Original Article

Routine assessment of cognitive function in older patients with hypertension seen by primary care physicians: why and how—a decision-making support from the working group on 'hypertension and the brain' of the European Society of Hypertension and from the European Geriatric Medicine Society

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The guidelines on hypertension recently published by the European Societies of Hypertension and Cardiology, have acknowledged cognitive function (and its decline) as a hypertension-mediated organ damage. In fact, brain damage can be the only hypertension-mediated organ damage in more than 30% of hypertensive patients, evolving undetected for several years if not appropriately screened; as long as undetected it cannot provide either corrective measures, nor adequate risk stratification of the hypertensive patient.
The medical community dealing with older hypertensive patients should have a simple and pragmatic approach to early identify and precisely treat these patients. Both hypertension and cognitive decline are undeniably growing pandemics in developed or epidemiologically transitioning societies. Furthermore, there is a clear-cut connection between exposure to the increased blood pressure and development of cognitive decline.
Therefore, a group of experts in the field from the European Society of Hypertension and from the European Geriatric Medicine Society gathered together to answer practical clinical questions that often face the physician when dealing with their hypertensive patients in a routine clinical practice. They elaborated a decision-making approach to help standardize such clinical evaluation.

Keywords: arterial stiffness, assessment, cognition, dementia, hypertension, hypertension-mediated organ damage, prevention

Abbreviations: BP, blood pressure; CT, computed tomography; DALYs, disability adjusted life years; HMOD, hypertension-mediated organ damage; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment; PWV, pulse wave velocity; SPRINT, Systolic Blood Pressure Intervention Trial

RATIONALE OF THE CURRENT STATEMENT

The growing prevalence of dementia is a major concern at different social levels (healthcare, research, social security, etc). The lack of effective treatment for a long-lasting, disabling condition is leading to a 'rise in pseudomedicine' [1].

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TABLE 1. Entry questionnaire

	Question	Physician opinion and knowledge
	Why	
1	How would you rank the occurrence of dementia and its burden?	
2	Do you think hypertension is a major risk factor for cognitive impairment and dementia?	
3	Which are the key factors in the management of hypertension that can modify onset and progression to dementia? How often should they be monitored over time for an effective prevention and/or postponement of dementia?	
4	Are there any additional factors for cognitive impairment of greater relevance when managing patients with hypertension 75 years or older?	
5	If the equipment is/was available, would you consider useful and appropriate an assessment of arterial stiffness (PWV) in patients with hypertension, to identify those at risk of cognitive decline?	
	How	
6	Is it relevant to screen for cognitive function in hypertensive patients? Which cognitive test to adopt?	
7	Would you request neuroimaging (CT or MRI scan) in your hypertensive patient with complaints of memory loss? Why?	

CT, computed tomography; PWV, pulse wave velocity.

Clinicians and Researchers should rather focus on *interventions that may delay the onset, progression, and disabling outcomes of dementia*. In fact, decline in average global cognitive function may begin at least 10 years before clinical diagnosis of dementia, with the decline accelerated about 3 years before clinical diagnosis [2]. In addition, patients with either slower or accelerating decline in cognitive function over time can be identified [3]. Even vascular brain lesions can accumulate silently, and this is far more common than overt stroke [4].

Several modifiable risk factors for cognitive decline and dementia have emerged in the last years [4], hypertension being the most prevalent. Associations between hypertension and cognitive impairment are modified by the age at which blood pressure (BP) is measured, with midlife hypertension being associated with later-life cognitive decline across numerous studies [5]. This finding emphasizes the relevance of a life-course approach to reduce the burden of high BP [6], including preventive strategies at older ages [7].

Therefore, the overarching goal of the present Statement is to promote a more appropriate approach to the routine assessment of cognitive function in older patients with hypertension. To achieve this goal, Part 1 of the article is aimed at increasing general practitioners (GPs) awareness about the relations between hypertension (and its management) and cognitive function, whereas Part 2 is aimed at providing a quick and manageable support for decision-making in daily clinical practice regarding the minimum cognitive screening for older patients with hypertension.

It is important to draw attention to the multifactorial nature of cognitive impairment. Consequently, several reasons support the search of early cognitive impairment: from identifying and treating reversible causes of dementia, to management of co-morbid health conditions, empowering patients to a more appropriate BP monitoring, increasing of family and doctors awareness of the relevance in understanding, adhering, and periodically reviewing the recommended therapy.

Hoping to simplify and encouraging its reading we have articulated the present Statement in seven simple questions. These bullet questions correspond to daily practice situations that the clinician is faced with, when fully evaluating a patient with hypertension. The main intention is to present evidence from a panel of experts gathered by the working group on Hypertension and the Brain of the European Society of Hypertension and by the European Geriatric Medicine Society to address these issues, and help decision-making more fluent and accurate in the clinic practice.

It was obvious to the working group that the medical community dealing with these patients should have a simple and pragmatic approach to early identification and appropriate treatment of these patients. Both hypertension and cognitive decline are undeniably growing pandemics in developed or epidemiologic transitioning societies. Furthermore, there is a clear-cut connection between exposure to the increased BP and development of cognitive decline.

ENTRY QUESTIONNAIRE

To promote the physician's active approach and initiative to the issue of cognitive function in patient with hypertension we propose each reader to firstly answer the Questions in Table 1.

A summary of the decision-making approach is shown in Table 2 near the end of this article.

Each reader may compare her/his original opinion and evaluate whether this statement has helped her/him in agreeing with the proposed Clinical Practice.

Question 1: How would you rank the occurrence of dementia and its burden?

Dementia is one of the major determinants of loss of autonomy in activities of daily living and the main reason for the institutionalization of older people. Epidemiological studies conducted over the past 20 years have shown that the prevalence of dementia is around 5.6–7.6% in the population over 60 years of age. Moreover, it has been estimated that there would be currently around 50 million dementia cases worldwide [8,9]. Projections show that this number has almost doubled over the past 20 years and that the number of dementia cases in 2050 will be above 100 million [9].

Epidemiologic studies have also shown that the incidence exponentially increases with age and, as the world's population ages, the number of dementia cases increases dramatically around the world: it has been estimated one new case every 3–4 s [9]. Importantly, the vast majority of new cases are expected to occur in very low-to-median income countries. For example, the number of people with

TABLE 2. Proposed approach to the cognitive evaluation of hypertensive patients

	Question	Physician opinion and knowledge
	Why	
1	How would you rank the occurrence of dementia and its burden?	Dementia is a profoundly disabling disease Early identification of patients at risk or with cognitive impairment and concurrent prevention strategies are highly recommended to postpone clinical onset and progression of dementia
2	Do you think hypertension is a major risk factor for cognitive impairment and dementia?	Dementia cannot be healed, yet it is still potentially preventable Long-term elevated BP, especially when occurring in midlife and young-old adults, is an established risk factor for accelerated cognitive decline and dementia Current evidence points towards the potential benefit of an optimal management of BP to reduce the risk of cognitive decline and dementia
3	Which are the key factors in the management of hypertension that can modify onset and progression to dementia? How often should they be monitored over time for an effective prevention and/or postponement of dementia?	Routinely assess cognitive decline in hypertensive patients after the age of 65 Periodically evaluate BP variability and the presence of – spontaneous or iatrogenic – orthostatic hypotension Promote home BP monitoring of BP and instruct patients to look for medical advice if BP is not kept in established limits and/or great BP variability is observed Promote treatment adherence and persistence on treatment by using single pill combination treatment strategies and periodic programmed monitoring Comply with current recommendations concerning periodic HMOD evaluation (as red-flags for cognitive screening) assess HMOD at least every 2 years in lower risk patients and every year in higher risk patients Assess cognitive function every year in asymptomatic patients and those younger than 75 years and every 6 months in those with subjective complaints of memory loss or in those $\geq$75 years
4	Are there any additional factors for cognitive impairment of greater relevance when managing patients with hypertension 75 years or older?	Never exclude the risk of hypotensive episodes in older hypertensive patients, especially in the presence of new onset and/or quickly evolving cognitive symptoms Promote standardized home BP measurements in three different hours of the day to identify transient hypotensive episodes (planning 24-h ABPM as needed) Periodically reasses therapy (dosage, schedule, association) to avoid overprescription and therapeutic inertia
5	If the equipment is/was available, would you consider useful and appropriate an assessment of arterial stiffness (PWV) in patients with hypertension, to identify those at risk of cognitive decline?	PWV provides information about vascular system aging (and biological age). Thus, PWV bears superior power than BP to detect the patients at risk of progression to dementia PWV has the ability to detect accelerated arterial aging early in the life-course and, thus, allows a more intensive management of CV morbidity and disability – including dementia
	HOW	
6	Is it relevant to screen for cognitive function in hypertensive patients?	Short cognitive screening tests should be performed in hypertensive patients by attending physicians (primary care physician or referral hypertension specialist) in hypertensive patients >65 years Its goal is screening and referral rather than making diagnosis of dementia MMSE and MoCA tests are simple and fast screening tools, performable in 10 min each, useful for periodic reassessment and pinpointing those hypertensive patients that require referral for more refined cognitive characterization
7	Would you request neuroimaging (CT or MRI scan) in your hypertensive patient with complaints of memory loss? Why?	The diagnosis of dementia is clinical, and neuroimaging exams should be used to rule out treatable causes of cognitive decline Neuroimaging is a part of specialized evaluation and follow-up in patients with dementia

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CT, computed tomography; CV, cardiovascular; HMOD, hypertension mediated organ damage; MMSE, Mini–Mental State Examination; MoCA, Montreal Cognitive Assessment; PWV, pulse wave velocity.

dementia in China and India is estimated to increase by 300% during the next decade [10]. The management of dementia is therefore a major challenge in most countries of the world.

In terms of mortality, dementia was the fifth leading cause of death worldwide in 2016 (2.4 million deaths) [8]. Dementia is a profoundly disabling disease in its late stages, the key indicator used to study its global impact is the disability adjusted life years (DALYs) which is the sum of years lived with disability and years of life lost, thus combining the effect of the disease on both quality and quantity of life. Globally, dementia was responsible for 28.8 million DALYs in 2016 which makes it the 23rd cause of DALYs globally [8]. As a result, the annual cost of dementia is estimated at $818 billion [9] (https://www.who.int/mental_health/neurology/dementia/policy_guidance/en/) [accessed April 2019.

The dramatic increase in the number of dementia cases is all the more worrying as we currently have no curative or disease-modifying treatment and the vast majority of recent trials have failed [11,12]. With such a bleak picture of a global epidemic of a disease associated with high morbidity and mortality and without any treatment in the short to medium term, a glimmer of hope comes from possible prevention strategies. Indeed, several population-based cohort studies have shown that vascular risk factors are associated with the risk of Alzheimer's disease [4]. These data, supplemented by anatomo-pathological studies that show a combination of vascular and neurodegenerative lesions in the vast majority of dementia cases, have raised hopes that a better control of metabolic and vascular factors, including hypertension, could help reduce the incidence of dementia [13].

'Dementia is a profoundly disabling disease.

Early identification of patients at risk or with cognitive impairment and concurrent prevention strategies are highly recommended to postpone clinical onset and progression of dementia'.

Question 2: Do you think hypertension is a major risk factor for cognitive impairment and dementia?

It has been reported that about 37% of patients affected by dementia have hypertension [14]. In older patients, hypertension was reported in 62% of patients 65–74 years old with dementia [15].

Hypertension is one of the major modifiable cardiovascular risk factors for accelerated cognitive decline in aging,

which provides a potential for interventions to decrease the rate of decay and delay the onset of clinical mild cognitive impairment and dementia [4,16–18].

Long-standing arterial hypertension is known to confer a cumulative effect on cerebrovascular damage, including atherosclerosis, white matter lesions, silent brain infarcts, microinfarcts, microbleeds, and brain atrophy [19], and more especially hippocampal atrophy [20]. Thus, chronic hypertension is the most powerful risk factor not only for clinical stroke, but also for subclinical cerebral small vessel disease. Improvement in BP control has contributed to a substantial reduction in incidence and mortality of clinical stroke in high-income countries over the past four decades. In addition, evidence has been accumulating that not only clinical stroke but also the load of subclinical cerebral small vessel disease has been strongly associated with cognitive decline and dementia [19].

Indeed, observational cohort studies have provided rather consistent evidence supporting the deleterious effect of chronic hypertension at young-adulthood or midlife on late-life cognitive function, but the cognitive consequence of late-life hypertension is less clear [4]. In addition, numerous prospective cohort studies have shown that use of antihypertensive drugs is associated with reduced risk of cognitive impairment and dementia in older people [21]. In 2019, the working group on Hypertension and Brain of the European Society of Hypertension (ESH) has produced a practice newsletter including a full review of the effect of antihypertensive treatment in cognitive decline [22].

However, evidence from randomized clinical trials remains inconclusive with regard to cognitive benefits of antihypertensive treatment in older adults with hypertension. Systematic reviews and meta-analyses of randomized controlled trials of BP-lowering therapy and risk of cognitive impairment and dementia were inconclusive among older patients with hypertension [21] as well as in patients with a history of clinical stroke or transient ischemic attacks. Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) showed that in people aged at least 50 years and free of diabetes and preexisting stroke, intensive control of BP (a goal of SBP < 120 vs. <140 mmHg) reduced the risk of mild cognitive impairment, but not the risk of probable dementia [23]. Of note, BP intervention in SPRINT was terminated earlier owing to cardiovascular benefit of intensive control group, which might limit the power to demonstrate an evident effect on risk reduction of dementia. Further, the randomized controlled trial of the Heart Outcomes Prevention Evaluation-3 failed to show an effect of BP-lowering therapy alone or in combination with lipid-lowering therapy on cognitive function in older people (age $\geq$70 years) without cardiovascular disease [24]. There is no controlled study comparing the effects on cognition of different classes of antihypertensive drugs. Meta-analyses of randomized controlled clinical trials suggesting the superiority of certain classes of antihypertensive drugs in older adults [25,26] have methodological limitations (combined analysis of observational and randomized controlled studies, for example). Therefore, the 'superiority' of some drugs as compared with others is just a hypothesis without any solid evidence. Also, most of the research in the field still uses global measures of cognition such as mini-mental state examination (MMSE) and/or MoCA, therefore, reducing the interpretability of the specific domains potentially involved and the detection of the treatment efficacy on specific cognitive performances.

Future research should seek to clarify cognitive benefits of different classes of antihypertensive medication, that has been identified as one of the gaps in knowledge and priority for future research by current ESH European Society of Cardiology (ESC) Guidelines [27].

'Dementia cannot be healed, yet it is still potentially preventable.

Long-term elevated BP, especially when occurring in midlife and young-old adults, is an established risk factor for accelerated cognitive decline and dementia.

Current evidence points towards the potential benefit of an optimal management of BP to reduce the risk of cognitive decline and dementia'.

Question 3: Which are the key factors in the management of hypertension that can modify onset and progression to dementia? How often should they be monitored over time for an effective prevention and/or postponement of dementia?

In view of a life-course approach to hypertension and the associated disabling health conditions [6], early life and midlife detection and control of BP, glucose and lipid levels appears reasonable with the potential to delay or prevent the disease onset.

Antihypertensive drug treatment along with lifestyle changes (i.e. smoking cessation, maintaining healthy body weight, and physical activity) should start as soon as possible and particularly in middle aged patients with the aim of achieving BP control to prevent also cognitive impairment and dementia in later life.

Key factors for a successful achievement of this goal are: periodic BP, measurement, improving, and promoting adherence and persistence in medical prescription, periodic evaluation of hypertension-mediated organ damage (HMOD).

Blood pressure variability

Both 24-h BP profile and variability have been associated with cerebral white matter lesions [28,29]. MRI detected lacunae and white matter lesions correlated not only with nondippers status (i.e. with a blunted nocturnal fall in BP levels) [30], but also with the condition of extreme dipper (i.e. with a marked nocturnal fall in BP levels) [31]. BP variability has also been associated with accelerated arterial aging [32].

Notably, hypertension loses its predictive role for cognitive decline in later life, leaving open the door to the risk of over-treatment and hypotension in the onset and progression of cognitive impairment in oldest old patients (see Question 4 below).

Therefore, measuring and targeting BP variability might help to identify hypertensive patients who are at higher risk

of developing silent cerebral damage, predisposing to the onset and progression of cognitive impairment.

Orthostatic hypotension

Orthostatic hypotension, classically defined as a sustained drop in SBP of at least 20 mmHg or DBP of at least 10 mmHg (≥15 mmHg with SH) within 3 min after moving from the supine to the upright position [33], is common in older patients [34]. Of note, orthostatic hypotension is a common feature of Parkinson's disease (prevalence 30–65%) and dementia with Lewy bodies (prevalence up to 69%) [35,36].

The causal relationship between orthostatic hypotension and cognitive impairment remains controversial [37,38]. However, treating and preventing orthostatic hypotension is able to minimize symptoms like mental fluctuations, falls, lethargy, fatigue, and dizziness and, thus, improving quality of life in both patients with or without dementia [39]. This is to remark once more the relevance of periodic revision of the patients' therapy to avoid cognitive iatrogenic effects of antihypertensive medication, alpha-blockers for urinary dysfunction, and drugs for neurobehavioural, psychiatric, and motor symptoms (e.g. antipsychotics, cholinesterase inhibitors, anxiolytics, sedatives, and dopamine agonists) [40,41].

Periodic home blood pressure measurement

Home BP values were more strongly associated with cognitive decline compared with office BP values, and day-to-day home BP variability predicts cognitive decline as well [42].

There is clear evidence that patient self-monitoring has a beneficial effect on medication adherence and BP control [27]. Promoting standardized home BP assessment, with the use of validated BP devices, and patient education and counselling as needed, is also a simple and effective way to increase patient awareness on BP levels and empowerment (the patient as the primary actor responsible of his/her health). Home BP measurements are more reproducible, more indicative of hypertension-mediated organ damage (especially left ventricular hypertrophy) and have greater prognostic significance than conventional office BP measurements [27].

Adherence and persistence

Multimorbidity, that is the simultaneous occurrence of at least two diseases, is extremely common in older patients and is often accompanied by polypharmacy, that is the daily intake of at least five drugs, that may lead to adverse drug reaction because of drug–drug or drug–disease interaction [43]. Not surprisingly, adverse drug reaction as the result of inappropriate medical prescription and/or inappropriate and inconsistent drug intake are a major cause of healthcare resource use and hospitalization.

Early discontinuation of treatment and inconsistent daily use of prescribed antihypertensive treatment are the most common contributors to poor adherence. Active participation in the treatment as well as routine evaluation of patient's adherence and drug side effects may prevent the development of complications and progressing decline in daily cognitive functioning [44].

Notably, poorer medication adherence may contribute to progression to dementia. In a prospective community-based cohort study including 4368 participants aged at least 65 years the risk of dementia was three times greater in those with moderate antihypertensive adherence compared with those with near perfect treatment adherence [45].

Routine assessment of cognitive function

Routine evaluation of cognitive function should be mandatory in hypertensive patients from at least 65 years of age and beyond (see Question 6 for more details).

Periodic follow-up and monitoring

The accurate and periodic assessment of HMOD is an important tool for detecting cardiovascular risk, systemic vascular 'health status', and safety and efficacy of treatment. These measures are likely to be largely effective for preventing or postponing onset and progression of clinical overt dementia.

Current Hypertension Guidelines [27], suggest that an interval between medical evaluations of 6 months is reasonable (in controlled hypertensive patients). A synthesis of the evidence on effectiveness, cost, and potential response to therapy, would render advisable:

1. Empowerment and reinforcement of patients and their family for routine weekly home BP measurement in the morning and in the evening;
2. Assessment of cardiovascular risk factors every year in lower risk patients and every 6 months in higher risk patients;
3. Assessment of heart, vascular, and kidney HMOD at least every 2 years in lower risk patients and every year in higher risk patients;
4. Assessment of cognitive function every year in asymptomatic patients and those younger than 75 years and every 6 months in those with subjective complaints of memory loss or in those at least 75 years.

To avoid physician inertia and a sort of 'carry-over' of long-lasting antihypertensive medical prescription, frequent (every 3–6 months depending on the patient complexity) and greater attention to periodic evaluation of adherence is recommended. The paragraph 10.4 of current Guidelines [27] provides more detailed consideration regarding the complex and multifaceted issue of adherence.

'Routinely assess cognitive decline in hypertensive patients after the age of 65.

Periodically evaluate BP variability and the presence of – spontaneous or iatrogenic – Orthostatic Hypotension.

Promote Home Blood pressure monitoring of BP and instruct patients to look for medical advice if BP is not kept in established limits and/or great BP variability is observed.

Promote Treatment Adherence and Persistence on treatment by using single pill combination treatment strategies and periodic programmed monitoring.

Comply with current recommendations concerning periodic HMOD evaluation (as red-flags for cognitive

screening) Assess HMOD at least every two years in lower risk patients and every year in higher risk patients.

Assess cognitive function every year in asymptomatic patients and those younger than 75 years and every six months in those with subjective complaints of memory loss or in those ≥75 years'.

Question 4: Are there any additional factors for cognitive impairment of greater relevance when managing patients with hypertension 75 years or older?

Recently, the SPRINT MIND Investigators published a study showing that intensive BP control (target SBP of <120 mmHg compared with a target of <140 mmHg) did not significantly reduce the risk of probable dementia in a large population of a broad age range [23]. In other terms, a greater lowering of BP does not provide an extra protection against dementia, at least in the whole population. A more careful reading of the Results revealed that intensive BP was beneficial on the composite outcome of Mild Cognitive Impairment or Probable Dementia in patients less than 75 years (hazard ratio 0.80, 95% confidence interval 0.65–0.98), but not in patients at least 75 years. One possible explanation of the lack of benefits of a greater BP lowering in patients older than 75 years on the prevention of dementia is represented by the fact that hypotension – that is not captured by the variable 'orthostatic hypotension' adopted to stratify SPRINT MIND participants – is a quite common phenomenon in older patients [46], affecting approximately 50% of older treated hypertensive patients [46].

Certainly, a greater BP variability [47] can both contribute to increase progression of cognitive impairment.

Another study in population showed that SBP lower than 120 mmHg was associated with a greater risk of new onset dementia, a risk comparable with that conferred by a SBP at least 160 mmHg [48].

Further evidence from clinical studies reported that episodes of hypotension were associated with significantly greater odds of progression to dementia in older patients with normal cognitive function [49].

Given that in a stiffer arterial system, hypotension result in cerebral hypoperfusion, assessment of arterial stiffness – where equipment is available – is encouraged to insure a more accurate management of antihypertensive therapy (dosage, adherence, home BP routine control, etc) (see Question 5).

The role of antihypertensive therapy in preventing cognitive disorders in older people remains a matter of debate, especially in free of stroke patients.

'Never exclude the risk of hypotensive episodes in older hypertensive patients, especially in the presence of new onset and/or quickly evolving cognitive symptoms.

Promote standardized home BP measurements in three different hours of the day to identify transient hypotensive episodes (planning 24-h ABPM as needed).

Periodically re-asses therapy (dosage, schedule, association) to avoid over-prescription and therapeutic inertia'.

Question 5: If the equipment was/is available, would you consider useful and appropriate an assessment of arterial stiffness (pulse wave velocity) in hypertensive patients to identify those at risk of cognitive decline?

In 2001 for the first time a large clinical study showed that in hypertensive patients, aortic pulse wave velocity was an independent determinant of mortality [50]. Since that publication, arterial stiffness, indexed as aortic pulse wave velocity (PWV), has progressively emerged as a proxy of arterial aging – from the Early Vascular Aging to the 'successful' Healthy Vascular Aging [51,52], and a predictor of cardiovascular events independent of traditional cardiovascular risk factors levels. Arterial stiffness has also been reported to be associated with multiple HMOD [53] as well as with BP variability [32].

For the most part of this document, the case has been made for a significant contribution of vascular dysfunction to the development of neurocognitive decline. The argument has been centred in BP, as a marker of arterial dysfunction. Still, evidence has been surfacing concerning other features of arterial function that can influence the development of brain damage, namely the level of arterial stiffness measured through PWV. The question is to learn if PWV (itself a HMOD marker) can identify asymptomatic hypertensive patients at higher risk of cognitive dysfunction, beyond the associated risk already consigned by increased BP per se. Recently, it has been reported that PWV levels may modify the response to antihypertensive treatment [54].

The predictive value of arterial stiffness as a marker of risk for cognitive decline and dementia independently of age and traditional cardiovascular risk factors has been reported starting 15 years ago [55]. Even if evaluating distinct domains of cognition with different metrics, aggregate evidence reported in meta-analysis finds an increased risk of global cognitive decline with increased arterial stiffness, with lower quality evidence reporting the same risk for memory decline [56]. More recently, a study evaluating cognition, BP, and PWV in middle-aged patients documented that PWV was superior to BP in predicting cognitive decline across multiple domains (even after adjustment for hypertensive status) [57]. The negative association between arterial stiffness and cognition over time, independently of other risk factors, was confirmed in older patients participating in the Rotterdam Study [58], in very old patients living in nursing homes participating in the PARTAGE [59] and in old hypertensive patients participating in the ADELAHYDE study [60].

Though the pathophysiological mechanism linking higher PWV to a greater cognitive decline have not been fully elucidated, it is likely that PWV represents a marker of vascular health status, integrating the cross-talk between macrocirculation and microcirculation damage and the ability of large vessel to adapt to sudden hemodynamic changes [61,62].

Therefore, a triple role for PWV in clinical management of the progression of cognitive decline can be envisioned:

1. PWV has superior power to detect those patients at risk of progression to dementia than other risk factors

(including BP and/or hypertensive status), identifying those requiring a more accurate assessment and frequent follow-up – including revision of therapy and adherence;
2. PWV could represent a therapeutic target to reduce the risk of cognitive dysfunction (issue to be confirmed by new trials with such purpose);
3. PWV has the ability to detect early and with more sensitivity the effect of antihypertensive treatment, enabling the physician to understand if the strategy used is moving in the correct direction [27].

In conclusion, the routine measurement of PWV in patients with hypertension, whenever available, provides added value in the evaluation of the risk of progression of the cognitive decline.

It is not task of the Primary Care Physician to perform such a test, rather to get information on nearby Centres performing PWV measurement where to address patients with hypertension.

'PWV provides information about vascular system aging (and biological age). Thus, PWV bears superior power than BP to detect the patients at risk of progression to dementia.

PWV has the ability to detect accelerated arterial aging early in the life-course and thus, allows a more intensive management of CV morbidity and disability – including dementia'.

Question 6 Is it relevant to screen for cognitive function in patients with hypertension? Which cognitive test to adopt?

In spite of the large number data in support of the detrimental role of hypertension on the alteration in brain structure and in the onset and progression of cognitive decline and dementia briefly mentioned above, randomized controlled trials of antihypertensive medications have not still demonstrated consistent delays in cognitive decline, despite reductions in BP [21,63]. Thus, the indication to screen for cognitive function in patients with hypertension remains controversial.

Current ESC ESH Hypertension Guidelines mention investigation for history of cognitive impairment (Table 12) and neurological examination and cognitive status (Table 13) as key information and steps in the routine evaluation of patient with hypertension. Similarly, testing for cognitive function is mentioned as a 'More detailed screening for HMOD' (Table 15) [27].

Nonetheless, no clear recommendation on routine screening for cognitive function – neither if limited to specific age groups – is present.

In addition, ethic considerations contribute to the complexity and controversy about screening for cognitive functions in patients with hypertension. Briefly, if dementia is largely not reversible and not treatable do patients with hypertension really want to know their prognosis about dementia? Which is the impact of a false positive to the test adopted to screen cognition? The likelihood of a false-positive result when adopting the MMSE test is 10–14% when screening for dementia and about 13% when screening for mild cognitive impairment [64].

Because evidence for screening cognitive impairment in asymptomatic older adults living in the community is lacking, the balance of benefits and harms cannot be determined [65,66].

However, we should consider that dementia is not a reversible nor a treatable condition, BUT it is largely preventable and the progression of cognitive decline may be slowed down.

In fact, improvement in control of multiple cardiovascular risk factors (e.g. high BP and high cholesterol) might partially contribute to the declining incidence of dementia [13] and the optimal cardiovascular health metrics was associated with a lower risk of cognitive and dementia in older adults [67]. In addition, silent cerebrovascular lesions (white matter lesions, lacunar infarcts, or microbleeds) are even more prevalent (44%) than cardiac (21%) and renal (26%) subclinical organ damage, and do frequently occur (35%) in the absence of other signs of organ damage [68].

Benefits of routine screening of cognitive function may regard treatment of reversible causes of dementia, a tighter management of cardiovascular risk factors – avoiding the excess of 'intensive' control of their levels – and additional comorbid heath conditions, empowerment of patient, family, and clinician about the relevance of adhering to recommended therapy.

It is fundamental to remark that in the routine clinical practice, there is no reason why a short cognitive screening in patients with hypertension should be administered only by a cognitive health specialist (neurologist, psychiatrist, or geriatrician). To the contrary, it should be administered by either GPs or hypertension specialists [69].

The most used test for cognitive screening is the MMSE [68], requiring about 10 min for the administration. Briefly, MMSE explores seven cognitive domains with a maximum score of 30; its score is influenced by age and education; its major limitation is the ceiling effect and the absence of items exploring the executive function.

The newer Montreal Cognitive Assessment (MoCA) [69], that is a little longer than MMSE to be administered, explores ten cognitive domains, including executive functions, with a maximum score of 30; it is available on-line and has been validated in more than 35 languages. A higher correlation of the MoCA than MMSE with neuropsychological tests for memory, executive functioning, visuospatial, and the Mattis Dementia Rating Scale has been reported [70]. The MoCA further allows to formulate hypotheses on the processes underlying the memory deficits in the recall subtest (i.e. mnesic/hippocampal vs. executive/frontal). This test offer parallel versions in various languages.

In clinical practice, the MMSE is the most used test; the MoCA can be preferred for people with executive problems.

Given that the diagnosis of dementia is not the task of GP nor of the hypertension specialist, the superiority of each test in sensitivity and specificity for the diagnosis of dementia and/or Mild Cognitive Impairment will not be discussed here. As both tests are highly influenced by the level of education (but also psychological and sensorial status), their evolution over time is considered by many specialists as more informative than the absolute value measured on one occasion.

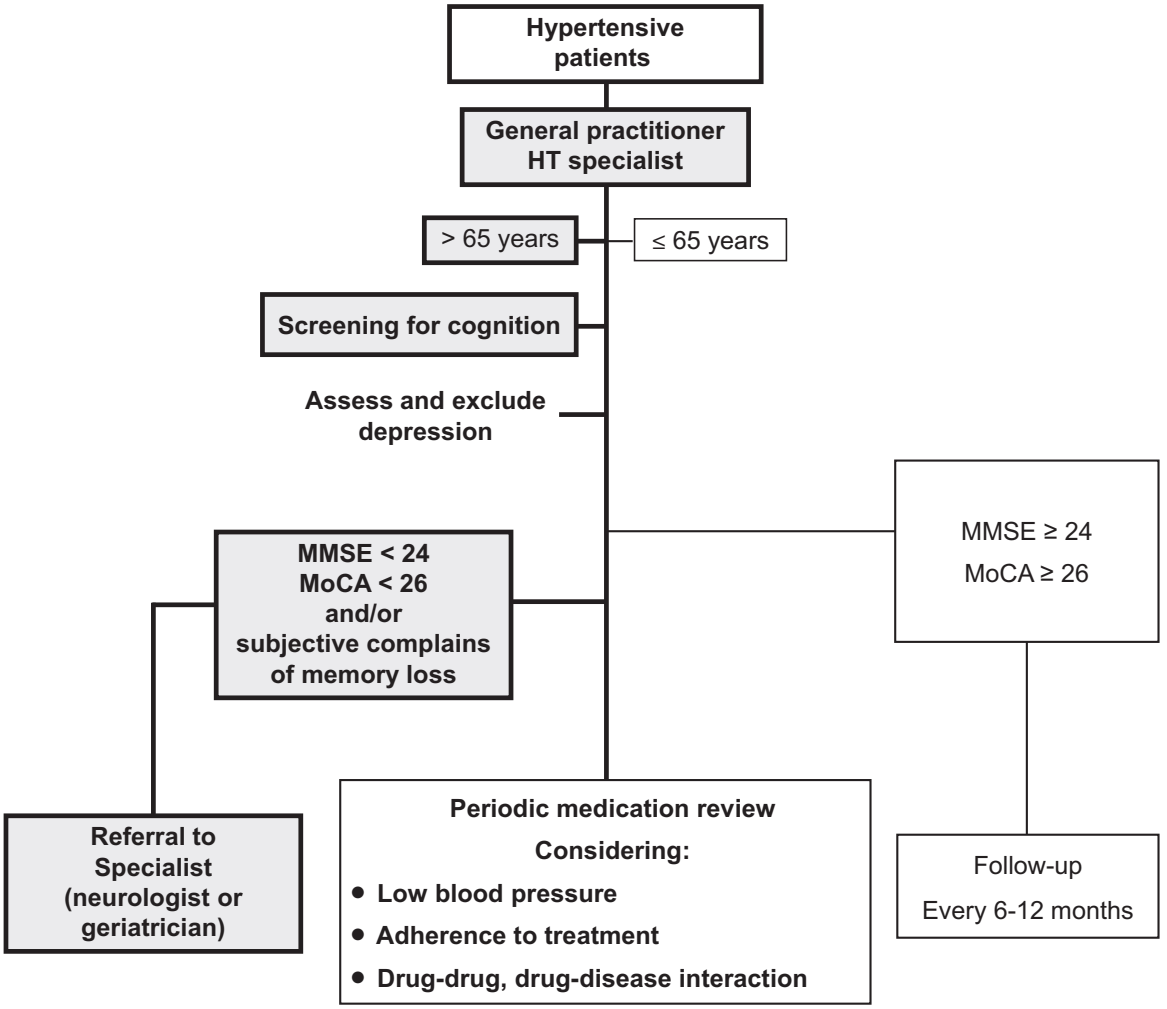

FIGURE 1 General practitioners or hypertension specialists should routinely screen for cognition all hypertensive patients aged over 65 years, and assess and exclude depression. If the Mini–Mental State Examination score less than 24 or the Montreal Cognitive Assessment test score less than 26 or subjective complains of memory loss are detected, the patient should be referred to a neurologist or a geriatrician.

A novel perspective is represented by the development of digital and/or web-based cognitive screening tests batteries. Of particular interest, tests for perceptive-motor tasks such as computerized simple decision times and/or processing speed tasks (with increased attentional load), finger tapping and manual dexterity (assessed for either hand separately) could be included for a more accurate screening of cognitive deficits in hypertensive patients. They require an additional 15 min and their wider use needs to be evaluated in properly designed studies.

In summary, screening for cognitive function in patients with hypertension should be routinely performed at least after the age of 65 years.

Though optimum sensitivity and specificity of the MMSE depends on the patient's age and education level, a general cut point of 24 is appropriate for discriminating patients with cognitive decline in most primary care populations [71].

The MoCA test adds the evaluation of executive function not evaluated by the MMSE, that is the most common cognitive domain affected in hypertensive patients.

Blood tests and neuroradiologic examinations should NOT be used as SCREENING TOOLS. Their use after a positive screening test remains more helpful for the neurologist and/or geriatrician to confirm the diagnosis of dementia and, if needed, to determine its subtype.

'Short cognitive screening tests should be performed in hypertensive patients by attending physicians (primary care physician or referral hypertension specialist) in hypertensive patients >65 years.

Its goal is screening and referral rather than making diagnosis of dementia.

MMSE and MoCA tests are simple and fast screening tools, performable in 10 min each, useful for periodic re-assessment and pinpointing those hypertensives that require referral for more refined cognitive characterization'.

Question 7: Would you request neuroimaging (computed tomography or MRI scan) in your hypertensive patient with complaints of memory loss? Why?

Elevated BP has been shown to be associated with brain abnormalities of both vascular and neurodegenerative mechanisms [72]. Specific brain regions that are known

to be vulnerable to elevated BP include hippocampal, frontal, and parietal areas [64,73]. In those regions it has been observed functional reorganization, reduced and dampened cerebral perfusion, lower grey matter volumes and higher numbers of hippocampal and cortical neuritic plaques, white matter injury [74,75].

It is critical to recall that neuroimaging represents a key element in the diagnosis of dementia, NOT for screening purposes. American and European Guidelines for dementia recommend neuroimaging in all patients at the time of initial diagnosis of dementia [75,76] to rule out treatable causes of dementia syndromes, such as tumour, intracranial haemorrhage, or normal pressure hydrocephalus.

Beyond excluding potentially treatable diseases, neuroimaging serves for another two purposes in the diagnostic process of patients with cognitive impairment: to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia.

Structural MRI is superior to computed tomography (CT) for the demonstration of markers of specific diseases, particularly hippocampal atrophy for Alzheimer's Disease; very focal temporal and/or frontal atrophy for frontotemporal dementia [72]. However, where MRI is not available or when patients cannot undergo MRI, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus.

Though it still remains a domain of specialist and researcher, it is worth mentioning that MRI may be used to evaluate progression of microvascular brain damage by periodic evaluation of topography and severity of vascular lesions [77], their spontaneous evolution and the possible response to antihypertensive therapy [28].

In conclusion, BP-related brain damage and cognitive dysfunction may be detected both by neurocognitive tests and brain imaging. The former could serve as screening tests, the latter may be used as their verification and clarification in clinical evaluation of patients with hypertension with some kind of cognitive impairment. Longitudinal progression of measures of brain vascular and nonvascular injury and neurocognitive function may be warranted.

'The diagnosis of dementia is clinical, and neuroimaging exams should be used to rule out treatable causes of cognitive decline.

Neuroimaging is a part of specialized evaluation and follow up in patients with dementia'.

Figure 1 illustrates the suggested flowchart for screening cognitive function in older hypertensive patients.

CONCLUSION

A set of recommendations are herein included, answering to everyday clinical practice question that concern the evaluation of cognitive function, a new HMOD, in hypertensive patients.

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Conflicts of interest

There are no conflicts of interest.

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