Cognitive dysfunctions in patients with hypertension — pathogenesis and treatment

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Abstract

Memory disorders are one of the most frequent abnormalities found in the elderly. The dominant cause of the disorder is dementia of Alzheimer's type (about 60%), vascular dementia is responsible for 15–20% of cases, and the rest are mixed forms. One of the basic symptoms is a weakening of the ability to remember. With time, dementia becomes more severe and the cognitive and mental disorders are accompanied by progressive somatic infirmity, leading in the final stage to bed immobilization and total dependence on the care of other people. Treatment of vascular dementia comes down to counteracting stroke risk factors and treating hypertension, as well as diabetes and other cardiovascular diseases. It has been clearly demonstrated that hypotensive drugs can reduce the risk of dementia. When choosing therapy for elderly patients, we should also bear in mind the effects on blood pressure and blood pressure variability, as these have been shown to be associated with a higher risk of dementia. The guidelines indicate the benefit of using a combination of a thiazide-like diuretic (indapamide) and a calcium antagonist (amlodipine) in elderly. Combination treatment with a converting enzyme inhibitor (perindopril) and a thiazide-like diuretic (indapamide) is also particularly beneficial in this age group.

Key words: hypertension; dementia; treatment

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Introduction

Societies throughout the world are aging rapidly. Current demographic projections predict an increase in life expectancy and a significant increase in the elderly population. In economically developed countries about 14–15% of the population and in developing countries about 5% are already over 65 years of age [1, 2]. Similarly, the Polish population is aging very rapidly. The group of people over 80 is growing the fastest. The number of people aged over 80 will double to over 3.5 million by 2050 and will account for 10.4% of the country's population, compared to 3.9% in 2013 [3]. In the general population, cardiovascular mortality in Poland in 2013 was about 46%, in people over 65 years of age 53%, and in those over 80 years of age more than 80% [4]. Hypertension is one of the most important risk factors for cardiovascular diseases: coronary heart disease, heart failure, and stroke [5]. Hypotensive treatment in very elderly patients significantly reduces the frequency of cardiovascular incidents and total mortality [6–8]. According to the WOBASZ II study, 43% of the Polish population aged 19–99 years suffers from hypertension, more often men than women (43.7% *vs.* 40.4%) [9, 10]. Over 3 mil-

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lion of the population (more than 40% of adult Poles with hypertension) are unaware of their disease [9]. The prevalence of hypertension and dementia increases with age [10, 11]. It is estimated that over 50 million people in the world already suffer from it, and by 2050 this number will triple. In Poland dementia affects approximately 12% of the population [12]. A significant percentage of people also suffer from mild cognitive impairment (MCI).

There are various causes of cognitive decline, which is documented in a rich scientific literature, listing among others, depression, diabetes, deficiency syndromes (vitamin B12, folic acid, iron), thyroid disease (especially hypothyroidism), heart failure, stroke, chronic obstructive pulmonary disease, cancer, and finally Alzheimer's disease (AD) or Parkinson's disease (PD) [13]. A team set up by the journal "Lancet" to prepare a report on dementia identified the 12 most significant risk factors for its development. Among low levels of education, hearing loss, brain injury, alcohol abuse > 21 drinks per week, obesity, smoking, depression, social isolation, physical inactivity, diabetes, environmental pollution — hypertension takes the top position.

The experts of the study stressed that hypotensive drugs are the only known and effective drugs to prevent dementia [14]. Age is of course a major factor in the development of dementia; however, it is currently estimated that within four years of diagnosis, mild cognitive impairment in about half of patients will progress to Alzheimer-type dementia [15, 16]. The annual rate of conversion of MCI to AD is most commonly reported to range from 6% to 14% [17]. This applies mainly to the most common form of MCI — amnestic, in which the deficit is mainly in memory, initially episodic, i.e. related to current events [18]. It is possible to have a form of MCI in which the impairment of one function is predominant or several areas of cognitive functioning, other than memory, e.g. language, visuospatial functions, attention, or executive functions, are impaired [19]. Mild cognitive impairment, in which only one cognitive domain, but other than memory, is impaired, has an increased likelihood of conversion to multiple types of other neurodegenerative diseases such as frontotemporal dementia, dementia with Lewy bodies, primary progressive aphasia, PD, and AD. The multi-domain type of MCI paradoxically has the least tendency to evolve into AD and often simply transforms into a physiological aging process [20].

Mild memory impairment is therefore associated with preclinical signs of dementia [21]. This condition is considered a risk factor for dementia [22]. Findings support the existence of a preclinical phase of dementia characterized by memory impairment that is present at least 5 years before its diagnosis [23]. De Carli has shown that elderly patients diagnosed with MCI are 3 to 15 times more likely to develop dementia than those of the same age without MCI. Approximately 20% of people over 65 years of age suffer from MCI, indicating a four times higher prevalence of this disorder than dementia [24]. Some clinical studies show that 10–15% of people who develop MCI, later develop dementia. Community-based studies show a prevalence of dementia of 3.8–6.3% [25].

Hypertension and risk cognitive impairment

The incidence of MCI has been shown to increase with age and is not dependent on gender or education, although mentally active older people are significantly less likely to develop dementia [26]. The presence of several vascular risk factors increases the risk of incident MCI (whether defined as cognitive or functional), but these were mostly associated with non-amnestic MCI. Thus, controlling vascular risk can potentially reduce the risk of cognitive impairment, including later dementia [27]. Trouble with memory can occur at any time in life, but is much more common in older age and may or may not be the onset of dementia. Memory along with thinking, perceptual processes, language functions, and visuospatial functions are part of cognitive functions that deteriorate with age. Cognitive processes allow people to gain knowledge about their environment and to communicate with it. They are also an integral part of acquiring and retaining knowledge. However, a cognitive impairment that may be related to hypertension has still received little attention in the literature [28]. Hypertension and hypercholesterolemia play a key role in the atherosclerotic etiology of cognitive impairment. In the Polish population, in elderly patients, they coexist in 58%, 60%, and 52% of patients over 60, 70, and 80 years of age, respectively [29]. In large caliber vessels, atherosclerotic plaques, especially unstable ones, may cause acute occlusion of the artery and be the direct cause of a stroke. In smaller caliber vessels, vascular remodeling plays a greater role [30]. The potential impact of hypertension and lipid disorders and coexisting diabetes on cognitive impairment is shown in Figure 1.

The study, which included 559 patients (mean age 67.8 ± 8.8 years), analyzed the influence of hypertension in patients with organ damage, on cerebral small vessel pathology and the occurrence of

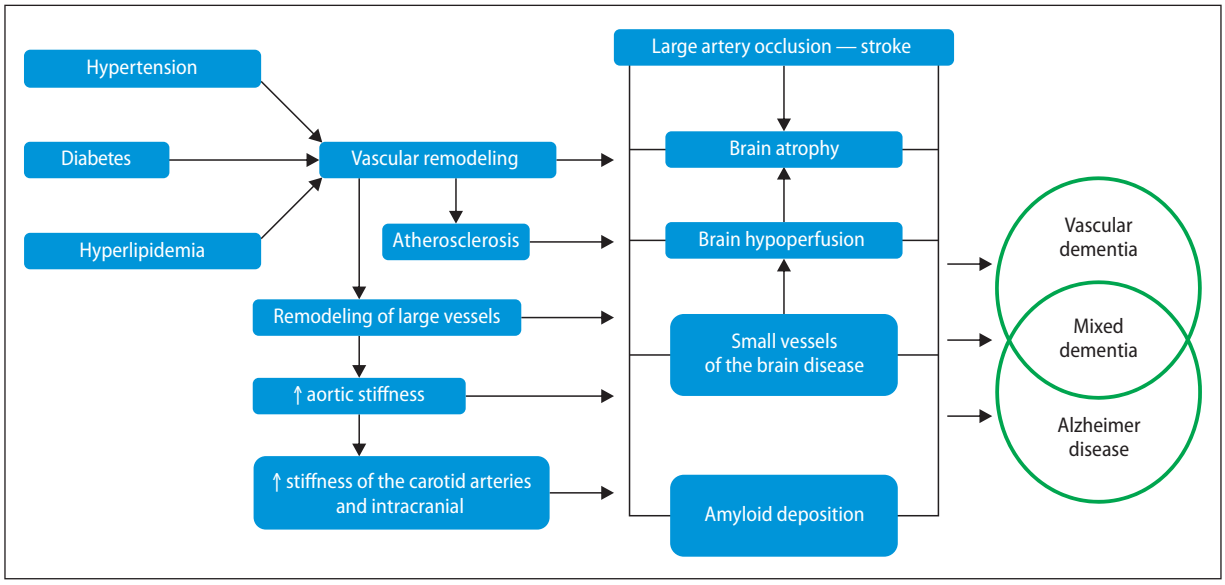

Figure 1. The influence of hypertension and lipid disorders as well as coexisting diabetes mellitus on cognitive disorders

dementia-like disorders. Cerebral small vessel disease was confirmed by an MRI in more than two-thirds of the subjects, and cognitive impairment in more than a quarter of the patients in one range. Increased pulse wave velocity was shown to increase the risk of cerebral small vessel lesions by 17%. Increased left ventricular mass index increased the risk of small vessel lesions by nearly 2-fold [31]. Ischemic lesions of the central nervous system are usually associated with severe strokes leaving permanent sequelae, including cognitive deficits. Cerebral ischemia can also be caused by clinically silent lacunar strokes, with an incidence of 10–30% [32], and white matter damage (periventricular leukoencephalopathy, leukoaraiosis), which can be detected in almost all elderly people with hypertension [33]. It is progressive and clinically manifested by cognitive decline, gait disturbances, and falls. The above changes are associated with an increased risk of stroke, cognitive decline, and dementia [33–36]. Disease progression is more rapid in elderly patients with highly variable blood pressure values and high pulse pressure [37]. These observations were confirmed by the HYVET study (Hypertension in the Very Elderly Trial), which showed, both in the placebo group and in the indapamide-treated group, that elevated BP increases the risk of dementia. In addition, it was observed that the effect of diastolic blood pressure elevation on the appearance of dementing changes takes the shape of a "u" curve [38].

In addition to its well-known effect on the occurrence of strokes, hypertension is also associated with a risk of asymptomatic brain damage, especially in the elderly, detected only by magnetic resonance imaging [32, 33]. Hypertension, usually beginning in middle age, is, therefore, one of the most important risk factors for dementia in old age.

Dementia is a syndrome of general cognitive impairment that interferes with social and occupational functioning. The two most common forms of dementia are AD, caused by degenerative changes in the nervous system, and vascular dementia, caused by cerebrovascular disease. Both of these causes often co-occur (so-called mixed dementia), especially in people over 80 years of age.

Impact of hypotensive treatment on cognitive functions

Epidemiological studies of people over the age of 50 show that blood pressure levels and their treatment play an important role in the onset of cognitive impairment.

Hypertension occurring in middle-aged patients has been associated with the onset of dementia and broad cognitive impairment later in life [39, 40]. In patients with uncontrolled hypertension, the risk of cognitive impairment increases more than 4-fold. Several observational studies have found an association between pre-existing high blood pressure values and later development of dementia, including AD [41, 42]. High blood pressure in middle age has also been linked to the occurrence of senile plaques and fibrotic neuronal degeneration — characteristic changes of AD later in life [43]. At the same time,

observational population studies have shown that the use of hypotensive drugs can reduce the incidence of AD and dementia [41, 44, 45]. Some observational studies have also found that patients with AD taking hypotensive drugs, compared to patients not receiving such drugs, show better cognitive performance [46, 47].

In addition, it has been observed that an association between high blood pressure values and the development of dementia later in life occurs especially in those individuals who were not taking hypotensive medication [48]. The study by Mahinrad et al. under the Coronary Artery Risk Development in Young Adults (CARDIA) program, in which subjects aged 18–30 years were followed up for 30 years, seems interesting. It showed that already at a young age, prolonged exposure to high blood pressure values affects cognitive decline [49]. Similarly, a study by Hisayama et al. conducted in Japan over 32 years, comparing blood pressure values in middle-aged and older adults showed a 24% increase in the development of vascular dementia for every 10 mm Hg increase in systolic blood pressure and a 37% increase for every 10 mm Hg increase in diastolic blood pressure [50]. Analysis of the Pol-Fokus study in approximately 2,000 elderly and very elderly patients showed that poorer BP control was associated with more pronounced cognitive impairment and more severe mood disturbance [51]. Abell et al. showed that in patients aged 50 years, a systolic blood pressure ≥ 130 mm Hg, which is below the traditional threshold of ≥ 140 mm Hg used to define hypertension, was associated with an increased risk of dementia and that in these patients the increased risk was independent of cardiovascular comorbidity [52]. Data from the Framingham study cohort suggest that subtle vascular brain damage in hypertensive patients develops insidiously during life and is already evident even in young individuals [53]. In contrast, the results of some previous meta-analyses from randomized clinical trials that assessed the association of hypotensive treatment with the risk of MCI and AD in both primary and secondary prevention did not yield conclusive results [54, 55]. Also, the published SPRINT MIND and HOPE 3 studies showed conflicting data.

The SPRINT MIND trial was conducted at 102 centers in the United States and Puerto Rico among 9361 patients aged 50 years or older, with hypertension, but without a history of coexisting diabetes or stroke. Participants were randomly assigned to a target systolic blood pressure of less than 120 mm Hg (intensive treatment group; n = 4678) or less than 140 mm Hg (standard treatment group; n = 4683). After more than 5 years of follow-up, dementia occurred in 7.2 *vs.* 8.6 cases per 1000 person-years in the intensive treatment group compared with standard treatment [hazard ratio (HR), 0.83; 95% confidence interval (CI): 0.67–1.04). Statistical significance was not reached due to the low incidence of dementia (149 *vs.* 176), as the SPRINT study was terminated prematurely. Intensive blood pressure control significantly reduced the risk of mild cognitive impairment (14.6 *vs.* 18.3 cases per 1000 person-years; HR: 0.81; 95% CI: 0.69–0.95) and the overall rate of mild cognitive impairment or dementia (20.2 *vs.* 24.1 cases per 1000 person-years) (HR: 0.85; 95% CI: 0.74–0.97) [56]. The opposite results were obtained in the HOPE-3 trial, which showed no significant reduction in the risk of cognitive impairment or dementia, with a combination of antihypertensive therapy based on candesartan and hydrochlorothiazide plus rosuvastatin compared with placebo [57]. The question of the effect of hypotensive treatment on cognitive impairment and dementia may be answered by the results of a meta-analysis published in 2020. [58]. It included 14 randomized clinical trials involving nearly 100,000 patients. The mean age of participants was 69 years and the mean follow-up time was 49.2 months. Lowering blood pressure with hypotensive drugs resulted in a significant reduction in the risk of dementia or cognitive impairment compared with the control group (7.0% *vs* 7.5% of patients over a mean follow-up of 4.1 years); odds ratio (OR): 0.93 (95% CI: 0.88–0.98) absolute risk reduction 0.39% (95% CI: 0.09–0.68%); and reduced cognitive decline (20.2% *vs.* 21.1% of participants over a mean follow-up period of 4.1 years) [OR: 0.93 (95% CI: 0.88–0.99)]; absolute risk reduction 0.71% (95% CI: 0.19–1.2%). Lowering blood pressure did not alter the results of tests assessing cognitive function. The results of this meta-analysis showed the importance of effectively lowering blood pressure to the recommended values. In conclusion, we have many studies documenting that hypertension is an important risk factor for cognitive impairment and dementia. A detailed analysis of these data shows that the culprit for these complications is elevated blood pressure in middle age, and the older the patient, the less important risk factor hypertension becomes. As patients age, elevated blood pressure gradually becomes a less important risk factor for dementia, and excessively low blood pressure increasingly becomes the main hemodynamic factor in the described disorders. At ages above 85 years, low systolic blood pressure may even predict the onset of dementia [59]. In cente-

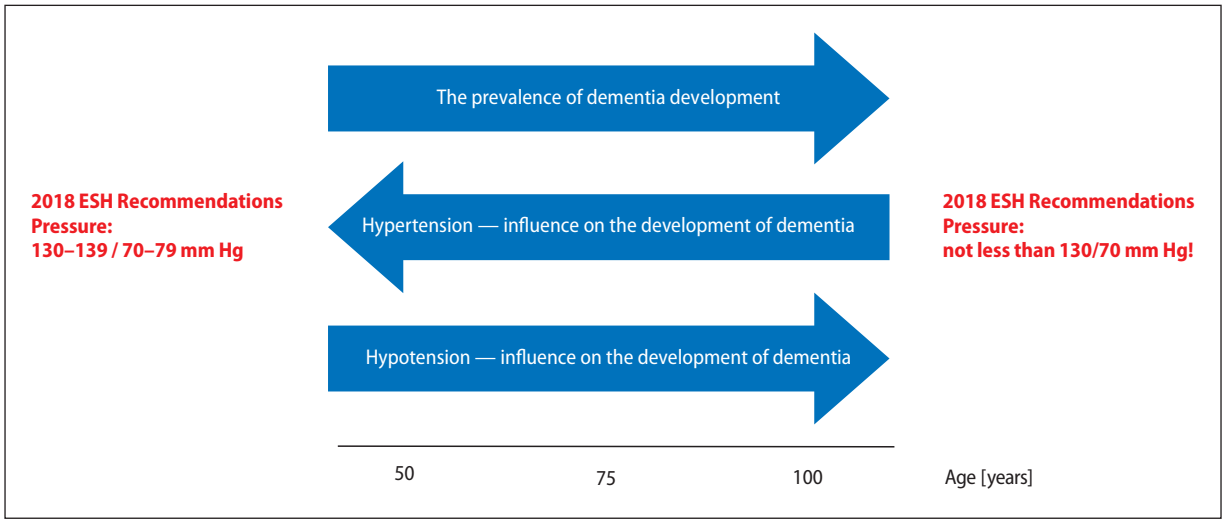

Figure 2. Influence of hypotension and arterial hypertension on cognitive impairment. ESH — European Society of Hypertension

narians, better mental and physical performance was associated with higher blood pressure [60]. An important observation was made by Streit et al. — they demonstrated an association between accelerated cognitive decline and lower blood pressure in the oldest old patients taking hypotensive drugs (mean annual change –0.35 points per 10 mm Hg lower systolic pressure, 95% CI: –0.60 to –0.11, p = 0.004] [61, 62] (Fig. 2).

Peters et al. analyzed 3121 hypertensive patients over 80 years of age (the population of the HYVET study) to determine whether there was an association between orthostatic hypotonia with cognitive impairment and dementia. In this study, they observed that an orthostatic fall in systolic blood pressure of at least 15 mm Hg and/or a fall in diastolic blood pressure of 7 mm Hg was associated with an increased risk of cognitive decline of 36% [risk ratio (HR) 1.36, 95% CI: 1.15–1.59]. When any fall in systolic blood pressure of more than 15 mm Hg on and any fall in diastolic blood pressure of more than 7 mm Hg, while standing together, and neurological symptoms were present, this was associated with a 56% increased risk of cognitive decline and a 79% increased risk of dementia. They also performed a meta-analysis combining the HYVET study results with other reports and found that orthostatic hypotonia was associated with a 21% increased risk of dementia [63]. The prevalence of orthostatic hypotonia increases with age. In people over 65 years of age, it occurs in 14–30% of the general population [64]. Hypotonia very often accompanies some neurological conditions; in people with diabetes it occurs in 12 to 28%, and in nursing homes for the elderly it is found in almost 59% of the subjects [65, 66]. The Honolulu Heart Program study, which included 3522 people aged 71 to 93 years, showed that mortality was 64% higher in people with orthostatic hypotension. Orthostatic hypotension was more common in people who smoked cigarettes, had a history of stroke or comorbid cardiac ischemia or diabetes, and was significantly lower in people with higher physical activity [67].

Why do hypertension and hypotension increase the risk of dementia?

Certainly, regulation of cerebral flow plays a key role [62]. A cohort study involving 4795 participants (median age 61.3 years) followed for nearly 7 years showed that cerebral vascular hypoperfusion assessed by MRI was associated with significantly accelerated cognitive decline and increased risk of dementia [68].

It has long been known that hypertension is a strong risk factor for atherosclerosis in all arterial vessels regardless of their caliber. Long-term hypertension in middle age increases many times the risk of advanced atherosclerosis in later life. The risk of AD and vascular dementia is three times higher in patients with advanced atherosclerotic lesions [69]. In elderly patients, there is increased vascular stiffness and the mechanisms of autonomic regulation of cerebral flow are disturbed. Therefore, in addition to hypertension and hypotension, increased pressure variability is also very important. This is confirmed, among others, by the work of Oshi et al. In nearly 1700 hypertensive patients over 60 years of age, increased pressure variability in home measurements, irrespective of mean pressure, was a strong risk factor

for the development of all-cause dementia, vascular dementia and AD [70]. The association with increased BP variability and cognitive decline in 40–75-year-olds was also demonstrated by Zhou et al. in the Maastricht Study [71]. Also, Fujiwara et al. showed that in people over 80 years of age, BP variability correlated with cognitive decline [72].

In conclusion, any decrease in blood pressure in the elderly population not only negatively affects cognitive function, as shown by Streit and Peters cited earlier, but is associated with an increased incidence of depression [73], delirium [74], or finally falls and fractures [75].

The aim of the meta-analysis by Roush et al. covering 16 clinical trials was to answer the question of whether the benefits of intensive hypotensive treatment depend on the age of the patients. This work showed that the risk of cardiovascular events was about 14.4% lower in the group of patients treated intensively (systolic pressure oscillated between 120–140 mm Hg). At the same time, it was demonstrated that older patients (mean age 77 years) benefited more from intensive treatment than younger patients (mean age 61 years), especially in terms of reduction in cardiovascular events (RR: 0.767, p = 0.025) and reduction in heart failure events (RR: 0.626, p = 0.043) [76].

Should intensive hypotensive treatment be a concern in elderly patients?

Although intensive hypotensive therapy results in a reduction in cardiovascular incident rates, there are concerns among practitioners that it may be associated with an increased incidence of orthostatic hypotension. So should we be concerned about intensive hypotensive treatment in elderly patients? This question was answered by a meta-analysis by Juraschek et al. published in 2021. Its aim was to assess the association between intensive hypotensive therapy and the occurrence of orthostatic hypotension. In total, 9 large clinical trials involving 18466 patients with a mean age of 65 years were analyzed. Five trials were randomized to different therapeutic targets (intensive *vs* less intensive treatment), and four trials were randomized to active treatment *vs* placebo. Orthostatic hypotension was defined as a fall in systolic blood pressure of 20 mm Hg or more or diastolic blood pressure of 10 mm Hg or more after a change in position from sitting to standing. Intensive treatment was defined as achieving a systolic pressure < 120–130 mm Hg, traditional treatment as a systolic pressure < 140–150 mm Hg. Intensive hypotensive treatment even reduced the risk of orthostatic hypotension by 7% [OR: 0.93 (95% CI: 0.86–0.99)]. In a pooled analysis of studies comparing lower and higher therapeutic targets and studies comparing active treatment with placebo, intensive hypotensive therapy was also associated with a significantly lower incidence of orthostatic hypotension — a difference of also 7%. In patients without coexisting diabetes, intensive hypotensive therapy was associated with a significant reduction in the incidence of orthostatic hypotension (OR: 0.9, 95% CI: 0.83–0.98). In this meta-analysis, the effect of intensive hypotensive therapy on reducing the incidence of orthostatic hypotension was not shown to be dependent on age (patients ≤ 75 years *vs.* > 75 years), sex, blood pressure level before inclusion in the study, history of stroke, presence of chronic kidney disease, the coexistence of obesity and a history of other cardiovascular diseases [77]. The results obtained in this meta-analysis consisted mainly of the SPRINT MIND study [78].

Analysis of the SPRINT study gave us another interesting observation. Intensive hypotensive therapy in 50-year-olds prolonged survival by 2.9 years, in 65-year-olds by 1.1 years, and in 80-year-olds by 0.8 years [79] (Fig. 3A–C).

In the ongoing care of hypertensive elderly patients, frequent monitoring of blood pressure and its variability, repeated blood pressure measurements in the sitting position and after standing upright must not be forgotten. In this group of patients, it is also important to avoid the use of hypotensive drugs from the group of beta-blockers, alpha-blockers, and short-acting diuretics. Blockers of the renin-angiotensin system should be used with caution. It should also be remembered that some drugs used in Parkinson's disease and psychotropic drugs commonly used in this group of patients, including benzodiazepines, especially those with sleep-inducing effects, may also cause orthostatic falls in blood pressure. It is therefore important, as emphasized in the Polish Society of Hypertension (PTNT) 2019 guidelines, not to lower blood pressure below 130/70 mm Hg in elderly patients [80].

There has also been a long-standing debate as to whether elevated blood pressure should be lowered in people aged 80 and over, and if so, to what blood pressure value. A number of studies conducted up to the end of the 20th century, evaluating hypotensive therapy in people over 80 years of age, showed that although lowering blood pressure significantly reduced the number of strokes, it increased overall mortality [81] and that in people over 85 years of age (very old age) it was low systolic pressure

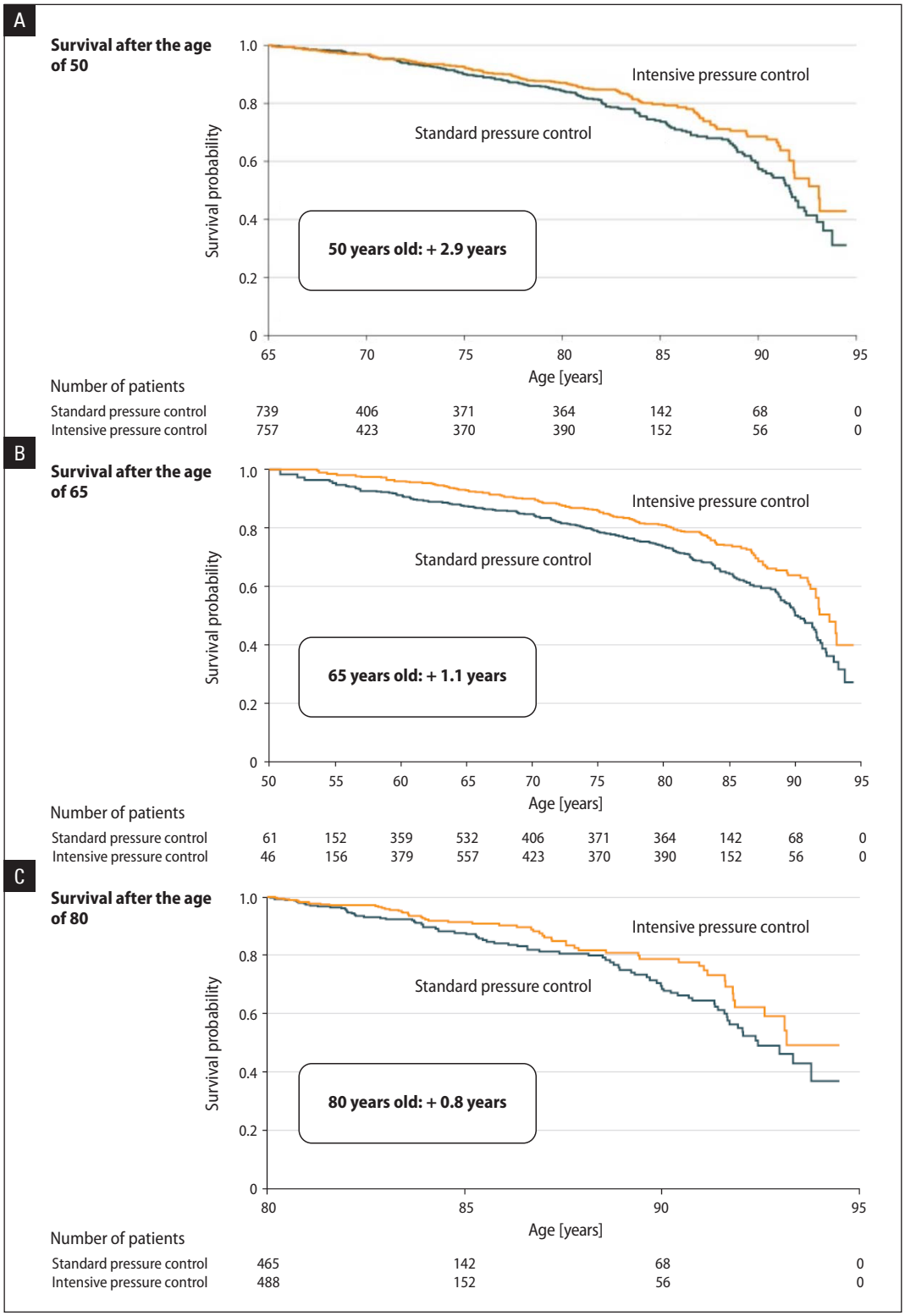

Figure 3A–C. Comparison of intensive and standard antihypertensive therapy for life extension in patients with arterial hypertension

(and not high pressure) that was associated with a higher risk of developing dementia. Controversy, therefore, arose as to whether hypertension in the elderly requires hypotensive therapy and whether it nonetheless adversely affects cognitive impairment? In order to finally clarify the validity of hypertension therapy in the oldest patients, the HYVET study was planned, which was a randomized, double-blind

trial conducted in 195 centers from 13 countries. The study was stopped prematurely, after a mean follow-up of 2.1 years, because of measurable benefits in the actively treated group. The study drug was indapamide SR with a possible combination with perindopril. Patients aged 80 years with hypertension defined as SBP 160 mm Hg and DBP between 90–109 mm Hg were eligible for the study. However, after three years, the criterion for DBP values was changed to < 110 mm Hg in 2003, allowing the inclusion of patients with isolated systolic hypertension. The criterion for SBP at the time of upright-ing throughout the study remained unchanged at 140 mm Hg. After randomization, patients were given indapamide SR 1.5 mg or a placebo. At each visit, if the target BP value was not reached, 2 and then 4 mg of perindopril or placebo were added. Target BP values were defined as SBP < 150 mm Hg and DBP < 80 mm Hg. In the placebo phase, 4761 patients were enrolled before randomization, of whom 3845 were randomized to one of the two groups. The two study groups were not significantly different at baseline. The age range at the start of the study was 80 to 105 years, with 73% of patients aged 80–84 years, 22.4% aged 85–89 years, and 4.6% aged 90 years. More than 90% of the patients knew they had hypertension, of which 1/3 had not been previously treated. A history of cardiovascular disease was positive in 11.8% of patients, and for diabetes in 6.9%. The mean length of patient follow-up was 1.8 years. The number of patient-years in the placebo group was 3964 and 4159 in the treatment group. The primary endpoint assessed in the HYVET trial was stroke and stroke-related death. This endpoint did not include transient ischemic attack (TIA). Secondary endpoints were death from all causes, death from cardiovascular disease, death from cardiac causes, and death from stroke. Death from cardiac causes included fatal myocardial infarction, fatal heart failure, and sudden cardiac death. Heart failure was diagnosed if the patient presented with at least one of four symptoms [paroxysmal nocturnal dyspnea, dyspnea at rest, orthopnea or symptoms consistent with New York Heart Association (NYHA) class III heart failure] and at least two of seven symptoms [rales or crackles, moderate swelling around the ankles, tachycardia (120 beats/min), third heart tone, elevated jugular venous pressure, cardiomegaly or radiological exponents of heart failure]. A third symptom was required for rales over the pulmonary fields and swelling around the ankles. In the active treatment group, there was a reduction in stroke [relative risk (RR): 0.59; 95% CI: 0.40–0.88, p = 0.009] and, unexpectedly, fewer deaths from all causes (RR: 0.76; 95% CI: 0.62–0.93, p = 0.007). Mean SBP and DBP measured in sitting decreased by 14.5 ± 18.5 mm Hg and 6.8 ± 10.5 mm Hg in the placebo group and 29.5 ± 15.4 mm Hg and 12.9 ± 9.5 mm Hg in the treatment group, respectively. Mean SBP and DBP measured standing decreased by 13.6 ± 18.9 mm Hg and 7.0 ± 10.9 mm Hg in the placebo group and 28.3 ± 16.5 mm Hg and 12.4 ± 10.3 mm Hg in the treatment group, respectively. Consequently, the mean difference in systolic and diastolic blood pressure between the groups after two years of follow-up was 15.0/6.1 mm Hg [7]. A detailed subgroup analysis of the HYVET trial results showed that active indapamide-based treatment reduced total mortality by 29% (95% CI: 13–32, p = 0.001). Cardiovascular mortality was reduced by 27% (95% CI: 3–45, p = 0.029) and the incidence of fatal stroke was reduced by 45% (95% CI: 8–67, p = 0.022). A 68% reduction in the rate of fatal heart failure (p = 0.05) and a 40% reduction in cardiac mortality (p = 0.077) were also observed, at the limit of statistical significance. There was also a significant reduction in all strokes by 34% (95% CI: 5–54, p = 0.026) and a reduction in heart failure exacerbation episodes by 72% (95% CI: 52–83, p < 0.001). All cardiovascular events were reduced by 27% (95% CI: 12–40, p < 0.001) [82].

So how to safely treat hypertensive elderly patients?

Diuretics

In elderly hypertensive patients, following the results of the HYVET study (described above), indapamide has a strong position. In some of the patients included in the HYVET study, the effect of hypotensive treatment on the cognitive abilities of hypertensive patients was also evaluated (HYVET-COG study) [83]. A statistically insignificant 14% reduction in the incidence of dementia was observed. It is very likely that a longer study on a larger number of patients would have shown significant inhibition of the development of cognitive impairment. When the results of the HYVET-COG study were combined with the results of three other studies comparing drug treatment with placebo in elderly and very elderly patients, hypotensive treatment was found to be associated with a significant 13% reduction in the risk of developing dementia [7] .

In another large clinical trial Systolic Hypertension in Elderly Program (SHEP), in 4736 hypertensive patients after 5 years of follow-up, it was shown that in the subgroup of patients treated with

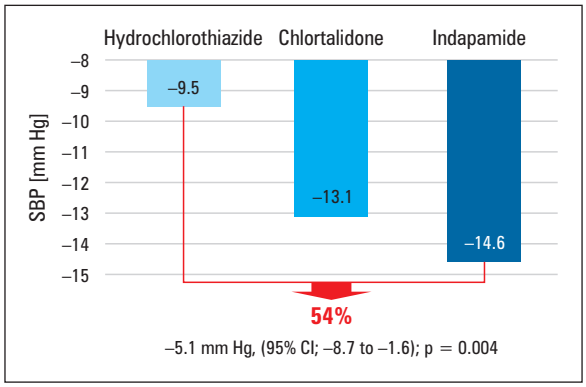

Figure 4. Comparison of the antihypertensive effects of hydrochlorothiazide, chlorthalidone and indapamide. SBP — systolic blood pressure

the thiazide-like diuretic, chlorthalidone at a dose of 12.5–25 mg reduced the risk of non-fatal myocardial infarction and cardiac death by 27%, stroke by 36%, heart failure by 49%, major cardiovascular events by 32% and overall mortality by 13% [84]. Although chlorthalidone is a popular thiazide-like diuretic in the USA, it is relatively rarely used in Poland and Europe. Compared to indapamide, it has a lower potency of hypotensive action (Figure 4).

The PTNT 2019 and European Society of Hypertension (ESH) 2018 guidelines emphasize that a thiazide/thiazide-like diuretic or a dihydropyridine calcium antagonist, or a combination of both, should be used as monotherapy in elderly patients [80]. Is there really a place for thiazide diuretics (hydrochlorothiazide) in modern hypertension pharmacotherapy and should not thiazide-like diuretics (indapamide) be preferred? The answer to this question can be found, among others, in the meta-analysis by Chen et al. [85]. On the basis of 19 randomized clinical trials involving 112113 patients, it was shown that only thiazide-like diuretics (including indapamide) significantly reduced the risk of stroke by 18%, cardiovascular events by 22% and heart failure exacerbations by 43%. Classical thiazide diuretics (including hydrochlorothiazide) reduced the risk of stroke (HF) by 3% and non-significantly reduced cardiovascular events (8%) and heart failure episodes (29%).

It should be emphasized that loop diuretics should not be used as first-line drugs in elderly patients because of their rapid and short-term hypotensive effects.

Combination of diuretic and RAA blocker

In the previously cited studies involving indapamide, therapy was extended according to the protocol to include a combination with perindopril. This is a good therapeutic option also in the group of elderly patients. This choice is confirmed by numerous clinical trials, e.g.: the aim of a meta-analysis that appeared in 2019 in the Journal of Hypertension was to evaluate the effect of indapamide treatment (in monotherapy or in combination with perindopril) compared to placebo on total mortality, cardiovascular deaths, and fatal strokes. Four large clinical trials were included: the PATS study (a 2-year Chinese study in which indapamide 2.5 mg was administered once daily), the PROGRESS study (a 4-year international study in which indapamide 2.5 mg and perindopril 4 mg were administered to patients after ischemic stroke or transient cerebral ischemia), the HYVET study (a 2-year international study in elderly hypertensive patients, administered indapamide SR 1.5 mg with optional 2–4 mg perindopril) and the ADVANCE study (a 4-year international study in patients with type 2 diabetes and a cardiovascular risk factor, administered perindopril 4 mg and indapamide 1.25 mg). In relatively heterogeneous patient populations, indapamide treatment led to a 15% reduction in the risk of mortality from any cause (HR: 0.85, 95% CI: 077–0.94, p = 0.0012), a 21% reduction in death from a cardiovascular cause (HR: 0.79, 95% CI: 0.70ľ0.90, p < 0.001) and a 37% reduction in the incidence of fatal stroke (HR: 0.63; 95% CI: 0.51–0.78, p < 0.001) [86].

At what dose of indapamide in combination with perindopril should treatment be started in elderly patients? Due to the risk of hypotension in the elderly (described above), a halved dose should be considered. Such a treatment regimen has been studied by Chalmers et al. In their study, they evaluated the long-term efficacy and safety of single-pill combination of 2 mg perindopril and 0.625 mg indapamide as first-line treatment in elderly patients (patients aged 65–85 years, with mild to moderate primary hypertension or isolated systolic hypertension). The primary endpoint was the proportion of patients with blood pressure normalization between 0 and 60 weeks of treatment. After one year of treatment (intent-to-treat), systolic and diastolic blood pressure in the supine position decreased by 23.0 ± 15.3 mm Hg and 13.3 ± 9.4 mm Hg, respectively. Mean systolic blood pressure decreases were similar in spontaneous hypertension and isolated systolic hypertension groups. After one month of treatment, normalization of blood pressure was achieved in 68.8% of patients, and after 3, 6, 9, 12 months in 90.3%, 94.6%, 95.7%, 96.2% of patients, respectively.

The efficacy and safety of such therapy were similar in subgroups below and above 75 years. The results

of this study suggest that in the elderly population the interval between the escalations of the intensity of pharmacological treatment should be prolonged even to 3 months [87].

In addition, the already cited PROGRESS study, which included approximately 6000 middle-aged patients over 60 years of age, demonstrated the benefit of treatment with perindopril with indapamide due to a significant reduction in the rate of cognitive decline [88]. In contrast, the SCOPE study (including patients aged 70–89 years) found no significant difference in the rate of dementia development between the groups treated with candesartan and placebo. A beneficial effect of candesartan treatment was noted only in patients with a baseline decreased cognitive function score (Mini-Mental State Examination ≤ 28) [89]. It is therefore possible to propose the thesis that angiotensin-converting enzyme inhibitors also differ from sartans in their effects on cognitive function.

Calcium antagonists

Apart from diuretics, calcium antagonists, especially dihydropyridine derivatives, are very often used in patients with hypertension. Their effectiveness was confirmed in the Syst-Eur study (Systolic Hypertension in Europe) [90]. It was shown that nitrendipine reduced the risk of myocardial infarction by more than 50% and the risk of stroke by 24% in hypertensive patients over 60 years of age. Treatment with nitrendipine resulted in a 55% reduction in the risk of dementia symptoms in addition to a reduction in stroke frequency. Detailed analysis showed that not only was there a statistically significant reduction in the number of patients with dementia caused by vascular lesions typical of hypertension, but the number of patients diagnosed with Alzheimer's disease also decreased. Such favorable results of this study led to its extension. For ethical reasons, nitrendipine was administered to all patients (including those in the placebo group). In the following years of follow-up, the difference in the risk of developing dementia lesions in favor of those treated with nitrendipine from the beginning increased further. These favorable results were related to the use of the dihydropyridine derivative of the calcium antagonist and could not be explained by the recorded difference in blood pressure between the active treatment group and the placebo group alone.

In contrast, Wang et al. analyzed 12 clinical trials in which 94338 patients were treated with amlodipine. Amlodipine conferred better protection against stroke — compared to placebo by –37% ($p = 0.06$), compared to sartans by –16% ($p = 0.02$), and compared to angiotensin-converting enzyme inhibitors by –18% ($p = 0.004$) [91].

Amlodipine in monotherapy has a beneficial effect on reducing BP variability [92]. This variability, according to the analysis by Howard et al. is the greater the more preparations the patient takes [93]. Thus we have another argument for limiting the number of tablets taken and the use of combined preparations in order to have not only a positive effect on blood pressure control, but also on its variability.

Combination of diuretic with amlodipine

As already mentioned, the 2019 PTNT guidelines recommend thiazide/thiazide diuretics and dihydropyridine calcium antagonists as first-line drugs in elderly patients with stage I hypertension. These drug groups can also be used in monotherapy. According to these guidelines, in uncomplicated hypertension, a combination of a thiazide-like diuretic and a dihydropyridine calcium antagonist should be preferred in the discussed age group. It is worth noting that also the 2018 ESH/ESC European guidelines recommended the use of a combination of a thiazide-like diuretic and a dihydropyridine calcium antagonist in elderly patients, especially when isolated systolic hypertension is present [94]. This guideline was influenced in part by the EFFICIENT study (EFfects of a FIxed Combination of Indapamide sustained-release with amlodipine on blood prEssure iN hyperTension), which included 196 patients with a mean age of 52.3 years with newly diagnosed stage II or III hypertension (65%) or patients previously treated with a calcium antagonist who did not achieve a blood pressure drop below 140/90 mm Hg. This multicenter, prospective, comparative, non-placebo-controlled phase IV study lasted 45 days. A fall in systolic blood pressure of 28.5 ± 2.1 mm Hg (95% CI: 26.4–30.6) and diastolic blood pressure of 15.6 ± 1.1 mm Hg (95% CI: 14.5–16.7) was achieved. Good blood pressure control (< 140/90 mm Hg) was observed in 85% of patients in the whole group, in 87% in the previously untreated group, and in 82% of those previously treated with a calcium antagonist [95] (Fig. 5).

In the EFFICIENT trial, a significant reduction in blood pressure, especially systolic blood pressure, was demonstrated at 45-day follow-up with the combination of indapamide and amlodipine. On the other hand, in the NESTOR study, a significant decrease of 20.1/10.1 mm Hg ($p < 0.001$) in blood pressure was achieved in the group of patients treated with indapamide and amlodipine 5 mg, and a decrease of 10.0/6.0 mm Hg ($p < 0.001$) compared

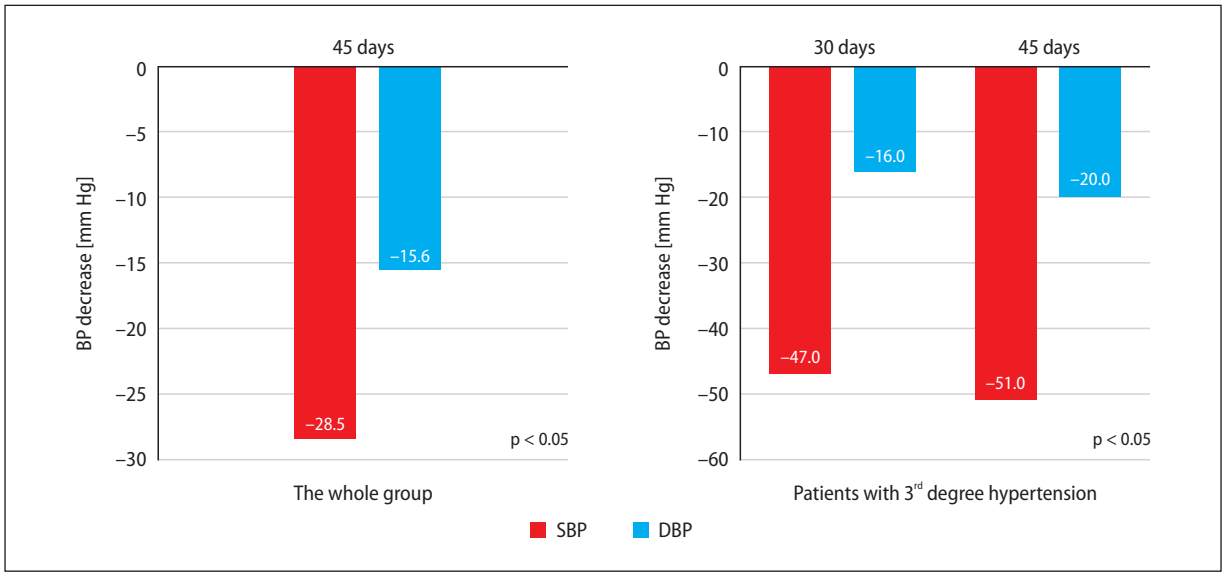

Figure 5. Decrease in systolic (SBP) and diastolic blood pressure (DBP) in patients treated with a combination of indapamide and amlodipine in the EFFICIENT study. BP — blood pressure

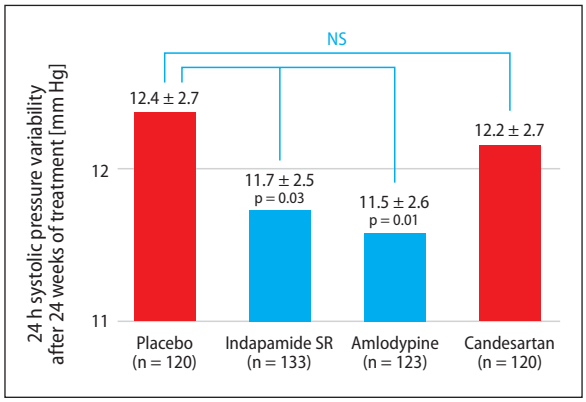

Figure 6. Decrease in systolic and diastolic blood pressure in patients treated with a combination of indapamide and amlodipine in the EFFICIENT study

to indapamide monotherapy. When the dose of amlodipine was increased to 10 mg, a decrease in blood pressure of 26.1/12.5 mm Hg was achieved. BP control was better in the group of patients treated with indapamide and amlodipine compared to those taking enalapril with amlodipine, at 86% and 78%, respectively. This study also proved the beneficial effect of this combination on BP reduction, associated (as previously described) with a significant risk of dementia [96].

The combination of indapamide and amlodipine, two long-acting hypotensive drugs, also has a beneficial effect on reducing BP variability. This positive effect of these drugs was proven, among others, in the X-Cellent study (Fig. 6).

Summary

Societies are aging rapidly. Current demographic projections predict an increase in life expectancy and a significant increase in the elderly population. The prevalence of hypertension and dementia increases with age. Disease progression is more rapid in elderly patients with highly variable blood pressure values and high pulse pressure.

Hypertension occurring in middle-aged patients has been associated with the onset of dementia and broad cognitive impairment later in life. In patients with uncontrolled hypertension, the risk of cognitive impairment increases. High blood pressure in middle age has also been linked to the occurrence of senile plaques and fibrotic neuronal degeneration.

Intensive blood pressure control significantly reduces the risk of mild cognitive impairment.

The guidelines indicate the benefit of using a combination of a thiazide-like diuretic (indapamide) and a calcium antagonist (amlodipine) in elderly. Combination treatment with a converting enzyme inhibitor (perindopril) and a thiazide-like diuretic (indapamide) is also particularly beneficial in this age group.

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