
Unnecessary treatment of patients with "pseudohypertension"

Table 17: Pharmacokinetic Alterations in Old Age

Rate of absorption ↓
Distribution altered
Altered apparent volume of distribution secondary to
↓ body fluids
↑ body fat
Protein binding ↓
Red cell binding ↓
Cardiac output and regional blood flows ↓
Drug penetration in tissues ↑
↑ permeability of blood-brain barrier
Metabolism altered
Hepatic clearance of drugs ↓
enzymatic degradation } ↓ by aging
enzymatic conjugation } ↑ by drug induction
activation
inactivation
solubilization
biliary excretion
Plasma clearance ↓ } except for protein-bound drugs
Plasma half-life ↑ }
Renal excretion ↓
Effective renal plasma flow ↓
Glomerular filtration rate ↓

As a general rule, it is best to start drug therapy with a low dose and adjust the dose gradually. In selecting the drugs for the elderly, several factors should be considered:

1: Concomitant medical problems
2: Concurrent drug therapy
3: Postural blood pressure response
4: Altered pharmacokinetics
5: Drug interactions
6: Cerebral blood flow and function
7: Renal function
8: Cardiac status

Adverse effects of antihypertensive drugs in the elderly are similar to those observed in the young but more pronounced.

Until recently, the long term effects of antihypertensive drugs in the elderly were virtually unknown and, therefore, the therapy was largely empiric. With the availability of the results from the EWPHE, SHEP, STOP and MRC trials, we are now better equipped with the knowledge about the consequences of long-term administration of antihypertensive drugs in the elderly. It is possible to understand the adverse effects of antihypertensive drugs in the elderly. Since most data were obtained with patients on diuretics, ß-blockers, and sympathetic inhibitors (reserpine), we do not have comparative data on the effects of other classes of drugs like angiotensin converting enzyme (ACE) inhibitors, calcium antagonists, and α_1-receptor blockers in older patients. Diuretics alone or in combination with ß-blockers have been used in the controlled trials that have shown a reduction in cardiovascular mortality and morbidity. The MRC trial, SHEP, and STOP-Hypertension have included low dose diuretic therapy or ß-blockers. Particular care was taken in these studies to avoid hypokalemia, a noteworthy fact.

DIURETICS

Diuretics have been shown to be consistently effective in the management of diastolic hypertension and/or isolated systolic hypertension. In most studies which utilized a diuretic as initial therapy, marked reduction in the complication rate was seen. In all of the recent trials in the elderly (EWPHE, MRC, SHEP, STOP-Hypertension, and the Department of Veterans Affairs Cooperative study), diuretic therapy was employed. Of course, the therapy was generally accompanied by a reduction in the blood pressure level and, thus, it may be the hemodynamic effect which is the final consequence of cardiovascular therapy. Low dose therapy can yield satisfactory results in uncomplicated hypertension (Table 18).

Table 18: Treatment Outcomes During Titration Phase by Final Hydrochlorothiazide Dosage Level* (From Cushman et al, 1991).

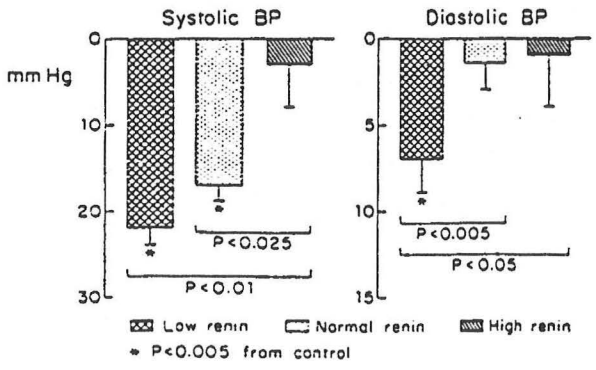
	Hydrochlorothiazide Dosage, mg				
	25 QD (n=13)	25 BID (n=10)	50 QD (n=18)	50 BID (n=10)	P
Systolic BP, mm Hg					
Baseline	168.6±9.1	178.4±15.3	166.6±6.5	172.4±10.2	.47
End titration	140.0±9.5	157.2±11.6	134.9±12.3	148.4±12.7	...
Change from baseline	-28.6±11.0	-21.2±20.1	-31.7±11.0	-24.0±16.1	.45
Diastolic BP, mm Hg					
Baseline	81.9±8.5	84.6±4.0	84.2±3.4	84.4±3.5	.36
End titration	75.2±9.6	77.6±6.8	75.8±7.5	78.8±9.7	...
Change from baseline	-6.6±10.7	-7.0±8.4	-8.4±7.7	-5.6±9.4	.58
Weight, kg					
Change from baseline	-1.7±1.0	-1.3±1.7	-1.3±1.5	-1.7±1.4	.45
Serum potassium, mmol/L					
Baseline	4.34±0.41	4.32±0.28	4.51±0.43	4.41±0.36	.27
End titration	4.28±0.36	3.99±0.65	4.03±0.38	3.67±0.45	...
Change from baseline	-0.06±0.45	-0.33±0.65	-0.48±0.49	-0.74±0.51	.02
Serum glucose, mmol/L					
Baseline	6.7±2.7	5.7±0.3	6.4±1.7	7.2±2.6	.81
End titration	6.7±1.9	5.9±0.5	6.8±1.5	7.6±2.5	...
Change from baseline	0±1.3	0.2±0.7	0.4±0.9	0.4±1.9	.36

*Data are expressed as mean±SD, and *P* values reflect differences across final hydrochlorothiazide dosage levels. QD indicates daily; BID, twice daily; and BP, blood pressure.

ADVANTAGES

Diuretics, as stated above, have proven efficacy in the elderly, are inexpensive, and are generally well tolerated. They are also effective in the management of isolated systolic hypertension (Cushman et al, 1991). From a pathophysiological standpoint, there is evidence that diuretics work best in low renin hypertension (Niarchos and Laragh, 1984), as is often the case in the elderly (Figure 26). Although not conclusive, diuretic therapy has been shown to be associated with reduced incidence of hip fractures (Ray et al, 1989; Wasnich et al, 1983). Furthermore, diuretics reverse the pathophysiological hallmark of established hypertension i.e. elevated vascular resistance (Vardan et al, 1983) (Figure 27). In most of the clinical trials including SHEP, EWPHE, MRC, and STOP-Hypertension, diuretics were well tolerated by the participants. Certainly diuretics are especially indicated in the treatment of hypertension associated with heart failure (Ram, 1993).

Figure 26: Effect of diuretic therapy on systolic and diastolic blood pressure (BP) in low-, normal- and high-renin isolated systolic hypertension. (From Niarchos & Laragh, 1984)



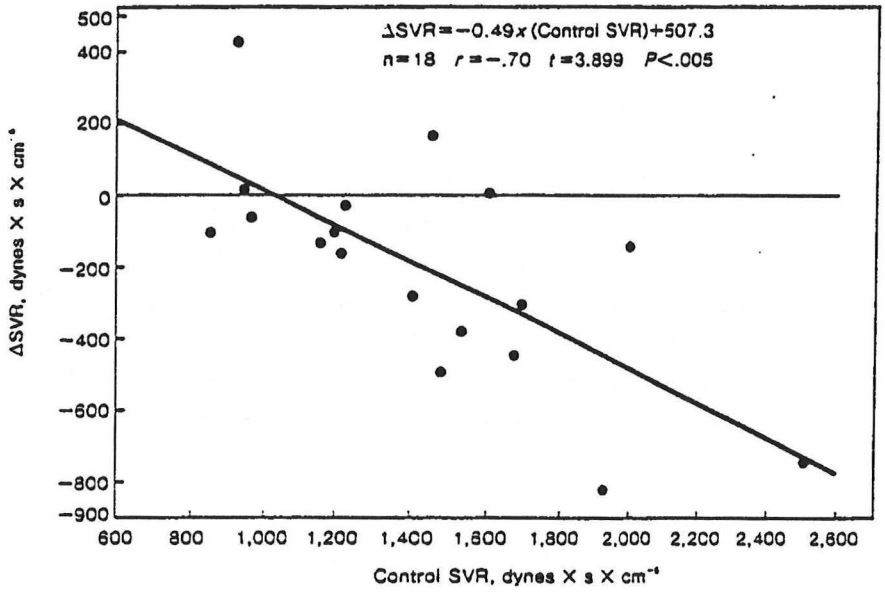


Figure 27: Relationship between initial systemic vascular resistance (SVR) and its change (Δ) after one month of therapy with hydrochlorothiazide in systolic hypertension. Higher the control SVR, greater the fall with therapy. (From Vardan et al, 1983).

DISADVANTAGES

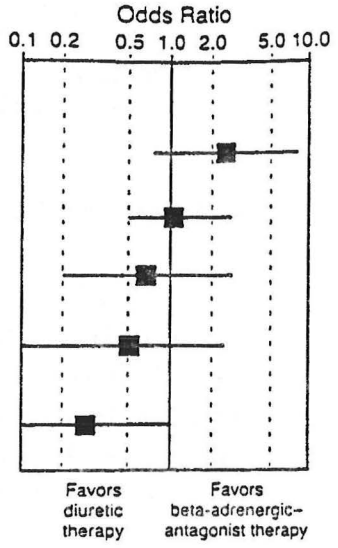
Diuretic therapy has a number of disadvantages, mainly biochemical in nature. Diuretics may cause hypokalemia, hyperuricemia, hyperlipidemia, hyperglycemia, etc. The significance of diuretic induced hyperlipidemia (↑ LDL, ↑ triglycerides) is not fully known despite years of debate and vigorous discussion. Long-term diuretic therapy has been associated with excess mortality in diabetic hypertensives (Warram et al, 1991). In a recent report, thiazide usage was associated with a significant risk of primary cardiac event (Siscovick et al, 1994) (Figure 28). The addition of a potassium sparing drug has been associated with a reduced risk of primary cardiac arrest, implying the need to maintain positive potassium balance during administration of diuretics.

Figure 28: Risk of Primary Cardiac Arrest Associated with Thiazide Therapy with an without Potassium-Sparing Diuretic Therapy, as Compared with Beta-Adrenergic-Antagonist Drug Therapy, among Patients Treated with Single Antihypertensive Drugs.

The odds ratios were adjusted for age, sex, pretreatment systolic blood pressure and heart rate, duration of hypertension, current smoking, and diabetes mellitus. Eleven case patients and 47 control patients were treated with a beta-adrenergic-antagonist drug alone. CI denotes confidence interval.

(From Siscovick et al, 1994).

Therapy	Odds Ratio (95% CI)
100-mg Thiazide	2.4 (0.7–8.0)
50-mg Thiazide	1.1 (0.5–2.5)
25-mg Thiazide	0.7 (0.2–2.5)
50-mg Thiazide and potassium-sparing diuretic	0.5 (0.1–2.2)
25-mg Thiazide and potassium-sparing diuretic	0.3 (0.1–1.0)



BETA-BLOCKERS

Like diuretics, ß-blockers have been extensively studied in the management of hypertension in the elderly. Although they are efficacious and have proven to be useful (Perry et al, 1994; LaPalio et al, 1992; Bracchetti et al, 1990), from a physiologic point of view, ß-blockers may not be ideal to treat hypertension in the elderly. Hypertension in the elderly is associated with suppressed activity of the renin angiotensin system and hence ß-blocker therapy may not yield maximal efficacy in this subgroup of patients (Figure 29).

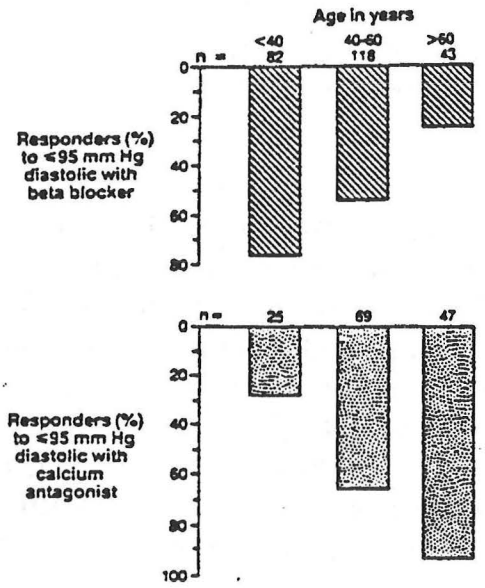


Figure 29: The percentage of patients of varying ages whose blood pressure was normalized, i.e.e, to below 95 mm Hg diastolic, with a ß-blocker (top) or a calcium antagonist (bottom). (From Bühler FR et al: Am J Med 1984;20:36-42).

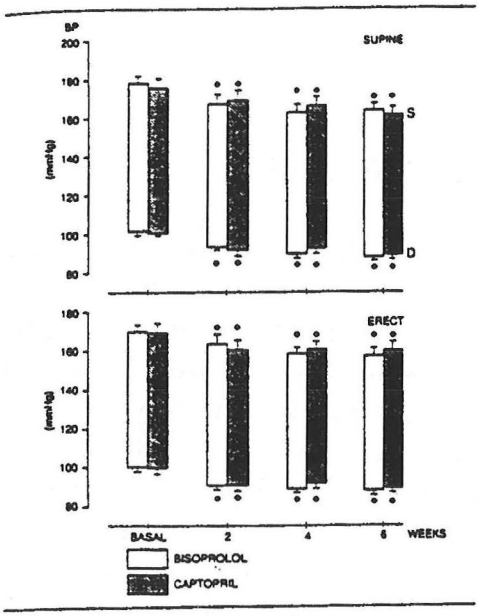


Figure 30: Mean systolic (SBP) and diastolic (DBP) blood pressure values ± SE in basal conditions and at 2, 4, and 6 weeks of treatment with bisoprolol and captopril (supine and erect positions). n = 24; *p < 0.01. (From Bracchetti et al, 1990).

ADVANTAGES

ß-Blockers have been used in the clinical trials that have documented the value of blood pressure reduction in elderly hypertensives (Table 19). Despite their established property of cardioprotection, in the MRC trial no such advantage was shown, thus raising doubts about the previously held favorable notions about ß-blockade. In a recently published large clinical trial, metoprolol showed impressive blood pressure reduction in a cohort of elderly hypertensives (LaPalio et al, 1992). Similarly, the newly released ß-blocker, bisoprolol, effectively reduced the blood pressure in elderly hypertensives (Bracchetti et al, 1990) (Figure 30). In 245 elderly

patients receiving antihypertensive drugs, ß-blockers, ACE inhibitors, and calcium antagonists were all equally effective in reducing the blood pressure (Perry et al, 1994). ß-Blockers have been demonstrated to offer secondary prevention of coronary disease (Yusef et al, 1990).

Table 19: Summary of Change in Diastolic and Systolic Blood Pressures from Baseline to Weeks 8 and 16* (From Applegate WB. Arch Intern Med 1991;151, p. 81).

	Diltiazem (D) (n=79)	Atenolol (A) (n=79)	Enalapril (E) (n=84)	Test (P)†
Diastolic blood pressure				
Baseline	98.0±0.4	98.9±0.5	98.1±0.3	...
Week 8	−14.9±0.7	−11.3±1.0	−10.1±0.8	TRT (<.001) D vs A (.002) D vs E (<.001) A vs E (.440)
Week 16	−13.7±0.7	−10.8±1.1	−10.5±0.9	TRT (.016) D vs A (.019) D vs E (.009) A vs E (.818)
Systolic blood pressure				
Baseline	161.4±1.7	164.7±2.0	165.7±1.6	...
Week 8	−15.3±1.6	−9.5±2.0	−12.6±1.7	TRT (.026) D vs A (.007) D vs E (.104) A vs E (.265)
Week 16	−14.2±1.6	−11.0±2.1	−12.7±1.9	TRT (.157)

*Values are mean ± SE.
†TRT indicates any treatment effect across groups.

DISADVANTAGES

Due to possible CNS effects, ß-blockers may be poorly tolerated by the elderly. ß-Blockers are contraindicated in patients with CHF, A-V block, COPD, etc. — which are not uncommon conditions in the elderly. ß-Blockers can worsen insulin resistance, raise blood sugar, triglyceride, and LDL levels. ß-Blockers (without intrinsic sympathomimetic activity — ISA) may not be effective in smokers. Although ß-blockers lower the blood pressure in the elderly, best antihypertensive effects with this class of drugs are obtained in younger subjects.

ACE INHIBITORS

As a pharmacotherapeutic drug class, ACE inhibitors exert important cardiovascular and renal effects. They are widely used in clinical medicine. Despite certain structural differences, all ACE inhibitors produce similar antihypertensive actions.

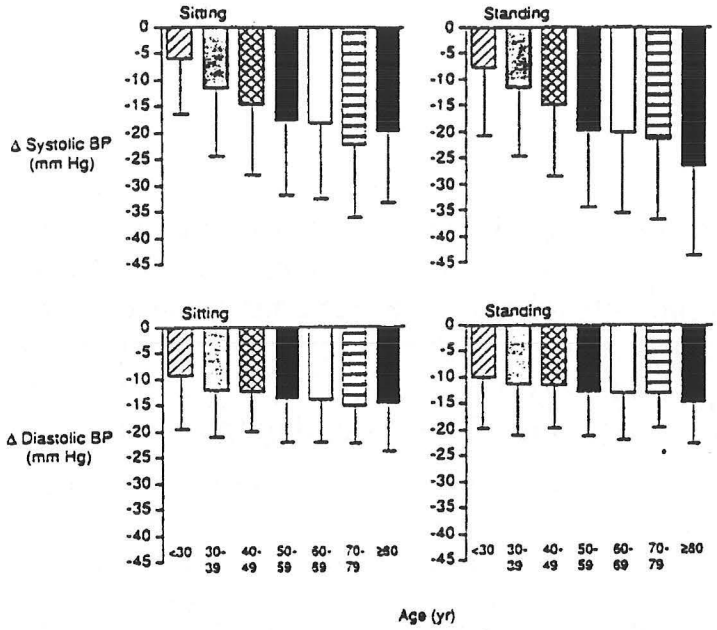
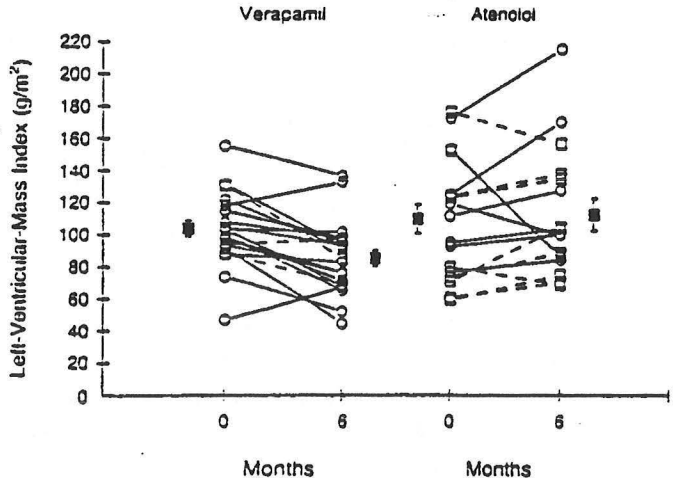


Figure 34: Response to nifedipine monotherapy: Changes in blood pressure from baseline to final visit in patients grouped according to age by decade. All changes from baseline are statistically significant at P ≤ 006. (From Bravo et al, 1990).

In a comparative study, verapamil and atenolol lowered the blood pressure equally in elderly hypertensives, but it is the former, not the latter, that caused regression of LVH (Schulman et al, 1990) (Figure 35). These observations imply that mechanisms of LVH in the elderly may be mediated by calcium fluxes, not by adrenergic influences. There is some evidence to indicate that calcium antagonists may have a vasculoprotective and anti-atherosclerotic effects (Ram, 1990).

Figure 35: Individual and Mean Changes in the Left-Ventricular-Mass Index from Bas Line to the Six-Month Follow-up, as Determined by Two-Dimensional Echocardiography.

Open squares with dashed lines indicate that a diuretic was added to the regimen. The solid squares and I bars indicate the mean ± SE. Left ventricular hypertrophy was considered to be present when the left-ventricular-mass index was ≥ 134 g per square meter of body-surface area for men and ≥ 110 g per square meter for women. After six months of treatment with verapamil, values were significantly lower ($P < 0.0001$) than base-line values. (From Schulman et al, 1990).



DISADVANTAGES

Occasionally, dihydropyridine derivatives such as nifedipine capsules may cause marked hypotension which can precipitate hypoperfusion to the vital organs. Ankle edema, tachycardia, and headache are known adverse effects of dihydropyridines. Drugs like verapamil and diltiazem may precipitate CHF and cause or aggravate heart block. Verapamil can cause constipation — a common inherent problem in the elderly.

α-BLOCKERS

α-Blockers such as doxazosin, prazosin, and terazosin have been shown to be efficacious in the management of hypertension in the elderly. Their efficacy matches that of other first-line antihypertensive drugs (Scott et al, 1988).

ADVANTAGES

α-Blockers are known to exert a lipid lowering effect, and they do not cause CNS side-effects. They are also advantageous to relieve bladder outlet obstruction in patients which prostatism. They do not decrease the cerebral blood flow (CBF) (Ram et al, 1987).

DISADVANTAGES

The dose response is highly variable and several dose adjustments have to be made to obtain a desired goal blood pressure. Orthostatic hypotension can occur if the dose is escalated rapidly or the patient is volume depleted. However, with a new α-blocker such as doxazosin which has a more gradual and smooth antihypertensive effect, postural hypotension is uncommon.

CENTRAL α_2-ADRENERGIC AGONISTS

This class includes drugs like methyldopa, clonidine, guanabenz and guanfacine — which have been successfully used to treat hypertension in the elderly. In the EWPHE trial, methyldopa was used as the second agent. These drugs are not popular in the clinical management of the elderly because of their CNS side-effects such as sedation, dry mouth, impotence, etc.

OTHER ANTIHYPERTENSIVE DRUGS

Labetalol, a combined α- and ß-adrenergic blocking drug, has been shown to reduce blood pressure in the elderly (Eisalo et al, 1984), but there is no large-scale or long-term experience with clinical use of labetalol in the elderly. Direct vasodilators such as hydralazine and minoxidil are reserved for managing severe, refractory, and complicated forms of hypertension. They can not be used as monotherapy because of the accompanying adverse counterregulatory mechanisms which are best managed by the co-administration of a ß-blocker and a diuretic-usually of loop variety. The following figure shows the therapeutic response rate to various antihypertensive drugs and relationship to age and race.

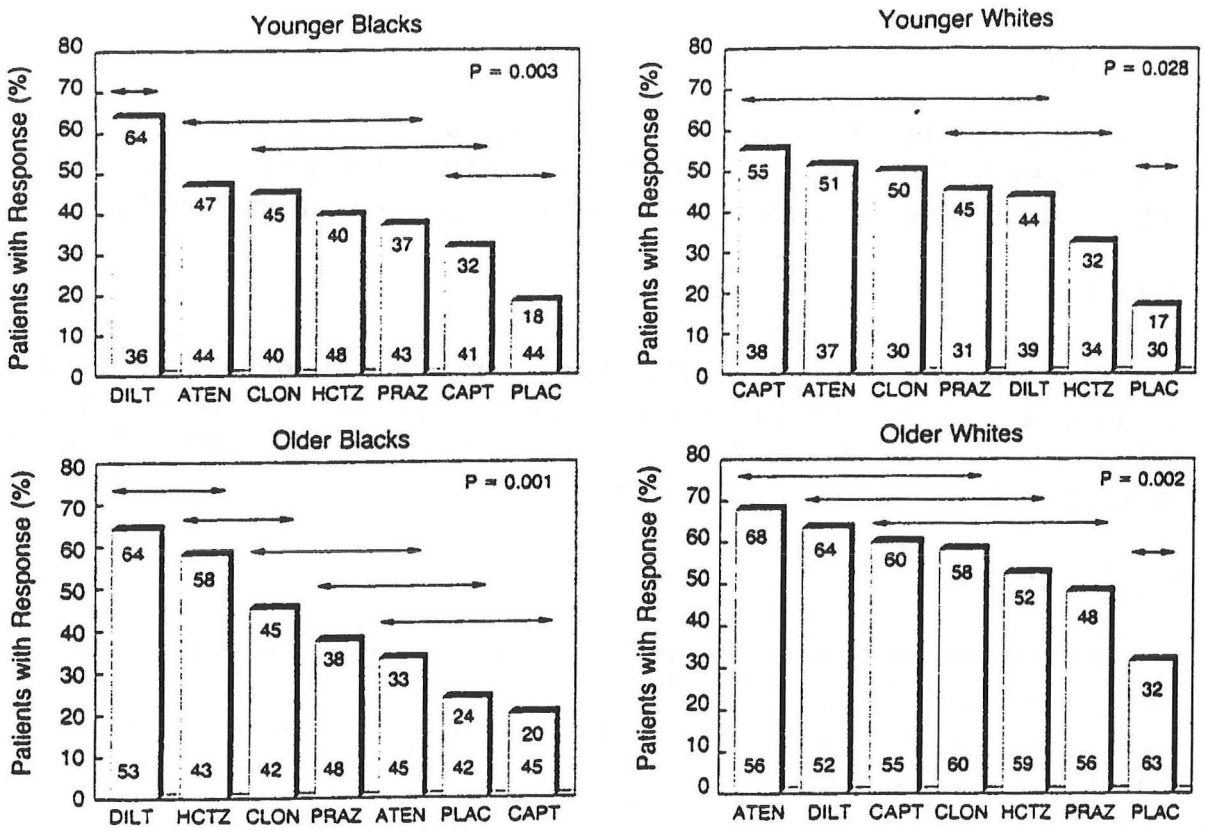


Figure 36: Responsiveness to various antihypertensive drugs - VA Cooperative Study Group. (From Materson et al. Single drug therapy for hypertension in men. N Engl J Med 1993;328:914-21).

XIII. SECONDARY CAUSES OF HYPERTENSION IN THE ELDERLY

The effect of aging on the prevalence of secondary causes of hypertension has not been thoroughly investigated. With advancing age and atherosclerosis, renal artery stenosis is more commonly seen in the elderly than in younger subjects. Older patients with hypertension should be considered for work-up, as in other age groups, on the basis of clinical course, physical examination, and laboratory findings. Correction or specific treatment of the underlying cause is likely to restore better blood pressure control in patients with a secondary form of hypertension (Ram, 1994). Of all the secondary forms, renovascular hypertension is perhaps the most common among the elderly (Ram, 1988). The concomitant presence of atherosclerosis significantly increases the prevalence of renovascular hypertension (Anderson et al, 1994; Libertino, 1991; Laugesen et al, 1983) (Figure 37). Not surprisingly, there is a higher incidence of renal artery stenosis in populations undergoing cardiac catheterization (Ramirez et al, 1987) (Figure 38).

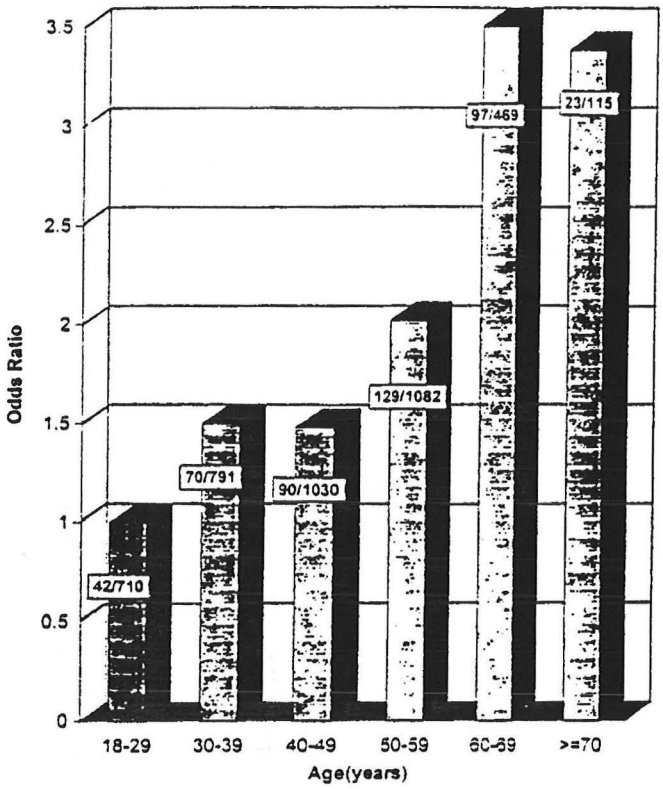


Figure 37: Odds ratio by χ^2-analysis for the prevalence of secondary hypertension for different age groups. The numbers on the bars are the number of secondary hypertensives/the number of essential hypertensives. Linear trend 53.3, $P < 0.000\ 001$. (From Anderson et al, 1994).

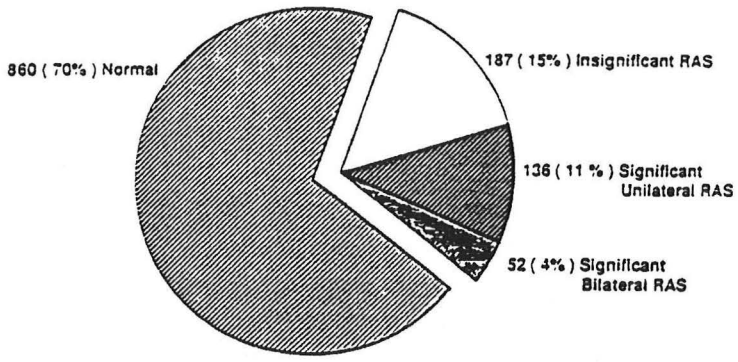


Figure 38: The prevalence of renal artery stenosis as determined by cine abdominal aortography at the time of cardiac catheterization (N = 1,235). Insignificant renal artery stenosis is determined as <50% luminal narrowing. Significant renal artery stenosis is defined as ≥50% luminar narrowing. (From Harding et al. J Am Soc Nephrol 1992;2:1608-16).

XIV. CONSEQUENCES OF INAPPROPRIATE ANTIHYPERTENSIVE THERAPY IN THE ELDERLY

Cerebral Hypoperfusion

Overzealous blood pressure reduction in the elderly can lead to disastrous consequences — syncope, stroke, myocardial infarction, etc. Sudden hypotension in elderly patients with carotid artery stenosis has been shown to cause focal cerebral ischemia (Ruff et al, 1981; Jackson et al, 1976). In these case reports, excessive hypotension played a significant role in causing cerebrovascular morbidity.

In normal (or young) subjects, cerebral blood flow (CBF) is auto-regulated such that it remains constant across a wide range of systemic blood pressure levels. However, in elderly patients, the limits of CBF autoregulation are restricted, and, as such, marked systemic hypotension can cause cerebral hypoperfusion (Wollner et al, 1979; Strandgaard, 1983; 1989). This unfortunate complication can be

avoided by gentle lowering of the blood pressure in the elderly. In a study we conducted here, systemic blood pressure was reduced gradually over a period of weeks; CBF did not change in the elderly patients receiving antihypertensive drug therapy (Ram et al, 1987) (Figure 39).

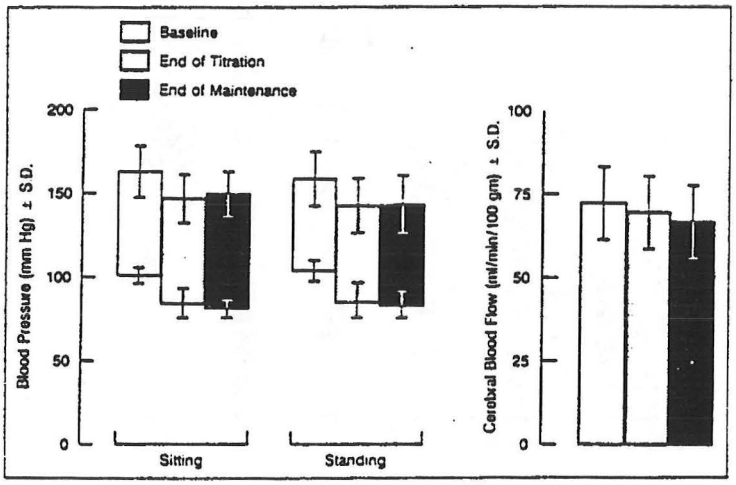


Figure 39: The blood pressure and cerebral blood flow responses in the subset of eight subjects who underwent cerebral blood flow studies. (From Ram et al, 1987).

THE J-SHAPED CURVE IN THE ELDERLY

In the earlier trials of antihypertensive drug therapy in the elderly, coronary mortality was not reduced. This raises speculation as to whether myocardial hypoperfusion (the J-Curve) from excessive lowering of systemic blood pressure was the underlying etiology for lack of protection against coronary deaths. From observational studies (Cox et al, 1992; Coope et al, 1988; Staessan et al, 1989), it does appear that excessive coronary mortality occurred in elderly patients in whom the blood pressure was reduced to the lower part of normal range. Whether this so called J- or U-shaped curve is solely due to the hemodynamic compromise or due to the underlying myocardial dysfunction, or due to deterioration of general health is not known. While it is premature to conclude that reduction of blood pressure in the elderly is harmful, it appears prudent not to lower the blood pressure excessively in this age group (Figure 40).

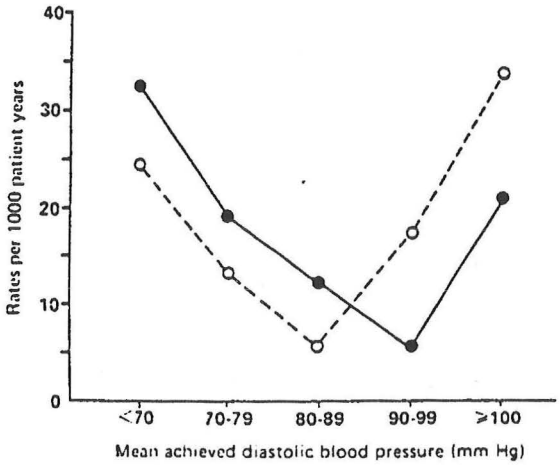


Figure 40: Mean rates from coronary artery disease per 1000 patient-years in patients in treated (0—0) and control (●—●) groups from the Hypertension in Elderly Patients in primary care study. (Adapted From Coope and Warrender, 1988).

The very old (>75 years) are particularly susceptible to poor prognosis if their systemic blood pressure achieves a relatively low level (Langer et al, 1993; Heikinheimo et al, 1990, Ho et al, 1992). Therefore, this subgroup has to be watched carefully and therapeutic decisions have to be made with caution.

XV. PATIENT COMPLIANCE AND DRUG PRESCRIBING FOR THE ELDERLY

In contrast to other age groups, elderly patients achieve a high level of adherence to prescribed antihypertensive drugs (Black et al, 1987; Traub et al, 1988). One can easily expect a compliance rate of 85-90% in the elderly (Figure 41).

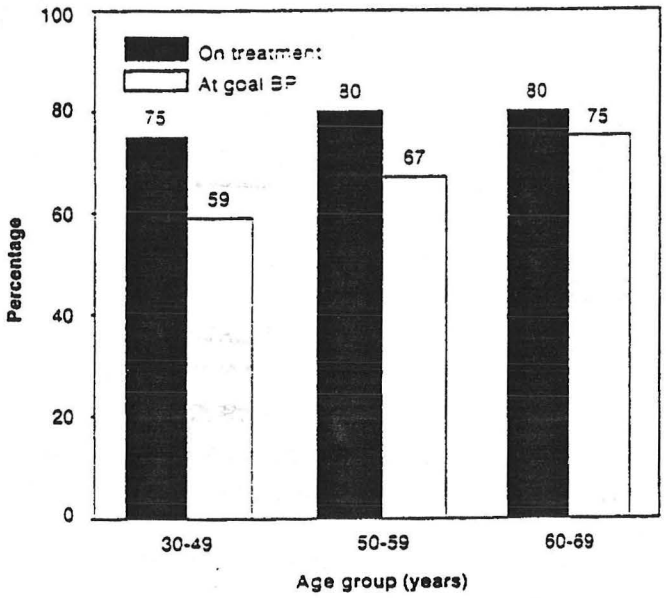


Figure 41: Adherence to therapy according to age among stepped-care group in the Hypertension Detection and Follow-up Program.

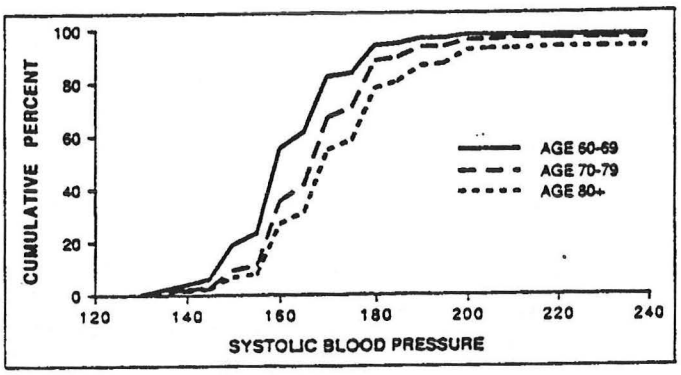


Figure 42: Lowest SBP for use of drug therapy in patients aged 60 to 69, 70 to 79, and 80 and over who have sustained ISH: cumulative percent of 1,179 respondents who report using drug therapy. (From Breckenridge and Kostis, 1989).

It is of interest to note that even prior to the publication of the SHEP data, 89% of physicians in a survey were prescribing antihypertensive drugs to elderly patients with isolated systolic hypertension (Breckenridge and Kostis, 1989) (Figure 42). Most were then prescribing either a diuretic or a beta-blocker to their elderly patients (Table 20). The prescription habits appear to be changing rather rapidly. In a more recent survey, physicians were increasingly prescribing ACE inhibitors and calcium antagonists in place of ß-blockers and diuretics for the treatment of

hypertension in elderly patients (Psaty et al, 1993) (Table 21). This trend was particularly striking for new prescriptions. On the other hand, in some communities, physicians prescribed inappropriate medication for nearly 25% of the elderly, thus placing them at a risk of adverse effects, especially mental impairment and sedation (Wilcox et al, 1994) (Table 22). It was surprising to note that nearly 600,000 elderly patients were still receiving reserpine and that nearly a million and a quarter elderly patients were still receiving methyldopa. Both of these drugs can cause a variety of cognitive and other adverse effects.

Table 20: Ranked Distribution of First- and Second-Line Drug Choices

First-Line Drug	Total Responses	Percent*	Second-Line Drug	Total Responses	Percent†
Thiazide diuretic	604	51.2	Beta blocker	334	28.3
Combination diuretic	179	15.2	Central alpha agonist	226	19.2
Beta blocker	132	11.2	Thiazide diuretic	125	10.6
Central alpha agonist	83	7.0	Beta blocker-diuretic	87	7.4
Calcium channel blocker	27	2.3	Prazosin	65	5.5
Potassium-sparing diuretic	26	2.2	Combination diuretic	64	5.4
Prazosin	23	2.0	Calcium channel blocker	50	4.2
Beta blocker-diuretic	16	1.4	ACE inhibitor	39	3.3
Reserpine	12	1.0	Hydralazine	30	2.5
Hydralazine	10	0.8	Potassium-sparing diuretic	22	1.9
Loop diuretic	10	0.8	Reserpine	19	1.6
Tranquilizer/sedative	8	0.7	Loop diuretic	11	0.9
ACE inhibitor	4	0.3	Tranquilizer/sedative	9	0.8
Guanethidine	—	—	Guanethidine	4	0.3
Other	11	0.9	Other	16	1.4
>2 checked	71	6.0	>2 checked	62	5.3
Decline choice	25	2.1	Decline choice	88	7.5

*Sixty-two responders (5.3 percent) checked two first-line drugs. "Percent" refers to percent of 1,179 respondents (not percent of 1,241 responses).
†Seventy-two respondents (6.1 percent) checked two second-line drugs. "Percent" refers to percent of 1,179 respondents (not percent of 1,251 responses).

(From Breckenridge and Kostis, 1989).

Table 21: Adjusted Odds of Receiving Various Types of Antihypertensive Drugs Among Starters Compared with Users*

	Women		Men		Combined	
	OR	P	OR	P	OR	P
Diuretics	0.72	.20	0.45	.01	0.59	.008
β-Blockers	0.39	.03	0.65	.22	0.52	.01
Vasodilators	0.61	.22	0.88	.76	0.69	.21
ACE inhibitors	2.84	<.001	1.98	.03	2.40	<.001
Calcium channel blockers	1.62	.12	2.18	.01	1.88	.004

*OR indicates odds ratio; and ACE, angiotensin converting enzyme. The odds ratios were adjusted for age, systolic blood pressure, number of antihypertensive drugs at 1 year, glucose intolerance, diabetes, self-reported urinary incontinence, coronary heart disease (at baseline and during follow-up), and congestive heart failure (at baseline and during follow-up).

(From Psaty et al, 1993).

Table 22: Number and Percentage of US Community Residents Aged 65 Years or Older Using Inappropriate Drugs*

Drugs	No. of People Receiving Drug	Percentage of Total Population Receiving Drug	No. of Prescriptions
Antihypertensives			
Propranolol	1 774 370	6.27	4 995 356
Methyldopa	1 280 297	4.52	3 663 512
Reserpine	597 655	2.11	1 467 226

*All figures are estimates for the noninstitutionalized US population. NSAIDs indicates nonsteroidal anti-inflammatory drugs. (From Wilcox et al, 1994)

XVI. EVALUATION AND MANAGEMENT OF ELDERLY PATIENTS WITH HYPERTENSION

In the last two decades, it has become increasingly clear that hypertension in the elderly is a major risk factor for cardiovascular and cerebrovascular morbidity and mortality. Trials conducted in the recent past have demonstrated that not only is the treatment of hypertension in the elderly feasible but also that reduction of blood pressure provides significant protection from stroke and cardiac diseases. It is no longer tenable to ignore the significance of isolated systolic hypertension. Careful treatment of diastolic and/or systolic hypertension provides a great opportunity to avoid the ravages of hypertension in the elderly.

Table 23: Recommendations for Treatment of Hypertension in Elderly Persons

Diastolic blood pressure >100 mm Hg - pharmacologic treatment.
Diastolic blood pressure of 90 to 100 mm Hg - nonpharmacologic therapy. If after 3 to 6 months, diastolic pressure is more than 95 mm Hg - pharmacologic therapy.
Systolic blood pressure of more than 160 mm Hg and diastolic pressure of less than 90 mm Hg - physician discretion.
Alternative first-step and second-step drugs should be based on individual characteristics of patients.

*Blood pressures are based on an average of three measures at three visits.

Whereas the clinical trials have demonstrated the value of treating hypertension in the aging population, we should be aware that the participants in the trials were basically healthy and mobile with no significant concurrent medical problems. Can we then extrapolate the results to the sick elderly patients who may have diabetes, arthritis, or lung disease? Will the frail, elderly hypertensive patient tolerate the treatment? Are there any gains in lowering the blood pressure of the elderly patient with too many co-existing medical conditions? Herein lies the call for clinical judgement. Physicians should carefully evaluate and individualize the therapeutic goals in such situations.

The following evaluation should be considered in management of hypertension in the elderly.

1: Assessment of cardiovascular risk factors
2: Review of the past and concurrent disease states
3: Target organ function
4: Careful examination of the cardiovascular system
5: ? Secondary forms of hypertensive such as renal artery stenosis

Upon deciding to treat hypertension, a therapeutic goal should be established — systolic blood pressure close to 140 mm Hg and diastolic blood pressure close to 90 mm Hg. If the non-pharmacological therapy is not enough, appropriate drug(s) in low doses should be chosen and titrated gradually taking into account the following considerations.

1: Cost
2: Drug interactions
3: Orthostatic hypotension
4: ? Adverse effects (quality of life)
5: Psycho-social factors
6: Patient education and adherence to therapy

Table 24: COST DIFFERENCES WITHIN AND BETWEEN CLASSES OF ANTIHYPERTENSIVE DRUGS

	Median Price		Absolute Price	
	Lowest	Highest	Lowest	Highest
Diuretics	5.10	36.84	2.59	40.37
β-Blockers	9.71	50.26	5.11	52.29
α-1 Blockers	18.92	40.28	11.67	42.49
Peripheral adrenergic inhibitors	5.85	49.60	3.96	53.31
α-2 Agonists	9.20	52.80	6.07	59.99
Direct vasodilators	10.49	20.00	6.37	21.71
ACE inhibitors	24.57	65.70	20.21	79.93
Calcium channel blockers	22.29	59.92	10.02	67.88

Prices in $ for one month's supply. (From Reif and Carter, 1994)

Table 25: Approximate Cost of Medication for 1 Year	
	Cost, $
Initial therapy	
Diuretic	
(appropriate in a large majority of patients)	50-150
Angiotensin-converting enzyme inhibitor	350-600
Difference in cost per patient*	300-450
Difference in cost per 5 million patients	1.5-2.25 billion
Therapy in nonresponsive patients	
Diuretic + ß-blocker	100-300
Angiotensin-converting enzyme inhibitor + calcium antagonist	800-1300
Difference in cost per patient	700-1000
Difference in cost per 5 million patients	3.5-5 billion

*Some calcium antagonists are more expensive than angiotensin-converting enzyme inhibitors, difference in cost is greater. (From Moser M. Arch Intern Med 1994;154, p. 1670).

In prescribing what might be indefinite drug therapy, physicians should consider financial implications (Tables 24 and 25) and make the right therapeutic choices (Reif and Carter, 1994; Kaplan, 1994). With the application of the above guidelines and periodic assessment and appraisal of therapeutic management, hypertension in the elderly can be successfully treated. It is the standard of total care rendered by the health care professionals that will determine if the elderly feel lucky (or unlucky) to be alive.

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