CNS Drugs (2015) 29:113–130
DOI 10.1007/s40263-015-0230-6

SYSTEMATIC REVIEW

Antihypertensive Drugs, Prevention of Cognitive Decline and Dementia: A Systematic Review of Observational Studies, Randomized Controlled Trials and Meta-Analyses, with Discussion of Potential Mechanisms

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Published online: 21 February 2015

Abstract
Background Chronic hypertension, particularly midlife high blood pressure, has been associated with an increased risk for cognitive decline and dementia. In this context, antihypertensive drugs might have a preventive effect, but the association remains poorly understood.
Objectives The aim of this systematic review was to examine all published findings that investigated this relationship and discuss the mechanisms underlying the potential benefits of antihypertensive medication use.
Methods A literature search was conducted using MEDLINE, Embase, and the Cochrane Library for publications from 1990 onwards mentioning hypertension, antihypertensive drugs, cognitive decline, and dementia.
Results A total of 38 relevant publications, corresponding to 18 longitudinal studies, 11 randomized controlled trials, and nine meta-analyses were identified from the 10,251 articles retrieved in the literature search. In total, 1,346,176 subjects were included in these studies; the average age was 74 years. In the seven longitudinal studies assessing the effect of antihypertensive medication on cognitive impairment or cognitive decline, antihypertensive drugs appeared to be beneficial. Of the 11 longitudinal studies that assessed the effect of antihypertensive medication on incidence of dementia, only three did not find a significant protective effect. Antihypertensive medication could decrease the risk of not only vascular dementia but also Alzheimer's disease. Four randomized controlled trials showed a potentially preventive effect of antihypertensive drugs on the incidence of dementia or cognitive decline: SYST-EUR (Systolic Hypertension in Europe Study) I and II, with a 55 % reduction in dementia risk (3.3 vs. 7.4 cases per 1,000 patient years; $p < 0.001$); HOPE (Heart Outcomes Prevention Evaluation), with a 41 % reduction in cognitive decline associated with stroke (95 % confidence

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interval [CI] 6–63); and PROGRESS (Perindopril Protection against Recurrent Stroke Study), with a 19 % reduction in cognitive decline (95 % CI 4–32; $p = 0.01$). Meta-analyses have sometimes produced conflicting results, but this may be due to methodological considerations. The lack of homogeneity across study designs, patient populations, exposition, outcomes, and duration of follow-up are the most important methodological limitations that might explain the discrepancies between some of these studies.

Conclusion Antihypertensive drugs, particularly calcium channel blockers and renin–angiotensin system blockers, may be beneficial in preventing cognitive decline and dementia. However, further randomized controlled trials with longer periods of follow-up and cognition as the primary outcome are needed to confirm these findings.

Key Points

Antihypertensive therapy may decrease the incidence and progression of cognitive decline and dementia, not only vascular dementia but also Alzheimer's disease.

Most observational studies have suggested this potential preventive effect. Randomized controlled trials and meta-analyses have sometimes produced conflicting results, but these are probably due to methodological considerations.

Calcium channel blockers and renin–angiotensin system blockers would be the most beneficial. They could reduce the risk for and progression of cognitive impairment and dementia by lowering blood pressure and through a neuroprotective specific effect.

1 Introduction

Dementia represents a major public health concern because of global increases in population size and life expectancy. The estimated number of people with dementia worldwide is 24 million. This amount will double every 20 years to 42 million by 2020 and 81 million by 2040, leading to a costly burden of disease [1]. To date, no curative treatments are available and it is critically important that risk factors whose modification could potentially prevent or delay the onset of disease are identified. Dementia has many etiologies, but the most common are Alzheimer's disease (AD) and vascular dementia (VaD). VaD had traditionally been considered secondary to vascular disease and distinguished from AD, considered to be a purely neurodegenerative form of dementia. However, these two conditions often coexist and there is strong evidence for a continuous spectrum of disease [2], suggesting an association between vascular risk factors and dementia, including AD. Chronic hypertension, particularly midlife high blood pressure (BP), has been associated with an increased risk for cognitive decline, VaD, and AD [3]. In this context, work has generally focused on the use of antihypertensive (AH) medication for the prevention of cognitive decline and dementia. However, there is almost no recent work aiming to provide an exhaustive summary of current literature relevant to this relationship that discusses both methodological limitations of the different studies and their implications and highlights the mechanisms underlying the potential benefits of the different classes of AH drugs. Thus, the aim of this systematic review was to examine all published findings that investigated the relationship between AH drug use and the incidence and progression of cognitive decline or dementia and to discuss the mechanisms that could explain the potential benefits of AH therapy.

2 Methods

2.1 Literature Search and Data Sources

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4]. It was carried out to identify observational epidemiological studies, randomized controlled trials (RCTs), and meta-analyses that compared the incidence of any dementia, VaD, AD, cognitive impairment, or the progression of cognitive decline between patients, whatever their age and cardiovascular comorbidities, with and without AH medication therapy or with different AH drug regimens. In March 2014, an electronic database search was performed in MEDLINE, Embase, and the Cochrane Library. The following search strategy was applied: [(hypertension OR hypertensive OR blood pressure OR systolic blood pressure (SBP) OR diastolic blood pressure (DBP)] AND [antihypertensive drugs OR calcium channel blockers (CCBs) OR diuretics OR beta blockers (BBs) OR angiotensin-converting enzyme inhibitors (ACEIs) OR angiotensin II receptor blockers (ARBs)] AND [dementia OR alzheimer OR vascular dementia OR severity of dementia OR cognition OR cognitive function OR cognitive performance OR cognitive impairment OR mild cognitive impairment (MCI) OR cognitive decline OR progression of severity of cognitive impairment OR prevalence OR incidence)]. We searched for studies from 1990 onwards because the relationship

between vascular risk factors and all forms of dementia was not widely recognized before this time. The searches were restricted to articles published in English and related to human studies. First, articles were scanned on titles and abstracts and were retained if they met the following inclusion criteria. Reference lists of all articles identified were searched. The resultant information was supplemented by extensive manual searching of references. Finally, all identified studies were cross-referenced to identify any reports that may have been missed.

2.2 Study Eligibility Criteria

The inclusion criteria were as follows: (1) the incidence of AD, VaD, any dementia or cognitive decline as well as the progression of cognitive impairment should be compared between patients with and without AH medication use or with different AH drug regimens; (2) AH drug use was the exposure variable of interest; (3) any dementia and cognitive impairment were defined according to the standardized diagnostic, *Diagnostic and Statistical Manual of Mental Disorders* (DSM) for overall dementia, National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA) for AD, National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) for VaD; (4) all studies were case-control, cohort studies, RCTs, or meta-analyses to provide definite information about cause-and-effect relationships with an increasing level of evidence; (5) sample sizes were 500 or more for observational studies in order to have the power to detect meaningful relationships; (6) confidence intervals (CIs) or other information that allowed estimation of standard errors were available; (7) results were adjusted for, at a minimum, age and sex.

The exclusion criteria were as follows: (1) studies that did not use neuropsychological tests or diagnostic criteria as outcome measures were excluded to maintain homogeneity in the presentation of findings from the literature; (2) cognitive decline or dementia was not a primary or secondary outcome; (3) cross-sectional studies; (4) animal studies; (5) the relationship between AH drugs, cognitive decline, and dementia was not studied.

For each study, study design, sample size, characteristics of study population at inclusion (age, cardiovascular comorbidities, range of SBP and DBP if available, and cognitive status) were extracted as was length of follow-up and covariates. In RCTs, the differential drop of SBP and DBP was extracted in both placebo and active treatment groups. AH medication use was identified with specific attention for different subclasses and drug combinations. The presence of cognitive impairment, cognitive decline, any dementia, VaD, and AD during follow-up was extracted. Cognitive outcomes were sometimes defined differently by different authors in the selected studies. Thus, cognitive tests and criteria used for assessment of dementia were also extracted as was the definition of cognitive impairment or cognitive decline. Quantitative data regarding the association of AH therapy and the incidence or progression of cognitive impairment, cognitive decline, or dementia were extracted. Studies were considered as reporting significant associations or not. The main limitations of each study were identified as were the main strengths. Data related to the assessment of methodological quality of studies according to the Jadad criteria [5, 6] adapted, as reported below, were also collected.

2.3 Quality Assessment

To provide an overview of the quality of epidemiological studies, we used an adaptation of the Jadad criteria [5, 6], which were initially developed for measuring the quality of RCTs. Two independent reviewers used this quality-assessment tool to grade each article according to the strength of the evidence. The maximum score for an RCT was 8 points: 1 point each was given for randomization, description of the method of randomization, local or national representativeness, explanation of the reasons for loss to follow-up, double-blind design, description of the method of double-blinding, description of the method of diagnosing dementia or cognitive impairment, and concordance of the diagnostic method with established guidelines. For other types of studies, the first two items described here were omitted, and the maximum score was 6 points. We focused on cohort studies and RCTs. Meta-analyses were also included in this systematic review because they provide an overview of the role of AH treatments on cognition.

3 Results

3.1 Study Selection and Populations

The MEDLINE, Embase, and Cochrane Library initial search returned 10,251 articles, 9,830 of which were excluded because their title or abstract were not relevant. The results of the literature search are shown in Fig. 1. By applying the criteria described above, 38 publications corresponding to 18 longitudinal studies, 11 RCTs, and nine meta-analyses were included in this systematic review. Study populations consisted of 1,346,176 subjects, with a mean age of 74 years. Most observational studies

(78 %) were conducted in general population except five that, respectively, referred to subjects with cardiovascular risk factors [7], hypertension [8], cardiovascular disease [9], diabetes [10], or mild to moderate AD [11]. As expected, RCTs mainly included hypertensive patients. Some of them focused on more specific populations, particularly subjects at high risk of cardiovascular events [12], with previous stroke [13] and/or transient ischemic attack [14], with coronary, peripheral, or cerebrovascular diseases or diabetes associated with end-organ damage [15].

3.2 Observational Studies

3.2.1 Antihypertensive Treatment and Cognitive Decline

Several observational studies, summarized in Table 1, have examined the relationship between AH treatments and cognitive functions, suggesting that their consumption could be beneficial. The EVA (Epidemiology of Vascular Aging) study [16] found that cognitive decline was lower in treated than in untreated hypertensive patients (relative risk [RR] 1.9; 95 % CI 0.8–4.4 vs. RR 4.3; 95 % CI

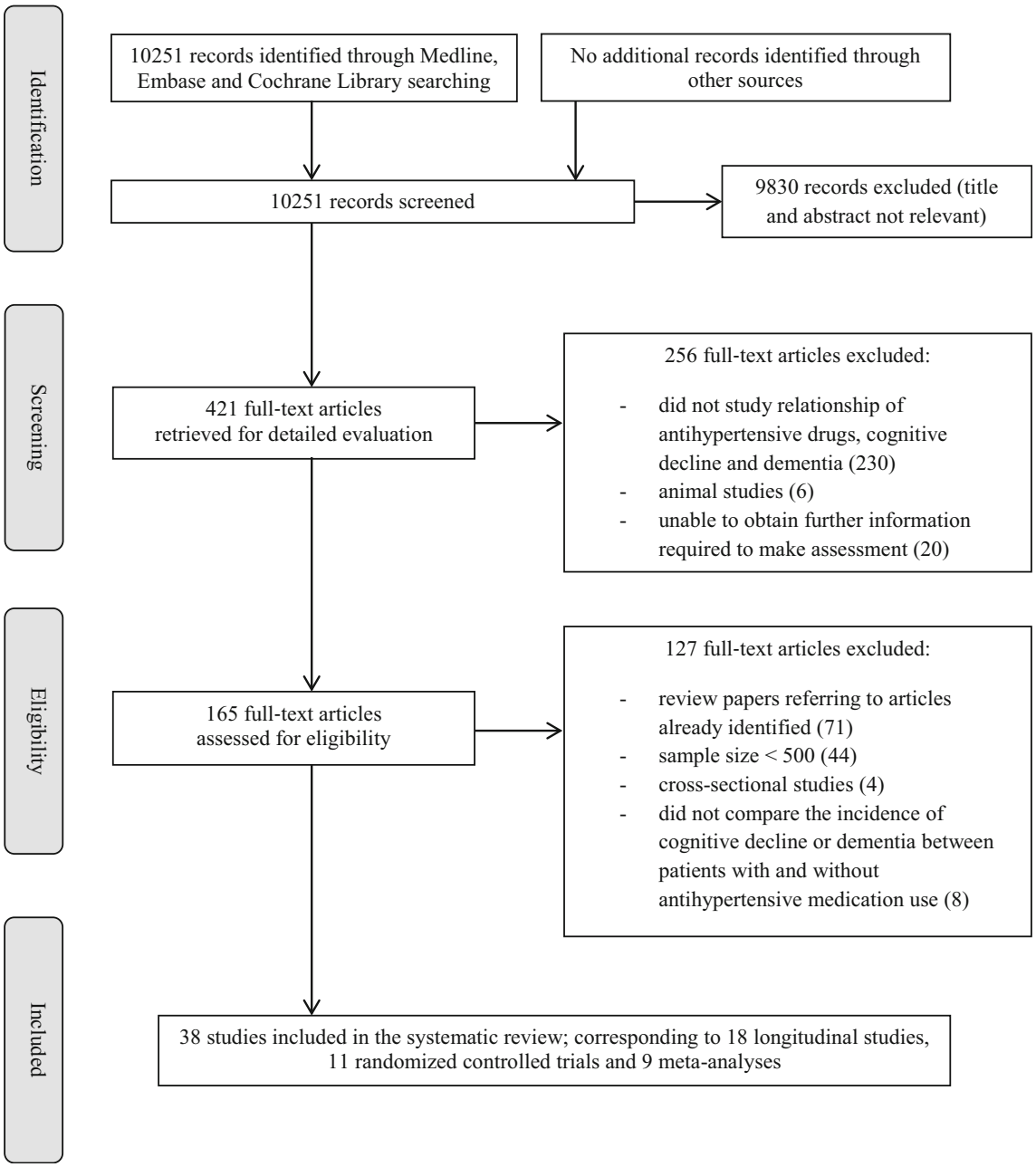

Fig. 1 PRISMA flowchart of systematic review

Table 1 Observational studies assessing the effect of antihypertensive medication use on cognitive decline

References	Study settings	Participants	Follow-up (years)	AH medication	Outcomes	Covariates	Quality score	Main results
Tzourio et al. [16]	EVA study, France	1,373 Subjects; age 59–71 at BL	4	BBs, CCBs, ACEIs, diuretics	CD: MMSE dropped ≥4 points over 4 years	Age, sex, education, income, depression, alcohol, ApoE, BL MMSE	2/6	CD was lower in treated vs. untreated hypertensives (RR 1.9; 95 % CI 0.8–4.4) vs. (RR 4.3; 95 % CI 2.1–8.8)
Murray et al. [17]	Community-based cohort study, Indiana, USA	1,617 African Americans; age ≥65 at baseline	5	AH medications	Performance on MMSE	Age, sex, education, heart disease, BP, BL cognitive test	4/6	Reduced risk of cognitive impairment by 38 %: (OR 0.62; 95 % CI 0.45–0.84)
Hajjar et al. [18]	Community-based cohort study, South Carolina, USA	350 Subjects; mean age at BL 77	2 (mean)	ACEIs, ARBs, CCBs, BBs, α-blockers, diuretics, clonidine, others	Performance on MMSE	Age, sex, ethnicity, anthropometrics, education, family history of dementia, alcohol and smoking, stroke, diabetes, BP, LDL-C and HDL-C, BL cognitive test	2/6	AH use associated with a lower rate of CD on the MMSE (-0.8 ± 2 in users vs. -5.8 ± 2.5 points in non-users; $p = 0.007$)
Sink et al. [7]	Cardiovascular Health Study, USA	1,054 Subjects with CV risk factors; mean age at BL 75	6	ACEIs vs. other AH agents	Performance on 3MSE	Age, sex, ethnicity, education, income, alcohol and smoking, diabetes, coronary artery disease, stroke, depression, creatinine and LDL levels, SBP, use of other AH drugs	4/6	No significant association between exposure to ACEIs and difference in 3MSE scores vs. other AH drugs; centrally active ACEIs associated with 65 % less decline in 3MSE scores per year of exposure ($p = 0.01$)
Hanon et al. [8]	OSCAR study (multicenter)	25,745 Subjects with HTN; age ≥50 at BL	0.5	Eprosartan ± other AH agents	Performance on MMSE	Age, sex, diabetes, hypercholesterolemia, BP, BL MMSE	2/6	BP reduction associated with an increase of MMSE by 0.8 points at 6 months ($p < 0.001$)
Gelber et al. [19]	HAAS, USA	2,197 Subjects; mean age at BL 77	9	BBs, ACEIs, diuretics, CCBs, vasodilators	Cognitive impairment: CASI score <74	Age, education, ApoE, BL CASI scores, BMI, alcohol and smoking, physical activity, diabetes, CV diseases, pulse pressure, heart rate	4/6	BBs as the sole AH medication was significantly associated with a lower risk of cognitive impairment vs. untreated subjects (incidence rate ratio 0.69; 95 % CI 0.5–0.94)
Soto et al. [11]	REAL.FR Study, France	616 Subjects with mild to moderate AD; mean age at BL 78	4	ACEIs, BBs, CCBs, thiazides, central and peripheral α-blockers, ARBs	Performance on MMSE	Age, sex, education, HTN	4/6	Continuous or intermittent use of ACEIs was associated with a significant difference in 4-year MMSE decline vs. no ACEI consumption (7.5 ± 0.9 vs. 9.7 ± 0.4 points; $p = 0.03$)

ACEI angiotensin-converting enzyme inhibitor, *AH* antihypertensive, *ApoE* apolipoprotein E, *ARB* angiotensin II receptor blocker, *BB* beta blocker, *BL* baseline, *BP* blood pressure, *BMI* body mass index, *CASI* Cognitive Abilities Screening Instrument, *CCB* calcium channel blocker, *CD* cognitive decline, *CI* confidence interval, *CV* cardiovascular, *HDL-C* high-density lipoprotein cholesterol, *HTN* hypertension, *LDL-C* low-density lipoprotein cholesterol, *MMSE* Mini Mental State Exam, *OR* odds ratio, *p* p-value, *RR* relative risk, *SBP* systolic blood pressure, *3MSE* Modified Mini Mental State Exam

2.1–8.8). Later work by Murray et al. [17] showed a 38 % reduced risk of cognitive impairment with AH medication (odds ratio [OR] 0.62; 95 % CI 0.45–0.84). This study is of particular interest since it was conducted among African-Americans, in whom hypertension is more prevalent than in Caucasians. Hajjar et al. [18] also found a lower rate of cognitive decline among patients with AH treatment (-0.8 ± 2 points in users vs. -5.8 ± 2.5 points in non-users; $p = 0.007$) in their longitudinal analysis, although it was conducted in few subjects. Nevertheless, the Cardiovascular Health Study [7] reported no significant association between ACEI exposure and difference in Modified Mini Mental Status Examination (3MSE) scores compared with other AH drugs, except for centrally acting ACEIs, which were associated with 65 % less decline in 3MSE scores per year of exposure ($p = 0.01$). Other studies among specific populations suggested some benefits of specific classes of AH drugs. In the OSCAR (Observational Study on Cognitive function And systolic blood pressure Reduction) study [8], use of eprosartan as sole or primary BP-lowering medication in patients with hypertension was associated with an increase of Mini Mental State Examination (MMSE) by 0.8 points at 6 months ($p < 0.001$). This open-label trial was not subject to the methodological restrictions of RCTs and was therefore offering a study population more similar to the general population. Recent work by Gelber et al. [19] in the HAAS (Honolulu Asia Aging Study) disclosed benefits of BB use on the risk of developing cognitive impairment (incidence rate ratio 0.69; 95 % CI 0.5–0.94). Lastly, Soto et al. [11] indicated a beneficial effect of ACEIs in reducing cognitive decline among 616 patients with mild to moderate AD from the REAL.FR (Réseau Alzheimer Français) study (4-year MMSE decline 7.5 ± 0.9 vs. 9.7 ± 0.4 points; $p = 0.03$).

3.2.2 Antihypertensive Treatment and Dementia

The main observational studies that investigated the relation between AH drug use and dementia are summarized in Table 2. As with those mentioned above, most have been conducted in the short and medium term. Of 11 studies, eight found AH medication to have a protective effect on the incidence of dementia. In the Kungsholmen Project, Qiu et al. [20] found a reduced risk of dementia and AD with AH medication (RR 0.7; 95 % CI 0.5–0.9). This result was further confirmed by the Cache County Study [21], which reported a preventive effect of AH drug consumption, especially diuretics, on the incidence of AD. The greatest reduction in AD risk was specifically observed with potassium-sparing diuretics (adjusted hazard ratio [HRa] 0.26; 95 % CI 0.08–0.64). Peila et al. [22] also showed, in HAAS, that AH treatment may protect against dementia and AD (HR 0.35; 95 % CI 0.16–0.78). This analysis is particularly interesting because it considers the duration of AH use. The work conducted by Li et al. [9] in the US Veterans Affairs Health System also disclosed similar results. ARBs were associated with a reduced incidence of AD compared with lisinopril (HR 0.81; 95 % CI 0.68–0.96) or the 'cardiovascular comparator' (HR 0.84; 95 % CI 0.71–1.00; $p = 0.045$). In the same field, Johnson et al. [10] demonstrated a decreased risk of dementia with AH medications, even among patients without hypertension (for ACEIs: HR 0.81; 95 % CI 0.69–0.94 and for ARBs: HR 0.55; 95 % CI 0.34–0.88), suggesting that AH drugs could be beneficial to cognition beyond their effect on hypertension. Recently, in the GEM (Ginkgo Evaluation of Memory) study, Yasar et al. [23] found a reduced risk of AD with consumption of diuretics, ARBs, ACEIs, and BBs. HRs were, respectively, 0.51 (95 % CI 0.31–0.82), 0.31 (95 % CI 0.14–0.68), 0.5 (95 % CI 0.29–0.83), and 0.58 (95 % CI 0.36–0.93). Finally, the work by Haag et al. [24] in the Rotterdam study, among 6,249 subjects followed over 13 years, showed a reduced risk of all dementia with AH drug use (HRa per year of use 0.95; 95 % CI 0.9–0.99). This association was not statistically significant in a previous report by In't Veld et al. [25] in the Rotterdam study, probably due to a shorter follow-up period (2.2 years). However, AH drug use was associated with a reduced incidence of VaD (RR 0.33; 95 % CI 0.11–0.99). Although many longitudinal studies have suggested a benefit of AH drug use on the prevention of dementia, others have shown no statistically significant association. Neither the East Boston Cohort Study (OR 0.66; 95 % CI 0.68–2.61) [26] nor the CSHA (Canadian Study of Health and Aging) (RR 0.91; 95 % CI 0.64–1.3) [27] found AH drug consumption to be preventive for AD. Similarly, in the BLSA (Baltimore Longitudinal Study of Aging) [28], the authors found that the use of CCBs was not associated with a significantly reduced risk of AD (dihydropyridine [DHP]-CCB: RR 0.3; 95 % CI 0.07–1.25; $p = 0.1$ and non-DHP-CCB: RR 0.82; 95 % CI 0.37–1.83; $p = 0.63$).

3.3 Randomized Controlled Trials

Intervention studies are more relevant in terms of analyzing causality. Several large RCTs have evaluated the effect of AH drugs on cognitive function and dementia, with inconsistent results.

3.3.1 Antihypertensive Treatment and Cognitive Decline

RCTs assessing the potential benefits of AH therapy on cognitive impairment and prevention of cognitive decline are presented in Table 3.

The HOPE (Heart Outcomes Prevention Evaluation) [12, 29] study showed a significant 41 % reduction in

Table 2 Observational studies assessing the association between antihypertensive treatments and dementia

References	Study settings	Participants	Follow-up (years)	AH medication	Outcomes	Covariates	Quality score	Main results
Qui et al. [20]	Kungsholmen Project, Sweden	1,270 Subjects; age ≥75 at BL	6	Diuretics (mainly), CCBs, BBs, adrenolytic AH	Incidence of dementia (DSM-III-R) and AD (NINCDS-ADRDA)	Age, sex, education, vascular disease, BP, baseline MMSE score	4/6	AHs associated with a reduced incidence of AD (RR 0.7; 95 % CI 0.5–0.9)
Khachaturian et al. [21]	Cache County Study, USA	3,227 Subjects; age ≥65 at BL	3	ACEIs, BBs, CCBs, diuretics	Incidence of dementia (DSM-III-R), AD (NINCDS-ADRDA), VaD (NINDS-AIREN)	Age, sex, education, heart disease, diabetes, hypercholesterolemia, ApoE	5/6	Reduced risk of AD with AHs (HRa 0.64; 95 % CI 0.41–0.98); diuretics and specifically potassium-sparing diuretics were associated with the greatest reduction in risk of AD (HRa 0.26; 95 % CI 0.08–0.64)
Peila et al. [22]	HAAS, Hawaii, USA	1,294 Subjects; mean age at BL 77	≥12	AH medications	Incidence of dementia (DSM-III-R and DSM-IV), AD (NINCDS-ADRDA), VaD (California AD Diagnostic and Treatment Centers guidelines)	Age, education, smoking, heart disease, BP, BMI, ApoE	4/6	Reduced risk of incident dementia for each additional year of treatment (HR 0.94; 95 % CI 0.89–0.99); reduced risk of dementia and AD in subjects >12 years of treatment (HR 0.35; 95 % CI 0.16–0.78)
Li et al. [9]	US Veterans Affairs health system, USA	819,491 Subjects with CVD; age ≥65 at BL	4	ARB, lisinopril, 'cardiovascular comparator' = BBs, CCBs	Incidence of dementia and AD (ICD-9)	Age, stroke, CVD, HTN, diabetes	3/6	ARBs associated with a reduced incidence of AD vs. lisinopril (HR 0.81; 95 % CI 0.68–0.96) or the 'cardiovascular comparator' (HR 0.84; 95 % CI 0.71–1.00; $p = 0.045$)
Johnson et al. [10]	Cohort from Veterans Administration, USA	37,7838 Subjects diagnosed with diabetes; age ≥65 at BL	2	BBs, α-adrenergic antagonists, diuretics, CCBs, ACEIs, ARBs	Incidence of dementia (ICD-9)	Age, sex, ethnicity, co-morbidities, co-medications	2/6	AH medications decreased risk of dementia even among pts without HTN (ACEIs: HR 0.81; 95 % CI 0.69–0.94 and ARBs: HR 0.55; 95 % CI 0.34–0.88)
Yasar et al. [23]	GEM study, USA	2,248 Subjects; age ≥75 at BL	6.1	Diuretics, ACEIs, ARBs, CCBs, BBs	Incidence of AD (DSM-IV, NINCDS-ADRDA)	Age, sex, education, smoking, income, BMI, SBP, DBP, MCI, number of vascular diseases	4/6	Among subjects with normal cognition, diuretic, ARB, ACEI, and BB use was significantly associated with a reduced risk of AD. HR were, respectively, 0.51 (95 % CI 0.31–0.82), 0.31 (95 % CI 0.14–0.68), 0.5 (95 % CI 0.29–0.83), and 0.58 (95 % CI 0.36–0.93). In participants with MCI, only diuretic use was associated with a decreased risk of AD (HR 0.38; 95 % CI 0.2–0.73)

Table 2 continued

References	Study settings	Participants	Follow-up (years)	AH medication	Outcomes	Covariates	Quality score	Main results
Haag et al. [24]	Rotterdam study, The Netherlands	6,249 Subjects; age ≥55 at BL	13	BBs, thiazide and loop diuretics, CCBs, ACEIs, ARBs, other AH drugs	Incidence of dementia (DSM-III-R), AD (NINCDS-ADRDA), VaD (NINDS-AIREN)	Age, sex, education, smoking, CVD and cerebrovascular disease, diabetes, cholesterol level, BP, BMI	3/6	AH use was associated with a reduced risk of all dementia (HRa per year of use 0.95; 95 % CI 0.9–0.99). Equivalent estimates were observed for AD
In't Veld et al. [25]	Rotterdam study, The Netherlands	7,046 Subjects; age ≥55 at BL	2.2	Diuretics, BBs, ACEIs, CCBs, other AH drugs	Incidence of dementia (DSM-III-R), AD (NINCDS-ADRDA), VaD (NINDS-AIREN)	Age, sex, stroke, diabetes, BP	4/6	No significant association between exposure to AHs and risk of dementia; AHs were associated with a reduced incidence of VaD (RR 0.33; 95 % CI 0.11–0.99)
Morris et al. [26]	East Boston Cohort study, USA	634 Subjects; age ≥65 at BL	4.5	AH medications	Incidence of AD (Modified NINCDS-ADRDA)	Age, sex, education, follow-up interval stratified sampling, stroke, heart disease, HTN, diabetes, BMI, ApoE	3/6	No significant association between exposure to AHs and risk of AD (OR 0.66; 95 % CI 0.68–2.61)
Lindsay et al. [27]	CSHA, Canada	4,615 Subjects; age ≥65 at BL	5	AH medications	Incidence of dementia (DSM-III-R), AD (NINCDS-ADRDA)	Age, sex, education, ApoE	4/6	No significant association between exposure to AHs and risk of AD (RR 0.91; 95 % CI 0.64–1.3)
Yasar et al. [28]	BLSA, USA	1,092 Subjects; age ≥60 at BL	11	CCBs	Incidence of AD (NINCDS-ADRDA)	Sex, education, smoking, heart disease, BP	3/6	No significant association between exposure to CCBs and risk of AD (DHP-CCB: RR 0.3; 95 % CI 0.07–1.25; $p = 0.1$ and non-DHP-CCB: RR 0.82; 95 % CI 0.37–1.83, $p = 0.63$)

ACEI angiotensin-converting enzyme inhibitor, *AD* Alzheimer's disease, *AH* antihypertensive, *ApoE* apolipoprotein E, *ARB* angiotensin II receptor blocker, *BB* beta blocker, *BL* baseline, *BMI* body mass index, *BP* blood pressure, *CCB* calcium channel blocker, *CI* confidence interval, *CVD* cardiovascular disease, *DBP* diastolic blood pressure, *DHP* dihydropyridine, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *HR* hazard ratio, *HRa* adjusted HR, *HTN* hypertension, *ICD* International Classification of Diseases, *MCI* mild cognitive impairment, *MMSE* Mini Mental State Exam, *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association, *NINDS-AIREN* National Institute of Neurological Disorders and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences, *pts* patients, *RR* relative risk, *SBP* systolic blood pressure, *VaD* vascular dementia

Table 3 Randomized controlled trials assessing the effect of antihypertensive treatments on cognitive decline

Trial	Subjects	Population characteristics	Follow-up (years)	Intervention	ΔSBP/DBP (active–PL)	Outcomes	Quality score	Main results
HOPE Bosch et al. [12]	9,297 Subjects; age ≥55	High risk of CV events	4.5	ACEI (ramipril) vs. PL	−3.8/2.8 mmHg	CD	5/8	Reduction in CD associated with stroke by 41 % (95 % CI 6–63)
PROGRESS Tzourio et al. [14]	6,105 Subjects; mean age 64	Previous stroke or TIA in 5 years; no age or BP inclusion criteria	3.9	ACEI (perindopril) ± diuretic (indapamide) vs. PL	−9/4 mmHg	CD (MMSE)	6/8	Reduction in CD by 19 % (95 % CI 4–32; $p = 0.01$)
MRC Prince et al. [31]	2,584 Subjects; age 65–74	SBP 160–209; DBP <115 mmHg	4.5	Diuretics (hydrochlorothiazide + amiloride) or BB (atenolol) vs. PL	−15.8/5 mmHg	Cognitive performance (PALT; TMT-A)	5/8	Non-significant differences in mean learning test coefficients between groups: (diuretic −0.31 [95 % CI −0.23 to −0.39], BB −0.33 [95 % CI −0.25 to −0.41], PL −0.3 [95 % CI −0.24 to −0.36]
SCOPE Lithell et al. [32]	4,964 Subjects; age 70–89	SBP 160–179; DBP 90–99 mmHg; MMSE at baseline ≥24	3.7	ARB (candesartan) ± diuretic (hydrochlorothiazide) vs. PL (with open-label active AH therapy if needed)	−3.2/1.6 mmHg	Cognitive impairment (MMSE)	5/8	Non-significant effect on cognitive function (MMSE decrease: 28.5–28 in the treatment group and 28.5–27.9 in the control group) ($p = 0.2$)
HYVET-COG Peters et al. [34]	3,336 Subjects; age ≥80	SBP 160–200; DBP <110 mmHg	2.2	Diuretic (indapamide) ± ACEI (perindopril) vs. PL	−15/5.9 mmHg	CD (fall in MMSE to <24 or >3 points in 1 year)	6/8	Non-significant effect on CD (HR 0.93; 95 % CI 0.82–1.05)
PROFESS Diener et al. [13]	20,332 Subjects; age ≥55	Ischemic stroke in the previous 90 days	2.4	ARB (telmisartan) vs. PL	−5.4 mmHg (ΔSBP)	Cognitive function (decrease in MMSE score of ≥3 points)	6/8	Non-significant differences in CD between groups (decrease in MMSE score of 3 points or more: RR 0.95; 95 % CI 0.87–1.05)
ONTARGET Anderson et al. [15]	25,620 Subjects; age ≥55	Coronary, peripheral, or cerebrovascular diseases or diabetes with end-organ damage	4.5	ACEI (ramipril) vs. ARB (telmisartan) vs. combination	−2.4/1.4 mmHg (combination vs ACEI); −0.9/0.6 mmHg (ARB vs. ACEI)	Cognitive impairment (diagnosis of dementia or significant cognitive dysfunction or MMSE ≤23); CD (−3 points or more on MMSE during follow-up)	7/8	CD: combination vs. ramipril OR 0.95; 95 % CI 0.88–1.04; $p = 0.28$, telmisartan vs. ramipril OR 0.97; 95 % CI 0.89–1.06; $p = 0.53$, telmisartan vs. PL OR 1.10; 95 % CI 0.95–1.27; $p = 0.22$
TRANSCEND Anderson et al. [15]	5,926 Subjects; age ≥55	Coronary, peripheral, or cerebrovascular diseases or diabetes with end-organ damage; history of intolerance to ACEIs	4.5	ARB (telmisartan) vs. PL	−4.0/2.2 mmHg			

ACEI angiotensin-converting enzyme inhibitor, *AH* antihypertensive, *ARB* angiotensin II receptor blocker, *BB* beta blocker, *BP* blood pressure, *CD* cognitive decline, *CI* confidence interval, *CV* cardiovascular, *DBP* diastolic BP, *HR* hazard ratio, *MMSE* Mini Mental State Examination, *OR* odds ratio, *PALT* Paired Associate Learning Test, *PL* placebo, *RR* relative risk, *SBP* systolic BP, *TIA* transient ischemic attack, *TMT-A* Trail-Making Test Part A

cognitive decline associated with stroke (95 % CI 6–63) in the ACEI group compared with the placebo group. These results were found despite a modest reduction in BP. In PROGRESS (Perindopril Protection against Recurrent Stroke Study) [14], the effects of an ACEI-based BP-lowering regimen were evaluated in 6,105 subjects with a history of stroke or transient ischemic attack (TIA). The active treatment was associated with a significant reduction in cognitive decline by 19 % in the whole population (95 % CI 4–32; $p = 0.01$) and particularly in subjects with recurrent strokes (RR 45 %; 95 % CI 21–61; $p = 0.001$). Other RCTs reported no statistically signification association. The Medical Research Council (MRC) trial of hypertension [30], conducted in a sub-group of 2,584 patients followed-up for 4.5 years, showed no effect of treatment across two specific neuropsychological tests : the Paired Associate Learning Test (PALT) and the Trail Making Test Part A (TMT-A). The mean learning test coefficients did not differ between the three treatment groups: diuretic −0.31 (95 % CI −0.23 to −0.39), BB −0.33 (95 % CI −0.25 to −0.41), placebo −0.3 (95 % CI −0.24 to −0.36). This lack of benefit may have been due to the assessment of only two cognition components [31]. The results of SCOPE (Study on Cognition and Prognosis in the Elderly) [32], conducted in subjects with an MMSE score at baseline ≥24, indicated no significant difference between the treatment group (candesartan ± hydrochlorothiazide) and the placebo group for cognitive decline. Mean MMSE decrease was from 28.5 to 28 in the treatment group and from 28.5 to 27.9 in the control group ($p = 0.2$). However, the MMSE is a test lacking in sensitivity to detect a cognitive decline in non-demented subjects, and this may have biased the results toward the null effect. HYVET-COG (Hypertension in the Very Elderly Trial—Cognitive Function Assessment) [33, 34], based on perindopril/indapamide versus placebo reported similar results (cognitive decline: HR 0.93; 95 % CI 0.82–1.05). In the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) study [13], no significant difference was observed in cognitive decline between the telmisartan and the placebo group (decrease in MMSE score of 3 points or more from the first evaluation: RR 0.95; 95 % CI 0.87–1.05). Lastly, in the parallel ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease) trials [15], designed to investigate the effect of renin–angiotensin system blockade on major cardiovascular outcomes, no significant benefits were found on cognitive function. Cognitive impairment: combination versus ramipril OR 0.95 (95 % CI 0.85–1.07), $p = 0.39$; telmisartan versus ramipril OR 0.9 (95 % CI 0.8–1.01), $p = 0.06$; telmisartan versus placebo OR 0.97 (95 % CI 0.81–1.17), $p = 0.76$. Cognitive decline: combination versus ramipril OR 0.95 (95 % CI 0.88–1.04), $p = 0.28$; telmisartan versus ramipril OR 0.97 (95 % CI 0.89–1.06), $p = 0.53$; telmisartan versus placebo OR 1.10 (95 % CI 0.95–1.27), $p = 0.22$.

3.3.2 *Antihypertensive Treatment and Dementia*

RCTs that investigated the relation between AH therapy and dementia are summarized in Table 4.

In the SYST-EUR (Systolic Hypertension in Europe) study [35], a total of 2,418 subjects were randomized to placebo or initially treated with a dihydropyridine CCB, possibly associated with an ACEI or a diuretic. This trial was the first to demonstrate a reduction by 50 % over 2 years in the incidence of dementia (7.7–3.8 cases per 1,000 patient-years; $p = 0.05$) [36]. After the double-blind placebo-controlled period, all participants were invited to continue or start on the active therapy for another 2 years. Compared with the controls, long-term AH drug use reduced the incidence of dementia by 55 % from 7.4 to 3.3 cases per 1,000 patient-years ($p < 0.001$) [37]. The results were even more significant than in the first trial. The incidence of AD and VaD was reduced. However, the MMSE scores did not change in either group. In PROGRESS [14], there was no clear benefit of ACEI therapy regarding prevention of dementia, except for patients who had recurrent stroke. However, there was a trend toward greater effects of treatment on dementia among participants treated with combination therapy (perindopril + indapamide) (relative risk reduction [RRR] 23 % [95 % CI 0–41], $p = 0.05$) than among participants treated with single-drug therapy (perindopril) (RRR −8 % [95 % CI −48 to 21], $p = 0.6$), but these results did not differ significantly (p for homogeneity 0.1). The SHEP (Systolic Hypertension in the Elderly Program) trial [38] did not find a significant difference in incidence of dementia between the treated group (diuretics ± BB) and the placebo group during 4.5 years of follow-up (4.2 vs. 3.6 dementia cases per 100 patient-years; RRR 14 %, 95 % CI 26–54; $p = 0.44$) [39]. However, differential drop-out rates might have biased results toward the null effect [40]. This result was consistent with SCOPE [32], which showed no significant difference between the treatment group (candesartan ± hydrochlorothiazide) and the placebo group. The proportion of patients who developed dementia was 62 per 1,000 patient-years in the candesartan group and 57 in the control group ($p = 0.2$). This lack of benefit may be due to small BP differences between groups, reducing the power to detect a preventive effect but also to the low sensitivity of MMSE to detect a slight cognitive decline in subjects without dementia. Finally, the HYVET-COG [33, 34], based on perindopril/indapamide

Table 4 Randomized controlled trials assessing the effect of antihypertensive treatments on dementia

Trial	Subjects	Population characteristics	Follow-up (years)	Intervention	ΔSBP/DBP (active–PL)	Outcomes	Quality score	Main results
SYST-EUR I Forette et al. [36]	2,418 Subjects; age ≥60	SBP 160–219; DBP <95 mmHg	2	CCB (nitrendipine) and/or (ACEI [enalapril] and/or diuretic [hydrochlorothiazide]) vs. PL	−8.3/3.8 mmHg	Dementia; AD, VaD, or mixed	6/8	Reduction in dementia by 50 % (3.8 vs. 7.7 cases per 1,000 pt years; $p = 0.05$)
SYST-EUR II (open follow-up) Forette et al. [37]	2,902 Subjects	Subjects from treatment and PL groups of SYST-EUR I	4	CCB (nitrendipine) and/or (ACEI [enalapril] and/or diuretic [hydrochlorothiazide]) vs. PL	−7/3.2 mmHg	Dementia; AD, VaD, or mixed	6/8	Reduction in dementia by 55 % (3.3 vs. 7.4 cases per 1,000 pt years; $p < 0.001$)
PROGRESS Tzourio et al. [14]	6,105 Subjects; mean age 64	Previous stroke or TIA in 5 years; no age or BP inclusion criteria	3.9	ACEI (perindopril) ± diuretic (indapamide) vs. PL	−9/4 mmHg	Dementia or dementia with recurrent stroke	6/8	Non-significant reduction in dementia except in stroke pts: 34 % (95 % CI 3–55; $p = 0.03$)
SHEP Applegate et al. [39]	4,736 Subjects; age ≥60	SBP 160–219; DBP <90 mmHg; no history of MI or stroke	4.5	Diuretic (chlorthalidone) ± (BB [atenolol] or reserpine) vs. PL	−12/4 mmHg	Dementia, diagnosed through expert evaluation (Short-Care Test)	6/8	Reduction in dementia by 16 % in treatment group, non-significant
SCOPE Lithell et al. [32]	4,964 Subjects; age 70–89	SBP 160–179; DBP 90–99 mmHg; MMSE at BL ≥24	3.7	ARB (candesartan) ± diuretic (hydrochlorothiazide) vs. PL (with open-label active AH therapy if needed)	−3.2/1.6 mmHg	Dementia (modified ICD-10 research criteria)	5/8	Non-significant decrease in incidence of dementia (62 per 1,000 pt-years vs. 57 in control group; $p = 0.2$)
HYVET-COG Peters et al. [34]	3,336 Subjects; age ≥80	SBP 160–200; DBP <110 mmHg	2.2	Diuretic (indapamide) ± ACEI (perindopril) vs. PL	−15/5.9 mmHg	Dementia, AD, VaD	6/8	Non-significant effect on incidence of dementia (HR 0.86; 95 % CI 0.67–1.09)

ACEI angiotensin-converting enzyme inhibitor, *AD* Alzheimer's disease, *AH* antihypertensive, *ARB* angiotensin II receptor blocker, *BB* beta blocker, *BL* baseline, *BP* blood pressure, *CCB* calcium channel blocker, *CI* confidence interval, *DBP* diastolic BP, *HR* hazard ratio, *ICD* International Classification of Diseases, *MI* myocardial infarction, *MMSE* Mini Mental State Examination, *PL* placebo, *pt* patient, *SBP* systolic BP, *TIA* transient ischemic attack, *VaD* vascular dementia

versus placebo, also reported similar results regarding incidence of dementia (HR 0.86; 95 % CI 0.67–1.09). The failure to have significant results is possibly due to a short follow-up period but also to the fact that the study was conducted in subjects over the age of 80 years.

3.4 Meta-Analyses

Recent meta-analyses, including either longitudinal studies or RCTs, have been performed. The meta-analysis conducted by Chang-Quan et al. [41] showed that AH medication could decrease the risk of VaD (RR 0.67; 95 % CI 0.52–0.87) and any dementia (RR 0.87; 95 % CI 0.77–0.96) but could not decrease that of AD (RR 0.9; 95 % CI 0.79–1.03) and cognitive decline (RR 0.97; 95 % CI 0.92–1.03). This result was consistent with the work by Guan et al. [42] (incidence of AD: RR 1.02; 95 % CI 0.91–1.14). Feigin et al. [43] included the PROGRESS, SCOPE, SHEP, and SYST-EUR trials in their meta-analysis and found no significant reduction in dementia (OR 0.8; 95 % CI 0.63–1.02). However, the analysis was based on studying aggregate data, which are potentially less relevant than individual patient data. Another meta-analysis, by Birns et al. [44], suggested a heterogeneous effect of AH therapy that would be beneficial for both immediate (weighted mean difference [WMD] 0.62; 95 % CI 0.21–1.02) and delayed memory (WMD 0.67; 95 % CI 0.23–1.11) but not on executive functions (trail-making test A: WMD −1.12 s; 95 % CI −1.22 to −1.02). In a meta-analysis by Birkenhäger et al. [45] that combined the results of the SHEP, SYST-EUR, and PROGRESS trials, AH therapy reduced the risk of dementia (OR 0.75; 95 % CI 0.6–0.94). This result was further confirmed by Peters et al. [34], who combined the HYVET-COG study in a meta-analysis with the PROGRESS, SYST-EUR, and SHEP trials. The pooled-ratio was borderline significant (HR 0.87; 95 % CI 0.76–1.00; $p = 0.045$), corresponding to a 13 % reduction in dementia risk. In 2009, the Cochrane review by McGuinness et al. [46] reported no significant reduction in incidence of dementia between treatment and placebo (OR 0.89; 95 % CI 0.74–1.07) but a significant improvement of MMSE. The studies included were HYVET-COG, SCOPE, SHEP, and SYST-EUR. The lack of benefit in terms of prevention of dementia may be explained by the exclusion of the PROGRESS study and that, in the SCOPE trial, many subjects originally assigned to the placebo group received AH drugs. Another Cochrane review, by López-Arrieta et al. [47], assessed the clinical efficacy of a CCB (nimodipine) and found a significant benefit on cognitive function in already declared dementia patients (standardized mean difference 0.61; 95 % CI 0.42–0.81; $p < 0.00001$). Very recently, the meta-analysis by Levi Marpillat et al. [48] disclosed benefits of AH treatment on overall cognition and risk of all-cause dementia, ARBs possibly being the most effective (adjusted effect size 0.6 ± 0.18; $p = 0.02$).

4 Discussion

Regarding the association between AH medication and cognitive impairment or cognitive decline, all seven observational studies showed a potential benefit. This result was further confirmed by two RCTs (HOPE and PROGRESS), whereas five (MRC trial of hypertension, SCOPE, HYVET-COG, PROFESS, and TRANSCEND) reported non-significant associations. The HOPE [12] and PROGRESS [14] study populations were more specific, including patients with previous, or at high risk of, cardiovascular events. The observed effects of study treatments reflected reductions in the risk of cognitive decline mainly associated with the occurrence of recurrent stroke during follow-up. This suggests that the benefits of treatment may have been the consequence of stroke prevention rather than a direct effect on cognitive decline. This is consistent with observational studies that have demonstrated that the risk of dementia after stroke is high [49, 50] and with RCTs that have shown that BP lowering reduces the risk of stroke [51]. Other RCTs including hypertensive patients without cardiovascular comorbidities did not report potential benefits of AH drugs on cognitive decline. This might have been due to methodological limitations but also to the characteristics of studies. The HYVET-COG RCT [34] was conducted in very elderly subjects, leading to selection bias in that hypertensive patients who survive to 80 years with no prior vascular event may not be representative of most elderly patients with vascular diseases. Moreover, there is strong evidence that hypertension in midlife, especially if not treated, negatively affects cognition in late life. This is due to the long-term cumulative effect of high BP at middle age, which leads to increased severity of atherosclerosis and vascular comorbidities in later life. However, there is less evidence that the same negative effect is present in later life [3]. This might explain the non-significant effect of AH drugs in preventing cognitive decline in this clinical trial of very elderly subjects. A total of 18 studies (11 observational studies and seven RCTs) compared the incidence of dementia between subjects with and without AH medication use or with different AH drug regimens. In the 11 observational studies, only three showed no significant association [26–28]. Three RCTs reported a lower incidence of dementia with AH drug use (SYST-EUR I, SYST-EUR II, and PROGRESS). Almost all studies focused, as a first step, on the relationship between AH medication and incidence of any dementia. Indeed, accumulating evidence has suggested

that there would be a continuous spectrum of dementias, ranging from patients with pure VaD to patients with pure AD and including a large majority of subjects with contributions from both AD and vascular diseases [2]. Some observational studies and RCTs investigated the potential benefit of AH medication either on VaD or AD. They produced inconsistent results due not only to methodological considerations but also to the fact that the distinction between VaD and AD is less clear than initially envisaged, both conditions sharing similar mechanisms and lesions to some extent. AH medication could decrease the incidence of VaD by lowering BP, disrupting the atherosclerotic process, and reducing the occurrence of cerebrovascular lesions [52]. Despite conflicting results, AH treatments may also be beneficial to reduce the incidence of AD by lowering BP since hypertension was reported to be associated with the neuropathological changes of AD [53]. Moreover, AH therapy could have some benefits in preventing AD through neuroprotective specific effects. However, a recent study suggested that participants in population-based studies may be misdiagnosed with AD when considerable cerebrovascular pathology is undetected [54].

Overall, accumulating evidence suggests that AH drugs may be beneficial in preventing cognitive decline and dementia. First, the potential benefits of AH therapy could be related to their BP-lowering properties. Several epidemiological studies have investigated the relation between BP and cognitive function and dementia. Evidence has emerged that high BP at midlife is an important risk factor for late-life cognitive decline and dementia [3]. Long-term hypertension increases arterial stiffness, leading to severe cerebral atherosclerosis and promotes small-vessel lipohyalinosis. These vascular changes might be the origin of stroke, chronic hypoperfusion, and hypoxia, resulting in white matter damage or leukoaraiosis [3, 55–57]. The ongoing hypothesis is that hypertension-related atherosclerotic and hemodynamic mechanisms would contribute to the early expression of a still subclinical AD [58]. By inducing vessel changes, high BP may also damage the blood–brain barrier, increasing vascular permeability and protein extravasation in cerebral parenchyma. This dysfunction would result in an amyloid accumulation [59]. Further, the involvement of hypoxia-induced factors increasing β-amyloid generation has also been suggested [60]. Hypertension may also influence the development of dementia, especially AD, by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [61]. The subsequent cerebral inflammatory response could trigger amyloid production. Thus, AH therapy may be helpful in reducing dementia risk via a BP-lowering effect.

Some AH subclasses may also be beneficial for cognitive function beyond their ability to reduce BP. Several studies have proposed that CCBs may possess neuroprotective properties. In the meta-analysis by Angeli et al. [62], CCBs were found to decrease the risk of stroke more effectively than other treatments in hypertensive patients, independently of the degree of BP reduction. These results are supported by the SYST-EUR study [36], in which the dihydropyridine CCB nitrendipine, the mainstay of active treatment, significantly reduced the incidence of dementia. A Cochrane review [47] also suggested a significant benefit of nimodipine on cognitive function in already declared dementia patients. In this context, a specific neuroprotective anti-degenerative action of CCBs may be hypothesized. Indeed, calcium is involved in many specific functions in the brain, particularly learning and memory [63]. Studies on rodents have reported age-related increases in L-type voltage-gated Ca^{2+} channel (L-VGCC) activity and calcium transport across the membrane of hippocampal and cortical neurons [64, 65]. This elevated intracellular calcium can cause apoptosis and increase neuronal vulnerability to neuro-degeneration. Indeed, sustained levels of intracellular calcium may induce favorable β-secretase cleavage of amyloid-β protein precursor (AβPP) [66], leading to the production of amyloid-β (Aβ) peptide [67]. Calcium has also been shown to contribute to hyperphosphorylation of Tau protein, underlying the formation of neurofibrillary tangles (NFTs) [68]. Calpains (calcium-dependent proteases), already known to have increased activity with aging and that are elevated in vulnerable neurons in early AD, may be implicated [69]. However, neuro-degeneration is also thought to cause calcium dysregulation [70]. Aβ deposition has been found to increase intracellular calcium in transgenic mouse models of AD by creating cation-selective pores through which calcium ions could enter [71]. Reactive oxygen species (ROS) caused by Aβ accumulation may have an effect on NMDA receptors and L-VGCCs, leading to a greater influx of calcium [72, 73]. Lastly, mutations in the Tau protein, as commonly encountered in AD, have also been shown to increase calcium influx into cells by altering the function of L-VGCCs [74]. Thus, CCBs that target L-VGCCs and attenuate intracellular rises of calcium can exert some therapeutic benefit in the prevention of cognitive decline and dementia, especially AD. Dihydropyridines that are able to cross the blood–brain barrier due to their lipophilic nature would be of considerable relevance [75].

Several lines of evidence also suggested that ACEIs and ARBs, both renin–angiotensin system blockers, may especially have benefits on cognition. Johnson et al. [10] demonstrated a decreased risk of dementia with ACEIs and ARBs, even among patients without hypertension. The potential benefit of ACEIs was also supported by two other observational studies [7, 11]. Lastly, in the PROGRESS study [14], a significant reduction of cognitive decline was

observed among patients who were assigned to perindopril therapy. The renin–angiotensin system is widely recognized as one of the most powerful signaling systems for controlling BP. Renin acts on angiotensinogen to produce angiotensin I, which in turn is cleaved by angiotensin-converting enzyme (ACE) to form the active angiotensin II. The latter, a potent vasoconstrictor, exerts its hypertensive effects following binding to its two receptors (AT1 and AT2). As previously described, hypertension negatively affects cognitive function. Angiotensin-II-mediated inhibition of acetylcholine release is also believed to impair cognition, especially for AD [76]. Conversely, although it has not been fully demonstrated, especially due to some paradoxes between in vitro and in vivo findings, ACE might be involved in degradation of Aβ, which is the major component of senile plaques [77]. Under this model, it is clear that ACEIs could be beneficial on cognitive function by preventing the negative effects of angiotensin II, but they may also reduce the positive benefits to Aβ degradation. Thus, ARBs, while still allowing ACE activity to go unaltered and potentially acting to positively reduce Aβ concentrations, might be more appropriate in preventing cognitive decline. Consistent with this idea was the work by Li et al. [9], in which ARBs were associated with a reduced incidence of AD compared with lisinopril. The meta-analysis by Levi Marpillat [48] also disclosed benefits of AH treatment, ARBs possibly being the most effective. Lastly, ACEIs could also be mediating clinical benefit through a reduction in the activation of inflammatory cytokines that is initiated by the renin–angiotensin system and could play a role in AD [78]. An increased upregulation of neprilysin (an Aβ-degrading enzyme) might be another possible mechanism for the beneficial effect of ACEIs [79]. Experimental studies have also suggested other specific effects of ARBs. Valsartan could promote the expression of insulin-degrading enzyme, known to be involved in the catabolism of Aβ [80]. Telmisartan, a partial agonist of peroxisome proliferator-activated receptor (PPAR)-γ, could also have a preventive effect on cognitive decline by increasing Aβ clearance [81].

Other AH subclasses were also suggested to be beneficial in terms of cognition. The recent work by Gelber et al. [19] in the HAAS disclosed benefits of BBs. The authors hypothesized that BBs could provide neuroprotection through improvement of microvascular integrity and possibly reduction of subsequent neuropathology, including cerebral angiopathy, amyloid deposition, widening of periarteriolar spaces, microinfarcts, and atrophy. However, these mechanisms remain unclear, and the potential preventive effect of BBs was not further confirmed in other longitudinal studies or clinical trials. Potassium-sparing diuretics were also found to be beneficial by reducing the incidence of dementia in the Cache County Study [21]. Consistent with this idea were observations that low potassium levels may be associated with oxidative stress [82, 83], inflammation [82, 83], platelet aggregation [84], and vasoconstriction [85], all of which are possible contributors to AD pathogenesis. However, this benefit was not confirmed further. Thus, regarding the potential preventive effect of BBs or potassium-sparing diuretics, there is currently insufficient evidence for this assertion.

Several methodological factors might explain the discrepancies between some of these studies and sometimes the lack of marked benefit of AH treatments on cognitive decline and dementia. First, observational studies have some limitations, particularly due to their design. The group of patients using AH drugs sometimes differed from those not using AH drugs, with regard to a number of factors potentially related to the risk of dementia. These limitations often lead to an underestimation of the association. Other potential limitations may have contributed to an overestimation of the potential benefits of AH therapy. Self-report of AH drug use by subjects with subtle impairment of memory in the pre-clinical phase of dementia may have produced less reliable answers and consequently led to an under-reporting of AH drug use in cases of dementia. In the same way, visual inspection of all available medication vials was better but less reliable than prescription-filling data. This misclassification of exposure might have been responsible for an overestimation of the beneficial effect of AH drugs in prevention of dementia. Indications for AH treatments may have also been associated with different vascular conditions, resulting in confusion bias. Misclassification of hypertension may also have happened because BP often drops in the pre-clinical phase of AD. This might have led to discontinuation of AH treatment, resulting in a potential overestimation of the protective effect. Attrition is also a common limitation, especially in cohort studies with older people. Another potential limitation is survival bias. Users of AH drugs might have been more likely to die before non-users, particularly due to their comorbidities. They may therefore have escaped detection of cognitive impairment or dementia and may have contributed to an overestimation of the potential benefits of AH therapy. On the other hand, users of AH drugs may have also had a longer survival due to better hypertension treatment, leading to increasing cases of dementia in the elderly since age is by far the strongest risk factor for dementia. RCTs also have methodological limitations. In our systematic review, the lack of benefit found in RCTs may have been due to the fact that, for ethical reasons, numerous subjects whose BP remained high crossed over from placebo to an active treatment group or were treated with more than one AH drug, leading to small BP differences between groups and consequently reducing the power to detect a preventive

effect. Moreover, due to their cost and complexity, RCTs are often designed with a relatively short duration of follow-up. Regarding the progression of cognitive impairment or the incidence of dementia, these RCTs may have been too short to detect a difference between treated and untreated groups since AH drugs would have the greatest effect when administered many years earlier in midlife. RCTs were not designed to assess the effect of AH drugs on cognition, cognitive decline, or dementia, being only secondary outcomes. Some RCTs, such as the SYST-EUR [35] or the HYVET-COG [34] studies, were stopped prematurely because of benefits on the primary endpoints. Thus, despite being the highest level of evidence, RCTs have several methodological limitations and are often of relatively poor quality in this field of prevention of dementia by AH therapy. This may explain some of the conflicting results that are observed with observational studies, leading to a greater consideration of observational data reporting an association.

We also acknowledge that our review has several limitations. First, studies lacked homogeneity across study designs, patient populations, variables, duration of follow-up, and overall methodological quality. All studies used different dosages of AH medications, and most did not mention patient compliance, which may raise questions about the reliability of the findings. Second, this review is based on published work and we cannot exclude the possibility that publication bias influences our findings. Statistically significant results are more likely to be published. Such publication bias often makes empirical effects seem larger than they are.

If confirmed in further RCTs with longer periods of follow-up and cognition as the primary outcome, the potential benefits of AH drugs on cognitive decline and dementia will have considerable clinical, public health, and economic implications. Indeed, in view of global increases in population size and life expectancy, the estimated number of people with dementia worldwide is expected to double every 20 years. To date, no curative treatments are available for AD, and with the modest benefits shown by the current AD-specific treatments (cholinesterase inhibitors and memantine), it is critically important that risk factors whose modification could potentially prevent or delay the onset of disease are identified. Hypertension is one of these potentially modifiable risk factors, suggesting a substantial impact of AH therapy in prevention of cognitive decline and dementia. This is crucially important in clinical medicine. In hypertensive patients, the potential preventive effect on cognitive decline and dementia will strongly add to the overall benefits of treatment. These additional benefits might also improve patient compliance with AH therapy. The results of our systematic review provide additional rationale and indicate the need for heightened efforts to detect hypertension, adequately treat it, and carefully monitor patients with the disease. If confirmed in further RCTs, the potential neuro-specific preventive effects of CCBs and renin–angiotensin system blockers could help the clinician choosing an AH medication based not only on BP control, but also on additional benefits. Overall, the potential benefits of AH drugs in preventing cognitive decline and dementia could have major public health implications in ageing populations. Recent estimates have suggested that around half of the AD cases worldwide might be attributed to potentially modifiable risk factors, one of which is hypertension [86]. Moreover, interesting projections suggested that, assuming a constant life expectancy, if the age at onset of clinical dementia could be delayed in all cases by just 5 years, the lifetime risk of dementia could be drastically reduced [87]. Thus, the potential benefits of AH drugs to reduce cognitive decline or incidence of dementia and to delay the onset of the disease could have a major public health impact. These potential preventive effects may also lead to a decrease in the tremendous burden of disability on dementia patients and caregivers. The primary cost drivers of dementia are informal costs due to home-based long-term care and nursing home expenditures [88]. Thus, the results of our systematic review could also have important economic implications.

5 Conclusion

Overall, the findings of this systematic review suggest that AH therapy may decrease the incidence and progression of cognitive decline and dementia; not only VaD but also AD. Several observational studies, RCTs, and meta-analyses have found positive results regarding prevention of cognitive decline and dementia; although the results are sometimes conflicting, this is probably due to methodological limitations as discussed above. Finally, accumulating evidence suggests that AH drugs, particularly CCBs and renin–angiotensin system blockers, could reduce the risk for and progression of cognitive impairment and dementia, not only by lowering BP but also through a neuroprotective specific effect. Further RCTs, particularly in populations at high risk of cognitive decline, with longer periods of follow-up and cognition as the primary outcome, are needed to confirm these findings. They would be of considerable importance, not only in terms of understanding the etiology of dementia but also in promoting BP-lowering strategies in a public health dimension.

Acknowledgments No funding was received related to the preparation of this article. Laure Rouch, Philippe Cestac, Charlène Cool, Bernard Chamontin, and Bruno Vellas have no conflicts of interest to

declare. Olivier Hanon reports receiving consulting fees or honorarium from Servier, Bayer, Sanofi, Boehringer-Ingelheim, Daiichi, Novartis, and Bristol-Myers Squibb. Catherine Helmer reports receiving fees from Schwabe Pharma. Béatrice Bouhanick has acted as a consultant for Lilly and Astra Zeneca for diabetic products. She has no conflict of interest with antihypertensive therapy. Jean-François Dartigues has received Grants from Ipsen and Novartis and consulting fees or honorarium from Ipsen, Novartis, and Newron. Sandrine Andrieu has a conflict of interest with the Ministry of Education. She has received Grants from Ipsen, Lilly, Lundbeck, and Nestlé. She has received consulting fees or honorarium and support for travel to meetings, manuscript preparation from Ipsen, Eisai, Pierre Fabre, Pfizer, Lilly, Janssen, Chiesi, Exonhit, Lundbeck, Nestlé, Novartis, Roche, Servier, and Sanofi. She has received fees for participating in review activities such as data monitoring boards from Enroll-HD and the CHDI Foundation and has received payments for lectures from Ipsen, Eisai, Pierre Fabre, Servier, Pfizer, Lundbeck, Nestlé, Novartis, Janssen, Chiesi, and Elan Pharmaceuticals.

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