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EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON COGNITIVE DECLINE

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Growing evidence supports the link between hypertension (HTN) in midlife and increased risk for cognitive decline and dementia in late-life. The Alzheimer's Disease (AD) International Association recognized HTN as the main modifiable vascular risk factor for cognitive decline and dementia. Clinical trials have demonstrated that antihypertensive treatment (AHT) and blood pressure (BP) control reduce the "burden" and "progression" of vascular brain injury and subsequently the risk of stroke, cognitive impairment and dementia. Given that the causes of dementia include a complex interplay between vascular and non-vascular risk factors, AHT could prevent cognitive decline or dementia risk beyond the presence of stroke or BP control. Results from several prospective studies seem to provide conflicting results on the effects of antihypertensive drugs on cognitive function or the incidence of dementia, partly explained by the fact that the vast majority of trials on BP were not designed to address cognitive function. Nevertheless, available data including meta-analysis suggest that AHT appears to have beneficial effects on cognitive function by lowering the incidence of dementia. Given the growing incidence of worldwide dementia, it is likely that BP control can minimize the risk or delay the onset of cognitive impairment, thereby reducing the burden of dementia and its adverse impact on public health.

PROSPECTIVE CONTROLLED TRIALS

Results on the positive effects of AHT in improving cognitive function, preventing dementia or AD are conflicting (Table 1). The Syst-Eur trial found that treatment initiated with nitrendipine with the possible addition of enalapril and/or hydrochlorothiazide, led to a reduction in the incidence of dementia by 50% and 55% in the extended phase [1]. The Rotterdam Study found that participants who received AHT at baseline had a significant reduction of the vascular dementia risk (70%) and a 13% nonsignificant reduction in the incidence of AD [2]. The HOPE [3] and the PROGRESS [1] studies were not designed to evaluate cognitive function in hypertensive patients. However, the sub-analysis of these trials demonstrated a reduction in cognitive decline associated with stroke decrease by 41% and 45% respectively. In addition, the PROGRESS sub-analysis study showed a 34% decrease in the risk of post stroke dementia. The HYVET-COG which was designed to assess the risk and benefit of AHT in elderly patients [1], was stopped early due to a substancial reduction in stroke and mortality in the treated group, but the incidence of dementia was not different between groups. The SHEP study showed similar findings but the total stroke incidence was reduced by 36% in patients with isolated systolic HTN [1]. However, a meta-analysis including HYVET-COG, SHEP, PROGRESS and Syst-Eur studies supported the use of AHT in reducing incidental dementia. The SCOPE study found no significant difference in reducing the incidence of dementia and cognitive decline using the Mini Mental Statement Examination (MMSE), but there was a trend in a reduction in cognitive decline in subjects with abnormal baseline MMSE [4].

The SPRINT MIND trial [5] demonstrated that the intensive BP control (systolic BP target less than 120 mmHg) significantly reduced the risk of mild cognitive impairment and the composite of mild cognitive impairment plus probable dementia compared to patients in the standard treatment group (systolic BP target less than 140 mmHg). A slow progression of the burden of the white matter hyperintensities (WMH) was also evident in the intensive-treatment group.

Regarding the elderly or very-old population, the Leiden 85-plus study found that therapy with calcium channel blockers (CCBs) reduced the annual cognitive decline assessed by MMSE. However, a more recent analysis showed that lower systolic BP in very-old taking antihypertensive drugs was associated with higher mortality and faster decline in cognitive function compared to patients not taking BP lowering therapy [6]. Accordingly, the 90+ study showed that developing HTN in older age may protect against dementia, particularly when the onset of HTN occurred between 80-89 years [7]. Additionally, the aggressive BP control in very old, frail patients has been linked to increase mortality and further deterioration of cognitive function and motor skills [8]. In this context, BP lowering therapy must be carefully monitored and managed in very old subjects.

EFFECTS OF DIFFERENT CLASSES OF ANTI-HYPERTENSIVE DRUGS

Benefits on cognitive function comes from controlling BP per se independently of the drug used. It has been documented that some drug classes could be superior to others in preventing cognitive decline. The use of Beta-Blockers (BB) in the SHEP study (monotherapy or in combination with diuretics) [1] did not induce significant changes in the cognitive test. The Honolulu-Asia Aging Study showed that patients receiving BB had a lower risk of cognitive impairment [9]. Diuretics were found not to improve cognitive performance or decrease the risk of dementia when used in monotherapy or combined with BB or angiotensin-converting-enzyme inhibitors (ACEi). However, the diuretic indapamide combined with perindopril have been shown to effectively prevent stroke, post stroke cognitive impairment and reduce the risk of dementia [1]. The Cache County Study showed that diuretics, specifically spironolactone, reduced incidence of AD by 70%. Another meta-analysis demonstrated that diuretics reduced the risk of dementia by 15% to 17% and the risk of AD by 18% [10]. The stratified analysis by diuretic subclass showed that spironolactone reduced dementia risk by approximately 30%, thiazide by 6% and loop diuretics by 14%.

CCBs used in Syst-Eur trial reduced the incidence of dementia by 50% [1]. The beneficial effects of CCB on cognitive function may be mediated by mechanisms other than BP lowering (i.e. calcium neuronal influx, imbalance intracellular calcium, dysregulation neuronal function). In another meta-analysis both CCBs and angiotensin II receptor blockers (ARBs) were independently associated with a decreased risk of dementia [11]. There is not clear evidence that CCBs decrease the risk of cognitive decline or dementia in the very elderly people [12].

Evidence indicates for the key role of the renin–angiotensin system (RAS) in the physiopathology of HTN, cognitive impairment, dementia and AD. The PRoFESS and TRANSCEND trials showed a reduction by 11% and 17% in cognitive impairment, respectively, without statistical significance. The ONTARGET trial showed no beneficial effect on cognitive outcome in patients with cardiovascular disease and diabetes [13]. The AVEC study documented that candesartan preserves the executive function, which is the most affected cognitive domain in hypertensive patients. In a study of 1,281 hypertensive patients the prevalence of executive dysfunction was 36.2% [14]. Another trial showed that candesartan improved executive function more than lisinopril and hydrochlorothiazide after 12 months follow-up. The U.S. Veterans Affairs demonstrated that ARBs are associated with a significant reduction in the incidence (55%) and progression (70%) of AD and dementia compared to lisinopril or other cardiovascular drugs [15].

The ability to cross the brain blood barrier (BBB) of the different antihypertensive drugs depends on the damage of the BBB and lipid solubility of the drugs. Centrally active ACEi (i.e. captopril, lisinopril, perindopril, ramipril) and ARBs (i.e. candesartan, irbersartan, valsartan, and telmisartan) have more capacity to penetrate cerebral tissues compared

to non-centrally active ACEi and ARBs (i.e. benazepril, enalapril, quinapril or losartan, olmesartan). RAS blocking drugs were associated with a lower likelihood to develop AD (33% vs 40%), whereas BBB-crossing RAS medications were associated with slower cognitive decline. The AD Neuroimaging Initiative [16] demonstrated that patients taking BBB-crossing ARBs had superior memory performance and less WMH volume over time compared to other non-BBB-crossing antihypertensive drugs. The Cardiovascular Health Study Cognition sub-study demonstrated a reduction in the risk of cognitive decline by 65% per year with ACEi, whereas the cumulative dosage of non-central ACEi was associated with a higher incidence of dementia. While centrally-acting ACEi were found to reduce rates of cognitive decline in patients with dementia, it remains unclear if all patients may benefit from this therapy [17].

META-ANALYSIS

Lowering of BP had a heterogenous effect on cognitive domains (Table 2). Birns et al. demonstrated an improvement in cortical but not in subcortical cognitive function [18]. Another meta-analysis showed that AHT lowers the incidence of vascular dementia without effect on cognitive impairment [19]. Further meta-analysis concluded that AHT, irrespective of drug class used, led to a reduction in the risk of all-cause dementia by 9% and an overall improvement of cognitive domains (except language) [20]. Other two systematic reviews indicated that ARBs are superior in improving episodic memory [21], whereas CCBs and ARBs appear to be beneficial in preventing cognitive decline and dementia [22]. A reduction in the incidence of dementia was also reported in another meta-analysis, without significant effect on the incidence of AD, cognitive impairment and cognitive decline [23].

CONCLUSION

AHT has been shown to be effective in controlling BP, slowing the progression of vascular injury and decreasing the incidence of stroke. These benefits could be extrapolated to prevention of cognitive impairment or dementia. Although, there is still a lack of properly designed clinical studies evaluating the impact of BP lowering therapy on cognitive function, the use of drugs that modulate the RAS (centrally-action) and CCBs seems to be superior in preserving the cognitive function by mechanisms independent of BP control, suggesting cerebroprotective effect. While more robust evidence needs to come, the current knowledge should be applied to reduce or delay the vascular brain injury and its cognitive consequences.

Table 1. Prospective Controlled Trials

Study	Population / follow-up	Drugs	Cognitive Outcome
Systolic Hypertension in Europe (Syst-Eur) [1]	n=2418, ≥60 y, no dementia baseline, (median FU 2 y)	Nitrendipine ± enalapril, HCTZ or both	Reduced incidence of dementia 50% (7.7 to 3.8 cases/1000p/y). AD=23, VaD=2 cases
Rotterdam study [2]	n=7046, ≥55 y, no dementia baseline, (mean FU 2,2 y)	Anti-hypertensive agents	Reduced incidence of VaD (RR 0.30, 95%CI: 0.11-0.99) and no-significant reduction of AD
Heart Outcome Prevention Evaluation (HOPE) [3]	n=9297, ≥55 y, vascular disease/diabetes (FU 4,5 y)	Ramipril	Reduced cognitive decline by 41% (RR 0.59, 95%CI 0.37 to 0.94)
Perindopril Protection Against Recurrent Stroke Study (PROGRESS) [1]	n=6105, mean 64 y, stroke or TIA previous, (FU 3,94 y)	Perindopril ± indapamide	Post-stroke cognitive decline by 45% (95%CI 21% to 61%) and post-stroke dementia risk by 34% (95%CI 3% to 55%)
Hypertension in Very Elderly Trial-Cognition (HYVET-COG) [1]	n=1687, ≥80 y, without dementia, (FU 2,2 y)	Indapamide ± perindopril	No significant difference in incident dementia (38 vs 33 cases/1000p/y)
Systolic Hypertension in the Elderly Program (SHEP) [1]	n=4736, >60 y, isolated systolic HTN (FU 2,2 y)	Chlorthalidone + atenolol	No significant difference in incident dementia (37 vs 44 cases)
Study Cognition and Prognosis in the Elderly (SCOPE) [4]	n=4937, 70-89 y, hypertension and MMSE ≥ 24, (FU 3,7 y)	Candesartan ± other anti-hypertensives	No significant difference in cognitive decline or dementia. Reduced MMSE score decline in pts with baseline MMSE 24-28 (-0.04 to -0.53, 95%CI 0.02-0.97)
Systolic Blood Pressure Intervention Trial-MIND (SPRINT-MIND) [5]	n=9361, >50 y, with CV risk and without stroke or dementia (FU 5,1 y)	Anti-hypertnesive agents	Reduced risk MCI (HR 0.81, 95%CI 0.69-0.95) and combined MCI or dementia (HR 0.85, 95%CI 0.74-0.97)
Leiden 85-plus study [6]	n=204, >85 y, at least one anti-hypertensive treatment	Anti-hypertensive agents	Only CCBs reduced anual cognitive decline (0.4 MMSE-point/year)
Leiden 85-plus study [6]	n=249, >85 y, at least one anti-hypertensive treatment	Anti-hypertensive agents	Increased all-mortality (HR 1.29/10 mmHg lower SBP, 95%CI 1.15-1.46). and cognitive decline (-0.35 MMSE-points/10 mm Hg; 95%CI -0.60, -0.11)
The 90+ study [7]	n=559, >90 y, no dementia (FU 2,8 y)	Anti-hypertensive agents	Reduced dementia risk with onset HTN at 90+ (HR 0.37, 95%CI 0.19-0.73)

Table 2. Meta-analysis

Meta-analysis	Number of studies	Number of subjects	Results
PROGRESS, Syst-Eur, SHEP, HYVET meta-analysis [1]	4 RCT	14,946	Reduced incident of dementia (HR 0.87, 95%CI 0.76-1.0)
Birns J et al. [18]	16 RCT	19,501	Heterogenous effect on different cognitive function
Chang-Quan H et al. [19]	14 longitudinal	69,563	Reduced incident of VaD (RR 0.67, 95%CI 0.52-0.87)
Levi Marpillat N et al. [20]	19 RCT + 11 studies	18,515 + 831,674	Reduced risk of dementia (HR 0.91, 95%CI 0.89-0.94)
Rouch L et al. [21]	11 RCT + 9 MA	1,346,176	Reduced incidence and progression of cognitive impairment and dementia (VaD and AD)
Guangli Xu et al. [23]	10 RCT	30,895	Reduced incidence of dementia (RR 0.86, 95%CI 0.75-0.99)

FU: Follow-up; y: years; AD: Alzheimer's disease; VaD: vascular dementia; MCI: mild cognitive impairment; MMSE: Mini-mental statement Exmination

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