Consensus Document

Twelve hot questions in the management of hypertension in patients aged 80+ years and their answers with the help of the 2023 European Society of Hypertension Guidelines

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Arterial hypertension is a major risk factor for cardiovascular morbidity and mortality, and highly prevalent in older age, underscoring the importance of its appropriate management. The population is ageing at an increasing rate, with those aged 80+ years being the fastest growing population characterized by high heterogeneity in terms of functionality and autonomy. The prevalence of hypertension rises with increasing age, due to a significant increase in SBP largely as a result of age-related stiffening of the aorta and other large arteries, affecting almost 80% of those aged 80+ years. Appropriate management of blood pressure in this population is a priority for clinicians. Frailty is a condition characterized by marked vulnerability to adverse health outcomes and is common among older adults including those with hypertension. Hypertension increases frailty level and at the same time, individuals with increasing frailty present with more drug-related adverse effects meaning they are less tolerant to blood pressure lowering by medication. Thus, frailty is a factor that should be integrated when treating hypertension in this population. The European Society of Hypertension 2023 Guidelines on the management of Hypertension are the first international guidelines to integrate the concept of adapting blood pressure management in older adults according to their frailty/functionality level, and to propose practical tools for the application of this concept in the daily practice of physicians and other healthcare professionals. The present article prepared by the European Society of Hypertension Working Group on Hypertension in Older Adults aims to further address some important aspects mentioned concisely in the 2023 European Society of Hypertension guidelines, in order to help physicians and other healthcare professionals including those practicing in primary care. To this end, this study discusses 12 'hot questions' which are answered with the help of the 2023 European Society of Hypertension Guidelines. We hope the present article and Working Group's actions will contribute to understanding and applying the ideal management of hypertension in this most vulnerable population.

Keywords: frailty screening, geriatric assessment, hypertension, older adults, practice, treatment

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; COST, European Cooperation in Science and Technology; CVD, cardiovascular disease; ESH, European Society of

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Hypertension; HBPM, home blood pressure monitoring; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; NIHR, National Institute for Health and Care Research; PROGRAMMING, PROmoting GeRiAtric Medicine IN countries where it is still eMerGing; RCT, randomized-controlled trial; SCORE2-OP, Systemic COronary Risk Evaluation-Older Persons; WCH, white-coat hypertension

INTRODUCTION

Arterial hypertension, the main risk factor for mortality in those aged over 70 years, is highly prevalent in older age affecting almost 80% of the oldest old (those aged 80+ years) [1]. As such, appropriate management of hypertension is essential to improve outcomes. The population is ageing at an increasing rate [2], resulting in a sharp increase both in the number of older adults, with those aged 80+ being the fastest growing population [3]. As a result, the number of people aged 80 years or older is expected to triple between 2020 and 2050 to reach 426 million globally [2]. Consequently, clinicians have an increasing number of older patients to care for and therefore are required to have an understanding about the challenges and considerations associated with hypertension treatment in these older adults.

The improvement in sanitary factors, nutrition, preventive medicine, control of infectious diseases, as well as medical and surgical/invasive management of common diseases underlying the major sources of mortality [i.e. cardiovascular diseases (CVDs), cancer, etc.] has resulted in many individuals living to very old ages. However, many of these people live with frailty, several comorbidities and accompanying use of multiple medications jointly affecting a variety of systems. In addition, ageing itself is naturally associated with progressive physiological changes that diminish physiologic reserves, and in turn lead to a decline of biological functions. Furthermore, older adults frequently suffer from 'geriatric syndromes', which do not fit into distinct organ-based disease categories, have often multifactorial causes, and have a major impact on quality of life and disability. These include, among others, falls, cognitive impairment, mobility problems, depressive symptoms, malnutrition, incontinence and sensory deficits, leading to frailty characterized by a diminished ability to adapt to stress as well as an increased vulnerability to adverse health outcomes including disability and mortality. In this context, hypertension and CVD act as causative factors for frailty [4]. Hence, on one side, treatment of factors underlying CVD, including hypertension, is essential to prevent emergence and/or progression of frailty [5]. On the other hand, individuals with frailty suffer from an increased burden of symptoms, medical complexity, and reduced tolerance to medical and surgical interventions. Older adults with frailty have a higher CVD risk than nonfrail persons and have more than double the likelihood of CVD mortality, even after accounting for traditional CVD risk factors [6]. Moreover, frailty is highly prevalent in older hypertensive patients [7]. Thus, evaluation of frailty in older age becomes essential and should be considered as part of the management of hypertension in older adults.

The older the age, the higher are the risk, prevalence and impact of frailty. However, one should note that while frailty is partially associated with a person's age in years [2], the factors underlying frailty (e.g. biological ageing, comorbidities, environmental factors) are neither linear nor consistent across ages. This can display as the presence of frailty in some of the youngest and middle old individuals, while, in contrast very old individuals may be robust. Nevertheless, one should also recognize that the dynamics of health change more rapidly in older ages of life [8] and thus apparently robust oldest old individuals are at a higher risk for health deterioration and may become frail rapidly, especially in the settings of an acute condition.

Heterogeneity in terms of health status is very common among older adults. As a result, the evidence that underpins clinical guidance for the management of hypertension in older adults is still limited, with many patients who commonly present in the community excluded from clinical trials [9]. This is especially true and important for those aged 80+ years and also younger adults with multiple long-term conditions and frailty. Considering the significantly high prevalence of hypertension and its impact in older age, the European Society of Hypertension (ESH) has established a new working group on Hypertension in Older Adults in 2022 [10]. The working group involves experts from different disciplines (cardiology, geriatrics, internal medicine, epidemiology, public health, pathophysiology, life-health and environment sciences, clinical and experimental medicine) from countries across Europe and beyond (Belgium, France, Germany, Greece, Ireland, Italy, Korea, Poland, Portugal, Spain, The Netherlands, Turkiye, United Kingdom) [11].

Management of hypertension continuously evolves with emerging new evidence from high quality trials. Consequently, dedicated guidelines on hypertension are updated regularly. The 2023 ESH Guidelines for the management of arterial hypertension were first presented at the 32nd European meeting on hypertension and cardiovascular protection in June 2023 [12]. The guidelines include detailed 22 sections and subsections outlined in nearly 200 pages and focused on specific issues including the impact of ageing on blood pressure (BP) regulation and hypertension in older persons (section 15.3).

Given the significance and intricacies of the management of hypertension in old age and the wide content of the guideline, the ESH working group (WG) on Hypertension in Older Adults took the initiative to compose a practical paper to facilitate understanding of the 2023 Guideline's suggestions/recommendations on management of this condition in older patients and widen its content whenever needed in areas which were concisely noted due to space constraints. We hereby discuss 12 important questions on specific aspects mentioned concisely in the guidelines, in order to clarify some key understandings concerning the management of hypertension in older adults.

MATERIALS AND METHODS

Following the presentation of the 2023 ESH Guidelines on Hypertension during the 32nd European ESH meeting in Milano, the members of the WG on Hypertension in Older

Adults prepared a document listing a number of questions commonly encountered in clinical practice while managing older adults. These were refined through e-mail communications and online meetings and the final list of 12 items was agreed by all WG members in November 2023 (Box). The questions were assigned to a minimum of two WG members who discussed and finalized the answers to the questions together. The answers were completed, reviewed and approved by the whole group in June 2024.

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Box. Twelve hot questions in the management of hypertension in patients aged 80+ years identified by ESH WG on Hypertension in Older Adults

1 How can one outline the mechanisms and consequences of systolic, diastolic and pulse pressure evolution with age?
2 Is it useful to evaluate global cardiovascular risk in very old adults?
3 What is the impact of neurocognitive disorders in the management of hypertension?
4 What is the impact of noncardiovascular drugs on blood pressure variations?
5 What are the considerations for 24-h ambulatory blood pressure monitoring and self-monitoring of BP in older adults?
6 How to deal with the high blood pressure variability (postural variations, post prandial, etc.)?
7 How to assess frailty in patients with hypertension? -From the concept to the everyday clinical practice
8 Are there differences in the management of hypertension between men and women in older age?
9 Which nonpharmacological therapies should be considered in older adults?
10 How to start and up-titrate pharmacological treatment in patients aged 80+ years?
11- What are the specific precautions/problems related to antihypertensive drugs?
12 In which situations antihypertensive treatment could be decreased?

TWELVE HOT QUESTIONS AND ANSWERS

Question 1. How can one outline the mechanisms and consequences of systolic, diastolic and pulse pressure evolution with age?

The 2023 ESH guidelines outline the mechanisms and consequences of systolic, diastolic and pulse pressure evolution with age (Chapter 5.5.2.2, Table 11, and Chapter 14.6). Available studies of BP in the general population report three main observations: First, during adult life, until middle age, there is a concomitant increase in SBP and DBP due to progressive age-related increase in peripheral vascular resistance. Second, elevated SBP and DBP are associated with a higher risk of cardiovascular morbidity and mortality, and third, lowering BP can consistently reduce cardiovascular risk, especially among those younger than 85 years [13]. In older adults, SBP shows a more pronounced increase than in younger individuals, while DBP decreases with age, leading to a higher prevalence of isolated systolic hypertension. The combination of high SBP with low DBP with a subsequent consequent high pulse pressure, defined as SBP minus DBP, in older people indicates significant arterial stiffness, the most typical manifestation of arterial ageing [14–16]. Hemodynamically, high SBP and high pulse pressure increase left ventricular afterload, while low DBP can markedly compromise coronary perfusion [16]. Once present, arterial hypertension further accelerates the process of vascular ageing, emphasizing the importance of its management. However, in very old individuals and those with frailty, presenting with several comorbidities and significant functional decline, low SBP levels may not necessarily be a sign of so-called 'good arterial health,' but in fact a sign of other disorders such as heart failure or neurological diseases, leading to poor prognosis [17,18]. Additionally, individuals with marked frailty might exhibit impaired circulatory autoregulation, causing tissue hypoperfusion in the presence of relatively low BP.

Taking all these into account, the relationship between BP levels and cardiovascular risk in older adults is not linear and follows a U-shaped curve. This U-shaped curve (i.e., high morbidity and mortality for very low BP levels) is explained by two different age-related processes: a decrease in DBP levels which reflect high arterial stiffness that many individuals develop after the age of 65 years, and a decrease in SBP levels occur generally very late in life due to multimorbidity and marked frailty. Consequently, the relationships between BP levels and cardiovascular risk are much more complex than in younger populations and must always be assessed, taking into account the overall health and frailty of an individual, their intrinsic capacity for BP regulation and the impact of arterial ageing on the observed BP.

Question 2. Is it useful to evaluate global cardiovascular disease risk in very old adults?

The 2023 ESH guidelines recommend estimation of total CVD risk according to grade and stage of hypertension in each hypertensive patient because of its relevance for hypertension management (Chapter 3.5) [12]. CVD risk assessment with the Systemic Coronary Risk Evaluation-Older Persons (SCORE2-OP) system is recommended for older hypertensive patients (70–89 years old) who are not already at high or very high risk [19].

Stratifying risk in the very old and hence developing patient-centred management strategies is really challenging due to the vast heterogeneity seen in these individuals. CVD risk estimation is recommended to better identify individuals in primary prevention, for whom the risk is not yet confirmed by manifest CVD. Risk stratification is particularly important in individuals with a high-normal BP or grade 1 hypertension, in whom it may influence the decision of whether or how fast to initiate BP-lowering drug treatment [12]. In those aged between 70 and 79 years, SCORE2-OP has greater risk differentiating capacity, especially in population at low CVD risk.

Most older hypertensive patients, especially those aged 80+, are considered in general at high/very high risk mainly because the risk of CVD increases with age [20]. Due to their high/very high risk for both the risk of CVD and significant adverse drug events, the initiation of antihypertensive treatment should always take into account benefits and risks of treatment such as the development of adverse drug

events [21,22]. In addition, the risk of non-CVD mortality generally also rises with age (so that remaining life expectancy inevitably decreases with age). Thus, prevention of disability-adjusted life-years in older adults is still a major challenge in the field of preventive cardiology.

Estimating incident CVD risk may facilitate shared decision-making in CVD prevention in older persons. In addition, a comprehensive geriatric-based evaluation incorporating all contributing factors is essential to provide the most accurate assessment for the evaluation of absolute risk and benefit of treatment strategies in older adults [23].

In conclusion, CVD risk stratification is recommended for the implementation of primary prevention strategies in apparently healthy older individuals. Stratifying risk in the very old and hence developing patient-centred management strategies is really challenging due to the vast heterogeneity seen in these individuals. As such, in addition to CVD risk stratification, a comprehensive geriatric-based evaluation is essential to guide management decisions in these older adults since individualized decisions are often needed.

Question 3. What is the impact of neurocognitive disorders in the management of hypertension?

Epidemiological and clinical research has shown associations between midlife hypertension and cognitive decline in older age [24,25]. In the 2023 ESH Guidelines for the management of arterial hypertension, recommendations are made on how optimal antihypertensive treatment can contribute to the prevention of cognitive decline (Chapter 17.5.3) and how to manage hypertension in the presence of (severe) cognitive impairment (Chapter 15.3.3).

Although evidence on the benefit of BP-lowering on cognitive decline has been conflicting, a recent individual participant data meta-analysis of five randomized controlled trials (RCTs) (28 008 patients, mean age 69.1 years) showed that a SBP/DBP lowering of 10/4 mmHg was associated with a lower incidence of dementia (odds reduction of 13% after a median follow-up of 4.3 years) [26], underlying the importance of timely initiation of antihypertensive treatment when indicated. Apart from optimal hypertension management, routine clinical screening of possible cognitive impairment using, for example, the Mini-Cog [27], Mini Mental State Examination (MMSE) [28], or the Montreal Cognitive Assessment (MoCA) [29], is recommended in participants aged 65 years and older [30,31]. Moreover, in a screening study conducted in hypertensive patients without a diagnosis of dementia (mean age 76 years), cognitive impairment was observed in more than one-third of older adults without a prior diagnosis of dementia. MoCA, MMSE and Mini-Cog demonstrated comparable discriminative ability for cognitive impairment, with MoCA and MMSE having the greater sensitivity and Mini-Cog having the highest specificity [31]. Based on a recent posthoc analysis of two large trials [32,33], angiotensin II receptor blockers (ARB), dihydropyridine calcium channel blockers (CCB) and thiazide/thiazide-like diuretics seem to be preferable drug options for the prevention of cognitive decline.

The 2023 ESH Guidelines also adapted treatment strategies, based on clinical frailty scale [34] for older adults with substantial alterations of functional status and autonomy, including clinically significant dementia. For patients aged 80 years and older with clinically significant dementia but with moderate functional impairment and partial loss of autonomy, antihypertensive treatment strategies may be started when SBP is at least 160 mm Hg, with an SBP target between 140 and 150 mmHg. Reduction of antihypertensive treatment should be considered if SBP is less than 120 mmHg or in the presence of orthostatic hypotension or significant frailty. For patients with severe dementia, an indication of treatment should be individualized according to symptoms, comorbidities and polypharmacy. In particular, cholinesterase inhibitors, which are frequently prescribed in patients with Alzheimer disease, are associated with an increased risk of adverse drug reactions when used concomitantly with diuretics or beta-blockers or non-dihydropyridine CCB [35]. Since most RCTs on the management of hypertension only included fit older adults, the results of ongoing RCTs in very frail older individuals, including those with varying degrees of cognitive impairment, will provide more evidence on the benefits/risks of the aforementioned treatment strategies. Nevertheless, in the presence of progressing cognitive impairment, timely involvement of proxies is not only important for assistance with treatment adherence but also for discussing the goals of care and the benefits/risks of antihypertensive treatment [36,37].

Question 4. What is the impact of noncardiovascular drugs on blood pressure variations?

Apart from desired beneficial effects, older people are more likely to experience side effects from various medications [38]. Accordingly, a fundamental principle during medical treatment is 'any symptom should be considered as drug-related until proven otherwise' [39]. The 2023 ESH Guidelines for the management of arterial hypertension recommend obtaining information on use of noncardiovascular medications potentially increasing BP (Table 1). Another drug with this potential is mirabegron, a beta-3 agonist, utilized commonly for overactive bladder syndrome [40]. The consideration when using noncardiovascular drugs involves the potential decrease in BP (including but not limited to orthostatic hypotension). The BP may decrease beyond the ideal values, resulting in falls, cognitive problems, fatigue, decrease in functionality and even ischemic vascular events [41]. Commonly prescribed noncardiovascular drugs that have the potential to decrease BP are listed in Table 2.

In summary, in older adults being treated for hypertension, management decisions should take into account accurate information on use of noncardiovascular drugs/supplements to check a possible interference on BP management related to their use, focusing on both the potential hypertensive and hypotensive effects.

TABLE 1. Medications and other substances that may increase blood pressure

Medication/substance	Proposed mechanism	Comments
NSAIDs	Inhibition of COX-1 and 2, decreasing PG I2 and E2 synthesis with subsequent reduction in urinary Na excretion and an increased systemic vascular resistance	Mild, dose-dependent increase in BP. Increased risk with age, preexisting hypertension, salt-sensitive patients, patients with renovascular hypertension.
Paracetamol (acetaminophen)	Presumably via inhibition of cyclooxygenases and reduced production of prostaglandins.	Increased relative risk of 1.34 of hypertension with almost daily paracetamol use.
Oestrogens and progestins	Increased renin synthesis (by oestrogens) leading to RAS activation and subsequent Na and water retention.	Mild, sustained increase in BP (6/3 mmHg increase with high doses of oestrogen (>50 μg of oestrogen and 1–4 μg progestin) but can be severe, common in premenopausal women, cause hypertension in 5% of women.
Glucocorticoids	Enhanced Na reabsorption and fluid retention via stimulation of mineralocorticoid receptors. Increased systemic vascular resistance due to upregulation of AT1 receptors on vascular smooth muscle cells.	Dose-dependent, low doses have less effect on BP, more common in older patients, or with a family history of primary hypertension.
Calcineurin inhibitors	Reduced NO production, ET-1 over production, systemic and renal vasoconstriction, renal Na retention.	Dose-dependent, mild-to-moderate increase in BP. Severe hypertension has been reported. Increased risk with preexisting hypertension, elevated creatinine levels and maintenance therapy with corticosteroids.
Antidepressants SNRIs	Increased noradrenaline release causing adrenergic activation and increased SNS activity.	Dose-dependent, mild (2/1mmHg) increase in BP.
Nasal decongestants	Vasoconstriction due to stimulation of alpha-1 receptors on vascular smooth muscles.	Dose-dependent, sustained increase in BP
Erythropoietin-stimulating agents	Increased thromboxane, reduced prostacyclin levels and activation of the local RAS. Increased ET-1 production, decreased NO synthesis with subsequent vasoconstriction.	Dose-dependent, mild increase in BP, increased risk with preexisting hypertension, or when the initial haematocrit level is low
Stimulants -Modafinil -Amphetamines -Methylphenidate	Block noradrenaline or dopamine reuptake Promote release of catehcholamines	
VEGF inhibitors	Decreased NO production via VEGFR-2 antagonism and stimulation of ET-1 receptors promoting vasoconstriction	A class effect. The incidence of hypertension is dose related, risk is increased by preexisting hypertension, old age and overweight
Substances of abuse -MDMA -PCP -Methamphetamine -Cocaine -Alcohol	Increased release and inhibited reuptake of monoamine neurotransmitters with subsequent SNS activation. Increased CNS catecholamine release with decreased neuronal uptake. Cocaine induces acute sympathomimetic effects and chronic HMOD, i.e., an increase in arterial wall stiffness.	Cocaine induces both acute and chronic increase in BP. Alcohol causes a dose-dependent, sustained increase in BP.
Herbal products -Licorice -Ephedra -St. John's wort -Yohimbine -Ginseng (high doses) -Ma huang	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism. Ephedra activates the alpha-1receptor, increasing SNS activity	Licorice: Dose-dependent, sustained increase in BP characterized by hypokalaemia, metabolic alkalosis and suppressed plasma renin activity and aldosterone levels. Yohimbine causes acute, dose-dependent increase in BP.
Diet pills -Sibutramine -Phenylpropanolamine	Increased levels of norepinephrine with subsequent activation of noradrenergic transmission	Mild increase in BP

AT1 receptors, type-1 angiotensin receptors; CNS, central nervous system; COX, cyclooxygenase; ET-1, endothelin-1; HMOD, hypertension-mediated organ damage; MDMA, methylenedioxymethamphetamine; NO, nitric oxide; NSAID, nonsteroid anti-inflammatory drugs; PCP, phencyclidine (phenylcyclohexyl piperidine); PG, prostaglandin; RAS, renin-angiotensin system; SNRI, serotonine-norepinephrine reuptake inhibitor; SNS, sympathetic nervous system; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2.
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Question 5. What are the considerations for 24-h ambulatory blood pressure monitoring and self-monitoring of blood pressure in older adults?

In the ESH 2023 guidelines [12] – due to the limited available evidence – this question is not definitively addressed in the sections dealing with BP measurement (Chapters 4.7–4.9 on home BP monitoring, HBPM; ambulatory BP monitoring, ABPM), diagnostic hypertension phenotypes [Chapters 14.2 and 14.3 on white-coat hypertension (WCH) and masked hypertension]; and the dedicated section for management of hypertension in 80+ years (Chapter 15.3.2).

Selecting the optimal method to measure BP in those aged 80+ years is challenging since numerous issues must be considered. The prevalence of WCH is quite high (reaching > 50%) [42], therefore increasing the interest of applying out-of-office methods (ABPM and/or HBPM). Specific BP phenotypes (reverse-dipping, extreme-dipping; postural or postprandial hypotension) are more frequently encountered in older age groups than in younger age groups, due to multiple and often combined etiological factors, including among others: primary or secondary autonomic dysfunction, polypharmacy, tendency for volume depletion, vascular ageing (increased arterial stiffness) and increased BP variability [12]. Moreover, in this population, data from HBPM should be interpreted very cautiously, keeping in mind that these individuals are often incapable for BP self-measurement, and perform unreliable or anxious self-measurement. ABPM is the optimal method to measure BP, yet it has very low applicability due to practical

TABLE 2. Noncardiovascular drugs that can decrease blood pressure beyond ideal levels (hypotension and/or orthostatic hypotension) under antihypertensive treatment[a]

Alpha-1 receptor antagonists (for lower urinary tract symptoms related to benign prostatic hyperplasia, esp. with doxazosin, terazosin)
Antipsychotics (for behavioural and psychological symptoms of dementia or as sleep aid, with esp. clozapine, quetiapine among second-generation antipsychotics; chlorpromazine and thioridazine among first-generation antipsychotics)
Some antidepressants (tricyclic antidepressants, trazodone) (for depression, anxiety, pain or as sleep aid)
Benzodiazepines (for anxiety or as sleep aid)
Opioids (for pain)
Levodopa (for treatment of Parkinson's disease and Parkinsonism)
Sodium glucose co-transporter inhibitors (for type II diabetes or heart failure)
First generation antihistamines (for allergic conditions or as sleep aid, e.g. pheniramine, chlorpheniramine, hydroxyzine, cyproheptadine, dimenhydrinate, diphenhydramine)

[a]Currently (or increasingly) commonly used in clinical practice in older adults.

restrictions, such as limited availability. It should be also highlighted that the relationship between office and out-of-office BP are age-dependent. Evidence suggests that individuals aged 80+ years have awake-ambulatory BP, which is lower than home BP, which in turn is lower than office BP [43,44]. Finally, due to lack of data, usual gaps in knowledge are even wider in this age group, regarding the prognostic ability of HBPM, ABPM and office BP; whether HBPM/ABPM-guided therapy provides greater reductions in mortality than office BP-guided treatment, and the out-of-office BP thresholds and treatment targets to be used.

Therefore in conclusion, in individuals aged 80+ years, ABPM and/or BP self-measurement should be part of daily clinical practice. However, precautions regarding their interpretation are needed. Ideally, these two methods should be regarded as complementary to office BP.

Question 6. How to deal with the high blood pressure variability (postural variations, post prandial, etc.)?

BP variability is exacerbated in older adults, contributing to organ damage and risk of adverse events independently of 24 h average BP [45–47]. The 2023 ESH guidelines discuss determinants of BP variability and possible strategies to address high variability at old age (Chapter 4.10).

In older patients, BP variability mainly derives from age-related changes in autonomic function, increased arterial stiffness and comorbidities such as diabetes, Parkinson's disease and Parkinson-plus syndromes, and atrial fibrillation, predisposing to short and long-term BP fluctuations including orthostatic and postprandial hypotension. A high prevalence of the white-coat effect, difference in the duration of action of antihypertensive medications as well as poor drug adherence or irregular treatment intake may further contribute to BP variability [43,48].

Orthostatic hypotension (i.e., SBP fall $\geq$20 mmHg and/or DBP fall $\geq$10 mmHg within 3 min of standing and/or symptoms of cerebral hypoperfusion, such as dizziness) [49] and postprandial hypotension (i.e., SBP fall $\geq$20 mmHg within 2 h after start of a meal) [50] carry an increased risk of mortality, cardiovascular disease events and injurious falls [51–54]. Both conditions might be associated with supine hypertension in patients with autonomic failure.

Considering this high variability and the increased predisposition to hypotension, office and out-of-office BP measurements should be implemented in older adults to better define BP profile, detect possible patterns behind hypotensive episodes and guide therapeutic strategies, while avoiding overtreatment. The implementation into clinical practice and the methodology of measuring BP in the standing position is an important question for both office and out-of-office measurements. Out-of-office measurements are feasible even in patients with mild-to-moderate dementia, who show higher vulnerability to hypotension-related complications [55].

The 2023 ESH guidelines recommend that standing BP should be routinely assessed in all older adults and progressive down-titration of antihypertensive therapy should be considered in patients with orthostatic hypotension, particularly in patients with high frailty and/or impaired functional autonomy regardless of symptoms (Chapter 10.5 and Chapter 15.5.1.4). ABPM should be performed if white-coat effect or hypotensive episodes are suspected. Medications worsening orthostatic hypotension (e.g., diuretics, alpha-blockers, vasodilators, etc.) should preferably be avoided and nonpharmacological measures (i.e., standing up slowly, lower extremity resistance exercises, wearing stockings for varices, adequate fluid intake [2–3 L/day], avoiding alcohol, eating less and frequently, adequate salt intake [6–10 g/day], avoiding carbohydrate-rich foods, avoiding intense exercise in hot weather, keeping the head 30 to 45 degrees high while lying) should be implemented [41,56,57]. Pharmacological treatment of supine hypertension might be considered in selected patients with very high supine BP, balancing potential cardiovascular protection against hypotensive risk and overall patients' prognosis [58]. In this case, the pharmacological treatment is preferred to be rather short acting and not at too aggressive dose (e.g., captopril, losartan).

Question 7. How to assess frailty in patients with hypertension? From concept to everyday clinical practice

The 2023 ESH guidelines outlined the concept and assessment of frailty in patients with hypertension in everyday clinical practice in chapter 15.3.3, including Table 21.

Frailty is the increased susceptibility to adverse outcomes resulting from diminished reserve and resistance to stressors [59]. Prevalence of frailty substantially increases in older individuals especially after the age of 80 years due to the loss of functional capacities (cognitive decline, mobility problems, sensorial disorders, etc.), geriatric conditions and syndromes (sarcopenia, osteoporosis falls, incontinence, confusion, etc.), age-related diseases (heart failure, stroke, neurodegenerative diseases, etc.) and iatrogenic complications.

Frailty should be assessed by general practitioners and other qualified healthcare professionals before starting antihypertensive treatment and at least once yearly after treatment initiation, in all patients 80 years and older and in younger selected populations who present with multimorbidity and/or frailty profiles. Healthcare professionals should be educated to use validated simple and rapid (<10 min)

tools such as the Clinical Frailty Scale [34] (less than 5 min, no need for specific tools, a score ≥5/9 indicates frailty), Fried Frailty Score [59] (about 5 min for answering the questions, plus assessment of hand grip strength [needs dynamometer] and balance tests, therefore a rather time demanding test). One can consider the use of Simplified Fried Frailty Scale, which is a very simplified, easy, nontime-consuming adaptation of Fried criteria performed in less than 5 min and has been clinically validated [60]. Antihypertensive treatment should be adapted according to this frailty level as proposed in the ESH 2023 Guidelines. In addition, patients diagnosed with a high level of frailty could be referred to a geriatrician for a comprehensive geriatric assessment in order to avoid further functional decline and loss of autonomy.

Question 8. Are there differences in the management of hypertension between men and women in older age?

According to the current ESH 2023 Guidelines, there is insufficient evidence to support the existence of differential effects of antihypertensive therapy on long-term prognosis based on sex [12]. The prevalence of hypertension rises with advancing age, reaching over 80% in octogenarians, with majority of them being women [12,61].

Recent studies indicate worse control of BP in women than in men and these disparities increase with age, being largest over 75 years of age [62]. Different biological factors, faster development of arterial stiffening, kidney failure, insufficient treatment intensity or inappropriate drug choice may play a role in this phenomenon [63].

The choice of antihypertensive medication in older women should be determined by functional capacity, comorbidities and drug properties. CCB and beta-blockers may have stronger BP-lowering effects in women than in men; however, the latter may be less effective in stroke prevention [64]. Moreover, due to the high prevalence of isolated systolic hypertension in older women, CCB may be considered as an optimal drug choice [65]. Thiazide and thiazide-like diuretics may have the potential to prevent osteoporosis-a significant problem in older women, via increased calcium reabsorption [66]. However, adverse drug effects like hyponatremia, hypokalaemia and arrhythmia during treatment with diuretics, ankle oedema with dihydropyridine CCB and cough with angiotensin-converting enzyme inhibitors (ACEIs) are more common in women than in men [64]. This is one of the arguments for preferring low-dose antihypertensive combination therapy in older women, if they do not have frailty.

In summary, women predominate among older adults with hypertension. BP control is less frequently achieved in older women than men. Differences in age-related comorbidities in women as well as higher susceptibility to adverse drug reactions influence the BP management and necessitate its individualization.

Question 9. Which nonpharmacological therapies should be considered in older adults?

According to ESH 2023 guidelines, hypertension treatment in older adults should include lifestyle measures (Chapter 7). However, if people are older than 80 years, these recommendations may have to be adapted given their potential to have negative impact on health status and frailty.

Despite weak evidence, older adults benefit from smoking abstinence and reducing alcohol consumption, which are also associated with falls and cognitive impairment. Structured exercise interventions, preferably collectively and adjusted to functionality and preferences, are cornerstones in lifestyle interventions. They have multiple effects that may benefit not only BP, but also other outcomes related to physical and cognitive functions, and promote social contacts and fight loneliness/isolation. Reduction of risk is most prominent in those who were initially least active. BP reductions and cardiometabolic benefits have been reported with low-intensity physical activity (6 min hourly) in highly sedentary people [12].

In younger adults with elevated BP who are overweight/obese, weight reduction is recommended to reduce BP and improve cardiovascular outcomes. However, undernutrition (risk of malnutrition and/or overt malnutrition) is common in older adults. Even individuals with excess body weight are not spared from undernutrition (reported as ∼20% in overweight and ∼30% in obese) [12]. Low skeletal muscle mass is one of the major criteria of malnutrition [67] and is a prevalent presentation in overweight/obese older adults. Weight loss, whether intentional or not, enhances the age-related loss of muscle mass. Because meta-analyses indicate that the mortality risk of healthy older people is lowest in the *overweight* range, experts generally agree there is usually no need for *overweight* older people to lose weight [68]. In obese robust older people, considering that a slow weight reduction outweighs the risks, promotion of endurance (aerobic) physical activity, importantly also incorporating resistance exercise and personalized dietary supplementation (protein intake of at least 1 g/kg/day, with a maximally moderate caloric restriction ∼500 kcal/day less than estimated needs) is required [68].

The relation between sodium-restricted diets and improved BP control has been widely recognised and this effect is more prominent in older adults [69]. However, it is good clinical practice to avoid dietary restrictions in older persons to reduce the risk of malnutrition and related loss of fat-free mass and functional decline [68]. Hence in older adults, advising salt restriction should be limited to individuals with very high consumption (>10 g/day; in this case, we should propose a *moderately* decrease salt intake), considering the association between this intervention and malnutrition, hyponatremia, orthostatic hypotension and falls [70,71]. Measuring the 24-h urinary sodium excretion is the reference method but may be complex with poor adherence in older adults. For clinical purposes, the technique can be simplified by measuring sodium excretion only once in a single morning (or second morning) voiding urine sample simultaneously with creatinine and/or total daily urine volume (measured or inferred) [72,73]. One should consider that dietary assessment of sodium consumption (diet records or diet recall) is time-consuming and it is difficult quantifying sodium concentration in recipes [73]. The sodium tracker is suggested as an easy way to keep tabs on how much sodium are received in diet [74]. Such a recording can also help the patient make better choices.

In summary, lifestyle interventions should be based on a personalised exercise programme and smoking and alcohol consumption restriction, preventing individual's deterioration and improving CVD and other health outcomes. Salt reduction and weight loss should considered with caution, typically in specific cases where the benefits appear to outweigh risk, usually after careful geriatric assessment.

Q10. How to start and up-titrate pharmacological treatment in patients aged 80+ years?

The 2023 ESH guidelines commented on how to start and uptitrate pharmacological treatment in patients 80+ in Chapter 11.10.8 and Figure 12, Chapter 15.3.1.2 and Chapter 15.3.3 in Table 21.

It is important to recognize that:

1. Initiation with monotherapy should be considered in patients with frailty and/or advanced age.
2. Frailty assessment is crucial: fit older (80+) adults should be regarded in a similar way as in the 65–79 age range, while severely dependent patients should be treated considering their comorbidity burden, with highly individualized treatment.

It is recommended to start treatment when SBP is above 160 mmHg, but a lower threshold may be considered in fit individuals. Office SBP target is 140–150 mmHg. In fit patients and if tolerated, this may be lowered to 130–139 mmHg and cautiously, if DBP is already less than 70 mmHg. The guideline suggests considering monotherapy for patients aged 80+ years. Initial dual therapy could be considered in very fit patents especially in those with severe hypertension and/or very high cardiovascular risk profiles where low-dose combination therapy could be considered. Concerning uptitration, clear evidence is lacking. However, clinical inertia should be avoided with respect to the specified goals. It is also clear that most of these patients will eventually need combination therapy. Therefore, uptitration will be necessary, in order to reach the fixed BP targets, but at a slower pace than in younger patients in order to avoid adverse drug events.

In summary, the SBP threshold of treatment initiation (140 or 160 mmHg) and the SBP targets (between 130 and 150 mmHg) depend on an individual's level of frailty, with the lowest values for the most fit patients. The general rule is that treatment should be initiated with monotherapy and uptitration should be slower than in younger patients (start low/go slow) [75].

Q11. What are the specific precautions/ problems related to antihypertensive drugs?

The 2023 ESH guidelines discuss the specific problems and precautions related to antihypertensive drugs at chapters 9.4 and 11, including table 15. Prescription of antihypertensive drugs and monitoring of ongoing treatment is addressed in Chapter 15.3.

The guidelines state that in the absence of specific indications, there is no evidence of more pronounced long-term benefits or harms of any specific drug class. Therefore, any of the five major drug classes, that is, ACEIs, ARBs, CCBs, thiazide/thiazide-like diuretics and beta-blockers can be used. This recommendation is caveated with the fact that older patients may be more susceptible to side effects of drugs due to age by itself and health condition changes/comorbidities which at their turn might lead to pharmacodynamic and pharmacokinetic changes, for example, increased susceptibility to side effects associated with beta-blockers, most importantly fatigue or sleep-related disorders (unusual dreams or insomnia), which can negatively impact on the quality of life.

The guidelines further refer to specific prescription rules for older patients that may be of major help for reducing drug-related adverse effects [76]. In the light of monitoring antihypertensive treatment, the guidelines recommend a systematic search for orthostatic hypotension in older people, even in the absence of symptoms.

Antihypertensive medication can effectively reduce the risk of cardiovascular disease in people of all ages [13], but can also have harmful side effects. Although common side effects such as dizziness, fatigue and headaches are often manageable through medicines optimization, there is evidence of more serious adverse events that must be taken into account when prescribing medication to older people [38,77].

For any patient, careful consideration of the benefit-risk ratio of each antihypertensive drug strategy is needed for optimal treatment. Adverse events might be drug specific (e.g., electrolyte abnormalities) or related to the BP lowering effect (e.g., syncope and falls). Orthostatic hypotension, a common adverse effect of most antihypertensive medications, could remain asymptomatic until the occurrence of a major complication such as fall, dizziness, confusion. For this reason, BP measurements at 1 and 3 min in upright position should systematically be performed in older adults even in the absence of symptoms [18].

Drug specific side effects can include:

1. Hyperkalaemia in patients prescribed ACEI, ARB and mineralocorticoid receptor antagonists
2. Bradycardia and cardiac decompensation in patients prescribed beta-blockers or non-dihydropyridine CCB especially when both these drug classes are used
3. Hypokalaemia, hyponatremia (with mineralocorticoid receptor antagonists) and gout in patients prescribed diuretics, thiazides and loop diuretics
4. Orthostatic or postprandial hypotension and syncope in patients prescribed alpha- blockers, centrally acting antihypertensives and vasodilators

Whilst these adverse events can affect people of any age, their incidence is much more common in older adults and those with frailty, due to an increase in underlying risk factors for these conditions, such as polypharmacy and reduction in kidney function [78,79].

Further important age-related adverse events to consider in older adults include aggravation of urinary incontinence with diuretics, risk of cognitive deterioration and delirium due to anticholinergic effects of some drugs (e.g. furosemide, metoprolol esp. when used in combination with other anticholinergic drugs) [80], lower limb oedema leading to gait problems, falls and excessive fatigue and

depression which are both aggravated by prescription of beta-blockers, α-blockers and central alpha-adrenoreceptor agonists [81].

In summary, while antihypertensive medication is crucial for managing hypertension, physicians should be mindful of its potential harms, particularly in older adults and those with frailty. A personalized approach to care should be taken that considers the benefits of medication alongside the potential risks. Once treatment has been initiated, physicians should regularly monitor for orthostatic hypotension, hypotensive episodes and other adverse events.

Q12. In which situations antihypertensive treatment could be decreased?

The 2023 ESH guidelines discuss situations at which antihypertensive treatment could be decreased in Chapters 9.4 and 15.3.3, including table 21.

The benefits and risks of antihypertensive treatment in older people are mostly studied through controlled clinical trials. These trials have shown that the treatment reduces the risk of stroke, heart attack, heart disease, and death from any cause [13,82]. However, it is important to note that these trials typically involve healthier individuals who may not have multiple long-term conditions, frailty or be on multiple medications, such as those that might be encountered in the community [9]. In such community-dwelling patients, there may be an increased risk of harm from adverse events, which could outweigh the benefits of continued treatment [38,83,84].

If the benefits of treatment are considered to be outweighed by the potential harms, clinicians may consider *deprescribing (reducing the dose and/or stopping the medication)* antihypertensive treatment [85]. This is most commonly performed after an adverse event that is considered to be caused by the medication. Deprescribing may also be considered if an individual experiences significant syncope, falls, acute kidney injury or electrolyte abnormalities such as hyperkalaemia (in the presence of renin-angiotensin-aldosterone blockers) or hypokalaemia (in the presence of thiazide and thiazide-like diuretics). Moreover, antihypertensive deprescribing may be considered in older individuals who have low SBP, defined in the ESH 2023 guidelines as less than 120 mmHg. This may indicate that they are at reduced risk of cardiovascular disease [86], particularly if the lower BP persists and is not due to other conditions. A decrease in BP has also been reported during the last 2 years before death pointing out the importance of regular follow-ups [87]. Caution is required, since some individuals may experience symptoms like syncope or orthostatic hypotension, which are associated with an increased risk of all-cause mortality, cardiovascular events or stroke [88]. This underscores the importance of balancing the prevention of cardiovascular diseases with the need to mitigate drug-induced adverse events in older adults.

PERSPECTIVES AND CONCLUSION

The most crucial question regarding guidelines for disease management is whether these guidelines will be read, understood, and primarily applied in daily clinical practice. To this end, the ESH Working Group on Hypertension in Older Adults offers this article in which we further elaborate on 12 'hot' questions regarding the management of hypertension in older adults, as concisely mentioned in the ESH 2023 guidelines, to further assist physicians and other healthcare professionals, to better understand and apply these guidelines.

The key element is the education of general practitioners and other physicians as well as nurses and other healthcare professionals practicing the management of hypertension in older people. This is related to the pathophysiology of hypertension in older adults, and an impressively high heterogeneity among the individuals of this age group in terms of numbers of comorbidities and medications, level of frailty, cognitive status, functional capacities and many other age-related syndromes and diseases. At the same time, cardiovascular complications are by far the most important causes of morbidity, loss of autonomy and mortality in this population.

Our WG aims to develop such educational programs in collaboration with the local ESH expert centres and several European Societies such as the European Geriatric Medicine Society (EuGMS) [89] and the European COST PROGRAMMING action (PROmoting GeRiAtric Medicine in countries where it is still eMergING, CA21122) [90]. This action aims the development of geriatric skills and education for the nongeriatricians especially in countries in which geriatric medicine is still emerging. We hope and expect that the present article and WG's actions will contribute to a patient-centred management of hypertension in this rapidly increasing population.

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Conflicts of interest

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