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Blood Pressure and Aging

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KEYPOINTS

- Isolated systolic hypertension is the predominant type of hypertension in the elderly and is associated with an increased cardiovascular risk. Isolated systolic hypertension is characterized by an increase in pulse pressure.
- Increased pulse pressure is a late manifestation of increased arterial stiffness, which is generally recognized as an important factor underlying cardiovascular complications in the elderly.
- Placebo-controlled intervention trials have clearly shown that pharmacological treatment of isolated systolic hypertension improves outcome in the elderly.

SUMMARY

Isolated systolic hypertension is the predominant type of hypertension in the elderly and is associated with cardiovascular complications such as stroke, coronary heart disease, and heart failure. In this chapter, the role of arterial stiffness, endothelial function, atherosclerosis, and oxidative stress in the pathogenesis of isolated systolic hypertension is extensively discussed. Placebo-controlled intervention trials such as the Systolic Hypertension in Europe Trial and the Systolic Hypertension in the Elderly Program have clearly shown that pharmacological treatment of isolated systolic hypertension improves outcome in the elderly. Nevertheless, isolated systolic hypertension remains the major subtype of untreated and uncontrolled hypertension.

I. INTRODUCTION

Hypertension refers to a lasting elevation of blood pressure with heterogeneous genetic and environmental causation. The increasing prevalence of hypertension with aging has been noted in numerous epidemiological studies. The process of vascular aging is characterized by a wider pulse pressure. In cross-sectional and longitudinal population studies, systolic blood pressure increase with age until the eighth decade of life (Fig. 44.1) (1). In contrast, diastolic blood pressure rises only until 50 years of age, after which it either becomes constant or even decreases slightly. Isolated systolic hypertension in older patients is a separate disease entity due to stiffening of the large arteries with advancing age. This chapter gives an overview of the epidemiological and pathophysiolocal consequences of the blood pressure–age relationship and the clinical consequences in the elderly.

II. EPIDEMIOLOGY

In the Framingham Heart Study, diastolic pressure was the strongest predictor below age 50, all three blood pressure indexes were comparable predictors at age 50–59, and from 60 years on, diastolic pressure was negatively related to risk of coronary events, so that pulse pressure became superior to systolic pressure (2). The predictive role of pulse pressure in the elderly is consistent in men and women, in treated and untreated hypertensive subjects (3), and in patients with a history of myocardial infarction (4) or renal failure (5). Furthermore, in older patients with isolated systolic hypertension, pulse pressure (6), and especially ambulatory pulse pressure (7), are a stronger predictor of cardiovascular risk than mean pressure.

According to guidelines proposed by the ESH/ESC, hypertension is defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or taking antihypertensive drug treatment. The prevalence of hypertension is ~25% in the general adult population and increases to 60–70% in the age group >60 years (1). In the general US population, studied in the National Health and Nutrition Examination Survey III (NHANES III), men had a higher prevalence of hypertension than women up to 59 years, whereas the reverse was true from 60 years on (1).

In a random Belgian population sample of 2241 men and 2362 women with a median age (IQR) of 41 (29–56), systolic blood pressure averaged 119 mmHg in subjects below the age of 41 and 131 mmHg in subjects above the age of 41 (8). The corresponding mean values for diastolic blood pressure were 71 and 78 mmHg. The distribution of blood pressure according to the WHO criteria in the Belgian population is given in Table 44.1. The prevalence of hypertension in the Belgian population was 25.6% of whom, 52.5% was treated. Blood pressure

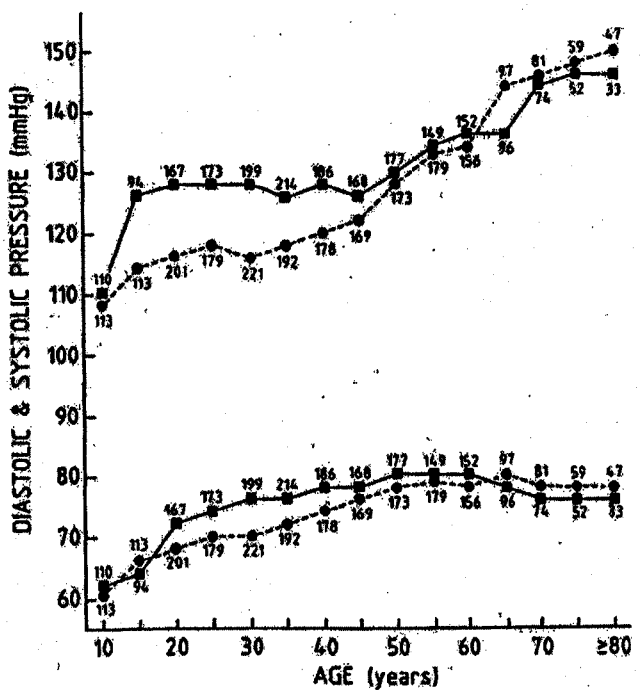

Figure 44.1 Systolic and diastolic blood pressure in 5 year age classes in a representative sample ($n = 4202$) of the population of five Belgian districts. ● represents women; ■ represents men. [From Burt et al. (1).]

Table 44.1 Classification of Blood Pressure Levels (mmHg) Based on Conventional Blood Pressure Measurement in Adults Aged 10 and Older in a Random Population Sample by Median Age

	Age ≤42 ($n = 2241$)	Age >42 ($n = 2362$)
Normotension		
Optimal (SBP <120 and DBP <80)	1573 (49.8%)	591 (19.5%)
Normal (SBP <130 and DBP <85)	828 (26.2%)	600 (19.8%)
High-normal (SBP 130–139 or DBP 85–89)	425 (13.5%)	478 (15.8%)
Hypertension		
Controlled on medication	59 (1.9%)	356 (11.8%)
Fase 1 (SBP 140–159 or DBP 90–99)	245 (7.8%)	739 (24.4%)
Fase 2 (SBP 160–179 or DBP 100–109)	20 (0.6%)	195 (6.4%)
Fase 3 (SBP ≥180 or DBP ≥110)	8 (0.3%)	66 (2.2%)

was well controlled in half of the treated subjects (8). Above the age of 41, only 20% of the subjects had an optimal blood pressure (systolic pressure <120 mmHg and diastolic pressure <80 mmHg).

Isolated systolic hypertension, defined as a systolic blood pressure ≥140 mmHg and a diastolic blood pressure <90 mmHg, is the predominant type of hypertension in the elderly. The NHANES III data demonstrated that below the age of 50, isolated diastolic hypertension (SBP <140 mmHg and DBP ≥90 mmHg) was most common (46.9%) among untreated hypertensives, whereas combined systolic/diastolic hypertension (SBP ≥140 mmHg and DBP ≥90 mmHg) was most common (45.1%) among inadequately treated individuals. In both untreated and inadequately treated groups, isolated systolic hypertension became the primary hypertensive subtype for subjects after the age of 50.

Few studies provide information on the incidence of hypertension in the general population. In the Framingham Heart Study, 5.3% of participants with optimal blood pressure, 17.6% with normal, and 37.3% with high-normal blood pressure below the age of 65 developed hypertension over a period of 4 years (9).

III. PATHOPHYSIOLOGY

Pulse pressure, the difference between systolic and diastolic blood pressure, is determined by the compliance of the arterial vascular bed and the stroke volume, and to a lesser extent by the ejection rate of the left ventricle. Mean arterial pressure, a weighted average of systolic and diastolic blood pressure, is dependent on cardiac output and total peripheral resistance.

A. Arterial Stiffness as Determinant of Systolic Hypertension

Arterial stiffness is emerging as the most important determinant of primary isolated hypertension in our aging community. Arterial distensibility and pulse wave velocity reflect the elasticity of an artery. Aortic pulse wave velocity doubles while distensibility coefficients halve between 20 and 70 years of age [Fig. 44.2(A) and (B)]. The arterial pressure wave consists of a forward component generated by the heart and reflected waves returning to heart form peripheral sites (5). In healthy young adults, the reflected waves coincide with diastole, raise diastolic pressure, and boost coronary perfusion. With arterial stiffening, the reflected waves move faster, reach the proximal aorta during systole, and cause an augmentation of late systolic pressure, whereas diastolic pressure decreases. The early return of the reflected pulse wave to the aorta during systole is the primary mechanism accounting for the rise in systolic blood pressure and the decline in diastolic blood pressure that occurs with arterial stiffening. Lowered diastolic pressure may impair coronary blood flow and predispose to myocardial ischemia. The higher systolic pressure augments cardiac work and may lead to heart failure (5). Histopathologic examination of the aorta of the elderly reveals thickening of the media because of the accumulation of collagenous fibers as well as calcium deposition (10). A functional component may be superimposed on these structural changes. Indeed, the vasoconstrictor tone in the large arteries may well rise with age, when the number of β_2-adrenoreceptors that mediate vasodilatation decreases (11).

B. Endothelial Function and Arterial Stiffness

Endothelial function estimated as flow-mediated vasodilatation apparently starts to deteriorate at about 50 years [Fig. 44.2 (C)], that is, when pulse pressure begins to rise. Endothelial function is more per formant in premenopausal women than in men. This observation suggests that estrogens might enhance endothelial function [Fig. 44.2 (C)]. Indeed, estrogens activate endothelium-dependent vascular relaxation mechanisms, including the nitric oxide-cGMP and prostacyclin-cAMP pathways (12).

The endothelium generates a variety of biological mediators which influence the tone and structure of the blood vessel and determine the susceptibility of the vessel wall to atherogenesis. One of these mediators is nitric oxide, which is synthesized from the amino acid L-arginine via the action of the enzyme nitric oxide synthase.

Endothelin-1 is an important vasoconstrictor released by the endothelium and may also increase arterial stiffness. Indeed, plasma endothelin-1 concentration, shows a significant positive correlation with aortic stiffness in patients with coronary artery disease (13). This observation illustrates that endothelial function affects the function of large arteries. Thus large arteries are more than simply passive conduits.

C. Atherosclerosis in Hypertension

Many of the histological alterations that occur in the vessel wall with aging resemble those that come with atherosclerosis. Figure 44.2 (D) shows the increase in carotid intima media thickness, a sign of early atherosclerosis associated with advancing age. Nevertheless, the role of atherosclerosis in the pathogenesis of isolated systolic hypertension remains debatable. In autopsy specimens of human aorta, compliance decreases with age, but the relative contributions of aging and atherosclerosis remain unknown (14). Moreover, clinical experience shows that many patients with severe generalized atherosclerosis

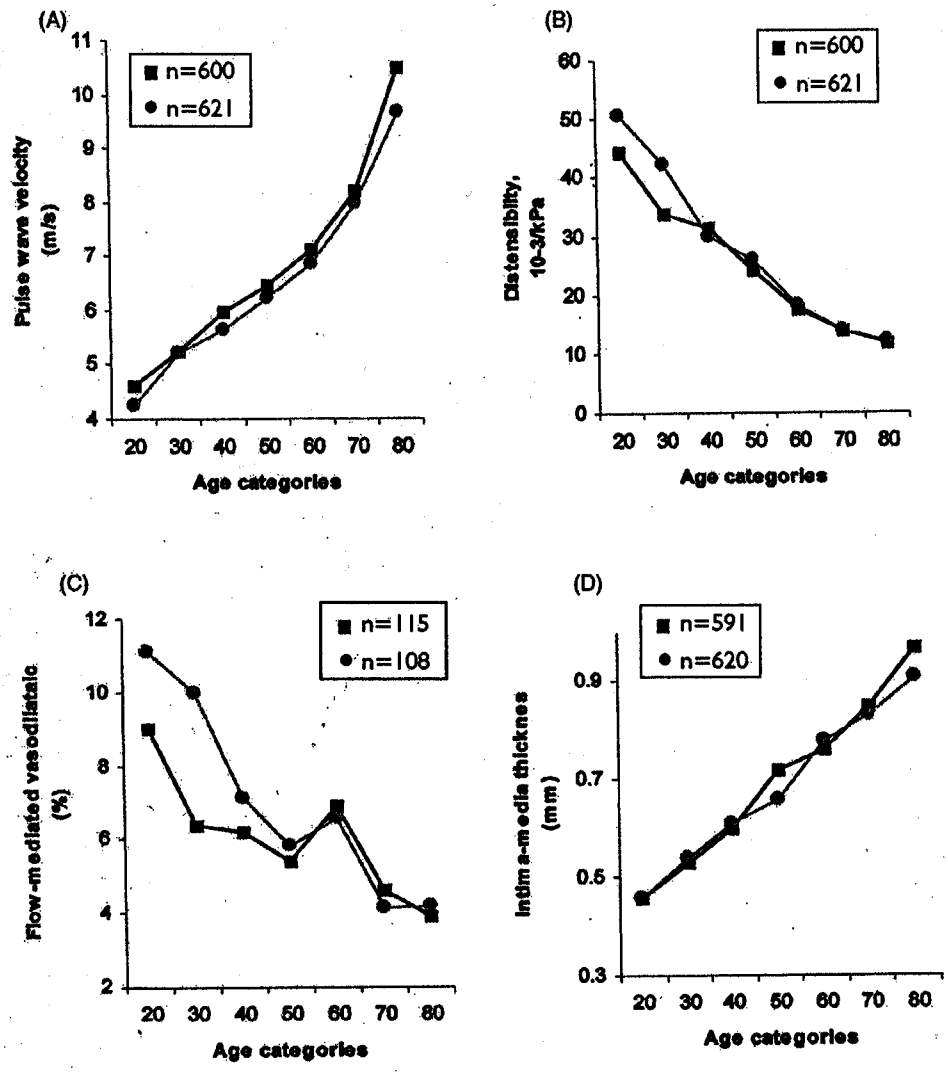

Figure 44.2 Wall characteristics by gender and age in a sample of the general population. ■ represents men and ● represents women. (A) Pulse wave velocity; (B) carotid artery distensibility; (C) endothelial function; (D) Intima-media thickness of the carotid artery. Data are mean for each age group.

maintain a normal central complaince. In contrast, in some populations with a low prevalence of atherosclerosis, systolic pressure does rise with age and isolated systolic hypertension is observed (15).

D. Hypertension Cause or Effect of Arterial Stiffness?

Whether the acceleration of the aging process occurs through an increase in arterial stiffness or through hypertension-associated changes in large artery structure has been debated. Liao et al. (16) evaluated the prospective relation between the baseline arterial elasticity and the development of hypertension in a population sample. After 6 years of follow-up, one standard deviation decrease in arterial elasticity was associated with a 15% greater risk of hypertension, independent of established risk factors for hypertension, and the level of baseline blood pressure. These results suggest that lower arterial elasticity is causally related to the development of systolic hypertension.

E. Chronological and Biological Aging in Arterial Hemodynamics

The age-related changes in cardiac function, circulatory hemodynamics, lipid metabolism, and detoxification of reactive oxygen species all contribute to morbidity and mortality in the elderly. Although age is an outstanding risk factor for high blood pressure, stroke, and coronary

artery disease, the precise pathophysiological mechanisms underlying these observations are presently unknown.

Telomeres are long stretches of characteristic DNA repeat sequences and associated proteins at the ends of chromosomes. These structures are essential to the life of the cell—they cap the ends of the chromosomes and therefore protect them from degradation and fusion. Recent experimental data support the concept that telomere length might serve as a biological clock not only at the cellular level but also probably at the systemic level (17,18). Telomerase is an enzyme that compensates for telomere shortening during DNA replication by adding telomere repeat sequences to the 5′ ends of the DNA strands. Its expression decreases with aging. Consequently, telomeres shorten each time DNA in a somatic cell replicates. The progressive loss of telomere length during life might contribute to cellular aging.

Evidence in support of this hypothesis comes from several observations:

- telomeres are shorter in somatic than in germline cells (17);
- fibroblasts from children suffering from progeria (a congenital disease characterized by accelerated aging) have shorter telomeres (18);
- telomere length in white blood cells decreases with age at a faster rate in men than women (19).

Of interest is the fact that homocysteine, a known risk factor for atherosclerosis (20), enhances the rate of telomere attrition per replicative cycle in cultured human vascular endothelial cells (21). To a large extent, this effect appears to be mediated by reactive oxygen species. Recently, it was shown that both pulse pressure and pulse wave velocity are inversely correlated with telomere length independent of chronological age (22). These observations suggest that pulse pressure and pulse wave velocity might be markers of the biological age of the vascular system.

F. Established Cardiovascular Risk Factors and Arterial Stiffness

Obesity is associated with decreased aortic elasticity. The rise in blood pressure following gain in body-weight is associated with profound changes in cardiovascular–renal physiology, including increased plasma volume, enhanced tubular sodium reabsorption, an initial decrease in total peripheral resistance, increased heart rate, activation of the sympathetic nervous system, and activation of the systemic renin–angiotensin–aldosterone axis (23). Adipose tissue secretes the hormone leptin, which increases sympathetic activity (23).

Adults with familial hypercholesterolemia have a significantly lower aortic distensibility than control subjects (24). The changes in vessel wall properties due to hypercholesterolemia may due to (1) impaired responses to endothelial relaxing factors (such as nitric oxide); (2) an increased content of collagen and calcium subsequent to deposition of cholesterol in the vessel wall; (3) a toxic effect of oxidized lipoproteins on the endothelium (25).

Even in the young, cigarette smoking increases arterial stiffness (26), aortic blood pressure (26), and plasma von Willebrand factor (a marker of endothelial damage) (27). More than 3800 chemicals present in tobacco smoke cause oxidative stress either directly or via biotransformation of these compounds. Smoking acutely increases sympathetic tone (28). Furthermore, smoking decreases nitric oxide production, the primary vasodilator produced by endothelial cells (26).

Diabetes is associated with increase arterial stiffness and decreased endothelial function (29). Glycation of proteins due to alterations in cellular metabolism remain a reasonable pathophysiological link between the hyperglycemia and the development of complication in diabetes. These chemically modified proteins may interact with cells in the vascular wall, inducing expression of cytokines and growth factors, which cause cross-linking of collagen molecules to each other (30), leading to an enhanced loss of collagen elasticity with a subsequent reduction in arterial distensibility.

Homocysteine a sulfur containing amino acid, which is formed in the metabolism of methionine to cysteine, behaves as an independent risk factor for cardiovascular disease. The two most important determinants of the plasma homocysteine concentration are folate status and renal function. From *in vitro* and animal models, there is evidence that high homocysteine concentrations are associated with endothelial toxicity attributed to oxidative stress that results from auto-oxidation of homocysteine (31). During this process, hydrogen peroxide and superoxide are formed that may increase low-density lipoprotein oxidation, and decrease the biovailability of nitric oxide (31). The decrease in nitric oxide leads to vasoconstriction. In hypertensive patients, plasma homocysteine is positively correlated with aortic stiffness as assessed by carotid–femoral pulse wave velocity, independent of sex, age, blood pressure, and renal function (32). However, homocysteine lowering therapy had no beneficial effect on carotid distensibility in patients with end-stage renal disease (33), nor in healthy siblings of patients with premature atherosclerosis (34).

G. Risk Factors Tracking During Aging

Traditionally, research on aging deals with processes that begin late in life, but many of these processes may have origins at young age. Hypertension, hypercholesterolaemia, and overweight are usually well tolerated at

younger age and are therefore barely perceived as harmful, but over time they may track and lead to excess morbidity and mortality from cardiovascular causes in middle-aged people (35–37). Findings from the Bogalusa Heart Study in the USA demonstrated that childhood blood pressure levels at or above the 80th percentile, not necessarily in hypertensive ranges, were associated with an increased prevalence of elevated blood pressure during adulthood (36). A follow-up study (35), showed that blood pressure in a group of male students at the age of 20.5, was associated with the incidence of cardiovascular diseases in the following 41.3 years. These findings suggest that elevated blood pressure during youth may have later clinical significance. Moreover, epidemiological studies have shown that cardiovascular risk factors tend to cluster within young persons (38) and that clustering of cardiovascular risk factors increases the risk of coronary heart disease. From the public health point of view, prevention is better than cure. Among 17-year-old Flemish adolescents, we recently found that 4.5% had hypertension, 9.0% were overweight (body mass index >25 kg/m^2), and 13.5% had a serum cholesterol concentration of 200 mg/dL or higher (38). Girls on oral contraceptive pills had a 4.6 mmHg higher blood pressure and an increase of 4.27 in the odds of not having an optimal blood pressure (systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg) (39). If smoking and excessive alcohol intake were considered, 41.0% of the youngsters had one cardiovascular risk factor and 8% combined two or more risk factors. Prevention should therefore start at a young age. In Belgium, school attendance is compulsory until 18 years. Trained physicians examine the students at regular intervals. Unfortunately, the physical examination does not include blood sampling for the measurement of cholesterol and new directives are being implemented which place less emphasis on physical health.

IV. OUTCOME TRIALS

A. Placebo-Controlled Trials

The ultimate goal of treating patients with hypertension is not only to reduce blood pressure, but also to prevent the cardiovascular and renal complications of an elevated blood pressure, so that survival is prolonged and the quality of life is improved. Since 1991, three outcome trials have been published, which addressed the question whether in the elderly the cardiovascular risk conferred by hypertension is reversible by antihypertensive drug treatment. In all trials and subgroups combined (40), among 7757 control patients, 734 deaths and 835 major cardiovascular complications occurred; in 7936 patients allocated active treatment, these numbers were 656 and 647, respectively. Median follow-up amounted 3.8 years. Overall, active treatment reduced total mortality by 13%, cardiovascular mortality by 18%, all cardiovascular complications by 26%, stroke by 30%, and coronary events by 23% (40).

In the Systolic Hypertension in Europe (Syst-Eur) trial, patients (≥60 years) with isolated systolic hypertension were randomized to active treatment ($n = 2398$), that is, nitrendipine, with the possible addition of enalapril and hydrochlorothiazide, or to matching placebos ($n = 2297$) (41). The between-group difference in blood pressure amounted to 10.1/4.5 mmHg ($P < 0.001$). Active treatment reduced the incidence of fatal and nonfatal stroke by 42% and that of major cardiovascular complications by 30%. Cardiovascular mortality tended to be lower on active treatment (−26%, $P = 0.08$), but all-cause mortality was not significantly influenced (−13%, $P = 0.28$) (41,42). Furthermore, active treatment reduced the incidence of mild renal dysfunction (serum creatinine ≥176.8 μmol/L) by 64% (13 vs. 5 cases, $P = 0.04$) (43). The relative benefits of active treatment were evenly distributed across the two sexes and across patients with and without a history of cardiovascular complications (44). Further analysis also suggested similar benefit in patients who remained on nitrendipine monotherapy (45).

At randomization into the Syst-Eur trial, 492 patients (10.5%) had diabetes mellitus. In these patients, with adjustments for possible confounders, active treatment reduced all-cause mortality by 55%, cardiovascular mortality by 76%, all cardiovascular endpoints by 69%, fatal and nonfatal strokes by 73%, and all cardiac endpoints by 63%. The reductions in total mortality ($P = 0.04$), cardiovascular mortality ($P = 0.02$), and all cardiovascular endpoints ($P = 0.01$) were significantly larger in diabetic than in nondiabetic patients (Fig. 44.3) (46). Furthermore, active treatment reduced the risk of proteinuria more ($P = 0.04$) in diabetic than in nondiabetic patients (71 vs. 20%).

The Syst-Eur Vascular Dementia Substudy (47) investigated whether antihypertensive treatment could reduce the incidence of dementia. In total, 2418 patients were enrolled. After a median follow-up of 2 years in the double-blind trial, active treatment reduced the incidence of dementia by 50% ($P = 0.05$) from 7.7 to 3.8 cases per 1000 patient years (11 vs. 21 patients). Active treatment prevented mainly Alzheimer's dementia (8 vs. 15 cases). These results were confirmed in the open-label follow-up study (48). During extended follow-up, the number of incident cases of dementia increased from 32 to 64. Long-term active treatment ($n = 1485$), compared with control ($n = 1417$), reduced the incidence of dementia by 55% from 7.4 to 3.3 cases per 1000 patient-years (43 vs. 2 patients) (48). Several reports suggest that calcium channel blockers, which cross the blood–brain barrier

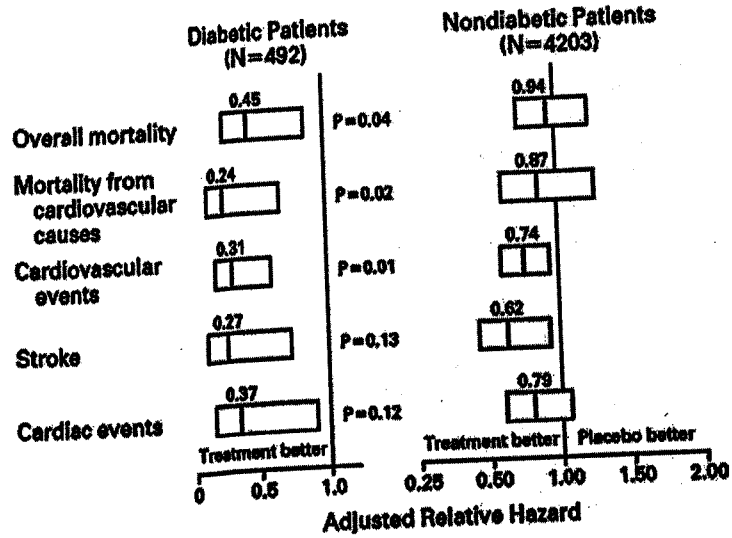

Figure 44.3 Adjusted relative hazard rates associated with active treatment as compared with placebo in diabetic and nondiabetic patients participating in the Syst-Eur trial. The relative hazard rates were adjusted for sex, age, previous cardiovascular complications, systolic blood pressure at enrolment, smoking status, and residence in eastern or western Europe. The *P*-values are for the interaction between treatment and diabetes and indicate whether the treatment effect was significantly associated with the presence or absence of diabetes at enrolment. Cardiovascular events, stroke, and cardiac events included fatal and nonfatal events. The bars indicate the 95% confidence intervals. The numbers above the bars indicate the benefit of the active treatment when compared with placebo. [From Tuomilehto et al. (46).]

and bind to brain receptors located in areas affected by Alzheimer's disease, may confer specific neuroprotection (49). However, the concept that antihypertensive therapy with long-acting dihydropyridines might protect against dementia needs further testing in controlled clinical trials.

The double-blind Syst-Eur trial ($P = 0.009$) (44) showed an interaction between treatment allocation and age. Randomization to active treatment was associated with a decreased relative risk of death in subjects aged 60–69 (59%) and 70–79 (58%), but with a slightly increased risk of death in patients aged ≥80 (11%). Similarly, a meta-analysis of the results of controlled trials in hypertensive patients over the age of 80 showed a nonsignificant of 6% excess death from all causes (50). In view of the remaining uncertainty, the Hypertension in the Very Elderly Trial (HYVET) is currently investigating the potential benefit of antihypertensive drug treatment on stroke and other cardiovascular endpoints in the very elderly (51). This trial will include a subgroup of patients with isolated systolic hypertension.

B. Guidelines for Antihypertensive Drug Therapy

Most experts recommend an integrated approach of risk management to prevent the complications of raised blood pressure. Accordingly, the need to start treatment increases in the presence of other cardiovascular risk factors or when absolute risk reaches a specified threshold (e.g., in the British population, a 10 year risk of coronary heart disease ≥15%).

On the basis of evidence from trials, most but not all guidelines suggest that low-dose thiazides might be the most cost-effective way to start pharmacological treatment in most patients. However, for each class of antihypertensive drugs, compelling indications or contraindications exist. For instance, β-blockers or calcium channel blockers can be used in patients with angina pectoris. Stable heart failure is an indication for thiazides, aldosterone receptor blockers, β-blockers, or ACE inhibitors, but not for angiotensin receptor blockers (52). A history of myocardial infarction favors the use of β-blockers or ACE inhibitors. Renal impairment, microalbuminuria, or proteinuria is an indication for ACE inhibitors and/or angiotensin receptor blockers. Systolic hypertension warrants the use of thiazides or long-acting dihydropyridines. In black people, hypertension responds better to thiazides or calcium channel blockers than to inhibitors of the renin system, in terms of both blood pressure reduction and prevention of complications. In the absence of renal impairment at the initiation of antihypertensive treatment, all major drug classes equally prevent end-stage renal disease (52).

V. CONCLUSIONS

Since age and blood pressure are continuous variables with no discernible transition points where there is a sudden increase in morbidity and mortality, arbitrary definitions

must be used for classification. Unlike diastolic blood pressure, systolic blood pressure increases progressively with age. The characteristic changes of systolic and diastolic blood pressure with age lead to an increase in pulse pressure, which has emerged as a new and potentially independent risk factor reflecting the biological aging of the vascular system. Arterial stiffness increasingly recognized as an important factor underlying cardiovascular complications in the elderly.

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HYPERTENSION

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