

Hypertension Treatment and Alzheimer’s Disease Risk by APOE Genotype

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Take-Home Message: Results of this study support the use of diverse antihypertensive drug classes, rather than specific types, for AD prevention, suggesting that lowering BP itself may be more important for AD prevention than the specific mechanism by which BP is reduced. AD-protective effects were smaller in APOE4 non-carriers compared with the overall sample. Results in APOE4 carriers did not reach statistical significance and will require confirmation in larger datasets.

INTRODUCTION	METHODS	RESULTS	RESULTS	CONCLUSIONS																																																																																							
Hypertension is considered a risk factor for Alzheimer’s disease (AD). It is also a very common condition affecting more than 70% of older adults. Since only about 11% of older adults over age 65 will receive AD diagnosis, hypertension alone may not be a strong predictor of AD risk. Prior research suggested that antihypertensive (HTN) treatment may delay AD onset and that some HTN drugs might provide more neuroprotection than others, though the evidence remains inconclusive. Considering genetic risk factors for AD may help further personalize AD prevention with HTN treatments. Here, we investigated how various HTN drugs initiated before age 70 may influence the odds of AD onset after age 75, taking into account APOE4 carrier status, the strongest genetic risk factor for AD.	The Long Life Family Study (LLFS) and the Health and Retirement Study (HRS) data were used. Logistic regression models were first applied to the LLFS data and then validated in the independent HRS cohort. The analysis was run in the full sample and separately for APOE4 carriers and non-carriers. Binary indicators of treatment with ACE inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta-blockers (BB), and calcium channel blockers (CCB) served as individual predictors. We also used two broader groups of HTN medications that included multiple drug classes: AAD (ACEI, ARB, diuretics) and BC (BB, CCB). The outcome was AD diagnosis at age 75+ vs. remaining AD-free past age 75. Sex, education, and smoking status were included as covariates.	Table. Associations of antihypertensive drugs initiated before age 70 with odds of AD onset after age 75 in LLFS. <table><tr><th>Data</th><th>Predict</th><th>Estim</th><th>SD</th><th>OR</th><th>Z-val</th><th>P-val</th><th>N</th><th>N events</th></tr><tr><td>all</td><td>AAD</td><td>-1.44</td><td>0.61</td><td>0.24 (0.069, 0.679)</td><td>-</td><td>2.38</td><td>0.0174</td><td>1887</td><td>91</td></tr><tr><td>all</td><td>BC</td><td>-1.85</td><td>0.31</td><td>0.16 (0.090, 0.298)</td><td>-</td><td>4.11E-09</td><td>1988</td><td>94</td></tr><tr><td>all</td><td>ACEI</td><td>-1.29</td><td>0.50</td><td>0.28 (0.125, 0.761)</td><td>-</td><td>2.62</td><td>0.0089</td><td>2567</td><td>140</td></tr><tr><td>all</td><td>ARB</td><td>-1.18</td><td>0.51</td><td>0.31 (0.141, 0.859)</td><td>-</td><td>2.31</td><td>0.0207</td><td>2739</td><td>151</td></tr><tr><td>all</td><td>BB</td><td>-1.39</td><td>0.41</td><td>0.25 (0.128, 0.573)</td><td>-</td><td>3.38</td><td>0.0007</td><td>2309</td><td>112</td></tr><tr><td>APOE4 noncarrier</td><td>BC</td><td>-1.48</td><td>0.31</td><td>0.23 (0.128, 0.427)</td><td>-</td><td>1.17E-06</td><td>1554</td><td>66</td></tr><tr><td>APOE4 noncarrier</td><td>ACEI</td><td>-1.09</td><td>0.53</td><td>0.34 (0.125, 1.007)</td><td>-</td><td>2.06</td><td>0.0399</td><td>2030</td><td>105</td></tr><tr><td>APOE4 noncarrier</td><td>BB</td><td>-1.05</td><td>0.42</td><td>0.35 (0.165, 0.806)</td><td>-</td><td>2.49</td><td>0.0126</td><td>1804</td><td>80</td></tr></table> Outcome: AD odds after age 75. OR: Odds Ratio. Predictors: initiating these anti-hypertensives before age 70: ACE inhibitors (ACEI); angiotensin II receptor blockers (ARB); diuretics; beta-blockers (BB); calcium channel blockers (CCB); and two broader groups: AAD (ACEI, ARB, diuretics) and BC (BB, CCB). Covariates: sex, education, smoking status. Model: logistic regression with familial bootstrapping (N=1000), no PSM. Sample: all LLFS participants. N.B. Results for APOE4 carriers and CCB were not significant (not shown).	Data	Predict	Estim	SD	OR	Z-val	P-val	N	N events	all	AAD	-1.44	0.61	0.24 (0.069, 0.679)	-	2.38	0.0174	1887	91	all	BC	-1.85	0.31	0.16 (0.090, 0.298)	-	4.11E-09	1988	94	all	ACEI	-1.29	0.50	0.28 (0.125, 0.761)	-	2.62	0.0089	2567	140	all	ARB	-1.18	0.51	0.31 (0.141, 0.859)	-	2.31	0.0207	2739	151	all	BB	-1.39	0.41	0.25 (0.128, 0.573)	-	3.38	0.0007	2309	112	APOE4 noncarrier	BC	-1.48	0.31	0.23 (0.128, 0.427)	-	1.17E-06	1554	66	APOE4 noncarrier	ACEI	-1.09	0.53	0.34 (0.125, 1.007)	-	2.06	0.0399	2030	105	APOE4 noncarrier	BB	-1.05	0.42	0.35 (0.165, 0.806)	-	2.49	0.0126	1804	80	In LLFS, familial bootstrap–adjusted analyses (N = 1000 replicates) found significant reduction in AD risk for two groups of HTN medications: AAD (OR =0.24) and BC (OR=0.16) in the full sample. Similar protective effects were seen for specific drug classes: ACEI, ARB, BB (Table). Stratified analysis found smaller (but still significant) benefits in APOE4 non-carriers taking BC, ACEI, BB; however, no significant effects were seen in APOE4 carriers. Replication analysis in the HRS broadly supported the protective associations with AD for AAD (OR=0.44) and BC (OR=0.55). Confidence intervals overlapped across cohorts, supporting the robustness of these associations. The larger AD-protective effects of HTN meds in LLFS (~80% risk reduction) may reflect the familial aggregation of exceptional health and longevity. Non-significant results in APOE4 carriers are likely due to the small sample size, so confirmation in larger datasets will be necessary.	Starting antihypertensive treatment before age 70 was associated with lower odds of AD after age 75 in LLFS and HRS. Unstratified analyses showed comparable AD-protective effects for both AAD and BC drug categories (LLFS: AAD OR=0.24, BC OR=0.16; HRS: AAD OR=0.44, BC OR=0.55). This suggests that <u>lowering BP itself may be more important for AD prevention than the specific mechanism by which BP is reduced</u>. Overall, our results support the use of various HTN medications, rather than specific drugs, for AD prevention. Acknowledgements This research was supported by the National Institutes of Health's National Institute on Aging (NIA/NIH) grants U19AG063893, R01AG062623. This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA/NIH. The research was conducted using the data provided by the Long Life Family Study (LLFS) and the Health and Retirement Study (HRS).  ALZHEIMER'S ASSOCIATION AAIC 26
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