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REVIEW ARTICLE

Can the Treatment of Hypertension in the Middle-Aged Prevent Dementia in the Elderly?

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Abstract Hypertension, one of the main risk factors for cardiovascular disease, is thought to play a crucial role in the pathophysiology of cognitive impairment. Studies have associated hypertension with subjective cognitive failures and objective cognitive decline. Subjective cognitive failures may reflect the early phase of a long pathological process leading to cognitive decline and dementia that has been associated with hypertension and other cardiovascular risk factors. The underlying cerebral structural change associated with cognitive decline may be a consequence of the cerebral small-vessel disease induced by high blood pressure and may be detected on magnetic resonance imaging as white matter hyperintensities, cerebral microbleeds, lacunar infarcts or enlarged perivascular spaces. The increasing interest in the relationship between hypertension and cognitive decline is based on the fact that blood pressure control in middle-aged subjects may delay or stop the progression of cognitive decline and reduce the risk of dementia in the elderly. Although more evidence is required, several studies on hypertension have shown a beneficial effect on the incidence of dementia.

Keywords Hypertension · Cognitive impairment · Dementia · Silent brain damage

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1 Introduction

Cardiovascular disease (CVD) remains the leading cause of death worldwide. The Global Burden of Disease study estimated that 29.6 % of all deaths were caused by CVD in 2010, more than all communicable, maternal, neonatal and nutritional disorders combined, and twice the number of deaths caused by cancer [1]. The burden of CVD in Europe remains heavy, although the prevalence varies dramatically among countries. More than four million Europeans die of CVD every year, and many more are hospitalized after acute episodes or are treated for chronic CVD [2]. The percentage of the population affected by hypertension, one of the main risk factors for CVD, is remarkably high and, according to numerous studies, this prevalence is expected to continuously increase as will that of co-existing diseases [3, 4].

Although the silent effects of high blood pressure on the heart, large vessels and kidneys are routinely assessed in hypertensive patients in the clinical setting, evaluation of these effects on the brain remains is rarely carried out. However, the progress in imaging techniques and the introduction of more sensitive cognitive tests has led to an improvement in silent cerebral disease evaluation over the last decade. In fact, impaired cognitive function, along with hypertension, has become one of the leading and most devastating health problems in Europe. The incidence of cognitive decline is increasing rapidly in tandem with the ageing population and the rise of vascular disease. Over time, this will lead to a significantly large number of people suffering a loss of autonomy and are becoming disabled. However, the increase in the diagnosis of cognitive disorders comprises not only severe disorders such as Alzheimer's disease and vascular dementia, but also slighter changes in cognition. This short review is aimed to call

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attention on the importance of the problem. For this purpose, we have synthesized currently available evidence on cognitive impairment and its relationship with hypertension, as well as highlighting the effects of antihypertensive treatment on the incidence of dementia.

2 Subjective and Objective Cognitive Impairment

Subjective cognitive failures (SCF), also known as subjective cognitive complaints, are concerns about a person's cognitive function. They may be due to one's self-awareness or may be reported by someone close to the subject. SCF express complaints of poor cognitive function such as forgetting to do things previously proposed, difficulties in remembering the names of familiar buildings or landmarks, or difficulties in remembering the names of close friends. SCF are especially common in elderly people and, normally, the first report of this memory complaint is presented to the family physician, who must decide whether it may be clinically relevant. These changes in cognition have been included as one of the diagnostic criteria for mild cognitive impairment [5]. In addition, some experts are starting to consider SCF as early markers or predictors of cognitive decline and even dementia, after finding independent associations between objective and subjective cognitive impairment [6]. In other words, these complaints are related to objective changes in cognition and, accordingly, might represent an early sign of cognitive dysfunction [7]. Thus, they provide a way of identifying subjects at risk of dementia.

Objective cognitive impairment is defined as a progressive decline in some cognitive functions that does not satisfy the diagnostic criteria of dementia. It precedes at least 50 % of dementia onsets. Cognitive impairment can be assessed by neuropsychological tests, because is not necessarily evident in daily living, and can affect the memory or others domains such as perception, abstract thought, judgment, planning ability and attention. Dementia is characterized by an intellective deterioration that includes memory loss and one or more other neuropsychological alterations, such as apraxia, agnosia and aphasia, which interfere with social and occupational living. Mental alterations include progressive memory loss, spatial and temporal disorientation, loss of self-sufficiency, and emotional depersonalization. Cognitive impairment and dementia are one of the principal neurological disorders in the elderly. The estimated prevalence is around 8 % in people aged $\geq$65 years and 15–20 % in those aged >80 years [8]. Alzheimer's disease (AD) accounts for 50–60 % of cases of dementia and vascular dementia (VD) for 30 % [9].

Hypertension is a major risk factor for cerebrovascular disease and, therefore, for vascular dementia. Traditionally, AD has been considered as a primary neurodegenerative disorder and not of vascular origin. However, emerging evidence supports the view that vascular risk factors and disorders may be also involved in AD [10–12]. It appears that there is a continuous spectrum ranging from patients with pure VD to patients with pure AD and including a large majority of patients with contributions from both AD and vascular pathologies [13].

3 Pathophysiology of Impairment in Cognitive Function

Several factors have been associated with cognitive impairment, including cardiovascular risk factors such as hypertension, aging or mood disorders, and others that may be unexpected, like higher social class and a college education, worse physical health and even gender. Age stands out as one of the most studied factors. However, despite often being associated with the elderly as a result of physiological ageing, cognitive impairment is not by any means confined to a specific age group, as found by numerous studies carried out in middle-aged rather than elderly people during recent decades [14]. Hence, age is considered a confounding factor in the presentation of cognitive decline, even though it has been shown that it may appear at younger ages. Another confounding factor is represented by some affective disorders, particularly depression [15, 16]. Moreover, affective disorders have not only been considered crucial contributors to the presentation of SCF and objective cognitive decline, but also to their severity [17]. In any case, it is clear that depression is, practically without exception, related to cognitive impairment, which leads to the need to develop successful markers for the decline in cognition in order to decide whether a complaint is related to mood disorders or may be independently associated with objective impairment.

4 The Role of Hypertension in Cognitive Decline

Although the mechanisms by which high blood pressure causes silent brain damage are yet not fully understood, both the macrovascular and microvascular levels are involved, with important interactions between the two levels [18, 19]. The association between large artery stiffening and cognitive impairment has been reported by several cross-sectional studies and has been confirmed in longitudinal studies [20]. The mechanism of this association has not yet been firmly established. It is hypothesized that the relationship between arterial stiffness and cognition may be mediated by small vessel disease. A recent systematic review suggests an association between arterial

stiffness and cerebral small vessel disease, and arterial stiffness and decreased cognitive function [20]. However, the clinical use of arterial stiffness as a predictor of cognitive decline is yet to be established.

Furthermore, it is likely that the vascular damage caused by hypertension represents a potential risk factor for cognitive dysfunction, and that it contributes to cognitive decline through complex mechanisms which include: hypertrophy and contraction of smooth muscle vascular vessels—leading to a reduced lumen and increased vascular resistance—, endothelial lesions and dysfunction, and increased vascular stiffness due to the synthesis of collagen fibres [21]. These mechanisms may alter cerebral blood flow, metabolism and structure (Fig. 1).

5 Structural Bases of Cognitive Decline

There are four main signs of cerebral small vessel disease (cSVD) that may appear as a result of hypertension and can be detected and seen by MRI. These are: white matter hyperintensities (WMH), cerebral microbleeds (CMB), lacunar infarcts (LI) and enlarged perivascular spaces (EPS).

5.1 White Matter Hyperintensities

Microvascular alterations caused by hypertension may lead to hypoperfusion, hypoxia and ischemia in the terminal distributions of the affected vessels [21]. When these territories contain white matter, this process may alter it and cause a loss of myelin. These white matter lesions can be seen as hyperintensities in T2-weighted MRI images (see Fig. 2). Large artery stiffening and endothelial dysfunction correlate with cognitive impairment and WMH in elderly hypertensive subjects who present memory complaints. Moreover, the severity of WMH is inversely associated with memory function scores [22].

5.2 Cerebral Microbleeds

CMB are another sign of hypertension-related cSVD. They also participate, as vascular factors, in neurodegenerative disorders and can be seen on MRI, where they are defined as punctate homogeneous foci of low signal intensity on gradient-echo-T2-weighted images (GRE-T2) as shown in Fig. 3. It has been proposed that, depending on the location in the brain, CMB might have different etiologies. Hypertension, together with atherosclerosis, is thought to increase the risk of CMB in deep or infratentorial areas [23]. CMB have been associated with SCF [24, 25] and with objective cognitive impairment [21, 26, 27].

5.3 Lacunar Infarcts

These are identified as sharply-demarcated hyperintense lesions in T2-weighted images, with corresponding hypointense lesions with a hyperintense rim on FLAIR. They have also been linked to cognitive functioning, although their contribution to impairment has not yet been definitively established. The number of LI has been found to be a significant predictor of executive performance, with

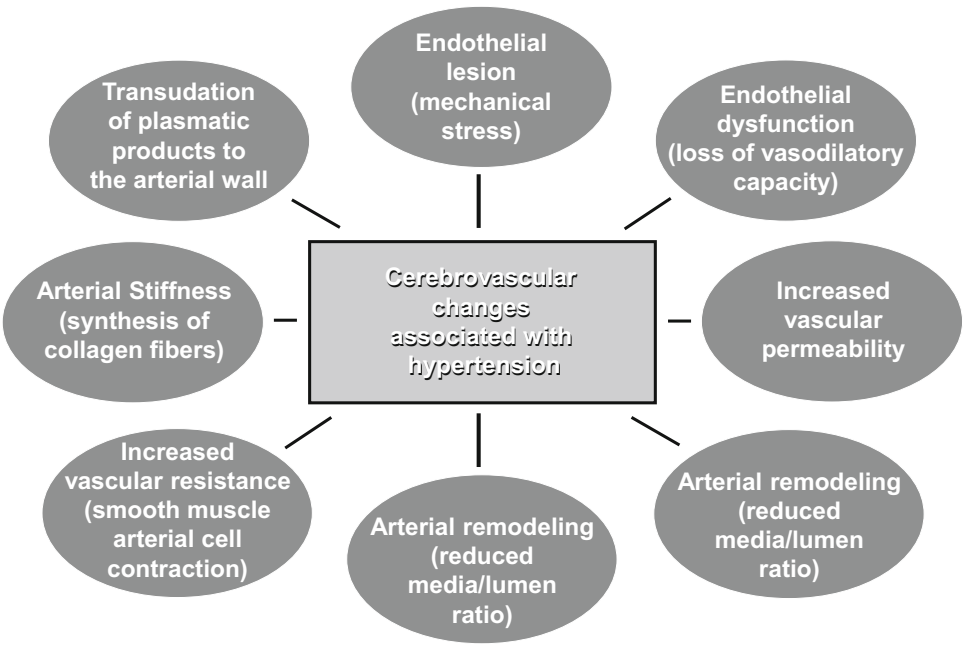


Fig. 1 Main cerebrovascular pathophysiological changes related to hypertension

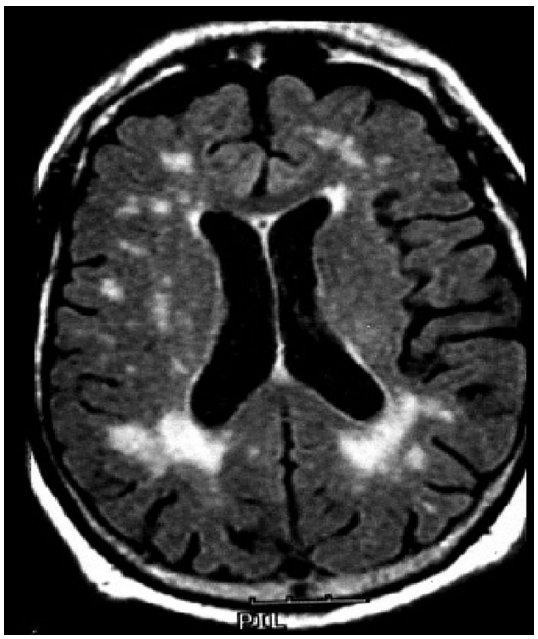


Fig. 2 Axial plane of a FLAIR MRI sequence. The hyperintense areas in the parenchyma correspond to white matter lesions that appear as a result of microvascular alterations and ischemia

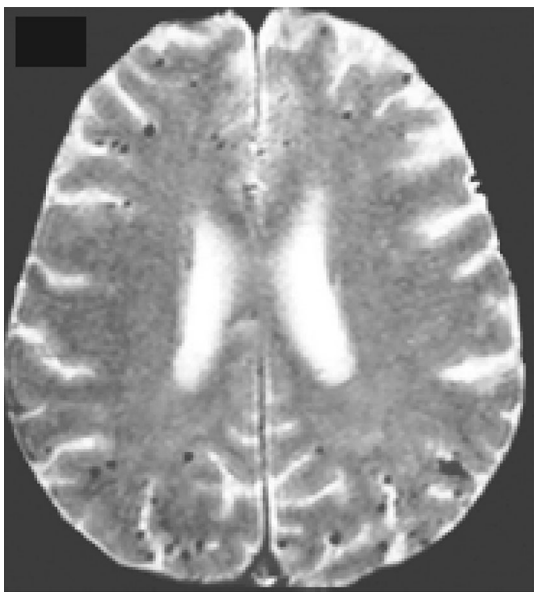


Fig. 3 Gradient-echo-T2-weighted (GRE-T2) MRI sequence of small foci of hypointensities. These low signal intensity lesions correspond to cerebral microbleeds

a higher number of LI being associated with poorer execution, even in subjects considered to be cognitively and functionally normal [28]. New LI onset on MRI has been associated with a steeper decline in executive functioning and psychomotor speed, although no relationship was found with memory or global cognitive function [29]. Another study focused on both LI and WMH and the domains of memory, processing speed and motor function, and found a solid association between the two signs of cSVD in all three domains in an elderly population. The study concluded that both WMH and LI had negative effects on cognition, which were greater when the two brain lesions were combined rather than presenting alone [30].

5.4 Enlarged Perivascular Spaces

EPS (also known as Virchow–Robin spaces) are also a marker of cSVD [31] and are thought to determine cognitive impairment in small vessel disease. They appear as rounded or linear-shaped lesions with a smooth margin and an absence of mass effect and are isointense to cerebrospinal fluid on T2-weighted images but hypointense on FLAIR images without a hyperintense rim. Like LI, they frequently coexist with WMH and other brain lesions. Although there are few studies on the subject, it has been postulated that an MRI finding of EPS probably implies decreased cognitive function, even in healthy subjects [32].

In summary, WMH, CMB, LI and EPS have all been identified as lesions which appear as a result of cSVD. They represent silent damage to the brain and, although they have mostly been studied individually and each has been linked to impaired cognition, they also correlate strongly with each other. A study which investigated the combined effect of these markers on different domains of cognitive function (memory, executive function, information processing speed, and overall cognition) found that the accumulation of these markers of brain damage resulted in worse cognitive functioning [33]. All four markers of silent damage have been linked to hypertension and cognitive function and, as stated, relationships between objective and subjective cognitive impairment have been shown [6].

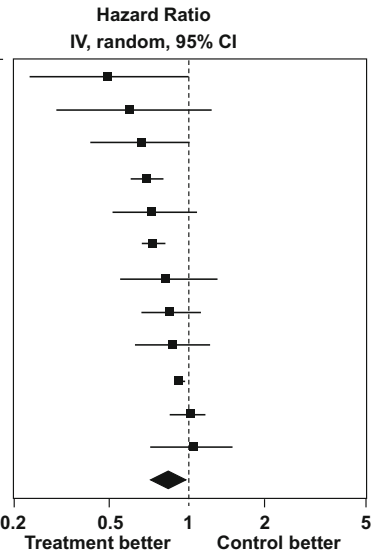
6 Prevention of Cognitive Impairment by Antihypertensive Treatment: Current Evidence

Is it possible to stop or delay the onset and progression of cognitive impairment and dementia by reducing blood pressure levels, if changes in cognitive function have already been detected?

Many studies have investigated the potential effects of blood pressure reduction on cognition. A meta-analysis by Levi et al. [34] investigated the impact that different antihypertensive drugs had on dementia and cognitive functioning, and concluded that treating high blood pressure reduced the incidence of cognitive impairment and dementia (Table 1). This beneficial effect was observed for

Table 1 Incidence of dementia in antihypertensive treatment trials

Study	Treatment	Hazard Ratio IV, random, 95% CI
Syst-Eur trial 1998	CA+ACEI vs pl	0.49 [0.24, 1.00]
BLSA 2005	CA vs others	0.63 [0.31, 1.28]
Cache County Study 2006	CA vs others	0.64 [0.41, 1.00]
Kungsholmen 1999	DIU vs pl	0.70 [0.60, 0.82]
Rotterdam 2001	Treat vs pl	0.76 [0.52, 1.11]
US Veteran 2010	ARB vs others	0.76 [0.69, 0.84]
SHEP 1991	DIU +BB vs pl	0.84 [0.54, 1.31]
Hyvet-Cog 2008	ACEI+Diu vs pl	0.89 [0.69, 1.15]
CSHA 2002	Treat vs pl	0.91 [0.64, 1.29]
US Veteran 2010	ACEI vs others	0.94 [0.91, 0.97]
CHS 2009	ACEI vs others	1.01 [0.87, 1.17]
SCOPE 2003	ARB vs Diu	1.08 [0.75, 1.56]
Total (95% CI)		0.84 [0.75, 0.93]



overall cognition and all cognitive functions except for language, with a reduction in risk of dementia of 9 %. Their suggestion for the absence of a favourable effect on language was that the area that controls this function might remain unaffected by hypertension. However, not all studies have shown this beneficial effect, and there is, as yet, no consensus [35].

Godin et al. [36] investigated the incidence and progression of WMH in hypertensive patients. Blood pressure and WMH total volume were measured in patients aged ≥65 years over a 4-year period, with the difference in WMH volume being measured by MRI at baseline and after four years. The study found that WMH were not only much more frequent in older patients and those diagnosed with hypertension, diabetes or stroke, but also in patients with uncontrolled blood pressure despite sustained antihypertensive treatment. Moreover, more-rapid progression of the lesions was associated with a steeper decrease in global cognitive performance throughout the 4-year follow-up. Two aspects associated with blood pressure were considered strong predictors of the progression of WMH volume, independently of confounders: blood pressure levels at baseline and changes in blood pressure during the 4-year follow-up. With respect to the effects of antihypertensive treatment on the progression of WMH, the study found a slower progression in patients who had started effective treatment on entry to the study, especially those who had higher systolic blood pressure at baseline. Comparison of the volumes of WMH of treated patients who achieved strict blood pressure control with those who did not, despite receiving treatment, showed the former had less WMH progression. Figure 4 shows the interaction between high blood pressure levels and antihypertensive treatment and their relationship with WMH load at baseline and their progression over 4 years.

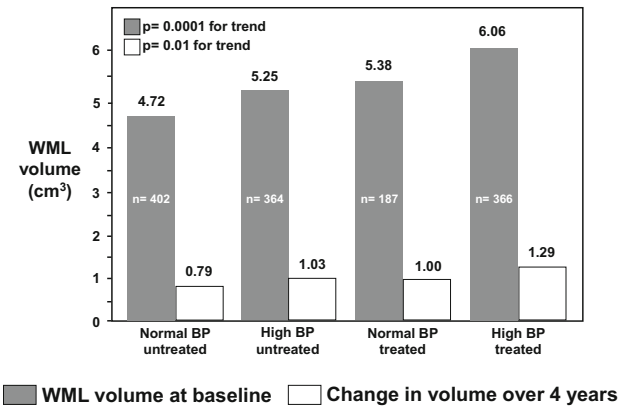


Fig. 4 Association between high blood pressure and antihypertensive treatment and WMH load and change in volume over 4 years. Adapted from reference [36]

7 Are There Preferred Antihypertensive Drugs to Prevent Cognitive Impairment and Dementia?

Antihypertensive drugs that have been shown to have a beneficial effect include calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs) and their combination with thiazide or thiazide-like diuretics,

and angiotensin receptor blockers (ARBs) [34, 35, 37]. Not all studies investigating specific classes of antihypertensive drugs or their combinations have reached the same conclusions, and some have even found that some drugs may have a detrimental effect on cognition. In addition, the effects on the reduction in the progression of cognitive decline have been found to differ in patients with normal cognition or with mild cognitive decline. In a study performed in Chinese hypertensive subjects aged >75 years, all antihypertensive drug classes reduced the risk of AD in subjects with baseline normal cognition, but only diuretics significantly reduced the risk in subjects with baseline mild cognitive decline after 6 years of treatment [35].

On the other hand, ARBs have shown an important beneficial effect, and have been proposed by some authors as the most effective agents in preventing dementia and cognitive decline, not only when compared to placebo but also when studied in comparison with other drugs like β-blockers, ACEIs or thiazide diuretics [34, 38]. In addition, patients receiving higher cumulative doses of ARBs were better protected against dementia and its subtypes. Although there was a significant benefit in receiving these agents for >180 days, the effect was greater after at least 4 years of ARB prescription [38]. This superiority was also seen over the other types of drugs, except for CCBs, suggesting that ARBs and CCBs have a greater protective effect. The mean decrease in blood pressure was similar between the different drugs, which might be interpreted as meaning that not only reductions in blood pressure are favourable for cognitive function, but that there might perhaps be specific mechanisms of action that differ between the diverse classes of antihypertensive drugs and may also play a role in their effect on cognition. ARBs might accomplish their beneficial effect by blocking AT1 receptors which, in turn, increase the action of endogenous angiotensin II via AT2 receptors, leading to a memory-enhancing effect. The blockade of AT1 receptors might also increase the synthesis of angiotensin IV which, in turn, activates AT4 receptors, which are involved in memory acquisition and recall [34].

The Systolic hypertension in Europe trial (SYST-EUR) found a 50 % reduction in incident dementia, both VD and AD, over a median 2-year follow-up in participants aged ≥60 years [39, 40]. To date, SYST-EUR has been the only large trial using a CCB-based regimen. It has been suggested that this class of antihypertensive may have neuroprotective effects in addition to BP lowering, for example, protecting against calcium dysregulation, and reducing neuronal calcium influx and the consequent neuronal damage [34, 41]. Lipophilicity is also an outstanding characteristic shared by some CCBs that could explain their beneficial effects on cognition. Lercanidipine has a highly-lipophilic profile and might have an anti-atherogenic effect, but may also inhibit the death of cerebral neurons, as shown in rat models [37]. However, epidemiological studies provide conflicting results, with some suggesting that CCBs are associated with less decline in cognitive function [42, 43], while others found that subjects taking CCBs were more likely to decline cognitively over 10 years than those taking other antihypertensives [44]. In a systematic review of the relationship between the use of CCBs and later cognitive decline or incidental dementia in very-elderly subjects, no clear evidence was found to suggest a protective effect of CCBs on the incidence of AD [45]. However, the same authors recently reported the results of the Newcastle 85+ Study, a population-based cohort study in subjects aged ≥85 years, which found an association between CCBs and less cognitive decline over 3 years compared with other antihypertensive classes [46]. Therefore, it is unclear whether CCB use in the very-elderly is beneficial with respect to cognitive decline and/or incident dementia. Evidence that some antihypertensive drugs are better than others in reducing cognitive decline is not robust or supported by randomized clinical trials. At present, the evidence only shows that reductions in blood pressure due to antihypertensive drugs delay the incidence of dementia compared with placebo. Randomized controlled clinical trials are warranted to establish the best antihypertensive strategy and which mechanisms may prevent or delay cognitive impairment related to hypertension.

8 Conclusions

Cognitive decline is a reflection of a pathological process occurring in the brain, for which hypertension, together with other associated cardiovascular risk factors, may bear a large share of the blame. For this reason, the detection of early cognitive complaints in hypertensive patients is important. Middle-aged patients with hypertension should be routinely tested for cognitive dysfunction because, although further studies are required to examine the long-term predictive value of mild cognitive impairment in hypertensive patients, it may be an early predictor of dementia. In addition, extensive study of the brain function and structure in these patients should be part of the target organ damage evaluation to stratify the total cardiovascular risk. This evaluation should include both a neuropsychological assessment and brain MRI, if possible. With respect to the neuropsychological assessment, further research is required to develop more valid, sensitive and adequate cognitive tests capable of detecting hypertensive patients with cognitive complaints at the general practitioner's office, in order to instigate preventive measures aimed at stopping or delaying the progression of cognitive decline in

patients at risk as early as possible. Randomized double-blind controlled clinical trials of antihypertensive treatments are required to determine the best blood pressure target and the best antihypertensive strategy in these patients.

Compliance with Ethical standards

Conflict of interest The authors do not declare any conflict of interest related to this manuscript.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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