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EFFECTS OF ANTIHYPERTENSIVE TREATMENT ON COGNITIVE DECLINE

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The link between hypertension (HTN) in midlife and increased risk for cognitive decline and dementia in late-life is well-established. HTN is recognized 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. Causes of dementia include a complex interplay between vascular and non-vascular risk factors, thus AHT could prevent cognitive decline or dementia risk. Prospective studies seem to provide conflicting results, partly due to the fact that the vast majority of trials on BP were not designed to address cognitive function. Available data including meta-analysis suggest that AHT appears to have beneficial effects by minimizing 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 Alzheimer's disease (AD) are conflicting (Table 1). The Syst-Eur trial found that AHT reduced the incidence of dementia by 50% and 55% in the extended phase [1]. The Rotterdam Study showed that AHT reduced the vascular dementia risk by 70% and the incidence of AD by 13% (non-significant) [2]. The sub-analysis of the HOPE [3] and the PROGRESS [1] studies demonstrated a reduction in cognitive decline associated with stroke (41% and 45%, respectively). In addition, the PROGRESS study showed a 34% decrease in the risk of post stroke dementia. The HYVET-COG demonstrated a substancial reduction in stroke and mortality in the treated group, but not in the incidence of dementia [1]. The SHEP study found a reduction in the total stroke incidence 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. In the SCOPE study the incidence of dementia was not reduced, but there was a trend in a reduction in cognitive decline in subjects with abnormal baseline Mini-Mental test [4].

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

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 [1] induce no significant changes in the cognitive test. The Honolulu-Asia Aging Study showed that patients receiving BB had a lower risk of cognitive impairment [9]. 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. However, another 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 AHT [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, AHT must be carefully monitored and managed in very old subjects.

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 effectively prevented stroke, post stroke cognitive impairment and reduced the risk of dementia [1]. In the Cache County Study 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 the 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, neuronal dysfunction). 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 non-significant reduction by 11% and 17% in cognitive impairment, respectively. 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 (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. In the U.S. Veterans Affairs ARBs were associated with a 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, however 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 AHT on cognitive function, the use of drugs that modulate the RAS (centrally-action) and CCBs seems to be superior in preserving 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-hypertensive agents	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. [22]	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

REFERENCES

1. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the hypertension in the very elderly trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7:683–689.
2. In't Veld BA, Ruitenberg A, Hofman A, et al. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001;22:407-12.
3. Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke: double blind randomised trial. Br. Med. J. 2002;324:699-702.
4. Skoog I, Lithell H, Hansson L, et al. SCOPE Study Group. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). Am J Hypertens. 2005;18:1052-9.
5. The SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA 2019;321(6):553-61.
6. Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old-data from the Leiden 85-plus Study. Age Ageing. 2018 May 8. [Epub ahead of print]
7. Corrada MM, Hayden KM, Paganini-Hill A, et al. Age of Onset of Hypertension and Risk of Dementia in the Oldest-Old: The 90+ Study. Alzheimers Dement. 2017;13:103–110.
8. Benetos A, Bulpitt CJ, Petrovic M, et al. An Expert Opinion From the European Society of Hypertension-European Union Geriatric Medicine Society Working Group on the Management of Hypertension in Very Old, Frail Subjects. Hypertension. 2016;67:820-5.
9. Gelber RP, Webster RG, Petrovitch H, et al. Antihypertensive medication use and risk of cognitive impairment. The Honolulu-Asia Aging Study. Neurology. 2013;81:888–895.
10. Tully PJ, Hanon O, Cosh S, Tzourio C. Diuretic antihypertensive drugs and incident dementia risk: a systematic review, meta-analysis and meta-regression of prospective studies. Journal of Hypertension. 2016, 34:1027-1035.
11. van Middelaar T, van Vught LA, Moll van Charante EP, et al. Lower dementia risk with different classes of antihypertensive medication in older patients. J Hypertens 2017;35:2095-2001.
12. Peters R. No clear relationship between antihypertensive class and cognitive function over 12 months in a cohort study of community-dwelling adults aged 80 and over. Ther Adv Chronic Dis. 2019 Jan 31;2019 Jan 31. doi: 10.1177/2040622318820849.
13. Anderson C, Teo K, Gao P, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurol. 2011;10:43–53.
14. Vicario A, Cerezo GH, del Sueldo M, et al. On behalf of the Heart-Brain Research Group in Argentina with the support of the Argentine Federation of Cardiology (FAC). Neurocognitive disorder in hypertensive patients. Heart-Brain Study. Hipertens Riesgo Vasc. 2018;35:169-176.
15. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. Br. Med. J. 2010;340:b5465.
16. Ho JK and Nation DA. Memory is preserved in older adults taking AT1 receptor blockers. Alzheimers Res Ther. 2017;9:33.
17. Gao Y, O'Caoimh R, Healy L, et al. Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. BMJ Open. 2013;3:1–8.
18. Birns J, Morris R, Donaldson N, Kalra L. The effects of blood pressure reduction on cognitive function: a review of effects based on pooled data from clinical trials. J Hypertens. 2006;24:1907-14.
19. Chang-Quan H, Hui W, Chao-Min W et al. The association of antihypertensive medications use with risk of cognitive decline and dementia: a meta-analysis of longitudinal studies. In J Clin Pract. 2011;65:1295-305.
20. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, et al. Antihypertensive classes, cognitive declineand incidence of dementia: a network meta-analysis. J. Hypertens. 2013;31:1073–1082.
21. Stuhec M, Keuschler J, Serra-Mestres J, et al. Effects of different antihypertensive medication groups on cognitive function in older patients: A systematic review. Eur Psychiatry. 2017;46:1-15.
22. Rouch L, Cestac P, Hanon O, et al. 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. CNS Drugs. 2015;29:113-30.
23. Guangli Xu, Feng Bai, Xin Lin, et al. Association between Antihypertensive Drug Use and the Incidence of Cognitive decline and Dementia: A Meta-Analysis of Prospective Cohort Studies. BioMed Research International. 2017, Article ID 4368474.