

Arterial hypertension in the elderly and treatment targets

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Introduction

Arterial hypertension (HTN) is the most common cardiovascular disease, and through its evolution and complications – atherosclerotic coronary disease, stroke, heart failure, and chronic kidney disease – is a major cause of cardiovascular mortality. The prevalence of hypertension is estimated at 30–40% of the population over 18 years old [1]. According to the SEPHAR Study, the prevalence in Romania was 46% [2]. The prevalence of hypertension is also high in the elderly population and depends on the age that is considered ≥ 65 years, ≥ 75 years or ≥ 80 years (very old). The increase in the population's life expectancy, especially in countries with efficient medical systems and good socio-economic conditions, has also increased the number of elderly people with HTN. In the states of the European Union, in a period of 10 years (2006–2016), the elderly population over 80 increased from 4.6% to 5.4% [3]. The increase in the elderly population, especially over 80, is accompanied by an increasing number of frailty or vulnerable, fragile people. Vulnerable people (frailty) with HTN have special treatment

problems of HTN, in addition to general medical and social care measures.

In people aged ≥ 65 years, HTN develops in 60–80% of cases due to the morphofunctional changes that occur in the cardiovascular system.

Isolated arterial hypertension is the most common form of hypertension in the elderly, estimated at 60–80% of cases. It is defined by an increase in SBP ≥ 140 mmHg and a decrease in DBP ≤ 80 mmHg [4]. It is accompanied by an increase in pulse pressure (PP), representing an independent cardiovascular risk factor.

Arterial hypertension in the elderly evolves into complications related to the pressure level but also the consequences of advanced age – atherosclerosis with multiple vascular determinations and impairment of cognitive function. In addition, comorbidities can be added – diabetes, chronic kidney disease, and chronic obstructive pulmonary disease. The additional presence of complications and comorbidities generates complex problems for the evaluation of HTN in the elderly and especially problems of HTN management.

The European Society of Cardiology (ESC) guidelines (ESH, ACC/AHA, ISH) for diagnosis and treatment of HTN extensively present the characteristics of hypertension in the elderly, the particularities (of antihypertensive treatment) and the new targets of antihypertensive treatment recommended in clinical practice [4–6]. How these treatment targets were arrived at, and the legitimate question of whether they can be applied in clinical practice are addressed in this paper.

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Cardiovascular morphological and functional changes in the elderly

After the age of 50–60 years, the systolic blood pressure (SBP) values increase slowly and the diastolic blood pressure (DBP) values decrease or remain stable, both in people considered normal and in untreated hypertensives. With advancing age, the difference between SBP and DBP increases, so in most cases, isolated HTN develops, prevalent in the elderly. The major cause of increased SBP and decreased DBP is arterial stiffness (large vessels).

Arterial stiffness increases as a result of some morphological and functional changes in the large arteries: hypertrophy of the vascular wall, development of atherosclerosis, calcifications and collagen growth and decrease in elasticity. The accumulation of collagen is favored by the increase in transforming growth factor (TGF) activity and the decline in elastin by the activation of elastases, especially metalloproteinases. Such changes in the extracellular matrix in the aorta (and large vessels) contribute to the decrease in arterial distensibility (aorta elasticity and loss of “recoil” during diastole) [7].

Arterial stiffness increases the pulse wave’s velocity and the reflected wave’s precocity, which adds to the incident pressure and further contributes to the increase in SBP and pulse wave. Heart rate – carotid-femoral artery is the gold standard for measuring arterial stiffness [8]. The increase in the pulse wave and the level of SBP/DBP are major risk factors for cardiovascular events.

Arterial stiffness in the elderly is associated with endothelial dysfunction and changes in vascular smooth fiber reactivity, processes that further contribute to the development of arterial stiffness [7]. Arterial stiffness is associated with endothelial dysfunction and increased endothelin, and reduced nitric oxide (NO) bioavailability, which affects arterial dilation. In HTN in the elderly, neurohormonal changes also occur, such as a decrease in renin-angiotensin system (RAS) activity and increases in plasma norepinephrine, elements that contribute to vascular reactivity and variable blood pressure (BP) values [3, 7].

Arterial hypertension in the elderly and adults is accompanied by BP variability in the short or long term, increasing cardiovascular morbidity [9]. Arterial stiffness affects the baroreflex activity and contributes to the disruption of arterial pressure homeostasis mechanisms and increased BP variability.

The increase in BP values in the elderly also has consequences at the myocardial level through the development of myocardial hypertrophy and fibrosis. The increase in afterload and the decrease in coronary perfusion pressure (low DBP) create conditions for the development of myocardial dysfunction and heart failure [10–12], especially with preserved ejection fraction (EF). The evolution towards

HF variably modifies BP values in the elderly and requires unique therapeutic approaches.

BP target values in HTN

The problems of pressure values that define HTN were the starting point of the research to establish the target level from which the antihypertensive treatment starts and the target values of HTN treatment for an indefinite period (HTN control). The scientific basis for the definition of these targets is represented by the studies that showed the direct relationship between the level of SBP/DBP ≥ 115 mmHg and cardiovascular risk. Establishing these targets has also become pressing for HTN in the elderly, which have many cardiovascular risk factors (age, dyslipidemia, diabetes, obesity).

Over the past 20 years, more research has been published regarding the treatment of hypertension in the elderly and cardiovascular risk reduction for different treatment targets. The results of the main SHEP, HYVET, STEP and SPRINT studies [10–12] led to the development of the current diagnostic and treatment guidelines by the academic societies: ESC/ESH, ACC/AHA and ISH.

The SHEP study included 4736 hypertensive patients, mean age of 71.6 years, with SBP values between 160–219 mmHg and DBP < 90 mmHg, followed for 9.5 years with chlorthalidone \pm atenolol treatment *versus* placebo [10]. At five years, 65% of participants with active treatment and 40% with placebo reached the target BP < 160 mmHg. A decrease in the incidence of stroke by 33% and major cardiovascular events by 35% was recorded [10].

The results of the SHEP study were confirmed by the HYVET study [11]. The HYVET study included 1845 patients over 80 years of age and SBP between 160–190 mmHg/90 mmHg. The benefits of the treatment with indapamide \pm perindopril *vs.* placebo were followed to achieve target BP values $\leq 150/80$ mmHg. After two years of therapy, target BP was reached in 48% of the active *versus* placebo group. In the group with active treatment, the fatal stroke rate decreased by 30%, cardiovascular death by 23% ($p=0.06$), and heart failure by 64% ($p=0.001$) [11].

The STEP study included 8511 hypertensive patients in two equal groups, aged 60–80 years, who received antihypertensive treatment (olmesartan, amlodipine, hydrochlorothiazide) *versus* standard treatment. Treatment targets were between 110–130 mmHg for intensive treatment and 130–150 mmHg for standard treatment. The percentage of patients who reached the target of $110 < 130$ mmHg was between 67% and 77%, respectively for 1 and 3 years. The benefits of intensive treatment were the reduction of stroke (HR 0.67),

acute coronary syndrome (ACS) (HR 0.67), acute decompensated heart failure (HR 0.27), and death from cardiovascular causes (HR 0.72). The STEP study provided evidence regarding the efficiency and safety of intensive antihypertensive treatment (average SBP of 127 mmHg) in elderly patients *versus* standard treatment [14]. The SPRINT study and its results have been the most widely commented on in recent years [12].

The SPRINT study enrolled 9361 participants over 50 years old (average age of 67.9 years) with high cardiovascular risk; 28.7% of patients were over 75 years old. The effectiveness and safety of lowering SBP through intensive treatment (target <120 mmHg) *versus* standard treatment (target <140 mmHg) was monitored over an average period of 3.26 years. The study was terminated early due to evidence of effectiveness. The primary endpoint achieved (myocardial infarction, ACS, stroke, heart failure (HF) or cardiovascular death) was lower for intensive treatment (5.2%) *versus* standard treatment (6.8%); HR 0.75 (CI 95), $p < 0.001$. The individual components of the primary objective – stroke, heart failure, and cardiovascular death were significantly lower in the intensive treatment group. Adverse effects in the intensive group – arterial hypotension, syncope, acute kidney injury and disability were more numerous than in the standard treatment group [11]. The SPRINT study and its final results provide evidence that lowering SBP <120 mmHg is superior to treatment with a target SBP <140 mmHg in high-risk nondiabetic hypertensive patients, including elderly patients [13].

The results of the cited clinical studies led to the development of the latest guidelines for the diagnosis and treatment of hypertension; ACC/AHA (2017); ESC/ESH (2018), and ISH (2020) which specify the levels of HTN definition and its stages, BP levels when pharmacologic treatment of HTN begins and HTN treatment targets for disease control. The parameters are different for the tactics of antihypertensive treatment in the elderly population.

Arterial hypertension is defined in the ESC/ESH guidelines by values ≥ 140 mmHg and or ≥ 90 mmHg for SBP and DBP, respectively, and the ACC/AHA guidelines by values ≥ 130 mmHg for SBP or 80 mmHg for DBP [4, 5].

The decision to initiate antihypertensive medication is based on the BP level and the assessment of the risk of cardiovascular disease:

- ESC recommendations: Treatment in all adults with SBP ≥ 140 mmHg. Treatment for SBP 130–139 mmHg or DBP 80–89 mmHg may be considered in patients at high cardiovascular risk, especially coronary artery disease [4];
- ACC/AHA recommendations are largely similar: treatment in all adults with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Also, in adults with SBP 130–139 mmHg and DBP

≥ 80 –89 mmHg and cardiovascular disease with cardiovascular risk $\geq 10\%$ at 10 years [5].

Targets for HTN control with antihypertensive agents in the two guidelines are different. The control of hypertension involves reducing blood pressure for an indefinite period through pharmacological and non-pharmacological measures, but also the stopping or regression of morphofunctional changes, which implies the reduction of stiffness and vascular disease [15].

For 18–65-year-olds, the ESC/ESH guideline provides a treatment target of 130 mmHg (SBP) or lower if tolerated, but not lower than 120 mmHg. In the elderly ≥ 65 years, the treatment target for controlling hypertension is 130–139 mmHg if tolerated. The ACC/AHA recommendations for hypertension control provide a single target <130/80 mmHg for most adults and SBP <130 mmHg for the elderly – if tolerated [5].

In summary, the treatment targets for an indefinite duration in adults are similar to ≤ 130 mmHg for SBP, which implies intensive pharmacological treatment; for the elderly, BP target levels are prudent 130–139 mmHg (ESC/ESH) *versus* <130 mmHg (ACC/AHA). In a recent study, the harmonization of the two guidelines was discussed, and recommendations were formulated [16].

The current recommendations for the treatment of HTN in the elderly are concordant with the results of the STEP and SPRINT studies, which proved significant cardiovascular benefits for intensive treatment, usually obtained by therapy with two antihypertensive agents.

In a comment on BP targets specified by clinical trials, especially SPRINT, Messerli is more skeptical and notes “the near impossibility of achieving an SBP ≤ 130 mmHg in some elderly patients with systolic hypertension and low cardiovascular compliance” [17].

Can the current treatment targets of HTN in the elderly be practically achieved?

Limits in achieving treatment targets in HTN

There are several elements that reduce the possibility of BP control in hypertensive patients provided by the current guidelines. The problem is present in hypertensive adults but especially in the elderly. It is estimated that approx. 35–50% of older adults do not achieve HTN control at the limits defined by the guidelines [1]. In general, failure to achieve BP targets in hypertensives (especially the elderly) depends on the actual disease and its characteristics and the patient – with his particular problems.

Arterial hypertension in the elderly, especially isolated systolic hypertension, develops under special physiopathological conditions. At the level of large arterial vessels, characteristic morphological changes occur – hypertrophy of the vascular wall, atherosclerotic lesions in various stages of evolution, collagen accumulation and elastin disruption, ultimately decreasing arterial distensibility, increasing arterial stiffness and pulse wave velocity [7, 8]. The stiffness of the large arteries and the main cause of the increase in hypertension in the elderly cannot be modified by pharmacological therapy.

Stiffness is not reversible or, at most, stabilized by current antihypertensive therapy. The physiopathological elements of HTN in adults – neurogenic factors, involvement of the renin-angiotensin system, endothelial dysfunction and modulation of vascular tone – act in HTN in the elderly [1, 16] and explain the partial response to therapy.

Arterial hypertension, especially in the elderly, is accompanied by additional risk factors in more than 50% of cases – diabetes, dyslipidemia, obesity, metabolic syndrome, and hyperuricemia – which can modify the antihypertensive treatment tactics, the treatment targets and the tolerance of the hypertensive agents used [6]. A similar problem is present in the case of major complications in hypertensive patients – acute coronary syndromes, stroke, renal dysfunction of various degrees, and heart failure [18, 19]. The targets for HTN treatment in these situations are at values <140/80 mmHg, but in most cases, with the limit of 130/80 mmHg. Using a target with values of 120–130/80 mmHg – through intensive treatment – is used in chronic kidney disease and stroke and requires special surveillance to identify adverse effects, such as orthostatic hypotension, worsening renal function, signs of cerebral hypoperfusion [4, 16].

Resistant arterial hypertension is a typical example of the failure of antihypertensive therapy in intensive treatment. The prevalence is estimated at <10% of treated hypertensives [5]. The real resistance of HTN is established after eliminating secondary causes and after checking adherence to treatment. To treat resistant hypertension, other treatment tactics must be used: e.g., renal denervation plus pharmacological treatment in maximum tolerated doses.

Adverse effects of hypertensive agents and treatment tolerance are factors that limit the achievement of BP control targets.

The adverse effects that appear during the treatment of HTN in the elderly are found especially in old age (>80 years), in people who receive combinations of antihypertensive agents, in the “intensive” treatment of HTN, in comorbidities or vulnerable frailty people).

The main adverse effects reported by clinical studies in hypertension are orthostatic hypotension, syncope, renal dysfunction, dyselectrolytemia, and falls with traumatic injuries [4–6].

Arterial hypotension would occur in up to 20% of treated elderly patients [8]. It is the result of the dysregulation of baroreceptors, the decrease in autoregulation of cerebral circulation or volume depletion and finally, cerebral hypoperfusion. The incidence of arterial hypotension in standing or postprandial was approx. 2.4% in the final SPRINT study [13] with intensive treatment *versus* 1.4% in the standard treatment group (HR 1.71, $p=0.001$). Similar incidence values were recorded in the SPRINT senior and STEP studies [14, 20–23].

Syncope in the elderly with intensive antihypertensive treatment in the SPRINT senior trial was 3.0% *vs.* 2.4% in the case of standard therapy. Falls with traumatic injury have a much higher incidence in frailty patients.

The development of acute renal injury or renal failure is possible in elderly hypertensives treated intensively or standardly with RAS inhibitory agents [18]. The situation occurs especially in patients with intensive treatment and without kidney disease before the start of antihypertensive therapy, elements reported in SPRINT (respectively 3.8% *vs.* 1.1% $p<0.001$ intensive or standard treatment) [2].

Renal dysfunction is functional and temporary in hypertensives with GFR within normal limits, or it can be a factor in worsening renal function in the case of hypertensives with chronic kidney disease.

Dyselectrolyteemia, especially hyponatremia when taking thiazides, is also found in hypertensive patients treated intensively *versus* standard (3.8% *vs.* 2.1% $p<0.001$) [13]. When sodium levels fall below 130 mEq, cognitive disorders or changes in the neurological condition can occur, which can be confused with stroke in the elderly.

The variability of BP values which is dependent on time has to be differentiated from large and transitory rises in BP, especially recorded in untreated hypertensive patients or in old patients and which are produced by unseen physical and emotional stress factors. The problems of BP variability are related to the hypertensive load, the morning surge and the possibility of being the target of pharmacological therapy.

Morning surge is a component of BP variability and is defined by the difference between BP in the morning (1–2 hours after waking up) and the lowest BP value, measured by ABPN. In the morning, after a night's sleep, pressor mechanisms are activated for 1–2 hours (sympathetic activity, pressor neurohormonal factors – RAS) and the increase in vascular tone in resistance arteries. In addition, as a result of the morning surge, stiffness in the arteries increases – an important cause of exaggerated BP variability [24]. The clinical significance of BP variability in people with hypertension was initially reported by Mancia *et al.* [25]. Subsequently, numerous observational data and clinical studies have accumulated elements that show the significant association – for various types or indices of variability – with cardiovascular damage and mortality.

Short-term (days) or long-term BP variability is associated with cardiovascular events and mortality [9]. An analysis of data (IDACO) from 7112 untreated hypertensives showed that the SD (standard deviation) of nocturnal systolic BP is an independent predictor of cardiovascular events, cardiovascular death and mortality, in contrast to values recorded during the day [26]. Similar results were obtained by numerous meta-analyses. A frequently cited meta-analysis [9], with data from prospective cohorts and clinical trials, looked at the long- and medium-term association of systolic BP variability with cardiovascular events and mortality. The results showed that in the long term, SBP variability was significantly associated with the risk of general mortality, cardiovascular mortality, cardiovascular events, coronary disease and stroke. Short- and medium-term variability data showed a similar association [9]. In general, BP variability in hypertensive people is influenced by many factors: age, severity of hypertension, comorbidities, antihypertensive medication and treatment compliance.

The clinical significance of the morning surge is related to the observations that showed that acute cardiovascular accidents (myocardial infarction, stroke, atrial fibrillation, acute pulmonary edema) frequently occur early in the morning in conditions of exaggerated morning surge.

On the other hand, non dippers have a higher hypertensive load with long-term adverse cardiovascular effects. Morning surge, like variability, is associated with organ damage (e.g., left ventricular hypertrophy), arterial stiffness, carotid atherosclerosis, microalbuminuria or other adverse cardiovascular events, especially stroke [27, 28].

The presence of exaggerated morning surge, the type of non dippers component of variability, led to the suggestion of administering antihypertensive medication in the evening instead of in the morning to control both processes [29, 30]. Two randomized clinical trials (MAPEC with 2156 patients and chronotherapy trial with 19048) with medication administration in the evening or the morning indicated that antihypertensive therapy administered in the evening led to a significant reduction in cardiovascular events (cardiovascular death, myocardial infarction, ischemic or hemorrhagic stroke) [31, 32].

In the very recently published study (2022), the TIME (Treatment in Morning *versus* Evening) study looked at the results of morning *versus* evening antihypertensive dosing in hypertensive patients treated with standard medication (24,610 patients, with a mean follow-up of 5.2 years). The primary endpoint (vascular death or hospitalization for MI or nonfatal stroke) was recorded in 3.4% of participants with evening treatment and 3.7% with morning treatment. The TIME study concluded that the usual administration of antihypertensive medication in the evening or morning “did not provide different results in the cardiovascular assessment over time”

[33]. A recent statement (2022) of the International Society of Hypertension (ISH) reached similar conclusions: “the preferred use of antihypertensive medication at bedtime, in the evening, should not be routinely recommended” [6].

Given the conditions in which short-term or long-term BP variability and excessive morning surge lead to adverse cardiovascular elements, the question arises as to whether there is a therapeutic possibility to control them and whether they are treatment targets [30].

A variant of treatment refers to the use of antihypertensive agents with a long duration of action. Calcium blockers, especially amlodipine, and SRA inhibitors (candesartan) fulfill these conditions. Amlodipine – administered as a single dose is preferred, given its better tolerability and reduced cardiovascular and renal adverse effects. The patient’s adherence to pharmacological treatment is a necessary condition for the control of hypertension. Adherence to the pharmacological treatment of hypertension one year after the initiation of therapy is <50%. The proportion of patients with controlled hypertension (<140 mmHg) varies and depends on regions and countries, between 20 and 50% and reflects both the effectiveness of the prescribed therapy and adherence to treatment [8].

Non-adherence to antihypertensive treatment is common at all ages. In general, the elderly are more concerned about the proper administration of medication than mature adults. Anxiety, depression, and disorders of cognitive function are causes of decreased adherence in the elderly. Non-adherence to antihypertensive treatment is the most frequent cause of suboptimal control of hypertension at any age of the patient. It is associated with increased cardiovascular risk, disease progression – including stiffness and organ damage – and decreased quality of life [34, 35]. In the SPRINT senior trial, in patients >75 years (n=2636), more intensive BP-lowering treatment (achieved 124/62 mmHg and adherence) significantly reduced the risk of major cardiovascular events (heart failure, cardiovascular and overall mortality) compared with standard treatment (135/67 mmHg) [20].

The causes of non-adherence are multiple and depend on the patient, the doctor, the type of medication used, comorbidities, socio-economic conditions and the health system. The patient (and the family) is advised by the medical team to understand the need to administer the prescribed medication for the prevention of cardiovascular events and to monitor its effectiveness on BP levels at home [8, 35]. The tolerability of the medication may decrease in conditions of polypharmacy. Administering medication (mono or combined therapy) in a single tablet (pill) once a day increases adherence to treatment and BP control [4, 5]. The doctor’s communication methods are important for the doctor-patient relationship. The attending physician has an

educational role through the complete explanations given to the patient, with special references to the benefits achieved through pharmacological and non-pharmacological therapy. In addition, the doctor can control adherence to the treatment through specific tests.

The antihypertensive agents used and the recommendation for achieving BP targets in the elderly are non-dihydropyridine calcium channel blockers, SRA inhibitors and thiazide diuretics in monotherapy or a combination of 2 [4, 5].

Beta-blockers are not recommended as the first line of treatment except for indications for comorbidities. Alpha-blockers, loop diuretics (risk of orthostatic hypotension) and agents with central action (drowsiness, cognitive impairment) should be avoided in the elderly [3]. In the ESC/ESH guideline, calcium blockers are preferred as monotherapy and SRA antagonists according to the ACC/AHA guideline. Treatment adherence and antihypertensive treatment targets are conditioned by the functional status of elderly patients.

Treatment targets in elderly patients (frailty)

The increase in life expectancy and the elderly or very elderly population (>80 years) has led to the complex problems of frailty (vulnerable) patients, more and more numerous in most European countries and in the United States of America and Canada.

The term frailty defines a state of vulnerability after a stressful event as a result of a cumulative decline in several physiological systems during life [8]. In fact, the term frailty for an older adult is used to define a multi-functional syndrome that includes physical, cognitive, psychological and social decline.

The level of “vulnerability” (frailty) is assessed on a 6-step scale in relation to the extent of the disorders that lead to addiction, hospitalization or institutionalization. The very elderly have, in more than 80% of cases, systolic hypertension and low SBP values (approx. 60 mmHg), a condition that decreases myocardial perfusion and increases ischemic risk. In addition to the impact of HTN on cardiovascular risk (SAH, TAD, PP), comorbidities are added in the elderly, which lead to the decline of cognitive function up to dementia.

Cardiovascular risk reduction in people >75 years with hypertension was reported by the SPRINT (senior) Study (n=2636 patients). More intensive BP-lowering treatment (achieved 124/62 mmHg) significantly reduced the risk of major cardiovascular events by 30% (myocardial infarction, cardiovascular mortality) compared with standard treatment 135/67 mmHg [20]. The treatment targets of HTN

in patients over 65 years old are provided differently in the current guidelines: ESC/ESH – TAS 130–139 mmHg, ACC/AHA <130/80 mmHg [4, 5]. The Canadian guideline for arterial hypertension provides values <120 mmHg for over 50 years. The condition of BP tolerance is added to the treatment recommendations.

Basic (classic) antihypertensive agents are used for treating hypertension in the elderly: calcium blockers, ACE/ARB, and thiazide diuretics. Low doses are used initially, preferably in monotherapy and in long-term combined therapy (2 agents) [35]. In elderly patients, the adverse effects of the medication are more frequent and of greater severity, which requires monitoring for arterial hypotension, fatigue, confusion, fall trauma and the development of acute kidney injury.

The adaptation of antihypertensive doses in the elderly must be individualized and evaluated in relation to the benefit/risk. In frail people, the benefits of HTN treatment are small, and in the long term, residual atherosclerosis becomes the predominant risk factor [17].

Some frailty patients do not need pharmacological treatment and only general therapy, recovery and medico-social supervision. Moderation and individualization are necessary for establishing treatment targets for hypertensive frailty people. The conditions in SPRINT are not encountered in the real world, and a target of 130–139 mmHg is probably better in frailty hypertensive patients.

Conflict of interest

The authors declare no conflict of interest.

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