Prevalence, pathophysiology and treatment of isolated systolic hypertension in the elderly

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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 review, 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.

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Prevalence

Isolated systolic hypertension affects between 10 and 20% of the elderly. In cross-sectional and longitudinal population studies, systolic blood pressure increases with age, while diastolic blood pressure rises until 50 years of age and then levels off or even slightly decreases [1–3]. This explains why the prevalence of isolated systolic hypertension – defined as a systolic blood pressure of 140 mmHg or higher and a diastolic blood pressure below 90 mmHg – rises with age and becomes the predominant type of hypertension in both treated and untreated elderly subjects (~60%) [4–6].

Estimates of the prevalence of isolated systolic hypertension are influenced not only by age distribution, but also by gender and race. The prevalence of isolated systolic hypertension is reported to be higher in women and in black subjects than in men and Caucasians [7,8].

Risk

With increasing age, there is a shift from diastolic pressure to systolic pressure and pulse pressure as the predominant predictor of cardiovascular risk. The predominance of systolic over diastolic blood pressure as a cardiovascular risk factor in the elderly is not

due to the larger range of systolic compared with diastolic pressure, since the observation still holds when systolic and diastolic blood pressures are expressed on a similar scale in units of standard deviation.

In the Framingham Heart Study, diastolic pressure was the strongest predictor of cardiovascular risk below the age of 50 years, all three blood pressure indexes were comparable predictors at age 50 to 59, and from 60 years on, the correlation between blood pressure and the risk of coronary events was positive for systolic pressure and negative for diastolic pressure, so that pulse pressure became the most important risk factor [9]. The predictive role of pulse pressure in the elderly is consistent in men and women, in treated and untreated hypertensive subjects [10], and in patients with a history of myocardial infarction [11] or renal failure [12]. Furthermore, in older patients with isolated systolic hypertension, pulse pressure [13] and especially ambulatory pulse pressure [14], is a stronger predictor of cardiovascular risk than mean pressure.

In eight studies, 15,693 patients with isolated systolic hypertension were followed up for 3.8 years (median). After correction for regression dilution bias, sex, age and diastolic blood pressure, the relative hazard rates associated

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with a 10 mmHg higher initial systolic blood pressure were 1.26 ($p < 0.001$) for total mortality, 1.22 ($p = 0.02$) for stroke, but only 1.07 ($p = 0.37$) for coronary events. Independent of systolic blood pressure, diastolic blood pressure was inversely correlated with total mortality, again highlighting the role of pulse pressure as a risk factor [15].

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 pressures, is dependent on cardiac output and total peripheral resistance. Isolated systolic hypertension, by definition, is characterized by an increase in pulse pressure, but not necessarily by an increase in mean arterial pressure.

Arterial stiffness as a determinant of systolic hypertension

Arterial stiffness is emerging as the most important determinant of primary isolated hypertension in the aging community. Arterial distensibility and pulse-wave velocity reflect the elasticity of an artery. Aortic pulse-wave velocity doubles, while distensibility coefficients halve between the ages of 20 and 70 years (FIGURE 1A & B). The arterial pressure wave consists of a forward component generated by the heart and reflected waves returning to the heart from peripheral sites [12]. 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 pressures, 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 the person to myocardial ischemia. Higher systolic pressure augments cardiac work and may lead to heart failure [12]. Histopathologic examination of the aorta of the elderly reveals thickening of the media due to the accumulation of collagenous fibers, as well as calcium deposition [16]. 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 [17].

Endothelial function & arterial stiffness

Endothelial function, estimated as flow-mediated vasodilatation, apparently starts to deteriorate at approximately 50 years of age (FIGURE 1C), when pulse pressure begins to rise. Endothelial function is more performant in premenopausal women than in men. This observation suggests that estrogens might enhance endothelial function (FIGURE 1C). Indeed, estrogens activate endothelium-dependent vascular relaxation mechanisms, including the nitric oxide–cyclic guanosine monophosphate (cGMP) and prostacyclin–cyclic adenosine monophosphate (cAMP) pathways [18].

The endothelium generates a variety of biological mediators that 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 [19]. This observation illustrates that endothelial function affects the function of large arteries. Thus, large arteries are more than simply passive conduits.

Atherosclerosis in isolated systolic hypertension

Many of the histological alterations that occur in the vessel wall with aging resemble those that come with atherosclerosis. The increase in carotid intima-media thickness, a sign of early atherosclerosis associated with advancing age is shown in FIGURE 1D. Nevertheless, the role of atherosclerosis in the pathogenesis of isolated systolic hypertension remains debatable. In autopsy specimens of the human aorta, compliance decreases with age, but the relative contributions of aging and atherosclerosis remain unknown [20]. Moreover, clinical experience shows that many patients with severe generalized atherosclerosis maintain a normal central compliance. In contrast, in some populations with a low prevalence of atherosclerosis, systolic pressure rises with age and isolated systolic hypertension is observed [21].

Hypertension: cause or effect of arterial stiffness?

Whether acceleration of the aging process occurs through an increase in arterial stiffness or through hypertension-associated changes in the large artery structure has been debated. Liao and colleagues evaluated the prospective relationship between baseline arterial elasticity and the development of hypertension in a population sample [22]. After 6 years follow-up, a 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.

Chronological & 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 [23,24].

Due to the fact that in the absence of telomerase (an enzyme that compensates for telomere shortening during DNA replication by adding telomere repeat sequences to the 5' ends of the DNA strands) telomeres shorten each time DNA replication takes place, and aging is assumed to depend on cell division, the progressive loss of telomere length has been proposed to contribute to the process of cellular aging. Evidence in support of this hypothesis comes from several observations:

- Telomeres are shorter in somatic than in germline cells [25]
- Fibroblasts from children suffering from progeria (a genetic disease that accelerates the aging process) have shorter telomeres, which has been found to be consistent with the reduced division potential of these cells observed *in vitro* [26]
- Telomere length in white blood cells decreases with age in both men and women [27]

Of interest is the fact that homocysteine, a known risk factor for atherosclerosis [28], enhances the rate of telomere attrition per replicative cycle in cultured human vascular endothelial cells [29]. 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 independently of chronological age [23]. These observations suggest that pulse pressure and pulse-wave velocity might be markers of the biological age of the vascular system.

Established cardiovascular risk factors & 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 [30]. Adipose tissue secretes the hormone leptin, which increases sympathetic activity [30].

Adults with familial hypercholesterolemia have a significantly lower aortic distensibility than control subjects [31]. The changes in vessel wall properties due to hypercholesterolemia may be due to [32]:

- Impaired responses to endothelial relaxing factors (such as nitric oxide)
- Increased content of collagen and calcium subsequent to deposition of cholesterol in the vessel wall
- Toxic effect of oxidized lipoproteins on the endothelium

Even in the young, cigarette smoking increases arterial stiffness [33], aortic blood pressure [33] and plasma von Willebrand factor (a marker of endothelial damage) [34]. More than 3800 chemicals present in tobacco smoke cause oxidative stress either directly or via biotransformation of these compounds. Smoking acutely increases sympathetic tone [35]. Furthermore, smoking decreases nitric oxide production, the primary vasodilator produced by endothelial cells [33].

Diabetes is associated with increased arterial stiffness and decreased endothelial function [36]. Glycation of proteins due to alterations in cellular metabolism remain a reasonable pathophysiological link between 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 [37], leading to enhanced loss of collagen elasticity with a subsequent reduction in arterial distensibility.

Figure 1. Mean wall characteristics by gender and age in a sample of the general population. (A) Pulse wave velocity; (B) Carotid artery distensibility; (C) Endothelial function; (D) Intima-media thickness of the carotid artery. Squares represent men and circles represent women.

Homocysteine, a sulfur-containing amino acid that 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. There is evidence from *in vitro* and animal models that high homocysteine concentrations are associated with endothelial toxicity attributed to oxidative stress that results from autooxidation of homocysteine [38]. During this process, hydrogen peroxide and superoxide are formed, which may increase low-density lipoprotein oxidation and decrease the bioavailability of nitric oxide [38]. 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 [39]. However, homocysteine-lowering therapy had no beneficial effect on carotid distensibility in patients with end-stage renal disease [40], nor in healthy siblings of patients with premature atherosclerosis [41].

Diagnosis

According to the 2003 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines for the Management of Arterial Hypertension (World Health Organization/International Society of Hypertension) [42], the diagnosis of hypertension should be based on multiple conventional blood pressure measurements, taken on separate occasions. Isolated systolic hypertension is defined as a conventional systolic blood pressure of 140 mmHg or more, with a Phase V diastolic blood pressure below 90 mmHg. However, the ESH/ESC recommend that consideration should be given to performing self-recorded and/or ambulatory blood-pressure monitoring before making therapeutic decisions. A 24 h ambulatory blood pressure of 125/80 mmHg or over, or a self-recorded blood pressure of 135/85 mmHg or over, may be regarded as hypertensive. Devices for self-recorded and ambulatory monitoring should be validated according to international standardized protocols and their accuracy should be checked periodically by comparison against values from a mercury sphygmomanometer [42].

In the clinical setting, the main use of ambulatory blood-pressure monitoring is to identify patients with white-coat hypertension in whom antihypertensive drug treatment may be avoided. White-coat or isolated office hypertension is usually defined as an elevation of the clinic blood pressure in the presence of a normal daytime ambulatory blood pressure. In older patients with isolated systolic hypertension, clinic and daytime ambulatory blood-pressure measurements may differ largely. Event-based studies have clearly demonstrated that the risk of cardiovascular disease is lower in patients with white-coat hypertension than in those with higher ambulatory blood pressure, even after controlling for concomitant risk factors [43]. In the Systolic hypertension in Europe (Syst-Eur) trial, patients with isolated systolic hypertension on conventional measurement (systolic blood pressure ≥ 160 mmHg) were classified

according to their daytime systolic blood pressure in one of three subgroups: nonsustained hypertension (<104 mmHg), mild sustained hypertension (140–159 mmHg), and moderate sustained hypertension (≥ 160 mmHg). Patients with nonsustained hypertension had smaller electrocardiogram voltages and a lower incidence of stroke and cardiovascular complications than patients with moderate sustained hypertension [44].

The diagnosis of isolated systolic hypertension should always comprise an evaluation of the overall cardiovascular risk by searching for other risk factors, target organ damage and concomitant diseases. In the absence of other cardiovascular risk factors, therapy of patients with white-coat hypertension may be limited to lifestyle measures and annual follow-up.

Treatment

Once the diagnosis of isolated systolic hypertension is made, the physician may consider starting pharmacological treatment. The ESH/ESC recommend an integrated approach to risk management in order to prevent the complications of hypertension. Accordingly, the necessity to initiate antihypertensive therapy increases in the presence of other cardiovascular risk factors or when absolute risk reaches a specific threshold. The primary goal of treatment should be to achieve the maximum reduction in overall cardiovascular risk, through treatment of all reversible risk factors including smoking, dyslipidemia, diabetes mellitus and high blood pressure itself. The target of antihypertensive treatment should be to lower blood pressure to at least 140/90 mmHg in all hypertensive patients and to below 130 mmHg in diabetic patients. However, care should be taken not to lower diastolic blood pressure too much. In the Systolic Hypertension in the Elderly Programme (SHEP), an on-treatment diastolic blood pressure of less than 60 mmHg was associated with a poorer outcome [45]. More studies are needed to determine how far diastolic blood pressure can be lowered [42].

The discussion of which drug class is better suited to start antihypertensive therapy is largely elusive. In most patients, optimization of treatment at acceptable tolerance requires rotation through and the combination of several drug classes. Diuretics and calcium-channel blockers have been shown to be particularly useful for the treatment of isolated systolic hypertension in the elderly [46,47].

Several studies on the prevalence and control of hypertension have indicated that systolic hypertension is less frequently treated than diastolic hypertension and that overall blood pressure control in treated patients with isolated systolic hypertension is poor [4,48–51]. Among 16,095 adults participating in the third National Health and Nutrition examination survey, 27% had hypertension, defined as a blood pressure of at least 140 mmHg systolic or 90 mmHg diastolic. Only 23% of those with hypertension were taking medications that controlled their blood pressure. The remaining 77% of the hypertensive patients did not take any antihypertensive drugs or their blood pressure was inadequately treated. Most cases of uncontrolled hypertension consisted of isolated,

mild systolic hypertension in older adults [48,51]. Controlling systolic blood pressure seems to be more difficult than controlling diastolic blood pressure. However, in the follow-up study of the Syst-Eur trial, 74% of the 3786 patients with isolated systolic hypertension reached the target blood pressure of 150 mmHg [52]. In view of the evidence from randomized controlled trials that older patients with isolated systolic hypertension benefit from antihypertensive treatment in terms of reduced cardiovascular mortality and morbidity, physicians should be further motivated to base treatment decisions on systolic blood pressure rather than on diastolic blood pressure alone.

Outcome trials

Placebo-controlled trials

The ultimate goal of treating patients with isolated systolic hypertension is not to reduce blood pressure, but to prevent the cardiovascular and renal complications of an elevated systolic blood pressure, so that survival is prolonged and the quality of life is improved. Since 1991, three outcome trials have been published that have addressed the question of whether the cardiovascular risk conferred by isolated systolic hypertension is reversible by antihypertensive drug treatment in the elderly [46,47,53]. Five earlier published trials also included groups of older patients with isolated systolic hypertension [15]. In all trials and subgroups combined, among 7757 control patients, 734 deaths and 835 major cardiovascular complications occurred [15]; in 7936 patients allocated active treatment, these numbers were 656 and 647, respectively. Median follow-up was 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% [15]. Thus, overall, the evidence available today indicates that pharmacological treatment of isolated systolic hypertension in the elderly improves outcome.

In the Syst-Eur trial patients (≥ 60 years) with isolated systolic hypertension were randomized to active treatment ($n = 2398$), in other words, nitrendipine (Pressodipin[®], Genepharm), with the possible addition of enalapril (Innovace[®], Merck Sharpe and Dohme) and hydrochlorothiazide, or to matching placebos ($n = 2297$) [46]. 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% , $p = 0.28$) [46,54]. Furthermore, active treatment reduced the incidence of mild renal dysfunction (serum creatinine $\geq 176.8 \mu\text{mol/l}$) by 64% (13 vs. five cases, $p = 0.04$) [55]. The relative benefits of active treatment were evenly distributed across the two sexes and across patients with and without a history of cardiovascular complications [56]. Further analysis also suggested a similar benefit in patients who remained on nitrendipine monotherapy [57].

At the time of 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 end points by 69%, fatal and nonfatal strokes by 73% and all cardiac end points by 63%. The reductions in total mortality ($p = 0.04$), cardiovascular mortality ($p = 0.02$) and all cardiovascular end points ($p = 0.01$) were significantly larger in diabetic compared with nondiabetic patients [58]. Furthermore, active treatment reduced the risk of proteinuria more in diabetic than in nondiabetic patients (71 vs. 20%; $p = 0.04$).

After the second of two interim analyses, the Syst-Eur trial ended prematurely due to a 42% reduction in stroke, the primary end point. To evaluate the effects of early and delayed antihypertensive therapy on the long-term outcomes of the Syst-Eur patients, the double-blind Syst-Eur trial was extended into an open-label, follow-up study. All patients still available for follow-up after the termination of the placebo-controlled phase received active treatment based on the dihydropyridine nitrendipine for a further 4 years. Median follow-up increased from 2.0 to 6.1 years. During extended follow-up, the rates of stroke and cardiovascular complications in patients formerly randomized to placebo and in patients continuing active treatment were similar to those observed on active treatment during the double-blind trial. Considering total follow-up, early compared with delayed blood pressure lowering treatment, lowered the rates of stroke (28%, $p = 0.01$) and all cardiovascular complications (15%, $p = 0.03$), with a similar trend for total (13%, $p = 0.09$) mortality. Thus, delaying treatment by 2 years in 1000 patients followed for 6 years, caused 17 preventable strokes or 25 avoidable major cardiovascular events [59]. These estimates underscore the necessity of early and adequate treatment of systolic hypertension.

The Syst-Eur Vascular Dementia substudy investigated whether antihypertensive treatment could reduce the incidence of dementia [60]. 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 mainly prevented Alzheimer's dementia (eight vs. 15 cases). These results were confirmed in the open-label follow-up study [61]. During extended follow-up, the number of 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. 21 patients) [61]. Several reports suggest that calcium-channel blockers, which cross the blood-brain barrier and bind to brain receptors located in areas affected by Alzheimer's disease, may confer specific neuroprotection. However, the concept that antihypertensive therapy with long-acting dihydropyridines might protect against dementia needs further testing in controlled clinical trials.

Both the double-blind Syst-Eur trial ($p = 0.009$) [56] and the extended follow-up study ($p = 0.06$) [59] 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 to 69 years (59 and 29% in the double-blind and extended follow-up study, respectively) and 70 to 79 years (58 and 19%), but with a slightly increased risk of death in patients aged 80 years or more (11 and 19%). Similarly, a meta-analysis of the results of controlled trials in hypertensive patients over the age of 80 years, showed a nonsignificant 6% excess of death from all causes [62]. 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 end points in the very elderly [63]. This trial includes a subgroup of patients with isolated systolic hypertension.

All available outcome trials in isolated systolic hypertension recruited patients with a systolic blood pressure of 160 mmHg or more (Grade II and III hypertension). Currently no data are available demonstrating that antihypertensive drug treatment reduces the risk of cardiovascular events in patients with Grade I isolated systolic hypertension (systolic pressure between 140 and 159 mmHg). Since the prevalence of this condition may be estimated to be approximately 20% and as Grade I isolated systolic hypertension is probably associated with an increased cardiovascular risk, an outcome trial in these patients is urgently needed.

Comparative trials

During the last few years, many randomized, controlled outcome trials have compared antihypertensive treatment regimens from older drug classes (diuretics and β -blockers) with newer agents (calcium-channel blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II antagonists and β -blockers). However, none of these trials have specifically examined patients with isolated systolic hypertension. The double-blind Losartan Intervention For End-point reduction trial (LIFE) in patients with left ventricular hypertrophy included a subgroup of 1326 patients with isolated systolic hypertension. In this subgroup the main outcome (composite of cardiovascular death,

stroke and myocardial infarction) tended to be 25% ($p = 0.06$) lower in the losartan (Cozaar[®], Merck Sharp and Dohme) compared with the atenolol group [64]. However, in a meta-analysis of 16 recent outcome trials including 135,842 patients with predominantly combined systolic and diastolic hypertension, old and new drugs provided similar protection against total and cardiovascular mortality and fatal and nonfatal myocardial infarction [65]. Calcium-channel blockers, including (+8%; $p = 0.07$) or excluding verapamil (+10%; $p = 0.02$), as well as angiotensin Type-1 receptor blockers (+24%; $p = 0.0002$) resulted in better stroke prevention than did the old drugs, whereas the opposite trend was observed for ACE inhibitors (-10%; $p = 0.03$). The risk of heart failure was higher ($p < 0.0001$) with calcium-channel blockers (+33%) and β -blockers (+102%) than with conventional therapy involving diuretics. These results should be interpreted with caution. Indeed, more detailed analyses demonstrated that most differences in specific cardiovascular end points were due to design features, gradients in achieved systolic blood pressure, or both [65]. In conclusion, currently there is little evidence for specific drug effects in minimizing cardiovascular events in hypertension. The benefits of antihypertensive therapy largely depend on blood pressure reduction itself.

Expert opinion & five-year view

Currently, intervention studies support the need for antihypertensive treatment of Grade II and III isolated systolic hypertension (systolic pressure ≥ 160 mmHg). However the benefit of antihypertensive treatment in Grade I isolated systolic hypertension (systolic pressure 140–160 mmHg) has yet to be tested in randomized, controlled trials. In addition, further research is needed to determine to what level systolic blood pressure need to be reduced for optimal prevention. These uncertainties should be resolved, since the number of elderly will substantially increase in the next 10 years. Consequently, they will strengthen their influence on the decision-making process in all aspects of life. Older people will increasingly stand up for their rights and strengthen their position as the largest segment of the drug market.

Key issues

- 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 but not necessarily by an increase in mean arterial pressure. Observational studies have shown that in older people, pulse pressure is a better predictor of cardiovascular risk than mean 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, 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. Accordingly, international guidelines agree that older patients with isolated systolic hypertension must be treated.
- Despite these recommendations, isolated systolic hypertension in the elderly constitutes the main subgroup of uncontrolled hypertension.

Pulse pressure is recognized as an important risk factor in the elderly. However, trial data are not yet available to support recommendations to treat pulse pressure by itself.

Further research is needed to answer the question of whether specific drug effects play a role in the prevention of cardiovascular complications over and above their blood pressure-lowering effect.

In the more distant future, a profound integration of genetic, molecular, clinical and epidemiological research may disclose subsets of patients in whom specific combinations of

genetic and environmental factors raise blood pressure and may pave the way to individualized therapy.

Further efforts should be undertaken to obtain better control of systolic blood pressure, which has been shown to be a more important predictor of cardiovascular risk than diastolic blood pressure. In order to obtain better control of systolic blood pressure, physicians should pay greater attention to it as a parameter for diagnosing, treating and intensifying treatment. In addition, new drugs that are more active in reducing systolic blood pressure need to be developed.

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